Summary

Foreword ................................................................. 5
On the Cover ............................................................. 7
2017 Research ............................................................ 9
Facts and Figures ......................................................... 9
Research Quality ......................................................... 13
Assurance Policies ....................................................... 13
Evaluation of Research Quality (VQR 2011-2014) ................. 16
Research Organization and Services ................................ 18
  Centre for Integrated Research .................................. 19
  Academic Research Board ........................................ 19
  Research Administrative Area .................................... 19
    Technology and Transfer Office ............................... 19
    Project Financial Management and Reporting Office .... 19
    Clinical Research Office ....................................... 20
  The Library ............................................................ 20
  Document supply service ......................................... 20
  Doctoral dissertations theses repository ....................... 20
  Contacts .............................................................. 21
Ethics Committee .......................................................... 22
  Members of the Ethics Committee ................................ 23
Research Units – overview and main 2017 scientific outputs .... 24
  Allergology, Immunology, Rheumatology ..................... 25
  Anesthesia, Intensive Care and Pain Management ............ 27
  Automation and Control Theory ................................ 29
  Biochemistry and Molecular Biology ............................ 31
  Biomedical Robotics and Biomicrosystems ...................... 33
  Breast Care .......................................................... 35
  Cardiovascular Science ............................................ 37
  Chemical-Physics Fundamentals in Chemical Engineering .... 39
Clinical Laboratory Sciences .......................................................... 41
Computer Systems and Bioinformatics ........................................... 43
Developmental Neuroscience .......................................................... 45
Diagnostic Imaging. ................................................................. 47
Drug Sciences ............................................................................. 49
Electronics for Sensor Systems ..................................................... 51
Endocrinology and Diabetes .......................................................... 53
Food Science and Nutrition ............................................................ 55
Gastroenterology ........................................................................ 57
General Surgery ......................................................................... 59
Geriatrics .................................................................................... 61
Gynaecology and Obstetrics ......................................................... 63
Heart Surgery .............................................................................. 65
Hematology, Stem Cell Transplantation, Transfusion Medicine and Cellular Therapy .............. 67
Hygiene, Public Health and Statistics ............................................ 69
Institute of Philosophy of Scientific and Technological Practice (FAST) ........................................ 71
Internal Medicine and Hepatology ............................................... 73
Measurements and Biomedical Instrumentation ................................ 75
Microscopic and Ultrastructural Anatomy. ................................... 77
Molecular Medicine and Biotechnology ......................................... 79
Molecular Neurosciences ............................................................... 81
Molecular Psychiatry and Neurogenetics ....................................... 83
Neurology, Neurophysiology, Neurobiology .................................. 85
Neurophysiology and Neuroengineering of Human–Technology Interaction ............................... 87
Nonlinear Physics and Mathematical Modeling ................................ 89
Nursing Science .......................................................................... 91
Oncology .................................................................................... 93
Ophthalmology ......................................................................... 95
Orthopaedic and Trauma Surgery ............................................... 97
Otolaryngology .......................................................................... 99
Pathology ................................................................................ 101
Physical and Rehabilitation Medicine ........................................... 103
Plastic Surgery and Dermatology ................................................. 105
Process Engineering ................................................................... 107
Radiation Oncology ................................................................. 109
Tissue Engineering & Chemistry for Engineering ................................ 111
Urology .................................................................................... 113
Vascular Surgery ...................................................................... 115
Virology .................................................................................. 117
Dear Stakeholder,

This 2017 edition of the Research Yearbook provides you an overview of Research activities and organization at the Campus Bio-Medico University of Rome (UCBM). It presents our research policies and strategies, and it reports specifically about the main facts, projects, scientific and innovation outputs produced by our institution in the 2017 calendar year.

In line with past editions, the contents of this 2017 Research Yearbook have been selected and developed having in mind three main goals, namely:

- **Dissemination and Promotion.** The Yearbook aims at providing to all those interested in UCBM research a comprehensive digest of the main ongoing research projects, and a simplified directory of the expertise, scientific equipment, technological facilities and services, research units and other organisational structures available in our university. We expect that all our stakeholders (e.g. students, researchers, experts and decision-makers from companies and from public and private institutions), will be able to easily retrieve from this document the basic answers to their knowledge and innovation needs, and identify the specific group(s) in our community and networks that will best fit for the purpose of effectively satisfying such needs. Extended information on our research activities can be retrieved on the research section of our official website http://www.unicampus.it/eng/research/;

- **Accountability.** This Yearbook is also intended to provide our main sponsors and external supporters a direct, basic source of information on how resources have been used, on which main outputs such resources contributed to generate and on the innovation potential of those outputs. From our perspective, it is a very important, crucial action of transparency and acknowledgement toward that part of the society which expressed trustiness in our research and innovation capabilities;

- **Self-assessment.** The facts and data briefly presented in this Yearbook are fully instrumental in providing a clear set of internal and external benchmarks to our research community, to stimulate continuous improvement of our performance and of the quality of our research work. The Yearbook also includes a brief description of the internal quality assurance policies.

Overall, the 2017 research facts and figures clearly confirm that UCBM Research stands at the same level, both in qualitative and quantitative terms, of the top Italian universities: about 60% of our publications appeared on journals belonging to the first quartile (Q1) of the Scopus/Scimago international periodicals ranking; 20% of the faculty members are now included in the so-called Top Italian Scientists community; and an overall success rate higher than 17% has been reached on competitive calls.

Finally, we want to acknowledge all researchers, clinical personnel and administrative and technical staff for their continued effort to keep the high-quality standards of our activities and outputs. Special thanks to the many contributors to this Yearbook, and especially to Maria Dora Morgante, Head of the Library Services, Riccardo Adriani, Head of the Graphics and Editing Services, and Antonella Benvenuto, Head of the Grant Office, for the hard work in the preparation of this document.

We do hope that you will enjoy this 2017 Yearbook and use it as the main reference to get in touch with those actors in our university who could best fit your expectations. We will be very happy to receive any remarks and suggestions aimed at improving its structure and contents; please address your feedback message to the mailbox of our Center for Integrated Research (CIR), that is cir@unicampus.it.

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Pro-Rector for Research  
Campus Bio-Medico  
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Raffaele Calabrò  
Rector (Chancellor)  
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University of Rome
On the Cover
Feedback quadratic filtering

A fundamental engineering tool of the twentieth century is the Kalman Filter, an algorithm that provides a recursive estimate of the state of a stochastic dynamical systems starting from noisy measurements. The Kalman Filter is the optimal estimator for linear systems driven by Gaussian noise. The applications of the Kalman Filter are numerous: tracking objects (e.g. faces, heads, hands, etc), economics, navigation and many computer vision applications.

In many modern applications, for example in biology, bio-engineering, finance, etc, non-Gaussian disturbances are commonly found. In these cases the Kalman Filter is still the optimal linear estimator but better estimators can in principle be found, even if their structure becomes usually more complicated. In this research we show how the knowledge of the noise distribution can be exploited to improve the estimate accuracy with respect to the Kalman Filter while still remaining the same simple structure and nice properties of the original algorithm. Mathematically, the estimator is defined as the projection of the state over the space of quadratic (or, in general, polynomial) functions of the measurements. To this aim we need to solve several theoretic issues such the difference between recursive and non recursive estimates, non stationary noise processes, etc. The paper provides new insights on these issues and a solution to the stability problem by introducing an output injection term in the filter structure.

Cacace F., Conte F., Germani A., Palombo G.

Feedback quadratic filtering

Automatica 2017, vol.82, 158-164

Campus Bio-Medico University of Rome - Department of Engineering - Research Unit of Computer Systems and Bioinformatics
The research activities carried out in 2017 at the Campus Bio-Medico University of Rome have produced important outputs in terms of scientific publications, research projects, clinical trials and patents. Notably, the number of scientific publications, as shown in the Figures below, has grown over the past years and has confirmed in 2017 a level, both in qualitative and quantitative terms, comparable to that of the best Italian universities, in relation to the size of the University and to the number of faculty members. In particular, number of publications, impact factor (I.F.) and normalized impact factor (N.I.F.) have increased respectively of 14%, 35% and 19% with respect to 2016.

As shown in Figure 2 the number of publications per faculty member is about 4 and increased by 7% with respect to 2016; the number of faculty members increased of 21% in the last five years as shown in Figure 3.

Figure 5 shows the overall scientific production in 2017 in terms of number of publications, Impact Factor (IF) and Normalized Impact Factor (NIF) for each of the 47 Research Units of the University.

There are several indicators, which provide objective evidence of the quality of the research carried out at the University such as, for example:

- Average of 4+ publications with Impact Factor per faculty member in 2017;
- 19% of faculty members (25 faculty members) with total Hirsch-index (h papers each of which has been cited in other papers at least h times) higher than 30 and included in the Top Italian Scientists list (www.topitalianscientists.org);
- 60% publications in the first quartile (Q1) according to ScImago ranking, which includes the top 25% journals in each subject category.
In 2017, more than 70 research projects, including clinical trials, were funded. The following figure illustrates the success rate on competitive calls during the period 2015-2017.

![Figure 4 - Competitive calls success rate (2014-2017)](image)

As regards the activities related to exploitation of research results, in 2017, two Italian and international patents have been granted, two applications for Italian patents, of which one co-owned with an Italian SME, were filed and two patents have been entered in the national phase. One contract has been signed with an Italian SME for the exploitation of an Italian pending patent.

As of 31st December 2017 patent portfolio owned or co-owned by the University includes 19 families of patents (with a total of 43 patents, 29 already granted) in the field of rehabilitation engineering, microengineering, regenerative medicine, biomedical instrumentation, cancer diagnostics and food analysis.

In 2017 two new startups have been accredited as spin off of the University.

More detailed information on ongoing projects is available in the section “Research projects” of this Yearbook, whereas in the section “The University Third Mission” the activities related to commissioned research, clinical trials, University patents and University accredited spin-off companies are presented along with information about Public Engagement and other dissemination activities promoted by the University to enhance the impact on society of our research activities.
Figure 5 - Number of publications, Impact Factor (I.F.) and Normalized Impact Factor (N.I.F.) per Research Unit
Research Quality Assurance Policies
Research Quality Assurance Policies

In accordance to relevant legislation and in conformity with the guidelines issued by the Italian National Agency for the Evaluation of the University and Research Systems (ANVUR), the Campus Bio-Medico University of Rome recognizes that quality is a fundamental value. Furthermore, it considers it its inspiring feature in the incessant effort to implement the University general mission as defined in its “Charter of the Aims”. The main UCBM source of reference for the quality assurance policy has been the “2014-2016 Strategic Guidelines” document. Its motto, “More Quality, More Person”, specifically identifies the strategic vision of combining the continuous improvement of all university activities with a systematic attention to the person, in teaching, research and healthcare.

The general principles guiding the quality assurance policy are:

- centrality of the person;
- special attention to the social impact and to the ethical implications of research;
- inseparable nature of teaching and research (or healthcare activities);
- efficient and effective use of resources;
- development of international cooperation activities and of research mobility programs;
- commitment to grant equal opportunities, to protect from discrimination and to remove barriers for the disabled;
- support to translational research to allow fast transfer of research results into medical practice and meaningful health outcomes;
- support to technological innovation and encouragement of socio-economic development, by promoting cooperation with local enterprises and institutions;
- support of University spin-off for the exploitation of research products.

Moreover, the University pursues systematic application of its “Charter of the Aims” and of its “Code of Ethics” to all research activities.

The Departments of Engineering and of Medicine and Surgery, supported by the Centre for Integrated Research, pursue continuous improvement of research activities paying special attention to the possible social impact of research outcomes by following these general guidelines:

- improvement of key performance indicators in terms of quality and impact of scientific production. Faculty and research staff are assessed annually using criteria and parameters recognized by the scientific community of reference, specifically by indicators defined by ANVUR for assessing quality of research (Evaluation of Research Quality - VQR);
- multidisciplinary and transdisciplinary dimension of research: implementation of measures aimed at fostering collaboration among the various Research Units (RU), especially those within different Departments. Collaborative activities within the Institute of Philosophy of Scientific and Technological Practice are specifically promoted;
- international dimension of research: implementation of activities aimed at encouraging international programs of incoming and outgoing mobility. The University also aims at increasing its ability to attract external resources through participation in competitive calls, especially at a European level and at promoting cooperation with foreign centres of excellence including “visiting professors” programs which encourage the assignment of foreign scientists at our University for extended periods of research and teaching;
- policies for young researchers: the goal is to enhance the collaboration among researchers in an integration and skill enhancement logic. Furthermore, the University wishes to help to achieve outcomes and scientific growth of young researchers through promotion of participation in internally or externally funded competitive calls;
- policies for Ph.D courses: programs to be activated are selected according to scientific areas of excellence and scientific sectors active in the Departments; the University is implementing strategies to ensure an adequate number of Ph.D scholarships provided both by University funding, and by external sources of funding, i.e. research competitive grants. Furthermore, it prefers to focus resources on its strategic research lines and anyhow on sectors that demonstrate high quality standards and scientific self-sustainability and productivity; it also promotes consolidation of Ph.D programs on topics of interest in industrial activities by seeking external funding; it encourages the international dimension...
of Ph.D programs through participation in schools, conferences and visits to other universities or research centres featuring excellence in research;

• policies for the Third Mission: the University promotes initiatives to pursue its Third Mission through research, such as:
  ▸ initiative to involve companies and other parties potentially interested in patents exploitation;
  ▸ measures to promote the incubation and acceleration of spin-off companies;
  ▸ initiatives to improve diffusion and dissemination of scientific results;
  ▸ fostering collaboration with public and private institutions, and companies, by publishing an annual report of its research activities, and by organizing a public engagement initiative, the Research Day with the aim of communicating the main research results.

The system for Quality Assurance in Research (QAR) intends to set research goals and objectives, to identify and plan what is required to achieve them, to monitor the regular course of each activity, as well as to verify the level of achievement of these objectives and propose corrective actions as appropriate.

Therefore, through the Quality Assurance in Research, the University implements its Quality Policy.

The boards and structures involved in the Quality Assurance in Research are:
• Quality Assurance Committee (Presidio di Qualità);
• Evaluation Committee (Nucleo di Valutazione);
• Academic Senate;
• Academic Research Board;
• Faculty Councils;
• Faculty Boards.

The Academic Research Board plays a key role as the QAR main body, in tight cooperation with the university Quality Assurance Committee.
Evaluation of Research Quality
(VQR 2011-2014)
Evaluation of Research Quality (VQR 2011-2014)

The VQR (Valutazione della Qualità della Ricerca, Evaluation of Research Quality) is the Italian research assessment exercise that ANVUR (the National Agency for the Evaluation of the University and Research system) regularly carries out on behalf of the Italian Ministry of Education, University and Research (MIUR). On February 21, 2017, ANVUR presented the new VQR Report, which is referred to the period January 2011-December 2014 (www.anvur.org/rapporto-2016).

With more than 130 participant organizations, almost 65,000 contributors, and 118,000 research products having been evaluated, the VQR is by far the most important and comprehensive research evaluation exercise ever attempted in Italy. For the period 2011-2014, the VQR has ranked UCBM second in the area of Biological Sciences among all Italian universities. UCBM was ranked fourth in other two areas, namely Chemical Sciences and Industrial and Information Engineering Areas, and UCBM was ranked tenth in the area of Medical Sciences.

The VQR Report also shows that, as regards the single scientific disciplinary sectors, UCBM gained the first place (out of twenty-three universities) in Orthopaedics sector and the second place (out of thirty-two universities) in Neurology sector. Moreover, UCBM has been ranked third in Computer Systems, Diagnostic Imaging and Pathology sectors, out of fifty-three, thirty-seven and thirty-four universities respectively. These results are based on the very good UCBM performance as measured by the specific indicators used for this ANVUR assessment: UCBM stands well above the average performance of all other universities in terms of scientific products classified of “excellent” or “good” quality.

VQR results are presented in the table below, where also information about the separate ranking regarding only small universities is reported (i.e. dimensional range ranking) along with the percentage of UCBM scientific products classified in excellent and good classes.

<table>
<thead>
<tr>
<th>Area</th>
<th>Overall ranking</th>
<th>Dimensional range ranking</th>
<th>% of publications in excellent and good levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area 03 Chemical Sciences</td>
<td>4° out of 56</td>
<td>4° out of 35</td>
<td>100%</td>
</tr>
<tr>
<td>Area 05 Biological Sciences</td>
<td>2° out of 62</td>
<td>2° out of 31</td>
<td>95.24%</td>
</tr>
<tr>
<td>Area 06 Medical Sciences</td>
<td>10° out of 52</td>
<td>8° out of 21</td>
<td>75.40%</td>
</tr>
<tr>
<td>Area 09 Industrial and Information Engineering</td>
<td>4° out of 63</td>
<td>4° out of 43</td>
<td>81.25%</td>
</tr>
</tbody>
</table>
Research Organization and Services
Research Organization and Services

Centre for Integrated Research
The Centre for Integrated Research (CIR) provides support to the Department of Medicine and Surgery and to the Department of Engineering for promotion, exploitation and administrative management of the research activities. It guarantees the proper management of funds for research activities, publications and scientific collaborations; it also ensures a correct execution of clinical trials according to relevant regulations, Good Clinical Practice and the Joint Commission International’s standards. Amongst CIR’s roles is the possibility of setting up and financing research units, groups and research programs open to the participation of scholars and researchers from national and international universities or research and cultural centres.

Academic Research Board
The Pro-Rector for Research chairs the Board, which is also composed of the Research Coordinators of the two UCBM Departments and of the Head of Research Administrative Area. The Board ensures the necessary link between the two boards of the Departments, addressing and monitoring scientific research, and fostering their collaboration. The Board is primarily in charge of elaborating the University strategic plan for research development and of guiding the research quality assurance system (QAR).

Research Administrative Area
The Research Administrative Area promotes and fosters access to research funding sources, guarantees administrative management of research projects and of clinical trials, as well as exploitation of research results. The Research Administrative Area includes the following offices: Grant Office, Technology Transfer Office, Project Financial Management and Reporting Office. Activities of the offices are described below.

Grant Office
The Grant Office main objective is to assist researchers in finding the most appropriate funding sources, also carrying out internal scouting activities in order to promote and consolidate collaborations among different UCBM Research Units. With this aim, the Office provides researchers with the support during the whole process of presenting research projects, from identification and notification of the most suitable financing opportunities to assistance in preparation and submission under national, European Commission and international competitive calls. It also offers support and follow up of project management in close synergy with the Project Financial Management and Reporting Office.

At the same time, the Office organizes seminars, workshops and informative events on competitive calls announcements. The Office also provides technical-scientific support to activities of the Academic Research Board.

Technology and Transfer Office
The Technology Transfer Office assists UCBM researchers in finding and assessing the best strategy to protect intellectual property and valorize research results, it manages the University patent portfolio in strict synergy with inventors, and promotes research results to SME and companies with the aim to exploit research activities through licensing of patents and implementation of joint research projects. Furthermore the Office supports the promotion of joint laboratories with industries and spin-off research processes as well as incubation and acceleration of spin-off companies. Finally, it organizes seminars and workshops on technology transfer research issues.

Project Financial Management and Reporting Office
The Project Financial Management and Reporting Office assists the Research Units in the daily administrative management of the research projects. It guarantees the proper post-award management of all grants, research contracts and clinical trials, analytical accounting management of research projects, expense analysis and monitoring. It also takes care of the projects periodic financial reports according to national and international regulations. Furthermore, it assists Research Units in the accounting administrative auditing of projects carried out by external auditing companies. The office manages also the Unique Code Project a distinctive code for the identification of the project
Finally, it also interacts with other administrative areas, such as Purchasing, Economics-Finance, Personnel Areas and Management Secretary’s Offices for an optimized administrative management of the research activities.

Clinical Research Office
The Clinical Research Office promotes the quality system of the University’s clinical research. This is an essential condition to make our University more and more competitive in the field of clinical research and, therefore, able to attract the main industrial players of pharmaceutical and biomedical sectors.

The office is in charge of the preliminary feasibility analysis of the clinical studies, which is carried on in collaboration with the departments involved in the process of clinical trial authorization (University Hospital Board, Pharmacy, Clinical and Nursing Management, Research Administrative Area).

The Clinical Research Office follows all the administrative and management steps of the study including the finalization of the formal contracts and agreements with the sponsoring partners.

During the execution of the clinical trials, the office carries out a regular reporting activity. It also performs scientific and technical advice and supports for the investigator during the study, where required.

The Clinical Research Office prepares all the needed documentation for Ethics Committee’s assessment and assists the subsequent authorization steps, performing the role of EC technical-scientific secretariat, in accordance with the current regulation on the execution of clinical trials (Legislative Decree 211 / 2003 and ss) and the UCBM Ethics Committee Regulation.

The office is also in charge of ensuring the full compliance with the quality standards established by the Joint Commission International (JCI) accreditation, including Principal Investigators training and updating on the best clinical research practices. The office, within the scope of its responsibilities, also takes care of relationships with the Regulatory Authorities (Ministry of Health, Istituto Superiore Sanità, AIFA, EMA, FDA) and of the registration of clinical trials to the competent authorities, as required.

The Library
The Library mission is to provide comprehensive resources and services in support of the research, teaching, and learning needs. To fulfil this mission, the Library is committed to acquire, deliver and integrate information to support excellence in research, in education, and in patient care. The focus is to build broad print and e-resources collections, including access to specific databases and striving to make electronic content easily accessible to all users.

The concrete support given to research activities, with reference to the scientific productivity, deals with the use of research evaluation metrics and its application to the analysis of research systems.

Specifically it assists single users, departments or research units in the recovery of bibliometric indicators, such as the Impact Factor and the normalized Impact Factor, as well as the citation index data from Web of Science and Scopus.

Document supply service
The Library operates an advanced system for handling users’ requests of documentation. The service allows registered users to request items, which are not available in the University Library.

The service is accessible also off-campus, upon registration through the online form available on the Library website.

Doctoral dissertations theses repository
The Library offers a storage and consultation service of doctoral dissertations repository. Full text doctoral dissertations theses repository are stored in the open access repository ILITHIA. The repository is indexed in OpenDOAR, an authoritative worldwide directory of academic open access repositories.
Research Organization and Services

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Ethics Committee
Ethics Committee

The Ethics Committee is an independent body whose tasks involve assessment, approval and monitoring of clinical trials, researcher training and consultancy services. The Ethics committee is composed of experts from the various fields of biomedical research, health care and safeguarding patients’ rights. It protects and promotes respect for human life, from the moment of conception to natural death by taking inspiration from the Charters of Human Rights, recommendation from international bodies, medical deontology and, in particular, the Helsinki Declaration and Good Clinical Practice guidelines. The Ethics Committee meets once a month for evaluation the studies.

Members of the Ethics Committee

President  Claudio Buoni

Alessandro Calisti, pediatrician
Fiorella Gurrieri, genetist
Giovanni Marino, local medicine representative
Giuseppe V. La Spina, clinician
Gemma Berta, voluntary work representative
Modesto D’Aprile, clinician
Paolo Pozzilli, biostatistician
Giorgio Minotti, pharmacologist
Giovanni Sironi, pharmacist
Domenica Tassielli, pharmacist, biomedical devices expert
Valentina Pepe, pharmacist
Norberto Silvestri, Hospital Administrator
Giuseppe La Monaca, legal matters expert
Maddalena Pennacchini, bioethics expert
Daniela Tartaglini, healthcare professions representative
Sara Emerenziani, nutrition expert
Salvatore Sciuto, clinical engineer
Francesco Di Matteo, clinical expert in diagnostic procedures and invasive techniques
Research Units
overview and main 2017 scientific outputs
Allergology, Immunology, Rheumatology

Head A. Afeltra
Faculty D.P.E. Margiotta
Other Personnel L. Arcarese, M. Lo Vullo, L. Navarini, A. Rigon, A. Soriano, M. Vadacca, A. Vernuccio

Description
The unit’s research interests concern epidemiology, pathogenesis, diagnosis and therapy of the systemic autoimmune diseases. The most important research topics are Systemic Lupus Erythematosus and Inflammatory Arthritis. The unit’s research methodology is based on the integration of clinical tools, diagnostic imaging (musculoskeletal ultrasonography and capillaroscopy) and laboratory methods (immunofluorescence, enzyme immunoassay, immunoblot).

Main research activities
- Cardiovascular involvement in Autoimmune Diseases;
- Metabolic Syndrome in Rheumatoid Arthritis and Systemic Lupus Erythematosus;
- Prevention of Cardiovascular Disease in Systemic Lupus Erythematosus;
- Lipid mediators and Systemic Lupus Erythematosus;
- Automation of auto-antibody determination by indirect immunofluorescence;
- Epidemiology of infection during biologic therapy in Rheumatoid Arthritis;
- New bone formation and p40 inhibition;
- Angiogenic and angiostatic factors in Systemic Sclerosis vasculopathy.

Main collaborations
- Forum Interdisciplinare per la Ricerca sulle Malattie Autoimmuni, (FIRMA);
- Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale (GIRRCS);
- Laboratory of Tissue Homostasis and Disease (THD), Skeletal Biology and Engineering Research Center (SBE), KU Leuven;
- Rheumatology Day Hospital, Gaetano Pini Institute, Milan;
- The Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Israel;
- Unit of Microbiology, San Carlo Borromeo Hospital, Milan;
- Unit of Rheumatology, Spedali Civili Brescia.

Most important publications

International consensus: what else can we do to improve diagnosis and therapeutic strategies in patients affected by autoimmune rheumatic diseases (rheumatoid arthritis, spondyloarthritides, systemic sclerosis, systemic lupus erythematosus, antiphospholipid syndrome and Sjogren’s syndro-
me)? The unmet needs and the clinical grey zone in autoimmune disease management. 
Autoimmun Rev. 2017 Sep;16(9):911-924. PubMed PMID: 28705780. IF 8,961

Autoimmune diseases are a complex set of diseases characterized by immune system activation and, although many progresses have been done in the last 15 years, several unmet needs in the management of these patients may be still identified. Recently, a panel of international Experts, divided in different working groups according to their clinical and scientific expertise, were asked to identify, debate and formulate a list of key unmet needs within the field of rheumatology, serving as a roadmap for research as well as support for clinicians. After a systematic review of the literature, the results and the discussions from each working group were summarized in different statements. Due to the differences among the diseases and their heterogeneity, a large number of statements was produced and voted by the Experts to reach a consensus in a plenary session. At all the steps of this process, including the initial discussions by the steering committee, the identification of the unmet needs, the expansion of the working group and finally the development of statements, a large agreement was attained. This work confirmed that several unmet needs may be identified and despite the development of new therapeutic strategies as well as a better understanding of the effects of existing therapies, many open questions still remain in this field, suggesting a research agenda for the future and specific clinical suggestions which may allow physicians to better manage those clinical conditions still lacking of scientific clarity.


The inter-observer reading variability in anti-nuclear antibodies indirect (ANA) immunofluorescence test: A multicenter evaluation and a review of the literature. 

Recently there has been an increase demand for Computer-Aided Diagnosis (CAD) tools to support clinicians in the field of Indirect ImmunoFluorescence (IIF), as the novel digital imaging reading approach can help to overcome the reader subjectivity. Nevertheless, a large multicenter evaluation of the inter-observer reading variability in this field is still missing. This work fills this gap as we evaluated 556 consecutive samples, for a total of 1679 images, collected in three laboratories with IIF expertise using HEp-2 cell substrate (MBL) at 1:80 screening dilution according to conventional procedures. In each laboratory, the images were blindly classified by two experts into three intensity classes: positive, negative, and weak positive. Positive and weak positive ANA-IIF results were categorized by the predominant fluorescence pattern among six main classes. Data were pairwise analyzed and the inter-observer reading variability was measured by Cohen's kappa test, revealing a pairwise agreement little further away than substantial both for fluorescence intensity and for staining pattern recognition ($k=0.602$ and $k=0.627$, respectively). We also noticed that the inter-observer reading variability decreases when it is measured with respect to a gold standard classification computed on the basis of labels assigned by the three laboratories. These data show that laboratory agreement improves using digital images and comparing each single human evaluation to potential reference data, suggesting that a solid gold standard is essential to properly make use of CAD systems in routine work lab.

Rosato E., Navarini L., Gigante A., Cianci R., Margiotta D., Barbano B., Afeltra A.

Intrarenal arterial stiffness is increased in systemic sclerosis patients with anti-ribonucleic acid polymerase III antibodies. 
Anesthesia, Intensive Care and Pain Management

Head  F.E. Agrò
Faculty  M. Carassiti, R. Cataldo

Description

The AIC&PM Research Unit works in different areas of research and applications concerning:

- Airway management:
  - Difficult airway management in Operating Theatre and ICU;
  - Tracheal intubation: advanced techniques;
  - Research on extraglottic devices and oxygenation rescue techniques;
  - Forces and pressures during direct and video laryngoscopy.
- Mechanical ventilation in Operating Theatre and ICU;
- Pain therapy;
- Loco-regional anesthesia;
- Procedures for obese patients.

Main research activities

The AIC&PM Research Unit focuses its activities on:

- Anesthesia
  - Loco-Regional anesthesia techniques
  - Airway management in Emergency and Elective scenarios
  - Airway management devices and innovations
  - Cardiac anesthesia and drugs
  - Obesity and perioperative safety
  - Pain management in perioperative medicine
  - Multimodal care in pancreatic Surgery
  - “in vitro” airway management strategies simulation to improve patients safety
- Cardiac surgery and controlled trial of volatile anesthetics
- Intensive therapy
- Cardiac output monitoring innovations in mechanically ventilated patients
- Advanced pain control strategies in ICU
- Ecocardiography in post cardio-surgical patients in ICU
- Pain Management and epidural space detection in vitro and in vivo
- FBSS (Patents development) Post Herpetic pain and neuro-biological modifications.

Most important publications


Mortality in cardiac surgery (MYRIAD): A randomized controlled trial of volatile anesthetics. Rationale and design.

OBJECTIVE: There is initial evidence that the use of volatile anesthetics can reduce the postoperative release of cardiac troponin I, the need for inotropic support, and the number of patients requiring prolonged hospitalization following coronary artery bypass graft (CABG) surgery. Nevertheless, small randomized controlled trials have failed to demonstrate a survival advantage. Thus, whether volatile anesthetics improve the postoperative outcome of cardiac surgical patients remains uncertain. An adequately powered randomized controlled trial appears desirable. DESIGN: Single blinded, international, multicenter randomized controlled trial with 1:1 allocation ratio. SETTING: Tertiary and University hospitals. INTERVENTIONS: Patients (n=10,600) undergoing coronary artery bypass graft will be randomized to receive either volatile anesthetic as part of the anesthetic plan, or total intravenous anesthesia. MEASUREMENTS AND MAIN RESULTS: The primary end point of the study will be one-year mortality (any cause). Secondary endpoints will be 30-day mortality; 30-day death or non-fatal myocardial infarction (composite endpoint); cardiac mortality at 30day and at one year; incidence of hospital re-admission during the one year follow-up period and duration of intensive care unit, and hospital stay. The sample size is based on the hypothesis that volatile anesthetics will reduce 1-year unadjusted mortality from 3% to 2%, using a two-sided alpha error of 0.05, and a power of 0.9. CONCLUSIONS: The trial will determine whether the simple intervention of adding a volatile anesthetic, an intervention that can be implemented by all anesthesiologists, can improve one-year survival in patients undergoing coronary artery bypass graft surgery.

Carassiti M., Mattei A., Quarta R., Massaroni C., Saccomandi P., Tesei M., Setola R., Schena E.

A new pressure guided management tool for epidural space detection: feasibility assessment on a simulator.

The detection of epidural space is usually performed by the technique of loss of resistance (LOR) without technological support, although there are few commercial options. We sought to design and develop a new noninvasive system able to detect the LOR without any changes to the conventional procedure. It allows detecting the LOR by a custom made algorithm. The system provides a visual and acoustic feedback when the LOR is detected. We optimized the detection algorithm and investigated the performance of the system during experiments on a custom simulator. During the experiments performed by 10 anesthetists and 10 trainees, the pressure exerted on the syringe plunger was monitored using the custom-made system. Each participant performed four experiments using the system on the simulator. The performance of the system in LOR detection was evaluated comparing the feedback activation and the breaches of the last layer of the simulator. Moreover, each participant filled out a questionnaire to assess how the procedure with the simulator mimics the clinical scenario. A higher questionnaire score corresponds to a more realistic condition (0 = not real, 5 = extremely real). Results showed that the LOR was detected in 74 of the 80 trials (92.5% of the cases); the anesthetists obtained better results than trainees: 97.5 versus 87.5%. The questionnaires showed that all the participants found the trial realistic (score ≥3); anesthetists found it more realistic than trainees (4.2 ± 0.78 vs. 3.8 ± 0.78, mean ± SD). In summary, the proposed system successfully detected the LOR in the large part of the trials. The participants found the trials realistic. A higher success rate was observed in the anesthetists group.


Regional anesthesia: the best is yet to come.

A lot is yet to be done in order to make the adoption of RA more widespread, 2, 5 and to investigate the effect of RA on short- and long-term outcomes (like persistent pain and cancer prognosis), but available data endorse the use of RA whenever not dangerous for the patient, and support the development of new research with large population studies. Hopefully, the best is yet to come.
Automation and Control Theory

**Description**

The Unit of Automation and Control Theory aims at modeling, analyzing and controlling complex dynamic systems, ranging from biological and healthcare systems to industrial, home automation and Critical Infrastructure systems. A particular emphasis is posed on the security issues underlying such complex systems, with the aim to develop robust, flexible and effective solutions. The activities of the Unit are focused on the development of innovative and strongly multi-disciplinary methodologies, tools and technologies. Among others, the Unit provided both theoretical and applicative contributions in the fields of cyber-physical systems, optimization, sparse and distributed algorithms, sensorial data, localization, security of critical infrastructure. The Unit is involved in several European and national research projects and cooperates with a wide spectrum of research bodies and industrial partners.

**Main research activities**

The unit has contributed to several projects and collaborations:
- **SMARTBENCH**: development of innovative integrated tools and methodologies to assess the safety and security of workers in dangerous zones.
- **HANSEL**: development of an integrated industry 4.0 platform to offer services in terms of overall validation of SCADA security architectures, stress test of hardware/software with respect to cyberattacks and training of operators and technicians.

**Main collaborations**

The Unit has established and strengthened the cooperation with several prestigious institutions; among others:
- **University of Cyprus**: development of distributed agreement algorithms;
- **University of Sapporo (Japan)**: finding the nodes in a network that are more vulnerable to a terrorist attack;
- **Institute for Complex Systems (CNR), Italy**: development of distributed decision-making algorithms with partial information;
- **National Institute for Insurance against Accidents at Work (INAIL)**: solution to improve safety in working environments;
- **University “Roma Tre”, Italy**: security of cyber-physical systems.
Most important publications

Oliva G., Setola R., Scala A

**Sparse and distributed Analytic Hierarchy Process**

The Analytic Hierarchy Process (AHP) is a de-facto standard technique in centralized decision-making for ranking alternatives by using knowledge on the ratio of their values, eventually affected by distortions or biases. However, AHP requires complete information. In this paper, we extend the AHP technique to the case of sparse information, modeled as an undirected connected graph. We complement our sparse framework by developing novel criteria and metrics to evaluate the degree of consistency of the data at hand. Moreover, we provide a distributed formulation of AHP where agents compute their own values by only knowing the ratio of their values with respect to their neighbors.

Carassiti M., Mattei A., Quarta R., Massaroni C., Saccomandi P., Tesei M., Setola R., Schena E.

**A new pressure guided management tool for epidural space detection: feasibility assessment on a simulator.**

In the paper it is proposed an innovative loss of resistance (LOR) devices to support doctor in the detection of epidural space during epidural procedures. The device is noninvasive and able to detect the LOR without any changes to the conventional procedure. The system provides a visual and acoustic feedback when the LOR is detected.

Papi M., Porzio M. M., Smarrazzo F.

**Existence of solutions to a class of weakly coercive diffusion equations with singular initial data.**
*Advances in Differential Equations* 2017; 22(11/12): 893-962. IF 1.236

Initial-boundary value problems for nonlinear parabolic equations having Radon measures as initial data have been widely investigated, looking for solutions which take values in some function space. If the diffusivity degenerates too fast at infinity, function-valued solutions may not exist and it is natural to consider solutions, which describe an orbit in the space of the finite Radon measures. We discuss existence of measure-valued solutions to the homogeneous Dirichlet initial-boundary value problem for a class of parabolic equations without strong coercivity and we examine qualitative properties of the solutions concerning the evolution of their singular part.
Biochemistry and Molecular Biology

**Head**  M. Maccarrone

**Faculty**  V. Chiurchiù, L. Dugo

**Other Personnel**  T. Bisogno, A. Leuti, A.M. Sardanelli

**Description**

The Research Unit has a long and widely recognized experience in chemistry, biochemistry, molecular biology, pharmacology and epigenetics of lipid signaling, that is interrogated under different disease conditions (most notably, neurodegenerative disorders [Alzheimer’s disease (AD) and Multiple Sclerosis (MS)], and defective reproductive events). In this context, up-to-date techniques are used to determine the drivers of signal transduction mediated by bioactive lipids like endocannabinoids (N-arachidonoylethanolamine and 2-arachidonoyl-glycerol) and specialized pro-resolving mediators (i.e. resolvins and maresins), through their specific receptor targets. In addition, metabolism of these ω-3 and ω-6 polyunsaturated fatty acid derivatives through multiple biosynthetic and degradative routes is studied by means of radiometric assays, in order to disclose the impact of metabolic regulation on the biological activity of these compounds. The effect of bioactive food components on lipid signaling is an additional focus of the Research Unit.

**Main research activities**

In collaboration with Prof. Mario van der Stelt (Leiden University, The Netherlands) and Prof. Benjamin F. Cravatt (The Scripps Research Institute, USA), we demonstrated that the endocannabinoid-degrading enzyme FAAH is not a selective target of BIA-10-2474, a compound that caused severe neurotoxicity in human patients with a major impact on health authorities worldwide. In addition, in collaboration with Prof. Pal Pacher (National Institutes of Health, USA) we fully profiled the endocannabinoid-binding receptor CB2, and with Dr. Silvia Marinelli (EBRI Foundation, Rome) we showed that, the endocannabinoid-binding receptor TRPV1 acts as an inflammation detector in the brain, and as a sentinel against neuroinflammation. These studies are clearly relevant for AD and MS, and may be useful for treating chronic inflammatory and autoimmune diseases.

**Main collaborations**

- Leiden University, The Netherlands;
- The Scripps Research Institute, USA;
- National Institutes of Health, USA;
- EBRI Foundation, Rome.
Most important publications


Activity-based protein profiling reveals off-target proteins of the Fatty Acid Amide Hydrolase inhibitor BIA 10-2474


A recent phase 1 trial of the fatty acid amide hydrolase (FAAH) inhibitor BIA 10-2474 led to the death of one volunteer and produced mild-to-severe neurological symptoms in four others. Although the cause of the clinical neurotoxicity is unknown, it has been postulated, given the clinical safety profile of other tested FAAH inhibitors, that off-target activities of BIA 10-2474 may have played a role. Here we use activity-based proteomic methods to determine the protein interaction landscape of BIA 10-2474 in human cells and tissues. This analysis revealed that the drug inhibits several lipases that are not targeted by PF04457845, a highly selective and clinically tested FAAH inhibitor. BIA 10-2474, but not PF04457845, produced substantial alterations in lipid networks in human cortical neurons, suggesting that promiscuous lipase inhibitors have the potential to cause metabolic dysregulation in the nervous system.


Cannabinoid CB2 receptor ligand profiling reveals biased signaling and off-target activity: Implications for drug discovery

*Nature Commun.* 2017;8:13958. DOI: 10.1038/ncomms13958. IF 12,124

The cannabinoid CB2 receptor (CB2R) represents a promising therapeutic target for various forms of tissue injury and inflammatory diseases. Although numerous compounds have been developed and widely used to target CB2R, their selectivity, molecular mode of action and pharmacokinetic properties have been poorly characterized. Here we report the most extensive characterization of the molecular pharmacology of the most widely used CB2R ligands to date. In a collaborative effort between multiple academic and industry laboratories, we identify marked differences in the ability of certain agonists to activate distinct signalling pathways and to cause off-target effects. We reach a consensus that HU910, HU308 and JWH133 are the recommended selective CB2R agonists to study the role of CB2R in biological and disease processes. We believe that our unique approach would be highly suitable for the characterization of other therapeutic targets in drug discovery research.


TRPV1 channels as brain inflammation detectors and neuropathic pain biomarkers in mice


The capsaicin receptor TRPV1 has been widely characterized in the sensory system as a key component of pain and inflammation. A large amount of evidence shows that TRPV1 is also functional in the brain although its role is still debated. Here we report that TRPV1 is highly expressed in microglial cells rather than neurons of the anterior cingulate cortex and other brain areas. We found that stimulation of microglialTRPV1 controls cortical microglia activation per se and indirectly enhances glutamatergic transmission in neurons by promoting extracellular microglial microvesicles shedding. Conversely, in the cortex of mice suffering from neuropathic pain, TRPV1 is also present in neurons affecting their intrinsic electrical properties and synaptic strength. Altogether, these findings identify brain TRPV1 as potential detector of harmful stimuli and a key player of microglia to neuron communication.
Biomedical Robotics and Biomicrosystems

**Head** E. Guglielmelli

**Faculty** D. Accoto, F. Taffoni, L. Zollo


### Description

Biomedical Robotics investigates the application of mechatronic and robotic technologies to medicine and biology, by proposing innovative solutions for diagnosis, healthcare and improvement of patient quality of life. 

The Biomedical Robotics and Biomicrosystems Lab strongly benefits from the tight link with the Department of Medicine and Surgery and the University Hospital for developing and experimentally validating innovative robotic and mechatronic technologies based on a human-centered design approach.

Main research areas are:
- **Rehabilitation and assistive technologies:** upper-limb and lower-limb therapy robots, motor and functional assessment, behavioral analysis, technical aids for independent living and work reintegration, assistive robots, upper limb prostheses, man-machine interfaces;
- **Surgical Robotics:** mechatronic tools for urological applications, haptic interfaces and bio-feedback, master-slave robotic systems, teleoperated control;
- **Biomicrosystems:** miniaturized sensors, invasive neural micro-interfaces, microfluidic platforms;
- **Neuroengineering and Neuro-developmental Engineering:** design of mechatronic components and systems to study and modelling motor behavior both in adults (healthy and suffering from neurological disorders) and in infant/children during development.

### Main research activities

- **PPRAS 1/3-** funded by the National Institute for Insurance against Accidents at Work 2017-2020
- **RehabRobo@Work** Bio-cooperative robotic system for upper-limb rehabilitation in working contests- funded by the National Institute for Insurance against Accidents at Work- 2017-2019
- **PPR2** - funded by the National Institute for Insurance against Accidents at Work, 2014-2017
- **AIDE** - funded by EC-H2020\ICT 22 - 2014-2017
- **PD-meter** - funded by the Ministry of Health, 2014-2017
- **START-DISC** - University Strategic Project, 2015-2017

### Most important publications


**NLR, MLP, SVM, and LDA: a comparative analysis on EMG data from people with trans-radial amputation.**


**Background:** Currently, the typically adopted hand prosthesis surface electromyography (sEMG) control strategies do not provide the users with a natural control feeling and do not exploit all the potential of commercially available multi-fingered hand prostheses. Pattern reco-
gnition and machine learning techniques applied to sEMG can be effective for a natural control based on the residual muscles contraction of amputated people corresponding to phantom limb movements. As the researches has reached an advanced grade accuracy, these algorithms have been proved and the embedding is necessary for the realization of prosthetic devices. The aim of this work is to provide engineering tools and indications on how to choose the most suitable classifier, and its specific internal settings for an embedded control of multigrip hand prostheses. **Methods:** By means of an innovative statistical analysis, we compare 4 different classifiers: Nonlinear Logistic Regression, Multi-Layer Perceptron, Support Vector Machine and Linear Discriminant Analysis, which was considered as ground truth. Experimental tests have been performed on sEMG data collected from 30 people with trans-radial amputation, in which the algorithms were evaluated for both performance and computational burden, then the statistical analysis has been based on the Wilcoxon Signed-Rank test and statistical significance was considered at p < 0.05. **Results:** The comparative analysis among NLR, MLP and SVM shows that, for either classification performance and for the number of classification parameters, SVM attains the highest values followed by MLP, and then by NLR. However, using as unique constraint to evaluate the maximum acceptable complexity of each classifier one of the typically available memory of a high performance microcontroller, the comparison pointed out that for people with trans-radial amputation the algorithm that produces the best compromise is NLR closely followed by MLP. This result was also confirmed by the comparison with LDA with time domain features, which provided not significant differences of performance and computational burden between NLR and LDA. **Conclusions:** The proposed analysis would provide innovative engineering tools and indications on how to choose the most suitable classifier based on the application and the desired results for prostheses control.

Simonetti D., Zollo L., Milighetti S., Miccinilli S., Bravi M., Ranieri F., Magrone G., Guglielmelli E., Di Lazzaro V., Sterzi S.

**Literature review on the effects of tDCS coupled with robotic therapy in post stroke upper limb rehabilitation.**

Today neurological diseases such as stroke represent one of the leading cause of long-term disability. Many research efforts have been focused on designing new and effective rehabilitation strategies. In particular, robotic treatment for upper limb stroke rehabilitation has received significant attention due to its ability to provide high-intensity and repetitive movement therapy with less effort than traditional methods. In addition, the development of non-invasive brain stimulation techniques such as transcranial Direct Current Stimulation (tDCS) has also demonstrated the capability of modulating brain excitability thus increasing motor performance. The combination of these two methods is expected to enhance functional and motor recovery after stroke; to this purpose, the current trends in this research field are presented and discussed through an in-depth analysis of the state-of-the-art. The heterogeneity and the restricted number of collected studies make difficult to perform a systematic review. However, the literature analysis of the published data seems to demonstrate that the association of tDCS with robotic therapy has the same clinical gain derived from robotic therapy alone. Future studies should investigate combined approach tailored to the individual patient's characteristics, critically evaluating the brain areas to be targeted and the induced functional changes.

Romeo R.A., Oddo C.M., Carrozza M.C., Guglielmelli E., Zollo L.

**Slippage detection with piezoresistive tactile sensors.**

One of the crucial actions to be performed during a grasping task is to avoid slippage. The human hand can rapidly correct applied forces and prevent a grasped object from falling, thanks to its advanced tactile sensing. The same capability is hard to reproduce in artificial systems, such as robotic or prosthetic hands, where sensory motor coordination for force and slippage control is very limited. In this paper, a novel algorithm for slippage detection is presented. Based on fast, easy-to-perform processing, the proposed algorithm generates an ON/OFF signal relating to the presence/absence of slippage. The method can be applied either on the raw output of a force sensor or to its calibrated force signal, and yields comparable results if applied to both normal or tangential components. A biomimetic fingertip that integrates piezoresistive MEMS sensors was employed for evaluating the method performance. Each sensor had four units, thus providing 16 mono-axial signals for the analysis. A mechatronic platform was used to produce relative movement between the finger and the test surfaces (tactile stimuli). Three surfaces with submillimetric periods were adopted for the method evaluation, and 10 experimental trials were performed per each surface. Results are illustrated in terms of slippage events detection and of latency between the slippage itself and its onset.
Over the past years, the research activity related to breast cancer has significantly expanded. The research unit is actively enrolled in the field of tailored therapies, in order to individualize the treatment with an integrated approach, in the era of precision medicine. The mission of the Breast Care Unit is to provide the highest quality clinical service, research and education to guarantee the reduction of breast cancer mortality together with the quality of life improvement, in the context of a multidisciplinary setting with complex intellectual architecture.

Specifically, Breast Cancer Surgeons are committed to:

- Providing the highest quality in all aspects of diagnosis, resection, reconstruction and clinical management.
- Achieving competence in a broad range of comprehensive oncological, radioguided and reconstructive procedures with structured educational supervision, assessment and feedback.
- Continuously increasing the use of oncoplastic conserving procedures to offer solutions for challenging scenarios, while preserving the natural shape and appearance of the breast.
- Providing the highest quality in all aspects of diagnosis, resection, reconstruction and clinical management.
- Continuously increasing the use of oncoplastic conserving procedures to offer solutions for challenging scenarios, while preserving the natural shape and appearance of the breast.

**Main research activities**

- New techniques of loco-regional anaesthesia performed by breast surgeon to improve surgical outcomes (pain control, opioid-free analgesia, prevention of chronic pain)
- Multicentric study “Prevention of the third millennium: liquid biopsy”, to detect fragments of circulating DNA in peripheral blood. This approach considers breast cancer as a “moving target”, an heterogeneous disease continuously evolving and changing.
- Management of B3 lesions (lesions of unknown biological potential) to investigate the role of possible new biomarkers for high risk patients
- International collaboration with Ministry of Health of Palestine to study the epidemiology of breast cancer in West Bank Area and the role of mini-invasive diagnostic techniques to improve surgical outcome and quality of life
- Oncoplastic breast surgery as an innovative approach that aims at the safe and effective treatment of the cancerous lesion while achieving the best possible aesthetic outcome, consisting of large lumpectomy and remodelling techniques such as breast-reshaping by therapeutic reduction mammoplasty or volume replacement by local glandular flaps or regional/distant flaps.

**Main collaborations**

- University Hospital of Tor Vergata, Rome;
- University Hospital of Perugia;
- Institut du Sein of Paris, France;
- Ministry of Health of Palestine.
Most important publications


Limitations in predicting PAM50 intrinsic subtype and risk of relapse score with Ki67 in estrogen receptor-positive HER2-negative breast cancer.


PAM50/Prosigna gene expression-based assay identifies three categorical risk of relapse groups (ROR-low, ROR-intermediate and ROR-high) in post-menopausal patients with estrogen receptor estrogen receptor-positive (ER+)/HER2-negative (HER2-) early breast cancer. Low risk patients might not need adjuvant chemotherapy since their risk of distant relapse at 10-years is below 10% with endocrine therapy only. In this study, 517 consecutive patients with ER+/HER2- and node-negative disease were evaluated for Ki67 and Prosigna. Most of Luminal A tumors (65.6%) and ROR-low tumors (70.9%) had low Ki67 values (0-10%); however, the percentage of patients with ROR-medium or ROR-high disease within the Ki67 0-10% group was 42.7% (with tumor sizes ≤2 cm) and 33.9% (with tumor sizes > 2 cm). Finally, we found that the optimal Ki67 cutoff for identifying Luminal A or ROR-low tumors was 14%. Ki67 as a surrogate biomarker in identifying Prosigna low-risk outcome patients or Luminal A disease in the clinical setting is unreliable. In the absence of a well-validated prognostic gene expression-based assay, the optimal Ki67 cutoff for identifying low-risk outcome patients or Luminal A disease remains at 14%.


Current trends and outcomes of breast reconstruction following nipple-sparing mastectomy: results from a national multicentric registry with 1006 cases over a 6-year period.


Background: Reconstruction options following nipple-sparing mastectomy (NSM) are diverse and not yet investigated with level IA evidence. The analysis of surgical and oncological outcomes of NSM from the Italian National Registry shows its safety and wide acceptance both for prophylactic and therapeutic cases. A further in-depth analysis of the reconstructive approaches with their trend over time and their failures is the aim of this study. Methods: Data extraction from the National Database was performed restricting cases to the 2009-2014 period. Different reconstruction procedures were analyzed in terms of their distribution over time and with respect to specific indications. A 1-year minimum follow-up was conducted to assess reconstructive unsuccessful events. Univariate and multivariate analyses were performed to investigate the causes of both prosthetic and autologous failures. Results: 913 patients, for a total of 1006 procedures, are included in the analysis. A prosthetic only reconstruction is accomplished in 92.2 % of cases, while pure autologous tissues are employed in 4.2 % and a hybrid (prosthetic plus autologous) in 3.6 %. Direct-to-implant (DTI) reaches 48.7 % of all reconstructions in the year 2014. Prophylactic NSMs have a DTI reconstruction in 35.6 % of cases and an autologous tissue flap in 12.9 % of cases. Failures are 2.7 % overall: 0 % in pure autologous flaps and 9.1 % in hybrid cases. Significant risk factors for failures are diabetes and the previous radiation therapy on the operated breast. Conclusions: Reconstruction following NSM is mostly prosthetic in Italy, with DTI gaining large acceptance over time. Failures are low and occurring in diabetic and irradiated patients at the multivariate analysis.
The Cardiovascular Science Research Unit comprises clinical cardiologists, interventional cardiologists, expert cardiologists in echocardiography and electrophysiology. Our Unit is involved in several national and international multicentre clinical trials, mainly focusing on new devices for percutaneous coronary intervention and new drugs for management of patients with cardiovascular diseases. Moreover, we performed and are performing several prospective experimental studies on a wide range of clinical settings such as interventional pharmacology, glycaemic variability assessment, biological markers and cardiac electrophysiology.

The randomized RIVENDEL study, investigating the effects of Ivabradine on vascular endothelial function, has been finalized and published; Substudies of the multicentre MATRIX study, comparing radial versus femoral approach in patients with acute coronary syndromes treated with PCI, have been published.

Ongoing research projects:
- Predictive role of a combined evaluation of carotid atherosclerosis and peripheral endothelial function on the presence and extent of coronary artery disease;
- Comparison of prasugrel and ticagrelor in protecting coronary microcirculation in patients with stable coronary artery disease undergoing PCI (PRO-MICRO 3 study);
- Impact of glycaemic variability assessed by a glucose continuous monitoring on platelet reactivity;
- Effects of ranolazine on glycemic control in diabetic patients;
- Impact of micro-RNA evaluation on cardiac resynchronization therapy outcome.

Our Unit collaborates with several other Italian and international universities and research institutions:
- Cardiovascular Research Center Aalst, Belgium;
- Harvard Clinical Research Institute, Boston, USA;
- Technical University of Eindhoven, The Netherlands;
- Virginia Commonwealth University, USA.
Most important publications

Mangiacapra F., Colaiori I., Ricottini E., Balducci F., Creta A., Demartini C., Minotti G., Di Sciascio G.

**Heart Rate reduction by IVabradine for improvement of ENDothELial function in patients with coronary artery disease: the RIVENDEL study.**


RIVENDEL was a randomized controlled trial evaluating the effect of ivabradine on endothelial function in patients with coronary artery disease (CAD) after complete revascularization with percutaneous coronary angioplasty (PCI).

Compared with standard medical treatment, the adjunct of ivabradine resulted in a significant reduction of heart rate, and an improvement of flow mediated dilatation (FMD) and nitroglycerin mediated dilatation. In the ivabradine group, a moderate negative correlation was observed between the heart variation and FMD variation over time.

In patients with CAD undergoing complete revascularization with PCI, addition of ivabradine to the standard medical therapy produces a significant improvement in endothelial function. This effect seems to be related to HR reduction.

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**Acute kidney injury after radial or femoral access for invasive acute coronary syndrome management: AKI-MATRIX.**


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Di Gioia G., Mega S., Nenna A., Campanale C.M., Colaiori I, Scordino D., Ragni L., Miglionico M., Di Sciascio G.

**Should pre-operative left atrial volume receive more consideration in patients with degenerative mitral valve disease undergoing mitral valve surgery?**


We assessed the role of Left Atrial Volume Indexed (LAVI) as predictor of adverse events after mitral valve surgery.

Pre-operative LAVI was an independent risk factor for post-operative and late atrial fibrillation, as well as for atrial and ventricular remodeling. LAVI should therefore be given more weight into decision making for patients with mitral regurgitation.
The Research Unit follows a methodology at the very basis of Process Engineering operative methods. To develop a new technology in the field, two steps are required:

- first, the theoretical elements characterizing the technology must be assessed, supported by purposed experimental campaigns;
- second, mathematical modelling, process simulation and economical assessment provide the essential framework to fully develop the technology.

Main research activities

- Predictive models development for artificial pancreas (in collaboration with the Unit of Endocrinology and Diabetes, Campus Bio-Medico University of Rome, Italy)
- Functionalized nanoparticles development for artificial Liver optimization (in collaboration with the Unit of Tissue Engineering & Chemistry for Engineering, Campus Bio-Medico University of Rome).
- Gastro-intestinal system modelling for in silico trials of drug bioavailability (in collaboration with Unit of Gastroenterology and Unit of Biochemistry and Molecular Biology, Campus Bio-Medico University of Rome).
- Computational biochemistry: proteins as networks (in collaboration with National Institute of Health, Italy, National Research Council (CNR), Italy, University of Rome “Tor Vergata”, University of Catania, Italy).
- Computational approach for developmental biology (in collaboration with Sapienza University, Italy and John Innes Centre, UK);
- Bioartificial liver optimization (in collaboration with Piaggio Research Centre, University of Pisa, Italy).
- Biogas production by anaerobic co-digestion of sludge and food waste (in collaboration with IRSA, Italy).

Main collaborations

- IRSA, Italy;
- Italian National Agency for New Technologies, Energy and Sustainable Development - ENEA, Casaccia Research Centre, Rome, Italy;
- John Innes Centre, UK;
- National Institute of Health, Italy;
- National Research Council (CNR), Italy;
- Piaggio Research Centre, University of Pisa, Italy;
- University of Catania, Italy;
- Sapienza University, Italy;
- University of Rome “Tor Vergata”, Italy.
**Most important publications**


**Auxin minimum triggers the developmental switch from cell division to cell differentiation in the Arabidopsis root.**

In multicellular organisms, a stringent control of the transition between cell division and differentiation is crucial for correct tissue and organ development. In the Arabidopsis root, the boundary between dividing and differentiating cells is positioned by the antagonistic interaction of the hormones auxin and cytokinin. Cytokinin affects polar auxin transport, but how this impacts the positional information required to establish this tissue boundary, is still unknown. By combining computational modeling with molecular genetics, we show that boundary formation is dependent on cytokinin’s control on auxin polar transport and degradation. The regulation of both processes shapes the auxin profile in a well-defined auxin minimum. This auxin minimum positions the boundary between dividing and differentiating cells, acting as a trigger for this developmental transition, thus controlling meristem size.

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Prisciandaro M., Piemonte V., Di Celso G.M., Ronconi S., Capocelli M.

**Thermodynamic features of dioxins’ adsorption.**

In this paper, the six more poisonous species among all congeners of dioxin group are taken into account, and the P-T diagram for each of them is developed. Starting from the knowledge of vapour tensions and thermodynamic parameters, the theoretical adsorption isotherms are calculated according to the Langmuir’s model. In particular, the Langmuir isotherm parameters (K and vmax) have been validated through the estimation of the adsorption heat (ΔHads), which varies in the range 20–24 kJ/mol, in agreement with literature values. This result will allow to put the thermodynamical basis for a rational design of different process units devoted to dioxins.

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De Falco M., Capocelli M., Losito G., Piemonte V.

**LCA perspective to assess the environmental impact of a novel PCM-based cold storage unit for the civil air conditioning.**

Cold storage is a valid solution for the energy peak reduction in the air conditioning field, which strongly affects the energy consumption in the civil sector. An innovative storage device, called ColdPeak, has been already tested in a recently published work, demonstrating unparalleled properties in terms of charging/discharging storage power. Now, the unit is analyzed from the environmental point of view by means of a LCA (Life Cycle Assessment) methodology: the air conditioning system integrating the ColdPeak unit has been compared with a conventional system from the environmental point of view, assuming the same potentiality of cold energy and including a sensitive analysis on the energy saving potential of the innovative device (5 e 25% of the energy required by the conventional system). In the sensitivity analysis, the energy saving is counter-balanced by the energy load required for the manufacturing and installation of an additional component in the air conditioning system (the ColdPeak device itself). The environmental footprint that considers the material and the energy to fabricate the ColdPeak is very low if compared with the amount of energy saved thanks to its application. As a matter of fact, the LCA study reports that the integration of the cold storage unit allows a significant reduction of environmental footprint in terms of Global Warming Potential (17%), Acidification Potential (15.5%), Eutrophication Potential (18%), Eco-toxicity (16%), Human Health (18%) and Fossil Depletion (18%). The paper also reports the temporal trend of the environmental footprint that shows a pay-back period for the construction of the innovative integrated system of less than one year for all the investigated categories.
Clinical Laboratory Sciences

**Head**  S. Angeletti  
**Faculty**  M. Ciccozzi, G. Gherardi  
**Other Personnel**  F. Antonelli, A. Crescenzi, A. Conti, M. De Cesaris, L. De Florio, G. Dicuonzo, M. Fogolari  
**External Members**  E. Cella, M. Giovannetti, A. Lai

**Description**

The research unit is actively interested in research studies aimed to investigate bioumoral markers involved in the diagnosis and prognosis of important disease such as diabetes or sepsis. Further fields of research included the molecular evolution of microorganisms causing important epidemic in Italy as well as worldwide and the antimicrobial resistant microorganisms circulating in different settings, especially in nosocomial. Furthermore, the activity of the research unit was extended also to the evaluation of interesting clinical case diagnosed at the Internal medicine Department of the University Campus Bio-Medico in terms of prompt diagnosis and treatment.

**Main research activities**

In the year 2017, the most important activities developed by the research unit have been in the areas of infectious disease, antibiotic resistance and their pathogenesis. Different collaboration were established with several Department of Internal medicine, Surgery and Geriatrics of the University Hospital Campus Bio-Medico. Furthermore, the research unit by a scientific agreement with the Auxilium Society managing the CARA Centre of Castelnuovo di Porto in Rome for migrants and refugees has continued the collaboration began in the year 2016. By this agreement, a protocol for migrants microbiological surveillance was developed and results of the surveillance reported in some publication on international peer-reviewed scientific journals.

**Main collaborations**

- Auxilium Society, CARA Centre of Castelnuovo di Porto, Italy;  
- Department of Pathology and Laboratory Medicine, University of Florida, Gainesville, USA.  
- Public Health Institute, Montenegro;  
- Public Institute, Bulgaria.

**Most important publications**

Maddaloni E., Pastore G., Del Buono M.G., Porcari A., Fittipaldi M., Garilli F., Tiberti C., Angeletti S., Pozzilli P., Mottini G., Napoli N.

*High prevalence of autoimmune diabetes and poor glycaemic control among adults in Madagascar: a brief report from a humanitarian health campaign in Ambanja.*  
Madagascar is a geographically isolated country considered a biodiversity hotspot with unique genomics. Both the low-income and the geographical isolation represent risk factors for the development of diabetes. During a humanitarian health campaign conducted in Ambanja, a rural city in the northern part of Madagascar, we identified 42 adult subjects with diabetes and compared their features to 24 randomly enrolled healthy controls. 42.9% (n = 18) of diabetic subjects showed HbA1c values ≥ 9.0%. Unexpectedly, waist circumference and BMI were similar in people with diabetes and controls. Different from the healthy controls, diabetic subjects showed a low prevalence of obesity (5.7% versus 30%, p = 0.02). Accordingly, we found a high prevalence of autoimmune diabetes as 12% of people with diabetes showed positivity for the autoantibody against glutamic acid decarboxylase. Diabetic subjects with positive autoantibody had higher HbA1c values (11.3 ± 4.1% versus 8.3 ± 2.6%, p = 0.03) compared to diabetic subjects with negative autoantibody. In conclusion, here we describe the presence of diabetes and its features in a rural area of Northern Madagascar, documenting poor glycaemic control and a high prevalence of autoimmune diabetes. These data highlight that the diabetes epidemic involves every corner of the world possibly with different patterns and features.

First epidemiological and phylogenetic analysis of Hepatitis B virus infection in migrants from Mali.

The armed conflict in Mali caused a migration crisis since 2012. Most Malian refugees were in Italy. In Sub-Saharan Africa, the seroprevalence of anti-HBV antibodies is particularly high. Genotype E is the most prevalent throughout a crescent covering area from Angola to Senegal, including Mali. We report 16 HBV positive individual from 136 Malian asylum seekers in order to investigate the genetic diversity of HBV in this population. Sequencing and phylogenetic analysis has been used. The HBV genotype E isolates from Mali did not cluster together but were intermixed, with the other African sequences. Only three supported clade were evidenced and closely related to sequences from Burkina Faso. The estimated evolutionary rate was 9.29 × 10^4 . The root of the tree dated back to February 2008 in (95% HPD: 2006-2011). From this ancestor six main statistically supported clusters (pp > 0.80) were identified. The most recent Clade dated back to May 2015. The BSP showed that the effective number of infections softly increased from 2011 to the 2015. Phylogenetic analysis helped in understanding how two on sixteen individuals, have been infected in Italy, and give an important improvement in prevention campaigns and monitoring of the viral infection in migrants. J. Med. Virol. 89:639-646, 2017.

Multi-drug resistant Klebsiella pneumoniae strains circulating in hospital setting: whole-genome sequencing and Bayesian phylogenetic analysis for outbreak investigations.

Carbapenems resistant Enterobacteriaceae infections are increasing worldwide representing an emerging public health problem. The application of phylogenetic and phylodynamic analyses to bacterial whole genome sequencing (WGS) data have become essential in the epidemiological surveillance of multi-drug resistant nosocomial pathogens. Between January 2012 and February 2013, twenty-one multi-drug resistant K. pneumoniae strains, were collected from patients hospitalized among different wards of the University Hospital Campus Bio-Medico. Epidemiological contact tracing of patients and Bayesian phylogenetic analysis of bacterial WGS data were used to investigate the evolution and spatial dispersion of K. pneumoniae in support of hospital infection control. The epidemic curve of incident K. pneumoniae cases showed a bimodal distribution of cases with two peaks separated by 46 days between November 2012 and January 2013. The time-scaled phylogeny suggested that K. pneumoniae strains isolated during the study period might have been introduced into the hospital setting as early as 2007. Moreover, the phylogeny showed two different epidemic introductions in 2008 and 2009. Bayesian genomic epidemiology is a powerful tool that promises to improve the surveillance and control of multi-drug resistant pathogens in an effort to develop effective infection prevention in healthcare settings or constant strains reintroduction.
Description

The research activities of the Computer Science and Bioinformatics (CoSBI) Research Unit are focused on the analysis of data, signals, and images with a special attention to biomedical applications. The Unit has also experience on high performance computing, machine learning and data analytics, computer networks with special focus on wireless networks, and modeling dynamic stochastic system.

Main research activities

- Ultra terabyte image processing techniques, i.e. methods for processing microscopy images with sizes that exceed the terabyte size for restoring, visualization, segmentation, information extraction.
- CAD systems for automatic analysis of Indirect Immunofluorescence (IIF) images.
- Decision Support Systems for clinical applications.
- Radiomics that is decoding tumour phenotypes by non-invasive quantitative imaging.
- Algorithms for the analysis of EEG and EEG-TMS signals, and of fMRI images.
- Control and estimation theory for stochastic, distributed and time-delayed systems, and control and systems technology for health-care applications: artificial pancreas, control of tumor growth.
- A system to detect risk conditions for COPD patients, identify COPD phenotypes, forecast clinical course and plan the therapeutic strategy with unsupervised/supervised machine learning methods.
- Identification of age-related cortical changes in excitability and connectivity.
- Definition and implementation of a general framework for the management of wearable sensors.
- Research on radiomics to collect repositories of images and predict therapy response of cancer patients.
- Development of estimation methods for mathematical models of biological systems.
- Development the CAD system to classify ANA samples in IIF.
- Analysis of social microblogs and rumour detection.
- Development tools for processing ultra terabyte images.

Main collaborations

- Allen Institute, USA;
- Catholic University of the Sacred Heart, Italy;
- Centro Diagnostico Italiano SpA;
- Department of Computer Science, Eindhoven University of Technology, The Netherlands;
- Departments of Information and Electrical Engineering, University of L’Aquila, Italy;
- European Laboratory for Non-Linear Spectroscopy (LENS), Italy;
- Informatics and Automation Sapienza University, Italy;
- Institute for Systems Analysis and Computer Science, Italy.
Most important publications

Merone M., Pedone C., Capasso G., Incalzi R.A., Soda P.

**A decision support system for tele-monitoring COPD-related worrisome events.**

Chronic Obstructive Pulmonary Disease (COPD) is a progressive disease, whose course is aggravated by a periodic worsening of symptoms and lung function lasting for several days. This paper presents a decision support system (DSS) detecting the onset of worrisome events in COPD subjects. It uses the heartbeat rate and the oxygen saturation, which can be collected via a pulse oximeter. The DSS consists in a binary finite state machine, whose training stage allows a subject-specific personalized model to trigger warnings and alarms as the health status evolves over time. The experiments on data collected from 22 COPD patients tele-monitored at home for six months show that the system recognition performance is better than the one achieved by medical experts. Furthermore, the support offered by the system in the decision-making process allows increasing the agreement between the specialists, largely impacting the recognition of the worrisome events.

Ferreri F., Guerra A., Vollero L., Ponzo D., Maatta S., Mervaala E., Iannello G., Di Lazzaro V.

**Age-related changes of cortical excitability and connectivity in healthy humans: non-invasive evaluation of sensorimotor network by means of TMS-EEG.**

The sensorimotor cortical system undergoes structural and functional changes across its lifespan. Some of these changes are physiological and parallel the normal aging process, while others might represent pathophysiological mechanisms underlying neurodegenerative disorders. In this work we have used the transcranial magnetic stimulation (TMS)-electroencephalography (EEG) navigated co-registration to investigate the influence of physiological aging on the excitability and connectivity of the human sensorimotor cortical system. We show that, after stimulation of the left motor cortex, TEPs are significantly affected by physiological aging. This phenomenon has a clear spatio-temporal specificity and we speculate that normal aging per se leads to some changes in the excitability of specific cortical neural assemblies whereas other alterations could reflect compensatory mechanisms to such changes.


**Luenberger-like observers for nonlinear time-delay systems with application to the artificial pancreas: the attainment of good performance.**
*IEEE Control Systems 2017;37(4):33-49. DOI: 10.1109/MCS.2017.2696759. IF 5,196*

The aim of this article is to show the good performance obtained by the state observer applied to a delay differential equations (DDE) model of the glucose-insulin system recently used in the artificial pancreas (AP) framework. Validation is carried out by real clinical measurements available from 20 healthy subjects who underwent an intravenous glucose tolerance test (IVGTT). The results show that the observer behavior is robust with respect to the initial conditions, which have been set according to a pair of very critical cases of under- and overestimation. Also, the robustness of the observer with respect to some model parameters, such as the delay in the pancreatic insulin production, is discussed.
The Developmental Neuroscience unit investigates developmental mechanisms at the molecular, cellular and systemic levels, both in animal models and in human infants. One major focus of the lab has been the interaction between reelin, a protein of the extracellular matrix and environmental factors, in particular gonadal hormones, during brain development. The reelin gene is a candidate gene for autism, a pervasive developmental disorders that is more frequent in males. The other major focus of the lab is the role of motor development and other embodied functions for development of cognitive functions and mental processes. Specifically, we are investigating early motor signs of autism risk in high-risk babies, who have an older sibling affected by this disorder. A new research focus of the lab is the investigation of embodied music perception in children.

Main collaborations

- Dr. Alessandra Micera, G. B. Bietti Foundation for Study and Research in Ophthalmology, Italy (interaction between NGF and reelin in the mouse retina);
- Dr. Nicola Di Stefano, Istituto FAST; Dr. Fabrizio Taffoni, Lab of Biomedical Robotics (music perception in young children);
- Prof. Jana M. Iverson, University of Pittsburgh (motor development in siblings who are at high risk for autism).
Most important publications


Dopamine neuronal loss contributes to memory and reward dysfunction in a model of Alzheimer’s disease.

Alterations of the dopaminergic (DAergic) system are frequently reported in Alzheimer’s disease (AD) patients and are commonly linked to cognitive and non-cognitive symptoms. However, the cause of DAergic system dysfunction in AD remains to be elucidated. We investigated alterations of the midbrain DAergic system in the Tg2576 mouse model of AD, overexpressing a mutated human amyloid precursor protein (APPswe). Here, we found an age-dependent DAergic neuron loss in the ventral tegmental area (VTA) at pre-plaque stages, although substantia nigra pars compacta (SNpc) DAergic neurons were intact. The selective VTA DAergic neuron degeneration results in lower DA outflow in the hippocampus and nucleus accumbens (NAc) shell. The progression of DAergic cell death correlates with impairments in CA1 synaptic plasticity, memory performance and food reward processing. We conclude that in this mouse model of AD, degeneration of VTA DAergic neurons at pre-plaque stages contributes to memory deficits and dysfunction of reward processing.

Di Stefano N., Focaroli V., Giuliani A., Formica D., Taffoni F., Keller, F.

A new research method to test auditory preferences in young listeners: results from a consonance versus dissonance perception study.

To date, behavioural procedures adopted to assess sound preferences in young children have evaluated the responses of participants while listening to the stimuli administered by the experimenter. Due to the difficulties, which may arise in the interpretation of the results, recent studies have suggested some limitations to these procedures, stimulating the further development of behavioural methods. Here, we introduce a new method for testing sound preferences in children, in which participants actively produce the stimuli during the experimental session. The apparatus consists of a musical lever which emits different sounds depending on its rotation around a hinge. The device was programmed to emit consonant and dissonant harmonic intervals. The procedure has been tested with 22 participants from 19 to 40 months of age. Results show that: (a) sound emission strongly stimulates toy manipulation; (b) the examined participants distinguished the two types of sounds, showing a preference for producing consonant over dissonant stimuli. This method could be used to study a wide range of sound qualities in young listeners, such as rhythm or pitch. Grounded in the mutual interaction between perception and action, this procedure is in line with recent research highlighting the role of embodiment in the perception of music.

Taffoni F., Perna L. D., Formica D., Focaroli V., Keller F., Di Stefano N.

A sensor-based approach to study sound perception in children.

In the present paper, we describe an instrumented toy to study auditory preferences in young children. After brief considerations on the theoretical framework, the design of the mechanical, electronic and software components of the system is presented. The system allows for: (a) producing audio stimuli according to how children play with the toy; (b) assessing children’s motor behaviour during the interaction. The device is provided with a sensor core enabling the assessment of manipulation in terms of angular displacement with errors lower than 1°. The laboratory validation is presented and discussed in details. Moreover, a pilot trial on two children aged 34 and 35 months is described and discussed. Results show the appropriateness of the technology to the experimental aims, and encourage research on methods based on the interaction between perception and action to investigate music preferences in young listeners.
Research is carried out following different lines, in cooperation with other research units of our University:

- **Neuroimaging**, that studies mainly the correlation of MRI with diagnosis, treatment or rehabilitation of different diseases;
- **Interventional radiology**, that studies how radiologists can use small invasive approaches for the diagnosis and the treatment of several diseases;
- **Image based navigations systems**, that studies the use of mechatronics and images acquired directly from the patients to guide diagnostic and therapeutic procedures in medicine;
- **Elderly people imaging**, that studies how senescence processes can modify the functionality and the morphology of different organs and tissues;
- **Oncologic imaging**, that studies how radiologists can help in the diagnosis, in the treatment and in the follow-up of oncologic patients;
- **Precision imaging**, that studies the correlation between some imaging biomarkers and genetic characteristics of different diseases.

### Most important publications


**Osteitis pubis in professional football players: MRI findings and correlation with clinical outcome.**


**Background and Purpose:** Osteitis pubis (OP), a common pathology in elite athletes, is an aseptic inflammatory process of the pubic symphysis bone, and may involve surrounding soft tissues, tendons and muscles. OP is typically characterized by (often recurring) groin pain and is an important cause of time-off from sports activity in athletes. Aim of this retrospective study was to analyze magnetic resonance imaging (MRI) findings in professional football players with clinical diagnosis of OP and to correlate MRI findings with clinical outcome.

**Material and Methods:** All professional football players (23 males, 1 female; mean age: 21±3.7 years; range: 16-30 years) with groin pain and clinical diagnosis of OP, who underwent pelvic MRI in our institution were retrospectively analyzed. The MR images were analyzed regarding the presence of bone marrow edema and its extension, whether fluid in the symphysis pubis or periarticular soft tissue edema with a rim-like periosteal distribution or edema in the muscles located around the symphyseal joint were present, whether degenerative changes of the symphysis pubis...
and of signs of symphyseal instability were encountered. A quantitative measurement of the signal intensity in bone marrow edema on 3T STIR sequences was performed, normalizing these values to the mean signal intensity values in the ipsilateral iliopsoas muscle. All patients were classified according to a 3-point grading scale. For each patient, both the symptoms 18 months after the initial MRI examination, the duration of time off from playing football and the kind of treatment applied were evaluated. Results: Among all professional athletes, in 20/24 (83.3%) MRI showed signs of OP with bone marrow edema at the pubic bone. 12 of these patients showed complete clinical recovery without any symptoms after 18 months, while in 8 patients partial recovery with persistence of groin pain during higher sports activity was observed. Patients with edema in periarticular soft tissues or in the muscles around the symphyseal joint on MRI at the beginning of symptoms presented significantly more often with a partial recovery after returning to high sports activity (p=0.042 and p=0.036, respectively). A partial recovery was also significantly associated with higher normalized mean signal intensity values in bone marrow edema on STIR sequences at the beginning of symptoms (mean=4.77±1.63 in the group with partial recovery vs. mean=2.86±0.45 in the group with complete recovery; p=0.0019). No significant association was noticed between MRI findings and time of abstinence from high sports activity, as well as between the 3-point grading scale and the time off from high sport activity and recovery at 18 months. Conclusions: Edema in periarticular soft tissues, edema with extension to the muscles located around the symphyseal joint, as well as higher normalized signal intensity values in bone marrow edema on STIR sequences in the pubic bones at the beginning of groin pain are the most reliable MRI findings of a poor clinical long-term outcome of OP in professional football players and should be regarded as negative prognostic factors.

Gaudio S., Quattrocchi C.C., Piervincenzi C., Zobel B.B., Montecchi F.R., Dakanalis A., Riva G., Carducci F.

White matter abnormalities in treatment-naive adolescents at the earliest stages of anorexia nervosa: a diffusion tensor imaging study.

Few studies have examined white matter (WM) integrity in long-lasting Anorexia Nervosa (AN) patients using Diffusion Tensor Imaging (DTI). In this paper, we investigated WM integrity at the earliest stages of AN (i.e. less than 6 months duration). Fourteen treatment-naive female adolescents with AN restrictive type (AN-r) in its earliest stages and 15 age-matched healthy females received brain MRI. Fractional Anisotropy (FA), Axial Diffusivity (AD), Radial diffusivity (RD), and Mean Diffusivity (MD) maps were computed from DTI data using Tract-Based Spatial Statistics analysis. AN-r patients showed FA decreases compared to controls (pFWE < 0.05) mainly in left anterior and superior corona radiata and left superior longitudinal fasciculus. AN-r patients also showed decreased AD in superior longitudinal fasciculus bilaterally and left superior and anterior corona radiata, (pFWE < 0.05). No significant differences were found in RD and MD values between the two groups. FA and AD integrity appears to be specifically affected at the earliest stages of AN. Alterations in the microstructural properties of the above mentioned tracts, also involved in cognitive control and visual perception and processing, may be early mechanisms of vulnerability/resilience of WM in AN and sustain the key symptoms of AN, such as impaired cognitive flexibility and body image distortion.

Macchi M., Belfiore M. P., Floridi C., Serra N., Belfiore G., Carmignani L., Grasso R. F., Mazza E., Pusceddu C., Brunese L., Carrafiello G.

Radiofrequency versus microwave ablation for treatment of the lung tumours: LUMIRA (lung microwave radiofrequency) randomized trial.

The LUMIRA trial evaluated the effectiveness of radiofrequency (RFA) and microwave ablation (MWA) in lung tumours ablation and defining more precisely their fields of application. It is a controlled prospective multi-centre random trial with 1:1 randomization. Fifty-two patients in stage IV disease (15 females and 37 males, mean age 69 y.o., range 40-87) were included. We randomized the patients in two different subgroups: MWA group and RFA group. For each group, we evaluated the technical and clinical success, the overall survival and complication rate. Inter-group difference was compared using Chi-square test or Fisher’s exact test for categorical variables and one-way ANOVA test for continuous variables. For RFA group, there was a significant reduction in tumour size only between 6 and 12 months (p value = 0.0014). For MWA group, there was a significant reduction in tumour size between 6 and 12 months (p value = 0.0003) and between pre-therapy and 12 months (p value = 0.0215). There were not significant differences between the two groups in terms of survival time (p value = 0.883), while the pain level in MWA group was significantly less than in RFA group (1.79 < 3.25, p value = 0.0043). In conclusion, our trial confirms RFA and MWA are both excellent choices in terms of efficacy and safety in lung tumour treatments. However, when compared to RFA therapy, MWA produced a less intraprocedural pain and a significant reduction in tumour mass.
Drug Sciences

Head G. Minotti
Faculty E. Salvatorelli
Other Personnel P. Menna

Description

This Research Unit is committed to elucidating pharmacological foundations and clinical correlates of cardiovascular liability of antitumor drugs. It designs and performs experiments by molecular modelling, cell biology, ex vivo human tissue biopsies, optical and mass spectrometry techniques.

Main research activities

Recalculation of cumulative anthracycline doses associated with 5% risk of heart failure. Cardiac pharmacokinetics and pharmacodynamics of pixantrone.
Most important publications


**Early diagnosis of acute coronary syndrome.**

The diagnostic evaluation of acute chest pain has been augmented in recent years by advances in the sensitivity and precision of cardiac troponin assays, new biomarkers, improvements in imaging modalities, and release of new clinical decision algorithms. This progress has enabled physicians to diagnose or rule-out acute myocardial infarction earlier after the initial patient presentation, usually in emergency department settings, which may facilitate prompt initiation of evidence-based treatments, investigation of alternative diagnoses for chest pain, or discharge, and permit better utilization of healthcare resources. A non-trivial proportion of patients fall in an indeterminate category according to rule-out algorithms, and minimal evidence-based guidance exists for the optimal evaluation, monitoring, and treatment of these patients. The Cardiovascular Round Table of the ESC proposes approaches for the optimal application of early strategies in clinical practice to improve patient care following the review of recent advances in the early diagnosis of acute coronary syndrome. The following specific ‘indeterminate’ patient categories were considered: (i) patients with symptoms and high-sensitivity cardiac troponin <99th percentile; (ii) patients with symptoms and high-sensitivity troponin <99th percentile but above the limit of detection; (iii) patients with symptoms and high-sensitivity troponin >99th percentile but without dynamic change; and (iv) patients with symptoms and high-sensitivity troponin >99th percentile and dynamic change but without coronary plaque rupture/erosion/dissection. Definitive evidence is currently lacking to manage these patients whose early diagnosis is ‘indeterminate’ and these areas of uncertainty should be assigned a high priority for research.

Menna P., Salvatorelli E., Minotti G.

**Cancer drugs and QT prolongation: weighing risk against benefit.**

We briefly summarize how QT prolongation occurs, what clinical conditions may expose cancer patients to an increased risk of QT prolongation, what can be done to minimize risk while also maximizing clinical benefit from the new drugs. Regulatory aspects of drug development and post approval surveillance are also discussed.

Salvatorelli E., Menna P., Chello M., Covino E., Minotti G.

**Modeling human myocardium exposure to doxorubicin defines the risk of heart failure from low-dose doxorubicin.**

The antitumor anthracycline, doxorubicin (DOX), can cause heart failure (HF) upon cumulative administration. Lowering the cumulative dose of DOX proved useful to minimize HF risk, and, yet, there is a growing concern that HF might occur after doses that were thought to be safe. Clinical trials that prospectively address such concerns are lacking. Because HF risk correlates with cardiac exposure to DOX, cumulative doses associated with HF risk were re-explored by modeling the accumulation of anthracycline pools in human myocardium. Ex vivo myocardial samples were used in vitro to simulate DOX rapid infusions. The accumulation of anthracycline pools was measured and incorporated into equations from which a risk versus dose curve was obtained. The experimental curve identified a 5% risk dose that was congruent with a previously reported clinical value (380 versus 400 mg/m2, respectively); however, 1-2% risk occurred after lower doses than reported. Simulations of gain-of-function polymorphism of carbonyl reductase 3, which converts DOX to its poorly diffusible alcohol metabolite, doxorubicinol (DOXOL), expanded anthracycline pools and caused 5% or 1-2% risk doses to decrease to 330 or 180-230 mg DOX/m2, respectively. These data show there is no safe dose of DOX. Diminishing cardiac exposure to circulating DOX may represent a cardioprotective strategy. We show that DOX slow infusions or liposomal DOX, which reduce cardiac exposure to DOX, caused formation of smaller anthracycline pools, did not generate DOXOL, increased the 5% risk dose to 750-800 mg/m2, and prevented HF risk aggravation by carbonyl reductase polymorphism.
Electronics for Sensor Systems

Head  G. Pennazza
Faculty:  M. Santonico
Other Personnel  S. Grasso, A. Sabatini, A. Zompanti

Description

The Unit of Electronics for Sensor Systems (ESS) has a long experience in the study, design, development and test of sensors and electronic interfaces for sensor systems, especially for medical applications and food monitoring. Its main characteristic is the multidisciplinary approach: designing sensors and electronic interfaces is the core activity, and it is addressed to specific issues in the bio-medical context or coming from food-industry. ESS staff includes Electronic Engineers, Biomedical Engineers and a Biotechnologist. This unit is able to cover many steps of the development process of innovative technologies, starting from the basic research on electronic circuits and on new sensing materials. ESS transforms this research in a new technology concept and it is also able to integrate a prototype system in an engineered version, and to test them in the lab and in a relevant environment. This unit also applies multivariate data analysis techniques for the elaboration of the data.

Main research activities

This unit has contributed in 2017 to the study of exhaled breath with: a multi-centre and multi-disease monitoring campaign (started many years ago), which has overcome the threshold of 1200 patients; further technological improvement in the electronic interface and sensor performance of the BIONOTE system; contribution to the European respiratory society technical standard on exhaled biomarkers in lung disease (just published).

This Unit is partner of a FLAG-ERA project, Convergence, started in 2017; unit’s task consists of developing low-power and wireless wearable sensors for the monitoring of ECG-like signals and for the detection of CO2, O2 and RH in the environment. This Unit started in 2017 a collaboration with the CNR Institute of Biomedicine and Molecular Immunology for the monitoring of paediatric asthma.

The collaboration with the department of Microelectronics of the University of Delft (NL) provided in 2017 novel microfabricated electrodes for the BIONOTE liquid sensors.

Main collaborations

• CNR-IBIM: Institute of Biomedicine and Molecular Immunology “A. Monroy”, Palermo, Italy;
• Department of Microelectronics, University of Delft, (NL).
Most important publications


**An Electronic System for the Contactless Reading of ECG Signals.**

The aim of this work is the development of a contactless capacitive sensory system for the detection of (Electrocardiographic) ECG-like signals. The acquisition approach is based on a capacitive coupling with the patient body performed by electrodes integrated in a front-end circuit. The proposed system is able to detect changes in the electric charge related to the heart activity. Due to the target signal weakness and to the presence of other undesired signals, suitable amplification stages and analogue filters are required. Simulated results allowed us to evaluate the effectiveness of the approach, whereas experimental measurements, recorded without contact to the skin, have validated the practical effectiveness of the proposed architecture. The system operates with a supply voltage of ±9 V with an overall power consumption of about 10 mW. The analogue output of the electronic interface is connected to an ATmega328 microcontroller implementing the A/D conversion and the data acquisition. The collected data can be displayed on any multimedia support for real-time tracking applications.


**Equivalent electric circuits for chemical sensors in the Langmuir regime.**
*Senors and Actuators B: Chemical, 238, 214-220. DOI: 10.1016/j.snb.2016.07.011 IF 5,401*

This paper presents an equivalent electric circuit model that describes adsorption-desorption processes occurring on bio and chemical sensor surfaces under the Langmuir hypothesis and considers the following practical case: the pressure or concentration of the particles in the test chamber is not perturbed by these processes and keeps its initial value, as in the cases of relatively high pressure or concentration values with zero molecular flow, or in the presence of a molecular flow at any pressure or concentration value. It is also pointed out that the equivalent circuit for Langmuir adsorption is similar to the circuit proposed for enzymatic reactions. Even if this work essentially covers theoretic aspects, a way is suggested for the possible experimental determination of both adsorption-desorption parameters and adsorption-desorption site density.


**A European Respiratory Society technical standard: exhaled biomarkers in lung disease.**
*Eur Respir J. 2017 Apr 26;49(4): 1600965. PubMed PMID: 28446552. IF 10,569*

Breath tests cover the fraction of nitric oxide in expired gas (FeNO), volatile organic compounds (VOCs), variables in exhaled breath condensate (EBC) and other measurements. For EBC and for FeNO, official recommendations for standardised procedures are more than 10 years old and there is none for exhaled VOCs and particles. The aim of this document is to provide technical standards and recommendations for sample collection and analytic approaches and to highlight future research priorities in the field. For EBC and FeNO, new developments and advances in technology have been evaluated in the current document. This report is not intended to provide clinical guidance on disease diagnosis and management. Clinicians and researchers with expertise in exhaled biomarkers were invited to participate. Published studies regarding methodology of breath tests were selected, discussed and evaluated in a consensus-based manner by the Task Force members. Recommendations for standardisation of sampling, analysing and reporting of data and suggestions for research to cover gaps in the evidence have been created and summarised. Application of breath biomarker measurement in a standardised manner will provide comparable results, thereby facilitating the potential use of these biomarkers in clinical practice.
Endocrinology and Diabetes

**Head**  P. Pozzilli

**Faculty**  S. Manfrini, N. Napoli


**Lab Technician**  L. Valente

**Scientific Secretary**  S. Miglietta, M. Delfonso

**Secretary**  A. Suppa

**Description**

Over the years, the research activity related to endocrine and metabolic diseases has expanded significantly placing the Area of Endocrinology, Campus Bio-Medico University of Rome as a reference point for a range of national and international projects. Our area has been and still is the Coordinator Center of scientific projects of the Ministry of Education and Ministry of Health and of clinical trials of novel therapies, especially in the field of diabetes. Our group collaborates with centres of excellence in Europe, Asia and North America. In these areas, our group works closely with scientific communities and governmental and non-governmental organizations on joint research programs.

**Main research activities**

- Pathogenesis and immunotherapy of type 1 diabetes (T1D);
- Type 2 diabetes (T2D), obesity and nutrition;
- Pathophysiological mechanisms of bone loss in diabetes, obesity and in post-menopause;
- Early diagnosis of thyroid cancer (microbiopsy and RAMAN technology);
- Extraskeletal effects of vitamin D; risk of fracture in T1D and T2D.

**Main results**

- Discovery of predictive markers for T1D using antibodies to post-translationally modified insulin;
- Protection of β-cell function in T1D;
- First report of beneficial effect of an oral hypoglycaemic agent (sotagliflozin) in the management of T1D;
- New markers of bone disease in T1D;
- Novel protocols for treatment of secondary hypoparathyroidism;
- Macrobiotic diet in treatment of diabetes and obesity.
Most important publications


Effects of sotagliflozin added to insulin in patients with type 1 diabetes.

We evaluated the safety and efficacy of sotagliflozin, an inhibitor of sodium-glucose cotransporters 1 and 2, in combination with insulin treatment in patients with type 1 diabetes (T1D). The least-squares mean change from baseline was greater in the sotagliflozin group than in the placebo group for HbA1c, weight (-3 kg), systolic blood pressure (-4 mm Hg), and mean daily bolus dose of insulin (-2.8 units/day) (P≤0.002 for all comparisons). Among patients with T1D treated with insulin, the proportion of patients who achieved a HbA1c level lower than 7.0% with no severe hypoglycemia or diabetic ketoacidosis was larger in the group that received sotagliflozin than in the placebo group.

Strollo R., Vinci C., Napoli N., Pozzilli P., Ludvigsson J., Nissim A.

Antibodies to post-translationally modified insulin as a novel biomarker for prediction of type 1 diabetes in children.

We studied if antibodies to post-translationally modified insulin (oxPTM-INS-Ab) antedate clinical onset of type 1 diabetes (T1D), and can identify children progressing to T1D (progr-T1D), compared with the standard islet-autoantibodies (AAB) to GADA, IAA, IA-2A, ZnT8A. oxPTM-INS-Ab were present in 91% of progr-T1D children. oxPTM-INS-Ab identified 17% to 41% of progr-T1D who tested negative to one or more standard AAB. oxPTM-INS-Ab allowed discrimination between progr-T1D and AAB+ children who did not progress to T1D (p<0.001), with 74% sensitivity and 91% specificity. In conclusion, oxPTM-INS-Ab are present before the clinical onset of T1D and can identify children progressing to T1D.


Placebo-controlled, randomized trial of the addition of once-weekly glucagon-like peptide-1 receptor agonist dulaglutide to titrated daily insulin glargine in patients with type 2 diabetes (AWARD-9).

Aim: To compare the addition of weekly dulaglutide vs the addition of placebo to titrated glargine in patients with type 2 diabetes (T2D) with sub-optimum glycated haemoglobin (HbA1c) concentration.

Results: HbA1c changes from baseline were -1.44 ± 0.09% with dulaglutide/glargine and -0.67 ± 0.09% with placebo/glargine at 28 weeks (P < .001). Body weight decreased with dulaglutide/glargine and increased with placebo/glargine (P < .001). Increases from baseline in mean glargine dose were smaller with dulaglutide/glargine vs placebo/glargine (P < .001).

Conclusions: Weekly dulaglutide 1.5 mg added to basal insulin is an efficacious and well tolerated treatment option for patients with T2D.
Food Science and Nutrition

Head  L. De Gara
Faculty  L. Dugo, C. Fanali, V. Locato, M. Russo
Other Personnel  S. Cimini, F. Orsini, V. Pasqualetti, M. B. Ronci, G. Tripodo, A. Vilmercati
External Members  P. Dugo, E. Marconi, L. Mondello

Description

Research unit interests:
• metabolism in plants and characterization of bio-active phytochemicals;
• food supplements and functional food with particular attention to “antioxidant” and prebiotics properties;
• validation of multisensorial platform based on electronic sensors for its use on shelf life monitoring and food quality assessment;
• in vitro and ex vivo tests evaluating nutritional / health value of food matrixes and nutraceutical compounds;
• plant redox signalling in response to environmental stresses affecting plant development and food security, with particular attention to climate change scenario;
• chemical characterization of bioactive compounds foods employing liquid and gas chromatography techniques.

Research unit expertise:
• plant molecular biology and biochemistry, plant and animal cell cultures, analytical chemistry of metabolites with traditional and omics approaches, food chemistry, plant and food biotechnology.

Main research activities

• Prof. De Gara, PI – project granted by Italian Space Agency. Antioxidant rich – food supplements for the protection against cosmic radiations- PAPARD;
• Prof. Fanali, PI – project granted by AGER2 “VIOLIN - Valorization of Italian Olive products through Innovative analytical tools”;
• Prof. De Gara, PI – Project granted by MIUR – PRIN “Adattamento e tolleranza delle piante agli stress abiotici in condizioni ambientali mutevoli”.

Main collaborations

• Electronics for Sensor Systems: validation of sensorial platforms for food quality/safety assessment;
• Gastroenterology: fructans in support to therapy for gastro-intestinal disorders;
• Geriatrics: Mediterranean Diets. New biochemical methods for testing oxidative stress status in diseases.
**Most important publications**

**Fanali C., D’Orazio G., Fanali S., Gentili A.**

**Advanced analytical techniques for fat-soluble vitamin analysis.**


This review presents advancements in sample preparation and liquid chromatographic methods made during the last 10 years for the fat-soluble vitamin (FSV) analysis in foods. Since activity and bioavailability of organic micronutrients (MOs) depend on the form in which they are present in a food, special emphasis has been given to the most recent techniques, instruments and approaches which have allowed the extraction and separation of various vitamin homologues as well as the comprehensive MO profiling in foods. Due to the numerous ancillary advantages, miniaturized techniques which have been applied in this analysis field are also discussed in this review. A number of selected applications are proposed to enable readers to access the most recent developments and trends aimed at gaining more in-depth knowledge of the vitamin composition of foods.

**De Gara L., Foyer C. H.**

**Ying and yang interplay between reactive oxygen and reactive nitrogen species controls cell functions.**


**Dugo L., Belluomo M. G., Fanali C., Russo M., Cacciola F., Maccarrone M., Sardanelli A. M.**

**Effect of Cocoa polyphenolic extract on macrophage polarization from proinflammatory M1 to anti-inflammatory M2 state.**


Polyphenols-rich cocoa has many beneficial effects on human health, such as anti-inflammatory effects. Macrophages function as control switches of the immune system, maintaining the balance between pro- and anti-inflammatory activities. We investigated the hypothesis that cocoa polyphenol extract may affect macrophage proinflammatory phenotype M1 by favoring an alternative M2 anti-inflammatory state on macrophages deriving from THP-1 cells. Chemical composition, total phenolic content, and antioxidant capacity of cocoa polyphenols extracted from roasted cocoa beans were determined. THP-1 cells were activated with both lipopolysaccharides and interferon-γ for M1 or with IL-4 for M2 switch, and specific cytokines were quantified. Cellular metabolism, through mitochondrial oxygen consumption, and ATP levels were evaluated. Here, we will show that cocoa polyphenolic extract attenuated in vitro inflammation decreasing M1 macrophage response as demonstrated by a significantly lowered secretion of proinflammatory cytokines. Moreover, treatment of M1 macrophages with cocoa polyphenols influences macrophage metabolism by promoting oxidative pathways, thus leading to a significant increase in O2 consumption by mitochondrial complexes as well as a higher production of ATP through oxidative phosphorylation. In conclusion, cocoa polyphenolic extract suppresses inflammation mediated by M1 phenotype and influences macrophage metabolism by promoting oxidative pathways and M2 polarization of active macrophages.
The Research Unit carries out basic and translational research projects through molecular biology analysis and electrophysiological study of muscle contraction with dedicated devices (Radnoti organ bath system and Ussing Chamber System for measuring epithelial membrane properties). The Gastrointestinal Laboratory collaborates with several Research Units of the University, such as Food Sciences and Human Nutrition Unit, Nonlinear Physics and Mathematical Modeling Laboratory and Biochemical Laboratory. Through the employment of high-quality instruments (high-resolution manometry and pH-impedance measuring), it also conducts clinical research protocols, both spontaneous and sponsored, for the study of pathophysiology and diagnosis of gastroesophageal reflux disease and esophageal motility disorders.

The Gastrointestinal laboratory works on the following research areas: immunomodulation of intestinal motility, modulation of microbiota and effect of prebiotics and probiotics in Health and Gastrointestinal diseases, physio-pathological mechanisms of functional gastrointestinal disorders (Irritable Bowel Syndrome, Paralytic ileus and chronic constipation). Nutritional Unit carries out the following projects: Impact of pre-operative nutritional status on surgical outcome in pancreatic cancer patient and on nutritional factors in Inflammatory Bowel Disease patients; immune-nutrition in onco- logical surgical patients. Moreover, the Research Unit carries on phase II and III clinical research trials to test new biological molecules for Inflammatory Bowel Disease treatment and a study with High Resolution manometry on motility pattern in patients affected by Achalasia.

- Farrè R., Leuven University, Belgium;
- Roman S., Centre Hospitalier Universitaire Edouard-Henriot de Lyon, Lyon, France;
- Putignani L., Human Microbiome Unit, Bambino Gesù Children’s Hospital and Research Institute, Rome, Italy.
Most important publications

Savarino V., Pace F., Scarpignato C.; Esoxx Study Group [Cicala M.]

**Randomised clinical trial: mucosal protection combined with acid suppression in the treatment of non-erosive reflux disease - efficacy of Esoxx, a hyaluronic acid-chondroitin sulphate based bioadhesive formulation.**


The aim of this study was to evaluate whether combined therapy would improve symptom relief compared to PPI treatment alone in 154 patients with NERD, randomised to receive Esoxx, a hyaluronic acid-chondroitin sulphate formulation, or placebo. Symptoms and quality of life were evaluated before and after treatment. The primary endpoint was the proportion of patients with a 3-point reduction in the symptom score. At the end of treatment, the primary endpoint was reached by 52.6% of patients taking Esoxx compared to 32.1% of those given placebo (P < 0.01). The effect of Esoxx with PPI treatment suggests that mucosal protection plus acid suppression could improve symptoms in NERD patients.


**Nutritional status and bioelectrical phase angle assessment in adult Crohn disease patients receiving anti-TNFα therapy.**


This study has investigated the nutritional status, and the effect of different therapeutic regimes in adult Crohn’s disease (CD) patients. Fat free mass (FFM) and BIA-derived phase angle (PhA) were assessed in 45 CD patients, 22 on conventional therapy (CT) and 23 on maintenance therapy with infliximab (MT), compared with 20 healthy volunteers. The mean values of PhA and of FFM were significantly lower in CT patients when compared with control group and MT patients. Following the induction protocol with infliximab (in 12 patients) the mean phase angle score normalized. PhA could be considered as an additional tool for assessing response to treatment in CD patients.


**Effect of Inulin on Proteome Changes Induced by Pathogenic Lipopolysaccharide in Human Colon.**


The protective role of inulin against lipopolysaccharide (LPS)-induced oxidative stress was evaluated on human colonic mucosa using a proteomic approach. Human colonic mucosa was sealed between two chambers and overlaid with Krebs (control), LPS or LPS+ inulin IQ solution. The solutions on the submucosal side were collected after 30 min of mucosal exposure. iTRAQ based analysis was used to analyze the proteomes from the colonic mucosa. Colonic muscle strips were exposed to the solutions to evaluate the response to acetylcholine. Exposure of colonic mucosa to inulin seems to prevent LPS-induced alteration in expression of some key proteins, which promote intestinal motility and inflammation.
General Surgery

Head  R. Coppola
Faculty  R. Alloni, D. Borzomati, D. Caputo, M. Caricato, P. Crucitti, V. Ripetti
Other Personnel  V. Bruni, G. Capolupo, V. La Vaccara, S. Valeri

Description

The General Surgery research unit includes seven academic surgeons (one full professor, three associate professors and three assistant professors). In 2017, the research unit has published 14 papers in English language international journals (IF: 49,355).

Main research activities

Pancreas Surgery
- Novel Biomarkers for the diagnosis and treatment of pancreatic cancer (promoted by R. Coppola, D. Caputo).
- Prognostic impact of metastatic nodal stations according to JPS classification after pancreaticoduodenectomy for periampullary cancer (promoted by R. Coppola, D. Borzomati).
- Prospective multicentric study on antibiotic prophylaxis in patients undergoing pancreaticoduodenectomy (promoted by R. Coppola, D. Borzomati).
- Prognostic role of preoperative inflammatory markers for surgically resected pancreatic head cancer (promoted by R. Coppola, D. Caputo).
- New technologies for protein biomarkers discovery in pancreatic cancer

Colorectal Surgery
- Impact of different types of cartridges for linear staples in laparoscopic colorectal surgery: a prospective randomized study (R. Coppola, D. Borzomati, V. La Vaccara).
- Comprehensive multidisciplinary approach to colorectal cancer microenvironment (promoted by M. Caricato, G. Capolupo, V. La Vaccara, A. Crescenzi).
- Impact of different types of cartridges for linear staples in laparoscopic colorectal surgery: a prospective randomized study (R. Coppola, D. Borzomati, V. La Vaccara).
- Comprehensive multidisciplinary approach to colorectal cancer microenvironment (promoted by M. Caricato, G. Capolupo, V. La Vaccara, A. Crescenzi).

Thoracic Surgery
- e-NOSE/BIONOTE evaluation of the “breath print” for patients with a diagnosed lung cancer undergoing surgical resection (promoted by P. Crucitti, F. Longo, R. Antonelli Incalzi) in collaboration with ECBM biomedical engineering.
- Low-dose CT scan lung cancer screening (promoted by P. Crucitti, F. Longo).

Bariatric Surgery
- Long-term weight regain after Gastric Bypass (promoted by Vincenzo Bruni, Domenico Borzomati, Ida Gallo and Rossella D’Alessio).
- Incidence and prevention of thromboembolic events after bariatric surgery (promoted by Vincenzo Bruni, Domenico Borzomati, Ida Gallo and Rossella D’Alessio).

Main collaborations

- Department of Pathology, Catholic University of the Sacred Heart, Italy;
- Department of Pathology, University of Florence, Italy;
- Edouard Herriot Hospital, France;
- Humanitas Research Hospital, Milan, Italy;
- Jagiellonian University, Poland;
- University of Hamburg, Germany;
- University of Lausanne, Switzerland;
- University of Pisa, Italy;
- University of Verona, Italy.
Most important publications

Caputo D., Papi M., Coppola R., Palchetti S., Digiacomo L., Caracciolo G., Pozzi D.

**A protein corona-enabled blood test for early cancer detection.**

Pancreatic cancer is a very aggressive malignancy that is often diagnosed in the advanced stages, with the implication that long-term survivors are extremely rare. Thus, developing new methods for the early detection of pancreatic cancer is an urgent task for current research. To date, nanotechnology offers unprecedented opportunities for cancer therapeutics and diagnosis. The aim of this study is the development of a new pancreatic cancer diagnostic technology based on the exploitation of the nano-biointeractions between nanoparticles and blood samples. In this study, blood samples from 20 pancreatic cancer patients and 5 patients without malignancy were allowed to interact with designed lipid nanoparticles, leading to the formation of a hard “protein corona” at the nanoparticle surface. After isolation, the protein patterns were characterized by sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE). We found that the protein corona of pancreatic cancer patients was much more enriched than that of healthy individuals. Statistical analysis of SDS-PAGE results allowed us to discriminate between healthy and pancreatic cancer patients with a total discriminate correctness rate of 88%.

Papi M., Caputo D., Palmieri V., Coppola R., Palchetti S., Bugli F., Martini C., Digiacomo L., Pozzi D., Caracciolo G.

**Clinically approved PEGylated nanoparticles are covered by a protein corona that boosts the uptake by cancer cells.**

Today, liposomes are an advanced technology of drug carriers with a dozen drugs in clinical practice and many more in clinical trials. A bottleneck associated with the clinical translation of liposomes has long been ‘opsonization’, i.e. the adsorption of plasma proteins at the liposome surface resulting in their rapid clearance from circulation. For decades, the most popular way to avoid opsonization has been grafting polyethylene glycol (PEG) to liposome surface. Recent studies have clarified that grafting PEG to liposome surface reduces, but does not completely prevent protein binding. In this work, we employed dynamic light scattering, zeta-potential analysis, one-dimensional sodium dodecyl sulfate polyacrylamide gel electrophoresis (1D-SDS-PAGE), semi-quantitative densitometry and cell imaging to explore the bionano-interactions between human plasma (HP) and Onivyde, a PEGylated liposomal drug that has recently been approved by the Food and Drug Administration (FDA) for the treatment of metastatic pancreatic ductal adenocarcinoma (PDAC). To properly evaluate the role of PEGylation, an unPEGylated variant of Onivyde was used as a reference. Collectively, our findings suggest that: i) although PEGylated, Onivyde is not “stealth” in HP; ii) surface chemistry is more important than PEGylation in controlling the bio-nano-interactions between Onivyde and plasma components. Of note, the PC was found to boost the cellular uptake of Onivyde in pancreas ductal adenocarcinoma cell line (PANC-1) thus suggesting its prominent role in its indication for PDAC treatment. Relevant implications for drug delivery and drug design are discussed.


**Phase II study of induction chemotherapy followed by chemoradiotherapy in patients with borderline resectable and unresectable locally advanced pancreatic cancer.**

There is not a clear consensus regarding the optimal treatment of locally advanced pancreatic disease. There is a potential role for neoadjuvant therapy to treat micrometastatic disease with chemotherapy, as well as for the treatment of local disease with radiotherapy. We evaluated the safety and efficacy of induction chemotherapy with oxaliplatin and gemcitabine followed by a high weekly dose of gemcitabine concurrent to radiation therapy in patients with borderline resectable and unresectable locally advanced pancreatic cancer. In our study, 41 patients with pancreatic cancer were evaluated. In all cases an accurate pre-treatment staging was performed. Patients with evidence of metastatic disease were excluded, and thus a total of 34 patients were consequently enrolled. Of these, twenty-seven patients (80%) had locally advanced unresectable tumours, seven patients (20%) had borderline resectable disease. This protocol treatment represents a well-tolerated promising approach. Fifteen patients (55.5%) underwent surgical radical resection. With a median follow-up of 20 months, the median PFS and OS were 20 months and 19.2 months, respectively. The median OS for borderline resectable patients was 21.5 months compared with 14 months for unresectable patients (p = 0.3). Continued optimization in multimodality therapy and an accurate patient selection remain crucial points for the appropriate treatment of these patients.
Geriatrics

Head R. Antonelli Incalzi
Faculty C. Pedone, S. Scarlata

Description

This Unit is made up by researcher and clinicians that bring together their skills to produce cutting-edge scientific evidences and provide the best available care for older people. About 50% of the research is based on the clinical activities carried on by the Unit, while the remaining includes analysis of data from epidemiological studies (such as the InCHIANTI and the SARA study) and systematic reviews and meta-analysis.

The lines of research currently ongoing are:
• Evaluation of health status and frailty;
• Evaluation of respiratory function with special focus on the interpretation of spirometric results;
• Evaluation of the diagnostic/prognostic properties of volatile organic compounds (VOCs) in different chronic and acute diseases;
• Development and implementation of system for remote telemonitoring of chronic diseases;
• Evaluation of nutritional intake as a determinant of the health status;
• Assessing the biological bases of and risk factors for antibiotic resistance and its spreading.

Main research activities

We tested the classificatory and predictive properties of e nose based assessment of volatile organic compounds (VOCs) and found that VOCs can significantly improve the traditionally HRCT-based screening of lung cancer, characterize lower limb ulcers having different severity and microbial contamination, predict liver patients’ survival.

Our research in the field of the determinants of functional decline in older people allowed to point out the role of seemingly trivial conditions (e. g. masticatory problems) and of novel markers of risk (e. g., liver fibrosis). We also showed that the current methods to identify frailty are useful to identify people at low risk for subsequent physical decline and mortality, but they cannot reliably identify people who will actually develop these outcomes. We are also investigating the role of diet and nutritional status on health outcomes, especially in people with heart failure, and we have shown that in older people current recommendation for decreasing sodium intake should be applied with caution.

With respect to respiratory diseases, we showed that the new reference standards for lung function are not better than the older ones in stratifying the mortality risk in people with COPD. Furthermore, we demonstrated the effects of an innovative vibro-tactile device in patients with sleep apnea.

Most important publications

Scarlata S., Annibali O., Santangelo S., Tomarchio V., Ferraro S., Armiento D., Scardocci A., Arcese W., Antonelli Incalzi R., Avvisati G.

Pulmonary complications and survival after autologous stem cell transplantation: predictive role of pulmonary function and pneumotoxic medications.
Research Yearbook 2017 | Campus Bio-Medico University of Rome

Autologous stem cell transplantation (ASCT) is the standard of care for multiple myeloma patients eligible for high-dose therapy, lymphoma patients undergoing second-line treatments and for acute myelogenous leukaemia (AML). Immune system impairment and chemotherapies significantly increase the risk of infections, particularly pneumonia. Overall, pulmonary complications, both infectious and non-infectious, occur in 40–60% of patients after stem cell transplantation, and are usually classified as early or late onset, depending on whether they occur within 100 days of the transplant. The underlying disease and baseline pulmonary function, along with conditioning regimens consisting of carmustine, etoposide, ara-cytin and melphalan for lymphoma, melphalan alone for multiple myeloma or busulphan and cyclophosphamide for acute myeloid leukaemia, all concur to cause pulmonary complications. Many reports focus on allogenic transplantation alone, but the only report dealing with ASCT displayed a 25% prevalence of pulmonary complications within the first year post-ASCT and a severe associated risk of death.

The aim of our study was to assess whether baseline pulmonary function tests help to define the risk of pulmonary complications/adverse events or death after ASCT, and determine whether pneumotoxic induction treatment affects this risk. […] In conclusion, exposure to pneumotoxic agents before ASCT increases the risk of pulmonary function abnormalities and to affect infection-free interval and event-free survival, as well as overall survival. If confirmed by a larger, multicentre study, these findings could influence pre-transplant assessment and management.

Lelli D., Antonelli Incalzi R., Pedone C.

Hemoglobin concentration influences N-terminal Pro B-Type natriuretic peptide levels in hospitalized older adults with and without heart failure.


**Objectives:** To investigate the relationship between hemoglobin and N-terminal pro B-type natriuretic peptide (NT-proBNP) concentration in hospitalized older adults with or without a diagnosis of heart failure (HF). **Setting:** Cross-sectional study based on retrospective hospital records review. **Participants:** Individuals aged 65 and older (N = 226; mean age 81.1), with (n = 104) and without (n = 122) a diagnosis of HF. **Measurements:** Information was collected on demographic characteristics, comorbidities, and laboratory and echocardiographic data. The relationship between hemoglobin and NT-proBNP was evaluated using linear regression models adjusted for potential confounders. **Results:** A negative association was found between NT-proBNP and hemoglobin (β = -0.226, P < .001). The regression coefficient was -0.114 (P = .04) in the subsample with HF and -0.191 (P < .001) in the subsample without HF. After adjustment for potential confounders, the inverse association between hemoglobin and NT-proBNP was confirmed in the whole sample (β = -0.182, P < .001), in those with HF (β = -0.136, P = .007), and in those without HF (β = -0.165, P = .003). **Conclusion:** Hemoglobin concentration should be taken into account in the interpretation of NT-proBNP in hospitalized older adults, especially those without HF.


Screening of obstructive sleep apnea syndrome by electronic-nose analysis of volatile organic compounds.


Obstructive Sleep Apnea Syndrome (OSAS) carries important social and economic implications. Once the suspicion of OSAS has arisen, Polysomnography (PSG) represents the diagnostic gold standard. However, about 45% of people who have undergone PSG are free from OSAS. Thus, efforts should be made to improve the selection of subjects. We verified whether the pattern of Volatile Organic Compounds (VOCs) helps to select patients amenable to PSG. We studied 136 subjects (20 obese non-OSAS, 20 hypoxic OSAS, 20 non-hypoxic OSAS, and 20 non-hypoxic Chronic Obstructive Pulmonary Disease (COPD) vs 56 healthy controls) without any criteria of exclusion for comorbidity to deal with a real-life population. VOCs patterns were analyzed using electronic-nose (e-nose) technology. A Discriminant Analysis (Partial Least Squares-Discriminant Analysis) was performed to predict respiratory functions and PSG parameters. E-nose distinguished controls (100% correct classification) from others and identified 60% of hypoxic, and 35% of non-hypoxic OSAS patients. Similarly, it identified 60% of COPD patients. One-by-one group comparison yielded optimal discrimination of OSAS vs controls and of COPD vs controls (100% correct classification). In conclusion, e-nose technology applied to breath-analysis can discriminate non-respiratory from respiratory deceased populations in real-life multimorbid populations and exclude OSAS. If confirmed, this evidence may become pivotal for screening purposes.
Gynaecology and Obstetrics

**Head**  R. Angioli  
**Faculty**  F. Plotti,  
**Other Personnel**  C. Battista, C. De Cicco Nardone, R. Montera, G.B. Serra, C. Terranova

**Description**

The Unit’s work is mainly focused on gynecologic oncology, gynecological surgery for both benign and malignant diseases, endoscopy (laparoscopy and hysteroscopy), endometriosis and uro-gynecology.

**Main research activities**

Our research activity is mainly focused on the identification of biomarkers for the early diagnosis and prognosis of endometrial cancer, on the evaluation of the quality of life of patients affected by gynecological cancers and on the different chemotherapy schemes for cervical cancer.

In collaboration with Yale University we synthesized and characterized polylactic-co-glycolic-acid (PLGA) nanoparticles (NPs) modified with the carboxy-terminal-binding domain of CPE (c-CPE-NP) for the delivery of suicide gene therapy to chemotherapy-resistant ovarian cancer cells. Besides, with the George Mason University and the University of Arizona Cancer Center we explored the kinase-driven metabolic signalling in early and advanced epithelial ovarian cancers, and its role in tumor progression and response to carboplatin-paclitaxel treatment.

**Most important publications**


**Dual-targeting nanoparticles for in vivo delivery of suicide genes to chemotherapy-resistant ovarian cancer cells.**


Ovarian cancer is the most lethal gynecologic cancer. Claudin-3 and -4, the receptors for Clostridium perfringens enterotoxin (CPE), are overexpressed in more than 70% of these tumors. Here, we synthesized and characterized poly(lactic-co-glycolic-acid) (PLGA) nanoparticles (NPs) modified with the carboxy-terminal-binding domain of CPE (c-CPE-NP) for the delivery of suicide gene therapy to chemotherapy-resistant ovarian cancer cells. As a therapeutic payload, we generated a plasmid encoding for the diphtheria toxin subunit-A (DT-A) under the transcriptional control of the p16 promoter, a gene highly differentially expressed in ovarian cancer cells. Flow cytometry and immunofluorescence demonstrated that c-CPE-NPs encapsulating the cytomegalovirus (CMV) GFP plasmid (CMV GFP c-CPE-NP) were significantly more efficient than control NPs modified with a scrambled peptide (CMV GFP scr-NP) in transfecting...
primary chemotherapy-resistant ovarian tumor cell lines in vitro (P = 0.03). Importantly, c-CPE-NPs encapsulating the p16 DT-A vector (p16 DT-A c-CPE-NP) were significantly more effective than control p16 DT-A scr-NP in inducing ovarian cancer cell death in vitro (% cytotoxicity: mean ± SD = 32.9 ± 0.15 and 7.45 ± 7.93, respectively, P = 0.03). In vivo biodistribution studies demonstrated efficient transfection of tumor cells within 12 hours after intraperitoneal injection of CMV GFP c-CPE-NP in mice harboring chemotherapy-resistant ovarian cancer xenografts. Finally, multiple intraperitoneal injections of p16 DT-A c-CPE-NP resulted in a significant inhibition of tumor growth compared with control NP in chemotherapy-resistant tumor-bearing mice (P = 0.041). p16 DT-A c-CPE-NP may represent a novel dual-targeting therapeutic approach for the selective delivery of gene therapy to chemotherapy-resistant ovarian cancer cells. Mol Cancer Ther; 16(2); 323-33.

Luvero D., Plotti F., Aloisi A., Angioli R.
The tip of the iceberg.

Epithelial ovarian cancer is the leading cause of death among patients diagnosed with gynecologic malignancies worldwide, and two thirds of the patients are diagnosed at advanced stages. Although primary cytoreductive surgery (PCS) followed by chemotherapy has been the standard of care for these patients for many years, neoadjuvant chemotherapy (NACT) followed by interval cytoreductive surgery has recently emerged as a new alternative treatment for advanced-stage ovarian cancer, which opens the door to scientific discussion about which treatment is best in which situations.<…>

There is a need to centralize ovarian cancer treatment and gather patients at large centers of excellence in which a skilled multidisciplinary team (pathologists, radiologists, surgeons, and oncologists) can work together to assess the patient and to responsibly decide which is the best treatment for that patient. The fear is that the problem is actually larger than it seems and that we are seeing only the tip of iceberg. It is discouraging to know that our patients, who rely on us to provide the best treatment possible, will likely be referred to more convenient local treatment facilities instead of being sent to expert centers where optimal treatment can be offered. The risk is that the introduction of NACT into common practice may deny optimal management to a large group of patients. That is the new challenge that international gynecologic cancer societies should embrace: Will we be able to choose the best strategy and to make an optimal surgery in the future?

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Plotti F., Scaletta G., Capriglione S., Montera R., Luvero D., Lopez S., Gatti A., De Cicco Nardone C., Terranova C., Angioli R.
The role of HE4, a novel biomarker, in predicting optimal cytoreduction after neoadjuvant chemotherapy in advanced ovarian cancer.

**Objectives:** This study aimed to evaluate serum human epididymis protein 4 (HE4) changes during neoadjuvant chemotherapy (NACT) to establish HE4 predebulting surgery cutoff values and to demonstrate that CA125, HE4, and computed tomography (CT) taken together are better able to predict complete cytoreduction after NACT in advanced ovarian cancer patients.

**Methods:** From January 2006 to November 2015, patients affected by epithelial advanced ovarian cancer (International Federation of Gynecology and Obstetrics stage III-IV), considered not optimally resectable, were included in this prospective study. After 3 cycles of NACT, all patients underwent debulking surgery and were allocated, according to residual tumor (RT), into group A (RT = 0) and group B (RT > 0). Serum CA125, HE4, and CT images were recorded during NACT and compared singularly and with each other in term of accuracy, sensitivity, specificity, and positive and negative predictive value.

**Results:** A total of 94 and 20 patients were included in group A and group B, respectively. The HE4 values recorded before debulking surgery correlated with RT. The identified HE4 cutoff value of 226 pmol/L after NACT was able to classify patients at high or low risk of suboptimal surgery, with a sensitivity of 75% and a specificity of 85% (positive predictive value, 0.87; negative predictive value, 0.70). The combination of CA125, HE4, and CT imaging resulted in the best combination with a sensitivity of 96% and a specificity of 92% (positive predictive value, 0.96; negative predictive value, 0.94).

**Conclusions:** The novel biomarker HE4, in addition to CA125 and CT, is better able to predict the RT at debulking surgery and the prognosis of patients.
Heart Surgery

**Head** M. Chello (E. Covino until October 31st)

**External Members** F. Nappi, C. Spadaccio

### Description

This research unit focuses both on clinical research and on basic, translational and surgical research in the field of cardiac surgery. Current and future research focuses on the clinical evaluation of patients undergoing adult cardiac surgery procedures, with regards to preoperative strategies to reduce complications. Also, intraoperative research on myocardial protection and early postoperative care play a pivotal role in the surgical outcomes and are under continuous development. The preclinical field of research, experienced in aging and in the development of bioresorbable scaffolds and biomaterials, offers parallelism with the clinical research by means of an introduction of materials and methods of research in the surgical scenario.

A new area of research has been achieved in the field of safety during cardiac surgery. It is geared to develop a model for analysing and preventing the risk of electric microshock.

### Main research activities

Research results for 2017 focused on the effect of statin in postoperative atrial fibrillation and bleeding (unpublished results), development of an experimental model of the Ross operation and the effect of aging in conduction system. Collaborations with other departments within the institution, such as the Biomaterials and Bioengineering Dept., or other departments in other institutions (Centre Cardiologique du Nord, Golden Jubilee National Hospital) set the basis for ongoing researches.

Current project include the evaluation of the heart rate variability in postoperative cardiac surgery patients to prevent atrial fibrillation and complications (submitted for PRIN), effect of statins in postoperative bleeding, degeneration of native and prosthetic aortic valve and their connections with pharmacologic approaches, the role of advanced glycation end products in aging and potential therapeutic approaches in cardiac surgery. In addition, myocardial protection with a detailed cardioplegia protocol comparison and intraoperative bleeding depending on preoperative treatment with newer antiplatelet agents are currently under investigation.

In the field of safety during cardiac surgery a study has been carried out that produced an interesting increase of knowledge, in partnership with Dept. of Astronautics, Electrical and Energetics Engineering of Sapienza University of Rome, and with the Dept. of Technological Innovations and Safety of Power Plants, Apparatus and Human Settlements of INAIL, Italy.

The study provides a scientific method, based on quantitative data obtained by models, measurements and literature reviews, to assess the microshock risk during a real surgical intervention.

### Most important publications

Nenna A., Lusini M., Spadaccio C., Nappi F., Prestipino F., Barbato R., Casacalenda A., Pugliese G., Barberi F., Giacinto O., Petitti T., Covino E., Chello M.

**Preoperative atorvastatin reduces bleeding and blood products use in patients undergoing on-pump coronary artery bypass grafting.**


**Aims:** Statins are a widely recognized weapon in the primary and secondary prevention of coronary artery disease for their pleiotropic effects. However, recent reports from the cerebrovascular and pharmacological literature are insinuating concerns about a potential increase in the haemorrhagic risk among statin users. The effect of statins in postoperative bleeding should be carefully investigated.

Implantation of a poly-L-lactide GCSF-functionalized scaffold in a model of chronic myocardial infarction.


A previously developed poly-L-lactide scaffold releasing granulocyte colony-stimulating factor (PLLA/GCSF) was tested in a rabbit chronic model of myocardial infarction (MI) as a ventricular patch. Control groups were constituted by healthy, chronic MI and nonfunctionalized PLLA scaffold. PLLA-based electrospun scaffold efficiently integrated into a chronic infarcted myocardium. Functionalization of the biopolymer with GCSF led to increased fibroblast-like vimentin-positive cellular colonization and reduced inflammatory cell infiltration within the micrometric fiber mesh in comparison to nonfunctionalized scaffold; PLLA/GCSF polymer induced an angiogenetic process with a statistically significant increase in the number of neovessels compared to the nonfunctionalized scaffold; PLLA/GCSF implanted at the infarcted zone induced a reorganization of the ECM architecture leading to connective tissue deposition and scar remodeling. These findings were coupled with a reduction in end-systolic and end-diastolic volumes, indicating a preventive effect of the scaffold on ventricular dilation, and an improvement in cardiac performance.

Nappi F., Spadaccio C., Nenna A., Lusini M., Fraldi M., Acar C., Chello M.

Is subvalvular repair worthwhile in severe ischemic mitral regurgitation? Subanalysis of the papillary muscle approximation trial.


**Objective:** The symmetry of mitral valve tethering and regional left ventricle wall dysfunction are reported to play a fundamental role in the outcomes and long-term durability of surgical repair in ischemic mitral regurgitation (IMR). We recently demonstrated in a randomized clinical trial (the Papillary Muscle Approximation trial) the superiority of papillary muscle approximation (PMA) in combination with standard restrictive annuloplasty (RA) in severe IMR over annuloplasty alone in terms of adverse left ventricular remodeling and mitral regurgitation (MR) recurrence. This approach, however, failed to produce a survival advantage and was still plagued by a high incidence of reoperation. We therefore performed a subanalysis of the PMA trial on the basis of preoperative parameters to elucidate the value of subvalvular surgery in certain subcategories of patients with the aim of creating a decisional algorithm on the best operative strategy. **Methods:** We performed a subanalysis of PMA trial, evaluating 96 patients with severe IMR and eligible for myocardial revascularization randomized to PMA + RA (n = 48) versus RA alone (n = 48) in association with coronary artery bypass grafting. Endpoints included left ventricular remodeling, MR recurrence, overall mortality, reoperation, and a composite cardiac endpoint (cardiac death, stroke, reintervention, hospitalization for heart failure, or New York Heart Association class worsening). Stratification variables were preoperative symmetry of mitral valve tethering and regional wall motion abnormality. **Results:** PMA improved ventricular remodeling and recurrence of MR in both preoperative symmetric and asymmetric tethering and in case of inferior wall dyskinesia but did not produce an additional benefit in anterolateral wall dysfunction. **Conclusions:** Preoperative symmetric and asymmetric tethering and isolated inferior wall dyskinesia are an indication for subvalvular apparatus surgery in IMR.

Nappi F., Spadaccio C., Nenna A., Lusini M., Fraldi M., Acar C., Chello M.

In major cardiac surgery that exposes per se to risk of bleeding. **Methods:** In this retrospective cohort study, we evaluated 441 patients who received atorvastatin until surgery and 213 patients who had never been treated with statins, undergoing elective primary isolated on-pump coronary artery bypass grafting. Postoperative bleedings, blood products use and complications were monitored during hospitalization. **Results:** Preoperative and intraoperative variables were similar between groups. Early and overall postoperative bleedings were reduced among statin users, who had lower C-reactive protein values in the first postoperative day. Atorvastatin carries a strong protective effect against major bleedings, with a propensity score-adjusted odds ratio of 0.28 (P<0.01). Also, blood products use for statin-treated patients was lower compared with controls, with fewer transfused patients and fewer red-packed cells units per transfused patient. **Conclusion:** Preoperative atorvastatin use is associated with reduced risk of bleeding and blood products use after coronary artery bypass grafting, likely due to a reduction in the postoperative inflammatory response. Statin continuation at the highest tolerable dose should be encouraged before cardiac surgery. The preoperative use of statins in cardiac surgery as ‘bleeding-preventers’ might have profound clinical implications.
Hematology, Stem Cell Transplantation, Transfusion Medicine and Cellular Therapy

**Head**  G. Avvisati  
**Faculty**  M.C. Tirindelli, O. Annibali  

**Description**

The research unit is involved in several trials on the treatments of adult lymphoproliferative and myeloproliferative disorders and their main complications. Laboratory’s Instrumentations to perform research activities are located by the Policlinic Blood Bank.

**Main research activities**

The Unit, as member of the Rome transplant network (RTN), performs autologous hematopoietic stem cells (HSC) transplantation and, in collaboration with the Urology Unit, has a leading national position in the treatment of severe resistant hemorrhagic cystitis, which may appear in these patients. In addition, the unit participate in several clinical Trials, proposed by the following cooperative Group: FIL (Fondazione Italiana Linfomi), IELSG (International Extranodal Lymphoma Study Group), GIMEMA (Gruppo Italiano Malattie Ematologiche dell’Adulto). Moreover, in cooperation with the Orthopaedic and Trauma Surgery Unit, performs research studies on the use of platelet rich plasma in degenerative articular pathologies. Furthermore, the unit is deeply involved in a multicentre cytofluorimetric standardization project for the detection of circulating endothelial cells (CEC) and their progenitors (endothelial progenitor cells: EPC). Finally, in cooperation with the Virology Unit, is conducting a study dealing with CMV reactivation in HSC transplanted patients.

The Unit collaborates with the Computer Systems and Bioinformatics of this University to develop a mobile App for monitoring of side effects during treatment with kinase inhibitors in chronic lymphoproliferative diseases. In addition, the unit collaborate with the Pathology Unit for the study of PD-1/PD-L1 axis in lymphoproliferative diseases. The head of the Unit has a leading international role in the treatment of acute promyelocytic leukemia and from January 2008 to December 2013 has served as a member of the editorial board of Blood (official journal of the American Society of Hematology).

**Main collaborations**

- Italian Lymphoma Foundation, Italy;
- Italian Group of Hematologic Diseases in the Adult (GIMENA), Italy;
- Rome Transplant Network (RTN), Italy.

**Most important publications**


**Role of treatment on the development of secondary malignancies in patients with essential thrombocythemia.**  
Aim of this study is to explore the role of different treatments on the development of secondary malignancies (SMs) in a large cohort of essential thrombocythemia (ET) patients. We report the experience of a regional cooperative group in a real-life cohort of 1026 patients with ET. We divided our population into five different groups: group 0, no treatment; group 1, hydroxyurea (HU); group 2, alkylating agents (ALK); group 3, ALK + HU sequentially or in combination; and group 4, anagrelide (ANA) and/or α-interferon (IFN) only. Patients from groups 1, 2, and 3 could also have been treated either with ANA and/or IFN in their medical history, considering these drugs not to have an additional cytotoxic potential. In all, 63 of the 1026 patients (6%) developed 64 SM during the follow-up, after a median time of 50 months (range: 2-158) from diagnosis. In univariate analysis, a statistically significant difference was found only for gender ($P = 0.035$) and age ($P = 0.0001$). In multivariate analysis, a statistically significant difference was maintained for both gender and age (gender HR1.7 [CI 95% 1.037-2.818] $P = 0.035$; age HR 4.190 [CI 95% 2.308-7.607] $P = 0.0001$). The impact of different treatments on SMs development was not statistically significant. In our series of 1026 ET patients, diagnosed and followed during a 30-year period, the different therapies administered, comprising HU and ALK, do not appear to have impacted on the development of SM. A similar rate of SMs was observed also in untreated patients. The only two variables which showed a statistical significance were male gender and age >60 years.

Scarlata S., Annibali O., Santangelo S., Tomarchio V., Ferraro S., Armiento D., Scardocci A., Arcese W., Antonelli Incalzi R., Avvisati G.

**Pulmonary complications and survival after autologous stem cell transplantation: predictive role of pulmonary function and pneumotoxic medications.**

*Eur Respir J. 2017 Mar 29;49(3): 1601902. PubMed PMID: 28356372. IF 10,569*

Exposure to pneumotoxic agents before ASCT increases the risk of pulmonary function abnormalities and to affect infection-free interval and event-free survival, as well as overall survival. If confirmed by a larger, multicentre study, these findings could influence pre-transplant assessment and management.


**Improved outcomes with retinoic acid and arsenic trioxide compared with retinoic acid and chemotherapy in non-high-risk acute promyelocytic leukemia: final results of the randomized Italian-German APL0406 trial.**


Purpose The initial results of the APL0406 trial showed that the combination of all-trans-retinoic acid (ATRA) and arsenic trioxide (ATO) is at least not inferior to standard ATRA and chemotherapy (CHT) in first-line therapy of low- or intermediate-risk acute promyelocytic leukemia (APL). We herein report the final analysis on the complete series of patients enrolled onto this trial. Patients and Methods The APL0406 study was a prospective, randomized, multicenter, open-label, phase III noninferiority trial. Eligible patients were adults between 18 and 71 years of age with newly diagnosed, low- or intermediate-risk APL (WBC at diagnosis ≤ 10 × 10⁹/L). Overall, 276 patients were randomly assigned to receive ATRA-ATO or ATRA-CHT between October 2007 and January 2013. Results Of 263 patients evaluable for response to induction, 127 (100%) of 127 patients and 132 (97%) of 136 patients achieved complete remission (CR) in the ATRA-ATO and ATRA-CHT arms, respectively ($P = .12$). After a median follow-up of 40.6 months, the event-free survival, cumulative incidence of relapse, and overall survival at 50 months for patients in the ATRA-ATO versus ATRA-CHT arms were 97.3% v 80%, 1.9% v 13.9%, and 99.2% v 92.6%, respectively ($P < .001$, $P = .0013$, and $P = .0073$, respectively). Postinduction events included two relapses and one death in CR in the ATRA-ATO arm and two instances of molecular resistance after third consolidation, 15 relapses, and five deaths in CR in the ATRA-CHT arm. Two patients in the ATRA-CHT arm developed a therapy-related myeloid neoplasm. Conclusion These results show that the advantages of ATRA-ATO over ATRA-CHT increase over time and that there is significantly greater and more sustained antileukemic efficacy of ATO-ATRA compared with ATRA-CHT in low- and intermediate-risk APL.
Hygiene, Public Health and Statistics

Head  T. Petitti
Other Personnel  A. Ianni

Main research activities and collaborations

In 2017 collaborations with internal research groups at the Campus Bio-Medico University of Rome (General Surgery, Digestive Endoscopy, Respiratory Pathophysiology, Medical Imaging, Nursing) as well as National and European research institutions (National Cancer Institute - IRCCS “Fondazione G. Pascale” - Naples; Department of Public Health, Section of Hygiene, Catholic University of the Sacred Heart – Rome; Hôpital de Hautepierre, Strasbourg) were initiated. As part of these collaborations there are ongoing scientific studies that have produced results published in national and international journals in 2017 and are currently being published.

Description

Main research interests include:
• Methodological and operational support to the research unit of the Faculty of Medicine and other national research institutions for the definition of the research protocol activities, collection and organization of data, analysis and presentation of results;
• Models data scouting and data analysis of hospital current database (management and clinical) with the objective of identifying useful indicators to management and clinicians.
**Most important publications**

Piredda M., Ghezzi V., Fenizia E., Marchetti A., Petitti T., De Marinis M.G., Sili A.

**Development and psychometric testing of a new instrument to measure the caring behaviour of nurses in Italian acute care settings.**


Aim: To develop and psychometrically test the Italian-language Nurse Caring Behaviours Scale, a short measure of nurse caring behaviour as perceived by inpatients.

Background: Patient perceptions of nurses’ caring behaviours are a predictor of care quality. Caring behaviours are culture-specific, but no measure of patient perceptions has previously been developed in Italy. Moreover, existing tools show unclear psychometric properties, are burdensome for respondents, or are not widely applicable.

Design: Instrument development and psychometric testing.

Method: Item generation included identifying and adapting items from existing measures of caring behaviours as perceived by patients. A pool of 28 items was evaluated for face validity. Content validity indexes were calculated for the resulting 15-item scale; acceptability and clarity were pilot tested with 50 patients. To assess construct validity, a sample of 2,001 consecutive adult patients admitted to a hospital in 2014 completed the scale and was split into two groups. Reliability was evaluated using nonlinear structural equation modelling coefficients. Measurement invariance was tested across subsamples.

Results: Item 15 loaded poorly in the exploratory factor analysis (n = 983) and was excluded from the final solution, positing a single latent variable with 14 indicators. This model fitted the data moderately. The confirmatory factor analysis (n = 1018) returned similar results. Internal consistency was excellent in both subsamples. Full scalar invariance was reached, and no significant latent mean differences were detected across subsamples.

Conclusion: The new instrument shows reasonable psychometric properties and is a promising short and widely applicable measure of inpatient perceptions of nurse caring behaviours.


**Methodological issues in the observational studies conducted in older population: a narrative review.**

*Epidemiology, biostatistics and public health.* 2017; 14(2): e12627-e12627. DOI: 10.2427/12627

Introduction: Well-conducted observational studies may represent valuable tools for getting insight to disease etiology, detecting the effect of age-related changes, and providing an important perspective on health risk factors and disabilities in an aging population. Nevertheless, this kind of research poses several challenges for researchers. The main aim of this narrative review was to address the potential methodological issues in performing the observational studies in the elderly, the factors that influence their participation, and the possible solutions for overcoming the barriers to research in this population.

Methods: Comprehensive search for the papers published in the period from January 1st 1980 until 31st July 2016 in English or Italian was conducted through MEDLINE, Scopus and Web of Science electronic databases. Findings from the included papers were finally summarized.

Results: In cohort studies, the following barriers were addressed: sample size calculation, ascertainment of the target population, frequency of data collection, exposure determination, multifactorial loss to follow-up (drop-outs), cognitive impairment, definition of confounders, and ethical aspects. Case-control studies were reported to be prone to the issues like ascertainment of cases and controls, willingness to participate, data accuracy, recall bias, issues related to patients’ multimorbidity, and cognitive impairment.

Conclusions: Important factors to consider in research in elderly people include: precise definition of the study population, well-conducted recruitment process, engagement with family and home care staff, cognitive impairment assessment and the consequent relevant ethical and legal issues, relief of participant burden in order to minimize withdrawal, and engagement with the media.
Institute of Philosophy of Scientific and Technological Practice (FAST)

**Head**  L. Borghi (*E. Covino until October 31st*)

**Faculty**  M. Bertolaso, L. Borghi, G. La Monaca, V. Tambone


**External Members**  G. Tanzella-Nitti, M. T. Bettetini, M. Cerro (student), S. Rampello (student)

### Description

The Institute coordinates the University’s educational and research activities in the following fields: Anthropology, General Ethics, Professional Ethics, General Bioethics, Clinical Bioethics, Moral Philosophy, Logic and Philosophy of Science, Forensic Medicine, History of Medicine, History of Science and Technology, Social Psychology, Philosophy of Law and Social Medicine. FAST’s education and research are conducted via interdisciplinary work carried out both within the borders of the Campus Bio-Medico University and in collaboration with other Institutions, with the scope of creating a dialogue between philosophers, researchers and teachers of the various scientific disciplines.

### Main research activities

#### Marta Bertolaso
- New epistemological and philosophical challenges in the fields of biological and systemic development, scientific advancement, in silico medicine, modeling and validation processes.
- PI of some research programs, including: “Will Science Remain Human? Frontiers of the Incorporation of Technological Innovations in the Biomedical Sciences” (STI); “Evolving Embodied Habitats” (FAS); “Self-on-a-Chip: A Study of Embodiment in Innovative 3D Cell-Culture Models” (UCBM).

#### Luca Borghi
- Participation in the THESA research group of the Italian Society for the History of Medicine on the Anatomical Theatres in Italy.
- Starting research on “William Osler and Italy” (McGill University, Montreal).

#### Laura Campanozzi
- Collaboration with McGill University about an international project on the Teaching Clinical Reasoning in Medical School. I won a research Grant promoted by UCBM to carry out this project.

#### Nicola di Stefano
- Media Project (Embodiment Grant 2015): progresses in data gathering and analysis. Recruitment of the sample for the study with the musical toy.
- Participation in the research group Sensibilia: Colloquium on Perception (Director T.Griffer).
Leonardo’s mistake: not evidence-based medicine?

Renowned as one of the most influential figures in many different fields, Leonardo da Vinci (1452–1519) was also a revolutionary anatomist. In his research on the human body and reproductive system, da Vinci devoted a series of drawings to conception and the fetus, in which the fetal membranes are represented for the first time. Additionally, when depicting coitus, da Vinci introduced two errors: a canal in the penis connected to the spinal cord, and a canal linking the uterus to the breasts.

A proposed road map for the ethical evaluation of sham (placebo) surgery.

**Objective:** The study proposes a possible roadmap for the ethical assessment of sham surgery clinical trials (CTs), focusing on methodological aspects, as a result of the lack of this type of practical tool in the literature/practice.

**Background:** Surgical procedures are frequently conducted without closely controlled studies. For this reason, these procedures are less rigorous than those for drug/device clinical trials. The aim of a sham (placebo) surgery CT is to carry out a surgical CT with a legitimate control group. The use of sham surgery is controversial from an ethical point of view.

**Methods:** This evaluation system is set up according to ICH/GCP, World Medical Association Declaration of Helsinki, CONSORT 2010 standards. The proposed roadmap is based on the following 4 steps/levels: safety/clinical indications; adequacy of trial methodology/design adopted for a sham surgery CT; specific informed consent, and economic issues.

**Results:** A flowchart is proposed which can be used at two levels: as a basic guideline for the design of a surgical protocol representing a benchmark level of care; and a multiaxial assessment considering the first two sources of morality of human acts according to Aristotelian ethics: the object of the act (step 1) and some of its circumstances (steps 2-4).

**Conclusions:** The use of a placebo and of double-blind control groups in surgery CTs would improves the quality of results, providing that an accurate ethical assessment procedure is in place, firstly to ensure patient safety and secondly to prevent abuses/procedural biases. Future testing of the proposed flowchart is outlined.

The hand: perception, cognition, action.

Drawing on shared research experiences and collaborative projects, this book offers a broad and timely perspective on research on the hand and its current challenges. It especially emphasizes the interdisciplinary context in which researchers need to be trained in contemporary science. From language to psychology, from neurology to the social sciences, and from art to philosophy and religion, the chapters discuss various aspects involved in hand research and therapy. Based on concrete and validated case studies, they approach hand function and gestures from different perspectives — not only neurological and medical, but also philosophical, evolutionary and anthropological. By highlighting the overlaps between different areas of research, the book seeks to foster better communication between researchers, and ultimately a better understanding of hand function and its recovery. It offers essential information and inspirations for students, researchers and practitioners in the fields of psychology, epistemology, bioengineering, neuroscience, anthropology and bioethics.
Internal Medicine and Hepatology

Head  A. Picardi
Faculty  U. Vespasiani Gentilucci
Other Personnel  G. Galati, P. Gallo

Description

Our Unit is involved in both spontaneous and collaborative studies on liver injury, inflammation and fibrogenesis. Collaborative studies are coordinated by scientific societies, mainly the Italian Society of Internal Medicine (SIMI) and the Italian Association for the Study of the Liver (AISF). We are also involved in clinical trials on new drugs for the treatment of liver steatohepatitis (NASH). Main collaborations are set with other research Units from our University, from the University of Navarra, Spain, with the Children’s Hospital and Research Institute “Bambino Gesù” of Rome, and with the University of Rome “Tor Vergata”. Specifically, we have advanced in the knowledge of the mechanisms of activation, maintenance and progression of portal inflammation in chronic liver disease. All those processes may involve and activate the compartment of liver staminal cells that are also involved in liver carcinogenesis. Other important collaborations are set with the Area of Geriatrics and of Oncology, and with the Unit of Electronics for Sensor Systems of the Faculty of Engineering. Some clinical investigations have been initiated in the non-invasive evaluation of liver fibrosis through transient elastometry.

Main research activities

Our most relevant research results refer to chronic liver disease and liver cancer pathology and treatment. New insights in the characterization of some of the most frequent genetic polymorphisms implied in the pathogenesis of fatty liver disease and in cirrhosis (PNPLA3 and LIPA), and the role of platelets in the methods used to identify some enzyme deficiencies (such as LAL deficiency). Other achievements refer to the “functional” characterization of patients with liver cirrhosis by electronic nose.
Most important publications


Metformin and insulin impact on clinical outcome in patients with advanced hepatocellular carcinoma receiving sorafenib: Validation study and biological rationale.

The aim of the present study was to validate the prognostic significance of metformin in HCC patients treated with sorafenib, and to clarify the role of sirtuin-3 (SIRT-3) in this resistance.

We analysed 279 patients consecutively treated with sorafenib.

Our findings could be attributed to increased tumour aggressiveness and resistance to sorafenib caused by chronic treatment with metformin.


Breath-print analysis by e-nose may refine risk stratification for adverse outcomes in cirrhotic patients.

We aimed to evaluate the association between BPs, mortality and hospitalization in cirrhotic patients.

Eighty-nine cirrhotic patients (M/F 59/30, mean age 64.8 ± 11.3, CPC A/B/C 37/33/19) were recruited and followed up for a median time of 23 months. We identified four different BP clusters (A, B, C, D).

This pilot study demonstrates that BP clusters are associated with significant clinical endpoints (mortality and hospitalization) even independently from “classical” prognostic indices. Our findings suggest that the e-nose may become an adjunctive aid to stratify the risk of adverse outcomes in cirrhotic patients.


Platelet count may impact on lysosomal acid lipase activity determination in dried blood spot.

We aimed to evaluate the influence of white blood cell (WBC) and platelet (PLT) counts on dried blood spot (DBS)-determined lysosomal acid lipase (LAL) activity in a large group of healthy subjects.

172 healthy subjects aged ≥18 were enrolled. Univariate and multivariate analyses to DBS-LAL activity were performed.

LAL activity in WBCs was significantly higher than in PLTs (458.9±133.6 vs 235.0±88.3nmol/mg/h, p<0.001). However, LAL activity in DBS correlated more strongly with that in PLTs (r=0.65, p<0.001) than with that in WBCs (r=0.49, p<0.01). In the multivariate model, DBS-LAL activity was independently associated only with PLT count (β=0.39, p<0.001). In conclusion, PLT number may impact on the result of the DBS-LAL test, and a consideration of PLT count is recommended before interpreting LAL activity in DBS.
Measurements and Biomedical Instrumentation

**Head**  
S. Silvestri

**Faculty**  
E. Schena

**Other Personnel**  
D. Lo Presti, C. Massaroni

**External Members**  
P. Saccomandi

**Description**

The Research Unit scientific activity is mainly focused on measurements and measurement systems for clinical diagnostics and applied to human wellbeing. The research activity is particularly focused on the development of novel sensors and measurement systems for measuring forces, gas flow-rate, cardiac output, temperature, human motion, optical absorption and respiratory parameters. The research unit realized instruments for the respiratory simulation and performance testing of artificial ventilators and optoelectronic systems dedicated to respiratory mechanics along with uncertainty evaluation. Researches are carried out on novel modalities and procedures to obtain measurements and/or information from physio-pathological processes, organs opto-mechanical variables, performance assessment and quality evaluation of medical instruments and their clinical efficacy with a particular emphasis on non-invasive processes.

**Main research activities**

The research activity has been focused on innovative methods to obtain a temperature map of organs by means of magnetic resonance imaging, innovative MR-compatible optical fibre sensors for force measurement and experimental estimation of optical properties of neuroendocrine pancreatic tumor and other organs for modelling laser absorption during interstitial ablation therapy. A research project has been funded by the Italian Ministry of University and Scientific Research: “Mechanical measurements for the musculoskeletal apparatus: novel and standardizable methodologies for metrological assessment of measurement systems”. A research project has been funded by Campus Bio-Medico University of Rome: “Evaluation of bone strength and Wnt pathway in obese patients”.

**Most important publications**

Massaroni C., Senesi G., Schena E., Silvestri S.

**Analysis of breathing via optoelectronic systems: comparison of four methods for computing breathing volumes and thoraco-abdominal motion pattern.**


Breathing parameters can be measured by motion capture systems by placing photo-reflective markers on the chest wall. A computational model is mandatory to compute the breathing volume and to calculate temporal and kinematical features by the gathered markers trajectories. Despite different methods based on different geometrical approaches can be adopted to compute volumes, no information about their differences in the respiratory evaluation are available. This study investigated the performances of four methods (conventio-
ral, prism-based, convex hull with boundary condition, based on Delaunay triangulation) using an optoelectronic motion capture system, on twelve healthy participants during 30 s of breathing. Temporal trends of volume traces, tidal volume values, and breathing durations were compared between methods and spirometry (used as reference instrument). Additionally, thoraco-abdominal motion patterns were compared between methods by analysing the compartmental contributions and their variability. Results show comparable similarities between the volume traces obtained using spirometry, prism-based and conventional methods. Prism-based method shows maximum differences of 0.06 L in the comparison of compartmental contributions to the total volume, by resulting in a maximum deviation of 1.6% in the percentage contribution analysis. In conclusion, our finding demonstrated the accuracy of the non-invasive MoCap-based breathing analysis with the prism-based method tested. Data provided in this study will lead researchers and clinicians in the computational method choice for temporal and volumetric breathing analysis.

Lo Presti D., Massaroni C., Formica D., Saccomandi P., Giurazza F., Calonero M.A., Schena E.

**Smart textile based on 12 fiber Bragg gratings array for vital signs monitoring.**
*IEEE Sensors Journal 2017;17(18): 6037-6043. DOI: 10.1109/JSEN.2017.2731788. IF 2.512*

Over the last decades, wearable systems have gained interest for vital signs monitoring. Among several technologies, fiber Bragg grating (FBG) sensors are becoming popular for some advantages, such as high sensitivity, magnetic resonance compatibility, and the capability of performing distributed measurements. The aim of this paper is twofold: the description of the design and the fabrication of a smart textile based on an array of 12 FBGs; its feasibility assessment for monitoring respiratory parameters (i.e., respiratory rate, respiratory period, and inspiratory and expiratory periods) and heart rate on healthy volunteers in two positions (standing and supine). The increased number of FBGs embedded in this system with respect to previous developed prototypes aims at improving its accuracy in the estimation of the mentioned parameters. Future testing will be performed to investigate if the proposed solution allows improving the measurements of respiratory volumes exchanges and in new scenarios (e.g., sports medicine, including walking, running, and cycling activities).

Nicolò A., Massaroni C., Passfield L.

**Respiratory frequency during exercise: the neglected physiological measure.**

The use of wearable sensor technology for athlete training monitoring is growing exponentially, but some important measures and related wearable devices have received little attention so far. Respiratory frequency (fR), for example, is emerging as a valuable measurement for training monitoring. Despite the availability of unobtrusive wearable devices measuring fR with relatively good accuracy, fR is not commonly monitored during training. Yet fR is currently measured as a vital sign by multiparameter wearable devices in the military field, clinical settings, and occupational activities. When these devices have been used during exercise, fR was used for limited applications like the estimation of the ventilatory threshold. However, more information can be gained from fR. Unlike heart rate, V·O2, and blood lactate, fR is strongly associated with perceived exertion during a variety of exercise paradigms, and under several experimental interventions affecting performance like muscle fatigue, glycogen depletion, heat exposure and hypoxia. This suggests that fR is a strong marker of physical effort. Furthermore, unlike other physiological variables, fR responds rapidly to variations in workload during high-intensity interval training fR, with potential important implications for many sporting activities. This Perspective article aims to (i) present scientific evidence supporting the relevance of fR for training monitoring; (ii) critically revise possible methodologies to measure fR and the accuracy of currently available respiratory wearables; (iii) provide preliminary indication on how to analyze fR data. This viewpoint is expected to advance the field of training monitoring and stimulate directions for future development of sports wearables.
Microscopic and Ultrastructural Anatomy

Head  S. Morini
Faculty  S. Carotti, F. Zalfa
External Members  F. Cimini, M. Francesconi, V. Panasiti, M. Zingariello, L. Sancillo

Description
The Microscopic and Ultrastructural Anatomy Unit applies techniques for morphological and molecular analysis of cells and tissues with particular reference to the digestive system and skin. The main research fields are the study of the liver diseases, focusing on the morphological features and molecular mechanisms of hepatic fibrogenesis and carcinogenesis. Structural, ultrastructural analysis by light, fluorescence, confocal and transmission electron microscopy are performed using histochemical, immunohistochemistry, immunofluorescence and immunogold techniques; morphometry by systems and softwares for image analysis is used. Molecular analysis and cell biology are applied to the study of liver, pancreas and skin diseases. In particular, gene expression analysis and post-transcriptional regulation mechanisms are investigated using advanced technologies.

Main research activities
The histological features of liver tissue, the biochemical serological parameters and the genetic signatures were investigated in order to identify factors connecting liver inflammation and fibrosis during non-tumoral liver diseases. Histo-morphology, cellular and molecular biology techniques were applied to the study of the intracellular pathways regulating, proliferation and aggressiveness of melanoma in collaboration with Prof. C Bagni (University of Rome “Tor Vergata” and University of Lausanne, Switzerland) and Prof. JC Marine (Catholic University of Leuven, Belgium). Histo-morphology and molecular approaches were applied also to the study of liver cancers (HCC and ICC), at both cellular and tissue level, in collaboration with Prof. MA Avila (Gene Therapy & Hepatology, University of Navarra, Pamplona, Spain).

Main collaborations
- University of Rome “Tor Vergata”, Italy;
- University of Lausanne, Switzerland.

Most important publications

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide. Its pathogenesis is complex and not yet fully understood. Over the years, many studies have proposed various pathophysiological hypotheses, among which the currently most widely accepted is the “multiple parallel hits” theory. According to this model, lipid accumulation in the hepatocytes and insulin
resistance increase the vulnerability of the liver to many factors that act in a coordinated and cooperative manner to promote hepatic injury, inflammation and fibrosis. Among these factors, adipose tissue dysfunction and subsequent chronic low-grade inflammation play a crucial role. Recent studies have shown that vitamin D exerts an immune-regulating action on adipose tissue, and the growing wealth of epidemiological data is demonstrating that hypovitaminosis D is associated with both obesity and NAFLD. Furthermore, given the strong association between these conditions, current findings suggest that vitamin D may be involved in the relationship between adipose tissue dysfunction and NAFLD. The purpose of this review is to provide an overview of recent advances in the pathogenesis of NAFLD in relation to adipose tissue dysfunction, and in the pathophysiology linking vitamin D deficiency with NAFLD and adiposity, together with an overview of the evidence available on the clinical utility of vitamin D supplementation in cases of NAFLD.


The fragile X mental retardation protein regulates tumor invasiveness-related pathways in melanoma cells.


The fragile X mental retardation protein (FMRP) is lacking or mutated in patients with the fragile X syndrome (FXS), the most frequent form of inherited intellectual disability. FMRP affects metastasis formation in a mouse model for breast cancer. Here we show that FMRP is overexpressed in human melanoma with high Breslow thickness and high Clark level. Furthermore, metaanalysis of the TCGA melanoma data revealed that high levels of FMRP expression correlate significantly with metastatic tumor tissues, risk of relapsing and disease-free survival. Reduction of FMRP in metastatic melanoma cell lines impinges on cell migration, invasion and adhesion. Next-generation sequencing in human melanoma cells revealed that FMRP regulates a large number of mRNAs involved in relevant processes of melanoma progression. Our findings suggest an association between FMRP levels and the invasive phenotype in melanoma and might open new avenues towards the discovery of novel therapeutic targets.


Reelin expression in human liver of patients with chronic hepatitis C infection.


Reelin is a secreted extracellular glycoprotein that plays a critical role during brain development. Several studies have described Reelin expression in hepatic stellate cells of the human liver. In order to investigate the possible role of Reelin in the process of hepatic fibrogenesis, in this study we investigated Reelin expression in the liver tissue of patients infected with the Hepatitis C Virus (HCV). On this basis, Reelin expression was analysed by immunohistochemistry during liver biopsies of 81 patients with HCV-related chronic hepatitis. A Knodell score was used to stage liver fibrosis. Hepatic stellate cells/myofibroblast immunohistochemical markers (CRBP-1, alpha-SMA) were also evaluated. As further confirmed by colocalization experiments (Reelin +CRBP-1), Reelin protein was expressed by hepatic stellate cells/myofibroblasts, and a significant positive correlation was found between Reelin expression and the stage of liver fibrosis (P=0.002). Moreover, Reelin correlated with CRBP-1 positive cells (P=0.002), but not with alpha-SMA, suggesting that Reelin should not be regarded as a marker of hepatic stellate cells/myofibroblasts differentiation but rather as a functional protein expressed during some phases of liver fibrosis. Furthermore, Disabled-1 (Dab1), a Reelin adaptor protein, was expressed in cells of ductular reaction suggesting a paracrine role for Reelin with regards these elements. In conclusion, Reelin was expressed by human hepatic stellate cells/myofibroblasts and the number of these cells increased significantly in the lobule as the liver fibrosis progressed, suggesting a role for Reelin in the activation of hepatic stellate cells/myofibroblasts during liver injury. Reelin may potentially be incorporated into liver injury evaluations in combination with other histological data.
The RU Molecular Medicine and Biotechnology has only one person in the academic and scientific permanent staff (VMF) and one person for the academic administrative activities (SV). The RU comprises the post graduate School of Specialization (Residency) in Clinical Pathology and Clinical Biochemistry (AP, MV, AP, EM) and one PhD student (FP). Researchers from other Universities, IRCCS and CNR actively cooperate both on research projects and the didactic activities. Since 2014 CE has approved the clinical UOS (Unità Operativa Semplice) of genetic onco-hematology in order to guarantee diagnostic services of cytofluorimetry, cytogenetics and molecular genetics in hematology.

Study of the leading epigenetic and genetic mechanisms that control the reprogramming of stem cells during the first phases of carcinogenesis and the tumor progression up to CTC, in the two-way connection with the microenvironment, including exosomes and circulating nucleic acids. Study of genetic and epigenetic biomarkers for the development of multilevel genomics-based cancer taxonomy, prediction of cancer progression and metastasization, response to therapy (renal, colorectal, lung, breast tumors). Cytofluorimetric analysis and genetics in oncohematology. Biotechnologies for diagnostic molecular assays and gene transfer.

• Integrative Tumor Biology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Bethesda, MD, US;
• MASMEC Biomed SpA, Bari, Italy;
• Dpt of Hematology and Immunology, Clinica Universidad de Navarra (CUN) University of Navarra, Pamplona, Spain;
• Centro de Investigaciones Medicas Aplicadas (CIMA), Flow Cytometry Core, University of Navarra, Pamplona, Spain;
• Dpt of Tumor Biology, University of Hamburg, University Medical Center Hamburg-Eppendorf, Germany
• IRCCS Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo (Fg)
• IFO Istituto Nazionale Tumori Regina Elena, Rome
• Dpt Bioscienze, Biotecnologie e Biofarmaceutica Università degli studi di Bari
• Core Facilities - Cytometry unit, Italian National Institute of Health, Italy.


Dysregulation of EGFR pathway in EphA2 cell subpopulation significantly associates with poor prognosis in colorectal Cancer.


Purpose: EphA2 receptor is involved in multiple cross-talks with other cellular networks, including EGFR, FAK, and VEGF pathways, with which it collaborates to stimulate cell migration, invasion, and metastasis. Colorectal cancer (CRC) EphA2 overexpression has also been correlated to stem-like properties of cells and tumor malignancy. We investigated the molecular cross-talk and miRNAs modulation of the EphA2 and EGFR pathways. We also explored the role of EphA2/EGFR pathway mediators as prognostic factors or predictors of cetuximab benefit in patients with CRC.
**Experimental design:** Gene expression analysis was performed in EphA2high cells isolated from CRC of the AOM/DSS murine model by FACS-assisted procedures. Six independent cohorts of patients were stratified by EphA2 expression to determine the potential prognostic role of a EphA2/EGFR signature and its effect on cetuximab treatment response.

**Results:** We identified a gene expression pattern ( EphA2, Efna1, Egfr, Ptpn12, and Atf2) reflecting the activation of EphA2 and EGFR pathways and a coherent dysregulation of mir-26b and mir-200a. Such a pattern showed prognostic significance in patients with stage I-III CRC, in both univariate and multivariate analysis. In patients with stage IV and WT KRAS, EphA2/Efna1/Egfr gene expression status was significantly associated with poor response to cetuximab treatment. Furthermore, EphA2 and EGFR overexpression showed a combined effect relative to cetuximab resistance, independently from KRAS mutation status.

**Conclusions:** These results suggest that EphA2/Efna1/Egfr genes, linked to a possible control by miR-200a and miR-200b, could be proposed as novel CRC prognostic biomarkers. Moreover, EphA2 could be linked to a mechanism of resistance to cetuximab alternative to KRAS mutations. Clin Cancer Res; 23(1); 159-70. ©2016 AACR.

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**Keap1/Nrf2 pathway in kidney cancer: frequent methylation of KEAP1 gene promoter in clear renal cell carcinoma.**


The Keap1/Nrf2 pathway is a master regulator of the cellular redox state through the induction of several antioxidant defence genes implicated in chemotherapeutic drugs resistance of tumor cells. An increasing body of evidence supports a key role for Keap1/Nrf2 pathway in kidney diseases and renal cell carcinoma (RCC), but data concerning the molecular basis and the clinical effect of its deregulation remain incomplete. Here we present a molecular profiling of the KEAP1 and NFE2L2 genes in five different Renal Cell Carcinoma histotypes by analysing 89 tumor/normal paired tissues (clear cell Renal Carcinoma, ccRCCs; Oncocytomas; Papillary Renal Cell Carcinoma Type 1, PRCC1; Papillary Renal Cell Carcinoma Type 2, PRCC2; and Chromophobe Cell Carcinoma). A tumor-specific DNA methylation of the KEAP1 gene promoter region was found as a specific feature of the ccRCC subtype (18/37, 48.6%) and a direct correlation with mRNA levels was confirmed by in vitro 5-azacytidine treatment. Analysis of an independent data set of 481 ccRCC and 265 PRCC tumors corroborates our results and multivariate analysis reveals a significant correlation among ccRCCs epigenetic KEAP1 silencing and staging, grading and overall survival. Our molecular results show for the first time the epigenetic silencing of KEAP1 promoter as the leading mechanism for modulation of KEAP1 expression in ccRCCs and corroborate the driver role of Keap1/Nrf2 axis deregulation with potential new function as independent epigenetic prognostic marker in renal cell carcinoma.

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**Stepwise analysis of MIR9 loci identifies miR-9-5p to be involved in Oestrogen regulated pathways in breast cancer patients.**


miR-9 was initially identified as an epigenetically regulated miRNA in tumours, but inconsistent findings have been reported so far. We analysed the expression of miR-9-5p, miR-9-3p, pri-miRs and MIR9 promoters methylation status in 131 breast cancer cases and 12 normal breast tissues (NBTs). The expression of both mature miRs was increased in tumours as compared to NBTs (P < 0.001) and negatively correlated with ER protein expression (P = 0.005 and P = 0.003, for miR-9-3p and miR-9-5p respectively). In addition, miR-9-5p showed a significant negative correlation with PgR (P = 0.002). Consistently, miR-9-5p and miR-9 3p were differentially expressed in the breast cancer subgroups identified by ER and PgR expression and HER2 amplification. No significant correlation between promoter methylation and pri-miRNAs expressions was found either in tumours or in NBTs. In the Luminal breast cancer subtype the expression of miR-9-5p was associated with a worse prognosis in both univariable and multivariable analyses. Ingenuity Pathway Analysis exploring the putative interactions among miR-9-5p/miR-9-3p, ER and PgR upstream and downstream regulators suggested a regulatory loop by which miR-9-5p but not miR-9-3p is induced by steroid hormone receptor and acts within hormone-receptor regulated pathways.
Molecular Neurosciences

**Head**  M. D’Amelio

**Other Personnel**  A. Candela, R. Marino, A. Nobili

**External Members**  L. La Barbera, P. Krashia

**Description**

The Molecular Neurosciences Unit focuses on neurodegenerative diseases and other neuropsychiatric conditions by means of the application of biologic techniques. We have a particular interest in the pathogenesis of β-amyloid neurodegenerative disorders such as Alzheimer’s disease (AD). We use cell and transgenic mouse models to gain an understanding of the pathogenesis of the disorder, and also to assist in the development of novel therapeutic techniques. We have applied similar techniques for the study of Parkinson’s disease (PD) and spinal muscular atrophy (SMA). We have identified several novel proteins involved in the pathogenesis of AD, and we have cell and mouse models of the disease. We are also applying similar techniques to psychiatric conditions such as autism and schizophrenia. The laboratory offers research opportunities to undergraduates, graduate students, postdoctoral fellows and other interested scientists.

**Main collaborations**

During last year, the Molecular Neurosciences Unit consolidated scientific collaborations with national and international partners. In particular, the Laboratory collaborated with the National Research Council (CNR) of Rome, “Roma Tre” University, Sapienza University of Rome, Université Libre de Bruxelles, Center of Excellence for Biomedical Research, University of Genova and University of Perugia. The aforementioned collaborations involve the study of neuronal function alterations in several models of human neurodegenerative disease.

During last year, the Molecular Neurosciences Unit published several papers in the field of neurodegenerative disorders. Among these, a Nature Communication paper disclosing the crucial role of dopaminergic brain stem in early phase of Alzheimer’s disease by using a validated model of the disease.

**Most important publications**


**Dopamine neuronal loss contributes to memory and reward dysfunction in a model of Alzheimer’s disease.**

*Nat Commun. 2017Apr 3;8:14727. PubMed PMID: 28367951. IF 12,124*

Alterations of the dopaminergic (DAergic) system are frequently reported in Alzheimer’s disease (AD) patients and are commonly linked to cognitive and non-cognitive symptoms. However, the cause of DAergic system dysfunction in AD remains to be elucidated. We investigated alterations of the midbrain DAergic system in the Tg2576 mouse model of AD, overexpressing a mutated human amyloid precursor protein (APPswe). Here, we found an age-dependent DAergic neuron loss in the ventral tegmental area (VTA) at pre-plaque...
Research Yearbook 2017 | Campus Bio-Medico University of Rome


**Autophagy inhibition favors survival of rubrospinal neurons after spinal cord hemisection.**

Spinal cord injuries (SCIs) are devastating conditions of the central nervous system (CNS) for which there are no restorative therapies. Neuronal death at the primary lesion site and in remote regions that are functionally connected to it is one of the major contributors to neurological deficits following SCI. Disruption of autophagic flux induces neuronal death in many CNS injuries, but its mechanism and relationship with remote cell death after SCI are unknown. We examined the function and effects of the modulation of autophagy on the fate of axotomized rubrospinal neurons in a rat model of spinal cord dorsal hemisection (SCH) at the cervical level. Following SCH, we observed an accumulation of LC3-positive autophagosomes (APs) in the axotomized neurons 1 and 5 days after injury. Furthermore, this accumulation was not attributed to greater initiation of autophagy but was caused by a decrease in AP clearance, as demonstrated by the build-up of p62, a widely used marker of the induction of autophagy. In axotomized rubrospinal neurons, the disruption of autophagic flux correlated strongly with remote neuronal death and worse functional recovery. Inhibition of AP biogenesis by 3-methyladenine (3-MA) significantly attenuated remote degeneration and improved spontaneous functional recovery, consistent with the detrimental effects of autophagy in remote damage after SCH. Collectively, our results demonstrate that autophagic flux is blocked in axotomized neurons on SCI and that the inhibition of AP formation improves their survival. Thus, autophagy is a promising target for the development of therapeutic interventions in the treatment of SCIs.

Gelfo F., Cutuli D., Nobili A., De Bartolo P., D’Amelio M., Petrosini L., Caltagirone C.

**Chronic lithium treatment in a rat model of basal forebrain cholinergic depletion: effects on memory impairment and neurodegeneration.**

Alzheimer’s disease (AD) is an age-related neurodegenerative disorder with multifactorial etiopathogenesis, characterized by progressive loss of memory and other cognitive functions. A fundamental neuropathological feature of AD is the early and severe brain cholinergic neurodegeneration. Lithium is a monovalent cation classically utilized in the treatment of mood disorders, but recent evidence also advances a beneficial potentiality of this compound in neurodegeneration. Interestingly, lithium acts on several processes whose alterations characterize the brain cholinergic impairment at short and long term. On this basis, the aim of the present research was to evaluate the potential beneficial effects of a chronic lithium treatment in preventing the damage that a basal forebrain cholinergic neurodegeneration provokes, by investigating memory functions and neurodegeneration correlates. Adult male rats were lesioned by bilateral injections of the immunotoxin 192 IgG-Saporin into the basal forebrain. Starting 7 days before the surgery, the animals were exposed to a 30-day lithium treatment, consisting of a 0.24% Li2CO3 diet. Memory functions were investigated by the open field test with objects, the sociability and preference for social novelty test, and the Morris water maze. Hippocampal and neocortical choline acetyltransferase (ChAT) levels and caspase-3 activity were determined. Cholinergic depletion significantly impaired spatial and social recognition memory, decreased hippocampal and neocortical ChAT levels and increased caspase-3 activity. The chronic lithium treatment significantly rescued memory performances but did not modulate ChAT availability and caspase-3 activity. The present findings support the lithium protective effects against the cognitive impairment that characterizes the brain cholinergic depletion.
Molecular Psychiatry and Neurogenetics

Head  A.M. Persico

Other Personnel  G. Barbieri, M. Canali, C. Cannizzaro, A. Costa, S.C. Lintas, R. Sacco

Genomics Lab. Mafalda Luce Centre, Milan  M. Baccarin, P. Castronovo, C. Picinelli, P. Tomaiuolo

Description

The Unit is responsible for investigating the pathogenic aspects, especially of a genetic nature, the biochemical and the neuroimmunological aspects applicable to childhood psychiatric disorders, such as autism and ADHD. The aim of these studies is to place them in connection with specific clinical signs and/or symptoms, psychopathological traits and behavioral response patterns. The study of biomarkers is intended not only to obtain a better understanding of the pathophysiology, related to the organic components of these disorders, but is also aimed at early detection of the disorder for the benefit of the child’s development. Privileged methods of study are array-CGH, genomic sequencing and qPCR (Neurogenetics and transcriptomics); analysis by western blotting and ELISA both associated with anti-brain antibodies tissues as well as with specific cytokines (Neuroimmunology); the HPLC for assay of plasma serotonin and specific urinary metabolites (biochemical). Finally, in clinical research settings EEG and eye tracking (Tobii TX300) are also used.

Main collaborations

- Biological Science Department and Interdepartmental Centre for Stem Cell Research Milano University, Italy.
- Brain Centre Rudolf Magnus, The Netherlands;
- Department of Translational Neuroscience, University Medical Centre Utrecht, The Netherlands;
- Institute of Psychiatry, King’s College London, UK.
- Neurotoxicology & Neuroendocrine Department, Italian National Institute of Health (ISS), Italy;
- Proteomics Laboratory, Tuscia University, Viterbo, Italy
- Psychology Department Sapienza University, Italy

Most important publications

Lintas C., Picinelli C., Piras I.S., Sacco R., Brogna C., Persico A.M.

Copy number variation in 19 Italian multiplex families with autism spectrum disorder: importance of synaptic and neurite elongation genes.

Autism Spectrum Disorder (ASD) is endowed with impressive heritability estimates and high recurrence rates. Its genetic underpinnings are nonetheless very heterogeneous, with common, and rare contributing variants located in hundreds of different loci, each characterized by variable levels of penetrance. Multiplex families from single ethnic groups represent a useful means to reduce heterogeneity and enhance genetic load. We screened 19 Italian ASD multiplex families (3 triplets and 16 duplets, total N= 41 ASD subjects), using array-CGH (Agilent 180K). Causal or ASD-relevant CNVs were detected in 36.6% (15/41) of ASD probands, corresponding to 36.8% (7/19) multiplex families with at least one affected sibling genetically positive. However, only in less than half (3/7) of positive families, affected siblings share the same causal or ASD-relevant CNV. Even in these three families, additional potentially relevant CNVs not shared by affected sib pairs were also detected. These results provide further evidence of genetic heterogeneity in ASD even within multiplex families belonging to a single ethnic group. Differences in CNV burden may likely contribute to the substantial clinical heterogeneity observed between affected siblings. In addition, Gene Ontology enrichment analysis indicates that most potentially causal or relevant ASD genes detected in our cohort belong to nervous system-specific categories, especially involved in neurite elongation and synaptic structure/function. These findings point toward the existence of genomic instability in these families, whose underlying genetic and epigenetic mechanisms deserve further scrutiny.

The EU-AIMS Longitudinal European Autism Project (LEAP): design and methodologies to identify and validate stratification biomarkers for autism spectrum disorders.


Background: The tremendous clinical and aetiological diversity among individuals with autism spectrum disorder (ASD) has been a major obstacle to the development of new treatments, as many may only be effective in particular subgroups. Precision medicine approaches aim to overcome this challenge by combining pathophysiologically based treatments with stratification biomarkers that predict which treatment may be most beneficial for particular individuals. However, so far, we have no single validated stratification biomarker for ASD. This may be due to the fact that most research studies primarily have focused on the identification of mean case-control differences, rather than within-group variability, and included small samples that were underpowered for stratification approaches. The EU-AIMS Longitudinal European Autism Project (LEAP) is to date the largest multi-centre, multi-disciplinary observational study worldwide that aims to identify and validate stratification biomarkers for ASD.

Methods: LEAP includes 437 children and adults with ASD and 300 individuals with typical development or mild intellectual disability. Using an accelerated longitudinal design, each participant is comprehensively characterised in terms of clinical symptoms, comorbidities, functional outcomes, neurocognitive profile, brain structure and function, biochemical markers and genomics. In addition, 51 twin-pairs (of which 36 had one sibling with ASD) are included to identify genetic and environmental factors in phenotypic variability.

Results: Here, we describe the demographic characteristics of the cohort, planned analytic stratification approaches, criteria and steps to validate candidate stratification markers, pre-registration procedures to increase transparency, standardisation and data robustness across all analyses, and share some ‘lessons learnt’. A clinical characterisation of the cohort is given in the companion paper (Charman et al., accepted).

Conclusions: We expect that LEAP will enable us to confirm, reject and refine current hypotheses of neurocognitive/neurobiological abnormalities, identify biologically and clinically meaningful ASD subgroups, and help us map phenotypic heterogeneity to different aetiologies.
Research Units

Neurology, Neurophysiology, Neurobiology

**Head**  V. Di Lazzaro

**Faculty**  F. Ferreri, F. Vernieri, M. Tombini


**Description**

The activity of the Research Unit aims at understanding the pathophysiology of a variety of neurological disorders, including stroke, degenerative diseases (dementias, Parkinson’s disease, tremor, amyotrophic lateral sclerosis), inflammatory diseases of the central nervous system (multiple sclerosis), spinal cord diseases, epilepsy, and headache. Another relevant area of interest is the use of electrophysiological techniques (EEG, EMG, evoked potentials), noninvasive brain stimulation (TMS, tDCS, tACS, vagal stimulation) and neurosonology (cerebral hemodynamics evaluation, functional TCD, TCD with bubble test), for the diagnosis of neurological disorders, and for the evaluation of the effects of drugs on the intact human brain and the study of human brain plasticity.

**Main research activities**

The research Unit has provided a relevant contribution in the development of innovative methods of neuromodulation useful to promote recovery in patients with chronic stroke and neuroprotection in the acute phase of stroke as well as developed cerebral hemodynamics markers to predict the risk of stroke and cognitive deterioration.

**Most important publications**


**Tremor stability index: a new tool for differential diagnosis in tremor syndromes.**


Misdiagnosis among tremor syndromes is common, and can impact on both clinical care and research. To date no validated neurophysiological technique is available that has proven to have good classification performance, and the diagnostic gold standard is the clinical evaluation made by a movement disorders expert. We present a robust new neurophysiological measure, the tremor stability index, which can discriminate Parkinson’s disease tremor and essential tremor with high diagnostic accuracy. The tremor stability index is derived from kinematic measurements of tremulous activity. It was assessed in a test cohort comprising 16 rest tremor recordings in tremor-dominant Parkinson’s disease and 20 postural tremor recordings in essential tremor, and validated on a second, independent...
Cirillo G., Di Pino G., Capone F., Ranieri F., Florio L., Todisco V., Tedeschi G., Funke K., Di Lazzaro V.

**Neurobiological after-effects of non-invasive brain stimulation.**

In recent years, many studies have evaluated the effects of noninvasive brain stimulation (NIBS) techniques for the treatment of several neurological and psychiatric disorders. Positive results led to approval of NIBS for some of these conditions by the Food and Drug Administration in the USA. The therapeutic effects of NIBS have been related to bi-directional changes in cortical excitability with the direction of change depending on the choice of stimulation protocol. Although after-effects are mostly short lived, complex neurobiological mechanisms related to changes in synaptic excitability bear the potential to further induce therapy-relevant lasting changes. To review recent neurobiological findings obtained from in vitro and in vivo studies that highlight molecular and cellular mechanisms of short- and long-term changes of synaptic plasticity after NIBS. Long-term potentiation (LTP) and depression (LTD) phenomena by itself are insufficient in explaining the early and long term changes taking place after short episodes of NIBS. Preliminary experimental studies indicate a complex scenario potentially relevant to the therapeutic effects of NIBS, including gene activation/regulation, de novo protein expression, morphological changes, changes in intrinsic firing properties and modified network properties resulting from changed inhibition, homeostatic processes and glial function. This review brings into focus the neurobiological mechanisms underlying long-term after-effects of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) recently obtained from in vitro and in vivo studies, both in animals and humans.

Capone F., Liberti M., Apollonio F., Camera F., Setti S., Cadossi R., Quattrocchi C.C., Di Lazzaro V.

**An open-label, one-arm, dose-escalation study to evaluate safety and tolerability of extremely low frequency magnetic fields in acute ischemic stroke.**

Extremely low frequency magnetic fields (ELF-MF) could be an alternative neuroprotective approach for ischemic stroke because preclinical studies have demonstrated their effects on the mechanisms underlying ischemic damage. The purpose of this open-label, one arm, dose-escalation, exploratory study is to evaluate the safety and tolerability of ELF-MF in patients with acute ischemic stroke. Within 48 hours from the stroke onset, patients started ELF-MF treatment, daily for 5 consecutive days. Clinical follow-up lasted 12 months. Brain MRI was performed before and 1 month after the treatment. The distribution of ELF-MF in the ischemic lesion was estimated by dosimetry. Six patients were stimulated, three for 45 min/day and three for 120 min/day. None of them reported adverse events. Clinical conditions improved in all the patients. Lesion size was reduced in one patient stimulated for 45 minutes and in all the patients stimulated for 120 minutes. Magnetic field intensity within the ischemic lesion was above 1 mT, the minimum value able to trigger a biological effect in preclinical studies. Our pilot study demonstrates that ELF-MF are safe and tolerable in acute stroke patients. A prospective, randomized, placebo-controlled, double-blind study will clarify whether ELF-MFs could represent a potential therapeutic approach.
Neurophysiology and Neuroengineering of Human–Technology Interaction

**Description**

The Research Unit investigates the neurophysiological processes underlying complex interaction between the human nervous system and technological artifacts.

Today, more and more often, the man is part of artificial/organic mixed complex, interacting with devices, robots, or with tool for functional replacement (e.g. prostheses). From a neuroscience perspective, this may strongly impact on well-known concepts, such sensory feedback, motor control, biomechanics, learning, functional recovery.

The Unit object of study is no longer humans as such, but modern humans in the era of the confluence with the technology, both in their physiological and pathological manifestations.

Furthermore, the Research Unit aim to investigate classical themes of neurophysiology of systems (motor control, body representation) using typical neuroengineering tools (e.g. modeling, objectification, automation).

Its multidisciplinary flavor favors direct applications on the healthy subjects and patients.

**Main research activities**

- Development of enabling technology of ERC RE-SHAPE project.
- Design and development of Hardware and Software Systems of virtual and augmented reality, and of cognitive studies that integrate VR-AR stimuli, external stimulations (e.g. tDCS, TMS) and the recording and processing of biological signals (EEG, fMRI, EMG)
- Development of a robot aided transcranial magnetic stimulation guided by artificial vision
- Investigation protocols to neuromodulated ownership during the rubber hand illusion paradigm.
- Effect of tDCS neuromodulation on redundant task with the wrist.
- Design and validation of the PDMeter, a wearable device to monitor Parkinson Disease motor state at home.
- Clinical trial of implanted intraneural electrodes.

**Head**  G. Di Pino  
**Faculty**  D. Formica  
**Other Personnel**  A. Mioli, A. Noccaro, J. Tosi, M. D’Alonzo, M. Pinardi, L. Raiano, A. Zangrandi
Most important publications

Lotti F., Ranieri F., Vadalà G., Zollo L., Di Pino G.

**Invasive intraneural interfaces: foreign body reaction issues.**

Intraneural interfaces are stimulation/registration devices designed to couple the peripheral nervous system (PNS) with the environment. Over the last years, their use has increased in a wide range of applications, such as the control of a new generation of neural-interfaced prostheses. At present, the success of this technology is limited by an electrical impedance increase, due to an inflammatory response called foreign body reaction (FBR), which leads to the formation of a fibrotic tissue around the interface, eventually causing an inefficient transduction of the electrical signal. Based on recent developments in biomaterials and inflammatory/fibrotic pathologies, we explore and select the biological solutions that might be adopted in the neural interfaces FBR context: modifications of the interface surface, such as organic and synthetic coatings; the use of specific drugs or molecular biology tools to target the microenvironment around the interface; the development of bio-engineered-scaffold to reduce immune response and promote interface-tissue integration.

Cirillo G., Di Pino G., Capone F., Ranieri F., Florio L., Todisco V., Tedeschi G., Funke K., Di Lazzaro V.

**Neurobiological after-effects of non-invasive brain stimulation.**

In recent years, many studies have evaluated the effects of noninvasive brain stimulation (NIBS) techniques for the treatment of several neurological and psychiatric disorders. Positive results led to approval of NIBS for some of these conditions by the Food and Drug Administration in the USA. The therapeutic effects of NIBS have been related to bi-directional changes in cortical excitability with the direction of change depending on the choice of stimulation protocol. Although after-effects are mostly short lived, complex neurobiological mechanisms related to changes in synaptic excitability bear the potential to further induce therapy-relevant lasting changes. Long-term potentiation (LTP) and depression (LTD) phenomena by itself are insufficient in explaining the early and long term changes taking place after short episodes of NIBS. Preliminary experimental studies indicate a complex scenario potentially relevant to the therapeutic effects of NIBS, including gene activation/regulation, de novo protein expression, morphological changes, changes in intrinsic firing properties and modified network properties resulting from changed inhibition, homeostatic processes and glial function.

Tosi J., Taffoni F., Santacatterina M., Sannino R., Formica D.

**Performance evaluation of bluetooth low energy: a systematic review.**

Small, compact and embedded sensors are a pervasive technology in everyday life for a wide number of applications (e.g., wearable devices, domotics, e-health systems, etc.). In this context, wireless transmission plays a key role, and among available solutions, Bluetooth Low Energy (BLE) is gaining more and more popularity. The aim of this work is to review the main methodologies adopted to investigate BLE performance. The first part of the paper is an in-depth description of the protocol, highlighting the main characteristics and implementation details. The second part reviews the state of the art on BLE characteristics and performance, in particular throughput, maximum number of connectable sensors, power consumption, latency and maximum reachable range.
The nonlinear physics and mathematical modeling research Unit investigates different problems belonging to Physics, Mathematics, Engineering, Biology and Medicine. Theoretical, analytical and numerical tools are applied to investigate complex dynamics underlying biological systems as well as astrophysics and classical and quantum field theories, with particular attention to fluid dynamics, nonlinear solid mechanics, condensed matter physics and stellar and black hole dynamics. Regarding biophysics, research activities focus on animal and human physiopathology of cardiac, intestine, neural, endocrine systems through the derivation and solution of mathematical models calibrated on experiments. To this aim, advanced tools of numerical calculus, atomistic simulations, biomedical imaging as well as data analysis are implemented with the aim of obtaining predictive information regarding complex systems. The Unit moreover extends its skills through national and international networks of collaborations.

In 2017 the research Unit has continued its long-lasting collaboration with the International Center for Relativistic Astrophysics Network (ICRANet) being awarded of the ICRANet Grant UCB-151020 for the research lines “Interdisciplinary Complex Systems: Theoretical Physics Methods in Systems Biology” and “Self Gravitating Systems, Galactic Structures and Galactic Dynamics” which lead the Unit to several publications on international journals. In the framework of a scientific agreement between UCBM and the Italian Institute for Technology (IIT), the group is working at a neuroscience project focused on computational and experimental investigation of physiological neural networks.
Most important publications

Loppini A., Pedersen M.G., Braun M., Filippi S.

**Gap-junction coupling and ATP-sensitive potassium channels in human β-cell clusters: effects on emergent dynamics.**


The importance of gap-junction coupling between β cells in pancreatic islets is well established in mouse. Such ultrastructural connections synchronize cellular activity, confine biological heterogeneity, and enhance insulin pulsatility. Dysfunction of coupling has been associated with diabetes and altered β-cell function. However, the role of gap junctions between human β cells is still largely unexplored. By using patch-clamp recordings of β cells from human donors, we previously estimated electrical properties of these channels by mathematical modeling of pairs of human β cells. In this work we revise our estimate by modeling triplet configurations and larger heterogeneous clusters. We find that a coupling conductance in the range 0.005-0.020 nS/pF can reproduce experiments in almost all the simulated arrangements. We finally explore the consequence of gap-junction coupling of this magnitude between β cells with mutant variants of the ATP-sensitive potassium channels involved in some metabolic disorders and diabetic conditions, translating studies performed on rodents to the human case. Our results are finally discussed from the perspective of therapeutic strategies. In summary, modeling of more realistic clusters with more than two β cells slightly lowers our previous estimate of gap-junction conductance and gives rise to patterns that more closely resemble experimental traces.

Gizzi A., Loppini A., Cherry E.M., Cherubini C., Fenton F.H., Filippi S.

**Multi-band decomposition analysis: Application to cardiac alternans as a function of temperature.**


It has long been known that variations in temperature can facilitate the development of cardiac arrhythmias. Here, we aim to quantify the effects of temperature on cardiac alternans properties. **Approach:** in this work, we use optical mapping recordings of canine ventricular epicardial preparations to demonstrate that hypothermia can promote the formation of alternans, which is an important precursor to potentially lethal arrhythmic like fibrillation. We then present a novel quantification of alternans properties for a broad range of cycle lengths under different thermal states. Specifically, we apply the recently developed multi-band-decomposition analysis (MBDA) in the context of cardiac action potential dynamics. **Main Results:** We show that the MBDA offers several advantages compared with traditional analysis of action potential durations. First, MBDA allows a depiction and quantification of the magnitude of alternans at all threshold values simultaneously and thus offers more information about how alternans relates to the action potential morphology while also removing the necessity of choosing a single threshold value. Second, the MBDA technique offers simple ways for assessing action potential amplitude alternans. Finally, MBDA provides a quantification of signal quality without any additional processing. **Significance:** We find that the MBDA technique shows promise in leading to a deeper understanding of cardiac alternans properties.


**Strongly bound excitons in anatase TiO(2) single crystals and nanoparticles.**


Anatase TiO2 is among the most studied materials for light-energy conversion applications, but the nature of its fundamental charge excitations is still unknown. Yet it is crucial to establish whether light absorption creates uncorrelated electron-hole pairs or bound excitons and, in the latter case, to determine their character. Here, by combining steady-state angleresolved photoemission spectroscopy and spectroscopic ellipsometry with state-of-the-art ab initio calculations, we demonstrate that the direct optical gap of single crystals is dominated by a strongly bound exciton rising over the continuum of indirect interband transitions. This exciton possesses an intermediate character between the Wannier-Mott and Frenkel regimes and displays a peculiar two-dimensional wavefunction in the three-dimensional lattice. The nature of the higher-energy excitations is also identified. The universal validity of our results is confirmed up to room temperature by observing the same elementary excitations in defect-rich samples (doped single crystals and nanoparticles) via ultrafast two-dimensional deep-ultraviolet spectroscopy.
The Unit investigates topics within clinical, pedagogical and organizational areas using quantitative and qualitative methods. Clinical areas include mainly palliative care, chronic disease, geriatric and cancer nursing. Palliative care topics include pressure ulcers, family caregivers’ satisfaction, care for adolescents who lose a parent and place of death. Geriatric topics include self-care (of elderly living at home and of elderly with chronic diseases), nutrition, quality of life, discharge process and continuity of care. Cancer nursing topics include prevention of chemo-induced oral mucositis, protective isolation in patients undergoing bone marrow or haematopoietic stem cell transplantation and nursing care dependence. Chronic disease topics regards self-care of patients and the contribution of their caregivers in COPD and multiple morbidity. Pedagogical topics focus on Nursing Students’ Perception of Instructor Caring, involvement of stakeholders in nursing education and hidden curriculum in nursing education. Organizational topics include care complexity, nursing documentation and prevention of errors during administration of intravenous therapy in critical care. Other key topics are caring behaviour of nurses and centrality of body and embodiment in nursing care and education.

The following ongoing multicentre research projects have been funded by the Center of Excellence for Nursing Culture and Research (CECRI):

- Self-care experiences from the perspective of the people with COPD;
- Self-care and quality of life in older adults with chronic diseases;
- Development and psychometric testing of a measure of cancer patients’ perception of care dependency;
- Exploration of care complexity in nurses’ views. A multicentre study;
- Nursing documentation in medical wards and in geriatric nursing homes;
- Self-care and contribution of self-care of caregivers in COPD.
Most important publications

Piredda M., Facchinetti G., Biagioli V., Giannarelli D., Armento G., Tonini G., De Marinis M.G.

Propolis in the prevention of oral mucositis in breast cancer patients receiving adjuvant chemotherapy: a pilot randomised controlled trial.


Chemo-induced oral mucositis (OM) is associated with significant symptoms and increased costs. This pilot trial evaluated safety, tolerability, compliance with, and tested clinical efficacy of propolis in breast cancer patients receiving doxorubicin and cyclophosphamide. Sixty patients were randomised to receive a dry extract of propolis plus mouth rinsing with sodium bicarbonate (experimental arm) or mouth rinsing with sodium bicarbonate (control arm). No patient in the experimental arm developed OM > G1, while in the control arm OM > G1 was 16.7% (p=.02). Propolis plus bicarbonate was safe, well tolerated and promisingly effective in the prevention of OM in patients with breast cancer.

Clari M., Matarese M., Ivziku D., De Marinis M.G.

Self-care of people with chronic obstructive pulmonary disease: a meta-synthesis.


Self-care in people with COPD can improve quality of life and reduce hospital admissions. This review synthesised qualitative literature on self-care behaviours and strategies used by people with COPD using the Joanna Briggs Institute meta-aggregative method. Self-care is directed towards prevention, control and management of physical consequences of COPD; self-care focuses on management of psychological effects of COPD; self-care is aimed at reducing the impact of COPD on social life; self-care is influenced by healthcare services and requires the acquisition of knowledge and skills. The findings can help to tailor self-care educational programs to experiences and priorities of people with COPD.

D’Angelo D., Punzano A.C., Mastroianni C., Marzi A., Latina R., Ghezzi V., Piredda M., De Marinis M.G.

Translation and testing of the Italian version of FAMCARE-2: measuring family caregivers’ satisfaction with palliative care.


Family satisfaction is critical to assess quality of palliative care. FAMCARE-2 is a measure of family satisfaction with healthcare received in palliative care that was adapted and tested with 185 caregivers of Italian patients admitted into 2 palliative care services. It showed excellent internal consistency (α=.96) and test–retest reliability (r=.98, p<.01). Confirmatory factor analysis showed a one-factor structure with good fit. Satisfaction levels were significantly correlated with female caregivers with less education, patient length of care, and place of assistance and death. The scale can help to identify which aspects of care need improvement, enabling caregivers to manage their role.
Oncology

Head  G. Tonini
Faculty F. Pantano, D. Santini, B. Vincenzi
Data manager T. Grassani, C. Potestà, T. Pignatelli

Description

The Oncology Research Unit is a multidisciplinary group of clinicians and scientists with expertise across the fields of clinical medicine, cancer care, epidemiology, bioinformatics and statistics, cell and molecular biology and immunology. A key aim of the Department of Oncology is the optimal translation of fundamental research into patient benefit. Our Translational Laboratory is physically closely located with the hospital and our strategy is to promote a tight interaction between basic scientists and clinicians. Research activities are mainly focused on diagnosis, treatment and prevention of cancers and can be divided into two broad disciplines: Translational and Clinical Research.

Teaching is one of our principal mission promoted by training and education activities including PhD and Resident-Specialty programs in Medical Oncology.

Main research activities

Translational research is focused on the:
- Evaluation of the effects of the new anticancer agents on tumor bone microenvironment including osteoblasts, osteoclasts and immune cells;
- Identification of new biomarkers for diagnosis, prognosis and prediction of response to novel anticancer treatments with a special focus on immunotherapies;
- Identification of new biomarkers involved in tumor progression and resistance to anticancer treatments in patients affected by soft tissue sarcomas.

Clinical Trial Unit focuses on: breast, prostate, renal, colorectal and lung cancers, but it also run trials in other rarer cancer types, including sarcoma. The unit is specialized in phase II exploratory and phase III randomized trials of new treatments.

Main collaborations

- Department of Clinical and Experimental Medicine, University of Pisa, Italy;
- Department of Surgery, Oncology and Gastroenterology, University of Padua, IOV-IRCCS, Italy;
- National Institute of Health and Medical Research (INSERM), France;
- Osteoncology and Rare Tumors Center, IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST), Italy.
Human equilibrative nucleoside transporter 1 gene expression is associated with gemcitabine efficacy in advanced leiomyosarcoma and angiosarcoma.


We investigated the correlation between human equilibrative nucleoside transporter 1 (hENT1) expression and gemcitabine efficacy in patients with advanced leiomyosarcoma and angiosarcoma.

We found a significant association between high hENT1 expression levels and favourable outcome in terms of PFS and OS compared to cases with low hENT1 expression in leiomyosarcoma treated with gemcitabine (PFS: 6.8 vs 3.2 months; OS: 14.9 vs 8.5 months). In addition, hENT1 overexpression correlated with a significant improvement in PFS (9.3 vs 4.5 months) and OS (20.6 vs 10.8 months) in angiosarcoma patients treated with gemcitabine.

Cabozantinib targets bone microenvironment modulating human osteoclast and osteoblast functions.


We investigate the effect of cabozantinib, c-Met and VEGFR2 inhibitor, on bone microenvironment using human primary osteoclasts and osteoblasts. Our results show that cabozantinib significantly inhibit osteoclast differentiation and activity. Moreover, the treatment has no effect on osteoblast differentiation, but it increases osteoprotegerin levels and down-modulates RANKL. Direct cell-to-cell contact between cabozantinib pre-treated osteoblasts and untreated osteoclasts confirmed the indirect anti-resorptive effect of cabozantinib. We demonstrate that cabozantinib inhibits osteoclast functions “directly” and “indirectly” reducing the RANKL/osteoprotegerin ratio in osteoblasts.

Outcome of oligoprogressing metastatic renal cell carcinoma patients treated with locoregional therapy: a multicenter retrospective analysis.


Locoregional treatment with radical intent should be considered during therapy with targeted agents in patients with metastatic renal cell carcinoma (mRCC) in order to achieve a complete response, especially in the setting of an oligo-progression in one or more metastatic sites. We retrospectively enrolled 55 patients who experienced a disease oligo-progression after at least 6 months from the beginning of first-line therapy in one or more metastatic sites radically treated with locoregional treatments. Post-first-oligo-progression overall survival (PFOPOS) and post-first-oligo-progression free survival (PFOPFS) were evaluated. We demonstrated that continuing the same systemic therapy, after a radical locoregional treatment on a site of progression, seems to be associated with a prolongation of mPFOPOS.
Description

The Ophthalmology area with its diagnostic and research laboratory of Ocular surface performs diagnostic activities focused on the eye surface, corneal, conjunctival dealing with an extremely peculiar eye section. Moreover, several research studies are investigating clinical and molecular aspects of retinal diseases; such age-related macular degeneration, diabetic retinopathy and vitreo-retinal interface abnormalities.

Main research activities

The research activities of the Ophthalmology Unit has been significant since many years, being among the top teams in the national landscape. An advanced research lab is part of this area, allowing to mix the most innovative techniques and discoveries of basic research in daily clinical activity. The research areas are developed in various fields:

- Pathogenesis of allergic eye diseases;
- Pathogenesis and therapy of dry-eye disease;
- Corneal transplants, indications and treatment;
- Immunological Management of Graft-Versus Host Disease (GVHD) and related complications;
- Neuromediators and Nerve Growth Factor (NGF) at ocular surface;
- Endocrine System effect at ocular surface.

The clinical and chirurgic team has a very pronounced international background that still offers educational, clinical and research exchanges with the major national and international institutions such as the one below.

Main collaborations

- Schepens Eye Research Institute, Harvard Medical School, Boston (Usa)
- World Health Organization (WHO), Geneva
- Italian Medicines Agency (AIFA), Rome
- Bascom Palmer Institute, Miami (Usa)
- Moorfield Eye Hospital, London (Great Britain)
- LV Prasad Eye Institute, Hyderabad (India)
- Beirut Eye and Ear Hospital, Beirut (Lebanon)
- DED research clinic at Pen University, Philadelphia (Usa)
- National Research Council (CNR), Rome
- Foundation G.B. Bietti, Rome
- Higher Health Institute, Rome
- University of Genoa, Messina, Padua, Bologna
**Most important publications**

Sabatino F., Di Zazzo A., De Simone L., Bonini S.

**The intriguing role of neuropeptides at the ocular surface.**

In recent decades, the role of neuropeptides in physiology and pathology has been elucidated. Various neuropeptides are expressed at the ocular surface, where they facilitate the crosstalk between immune and nervous systems. They actively regulate trophic and immune functions and orchestrate neuroinflammation. The purpose of this manuscript is to review the expression of the neuropeptides SP, VIP, CGRP, and NPY at the ocular surface, focusing on their role in tropism and immunity, and to summarize their functions in ocular immune privilege, infection, dry eye, and allergic eye disease.


**TFOS DEWS II pathophysiology report.**

The TFOS DEWS II Pathophysiology Subcommittee reviewed the mechanisms involved in the initiation and perpetuation of dry eye disease. Its central mechanism is evaporative water loss leading to hyperosmolar tissue damage. Research in human disease and in animal models has shown that this, either directly or by inducing inflammation, causes a loss of both epithelial and goblet cells. The consequent decrease in surface wettability leads to early tear film breakup and amplifies hyperosmolarity via a Vicious Circle. Pain in dry eye is caused by tear hyperosmolarity, loss of lubrication, inflammatory mediators and neurosensory factors, while visual symptoms arise from tear and ocular surface irregularity. Increased friction targets damage to the lids and ocular surface, resulting in characteristic punctate epithelial keratitis, superior limbic keratoconjunctivitis, filamentary keratitis, lid parallel conjunctival folds, and lid wiper epitheliopathy. Hybrid dry eye disease, with features of both aqueous deficiency and increased evaporation, is common and efforts should be made to determine the relative contribution of each form to the total picture. To this end, practical methods are needed to measure tear evaporation in the clinic, and similarly, methods are needed to measure osmolarity at the tissue level across the ocular surface, to better determine the severity of dry eye. Areas for future research include the role of genetic mechanisms in non-Sjögren syndrome dry eye, the targeting of the terminal duct in meibomian gland disease and the influence of gaze dynamics and the closed eye state on tear stability and ocular surface inflammation.

Busanello A., Santucci D., Bonini S., Micera A.

**Review: Environmental impact on ocular surface disorders: possible epigenetic mechanism modulation and potential biomarkers.**

Throughout life, external and the internal environments interact in normal development and tissue homeostasis as well as in onset of disease. Epigenetic modifications occur in response to environmental changes and play a fundamental role in controlling gene expression without modification of the DNA base sequence. Aging, inflammation, drugs, infections and ultraviolet exposure may have profound effects on epigenetic modifications and trigger susceptibility to diseases. Increasing evidence has demonstrated that epigenetic mechanisms play a key role in regulating the physiopathology of the ocular surface. The evaluation of epigenetic factors in ocular disease would lead to further investigation regarding the potential use of therapeutic targets and diagnostic biomarkers. This review examines specific epigenetic and biochemical mechanisms that may occur in the ocular surface microenvironment. Potential correlation between epigenetic factors and targets should be considered in future approaches to prevention and/or treatment of specific ocular surface disorders.
**Orthopaedic and Trauma Surgery**

**Head**  R. Papalia  
**Faculty**  A.C. Di Martino, F. Franceschi, U.G. Longo, A. Marinozzi, G. Vadala  
**Other Personnel**  C. Amato, S. Campi, F. Cancilleri, V. Denaro, G. Di Giacomo, F. Franceschetti, G. Marineo, A. Palumbo, N. Papapietro, G. Rizzello  
**PhD Students**  L. Diaz, A. Berton, F. Russo, G. Salvatore, S. Vasta, B. Zampogna  
**Residents**  E. Albo, A. Alifano, A. Baldari, F. Buschini, V. Candela, M. Ciuffreda, G. De Angelis, S. De Salvatore, C. Di Naro, A. Gambineri, A. Guarnieri, M. Paciotti, A. Perrino, S. Petrillo, S. Santini, A. Tecame, F. Vorini  

**Description**

The UCBM Research Unit of Orthopaedic Surgery and Trauma Surgery is devoted to the study of new surgical and biological strategies for the treatment of degenerative and traumatic diseases of the musculoskeletal system, in particular upper and lower limbs and spine. The research topics are related to the use of Adult Stem Cells and Platelet Rich Plasma for the treatment cartilage, disc, bone and tendon regeneration. Moreover, research on bone tumors and sport related trauma with the use of finite elements models are also being investigated. As part of the Centre of Integrated Research, research is approached with a multidisciplinary view in order to get new cutting edge hypothesis and objectives to achieve the best results for the patients. The Research Unit is also equipped with a Laboratory of Regenerative Orthopaedic where basic and preclinical researches are performed. Two full time biologist with cell and molecular biology expertise as well as histology work in the laboratory. Preclinical studies have been carried out for several years at the Animal Facility of Tor Vergata University of Rome and in collaboration with the Veterinary Hospital at University of Padua.

**Main research activities**

- Mesenchymal Stem Cell (MSC) application for intervertebral disc regeneration under the frame work of the H2020 project RESPINE: a double blind phase 2b trial of intradiscal injection of MSCs;
- Development of smart surgical platform for spine surgery: UCBM internal grant START-DISC;
- Clinical applications of stromal vascular fraction cells from adipose tissue and platelet rich plasma for the treatment of osteoarthritis;
- Surgical applications of invasive neural interfaces for bidirectional interaction between robotic superior limb prostheses and biological systems;
- Targeted muscle reinnervation for improved control of myoelectric upper limb prostheses;
- New biocompatible materials for bone and cartilage regeneration;
- Degenerative tendon alterations following post-traumatic pathologies;
- Finite element analysis of the metastatic spine to evaluate the risk of fracture and the role of preventive vertebroplasty;
- Translational computational analysis to optimize surgical treatment for patellar instability;
- Development of a computer model to study shoulder instability;
- Subchondroplasty for the treatment of bone edema of the knee.

**Main collaborations**

- Animal Facility, University of Rome “Tor Vergata”, Italy
- Veterinary Hospital, University of Padua, Italy.

**Most important publications**

Vadalà G., Russo F., Musumeci M., D’Este M., Cattani C., Catanzaro G., Tirindelli M.C., Lazzari L., Alini M., Giordano R., Denaro V.  

**Clinically relevant hydrogel-based on hyaluronic acid and platelet rich plasma as a carrier for mesenchymal stem cells: rheological and biological characterization.**

Intervertebral disc regeneration is quickly moving towards clinical applications. However, it is still missing an ideal injectable hydrogel to support mesenchymal stem cells (MSC) delivery. Herein, a new injectable hydrogel composed of platelet rich plasma (PRP) and hyaluronic acid (HA) blended with batroxobin (BTX) as gelling agent, was designed to generate a clinically relevant cell carrier for disc regeneration. PRP/HA/BTX blend was tested for rheological properties. Amplitude sweep, frequency sweep and rotational measurements were performed and viscoelastic properties were evaluated. Human MSC encapsulated in PRP/HA/BTX hydrogel were cultured in both growing medium and medium with or without TGF-β1 up to day 21. The amount of glycosaminoglycan was evaluated. Quantitative gene expression evaluation for collagen type II, aggrecan and Sox9 was also performed. Rheological tests showed that the hydrogel jellifies in 15 minutes at 20°C and in 3 minutes at 37°C. Biological test showed that MSCs cultured in the hydrogel maintain high cell viability and proliferation. Human MSC within the hydrogel cultured with or without TGF-β1 showed significantly higher GAG production compared to control medium. Moreover, MSCs in the hydrogel underwent differentiation to chondrocyte-like cells with TGF-β1, as shown by histology and gene expression analysis. This novel hydrogel improves viability and proliferation of MSCs supporting the differentiation process toward chondrocyte-like cells. Rheology tests showed optimal gelation kinetics at room temperature for manipulation and faster gelation after transplantation (37°C). The clinical availability of all components of the hydrogel will allow a rapid translation of this regenerative approach into the clinical scenario.


Meniscal extrusion as booster of osteoarthritis.


Meniscal extrusion (ME) has shown to play a critical but still unclear role in osteoarthritis (OA) development. ME has been described as an important risk factor in the progression of knee OA, as it is involved in the thinning of articular cartilage, joint space narrowing, spontaneous osteonecrosis of the knee and subchondral bone marrow lesions. Meniscal damage of any degree of severity could cause ME in both compartments, but it is commonly associated with severe meniscal tears or root tears mainly in the medial meniscus. Magnetic resonance imaging is the most commonly used imaging modality in the assessment of ME, while ultrasonography may represent a valid alternative with high sensitivity and specificity. Conservative treatment for ME includes physical therapy and rehabilitation to maintain range of motion, corticosteroid injections and intra-articular injections of hyaluronic acid to provide short-term relief of knee pain. The goal of this study is to review standards of current diagnosis and treatment of ME and its relationship to knee OA.

Longo U.G., Ciuffreda M., D’Andrea V., Mannering N., Locher J., Denaro V.

All-polyethylene versus metal-backed tibial component in total knee arthroplasty.


**Purpose:** The aim of this systematic review was to evaluate the clinical outcomes, rate of revisions and complications of all-polyethylene tibial and metal-backed tibial components in patients treated with knee arthroplasty for primary or secondary osteoarthritis.

**Methods:** A systematic review of the literature according to the PRISMA guidelines was performed. A comprehensive search of PubMed, Medline, CINAHL, Cochrane, Embase, and Google Scholar databases using various combinations of the keywords such as “knee”, “arthroplasty”, “metal-backed”, and “all-polyethylene”, since inception of databases to 2016, was performed.

**Results:** Thirty-two articles, describing patients with all-polyethylene tibial or metal-backed tibial components in the setting of osteoarthritis, were included. A total of 68,202 knees in 58,942 patients were included, with an average age at surgery of 69.3 years, ranging from a mean age of 57.9-82 years. The mean KSS was 82.4 and 81.3 (n.s.), the mean KSS(F) was 73.6 and 74.9 (p = 0.04), the mean ROM was 104.5 and 104.6 (n.s.), and the mean HSS was 87 and 86, each, respectively, for the metal-backed tibial components group and all-polyethylene tibial components group. The overall rate of revisions was 1.90 %. The rate of revision in the metal-backed tibial components group was 1.85 %, whilst the rate of revision in the all-polyethylene tibial components group was 2.02 % (p < 0.00001).

**Conclusion:** Metal-backed tibial and all-polyethylene tibial components did not show any significant difference in most of the included outcome scores, but statistical differences were found in terms of complications and revision rate. These items have a negative impact on the cost-effectiveness of all-polyethylene tibial components. Even if all-polyethylene tibial components show similar clinical outcome score, equivalent range of knee motion, and long-term survival compared to metal-backed tibial components, complications and revision rate seem to lead the surgeon to prefer the last ones. The clinical relevance of this study is that metal-backed tibial components should be preferred in TKA surgery because complications are higher using all-polyethylene tibial components. On the other hand, the quality of evidence, according to GRADE system, is low underling the necessity of more randomised study to clarify these items.
Otolaryngology

Description

The research unit has been working for years in the design of new devices for topical therapy of upper airway, we are studying the endothelial dysfunction and the potential role of Nerve growth factor (NGF) and the inner ear disorders. We are working on new hearing aids and new methods of nasal breathing evaluation and innovative techniques for vertigo and sinus-nasal diseases.

Main research activities

• New devices for topical therapy for upper airway;
• Development of hearing aids “transparent” to maintain the spectral characteristics of the sound;
• New surgical techniques for the treatment of Ménière disease. Prospective study;
• Otologic disorders, temporo-mandibular dysfunction and serotonergic pattern;
• Topical hyaluronic acid use in the upper airway inflammation;
• Endothelial dysfunction and inner ear disorders;
• New device to evaluate nasal breathing;
• The level of NGF and the expression of NGF receptors in nasal cavity and in the olfactory bulb.

Head  F. Salvinelli
Faculty  M. Casale
Most important publications

Lopez M.A., Manzulli N., D’Angelo A., Lauritano D., Casale M., Candotto V.

The use of hyaluronic acid as an adjuvant in the management of periodontitis.

The emollient and restructuring action exerted on the mucous membranes by hyaluronic acid is of particular significance. This is thanks to its reparative (it stimulates angiogenesis) and soothing properties (hyaluronic acid is used in wound care to improve the processes of wound healing), which are effective in treating the symptoms of local inflammation and irritation. The purpose of this clinical trial is to evaluate the potential efficacy of nebulized hyaluronic acid in the management of chronic periodontitis in adults. The results of the statistical analysis demonstrate that there was a slight improvement in the measurement of pocket depth in the side treated with HA at time 0 (pre-treatment) and time 1 (15 days post-treatment). Furthermore, the difference between bleeding on probing as measured at time 0 and time 1 indicated an improvement on both sides, with a slightly greater improvement on the side treated with HA.

Lopez M.A., Manzulli N., D’Angelo A., Candotto V., Casale M., Lauritano D.

The use of hyaluronic acid as an adjuvant in the management of gingivitis.

Recently, a specifically designed device was proposed that is able to nebulize particles with a diameter of approximately 16 micrometres to be used mainly in the management of diseases of the upper airway respiratory tract. The purpose of this pilot study is to evaluate the potential efficacy of nebulized hyaluronic acid in the management of gingivitis. The results of the statistical analysis demonstrate that there was no difference between the pocket depth as measured in the treated sites at time 0 (pre-treatment) and time 1 (15 days post-treatment). However, the difference between bleeding on probing as measured at time 0 and time 1 indicated an improvement on both sides, with a slightly greater improvement on the side treated with HA.


The efficacy of topical hyaluronan in rhinosinusitis: a systematic review.

Rhinosinusitis is one of the most common inflammatory conditions of the nasal cavity and paranasal sinuses and is one of the most common causes of absence from work and for visits to the family doctor. The treatment strategy in both acute rhinosinusitis (ARS) and chronic rhinosinusitis (CRS) is to reduce the severity of the symptoms, minimize the duration of the disease and prevent complications. Topical therapy has become an important tool in otolaryngologists’ armamentarium for rhinosinusitis treatment. Recently, topical hyaluronic acid (HA), the major component of many extracellular matrices that promotes tissue healing, including activation and moderation of the inflammatory responses, cell proliferation, migration and angiogenesis, has been proposed for ARS and CRS adjuvant tool. The aim of the study is to systematically review the published literature regarding all the therapeutic effects of HA on the ARS and CRS. Relevant published studies were found in PubMed, Google Scholar and Ovid, using a combined keyword search or medical subject headings. At the end of our study selection process, 5 relevant publications were included: 2 of them investigated the potential role of HA in reducing symptoms and preventing exacerbations of CRS in adult population, two of them in paediatric patients affected by upper respiratory tract infections and one of them in cystic fibrosis patients with bacterial rhinopharyngitis. Data deriving from the present review of 5 clinical studies showed that the use of topical HA represents a relevant therapeutic advance in rhinosinusitis to minimize symptoms and prevent reacutization with a significant improvement of their quality of life, as it avoids systemic side effects and increases local drug activity. Further studies on larger populations and with new specific nebulization devices for upper airway are needed to confirm these encouraging results.
Pathology

Head G. Perrone
Faculty A. Onetti Muda, C. Rabitti
Other Personnel M. Amato, M. Donati, G. Nicolò, S. Ferrari

Description

The Anatomic Pathology Lab is dedicated to medical diagnosis and scientific research activities. The latter is in turn divided into two main operative fields, i.e. development of research lines that are specific to the area, and collaboration within research lines in other areas. Over the years, the laboratory has been furnished with a wide range of technologically advanced equipment, which allows it to better implement activities. Highly specialized engineers manage equipment. Currently, standard procedures include:

- Histopathology and cytopathology
- Histochemistry
- Immunohistochemistry
- Transmission electron microscopy
- Pyrosequencing station
- Fluorescence microscope with FISH equipment
- Real-time PCR equipment
- N-Counter Nanostring

A dissecting room is also available.

Main research activities

Research topics:
- Application of morphological and molecular technologies for cancer characterization and correlation with disease progression/treatment outcome
- Breast cancer - morphological and molecular characterization of breast cancer supporting innovative medical and surgical procedures
- Pancreatic and peripancreatic neoplasms - histological and immunohistochemical subtyping; multicenter standardization of resection margins status; validation of pre-operative molecular analysis as an additional mutodiagnostic tool for cancer
- Neoplastic, metabolic and inflammatory liver diseases: morphological characterization and correlation with disease progression.

Funded projects:
- Extension of the RealQuant® Lung Fusion Genes kit validation to cytological specimens (OSLO) - Principal Investigator: Giuseppe Perrone
- Funded by Diatech Pharmacogenetics
- Concordance value between PAM50 and immunohistochemical evaluation of Ki-67
- Principal Investigator: Giuseppe Perrone
- Funded by TCI Telecomunicazioni
- Optimization of the biopsy tissue for complete morphological and molecular characterization of pulmonary adenocarcinoma
- Principal Investigator: Giuseppe Perrone
- Funded by Astrazeneca
- Bone strength and WNT signalling in obese patients
- Research Collaborator: Carla Rabitti
- Funded by Institutional Grant

Main collaborations

- Medical Oncology Department, Hospital Clinic, Universitat de Barcelona, Barcelona, Spain;
- Dept. of Pathology, Harvard University School of Medicine, Boston, USA
- Department of Fundamental Neuroscience, Faculty of Biology and Medicine, University of Lausanne, Switzerland
- Dipartimento di Medicina Sperimentale e Clinica, Università di Firenze

Most important publications


Human equilibrative nucleoside transporter 1 gene expression is associated with gemcitabine efficacy in advanced leiomyosarcoma and angiosarcoma.


Background: The expression of human equilibrative nucleoside transporter 1 (hENT1), the major gemcitabine transporter into cells, has been thoroughly investigated as a predictive marker of response to gemcitabine in pancreatic cancer and biliary tract cancers. Since
gemcitabine is widely used in the treatment of leiomyosarcoma and angiosarcoma, we investigated the correlation between hENT1 expression and gemcitabine efficacy in these sarcoma subtypes.

**Methods:** We retrospectively identified 71 patients affected by advanced angiosarcoma (26) or leiomyosarcoma (45) treated within five Italian referral centres for sarcoma; among them, 49 patients (15 angiosarcoma, 34 leiomyosarcoma) were treated with gemcitabine. All tumour samples were analysed for hENT1 expression by real-time PCR. Median 2-ΔCt value was used as the cutoff to dichotomise patients into ‘high’ expression and ‘low’ expression groups. Kaplan-Meier analysis was performed to estimate progression-free survival (PFS) and overall survival (OS).

We found a significant association between high hENT1 expression levels and favourable outcome in terms of PFS and OS compared to cases with low hENT1 expression in leiomyosarcoma treated with gemcitabine (PFS: 6.8 vs 3.2 months, P=0.004; OS: 14.9 vs 8.5 months, P=0.007). In addition, hENT1 overexpression correlated with a significant improvement in PFS (9.3 vs 4.5 months; P=0.02) and OS (20.6 vs 10.8 months; P=0.001) in angiosarcoma patients treated with gemcitabine.

**Conclusions:** Our study suggests that higher hENT1 expression are associated to gemcitabine efficacy both in patients with advanced leiomyosarcoma and angiosarcoma.

**Limitations in predicting PAM50 intrinsic subtype and risk of relapse score with Ki67 in estrogen receptor-positive HER2-negative breast cancer.**


PAM50/Prosigna gene expression-based assay identifies three categorical risk of relapse groups (ROR-low, ROR-intermediate and ROR-high) in post-menopausal patients with estrogen receptor estrogen receptor-positive (ER+)/ HER2-negative (HER2-) early breast cancer. Low risk patients might not need adjuvant chemotherapy since their risk of distant relapse at 10-years is below 10% with endocrine therapy only. In this study, 517 consecutive patients with ER+/HER2- and node-negative disease were evaluated for Ki67 and Prosigna. Most of Luminal A tumors (65.6%) and ROR-low tumors (70.9%) had low Ki67 values (0-10%); however, the percentage of patients with ROR-medium or ROR-high disease within the Ki67 0-10% group was 42.7% (with tumor sizes ≤2 cm) and 33.9% (with tumor sizes > 2 cm). Finally, we found that the optimal Ki67 cutoff for identifying Luminal A or ROR-low tumors was 14%. Ki67 as a surrogate biomarker in identifying Prosigna low-risk outcome patients or Luminal A disease in the clinical setting is unreliable. In the absence of a well-validated prognostic gene expression-based assay, the optimal Ki67 cutoff for identifying low-risk outcome patients or Luminal A disease remains at 14%.

Amato M., Perrone G., Righi D., Pellegrini C., Rabitti C., Di Matteo F., Crucitti P., Caputo D., Coppola R., Tonini G., Santini D., Onetti Muda A.

**HER2 status in gastric cancer: comparison between primary and distant metastatic disease.**


HER2 (human epidermal growth factor receptor-2) assessment in histological samples of gastric cancer is essential to determine which patients might benefit from trastuzumab therapy. HER2 is often evaluated in primary tumor even if trastuzumab therapy is used to treat metastatic disease. However, the exact relationship in terms of HER2 status between primary and metastatic tumors has not been fully clarified. We aimed to evaluate the HER2 status concordance between primary gastric cancer and corresponding distant metastasis. HER2 status was evaluated by IHC (immunohistochemistry) and/or FISH (fluorescence in situ hybridization) in 41 patients in primary gastric cancer and in paired metastasis. HER2 was assessed according scoring criteria applied in clinical approach. HER2 positivity was found in 14.6% primary tumors and in 24.4% corresponding metastasis. HER2 concordance rate between primary and metastasis was 80.5% (K-value = 0.388). Eight/41 (19.5%) cases resulted discordant: 6 patients with metastatic HER2 positive lesions were found HER2 negative in primary cancers while 2 patient HER2 positive in primary lesion showed a negative conversion in metastasis. Our results showed a good concordance in terms of HER2 status between primary and metastatic lesions, as well as in biopsy and surgical removed specimens. However, the higher rate of HER2 positive status found in metastatic lesions underlined the importance of HER2 assessment in all samples obtained from different sites of gastric cancer disease.
Physical and Rehabilitation Medicine

Head  S. Sterzi
Faculty  F. Bressi
Other Personnel  M. Bravi, S. Miccinilli, M. Morrone, F. Santacaterina

Description

The research unit is equipped with a movement analysis laboratory, consisting in a stereophotogrammetric system of 8 cameras, two force platforms, a surface electromyography system and a dedicated software for the analysis of collected data. The main activities conducted in the laboratory are: optoelectronic plethysmography, gait analysis and analysis of the upper limb kinematics. Our unit is also equipped with two MIT-MANUS robots (InMotion 2 and InMotion3) that are used for clinical trials involving the upper limb functional recovery after stroke. A virtual reality tool for the treatment of phantom limb syndrome in upper limb amputees is also present.

Recently we have available a new tool for hand rehabilitation post-stroke. It is a hand rehabilitation glove, Gloreha, that provides computer-controlled, repetitive, passive and active assisted mobilization of the fingers, with multisensory feedback.

Main research activities

- Gait analysis in hemiparetic/hemiplegic patients for optimization of orthotic prototypes;
- Rehabilitation with robotic platforms of upper and the lower limbs in patients with hemiplegia/hemiparesis after stroke;
- Non-Invasive Brain Stimulation techniques in Upper Limb-Impaired Chronic Stroke patients;
- Study of the kinematics of the rib cage with optoelectronic plethysmography in patients with lung cancer, COPD, stroke and spinal cord injuries;
- Stereophotogrammetric analysis of postural alterations in patients with movement disorders;
- Implantation of neural invasive interfaces for the bidirectional control of an upper limb cybernetic prosthesis and pain control in upper limb amputees;
- Dysphagia management in elderly people.

Main collaborations

- Bambino Gesù Pediatric Hospital, Italy;
- Burke Hospital, USA;
- INAIL Prosthesis Center, Italy;
- San Raffaele Foundation IRCCS, Italy;
- Santa Lucia Foundation IRCCS, Italy;
- Thoracic Surgery Unit of the University Hospital A. Gemelli, Italy.

Literature review on the effects of tDCS coupled with robotic therapy in post stroke upper limb rehabilitation.


Most important publications

Simonetti D., Zollo L., Milighetti S., Miccinilli S., Bravi M., Ranieri F., Magrone G., Guglielmelli E., Di Lazzaro V., Sterzi S.
Today neurological diseases such as stroke represent one of the leading cause of long-term disability. Many research efforts have been focused on designing new and effective rehabilitation strategies. In particular, robotic treatment for upper limb stroke rehabilitation has received significant attention due to its ability to provide high-intensity and repetitive movement therapy with less effort than traditional methods. In addition, the development of non-invasive brain stimulation techniques such as transcranial Direct Current Stimulation (tDCS) has also demonstrated the capability of modulating brain excitability thus increasing motor performance. The combination of these two methods is expected to enhance functional and motor recovery after stroke; to this purpose, the current trends in this research field are presented and discussed through an in-depth analysis of the state-of-the-art. The heterogeneity and the restricted number of collected studies make difficult to perform a systematic review. However, the literature analysis of the published data seems to demonstrate that the association of tDCS with robotic training has the same clinical gain derived from robotic therapy alone. Future studies should investigate combined approach tailored to the individual patient's characteristics, critically evaluating the brain areas to be targeted and the induced functional changes.


**Transcutaneous vagus nerve stimulation combined with robotic rehabilitation improves upper limb function after stroke.**

The efficacy of standard rehabilitative therapy for improving upper limb functions after stroke is limited; thus, alternative strategies are needed. Vagus nerve stimulation (VNS) paired with rehabilitation is a promising approach, but the invasiveness of this technique limits its clinical application. Recently, a noninvasive method to stimulate vagus nerve has been developed. The aim of the present study was to explore whether noninvasive VNS combined with robotic rehabilitation can enhance upper limb functionality in chronic stroke. Safety and efficacy of this combination have been assessed within a proof-of-principle, double-blind, semirandomized, sham-controlled trial. Fourteen patients with either ischemic or haemorrhagic chronic stroke were randomized to robot-assisted therapy associated with real or sham VNS, delivered for 10 working days. Efficacy was evaluated by change in upper extremity Fugl-Meyer score. After intervention, there were no adverse events and Fugl-Meyer scores were significantly better in the real group compared to the sham group. Our pilot study confirms that VNS is feasible in stroke patients and can produce a slight clinical improvement in association to robotic rehabilitation. Compared to traditional stimulation, noninvasive VNS seems to be safer and more tolerable. Further studies are needed to confirm the efficacy of this innovative approach.


**Optoelectronic plethysmography in clinical practice and research: a review.**

**Background:** Optoelectronic plethysmography (OEP) is a non-invasive motion capture method to measure chest wall movements and estimate lung volumes.

**Objectives:** To provide an overview of the clinical findings and research applications of OEP in the assessment of breathing mechanics across populations of healthy and diseased individuals.

**Methods:** A bibliographic research was performed with the terms “opto-electronic plethysmography,” “optoelectronic plethysmography,” and “optoelectronic plethysmograph” in 50 digital library and bibliographic search databases resulting in the selection of 170 studies.

**Results:** OEP has been extensively employed in studies looking at chest wall kinematics and volume changes in chest wall compartments in healthy subjects in relation to age, gender, weight, posture, and different physiological conditions. In infants, OEP has been demonstrated to be a tool to assess disease severity and the response to pharmacological interventions. In chronic obstructive pulmonary disease patients, OEP has been used to test if patients can dynamically hyperinflate or deflate their lungs during exercise. In neuromuscular patients, respiratory muscle strength and chest kinematics have been analyzed. A widespread application of OEP is in tailoring post-operative pulmonary rehabilitation as well as in monitoring volume increases and muscle contributions during exercise.

**Conclusions:** OEP is an accurate and validated method of measuring lung volumes and chest wall movements. OEP is an appropriate alternative method to monitor and analyze respiratory patterns in children, adults, and patients with respiratory diseases. OEP may be used in the future to contribute to improvements in the therapeutic strategies for respiratory conditions.
Plastic Surgery and Dermatology

Head  P. Persichetti
Faculty  C. Dianzani, G.F. Marangi, S. Tenna
Other Personnel  A. Aveta, M. Barone, B. Brunetti, B. Cagli, A. Cogliandro, V. Panasiti, S. Santoro, F. Segreto, P. Simone, V. Toto

Description

Fields of interests and research:
• Reconstructive surgery following neoplasms, malformations or trauma of:
  ▶ head and neck
  ▶ upper and lower limb
  ▶ thorax
  ▶ abdomen
  ▶ perineum
• Screening, diagnosis and treatment of skin cancer
• Breast reconstruction (Implants, Flap, Lipofilling)
• Treatment of ulcers:
  ▶ vascular
  ▶ diabetes
  ▶ pressure sore
• Application of regenerative medicine with autologous fat plus Platelet Rich Plasma (PRP)
• Burns
• Body contouring procedures after bariatric surgery
• Cosmetic surgery and aesthetic medicine:
  ▶ Head and neck (rhinoplasty, blepharoplasty, face lift, otoplasty)
  ▶ Breast (augmentation, mastopexy, reduction mammoplasty)
  ▶ Abdomen (abdominoplasty, liposuction)
  ▶ Upper and lower limb (thigh lift, brachioplasty, liposuction)
  ▶ Filler
  ▶ Botulinum toxin
• Application of regenerative medicine in skin rejuvenation
• Application of regenerative medicine in the treatment of atrophic acne scars
• Lasers treatment of:
  ▶ Hemangiomas
  ▶ Scars
  ▶ Cutaneous lesions
  ▶ Photoaging
  ▶ Hypertrichosis

Main research activities

• Application of regenerative medicine in treatment of atrophic acne scars: nanofat plus PRP infiltration and fractional CO2 laser resurfacing;
• The use of PRP in breast implant capsule contracture;
• Treatment of venous ulcers with different combinations of fat graft and platelet rich plasma: a prospective comparative evaluation;
• Quality of life in patients affected by breast cancer treated with reconstructive procedures: application of the BREAST-Q questionnaire;
• Evaluation of the postero-medial scar brachioplasty technique associated to lipo-aspiration in the post-bariatric arm remodeling;
• Platelet-rich plasma in breast implant capsule contracture;
• IPL in the treatment of posterior blepharitis;
• The use of regenerative devices in chronic wounds: a prospective randomized control trial;
• Bioelectrochemical sensor to detect antibiotic-resistant Pseudomonas Aeruginosa;
• Evaluation of the periprosthetic breast capsule in patients subjected to breast reconstruction with tissue expanders with different surfaces;
• Association of human papilloma virus infection and keratoacanthoma clinical evolution;
• Correlation with dysfunction of the thyroid gland and skin pathology;
• Association of human papilloma virus infection and actinic cheilitis;
• CDKN2A involvement in melanoma and mesothelioma susceptibility in rare familial cancer syndromes;
• Clinical evaluation of topical treatment in papulo cystic acne.
• In the 2017 creation of a Multidisciplinary Research Group: “To be and to appear: Objective indication to Plastic Surgery” of Campus Bio-Medico University of Rome, Rome, Italy.

Main collaborations

• Department of Plastic and Reconstructive Surgery, Kansai Medical University Department of Plastic and Reconstructive Surgery, Kansai Medical University, Japan;
• Singapore Centre for Environmental Life Sciences Engineering, Nanyang Technological University, Singapore;
Human papilloma virus expression in immunocompetent patients with actinic keratosis: a case series.

Dianzani C., Paolini F., Conforti C., Riva E., Beninati E., Venuti A.


Actinic keratosis (AK) is a common skin disease that can develop into squamous cell carcinoma (SCC). Previous studies showed that human papilloma virus (HPV) skin infection might be related to an increased risk for AK and SCC in immunosuppressed patients. The purpose of this study was to detect the presence (HPV DNA) and the expression (HPV RNA) of this virus in the AK lesions of immunocompetent patients. The presence of HPV RNA was also assessed because detection of only genomic viral DNA does not mean that virus is interacting with host cell, and synthesis of viral RNA indicates biological activity of the virus.

Superficial temporal artery perforator flap: Anatomic study of number and reliability of distal branches of the superficial temporal artery and clinical applications in three cases.

Aveta A., Brunetti B., Tenna S., Segreto F., Persichetti P.


**Background:** Limited information is available about the anatomical feasibility and clinical applications of flaps based on distal divisions of the superficial temporal artery (STA). The aim of this study was to investigate the anatomy of the STA, focusing on the number and reliability of distal branches and to show representative cases for the use of such flaps for zygomatic, parieto-frontal and occipital reconstructions. **Methods:** Fifty volunteers were examined bilaterally by Doppler to investigate the presence and variability of the distal divisions of STA branches. Dissection was performed on 14 temporal regions of 7 fresh cadavers. Three cases of reconstruction following skin cancer in the zygomatic (7 × 5 cm defect), parieto-frontal (4 × 4 cm defect) and occipital areas (4 × 2 cm defect) are presented. All the flaps were pedicled and based on a single vessel. **Results:** In all the 50 volunteers, the parietal branch split into 2 ± 0 branches (anterior and posterior), bilaterally, while an average of 2.84 ± 0.46 and 2.82 ± 0.48 branches originated from the frontal vessel on the right and left side, respectively. 2 ± 0 parietal and 3 ± 0 frontal (superior, central, and inferior) cutaneous perforator branches were identified in all cadaveric specimens. Flaps (4 × 10 cm, 5 × 7 cm, and 2 × 5 cm, respectively, width × length) healed uneventfully providing stable coverage. **Conclusions:** STA distal perforator branches proved to be anatomically constant in both the cadaveric and clinical settings. Although a larger series of cases is needed, island flaps based on such vessels may represent a versatile surgical option, allowing a wide range of reconstructions in the different facial subunits.

A systematic review of patient-reported outcome measures after rhinoplasty.

Barone M., Cogliandro A., Di Stefano N., Tambone V., Persichetti P.


The literature still lacks a review regarding PROs applied for rhinoplasty. Thus, we performed a systematic review of the literature to identify PROMs that assess patient satisfaction and quality of life after rhinoplasty. The aim of our study was to identify existing questionnaires and to summarize their development, psychometric properties, and content. A multi-step search of the web-based PubMed database from the National Library of Medicine was performed to identify PROMs that are designed to evaluate satisfaction and quality of life following rhinoplasty. Each potential PROM was examined by three independent reviewers for adherence to inclusion/exclusion criteria. Questionnaires included in the analysis were appraised for their adherence to international guidelines for the development and validation of health outcome questionnaires, as outlined by the Scientific Advisory Committee of the Medical Outcome Trust and the U.S. Food and Drug Administration. Our search generated a total of 457 articles, 351 that were retrieved in the primary search, and 106 that were found in the references of the first set of articles. The process of development and validation of each of the included PROMs was examined. Only ten of these were identified as surgery-specific questionnaires about rhinoplasty. These were divided into three categories: (1) functional self-assessment (Nasal Surgical Questionnaire, Nasal Obstruction Symptoms Evaluation Scale, and Nasal Obstruction Septoplasty Effectiveness); (2) aesthetic self-assessment (Utrecht Questionnaire, FACE-Q rhinoplasty module, Glasgow Benefit Inventory); and (3) aesthetic and functional self-assessment (Rhinoplasty Outcomes Evaluation, Functional Rhinoplasty Outcome Inventory 17, RHINO Scale, and Evaluation of Aesthetic Rhinoplasty Scale).
Process Engineering

Head  M. De Falco
Faculty  M. Capocelli
Other Personnel  D. Barba, A. Germanà, N. Greco, G. Iaquaniello, R. Pizzi

Description

In the Research Unit, academic figures and business leaders (lecturers of the Master of Chemical Engineering for the Sustainable Development) work in close synergy with the objective to develop new technologies of industrial interest, aimed at increasing the compatibility of production systems with safeguarding the environment and human health. The scientific and technological approach derives from the belief that every production system should be equipped with advanced technologies able to improve the performance but, at the same time, reducing the pollutants emissions into the environment at the minimum values allowed by the state of technological knowledge, well below the legal limits. This approach is known as BAT (Best Available Technology) philosophy.

Main research activities

• Launch of a development program with Menarini S.p.A. in the design and fabrication of a new generation of tailored bioreactors for the growth of CHO cells. Submission of a research project to the Lazio Region.
• Collaboration with the company Serintel for an Advanced Training project in the Oil & Gas industry. The Research Unit has formulated short papers about innovative and sustainable technologies for the Oil & Gas sector, published on the international portal www.oil-gasportal.com.
• Design of an innovative Decentralized Fresh Water production process from Solar Multi Stage Humidification, tailored for the decentralized production of fresh water at low operating costs in rural areas. The process has been developed with the collaboration of the company Sitie and will be presented to private and public investors.
• Signing of a framework agreement with the Universidad National de la Colombia for the development of joint activities of scientific research and training.

Main collaborations

• Menarini, Italy;
• Serintel Company, Rome, Italy;
• Company Sitie, Italy;
• Universidad National de Colombia, Colombia.

Most important publications

De Falco M., Capocelli M., Basile A.

Selective membrane application for the industrial one-step DME production process fed by CO2 rich streams: modeling and simulation.

The integration of a microporous zeolite membrane, highly selective to steam water in a one-step DME synthesis reactor, is modeled and assessed. The membrane reactor performance and the comparison with a conventional reactor, are studied mainly for a CO2-rich feedstock, i.e. derived from a biogas-derived syngas. The continuous removal of water from the reaction environment reduces the inhibition effect of H2O on the CO2 hydrogenation and methanol dehydration reactions, thus allowing the achievement of high conversions, DME
yield and selectivity even at large CO2 composition in the inlet feedstock. If a CO2/CO ratio equal to 3 is imposed in the inlet stream, the DME yield reaches a value of 0.75 vs. 0.57 in a conventional reactor operating at the same conditions, the XCOx and XCO2 are 0.75 and 0.69, with an improvement of 15.4% and 30.2%, and the DME selectivity is close to 1.

The membrane reactor behavior is assessed by a one-dimensional, non-isothermal model. Fixing industrial scale parameters, the effect of the main operating conditions as temperature and pressure in the reactor environment, the Gas Hourly Space Velocity (GHSV), the feedstock composition in terms of CO2/CO and H2/COx ratios, the pressure and flow rate downstream to the selective membrane are analyzed and discussed.

The simulations confirm the improvement of the reactor performance, within large ranges of operating conditions, derived from the integration of the selective membrane. On this basis, membrane reactor for one-step DME synthesis process can be included in the “CO2 valorization” framework since the greenhouse gas CO2 can be used as a reactant in an industrial process and thus converted into a useful and marketable product.

De Falco M., Capocelli M., Giannattasio A.

**Membrane reactor for one-step DME synthesis process: industrial plant simulation and optimization.**

*J CO2 Util. 2017; 22; 33-43. DOI: 10.1016/j.jcou.2017.09.008. IF 4.292*

DME production represents a possible route of CO2 valorisation in the decarbonization pathway. This paper provides an insight into the basic design and process analysis of a DME production plant by implementing Membrane Reactors to convert CO2 at acceptable values. The paper provides the process analysis of the overall plant architecture related to an innovative DME production process configuration, called Double Recycling Loop DME (DRL-DME), enables the utilization of a pure CO2 stream as sweeping gas in the permeation zone (PZ) and a double recycling loop to reintroduces the un-reacted syngas and the outlet stream from the PZ. The mathematical model of the entire plant is presented and implemented to study the effect of the process parameters on the performances. This paper brings a step forward by determining the possible configuration and the performance of a whole industrial plant, able to realize the DME synthesis from CO2-rich streams in membrane reactor with recirculation. The whole process includes the utilization of a pure CO2 external feed, the steam production and all the necessary separation units. By fixing the set point of the process control variables, the recirculation streams are calculated though a mathematical algorithm founded on previous literature results. Through the mathematical model it is possible to estimate the CO2 conversion and DME yield as well as the main features of the plant, by varying some important process parameters (e.g. feedstock composition, reactor pressure, H2/COx).
Radiation Oncology

Head  S. Ramella
Faculty  R.M. D’Angelillo, M. Fiore, E. Ippolito

Description

The Radiation Oncology Research Unit’s strategy focuses on the association between radiotherapy and systemic agents and on radiobiological and technical issues. In particular, the combination of radiation and target agents, chemotherapy and immunotherapy in clinical and multidisciplinary setting is investigated. Special efforts are about combined treatment of lung cancer, prostate cancer, pancreatic cancer, rectal cancer. Modern breast irradiation techniques are explored to optimize dose distribution to the target and to the organs at risk. Special techniques such as stereotactic treatment, volumetric arc therapy and respiratory gating are implemented in radiation research protocols and in clinical practice. A rising interest of the research group is in the development of patients’ tools to monitor patients’ quality of life.

Main research activities

The main results in lung cancer have been obtained in exploring an adaptive approach in concurrent chemoradiation in locally advanced non-small cell lung cancer (NSCLC). Accordingly, two main topics have been developed: the evaluation of radiomics as a predictive tool for adaptive radiotherapy and the starting of a national project involving Medical and Engineering faculties in order to assess the predictive and prognostic value of radiomics in locally advanced and metastatic NSCLC. In castration resistant prostate cancer, a national project about the role of radiation therapy with new hormonal drugs was conducted. New research protocols have started about RT plus new drugs in locally advanced high risk patients, as well as a project to investigate the cardiotoxicity in hormonal patients. Multidisciplinary treatment protocols in gastrointestinal cancer are ongoing, exploring the intensification of the integrated approach in pancreatic patients and the reduced toxicity in rectal cancer.
Research Yearbook 2017 | Campus Bio-Medico University of Rome

Most important publications


Combining abiraterone and radiotherapy in prostate cancer patients who progressed during abiraterone therapy.

This multicentre ‘field-practice’ study investigated treatment outcomes of ongoing abiraterone therapy with the addition of radiotherapy initiated for oligoprogression or with a palliative intent. A total of 32 patients were enrolled in the study. Median duration of abiraterone treatment was 13.0 months (range=3.8-40.9 months). Median duration of abiraterone treatment before RT was 5.9 months (range=0.4-40.0 months), and 7.2 months after RT (range=0.1-29.7 months). Median progression-free survival (PFS) was 12.6 months (95%CI=10.5-14.7) from the initiation of abiraterone treatment. RT prolongs abiraterone treatment in mCRPC patients leading to better clinical outcomes with this molecule.

Ramella S., Fiore M., Silipigni S., Zappa M.C., Jaus M., Alberti A.M., Matteucci P., Molfese E., Cornacchione P., Greco C., Trodella L., Ippolito E., D’Angelillo R.M.

Local control and toxicity of adaptive radiotherapy using weekly CT imaging: results from the LARTIA trial in stage III NSCLC.

Anatomical change of tumor during radiotherapy contributes to target missing. However, in the case of tumor shrinkage, adaptation of volume could result in an increased incidence of recurrence in the area of target reduction. This study aims to investigate the incidence of failure of the adaptive approach and, in particular, the risk for local recurrence in the area excluded after replanning. Replanning was outlined in 50 patients selected from a total of 217 patients subjected to weekly simulation CT in our center from 2012 to 2014. The reduced toxicity and the documented low rate of marginal failures make the adaptive approach a modern option for future randomized studies.


Phase II study of induction chemotherapy followed by chemoradiotherapy in patients with borderline resectable and unresectable locally advanced pancreatic cancer.

There is not a clear consensus regarding the optimal treatment of locally advanced pancreatic disease. We evaluated the safety and efficacy of induction chemotherapy with oxaliplatin and gemcitabine followed by a high weekly dose of gemcitabine concurrent to radiation therapy. In our study, 41 patients with pancreatic cancer were evaluated. This is a well-tolerated promising approach. Fifteen patients (55.5%) underwent surgical radical resection. With a median follow-up of 20 months, the median PFS and OS were 20 months and 19.2 months, respectively. Continued optimization in multimodality therapy and an accurate patient selection remain crucial points.
**Tissue Engineering & Chemistry for Engineering**

**Head** M. Trombetta  
**Faculty** F. Basoli, A. Rainer  
**Other Personnel** F. Abbruzzese, M. Costantini, S.M. Giannitelli, M. Gori

**Description**

The Tissue Engineering and Chemistry for Engineering Research Unit works mainly on the following fields:

**Tissue engineering:** the Unit works on the synthesis and functionalization of biomaterials and manufacturing of scaffolds for regenerative medicine application. The Unit also develops advanced in vitro tissue and organ models for drug discovery and morphogenesis/pathogenesis studies. In particular, one of the most promising research lines is focused on the integration of micro-manufacturing technologies with tissue engineering ones, designed to miniaturize organ models to be combined with advanced imaging and spectroscopy techniques (organ-on-chip approach). At present, the Research Unit is involved in a Joint Laboratory for Nanotechnologies for the Life Sciences (nano4life), together with the Institute of Photonics and Nanotechnologies, National Research Council of Rome.

**Nanomaterials for energy:** sulphur, carbon and re-oxidation tolerant Solid Oxide Fuel Cells (SOFC) anodes.

**Food crime:** development of e-learning platforms to train Europol officers on food crime.

**Critical Infrastructure Protection:** creating added-value, decision-support capabilities with consequence analysis for national and multi-nation emergency management and CI owners.

**Main research activities**

Dr. Alberto Rainer has been awarded a research grant in the framework of the Internal Grant Program for the project “GUT2.0 - A multi-cellular ‘gut-on-chip’ technology for predictive human safety testing: an integrated experimental and modeling approach”. GUT 2.0 foresees the application of an organ-on-chip model in the field of predictive safety. The approach proposed by the present method represents a significant advance in the field of in vitro models, as we foresee to recapitulate, within the ‘chip’ footprint, a multicellular gut environment. This approach re-presents an increased level of complexity if compared with the in vitro toxicological models for the intestine. Hence, its development should provide the necessary degree of interplay among different cell populations for a robust safety testing model.

Prof. Marcella Trombetta is National Coordinator of a PRIN2012 project entitled “aCTion - Cells-on-chip technologies for the study of the endocannabinoid system in an in vitro model of tumor/immune system interaction”. The project aims to develop advanced models for the in vitro study of cellular interactions, taking advantage from 3D co-culture technologies within microfluidic devices. In particular, the on-chip technologies will be applied to a model of tumor stem compartment to study its interaction with immune system cells) to investigate the role of the endocannabinoid system in the crosstalk between the two populations.

Prof. Marcella Trombetta is Scientific Coordinator and Leader of the Operational Activity 4.10 “BACCUS Class: an e-learning platform for training law enforcement officers to combat food crime” of the Europol project coordinated by Carabinieri NAS “ASKLEPIOS-Actions on food Supplements, fake genuine (not) food exhibition, e-Learning platform, action on Pesticides, operation “In Our Sites” and JAD” funded by EU Commission- Europol for the EMPACT activities under the OAP Counterfeit Goods. Prof. Marcella Trombetta is partner of the project CIPR-Net, Critical Infrastructure Research and Resilience Network Co-funded by EU FP7. CIPRNet establishes a Network of Excellence in Critical Infrastructure Protection (CIP). CIPRNet performs research and development that addresses a wide range of stakeholders including (multi) national emergency management, critical infrastructure operators, policy makers, and the society.

**Most important publications**

Testa S., Costantini M., Fornetti E., Bernardini S., Trombetta M., Seliktar D., Cannata S., Rainer A., Gargioli C.v

**Combination of biochemical and mechanical cues for tendon tissue engineering.**  

Tendinopathies negatively affect the life quality of millions of people in occupational and athletic settings, as well as the general population. Tendon healing is a slow process, often with insufficient results to restore complete endurance and functionality of the tissue. Tissue engine-
Research Units

Costantini M., Testa S., Mozetic P., Barbetta A., Fuoco C., Fornetti E., Tamiro F., Bernardini S., Jaroszewicz J., Święszkowski W., Trombetta M., Castagnoli L., Seliktar D., Garstecki P., Cesareni G., Cannata S., Rainer A., Gargioli C.

Microfluidic-enhanced 3D bioprinting of aligned myoblast-laden hydrogels leads to functionally organized myofibers in vitro and in vivo.


We present a new strategy for the fabrication of artificial skeletal muscle tissue with functional morphologies based on an innovative 3D bioprinting approach. The methodology is based on a microfluidic printing head coupled to a co-axial needle extruder for high-resolution 3D bioprinting of hydrogel fibers laden with muscle precursor cells (C2C12). To promote myogenic differentiation, we formulated a tailored bioink with a photocurable semi-synthetic biopolymer (PEG-Fibrinogen) encapsulating cells into 3D constructs composed of aligned hydrogel fibers. After 3-5 days of culture, the encapsulated myoblasts started migrating and fusing, forming multinucleated myotubes within the 3D bioprinted fibers. The obtained myotubes showed high degree of alignment along the direction of hydrogel fiber deposition, further revealing maturation, sarcomerogenesis, and functionality. Following subcutaneous implantation in the back of immunocompromised mice, bioprinted constructs generated organized artificial muscle tissue in vivo. Finally, we demonstrate that our microfluidic printing head allows to design three dimensional multi-cellular assemblies with an exquisite compartmentalization of the encapsulated cells. Our results demonstrate an enhanced myogenic differentiation with the formation of parallel aligned long-range myotubes. The approach that we report here represents a novel approach for tendon tissue engineering, demonstrating how the combined effect of biochemical and mechanical stimuli ameliorates biological and mechanical properties of the artificial tissue compared to those obtained with single inducement.


Combining type I interferons and 5-Aza-2'-Deoxycytidine to improve anti-tumor response against melanoma.


Resistance to IFN-I-induced antineoplastic effects has been reported in many tumors and arises, in part, from epigenetic silencing of IFN-stimulated genes by DNA methylation. We hypothesized that restoration of IFN-stimulated genes by co-administration of the demethylating drug 5-aza-2'-deoxycytidine (decitabine [DAC]) may enhance the susceptibility to IFN-I-mediated antitumoral effects in melanoma. We show that combined administration of IFN-I and DAC significantly inhibits the growth of murine and human melanoma cells, both in vitro and in vivo. Compared with controls, DAC/IFN-I-treated melanoma cells exhibited reduced cell growth, augmented apoptosis, and diminished migration. Moreover, IFN-I and DAC synergized to suppress the growth of three-dimensional human melanoma spheroids, altering tumor architecture. These direct antitumor effects correlated with induction of the IFN-stimulated gene Mx1. In vivo, DAC/IFN-I significantly reduced melanoma growth via stimulation of adaptive immunity, promoting tumor-infiltrating CD8+ T cells while inhibiting the homing of immunosuppressive CD11b+ myeloid cells and regulatory T cells. Accordingly, exposure of human melanoma cells to DAC/IFN-I induced the recruitment of immune cells toward the tumor in a Matrigel (Corning Life Sciences, Kennebunkport, ME)-based microfluidic device. Our findings underscore a beneficial effect of DAC plus IFN-I combined treatment against melanoma through both direct and immune-mediated anti-tumor effects.
Urology

Head  G. Muto
Faculty  M. Buscarini, R. Papalia

Description
The research unit of urology is mainly focused on clinical research. Minimally invasive surgery, modern source of energy in the treatment of BPH and bladder cancers urinary diversions with sexual function preservation are the main field of interest.

Main research activities
- Keap1/Nrf2 pathway in kidney cancer: Frequent methylation of KEAP1 gene promoter in clear renal cell carcinoma
- Pros-IT CNR: an Italian prostate cancer monitoring project
- Multiparametric magnetic resonance imaging of the prostate with computer-aided detection: experienced observer performance study
- Integrated Biosensor Assay for Rapid Uropathogen Identification and Phenotypic Antimicrobial Susceptibility Testing
- Anterior colporrhaphy plus inside-out tension-free vaginal tape for associated stress urinary incontinence and cystocele: 10-year follow up results
- Oncological outcomes of minimally invasive partial versus minimally invasive radical nephrectomy for cT1-2/N0/M0 clear cell renal cell carcinoma: a propensity score-matched analysis

Most important publications

Keap1/Nrf2 pathway in kidney cancer: frequent methylation of KEAP1 gene promoter in clear renal cell carcinoma.

The Keap1/Nrf2 pathway is a master regulator of the cellular redox state through the induction of several antioxidant defence genes implicated in chemotherapeutic drugs resistance of tumor cells. An increasing body of evidence supports a key role for Keap1/Nrf2 pathway in kidney diseases and renal cell carcinoma (RCC), but data concerning the molecular basis and the clinical effect of its deregulation remain incomplete. Here we present a molecular profiling of the KEAP1 and NFE2L2 genes in five different Renal Cell Carcinoma histotypes by analysing 89 tumor/normal paired tissues (clear cell Renal Carcinoma, ccRCCs; Oncocytomas; Papillary Renal Cell Carcinoma Type 1, PRCC1; Papillary Renal Cell Carcinoma Type 2, PRCC2; and Chromophobe Cell Carcinoma). A tumor-specific DNA methylation of the KEAP1 gene promoter region was found as a specific feature of the ccRCC subtype (18/37, 48.6%) and a direct correlation with mRNA levels was confirmed by in vitro 5-azacytidine treatment. Analysis of an independent data set of 481 ccRCC and 265 PRCC tumors corroborates our results and multivariate analysis reveals a significant correlation among ccRCCs epigenetic KEAP1 silencing and staging, grading and overall survival. Our molecular results show for the first time the epigenetic silencing of KEAP1 promoter as the leading mechanism for modulation of KEAP1 expression in ccRCCs and corroborate the driver role of Keap1/Nrf2 axis deregulation with potential new function as independent epigenetic prognostic marker in renal cell carcinoma.
Giannini V., Mazzetti S., Armando E., Carabalona S., Russo F., Giacobbe A., Muto G., Regge D.

**Multiparametric magnetic resonance imaging of the prostate with computer-aided detection: experienced observer performance study.**

**Objectives:** To compare the performance of experienced readers in detecting prostate cancer (PCa) using likelihood maps generated by a CAD system with that of unassisted interpretation of multiparametric magnetic resonance imaging (mp-MRI).

**Methods:** Three experienced radiologists reviewed mp-MRI prostate cases twice. First, readers observed CAD marks on a likelihood map and classified as positive those suspicious for cancer. After 6 weeks, radiologists interpreted mp-MRI examinations unassisted, using their favourite protocol. Sensitivity, specificity, reading time and interobserver variability were compared for the two reading paradigms.

**Results:** The dataset comprised 89 subjects of whom 35 with at least one significant PCa. Sensitivity was 80.9% (95% CI 72.1-88.0%) and 87.6% (95% CI 79.8-93.2; p = 0.105) for unassisted and CAD paradigm respectively. Sensitivity was higher with CAD for lesions with GS > 6 (91.3% vs 81.2%; p = 0.046) or diameter ≥10 mm (95.0% vs 80.0%; p = 0.006). Specificity was not affected by CAD. The average reading time with CAD was significantly lower (220 s vs 60 s; p < 0.001).

**Conclusions:** Experienced readers using likelihood maps generated by a CAD scheme can detect more patients with ≥10 mm PCa lesions than unassisted MRI interpretation; overall reporting time is shorter. To gain more insight into CAD-human interaction, different reading paradigms should be investigated.

**Key Points:** With CAD, sensitivity increases in patients with prostate tumours ≥10 mm and/or GS > 6. • CAD significantly reduces reporting time of multiparametric MRI. • When using CAD, a marginal increase of inter-reader agreement was observed.


**Pros-IT CNR: an Italian prostate cancer monitoring project.**

**Aims:** The Pros-IT CNR project aims to monitor a sample of Italian males ≥18 years of age who have been diagnosed in the participating centers with incident prostate cancer, by analyzing their clinical features, treatment protocols and outcome results in relation to quality of life.

**Methods:** Pros-IT CNR is an observational, prospective, multicenter study. The National Research Council (CNR), Neuroscience Institute, Aging Branch (Padua) is the promoting center. Ninety-seven Italian centers located throughout Italy were involved. The field study began in September 1, 2014. Subjects eligible were diagnosed with biopsy-verified prostate cancer, naive. A sample size of 1500 patients was contemplated. A baseline assessment including anamnestic data, clinical history, risk factors, the initial diagnosis, cancer staging information and quality of life (Italian UCLA Prostate Cancer Index; SF-12 Scale) was completed. Six months after the initial diagnosis, a second assessment evaluating the patient’s health status, the treatment carried out, and the quality of life will be made. A third assessment, evaluating the treatment follow-up and the quality of life, will be made 12 months after the initial diagnosis. The 4th, 5th, 6th and 7th assessments, similar to the third, will be completed 24, 36, 48 and 60 months after the initial diagnosis, respectively, and will include also a Food Frequency Questionnaire and the Physical Activity Scale for the Elderly.

**Discussion:** The study will provide information on patients’ quality of life and its variations over time in relation to the treatments received for the prostate cancer.
Our interests focus on all the aspects of arterial surgery, from the carotid artery endarterectomy/bypass for prevention of cerebral ischemia, down to the plantar revascularization for limb salvage, through all the diseases of the aorta. When endovascular treatment is the best choice for the patient, it strictly follows the Instructions for Use from the manufacturer. Large vessels reconstruction after tumor resection is one of our specific interest.

Main research activities

Decision making impacts on survival in Critical Limb Ischemia.

We already showed that the Endovascular technique and open bypass are complementary in treatment of CLI, as these apply to different patterns of disease. While the majority of patients with rest pain can be successfully treated by endovascular techniques despite the TASC II class, those with advanced necrosis and tissue loss are best treated by an open bypass whenever possible. In the last year we could update our series and refine our ultrasound-based decision algorithm. The significant improvement of late survival of our patients, compared to most of the current series, confirmed the value of this approach.

EVAR: How to make open conversion after supra renal grafts a safe operation.

EV treatment of endoleaks is not always possible, and an open conversion is occasionally needed. In the case of suprarenal grafts this can be a hazardous procedure. Following the principle of minimally invasive laparotomic aneurysm repair, we propose a technique to make open conversion safer, avoiding the removal of the whole suprarenal graft. This is based on the following principles:
1. Clamp the aorta horizontally, flush to the renal arteries, without mobilizing the endograft.
2. Open the sac and clamp the iliac branches by soft jaw external clamps close to the aortic bifurcation.
3. Divide the graft 5 to 10 millimetres below the proximal clamp, and divide the iliac branches inside the sac as distal as possible. The metallic struts can be sectioned by a steel wire cutter. Remove the central part of the graft, leaving the aortic and iliac stumps in place.
4. Clear the thrombus and oversaw the lumbar arteries.
5. Pass a teflon felt band around the aorta near the proximal clamp and implant a new bifurcation graft by sawing the residual inner endograft, the native aortic wall and the external teflon band altogether in order to obtain a firm and secure proximal anastomosis, double reinforced by the internal endograft and the external felt, without removing the suprarenal stent.
6. Anastomose the iliacs to the residual iliac endografts and close the sac.

By avoiding the need to gain distal control, a mini laparotomy is fully adequate, and the patient can benefit of this less invasive technique.

In the last two years we treated eleven patients without complications, a mean blood loss of 380 ml, and a mean postoperative hospital stay of 5 days.

Restenosis after CEA: carotid graft versus CAS.

Restenosis after CEA is currently treated by CAS. Late reports have shown suboptimal late results. We already reported our series of carotid restenosis treated by a carotid vein graft in patients with a long life expectancy. We have updated our series with the late controls favoring this option versus CAS.

Endovascular and Open treatment of aortic embolism causing distal disease.

Critical limb ischemia due to aortic atheroembolism is not as rare as it is currently believed. This is an insidious disease and if unrecognized can be at the origin of failures of treatment and bad outcomes. An endovascular aortic coverage, coupled with a femoral to popliteal or tibial graft seems to be a durable solution. We reviewed our series of such hybrid procedures, and described the diagnostic workflow, technique and results.
Elongation, coils, and kinks of carotid vessels are rare conditions, and these are often asymptomatic. Rarely, kinking may provide functional symptoms, requiring surgical correction. We report an unusual case of internal carotid artery kinking causing pharynx compression with dysphagia. Patient underwent carotid-carotid bypass graft. His dysphagic symptom improved markedly at 1-month follow-up control.

Stilo F., Sirignano P., Montelione N., Mansour W., Capocchia L., Catanese V., Spinelli F., Speziale F.

**Bypass for symptomatic in-stent carotid restenosis.**


**Methods:** Data were retrospectively collected from a prospectively compiled database on patients treated with CB in two high-volume Italian centers between 2008 and 2016, for symptomatic high-grade ISR after CAS. After carotid endarterectomy and stent removal, a greater saphenous vein (GSV) was preferentially employed as the graft; when the GSV was not accessible, a 6mm polytetrafluoroethylene (PTFE) graft was implanted. Standard follow-up protocol included clinical examinations, duplex scans (DUS) and computed tomographic angiography. Measures considered for analysis were perioperative (30-day) and long-term occurrence of new ipsilateral cerebral events, neurological deficits, death from all causes, and needs for reintervention. In addition, peripheral nerve palsy, cervical hematomas, and other local complications after surgery were noted. **Results:** The population of the study comprised 13 patients (11 men and two women; median age was 66.5years (range 56-88)). Mean times from index CAS to stent explantation were 38.9±18.2months. GSV grafts were used in seven cases (53.8%) and PTFE grafts in the remaining six (46.2%) cases. Intraoperative neurological complications rate was null. One patient presented a transient dysphagia. At 30-day, no new neurological complications, reinterventions or deaths occurred. At mean follow-up of 41.2±18.2months, three patients died in absence of further neurological events. None of the CB patients required reintervention. **Conclusions:** In our experience, CB offers satisfactory results in patients treated for symptomatic ISR with an acceptable risk of cranial nerve injury.


**Initial clinical experience with a polytetrafluoroethylene vascular dialysis graft reinforced with nitinol at the venous end.**


**Objective:** The purpose of this study was to examine the outcomes of a vascular hybrid polytetrafluoroethylene (PTFE) graft, provided with a nitinol-reinforced section (NRS) on one end, in hemodialysis vascular access placement.

**Methods:** A retrospective study was conducted including all the consecutive patients who underwent Gore Hybrid Vascular Graft (GHVG; W. L. Gore & Associates, Flagstaff, Ariz) implantation for hemodialysis access placement between October 2013 and November 2015. A propensity-matched control group was obtained from consecutive patients who underwent standard PTFE arteriovenous graft implantation between January 2010 and July 2013. The selection criteria were inadequate venous material for autogenous arteriovenous fistula placement, patent deep venous circulation, and vein diameter of 4 to 8.5 mm. The implantation technique involves the insertion of the NRS some centimeters into the target vein. Fluoroscopic guidance helps deploy the device in the desired landing zone (ie, position of the proximal end of the NRS), based on anatomic landmarks. Survival, functional patency rates, and complications were compared with a propensity-matched historical control group. Vein diameter, previous vascular access placement, and diabetes were tested as predictors of reintervention with a logistic regression analysis.

**Results:** There were 32 patients (14 men; mean age, 69 ± 14 years) who received the GHVG graft. The historical control group included 43 patients. Technical success was 100%. The graft configuration was brachial-axillary (n = 22 [69%]), brachial-basilic loop (n = 5 [16%]), brachial-an-tecubital loop (n = 3 [9%]), axilloaxillary loop (n = 1 [3%]), and femoral-femoral loop (n = 1 [3%]). Mean NRS oversize was 20% ± 7% (range, 3%-34%; median, 19%). Perioperative complications requiring revision included acute limb ischemia treated with thrombectomy (n = 1 [3%]) and graft infection requiring explantation (n = 2 [6%]). Two patients (6%) died in the hospital of unrelated causes. The mean follow-up was 15 ± 11 months (range, 0-33 months; median, 15.5). The propensity-matched groups included 25 patients each. Survival estimates at 24 months for the GHVG and standard PTFE groups were 91% ± 6% and 82% ± 9% (P > .05), respectively. The 12-month patency estimates were as follows: functional primary patency, 66% ± 10% vs 51% ± 10% (P > .05); functional assisted primary patency, 75% ± 9% vs 51% ± 10% (P > .05); and functional secondary patency, 79% ± 9% vs 67% ± 10% (P > .05). Reduction in vein diameter was associated with reintervention.

**Conclusions:** The GHVG is a safe and effective alternative to standard PTFE in hemodialysis access surgery. Careful planning for the landing zone is advisable, especially for small outflow veins. Larger studies and randomized trials are needed to define the role for this device. A study including a greater number of centers experienced with this device is currently under way.
Virology

Head  E. Riva

Other Personnel  L. Piccioni

Description

The Virology Research Unit is involved in both basic and clinical virology. Thesaurus main topics concern host’s and viral factors able to predict the outcome and the treatment response of persistent viral infections such as HCV infection (in terms of Progression and treatment response), CMV infection (in terms of reactivation and clinical progression in transplanted recipients) and HPV infections (in terms of HPV-related dysplasia progression).

Based on the past and the more recent experience, the Virology research staff is mainly involved in the field of molecular virology and in assays useful in identifying specific Single nucleotide polymorphisms (SNPs) such as Real Time PCR, Melting and Pyrosequencing analysis.

Main research activities

The specific SNPs that have been understudy are mainly rs12979860, rs8099917, ss46945590 TT/delta G SNPs in Interferon lamda III-IV region. These SNP are mainly involved in host’s innate immunity and in treatment response in chronic infectious diseases.

The Unit has been also involved in the comparison and validation of molecular methods applied for persistent virus (CMV, HCV, EBV and parvovirus) and emergent/acute infections (Chikungunya, respiratory viruses).

All these topics are addressed in ongoing studies, which involve different areas of Campus Bio-Medico University Hospital.

The team acts also in the contest of the project “Migrant and Health” aimed to prevent and monitoring infectious diseases in Migrants.

The Virology Unit is also in close collaboration with the Department of Molecular Medicine -Virology section-“Sapienza” University of Rome, AIFA/EMA and with the Virology Lab of Ospedale Pediatrico “Bambino Gesù” of Rome.

Main collaborations

- Department of Molecular Medicine -Virology section. Sapienza University, Rome, Italy;
- European Medicines Agency;
- Italian Medicines Agency (AIFA), Italy;
- Virology Lab. “Bambino Gesù” Paediatric Hospital, Italy.
**Most important publications**

Dianzani C., Paolini F., Conforti C., Riva E., Beninati E., Venuti A.

**Human papilloma virus expression in immunocompetent patients with actinic keratosis: A case series.**


Actinic keratosis (AK) is a common skin disease that can develop into squamous cell carcinoma (SCC). Previous studies showed that human papilloma virus (HPV) skin infection might be related to an increased risk for AK and SCC in immunosuppressed patients. The purpose of this study was to detect the presence and the expression of this virus in the AK lesions of immunocompetent patients. Fresh samples of AK lesions and healthy skin were collected from 40 immunocompetent patients. The rates of HPV positivity for AK lesions and healthy samples were 88.8% and 62%, respectively, with a statistically significant difference (*P* <0.0051). We detected many different HPV genotypes; the most commonly found types were HPV 36 and HPV 107 in AK lesions and healthy skin, respectively. These HPV types were previously reported to be highly frequent in normal and lesional skin, suggesting that different HPV types might be associated with different levels of risk for cutaneous lesions. Our results are an important contribution to the hypothesis that HPV might be involved in the pathogenesis of AK. To the best of our knowledge, this is the first report describing the presence of viral transcripts in immunocompetent patients, a finding that strongly supports the hypothesis that beta-HPVs are actively involved in the early stage of skin carcinogenesis.
Research Projects
EUROPEAN COMMISSION

AIDE
Adaptive Multimodal Interfaces to Assist Disabled People in Daily Activities

Url: http://www.aideproject.eu/
Coordinator: Universidad Miguel Hernández
Partners: Sant’Anna School of Advanced Studies, Campus Bio-Medico University of Rome (Research Unit of Biomedical Robotics and Biomicrosystems), Universidad Politécnica de Valencia, University of Tübingen, Cedar Foundation, Zed Worldwide S.A., Fraunhofer-Gesellschaft zur Förderung der angewandten Forschung e.V., B&J Adaptaciones
Funded under: H2020-ICT
End: 31/01/2018
Contacts: Loredana Zollo (l.zollo@unicampus.it), Research Unit of Biomedical Robotics and Biomicrosystems

The AIDE project has the ambition to strongly contribute to the improvement of the user technology interface by developing and testing a revolutionary modular and adaptive multimodal interface customizable to the individual needs of people with disabilities. Furthermore, the project will focus on the development of a totally new shared-control paradigm for assistive devices that merges together information on the user’s residual abilities, behavior, emotional state and intentions with information about the environment and context factors. UCBM is responsible for the design of a modular architecture supporting the development of the multi-modal interface and for the design and development of a shared control for the assistive device based on reinforcement learning. Moreover, UCBM will be involved in: (i) definition of the experimental scenario, (ii) identification of user needs, (iii) characterization of the AIDE system and (iv) experimental validation of the AIDE system on end-users, in collaboration with “Centro Protesi INAIL” of Budrio.

EU-AIMS
European Autism Interventions – A Multicentre Study for Developing New Medications

Url: http://www.eu-aims.eu/
Coordinator: Roche
Partners: King’s College London, Central Institute of Mental Health Mannheim, Radboud University, Cambridge University, deCODE Genetics, University Medical Centre, Universität Basel, Institut Pasteur, GABO:mi, Max-Planck Institute of Experimental Medicine, European Molecular, Biology Laboratory, NeuroSearch, Karolinska Institutet, Eli Lilly and Company Ltd., Janssen, Pharmaceutica, Institut de Recherches Servier, Vifor Pharma, Birkbeck College, Institute of Education, Campus Bio-Medico University of Rome (Research Unit of Molecular Psychiatry and Neurogenetics), Autism Speaks, Pfizer, CEA, Universität Ulm
Funded under: Innovative Medicine Initiatives
End: 31/03/2017
Contacts: Antonio Persico (a.persico@unicampus.it)

The main project objectives are development and validation of translational approaches for the advancement of novel therapies to treat ASD, setting new standards in research and clinical development to aid the drug discovery process, Identification and development of expert clinical sites across Europe to run clinical studies and trials, and the creation of an interactive platform for ASD professionals and patients. UCBM contributes to establish biomarkers of the autism phenotype.
**RESHAPE**  
Restoring the Self with Embodiable Hand Prostheses

**Principal Investigator:** Dr. Giovanni Di Pino, Campus Bio-Medico University of Rome  
**Funding under:** ERC-StG-2015 - ERC Starting Grant  
**End:** 31/08/2021  
**Contacts:** Giovanni Di Pino (g.dipino@unicampus.it), Research Unit of Neurophysiology and Neuroengineering of Human-Technology Interaction

RESHAPE aims to study prosthesis embodiment, identify what makes a hand prosthesis easily embodi-able, and test non-invasive brain stimulation to facilit-ate the embodiment.  
The first of three phases develops the enabling tech-nology and defines the embodiment protocol.  
The following phase evaluates thirty myoelectric-prosthesis users and the first of two amputees implanted with peripheral neural electrodes, for functional abili-ty, prosthesis embodiment and acceptability and for phantom limb pain (PLP), before and after neuro- modulation.  
In the last phase, a neuro-controlled prosthesis is opt-imized in line with the specifications defined in the previous phase and tested in the second implanted amputee.  
Patients are stimulated with a homeostatic plasticity-based rTMS either on premotor cortex or on intraparietal sulcus. A robot-aided TMS compensates head-coil relative displacement, allowing the subject to operate the prosthesis during the stimulation.

**RESPINE**  
Regenerative therapy of intervertebral disc: a double blind phase 2b trial of intradiscal injection of mesenchymal stromal cells in degenerative disc disease of the lomber spine unresponsive to conventional therapy

**Coordinator:** Centre Hospitalier Universitaire Montpellier  
**Partners:** Campus Bio-Medico University of Rome, Universidad De Navarra, Universidad De Valladolid, Univercell-Biosolutions, National University Of Ireland, Galway, Citospin S.L., Institut De Terapia Regenerativa Tisular Sl, Assistance Publique - Hôpitaux De Paris, Centre Hospitalier Universitaire De Nantes, Centre National De La Recherche Scientifique (CNRS), Ecrin European Clinical Research Infrastructure Network, Bg Klinikum Bergmannstrost Halle Gmbh, Universite De Montpellier  
**Funding under:** H2020-SC1-2016-RTD  
**End:** 31/12/2020  
**Contacts:** Gianluca Vadalà (g.vadala@unicampus.it), Research Unit of Orthopaedic and Trauma Surgery

The World Health Organisation (WHO) has included low back pain in its list of twelve priority diseases. Notably, Degenerative disc disease (DDD) presents a large, unmet medical need that results in a disabling loss of mechanical function. To develop the world’s first rigorously proven, effective treatment of DDD, RESPINE aims to assess, via a multicentre, randomized, controlled, phase 2b clinical trial including 112 patients with DDD, the efficacy of an allogeneic intervertebral mesenchymal stem cell (MSC)-based therapy. This innovative therapy aims to rapidly (within 3 months) and sustainably (at least 24 months) reduce pain and disability. In addition, the consortium aims to provide new knowledge on immune response & safety associated with allogeneic BM-MSC intradiscal injection. This simple procedure would be cost-effective, minimally invasive, and standardised.

**CONVERGENCE**  
Frictionless Energy Efficient Convergent Wearables for Healthcare and Lifestyle Applications

**Url:** https://www.convergence-era.org/  
**Coordinator:** Ecole Polytechnique Fédérale de Lausanne (EPFL)  
**Partners:** Campus Bio-Medico University of Rome, CEA LETI – Laboratoire d’Electronique et de Technologie de l’Information, Elektronikas un datorzinatnu instituts/Signal Processing Lab, Italian National Agency for New Technologies, Energy and Sustainable Economic (ENEA), ETHZ Eidgenössische Technische Hochschule Zürich / Department of Mechanical and Process Engineering, Institut Polytechnique de Grenoble, Hirslanden Clinic Cecil/Cardiovascular Center, Consorzio Nazionale Interuniversitario Per La Nano-elettronica (UNET), Middle East Technical University, National Institute for R&D in Microtechnologies/Laboratory of Microsystems for Biomedical & Environmental Applications, ST Microelectronics, TAGLIAFERRI Società Responsabilità Limitata, Tallinn University of
The project adopts a focused strategy centred on proofs-of-concepts related to energy efficient sensor networks for future wearables exploiting the convergence of multi-parameter biosensors and environmental sensors on an autonomous system technology platform, serving data fusion for preventive life-style and healthcare. We connect solidly a critical mass of research institutions in-between and to some end user, to set the foundation of future emerging research project in this field, at European level by connecting national competences and resources.

ITALIAN MINISTRY OF EDUCATION, UNIVERSITY AND RESEARCH

PRIN (Research Projects of National Interest) 2012

Cells-on-chip technologies for the study of the endocannabinoid system in an in vitro model of tumor/immune system interaction

Coordinator: Marcella Trombetta – Research Unit of Tissue Engineering and Chemistry for Engineering (UCBM),
Partners: Research Unit of Oncology (UCBM), Research Unit of Biochemistry and Molecular Biology (UCBM), National Research Council, University of Rome “Tor Vergata”

Mechanical measurements for the musculoskeletal apparatus: novel and standardizable methodologies for metrological assessment of measurement systems

Coordinator: Sapienza University

Partners: Research Unit of Measurements and Biomedical Instrumentation (UCBM), University “Roma Tre”

PRIN (Research Projects of National Interest) 2015

Adaptation and tolerance of plants to climate change-dependent abiotic stresses

Coordinator: Università di Milano
Partners: Research Unit of Food Science and Nutrition (UCBM), Università degli studi di Padova, Scuola Superiore di Studi Universitari e Perfezionamento Sant’Anna

Endocannabinoid Signaling in Alzheimer’s Disease: A Novel Target for Mechanistic Understanding and Potential Therapeutics

Coordinator: Mauro Maccarrone - Research Unit of biochemistry and molecular biology (UCBM)
Partners: Consiglio Nazionale delle Ricerche, Università degli Studi di Roma “La Sapienza”, Università degli Studi di Roma “Tor Vergata” Università degli Studi di Teramo

Pancreatic β-cell identity, glucose sensing and the control of insulin secretion

Coordinator: Paolo Pozzilli - Research Unit of endocrinology and diabetes
Partners: Università degli Studi di Verona, Università degli Studi di Catania, Università degli Studi di Parma, Università degli Studi di Roma “La Sapienza, Università Cattolica del Sacro Cuore, Università degli Studi di Siena, Università di PISA, Università degli Studi di Roma “Tor Vergata”, Libera Università “Vita Salute S. Raffaele” Milano

FARE ERC
ENABLE - Empowering Novel Augmentation of Limb Embodiment

Principal Investigator: Dr. Giovanni Di Pino, Campus Bio-Medico University of Rome
ITALIAN MINISTRY OF HEALTH
FINALISED RESEARCH

GR Ordinary 2011-2012
Daily at-home follow-up of Parkinson’s disease patients motor performance through robotic and portable devices
Coordinator: IRCCS San Raffaele Pisana
Partners: Research Unit of Neurology, Neurophysiology, Neurobiology (UCBM), Research Unit of Biomedical Robotics and Biomicrosystems (UCBM), IRCCS San Raffaele Pisana

Cross Sectional study to evaluate the interactions between gut microflora and immune system at the cross-road of the pathogenesis of Inflammatory Bowel Diseases and Irritable Bowel Syndrome
Coordinator: Istituto Superiore di Sanità
Partners: Research Unit of Gastroenterology (UCBM), Research Unit of Clinical Laboratory Sciences (UCBM), Istituto Superiore di Sanità, University of Roma “Tor Vergata”

Exploiting the Protein Corona effect for biomarker discovery and targeting of nanomedicines in pancreatic cancer
Coordinator: IRCCS Regina Elena (IFO-IRE)
Partners: Research Unit of General Surgery (UCBM), IRCCS Regina Elena, (IFO-IRE), Catholic University of the Sacred Heart

RF Ordinary 2011-2012
Cell-on-Chip technology as a novel tool to investigate the crosstalk between cancer and immune cell: role of the transcription factors Interferon Regulatory Factor 1 and 8 (IRF1, IRF8) in melanoma as a model system
Coordinator: Istituto Superiore di Sanità
Partner: Research Unit of Clinical Laboratory Sciences (UCBM), Research Unit of Tissue Engineering and Chemistry for Engineering (UCBM), Istituto Superiore di Sanità, National Research Council

RF – Network Project 2013
Italian autism spectrum disorders network: filling the gaps in the National Health Care System
Coordinator: Istituto Superiore di Sanità
Partners: Research Unit of Molecular Psychiatry and Neurogenetics (UCBM), IRCCS Eugenio Medea – Associazione La Nostra Famiglia, Fondazione Stella Maris, Bambino Gesù

RF Industrial Co-Financing 2013
Extremely low frequency magnetic field (ELF-MF) stimulation as a neuroprotective treatment in acute ischemic stroke
Coordinator: UCBM
Partners: Research Unit of Neurology, Neurophysiology, Neurobiology (UCBM), IGEA S.p.A.

GR Ordinary 2013
Coordinator: Santa Lucia Foundation
Partners: Research Unit of Neurology, Neurophysiology, Neurobiology (UCBM), Sapienza University, Rome

PE-Italian Researchers Abroad 2011-2012
Clinical and Genetic characterization of early complications in Juvenile Obesity
Coordinator: Bambino Gesù Paediatric Hospital
Partners: Research Unit of Endocrinology and Diabetes (UCBM), Washington University School of Medicine - Jewish Hospital of St. Louis
ITALIAN MINISTRY OF ECONOMIC DEVELOPMENT

B³ - Bioscience, Patents and Business – Exploitation of research in the bioscience sector through knowledge transfer, human resources development and industrial properties transfer.
Coordinator: UCBM

INAIL BRIC

Bio-cooperative robotic system for upper-limb rehabilitation in working contexts
Coordinator: Research Unit of Biomedical Robotics and Biomicrosystems (UCBM)

SmartBench - Smart Industrial Safety Workbench
Coordinator: University of Rome “Tor Vergata”
Partner: Research Unit of Automation and Control Theory (UCBM), University of Salento, University of Bologna, University of Messina

LAZIO REGIONAL AUTHORITY

INTESE – Innovation and Technology transfer to support exploitation of research results
Coordinator: UCBM

HEREMOS – HEalth REmote MOonitoring System
Coordinator: RDSLAB srl
Partners: Research Unit of Measurements and Biomedical Instrumentation (UCBM)

OTHER GRANTS

A novel approach to identify COPD phenotypes, forecast clinical course and plan the therapeutic strategy
Funding Body: Fondazione Roma

Coordinator: Research Unit of Geriatrics (UCBM)
Partner: Research Unit of Diagnostic Imaging (UCBM), Research Unit of Electronics for Sensor Systems (UCBM), Research Unit of Computer System and Bioinformatics (UCBM).

Evaluation of corneal innervation as a new tool to detect autonomic neuropathy in diabetes
Funding Body: Fondazione Roma
Coordinator: Research Unit of Endocrinology and Diabetes (UCBM)
Partner: Research Unit of Ophthalmology (UCBM), Sapienza University.

Reaching, posture, object exploration, and language in high and low risk infants
Funding Body: National Institutes of Health
Coordinator: University of Pittsburgh, USA
Partners: Research Unit of Developmental Neuroscience (UCBM)

VIOLIN – Valorization of Italian products deriving from Oliva through innovative analytical techniques
Funding Body: Fondazione Cariplo
Coordinator: University of Messina
Partners: University of Rome La Sapienza, Alma Mater Studiorum University of Bologna, University of Turin, Edmund Mach Foundation, University of Sannio, University of Tuscia, University of Genoa, Campus Bio-Medico University of Rome, University of Bari, University of Verona.

Trial to reduce IDDM in the genetically at risk – study TRIGR
Funding Body: National Institutes of Health
Coordinator: University of Helsinki
Partners: Research Unit of Endocrinology and Diabetes (UCBM), University of Turku, The National Institute for Health and Welfare Helsinki, The Children’s Hospital at Westmead NSW Australia, Charles University Prague, University of Tartu Estonia, Kinder und Jugendkran-kenhaus Auf der Bult Hannover Germany, Sommelweis University Budapest, ASRIS ONLUS Cagliari, Centre Hospitalier de Luxembourg, Erasmus MC Sophia Rotterdam, University of Medicine in Wroclaw Poland, Hospital de Cruces University of Pais Vasco Spain, Hospital Clinico San Carlos Madrid, Linkoping University Sweden, University Children’s Hospital Zurich, Children’s Ho-
spital of Pittsburgh, University of South Florida, Robarts Research Institute, Canada

“SERISM: Role of the endocannabinoid system in reprogramming human pluripotent stem cells under microgravity”

**Funding Body:** ASI – Italian Space Agency  
**Partners:** Research Unit of Biochemistry and Molecular Biology (UCBM)

Interdisciplinary complex systems: theoretical physics methods in systems biology; Self-gravitating systems, galactic structures and galactic dynamics

**Funding Body:** ICRANet  
**Partners:** Research Unit of Non Linear Physics and Mathematical Modeling (UCBM), ICRA

Hearth Remote monitoring – COR

**Funding Body:** ASI – Italian Space Agency  
**Coordinator:** Altec S.p.A.  
**Partner:** Research Unit of Electronics for Sensor Systems (UCBM)

Posttranslationally modified insulin as target for therapy in type 1 diabetes

**Funding Body:** JDRF (Juvenile Diabetes Research Foundation)  
**Partner:** Research Unit of Endocrinology and Diabetes (UCBM)

Continuity of care for terminally ill patients: Data collection-Observation-Sperimentation (CA-IOS)

**Funding Body:** ENPAPI  
**Partners:** Research Unit of Nursing Science (UCBM)

Bio-Medical Humanities: un crocevia a servizio di idee umanizzanti

**Funding Body:** Fondazione Cattolica Assicurazioni  
**Partners:** Institute of Philosophy of Scientific and Technological Practice (FAST)

Antibodies to post-translationally modified insulin as biomarker of type 1 diabetes

**Funding Body:** EFSD (European Foundation for the Study of Diabetes), JDRF and Lilly  
**Partner:** Research Unit of Endocrinology and Diabetes (UCBM)  
**PI:** Rocky Strollo (Endocrinology and Diabetes, UCBM);  
**CoPI:** Ahuva Nissim (Queen Mary University of London);  
**CoPI:** Paolo Pozzilli (Endocrinology and Diabetes, UCBM)

**EFSD Mentorship Programme supported by AstraZeneca**

**Funding Body:** EASD (European Association for the Study of Diabetes e V.)  
**Partner:** Research Unit of Endocrinology and Diabetes (UCBM)

Evaluation of bone fragility in type 1 diabetes

**Funding Body:** SIOMMMS (Società Italiana dell’Osteoporoosi, del Metabolismo Minerale e delle Malattie dello Scheletro)  
**Partner:** Research Unit of Endocrinology and Diabetes (UCBM)  
**PI (Young investigator):** Rocky Strollo  
**Supervisor:** Nicola Napoli (Endocrinology and Diabetes, UCBM)

Use of computer support for the evaluation and monitoring of kinase inhibitors in the course of treatment for Chronic Lymphoid Leukemia and Lymphoma Follicular.

**Funding Body:** GILEAD Health Program  
**Partner:** Research Unit of Hematology, Stem Cell Transplantation, Transfusion Medicine And Cellular Therapy (UCBM)  
**PI:** Dr. Ombretta Annibali  
**Other Research Units involved:** Research Unit of Computer Systems and Bioinformatics (UCBM)

An Electronic and Optical Investigation of Highly Ordered Switchable Molecular Layers for Optical Memories and Storage Devices (HiOrSMoL)

**Funding Body:** Iscrac-Cineca HPC  
**Partner:** Research Unit of Nonlinear Physics and Ma-
A full atomistic computational study of the ion permeation in the human alpha7 nicotinic receptor. Acronym (IONLGIC)

**Funding Body:** Iscra-Cineca HPC Computational grant  
**Partner:** Research Unit of Nonlinear Physics and Mathematical Modeling (UCBM)

A full atomistic computational study of the active and inactive states of the human α7 nicotinic receptor

**Funding Body:** ICHEC-Irish Centre for High-End Computing HPC Computational grant  
**Partner:** Research Unit of Nonlinear Physics and Mathematical Modeling (UCBM)

Investigating AMyloid Flbrils mechanical properties via MUltiscale Simulations (AmFiMuS).

**Funding Body:** ISCRA-CINECA (National HPC Italian Center)  
**Pi:** Letizia Chiodo, Research Unit of Nonlinear Physics and Mathematical Modeling (UCBM)

STREET-OF-NY - Study of optoelecTRonic propErties of titanium dioxide nanosystEms in The frame OF the maNy body perturbation theorY

**Funding Body:** Computational grants awarded by PRACE (Partnership for Advanced Computing in Europe)  
**Pi:** Letizia Chiodo, Research Unit of Nonlinear Physics and Mathematical Modeling (UCBM)

MDNICO-Molecular dynamics study of ion permeation in wild-type and mutants of the human α7 nicotinic receptor

**Funding Body:** Computational grants awarded by PRACE (Partnership for Advanced Computing in Europe)  
**Pi:** Letizia Chiodo, Research Unit of Nonlinear Physics and Mathematical Modeling (UCBM)
Strategic University Projects

A competitive call has been launched in 2014 with the aims of enhancing the capabilities of UCBM Research Units to oversee and participate in the HORIZON 2020 European research programme, promoting synergy and collaboration between the Engineering and Medicine and Surgery Departments as well as promoting young researchers.

Three multidisciplinary projects lasting 2 years, coordinated by young researchers (under 40 years) have been funded (total funding: 500 K€uro) and started in April 2015. All the projects passed interim review, performed by qualified external reviewers, with good results.

The final results of the projects are described below.

Evaluation of bone strength and WNT pathway in obese patients

PI: Dr. Nicola Napoli, Research Unit of Endocrinology and Diabetes

Other Research Units involved: Orthopaedic and Trauma Surgery, Pathology, Geriatrics, Radiology, Biochemistry, Measurements and Biomedical Instrumentation.

Obesity, inflammation and sarcopenia may affect bone health of elderly subjects and this may be driven by WNT pathway. The aim of the project was to assess whether obesity is involved in bone fragility and to investigate the mechanisms. 68 obese and lean elderly women subjected to standard hip arthroplasty were enrolled. Blood, bone, muscle and adipose tissue samples were analyzed by ELISA, gene/protein expression, histomorphometry and biomechanical tests. Gene/protein analyses showed WNT decrease; adiponectin and osteocalcin were highly lowered in adipose tissue and bone of obese. Bone showed a normal mineralization and both biomechanics (Young’s modulus) and densitometry were not different in obese vs leans. Both inflammatory and bone turnover markers were not altered in obese, suggesting that serum levels may have some limitations. For the first time, these data provided evidence of a low bone formation at tissue level, which may be involved in bone impairment of elderly obese.

Figure 6 - Gene and protein expression analyses in the three tissues; data are represented as mean ± SEM. Unpaired t test was performed (P > 0.05) for comparison between groups. A) Gene expression analysis of osteocalcin in normal weight (black) and obese (grey) subjects; p=0.0423. B) Protein expression of adiponectin in adipose tissue of leans (black) and obese (grey), p=0.0186. C) Protein analysis of WNT5A in muscle in normal weight (black) and obese (grey) subjects, p=0.0438.
Smart surgical platform for the transpedicular delivery of advanced regenerative therapies into the intervertebral disc space

**PI:** Prof. Rocco Papalia, Research Unit of Orthopaedic and Trauma Surgery  
**Other Research Units involved:** Biomedical Robotics and Biomicrosystems, Neurology, Neurophysiology, Neurobiology

The START-Disc goals are: i) developing a smart surgical platform for the delivery of ATMPs to the intervertebral disc (IVD) through the transpedicular approach; ii) selection of biomaterials for closing the transpedicular tunnel and biological therapeutic products for IVD degeneration treatment.

The developed surgical platform is composed by: i) a mechanical support with 5 DoF for positioning and orienting the surgical tool; ii) an ultrasonic driller for deep hole into the bones that preserves the soft tissues; iii) a rotary drill to characterize the mechanical impedance of bone tissues and iv) a pressure sensor for intraoperative measuring the IVD pressure during the ATMPs delivery. The surgical platform has been tested on two human cadaver at AO Research Institute (Davos, CH).

The conducted drilling tests showed that the measured bone mechanical impedance is related with the bone density evaluated using post operative CT scan of human cadavers: the impedance and density values detected near the transition between bone layers are less than 10%.

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**A multi-cellular ‘gut-on-chip’ technology for predictive human safety testing: an integrated experimental and modeling approach.**

**PI:** Dr. Alberto Rainer, Research Unit of Tissue Engineering and Chemistry for Engineering  
**Other Research Units involved:** Gastroenterology, Nonlinear Physics and Mathematical Modeling, Microscopic and Ultrastructural Anatomy

The project “GUT2.0 - A multi-cellular ‘gut-on-chip’ technology for predictive human safety testing: an integrated experimental and modeling approach” aims at developing a microfluidic model of the intestine barrier for predictive safety testing. The project has successfully established a micro-actuated multi-axial stretchable microfluidic device [Gizzi et al. Scientific Reports, 2017] that has been tested in combination with human enterocytes. The project results also include the establishment of micro-engineered substrates (micro-pillar arrays) in PDMS elastomer to be used as force sensors for the measurement of cell contraction forces at the single cell level. Micro-pillar arrays represent an easy and scalable route for the achievement of high-throughput mechanobiological characterization of living cells.
Grant Program on Embodiment

This novel internal grant program has been started in 2016, and aims at fostering the collaboration between researchers of the “Istituto FAST” and other researchers who operate at UCBM. The grant program has been financed through an ad hoc grant from the “Associazione Campus Bio-Medico”. The general idea behind this grant program is that researchers who operate in humanistic fields (philosophy, epistemology, history, music, education, etc.) should have the possibility not only to investigate fundamental theoretical questions, but also to explore the biological implications of theoretical concepts, through a rigorous experimental paradigm, thanks to the collaboration with researchers in biology, medicine, engineering etc. The first theme chosen for the first round of grants is “Embodiment”. Three research projects have been selected among the research proposals that have been submitted. Each proposal has been evaluated by 3 different external experts. The 3 funded projects are described below.

Self-on-a-Chip: A Study of Embodiment in Innovative 3D Cell-Culture Models (SOAC)

PI: Marta Bertolaso
Other Research Units involved: Tissue Engineering and Chemistry for Engineering, Nonlinear Physics and Mathematical Modeling, Oncology

Cells-on-chip are in vitro models of biological micro-environments that combine co-culture protocols and microfluidic technologies: they consist in interconnected compartments linked through a microfluidic circulatory system. They allow a high degree of control over the experimental parameters, and the use of modern microscopy. The Campus Bio-Medico University of Rome hosts an interdisciplinary consortium working on cell chips for several research projects. The consortium is formed by: a Tissue Engineering Unit, a Translational Oncology Unit and a Non-linear Physics and Mathematical Modelling Unit. The experimental part of the project is building an on-chip model of tumor interaction with different immune cell populations. This innovative experimental model raises issues of several kinds: technical and methodological, theoretical, epistemological and philosophical. On these questions, the scientific units collaborate with a Unit of Philosophy of Scientific and Technological Practice and Philosophy of Biology to determine the quality of the new model as a proof of concept not only for the study of cancer and tissue organization, but also for the consideration of cell chips as dynamic embodied selves (“selves-on-chips”). Following the proposed science-philosophy interaction methodology, the different Research Units involved in the project had several discussion meetings that succeeded in creating a common language and mutual cross-fertilization. In parallel, the RUs pursued their specific research programs within the project. Under the lead of philosophers, the project clarified the technological and conceptual innovation potential of integrated microfluidic 3D cell culture devices (organ-on-a-chip), on the background of a historical framework comprising two different but intertwined narratives. The first is the technological history of cell culture, since Ross Harrison to the evolution of 2D cell culture devices, particularly the latest evolution within 3D cell culture from floating collagen gels to tissue engineering methods aimed at the fabrication of artificial organs for regenerative medicine. The merging of nano- and microfabrication technology paved the way to an unprecedented exploitation of the specific properties of the nanoscale to sculpt and dynamically control key aspects of cell and tissue microenvironment. This shift not only allowed to “break the in-vitro impasse”, eliciting more realistic and truly “embodied” material models, but came to converge with the breakthrough of “3D thinking” in cell biology.

The second narrative is the history of cell biology – that is of the conceptual frameworks underlying and coevolving with the technological advancements in tissue culture – where cell culture techniques played the alternate functions. From Ross Harrison original “holistic” endeavor, cell culture techniques were increasingly subservient, since the middle of XX Century, to the molecularization of biology, promoting the
isolation – and therefore “disembodiment” of parts (identified as autonomous causal factors) from body. The trend has inverted since the end of XX Century, and current vindications of microfluidic devices as the most adequate experimental systems for Systems Biology highlight the potential role of such models not only for their cost-effectiveness, high-throughput and automation potential, and for partly solving the scientific as well as bioethical challenges of animal testing, but also for addressing crucial theoretical issues of contemporary philosophy of biology.

Experimental activities carried out by the scientific RUs have been aimed at developing microfabricated devices for lab-on-a-chip applications, and at using those devices to build in vitro models of tissues and organs. The devices were obtained by means of electronic, optical and soft litography. The new models were the following:

- **a liver-on-a-chip model** able to recapitulate hepatic sinusoid physiology. The device was used to achieve an in vitro model of nonalcoholic fatty liver disease (NAFLD) onset.
- **a gut-on-a-chip model** characterized by a PDMN actuated porous membrane for culturing intestinal epithelium cells (enterocytes) in cyclical stress conditions. The device was designed in silico by means of finite elements analysis in non linear elastic field for large deformations. The material model was calibrated by stretching and compression tests; the most appropriate geometry was implemented by means of soft-litographic process, and the chip was validated micromechanically in operation. Biological validation is in progress.
- **a system of hydrodynamic traps for cell pairing**, i.e., the pairing of two cells with different phenotypes replicated in large numbers (>5000) within the device, to study phenomena such as the modulation of inflammation by mesenchymal stem cells. The device was used successfully in an early model of inflammation, and experiments are prosecuting in collaboration with Centro di Medicina Traslazionale dell’Ospedale St.Anne di Brno (CZ).

In collaboration with Istituto di Fotonica e Nanotecnologie – CNR and Istituto Superiore di Sanità, the project carried out epifluorescence time lapse microscopy campaigns on devices that simulate the tumor-immune system interface.

**Music: embodiment in action (MEDIA)**

**PI:** Nicola Di Stefano  
**Other Research Units involved:** Laboratory of Developmental Neuroscience, Research Unit of Biomedical Robotics and Biomicrosystems, Research Unit of Neurophysiology and Neuroengineering of Human-Technology Interaction

Today, listening to music is a fundamental aspect of our everyday life: we habitually use music to regulate, enhance, or simply change our emotional states. Looking back to the history of humanity, we can easily state that no culture lacks music and that making music appears to be one of the most transcultural and permanent characters of mankind. Nevertheless, music is, puzzlingly, useless and essential for our survival. Why do we listen to music? Musical issues have been addressed from ancient Greek philosophy to contemporary neuroscience. Nowadays, scientific research has provided relevant results, drawing a fairly detailed picture of the biological and cultural elements that characterize music experience. While cognitive approach highlighted the importance of hierarchical structures and mental models for the comprehension of musical language, different studies have recently evidenced the mutual influences between perception, cognition and action, inviting researchers to overcome the old paradigm of a mere passive and receptive role of the body in the perceptual process. In this sense, music cognition can be considered as “grounded” in sensorimotor networks, due to the functional and neurophysiological linkage between cognition, human motor system, gestures and body movements. Therefore, what was conceived as a pure “cognitive” level now impacts on both understanding and perceiving music.

Our mental representations, traditionally considered as “cognitive”, clearly contain aspects of perception and action, most obviously present in the neural signatures of mental simulation, and likely in many other cognitive operations, especially in the case of music processing, which inherently engages multiple senses and bodily responses, from tears to movement. Starting from an embodied model of music perception, MEDIA suggests an original way to take into account traditional questions, introducing an innovative methodology and experimental devices. In particular, it aims at investigating the actual influence of auditory perception in motor behavior of children by integrating kinematic
data from wearable magneto-inertial sensors and neurophysiological data from EEG recording. In an ecological experimental design, children will freely interact with an instrumented device, opportuneely configured to emit different acoustic stimuli depending on how it is manipulated. Each session will be video-recorded. The analysis of videos, kinematic and EEG data will provide an innovative conceptual framework of embodied music perception.

Improve the dynamic ongoing organism-environment transaction (embodiment) of the frail older with Parkinson’s Disease (PD) through an integrated assistance service (PARKEMB)

PI: Maddalena Pennacchini
Other Research Units involved: Computer Systems and Bioinformatics, General Surgery, Neurology, Neurophysiology, Neurobiology

The PARKEMB project aims at evaluating the impact that new technologies and education may have on PD (Parkinson’s Disease) patients and their caregivers. The goal is to increase the awareness that patients and caregivers have, improve the communication between patients, caregivers, nurses and physicians, and to enhance the monitoring of conditions of patients and caregivers.

The project is organized into four phases:

• **P1:** Mobile App Development, devoted to the design and implementation of a mobile App for the monitoring of PD patients and their caregivers at their home. The monitoring is performed through the completion of a set of surveys, included into the App. Upon each survey completion, the App allows the user (patient or caregiver) to share the data with the physician. Based on collected data, the physician can take proper and prompt actions.

• **P2:** Implementation of a training program for patients and caregivers. Under this phase, a group of selected patients undergo a training process. Each patient/caregiver is instructed in using the App and is informed on the information that the App collects and distributes. Moreover, a set of preliminary data is collected as paper form surveys, in order to build up a baseline for successive data analysis.

• **P3:** Remote Monitoring of patients and caregivers, that consists in the collection of data from patients and caregivers. The users employ their mobile App to periodically compile surveys and to submit their data to the physician of the project. The physician interacts with a specific patient/caregiver as soon as he provides new data. Collected data is anonymized and stored in a database.

• **P4:** Data Analysis. All the data are analyzed and the impact of the proposed approach is evaluated. Other actions related to the dissemination of results and the definition of new projects are performed.
Research and the “Third Mission” of the University
Impact of Research on Society
Impact of Research on Society

The key factor of UCBM policy for Third Mission activities is the centrality of human being to foster society innovation. According to its main mission for healthy living and improvement of quality of life, UCBM systematically pursues the activities related to third mission with the aim of transferring both knowledge and technology in order to enhance the socio-economic development at local and national level.

The activities are mainly devoted to strengthen competitiveness by promoting process and product innovation and by networking with local SMEs and National and International companies with a twofold aim: placement of students and exploitation of the research activities of the Research Units of Engineering and Medicine and Surgery Departments. In this context the project “INTESE - Innovation and Technology transfer to support exploitation of research results” funded by Lazio Regional Authority is worth a mention. The main objectives of the project consist in developing collaborations with local companies of process and product innovation by exploiting competencies and technologies developed by UCBM Research Units and staff mobility so fostering a mutual beneficial approach to create a critical mass of competencies and resources. During 2017, an internal call for projects within INTESE has co-funded five actions for the technology transfer of the results of UCBM research units (RU):

- CYTO+: TRL increment of CytoMatrix technology, coordinated by the RU of Tissue Engineering & Chemistry for Engineering, with the collaboration of the RU of Clinical Laboratory Sciences and of UCS Diagnostics Srl;
- ITHACA: Integration of microfluidic devices within high content screening microscopy systems for Cell-on-a-chip applications, coordinated by the RU of Tissue Engineering & Chemistry for Engineering, with the collaboration of the RU of Clinical Laboratory Sciences and of BioNova Technologies Srl and Nikon Instruments SpA;
- PROBRA: Innovative design, development and commercialization of compression garments for the prevention of complications and pathological scarring in patients undergoing brachioplasty surgery, coordinated by the RU of Nonlinear Physics and Mathematical Modeling, with the collaboration of the RU of Plastic Surgery and Dermatology and of Laboratori Ortopedici Riuniti Piscitelli snc;
- SIRASI: Robotic system to support upper and lower limb rehabilitation, coordinated by the RU of Biomedical Robotics and Biomicrosystems, with the collaboration of the RU of Physical and Rehabilitation Medicine and of Ican robotics Srl;
- HANSEL: Health AutomatioN SystEm Laboratory, coordinated by the RU of Automation and Control Theory, with the collaboration of the RU of Computer Systems and Bioinformatics and of Vitrociset SpA, BV TECH SpA, ASPISEC, ASTER SpA, JOIN-TECH Srl, Page Europa Srl, Universidad de Malaga, University of Cyprus, Royal Halloway University, IOSight, DATONIX SpA, Servitecnico Srl, Beckhoff Automation Srl.

Moreover, specific attention is devoted to ethical and anthropological issues thanks to the contribution of the Institute of Philosophy of Scientific and Technological Practice (FAST) and its research activities developed in close synergy with Research Units in order to enhance the social impact of research results.

The main actions developed in the last five years to strengthen the third mission activities are related to accessing National networks such as NETVAL (Italian Network of Technology Transfer Offices of Universities and Public Research Organizations) for technology transfer and ALMALAUREA for placement, to creation of a University-Industry Committee with the aim of collaborating with enterprises not only for technology transfer, but also for defining education and research strategies.

Third mission activities, in particular commissioned research, clinical trials, UCBM patent portfolio, UCBM spin-off companies, and public engagement activities, are briefly reported below.

COMMISSIONED RESEARCH

PPR2 Project
Control of upper-limb prosthesis with neural invasive interfaces

Client: INAIL-Centro per la Sperimentazione ed Applicazione di Protesi e Presidi Ortopedici di Vigorso di
Budrio (BO)  
**Contractor:** Research Unit of Biomedical Robotics and Biomicrosystems (UCBM)  
**Other Research Units involved:** Research Unit of Physical and Rehabilitation Medicine (UCBM), Research Unit of Orthopaedic and Trauma Surgery (UCBM), Research Unit of Neurology, Neurophysiology, Neurobiology (UCBM)  

**PPP AS 1/3 Project**  
Implantable system for the control of upper-limb prosthesis with invasive neural interfaces and wireless communication  
**Client:** INAIL-Centro per la Sperimentazione ed Applicazione di Protesi e Presidi Ortopedici di Vigorso di Budrio (BO)  
**Contractor:** Research Unit of Biomedical Robotics and Biomicrosystems (UCBM)  
**Other Research Units involved:** Research Unit of Physical Medicine and Rehabilitation (UCBM), Research Unit of Orthopaedic and Trauma Surgery (UCBM), Research Unit of Neurology, Neurophysiology, Neurobiology (UCBM), Research Unit of Neurophysiology and Neuroengineering of Human-Technology Interaction (UCBM)  

**PCR 1/2 Project**  
New methods in the treatment of limb amputation for the application of bionic prostheses  
**Client:** INAIL-Centro per la Sperimentazione ed Applicazione di Protesi e Presidi Ortopedici di Vigorso di Budrio (BO)  
**Contractor:** Research Unit of Biomedical Robotics and Biomicrosystems (UCBM)  
**Other Research Units involved:** Research Unit of Orthopaedic and Trauma Surgery (UCBM); Research Unit of Biomedical Robotics and Biomicrosystems (UCBM); Research Unit of Physical and Rehabilitation Medicine (UCBM); Research Unit of Neurology, Neurophysiology, Neurobiology (UCBM); Research Unit of Neurophysiology and Neuroengineering of human-technology interaction (UCBM).  

**Support for the technical contents of the web portal www.oil-gasportal.com**  
**Client:** Serintel S.r.l.  
**Contractor:** Research Unit of Process Engineering (UCBM)  

**Liquid chromatography tandem mass spectrometry platforms to develop analytical protocols for drugs and metabolites in biologic fluids**  
**Client:** Eureka S.r.l.  
**Contractor:** Research Unit of Drug Sciences (UCBM)  

**Expert systems for early diagnosis of COPD exacerbation**  
**Client:** Laboratori Informatica Applicata (L.I.A.)  
**Contractors:** Research Unit of Geriatrics, Research Unit of Computer Systems and Bioinformatics (UCBM)  

**GEPIKID**  
**Client:** National Institutes of Health  
**Contractor:** Research Unit of Molecular Medicine and Biotechnology (UCBM)  

**“I care about myself” Self-care experiences from the perspective of the people with COPD**  
**Client:** IPASVI, Rome  
**Contractor:** Research Unit of Nursing Science (UCBM)  

**Development and psychometric testing of a measure of cancer patients’ perception of care dependency**  
**Client:** IPASVI Rome  
**Contractor:** Research Unit of Nursing Science (UCBM)  

**Determination of polyphenols in hazelnut kernels and their derived food products**  
**Client:** Soremartec Italia s.r.l. - FERRERO Group  
**Contractor:** Research Unit of Food Science and Nutrition (UCBM)  

**Endocannabinoid biomarkers in inflammatory bowel disease of pets**  
**Client:** Vetagro SpA  
**Contractor:** Research Unit of Biochemistry and Molecular Biology (UCBM)  

**A multicenter prospective randomized placebo-controlled double blind study to evaluate the effectiveness of low-frequency pul-
Third Mission

sed electromagnetic fields (ELF-MF) in acute ischemic stroke (I-NIC)
Client: Network Future in Research (Consorzio Futuro in Ricerca)
Contractor: Research Unit of Neurology, Neurophysiology, Neurobiology (UCBM)

Blood lysosomal acid lipase activity in patients with non-alcoholic fatty liver disease
Client: Alexion Pharma
Contractor: Research Unit of Internal Medicine and Hepatology (UCBM)

Evaluation of the in vitro effects of certain target compounds on an experimental model of epilepsy
Client: Phytexs, Inc.
Contractor: Research Unit of Biochemistry and Molecular Biology (UCBM)

Total laboratory automation: advantages in pre-analytical, analytical and post analytical process
Client: Siemens Healthcare S.r.l
Contractor: Research Unit Clinical Laboratory Sciences (UCBM)

IEEE Editorial Services Agreement
Client: The Institute of Electrical and Electronics Engineers, Incorporated (“IEEE”)
Contractor: Research Unit of Biomedical Robotics and Biomicrosystems (UCBM)

Assessment of neonatal oro-motor performance during bottle feeding
Client: Artsana S.p.A.
Contractor: Research Unit of Biomedical Robotics and Biomicrosystems (UCBM),
Other partners involved: “Santa Maria Goretti” Hospital

LCA perspective to assess the environmental impact of a PCM-based device for cold storage in the civil air conditioning
Client: Upgrading Services SpA
Contractor: Research Unit of Chemical – Physics

Fundamentals in Chemical Engineering (UCBM)

STS – Surgery Touchless System
Client: Proge Software srl
Contractor: Research Unit of Automation and Control Theory (UCBM)

Brand Protection on Marketplace
Client: Poste Italiane SpA
Contractor: Research Unit of Automation and Control Theory (UCBM)

Markers of the endocannabinoid system in inflammation
Client: Vetagro SpA
Contractor: Research Unit of Biochemistry and Molecular Biology (UCBM)

Biochemical markers of inflammatory bowel diseases
Client: University of Teramo
Contractor: Research Unit of Biochemistry and Molecular Biology (UCBM)

Biochemical profiling of new chemical entities with therapeutic potential
Client: F. Hoffmann-La Roche Ltd
Contractor: Research Unit of Biochemistry and Molecular Biology (UCBM)

Interleukin-8 and Programmed Cell Death Protein 1 Checkpoint in the Tumor Microenvironment
Client: Dompé Farmaceutici S.p.A.
Contractor: Research Unit of Biochemistry and Molecular Biology (UCBM)

Management of the technical contents of the Oil & Gas R&D portal
Client: Serintel srl
Contractor: Research Unit of Process Engineering

The contribution of caregiver and patient dyads to self-care in COPD: a mixed method study (1st phase)
Client: IPASVI  
Contractor: Research Unit of Nursing Science (UCBM)

**Automotive CyberSecurity**  
Client: NITEL Consortium  
Contractor: Research Unit of Automation and Control Theory (UCBM)

**Design and development of an electronic differential sensor system for water characterization**  
Client: Puretech srl  
Contractor: Research Unit of Electronics for Sensor Systems (UCBM)

**Autonomic Nervous System Study - Cardiac Autonomic Reflex tests. CARTs - Small Nerve Fiber (A-delta, B and C) health with in vivo corneal confocal microscopy**  
Client: Sapienza University of Rome  
Contractor: Research Unit of Endocrinology and Diabetes (UCBM)

**Integration of the SofTaxic (E.M.S. srl) neuro-navigation system in a platform for robot-aided transcranial magnetic stimulation**  
Client: EMS srl  
Contractor: Research Unit of Neurophysiology and Neuroengineering of Human-Technology Interaction (UCBM)

**In-Hospital Economic Burden of Anastomotic Leakage after Colorectal Anastomosis Surgery: A Real-World Cost Analysis**  
Client: Johnson & Johnson Medical SpA  
Contractor: Research Unit of General Surgery (UCBM)
CLINICAL TRIALS

During the year 2017, 98 studies have been approved by the independent Ethics Committee of the UCBM. 46 (46,9%) and 52 (53,1%) of these projects were interventional or observational studies, respectively. The distribution of studies among the different Research Units is summarized in Figure 9. The very majority of the interventional trials is of Phase 2 or 3.

UCBM promoted 36 of the new studies approved in 2016 (36,7 % of the total). On the other side, 25 projects were promoted by not-for-profit institutions / research networks, and 37 projects were sponsored by Companies (pharmaceutical or developing medical devices) (Figure 11).
RESEARCH EXPLOITATION

Patent portfolio owned/co-owned by UCBM

- **Sodium 2-Mercapt ethanol Sulfonate for use in the treatment of lumbar pain** (IT1402161, EP2629768, WO2012052888); Inventors: F. E. Agrò, M. Carassiti, V. Denaro, A.C. Di Martino.
- **Sodium 2-Mercapt ethanol Sulfonate for use in the treatment of lumbar pain** (EP2629768); Inventors: F. E. Agrò, M. Carassiti, V. Denaro, A.C. Di Martino.
- **System for the estimation of cardiac output** (IT1408989, EP20120815801); Inventors: M. Carassiti, S. Cecchini, E. Schena, S. Silvestri.
- **Apparatus and method for videorhinohygrometric (vri) measures** (US2009221927); Inventors: F. Salvinelli, R. Setola, M. Casale, P. Soda, V. Cusimano.
- **Locomotion device for endoscopic applications and related methods** (IT1397408, US20130324796); Inventors: D. Accoto, S. Passanisi.
- **Device and method for controlled adhesion upon moist substrate** (EP2806817); Inventors: D. Accoto, C. Esposito, M. T. Francomano.
- **Upper limb movement therapy device** (IT1388838); Inventors: D. Accoto, E. Cecchini, E. Guglielmelli, M. Orsini, F. Torchiani, L. Zollo.
- **Diagnostic method of pancreas cancer based on the determination of mutations of K-RAS gene** (IT0001417084); Inventors: A. Onetti Muda, G. Porrone.
- **Method for measuring slippage between surfaces** (IT102016000105302); Inventors: R. Romeo, L. Zollo, E. Guglielmelli. Co-owner: INAIL.
- **Method for positioning the units of an array of tactile sensors for obtaining a hyper spatial acuity and processing method thereof** (IT102016000076248); Inventors: C. Oddo, R. Romeo, L. Zollo, L. Beccai, E. Guglielmelli, M. Chiara Carrozza. Co-owners: Scuola Superiore Sant’Anna, Istituto Italiano di Tecnologia.
- **Haptic interface module** (IT1399399); Inventors: D. Accoto, E. Cecchini, E. Guglielmelli.
- **Coronary shunt positioner** (IT1410043); Inventors: E. Covino. Co-owner: Assut Europe SpA.
- **Technique of purification of adipose tissue to obtain a high concentration of adipose stem cells** (IT102017000003805); Inventors: P. Persichetti, G. F. Marangi, F. Segreto F. Pantano, M.C. Tirindelli, C. Gregorj.
UCBM spin-off companies

Three spin-off companies are accredited by UCBM, namely ICAN Robotics srl, BHL – Bio Health Lab srl and B.R.I.O. srl. The spin-off activities are related to robot-assisted rehabilitation, to software solutions for patients and physicians and to the commercialization of devices for otolaryngology.

ICAN Robotics (www.icanrobotics.com) is an innovative start-up company, founded in September 2014, active in the field of biomedical robotics, developing technologies for rehabilitation and physical assistance for patients with neurological, orthopedic or age-induced conditions. ICan robotics develops innovative and user-friendly products, which can be used not only in healthcare facilities, but also at patients’ abodes, for the benefit of the quality of life of patients and their caregivers.

BHL – Bio Health Lab (www.biohealthlab.it), accredited by UCBM in 2017, designs, develops and markets mobile app and software solutions related to healthcare sector. The solutions, with high innovative contents, are the result of research activities in several fields such as diagnostics, hospital organization and physician-patient communication.

Biomedical Research in Otolaryngology, in short B.R.I.O., accredited by UCBM in 2017, produces and distributes innovative biomedical devices for the healthcare sector. In particular, the company is involved in the distribution of an innovative device for otolaryngology, manually operable, dispensing substances in the form of aerosols.

Public engagement activities

One of the priorities for the Campus Bio-Medico University of Rome is to design specific public engagement activities to meet special social needs. Projects for the protection of health are carried out regularly as for example, lung cancer prevention campaigns for smokers and former smokers, prevention days and screening of thyroid cancer, information days on osteoporosis and rheumatoid arthritis. Furthermore, a counselling service for relatives of chronic degenerative disease patient has been active since 2011.

Guidance programs and interaction with high school students take place regularly. Undergraduate Open Days, the “Salone dello studente” and the RomeCup annual event, are great opportunities to get information or get to visit the University. The University publishes the magazine “Lettere dal Campus” accessible on line as well, which typically includes a section focused on ongoing research activities, latest achievements and news from the UCBM research community. Finally, the University is also active on social media (Facebook, Twitter, YouTube, Google+, Flickr, Linkedin, Pinterest) having 30,000 users and a pool of 8 million annual contacts.

Below a list of the main public engagement activities carried out at UCBM in 2017 is reported.

Rome, 16 January 2017

Post-operative strategies after knee surgery in athletes

Discussant: Dr. Stefano Della Villa, President of Isokinetic Medical Group - FIFA Medical Centre of Excellence.

Seminar promoted by the Postgraduate School of Orthopedics.
Rome, 17 January 2017
Nutrition and Energy
Discussant: Gianpaolo Mocetti, Acea S.p.A.
Seminar promoted by the Food Science and Nutrition Unit, Campus Bio-Medico University of Rome.

Rome, 18 January 2017
“The marriage of Tony the Italian-American”. Clinical decisions between caution and epic.
Discussant: Vittoradolfo Tambone; Giampaolo Ghilardi.

Rome, 18 January 2017
The rules of beverage and consumer protection
Discussant: Chiara Gentile, Birra Peroni S.p.A.
Seminar promoted by the Food Science and Nutrition Unit, Campus Bio-Medico University of Rome.

Rome, 18 January 2017
Wine and health
Discussant: Monica Minelli, Federdoc.
Seminar promoted by the Food Science and Nutrition Unit, Campus Bio-Medico University of Rome.

Rome, 13 February 2017
Presentation of internal research announcement
Development of joint research activities with companies within the INTESE project.

Rome, 17 February 2017
“Quo vadis science?” - Lunchtime meeting on the emerging orientations of scientific research.
What is not inside the brain: critical reflections between philosophy and neuroscience.
Seminar promoted by Institute of Philosophy of Scientific and Technological Practice.

Rome, 1 March 2017
Molecular basis of formation and fission of transport vesicles in cell secretion.
Discussant: Daniela Corda, PhD, Institute of Protein Biochemistry - CNR Napoli.
Seminar promoted by the Centre for Integrated Research (CIR), Campus Bio-Medico University of Rome.

Rome, 8 March 2017
Gender medicine. Theoretical aspects and the case of the Transformative Surgery: the feminization of the face.
Discussant: Dario Sacchini, Università Cattolica del Sacro Cuore; Paolo Persichetti, Campus Bio-Medico University of Rome.

Rome, 22 March 2017
Nutrition and Sport: Classification of sports disciplines, morphological biotype, body composition and energy metabolism.
Discussant: Dr. Raffaella Spada, Institute of Medicine and Science of Sport, CONI.
Seminar promoted by the Food Science and Nutrition Unit, Campus Bio-Medico University of Rome.

Rome, 29 March 2017
Nutrition and Sport: Use of nutrients in various sports.
Discussant: Dr. Francesca Base, Institute of Medicine and Science of Sport, CONI.
Seminar promoted by the Food Science and Nutrition Unit, Campus Bio-Medico University of Rome.

Rome, 30 March 2017
Biomedical Humanities and Technology: A challenge for scientific practice and editorial strategies and policies.
Discussant: Dr. Marta Bertolaso, Institute of Philosophy of Scientific and Technological Practice (FAST), Campus Bio-Medico University of Rome; Ties Nijsen, Springer Publishing Editor for History and Philosophy of Science & Logic; Emanuele Serrelli, Bio-Techno-Practice, Research Empowering Hub.

Rome, 5 April 2017
Nutrition and Sport: Timing of intake: nutritional support before, during and after training.
Discussant: Dr. Loredana Torrisi, Institute of Medicine and Science of Sport, CONI.
Seminar promoted by the Food Science and Nutrition Unit, Campus Bio-Medico University of Rome.

Rome, 11 April 2017
Transcranial Magnetic Stimulation: theoretical model.
Discussant: Prof. Luca Di Rienzo, Associate Professor, Department of Electronics, Information and Bioengineering - Electrical Section, Politecnico di Milano.
Seminar promoted by the Neurology Unit, Campus Bio-Medico University of Rome.

Rome, 27 April 2017
Hemodynamic assessment of coronary artery disease: state of the art and novel applications.
Discussant: Prof. Emanuele Barbato, Cardiovascular Research Center Aalst (Belgio) - Università degli Studi di Napoli “Federico II”. Seminar promoted by the Cardiology Unit, Campus Bio-Medico University of Rome.

**Rome, 3 May 2017**

**Kick-off meeting of project PCR 1\2**
New methods in the treatment of limb amputations, aimed at the application of bionic prostheses.

**Rome, 4 May 2017**

**Climate and Nutrition**
Discussant: Ing. Andrea Forni, Università degli Studi di Cassino e del Lazio Meridionale, Coordinatore Interventi sul Territorio Ufficio Studi ENEA. Seminar promoted by the Food Science and Nutrition Unit, Campus Bio-Medico University of Rome.

**Rome, 5 May 2017**

“**Quo vadis science?”** - Lunchtime meeting on the emerging orientations of scientific research. The openness of embodiment. Critical perspectives in cognitive neuroscience. Seminar promoted by Institute of Philosophy of Scientific and Technological Practice.

**Rome, 10 May 2017**

**Reprogrammed cells: from bench to bedside: “Principles and methods of adult cell reprogramming”**
Seminar promoted by the Tissue Engineering and Chemistry for Engineering Unit, Campus Bio-Medico University of Rome.

**Rome, 11 May 2017**

**Traditional and innovative technologies for the production of gluten-free pasta.**
Discussant: Dr. Alessandra Marti, DeFENS – Food Science and Technology Section, Università degli Studi Milano. Seminar promoted by the Food Science and Nutrition Unit, Campus Bio-Medico University of Rome.

**Rome, 11 May 2017**

**Vision for Robotic Manipulation**
Discussant: Prof. Bruno Siciliano, PRISMA Lab - Department of Electrical Engineering and Information Technology, Università degli Studi di Napoli “Federico II”. Seminar promoted by the Food Science and Nutrition Unit, Campus Bio-Medico University of Rome.

**Rome, 11 May 2017**

**Surface plasmon resonance and surface plasmon resonance microscopy: principle, instrumentation and applications**
Discussant: Dr. Nguyen Ly, PhD - Biosensing Instrument Inc., Tempe, AZ (USA). Seminar promoted by the Tissue Engineering and Chemistry for Engineering Unit, Campus Bio-Medico University of Rome.

**Rome, 12 May 2017**

**Introduction to atomic force microscopy (AFM) technique.**
Discussant: Stefano Schutzmann, PhD - LOT-QuantumDesign, Roma. Seminar promoted by the Tissue Engineering and Chemistry for Engineering Unit, Campus Bio-Medico University of Rome.

**Rome, 12 May 2017**

**Bioinstructive platforms for tissue engineering, cancer therapy and drug delivery: bridging the gap via electrofluidodynamics.**
Discussant: Vincenzo Guarino, PhD - Institute of Polymers, Composites and Biomaterials (IPCB), CNR. Seminar promoted by the Tissue Engineering and Chemistry for Engineering Unit, Campus Bio-Medico University of Rome.

**Rome, 16 May 2017**

**Reprogrammed cells: from bench to bedside: “In vitro models with iPSCs”**
Seminar promoted by the Tissue Engineering and Chemistry for Engineering Unit, Campus Bio-Medico University of Rome.

**Rome, 16 May 2017**

**Innovation in biomedicine: advanced in vitro and...**
in silico models.
Discussant: Alessio Gizzi; Fabrizio Mattei; Valeria Lucarini; Wolfgang Holnthoner; Giancarlo Forte; Alessandro Veneziani; Antonella Regnigni Wilson; Cesare Gargioli; Maurilio Sampaolesi.

**Rome, 17 May 2017**
**Research Day 2017**
Organized by the Centre for Integrated Research (CIR), Campus Bio-Medico University of Rome.

**Rome, 18 May 2017**
**Chromatography as a technique for the separation of complex mixtures**
Discussant: Prof. Ilaria D’Acquarica, Department of Chemistry and Pharmaceutical Technologies, Sapienza Università di Roma.
Seminar promoted by the Food Science and Nutrition Unit, Campus Bio-Medico University of Rome.

**Rome, 19 May 2017**
**Physiology of the motor cortex and mirror neurons.**
Discussant: Prof. Giacomo Rizzolatti, Università di Parma.

**Rome, 24 May 2017**
**Reprogrammed cells: from bench to bedside: “iPSCs for precision medicine & drug screening”.**
Seminar promoted by the Tissue Engineering and Chemistry for Engineering Unit, Campus Bio-Medico University of Rome.

**Rome, 25 May 2017**
**Computerized systems in the production and control of medicines: a conscious and safe use.**
Discussant: Prof. Giuseppe Ruggirello, CTP SYSTEM.

**Rome, 31 May 2017**
**Internet of Things: applications, technologies and business models.**
Discussant: Ing. Marco Sgroi.
Seminar organized by the Department of Engineering, Campus Bio-Medico University, Rome.

**Rome, 23 June 2017**
**Secure interconnection of complex control systems and resilience.**
Discussant: Cristina Alcaraz, PhD in Computer Science.
Seminar organized by the Laboratory of Complex Systems, Campus Bio-Medico University, Rome.

**Rome, 28 June 2017**
**Selective polymer-assisted transport: using di-block copolymers as solid polymer electrolytes and injectable tissue scaffolds.**
Discussant: Sergio Granados-Focil, PhD, Associate Professor, Gustaf H. Carlson School of Chemistry and Biochemistry, Clark University, Worcester, MA.
Seminar promoted by the Tissue Engineering and Chemistry for Engineering Unit, Campus Bio-Medico University of Rome.

**Rome, 28 June 2017**
**Aqueous organic flow batteries.**
Discussant: Diana De Porcellinis, graduated in Chemical Engineering for Sustainable Development at Campus Bio-Medico University of Rome and now PhD at John A. Paulson School of Engineering and Applied Science Harvard University, Cambridge, MA.
Seminar promoted by the Tissue Engineering and Chemistry for Engineering Unit, Campus Bio-Medico University of Rome.

**Rome, 7 July 2017**
**Imbalance of excitatory/inhibitory signaling leads to specific focal seizure onset patterns.**
Discussant: Prof. Massimo Avoli, M.D., Ph.D., Université McGill and Montreal Neurological Institute.
Seminar promoted by the Neurology Unit, Campus Bio-Medico University of Rome.

**Rome, 11 July 2017**
**The ethics of research**
Discussant: Prof. Ariberto Acerbi, Pontificia Università della Santa Croce.
Seminar promoted by the Institute of Philosophy of Scientific and Technological Practice (FAST), Campus Bio-Medico University of Rome.

**Rome, 11 July 2017**
**Prosigna update in breast cancer and nanostring perspective in immuno-oncology for the clinic.**
Discussant: Natalia de la Fuente, Ph.D., Associate Medical Affairs Director, Europe, NanoString Technology, Inc; Pascale Morel, Medical Affairs Director, Europe, NanoString Technology, Inc.

**Rome, 4 October 2017**
**Immediate breast reconstruction with heterolo-

Rome, 13 October 2017
“Quo vadis science?” - Lunchtime meeting on the emerging orientations of scientific research. Seminar promoted by Institute of Philosophy of Scientific and Technological Practice.

Rome, 19 October 2017
New Perspectives on Immunotherapy in Corneal Transplantation
Discussant: Prof. Takenori Inomata MD, PhD, MBA, Assistant Professor, Ophthalmology & Education Department, Juntendo University Hospital, Tokyo, Japan. Seminar promoted by the Ophthalmology Unit, Campus Bio-Medico University Rome.

Rome, 19 October 2017
How to use clinical research to make good treatment decisions for patients: Study Designs
Discussant: Dennis Black.

Rome, 26 October 2017
How to use clinical research to make good treatment decisions for patients: Making sense of data
Discussant: Dennis Black.

Rome, 21 November 2017
Epilepsy secondary to brain neoplasm: management of antiepileptic therapy, side effects and quality of life
Discussant: Marta Maschio, Responsible Centro per l’Epilessia Tumorale, UOSD Neurologia, Istituto Nazionale Tumori “Regina Elena”. Seminar promoted by the Neurology Unit, Campus Bio-Medico University of Rome.

Rome, 22 November 2017
Addressing global nutrition challenges in the 21st century. Why are we failing to achieve good results?
Discussant: Dott. Militezegga Abduk Mustafa and Boitshepo Giyose, Nutrition and Food Systems Division (ESN) – Economic and Social Development Department (ES), FAO. Seminar promoted by the Food Science and Nutrition Unit, Campus Bio-Medico University of Rome.

Rome, 28 November 2017
Optogenetics, synaptic plasticity and new treatments for addictions
Discussant: Prof. Antonello Bonci, MD, Scientific Director National Institute on Drug Abuse - Baltimore. Seminar promoted by the Neurology Unit, Campus Bio-Medico University of Rome.

Rome, 29 November 2017
Integrating exposures, genetic susceptibility and somatic changes in lung cancer etiology and progression
Discussant: Dott. Maria Tesera Landi, Senior Investigator dell’Integrative Tumor Epidemiology Branch dell’NIH, NCI/DCEG di Rockville (Md). Seminar promoted by General Pathology Unit, Campus Bio-Medico University Hospital, Rome.

Rome, 30 November 2017
Where nutrition becomes therapy
Discussant: Samantha Selicato, Brand Manager Out Of Hospital, Nestlé Health Science; Micaela Ferrante, Medical Delegate FF Hospital, Nestlé Health Science. Seminar promoted by the Food Science and Nutrition Unit, Campus Bio-Medico University of Rome.

Rome, 1 December 2017
Loads, structure and signaling in models of joint regeneration
Discussant: Dott. Riccardo Gottardi, Assistant Professor, Center for Cellular and Molecular Engineering, Department of Orthopaedic Surgery, University of Pittsburgh. Seminar promoted by the Orthopedics and Traumatology Unit, Campus Bio-Medico University of Rome.
simulation
Discussant: Prof. Flavio H. Fenton, School of Physics, Georgia Institute of Technology, Atlanta (USA).

**Rome, 15 December 2017**
The role of chemistry and chemical engineering in the development of a sustainable world
Discussant: Luigi Nataloni, Global Manufacturing Technology Leader Sweeteners and Polyols in Cargill; Gaetano Iaquaniello, CEO of Processi Innovativi (group Maire Tecnimont), Vice president of the Italian Association of Chemical Engineering (AIDIC).
Seminar promoted by the Chemical Engineering Unit, Campus Bio-Medico University of Rome in collaboration with the Italian Association of Chemical Engineering (AIDIC).

**Rome, 19 December 2017**
Neuroscience and rehabilitation: translational research and technological innovation in clinical practice
Discussant: Dott. Marco Molinari, Director UOC Neuroriabilitazione 1, Fondazione Santa Lucia IRCCS, Roma; Ing. Nevio Luigi Tagliamonte, Robotic Neurorehabilitation Laboratory, Midollary Injury Rehabilitation Laboratory, Fondazione Santa Lucia IRCCS, Roma.

**Rome, 20 December 2017**
Modeling, Surveillance, Mimicking of Human Motions & Human Robot Interaction
Discussant: Xanthi S. Papageorgiou, National Technical University of Athens (NTUA/ICCS), School of Electrical and Computer Engineering - Division of Signals, Control and Robotics.
Research Agreements and Collaborations
National agreements and collaborations

Altec S.p.A., Italy
Artsana S.p.A., Italy
ASRIS ONLUS Cagliari, Italy
Autentica Srl, Italy
Bambino Gesù Paediatric Hospital, Italy
Banca Nazionale del Lavoro, Italy
Carabinieri Headquarters for Healthcare, Italy
Catholic University of the Sacred Heart, Italy
Cell Factory, Foundation IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy
CNIT – Consorzio Nazionale Interuniversitario per le Telecomunicazioni, Italy
Confederazione Nazionale Coldiretti, Italy
Consorzio Ferrara Ricerche, Italy
Elesta S.r.l., Italy
ENEA, Italy
Eureka S.r.l., Italy
Fondazione IRCCS Istituto Nazionale dei Tumori, Italy
“Foro Italico” University of Rome, Italy
ICRA – International Center for Relativistic Astrophysics, Italy
IGEA S.p.A.
International School for Advanced Studies Trieste, Italy
IPASVI, Italy
IRCCS Eugenio Medea – Associazione La Nostra Famiglia, Italy
IRCCS Fondazione Santa Lucia, Italy
IRCCS Fondazione Stella Maris, Italy
IRCCS Regina Elena (IFO-IRE), Italy
IRCCS San Raffaele Pisana, Italy
Italian Ministry of Health, Italy
Italian National Institute of Health, Department of Therapeutic Research and Medicine Evaluation, Italy
Kell S.r.l., Italy
Medtronic International Trading Sarl, Italy
National Research Council (CNR), Italy
Network Future in Research (Consorzio Futuro in Ricerca), Italy
OpenSky, Italy
Pfizer Italia S.r.l., Italy
Politecnico di Torino, Italy
Polytechnic University of Marche, Italy
Polytechnic University of Milan, Italy
Poste Italiane SpA, Italy
Proge Software srl, Italy
Puretech S.r.l., Italy
Sant’Anna School of Advanced Studies, Italy
Sapienza University, Rome, Italy
Selex ES SpA, Italy
Serintel S.r.l., Italy
Siemens Healthcare S.r.l, Italy
SOREMARTEC ITALIA S.r.l., Italy
Studiare Sviluppo S.r.l., Italy
University “Roma Tre”, Italy
University of Bari, Italy
University of Bologna, Italy
University of Brescia, Italy
University of Cagliari, Italy
University of Calabria, Italy
University of Catania, Italy
University of Chieti-Pescara, Italy
University of Florence, Italy
University of Foggia, Italy
University of Genova, Italy
University of Insubria Varese-Como, Italy
University of Milan, Italy
University of Padova, Italy
University of Parma, Italy
University of Pisa, Italy
University of Rome “Tor Vergata”, Italy
University of Siena, Italy
University of Teramo, Italy
University of Turin, Italy
International agreements and collaborations

Alexion Pharma, USA
AO Research Institute Davos, Switzerland
Assistance Publique - Hôpitaux De Paris, France
Autism Speaks, USA
B&J Adaptaciones, Spain
Belgian Customs and Excise, Belgium
B&G Klinikum Bergmannstrost Halle Ggmbh, Germany
Birkbeck College, United Kingdom
Cambridge University, United Kingdom
CEA, France
Cedar Foundation, USA
Central Institute of Mental Health Mannheim, Germany
Centre Hospitalier de Luxembourg, Luxembourg
Centre Hospitalier Universitaire De Nantes, France
Centre Hospitalier Universitaire Montpellier, France
Centre National De La Recherche Scientifique (CNRS), France
Charles University Prague, Czech Republic
Children’s Hospital of Pittsburgh, USA
Citospin S.L., Spain
Commissariat à l’Energie Atomique et aux Energies Alternatives (Neurospin/CEA), France
deCODE Genetics, Iceland
Deltares, The Netherlands
ECRIN – European Clinical Research Infrastructure Network, France
Eli Lilly and Company Ltd., United Kingdom
Erasmus MC Sophia Rotterdam, The Netherlands
European Commission, Joint Research Centre, Belgium
European Molecular Biology Laboratory, Germany
F. Hoffmann-La Roche Ltd., Switzerland
Fraunhofer-Gesellschaft zur Förderung der angewandten Forschung e.V., Germany
GABO:mi, Germany
Hospital Clinico San Carlos Madrid, Spain
Hospital de Cruces University of Pais Vasco, Spain
Institut de Recherches Servier, France
Institut De Terapia Regenerativa Tisular S.l, Spain
Institut Pasteur, France
Institute of Education, United Kingdom
Janssen Pharmaceutica, Belgium
Karolinska Institutet, Sweden
Kinder und Jugendkrankenhaus Auf der Bult Hannover, Germany
King’s College London, United Kingdom
Linkoping University, Sweden
Max-Planck Institute of Experimental Medicine, Germany
National University of Ireland, Galway, Ireland
NeuroSearch, Denmark
Phytecs Inc., USA
Radboud University, The Netherlands
Robarts Research Institute, Canada
Sommelweis University Budapest, Hungary
The Children’s Hospital at Westmead NSW, Australia
The Institute of Electrical and Electronics Engineers, Incorporated (IEEE), USA
The National Institute for Health and Welfare Helsinki, Finland
The Netherlands Food and Consumer Product Safety Authority, The Netherlands
TNO, The Netherlands
Union des Industries Chimiques (UIC), France
Univercell-Biosolutions, France
Universidad De Navarra, School of Engineering (TECNUN), Spain
Universidad De Valladolid, Spain
Universidad Miguel Hernández, Spain
Universidad Politécnica de Valencia, Spain
Universitaet Ulm, Germany
Universität Basel, Switzerland
University Children’s Hospital Zurich, Switzerland
University Medical Centre Utrecht, The Netherlands
University of British Columbia, USA
University of Cyprus, Cyprus
University of Helsinki, Finland
University of Medicine in Wroclaw, Poland
University of Pittsburgh, USA
University of South Florida, USA
University of Tartu, Estonia
University of Technology and Life Sciences, Poland
University of Tübingen, Germany
University of Turku, Finland
Vifor Pharma, Switzerland
Wageningen University & Research Centre, The Netherlands
Washington University School of Medicine - Jewish Hospital of St. Louis, USA
Yale University, School of Medicine, USA
Zed Worldwide S.A., Spain
Editorial board membership
# Editorial board membership

<table>
<thead>
<tr>
<th>Name</th>
<th>Journals</th>
</tr>
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| Accoto D.             | Frontiers  
                          Springer Series on Biosystems and Biorobotics |
| Agrò F.               | La Clinica Terapeutica                                                  |
| Altamura C.           | World Journal of Neurology                                              |
| Angeletti S.          | Disease Marker  
                          EC Microbiology                                                         |
| Angioli R.            | Oncology Reports  
                          Minerva Ginecologica                                                    |
| Antonelli Incalzi R.  | Advances in Respiratory Medicine  
                          Journal of Frailty and Aging                                            |
| Avvisati G.           | Blood  
                          La Clinica Terapeutica                                                  |
| Bertolaso M.          | Bioethics Update  
                          Current Bioinformatics  
                          Filosofia e saperi.  
                          Medic - Metodologia didattica e innovazione clinica  
                          Medicina e Storia  
                          Organisms – An International Journal of Biological Sciences  
                          Per la Filosofia  
                          Scienze e Ricerche                                                   |
| Bonini S.             | Ocular Surface                                                          |
| Borghi L.             | Medicina Historica (Co-editor)                                          |
| Cacace F.             | Mathematical Problems in Engineering                                     |
| Carassiti M.          | Minerva Anestesiologica                                                 |
| Carotti S.            | Journal of Digestive Disease and Hepatology                              |
| Casale M.             | Austin Otolaryngology  
                          Global Journal of Otolaryngology                                        |
| Chello M.             | Journal of Geriatric Cardiology  
                          World Journal of Hypertension  
                          World Journal of Surgical Procedures                                    |
| Chiodo L.             | Thin Solid Films, Frontiers in Materials                                 |
| Cicala M.             | MEDIC: Metodologia e Didattica Clinica  
                          World Journal Gastroenterology                                           |
<p>| Caputo D.             | World Journal of Gastrointestinal Surgery                               |</p>
<table>
<thead>
<tr>
<th>Name</th>
<th>Publications and Roles</th>
</tr>
</thead>
</table>
| Coppola R.       | International Journal of Surgery  
                   International Journal of Surgery Case Reports  
                   Pancreatology  
                   Plos One                                                |
| D'Amelio M.      | Neuromolecular Medicine (Associate Editor)  
                   Scientific Reports (Neuroscience Section)                 |
| Di Lazzaro V.    | Behavioural Neurology  
                   Brain Stimulation  
                   Case Reports in Medicine  
                   Neurology Research International                            |
| Di Martino A.C.  | European Spine Journal  
                   Frontiers in Surgery  
                   Journal of Orthopaedics and Traumatology  
                   Musculoskeletal Surgery                                    |
| Di Paola L.      | Advances in Systems Biology  
                   International Journal of Biochemistry Research and Review (Editor in Chief)  
                   International Journal of Medical Biotechnology & Genetics  
                   Journal of Physical Chemistry and Biophysics           |
| Di Sciascio G.   | Cor et Vasa  
                   Heart and Brain  
                   Minerva Cardioangiologica  
                   Journal of Cardiovascular Medicine                           |
| De Gara L.       | Journal of Experimental Botany  
                   Methods in Molecular Biology  
                   Plant Cell and Environment                                      |
| Dugo P.          | Advisory Board di Flavour and Fragrance Journal                                         |
| Fanali C.        | Current Analytical Chemistry  
                   Open Chemistry  
                   Separations                                                  |
| Gizzi A.         | Mathematical Problems in Engineering  
                   JSM Head and Face Medicine                                       |
| Guarino M.P.L.   | Journal of Digestive Diseases and Hepatology                                          |
| Guglielmelli E.  | Applied Bionics and Biomechanics  
                   IEEE Robotics & Automation Society (Vice-President for Publications Activities)  
                   Springer Series on Biosystems and Biorobotics (Editor-in-Chief) |
<p>| Ippolito E.      | Musculoskeletal Surgery                                                                |
| Laudisio A.      | Frontiers in Geriatric Medicine                                                        |
| Locato V.        | Frontiers in Plant Science                                                            |</p>
<table>
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<tr>
<th>Name</th>
<th>Publications/Positions</th>
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<tbody>
<tr>
<td>Longo U.G</td>
<td>BMC musculoskeletal disorder</td>
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<tr>
<td>Maccarrone M.</td>
<td>Anti-Allergy and Anti-Inflammatory Agents in Medicinal Chemistry</td>
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<td>Cardiovascular Psychiatry and Neurology</td>
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<td>Encyclopedia of Life Sciences</td>
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<td>Frontiers in Membrane Physiology and Biophysics (Associate Editor)</td>
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<td>Frontiers in Molecular Neuroscience (Associate Editor)</td>
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<td>Journal of Alzheimer’s Disease (Associate Editor)</td>
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<td>Lipids in Health and Disease</td>
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<td>The Open Journal of Neuroscience</td>
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<td>Mangiacapra F.</td>
<td>Journal of Cardiovascular Translational Research</td>
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<td>Marinozzi A.</td>
<td>Applied Bionics and Biomechanics</td>
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<td>Minotti G.</td>
<td>Cardio-Oncology (Deputy Editor)</td>
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<td>Chemotherapy (Editor in Chief)</td>
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<td>Journal of Pharmacology and Experimental Therapeutics (Editorial Board Member)</td>
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<td>Mondello L.</td>
<td>Journal Separation Science</td>
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<td>Morini S.</td>
<td>Journal of Cardiology &amp; Cardiovascular Medicine</td>
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<td>Napoli N.</td>
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<td>Forum for Bone and Mineral Research</td>
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<td>Journal of Endocrinological Investigation</td>
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<td>Osteoporosis International</td>
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<td>Nusca A.</td>
<td>Plos ONE</td>
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<td>Oliva G.</td>
<td>International Journal of Control Science and Engineering</td>
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<td>Papalia R.</td>
<td>Musculoskeletal Surgery</td>
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<td>Patti G.</td>
<td>American Journal of Cardiovascular Disease</td>
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<td>Pedone C.</td>
<td>Advances in Respiratory Medicine (Vice Editor in Chief)</td>
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<tr>
<td>Perrone G.</td>
<td>Archives of Clinical Hepatitis Research</td>
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<td>International Journal of Clinical and Experimental Pathology</td>
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<tr>
<td>Persichetti P.</td>
<td>European Journal of Plastic Surgery</td>
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<tr>
<td>Persico AM.</td>
<td>Giornale di Neuropsichiatria dell’Età Evolutiva</td>
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<td>Molecular Autism</td>
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<td>Journal of Sensors</td>
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<td>World Journal of Respirology</td>
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<td>Petitti T.</td>
<td>European Journal of Plastic Surgery</td>
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<td>Piemonte V.</td>
<td>Advances in Systems Biology</td>
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<td>Artificial Organs</td>
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<td></td>
<td>International Journal of Biochemistry Research &amp; Review</td>
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<td></td>
<td>International Journal of Medical Biotechnology &amp; Genetics(IJMBG)</td>
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<td></td>
<td>Journal of Physical Chemistry &amp; Biophysics</td>
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<td></td>
<td>Journal of Sustainable Energy Engineering</td>
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<td>Journal of Technology Innovations in Renewable Energy</td>
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<tr>
<td>Picardi A.</td>
<td>Archives of Medical Science (Section Editor)</td>
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<td>World Journal of Gastroenterology</td>
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<td></td>
<td>World Journal of Hepatology</td>
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<td>Pozzilli P.</td>
<td>Diabetes Metabolism Research &amp; Reviews (DMRR) (Editor in Chief)</td>
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<td></td>
<td>La Clinica Terapeutica</td>
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<tr>
<td>Russo MT</td>
<td>Aurora. Papeles del seminario Maria Zambrano</td>
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<td></td>
<td>Book Series: Percorsi di Etica</td>
</tr>
<tr>
<td></td>
<td>British Journal of Education, Society &amp; Behavioral Science</td>
</tr>
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<td>Camillianum</td>
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<tr>
<td></td>
<td>Critical Hermeneutics</td>
</tr>
<tr>
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<td>MEDIC: Metodologia e Didattica Clinica</td>
</tr>
<tr>
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<td>Per la Filosofia</td>
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<tr>
<td></td>
<td>Clinical Cancer Drugs</td>
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<tr>
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<td>Clinical Medicine Insights: Oncology</td>
</tr>
<tr>
<td></td>
<td>Critical Reviews in Oncology/Hematology</td>
</tr>
<tr>
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<td>Expert Opinion on Biological Therapy</td>
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<td></td>
<td>Expert Opinion on Emerging Drugs</td>
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<td></td>
<td>Expert Opinion on Therapeutic Targets (Editor in Chief)</td>
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<td></td>
<td>Journal of Bone Oncology</td>
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<td>Journal of Chemotherapy</td>
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<td>Acta Imeko</td>
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<td>International Journal of Radiology</td>
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<td>Journal of Healthcare Engineering</td>
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<td>Advance Research in Textile Engineering</td>
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<td>Silvestri S.</td>
<td>The Open Biomedical Engineering Journal</td>
</tr>
<tr>
<td>Soda P.</td>
<td>The Open Medical Devices Journal</td>
</tr>
<tr>
<td>Spinelli F.</td>
<td>Italian Journal of Vascular and Endoovascular Surgery Medical Journal, International Angiology</td>
</tr>
<tr>
<td>Sterzi S.</td>
<td>European Journal of Physical and Rehabilitation Medicine (Associate Editor)</td>
</tr>
<tr>
<td>Tambone V.</td>
<td>MEDIC: Metodologia e Didattica Clinica, La Clinica Terapeutica</td>
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<td>Expert Opinion on Investigational Drugs (Editor in Chief), Expert Opinion on Pharmacotherapy, Expert Review of Anticancer Therapy, Future Oncology, La Clinica Terapeutica</td>
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<td>Vadalà G.</td>
<td>Journal Orthopaedic Research (JOR), Spine</td>
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<td>Vespasiani Gentilucci U.</td>
<td>World Journal of Hepatology</td>
</tr>
</tbody>
</table>
PhD Courses and XXX cycle theses (2015-2017)
Ph.D Courses

The Campus Bio-Medico University of Rome offers Ph.D courses to students motivated to gain autonomy and rigor in scientific research. Courses aim to provide doctoral students a scientific culture, methodological tools and advanced technical skills, thereby contributing to the growth of research and scholarship in Italy and internationally.

The primary purpose of PhD study is the preparation and presentation of a substantial piece of original research designed to be completed within three years of study.

Full text Ph.D dissertations are deposited in the open access repository ILITHIA. The repository is indexed in OpenDOAR, an authoritative worldwide directory of academic open access repositories. Link: <http://ilithia.unicampus.it/ilithia/Default.asp>.

Authors hold copyright of dissertation in accordance with current legislation (Law 633/1941) and subsequent amendments and additions. The dissertations present in the University repository are a guarantee for the author, certifying and dating intellectual property. The repository helps to ensure a high level of visibility of Ph.D dissertations increasing significantly their impact, for the benefiting of both researchers and Campus Bio-Medico University itself.

PH.D IN INTEGRATED BIOMEDICAL SCIENCES AND BIOETHICS

- **Duration**: 3 years
- **Coordinator**: Prof. Paolo Pozzilli

**Students enrolled**


**Learning outcomes**

The structure of the Ph.D in Integrated Biomedical Sciences and Bioethics is designed to produce graduates who have a thorough knowledge of the literature and comprehensive understanding of scientific methods and techniques applicable to their own research. This particular Ph.D focuses its attention in integration of the broader fields of biomedical research with a more philosophical approach, which include further study in anthropology, ethics, aesthetics, epistemology, and bioethics.

**Research fields**

The Ph.D in Integrated Biomedical Sciences and Bioethics is divided in various tracks:

- **Endocrinology**: MED/13, MED/09, MED/08, BIO/10, MED/16, MED/18
- **Bioethics**: MED/43, BIO/14, MED/26, BIO/16
- **Osteo-Oncology Pathology**: MED/06, MED/04, BIO/10, MED/15, MED/40, MED/16
- **Aging Sciences and of Tissue Regeneration**: MED/09, MED/19, MED/26, MED/15
PH.D IN BIOENGINEERING AND BIOSCIENCES

Duration 3 years
Coordinator Prof. Giulio Iannello

Students enrolled

Learning outcomes
The structure of the Ph.D in Bioengineering and Biosciences is designed to produce graduates with rigorous research and analytical skills, who are exceptionally well-equipped to carry out research in academic, industry, or government positions. The program is divided in two tracks: one oriented to biomedical engineering applications the other to Science and food technology and nutrition.
Ph.D program allows graduates to:
• develop new methods, instruments and systems, for biomedical engineering and for food sciences and nutrition;
• describe, plan, coordinate and carry out research programs developing technical and medical-biological skills;
• integrate traditional formation in the biomedicine, with knowledge such as maths and technology which can face the increasing complexity of “bioinspired” research fields.

Research fields
The main fields of study are:
• Bioengineering: study, design and development of new methods, systems and medical devices, medical and biological research, development of bioinspired medical technologies;
• Material science and nanotechnology: study, development and testing of materials for industrial applications with a particular consideration to medical and food applications;
• Modelling: study and use of complex systems models for applications in biology and medicine;
• Food chemistry and plant physiology: study and development of new knowledge and protocols for the characterization of bioactive molecules and their metabolism. Use of new technologies for the nutritional enhancement of traditional and innovative foods;
• Nutrition: use of advanced technological for the study of nutritional parameters and their impact in the prevention of diseases; Experimentation protocols and procedures applied to clinical nutrition.
PH.D IN SCIENCE AND ENGINEERING FOR HUMANS AND THE ENVIRONMENT

Duration  3 years
Coordinator  Prof. Giulio Iannello

Students enrolled

Learning outcomes
The PhD in Science and Engineering for Humans and the Environment aims at training experts capable of carrying out research activities for the care of the individual and the environment. The PhD is divided into courses that offer the development of complementary skills in engineering, as well as different scientific and technological fields, but likewise focused on improving the quality of life for individuals with reference to the environment they live in.

This goal is pursued thanks to the presence in the Academic Board of researchers from different macro-areas of study and having a long-standing commitment to the subject matter of the PhD course. The training courses also aim at stimulating doctoral students with a multi-disciplinary approach to problems regarding man and the environment.

Ph.D program allows graduates to:
• develop new methods, instruments and systems to promote health, well-being and personal safety, through the care of environment and also supported by the most up-to-date research results
• describe, plan, coordinate and carry out research programs in order to develop technical and multidisciplinary research combining different technical and scientific skills
• integrate the traditional type of education in biomedicine, with knowledge such as maths and technology which can help to face the increasing complexity of “bioinspired” research fields.

Research fields
The main fields of study are:
• study, design and development of new methods, systems and devices for biomedical applications, with particular reference to biorobotics, biomedical instrumentation, biomaterials, and tissue engineering;
• study and use complex systems models for applications in biology, medicine and environmental science;
• study and development of new knowledge and protocols for the characterization of bioactive molecules and their metabolism, their nutritional parameters and impact on diseases prevention, as well as experimentation of protocols and procedures applied to clinical nutrition;
• study, design and development of new methods, systems and devices based on information technology, with particular reference to the analysis of large amounts of data.
Graduate School – shared education platform

The Coordinating Board for Ph.D programs, formed by Doctoral program Coordinators and supported by the Centre for Integrated Research, in the academic year 2013/14 created a training event called ‘Graduate School – a shared education platform’. Its goal was to offer a training course in Scientific Research, cutting across individual Degree Programs, to investigate issues of common interest. The event is organized with a series of short lectures that address specific issues identified by Doctoral program Coordinators.

### Monday May 15th

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Location</th>
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<tbody>
<tr>
<td>09:30-10:00</td>
<td>Institutional greetings</td>
<td>Conference room PRABB</td>
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<tr>
<td>10:00-10:15</td>
<td>Presentation of the Doctoral School</td>
<td>R2</td>
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<tr>
<td>10:15-10:45</td>
<td>The relevance of the period abroad in the PhD program, P. Pozzilli</td>
<td>R2</td>
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<td>Coffee break</td>
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<tr>
<td>11:00-12:00</td>
<td>PhD: a complementary training path for the professions of the future, I. Screpanti</td>
<td>Conference room PRABB</td>
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<td>12:00-13:00</td>
<td>Dialysis therapy: technological principles, clinical approach and quality of life of the patient, M. L. Costantino</td>
<td>R2</td>
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<td>Welcome lunch</td>
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<tr>
<td>14:30-15:30</td>
<td>Identity, mission and cultural project of Campus Bio-Medico University of Rome, L. Anfossi</td>
<td>Conference room PRABB</td>
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<tr>
<td>15:30-17:00</td>
<td>Designing a clinical research study, A. Schwartz</td>
<td>R2</td>
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<tr>
<td>15:30-17:00</td>
<td>Pure hydrogen production in a membrane reformer: demonstration, macro-scale and atomic scale modeling, M. Sheintuch</td>
<td>R2</td>
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<tr>
<td>17:00-18:30</td>
<td>The future of research in biomedical engineering, M. C. Carrozzi</td>
<td>Conference room PRABB</td>
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### Tuesday May 16th

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<th>Event</th>
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<tr>
<td>09:00-11:00</td>
<td>Workshop “Innovation in biomedicine: advanced in vitro and in silico models”</td>
<td>Aula Magna Trapezzo</td>
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<td>Coffee break</td>
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<tr>
<td>11:30-13:30</td>
<td>Workshop “Innovation in biomedicine: advanced in vitro and in silico models”</td>
<td>Aula Magna Trapezzo</td>
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<td>13:15-14:15</td>
<td>Discussion on the exercise of “VQR 2011-2014”</td>
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<td>15:00-16:30</td>
<td>The importance of strengthening the skills of researchers in the field of exploitation of research results, A. Piccalunga</td>
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<tr>
<td>16:30-18:00</td>
<td>Robotic surgery and related technologies: open challenges and ongoing projects, A. Menciassi</td>
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<td><strong>Wednesday May 17th</strong></td>
<td><strong>Research Day</strong></td>
<td>Aula Magna Trapezo</td>
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<td>08.30-13.30</td>
<td><strong>Buffet in the Aula Magna foyer</strong></td>
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<td>14.45-15.30</td>
<td>How to survive a peer review process, G. A. FitzGerald, G. Yang</td>
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<td>15.30-16.45</td>
<td>Bioactive molecules of plants: from basic research to technology transfer, M. E. Maffei</td>
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<tr>
<td>16.45-17.30</td>
<td>Presentation of the best doctoral thesis</td>
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<tr>
<td><strong>Thursday May 18th</strong></td>
<td><strong>Guidelines and feasibility requirements of clinical trials</strong>, G. Gussoni</td>
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<td>09.00-11.00</td>
<td><strong>Coffee break</strong></td>
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<td>11.30-13.30</td>
<td>Workshop “Guidelines for clinical trials in the perspective of the new European regulation and the UCBM organizational model”</td>
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<td>14.00-16.30</td>
<td>From the idea to the research project: types of funding and structure of the proposal, C. Buonocore, A. Benevento, M. Fioretto</td>
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<tr>
<td>16.30-17.30</td>
<td>Bone Health and bone metastasis: a continuum of care, D. Santini</td>
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<tr>
<td><strong>Friday May 19th</strong></td>
<td><strong>Cortical motor system</strong>, G. Rizzolatti</td>
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<td>09.00-10.00</td>
<td><strong>Coffee break</strong></td>
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<td>10.00-11.00</td>
<td>Mirror neurons, G. Rizzolatti</td>
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<tr>
<td>11.30-12.30</td>
<td>Cell-based social networks: shaping and maintaining bone architecture, R. Civitelli</td>
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<tr>
<td>12.30-13.30</td>
<td>Multisensory systems for the health of the elderly, R. Antonelli Incalzi</td>
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<td>13.30-14.00</td>
<td>Conclusions</td>
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<tr>
<td>15.00-18.00</td>
<td>Open session of the Scientific Committee meeting of FAST - Institute of Philosophy of Scientific and Technological Practice of Campus Bio-Medico University of Rome</td>
<td>Conference room PRABB</td>
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<tr>
<td>15.00</td>
<td>Presentation of FAST, E. Covino</td>
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<tr>
<td>15.15</td>
<td>Presentation of research topics, FAST Researchers – part I</td>
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<tr>
<td>16.15</td>
<td><strong>Coffee Break</strong></td>
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<td>16.30</td>
<td>Presentation of research topics, FAST Researchers – part II</td>
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<td>17.30</td>
<td>Discussion with the components of the Scientific Committee</td>
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<td>18.00</td>
<td>End of works</td>
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Ph.D dissertations defended in 2017

*Link to full text dissertations: http://ilithia.unicampus.it/ilithia/Default.asp

**INSULIN RESISTANCE IN WOMEN WITH POLYCYSTIC OVARY SYNDROME: INSULIN AND BONE INTERACTION AND IMPLICATIONS OF DIET**

**Ph.D student** Anifa Chantal Amisi

**Tutor** Paolo Pozzilli

Looking at the current scientific literature, it seems that Polycystic Ovary Syndrome (PCOS) is a pathology mainly from developed and emerging countries. It looks like Africa is not interested in this pathology, which according to the current literature affects 8-10% of women around the world. However, a preliminary study carried out 10 years earlier on Congolese women showed that this pathology does indeed exist in Africa, and that insulin resistance, the main complication of this pathology, is found in a fairly high proportion. With the goal of improving PCOS women’s well-being, I continued my research on insulin resistance. On the recommendation of Professor Paolo Pozzilli, who is one of the pioneers in research on type 1 diabetes, I began to look for a simpler way to diagnose and treat this complication in Congolese women affected by PCOS. I present, in this thesis, the results of my research. The first part of this thesis focuses on markers of insulin resistance. It shows how the wrist circumference is the best marker known to date for the assessment of insulin resistance in women with PCOS. These results suggest that the wrist circumference may be the best easy-to-detect anthropometric marker known to date. They also suggest that insulin resistance has an impact on the bone system in PCOS women. The second part presents peculiarities of the Congolese PCOS woman’s diet having insulin resistance. With this study, we provide the first demonstration of the impact of imported white rice consumption on insulinemia and insulin resistance in Congolese women with PCOS. We demonstrate that there is a link between white rice consumption and insulin resistance in PCOS women. We also demonstrate that consumption of large amounts of white rice not only induces, but also worsens insulin resistance in women with PCOS regardless of BMI and central fat distribution. Finally, the third part of this thesis is about the beneficial effects of a 12 weeks antioxidant-rich diet on insulin resistance in PCOS women. Our results emphasize the fact that insulin resistance causes oxidative stress in women with PCOS. Therefore, by acting on this oxidative stress with a rich antioxidant diet, insulin resistance can be improved in these women.

**MENOPAUSE, ENDOMETRIAL CANCER AND METABOLIC SYNDROME: LINKS AND TREATMENTS**

**Ph.D student** Michela Angeluci

**Tutor** Paolo Pozzilli

Endometrial cancer (EC) is the most common gynecological malignancy in Europe and North America. The incidence of endometrial cancer is about 1 times higher in developed countries than developing countries. This could be due to an increased life expectancy, increased caloric intake, obesity, adjuvant Tamoxifen use for breast cancer, and a reduction in fertility rates. Endometrial cancer risk is found to be positively correlated with increasing age. Over 90% of the cases are diagnosed after the age of 50 years, therefore endometrial cancer is more common in post-menopausal women than in premenopausal women. Elevated serum estrogen level is associated with chronic anovulation, increasing the risk of developing endometrial cancer. Thus, women with Polycystic Ovary Syndrome (PCOS) and women with estrogen-secreting ovarian tumors. Insulin resistance and PCOS, both components of the metabolic syndrome, may play a central role in the pathogenesis of endometrial...
cancer. The risk of endometrial cancer becomes higher when obesity is associated with infertility or amenorrhea, as is the case for PCOS. Endometrial cancer risk increases by 1.2 fold for each 5 kilograms weight gain. Since obesity is also associated with insulin resistance and hyperinsulinemia the positive relationship with endometrial cancer risk becomes even stronger.

Metabolic syndrome (Mets) or Syndrome X has been studied since the early 80’s and Syndrome X was initially coined by Gerald Reaven in 1988. It comprises of the following components: obesity, elevated blood pressure, hyperglycemia or insulin resistance and dyslipidemia. All these are important cardiovascular risk factors. In particular, obesity is considered to be the biggest contributor of cardiac dysfunction in postmenopausal women. The decrease in estrogen levels in menopausal women is associated with the loss of subcutaneous fat and an increase in abdominal fat. Human subcutaneous and visceral adipose tissues express both estrogen receptors (ERα, ERβ). ERα plays a major role in the activity of adipocytes and sexual dimorphism of fat distribution. Estrogen exerted a direct positive effect on cardiovascular disease (CVD) risk in women, a benefit that was lost as women transitioned from a premenopausal to a postmenopausal state and experienced a loss of estrogen. Furthermore, the progressive androgenicity of the hormonal pattern exerts a direct negative effect on CVD risk. Testosterone is associated with insulin resistance, hyperinsulinemia, low HDL levels, high blood levels of glucose and triglycerides, and diabetes mellitus and from epidemiologic data showing that androgens are associated with inflammatory markers. Physiological changes during the menopausal transition, especially the alteration of reproductive endocrine function, might contribute to the risk of metabolic syndrome (MS). This is possibly but not totally related to increasing estrogenic deficiency. The prevalence of MS increases from 6.7% in the third decade to 43.5% in the seventh decade. The emergence of metabolic syndrome features may be a direct result of ovarian failure or, alternatively, an indirect result of the metabolic consequences of central fat redistribution with estrogen deficiency.

Metabolic syndrome has emerged as a possible clinical condition that predisposes to malignant disease, in addition to weight and other metabolic risk factors such as insulin resistance, diabetes, hypertension, and dysglycemia. A central feature of the metabolic syndrome is obesity, which is expressed by an increased waist-hip ratio (WHR) or body mass index (BMI), which reflects an increase in adipose tissue. Circulating concentrations of estradiol in postmenopausal women are directly related to BMI. Estradiol can be formed from the conversion of androgens via the cytochrome P450 enzyme complex known as aromatase, which is present in adipocytes and adipocyte stromal tissue. Many breast and endometrial cancers are dependent on estradiol for tumor growth. Consequently obesity (BMI >30 kg/m²) predisposes to increased estrogen production and is associated with a twofold to fivefold increase in risk of endometrial cancer and a twofold increase in risk of breast cancer in postmenopausal women. Circulating estrogens are an important pathological mechanism linking obesity with breast and endometrial cancer development in postmenopausal women. Increased adiposity raises interleukin (IL)-6 and tumor necrosis factor (TNF)-a cytokines production in obese women that are potent inducers of aromatase activity and thus to production of estradiol, which is a potent growth factor for estrogen receptor-positive breast and endometrial cancers. Adipocytes, or fat cells, are not only a simple storage sites for triglycerides but a complex endocrine organ able to secrete hormones, cytokines, and other proteins with signaling properties (collectively termed “adipokines”). Adipokines are a diverse group of signaling molecules that play roles in such processes as appetite and energy balance, inflammation, insulin resistance/sensitivity, angiogenesis, lipid metabolism, cell proliferation, and atherosclerosis. Many of these functions are related to either the metabolic syndrome or cancer, and they may serve as a link between these two pathologies. There are more than 50 adipokines with diverse functions affecting glucose homeostasis, insulin sensitivity, angiogenesis, adipogenesis, inflammation, cellular proliferation, apoptosis, and differentiation. These cytokines secreted by adipocytes are known to promote insulin resistance and increase circulating triglycerides, features of the metabolic syndrome. Inflammation has also been linked to many types of cancer, such as gastric, pancreatic, esophageal, liver, bladder, and colorectal cancers because it influences growth, apoptosis, and proliferation of tumor and stromal cells. TNF-a activates nuclear factor-KB, which increases production of NO, a substrate for Reactive Oxygen Species (ROS) formation and stimulates other inflammatory cytokines. ROS and inflammatory cytokines lead to insulin resistance and glucose intolerance. Thereby, increased circulating cytokines from adipocytes promote cancer
progression by contributing to inflammation. Leptin is an adipocyte-specific hormone that serves as a metabolic signal to the brain that results in inhibition of appetite and increased basal metabolism to promote use of the stored energy (fat). Thus, circulating leptin levels are directly related to adiposity. However, obese patients develop resistance to leptin and consequently become hyperleptinemic and more susceptible to the components of the metabolic syndrome. In addition to its association with obesity and insulin resistance, increased plasma leptin levels are associated with prostate, colon, breast, and it is inversely correlated with breast, endometrial, and gastric cancer risk. Angiogenesis is the process of new blood vessel formation from pre-existing vasculature and is a critical process for tumor formation and metastasis. One of the most important proangiogenic factors secreted by adipocytes is Vascular Endothelial Growth Factor (VEGF). The adipocytokine Visfatin, has been linked to several inflammatory disease states and cancer. Thus, visfatin may be an obesity-induced adipocytokine involved in the development of MetS-related cancers. Adipokines influence insulin resistance by increasing or decreasing insulin sensitivity. Because insulin resistance is directly related to the metabolic syndrome and cancer development, adipokines may play a crucial role in linking these two diseases. The evidence for adipokines and proinflammatory cytokines derived from adipose tissue promoting carcinogenesis (either via promoting insulin resistance or directly influencing cancer cells) is considered intermediate. Previous epidemiological data, showed a strong association between endometrial cancer risk and obesity, as measured by both BMI and waist circumference. In particular, metabolic syndrome and hyperinsulinemia resulted associated with endometrial cancer. Among premenopausal women with metabolic syndrome, there is almost a twofold increased risk of endometrial cancer, largely due to increasing waist sizes. After menopause, this jumps to a 60–230% elevated risk of endometrial cancer in women with metabolic syndrome.

PART II RESEARCH PROJECT N°1: EFFICACY OF MYOINOSITOL AND FLAVONOIDS IN POSTMENOPAUSAL WOMEN AFFECTED BY METABOLIC SYNDROME: A RANDOMIZED CROSSOVER STUDY. The aim of this study is to evaluate the efficacy of myo-inositol and soy isoflavones in reducing insulin resistance in postmenopausal patients with metabolic syndrome. Forty-two such patients were enrolled in the study and were randomized into two groups, G1 and G2. During the first year (time T0-T2), group G1 (21 patients) was administered myoinositol 2 g + soya isoflavones (genistein 200 mg) once daily while group G2 was treated with diet and exercise only. After one year, the treatments were crossed over: during the second year (time T2-T4), group G2 (21 patients) was administered myoinositol 2 g + soya isoflavones (genistein 200 mg) once daily, while group G1 stopped the pharmaceutical treatment and was treated with diet and exercise only. Patients were evaluated at baseline (T0) and every 6 months (T1-T4) for body mass index (BMI), abdominal circumference (CA), basal glucose (BG), triglycerides (TG), low density lipoprotein (LDL), and high-density lipoprotein (HDL). Myo-inositol in association with soy isoflavones produced a highly significant improvement in serum levels of BG and TG compared with the groups treated with diet and exercise only. There was no significant change in BMI in either group from T0 to T4. Supplementation with myo-inositol and soy isoflavones may be considered a reliable option in the treatment of metabolic syndrome in postmenopausal women.

RESEARCH PROJECT N°2: THE ROLE OF NOVEL BIOMARKER HE4 IN ENDOMETRIAL CANCER: A CASE CONTROL PROSPECTIVE The aim of the study was to explore the clinical of serum human epididymys secretory protein E4 (HE4) and CA125 in endometrial carcinoma. From January 2010 to April 2012, serum specimens were collected from consecutive cases of endometrial carcinoma and from cases of uterus benign disease (control group). The CA125 normal value is considered less than 35 U/mL. Two HE4 cut-off are considered: less than 70 pmol/L and less than 150 pmol/L. The specificity analysis was performed using the Mann–Whitney test for the CA125 and HE4 series. The level of statistical significance is set at p <0.05. The sensitivity of CA125 in detecting endometrial cancer is 19.8%, whereas the sensitivity of HE4 is 59.4 and 35.6% for 70 and 150 pmol/L cutoff, respectively. Thus the specificity of HE4 is 100% (positive predictive value = 100%, negative predictive value = 71.52 and 61.31% considering the two HE4 cut-offs, respectively), whereas the CA125 specificity is 62.14% (positive predictive value 033.9%, negative predictive value 044.14%) in detection of endometrial cancer. Combining CA125 and HE4, the sensitivity to detect endometrial cancer is 60.4 and 34.6%, at HE4 cut off of 70 and 150 pmol/L, respectively, with a specificity of 100%. HE4 may be a new tool for preoperative evaluation and postoperative surveillance of endometrial cancer patients, with a positive predictive value = 100%. HE4
at cut-off of 70 pmol/L yields the best sensitivity and specificity.

**PREHABILITATION IN PATIENTS UNDERGOING PANCREATICODUODENECTOMY: A RANDOMIZED CONTROLLED TRIAL.**

**Ph.D student** Fabio Ausania  
**Tutor** Giuseppe Tonini

**INTRODUCTION:** Prehabilitation has been postulated as an effective tool to prevent postoperative complications in patients undergoing major abdominal surgery. However, no studies have shown its effectiveness in pancreatic surgery patients. The aim of this study was to assess the impact of prehabilitation on postoperative complications in patients undergoing pancreaticoduodenectomy.

**METHODS:** This was a randomized controlled trial. Eligible candidates accepting to participate were randomized (1:1 ratio) to control (standard care) or intervention (standard care + prehabilitation) groups. All patients with periampullary tumours were included. Those patients receiving neoadjuvant treatment were excluded. Prehabilitation covered 3 actions: i) nutritional support ii) control of diabetes and exocrine pancreatic insufficiency iii) physical and respiratory training. The main study outcome was the proportion of patients suffering postoperative complications. Secondary outcomes included the occurrence of specific complications (pancreatic leak, delayed gastric emptying, etc) and hospital stay.

**RESULTS:** 38 patients were included in the intention-to-treat analysis. We randomized 20 patients to the control arm and 18 to intervention. No statistically significant difference was observed in terms of complications between prehabilitation group and standard care group. Pancreatic leak was less frequent in prehabilitation group, however this difference was not statistically significant. DGE and hospital stay were significantly lower in the prehabilitation group (P= <0.05).

**CONCLUSION:** Prehabilitation did not reduce postoperative complications in pancreaticoduodenectomy patients. However, a reduction of DGE and hospital stay was observed.

**IMPACT OF PRE-OPERATIVE IMMUNONUTRITION IN PATIENTS UNDERGOING PANCREATICODUODENECTOMY FOR PERI-AMPULLARY CANCER**

**Ph.D student** Paola Balestrieri  
**Tutor** Michele Cicala

**Background:** Cachexia and reduction in food intake due to anorexia represent the most important pathophysiological consequences of peri-ampullary cancer (PC). In addition, complex surgical procedure potentially leads to further depression of the immune response. Therefore, infective complications are not infrequent. Immunonutrition (IN) contains pharmacologic doses of nutrients including arginine, ω-3 polyunsaturated fatty acids, glutamine and ribonucleic acid. Available data show that IN, in patients suffering from gastrointestinal cancer, is safe and effective in decreasing postoperative infections and reduce length of hospital stay as compared with the control group. The effect of IN in patients with peri-ampullar cancer undergoing pancreaticoduodenectomy (PD) is still unclear.

**Aim:** The aim of the present study is to evaluate the effect of IN on post-operative infectious complications, average survival time, mortality and on frequency of re-hospitalization in patients with peri-ampullar neoplasms undergoing PD. Therefore, the impact of sarcopenia on post-operative outcome has been evaluated.

**Methods:** Thirty one consecutive patients who were candidates for a curative PD in either the pancreatic head or the periampullary region were prospectively enrolled. Patients were randomized to receive pre-operative IN or standard nutrition. The relationship between pre-operative body composition (assessed by BIA), percentage of weight loss and sarcopenia (assessed by means of computerized tomography) and post-operative outcome
was assessed.

Results: Malnutrition and sarcopenia were observed in 68% and 74% of patients, respectively, and 40% had lost >10% of their usual body weight. Malnutrition, impaired body composition and sarcopenia were associated with a longer hospital stay, higher rate of post-operative complications compared to well-nourished patients. No differences were observed in overall mortality, except for sarcopenia, and rate of re-admission. The frequency of infectious complication was lower, although not significantly, in the IN group compared to non-IN group. Median hospital stay was significantly lower in the IN group (n =10) compared to non-IN (n=21); (11 ± 5 days vs 17.3 ± 10, respectively). There were no significant differences in hospital re-admissions rate and intra-hospital mortality between IN and no-IN patients.

Conclusion: Pre-operative malnutrition and sarcopenia are highly prevalent in peri-ampullary cancer patients undergoing PD. Pre-operative IN is an effective and safe intervention to reduce postoperative infection complication and length of hospital stay. According to our results, it appears reasonable to monitor relevant nutritional parameters regularly in all PC cancer patients, in particular in pre-operative setting, and to initiate early interventions to prevent reversible elements of malnutrition in cancer patients.

DESIGN AND VALIDATION OF SAMPLING DEVICES FOR OCULAR SURFACE AND FLUIDS

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Personalized medicine is a growing field in which physicians and biologists use diagnostic tests to identify specific biological markers, which will determine medical treatments and procedures for each patient. Merging the researcher information with medical records, allows clinicians to develop targeted treatment and prevention plans (Offit K, 2011; Wilson B, 2015). Various scientific publications describe extensively the personalized medicine, health information management, biomarker discovery and targeted therapies (Zhang L, 2015). The market of molecular diagnostics devices is growing fast, nearly 4000 new diagnostic tests have been introduced only in 2015 (Pritchard DE, 2017). Equal for the molecular therapeutics market, nearly 28% of all the medicines the United States Food and Drugs Administration (FDA) approved in 2015 were personalized medicines (https://www.fda.gov/Drugs/DevelopApprovalProcess), and a recent study sponsored by the Personalized Medicine Coalition (PMC) demonstrated that 42% of all medicines and 73% of cancer medicines in development are potential personalized medicines (Pritchard DE, 2017). To realize a personalized approach new technology that endorses a person's biology, like DNA, RNA, or protein, to confirm a possible disease is required (Vogenberg FR, 2010). In human medicine, and in particular in Ophthalmology, suitable cellular markers can be used to recognize corneal and conjunctival pathologies; their use is very useful for the diagnosis of ocular diseases. These markers provide great help both from a diagnostic point of view and from a therapeutic point of view. This type of investigation would in fact determine benefits from the etiopathogenetic point of view, clinical, diagnostic and prognostic for the pathology in consideration. Hence, the main aim of my Ph.D. was to simplify the discovery of specific eye disorder biomarkers, through the development of new sampling and testing devices, that allow the identification of a specific biomarker, correlated to a specific pathology, in office. Therefore, my functional intent for the present thesis as shown in scheme 1 was to undergo the simplification of biomarker discovery, through the design and development of three different devices: • First a new sampling device, that incorporates a nitrocellulose membrane, that permits a fast and reliable imprinting and analysis of the ocular surface, as compared to other old sampling techniques, referring to biochemical and molecular analyses in order to identify and have an overview of the enormous field of the Biomarkers. • Second a solubilizing device, that attends to solubilize the proteins and nucleic acids contained in biological fluids, or from the nitrocellulose membrane of the new sampling device, obtaining therefore samples immediately available for analysis. • Third a biosensor, to facilitate the research of biomarkers of interest, I have participated in the development of a biosensor, for an already patented device, that will complete it, giving a quantifiable biomarker response, in collaboration with the ISM, IMM IFT institutes of the CNR of Tor Vergata. This last device will give an immediate and quantitative response of a
biomarker, solubilized in the second device in which both the biological fluids and the nitrocellulose membrane of the first device can be inserted, contributing to pursuing, therefore, the same goal, or the easiest identification of one or more specific pathology markers.

INFLUENCE OF THE ROTATIONAL MOVEMENT ON THE PATENCY OF PERFORATOR PEDICLES: PHYSICAL MODEL AND CLINICAL APPLICATIONS

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**Tutor**  Paolo Persichetti

**Purpose:** The purpose of the study is to evaluate risk factors and outcomes associated with the use of free style pedicled perforator flaps harvested at different anatomical sites (head and neck, trunk, extremities) with different degrees of rotation.

**Materials and Methods:** A retrospective review was performed including only patients who received reconstruction with a pedicled perforator based flap, islanded on a single perforator vessel, with sparing of the underlying source vessel. A statistical analysis based on Pearson’s chi-squared test and logistic regression was performed to evaluate if patient related variables (age, obesity, diabetes, hypertension, venous insufficiency, coronary heart disease, irradiation, tabagism) and flap related variables (anatomical location, flap movement, degree of pedicle rotation, flap surface, knowledge/exposure of the source vessels) had an impact on flap vascular complications rate (full thickness or partial thickness flap necrosis, epidermolysis, delayed healing).

**Results:** Patients reviewed were operated at our Institution between January 2010 and December 2016. There were 71 propeller flaps and 59 V-Y advancement flaps. Overall flap complications rate was 23% (16% for advancement flaps vs 30% for propeller flaps). Among patient related variables, coronary heart disease proved to be an independent risk factor for flap complications (p=0.020), while hypertension was found to be a protective factor (p=0.07). Among flap related variables, flap movement (advancement vs propeller), anatomical location, flap surface and knowledge of the source vessels did not show any influence on the outcome, while the increasing degree of pedicle rotation proved to have a significant impact on the development of flap vascular complications (p=0.018).

**Conclusions:** Free style pedicled perforator flaps, either advanced or rotated in a propeller fashion, proved to be a reliable tool to treat small to moderate size defects in different anatomical regions. Considering the clinical impact of the degree of pedicle rotation on flap performance, a surgical algorithm based on the reconstructive ladder concept is proposed to optimize outcomes.

LIVER AND PANCREATIC CANCERS: THE ROLE OF METABOLIC SYNDROME AND NOVEL AVENUES FOR TREATMENT

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**Tutor**  Paolo Pozzilli

MODULATION OF BRAIN PLASTICITY TO PROMOTE THE RECOVERY OF UPPER LIMB MOTOR FUNCTION IN CHRONIC STROKE

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Robot-assisted rehabilitation and non-invasive brain stimulation can produce a slight improvement in severe
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chronic stroke patients. However, it is unknown whether their combination can produce synergistic effects. Safety and efficacy effects of combined treatment were evaluated in a proof-of-principle, double-blinded, semi-randomized, sham-controlled trial. Inhibitory continuous Theta Burst Stimulation (cTBS) was delivered on the affected hemisphere, in order to improve the response to the following robot-assisted therapy. 20 chronic stroke patients with severe upper limb impairment were randomized to robot-assisted therapy associated with real or sham cTBS, delivered for ten consecutive working days. 8 real and 9 sham patients completed the study. The primary outcome was the change in Fugl-Meyer scale, while changes in several quantitative indicators of motor performance extracted by the robot were considered secondary outcomes. The treatment was well-tolerated by all patients and there were no adverse events. We found a small, but significant, Fugl-Meyer improvement (about 5%) in all patients. The difference between the real and the sham cTBS groups was not significant. Among several secondary end points, only the Success Rate (percentage of targets reached by the patient) improved more in the real than in the sham cTBS group. This study shows that a short intensive robot-assisted rehabilitation produces a slight improvement in severe upper-limb impaired chronic stroke patients, even years after the stroke. The association with homeostatic metaplasticity-promoting non-invasive brain stimulation does not augment the clinical gain in patients with severe stroke.

POST-TRANSLATIONAL MODIFICATIONS OF PROTEINS AND GENETIC POLYMORPHISMS ASSOCIATED TO METABOLIC DISEASES

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Tutor Paolo Pozzilli

Study 1: Antibodies to post-translationally modified insulin in LADA. Hypothesis/Aims: The general hypothesis is that oxPTM-Ins reactivity could be higher than the reactivity of the native insulin in LADA patients. It was also evaluated whether oxPTM-Ins antibodies can be used as biomarker to differentiate LADA from T2D. Methods: This study included 37 patients with LADA, 33 patients with T2D and 19 healthy controls (HC). OxPTM insulin was generated using ribose, CuCl2, H2O2 and HOCl. Autoreactivity to oxPTM-Ins was detected by ELISA using sera from study participants. Results: Reactivity to .OH-Ins was significantly higher than NT-Ins in LADA (NT-Ins median ± SE absorbance 0.050 ± 0.03; .OH-Ins median ± SE absorbance 0.122 ± 0.02) (p = 0.01). ELISA data showed that antibody binding to oxPTM-Ins was significantly higher in LADA compared to HC (.OH-Ins median ± SE absorbance in LADA vs. HC: 0.12 ± 0.02 vs. 0.046 ± 0.009, p = 0.02; Gly-Ins: 0.054 ± 0.017 vs. 0.002 ± 0.008, p <0.0001). Reactivity to NT-Ins and oxPTM-Ins was similar between LADA and T2D (NT-Ins median ± SE absorbance in LADA 0.05 ± 0.03; NT-Ins median ± SE absorbance in T2D 0.04 ± 0.028) (p=0.88). Antibody binding to Gly-Ins was also not different between LADA and T2D (Gly-Ins in LADA 0.093±0.020; Gly-Ins in T2D 0.093±0.019) (p=0.78). .OH-Ins antibodies were not different in LADA and T2D (.OH-Ins in LADA 0.122±0.023; .OH-Ins in T2D 0.095±0.021) (p=0.64). HOCl-Ins binding was also similar in LADA and T2D (HOCl-Ins in LADA 0.093±0.020; HOCl-Ins in T2D 0.05±0.017) (p=0.53). Conclusions: oxPTM-Ins antibodies are not prevalent in LADA compared to T2D.

Study 2: Post-translationally modified collagen type I antibodies in Osteoporosis and Diabetes. Hypothesis/Aims: The objective of this study was to test whether auto-reactivity to oxPTM of collagen type I (oxPTM-CI) is involved in osteoporosis in patients with T2D. Methods: This study included 12 patients with osteoporosis (OP) without diabetes, 12 patients with osteoporosis and T2D (OP + T2D) and 13 healthy controls (C). OxPTM-CI was generated using ribose, CuCl2, H2O2 and peroxynitrite (ONOO-). Reactivity to oxPTM-CI was observed by ELISA using sera from study participants. Statistical analysis revealed no significant differences for the .OH-CI antibody levels in OP, OP +T2D and C (.OH-CI median ± SE absorbance in OP 0.084 ± 0.032 vs. OP + T2D 0.097 ± 0.062 p = 0.46; vs. C 0.114 ± 0.026 p = 0.54.). ONOO-CI antibody binding was the lowest detected by the assay for all groups. Moreover, no differences among the three groups were observed (ONOO-CI in OP 0.044 ± 0.009 vs. OP + T2D 0.058 ± 0.033 p = 0.16; vs. C 0.065 ± 0.033p = 0.21). Conclusions: In conclusion, no reactivity against ox-PTM-CI was observed in osteoporosis, regardless
the presence of type 2 diabetes. Study 3: Establishing a genetic basis for parathyroid hormone secretion by studies of patients with normocalcaemic forms of hypoparathyroidism and hyperparathyroidism. Hypothesis/ Aims: The objective of this study was to investigate if alterations of the CASR, PTH and vitamin D metabolism genes may be responsible for hypoparathyroidism and hyperparathyroidism. Methods: Five groups of subjects (Euparathyroid forms of hypocalcaemia, n = 13; Euparathyroid forms of hypercalcaemia, n = 11; Normocalcaemic forms of hypoparathyroidism, n = 16; Normocalcaemic forms of hyperparathyroidism, n = 10; Healthy control subjects with normal calcaemia and PTH, n = 58) were selected on basis of serum albumin-adjusted calcium and PTH values for DNA sequence analysis of CASR, PTH and Vit D metabolism genes. DNA sequence analyses of the coding-region and exon-intron boundaries of CASR, PTH, GC and CYP24A1 genes were performed. All SNPs were processed by Sanger sequencing and an automated detection system. Departure from the Hardy-Weinberg equilibrium was determined by Chi-squared analysis (X2). Results: CASR rs1801725 (A986S) was more frequent in the low calcium group compared to the control group (p <0.01). Higher frequency of rs1801726 (Q1011E) in the low calcium group compared to controls was observed (p <0.001). CASR Exon 7 SNP rs1801726 was also observed more frequently in hypoparathyroid subjects compared to controls (p <0.0001). CASR rs4678174 SNP genotype frequencies were higher in hypoparathyroid subjects compared to controls (low PTH vs controls p <0.0001). Conclusions: No SNPs were detected in the causative relation between normal calcium levels and hyperparathyroidism or hypoparathyroidism; however, this study confirmed the involvement of the CASR SNPs rs1801725 and rs1801726 in the condition of hypocalcaemia.

DIABETES MELLITUS AND ATRIAL REMODELING IN PATIENTS WITH ATRIAL FIBRILLATION: ROLE OF ELECTRO-ANATOMICAL MAPPING AND CATHETER ABLATION

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Tutor  Germano Di Sciascio

Background and aim of the study Diabetes Mellitus (DM) and Atrial Fibrillation (AF) are two pandemic diseases. DM is one of the most important risk factors for AF and is a predictor of stroke and thromboembolism. The mechanisms of AF associated with DM are not fully understood and are represented by atrial autonomic, electrical, and structural remodeling, together with insulin resistance. AF ablation has become an established therapy for maintaining sinus rhythm in patients with symptomatic paroxysmal AF. This is primarily achieved through isolation of the pulmonary veins (PVI). In non-paroxysmal forms, more extensive ablations, i.e. substrate modification with complex fractionated atrial electrograms (CFAEs) ablation, may be required. The aim of this randomized study was to compare in terms of clinical outcome two strategies of catheter ablation (PVI vs PVI+CFAEs) for paroxysmal AF in DM patients. Methods The population of this study consisted of 64 patients with DM undergoing catheter ablation for AF: 32 of them were randomized to PVI and 32 to PVI+CFAEs ablation. The study population was also compared to a historical population of non-DM patients undergone catheter ablation (PVI) for paroxysmal, symptomatic drug-refractory AF. Follow-up consisted of outpatient visits and Holter monitoring performed after 1 month and each 3 months after the ablation procedure. Results In the study population (DM patients), with respect to a historical population of non-DM patients undergone paroxysmal AF ablation, a significant higher percentage of patients showed more than 25% of atrial area interested by CFAEs (Study Population 58% vs 15% Historical Group; P <0.05). A wider CFAEs area was reported in DM patients with Hb1Ac constantly above 7.5% during the 12 months preceding ablation (Hb1Ac >7.5% 41% vs. Hb1Ac <=7.5% 24%; P <0.05). Success rate of catheter ablation in study population was similar to that of historical population (Study Population 83% vs 85% Historical Group; P = NS). During follow-up the recurrences rate was similar in the two group (PVI 27% vs. PVI + CFAEs 21%; P = NS). In patients with recurrences the AF burden, expressed as number of AF episodes/patients, was similar in the two groups (PVI 4 ± 2 vs. PVI + CFAEs 3 ± 2; P = NS). In the PVI group, recurrences occurred with similar rate in patients with Hb1Ac >7.5% compare to those with Hb1Ac <=7.5% (Hb1Ac >7.5% 30% vs. Hb1Ac <=7.5% 22%; P=NS), but a greater AF burden was observed
in those with Hb1Ac >7.5% (6±2 Hb1Ac >7.5% vs. 1±2 Hb1Ac <=7.5%; P <0.05). This was not the case for PVI+CFAEs group. A significant benefit with PVI+CFAEs was identified in patients with Hb1Ac >7.5% (HR 1.28, CI 1.11-1.45, P <0.05), more than 25 years from DM diagnose (HR 1.25, CI 1.09-1.50, P <0.05) and more than 5 AF episodes/year (HR 1.2, CI 1.03-1.55, P <0.05). No significant interaction was identified for other subgroup of patient. Conclusions This is the first randomized study that investigated atrial remodeling in type 1 DM humans using electroanatomical mapping system. The main findings of this study are: a) DM patients had a more complex atrial "substrate" than non-DM patients; b) in study population at 1-year follow-up the recurrences rate was similar in the groups of patients; c) specific subgroup of patients may benefit from more complex ablations. Recurrences rate seem to be associated more with glycemic control than to simpler procedure. Upstream therapies targetting atrial remodeling may play a key role in the treatment of AF in DM pts.

EFFICACY AND TOXICITY OF AUTOLOGOUS STEM CELL TRANSPLANTATION IN NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS: FOCUS ON GASTROINTESTINAL ADVERSE EVENTS

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Background: Although multiple myeloma (MM) continues to be considered incurable, an Overall Survival Improvement has been achieved in a significant fraction of patients. High-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (Auto-HCT) is still the standard treatment for patients affected by MM younger than age 65. The superiority of Auto-HCT, in terms of complete response (CR), overall survival (OS) and disease-free survival, has been demonstrated in numerous studies, however is not yet free of adverse events (AEs). In the 40% of patients treated with conventional chemotherapy followed by Auto-HCT a severe oral mucositis (MO) appears, associated with disabling pain and further gastrointestinal toxicity. Our aim was to report the results of a monocentric, observational, retrospective study, which involved a cohort of patients with newly diagnosed MM treated with new or old drugs followed by single or tandem Auto-HCT. The research focused on evaluating the incidence of AEs, especially gastrointestinal.

Patients and Methods: The data collection, completed over two years, obtained a sample of 258 newly diagnosed MM patients between August 1989 and May 2014. The median age was 54 years (range, 37 – 69), 121 were women and 137 men. As induction treatment, between October 1988 and October 2008, 173/258 patients received old drugs, i.e. vincristine, doxorubicin and dexamethasone (VAD; n=166) or melphalan and prednisone (MP; n=7), while 85/258 patients, between February 2005 and November 2013, were treated with novel agents, i.e. velcade-based (n=67) or IMiD-based regimens (n=18). All 258 patients received high doses of melphalan and single (n=149) or tandem (n=109) auto-HCT.

Results: Among patients treated with old drugs, a CR/nCR/VGPR was achieved in 31/173 (17.9%) after induction, in 50/173 patients (28.9%) after single auto-HCT and in 19/55 patients (34.5%) after tandem auto-HCT. While for patients treated with novel agents, a CR/nCR/VGPR was observed in 36/85 patients (42.3%) after induction, in 35/85 patients (41.8%) after single auto-HCT and in 27/50 patients (54%) after tandem auto-HCT. From the detailed research on the new drugs, no differences were observed in terms of response and survival between IMiDs or velcade-based regimens. Overall survival (OS) and progression-free survival (PFS) at 10 years, for all 258 patients, was 44.4% and 22.5%, respectively. OS and PFS were better for patients in CR/nCR/VGPR after induction compared to those in partial response or stable disease (OS: 62.1% vs 40.7%, p=0.06 and PFS: 36.2% vs 17.2%, p=0.06). In addition, OS and PFS showed better results for patients treated with new drugs than those treated with old drugs (OS: 66.1% vs 51.5%, p=0.09; PFS: 55.0% vs 25.3%, p=0.0039). Non-hematological major toxicities after single auto-HCT were detected in 153/258 patients (59%) and in 52/126 patients (52%) after tandem. The highest incidence after single auto-HCT were gastrointestinal AEs (53.5%), followed by infectious toxicities (31.0%), Fever of Unknown Origin (22.1%), respiratory toxicity (6.9%), and lastly cardio
circulatory, neurological and genitourinary toxicity (3.1%). After tandem auto-HCT the infectious toxicities are more frequent (16.7%) than gastrointestinal (13.5%). A considerable reduction is observed for FUO and genitourinary toxicity between single and double auto-HCT (22.1% vs 7.94% and 3.11% vs 0.79% respectively). Among infections observed, the pathogen most involved is Herpes Zoster Virus (HZV) followed by Escherichia coli (E.coli). Since diarrhea and MO are the most frequent AEs observed among gastrointestinal (72.5% and 90% respectively), the research focused on correlation between diarrhea and MO or infectious agents. The incidence of patients with positive rectal swab is 22.5% (diarrhea caused specifically by E.coli, Candida albicans and Klebsiella pneumoniae), while a negative rectal swab appeared in 47.5% of patients, resulting in this case that diarrhoea was caused by MO. Among patients with mild MO (grade 1 and 2 considering the Common Terminology Criteria for Adverse Events - CTCAE version 4.0), the median of weight loss is 3 kg and the median of hospitalization is 18.5 days; for patients with severe MO (grade 3 and 4) the median of weight loss is 4 kg and the median of hospitalization is 22.5 days. Pearson’s index, Student’s T-Test and Mann Witney U Test have demonstrated that a weak but statistically significant correlation (p=0.03) exists between grade of severity of MO and weight loss. No correlation was instead observed with hospitalization.

Conclusions: The use of new drugs as first-line treatment allows obtaining better responses. However, responses obtained after tandem auto-HCT are better than induction with both old and new drugs. These results indicate that despite the current era of IMiDs and proteasome inhibitors, the auto-HCT remains the standard therapy for young, newly diagnosed MM patients. Our data suggest that the treatment choice is important for survival and quality of life. Among non-hematological toxicities, gastrointestinal are those that appear with a higher incidence after single auto-HCT. The MO is the most frequent gastrointestinal toxicity associated with auto-HCT, continuing therefore to be a serious clinical problem. Finally, the study of post-transplant complications not only helps to improve the patient’s quality of life but also the economic consequences and costs derived from such complications. Therefore, the impact of MO on the economic resources would be a considerable interest for national health system.

THE HOPE DIMENSION IN CANCER PATIENTS: BIOETHICAL AND CLINICAL PERSPECTIVES

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Hope is a multidimensional characteristic that involves different human dimensions, the construction of which has been studied several times in multiple disciplinary fields. Our clinical study aims to assess the impact of the pathology in relation to the level of hope and compare the level of hope with other clinical and socio-demographic variables. The results show that: a) the experimental sample, 84.3% of which was composed of stage IV cancer patients, had an average hope level (mean ± es = 35.47 ± 0.78); b) there was no significant correlation between health and hope; c) there were no significant differences in hope levels, while there were significant differences in physical health (PCS). The data collected would indicate that hope is a dimension independent of diagnosis, disease stage, sex, type of hospitalization, marital status and does not change in the various age groups. It would seem to be a construct that remains stable over time and is poorly influenced by other variables.

Given this phenomenological development, which shows that cancer patients have a high level of hope comparable with that of healthy subjects, it can be claimed that hope does not necessarily depend on the circumstances. Hope focuses more on sense (rather than on pain) without imposing it by will in accordance with predetermined schemes, gathering it from experience, looking for it day after day, in a humble attitude of surprise, wonder and gratitude.

It is therefore necessary to recognize hope as rooted in our being (ontological hope) which we must know and nurture (virtue). Therefore, it is not merely a natural hope understood as an instinct for survival, nor a theological virtue in the first instance, but it is the man’s free choice to adhere to what he truly is, the choice to generate or not generate, to live or die.
PERFORMANCE EVALUATION OF MOTION CAPTURE SYSTEMS FOR RESPIRATORY FUNCTION ASSESSMENT

Ph.D student  Carlo Massaroni
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Motion capture (MoCap) is the process of recording the movement of objects or people. Currently, within a large number of MoCap technologies, the most affordable and accurate analysis of the musculoskeletal system can be performed by using systems based on the tracking of markers positioned on specific body landmarks. Scientific literature outlines a validation issue for results from the same subject examined by different laboratories: to ensure a correct diagnosis, standard methods are required for the evaluation of the performances of measurement systems so that values and uncertainties of kinematics and dynamics quantities can be evaluated with repeatability and reproducibility. No established procedure based on metrological tools have been developed for a fast, in-situ evaluation of MoCap systems for small movement detection and breathing assessment purposes. Moreover, no volumetric platform have been developed to test performances of MoCap system in the calculation of volumes and volume changes, neither in static and dynamic conditions. So, the developing of a method for calibration assessment and measurement uncertainty evaluation of MoCap system applied to the movement as well as mechanical ventilation analysis should be useful to propose a new procedure to establish a standard for quality for mechanical measurements performed in movement analysis laboratories. Moreover, the exploration of alternative solutions for analysis of breathing with optical technologies is needed. The application of MoCap technology to extend the potentiality of currently available instruments to better understand the biomechanics of breathing in healthy subjects, pathological ones and in new populations like elite athletes, during exercise at the different level of effort and with dysfunctional breathing symptoms could be interesting to improve the knowledge of human physiology. Despite some attempts have been proposed, an easy-to-use software for the analysis of breathing values and kinematical parameters should improve the use of that tools by clinicians and researchers in general. The proposed procedure and software will be available for care centres of movement analysis and mechanical ventilation analysis as well as institutions where MoCap systems are used. To overcome some limitations of MoCap systems in some scenarios and in the environments in which the collection of a large number of markers are complicated for a prolonged time (i.e., sports activities), wearable textiles may be used to collect vital signs, breathing parameters and biomechanics in general. In the last years, the growing interest in smart textiles for medical applications is driven by the aim to increase the mobility of subjects who need a continuous monitoring of physiological parameters. Smart textiles can embed one or more sensors to monitor various mechanical, thermal and chemical parameters (e.g., strain, temperature, displacement, oxygen blood saturation). The lung volume and breathing temporal parameters (i.e., breathing rate, inspiratory/expiratory times and ratio) can be obtained by means of devices that measure flowrate at the mouth (i.e., portable pneumotachometers, flow sensors), requiring the use of a facemask. However, no information about the biomechanics of the breathing can be obtained. Since the chest and the abdomen show movements related to the alternation of inspiration and expiration, temporal and kinematical parameters of the breathing can be potentially evaluated by registering these movements. Wearables based upon the strain evaluation can be potentially employed at this scope. Within the large numbers of technologies can be adopted, during the last decades, the use of fiber optic-based sensors (FOSs) has been gaining acceptance in the development of systems to monitor respiration. Literature shows a lack of investigation in the placement of the sensors, as well as a limited number of trials aiming at validating the measurements performed by the smart textiles. The specific aims of this Thesis dissertation are: 1. Design, development, and test of a mechatronic platform for in-situ test of MoCap systems; 2. Test of marker-based systems for movement analysis in the range of small movements with the developed platform; 3. Design, development, and test of methods to ensure accurate measurements of breathing volumes and features from tridimensional coordinates collected by MoCap systems, in a range of application; 4. Design, development, and test of wearable solution to collect breathing parameters, and the relative algorithms to extract breathing features. This Thesis is structured in five chapters briefly described below.
to report the background, methodology and experimental results in accordance to the specific aims. Chapter I presents an in-depth analysis of the characteristics of MoCap system used in the musculo-skeletal system evaluation. By the analysis of the literature, the optoelectronic plethysmography seems to be a promising technology for the investigation not only of breathing parameters (as temporal parameters and lung volumes) but also of the biomechanics of breathing. The biomechanics of the chest wall during exercise can highlight breathing strategy and pathologies impossible to be detected with flow-based traditional technologies (i.e. spirometry). Moreover, there is the need of an instrument for the fast volume calibration for MoCap as well as for the assessment of the performance among the time of MoCap used in the field of breathing assessment. A the end of the Chapter a brief summary of wearable solutions for breathing monitoring have been also presented, highlighting the major limitations of available systems have been used in this promising field. Chapter II will be devoted to the description of the design, metrological evaluation, and test on a motion laboratory of a fully programmable mechatronic platform. This platform (two versions of the platform will be described) allows delivering known displacement and volume to MoCap system. Its metrological characterization will be described as well as the motion control strategy adopted to optimize its performances. The results of a calibration of one MoCap performed by the use of the platform will be also reported and discussed. In the third chapter, the description of all the methods used to compute volumes from tridimensional coordinates will be described and reviewed. Then, three new methods will be described and the performances of these methods will be discussed against a spirometry data collected on healthy subjects. Moreover, a paragraph is completely devoted to new approaches in the evaluation of breathing in sports science including the description of an ad-hoc developed software for the breathing analysis. Lastly, the comparison between full and reduced markers protocols in the breathing volumes and kinematics evaluation will be presented as well as the result of the application of MoCap system and the developed software in the non-invasive investigation of kinematics and breathing volumes in the dysfunctional breather. The fourth chapter will be devoted to the wearable technologies for the respiratory monitoring. The first section will describe the actual technologies based on the optical fibers used in this field; in the next sections different design of a smart textile design and made to measure vital signs will be described and its performances in the measure of breathing rate, temporal features, volume and compartmental volumes as well as heart rate in harsh environments will be described. Lastly, the fifth chapter will summarize the main findings of this dissertation as well as the limitations and areas of future development and application of the methods proposed in this research.

NEW TECHNOLOGIES AND ADJUVANT TREATMENTS FOR THE MANAGEMENT OF TYPE 1 DIABETES

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Tutor Paolo Pozzilli

Type 1 diabetes (T1D) is an immune-mediated chronic disease accounting for 5-10% of the total cases of diabetes and its incidence is growing worldwide. As a result of the autoimmune process, inducing the failure of insulin-producing cells, intensive insulin therapy represents the gold standard treatment to maintain blood glucose homeostasis. In 1993, the effectiveness of intensive insulin therapy in T1D has been widely established in Diabetes Control and Complications Trial (DCCT). Moreover, it was affirmed that optimal glycaemic control is directly related to the reduction of incidence and progression of long-term diabetes complications. Therefore, tight glycaemic control is overall recommended for T1D patients with near-normalization of blood glucose levels and an HbA1c <7.0% as the treatment goals. However, a great number of T1D patients have a suboptimal glycaemic control and 60% of people with T1D monitor less frequently than American Diabetes Association (ADA) recommendations of ≥3 tests daily. On the other hand, benefits of intensive insulin treatment observed in the DCCT came with a three times higher risk of severe hypoglycaemia compared to the conventional therapy with one or two daily insulin injections and the fear of hypoglycaemia keeps many patients away from intensive...
treatment and achievement of recommended glycaemic goals. Furthermore, treatment goals should be achieved safely and effectively by maintaining daily flexibility to fit individual lifestyle and without major variations in eating behaviours and physical activity promoting patients' compliance and their overall quality of life. Therefore, to reduce these main limiting factors supporting long-term diabetes management the newer technologies and adjuvant treatments represent areas of investigation with important clinical applications. The overall aim of my PhD was to find out if new technologies and adjuvant treatments may improve glycaemic control and patients compliance, reducing glucose variability in T1D patients. This thesis includes two sections: the first one section is focused on the effectiveness of a bolus advisor calculator on glycaemic control in T1D patients undergoing intensive insulin therapy; the second section evaluates the hypothesis that D-Chiro-Inositol (DCI) plus Folic Acid oral supplementation can act as adjuvant treatments to insulin therapy in overweight or obese T1D patients, reducing insulin resistance. 1st section: in order to achieve an optimal glycaemic control in insulin-treated T1D patients the rationale of this part of the thesis has been the higher frequency of errors with empirical calculations of mealtime insulin doses. In fact, 42% diabetic patients administer an uncorrected dose of prandial insulin and the few studies carried-out on bolus calculator systems have been published with controversial results. At the same time, we tested effectiveness and feasibility of a wireless meter integrated with a bolus calculator working with a telemedicine system. Furthermore, we investigated the efficacy of this automated bolus calculator (ABC) and wirelessly communicated blood glucose measurement on glucose variability, by the use of a continuous glucose monitoring system (CGMS). The rationale is clearly established from the DCCT results suggesting that glycaemic variability may be an additional risk factor for the long-term diabetes complications and the new treatment strategies are increasingly focusing on reducing post-prandial glycaemic excursions. The results of this section have demonstrated that an ABC system is a friendly wireless meter that helps to improve glycaemic control and patients compliance to SMBG. Moreover, patients using an ABC showed a significant reduction of time spent in hypoglycaemic range compared to the control subjects. 2nd section: The rationale of this section of the thesis was based on the worldwide rise of obesity in childhood and adolescence with the consequent increase of insulin resistance also in young patients with T1D. In fact suboptimal glucose control is often due to the higher insulin doses causing an increased risk of hypoglycaemic events, weight gain and poor glycaemic control. On this basis, the second part of this thesis was focused on a research project evaluating the hypothesis that D-Chiro-Inositol (DCI) plus Folic Acid oral supplementation may improve glucose control reducing insulin resistance in overweight or obese T1D patients. In fact, D-Chiro-Inositol (DCI), as putative mediator of intracellular insulin action can accelerate glucose disposal and act as insulin sensitizer. Moreover, folic acid administration seems to improve glycaemic control reducing insulin resistance in other insulin resistant conditions. Therefore, we carried-out a 24 weeks, prospective, randomized, control trial in 26 overweight or obese T1D patients, undergoing intensive insulin therapy. The results of this trial demonstrated for the first time that the DCI plus Folic Acid oral supplementation can improve glycaemic control in overweight T1D patients, as showed by the significant reduction of HbA1c at the end of the study period.

ANALYSIS AND DEVELOPMENT OF COMPUTER-BASED SOLUTIONS FOR IIF APPLICATIONS

Ph.D student Mario Merone
Tutor Carlo Sansone

The antinuclear antibodies (ANAs) can be found in rheumatic and non rheumatic conditions, but their importance depends strongly on the clinical suspect of ANA Associated Rheumatic Diseases (AARDs). The indirect immunofluorescence (IIF) on human epithelial cells (HEp-2) is considered the gold standard for ANA testing however, it is strongly influenced by several issues. This manuscript aims to provide significant contributions in the IIF research, in the biomedical field, which is a bridge between engineering and medicine. For this reason will be presented engineering solutions designed for medical applications. We discuss different issues that should be considered in a systematic way to provide effective and viable solution in IIF research: image segmentation; inter-observer reading IIF variability study, fluorescence intensity classification. With respect to the first issue, this
PhD Courses and XXX cycle theses (2015-2017)

manuscript tackles with HEp-2 cells segmentation, i.e. one of the open issue in HEp-2 image analysis, providing contributions into four main directions: we survey the literature on HEp-2 image segmentation dividing the works in the literature into three main categories. We introduce a segmentation pipeline employing a deformable model whose energy minimization, differently from the classical snakes and active contour models, it can detect objects with boundaries not necessarily defined by gradient since the stopping term is related to a particular segmentation of the image rather than on a derivative quantity. We make available new 24 HEp-2 images containing 985 cells, thus enlarging the reference image dataset publicly available that now contains 1964 cells. We experimentally benchmark the proposed segmentation method with most representative methods in the literature using the enlarged image repository, revealing that a segmentation pipeline using active contour better copes with the variability in cell appearance due to different fluorescence intensities and staining patterns as well as to irregular illumination. Let’s now turn the attention to inter-observer reading IIF variability study, the results archived in our analysis show that is necessary and crucial a standardization of ANA testing and how it is far from being completed. In fact the IIF method is labor intensive, subjective and prone to reader bias. A proposal of tight procedures both for users (working protocol) and for manufacturers (assay kits production) and a large use of international standards and independent calibrators could make easily the standardization process. Therefore, an international standardization of the HEp-2 assay kit (fixative used, conjugate etc.) and the introduction of a CAD system may represent two important elements of this process reducing operator time of work and improving the diagnostic efficacy. CAD systems may represent one of the most important novel elements of harmonization in the autoimmunity field, reducing intra- and inter-laboratory variability in a new vision of the diagnostic autoimmune platform. Furthermore, our study demonstrates that there can be marked discordance between ANA results drawn from different laboratories mostly for intensity and multiple patterns classification. Laboratories agreement improves using digital images and comparing each single human evaluation to a potential reference (gold standard) data that is essential for use CAD systems in routine work lab. Finally, with respect to fluorescence intensity classification, the results archived by the proposed system show that the method of Maximum Observation allows a gold standard that maximizes the agreement between expert physicians minimizing the probability of incorrect label on training sample and also that the system archives performances comparable to those archived by human experts and superior, to those obtained by method at the state-of-art.

TECHNIQUES FOR DEFORMABLE ORGAN REGISTRATION IN DCE FRAMEWORK

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In the last decades, the development of non-invasive medical imaging modalities enabled remarkable progress in clinical diagnostics. Many diseases are nowadays detected by medical imaging techniques, which allows for earlier diagnosis and therapeutic intervention with a higher efficiency. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a clinical technique devoted to the study of lesions in organs. It is based on the analysis of perfusion dynamics of a contrast agent (CA) in the examined tissues by acquiring an image series over time, before, during and after the arrival of the CA. The acquired signal is analyzed for a selected region of interest (ROI) or individual pixels in each 2D slice of the series to generate an enhancement curve (EC), which reflects the tissue’s response to the arrival of the CA by time-dependent enhancement value of the detected intensity. These curves provide a set of parameters, commonly visualized by 2D color maps, that yield valuable information for diagnosis. However, for a correct diagnosis, it is crucial to determine the EC with a high accuracy, which is often compromised by artifacts within the acquired time series due to patient motion. DCE algorithms assume that the analyzed ROI does not modify its shape and position over the entire time series, which is usually not a valid assumption, since the examined non-rigid structures are affected by patient motion and can change in position, shape and brightness. The compensation for such artifacts is complex, since the detected signal intensities intrinsically vary over time due to the diffusion of the CA. In this thesis, we present a novel technique to compensate artifacts in DCE induced by motion/deformation of the ROI. The algorithm uses deformable
active contours (AC), also called snakes, to define the deformation of the ROI in each image. We optimized the standard AC method by adding an additional term to the energy functional that is minimized during the procedure. Specifically, we included a distance map calculated with the Chamfer transform into the external forces that are responsible for the attraction of the snake to the edges in an image. This results in a considerably more accurate detection of the contour of the ROI by the snake and thus in a better segmentation. Subsequently, the center of mass and the principal axes for each frame are determined and used for a rototranslation compensation of misalignment between the frames. The algorithm was applied to different organs of the abdominal part and the results clearly show an improved accuracy of the corrected EC and the resulting parameters, when compared to the uncorrected EC. In addition to inter-frame misalignments, motion artifacts also cause displacements in the transverse direction relative to the image plane, thereby generating inconsistencies in the shape of the organ profiles in the same temporal series. Therefore, we extended our algorithm to four dimensions by using a hybrid approach based on ACs and a template matching algorithm based on the Chamfer distance. The frame-by-frame method segments the ROI of a particular frame via the AC model, subsequently, the final contour of the time frame is compared to the images of the same and adjacent planes of the successive frame and the best match is assigned to the previous image. Finally, we introduce a fast and user-friendly tool to analyze 4D DCE-MRI data. The results can be visualized in different 3D representations and provide quantitative volumetric information in order to improve the understanding of the contrast agent perfusion in pathological tissues and the resulting diagnosis.

**MOTION CAPTURE SYSTEMS FOR RESPIRATORY, GAIT AND POSTURE ANALYSIS**

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**Tutor**  Loredana Zollo

In this paper, we have presented some interesting clinical uses of optoelectronic motion analysis systems. Such systems have shown a great reliability as for detecting even small movements, like those of thoraco-abdominal wall. This is a major advantage of this kind of motion capture, as demonstrated by the diffusion of this kind of analysis for studying respiratory diseases. In particular, the possibility to measure several compartments independently has been shown to be very useful for clinical purposes. To point out this advantage, we showed how posture (sitting or supine) can influence breathing kinematics among spinal cord injured patients, and the synchronization between upper thoracic and abdominal compartments. Other examples of how useful marker-based stereophotogrammetric systems in clinical practice are represented by the analysis of trunk alignment in Parkinson disease and the assessment of ankle foot orthoses in gait analysis, as well as for postural stability in amputee patients. Future directions of research would be to make motion analysis systems even more invasive; in this way of research, wearable sensors as well as sensorized fabrics promise to enhance body movements analysis, thus avoiding the limits of a laboratory setting.

**BIOLOGICALLY ACTIVE PHENOLIC COMPOUNDS IN FRUITS AND LEAVES OF CYCLANTHERA PEDATA (L.) SCHRAD (CAIGUA) AND IN RELATED PLANT-DERIVED FOOD SUPPLEMENTS**

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**Tutor**  Laura De Gara

Cyclanthera pedata (L.) Schrad., known as caigua, is an edible plant belonging to the Cucurbitaceae family and native to South America, which is also used for therapeutic purposes. The local folk medicine recommends the daily intake of fruits and leaves of caigua for the treatment of several diseases, e.g. diabetes, high blood pressure and LDL-cholesterol. Recently, food supplements produced from caigua fruits are available on the European market. They would be associated with anti-hypercholesterolemic and anti-hypertensive properties, also
reported in literature. Recent scientific studies relate the anti-hyperglycaemic properties of this plant to the high content of phenolic compounds, the most abundant class of secondary metabolites, and in particular to the glycosylated flavonoids' subclass. Currently, high performance liquid chromatography (HPLC) is the technique of choice for the qualitative and quantitative analysis of phenolic compounds extracted from caigua. Nevertheless, high performance thin layer chromatography (HPTLC) is widely employed for the initial examination of plant extracts before HPLC analysis, because of well-known advantages, such as short separation times, amenable to detection reagents, possibility of running several samples simultaneously, and suitability to be hyphenated to mass spectrometry (HPTLC-MS). The aim of this work has been to investigate the occurrence and content of phenolic compounds in a commercial food supplement in comparison to those determined in leaves and fruits of caigua. As part of the research, an HPTLC-MS method was developed for the preliminary screening of phenolic compounds occurring in the above samples. Further studies were performed in order to investigate the influence of pedo-climatic conditions and vegetative state on the accumulation of phenolic compounds in the leaves and fruits of plants grown in different geographical areas, with the purpose to select the best growth conditions to get raw materials with a greater amount of beneficial molecules for food supplements manufacture. More in-depth analysis were performed by developing an HPLC-MS method and the resulting data were compared with previously obtained results. A total of ten glycosylated flavonoids were identified, nine of which already reported in literature, while one was never identified before. Both HPLC and HPTLC data converge in hypothesizing a strong influence of plant vegetative state on the accumulation of phenolic compounds in caigua leaves, while both techniques reveal the presence of more preserved phenolic patterns in the caigua fruits. Moreover, a simple hydrolysis procedure, having the advantages of miniaturisation (low sample and solvent consumption), simultaneous hydrolysis of multiple samples, use of inexpense glassware, and no need of instrumentation, was developed, in order to confirm the phenolics characterization in the studied plant. The redox activity and the levels of vitamin C in leaves and fruits of C. pedata were determined as well. All obtained results are reported and discussed in this thesis.

THE INDISPENSABILITY OF AN INTERDISCIPLINARY APPROACH IN BIOETHICS FOR INDIA

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This PhD thesis analyses the multi religious and multicultural background of India to propose a core curriculum for bioethics/medical ethics in the distinctive pluralistic context of the country. A detailed study of the multiplicity in the areas of ethnicity, religious affiliations, medical traditions, cultural priorities, linguistic barriers etc. allows to have a profound scrutiny into the unique Indian scenario where the ethics curriculum in the health care system is put forward. With a broader enquiry into the potential frameworks in the society that can foster the dissemination of bioethics in the country and a deeper investigation through the institutions where the medical ethics curriculum already exists, the research finds its ways to propose the core curriculum in bioethics/medical ethics for India.

ROLE OF PLATELET REACTIVITY AND LEPTIN IN CARDIOVASCULAR OUTCOME OF PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTIONS

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Research Project 1 Background. The incremental predictive value of high inflammatory status and high on-treatment platelet reactivity (HPR) on the occurrence of periprocedural myocardial infarction (PMI) after percutaneous coronary intervention (PCI) has not been characterized. Methods. 500 PCI patients (pts) treated with clopidogrel
had preprocedural measurement of CRP levels and platelet reactivity (PR) using VerifyNow P2Y12 assay. Elevated inflammatory status was defined as CRP >3 mg/L and HPR as P2Y12 reactivity units (PRU) >240. Results. Rates of PMI were increased in pts with CRP levels >3 mg/L (10.9% vs 4.6%, OR 2.4, 95% CI 1.2 to 4.5, P = 0.015) and in pts with HPR (11% vs 5.5%, OR 2.2, 95% CI 1.2 to 4.4, P = 0.018). The occurrence of PMI was highest in the subgroup with HPR and high inflammatory status (16.6% vs 3.6%, OR 4.3, 95% CI 1.5 to 12.6, P = 0.008). Conclusions. In pts who undergo PCI, baseline stratification according to PR and inflammatory status may identify those at higher risk for PMI. Research Project 2 Background. Growing evidence suggests that PR may predict bleeding. We investigate the incremental value of PR in predicting bleeding PCI via the femoral approach over a validated bleeding risk score (BRS). Methods and Results. 800 PCI pts were included. PR was measured before PCI with the VerifyNow P2Y12 assay and low PR was defined as a =1.78. Calculation of the BRS included the following: age, sex, intra-aortic balloon pump, glycoprotein IIb/IIIa inhibitors, chronic kidney disease, anemia, and low-molecular-weight heparin within 48-hour pre-PCI. A new risk score including low PR (BRS-PR) was developed and validated in an independent cohort of pts (n = 310). Bleeding events at 30 days after PCI were defined according to the REPLACE-2, and BARC criteria. Both BRS and PR showed high discriminatory power for bleeding (AUC >0.7 for all definitions). In the validation set, BRS-PR showed higher discriminatory power for TIMI bleeding than BRS alone (AUC = 0.788 versus 0.709; P = 0.036). Conclusions. PR has incremental predictive value on bleeding events after PCI via the femoral approach over a BRS. Research Project 3 Background. No comprehensive data are available on role of platelet indices (PI) in periprocedural risk stratification of pts undergoing PCI. Methods. 502 PCI pts had preprocedural measurement of PI and PR, the latter assessed by the point-of-care VerifyNow P2Y12 assay and expressed as PRU. Study endpoints were HPR and PMI according to tertiles of PI. Results. Incidence of PMI was 6.6%. Rates of PMI were not different among PI tertiles: platelet count (I: 6.0%, II: 7.1%, III: 6.5%; P = 0.74), mean platelet volume (I: 6.6%, II: 7.3%, III: 5.8%; P = 0.86), platelet distribution width (I: 7.2%, II: 7.2%, III: 5.4%; P = 0.74), MPV/P ratio (I: 6.6%, II: 6.0%, III: 7.1%; P = 0.91). A significant difference in the occurrence of PMI was identified among PRU tertiles (I: 3%, II: 5.4%, III: 11.4%; P = 0.006). Conclusion. This study showed no relation between PI and PMI in PCI pts, but confirms association of HPR with increased incidence of PMI. Research Project 4 Background. Leptin is an adipose tissue derived hormone, which is involved in the regulation of food intake and energy balance. No data are available on relation of leptin and PR and cardiovascular outcome in pts undergoing PCI. Methods. 155 PCI pts were enrolled in the study and had preprocedural measurement of plasma leptin levels and PR. Leptin levels were assessed by ELISA. Hyperleptinemia was defined as leptin levels ≥14 ng/ml. PR was evaluated by the VerifyNow P2Y12 assay and expressed as PRU. Pts were divided in three groups based on PRU values: LPR for PRU =178; NPR for PRU between 178 and 239; HPR for PRU =239. All pts were followed every 12 months for up 8 years. Results. Leptin plasma levels were significantly different among groups of PR (P = 0.047). In particular leptin levels were significantly higher in pts with HPR (12.61 ± 16.58 ng/ml) compared to LPR (7.83 ± 8.87 ng/ml, P = 0.044) and NPR (7.04 ± 7.03 ng/ml, P = 0.01) group. Incidence of PMI in the study was 8%. Rate of PMI was higher among hyperleptinemic pts (15.1% vs 6.5%, P = 0.22). Clinical long-term follow-up was complete in 140 pts (90.3%). Incidence of MACE was 40% in hyperleptinemic group and 21% in the normoleptinemic group. Pts with hyperleptinemia experienced a significantly higher rate of MACE compared with those in the normoleptinemic group (HR 2.3; CI 95% 1.14-4.6, P = 0.02). Conclusions. The present study suggests that high levels of leptin are associated with HPR and with a worse clinical outcome in pts treated with clopidogrel undergoing PCI.

TACTILE SENSING SYSTEM FOR BIOMECHATRONIC PROSTHETIC HANDS AND GRASP ANALYSIS

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Tutor Loredana Zollo

The development of the artificial tactile sensing began in the 1970s. During the last decades, tactile sensors
based on different sensing principles have been developed; the emulation of the physiological sense of touch has gained growing interest in fields such as robotics, as the modern robots are increasingly moving towards unstructured environments. Thus, the acquisition of information about interaction forces and surface properties (such as roughness, hardness, shape etc.) became highly desirable. Several technological solutions have been employed to design tactile sensors; nonetheless, their inclusion within artificial systems still remains problematic in several fields. This is also true when the prosthetic domain is considered. Although tactile sensing is an essential element for autonomous dexterous manipulation, no prosthesis endowed with tactile sensors is available in the market. The present PhD thesis deals with the sensorization of a mechatronic, prosthetic hand, featuring the twofold objective of: i) allowing the control system embedded in such a prosthesis to use sensory information in a closed-loop control, optimizing the applied forces (e.g., during a grasping task) and preventing the manipulated object from slipping; ii) providing the prosthesis user with the aforementioned sensory information, obtaining a closed-loop system which gives the amputee the possibility to properly interact with the external world through the tactile feedback. Starting from the study of human and robotic hands, particularly in terms of tactile characteristics, a solution for an artificial sensory system adoptable for prosthetic hands has been elaborated. This system has been evaluated on a mechatronic hand, namely IH2 Azzurra (Prensilia srl, Pontedera, Italy), similar to the commercial ones but conceived for research scenarios and thus open to both hardware and software modifications. In order to understand the pressure applied onto the objects and its hardness level, force regulation is crucial as well as the avoidance of slippage events. To this end, force and slip sensors are needed for an effective prosthesis sensorization. With the aim of deepening the comprehension of the aforementioned applied pressure, a preliminary evaluation of the grasping forces exerted by human subjects has been done by means of instrumented objects, purposely designed (through CAD software) and developed. These objects have common shapes and dimensions as objects of daily life, but are equipped with sensors for monitoring various physical quantities (such as force, acceleration, temperature etc.). The developed objects have been provided with piezo-resistive sensors for force measurement and with an accelerometer for estimating object orientation and detecting slippage. Suitability for the performance of some Activities of Daily Living (ADLs), such as bi-digital and tri-digital grasps, has driven the design of the objects. The quantities measured with the objects can help obtain insight into the grasping strategies employed by the users. The objective of measuring the force levels applied by an artificial hand can be accomplished by means of tactile sensors. This leads to the sensorization of the above mentioned prosthetic hand. First, a given transduction technology has been chosen within the available ones for the force measurement. This choice has been followed by the identification of the areas to sensorize, which have coincided with the five fingertips, with the metacarpophalangeal joints (MCP) and with the thenar eminence. These areas have been redesigned through CAD software for the inclusion of tactile sensors, given that the IH2 Azzurra (hereafter indicated as IH2) is not equipped with this kind of sensors. Piezo-resistive sensors have been employed: opportune circuitry has been developed for the conversion of the sensors output (i.e., electrical resistance variation) into a force signal, with the realization of dedicated PCBs for the sensors output collection and conditioning. Moreover, an algorithm for identification of slip phenomena has been developed. This algorithm can be easily applied on the force sensor output, allowing the measurement of the force and the generation of an ON/OFF signal relating to the presence or absence of slip events during grasp. The algorithm has rigorously been validated on different typologies of resistive sensors and used for an online implementation into a prosthetic control.

**STUDY OF THE MECHANISMS INVOLVED IN ROS SCAVENGING IN TWO RICE VARIETIES (ORYZA SATIVA SSP. JAPONICA) WITH DIFFERENT SENSITIVITY TO SALT STRESS**

**Ph.D student** Maria Beatrice Ronci  
**Tutor** Vittoria Locato

Soil salinization is a major constraint on crop production worldwide and affects at least 33% of arable lands,
and more areas are expected to deteriorate in the coming years due to changes in global climate. Plants differ greatly in their tolerance to salinity. Most crop species cannot withstand high concentrations of salt, and rice (Oryza sativa L.) is the most salt-sensitive species among cereals. Salt tolerance is a complex trait varying between and within species.

Soil salinity imposes two primary stresses on plants: first is osmotic stress and later ionic stress arises when Na⁺ concentrations reach toxic levels inside the cells. To cope with this adverse condition, plants have evolved a multifaceted range of physiological and metabolic responses activating many stress-responsive genes and synthesizing diverse functional proteins and metabolites through a complex signal transduction network. The molecular processes controlling early salt stress perception and signalling are not yet fully understood. High salinity is known to induce the formation of reactive oxygen species (ROS) within plant cells at very early stages of response.

While ROS have the potential to cause oxidative stress, several studies have shown that ROS also play a key role in plants as signal molecules. ROS-mediated signalling is controlled through a delicate balance between its production and scavenging. Low doses of H₂O₂ have been shown to induce protective mechanisms and acclimation responses against oxidative and various abiotic stress. Elevated concentrations of ROS, alone or in combination with other molecules, induced by several stresses can eventually trigger programmed cell death.

To prevent oxidative damage induced by high production of ROS, plants have evolved enzymatic and non-enzymatic antioxidative systems that are crucial for ROS homeostasis controlling the levels of ROS inside the cells. H₂O₂ profiles as well as antioxidative systems have been investigated in rice cultured cells obtained from Italian rice varieties (Baldo and Vialone Nano) having different salt-tolerance.

The tolerant variety (Baldo) had innate ROS scavenging systems allowing ROS, in particular H₂O₂, to act as signal molecule rather than as damaging one. Under salt stress, the tolerant variety also exhibited rapid upregulation of K⁺ transporter genes to cope with K⁺/Na⁺ impairment, not detected in presence of only the oxidative stress.

In their whole, these results underline the relevance of specific H₂O₂ signatures and innate antioxidative systems in modulating ionic and redox homeostasis for salt stress tolerance.

THE PRO-RESOLUTION PATHWAY IS ALTERED IN CHRONIC HEART FAILURE: IMPLICATIONS FOR ADAPTIVE IMMUNITY DYSREGULATION

**Ph.D student** Stefano Saracini  
**Tutor** Raffaele Antonelli Incalzi

Chronic Heart Failure (CHF) is a syndrome affecting humans with a relevant immune component which contributes to the severity of the condition. Inflammation in CHF is characterized by an increased plasma level of pro-inflammatory cytokines which are the signal of the onset of acute inflammation that in absence of resolution might become chronic. Resolution of inflammation is a finely regulated process mediated by specialized pro-resolving lipid mediators (SPMs) including arachidonic acid (AA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) derived molecules. In this work it has been shown that (DHA)-derived, also called D-series resolvins (RvDs), resolvin D1 (RvD1) and resolvin D2 (RvD2), are not able to modulate T cells immune responses in CHF patients and for this reason they could be involved in the failure of the resolution of chronic inflammation in this syndrome. Previously work has shown that RvD1 and RvD2 were able to modulate the immune activity of T lymphocytes, responsible for the adaptive immune response, in healthy humans. In this study we sought to investigate whether or not RvD1 and RvD2 are able to modulate the immune activity of T cells in CHF patients. ELISA test showed that plasma levels of RvD1 were greatly reduced in CHF patients compared with those of the healthy controls. In addition, both RvD1 and RvD2 were not able to modulate T cells immune responses in CHF patients. These results suggested that there might be a defective signaling in the pro-resolving pathway of RvDs in CHF. qRT-PCR reported a reduction of the expression in both key enzyme 15- lipoygenase (15-LOX),
involved in RvD1 and RvD2 biosynthesis, and RvD1 receptor GPR32 compared with controls, and western blotting analysis confirmed this reduction. These findings indicate that the failure of CHF patients to respond to the pro-resolving actions of RvDs is caused by defects in both biosynthetic and expression pathway of RvD1, and that this may participate in the progression of chronic inflammation. The pro-resolution pathway might be a potential candidate to design better treatments for CHF with the aim of reducing chronic inflammation.

ROLE OF PROTEIN AMBRA1 BETWEEN THE INHIBITION/EXCITATION IMBALANCE IN THE HIPPOCAMPUS: ITS IMPLICATIONS IN NEURODEVELOPMENTAL DISORDERS

Ph.D student Francesca Sciarra
Tutor Annalisa Nobili

Imbalances between excitatory and inhibitory synaptic transmission are implicated to the pathogenesis of neurodevelopmental disorders, like Autism and Schizophrenia (Durand, M.C. et al. Hippocampus plays an important role in neurodevelopmental 2008; Bozdagi O. et al, 2010) disorders, in fact this area is implicated in learning and social behavior. In this area the excitatory transmission is turned by Pyramidal neurons, the inhibitory transmission instead, is turned by Parvalbumin interneurons that are highly implicated in this imbalance (Filice F. and Swaller B.). Recent evidence shown an important role for Ambra1 gene and neurodevelopmental 2007) disorders in human studies and in mouse studies (Mitjans, M. et al, 2017; Heinreich, A. et al, 2013). Ambra1 is crucial protein for neurodevelopment, in fact homozygous (Dere, E. et al, 2014) Ambra1-/- mouse embryos show serious brain malformation, like aberrant cellular proliferation and spine bifida. So we decided to study the role of aplainsufficiency of (Fimia, G.M. et al., 2007) Ambra1 in Hippocampal excitation/inhibition balance. We show that heterozygous Ambra1+/- mice are characterized by loss of hippocampal Parvalbumin interneuron, decreases in the inhibition/excitation ratio and altered social behaviors only in female gender. Loss of Parvalbumin interneurons in Ambra1+/- females is further linked to reductions of inhibitory drive onto principal neurons and alterations in network oscillatory activity, CA1 synaptic plasticity and pyramidal neuron spine density. Parvalbumin interneuron loss in underlined by increased apoptosis in MGE (medial ganglionic area) during the embryonic development. Together, these findings identify an Ambra1-dependent mechanism that drives inhibition/excitation imbalance in the hippocampus, contributing to abnormal brain activity reminiscent of neurodevelopmental disorders.

MULTIMODAL ADAPTIVE INTERFACES FOR UPPER LIMB ROBOT-AIDED NEURO-REHABILITATION

Ph.D student Davide Simonetti
Tutor Loredana Zollo

Nowadays, stroke is one of the leading cause of permanent disability. Several rehabilitation methodologies can be adopted to counteract stroke motor impairments, but the optimal training approach remains unknown. In this perspective, rehabilitation robotics is one of the most active research fields in the neuro-rehabilitation panorama. Robotic devices for upper limb treatment may lead to improvements in motor recovery and neuro-plasticity due to their ability to deliver highly-intensive, repeatable, and accurate movement therapy. In addition, robotic machines provide objective measurements for patient assessment, while guaranteeing patient safety and unloading therapist workload with respect to conventional therapy. This work presents the development of multimodal adaptive interfaces tailored to human’s specific needs. Multimodal interfaces represent complex systems characterized by the simultaneous use of multiple human sensory modalities that can support combined input/output modes. They include different subsystems that can operate both as monitoring tools that record various levels of information as well as stimulation techniques (auditive, visual, haptic and neuromodulation).
The concept of multimodal interface is then applied to upper limb robot-aided neurorehabilitation with the ambition to maximize the therapeutic effects in post-stroke patients. Bio-cooperative systems and non-invasive neuromodulation techniques may represent a general extended vision of multimodal interfaces. In particular, bio-cooperative systems include several subsystems that communicate through a customized multimodal interface. They represent the new generation of robotic platforms that collocate the patient in the control loop, by employing his/her physiological, neurological, psychological and biomechanical measures, and automatically adapts the control strategy on the basis of the acquired patient states. The proposed work consists of two main research areas that include the concept of multimodal interface: i) design criteria of bio-cooperative robotic systems for upper limb rehabilitation, ii) application of multimodal interfaces for investigating effects of robotic therapy combined with non-invasive neuromodulation techniques. Regarding the first area, a novel taxonomy of bio-cooperative systems is proposed. In addition, the application of bio-cooperative system has been applied to two case studies grounded on end-effector machines (Kuka robotic arm and CBM-Motus). However, the approach can be easily extended to wearable robotic devices as shown in Chapter 5. A special attention has been paid to the design and development of an arm gravity support system integrated in a bio-cooperative upper limb robot-aided rehabilitation system. The bio-cooperative approach and an adaptive control strategy have been then applied to a robotic tele-rehabilitation system. Furthermore, a modular system aimed to control an upper arm robotic exoskeleton for assistive tasks has been presented and discussed. Finally, the development of a mechanical interfacing system for hand rehabilitation devices and upper arm exoskeletons is reported. As regards the second area, the concept of multimodal interface has been applied for quantitative assessment of the outcomes related to clinical studies involving stroke patients. These studies have been designed for investigating the effects of neuromodulation techniques paired with upper limb planar robotic therapy. The outcomes of two clinical studies combining Transcranial Magnetic Stimulation (TMS) and transcranial Direct Current Stimulation (tDCS) with upper limb robotic therapy are reported and discussed.

ANALYSIS OF THE DYNAMIC CHANGES IN THE NUMBER AND MOLECULAR PHENOTYPE OF RANK POSITIVE CIRCULATING TUMOR CELLS IN PATIENTS WITH BREAST CANCER WITH BONE METASTASES TREATED WITH DENOSUMAB

Ph.D student Luciano Stumbo
Tutor Giuseppe Tonini

BACKGROUND: Bone is the most common site of metastatic invasion in breast cancer. Skeletal metastases from breast cancer are mostly osteolytic, with histological evidence of an increase in the number and activity of osteoclasts. It is well known that the RANK / RANKL / OPG axis controls osteoclastogenesis and bone resorption. In particular, the RANKL / RANK / OPG signal is unregulated in several cancers, such as breast cancer, malignant bone tumors and multiple myeloma. Recent data have shown that human breast carcinoma cell lines and tissue samples express the RANK protein on their surface and it has been suggested that RANKL can act as a chemotactic factor for these tumor cells. The bone microenvironment is a rich source of RANKL that can stimulate tumor cells expressing RANK to migrate to the bone. The circulating tumor cells (CTC) are defined as cells that detach from the site of a primary or metastatic tumor and that circulate in the peripheral blood being able to settle in secondary sites forming metastases. It is hypothesized that the homing and spread of CTCs to the bone could be stimulated by the chemotactic attraction exerted by the presence of the RANKL reservoir on the RANK-positive CTCs. Denosumab, a fully humanized monoclonal antibody against RANKL, has been shown to prevent or delay related skeletal events in patients with solid tumors that have metastasized to bone. Given the pro-metastatic effect of RANKL, it is reasonable to assume that denosumab could have an antitumor effect through its activity on RANK-positive CTCs.

STUDY OBJECTIVES: 1. To identify, for the first time in the literature, the existence of CTC RANK positive in the blood of patients affected by breast cancer with bone metastases. 2. Evaluate any denosumab capacity to
modulate the number and type of CTCs in these patients. 3. To evaluate the correlation between the count of the RANK positive CTC and the evolution of skeletal and extra-skeletal disease.

MATERIALS AND METHODS: 56 patients, aged between 32 and 89, with breast cancer and bone metastases were enrolled. Patients were treated with denosumab. During the treatment period a blood sample was taken for the evaluation of CTC, observing in particular the subpopulation of the RCA positive CTCs. The presence of circulating tumor cells (CTC) in the peripheral blood of the patients enrolled in the present study were analyzed at time 0 and at days 2, 7, 14, 28 after the first administration of denosumab. For clinical features and molecular factors, frequency analysis was performed with the exact Fisher test and the chi-square test. Whole blood CTC counts are performed with the CellSearch® method and the counts were estimated using the Kaplan-Meier method, and the significance of differences in survival rates was ascertained using the log-rank test. Multivariate analysis using the Cox proportional hazards model was used to evaluate the independent contribution of each variable to progression-free skeletal survival. All statistical calculations were performed using IBM SPSS Statistics (version 21.0, SPSS Inc., Chicago, IL) or GraphPad Prism (version 5, San Diego, CA).

RESULTS: 1. Identification of the existence of CTC RANK positive in the blood. The study demonstrated for the first time that the expression of RANK is detectable by the CellSearch® method on CTCs in patients enrolled. The preliminary results obtained from the first 44 patients enrolled did not show significant differences in terms of percentage of CTC RANK positive in the different molecular tumor phenotypes of the breast. Subsequently, the analysis was extended to all 56 patients. 2. Evaluation of the effect of denosumab on the number of CTC RANK + / RANK- in the course of treatment. The preliminary results show a significant decrease in the number of CTC RANKpos after 2 days from the denosumab therapy compared to the number of CTC RANKpos detected at baseline. On the other hand, the number of CTC RANKneg does not decrease in response to denosumab treatment suggesting a specific effect on the subset of the RANK positive CTCs. 3. Correlation between the count of CTC RANK + / RANK- and the evolution of skeletal and extra-skeletal disease. The study showed that patients with CTC RANK positive who had a dose of these stable or increased at day 2 from the administration of Denosumab have a delay in the presentation of the first skeletal related event (SRE) (39 months for CTC RANK + increased or stable vs 18 months in CTC RANK + reduced). The analysis of time to bone progression in function of the CTC RANK + \ RANK-purity, although not showing significant (p = 0.396), showed that patients who have a time advantage in bone progression are those that have a count of CTC RANK- (37 months vs. 22 months in CTC RANK positive patients). Time analysis of visceral progression as a function of the CTC RANK + \ RANK setting was statistically significant (p = 0.011), demonstrating that CTC RANK- patients have a time advantage to visceral progression (39 months in CTC patients RANK- vs 9 months for CTC RANK + patients). Finally, the time has been evaluated for the appearance of the first SRE according to the CTC RANK + \ RANK- set-up. In this case the analysis showed a p = 0.058, confirming also in this case that patients with CTC RANK- have an advantage in terms of appearance of the first SRE (29 months vs. 19 months for CTC RANK + patients).

DISCUSSION AND CONCLUSIONS: The trial demonstrated the presence of the RANK receptor on human CTC using a method, the Cell Search, widely validated clinically. Furthermore, the presence of CTC RANK + would seem to confer a worse prognosis in terms of time to visceral disease progression. The Denosumab, on the other hand, would seem to modulate the share of the CTC RANK + without modifying the share of the CTC RANK-. Ultimately, the study found a counterintuitive relationship between the decrease in RANK + CTCs 2 days after the administration of Denosumab and the increase in SRE time. Continuing the study by expanding the series and the follow-up number, could lead to the consideration of RANK as a predictor marker of response to a drug that revolutionizes the clinical history of patients with bone metastases and contribute to improving the quality of life in patients with this pathology.
APPLICATION OF DIFFERENT EXTRACTION TECHNIQUES AND HPLC-PDA-ESI/MS METHODS TO THE ANALYSIS OF PHENOLIC COMPOUNDS IN FOOD SAMPLES

Ph.D student  Giusy Tripodo
Tutor  Chiara Fanali

Phenolic compounds encompass a major group of secondary plant metabolites that display a wealth of structural variety and a large diversity of significant biological activities. Over the last 15 years researchers and food manufactures have become increasingly interested in phenolic compounds. The chief reason for this interest is the recognition of their positive effects on human health, like antioxidant activity and their probable role in the prevention of various diseases associated with oxidative stress, such as cancer and cardiovascular and neurodegenerative diseases, and their great abundance in our diet. The present thesis study was based in the development and validation of quali-quantitative analysis methods of phenolic bioactive compounds by high performance liquid chromatography (HPLC) coupled to UV-visible detector (PDA) and mass spectrometry (MS). Two food samples were investigated: Goji berry (Lycium barbarum L.) and Hazelnut kernels (Corylus avellana L.). Goji berry fruits (Lycium barbarum L.) have generated particular interest in recent times for their potential beneficial effects on human health, such as antioxidant, anti-inflammatory and antitumor activities. It is believed that phenolic compounds are responsible for these effects. The study on Goji berry fruits was divided in two sections. A first study was based on the investigation of the effects of solvent type on the extraction of phenolic compounds through a solid-liquid method. Methanol, methanol 3% formic acid, ethyl acetate, ethyl acetate/methanol 3% formic acid (50:50 v/v) and water/methanol (90:10 v/v) were tested, in order to study their effect on the content of total phenolic compounds and on antioxidant activity, by Trolox antioxidant capacity (TEAC) assay, in Goji berry extracts. HPLC-PDA-ESI-QMS was employed for separation, identification and quantification of phenolic compounds in Goji berry samples. The analytical method was fully validated in terms of retention time and peak area precision, expressed as %RSD, limit of detection (LOD) and limit of quantitation (LOQ) and linearity range employing nine phenolic standard compounds belonging to phenolic acid and flavonoid classes as representative of each class of phenolics. The validated method was then applied in Goji berry extracts obtained by using different extraction solvents. Seven phenolic compounds, belonging to phenolic acid and flavonoid classes, were detected and tentatively identified in Goji berry extracts. Methanol 3% formic acid was the solvent presenting the highest amount of the seven phenolic compounds detected (18.32 µg/100 g of dried weight, DW) and the highest TEAC value (56.71 µmol TE/g DW), while ethyl acetate was the lowest one with an amount of phenolic compounds of 1.13 µg/100 g DW and a TEAC value of 0.56 µmol TE/g DW. A second study was based on the study of pressurized-liquid extraction (PLE) method by a design of experiments (DOE) based on response surface methodology (RSM) for the extraction of phenolic compounds from Goji fruits. The global yield (% w/dw, weight/dry-weight), total phenolic content (TPC), total flavonoid (TF) and antioxidant activity (determined via ABTS assay, expressed as TEAC value) were used as response variables to study the effects of temperature (50–180°C) and green solvent composition (mixtures of ethanol/water). The analysis of phenolic compounds were performed by HPLC-PDA-MS/MS. PLE optimum conditions (180°C and 86% ethanol in water) were obtained using the commercial sample as representative matrix. Once the experimental design was validated for commercial fruit samples, the optimum conditions were applied to three different varieties of fruit samples (Selvatico mongolo, Bigol and Polonia). Nine phenolic compounds were tentatively identified in these extracts, including phenolic acids and their derivatives, and flavonols. The optimized PLE conditions were compared to a conventional solid-liquid extraction (SLE), demonstrating that PLE is a useful alternative to extract phenolic compounds from Goji berry. Hazelnut (Corylus avellana L.) is one of the nuts most consumed in many countries including Turkey, Italy, Spain and United States. It is a rich source of dietary fibers and beneficial nutrients such as lipids, proteins, but also significant micronutrients like essential minerals, vitamin E, B complex vitamins and phenolic compounds, which contribute to its organoleptic properties such as astringent and bitter taste. The content of phenolic compounds may be a significant parameter in the assessment of hazel-
nuts quality. In fact, it depends on several factors like cultivar, geographical origin and processing condition such as roasting. Phenolic compounds were extracted from hazelnut kernels employing two extraction techniques: ultrasound-assisted solid-liquid extraction (UA-SLE) and solid-phase extraction (SPE). Different extraction solvents were tested evaluating total phenolic content, total flavonoids and antioxidant capacity. The individual phenolic compounds in hazelnut kernels of different cultivars were analyzed by HPLC-PDA-MS/MS. The best extraction conditions in terms of the highest value of total phenolic compounds extracted together to other parameters like simplicity and cost were selected for method validation and individual phenolic compounds analysis. Different protocols were performed using commercial hazelnut kernels. The UA-SLE protocol performed using 0.1 g of defatted sample and 15 mL of extraction solvent (methanol/water/methanol 0.1% HCOOH/acetonitrile (1:1:8:5, v/v/v/v)) was selected as best extraction conditions. The analytical method was developed and then validated using a mixture of six different phenolic acids and flavonoids standards. RSD % for intra-day e inter-day of retention time, LOD and LOQ were evaluated. The accuracy of the extraction was also assessed. Calibration curves were constructed with a good linearity and satisfactory determination coefficients R2 for quantitative analysis. Finally, the method was applied to the analysis of phenolic compounds in three different hazelnut kernel varieties.
Awards
Awards

Claudia Altamura, Fabrizio Vernieri
Best poster at the Congress of the European Headache Federation.

Giovanni Assenza
Nominated councilor for the Lazio-Abruzzo macro area of the Italian League against Epilepsy.

Alessandra Berton
Fellowship awarded by the Japanese Orthopaedic Society of Knee, Arthroscopy and Sports Medicine (JOSKAS) and the Italian Society of Knee Surgery, Arthroscopy, Sports Traumatology, Cartilage and New Arthroscopy Technologies (SIGASCOT)

Mauro Barone, Annalisa Cogliandro, Paolo Persichetti
“Memorial Prize Domenico Dioguardi” at the 66th National Congress of SICPRE.

Stefano Campi
European Knee Society travelling fellowship 2017

Carassiti Massimiliano, Mattei Alessia, Pizzo Carmen, Vallone Niccolò, Saccomandi Paola, Schena Emiliano

Pierfilippo Crucitti
Received the “Order of Merit of the Italian Republic” for the prevention and treatment activities carried out as part of the “A breath for life” campaign.

Francesca D’Auria

Laura De Gara
Nominated member of the Scientific Council for Agricultural Research and Analysis of Agrarian Economy (CREA).

Giuseppe Defeudis
Member of the Androyoung National Commission for under 40 researchers of the Italian Society of Andrology.

Vincenzo Denaro, Gianluca Vadala, Alberto Di Martino, Fabrizio Russo, Biagio Zampogna, Rocco Papalia
The team has been awarded the “AAOS Honorary Mention” for the surgical video “Laminectomy and instrumented fusion for multilevel cervical myelopathy” presented at the “Orthopaedic Video Theater” of the 84th congress of the American Academy of Orthopaedic Surgeons (AAOS), 14-18 March 2017, San Diego, CA, USA.

Lazzaro Di Biase
“Young researcher award” conferred at the 62nd Congress of the Italian Society of Clinical Neurophysiology.

Di Perna Leonardo, Spina Gabriele, Thackray-Nowescrea S. Crooks M.G., Morice A.H., Soda Paolo, den Brinker A.C.

Antonio Di Zazzo
Best paper and Travel grant awarded by the Japanese Ophthalmology Society

Francesco Franceschi
The “John J. Joyce award” and the “Caspari award” conferred to the Upper and lower limb surgery unit directed by prof. Francesco Franceschi during the 2017 ISAKOS International Congress.

Giovanni Galati
“Young investigator award” conferred by the Asian Pacific Association for a study of the liver.
Alessio Gizzi
Research in Pairs Scheme 4 grant awarded by the London Mathematical Society.
UCBM, Visiting Professor Grant Program, Technical University of Munich.
INdAM, International Scholarship Grant 2016-2017, Technical University of Munich.
Erasmus+, Staff Mobility for Teaching Assignment, Technical University of Munich.

Paolo Gallo, Antonio De Vincentis
Entered the Ultrasound Commission of the Youth Italian Gastroenterologists and Endoscopists Association, to collaborate in the organization of courses for young doctors.

Giulia Leanza
Travel grant awarded by the Italian Society of Diabetology.

Mauro Maccarrone
Appointed as Scientific Advisory Board (SAB) member of Phytecs (USA) and InMed Pharmaceuticals (Canada), due to his expertise in (endo)cannabinoid research.

Ernesto Maddaloni
Awarded for scientific merit by the Italian Society of Endocrinology during the recent National SIE Congress.

Ernesto Maddaloni, Andrea Palermo
“Early investigators award” conferred by the Endocrine Society.

Carlo Massaroni
“Best PhD thesis of 2017” awarded by the National Bioengineering Group.

Simona Mega
Regional Delegate of the Italian Society of Echocardiography and Cardiovascular Imaging.

Andrea Palermo
“Young investigator award” promoted by the American Society for Bone and Mineral Research.
“Best poster award” conferred by the Italian Society of Diabetology.

Giuseppe Patti
“Best poster in atrial fibrillation” awarded at the Congress of the European Society of Cardiology

Bianca Santo
“Best poster discussion” awarded by the Campus Bio-Medico University Alumni Association

Francesco Segreto
“GiovedìScienza award” conferred to under 35 researchers.

Sonia Silipigni
“Prof. Dario Cova award” conferred at the 5th Congress of the “Geriatric oncology Italian Group”.

Paolo Soda
Nominated chair of the “Technical Committee on Computational Life Sciences (TCCLS)”.

Rocky Strollo
“Renzo Navalesi award” conferred by the Italian Society of Diabetology.
“Young Investigator Travel Grant award” conferred by the American Diabetes Association
Award for the Parma Diabete XI ed. of the Italian Society of Diabetology

Lucio Trodella
“Maestro dell’Oncoologia” at the Congress of the Southern Italy Oncology Group.

Marcella Trombetta
Entered the “National Commission for the prediction and prevention of major risks” of the Civil Protection for the chemical, nuclear and industrial risks sector.

Gianluca Vadalà
Winner of the International Society of the Study of the Lumbar Spine (ISSLS) 2017 Clinical Travelling Fellowship Award.

Sebastiano Vasta
Travelling fellowship awarded by the Italian Society of Knee Surgery, Arthroscopy, Sports Traumatology, Cartilage and New Arthroscopy Technologies.
2017 Research papers awarded by Department of Medicine and Surgery as “UCBM Paper of the month”

January

Di Gioia G., Mega S., Nenna A., Campanale C. M., Colaiori I., Scordino D., Ragni L., Miglionico M., Di Sciascio G.

Should pre-operative left atrial volume receive more consideration in patients with degenerative mitral valve disease undergoing mitral valve surgery?


**Cannabinoid CB (2) receptor ligand profiling reveals biased signalling and off-target activity.**


February


**Autoantibodies to post-translationally modified type I and II collagen in Charcot neuroarthropathy in subjects with type 2 diabetes mellitus.**


**Determinants of bone specific metastasis in prostate cancer.**


March


**Placebo-controlled, randomized trial of the addition of once-weekly glucagon-like peptide-1 receptor agonist dulaglutide to titrated daily insulin glargine in patients with type 2 diabetes (AWARD-9).**


April


**Mechanisms of diabetes mellitus-induced bone fragility.**


May


**TRPV1 channels are critical brain inflammation detectors and neuropathic pain biomarkers in mice.**


Cimini F. A., Barchetta I., Carotti S., Bertoccini L., Baroni M. G., Vespasiani-Gentilucci U., Cavallo M. G., Morini S.

**Relationship between adipose tissue dysfunction, vitamin D deficiency and the pathogenesis of non-alcoholic fatty liver disease.**


Simonetti D., Zollo L., Milighetti S., Miccinilli S., Bravi M., Ranieri F., Magrone G., Guglielmelli E., Di Lazzaro V., Sterzi S.

**Literature Review on the Effects of tDCS Coupled with Robotic Therapy in Post Stroke Upper Limb Rehabilitation.**

Dig Liver Dis. 2017 Sep;49(9):1009-1013. PubMed PMID: 28539229. IF 2,875

June

Human equilibrative nucleoside transporter 1 gene expression is associated with gemcitabine efficacy in advanced leiomyosarcoma and angiosarcoma.  

July - August

Di Stefano N., Ghilardi G., Morini S.  
Leonardo’s mistake: not evidence-based medicine?  

October

Lelli D., Antonelli-Incalzi R., Bandinelli S., Ferrucci L., Pedone C.  
Association between sodium excretion and cardiovascular disease and mortality in the elderly: a cohort study.  

November

The fragile X mental retardation protein regulates tumor invasiveness-related pathways in melanoma cells.  

**December**

Segreto F., Carotti S., Marangi G.F., Tosi D., Zingariello M., Pendolino A.L., Sancillo L., Morini S., Persichetti P.  
The role of angiogenesis, inflammation and estrogen receptors in breast implant capsules development and remodeling.  
2017 Publications
Full List
ALLERGOLOGY, IMMUNOLOGY, RHEUMATOLOGY

**Head** A. Afeltra

**Articles**


*International consensus: what else can we do to improve diagnosis and therapeutic strategies in patients affected by autoimmune rheumatic diseases (rheumatoid arthritis, spondyloarthritides, systemic sclerosis, systemic lupus erythematosus, antiphospholipid syndrome and Sjogren’s syndrome)?: The unmet needs and the clinical grey zone in autoimmune disease management.*

*Autoimmun Rev. 2017 Sep;16(9):911-924. PubMed PMID: 28705780. IF 8,961*

Salvarani C., Soriano A., Muratore F., Shoenfeld Y., Blockmans D.

*Is PET/CT essential in the diagnosis and follow-up of temporal arteritis?*


*The inter-observer reading variability in anti-nuclear antibodies indirect (ANA) immunofluorescence test: A multicenter evaluation and a review of the literature.*


*Biologic therapies and infections in the daily practice of three Italian rheumatologic units: a prospective, observational study.*


Bertolotti M., Franchi C., Rocchi MB., Miceli A., Libbra MV., Nobili A., Lancellotti G., Carulli L., Mussi C.; REPOSI Investigators, [Afeltra A.].

*Prevalence and determinants of the use of lipid-lowering agents in a population of older hospitalized patients: the findings from the REPOSI (Registro Politerapie Società Italiana di Medicina Interna) study.*


*Disease phenotype and outcome depending on the age at disease onset in patients carrying the R92Q low-penetrance variant in TNFRSF1A gene.*


Di Lazzaro V., Rigon A., Soriano A., Capone F., Corbetto M., Florio L., Afeltra A., Onetti Muda A., Luigetti M.

*Sjögren’s syndrome presenting with isolated sensory axonal polyneuropathy.*


Pignataro F., Marigliano B., Sambataro G., Afeltra A.

*Darier’s disease and rheumatoid arthritis: a new association and a review of the literature.*


Nucera E., Basta F., Buonomo A., Mezzacappa S., Margiotta D.P., Antonelli Incalzi R., Schiavino D.

*A case of hypocomplementemic urticarial vasculitis syndrome successfully treated with omalizumab.*


Navarini L., Afeltra A., Gallo Afflitto G., Margiotta DPE.

*Polyunsaturated fatty acids: any role in rheuma-

Subclinical atherosclerosis and history of cardiovascular events in Italian patients with rheumatoid arthritis: Results from a cross-sectional, multicenter GIRRCS (Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale) study.

Angiogenic and angiostatic factors in renal scleroderma-associated vasculopathy.

Soriano A., Muratore F., Pipitone N., Boiardi L., Cimino L., Salvarani C.
Visual loss and other cranial ischaemic complications in giant cell arteritis.

Margiotta D.P.E., Basta F., Dolcini G., Batani V., Navarini L., Afeltra A.
The relation between, metabolic syndrome and quality of life in patients with systemic lupus erythematosus.

Rosato E., Navarini L., Gigante A., Cianci R., Margiotta D., Barbano B., Afeltra A.
Intrarenal arterial stiffness is increased in systemic sclerosis patients with anti-ribonucleic acid polymerase III antibodies.

Laudisio A., Margiotta D.P.E., Zuccalà G., Afeltra A., Antonelli Incalzi R.
Methotrexate-induced dysautonomia in a patient with rheumatoid arthritis.

**Book Chapters**

Margiotta D.P.M., Afeltra A.
Meccanismi di danno tissutale.

M. Vadacca, A. Afeltra:
Polimiosite-Dermatomiosite.
Pag. 261, UNIREUMA, Reumatologia per Studenti e Medici di Medicina Generale III Ediz. Idelson-Gnocchi

**ANESTHESIA, INTENSIVE CARE AND PAIN MANAGEMENT**

**Head** F.E. Agrò

**Articles**

Carassiti M., Mattei A., Quarta R., Massaroni C., Saccomandi P., Tesei M., Setola R., Schena E.
A new pressure guided management tool for epidural space detection: feasibility assessment on a simulator.

Menna P., Salvatorelli E., Mattei A., Cappiello D., Minotti G., Carassiti M.
Modified colistin regimen for critically ill patients with acute renal impairment and continuous renal replacement therapy.


**Mortality in cardiac surgery (MYRIAD): A randomized controlled trial of volatile anesthetics. Rationale and design.**


Cavaliere F., Rossi M., Allegri M., Apan A., Calderini E., Carassiti M., Coluzzi F., Di Marco P., Langeron O., Piastra M.

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**Head** E. Guglielmelli

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Head F. Keller
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Head B. Beomonte Zobel

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**Head** G. Minotti

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**Head** G. Pennazza

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Head P. Pozzilli

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Head L. De Gara

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Head M. Cicala

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**Head** R. Antonelli Incalzi

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Head  R. Angioli

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Head G. Avvisati

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Head T. Petitti

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Head E. Covino (L. Borghi)

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Head A. Picardi

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**Head** S. Silvestri

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Head S. Morini

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HEAD V.M. Fazio

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**Head** M. D’Amelio

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Head V. Di Lazzaro

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**Head** G. Di Pino

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**Books & book chapters**


ISBN 978-3-319-66880-2 DOI: 10.1007/978-3-319-66881-9_4

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Head S. Filippi

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*Head*  M.G. De Marinis

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**Head** G. Tonini

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**Head** S. Bonini

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**Head** R. Papalia

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Head A. Onetti Muda

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Head S. Sterzi

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Head M. De Falco

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Head S. Ramella

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Head M. Trombetta

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Name Index
### Name Index

#### A
- **Abbruzzese F.** 112, 266
- **Accoto D.** 34, 199
- **Afeltra A.** 26, 193
- **Afferni P.** 44, 206
- **Agrò F.E.** 28, 194
- **Albo E.** 98, 254
- **Alessi A.** 34, 199
- **Alifano A.** 98
- **Alloni R.** 60, 219
- **Altamura C.** 86, 240
- **Altavilla R.** 240
- **Altomare A.** 58, 218
- **Altomare V.** 36, 201
- **Amato C.** 98, 254
- **Amato M.** 102, 259
- **Angeletti S.** 42, 204
- **Angioli R.** 64, 224
- **Annibali O.** 68, 226
- **Antonelli F.** 42, 204
- **Antonelli Incalzi R.** 62, 221
- **Anzilotti S.** 72, 228
- **Arcarese L.** 26
- **Armento G.** 94, 248
- **Armiento D.** 68, 226
- **Assenza F.** 86, 240
- **Assenza G.** 86, 240
- **Aveta A.** 106, 262
- **Avvisati G.** 68, 226

#### B
- **Bacca M.** 84
- **Baldari A.** 98
- **Balestrieri P.** 58, 218
- **Barba D.** 108, 264
- **Barbieri G.** 84, 240
- **Barone M.** 72, 106, 228
- **Barone R.** 199
- **Basoli F.** 112, 266
- **Battista C.** 64
- **Becilli M.** 68, 226
- **Beomonte Zobel B.** 48, 209
- **Bertolaso M.** 72, 228
- **Berton A.** 98, 254
- **Bettetini M.T.** 72, 228
- **Bisogno T.** 32, 197
- **Bonini S.** 96, 253
- **Bono M.C.** 38, 201
- **Bonomo O.** 36
- **Borghi L.** 72, 228
- **Borzomati D.** 60, 219
- **Bravi M.** 104, 261
- **Bressi F.** 104, 261
- **Briganti S.I.** 54, 212
- **Brunelli N.** 86, 240
- **Brunetti B.** 106, 262
- **Buscarini M.** 114, 267
- **Buschini F.** 98, 254
- **Cacace F.** 44
- **Cagli B.** 106, 262
- **Calabrese V.** 38, 201
- **Campanozzi L.** 72, 228
- **Campi S.** 98
- **Canali M.** 84, 240
- **Cancilleri F.** 98, 254
- **Candela V.** 98, 254
- **Cannizzaro C.** 84, 240
- **Capocelli M.** 108, 264
- **Capolupo G.T.** 60, 219
- **Capone F.** 86, 240
- **Caputo D.** 60, 219
- **Carassiti M.** 28, 194
- **Caricato M.** 60, 219
- **Carnevale A.** 110, 265
- **Carotti S.** 78, 236
- **Carpino G.** 34, 199
- **Casale M.** 100, 258
- **Cascio Rizzo A.** 86, 240
- **Castronovo P.** 84
- **Cataldo R.** 28, 34, 194
- **Catania G.** 94
- **Cavallari I.** 54, 212
- **Cavallucci V.** 239
- **Cecchi G.** 86, 240
- **Celesti C.** 82
- **Cella E.** 42, 204
- **Cerchiaro E.** 68, 226
- **Cerro M.** 72, 228
- **Chello M.** 225
- **Cherubini C.** 90, 245
- **Chiarella I.** 62, 221
- **Chiodo L.** 90, 245
- **Chiurcilia V.** 32, 197
- **Ciancio A.L.** 34, 199
- **Cicala M.** 58, 218
- **Ciccozzi M.** 42, 204
- **Cimini F.** 78, 236
- **Cimini S.** 56, 215
- **Ciricchetta E.** 68, 226
- **Ciuffreda M.** 98, 254
- **Cogliandro A.** 106, 262
- **Conti A.** 42, 204
- **Coppola R.** 60, 219
- **Cordella F.** 34, 199
- **Cordelli E.** 44, 206
- **Cortese L.** 62, 221
- **Costa A.** 84, 240
- **Costa C.** 86, 240
- **Costantini M.** 80, 112, 238, 266
- **Costanzo L.** 62, 221
- **Covino E.** 66, 72, 225, 228
- **Crescenzi A.** 42
- **Crucitti P.** 60, 219
- **Cupo G.** 96
<table>
<thead>
<tr>
<th>Name Index</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cursano M.C.</strong> 94, 248</td>
</tr>
<tr>
<td><strong>D</strong></td>
</tr>
<tr>
<td><strong>Dabrowska M.</strong> 80, 238</td>
</tr>
<tr>
<td><strong>D’Alonzo M.</strong> 88</td>
</tr>
<tr>
<td><strong>D’Amelio M.</strong> 82, 239</td>
</tr>
<tr>
<td><strong>D’Angelillo R.M.</strong> 110, 265</td>
</tr>
<tr>
<td><strong>De Angelis G.</strong> 98, 254</td>
</tr>
<tr>
<td><strong>De Cesaris M.</strong> 42, 204</td>
</tr>
<tr>
<td><strong>De Cicco Nardone C.</strong> 64, 224</td>
</tr>
<tr>
<td><strong>De Cillis F.</strong> 30, 195</td>
</tr>
<tr>
<td><strong>De Falco M.</strong> 108, 264</td>
</tr>
<tr>
<td><strong>De Feudis G.</strong> 54, 212</td>
</tr>
<tr>
<td><strong>De Florio L.</strong> 42, 204</td>
</tr>
<tr>
<td><strong>De Gara L.</strong> 56, 215</td>
</tr>
<tr>
<td><strong>Delfonso M.</strong> 54, 212</td>
</tr>
<tr>
<td><strong>De Lisi D.</strong> 94, 248</td>
</tr>
<tr>
<td><strong>Dellacasa Bellingegni A.</strong> 34, 199</td>
</tr>
<tr>
<td><strong>Dell’Acqua M.C.</strong> 239</td>
</tr>
<tr>
<td><strong>Della Pepa C.</strong> 248</td>
</tr>
<tr>
<td><strong>Dell’Aquila E.</strong> 94, 248</td>
</tr>
<tr>
<td><strong>Del Toro R.</strong> 54, 212</td>
</tr>
<tr>
<td><strong>De Maggio M.C.</strong> 195</td>
</tr>
<tr>
<td><strong>De Marinis M.G.</strong> 92, 246</td>
</tr>
<tr>
<td><strong>De Muro M.</strong> 68, 226</td>
</tr>
<tr>
<td><strong>Denaro V.</strong> 98, 254</td>
</tr>
<tr>
<td><strong>De Salvatore S.</strong> 98</td>
</tr>
<tr>
<td><strong>Dianzani C.</strong> 106, 262</td>
</tr>
<tr>
<td><strong>Diaz L.</strong> 98, 254</td>
</tr>
<tr>
<td><strong>Di Biase L.</strong> 86, 240</td>
</tr>
<tr>
<td><strong>Di Cerbo M.</strong> 68, 226</td>
</tr>
<tr>
<td><strong>Dicuonzo G.</strong> 42, 204</td>
</tr>
<tr>
<td><strong>Di Donato A.</strong> 110, 265</td>
</tr>
<tr>
<td><strong>Di Giacomo G.</strong> 98, 254</td>
</tr>
<tr>
<td><strong>Di Gioia C.</strong> 62, 221</td>
</tr>
<tr>
<td><strong>Di Lazzaro V.</strong> 86, 240</td>
</tr>
<tr>
<td><strong>Di Martino A.</strong> 254</td>
</tr>
<tr>
<td><strong>Di Matteo F.M.</strong> 211</td>
</tr>
<tr>
<td><strong>Di Mauro A.</strong> 54, 212</td>
</tr>
<tr>
<td><strong>Di Naro C.</strong> 98</td>
</tr>
<tr>
<td><strong>Di Paola L.</strong> 40, 203</td>
</tr>
<tr>
<td><strong>Di Pino G.</strong> 88, 244</td>
</tr>
<tr>
<td><strong>Di Pumpo M.</strong> 62</td>
</tr>
<tr>
<td><strong>Di Santo A.</strong> 86, 240</td>
</tr>
<tr>
<td><strong>Di Sciascio G.</strong> 38, 201</td>
</tr>
<tr>
<td><strong>Di Stefano N.</strong> 72, 228</td>
</tr>
<tr>
<td><strong>Di Zazzo A.</strong> 96</td>
</tr>
<tr>
<td><strong>Donati M.</strong> 102, 259</td>
</tr>
<tr>
<td><strong>D’Onofrio L.</strong> 94, 248</td>
</tr>
<tr>
<td><strong>Dugo L.</strong> 32, 197</td>
</tr>
<tr>
<td><strong>Dugo P.</strong> 56, 215</td>
</tr>
<tr>
<td><strong>Emerenziani S.</strong> 58, 218</td>
</tr>
<tr>
<td><strong>Errante Y.</strong> 48, 209</td>
</tr>
<tr>
<td><strong>F</strong></td>
</tr>
<tr>
<td><strong>Faiella E.</strong> 48</td>
</tr>
<tr>
<td><strong>Falanga E.</strong> 62</td>
</tr>
<tr>
<td><strong>Falato E.</strong> 86, 240</td>
</tr>
<tr>
<td><strong>Fallacara A.</strong> 86, 240</td>
</tr>
<tr>
<td><strong>Fallucca S.</strong> 54, 212</td>
</tr>
<tr>
<td><strong>Fanali C.</strong> 56, 215</td>
</tr>
<tr>
<td><strong>Farrè R.</strong> 218</td>
</tr>
<tr>
<td><strong>Fazio V.M.</strong> 80, 238</td>
</tr>
<tr>
<td><strong>Ferrari S.</strong> 102, 259</td>
</tr>
<tr>
<td><strong>Ferraro S.</strong> 68, 226</td>
</tr>
<tr>
<td><strong>Ferreri F.</strong> 86, 240</td>
</tr>
<tr>
<td><strong>Ferrini A.</strong> 62, 221</td>
</tr>
<tr>
<td><strong>Filippi S.</strong> 90, 245</td>
</tr>
<tr>
<td><strong>Finamore P.</strong> 62, 221</td>
</tr>
<tr>
<td><strong>Fioramonti M.</strong> 248</td>
</tr>
<tr>
<td><strong>Fiore M.</strong> 110, 265</td>
</tr>
<tr>
<td><strong>Fioriti E.</strong> 54, 212</td>
</tr>
<tr>
<td><strong>Fioroni I.</strong> 94, 248</td>
</tr>
<tr>
<td><strong>Floreno B.</strong> 110, 265</td>
</tr>
<tr>
<td><strong>Florio L.</strong> 86, 240</td>
</tr>
<tr>
<td><strong>Focaroli V.</strong> 34, 46, 208</td>
</tr>
<tr>
<td><strong>Fogolari M.</strong> 42, 204</td>
</tr>
<tr>
<td><strong>Fontana D.</strong> 62, 221</td>
</tr>
<tr>
<td><strong>Formica D.</strong> 88, 244</td>
</tr>
<tr>
<td><strong>Franceschetti F.</strong> 98</td>
</tr>
<tr>
<td><strong>Franceschi F.</strong> 98, 254</td>
</tr>
<tr>
<td><strong>Francesconi M.</strong> 78, 236</td>
</tr>
<tr>
<td><strong>Frari V.</strong> 258</td>
</tr>
<tr>
<td><strong>Frezza A.M.</strong> 248</td>
</tr>
<tr>
<td><strong>G</strong></td>
</tr>
<tr>
<td><strong>Gabriele S.</strong> 240</td>
</tr>
<tr>
<td><strong>Galati G.</strong> 74, 232</td>
</tr>
<tr>
<td><strong>Galdi F.</strong> 62, 221</td>
</tr>
<tr>
<td><strong>Gallo P.</strong> 38, 74, 201, 232</td>
</tr>
<tr>
<td><strong>Gambineri A.</strong> 98</td>
</tr>
<tr>
<td><strong>Gaudio S.</strong> 48, 209</td>
</tr>
<tr>
<td><strong>Gentile C.</strong> 199</td>
</tr>
<tr>
<td><strong>Gentile V.</strong> 34</td>
</tr>
<tr>
<td><strong>Germanà A.</strong> 108, 264</td>
</tr>
<tr>
<td><strong>Gherardi G.</strong> 42, 204</td>
</tr>
<tr>
<td><strong>Ghilardi G.</strong> 72, 228</td>
</tr>
<tr>
<td><strong>Giannetti B.</strong> 68, 226</td>
</tr>
<tr>
<td><strong>Giannitelli S.M.</strong> 112, 266</td>
</tr>
<tr>
<td><strong>Giannunzio G.</strong> 62, 221</td>
</tr>
<tr>
<td><strong>Giovannetti M.</strong> 42, 204</td>
</tr>
<tr>
<td><strong>Giua R.</strong> 62, 221</td>
</tr>
<tr>
<td><strong>Giudici F.</strong> 30</td>
</tr>
<tr>
<td><strong>Giurazza F.</strong> 48, 209</td>
</tr>
<tr>
<td><strong>Giusti C.</strong> 96</td>
</tr>
<tr>
<td><strong>Gizzi A.</strong> 90, 245</td>
</tr>
<tr>
<td><strong>Goffredo C.</strong> 38, 201</td>
</tr>
<tr>
<td><strong>Gori M.</strong> 112, 266</td>
</tr>
<tr>
<td><strong>Grassani T.</strong> 94</td>
</tr>
<tr>
<td><strong>Grasso A.</strong> 36</td>
</tr>
<tr>
<td><strong>Grasso R.F.</strong> 48, 209</td>
</tr>
<tr>
<td><strong>Grasso S.</strong> 52, 211</td>
</tr>
<tr>
<td><strong>Greco C.</strong> 110, 265</td>
</tr>
<tr>
<td><strong>Greco N.</strong> 108, 264</td>
</tr>
<tr>
<td><strong>Gregorj C.</strong> 68, 226</td>
</tr>
<tr>
<td><strong>Greto V.</strong> 54, 212</td>
</tr>
</tbody>
</table>
Grilli C. 94, 248
Gruppioni E. 34, 199
Guarino M. P. L. 58, 218
Guarnieri A. 98, 254
Guerra A. 86, 240
Guglielmelli E. 34, 199
Guglielmi C. 54, 212
Lintas S. C. 84
Locato V. 56, 215
Loiacono L. 80, 238
Longo U. G. 98, 254
Loppini A. 90, 92, 245
Lotti F. 254
Lo Vullo M. 26, 193
Ludovisi M. 62, 221
Maccarrone M. 32, 197
Maddalonì E. 54, 212
Maggi D. 54, 212
Maioni M. 72, 228
Malagrìno I. 72, 228
Mallio C. A. 48, 209
Manfrini S. 54, 212
Mangiacapra F. 38, 201
Marangi G. F. 106, 262
Marano M. 86, 240
Marchetti A. 72, 228
Marconi E. 56
Marigliano B. 193
Marineo G. 98, 254
Marino R. 46, 82, 208
Marinozzi A. 98, 254
Marrelli L. 40, 203
Marrucci E. 94, 248
Martelli E. 269
Massaronì C. 76, 233
Matarese M. 92, 246
Matteucci P. 110, 265
Maurizì A. R. 54, 212
Mazzara C. 248
Mega S. 38, 201
Melfì R. 38, 201
Menci M. 30
Menna P. 50, 211
Merone M. 44, 206
Miccìlì S. 104, 261
Migletta S. 54, 212
Miglione C. 38, 201
Minotti G. 50, 211
Mioli A. 88, 244
Molfese E. 110, 265
Mondello L. 56, 215
Monte L. 54
Montelione N. 116
Montera R. 64, 224
Montoni L. M. 195
Morgia A. M. 68, 226
Morini S. 78, 236
Moro L. 221
Morrone M. 104, 261
Mottini G. 72, 228
Muto G. 114, 267
Nacì A. 54, 212
Napoli N. 54, 212
Napolitano A. 94
Napì F. 66, 225
Navarini L. 26, 193
Nicolò G. 102, 259
Nixon J. 72, 228
Nobile C. 68, 226
Nobili A. 82, 239
Noccarò A. 88, 244
Noce E. 34, 199
Nusca A. 38, 201
Oliva G. 30, 195
Onetti Muda A. 102, 259
Onorato A. 94
Orsaria P. 36
Orsini F. 56, 215
<table>
<thead>
<tr>
<th>Name</th>
<th>Research Yearbook 2017</th>
<th>Campus Bio-Medico University of Rome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paciotti M.</td>
<td>98, 254</td>
<td></td>
</tr>
<tr>
<td>Pagano A.</td>
<td>68, 226</td>
<td></td>
</tr>
<tr>
<td>Palermo A.</td>
<td>54, 212</td>
<td></td>
</tr>
<tr>
<td>Palumbo A.</td>
<td>98, 254</td>
<td></td>
</tr>
<tr>
<td>Panasiti V.</td>
<td>78, 106, 236, 262</td>
<td></td>
</tr>
<tr>
<td>Pantano F.</td>
<td>248</td>
<td></td>
</tr>
<tr>
<td>Paolasini S.</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Paolucci M.</td>
<td>86, 240</td>
<td></td>
</tr>
<tr>
<td>Papalia R.</td>
<td>98, 114, 254, 267</td>
<td></td>
</tr>
<tr>
<td>Papapietro N.</td>
<td>98, 254</td>
<td></td>
</tr>
<tr>
<td>Papi M.</td>
<td>30, 195</td>
<td></td>
</tr>
<tr>
<td>Parente F.R.</td>
<td>52, 211</td>
<td></td>
</tr>
<tr>
<td>Pasqualetti V.</td>
<td>56, 215</td>
<td></td>
</tr>
<tr>
<td>Patti G.</td>
<td>38, 201</td>
<td></td>
</tr>
<tr>
<td>Pedone C.</td>
<td>62, 221</td>
<td></td>
</tr>
<tr>
<td>Pellegrino P.</td>
<td>72, 228</td>
<td></td>
</tr>
<tr>
<td>Pennacchini M.</td>
<td>72, 228</td>
<td></td>
</tr>
<tr>
<td>Pennazza G.</td>
<td>52, 211</td>
<td></td>
</tr>
<tr>
<td>Pepe A.</td>
<td>86, 240</td>
<td></td>
</tr>
<tr>
<td>Perrino A.</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>Perrone G.</td>
<td>102, 259</td>
<td></td>
</tr>
<tr>
<td>Persichetti P.</td>
<td>106, 262</td>
<td></td>
</tr>
<tr>
<td>Persico A.M.</td>
<td>84, 240</td>
<td></td>
</tr>
<tr>
<td>Petitti T.</td>
<td>70, 228</td>
<td></td>
</tr>
<tr>
<td>Petrichella S.</td>
<td>44, 206</td>
<td></td>
</tr>
<tr>
<td>Petrillo S.</td>
<td>98, 254</td>
<td></td>
</tr>
<tr>
<td>Picardi A.</td>
<td>74, 232</td>
<td></td>
</tr>
<tr>
<td>Piccioni L.</td>
<td>118, 270</td>
<td></td>
</tr>
<tr>
<td>Piccoli A.</td>
<td>54, 212</td>
<td></td>
</tr>
<tr>
<td>Pinardi M.</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>Piras I.S.</td>
<td>240</td>
<td></td>
</tr>
<tr>
<td>Piredda M.</td>
<td>92, 246</td>
<td></td>
</tr>
<tr>
<td>Pizzi R.</td>
<td>108, 264</td>
<td></td>
</tr>
<tr>
<td>Plotti F.</td>
<td>64, 224</td>
<td></td>
</tr>
<tr>
<td>Poeta M.L.</td>
<td>80, 238</td>
<td></td>
</tr>
<tr>
<td>Portaccio I.</td>
<td>34, 199</td>
<td></td>
</tr>
<tr>
<td>Potestà C.</td>
<td>94, 248</td>
<td></td>
</tr>
<tr>
<td>Pozzilli P.</td>
<td>54, 212</td>
<td></td>
</tr>
<tr>
<td>Quattrocrochi C.C.</td>
<td>48, 209</td>
<td></td>
</tr>
<tr>
<td>Rabitti C.</td>
<td>102, 259</td>
<td></td>
</tr>
<tr>
<td>Raiano L.</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>Rainer A.</td>
<td>112, 266</td>
<td></td>
</tr>
<tr>
<td>Ramella S.</td>
<td>110, 265</td>
<td></td>
</tr>
<tr>
<td>Rampello S.</td>
<td>72, 228</td>
<td></td>
</tr>
<tr>
<td>Ranieri F.</td>
<td>86, 240</td>
<td></td>
</tr>
<tr>
<td>Ratta R.</td>
<td>94, 248</td>
<td></td>
</tr>
<tr>
<td>Ribelli G.</td>
<td>94, 248</td>
<td></td>
</tr>
<tr>
<td>Ribolsi M.</td>
<td>58, 218</td>
<td></td>
</tr>
<tr>
<td>Ricciardì D.</td>
<td>38, 201</td>
<td></td>
</tr>
<tr>
<td>Ricciardì R.</td>
<td>224</td>
<td></td>
</tr>
<tr>
<td>Ricci L.</td>
<td>86, 240</td>
<td></td>
</tr>
<tr>
<td>Ricci S.</td>
<td>221</td>
<td></td>
</tr>
<tr>
<td>Ricottini E.</td>
<td>38, 201</td>
<td></td>
</tr>
<tr>
<td>Rigon A.</td>
<td>26, 193</td>
<td></td>
</tr>
<tr>
<td>Rinaldi C.G.</td>
<td>110, 265</td>
<td></td>
</tr>
<tr>
<td>Ripetti V.</td>
<td>60, 219</td>
<td></td>
</tr>
<tr>
<td>Riva E.</td>
<td>118, 270</td>
<td></td>
</tr>
<tr>
<td>Riva L.</td>
<td>72, 228</td>
<td></td>
</tr>
<tr>
<td>Rivera C.</td>
<td>62, 221</td>
<td></td>
</tr>
<tr>
<td>Rizza W.</td>
<td>215</td>
<td></td>
</tr>
<tr>
<td>Rizzello G.</td>
<td>98, 254</td>
<td></td>
</tr>
<tr>
<td>Romeo R.</td>
<td>34, 199</td>
<td></td>
</tr>
<tr>
<td>Ronci M.B.</td>
<td>56, 215</td>
<td></td>
</tr>
<tr>
<td>Rossi Bartoli I.</td>
<td>221</td>
<td></td>
</tr>
<tr>
<td>Rossi E.</td>
<td>248</td>
<td></td>
</tr>
<tr>
<td>Rossini M.</td>
<td>34, 199</td>
<td></td>
</tr>
<tr>
<td>Rulli A.</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Russano M.</td>
<td>94, 248</td>
<td></td>
</tr>
<tr>
<td>Russo F.</td>
<td>98, 254</td>
<td></td>
</tr>
<tr>
<td>Russo M.</td>
<td>56, 215</td>
<td></td>
</tr>
<tr>
<td>Russo M.T.</td>
<td>72, 228</td>
<td></td>
</tr>
<tr>
<td>Saccomandi P.</td>
<td>233</td>
<td></td>
</tr>
<tr>
<td>Sacco R.</td>
<td>84, 240</td>
<td></td>
</tr>
<tr>
<td>Salvadori F.</td>
<td>34, 199</td>
<td></td>
</tr>
<tr>
<td>Salvati G.</td>
<td>38, 201</td>
<td></td>
</tr>
<tr>
<td>Salvatore G.</td>
<td>98, 254</td>
<td></td>
</tr>
<tr>
<td>Salvatorelli E.</td>
<td>50, 211</td>
<td></td>
</tr>
<tr>
<td>Salvinelli F.</td>
<td>100, 258</td>
<td></td>
</tr>
<tr>
<td>Sambataro G.</td>
<td>193</td>
<td></td>
</tr>
<tr>
<td>Sancillo L.</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>Santacaterina F.</td>
<td>104, 261</td>
<td></td>
</tr>
<tr>
<td>Santini D.</td>
<td>94, 96, 248</td>
<td></td>
</tr>
<tr>
<td>Santini S.</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>Santonico M.</td>
<td>52, 211</td>
<td></td>
</tr>
<tr>
<td>Santoro S.</td>
<td>106, 262</td>
<td></td>
</tr>
<tr>
<td>Santucci D.</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Sardanelli A.M.</td>
<td>32, 197</td>
<td></td>
</tr>
<tr>
<td>Sarlo C.</td>
<td>68, 226</td>
<td></td>
</tr>
<tr>
<td>Sartea C.</td>
<td>72, 228</td>
<td></td>
</tr>
<tr>
<td>Scardocci A.</td>
<td>68, 226</td>
<td></td>
</tr>
<tr>
<td>Scarlata S.</td>
<td>62, 221</td>
<td></td>
</tr>
<tr>
<td>Schena E.</td>
<td>76, 233</td>
<td></td>
</tr>
<tr>
<td>Sciarrà F.</td>
<td>239</td>
<td></td>
</tr>
<tr>
<td>Scotto di Luzio F.</td>
<td>199</td>
<td></td>
</tr>
<tr>
<td>Scotto Di Luzio F.</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Segreto F.</td>
<td>106</td>
<td></td>
</tr>
<tr>
<td>Serra G.B.</td>
<td>64, 224</td>
<td></td>
</tr>
<tr>
<td>Setola R.</td>
<td>30, 195</td>
<td></td>
</tr>
<tr>
<td>Sgrulletta R.</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>Sicilia A.</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>Sicilia R.</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Silipigni S.</td>
<td>110, 265</td>
<td></td>
</tr>
<tr>
<td>Silletta M.</td>
<td>94, 248</td>
<td></td>
</tr>
<tr>
<td>Silvestri S.</td>
<td>76, 233</td>
<td></td>
</tr>
<tr>
<td>Simone P.</td>
<td>106, 262</td>
<td></td>
</tr>
<tr>
<td>Simonetti D.</td>
<td>34, 199</td>
<td></td>
</tr>
<tr>
<td>Simonetti S.</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>Smarrazzo F.</td>
<td>30, 195</td>
<td></td>
</tr>
<tr>
<td>Name Index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Soare A.</strong></td>
<td>54, 212</td>
<td></td>
</tr>
<tr>
<td><strong>Soda P.</strong></td>
<td>44, 206</td>
<td></td>
</tr>
<tr>
<td><strong>Sorian A.</strong></td>
<td>26, 193</td>
<td></td>
</tr>
<tr>
<td><strong>Spadaccio C.</strong></td>
<td>66, 225</td>
<td></td>
</tr>
<tr>
<td><strong>Spalato Ceruso M.</strong></td>
<td>94, 248</td>
<td></td>
</tr>
<tr>
<td><strong>Spiezia F.</strong></td>
<td>252, 254, 257, 272</td>
<td></td>
</tr>
<tr>
<td><strong>Spinelli F.</strong></td>
<td>116, 269</td>
<td></td>
</tr>
<tr>
<td><strong>Spitaleri D.</strong></td>
<td>62, 221</td>
<td></td>
</tr>
<tr>
<td><strong>Spoto C.</strong></td>
<td>248</td>
<td></td>
</tr>
<tr>
<td><strong>Spurio S.</strong></td>
<td>68, 226</td>
<td></td>
</tr>
<tr>
<td><strong>Stefano M.</strong></td>
<td>34</td>
<td></td>
</tr>
<tr>
<td><strong>Stellato M.</strong></td>
<td>94, 248</td>
<td></td>
</tr>
<tr>
<td><strong>Sterzi S.</strong></td>
<td>104, 261</td>
<td></td>
</tr>
<tr>
<td><strong>Stilo F.</strong></td>
<td>116, 269</td>
<td></td>
</tr>
<tr>
<td><strong>Strollo R.</strong></td>
<td>54, 212</td>
<td></td>
</tr>
<tr>
<td><strong>Stumbo L.</strong></td>
<td>94, 248</td>
<td></td>
</tr>
<tr>
<td><strong>Summa S.</strong></td>
<td>244</td>
<td></td>
</tr>
<tr>
<td><strong>Suppa A.</strong></td>
<td>54, 212</td>
<td></td>
</tr>
<tr>
<td><strong>Tabacco G.</strong></td>
<td>54, 212</td>
<td></td>
</tr>
<tr>
<td><strong>Taffoni F.</strong></td>
<td>34, 199</td>
<td></td>
</tr>
<tr>
<td><strong>Tafuri M.A.</strong></td>
<td>68</td>
<td></td>
</tr>
<tr>
<td><strong>Tagliaboschi L.</strong></td>
<td>62</td>
<td></td>
</tr>
<tr>
<td><strong>Tagliamonte N.L.</strong></td>
<td>34, 199</td>
<td></td>
</tr>
<tr>
<td><strong>Tambone V.</strong></td>
<td>72, 228</td>
<td></td>
</tr>
<tr>
<td><strong>Tanzella-Nitti G.</strong></td>
<td>72, 228</td>
<td></td>
</tr>
<tr>
<td><strong>Tartaglini D.</strong></td>
<td>92, 246</td>
<td></td>
</tr>
<tr>
<td><strong>Tecame A.</strong></td>
<td>98, 254</td>
<td></td>
</tr>
<tr>
<td><strong>Tenna S.</strong></td>
<td>106, 262</td>
<td></td>
</tr>
<tr>
<td><strong>Terenzio A.</strong></td>
<td>94</td>
<td></td>
</tr>
<tr>
<td><strong>Terranova C.</strong></td>
<td>64, 224</td>
<td></td>
</tr>
<tr>
<td><strong>Tesei M.</strong></td>
<td>195</td>
<td></td>
</tr>
<tr>
<td><strong>Tirindelli M.C.</strong></td>
<td>68, 226</td>
<td></td>
</tr>
<tr>
<td><strong>Tomaiuolo P.</strong></td>
<td>84, 240</td>
<td></td>
</tr>
<tr>
<td><strong>Tomarchio V.</strong></td>
<td>68, 226</td>
<td></td>
</tr>
<tr>
<td><strong>Tombini M.</strong></td>
<td>86, 240</td>
<td></td>
</tr>
<tr>
<td><strong>Tonini G.</strong></td>
<td>94, 248</td>
<td></td>
</tr>
<tr>
<td><strong>Tosi J.</strong></td>
<td>88, 244</td>
<td></td>
</tr>
<tr>
<td><strong>Toto V.</strong></td>
<td>106, 262</td>
<td></td>
</tr>
<tr>
<td><strong>Trillo L.</strong></td>
<td>58, 218</td>
<td></td>
</tr>
<tr>
<td><strong>Tripodo G.</strong></td>
<td>56, 215</td>
<td></td>
</tr>
<tr>
<td><strong>Trodella L.</strong></td>
<td>110, 265</td>
<td></td>
</tr>
<tr>
<td><strong>Trodella L.E.</strong></td>
<td>110, 265</td>
<td></td>
</tr>
<tr>
<td><strong>Trombetta M.</strong></td>
<td>112, 266</td>
<td></td>
</tr>
<tr>
<td><strong>Tuccinardi D.</strong></td>
<td>54, 212</td>
<td></td>
</tr>
<tr>
<td><strong>U</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ulivì M.</strong></td>
<td>86, 240</td>
<td></td>
</tr>
<tr>
<td><strong>Ursini F.</strong></td>
<td>86, 240</td>
<td></td>
</tr>
<tr>
<td><strong>V</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vadacca M.</strong></td>
<td>26, 193</td>
<td></td>
</tr>
<tr>
<td><strong>Vadalà G.</strong></td>
<td>98, 254</td>
<td></td>
</tr>
<tr>
<td><strong>Valente L.</strong></td>
<td>54, 212</td>
<td></td>
</tr>
<tr>
<td><strong>Valentini S.</strong></td>
<td>34, 199</td>
<td></td>
</tr>
<tr>
<td><strong>Valenti R.</strong></td>
<td>44, 206</td>
<td></td>
</tr>
<tr>
<td><strong>Valeri S.</strong></td>
<td>60, 219</td>
<td></td>
</tr>
<tr>
<td><strong>Vasta S.</strong></td>
<td>98, 254</td>
<td></td>
</tr>
<tr>
<td><strong>Venditti O.</strong></td>
<td>248</td>
<td></td>
</tr>
<tr>
<td><strong>Verdecchia M.</strong></td>
<td>240</td>
<td></td>
</tr>
<tr>
<td><strong>Vernieri F.</strong></td>
<td>86, 240</td>
<td></td>
</tr>
<tr>
<td><strong>Vernuccio A.</strong></td>
<td>26</td>
<td></td>
</tr>
<tr>
<td><strong>Vespasiani Gentilucci U.</strong></td>
<td>74, 232</td>
<td></td>
</tr>
<tr>
<td><strong>Vilmercati A.</strong></td>
<td>56</td>
<td></td>
</tr>
<tr>
<td><strong>Vincenzi B.</strong></td>
<td>248</td>
<td></td>
</tr>
<tr>
<td><strong>Vinci C.</strong></td>
<td>54, 212</td>
<td></td>
</tr>
<tr>
<td><strong>Virga S.</strong></td>
<td>80, 238</td>
<td></td>
</tr>
<tr>
<td><strong>Virzi V.</strong></td>
<td>94, 248</td>
<td></td>
</tr>
<tr>
<td><strong>Vollero L.</strong></td>
<td>44, 206</td>
<td></td>
</tr>
<tr>
<td><strong>Vorini F.</strong></td>
<td>98</td>
<td></td>
</tr>
<tr>
<td><strong>Z</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Zalfa F.</strong></td>
<td>78, 236</td>
<td></td>
</tr>
<tr>
<td><strong>Zampogna B.</strong></td>
<td>98, 254</td>
<td></td>
</tr>
<tr>
<td><strong>Zangrandi A.</strong></td>
<td>88</td>
<td></td>
</tr>
<tr>
<td><strong>Zardi E.M.</strong></td>
<td>193, 271</td>
<td></td>
</tr>
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<td><strong>Zompanti A.</strong></td>
<td>52, 211</td>
<td></td>
</tr>
<tr>
<td><strong>Zingariello M.</strong></td>
<td>78, 236</td>
<td></td>
</tr>
<tr>
<td><strong>Zito A.</strong></td>
<td>62, 221</td>
<td></td>
</tr>
<tr>
<td><strong>Zollo L.</strong></td>
<td>34, 199</td>
<td></td>
</tr>
</tbody>
</table>