SUMMARY

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**Research projects**

- Grants from competitive calls
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**The University Third Mission: impact on society**

- Commissioned research
- Clinical trials
- Research exploitation
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Dear Stakeholder,

this Yearbook introduces you to Research at Campus Bio-Medico University of Rome (UCBM), and it specifically reports about the main facts, activities and scientific outputs achieved by our institution in the 2015 calendar year.

The Yearbook has been conceived and produced 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 answers to their knowledge and innovation needs, and identify the specific group(s) in our community that will fit for the purpose of effectively satisfying such needs. This Yearbook also includes a brief description of our research strategic objectives and quality assurance policies, with the aim of offering the possibility to other actors and potential partners to share and align with our strategy and possibly support its implementation plan. Extended information on our research activities can be retrieved on the new research section of our official website www.unicampus.it/research

• **Accountability.** This Yearbook is also intended to provide our main sponsors and external supporters a direct source of information on how resources have been used, on which 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 capabilities;

• **Self-assessment.** The facts and data briefly presented in this Yearbook are 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.

Key performance indicators have shown that, also in 2015, research at UCBM continued to grow, significantly, as it has been since the very beginning of our history, back in the early '90s.

Of note, the total cumulative Impact Factor of our publications raised for the first time beyond 2000 points. More than 70% of such publications appeared on journals belonging to the first quartile (Q1) of the Scopus\Scimago international periodicals ranking.

In addition, the amount of clinical research activities raised significantly: the economic value of contracts related to new clinical trials increased in 2014-2015 of more than 600% with respect to 2013. The associated turnover, directly related to the successful enrolment of patients in clinical trials, also increased of about 100% in the same period. Such impressive figures, even beyond our expectations, are strongly related to the excellence of the principal investigators and the research clinical staff involved in these studies. However, the results strongly rely also on the organisational solutions that have been brought forth during the last three years. They have been significantly implemented in a perspective of an efficient management of preparatory, authorisation and execution phases of clinical research. Based on such results, further refinements of the organisational model and quality assurance procedures are still being introduced to fully turn clinical research into a key asset of our university, which fully exploits the potential of our own research hospital.

The Academic Research Board, where we sit together with Paolo Sormani, General Manager of our University, and Gianfilippo Capriotti, Head of the Research Administrative Area, has worked in tight co-operation with the Scientific Research Committee to oversee and monitor research activities, with the competent and effective support of all the internal research offices.

From the research management viewpoint, it is particularly worth to recall that in October 2015 our university has volunteered, among the first ten Italian universities, to be visited by an independent
evaluation committee appointed by the National Agency for Evaluation of University and Research (ANVUR). Results of such visits have not been published yet, anyhow this exercise gave us already several, very important inputs for consolidating and further improving our internal quality assurance processes and procedures. Our personal gratitude goes to all the researchers and administrative staff who have been co-operating in producing the relevant documentation and other materials needed to implement and assess our Research Quality Assurance system.

Finally, we want to acknowledge all researchers, clinical personnel and administrative 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, Graphics and Editing Services, and Antonella Benvenuto, Research Promotion and Technology Transfer Office, for the hard work in the preparation of this document.

We do hope that you will enjoy this 2015 Yearbook.

We will be very happy to receive any remarks and suggestions aimed at improving its structure and contents; please address your feedback message to cir@unicampus.it

Eugenio Guglielmelli
Pro-Rector for Research
Campus Bio-Medico University of Rome

Andrea Onetti Muda
Rector
Campus Bio-Medico University of Rome
ON THE COVER
In 2013 State of the Union Address, President Obama called additive manufacturing (AM) a technology that has “the potential to revolutionize the way we make almost everything”. This is particularly true in the biomedical field, where the combination of smart biomaterials with AM is revolutionizing the approach to tissue engineering and regenerative medicine.

However, while the use of AM for the fabrication of custom-shaped bone graft substitutes using thermoplastic biopolymers is well established, AM techniques are still hampered by low resolution, limited materials selection, and smooth-surfaced struts, which affect initial cell adhesion and proliferation.

Moreover, conventional AM systems are not suitable to directly manufacture sub-micrometer structures that could mimic the features of natural ECM, or to achieve hierarchical porous architectures with multimodal pore size distributions.

As thoroughly reviewed in our work, a current trend in AM is represented by the development of hybrid manufacturing technologies by combining AM with other scaffolding fabrication methods, such as electrospinning, freeze-drying, etc., potentially reaping the advantages of both “worlds”. Another major issue regards the application of AM techniques to the deposition of hydrogels. Hydrogels are indeed particularly attractive for biofabrication, as they recapitulate several features of the natural extracellular matrix, providing a highly hydrated mechanically supportive three-dimensional environment for cell encapsulation, as well as biologically-relevant chemical and physical signals.

However, despite the progress made in modifying hydrogels for enhanced bioactivity, little has been done to optimize hydrogels for the physico-chemical requirements of additive manufacturing processes. This has been identified as one major hurdle for a more rapid progress of the field, with potential impact on the establishment of tissue analogues for regenerative medicine, as well as for in vitro drug screening and toxicology.

We have developed a new concept of extrusion-based bioprinting, which implements a microfluidic control in the dispensation of the bioink. Microfluidics enables the printing head to achieve a level of accuracy that was previously unachievable by extrusion-based systems. At the heart of the system, there is a coaxial extrusion head that induces the solidification of the bioink in the form of a hydrogel upon its deposition. Hydrogel fibers with dimensions ranging between 150 and 300 μm and high shape fidelity can be obtained. The printing conditions are mild since bioinks viscosity is low and crosslinking conditions can be tuned to be harmless toward encapsulated cells. Beside alginate – main component of all bioinks – other macromolecules of biological interest can be used as extracellular matrix components for cell encapsulation.
2015 RESEARCH FIGURES
The research activities carried out in 2015 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 growth rate of the number of scientific publications, as shown in the figures below, has been steady and significantly positive over the past five years and has reached in 2015 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, the number of publications with Impact Factor has increased by 6% with respect to 2014, exceeding for the first time the value of 500, the total Impact Factor (I.F.) has increased by 13%, exceeding for the first time the value of 2,000, the normalized Impact Factor (I.F.N.) is stable around the value of 2,300, which was a record level last year.

![Figure 1: Number of publications with I.F., total I.F. and total I.F.N. in the last five years](image)

As shown in Figure 2 the number of publications per faculty member is stable with respect to 2014 and increased by 59% with respect to 2011, despite the number of faculty members did not change significantly over the last five years, as shown in Figure 3.
Figure 4 shows the overall scientific production in 2015 in terms of number of publications, Impact Factor (IF) and Normalized Impact Factor (IFN) for each of the 48 Research Units of the university. The numbers confirm the positive trend of the last five years; in particular the average I.F. per Research Unit has increased by 7% with respect to 2014.
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 5 publications with Impact Factor per faculty member in 2015;
- 20 % of 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)
- 70% publications in the first quartile (Q1) according to SCImago ranking, which includes the top 25% journals in each subject category.

In 2015, 63 research projects, including clinical trials, were funded. As for research projects submitted under competitive calls in 2015, a success rate of 12% has been reached. The main funding bodies of ongoing projects were: European Commission, Italian Ministry of Education, University and Research, Italian Ministry of Health, Italian Ministry of Foreign Affairs and International Cooperation, Italian Ministry of Economic Development, Italian Space Agency, European Space Agency, Lazio Regional Authority, the National Institute for Insurance against Accidents at Work (INAIL) as well as several business companies which have been supporting commissioned research and clinical trials; 23 internal clinical trials were also started.
As regards the activities related to exploitation of research results, in 2015 3 Italian patents, 2 European patents and 2 US patents have been granted. 2 applications for Italian patents, co-owned with other Universities and Research Centers were filed and 3 patents have been entered in the national phase.
As of 31st December 2015 patent portfolio owned or co-owned by the University includes 17 families of patents (with a total of 39 patents, 17 already granted) in the field of rehabilitation engineering, microengineering, regenerative medicine, biomedical instrumentation, cancer diagnostics and food analysis.

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.
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 is 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;
  - Research Scientific Committee;
  - Faculty Councils;
  - Faculty Boards.

The Research Scientific Committee plays a key role as the QAR main body, in tight cooperation with the university Quality Assurance Committee.
MAIN RESEARCH STRATEGIC OBJECTIVES
(2014-2016)
The research strategy of the University is elaborated every three years, in line with the overall Strategic Guidelines 2014-2016 of the University as defined by the Administrative Board. Such strategy can be updated annually, based on the evaluation of the performance of the University when compared to the continuous evolution of the state-of-the-art in the target research areas.

For the period 2014-2016, the research strategic objectives of the University have been defined as the final outcome of an innovative process which involved the two Departments and the whole community of researchers of the University. An internal call for strategic projects has been launched, and three projects were selected based on an independent, external evaluation by experts having a solid track as evaluators of European research programmes. Such strategic projects helped to identify strategic objectives directly related to their research areas. These same projects have been supported by the University with 500 Keuros for two years, with the aim to pave the way to the start-up of long-term research initiatives which could attract a critical mass of resources and partnership at National, European and international level. Of note, the Principal Investigators leading the three strategic projects are young researchers and all the projects are multidisciplinary by nature with a balanced involvement of Research Units of both the university Departments.

In addition, each university Department has been solicited to define its own research strategic objectives. The Departments have been also offered the possibility to propose a few research objectives to be upgraded at the level of university strategic objectives, typically based on a clear evidence of success on the proposed research areas, in terms of scientific outcome and raising of competitive funding in the last three to five years.

As a result of this process, the main research strategic objectives of the university for the 2014-2016 period are defined as follows:

- **RSO1. NEW CLINICAL APPROACHES TO AGE-RELATED DISEASES.** Development of novel technological methods and tools for the prevention, the early detection and the treatment of age-related diseases. The objective is to carry out preclinical and/or clinical observational and correlative studies to identify the relationship between aging and endocrine diseases, metabolic syndrome, cardiovascular risk or alterations of bone metabolism. These topics are related to the many emerging aging-related issues, which have always been at the centre of the University mission as well as of many European competitive calls;

- **RSO2. IN-SILICO MEDICINE.** Development of “cell-on-chip” and “organ-on-chip” platforms, alternative to traditional descriptive animal or cellular models, which can be predictive of metabolic systems and of the interaction with the immune system. A high strategic impact is recognized to this research field mainly because it gives the opportunity of making “in-silico” models of physiological systems available in various areas of research. For example the possibility of identifying potentially dangerous substances for human health (environmental contaminants, additives, etc.), or develop new drugs with mechanism-based criteria can be enabled by these research approach. This research field is of great interest to the European Commission which has always been concerned with the problem of identifying and validating alternative drug testing methods.

- **RSO3. SUSTAINABLE SOLUTIONS FOR REGENERATIVE MEDICINE.** Development of new regenerative medicine strategies for improving the tolerability and efficacy of medical and surgical treatments, as well as pharmaco-economics opportunities for the National Health Service. Examples of these opportunities are: intervertebral disc repairs with polymers administered through robotic platforms, treatment of chemotherapy or radiation therapy induced mucositis with platelet-rich plasma that contains growth factors having a trophic-reparative action, fibrin glue therapy of severe hemorrhagic cystitis.

- **RSO4. BIOMARKERS FOR PRECISION MEDICINE.** Collaborative studies in oncology, onco-hematology, surgery and lab testing, using genetic and epigenetic biomarkers to improve the level
of diagnosis-prognosis and to evaluate the appropriateness of therapeutic drug monitoring. From these studies we expect an improvement in personalizing therapies with obvious benefits for the physician (at the decision making level), for the patient (better care, better survival), and for the National Health Service (money saving).

**Main strategic research objectives for the Medicine and Surgery Department are as follows:**

- Neurobiology and neurogenetic studies, as applied to the diagnosis of pervasive behavioural disorders, to cognitive-motor training of patients with senile dementia, to Alzheimer’s disease, or to the outcomes of acute or chronic stroke.
- Studies on inflammation and autoimmunity, starting from the development of new diagnostic platforms for preclinical evaluations of natural substances with anti-inflammatory activity, up to clinical trials of protective growth factors or biotechnological and anti-inflammatory agents.
- Periprocedural cardiac protection studies in patients with acute coronary syndromes, or cardio-prevention in patients exposed to cardiotoxic cancer drugs, accompanied by cardiac functional imaging studies and interpretation of predictive markers.
- New mechanism-based, diagnostic, and therapeutic approaches to complex and debilitating clinical conditions such as chronic obstructive pulmonary disease and viral or metabolic liver diseases.

**Main strategic research objectives for the Engineering Department are as follows:**

- Development of electronic interfaces for the management of artificial sensory systems for vapours, gases and liquids for medical, nutrition, environmental and space applications.
- Study and modelling of complex systems and study of nonlinear dynamics of complex systems at different scales, both spatial and temporal.
- Definition, development and optimization of industrial processes and new technologies for chemical implants based on sustainability and environmental compatibility.
- Development of cell-on-chip systems and organs-on-chips as advanced models for the study of morphogenesis, pathogenesis and drug screening.
- Development of advanced materials for chemical, physical and biomedical applications, with particular regard to the manufacturing of smart biomimetic materials for tissue engineering and regenerative medicine.
- Innovative solutions for people and object localization.
- Development of research topics specific to clinical engineering with respect to innovative and standardized methods for performance testing of measurements systems.
- Development of robotic systems for medical applications (diagnosis, acute treatment, rehabilitation), development of biomechatronic prosthesis and tools for independent living.
- Development of technologies for research in neuroscience, specifically for studies on pathophysiology of neurodevelopmental disorder and on sensory motor coordination in adults. Development of neural interfaces for bionic systems and integrated use of robotic systems with neuroimaging and neuromodulation technologies for neurorehabilitation.
- Use and development of signal processing methods and techniques, machine learning, multiparametric analysis to extract data, signals, pictures, video and information useful to users of biomedical applications.

In order to be fully compliant with the overall Strategic Guidance Lines 2014-2016 defined by the University Administrative Board, these objectives are to be achieved by promoting participation to national and international competitive calls for research, innovation and mobility; by consolidating and extending partnerships with public and private national and foreign institutions for common initiatives on all of the most important research sectors of the University; by increasing the capacity of attracting international scholars, and promoting participation in projects linked to large-scale European programmes, such as the EIT\KIC, the FET-Flagship and other similar programs; by
setting up attractive services and partnership opportunities to network with UCBM as a primary Innovation Hub and even to locate for industrial groups in health care, biomedical, biotechnology and food sectors which wish to network with UCBM as a primary Innovation Hub and even to locate in the University premises some of their own research units; by defining, together with the Institute of Philosophy of Scientific and Technological Practice (FAST) and the two university Departments, a multidisciplinary research strategy with the aim of generating a positive impact on the solution of anthropological, ethical or social issues.
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. The figure below schematically shows CIR organization.

Academic Research Board

The Pro-Rector for Research is the Head of CIR. The Academic Research Board, formed by the Rector, the University General Manager, the Pro-Rector for Research and the Head of Administrative Research Area, supervises the activities of CIR.

Research Scientific Committee

The Pro-Rector for Research chairs the Committee, which is also composed of the Research Coordinators of the two UCBM Departments. The Committee ensures the necessary link between the two boards of the Departments, addressing and monitoring scientific research, and fostering their collaboration. The Committee 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: Research Promotion and Technology Transfer Office, Project Financial Management and Reporting Office and Clinical Trials Office. Activities of the offices are described below.

Research Promotion and Technology Transfer Office
The Research Promotion and Technology Transfer Office main objective is to assist the researchers in finding the most appropriate funding sources and in the exploitation of research results. In this context the Office carries out mapping of both expertise and results obtained by the Research Units. It also performs internal scouting activities in order to promote and consolidate collaborations among the UCBM Research Units.

The office guarantees identification and wide dissemination, also by means of information days, of the most appropriate funding opportunities and assistance in preparation and submission of research projects under national, European Commission and international competitive calls. It also provides follow up of project management in close collaboration with the Project Financial Management and Reporting Office.

As regards the services strictly related to the exploitation of research activities, the Office assists faculty and staff in finding the best strategy to protect intellectual property, manages the University patent portfolio working closely with inventors, promotes research results to SME and companies; supports the promotion of joint labs, and supports spin-off research processes as well as incubation and acceleration of spin-off companies. Furthermore the Office organizes seminars and workshops on technology transfer research issues.

Finally, it assists the Research Scientific Committee.

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 (Law 3/2003 art.11; Law 136/2010).

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 Trials Office
The Clinical Trials Office (USPC) promotes the Quality System of University Clinical Trials, by monitoring them along the whole process, complying with best practices in European and US institutions. The aim is to assist the Institution in the dialogue with clinical trials Industrial Promoters and Sponsors in order to provide a contribution to the quality, internationality and profitability of trials.

The Office, in fact, carries out for each study an estimate and economic analysis as well as a feasibility study (numerical sufficiency and professional profile of staff, effective recruitment potential, adequacy of premises and equipments, tracking performance); it ensures staff training in Good Clinical Practice (GCP); it takes care of negotiating financial terms of the studies, until the agreement is finally signed. Such procedures are required by the European Regulation No 536/2014 on clinical trials, issued by the European Parliament.

Essential to the functions of USPC is a close cooperation with the governing bodies of the University Hospital.
Once the study is started, USPC conducts regular reporting making sure time frame is followed as per contract. When required, it also provides advice on the management of the drug on trial in cooperation with the Hospital Pharmacy. In case the University is the Coordinator Centre of non-profit experiments, USPC provides advice to Investigators on study reporting and management. Organizations such as the Italian Medicines Agency (AIFA), the Italian competent authority for drugs, consider non-profit studies the most genuine and qualifying expression of the Institution scientific interests. Upon request by Sponsors or Accreditation entities, the office may organize clinical research training courses for Principal Investigators of approved clinical trials, constantly monitoring their qualifications as required by current regulations. The course are chaired by certified Quality Assurance experts.

**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.
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RESEARCH UNITS: OVERVIEW AND MAIN 2015 SCIENTIFIC OUTPUTS
ALLERGOLOGY, IMMUNOLOGY, RHEUMATOLOGY

Head:
A. Afeltra


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 (ultrasonography and musculoskeletal capillaroscopy) and laboratory methods (immunofluorescence, enzyme immunoassay, molecular biology, flow cytometry).

- Pathogenesis of Lupus nephritis
- Automation of auto-antibody determination by indirect immunofluorescence
- Epidemiology and features of inflammatory rheumatic manifestation during therapy with aromatase inhibitors
- Epidemiology of infection during biologic therapy in a large Italian cohort of rheumatoid arthritis

- GIRRCS (Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale)
- Unit of Biochemistry and Molecular Biology, Campus Bio-Medico University of Rome, Prof. Mauro Maccarrone
- Rheumatology Day Hospital, Ospedale Gaetano Pini di Milano, Dott.ssa N. Del Papa
- Unit of Rheumatology, Spedali Civili di Brescia, Prof.ssa A. Tincani
- Unit of Microbiology, Ospedale San Carlo Borromeo di Milano, Dott.ssa A. Radice
- Forum Italiano di Ricerca sulle Malattie Autoimmuni, FIRMA
- Sheba Medical Center · Center for Autoimmune Diseases, Israel · Ramat Gan, Prof Yehuda Shoenfeld
Most important publications


The involvement of T regulatory lymphocytes in a cohort of lupus nephritis patients: a pilot study.


T regulator lymphocytes (Tregs) play a key role in the maintenance of immune tolerance and in the development of autoimmune diseases. Expression of Foxp3 is specific for Tregs, and can be used for the identification of these cells. This study investigated the variations of Tregs Foxp3+ in the kidney biopsies inflammatory infiltrate of different lupus nephritis classes compared to that of ANCA glomerulonephritis, acute tubulointerstitial nephritis and nephroangiosclerosis. Sections of paraffin-embedded tissue have been stained by immunohistochemistry with anti-CD3 and anti-FoxP3 antibodies. We find that the ratio of FoxP3+/CD3+ cells is significantly lower in patients with lupus nephritis class IV and in patients with vasculitides than in the course of nephroangiosclerosis, tubulointerstitial nephritis and lupus nephritis class V. The data presented herein demonstrate a decrease of FoxP3+ Treg cells in the inflammatory infiltrate of lupus nephritis, particularly during the most active phases of lupus nephritis, as observed in the course of a IV class nephritis.


Clinical comparison of QUANTA Flash dsDNA chemiluminescent immunoassay with four current assays for the detection of anti-dsDNA autoantibodies.


Introduction: The objective of the present study was to compare QUANTA Flash dsDNA, a chemiluminescent immunoassay (CIA) on the BIO-FLASH, a rapid-response chemiluminescent analyzer, to three other anti-dsDNA antibody assays and to Cri-thidia luciliae indirect immunofluorescence test (CLIFT).

Methods: In the first part of the study, 161 samples, 61 from patients suffering from systemic lupus erythematosus (SLE) and 100 from a disease control group, were tested by QUANTA Flash dsDNA CIA, QUANTA Lite dsDNA SC ELISA, BioPlex 2200 multiplex flow immunoassay (MF), ImmuLisa dsDNA ELISA, and NOVA Lite CLIFT. A second cohort of 69 SLE patients was then tested by QUANTA Flash dsDNA and CLIFT to expand the study.

Results: The overall qualitative agreements varied between 77.0% (NOVA Lite CLIFT versus QUANTA Lite) and 89.4% (ImmuLisa versus NOVA Lite CLIFT). The clinical sensitivities for the anti-dsDNA antibody tests varied from 8.2% (NOVA Lite CLIFT) to 54.1% (QUANTA Lite), while the clinical specificities varied from 88.0% (BioPlex 2200) to 100.0% (NOVA Lite CLIFT). Good correlation was found between QUANTA Flash dsDNA and NOVA Lite CLIFT. Conclusions: Significant variations among dsDNA methods were observed. QUANTA Flash dsDNA provides a good combination of sensitivity and specificity for the diagnosis of SLE and good agreement to CLIFT.
ANESTHESIA, INTENSIVE CARE AND PAIN MANAGEMENT

Head:
F.E. Agrò

Faculty: M. Carassiti, R. Cataldo
Other Personnel: S. Antonelli, M. Benedetto, F. Costa, A. Mattei, M. Vennari, M. Vitiello

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

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

Intensive therapy
- Colistin therapeutical targets in clostridium difficile infection during patient ultrafiltration
- Cardiac output monitoring innovations in mechanically ventilated patients
- Advanced pain control strategies in ICU
- Ecocardiography in post cardio-surgical patients in ICU

Pain Management
- FBSS (Patents development)

Post Herpetic pain and neurobiological modifications
Agrò F.E., Doyle D.J., Vennari M.
Use of GlideScope® in adults: an overview.

This paper is an overview of the literature concerning the “know how” of the GlideScope® use in adults. We summarized the main evidences of the last 10 years with particular attention to experts’ suggestions about clinical practice of the GlideScope®, noticing matters still debated on GlideScope® use. We used PubMed to search publications from January 2003 to June 2013 using the search terms “GlideScope”, “video laryngoscope” and “videolaryngoscopy”. These publications were searched manually or references to further publication not identified using PubMed. All works that made a point worth including were cited in the discussion. Our research confirms the value of GlideScope® use in airway management and highlights the debate about the use of videolaryngoscopes in routine cases and the operators who may use them in clinical practice.

Benedetto M., Romano R., Baca G., Sarridou D., Fischer A., Simon A., Marczin N.
Inhaled nitric oxide in cardiac surgery: evidence or tradition?

Inhaled nitric oxide (iNO) therapy as a selective pulmonary vasodilator in cardiac surgery has been one of the most significant pharmacological advances in managing pulmonary hemodynamics and life threatening right ventricular dysfunction and failure. However, this remarkable story has experienced a roller-coaster ride with high hopes and nearly universal demonstration of physiological benefits but disappointing translation of these benefits to harder clinical outcomes. Most of our understanding on the iNO field in cardiac surgery stems from small observational or single centre randomised trials and even the very few multicentre trials fail to ascertain strong evidence base. As a consequence, there are only weak clinical practice guidelines on the field and only European expert opinion for the use of iNO in routine and more specialised cardiac surgery such as heart and lung transplantation and left ventricular assist device (LVAD) insertion. In this review the authors from a specialised cardiac centre in the UK with a very high volume of iNO usage provide detailed information on the early observations leading to the European expert recommendations and reflect on the nature and background of these recommendations. We also provide a summary of the progress in each of the cardiac subspecialties for the last decade and initial survey data on the views of senior anaesthetic and intensive care colleagues on these recommendations. We conclude that the combination of high price tag associated with iNO therapy and lack of substantial clinical evidence is not sustainable on the current field and we are risking loosing this promising therapy from our daily practice. Overcoming the status quo will not be easy as there is not much room for controlled trials in heart transplantation or in the current atmosphere of LVAD implantation. However, we call for international cooperation to conduct definite studies to determine the place of iNO therapy in lung transplantation and high risk mitral surgery. This will require new collaboration between the pharmaceutical companies, national grant agencies and the clinical community. Until these trials are realized we should gather multi-institutional experience from large retrospective studies and prospective data from a new international registry. We must step up international efforts if we wish to maintain the iNO modality in the armamentarium of hemodynamic tools for the perioperative management of our high risk cardiac surgical patients.

Gaszynski T., Toker K., Carassiti M., Chalkias A., Carlson J.N.
Advances in airway management and ventilation strategies in emergency medicine.
AUTOMATION AND CONTROL THEORY

Head:
R. Setola

Faculty: G. Oliva, M. Papi, F. Smarrazzo
Other Personnel: F. De Cillis, M.C. De Maggio, E.E. Miciolino, L.M. Montoni, M. Tesei

The Unit of Automation and Control Theory aims at modeling, analyzing and controlling complex dynamic systems, ranging from networks of Critical Infrastructures, to biological systems and from sensor networks to cyber-physical systems. 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 strong multi-disciplinary methodologies, tools and technologies. Among others, the Unit provided both theoretical and applicative contributions in the field of indoor localization, critical infrastructure protection and innovative gesture-based tools for surgery rooms.

The Unit is involved in several European and national research projects and cooperates with a wide spectrum of research bodies, industrial partners and Critical Infrastructure firms.

The Unit coordinated one EU project and participated to 3 EU FP7 projects:
- RISING on the development of innovative tools to support situation awareness and localization of first responders in order to improve safety and effective
- CIPRNET to create a network of excellence on Critical Infrastructure protection and to develop a DSS to support civil protection and operator to manage more effectively emergency related to flooding, earthquake, etc.
- STRUCTURES to improve the security of critical infrastructures against electromagnetics attacks.

The Unit participated to 3 Lazio regional projects on data fusion for cyber security; biomedical image manipulation; and a touchless interfaces for surgery room (a video describing the device is available here https://www.youtube.com/watch?v=ngGum2FI1aY).

Moreover, the Unit participated to a project granted by Italian PNRM on use of game theory for anti-piracy and to a project funded by Poste Italiane on the cyber security.
Most important publications

Oliva G., Panzieri S., Pascucci F., Setola R.  
Sensor networks localization: extending trilateration via shadow edges.  
IEEE Trans Autom Control. 2015;60(10):2752-2755. DOI: 10.1109/TAC.2015.2404253. IF 2.779

In this paper a novel methodology to localize a sensor network in a distributed way is developed. In the proposed framework the sensors are able to measure their relative distance from a set of neighbors, and we propose a method to get rid of ambiguities by taking explicitly into account negative information, i.e., the fact that two nodes are not connected is indeed a valuable piece of information to find the correct position of the sensors.

Oliva G., La Manna D., Fagiolini A., Setola R.  
Distributed data clustering via opinion dynamics.  
Int J Distrib Sens N. 2015; N 753102. DOI: 10.1155/2015/753102. IF 0.665

We provide a distributed method to partition a large set of data in clusters, characterized by small in-group and large out-group distances. We assume a wireless sensors network in which each sensor is given a large set of data and the objective is to provide a way to group the sensors in homogeneous clusters by information type. In previous literature, the desired number of clusters must be specified a priori by the user. In our approach, the clusters are constrained to have centroids with a distance at least between them and the number of desired clusters is not specified. Although traditional algorithms fail to solve the problem with this constraint, it can help obtain a better clustering. In this paper, a solution based on the Hegselmann-Krause opinion dynamics model is proposed.

Setola R., Sforza A., Vittorini V., Pragliola C.  
Railway infrastructure security.  

This monograph addresses crucial issues in the protection of railway systems, with the objective of enhancing the understanding of railway infrastructure security. It explains how to assess terrorist and criminal threats, design countermeasures, and implement effective security strategies. In so doing, it draws upon a range of experiences from different countries in Europe and beyond. The book is the first to be devoted entirely to this subject. It will serve as a timely reminder of the attractiveness of the railway infrastructure system as a target for criminals and terrorists and, more importantly, as a valuable resource for stakeholders and professionals in the railway security field aiming to develop effective security based on a mix of methodological, technological and organizational tools.
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 and Multiple Sclerosis], 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-arachidonoylglycerol) and specialized pro-resolving mediators (lipoxins, resolvins, protectins 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.

In collaboration with Prof. Rafael Maldonado (Pompeu Fabra University, Barcelona), the group has developed an unprecedented animal model of eating addictive-like behavior in mice. This model has allowed identifying extreme subpopulations of mice related to addictive-like behaviour, where epigenetic and proteomic changes were interrogated for the very first time. Remarkable changes were found in proteins involved in impulsivity-like phenotype, synaptic plasticity and endocannabinoid signaling, overall demonstrating that the model provides an excellent tool to investigate neurobiological clues. Moreover, the group showed that endocannabinoids are secreted through extracellular membrane vesicles produced by microglial cells around neurons, with a clear impact on neurotransmission within the brain. Professor M. Maccarrone has also organized as Chair the 2015 Gordon Research Conference on “Cannabinoid Function in the CNS”, and has coordinated a community review where the state-of-the-art of endocannabinoid research was presented by some of the founding scientists 50 years after the discovery of THC.
Cannabis sativa, in 1964, the psychoactive ingredient of Δ9-tetrahydrocannabinol (THC), was isolated. Nearly 30 years later, the endogenous counterparts of THC, collectively termed endocannabinoids (eCBs), were discovered: N-arachidonoylthanolamine (anandamide) (AEA) in 1992 and 2-arachidonoylglycerol (2-AG) in 1995. Since then, considerable research has shed light on the impact of eCBs on human health and disease, identifying an ensemble of proteins that bind, synthesize, and degrade them and that together form the eCB system (ECS). eCBs control basic biological processes including cell choice between survival and death and progenitor/stem cell proliferation and differentiation. Unsurprisingly, in the past two decades eCBs have been recognized as key mediators of several aspects of human pathophysiology and thus have emerged to be among the most widespread and versatile signaling molecules ever discovered. Here some of the pioneers of this research field review the state of the art of critical eCB functions in peripheral organs. Our community effort is aimed at establishing consensus views on the relevance of the peripheral ECS for human health and disease pathogenesis, as well as highlighting emerging challenges and therapeutic hopes.

**Most important publications**


In 1964, the psychoactive ingredient of Cannabis sativa, Δ9-tetrahydrocannabinol (THC), was isolated. Nearly 30 years later, the endogenous counterparts of THC, collectively termed endocannabinoids (eCBs), were discovered: N-arachidonoylthanolamine (anandamide) (AEA) in 1992 and 2-arachidonoylglycerol (2-AG) in 1995. Since then, considerable research has shed light on the impact of eCBs on human health and disease, identifying an ensemble of proteins that bind, synthesize, and degrade them and that together form the eCB system (ECS). eCBs control basic biological processes including cell choice between survival and death and progenitor/stem cell proliferation and differentiation. Unsurprisingly, in the past two decades eCBs have been recognized as key mediators of several aspects of human pathophysiology and thus have emerged to be among the most widespread and versatile signaling molecules ever discovered. Here some of the pioneers of this research field review the state of the art of critical eCB functions in peripheral organs. Our community effort is aimed at establishing consensus views on the relevance of the peripheral ECS for human health and disease pathogenesis, as well as highlighting emerging challenges and therapeutic hopes.

Active endocannabinoids are secreted on extracellular membrane vesicles. EMBO Rep. 2015 Feb; 16(2): 213-20. PubMed PMID: 25568329. IF 9,055

Endocannabinoids primarily influence neuronal synaptic communication within the nervous system. To exert their function, endocannabinoids need to travel across the intercellular space. However, how hydrophobic endocannabinoids cross cell membranes and move extracellularly remains an unresolved problem. Here, we show that endocannabinoids are secreted through extracellular membrane vesicles produced by microglial cells. We demonstrate that microglial extracellular vesicles carry on their surface N-arachidonoylthanolamine (AEA), which is able to stimulate type-1 cannabinoid receptors (CB1s), and inhibit presynaptic transmission, in target GABAergic neurons. This is the first demonstration of a functional role of extracellular vesicular transport of endocannabinoids.


An increasing perspective conceptualizes obesity and overeating as disorders related to addictive-like processes that could share common neurobiological mechanisms. In the present study, we aimed at validating an animal model of eating addictive-like behavior in mice, based on the DSM-5 substance use disorder criteria, using operant conditioning maintained by highly palatable chocolate-flavored pellets. For this purpose, we evaluated persistence of food-seeking during a period of non-availability of food, motivation for food, and perseverance of responding when the reward was associated with a punishment. This model has allowed identifying extreme subpopulations of mice related to addictive-like behavior. We investigated in these subpopulations the epigenetic and proteomic changes. A significant decrease in DNA methylation of CNR1 gene promoter was revealed in the prefrontal cortex of addict-like mice, which was associated with an upregulation of CB1 protein expression in the same brain area. The pharmacological blockade (rimonabant 3 mg/kg; i.p.) of CB1 receptor during the late training period reduced the percentage of mice that accomplished addiction criteria, which is in agreement with the reduced performance of CB1 knockout mice in this operant training. Proteomic studies have identified proteins differentially expressed in mice vulnerable or not to addictive-like behavior in the hippocampus, striatum, and prefrontal cortex. These changes included proteins involved in impulsivity-like behavior, synaptic plasticity, and cannabinoid signaling modulation, such as alpha-synuclein, phosphatase 1-alpha, duallecin-kinase 2, and diacylglycerol kinase zeta, and were validated by immunoblotting. This model provides an excellent tool to investigate the neurobiological substrate underlying the vulnerability to develop eating addictive-like behavior.
BIOMEDICAL ROBOTICS AND BIOMICROSYSTEMS

Head:
E. Guglielmelli

Faculty: D. Accoto, D. Formica, F. Taffoni, L. Zollo

Biomedical Robotics investigates the application of mechatronic and robotic technologies to medicine and biology, for unveiling biological principles, for mimicking such principles in artificial systems and for developing innovative solutions for diagnosis, healthcare and improvement of patient quality of life.

Biomechatronic design methods and tools, human-centered design, bio-inspired systems for clinical and non-clinical applications, surgical robotics and micro-endoscopic systems, rehabilitation and assistive robotics, bionic prostheses, neuro-engineering and neurodevelopmental engineering.

- PPR2 - funded by the National Institute for Insurance against Accidents at Work, 2014-2017
- AIDE - funded by EC-H2020\CT 22 - 2014-2017
- DAHMS - funded by the Italian Ministry of Economic Development, 2010-2016
- NEMESIS - funded by the Italian Ministry of Health, 2012-2015
- PD-meter - funded by the Ministry of Health, 2014-2017
- START-DISC - University Strategic Project, 2015-2017
- NEUROHAND - funded by Lazio Regional Authority, 2012-2015

- INAIL - Prosthetic centre, Italy
- Sant’Anna School of Advanced Studies, Italy
- Cagliari University, Italy
- Politecnico di Milano, Italy
- Institute of Cognitive Sciences and Technologies, National Research Council (CNR), Italy
- Institute for Microelectronics and Microsystems, National Research Council (CNR), Italy
- Universidad Miguel Hernández de Elche, Spain
- Fraunhofer IBMT, St. Ingbert, Germany
- Division of Newborn Medicine, Boston Children’s Hospital / Harvard Medical School, MA, USA
- Latina Santa Maria Goretti Hospital/Unit of Pediatrics and Neonatology
- Physical Medicine and Rehabilitation Unit, “A. Gemelli” Polyclinic - Catholic University, Italy
- Infant Communication Lab, University of Pittsburg, USA
- MASMEC SpA, Italy
- ST Microelectronics, Italy
The assessment of Oral-Motor Behavior (OMB) represents one of the earliest noninvasive ways to evaluate the newborns’ well-being and neuromotor behavior. This work aimed at developing a new low-cost, easy-to-use and noninvasive system for a technology-aided assessment of newborns’ OMB during bottle feeding. A Sucking Monitoring Device (SUMOD) was designed and developed to be easily integrated on a typical feeding bottle. A software system was developed to automatically treat and analyze the acquired data: proper algorithms for a fully automatic segmentation and features extraction are proposed and implemented. A set of measures of motor control and coordination are introduced and implemented for the specific application to the OMB analysis. Experimental data were collected on two groups of newborns (Healthy vs. Low Birth Weight) with the SUMOD in a clinical setting. Statistical tests pointed out the effectiveness of AFOs in the gait recovery process or pointing out the therapeutic differences among the various types of AFOs available on the market. Aim: To perform a comparative analysis of solid and dynamic Ankle-foot Orthoses (AFOs) on hemiparetic patients affected by foot drop syndrome by means of spatio-temporal, kinematic and electromyographic indicators. Setting: A rehabilitation center for adults with neurologic disorders. Methods: Biomechanical gait analysis was carried out on ten chronic hemiparetic subjects with foot drop syndrome under 3 conditions with randomized sequences: 1) without AFO; 2) wearing a solid AFO; 3) wearing a dynamic AFO. Significant changes in spatio-temporal, kinematic and electromyographic features of gait were investigated. Results: Gait analysis outcomes showed that there were no significant differences among the solid and the dynamic AFO on the spatio-temporal parameters. Both AFOs led to a reduction of the range of motion of the ankle dorsiplantar-flexion during stance with respect to the ambulation without AFO. Conclusions: The proposed set of indicators showed that the AFOs were capable of limiting the effect of the foot-drop in hemiparetic patients and balancing the two limbs. Main differences between the two orthoses were related to muscular activity, being the level of co-contraction of the two couples of analysed muscles typically lower when the dynamic AFO was worn and closer to a normal pattern. Clinical Rehabilitation Impact: A more extensive use of the proposed indicators in the clinical practice is expected in order to enable the definition of clinical guidelines for the prescription of the two devices.

Guglielmelli E., Micera S., Migliavacca F., Pedotti A.

Moving along: in biomechanics, rehabilitation engineering, and movement analysis, Italian researchers are making great strides.


In Italy, biomechanics research and the analysis of human and animal movement have had a very long history, beginning with the exceptional pioneering work of Leonardo da Vinci. In 1499, da Vinci began investigating human anatomy, including an examination of human tendons, muscles, and the skeletal system. He continued this line of inquiry later in life, identifying what he called “the four powers – movement, weight, force, and percussion” – and how he thought they worked in the human body. His approach, by the way, was very modern – analyzing nature through anatomy, developing models for interpretation, and transferring this knowledge to bio-inspired machines.


Poor glycemic control is associated with unfavorable outcome in patients undergoing percutaneous coronary intervention (PCI), irrespective of diabetes mellitus. However, a complete assessment of glycemic status may not be fully described by glycated hemoglobin or fasting blood glucose levels.
whereas daily glycemic fluctuations may influence cardiovascular risk and have even more deleterious effects than sustained hyperglycemia. Thus, this paper investigated the effectiveness of a continuous glucose monitoring (CGM), registering the mean level of glycemic values but also the extent of glucose excursions during coronary revascularization, in detecting periprocedural outcome such as renal or myocardial damage, assessed by serum creatinine, neutrophil gelatinase-associated lipocalin (NGAL), and troponin I levels. High glycemic variability (GV) has been associated with worse postprocedural creatinine and NGAL variations. Moreover, GV, and predominantly hypoglycemic variations, has been observed to increase in patients with periprocedural myocardial infarction. Thus, our study investigated the usefulness of CGM in the setting of PCI where an optimal glycemic control should be achieved in order to prevent complications and improve outcome.


**Statin pretreatment and risk of in-hospital atrial fibrillation among patients undergoing cardiac surgery: a collaborative meta-analysis of 11 randomized controlled trials.**


Aims: Statin pretreatment in patients undergoing cardiac surgery is understood to prevent postoperative atrial fibrillation (AF). However, this is based on observational and limited randomized trial evidence, resulting in uncertainty about any genuine anti-arrhythmic benefits of these agents in this setting. We therefore aimed to quantify precisely the association between statin pretreatment and postoperative AF among patients undergoing cardiac surgery.

Methods and Results: A detailed search of MEDLINE and PubMed databases (1st January 1996 to 31st July 2012) was conducted, followed by a review of the reference lists of published studies and correspondence with trial investigators to obtain individual-participant data for meta-analysis. Evidence was combined across prospective, randomized clinical trials that compared the risk of postoperative AF among individuals randomized to statin pretreatment or placebo/control medication before elective cardiac surgery. Postoperative AF was defined as episodes of AF lasting ≥5 min. Overall, 1105 participants from 11 trials were included; of them, 552 received statin therapy preoperatively. Postoperative AF occurred in 19% of these participants when compared with 36% of those not treated with statins (odds ratio 0.41, 95% confidence interval 0.31-0.54, P < 0.00001, using a random-effects model). Atrial fibrillation prevention by statin pretreatment was consistent across different subgroups.

Conclusions: Short-term statin pretreatment may reduce the risk of postoperative AF among patients undergoing cardiac surgery.


**Bleeding and stent thrombosis on P2Y12-inhibitors: collaborative analysis on the role of platelet reactivity for risk stratification after percutaneous coronary intervention.**


Aims: Although platelet reactivity during P2Y12-inhibitors is associated with stent thrombosis (ST) and bleeding, standardized and clinically validated thresholds for accurate risk stratification after percutaneous coronary intervention (PCI) are lacking. We sought to determine the prognostic value of low platelet reactivity (LPR), optimal platelet reactivity (OPR), or high platelet reactivity (HPR) by applying uniform cut-off values for standardized devices.

Methods and Results: Authors of studies published before January 2015, reporting associations between platelet reactivity, ST, and major bleeding were contacted for a collaborative analysis using consensus-defined, uniform cut-offs for standardized platelet function assays. Based on best available evidence for each device (exploratory studies), LPR-OPR-HPR categories were defined as <95, 95-208, and >208 PRU for VerifyNow, <19, 19-46, and >46 U for the Multiplate analyser and <16, 16-50, and >50% for VASP assay. Seventeen studies including 20 839 patients were used for the analysis; 97% were treated with clopidogrel and 3% with prasugrel. Patients with HPR had significantly higher risk for ST [risk ratio (RR) and 95% CI: 2.73 (2.03-3.69), P < 0.00001], yet a slight reduction in bleeding [RR: 0.84 (0.71-0.99), P = 0.04] compared with those with OPR. In contrast, patients with LPR had a higher risk for bleeding [RR: 1.74 (1.47-2.06), P < 0.00001], without any further benefit in ST [RR: 1.06 (0.68-1.65), P = 0.78] in contrast to OPR. Mortality was significantly higher in patients with HPR compared with other categories (P < 0.05). Validation cohorts (n = 14) confirmed all results of exploratory studies (n = 3).

Conclusions: Platelet reactivity assessment during thienopyridine-type P2Y12-inhibitors identifies PCI-treated patients at higher risk for mortality and ST (HPR) or at an elevated risk for bleeding (LPR).
CHEMICAL-PHYSICS FUNDAMENTALS IN CHEMICAL ENGINEERING

Head: V. Piemonte
Faculty: L. Di Paola
Other Personnel: L. Marrelli

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 modeling, process simulation and economical assessment provide the essential framework to fully develop the technology.

- Transport phenomena in the artificial and bioartificial organs (In collaboration with “Campus Bio-Medico University Hospital of Rome” and “Umberto I University Hospital”, University of Rome “La Sapienza”, Italy)
- New bio-treatment technology platform for the elimination of toxic pollutants from water and soil. (In collaboration with “Queen’s” University of Kingstone, Ontario, Canada)
- Life cycle assessment (LCA) of petroleum-based products and bio-based products.
- Systems biology approach to structural biology: the complex network theory is applied to outline the structure-function relationship for protein structures (in collaboration with Istituto Superiore di Sanità e CNR-IASI)
- Multiscale modelling of tissue patterning: the concentration fields of key components in Arabidopsis Thaliana allows to understand the complex interaction between differentiation and growth (in collaboration with Università Sapienza Roma)
- Biofuels and bioplastics production, separation and purification technologies (In collaboration with Kinetics Technology KT, Rome, Italy)
- New technologies for Produced Water Treatment
Reverse osmosis membranes for treatment of produced water: a process analysis.


The purpose of this paper was to develop and present a process suitable for the purification of the so-called produced waters, a by-product of crude oil extraction, by devising a treatment train aimed at industrial and agricultural water reuse. If compared to municipal wastewaters, produced waters have a very high salinity that requires specific attention for designing and managing the specific treatment device. Membranes, commonly used in the production of desalted water, appear to be a suitable technique to deal with these issues. In this paper, we propose a comprehensive process scheme for produced water treatment train: A Vibratory Shear Enhanced Processing (VSEP) membrane system is in charge of the secondary treatment, whereas a reverse osmosis (RO) unit realizes the tertiary treatment. Material and energy balances are carried out on the whole process, while the RO process is simulated by the IMSDesign Software by Hydranautics. We analyzed three different scenarios, at increasing produced waters salinity, getting a stream outlet as purified water with such low pollutants concentration and salinity to be reusable for different purposes. The RO process is carried out with a single-step or a double-step filtration, a cost analysis, performed on the different case studies, allowed computing the final specific costs per cubic meter of treated water, showing that a double filtration step allows a lower salinity water, albeit raising the costs up to about 5 €/m³, a high price justified only if a ultrapure water should be required for specific applications.

Protein contact network topology: a natural language for allostery.


Protein molecules work as a whole, so that any local perturbation may resonate on the entire structure: allostery deals with this general property of protein molecules. It is worth noting a perturbation does not necessarily involve a conformational change but, more generally, it travels across the structure as an ‘energy signal’. The atomic interactions within the network provide the structural support for this ‘signaling highway’. Network descriptors, capturing network signaling efficiency, explain allostery in terms of signal transmission. In this review we will survey the key applications of graph theory to protein allostery. The complex network approach introduces a new perspective in biochemistry; as for applications, the development of new drugs relying on allosteric effects (allo-network drugs) represents a promising avenue of contact network formalism.

Performance assessment of water gas shift membrane reactors by a two-dimensional model.


There is currently a large world effort towards developing hydrogen power as the next generation of clean energy for both the transportation and the electricity sectors. Water gas shift is a thermodynamically limited reaction, which has to operate at low temperatures, reducing kinetics rate, and increasing the amount of catalyst required to reach valuable carbon monoxide conversions. It has been widely demonstrated that the integration of hydrogen selective membranes is a promising way to enhance water gas shift reactors’ performance: a Pd-based membrane reactor operated successfully overcoming the thermodynamic constraints of a traditional reactor thanks to the removal of hydrogen from the reaction environment. In this work, the effect of hydrogen removal in membrane water gas shift reactors will be investigated by a two-dimensional, non-isothermal model in order to analyze the water gas shift reactor performance. In particular, the effects on the reactor performance of the gas space hourly velocity, reactor temperature, pressure difference, sweeping gas flow rate, and inlet flow rate composition have been deeply assessed.
CLINICAL PATHOLOGY AND MICROBIOLOGY

Head:
S. Angeletti

Faculty: G. Gherardi

Other Personnel: F. Antonelli, M. Ciccozzi, A. Conti, M. De Cesaris, L. De Florio, E. Dedej, G. Dicuonzo, M. Fogolari, A. Lo Presti

The research unit is actively enrolled in the field of molecular evolution of microorganisms causing important epidemic worldwide. Furthermore, a large part of the research activity has been dedicated to the study of the spread of multi-drug resistance bacteria supporting the CIO Unit of the University Hospital Campus Bio-Medico. In general the research unit goes ahead in the multi-marker evaluation of septic patients, as demonstrated by the recent important publications produced.

In the year 2015, the most important activities developed by the research unit have been in the areas of infectious disease and antibiotic resistance. Several articles have been published on these issues in collaboration with important Italian department such as Department of Infectious, Parasitic and Immunomediated Diseases, National Institute of Health, Rome, Italy, National Institute of Health, Rome, Italy, as well as foreigners Institutions such as the Public Health Institute of Montenegro, Public Health Institute of Bulgaria and the Department of Pathology and Laboratory Medicine, University of Florida, Gainesville, FL, USA.
Carbapenem-resistant Klebsiella pneumoniae isolates are an important cause of nosocomial infections. This study evaluated a rapid cost-saving method based on MALDI-TOF technology, and compared it with phenotypic, genotypic and epidemiological data for characterization of KPC-Kp strains consecutively isolated during a supposed outbreak. Twenty-five consecutive KPC Klebsiella pneumoniae isolates were identified and clustered by the MALDI Biotyper (Bruker, Daltonics). To display and rank the variance within a data set, principal component analysis (PCA) was performed. ClinProTools models were generated to investigate the highest sum of recognition capability and cross-validation. A Class dendrogram of isolates was constructed using ClinProTool. MLST was performed sequencing gapA, infB, mdh, pgi, rpoB, phoE and tonB genes. blaKPC and cps genes were typed. Phylogenetic analysis and genetic distance of the KPC gene were performed using the MEGA6 software. PCA analysis defined two clusters, I and II, which were identified in a dendrogram by both temporal split and different antimicrobial susceptibility profiles. These clusters were composed mostly of strains of the same sequence type (ST512), the most prevalent ST in Italy, and the same cps (type 2). In cluster II, blaKPC genotype resulted more variable than in cluster I. Phylogenetic analysis confirmed the genetic diversity in both clusters supported by the epidemiological data. Our study confirms that MALDI-TOF can be a rapid and cost-saving method for epidemiological clustering of KPC K. pneumoniae isolates and its association with blaKPC genotyping represents a reliable method to recognize possible clonal strains in nosocomial settings.

MALDI-TOF mass spectrometry and blakpc gene phylogenetic analysis of an outbreak of carbapenem-resistant K. pneumoniae strains.


Carbapenem-resistant Klebsiella pneumoniae isolates are an important cause of nosocomial infections. This study evaluated a rapid cost-saving method based on MALDI-TOF technology, and compared it with phenotypic, genotypic and epidemiological data for characterization of KPC-Kp strains consecutively isolated during a supposed outbreak. Twenty-five consecutive KPC Klebsiella pneumoniae isolates were identified and clustered by the MALDI Biotyper (Bruker, Daltonics). To display and rank the variance within a data set, principal component analysis (PCA) was performed. ClinProTools models were generated to investigate the highest sum of recognition capability and cross-validation. A Class dendrogram of isolates was constructed using ClinProTool. MLST was performed sequencing gapA, infB, mdh, pgi, rpoB, phoE and tonB genes. blaKPC and cps genes were typed. Phylogenetic analysis and genetic distance of the KPC gene were performed using the MEGA6 software. PCA analysis defined two clusters, I and II, which were identified in a dendrogram by both temporal split and different antimicrobial susceptibility profiles. These clusters were composed mostly of strains of the same sequence type (ST512), the most prevalent ST in Italy, and the same cps (type 2). In cluster II, blaKPC genotype resulted more variable than in cluster I. Phylogenetic analysis confirmed the genetic diversity in both clusters supported by the epidemiological data. Our study confirms that MALDI-TOF can be a rapid and cost-saving method for epidemiological clustering of KPC K. pneumoniae isolates and its association with blaKPC genotyping represents a reliable method to recognize possible clonal strains in nosocomial settings.


Molecular epidemiology and phylogenetic analysis of Hepatitis B virus in a group of migrants in Italy.


Background: Hepatitis B virus infection (HBV) is widespread and it is considered a major health problem worldwide. The global distribution of HBV varies significantly between countries and between regions of the world. Among the many factors contributing to the changing epidemiology of viral hepatitis, the movement of people within and between countries is a potentially important one. In Italy, the number of migrant individuals has been increasing during the past 25 years. HBV genotype D has been found throughout the world, although its highest prevalence is in the Mediterranean area, the Middle East and southern Asia. We describe the molecular epidemiology of HBV in a chronically infected population of migrants (living in Italy), by using the phylogenetic analysis. Methods: HBV-DNA was amplified and sequenced from 43 HBV chronically infected patients. Phylogenetic and evolutionary analysis were performed using both maximum Likelihood and Bayesian methods. Results and conclusions: Of the 43 HBV S gene isolates from migrants, 25 (58.1 %) were classified as D genotype. Maximum Likelihood analysis showed an interfamiliality between Moldavian and foreigners sequences mostly respect to Italian ones. Italian sequences clustered mostly together in a main clade separately from all others. The estimation of the time of the tree’s root gave a mean value of 17 years ago suggesting the origin of the tree back to 1992 year. The skyplot showed that the number of infections softly increased until the early 2005s, after which reached a plateau. Comparing phylogenetic data to the migrants date of arrival in Italy, it should be possible that migrants arrived in Italy yet infected from their country of origin. In conclusion, this is the first paper where phylogenetic analysis and genetic evolution has been used to characterize HBV sub genotypes D1 circulation in a selected and homogeneous group of migrants coming from a restricted area of Balkans and to approximately define the period of infection besides the migration date.
COMPUTER SYSTEMS AND BIOINFORMATICS

Head:
G. Iannello

Faculty: F. Cacace, P. Soda, L. Vollero
Other Personnel: L. Acciai, P. Afferni, E. Cordelli, M. Merone, L. Onofri, S. Petrichella, R. Valenti

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, computer networks with special focus on wireless networks, and modeling dynamic stochastic system.

- 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.
- Support Decision Systems for clinical applications.
- Algorithms for the analysis of EEG and EEG-TMS signals, and of fRMI images.
- Bioinformatics tools for long non-coding RNAs analysis.
- Estimation methods for mathematical models of biological systems

- the European Non-linear Spectroscopy Laboratory: we have contributed to develop tools for processing ultra terabyte images.
- the Geriatrics Unit: we have developed a system to detect risk conditions for BPCO patients.
- IASI-CNR: we have designed algorithms to analyze the secondary structure of long non-coding RNAs.
- the Neurology, Neurophysiology, Neurobiology Unit: we have contributed in the identification of conditions and biomarkers of the Alzheimer’s disease.
- the Robotic Unit: we have contributed in the development of a system for robotic tele-rehabilitation of the upper limb.
- the Allergology, Immunology, Rheumatology Unit: we have further developed the CAD system to classify ANA samples in IIF.
- Università Cattolica del Sacro Cuore: we are developing new strategies for type 1 diabetes mellitus monitoring and treatment.
- the Department of Information and Electrical Engineering of L’Aquila: we developed new approaches for estimators and filters of uncertain dynamical systems and systems with delayed measurements.
## Most important publications


*A versatile clearing agent for multi-modal brain imaging.*


Extensive mapping of neuronal connections in the central nervous system requires high-throughput μm-scale imaging of large volumes. Here, we introduce a versatile brain clearing agent (2,2’-thiodie- thanol; TDE) suitable for various applications and imaging techniques. We demonstrate the effectiveness of this method in different applications: in fixed samples by imaging a whole mouse hippocampus with serial two-photon tomography; in combination with CLARITY by reconstructing an entire mouse brain with light sheet microscopy and in translational research by imaging immunostained human dysplastic brain tissue.

**Fiscon G., Paci P., Iannello G.**

*MONSTER v1.1: a tool to extract and search for RNA non-branching structures.*

BMC Genomics. 2015; 16: S1. PubMed PMID: 26047478. IF 0,921

Here, we present an updated version of our previous tool MONSTER, accounting for the peculiar feature of long non-coding RNAs that are not expected to have a unique fold, but appear to fluctuate among a large number of equally-stable folds. We improved our search engine for structural motifs shared between two full-length RNAs in order to take into account all the alternative equally-stable structures. We present an application of MONSTER v1.1 on long non-coding RNAs, which are a specific class of lncRNAs located in genomic regions which do not overlap protein-coding genes. In particular, we provide reliable predictions of the shared protein-coding genes. In particular, we provide reliable predictions of the shared protein-coding genes.

**Cacace F., Conte F., Germani A.**

*Filtering continuous-time linear systems with time-varying measurement delay.*

IEEE T Automat Contr. 2015 May; 60 (5): 1368-1373. doi: 10.1109/TAC.2014.2357138. IF 2,779

We consider the filtering problem of LTI continuous-time systems with known and bounded measurement delays. The aim of the technical note is the design of a finite-dimensional sub-optimal filter whose performance in terms of the estimation error is comparable to optimal infinite-dimensional approaches. We show that the proposed approach allows for a precise characterization of the relationship between measurement delay and the covariance of the estimation error. In the time-varying case no restrictive hypotheses on the delay function are needed. The proposed filter can therefore be applied to delay functions for which traditional infinite-dimensional approaches cannot be straightforwardly applied.
The Developmental Neuroscience unit investigates developmental at the molecular, cellular and systemic levels, mechanisms, both in animal models and in human infants. One major focus of the lab is 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 systems, in particular perception-action loops, 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.

- Interaction between NGF and reelin in the mouse retina
- Motor development in siblings who are at high risk for autism
- Novel behavioural tests of music perception in young children

- Dr. Alessandra Micera, Fondazione Bietti (interaction between NGF and reelin in the mouse retina)
- Prof. Jana M. Iverson, University of Pittsburgh (motor development in siblings who are at high risk for autism)
- Dr. Nicola Di Stefano, Istituto FAST; Dr. Fabrizio Taffoni, Biomedical Robotics and Biomicrosystems Unit (music perception in young children)
NGF expression in reelin-deprived retinal cells: a potential neuroprotective effect.


We recently reported that increased NGF and p75(NTR) as well as decreased trkA(NGFR) characterized the Reelin-deprived (E-Reeler) retina, prospecing a potential contribution of NGF during E-Reeler retinogenesis. Herein, retinal ganglion cells (RGCs), glial cells and rod bipolar cells (RBCs) were isolated from E-Reeler retinas, and NGF, trkA(NGFR)/p75(NTR) expression and apoptosis were investigated. E-Reeler (n = 28) and E-control (n = 34) retinas were digested, and RGCs, glial cells and RBCs were isolated by the magnetic bead separation. Expression of NGF, trkA(NGFR), p75(NTR), Annexin V/PI and Bcl2/Bax was quantified by flow cytometry and validated by real-time PCR or WB. In E-Reeler retinas, NGF was significantly increased in RGCs and glial cells, p75(NTR) was increased in both RBCs and RGCs, and trkA(NGFR) was unchanged. In E-control retinas, NGF and p75(NTR) were expressed mainly in RBCs and RGCs and faintly in glial cells, while trkA(NGFR) was weakly expressed by RBCs and RGCs. In RBCs and RGCs, Annexin V expression was unchanged, while Bc2 increased and Bax decreased selectively in E-Reeler RGCs. The data indicate that E-Reeler RBCs and RGCs overexpress NGF and p75(NTR) as a protective endogenous response to Reelin deprivation. The observation is strongly supported by the absence of apoptosis in both cell types.

False belief understanding and “cool” inhibitory control in 3-and 4-years-old Italian children.

Front Psychol. 2015 Jun 29; 6: 872. PubMed PMID: 26175700. IF 2.6

During preschool years, major developments occur in both executive function and theory of mind (ToM), and several studies have demonstrated a correlation between these processes. Research on the development of inhibitory control (IC) has distinguished between more cognitive, “cool” aspects of self-control, measured by conflict tasks, that require inhibiting an habitual response to generate an arbitrary one, and “hot,” affective aspects, such as affective decision making, measured by delay tasks, that require inhibition of a prepotent response. The aim of this study was to investigate the relations between 3- and 4-year-olds’ performance on a task measuring false belief understanding, the most widely used index of ToM in preschoolers, and three tasks measuring cognitive versus affective aspects of IC. To this end, we tested 101 Italian preschool children in four tasks: (a) the Unexpected Content False Belief task, (b) the Conflict task (a simplified version of the Day-Night Stroop task), (c) the Delay task, and (d) the Delay Choice task. Children’s receptive vocabulary was assessed by the Peabody Picture Vocabulary test. Children’s performance in the False Belief task was significantly related only to performance in the Conflict task, controlling for vocabulary and age. Importantly, children’s performance in the Conflict task did not significantly correlate with their performance in the Delay task or in the Delay Choice task, suggesting that these tasks measure different components of IC. The dissociation between the Conflict and the Delay tasks may indicate that monitoring and regulating a cool process (as flexible categorization) may involve different abilities than monitoring and regulating a hot process (not touching an available and highly attractive stimulus or choosing between a smaller immediate option and a larger delayed one). Moreover, our findings support the view that “cool” aspects of IC and ToM are interrelated, extending to an Italian sample of children previous findings on an association between self-control and ToM.
The Unit is organized in different lines where the research activities are performed in cooperation with other research units of our University: Neuroimaging, that studies the correlation of MRI with diagnosis, treatment or rehabilitation of different diseases, both in neurology or in oncology; Interventional Radiology, that studies how radiologists can use small invasive approaches for the diagnosis and the treatment of several diseases; Imaging based navigations systems, that studies the use of mechatronics and images acquired directly from the patients to guide diagnostic and therapeutic procedures in Medicine; Oncologic Imaging, that studies how radiologists can help in the diagnosis, in the treatment and in the follow-up of oncologic patients; Functional imaging, that studies the use of imaging to check the functionality of different organs or to highlight the accumulation of specific substances in the body.

The main research publications, during 2015, are in the following sectors: functional MRI to evaluate the rehabilitation efficacy in Parkinson’s disease, the abnormal neuronal connectivity in Alzheimer’s Disease, in collaboration with the Brain Center Rudolf Magnus, University Medical Center Utrecht, The Netherlands, and in the early stages of anorexia nervosa, Magnetic Resonance thermometry, Interventional Radiology for the palliation of bone metastases and in lung tumour ablation procedures, in collaboration with Institut Bergonie, Bordeaux, France, multimodality imaging to assess bone environment in cancer patients, in collaboration with The University of Minnesota, Minneapolis (USA), post mortem evaluation of coronary arteries, in collaboration with the Institute of Legal medicine, Catholic University Rome, functional heart parameters in thalassemic patients, in vivo brain Gadolinium deposition from currently used contrast agents.
Altered resting state functional connectivity of anterior cingulate cortex in drug naïve adolescents at the earliest stages of anorexia nervosa.


Previous Resting-State Functional Connectivity (RSFC) studies have shown several functional alterations in adults with or recovered from long Anorexia Nervosa (AN). The aim of this paper was to investigate whole brain RSFC in adolescents with AN in the earliest stages, less than 6 months, of the disorder. Sixteen drug-naïve outpatient female adolescents with AN-restrictive type (AN-r) (mean age: 15.8; SD 1.7) were compared to 16 age-matched healthy female (mean age: 16.3; SD 1.4). Relevant resting state networks (RSNs) were identified using independent component analysis (ICA) from functional magnetic resonance imaging data; a dual regression technique was used to detect between-group differences in the RSNs. Between-group differences of the functional connectivity differences in the RSNs. Between-group analyses indicated that the above mentioned network dering that the above mentioned network and its area are mainly involved in cognitive control and emotional processing, our conclusion that the above mentioned network and its area are mainly involved in cognitive control and emotional processing, our


Purpose: Cancer survivors are at an increased risk for fractures, but lack of effective and economical biomarkers limits quantitative assessments of marrow fat (MF), bone mineral density (BMD) and their relation in response to cytotoxic cancer treatment. We report dual energy CT (DECT) imaging, commonly used for cancer diagnosis, treatment and surveillance, as a novel biomarker of MF and BMD.

Methods: We validated DECT in pre-clinical and phase I clinical trials and verified with water-fat MRI (WF-MRI), quantitative CT (QCT) and dual-energy X-ray absorptiometry (DXA). Basis material composition framework was validated using water and small-chain alcohols simulating different components of bone marrow. Histologic validation was achieved by measuring percent adipocyte in the cadaver vertebrae and compared with DECT and WF-MRI. For a phase I trial, sixteen patients with gynecologic malignancies (treated with oophorectomy, radiotherapy or chemotherapy) underwent DECT, QCT, WF-MRI and DXA before and 12 months after treatment. BMD and MF percent and distribution were quantified in the lumbar vertebrae and the right femoral neck. Results: Measured precision (3 mg/cm3) was sufficient to distinguish test solutions. Adiposity in cadaver bone histology was highly correlated with MF measured using DECT and WF-MRI (r = 0.80 and 0.77, respectively).

In the clinical trial, DECT showed high overall correlation (r = 0.77, 95% CI: 0.69, 0.83) with WF-MRI. MF increased significantly after treatment (p = 0.002). Chemotherapy and radiation caused greater increases in MF than oophorectomy (p = 0.032). L4 BMD decreased 14% by DECT, 20% by QCT, but only 5% by DXA (p = 0.002 for all). At baseline, we observed a statistically significant inverse association between MF and BMD which was dramatically attenuated after treat-ment. Conclusion: Our study demonstrated that DECT, similar to WF-MRI, can accurately measure marrow adiposity. Both imaging modalities show rapid increase in MF following cancer treatment. Our results suggest that MF and BMD cannot be used interchangeably to monitor skeletal health following cancer therapy.

Quattrrochi C.C., Mallio C.A., Errante Y., Cirimele V., Caride L., Ax A., Zobel B.B. Gadodiamide and dentate nucleus T1 hyperintensity in patients with meningioma evaluated by multiple follow-up contrast-enhanced magnetic resonance examinations with no systemic interval therapy.


The dentate nucleus of the cerebellum may appear as hyperintense on unenhanced T1 magnetic resonance images (MRIs) of the brain. Recently, T1 signal hyperintensity has received attention owing to data on the association of this finding with the history of multiple injections of gadolinium-based contrast agents, specifically gadodiamide, in patients with multiple sclerosis and brain metastases. We conducted a retrospective study on patients with a meningioma who had routinely undergone follow-up enhanced MRI scans with gadodiamide. Across a time interval of 18 months (from January 2013 to July 2014), we identified 102 consecutive patients eligible for this study. A significant increase in T1 hyperintensity of the dentate nuclei of the cerebellum on non enhanced scans was observed between the first and the last MRI in the group of patients with a history of at least 6 enhanced MRIs scans (P < 0.01), whereas no differences were observed in the group with 1 to 5 enhanced MRI scans (P = 0.74). Further research is necessary to shed light on the mechanism of the T1 hyperintensity as well as on the histological and microstructural appearance of the dentate nucleus after multiple intravenous injections of gadodiamide. The finding raises the question of substantial dechelation of this agent in patients with normal renal function.
DRUG SCIENCES

Head:
G. Minotti

Faculty: E. Salvatorelli
Other Personnel: P. Menna

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.

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

Salvatorelli E., Menna P., Cantalupo E., Chello M., Covino E., Wolf F.I., Minotti G.  
*The concomitant management of cancer therapy and cardiac therapy.*  
Critical analysis of: i) molecular mechanisms and clinical correlates of cardiotoxicity from chemotherapeutics or new generation “targeted” drugs; ii) type I versus type II agents classification; iii) early versus delayed cardiovascular events; iv) genetic tests and pharmacologic measures to minimize cardiovascular risk; v) clinical toxicity versus asymptomatic systolic and/or diastolic dysfunction.

Minotti G., Graziani G., Delogu G.  
*Editorial.*  
On the rebuilding of Chemotherapy journal for anticancer and antimicrobial research.

Salvatorelli E., Menna P., Minotti G.  
*Managing anthracycline-induced cardiotoxicity: beginning with the end in mind.*  
Principles of diagnosis, treatment and prevention of anthracycline cardiotoxicity in contemporary oncology.
ELECTRONICS FOR SENSOR SYSTEMS

Head:
G. Pennazza

Faculty: M. Santonico
Other Personnel: S. Grasso, A. Zompanti

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.

- Development and test of a sensor for the monitoring of Extravergin Olive Oil, able of unmasking adulteration down to 5% of admixture. BIONOTE has been awarded (in the person of an UCBM young MD) for a study on Lung Cancer based on exhaled breath collected via Pneumopipe (ESS patent) daily used in different wards of the polyclinic.
- Design of a contactless device for ECG-like signals in the frame of a project (Remote Cardio Observation) financed by the Italian Space Agency.
- The partners of KOSMOMED project (financed by the European Space Agency) has used with promising results the devices provided by this unit.
- Tipitec, a project funded by Regione Lazio and coordinated by UCBM (M. Santonico, ESS unit), has involved other four Universities in a fruitful opportunity of interaction with the food industry in the frame of Expo 2015.

New collaborations: Unit of Authenticity and Novel Food of Wageningen University (PhD student activity); Siemens AG in Munich (thesis work financed by Erasmus+)
Most important publications


The lung cancer breath signature: a comparative analysis of exhaled breath and air sampled from inside the lungs.

Results collected in more than 20 years of studies suggest a relationship between the volatile organic compounds exhaled in breath and lung cancer. However, the origin of these compounds is still not completely elucidated. In spite of the simplistic vision that cancerous tissues in lungs directly emit the volatile metabolites into the airways, some papers point out that metabolites are collected by the blood and then exchanged at the air-blood interface in the lung. To shed light on this subject we performed an experiment collecting both the breath and the air inside both the lungs with a modified bronchoscopic probe. The samples were measured with a gas chromatography-mass spectrometer (GC-MS) and an electronic nose. We found that the diagnostic capability of the electronic nose does not depend on the presence of cancer in the sampled lung, reaching in both cases an above 90% correct classification rate between cancer and non-cancer samples. On the other hand, multivariate analysis of GC-MS achieved a correct classification rate between the two lungs of only 76%. GC-MS analysis of breath and air sampled from the lungs demonstrates a substantial preservation of the VOCs pattern from inside the lung to the exhaled breath.

Santonico M., Grasso S., Genova F., Zompanti A., Parente F.R., Pennazza G.

Unmasking of olive oil adulteration via a multi-sensor platform.

Methods for the chemical and sensorial evaluation of olive oil are frequently changed and tuned to oppose the increasingly sophisticated frauds. Although a plethora of promising alternatives has been developed, chromatographic techniques remain the more reliable yet, even at the expense of their related execution time and costs. In perspective of a continuous increment in the number of the analyses as a result of the global market, more rapid and effective methods to guarantee the safety of the olive oil trade are required. In this study, a novel artificial sensorial system, based on gas and liquid analysis, has been employed to deal with olive oil genuineness and authenticity issues. Despite these sensors having been widely used in the field of food science, the innovative electronic interface of the device is able to provide a higher reproducibility and sensitivity of the analysis. The multi-parametric platform demonstrated the capability to evaluate the organoleptic properties of extra-virgin olive oils as well as to highlight the presence of adulterants at blending concentrations usually not detectable through other methods.
The Research Unit focuses on the industrial and therapeutic applications of electromagnetic power. Main research interests include the study and modelling of electrical power systems, electrical circuits, and machines, and the efficiency analysis of the antennas used for heating biological tissues and exploring terrestrial areas.

- Evaluation of the energetic efficiency of pancake induction coils used for therapeutic heating of tissues (induction diathermy). Research activity aims at pinpointing the best planar coil configuration to guarantee the minimum energy consumption for a given power absorption average density (SAR) in the biological tissue. Different multi-leaf coil geometries are considered;
- Individuation of a hybrid analytical-numerical procedure for rapidly determining the geometric and electromagnetic parameters of a stratified medium, starting from a set of measurements of the electromagnetic field generated on its top surface by a current-carrying loop antenna (electromagnetic induction sounding technique);
- Derivation of exact electromagnetic fields produced by dipole antennas, circular antennas and transmission lines in the presence of conducting media. Exact closed-form expressions have already been obtained for sources positioned on the surface of a homogeneous ground.
Most important publications

Parise M.
Transverse magnetic field of infinite line source placed on ground surface.
Electronics Letters; 2015; 51(19): 1478-1480. DOI: 10.1049/el.2015.0636 IF 0.93
An exact explicit expression is derived for the Sommerfeld integral describing the surface transverse magnetic field generated by an infinite line source placed on a plane air-earth boundary. The spatial distribution of the transverse magnetic field is given in series form, as a linear combination of exponential functions. The accuracy and convergence rate of the proposed formulation are investigated through numerical simulations.

Parise M.
Improved Babylonian square root algorithm-based analytical expressions for the surface-to-surface solution to the Sommerfeld half-space problem.
IEEE Trans Antennas Propag. 2015; 63(12): 5832-5837. DOI: 10.1109/TAP.2015.2478958 IF 2.181
In a recent work, analytical explicit expressions have been derived for the Sommerfeld integrals describing the surface fields of a vertical electric dipole placed near a plane air-earth boundary. Such formulas have the advantage of being exact, but unfortunately consist of slowly convergent infinite sums of special functions. As a consequence, accurate evaluation of the fields is obtained at the cost of a non-negligible computational effort. The purpose of this communication is to derive improved explicit expressions for the Sommerfeld integrals, which assure the same degree of accuracy as the preceding ones, but are constituted by fast-convergent sums of Hankel functions.

Parise M.
On the surface fields of a small circular loop antenna placed on plane stratified earth.
Int J Antennas Propag. 2015; 2015: 187806.DOI: 10.1155/2015/187806 IF 0.66
An analytical method is presented which makes it possible to derive exact explicit expressions for the time-harmonic surface fields excited by a small circular loop antenna placed on the top surface of plane layered earth. The developed procedure leads to casting the complete integral representations for the EM field components into forms suitable for application of Cauchy’s integral formula. As a result, the surface fields are expressed as sums of Hankel functions. Numerical simulations are performed to show the validity and accuracy of the proposed solution.
ENDOCRINOLOGY AND DIABETES

Head:
P. Pozzilli

Faculty: S. Manfrini, N. Napoli

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 Area, collaborates with centers of excellence both European and Asian, and North America. Our group works closely with the scientific community and governmental and non-governmental organizations on joint research programs.

- Pathogenesis and immunotherapy of type 1 diabetes(T1D)
- Type 2 diabetes(T2D), obesity and nutrition
- Pathophysiological mechanisms of bone loss in patients with diabetes, obesity and in post-menopausal women
- Extraskeletal effects of vitamin D; risk of fracture in T1D and T2D patients

Main results
- Discovery of antibodies to post-translationally modified insulin in T1D
- Protection of β-cell function in T1D
- New markers of bone disease in T1D
- Novel protocols for treatment of secondary hypoparathyroidism
- Macrobiotic diet in treatment of diabetes and obesity

Main collaborations
- Biochemistry and Molecular Biology Research Unit, Campus Bio-Medico University of Rome
- Department of Clinical Sciences and Experimental Medicine, Sapienza University, Rome
- Centre for Diabetes & Metabolic Medicine, St. Bartholomew's and The London School of Medicine, Queen Mary's College, London, UK
- Washington University in St. Louis USA
- University of Harvard, Boston, USA
Pancreatic accumulation of 99mTc-IL-2 is a technique used to image chronic inflammatory-mediated disorders. We used this method to detect a signal consistent with the presence of insulitis in patients with autoimmune diabetes. Positive and negative controls (patients with pancreatic carcinoma and type 2 diabetes, respectively) also were studied.

**Methods:** We examined 25 patients with autoimmune diabetes (16 with recently diagnosed type 1 diabetes, 9 with latent autoimmune diabetes in adults [LADA]), 6 with type 2 diabetes, and 7 with pancreatic carcinoma (the latter two groups were used as negative and positive controls, respectively). All patients underwent 99mTc-IL-2 scintigraphy and contrast-enhanced MRI of the pancreas. To validate positive controls, samples were taken from patients with pancreatic carcinoma during surgery for histological and immunohistochemical investigations. Results: Pancreatic accumulation of 99mTc-IL-2 was detected in patients with autoimmune diabetes (61% positive) and, notably, in 6 of 9 patients with LADA; semiquantitative evaluation of pancreatic uptake of 99mTc-IL-2 showed higher values in patients with autoimmune diabetes (both childhood and LADA) and pancreatic carcinoma than in those with type 2 diabetes (4.45 6 1.99, 4.79 6 1.1, and 4.54 6 1.62 vs. 2.81 6 0.63; P = 0.06, P = 0.01, and P = 0.04, respectively). In patients with pancreatic carcinoma, pancreatic interleukin-2 receptor expression correlated with pancreatic 99mTc-IL-2 uptake (r = 0.8; P = 0.01). In patients with LADA, 99mTc-IL-2 uptake inversely correlated with duration of disease (r = 0.7; P = 0.03). Conclusions: Autoimmune diabetes in adults is associated with increased pancreatic 99mTc-IL-2 uptake, indicating the presence of insulitis, particularly within 1 year of the beginning of insulin therapy, similar to type 1 diabetes at diagnosis.

**References:**


Immunotherapies for type 1 diabetes mellitus (T1DM) have been the focus of intense basic and clinical research over the past few decades. Restoring β-cell function is the ultimate goal of intervention trials that target the immune system in T1DM. In an attempt to achieve this aim, different combination therapies have been proposed over the past few years that are based on treatments tackling the various mechanisms involved in the destruction of β-cells. The results of clinical trials have not matched expectations based on the positive results from preclinical studies. The heterogeneity of T1DM might explain the negative results obtained, but previous trials have not addressed this issue. However, novel promising combination therapies are being developed, including those that couple immunomodulators with drugs that stimulate β-cell regeneration in order to restore normoglycaemia. This strategy is an encouraging one to pursue the goal of finding a cure for T1DM. This Review summarizes the available data about combination immunotherapies in T1DM, particularly addressing their clinical importance. The available data supporting the use of registered drugs, such as proton pump inhibitors and incretin-based agents, that have been shown to induce β-cell regeneration will also be discussed.
FOOD SCIENCE AND NUTRITION

Head:  
L. De Gara

Faculty: C. Fanali, V. Locato

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

- Dr. Locato, PI - FIRB project “Cyclic nucleotides in biotic stress signalling in plant”
- Prof. De Gara, PI - project granted by Italian Space Agency. Antioxidant rich - food supplements for the protection against cosmic radiations- PAPARD

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

Locato V., Uzal E.N., Cimini S., Zonno M.C., Evidente A., Micera A., Foyer C.H., De Gara L.

**Low concentrations of the toxin ophiobolin A lead to an arrest of the cell cycle and alter the intracellular partitioning of glutathione between the nuclei and cytoplasm.**


Ophiobolin A, a tetracyclic sesterpenoid produced by phytopathogenic fungi, is responsible for catastrophic losses in crop yield but its mechanism of action is not understood. The effects of ophiobolin A were therefore investigated on the growth and redox metabolism of Tobacco Bright Yellow-2 (TYB-2) cell cultures by applying concentrations of the toxin that did not promote cell death. At concentrations between 2–5 μM, ophiobolin A inhibited growth and proliferation of the TYB-2 cells, which remained viable. Microscopic and cytofluorimetric analyses showed that ophiobolin A treatment caused a rapid decrease in mitotic index, with a lower percentage of the cells at G1 and increased numbers of cells at the S/G2 phases. Cell size was not changed following treatment suggesting that the arrest of cell cycle progression was not the result of a block on cell growth. The characteristic glutathione redox state and the localization of glutathione in the nucleus during cell proliferation were not changed by ophiobolin A. However, subsequent decreases in glutathione and the re-distribution of glutathione between the cytoplasm and nuclei after mitosis occurring in control cells, as well as the profile of glutathionylated proteins, were changed in the presence of the toxin. The profile of poly ADP-ribosylated proteins were also modified by ophiobolin A. Taken together, these data provide evidence of the mechanism of ophiobolin A action as a cell cycle inhibitor and further demonstrate the link between nuclear glutathione and the cell cycle regulation, suggesting that glutathione-dependent redox controls in the nuclei prior to cell division are of pivotal importance.

Fanali C., Beccaria M., Salvo S., Tranchida P., Tripodo G., Farnetti S., Dugo L., Dugo P., Mondello L.

**Non-polar lipids characterization of Quinoa (Chenopodium quinoa) seed by comprehensive two-dimensional gas chromatography with flame ionization/mass spectrometry detection and non-aqueous reversed-phase liquid chromatography with atmospheric pressure chemical ionization mass spectrometry detection.**

J Sep Sci. 2015 Sep; 38(18):3151–3160. DOI: 10.1002/jssc.201500466. IF 2,737

A chemical characterization of major lipid components, namely, triacylglycerols, fatty acids and the unsaponifiable fraction, in a Quinoa seed lipids sample is reported. To tackle such a task, non-aqueous reversed-phase high-performance liquid chromatography with mass spectrometry detection was employed. The latter was interfaced with atmospheric pressure chemical ionization for the analysis of triacylglycerols. The main triacylglycerols (>10%) were represented by OLP, OOL and OLL (P = palmitoyl, O = oleoyl, L = linoleoyl); the latter was present in the oil sample at the highest percentage (18.1%). Furthermore, fatty acid methyl esters were evaluated by gas chromatography with flame ionization detection. 89% of the total fatty acids was represented by unsaturated fatty acid methyl esters with the greatest percentage represented by linoleic and oleic acids accounting for approximately 48 and 28%, respectively. An extensive characterization of the unsaponifiable fraction of Quinoa seed lipids was performed for the first time, by using comprehensive two-dimensional gas chromatography with dual mass spectrometry/flame ionization detection. Overall, 66 compounds of the unsaponifiable fraction were tentatively identified, many constituents of which (particularly sterols) were confirmed by using gas chromatography with high-resolution time-of-flight mass spectrometry.


**Fructan biosynthesis and degradation as part of plant metabolism controlling sugar fluxes during durum wheat kernel maturation.**


Wheat kernels contain fructans, fructose based oligosaccharides with prebiotic properties, in levels between 2 and 35 weight % depending on the developmental stage of the kernel. To improve knowledge on the metabolic pathways leading to fructan storage and degradation, carbohydrate fluxes occurring during durum wheat kernel development were analyzed. Kernels were collected at various developmental stages and qualitative analysis of carbohydrates (mono- and disaccharides, fructans, starch) was performed, alongside analysis of the activities and gene expression of the enzymes involved in their biosynthesis and hydrolysis. High resolution HPAC-PAD of fructan contained in durum wheat kernels revealed that fructan content is higher at the beginning of kernel development, when fructans with higher DP, such as bifurcose and 1,1-nystose, were mainly found. The changes in fructan pool observed during kernel maturation might be part of the signaling pathways influencing carbohydrate metabolism and storage in wheat kernels during development. During the first developmental stages fructan accumulation may contribute to make kernels more effective Suc sinks and to participate in osmotic regulation while the observed decrease in their content may mark the transition to later developmental stages, transition that is also orchestrated by changes in redox balance.
The Research Unit carries out basic and translational research projects through molecular biology analysis and electrophysiological study of muscle contraction with dedicated devices. 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 digestive pathophysiology laboratory works on the following research areas: immunomodulation of intestinal motility though studying the intestinal motility functional alterations of human colonic smooth muscle in infective models and effect of prebiotics and probiotics and a study of the physio-pathological mechanisms of functional gastrointestinal disorders (Irritable Bowel Syndrome, Paralytic ileus and chronic constipation). The Nutritional Unit carries out the following projects: Impact of pre-operative nutritional status on surgical outcome in pancreatic cancer patient undergoing surgery; immune-nutrition in oncological surgical patients; oral supplement in lung cancer patients. Moreover, the Research Unit carries on phase II and III clinical research trials to test new biological molecules for Inflammatory bowel disease treatment.
Most important publications

Ribolsi M., Cicala M. 
Reply: To PMID 25109844. 

Intra-bolus pressure and esophagogastric gradient, assessed with high-resolution manometry, are associated with acid exposure and proximal migration of refluxate.

Carotti S., Guarino MP., Vespasiani-Gentilucci U., Morini S. 
Starring role of toll-like receptor-4 activation in the gut-liver axis.

Since the introduction of the term “gut-liver axis”, many studies have focused on the functional links of intestinal microbiota, barrier function and immune responses to liver physiology. Intestinal and extra-intestinal diseases alter microbiota composition and lead to dysbiosis, which aggravates impaired intestinal barrier function via increased lipopolysaccharide translocation. The subsequent increased passage of gut-derived product from the intestinal lumen to the organ wall and bloodstream affects gut motility and liver biology. The activation of the toll-like receptor 4 (TLR-4) likely plays a key role in both cases. This review analyzed the most recent literature on the gut-liver axis, with a particular focus on the role of TLR-4 activation. Findings that linked liver disease with dysbiosis are evaluated, and links between dysbiosis and alterations of intestinal permeability and motility are discussed. We also examine the mechanisms of translocated gut bacteria and/or the bacterial product activation of liver inflammation and fibrogenesis via activity on different hepatic cell types.
The Research Unit of General Surgery includes six academic surgeons (one full professor, two associate professors, and two assistant professors). In 2015, the research unit published 7 papers on English language international journals (IF: 23,936).

**Surgery of the pancreas**
- Novel Biomarkers for the diagnosis and treatment of pancreatic cancer (promoted by R. Coppola, D. Borzomati)
- Prognostic impact of metastatic nodal stations according to JPS classification after pancreaticoduodenectomy for periampullary cancer (promoted by R. Coppola, D. Borzomati and S. Valeri) in collaboration with Research Unit of Pathology, Istituto Clinico Humanitas Milan, Azienda Ospedaliera Universitaria Pisana, University of Cracow, Poland
- Prospective multicentric study on antibiotic prophylaxis in patients undergoing pancreaticoduodenectomy (promoted by R. Coppola, D. Borzomati and S. Valeri) in collaboration with Research Unit of Clinical Pathology and Microbiology, Istituto Clinico Humanitas Milan
- Prognostic role of preoperative inflammatory markers for surgically resected pancreatic head cancer (promoted by R. Coppola, D. Borzomati and S. Valeri) in collaboration with Edouard Herriot Hospital of Lyon France; University of Verona, Italy; University of Hamburg, Germany; University of Lousanne, Switzerland
- Insuline dosage, diabetes mellitus and pancreatic cancer. (promoted by R. Coppola, M. Caricato and G. Capolupo) in collaboration with Research Unit of Pathology, Research Unit of Endocrinology and Diabetes, Department of Pathology Catholic University Rome Italy
- The role of immunonutrition in patients undergoing pancreaticoduodenectomy for cancer. (promoted by R. Coppola, R. Alloni, D. Borzomati and S. Valeri) in collaboration with Research Unit of Gastroenterology

**Colorectal surgery**
- Comprehensive multidisciplinary approach to colorectal cancer microenvironment (promoted by M. Caricato, G. Capolupo, V. La Vaccara and A. Crescenzi). In collaborations with Department of Pathology and Department of tissue engineering
- Spectroscopy characterization of neoplastic tissue (promoted by M. Caricato, G. Capolupo, V. La Vaccara and A. Crescenzi). In collaborations with Research Unit of Pathology, Department of Pathology “La Sapienza” University of Rome, Department of Anatomy Catholic University of Rome
- Innovative technique for improving sensitivity of peritoneal washing cytology in gastric cancer (promoted by M. Caricato, G. Capolupo, V. La Vaccara and A. Crescenzi). In collaborations with Research Unit of Pathology, Department of Pathology “La Sapienza” University of Rome, Department of Anatomy Catholic University of Rome
Incidence and prognostic impact of para-aortic lymph nodes metastases during pancreaticoduodenectomy for peri-ampullary cancer.


Background: Standard lymphadenectomy during pancreaticoduodenectomy (PD) for peri-ampullary cancer does not include the routine removal of para-aortic lymph nodes (PALN) (station 16, according to the JPS staging system). The aim of this study was to report the incidence and the prognostic value of PALN metastases in patients undergoing PD for peri-ampullary cancer. Materials and methods: One hundred thirty-five consecutive patients who underwent PD and PALN dissection for peri-ampullary cancer were prospectively evaluated. The relationship between clinicopathological factors, including PALN metastases and survival was evaluated at univariate and multivariate analysis. Results: PALN metastases (N16+) were found in 11.1% of cases. At univariate analysis, R1 resection, metastatic nodes different from para aortic (N1) and N16+ significantly affected patients’ prognosis. Compared with N16+, the median overall survival (OS) of N0 patients was significantly longer (32 versus 69 months, respectively; P < 0.05), whereas no difference was found between N16+ and N1 patients (32 versus 34 months, respectively) (P > 0.05). At multivariate analysis, only R1 resection reached statistical significance and was confirmed an independent prognostic factor. Conclusions: Neoplastic involvement of PALN in peri-ampullary cancer is frequent and, so, their removal during PD could be justified. Moreover, PALN metastases should be not considered an absolute contraindication to radical surgery.

Incidence and prognostic impact of para-aortic lymph nodes metastases during pancreaticoduodenectomy for peri-ampullary cancer.


Background: Radio-chemotherapy is one of the steps of multidisciplinary management in locally advanced pancreatic cancer. The Epidermal Growth Factor Receptor (EGFR) plays an important role in the disease pathway. The purpose of this prospective study is to evaluate the safety and the efficacy of radiotherapy in combination with cetuximab and EGFR targeting therapy for patients with locally advanced disease. Materials and methods: From November 2008 through January 2012, 34 patients were included in this study. In all cases an accurate pre-treatment staging including CT scan, Endoscopic Ultra-Sonography (EUS), 18F-fluorodeoxyglucose (18F-FDG) PET-CT and laparoscopy with peritoneal washing was performed. External beam radiation was delivered with a total dose of 50.4 Gy (1.8 Gy per fraction). Patients were treated using 3D-conformal radiotherapy, and the clinical target volume was the primary tumor and involved lymph nodes. Cetuximab 300 mg/m2 and Cetuximab were given weekly during radiation therapy. Results: Ten patients (29.4 %) were excluded from the protocol because of the evidence of metastatic disease at the pre-treatment staging. Three patients refused radiochemotherapy. Twenty-one patients completed the therapy protocol. During the combined therapy grade 3-4 toxicities observed were only haematological (leukopenia 47.6 %, thrombocytopenia 4.8 %, elevated gamma-GT 23.8 %, elevated alkaline phosphatase 4.8 %). Non-haematological toxicity grade 3-4 was never reported. Post-treatment workup showed partial response in five patients (24 %), stable disease in 11 patients (52 %) and disease progression in 5 patients (24 %). Two-year Local Control was 49 % (median, 18.6 months), 2-year Metastases Free Survival was 24 % (median, 10.8 months). One and two Year Overall Survival were 66 % and 26 % respectively, with a median survival time of 15.3 months. Conclusions: The combination of cetuximab and gemcitabine with concurrent radiation therapy provides a feasible and well tolerated treatment for locally advanced pancreatic cancer. Patients’ selection is crucial in order to treat patients appropriately.

Prospective study of cetuximab and gemcitabine in combination with radiation therapy: feasibility and efficacy in locally advanced pancreatic head cancer.

Most important publications


hERG1 channels drive tumour malignancy and may serve as prognostic factor in pancreatic ductal adenocarcinoma.


Background: hERG1 channels are aberrantly expressed in human cancers. The expression, functional role and clinical significance of hERG1 channels in pancreatic ductal adenocarcinoma (PDAC) is lacking. Methods: hERG1 expression was tested in PDAC primary samples assembled as tissue microarray by immunohistochemistry using an anti-hERG1 monoclonal antibody (α-hERG1-MoAb). The functional role of hERG1 was studied in PDAC cell lines and primary cultures. ERG1 expression during PDAC progression was studied in Pdx-1-Cre,LSL-Kras(G12D/+),LSL-Trp53(R175H/+) transgenic (KPC) mice. hERG1 was expressed at high levels in 59% of primary PDAC; (ii) hERG1 blockade decreased PDAC cell growth and migration; (iii) hERG1 was physically and functionally linked to the Epidermal Growth Factor-Receptor pathway; (iv) in transgenic mice, ERG1 was expressed in PanIN lesions, reaching high expression levels in PDAC; (v) PDAC patients whose primary tumour showed high hERG1 expression had a worse prognosis; (vi) the α-hERG1-MoAb could detect PDAC in vivo. Conclusions: hERG1 regulates PDAC malignancy and its expression, once validated in a larger cohort also comprising of late-stage, non-surgically resected cases, may be exploited for diagnostic and prognostic purposes in PDAC either ex vivo or in vivo.


Prospective study of cetuximab and gemcitabine in combination with radiation therapy: feasibility and efficacy in locally advanced pancreatic head cancer.


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Nappo, G., Borzomati, D., Perrone, G., Valeri, S., Amato, M., Pettiti, T., Coppola, R.
GENETIC PATHOLOGY

Head:
V.M. Fazio


The RU of Genetic Pathology (first, Molecular Medicine and Biotechnology) was renamed on the basis of the Disciplinary Area of General and Clinical Pathology (MED/04-06A2), that comprises the post graduate School of Specialization (Residency) in Clinical Pathology and Clinical Biochemistry (MC, AP, EM, FP, MV) and the new instituting Clinical Laboratory of Genetic OncoHematology (VS, EM). To date the permanent staff is composed only by VM Fazio and S Virga. In addition, M De Robertis is involved as Research Fellow (Assegnista di Ricerca) on a colorectal cancer stem cell project, with the PhD students LL from the University of Foggia. Researchers from other University (MLP) and CNR (ES) actively cooperate both on research projects and the didactic activities.

The specific competences of the RU are focused on molecular genetics and epigenetics, development of cancer models, in vitro and in vivo gene transfer, histopathology technologies, cytofluorimetric analysis and cell sorting and application of bioinformatics studies in collaboration with leading groups.

Three main projects are in development:
- 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, 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, response to therapy and metastasization (renal, colorectal, lung, breast tumors).
- Cytofluorimetric analysis and genetics in oncohematology.

Main collaborations

- AB Analitica srl, Padova
- Bio-Ker srl, Naples - Milan (Multimedica SpA group)
- IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG)
- MASMEC BioMed SpA, Bari
- NCI, Div. Cancer Epidemiol.&Genetics, Bethesda, Md, USA.
- The Sidney Kimmel Comprehensive Cancer Center, The Johns Hopkins University, Baltimore (Md-USA)
- Translational Oncology Division, University Hospital Fundacion Jimenez Diaz, Madrid, Spain
Most important publications


**Competitive allele-specific TaqMan PCR (Cast-PCR) is a sensitive, specific and fast method for BRAF V600 mutation detection in Melanoma patients.**


BRAF codon 600 mutation testing of melanoma patients is mandatory for the choice of the most appropriate therapy in the clinical setting. Competitive allele specific TaqMan PCR (Cast-PCR) technology allows not only the selective amplification of minor alleles, but it also blocks the amplification of non-mutant allele. We genotyped codon 600 of the BRAF gene in 54 patients’ samples by Cast-PCR and bidirectional direct sequence analysis. All the mutations detected by sequencing were also identified by Cast-PCR. In addition, Cast-PCR assay detected four samples carrying mutations and was able to clearly identify two mutations of uncertain significance by Sanger sequencing. The limit of detection of Cast-PCR was evaluated by constructing dilution curves of BRAF600E and BRAF600K mutated clinical samples mixed with a not-mutated specimen. Both mutations could be detected until a 1:100 mutated/not mutated ratio. Cloning and sequencing of the clones was used to confirm mutations on representative discrepant cases. Cast-PCR performances were not affected by intra-tumour heterogeneity, and less affected by melanin content. Our results indicate that Cast-PCR is a reliable diagnostic tool for the identification of melanoma patients as eligible to be treated with TKIs and might be implemented in the clinical setting as elective screening method.


**TRIM8 downregulation in glioma affects cell proliferation and it is associated with patients survival.**


Background: Human gliomas are a heterogeneous group of primary malignant brain tumors whose molecular pathogenesis is not yet solved. In this regard, a major research effort has been directed at identifying novel specific glioma-associated genes. Here, we investigated the effect of TRIM8 gene in glioma. Methods: TRIM8 transcriptional level was profiled in our own glioma cases collection by qPCR and confirmed in the independent TCGA glioma cohort. The association between TRIM8 expression and Overall Survival and Progression-free Survival in TCGA cohort was determined by using uni-multivariable Cox regression analysis. The effect of TRIM8 on patient glioma cell proliferation was evaluated by performing MTT and clonogenic assays. The mechanisms causing the reduction of TRIM8 expression were explored by using qPCR and in vitro clonogenic assays. Results: We showed that TRIM8 expression correlates with unfavorable clinical outcome in glioma patients. We found that a restored TRIM8 expression induced a significant reduction of clonogenic potential in U87MG and patient’s glioblastoma cells. Finally we provide experimental evidences showing that miR-17 directly targets the 3’ UTR of TRIM8 and post-transcriptionally represses the expression of TRIM8. Conclusions: Our study provides evidences that TRIM8 may participate in the carcinogenesis and progression of glioma and that the transcriptional repression of TRIM8 might have potential value for predicting poor prognosis in glioma patients.


**Novel insights into Notum and glypicans regulation in colorectal cancer.**


The connection between colorectal cancer (CRC) and Wnt signaling pathway activation is well known, but full elucidation of the underlying regulation of the Wnt/β-catenin pathway and its biological functions in CRC pathogenesis is still needed. Here, the azoxymethane/dextran sulfate sodium salt (AOM/DSS) murine model has been used as an experimental platform able to mimic human sporadic CRC development with predictable timing. We performed genome-wide expression profiling of AOM/DSS-induced tumors and normal colon mucosa to identify potential novel CRC biomarkers. Remarkably, the enhanced expression of Notum, a conserved feedback antagonist of Wnt, was observed in tumors along with alterations in Glypican-1 and Glypican-3 levels. These findings were confirmed in a set of human CRC samples. Here, we provide the first demonstration of significant changes in Notum and glypicans gene expression during CRC development and present evidence to suggest them as potential new biomarkers of CRC pathogenesis.
GERIATRICS

Head: 
R. Antonelli Incalzi

Faculty: C. Pedone


The Unit of Geriatrics is involved in research projects focusing in:
- Evaluation of health status and frailty in elderly people, with special attention to multidimensional assessment techniques applied in specific diseases (e.g., heart failure, COPD)
- Evaluation of respiratory function in elderly patients with special focus on the interpretation of spirometric results
- Evaluation of the diagnostic/prognostic properties of volatile organic compounds (VOCs) in different diseases: heart failure, COPD, sleep apnea, skin ulcers, urinary infections, pleural effusions
- Development and implementation of system for remote telemonitoring of chronic diseases
- Evaluation of nutritional intake as a determinant of the health status of elderly people.

The research activity is supported by the availability of a wide array of instruments for functional evaluation and by a strong expertise in epidemiology and biostatistics for the design, implementation and analysis of epidemiological studies.

With respect to the evaluation of health status in elderly people, we have shown that depression is associate with neuro-autonomic derangements in Parkinson’s Disease, and that the association between these derangements and inflammatory status are influenced by gender and obesity in the general elderly population. We have also studied the complex relationship between renal function, disability and mortality, and have shown that leptin influences the rate of decline of renal function.

With respect to the study of VOCs, we have shown that in people with sleep apnoea, the pattern of change of these compounds after ventilation therapy is influenced by comorbidities. Finally, we have tested an innovative model of care based on a telemonitoring system, showing that it can reduce the rate of death/readmission of patients with heart failure by 40%.
Most important publications

Pedone C., Roshanravan B., Scarlata S., Patel K.V., Ferrucci L., Incalzi Antonelli R.

Longitudinal association between serum leptin concentration and glomerular filtration rate in humans.


Background: Obesity is a risk factor for decline in glomerular filtration rate (GFR). One proposed mechanism leading to glomerulosclerosis is an increase in leptin levels. However, the association between leptin and GFR has never been demonstrated. The aim of this study is to verify whether higher levels of leptin are associated with longitudinal changes of estimated GFR (eGFR). Methods and Findings: We selected 744 participants in the INCHANTI study (416 women). The association between eGFR and leptin changes over a 6-years follow-up was assessed using random effect models including leptin as a time-varying covariate and adjusted for potential confounders. We also compared the patients with rapid decline of renal function across tertiles of change in serum leptin between baseline and 6-years follow-up. Mean baseline eGFR was 82.2 ml/min/1.73 m, 78.7 ml/min/1.73 m, and 75.4 ml/min/1.73 m in the first, second and third tertile of baseline serum leptin concentration, respectively. After adjustment for potential confounders, leptin concentration was inversely associated with changes of eGFR over time (β for log-leptin: -1.288, 95% CI: -2.079 - -0.497). Relative to baseline levels, the estimated change in eGFR for unit-increase in log-leptin was -1.9% (95% CI: -2.977 - -0.761). After stratification by sex, the results were confirmed in women only. In women we also found an association between increasing leptin concentration over time and rapid decline of renal function. Conclusions: In women, serum leptin may contribute to eGFR decline independently from obesity and diabetes mellitus, although a cause-effect relationship cannot be established due to the observational nature of our study. A better characterization of adipokine profile of obese individuals may shed light on the accelerated renal function decline reported in a proportion of high-risk obese individuals.

Laudisio A., Bandinelli S., Gemma A., Ferrucci L., Incalzi R.A.

Associations of heart rate with inflammatory markers are modulated by gender and obesity in older adults.


Background: Faster resting heart rate (HR), which is associated with inflammation and elevated cortisol levels, is a risk factor for excess cardiovascular morbidity and mortality. Obesity is associated with increased cardiovascular morbidity and mortality, inflammation, and elevated cortisol levels. The aim of the present study was to evaluate the interaction of Body Mass Index (BMI) with inflammation and cortisol in modulating HR in older subjects. Methods: We analyzed data of 895 participants aged 65+ enrolled in the “INCHANTI” study, in sinus rhythm, and not taking beta blockers or digoxin. Linear regression was performed to assess the adjusted association between HR, IL-6, and cortisol levels. The model was also analyzed stratifying for BMI tertiles. Logistic regression was adopted for evaluating the association of HR exceeding the mean value with Il-6 and serum cortisol. Results: According to multivariable linear regression, IL-6 and cortisol levels were associated with HR (β = 1.42, 95% CI = 0.43-2.42; p = .005 and B = .34, 95% CI = 0.17-.51; p < .0001, respectively). The association was significant only among women in the highest BMI tertile (B = 4.16, 95% CI = 1.40-6.91; p = .003 for IL-6 and B = .57, 95% CI = 0.14-1.01; p = .010 for cortisol). Logistic regression confirmed that IL-6 and cortisol levels were associated with HR above the mean value in the highest BMI tertile (OR = 2.13, 95% CI = 1.15-3.97; p = .009 and OR = 1.14, 95% CI = 1.03-1.25; p = .009, respectively). Conclusions: Faster HR is associated with proinflammatory state in elderly patients; this association seems to be limited to women with higher BMI.

Pedone C., Rossi F.F., Cecere A., Costanzo L., Antonelli Incalzi R.

Efficacy of a physician-led multiparametric telemonitoring system in very old adults with heart failure.


Objective S: To evaluate the effect of an innovative model integrating telemonitoring of vital parameters and telephone support on 6-month survival and hospital admissions of elderly adults with heart failure (HF). Design: Parallel-arm, randomized trial. Setting: Geriatric acute care ward and outpatient clinic at Policlinico Campus Biomedico (Rome, Italy). Participants: Individuals with HF aged 65 and older (mean age 80) randomly assigned to intervention (n = 50) or control (n = 46). Participants had an average ejection fraction of 46%. Intervention: Telemonitoring system (receives and communicates oxygen saturation, heart rate, and blood pressure readings) and office-hours telephone support provided by a geriatrician. Measurements: Combination of all-cause death and hospital admissions. Results: The two groups were similar with the exception of the prevalence of women and of disability (both more common in the control group). Three patients for each group were lost to follow-up (final analyzed sample size: 90). Incidence of the main outcome was 42% in the control group and 21% in the intervention group (relative risk = 0.51, 95% confidence interval (CI) = 0.26-0.98). The results were unchanged after taking into account the setting of enrollment, sex, and disability (hazard ratio = 0.42, 95% CI = 0.19-0.94). Conclusion: Telemonitoring of elderly people with HF is feasible and reduces the risk of death and hospitalization. Further studies are needed to confirm these findings and evaluate the cost-ef ficacy of the service.
GYNAECOLOGY AND OBSTETRICS

Head:
R. Angioli

Other Personnel: A. Aloisi, C. Battista, C. De Cicco Nardone, R. Montera, F. Plotti, R. Ricciardi, G.B. Serra, C. Terranova

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

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 gynaecological cancers and on the different chemotherapy schemes for cervical cancer.

In collaboration with Yale University we have evaluated the sensitivity of gynaecological cancer to targeted therapy, in particular to PI3K/Akt/mTOR inhibitors and anti-HER2 agents and investigated how cancer cells escape the therapeutic pressure of these drugs, to better identify patients who are more likely to respond to a specific therapy and increase effectiveness of such therapies by testing novel combinations.
Research Units: overview and main 2015 scientific outputs

Most important publications

**Scaletta G., Plotti F., Aloisi A., Angioli R.**

Primary chemotherapy versus primary surgery for ovarian cancer.


Sean Kehoe and colleagues (July 18, p 249) recently reported the results of the CHORUS trial and concluded that survival in women with advanced ovarian cancer receiving primary chemotherapy is non-inferior to primary debulking surgery. However, the authors reported an optimal cytoreduction rate of 41% in the primary debulking surgery group, with a median overall survival of 22·6 months, which is towards the lower limit of overall survival according to the scientific literature; but considering that residual disease after surgery remains the most important prognostic factor of survival, we believe the low median overall survival could represent a fundamental bias that would affect the proper interpretation of data. In a study of 285 patients with FIGO stage IIIC/IV ovarian cancer who underwent primary debulking surgery, Dennis Chi and colleagues reported a 71% optimal cytoreduction with a median overall survival of 50 months, which is largely superior to that reported by Kehoe and colleagues. Moreover, the CHORUS trial results showed that 11% of patients did not present macroscopic abdominal involvement; considering that in this subgroup of patients, optimal cytoreduction is mostly achieved in 98% of cases, the cytoreduction rate for stages IC/IV could be considered rather low. On the basis of these considerations, we would be interested to know the reasons for the suboptimal cytoreduction and the cytoreduction rate for each centre, as the cytoreductive effort by all surgeons seems to have varied substantially, apparent from the operative times (median 120 min) that are lower than those usually reported. For these reasons, we believe that the CHORUS trial data should be interpreted with caution.


Dual HER2/PIK3CA targeting overcomes single-agent acquired resistance in HER2-amplified uterine serous carcinoma cell lines in vitro and in vivo.


HER2/neu gene amplification and PIK3CA driver mutations are common in uterine serous carcinoma (USC) and may represent ideal therapeutic targets against this aggressive variant of endometrial cancer. We examined the sensitivity to neratinib, taselisib, and the combination of the two compounds in in vitro and in vivo experiments using PIK3CA-mutated and PIK3CA wild-type HER2/neu-amplified USC cell lines. Dual HER2/PIK3CA blockade may represent a novel therapeutic option for USC patients harboring tumors with HER2/neu gene amplification and mutated or wild-type PIK3CA resistant to chemotherapy.

**Plotti F., Scaletta G., Aloisi A., Luvero D., Capriglione S., Miranda A., Monteria R., De Cicco Nardone C., Terranova C., Angioli R.**

Quality of life in platinum-sensitive recurrent ovarian cancer: chemotherapy versus surgery plus chemotherapy.


This study was designed to compare quality of life in a sample of Italian patients affected by platinum-sensitive recurrent ovarian cancer and submitted to chemotherapy alone or secondary cytoreductive surgery plus chemotherapy through validated questionnaires. After a diagnostic laparoscopy, surgical resectable patients were enrolled in group A (surgery plus chemotherapy). Patients not suitable for optimal debulking surgery and all patients who refused surgery were enrolled in group B (chemotherapy alone). At beginning of treatment, after the third and sixth cycle of chemotherapy, all eligible patients were asked to fill in QLQ-C30 (version 3.0) and EORTC QLQ-OV28 questionnaires. Both surgery followed by chemotherapy and chemotherapy alone seem to have a negligible impact on QOL. SCS plus chemotherapy seems to be an effective and tolerable therapeutic option in platinum-sensitive recurrences.
HEART SURGERY

Head:
E. Covino
Faculty: M. Chello

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.

Research results for 2015 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. Also, 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 a interesting increase of knowledge, in partnership with Dept. of Astronautics, Electrical and Energetics Engineering of Sapienza University of Rome, and with Dept. of Technological Innovations and Safety of Power Plants, Apparatus and Human Settlements of INAIL, Rome, 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.
An experimental model of transposition of the pulmonary trunk as an autograft in the aortic position has been developed and performed under cardiopulmonary bypass in 20 growing lambs, aged 3 months. The experimental design included: a control group that underwent PA transposition; a group in which the PA was reinforced with an external, synthetic, nonresorbable, polypropylene grid; and a group that received various combinations of resorbable meshes. Animals were followed up during growth for 6 months by angiography and echocardiography and eventually killed for pathologic analysis. All animals survived the procedure with no complications. The model was easy and reproducible. Resorbable meshes prevented PA dilation and preserved its progressive growth process, aiding histologic remodelling. We developed an easy and reproducible model of the Ross procedure, allowing for a reliable simulation of the clinical scenario. Resorbable PA reinforcement may represent an interesting option in this context.

Electrical modeling of an isolated surgical aortic valve replacement for microshock risk assessment.
IEEE Transactions on Industry Applications. 2015; PP(99): 1 DOI: 10.1109/TIA.2015.2480853 IF 1,756

The paper deals with the method and the concepts to obtain the circuit of the surgical layout and provides the most critical values of leakage current flowing through the heart of the patient during the phases of a surgical intervention. Different fault conditions to the electrical power supply installation of the operating room and to the involved Electrical Medical Equipment are simulated. The obtained currents are compared with the values experimented by the recent investigations on electrical current inducing ventricular fibrillation. The probability of this disruption of the normal heart action at different values of the leakage current is estimated. The risk estimation is obtained by the product of the probability of ventricular fibrillation when certain fault conditions occur and the probability of occurrence of the considered fault conditions. This in-depth investigation of the microshock probability provides the knowledge necessary to adopt suitable protection measures, additional to those already implemented for risk reduction.
HEMATOLOGY, STEM CELL TRANSPLANTATION, TRANSFUSION MEDICINE AND CELLULAR THERAPY

Head:
G. Avvisati

Faculty: M.C. Tirindelli

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.

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. Moreover, in cooperation with the Orthopedic 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 progenitors cells: EPC). Finally, in cooperation with the Virology unit, it is conducting a study dealing with CMV reactivation in HSC transplanted patients.
Acute promyelocytic leukemia in patients aged >70 years: the cure beyond the age.


All-trans retinoic acid (ATRA) has made acute promyelocytic leukemia (APL) a very curable disease also in patients aged >60 years; however, there are only few case reports in very elderly APL patients. To address this issue, we reviewed treatment results in 13 patients aged >70 years with newly diagnosed APL followed at our institution from January 1991 to December 2008. According to Sanz score, seven patients were at low risk, five at intermediate risk, and one at high risk. Induction therapy consisted of ATRA + idarubicin in nine patients (3/9 with reduced idarubicin dosage) and ATRA alone in four patients; in this latter group, however, 2/4 needed to add chemotherapy (CHT) due to hyperleukocytosis during ATRA treatment. All patients achieved both morphological and molecular complete remission (CR) after a median time of 51 [interquartile range (IR) 43-55] and 114 (IR 74-155) days, respectively. Infective complications were observed in 10/13 patients, APL differentiation syndrome in 3/13 patients. Twelve patients received consolidation therapy, followed by maintenance treatment in nine patients. Five patients relapsed after 7, 8, 11, 35, and 56 months. At present, seven patients are still alive, five died due to disease progression (four) or senectus while in CR (one), and one was lost to follow-up while in CR. The 5-year event-free survival was 56.1 % (95 % CI, 26.0-86.2); the 5-year overall survival (OS) was 64.5 % (95 % CI, 35.6-93.4). ATRA-based treatment of APL is safe and effective also in elderly patients, with long-lasting disease-free OS.


Ninety-seven patients affected by high-risk hematological malignancies underwent G-CSF primed, unmanipulated bone marrow (BM) transplantation from a related, haploidentical donor. All patients were prepared with an identical conditioning regimen including Thiopeta, Busulvex, Flu-darabine (TBF) and antithymocyte globulin given at myeloablative (MAC = 68) or re-duced (reduced intensity conditioning (RIC) = 29) dose intensity and received the same GvHD prophylaxis consisting of the combination of methotrexate, cyclosporine, mycophenolate-mofetil and basiliximab. Patients were transplanted in 1st or 2nd CR (early phase: n = 60) or in > 2nd CR or active disease (advanced phase: n = 37). With a median time of 21 days (range 12-38 days), the cumulative incidence (CI) of neutrophil engraftment was 94 ± 3%. The 100-day CI of III-IV grade acute GvHD and the 2-year CI of extensive chronic GvHD were 9 ± 3% and 12 ± 4%, respectively. Overall, at a median follow-up of 2.2 years (range 0.3-5.6), 44 out of 97 (45%) patients are alive in CR. The 5-year probability of overall survival (OS) and disease-free survival (DFS) for patients in early and advanced phase was 53 ± 7 vs 24 ± 6% (P = 0.006) and 48 ± 7 vs 22 ± 6% (P = 0.01), respectively. By comparing MAC with RIC patient groups, the transplant-related mortality was equivalent (36 ± 6 vs 28 ± 9 %) while the relapse risk was lower for the MAC patients (22 ± 6 vs 45 ± 11%), who showed higher OS (48 ± 7 vs 29 ± 10%) and DFS (43 ± 7 vs 26 ± 10%). However, all these differences did not reach a statistical significance. In multivariate analysis, diagnosis and recipient age were significant factors for OS and DFS. In conclusion, this analysis confirms, on a longer follow-up and higher number of patients, our previous encouraging results obtained by using MAC and RIC TBF regimen as conditioning for G-CSF primed, unmanipulated BM transplantation from related, haploidentical donor in patients with high-risk haematological malignancies, lacking a HLA-identical sibling or unrelated donor and in need to be urgently transplanted.
HYGIENE, PUBLIC HEALTH AND STATISTICS

Head:
T. Petitti

Other Personnel: A. Ianni

The areas of research interest of the research are:
- 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

In year 2015 collaborations with internal research groups at the Campus Bio-Medico University (General Surgery, Pediatrics, Digestive Endoscopy, Respiratory Pathophysiology, Diagnostic Imaging, Nursing Science) and 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 the year 2015 and are currently being published.
Standard lymphadenectomy during pancreaticoduodenectomy (PD) for peri-ampullary cancer does not include the routine removal of para-aortic lymph nodes (PALN) (station 16, according to the JPS staging system). The aim of this study was to report the incidence and the prognostic value of PALN metastases in patients undergoing PD for peri-ampullary cancer. One hundred thirty-five consecutive patients who underwent PD and PALN dissection for peri-ampullary cancer were prospectively evaluated. The relationship between clinicopathological factors, including PALN metastases and survival was evaluated at univariate and multivariate analysis. PALN metastases (N16+) were found in 11.1% of cases. At univariate analysis, R1 resection, metastatic nodes different from para-aortic (N1) and N16+ significantly affected patients’ prognosis. Compared with N16+, the median overall survival (OS) of N0 patients was significantly longer (32 versus 69 months, respectively; P < 0.05), whereas no difference was found between N16+ and N1 patients (32 versus 34 months, respectively; P > 0.05). At multivariate analysis, only R1 resection reached statistical significance and was confirmed an independent prognostic factor. Neoplastic involvement of PALN in peri-ampullary cancer is frequent and, so, their removal during PD could be justified. Moreover, PALN metastases should be not considered an absolute contraindication to radical surgery.


Extracapillary proliferation is an independent predictive factor in Immunoglobulin A nephropathy.


Oxford classification of Immunoglobulin A Nephropathy (IgAN) identifies four pathological features as predictors of renal outcome (MEST-score): mesangial proliferation (M); endocapillary proliferation (E); segmental glomerulosclerosis (S); tubular atrophy/interstitial fibrosis (T). In particular extracapillary proliferation (Ex) was not considered as an independent histological variable predicting renal outcome. Recently the VALIGA study provided a validation of the Oxford classification in a large European cohort of IgAN patients and re-stated that Ex is not associated with a worse renal prognosis. We propose a retrospective study to evaluate the predictive value of the MEST-score in a multi-centre, single region group of patients from central Italy and in addition, to investigate Ex as a marker predicting renal outcome. One hundred and seven patients were enrolled in this study. Clinical data of each patient were available at diagnosis and follow-up. The median age at diagnosis was 36.7 years; 72% of the patients were males. Histological parameters were those included in the MEST-score of the Oxford classification; in addition, Ex was also assessed. Multiple linear regression models for survey were used. Statistical analysis showed a correlation between the progression of renal decline, in terms of estimated glomerular filtration rate (slope eGFR), and M, S, T. Differently from Oxford and VALIGA studies, no correlation was found with E, while Ex correlated with a decline of eGFR. Our results suggest that Ex represents an additional independent variable associated with a faster decline of renal function in IgAN.

Petitti T., Candela M.L., Ianni A., de Belvis AG., Ricciardi W., De Marinis MG.

[Validation of the Italian version of the GHAA-9 m questionnaire on patient satisfaction in digestive Endoscopy].


There isn’t a validated questionnaire in Italian language to evaluate the quality perceived by the patient in Digestive Endoscopy. Objective was the validation of the translation of a questionnaire from English to Italian language to measure the level of patient satisfaction. We conducted a prospective study on validation in Italian of a short questionnaire adapted for Endoscopy by the American Society of Gastrointestinal Endoscopy, the GHAA-9m. It’s been tested with the technique of the questionnaire/interview on 80 out-patients who underwent in the month of September 2014 to endoscopic examinations of the gastrointestinal tract. The patients were divided into 2 groups of 40 patients: group 1 was administered before the questionnaire and subsequently the interview was conducted, on the contrary on the group 2 was administered before the interview and subsequently the questionnaire. The results of the two groups were compared using the inter-rater agreement. It was also evaluated the internal consistency of the questions. Results show that the instrument is experienced as simple and quick to use for patients. Data analysis allowed us to conclude that the Italian translation is valid and consistent. In the phase of the interview there were some aspects that suggest, in a development of this tool, some changes that could increase the accuracy and informational content. The Italian version of the questionnaire GHAA-9m has good validity, reliability, and shows property valuation comparable to those of the American version and can therefore be used in daily practice Digestive Endoscopy.

Most important publications

Nappo G., Borzomati D., Perrone G., Valeri S., Amato M., Petitti T., Coppola R.

Incidence and prognostic impact of para-aortic lymph nodes metastases during pancreaticoduodenectomy for peri-ampullary cancer.

INSTITUTE OF PHILOSOPHY OF SCIENTIFIC AND TECHNOLOGICAL PRACTICE (FAST)

Head: E. Covino

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

The FAST Institute aims at promoting the dialogue between Sciences and Humanities, both through teaching and research. The main interests of the members of the Institute cover a wide range of topics and disciplines, including anthropology, bioethics, philosophy of biology, philosophy of mind, aesthetics, history of medicine, history of science, philosophy of nursing, and others.

- History of the Gaslini Children’s Hospital in Genoa (Borghi)
- Bio-Techno-Practice: www.biotechnopractice.org (Bertolaso)
- Contemporary Issues in Metaphysics of Biological Sciences, funded by the Agencia de Ciencia y Tecnología de la Región de Murcia, Spain (Bertolaso)
- The unity of the human being: from embryogenesis to virtues development: an interdisciplinary approach for the comprehension of human nature, funded by the Templeton Foundation and Oxford University (Bertolaso)
- Proposal of Guidelines for Palliative Sedation (Tambone)
- Theory and Practice of the Aware and Cooperative Reduction (Tambone)
- The Indispensability of an Interdisciplinary Approach in Bioethics for India (Tambone)
- The role of the action-perception loop in human cognition (Di Stefano/Keller)

In addition to ongoing research activities, in 2015 the Institute has launched a call for pilot research proposals on “embodiment”, with the aim to foster research collaborations within the Institute and with the different research groups who operate at Campus Bio-Medico University of Rome.
Most important publications

Borghi L.
The monuments men: in the history of anesthesia, too.
A 2014 American-German war movie directed by and starring George Clooney popularized the work of a special United States Army unit devoted to the rescue of art treasures stolen or hidden by the Nazis during World War II. A similar story occurred in Paris to a curious little monument closely linked to the history of Anesthesia. This happened about 70 years ago, in December of 1944.

Bertolaso M., Capolupo A., Cherubini C., Filippi S., Gizzi A., Loppini A., Vitiello G.
The role of coherence in emergent behavior of biological systems.
In his research activity, Emilio Del Giudice explored the possibility to move towards a unified view of some long-range dynamics in nature, ranging from quantum field theory in physics up to biology. Such a view is adopted in this contribution by discussing a mathematical model for synchronized electrical behavior of pancreatic beta cells. The stochasticity is a fundamental component of the physiological synchronized behavior of this system. On the contrary, in a pathological type I diabetes scenario, the cells are destroyed by the autoimmune system and their coherent behavior is lost. This phenomenology conceptually links to ideas of coherent dynamics in quantum physics. Possible implications both for physical sciences and for the epistemology of life sciences are outlined.

Ghiardi G., Tambone V.
[For an ontological foundation of the “aware and cooperative reduction”].
Medicina e Morale 2015; 5: 781-804.
The present work develops the ontological presuppositions of scientific methodology labeled as “aware and cooperative reduction”. The idea of being underlying scientific reduction is analyzed by distinguishing among legitimate and improper reductionism. This framework is useful to assess within the context of clinical methodology the complexity of scientific practice. We also focus on the ontological roots of complexity in science, reaching to what Viktor Frankl has named “dimensional realism”. Thanks to this analytical model we recovered the theme of analogy as an important instrument of scientific rationality, which allows to keep together both the objective and the subjective instances of the epistemological domain. This speculative path lead us to ask about the conditions of possibility of human knowledge. In so doing, we have found the notion of “future potentiality” to be the mark of human knowledge. The result of our inquiry is that “analogue being” is the ontological foundation of scientific methodology. The ontological idea of “analogy” conveys an understanding of being constituted by different levels, or dimensions, which are not conceptually exhaustible within scientific research, but which are nevertheless accessible by human investigation.
INTERNAL MEDICINE AND HEPATOLOGY

Head:
A. Picardi

Other Personnel: G. Galati, U. Vespasiani Gentilucci

The unit is firstly devoted to clinical investigation in the field of metabolic and viral chronic liver disease, cirrhosis and hepatocellular carcinoma (HCC).

Our Unit is involved in both collaborative studies - coordinated by scientific societies such as the Italian Society of Internal Medicine (SIMI) and the Italian Association for the Study of the Liver (AISF) - and spontaneous investigation projects in the field of liver injury, inflammation and fibrogenesis. Main collaborations are set with other Units from our University and from the University of Navarra, Spain. Specifically, with the Unit of Human Anatomy and of Clinical Pathology 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 could be implied in hepato-carcinogenesis. Other important collaborations are set with the Area of Oncology and of Neurology. Some clinical investigations have been initiated in the non-invasive evaluation of liver fibrosis through transient elastometry.
Hepatic toll-like receptor 4 expression is associated with portal inflammation and fibrosis in patients with NAFLD.


There were no studies aimed to characterize hepatic Toll-Like Receptor 4 (TLR4) expression in Non-Alcoholic Fatty Liver Disease. We aimed to analyse hepatic TLR4 expression and to verify its relationship with disease activity/evolution in NAFLD patients. We found that TLR4 expression by regenerating and inflammatory cells at the porto-septal and interface level, favoured by increased LPS activity, is associated with activation of fibrogenic cells and with the degree of fibrosis. TLR4 has thus a role as a mediator between inflammation and fibrogenesis.

Matrix metalloproteinase 10 contributes to hepatocarcinogenesis in a novel crosstalk with the stromal derived factor 1/C-X-C chemokine receptor 4 axis.


Matrix metalloproteinases (MMPs) participate in tissue repair, but also participate in cancer by promoting a protumorigenic microenvironment. Herein, we investigated MMP10 expression and function in human hepatocellular carcinoma (HCC) and diethylnitrosamine (DEN)-induced mouse hepatocarcinogenesis. According to results, MMP10 contributes to HCC development, participating in tumor angiogenesis, growth, and dissemination. A new reciprocal crosstalk between MMP10 and the CXCR4/SDF1 axis contribute to HCC progression and metastasis. This is the first report addressing the role of a MMP in hepatocarcinogenesis in the corresponding genetic mouse model.

Altered metal metabolism in patients with HCV-related cirrhosis and hepatic encephalopathy.


Dysfunctional metal homeostasis contributes to oxidative stress and neuronal damage. These have been implicated in hepatic encephalopathy pathogenesis. To investigate whether altered metal metabolism is associated with hepatic encephalopathy. Serum iron, copper, ceruloplasmin, ceruloplasmin activity, transferrin, and ceruloplasmin/transferrin ratio were determined in 21 controls and 34 HCV-cirrhotic patients. Neuropsychological tests were performed by the repeatable battery of neuropsychological status. Magnetic resonance assessed basal ganglia volumes and metal deposition (pallidal index and T2*). According with our results, altered metal metabolism likely contributes to cirrhotic hepatic encephalopathy.
MEASUREMENTS AND BIOMEDICAL INSTRUMENTATION

Head:  
S. Silvestri

Faculty: E. Schena
Other Personnel: C. Massaroni, P. Saccomandi

The Research Unit scientific activity is mainly focused on measurements and measurement systems for clinical diagnostics and applied to human well-being. 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.

The research activity has been focused on innovative methods to obtain a temperature map of organs by means of magnetic resonance imaging and CT, innovative MR-compatible optical fibre sensors for force measurement and experimental estimation of optical properties of pancreas 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”

- Diagnostic and Interventional Radiology and Biophysics Institute of Johann Wolfgang Goethe Universität Frankfurt am Main
- Photonics Micro- and Nano-structures Laboratory, Centro Ricerche ENEA Frascati
- Biorobotics Institute S. Anna School of Advanced Studies, Italy.
Most important publications

Saccomandi P., Vogel V., Bazrafshan B., Maurer J., Schena E., Vogl T.J., Silvestri S., Mantele W.  
Estimation of anisotropy coefficient of swine pancreas, liver and muscle at 1064 nm based on goniometric technique.  
Optical properties of tissues are required for theoretical modeling of Laser Ablation in tumor therapy. The light scattering characteristic of tissues is described by the anisotropy coefficient, g. The relationship between the angular distribution of scattered light and g is given by the Heney-Greenstein (HG) phase function. This work describes the estimation of anisotropy coefficients of ex vivo swine pancreas, liver and muscle at 1064 nm. The intensities of scattered light at fixed angles were measured under repeatability conditions. Experimental data were fitted with a two-term HG, estimating the anisotropy coefficients for the forward (e.g., 0.956 for pancreas, 0.964 for liver and 0.968 for muscle) and the backward (e.g., -0.481 for pancreas, -0.414 for liver and -0.372 for muscle) scattering.

Allegretti G., Saccomandi P., Giurazza F., Caponero M.A., Frauenfelder G., Di Matteo F.M., Beomonte Zobel B., Silvestri S., Schena E.  
Magnetic resonance-based thermometry during laser ablation on ex-vivo swine pancreas and liver.  
Laser Ablation (LA) is a minimally-invasive procedure for tumor treatment. LA outcomes depend on the heat distribution inside tissues and require accurate temperature measurement during the procedure. Magnetic resonance imaging (MRI) allows a non-invasive and three-dimensional thermometry of the organ undergoing LA. In this study, the temperature distribution within two swine pancreases and three swine livers undergoing LA (Nd:YAG, power: 2 W, treatment time: 4 min) was monitored by a 1.5-T MR scanner, utilizing two T1-weighted sequences (IRTF and SRTF). The signal intensity in four regions of interest, placed at different distances from the laser applicator, was related to temperature variations monitored in the same regions by twelve fiber Bragg grating sensors. The relationship between the signal intensity and temperature increase was calculated to obtain the calibration curve and to evaluate accuracy, sensitivity and precision of each sequence. This is the first study of MR-based thermometry during LA on pancreas. More specifically, the IRTF sequence provides the highest temperature sensitivity in both liver (1.8±0.2 °C⁻¹) and pancreas (1.8 ± 0.5 °C⁻¹) and the lowest precision and accuracy. SRTF sequence on pancreas presents the highest accuracy and precision (MODSFR= -0.1 °C and LOASFRT=[-2.3; 2.1]°C).

Feedforward neural network for force coding of an MRI-compatible tactile sensor array based on fiber bragg grating.  
This work shows the development and characterization of a fiber optic tactile sensor based on Fiber Bragg Grating (FBG) technology. The sensor is a 3 x 3 array of FBGs encapsulated in a POMS compliant polymer. The strain experienced by each FBG is transduced into a Bragg wavelength shift and the inverse characteristics of the sensor were computed by means of a feedforward neural network. A 21 mN RMSE error was achieved in estimating the force over the 8 N experienced load range while including all probing sites in the neural network training procedure, whereas the median force RMSE was 199 mN across the 200 instances of a Monte Carlo randomized selection of experimental sessions to evaluate the calibration under generalized probing conditions. The static metrological properties and the possibility to fabricate sensors with relatively high spatial resolution make the proposed design attractive for the sensorization of robotic hands. Furthermore, the proved MRI-compatibility of the sensor opens other application scenarios, such as the possibility to employ the array for force measurement during functional MRI-measured brain activation.
The Microscopic and Ultrastructural Anatomy Unit applies techniques for morphological 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. Structural, ultrastructural and molecular analysis by light, fluorescence and transmission electron microscopy are performed using histochemical, immunohistochemistry, immunofluorescence and immunogold techniques. Morphometric analysis by systems and software for image analysis, molecular and cell biology are applied to the study of liver, pancreas and skin diseases. The analysis of the expression levels of RNA and proteins by approaches of Q-PCR, western blotting and nanostring and the study of the regulation of translation and stability of mRNA in cellular systems or tissues are investigated.

The role of the hepatic progenitor cells and their activation in the so called "ductular reaction" during non-alcoholic steatohepatitis was investigated in order to identify mediators, such as Toll-like receptor 4, connecting liver inflammation and fibrosis. The regenerative process and its dysregulation during hepatocarcinogenesis were also addressed in animal models and HCC patients in collaboration with Prof. MA Avila (University of Navarra, Gene Therapy & Hepatology-Pamplona, Spain). A significant role in determining the hepatic injury and degeneration was attributed to metalloproteinase 10.

Histomorphology and molecular biology techniques were applied to the study of the intracellular pathway regulators of differentiation, proliferation and aggressiveness of melanoma at both cellular and tissue level in collaboration with Prof. C Bagni (Università di Roma “Tor Vergata” and University of Lausanne, Switzerland) and Prof. JC Marine (Catholic University of Leuven, Belgium).
Most important publications

Carotti S., Vespasiani-Genti-
lucci U., Perrone G., Picardi
A., Morini S.
Portal inflammation during
NAFLD is frequent and as-
associated with the early pha-
se of putative hepatic pro-
genitor cell activation.
J Clin Pathol. 2015 Nov; 68(11):
883-90. PubMed PMID:
26124313. IF 2,641

We investigated whether portal tract in-
flammation observed in non-alcoholic
fatty liver disease (NAFLD) is associated
with hepatic progenitor cell compartment
activation, as thoroughly evaluated with
different markers of the staminal lineage.
Results of the present study show that
portal inflammation is frequent during
NAFLD and strongly associated with ac-
tivation of putative hepatic progenitor
cells since the first steps of their diffe-
rentiation, portal myofibroblast activity
and fibrosis.

García-Irigoyen O., Latasa
M.U., Carotti S., Uriarte I., Eli-
 zalde M., Urtasun R., Vespa-
siani-Gentilucci U., Morini S.,
Benito P., Ladero J.M., Ro-
driguez J.A., Prieto J., Orbe
J., Páramo J.A., Fernández-
Barrena M.G., Berasain C.,
Avila M.A.
Matrix metalloproteinase 10
contributes to hepatocarcin-
genesis in a novel crosstalk
with the stromal derived fac-
tor 1/C-X-C chemokine re-
ceptor 4 axis.
Hepatology. 2015 Jul; 62(1):
166-78. PubMed PMID: 25808184. IF
11,055

Matrix metalloproteinases (MMPs) parti-
cipate in tissue repair after acute injury,
but also participate in cancer by promoting
a protumorigenic microenvironment.
MMP10 contributes to HCC development,
participating in tumor angiogenesis,
growth, and dissemination. We identified
a new reciprocal crosstalk between
MMP10 and the CXCR4/SDF1 axis con-
tributing to HCC progression and meta-
stasis. To our knowledge, this is the first
report addressing the role of a MMP in
hepatocarcinogenesis in the corresponding
genetic mouse model.

Vespasiani-Gentilucci U., Ca-
rotti S., Perrone G., Mazzarelli
C., Galati G., Onetti-Muda A.,
Picardi A., Morini S.
Hepatic toll-like receptor 4
expression is associated with
portal inflammation and fi-
brosis in patients with
NAFLD.
Liver Int. 2015 Feb; 35(2): 569-
81. PubMed PMID: 24649857. IF
4,850

Notwithstanding evidences implicating
the lipopolysaccharides (LPS/toll-like re-
ceptor-4 (TLR4) axis in the pathogenesis
of NAFLD, there are no studies aimed to
characterize hepatic TLR4 expression in
NAFLD patients. We aimed to analyse
hepatic TLR4 expression and to verify its
relationship with disease activity/evolution
in NAFLD patients. Here we showed that
TLR4 expression by regenerating and in-
flammatory cells at the porto-septal and
interface level, favoured by increased
LPS activity, is associated with activation
of fibrogenic cells and the degree of fi-
brosis
MOLECULAR NEUROSCIENCES

Head:
M. D'Amelio

Other Personnel: A. Nobili, F. Sciarra

The Molecular Neurosciences Unit focuses on the application of biologic techniques to study neurodegenerative diseases and other neuropsychiatric conditions. 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.

During last year, the Molecular Neurosciences Unit consolidated scientific collaborations with national and international partners. In particular, the Laboratory collaborated with Roma Tre University, Sapienza University of Rome, Université Libre de Bruxelles, Center of Excellence for Biomedical Research, University of Genova.

The aforementioned collaborations involve the study of neuronal function alterations in several models of human neurological disease. Publications of research results are expected in the current year.
SAM68 is a physiological regulator of SMN2 splicing in spinal muscular atrophy.


Spinal muscular atrophy (SMA) is a neurodegenerative disease caused by loss of motor neurons in patients with null mutations in the SMN1 gene. The almost identical SMN2 gene is unable to compensate for this deficiency because of the skipping of exon 7 during pre-messenger RNA (mRNA) processing. Although several splicing factors can modulate SMN2 splicing in vitro, the physiological regulators of this disease-causing event are unknown. We found that knockout of the splicing factor SAM68 partially rescued body weight and viability of SMA Δ7 mice. Ablation of SAM68 function promoted SMN2 splicing and expression in SMA Δ7 mice, correlating with amelioration of SMA-related defects in motor neurons and skeletal muscles. Mechanistically, SAM68 binds to SMN2 pre-mRNA, favoring recruitment of the splicing repressor hnRNP A1 and interfering with that of U2AF65 at the 3’ splice site of exon 7. These findings identify SAM68 as the first physiological regulator of SMN2 splicing in an SMA mouse model.

Nisticò R., Fiorenzano F., Mangolo D., Ferraina C., Grilli M., Di Prisco S., Nobili A., Sac-}

93

Most important publications

Pagliarini V., Pelosi L., Bustamante MB., Nobili A., Berardinelli MG., D’Amelio M., Musaro A., Sette C.

SAM68 is a physiological regulator of SMN2 splicing in spinal muscular atrophy.


Spinal muscular atrophy (SMA) is a neurodegenerative disease caused by loss of motor neurons in patients with null mutations in the SMN1 gene. The almost identical SMN2 gene is unable to compensate for this deficiency because of the skipping of exon 7 during pre-messenger RNA (mRNA) processing. Although several splicing factors can modulate SMN2 splicing in vitro, the physiological regulators of this disease-causing event are unknown. We found that knockout of the splicing factor SAM68 partially rescued body weight and viability of SMA Δ7 mice. Ablation of SAM68 function promoted SMN2 splicing and expression in SMA Δ7 mice, correlating with amelioration of SMA-related defects in motor neurons and skeletal muscles. Mechanistically, SAM68 binds to SMN2 pre-mRNA, favoring recruitment of the splicing repressor hnRNP A1 and interfering with that of U2AF65 at the 3’ splice site of exon 7. These findings identify SAM68 as the first physiological regulator of SMN2 splicing in an SMA mouse model.


Presynaptic c-Jun N-terminal Kinase 2 regulates NMDA receptor-dependent glutamate release.


Activation of c-Jun N-terminal kinase (JNK) signaling pathway is a critical step for neuronal death occurring in several neurological conditions. JNKs can be activated via receptor tyrosine kinases, cytokine receptors, G-protein coupled receptors and ligand-gated ion channels, including the NMDA glutamate receptors. While JNK has been generally associated with postsynaptic NMDA receptors, its presynaptic role remains largely unexplored. Here, by means of biochemical, morphological and functional approaches, we demonstrate that JNK and its scaffold protein JIP1 are also expressed at the presynaptic level and that the NMDA-evoked glutamate release is controlled by presynaptic JNK-JIP1 interaction. Moreover, using knockout mice for single JNK isoforms, we proved that JNK2 is the essential isoform in mediating this presynaptic event. Overall the present findings unveil a novel JNK2 localization and function, which is likely to play a role in different physiological and pathological conditions.


Neuregulin 1 signalling modulates mGlur1 function in mesencephalic dopaminergic neurons.


Neuregulin 1 (NRG1) is a trophic factor that has an essential role in the nervous system by modulating neurodevelopment, neurotransmission and synaptic plasticity. Despite the evidence that NRG1 and its receptors, ErbB tyrosine kinases, are expressed in mesencephalic dopaminergic nuclei and their functional alterations are reported in schizophrenia and Parkinson’s disease, the role of NRG1/ErbB signalling in dopaminergic neurons remains unclear. Here we found that NRG1 selectively increases the metabotropic glutamate receptor 1 (mGlur1)-activated currents by inducing synthesis and trafficking to membrane of functional receptors and stimulates phosphatidylinositol 3-kinase-Akt-mammalian target of rapamycin (PI3K-Akt-mTOR) pathway, which is required for mGlur1 function. Notably, an endogenous NRG1/ErbB tone is necessary to maintain mGlur1 function, by preserving its surface membrane expression in dopaminergic neurons. Consequently, it enables striatal mGlur1-induced dopamine outflow in in vivo conditions. Our results identify a novel role of NRG1 in the dopaminergic neurons, whose functional alteration might contribute to devastating diseases, such as schizophrenia and Parkinson’s disease.
MOLECULAR PSYCHIATRY AND NEUROGENETICS

Head:
A.M. Persico


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.

The main research lines pursued include the identification of biomarkers for autism and ADHD (genomics, transcriptomics, electrophysiology, eye tracking, collaboration for urinary metabolomics, proteomics and brain imaging); genetics of neurodevelopmental disorders; contribution of cytogenetic abnormalities and gene expression; causes and implications of iperserotonemia in autism; immune genes and immune abnormalities in autism; environmental factors and autism (p-cresol urine); psychopharmacology of childhood neuropsychiatric disorders (ECNP).

- Istituto Superiore di Sanità, Neurotoxicology & Neuroendocrine Department, Rome
- Sapienza University of Rome, Psychology Department
- Tuscia University, Proteomics Laboratory, Viterbo
- Milano University, Biological Science Department and Interdepartmental Centre for Stem Cell Research
- University Medical Centre Utrecht, Department of Translational Neuroscience
- Brain Centre Rudolf Magnus - Netherlands
- King’s College London, The Institute of Psychiatry - UK
Macrocephaly and brain overgrowth have been associated with autism spectrum disorder. We performed a systematic review and meta-analysis to provide an overall estimate of effect size and statistical significance for both head circumference and total brain volume in autism. Our literature search strategy identified 261 and 391 records, respectively; 27 studies defining percentages of macrocephalic patients and 44 structural brain imaging studies providing total brain volumes for patients and controls were included in our meta-analyses. Head circumference was significantly larger in autistic compared to control individuals, with 822/5225 (15.7%) autistic individuals displaying macrocephaly. Structural brain imaging studies measuring brain volume estimated effect size. The effect size is higher in low functioning autistics compared to high functioning and ASD individuals. Brain overgrowth was recorded in 142/1558 (9.1%) autistic patients. Finally, we found a significant interaction between age and total brain volume, resulting in larger head circumference and brain size during early childhood. Our results provide conclusive effect sizes and prevalence rates for macrocephaly and brain overgrowth in autism, confirm the variation of abnormal brain growth with age, and support the inclusion of this endophenotype in multi-biomarker diagnostic panels for clinical use.

Autism genetics: methodological issues and experimental design.
Autism is a complex neuropsychiatric disorder of developmental origin, where multiple genetic and environmental factors likely interact resulting in a clinical continuum between “affected” and “unaffected” individuals in the general population. During the last two decades, relevant progress has been made in identifying chromosomal regions and genes in linkage or association with autism, but no single gene has emerged as a major cause of disease in a large number of patients. The purpose of this paper is to discuss specific methodological issues and experimental strategies in autism genetic research, based on fourteen years of experience in patient recruitment and association studies of autism spectrum disorder in Italy.

Endocannabinoid Signaling in Autism.
Autism spectrum disorder (ASD) is a complex behavioral condition with onset during early childhood and a lifelong course in the vast majority of cases. To date, no behavioral, genetic, brain imaging, or electrophysiological test can specifically validate a clinical diagnosis of ASD. However, these medical procedures are often implemented in order to screen for syndromic forms of the disorder (i.e., autism comorbid with known medical conditions). In the last 25 years a good deal of information has been accumulated on the main components of the “endocannabinoid (eCB) system”, a rather complex ensemble of lipid signals (“endocannabinoids”), their target receptors, purported transporters, and metabolic enzymes. It has been clearly documented that eCB signaling plays a key role in many human health and disease conditions of the central nervous system, thus opening the avenue to the therapeutic exploitation of eCB-oriented drugs for the treatment of psychiatric, neurodegenerative, and neuroinflammatory disorders. Here we present a modern view of the eCB system, and alterations of its main components in human patients and animal models relevant to ASD. This review will thus provide a critical perspective necessary to explore the potential exploitation of distinct elements of eCB system as targets of innovative therapeutics against ASD.
NEUROLOGY, NEUROPHYSIOLOGY, NEUROBIOLOGY

Head:
V. Di Lazzaro

Faculty: M. Tombini, F. Vernieri

The activity of the Research Unit is focused on the study of the pathophysiology of a variety of neurological disorders, including stroke, degenerative diseases (dementias, Parkinson’s disease, amyotrophic lateral sclerosis), movement disorders, inflammatory diseases of the central nervous system (multiple sclerosis), spinal cord diseases, epilepsy, cephalalgia. It also investigates the physiology of the central nervous system and, in particular, of the motor system and the mechanisms of brain plasticity, by means of electrophysiological techniques (EEG, EMG, evoked potentials), neurosonology and non-invasive brain stimulation (TMS, tDCS, vagal stimulation).

- “Progetto di Ricerca Finalizzata” of the Italian Ministry of Health (code: GR-2011-02352674): “Daily at-home follow-up of Parkinson’s Disease patients motor performance through robotic and portable devices”.
- “Progetto di Ricerca Finalizzata” of the Italian Ministry of Health (code: CO-2013-02358697): Extremely low frequency magnetic field (ELF-MF) stimulation as a neuroprotective treatment in acute ischemic stroke.
- Collaborating Unit in the “PPR2” INAIL-UCBM joint project, dedicated to the development of intraneural interfaces for the bidirectional control of robotic hand prostheses.
BDNF gene polymorphism impacts human motor cortex function and plasticity. Using transcranial magnetic stimulation (TMS), we investigated whether BDNF polymorphism influences cortical plastic changes in acute stroke. Twenty patients were recruited within 10 days of their first-ever ischemic stroke and genotyped for BDNF polymorphism. Blinded to the latter, we evaluated the excitability of the affected and unaffected hemisphere by measuring resting and active motor threshold and motor-evoked potential amplitude under baseline conditions and after intermittent theta burst stimulation, a protocol of repetitive TMS inducing LTP-like activity. We also computed laterality indexes to assess inter-hemispheric excitability imbalance. Demographics, threshold and amplitude of motor-evoked potentials did not differ between those with (8 patients) and without polymorphism. Excitability of the unaffected hemisphere was significantly higher than the excitability of the affected hemisphere as probed by each measure. This imbalance was exaggerated in those without polymorphism; laterality indexes of rest motor thresholds were 0.016 ± 0.050 and 0.139 ± 0.028 for patients with and without polymorphism [t = 2.270, P = 0.036]. Exaggerated hemispheric imbalance also persisted after intermittent theta burst stimulation, which failed to induce any difference between groups. Our results suggest that inter-hemispheric imbalance with greater excitability over unaffected hemisphere, is several times stronger in stroke patients without, as opposed to with, polymorphism.

Raffin E, Pellegrino G, Di Lazzaro V, Thielcher A, Siebner HR.

Bringing transcranial mapping into shape: Sulcus-aligned mapping captures motor somatotopy in human primary motor hand area.


Motor representations express some degree of somatotopy in human primary motor hand area (M1HAND), but within-M1HAND corticomotor somatotopy has been difficult to study with transcranial magnetic stimulation (TMS). Here we introduce a “linear” TMS mapping approach based on the individual shape of the central sulcus to obtain mediolateral corticomotor excitability profiles of the abductor digiti minimi (ADM) and first dorsal interosseus (FDI) muscles. In thirteen young volunteers, we used stereotactic neuronavigation to stimulate the right M1HAND with a small eight-shaped coil at 120% of FDI resting motor threshold. We pseudorandomly stimulated six targets located on a straight mediolateral line corresponding to the overall orientation of the central sulcus with a fixed coil orientation of 45° to the mid-sagittal line (STRAIGHT-450FIX) or seven targets in the posterior part of the crown of the central sulcus following the bending of the central sulcus (CURVED). CURVED mapping employed a fixed (CURVED-450FIX) or flexible coil orientation producing always a current perpendicular to the sulcal wall (CURVED-900FLEX). During relaxation, CURVED but not STRAIGHT mapping revealed distinct corticomotor excitability peaks in M1HAND with the excitability maximum of ADM located medially to the FDI maximum. This mediolateral somatotopy was still present during tonic contraction of the ADM or FDI. During ADM contraction, cross-correlation between the spatial excitability profiles of ADM and FDI was lowest for CURVED-900FLEX. Together, the results show that within-M1HAND somatotopy can be readily probed with linear TMS mapping aligned to the sulcal shape. Sulcus-aligned linear mapping will benefit non-invasive studies of representational plasticity in human M1HAND.


The effect of transcutaneous vagus nerve stimulation on cortical excitability.


There is great interest about the therapeutic potentialities of transcutaneous vagus nerve stimulation (tVNS) applied to neuropsychiatric disorders. However, the mechanisms of action of tVNS and its impact on cortical excitability are unclear. To this regard, transcranial magnetic stimulation (TMS) can be useful because it is able of evaluating non-invasively excitatory and inhibitory circuitry of the human cortex. Aim of the present study is to investigate the effects of tVNS on cerebral cortex excitability in healthy volunteers by means of TMS. Ten healthy subjects participated in this randomized placebo-controlled double-blind study. Real tVNS was administered at left external acoustic meatus, while sham stimulation was performed at left ear lobe, both of them for 60 min. We evaluated motor thresholds, motor evoked potential amplitude, recruitment curves, and short-interval intracortical inhibition (SICI) in right and left motor cortex. Such parameters were evaluated before and 60 min after the exposure to tVNS, for both the real and the sham stimulation. Cardiovascular parameters were monitored during the stimulation. A generalized linear model for repeated measures was implemented to assess the effect of time and stimulation type on cardiovascular and neurophysiological variables. SICI, a double-pulse TMS paradigm informative of GABA-A activity, was significantly increased in right motor cortex after real tVNS. Other neurophysiological parameters, as well as cardiovascular variables, remained unchanged. Our findings confirm that tVNS is a safe and effective way to stimulate vagus nerve and provide innovative data about the possible mechanisms of action that supports the potential therapeutic application of this technique.
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 and stellar and black hole physics. 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, 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 a networks of collaborations both at national and international levels.

In 2015 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 -141020 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. It has also participated to the internal UCBM funding call being awarded, as research Unit, of a grant for the project n.0015/14 “A multi-cellular ‘gut-on-chip’ technology for predictive human safety testing: an integrated experimental and modeling approach”.

NONLINEAR PHYSICS AND MATHEMATICAL MODELING

Head: 
S. Filippi

Faculty: C. Cherubini, L. Chiodo, A. Gizzi
Other Personnel: F. Cipolletta, A. Loppini, G. Nestola

Aims

Main research activities
The activity of pancreatic β cells can be described by biological networks of coupled nonlinear oscillators that, via electrochemical synchronization, release insulin in response to augmented glucose levels. In this work, we analyze the emergent behavior of regular and percolated clusters through a stochastic mathematical model where “functional” networks arise. We show that the emergence and robustness of the synchronized dynamics depend both on intrinsic and extrinsic parameters. In particular, cellular noise level, glucose concentration, network spatial architecture, and cell-to-cell coupling strength are the key factors for the generation of a rhythmic and robust activity. Their role in the functional network topology associated with β cells clusters is analyzed and discussed.

Cipolletta F., Cherubini C., Filippi S., Rueda J.A., Ruffini R.

Fast rotating neutron stars with realistic nuclear matter equation of state.


We construct equilibrium configurations of uniformly rotating neutron stars for selected relativistic mean-field nuclear matter equations of state (EOS). We compute, in particular, the gravitational mass (M), equatorial (Req) and polar (Rpol) radii, eccentricity, angular momentum (J), moment of inertia (I) and quadrupole moment (M2) of neutron stars stable against mass shedding and secular axial-symmetric instability. By constructing the constant frequency sequence f = 716 Hz of the fastest observed pulsar, PSR J1748–2040ad, and constraining it to be within the stability region, we obtain a lower mass bound for the pulsar, Mmin = [1.2–1.4]M☉ for the EOS employed. Moreover, we give a fitting formula relating the baryonic mass (Mb) and gravitational mass of nonrotating neutron stars, Mb/MO = M/MO + (13/20)(M/MO)2 [or M/MO = Mb/M–(1/2)(Mb/M)2], which is independent of the EOS. We also obtain a fitting formula, although not EOS independent, relating the gravitational mass and the angular momentum of neutron stars along the secular axisymmetric instability line for each EOS. We compute the maximum value of the dimensionless angular momentum, a/MoJ/GM2 (or “Kerr parameter”), (a/MoJ)max = 0.7, found to be also independent of the EOS. We then compare and contrast the quadrupole moment of rotating neutron stars with the one predicted by the Kerr exterior solution for the same values of mass and angular momentum. Finally, we show that, although the mass quadrupole moment of realistic neutron stars never reaches the Kerr value, the latter is closely approached from above at the maximum mass value, as physically expected from the no-hair theorem. In particular, the stiffer the EOS, the closer the mass quadrupole moment approaches the value of the Kerr solution.

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

Mathematical modeling of gap junction coupling and electrical activity in human β-cells.


Coordinated insulin secretion is controlled by electrical coupling of pancreatic β-cells due to connexin-36 gap junctions. Gap junction coupling not only synchronizes the heterogeneous β-cell population, but can also modify the electrical behavior of the cells. These phenomena have been widely studied with mathematical models based on data from mouse β-cells. However, it is now known that human β-cell electrophysiology shows important differences to its rodent counterpart, and although human pancreatic islets express connexin-36 and show evidence of β-cell coupling, these aspects have been little investigated in human β-cells. Here we investigate theoretically, the gap junction coupling strength required for synchronizing electrical activity in a small cluster of cells simulated with a recent mathematical model of human β-cell electrophysiology. We find a lower limit for the coupling strength of approximately 20 pS (i.e., normalized to cell size, ~2 pS pm-1) below which spiking electrical activity is asynchronous. To confront this theoretical lower bound with data, we use our model to estimate from an experimental patch clamp recording that the coupling strength is approximately 100–200 pS (10–20 pS pm-1), similar to previous estimates in mouse β-cells. We then investigate the role of gap junction coupling in synchronizing and modifying other forms of electrical activity in human β-cell clusters. We find that electrical coupling can prolong the period of rapid bursting electrical activity, and synchronize metabolically driven slow bursting, in particular when the metabolic oscillators are in phase. Our results show that realistic coupling conductances are sufficient to promote synchrony in small clusters of human β-cells as observed experimentally, and provide motivation for further detailed studies of electrical coupling in human pancreatic islets.

Cipolletta F., Cherubini C., Filippi S., Loppini A., Ruffini R.

Role of topology in complex functional networks of beta cells.


The activity of pancreatic β cells can be discussed with realistic nuclear matter equations of state. We compute, in particular, the gravitational mass bound for the pulsar, Mmin = [1.2–1.4]M☉ for the EOS employed. Moreover, we give a fitting formula relating the baryonic mass (Mb) and gravitational mass of nonrotating neutron stars, Mb/MO = M/MO + (13/20)(M/MO)2 [or M/MO = Mb/M–(1/2)(Mb/M)2], which is independent of the EOS. We also obtain a fitting formula, although not EOS independent, relating the gravitational mass and the angular momentum of neutron stars along the secular axisymmetric instability line for each EOS. We compute the maximum value of the dimensionless angular momentum, a/MoJ/GM2 (or “Kerr parameter”), (a/MoJ)max = 0.7, found to be also independent of the EOS. We then compare and contrast the quadrupole moment of rotating neutron stars with the one predicted by the Kerr exterior solution for the same values of mass and angular momentum. Finally, we show that, although the mass quadrupole moment of realistic neutron stars never reaches the Kerr value, the latter is closely approached from above at the maximum mass value, as physically expected from the no-hair theorem. In particular, the stiffer the EOS, the closer the mass quadrupole moment approaches the value of the Kerr solution.
NURSING SCIENCE

Head:  
M.G. De Marinis

Faculty: M. Matarese, D. Tartaglini  
Other Personnel: M. Piredda

The Unit is interested in clinical, pedagogical and organizational areas and uses quantitative and qualitative methods. Clinical areas include mainly palliative care, geriatric and cancer nursing. Palliative care topics include nursing care dependence, pressure ulcers and care for adolescents who lose a parent. Geriatric topics include self-care (of elderly living at home and of elderly with chronic diseases), nutrition and quality of life. Cancer nursing topics include prevention of chemo-induced oral mucositis; nursing care dependence, information about ports, decisional conflict. Pedagogical topics focus on involvement of stakeholders in nursing education, hidden curriculum in nursing education, predictors of academic success in nursing degrees. Organizational topics include care complexity, nursing documentation and prevention of errors during administration of intravenous therapy in critical care. A key focus is the 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

Other ongoing research projects funded by the Alberto Sordi Foundation are the following:
- The concept of Self-care for home-dwelling older people
- Self-care for the promotion of nutrition of older people
Most important publications


Objectives: To identify, critically appraise and synthesize qualitative evidence of self-care experiences in health promotion for home-dwelling elders. Design: A meta-synthesis was conducted following the Joanna Briggs Institute guidelines and using Qualitative Assessment and Review Instrument Software. Data sources: The literature search was conducted on PubMed, CINAHL, Embase, Psycinfo, Eric and ILISI databases from inception up until March 2015. Other articles were searched on Scopus and Web of Knowledge. The reference list of all the identified articles was also searched for additional studies. Studies published in English, Italian, French, Portuguese, and Spanish were considered for inclusion in the review. Review methods: Data from the selected qualitative articles were extracted independently by two reviewers using the data extraction tool of the Joanna Briggs Institute-Qualitative Assessment and Review Instrument. The meta-synthesis involved the following three steps: the production of a set of statements representing the aggregated data obtained by assembling the findings of qualitative studies; the categorization of findings on the basis of similarity in meaning; and the aggregation of these categories to produce a comprehensive set of synthesized findings. No studies were excluded due to methodological quality. Results: Of the 4001 records identified, 11 articles met the inclusion criteria. Most articles were conducted in Scandinavian countries and used a phenomenological design. Most elders in the sample were middle-class, cognitively intact, independent, and in good health. The meta-synthesis revealed that older people living at home make decisions about their self-care activities on the basis of their attitudes toward their life and future. These self-care activities are directed toward holistic wellness, prevention and treatment of aging effects, obtaining a sense of satisfaction, and self-realization. Furthermore, self-care activities are settled in a social and relational network that allows old people to take care of themselves and of others or to be cared for by others. Conclusions: This meta-synthesis presents the perspectives of home-dwelling old people on health-promoting self-care experiences. Such information can help healthcare professionals to maintain long-term autonomy of elders in self-care and to promote healthy aging. Further qualitative research describing self-care experiences of home-dwelling elders from different cultures, education levels, and social backgrounds is needed.


Aims: To determine the most accurate fall risk screening tools for predicting falls among patients aged 65 years or older admitted to acute care hospitals. Background: Falls represent a serious problem in older inpatients due to the potential physical, social, psychological and economic consequences. Older inpatients present with risk factors associated with age-related physiological and psychological changes as well as multiple morbidities. Thus, fall risk screening tools for older adults should include these specific risk factors. There are no published recommendations addressing what tools are appropriate for older hospitalized adults. Design: Systematic review. Data sources, MEDLINE, CINAHL and Cochrane electronic databases were searched between January 1981–April 2013. Only prospective validation studies reporting sensitivity and specificity values were included. Review methods: Recommendations of the Cochrane Handbook of Diagnostic Test Accuracy Reviews have been followed. Results: Three fall risk assessment tools were evaluated in seven articles. Due to the limited number of studies, meta-analysis was carried out only for the STRATIFY and Hendrich Fall Risk Model II. In the combined analysis, the Hendrich Fall Risk Model II demonstrated higher sensitivity than STRATIFY, while the STRATIFY showed higher specificity. In both tools, the Youden index showed low prognostic accuracy. Conclusion: The identified tools do not demonstrate predictive values as high as needed for identifying older inpatients at risk for falls. For this reason, no tool can be recommended for fall detection. More research is needed to evaluate fall risk screening tools for older inpatients.


Purpose: Care dependence can be associated with suffering and humiliation. Nurses’ awareness of patients’ perception of care dependence is crucial to enable them in helping the dependent persons. This study aimed to describe adult patients’ experience of nursing care dependence. Method: A metasynthesis was conducted to integrate qualitative findings from 18 studies published through December 2014 on adult patients’ experiences of care dependency. Procedures included the Joanna Briggs Institute approach for data extraction, quality appraisal, and integration of findings. Findings: The experience of dependence revealed the concept of the embodied person, particularly in relation to care of the physical body. The relationship between the individual and nurses within the context of care had a major impact for dependent patients. When the care relation was perceived as positive, the experience led to the development of the person in finding new balances in life, but when it was perceived as negative, it increased patient’s suffering. Conclusions: Care dependence is manifested mostly as bodily dependence and is consistent with its relational nature. The nurse–patient relationship is important to the dependent patients’ experience. Clinical Relevance: A greater understanding of patients’ experiences of dependence is crucial to enable nurses in improving care and decreasing patient suffering.
The research field of Oncological Science involves several clinical and non-clinical groups belonging to the Campus Bio-Medico University of Rome. The main research areas are the following: translational and clinical research in osteoncology, study of the molecular and cellular mechanisms associated with tumor progression and identification of new biomarkers for diagnosis, prognosis and prediction of response to anticancer treatments.

**Translational and clinical research in osteoncology**
- Preneoplastic niche: identification of novel cellular and molecular targets for the treatment of solid tumors
- Identification of molecular predictive targets of bone metastases onset in breast and prostate cancer
- Study of new therapies targeting the androgen pathway: evaluation of their antitumoral activity and their effect on the bone microenvironment

**Study of the molecular and cellular mechanisms associated with tumor progression**
- Development of microfluidic platforms (cells-on-chip) to analyze the cross-talk between tumors and the immune system and the mechanisms of tumor resistance and tumor immunoediting (in collaboration with Tissue Engineering Research Unit)
- Study the interplay between cancer stem cells (CSC) and tumor associated macrophages as the cause of CSC high chemo-resistance in order to develop novel improved therapeutic approaches for breast and non small cell lung cancer
- Development of a coculture of tumor cells and immune system cells (derived from patients), for a new in vitro model to evaluate the efficacy of immunotherapies (immune checkpoint inhibitors)
- Translational oncological studies focused on the evaluation of angiogenesis, apoptosis and the cell cycle regarding tumor onset and progression (pancreatic and ampullary carcinoma, colorectal cancer, breast, lung and soft tissue cancers)

**Identification of new biomarkers for diagnosis, prognosis and prediction of response to anticancer treatments**
- Identification of new biomarkers involved in tumor progression and resistance to anticancer treatments in patients affected by soft tissue sarcomas
- Identification of disseminated tumor cells in the bone marrow and circulating tumor cells in the peripheral blood of patients affected by epithelial tumors
- Identification of new biomarkers and new endocrine and biological treatment schedules in breast cancer
- Clinical studies on the management of chronic and breakthrough pain: role of early palliative and supportive care
were randomly assigned. At a median 17, 2008, and May 31, 2011, 508 patients NCT00719797. FINDINGS: Between July with ClinicalTrials.gov, number on Nov 30, 2014. The trial is registered intention to treat. TRIBE was concluded lecular subgroups. All analyses were by treatment efficacy in RAS and BRAF mo-

overall survival in the main cohort and we assessed the secondary endpoint of

mg/m(2) continuous infusion of fluorouracil given concurrently with 200 mg/m(2) leu-
mg/m(2) intravenous infusion of oxaliplatin irinotecan for 60 min, followed by an 85

of a 165 mg/m(2) intravenous infusion of fluorouracil for 46 h. FOLFOXIRI consisted and a 2400 mg/m(2) continuous infusion min followed by a 200 mg/m(2) intravenous

FOLFOXIRI plus bevacizumab. Bevacizumab to receive FOLFIRI plus bevacizumab or cancer who were recruited from 34 Italian oncology units. Patients were randomly assigned (1:1) via a web-based procedure to receive FOLFIRI plus bevacizumab or FOLFOXIRI plus bevacizumab. Bevacizumab was given as a 5 mg/kg intravenous dose. FOLFIRI consisted of a 180 mg/m(2) intravenous infusion of irinotecan for 60 min followed by a 200 mg/m(2) intravenous infusion of leucovorin for 120 min, a 400 mg/m(2) intravenous bolus of fluorouracil, and a 2400 mg/m(2) continuous infusion of fluorouracil for 46 h. FOLFOXIRI consisted of a 165 mg/m(2) intravenous infusion of irinotecan for 60 min, followed by an 85 mg/m(2) intravenous infusion of oxaliplatin given concurrently with 200 mg/m(2) leu-
covorin for 120 min, followed by a 3200 mg/m(2) continuous infusion of fluorouracil for 48 h. Tissue samples for RAS and BRAF mutational status analyses were centrally collected. In this updated analysis, we assessed the secondary endpoint of overall survival in the main cohort and treatment efficacy in RAS and BRAF mo-

molecular subgroups. All analyses were by intention to treat. TRIBE was concluded on Nov 30, 2014. The trial is registered with ClinicalTrials.gov, number NCT00719797. FINDINGS: Between July 17, 2008, and May 31, 2011, 508 patients were randomly assigned. At a median follow-up of 48-1 months (IQR 41-7-55-6), median overall survival was 29-8 months (95% CI 26-0-34-3) in the FOLFIRI plus bevacizumab group compared with 25-8 months (22-6-29-1) in the FOL-

FOXIRI plus bevacizumab group (hazard ratio [HR] 1-49, 95% CI 1-11-1-99) and 13-4 months (8-2-24-1) in the BRAF-mutation-positive subgroup (HR 2-79, 95% CI 1-75-4-46; likelihood-ratio test p < 0.0001). Treatment effect was not significantly different across mo-
molecular subgroups (interaction = 0-52).

Vincenzi B., Cremolini C., Sar-
tore-Bianchi A., Russo A., Man-
navola F., Perrone G., Pantano F., Loupakis F., Ros-
sini D., Ongaro E., Bonazzina E., Delli’Aquila E., Impe-
rатори M., Zoccoli A., Bronte G., De Magli
go G., Fontanini G., Natoli C., Falcone A., Santini D., Onetti-Muda A., Siena S., To-
nini G., Aprile G.

Prognostic significance of K-
Ras mutation rate in meta-
tastatic colorectal cancer pa-
tients.


Introduction: Activating mutations of K-
Ras gene have a well-established role as predictors of resistance to anti-EGFR mo-
noclonal antibodies in metastatic colorectal cancer (mCRC) patients. Their prognostic value is controversial, and no data regarding the prognostic value of mutation rate, defined as the percentage of mutated al-
leles/tumor sample, are available. We aimed to evaluate the prognostic value of K-Ras mutation rate in a homogenous co-
hort of mCRC patients receiving first-line dou-
belet plus bevacizumab. Patients and Methods: This retrospective study enrolled 397 K-Ras mutant mCRC patients from 6 Italian centers, and 263 patients were fully evalua-
table for our analysis. K-Ras mutation rate was assessed by pyrose-
quencing. Patients with less than 60% of cancer cells in tumor tissue were excluded. No patients received anti-EGFR containing anticanicancer therapy, at any time. Median mutation rate was 40% and was adopted as cut-off. The primary and secondary endpoints were PFS and OS respectively.

RESULTS: At univariate analysis, K-Ras mutation rate higher than 40% was si-
ificantly associated with lower PFS (7.3 vs 9.1 months; P < 0.0001) and OS (21 vs 31 months; P = 0.004). A multivariate model adjusted for age at diagnosis, site of origin of tumor tissue (primary vs me-
tastases), referral center, number of me-
tastatic sites, and first-line chemotherapy backbone, showed that K-Ras mutation rate remained a significant predictor of PFS and OS in the whole population.

Iuliani M., Pantano F., Butti-
giiero C., Fioramonti M., Ber-
taglia V., Vincenzi B., Zoccoli A., Ribelli G., Tucci M., Vignani F., Berruti A., Scagliotti G.V., Tonini G., Santini D.

Biological and clinical effects of abiraterone acetate in bone microenvironment.


Abiraterone acetate (ABI) is associated not only with a significant survival ad-

dvantage in both chemotherapy-naive and mCRC patients with metastatic castra-
tion-resistant prostate cancer (mCRPC), but also with a delay in time to develop-
mement of Skeletal Related Events and in radiological skeletal progression. These bone benefits may be related to a direct effect on prostate cancer cells in bone or to a specific mechanism directed to bone microenvironment. To test this hy-
pothesis we designed an in vitro study aimed at evaluating a potential direct effect of ABI on human primary osteoclasts/os-
teoblasts (OCLs/OCBu). We also assessed changes in bone turnover markers, serum carboxy-terminal collagen crosslinks (CTX) and alkaline phosphatase (ALP), in 49 mCRC patients treated with ABI. Our re-
sults showed that non-cytotoxic doses of ABI have a statistically significant inhi-
bitory effect on OCL differentiation and activity inducing a down-modulation of OCL marker genes TRAP, cathepsin K and metalloproteinase-9. Furthermore ABI promoted OCL differentiation and bone matrix deposition up-regulating OCL specific genes, ALP and osteocalcin. Finally, we observed a significant decrease of serum CTX values and an increase of ALP in ABI-treated patients. These findings suggest a novel biological mechanism of action of ABI consisting in a direct bone anabolic and anti-resorptive activity.
OPHTHALMOLOGY

Head:
S. Bonini

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.

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. The activities of diagnosis is focused on severe ophthalmological pathologies.
Sex hormones in allergic conjunctivitis: altered levels of circulating androgens and estrogens in children and adolescents with vernal keratoconjunctivitis.


Purpose: Vernal keratoconjunctivitis (VKC) is a chronic allergic disease mainly affecting boys in prepubertal age and usually recovering after puberty. To evaluate a possible role of sex hormones in VKC, serum levels of sex hormones in children and adolescents with VKC were assessed.

Methods: 12 prepubertal and 7 early pubertal boys with active VKC and 6 male patients with VKC in remission phase at late pubertal age and 48 healthy age and sex-matched subjects were included. Serum concentration of estrone, 17 beta-estradiol, dehydroepiandrosterone-sulfate, total testosterone and free testosterone, dihydrotestosterone (DHT), cortisol, delta-4-androstenedione, follicle-stimulating hormone, luteinizing hormone, and sex-hormones binding globuline (SHBG) were evaluated.

Results: Serum levels of Estrone were significantly increased in all groups of patients with VKC when compared to healthy controls (P < 0.001). Prepubertal and early pubertal VKC showed a significant decrease in DHT (P = 0.007 and P = 0.028, resp.) and SHBG (P = 0.01 and P = 0.002, resp.) when compared to controls and serum levels of SHBG were increased in late pubertal VKC in remission phase (P = 0.007). Conclusions AND RELEVANCE: VKC patients have different circulating sex hormone levels in different phases of the disease and when compared to nonallergic subjects. These findings suggest a role played by sex hormones in the pathogenesis and/or activity of VKC.

Preliminary evidence of neuropeptides involvement in keratoconus.


In vivo corneal confocal microscopy as a novel non-invasive tool to investigate cardiac autonomic neuropathy in Type 1 diabetes.


Aims: To investigate whether small nerve fibre degeneration detected using corneal confocal microscopy is associated with cardiac autonomic neuropathy in people with Type 1 diabetes.

Methods: Thirty-six people with Type 1 diabetes and 20 age- and sex-matched healthy control subjects were enrolled. Tests to determine heart rate response to deep-breathing (expiratory-to-inspiratory ratio), heart rate response to lying-to-standing test (30:15 ratio) and blood pressure response to standing were performed to detect cardiac autonomic neuropathy. Corneal confocal microscopy was performed to assess: corneal nerve density and corneal nerve beading; branching pattern; and nerve fibre tortuosity.

Results: Compared with control participants, participants with Type 1 diabetes had fewer (mean ± SD 45.4 ± 20.2 vs 92.0 ± 22.7 fibres/mm²; P < 0.001) and more tortuous corneal nerve fibres (20 participants with Type 1 diabetes vs four control participants had nerve tortuosity grade 2/3; P = 0.022) and fewer beading (mean ± SD 15.1 ± 3.5 vs 20.6 ± 5.0; P < 0.001). Of the participants with Type 1 diabetes, 11 met the criteria for the diagnosis of cardiac autonomic neuropathy. Corneal nerve density was significantly lower in participants with cardiac autonomic neuropathy than in those without (mean ± SD 32.8 ± 16.4 vs 51.7 ± 18.9 fibres/mm²; P = 0.008). This difference remained significant after adjustment for age (P = 0.02), gender (P = 0.04), disease duration (P = 0.005), insulin requirement (P = 0.02) and neuropathy disability score (P = 0.04). Conclusion: This study suggests that corneal confocal microscopy could represent a novel and non-invasive tool to investigate cardiac autonomic neuropathy in people with Type 1 diabetes. Larger studies are required to define the role of corneal confocal microscopy in the assessment of cardiac autonomic neuropathy.
ORTHOPAEDIC AND TRAUMA SURGERY

Head:
R. Papalia

Faculty: F. Franceschi, U.G. Longo, A. Marinozzi


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 age 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 are carried out at the Animal Facility of Tor Vergata University of Rome and in collaboration with the Veterinary Hospital at University of Padua for several years.

- Stem cell applications in intervertebral disc regeneration and the acceleration of spinal column healing processes (arthrodesis)
- Development of smart surgical platform for spine surgery
- Clinical applications of platelet rich plasma for the treatment of degenerative and traumatic musculoskeletal diseases
- Endothelial dysfunction in musculoskeletal disorders
- Surgical applications of invasive neural interfaces for bidirectional communication between robotic superior limb prostheses and biological systems
- New biocompatible materials for bone and cartilage regeneration
- Degenerative tendon alterations following post-traumatic pathologies

- Research Units of Biomedical Robotics and Biomicrosystems; Microscopic and Ultrastructural Anatomy; Tissue Engineering and Chemistry for Engineering; Neurology, Neurophysiology, Neurobiology; Vascular Surgery
- Centre for Sports and Exercise Medicine, Mile End Hospital, Barts and The London, United Kingdom
- Bambino Gesù Italian Paediatric Research Hospital, Rome
- Department of Neurosurgery, University of Padua, Padua, Italy
- University of Pittsburgh Medical Center (UPMC), Pittsburgh, USA
- AO Research Institute, Davos, Switzerland
- Mayo Clinic, Biomechanics Laboratory and Department of Orthopedics, Rochester, MN, USA
- Beth Israel Deaconess Medical Center, Center for Advanced Orthopedic Studies, USA
Harvard Medical School teaching hospital, Boston, MA, USA
- Sports Medicine and Shoulder Service, Departement Of Motion Analysis Hospital for Special Surgery, New York, USA
- Clinica do Dragão - Espregueira-Mendes Sports Centre, FIFA Medical Centre of Excellence, FC Porto Stadium
- Duke University, Division of Sports Medicine Duke, Sports Medicine Center, Durham, NC

Most important publications


Purpose: Spinal cord back shift has been considered the desired end point of posterior decompression procedures for cervical spondylotic myelopathy (CSM). However, the association with postoperative outcomes has not been definitively demonstrated. The aim of this review is to obtain an overview of the current knowledge on the spinal back shift after posterior decompression to clarify the main controversial aspects and provide recommendations for further studies on the subject. Methods: A comprehensive quantitative review of the literature was performed. Bibliographic databases were searched using the following keywords: spinal cord drift, spinal cord shift, CSM, ossification of posterior longitudinal ligament, posterior decompression, lamina-plasty, laminectomy and fusion. Results: Twelve eligible studies were included. The authors measured the spinal cord back shift in different ways, using the posterior edge, the center or the anterior margin of the spinal cord as reference points. Six studies analyzed the correlation between the spinal cord back shift and the recovery rate, but their results were discordant. The correlation between the posterior cord migration and cervical alignment was not confirmed in all studies. Conclusions: There is a need for a consensus on the best way to measure the spinal cord back shift. The action of multiple factors on spinal cord back shift can explain the difference in the results collected from the studies. We recommend further studies to clarify the behavior of the spinal cord after posterior decompression and its clinical meaning.


Purpose: To assess whether the portions of the semitendinosus and gracilis tendons harvested for anterior cruciate ligament reconstruction have the potential to regenerate and, if so, to evaluate the histologic properties and actual function of this newly formed tissue. Methods: We performed a comprehensive search of CINAHL (Cumulative Index to Nursing and Allied Health Literature), Embase, Medline, the Cochrane Central Registry of Controlled Trials, and SPORTDiscus from inception of the databases to July 2014, using various combinations of keywords. Studies focusing on hamstring tendon and muscle regeneration through imaging and histology, as well as on the related functional outcomes, were selected. We included studies assessing evidence of tissue regeneration with imaging (magnetic resonance imaging, 3-dimensional computed tomography, ultrasonography) or with histologic examination of biopsy samples (or a combination thereof). Results: Nineteen articles were included in this review, with a total of 400 patients observed. The overall rate of tissue regeneration was 86.0%, with similar values shown in most studies regardless of the methodology of the assessment. Biopsy confirmed that the tissue found at the site in 74% of the cases showed typical histologic features of the tendon. The mean modified Coleman Methodology Score of the studies included was 52.7 points, showing a modest methodologic quality for the studies published to date. Conclusions: In over 85% of the cases analyzed, regeneration signs of the harvested tendon were found through different imaging and histologic methodologies. A torque deficit in deep knee flexion is always present postoperatively, but the cause for this is still unclear. There is a need for better-designed trials featuring a higher level of evidence to further investigate this matter, and the effects of postoperative care and the surgical approach used on the regeneration process should be analyzed in the future.


The aim of this study was to compare different methods to create a cavity into ovine nucleus pulposus (NP) by enzymatic digestion (E), mechanical nucleotomy (N), or a combining technique (E+N), as a model to study NP regeneration strategies with intact annulus fibrosus (AF) in functional spinal units (FSU) in vitro. Methods: The transpedicular approach via the endplate route (2 mm tunnel) was performed on ovine FSU (IVD and superior and inferior endplate) to access the NP. FSUs were treated by N (Arthroscopic shaver), E (Trypsin/ Collagenase), or E+N. Treatments were evaluated macro- and microscopically. The degradation of proteoglycan (PG) around the cavity was assessed by gel electrophoresis. Cell viability was evaluated using the lactate dehydrogenase (LDH) assay. Conclusions: Mechanical nucleotomy leads to a more reproducible and less destructive cavity in the NP. Enzymatic methods perform better in terms of cavity volume; however, the cells and PG of the surrounding tissue may be affected. The mechanical nucleotomy enables the creation of a cavity into the IVD while keeping the AF intact, allowing the injection of reproducible volumes of hydrogel and tissue engineering construct for preclinical tests.
Objective: Nerve growth factor (NGF) is a neurotrophin which promote and regulate the survival of neurons in the peripheral nervous system. We aimed to evaluate the nasal NGF expressions of mast cells in healthy patients after stimulation with sterilized isotonic solution delivered at high pressure. Patients and Methods: The first part of the study was made with 21 voluntary individuals. The middle third of the inferior turbinate epithelial cells on the right nostril was scraped using a sterile curette and indicated
as (pre), than a spray of sterilized isotonic solution at high pressure on the left nostril was delivered and 25 minutes later a similar stimulation was delivered on the same nostril. The stimulation was made with a specific spray. The middle third of the inferior turbinate epithelial cells on the left nostril was scraped using a sterile curette and indicated as (post), RESULTS: Forced nasal stress induced by local delivery of high pressure physiological solution causes an increase in the number of mast cells and enhances level of NGF in the nasal fluid compared to the control subjects. So based on the first part of our study, since NGF is universally known as effective in protection and repairing of neural cells damage, we started the second part and gave a treatment on the same patients, to increase NGF levels with a six months daily therapy and observed the variations in Sensorineural Hearing Loss (SNHL) and tinnitus intensity from the beginning to the end of the therapy. All patients received sterilized isotonic solution at high pressure (pression emission level: PEL): 7 g/sec for 0.5 sec (emission time: ET) in both nostrils. 25 minutes later a similar stimulation was delivered twice a day. The control group (21 pts) received normal therapy with betahistine dihydrochloride 16 mg twice a day. Conclusions: Upon acuphenometry, there was a lower intensity of tinnitus and the improvement was signaled by the patients. Patients with SNHL treated with conventional therapy had a slight worsening, while the patients treated with our new therapy which increased NGF levels, showed improvement of hearing. This new therapy represents a new therapy of SNHL, tinnitus and hearing disorders.

Casale M., Moffa A., Sabatino L., Pace A., Oliveto G., Vitali M., Baptista P., Salvinelli F.


Background: To date, topical therapies guarantee a better delivery of high concentrations of pharmacologic agents to the mucosa of the upper aerodigestive tract (UADT). The use of topical drugs, which are able to reduce mucosal inflammation and to improve healing tissues, can represent a relevant therapeutic advance. Topical sodium hyaluronate (SH) has recently been recognized as adjuvant treatment in the chronic inflammatory disease of the UADT. Aims: The aim of our work was to review the published literature regarding all the potential therapeutic effects of SH in the chronic inflammatory disease of UADT. Methods: Relevant published studies were searched in Pubmed, Google Scholar, Ovid using keywords (“sodium hyaluronate” and “upper airways”) or Medical Subject Headings. Results: At the end of our selection process, sixteen publications have been included. Six of them in the postoperative phase of nasal-sinus surgery, 2 of them in pediatric patients affected by recurrent upper respiratory tract infections, 4 of them in reducing symptoms and preventing exacerbations of chronic upper airways in adult population, 4 of them in patients with chronic inflammatory disease of UADT including gastro-esophageal reflux disease (GERD). Conclusion: Topical administration of SH plays a pivotal role in the postoperative phase of patients undergoing FESS and nasal surgery, and positive results are generally observed in all the patients suffering from UADT chronic inflammatory disease.

Salvinelli F., Frari V., Rocco ML., d’Eramo A., Salvinelli E., Salvinelli B., Aloe L.

High-pressure physiological saline isotonic solution administration enhances brain NGF and NGF-receptors expression.

Objective: Nerve growth factor (NGF) is a neurotrophic which promotes and regulates the survival of neurons in the peripheral nervous system. The aim of this study was to investigate the effect of high-pressure administration of sterile physiological saline isotonic solution (HpPSIS) into nasal cavity of laboratory animals on NGF levels and NGF-receptor expression in the olfactory bulbs and brain. Materials and methods: For this study we used three weeks old female Sprague Dawley SD rats (n=48). Rats were divided into two groups, the first one treated delivering physiological saline solution with a normal syringe modified at the extremity to fit the rats’ nostril (5 ml) (n=24) and the second one treated spray with HpPSIS (n=24 rats). Rats were treated three times a day either for 5 consecutive days (short term treatment) or 10 consecutive days (longer treatment) in both nostrils of HpPSIS delivered at high pressure (pression emission level: PEL: 7 g/sec for emission time ET: 0.5 sec) with a specific forced spray ergatorium. Untreated rats received a similar manipulation three times a day through a syringe in the nostrils, but no HpPSIS administration. Results: The results of these studies highlight the possibility that endogenous enhancement of NGF by stimulation of NGF-producing cells within the nasal cavities and also in the CNS represent a novel experimental approach to enhance the brain NGF levels with a new therapy. HpPSIS treatment further enhances the presence of NGF in the four brains examined. Indeed, a significant increase of NGF was first observed after 5 days of HpPSIS treatment, compared to HpPSIS untreated rats. The increase was over 25% in the OB, ST, HI and in CX, while 10 days after HpPSIS treatments the levels of NGF were even higher. These differences were statistically significant, p < 0.05. Conclusions: It was found that forced administration of HpPSIS enhances the presence of these neurotrophic signals, not only in the olfactory bulbs, but also in forebrain cholinergic neurons, which are known to degenerate as result of memory loss and brain aging, including Alzheimer Disease. These findings for the first time in the literature demonstrate the possibility of enhancing the endogenous NGF to protect NGF-damaged neurons. Since the enhanced expression of NGF was first observed after 5 days of treatment and higher after 10 days of treatment, a reasonable hypothesis is that longer HpPSIS treatment might further enhance the level of NGF in brain and olfactory bulbs.
The Pathology Research Unit 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.

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 periampullary neoplasms - histological and immunohistochemical subtyping; multicenter standardization of resection margins status; validation of pre-operative molecular analysis as an additional diagnostic tool for cancer
- Morphologic bone changes related to metabolic diseases.

Funded projects:
- Clinical trial PAM50 PROSIGNA- Principal Investigator: Perrone; Funded by Banca d'Italia
- Concordance value between PAM50 and immunohistochemical evaluation of KI-67 - Principal Investigator: Perrone; Funded by TCI Telecomunicazioni
- Bone strength and WNT signalling in obese patients – Research Collaborator: Rabitti. Funded by Institutional Grant

- Harvard University School of Medicine, Dept. of Pathology - Boston, USA
- Hôpital Necker, INSERM U574 - Paris, France
- Bambino Gesù Hospital, Pathologic Anatomy, IRCCS - Rome, Italy
hERG1 channels drive tumour malignancy and may serve as prognostic factor in pancreatic ductal adenocarcinoma.

VespaSiani-Gentiucci U., Carritti S., Perrone G., Mazzarelli C., Galati G., Onetti-Muda A., Picardi A., Morini S. Hepatic toll-like receptor 4 expression is associated with portal inflammation and fibrosis in patients with NAFLD.


Notwithstanding evidences implicating the lipopolysaccharides (LPS)/toll-like receptor-4 (TLR4) axis in the pathogenesis of NAFLD, there are no studies aimed to characterize hepatic TLR4 expression in NAFLD patients. We aimed to analyse hepatic TLR4 expression and to verify its relationship with disease activity/evolution in NAFLD patients.

Liver tissue from 74 patients with NAFLD and 12 controls was analysed by immunohistochemistry using an anti-hERG1 monoclonal antibody (-hERG1-MoAb). The functional role of hERG1 was studied in PDAC cell lines and primary cultures. ERG1 expression during PDAC progression was studied in Pdx-1-Cre,LSL-Trp53(R175H+/+) transgenic (KPC) mice. ERG1 expression in vivo was determined by optical imaging using Alexa-680-labelled -hERG1-MoAb. hERG1 was expressed at high levels in 59% of primary PDAC. hERG1 blockade decreased PDAC cell growth and migration; hERG1 was physically and functionally linked to the Epidermal Growth Factor-Receptor pathway; in transgenic mice, ERG1 was expressed in PanIN lesions, reaching high expression levels in PDAC. PDAC patients whose primary tumour showed high hERG1 expression had a worse prognosis; the -hERG1-MoAb could detect PDAC in vivo. hERG1 regulates PDAC malignancy and its expression, once validated in a larger cohort also comprising of late-stage, non-surgically resected cases, may be exploited for diagnostic and prognostic purposes in PDAC either ex vivo or in vivo.

VespaSiani-Gentiucci U., Carritti S., Perrone G., Mazzarelli C., Galati G., Onetti-Muda A., Picardi A., Morini S. Hepatic toll-like receptor 4 expression is associated with portal inflammation and fibrosis in patients with NAFLD.


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PHYSICAL AND REHABILITATION MEDICINE

Head:
S. Sterzi

Other Personnel: V.M. Bravi, F. Bressi, S. Miccinilli, M. Morrone, F. Santacaterina

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.

- 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
- 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

- Engineering, Neurology and Geriatric Units of the University Hospital
- Thoracic Surgery Unit of the University Hospital A. Gemelli of Rome
- Burke Hospital (New York-USA)
- San Raffaele Foundation IRCCS of Rome
- Santa Lucia Foundation IRCCS of Rome
- Pediatric Hospital Bambino Gesù, Palidoro, Rome
- INAIL prosthesis center
Comparative analysis and quantitative evaluation of ankle-foot orthoses for foot drop in chronic hemiparetic patients.

Background: Ankle-foot-orthoses (AFOs) are frequently prescribed for hemiparetic patients to compensate for the foot drop syndrome. However, there is not a systematic study either on the effectiveness of AFOs in the gait recovery process or pointing out the therapeutic differences among the various types of AFOs available on the market. Aim: To perform a comparative evaluation of solid and dynamic Ankle-Foot Orthoses (AFOs) on hemiparetic patients affected by foot drop syndrome by means of spatio-temporal, kinematic and electromyographic indicators.

Design: Crossover design with randomization for the interventions. Setting: A rehabilitation center for adults with neurologic disorders. Population: Ten chronic hemiparetic patients with foot drop syndrome met inclusion criteria and volunteered to participate. Methods: biomechanical gait analysis was carried out on hemiparetic subjects with foot drop syndrome under 3 conditions with randomized sequences: 1) without AFO; 2) wearing a solid AFO; 3) wearing a dynamic AFO. Significant changes in spatio-temporal, kinematic and electromyographic features of gait were investigated. Results: Gait analysis outcomes showed that there were no significant differences among the solid and the dynamic AFO on the spatio-temporal parameters. Both AFOs led to a reduction of the range of motion of the ankle dorsi-planter-flexion during stance with respect to the ambulation without AFO. They also had the effect of reducing the asymmetry between the paretic and the contralateral limb in terms of ankle angle at initial contact and hip flexion. The solid AFO generally led to an increase of the co-contraction of the couples of muscles involved in the gait. Conclusion: The proposed set of indicators showed that the AFOs were capable of limiting the effect of the foot-drop in hemiparetic patients and balancing the two limbs. Main differences between the two orthoses were related to muscular activity, being the level of co-contraction of the couples of analysed muscles typically lower when the dynamic AFO was worn and closer to a normal pattern. Clinical rehabilitation impact: A more extensive use of the proposed indicators in the clinical practice is expected in order to enable the definition of clinical guidelines for the prescription of the two devices.

Upper-limb kinematic reconstruction during stroke robot-aided therapy.

The paper proposes a novel method for an accurate and unobtrusive reconstruction of the upper-limb kinematics of stroke patients during robot-aided rehabilitation tasks with end-effector machines. The method is based on a robust analytic procedure for inverse kinematics that simply uses, in addition to hand pose data provided by the robot, upper arm acceleration measurements for computing a constraint on elbow position; it is exploited for task space augmentation. The proposed method can enable in-depth comprehension of planning strategy of stroke patients in the joint space and, consequently, allow developing therapies tailored for their residual motor capabilities. The experimental validation has a twofold purpose: (1) a comparative analysis with an optoelectronic motion capturing system is used to assess the method capability to reconstruct joint motion; (2) the application of the method to healthy and stroke subjects during circle-drawing tasks with InMotion2 robot is used to evaluate its efficacy in discriminating stroke from healthy behavior. The experimental results have shown that arm angles are reconstructed with a RMSE of 8.3 x 10(-3) rad. Moreover, the comparison between healthy and stroke subjects has revealed different features in the joint space in terms of mean values and standard deviations, which also allow assessing inter- and intra-subject variability. The findings of this study contribute to the investigation of motor performance in the joint space and Cartesian space of stroke patients undergoing robot-aided therapy, thus allowing: (1) evaluating the outcomes of the therapeutic approach, (2) re-planning the robotic treatment based on patient needs, and (3) understanding pathology-related motor strategies.
PLASTIC SURGERY AND DERMATOLOGY

Head:
P. Persichetti

Faculty: C. Dianzani, S. Tenna
Other Personnel: B. Brunetti, B. Cagli, A. Cogliandro, G.F. Marangi, V. Panasiti, P. Simone

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 acne scars
- Lasers treatment of: hemangiomas - scars - cutaneous lesions - photoaging - hypertrichosis

- 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 liposuction in the post-bariatric arm remodeling
- Platelet-rich plasma in breast implant capsule contracture
- IPL in the treatment of posterior blepharitis

Kansai Medical University Department of Plastic and Reconstructive Surgery - Osaka, Japan
Resurfacing of soft tissue defects consequent to skin cancer, melanoma, or sarcoma excision in different anatomical districts represents a difficult challenge for the plastic surgeon. Classic reconstructive procedures are frequently charged by unsatisfactory results. The introduction of perforator flaps in the clinical practice represented a revolution in the field of reconstructive plastic surgery. The technique further evolved with the introduction of the freestyle concept, allowing one to harvest a skin flap from any region of the body where an appropriate and detectable Doppler signal is present and to resurface soft tissue defects mobilizing the surrounding tissues, which present similar features compared with the recipient site in terms of color and texture, on a consistent vascular source and in a tension-free manner. The authors present their personal approach to the reconstruction of soft tissue defects near the knee, which present a subjective dimension or to a rush toward an ideal objective perfection. Beauty must improve the quality of life in general, in an attempt to surpass the physical and relational problems of the patient. Cosmetic surgery doesn’t have to be reduced to a cosmetic medicine recognized in systematic connection with other medical branches, with which it actively cooperates in the planning, the definition, and the solution of the clinical problem.


Purpose: In this article we revisited the anatomy of the distal perforator of the descending genicular artery (DGA) and report the clinical application of its perforator propeller flap in the reconstruction of soft tissue defects around the knee. Methods: Forty fresh human lower limbs were dissected to redefine the anatomy of the branches of the DGA and their perforators and the anatomical landmarks for clinical applications. Five patients underwent “propeller” distal anteromedial thigh (AMT) flaps based on DGA perforators for the reconstruction of post-traumatic (n = 4) and post-oncologic (n = 1) soft tissue defects occurring near the knee with a size ranging from 4.8 cm x 6.2 cm to 10.5 cm x 18.2 cm. Results: A constant cutaneous perforator of the osteoarticular branch (OAB) of the DGA was found in the distal AMT fossa with a mean caliber of 1.2 ± 0.4 mm. It arose 9.4±±0.1 cm distally to the origin of the OAB and 4.0 ± 0.4 cm above the knee joint. The size of the harvested flaps ranged from 6.0 cm x 7.1 cm to 11.0 cm x 20.1 cm. All the flaps healed uneventfully at a mean period of 7.4 months. All the patients regained full range motion of the knee joint. Conclusion: Our study provided evidence of the vascular supply and the clinical application of the distal AMT flap based on a constant perforator arising from the OAB of the DGA. This flap may be a versatile alternative for the reconstruction of the defects around the knee because of its consistent vascular pedicle, pliability and thinness, adequate retrograde perfusion, and the possible direct suture of the donor site.
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.

- 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
An innovative process scheme for the industrial production of pure hydrogen through natural gas steam reforming reaction is proposed and assessed. The configuration, called CO2 Capture Reformer and Membrane Module (CC-RMM), is composed by a series of n reactor-separation unit modules, where the H2 production is supported and the hydrogen stream is separated by means of Pd-based dense selective membranes, an Air Separation Unit (ASU), which provides a pure oxygen stream, and an oxy-combustor, where the oxygen reacts with the outlet reactors stream producing pure CO2 and the overall heat required by the process, thus allowing a global energy balance of the plant.

After optimizing the operating parameters as number of reforming steps, reactor temperatures and pressures and feedstock mixture composition, an economic comparison among the CC-RMM and three conventional natural gas steam reforming hydrogen production plants has been performed, attesting that the proposed novel hybrid scheme is able to compete in terms of CO2 recovery costs (20.95 €/ton CO2) and of total energy requirement for pure hydrogen production and CO2 capture (3575 kcal/Nm3H2 versus 3867-4191 kcal/Nm3H2 of the conventional configurations).

The performed simulation analysis has demonstrated the application potentialities of the proposed hydrogen production process configuration.

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### Most important publications

- **De Falco M., Salladini A., Palo E., Iaquaniello G.**
  *Pd-alloy membrane reactor for natural gas steam reforming: an innovative process design for the capture of CO2.*
  Ind Eng Chem Res. 2015 Jul 15; 54 (27): 6950-6958. DOI: 10.1021/acs.iecr.5b01141. IF 2.587

- **Barba D., Brandani F., Capocelli M., Luberti M., Zizza A.**
  *Process analysis of an industrial waste-to-energy plant: theory and experiments.*

- **Piemonte V., De Falco M., Basile A.**
  *Performance assessment of water gas shift membrane reactors by a two-dimensional model.*

There is currently a large world effort towards developing hydrogen power as the next generation of clean energy for both the transportation and the electricity sectors. Water gas shift is a thermodynamically limited reaction, which has to operate at low temperatures, reducing kinetics rate, and increasing the amount of catalyst required to reach valuable carbon monoxide conversions. It has been widely demonstrated that the integration of hydrogen selective membranes is a promising way to enhance water gas shift reactors’ performance: a Pd-based membrane reactor operated successfully overcoming the thermodynamic constraints of a traditional reactor thanks to the removal of hydrogen from the reaction environment. In this work, the effect of hydrogen removal in membrane water gas shift reactors will be investigated by a two-dimensional, non-isothermal model in order to analyze the water gas shift reactor performance. In particular, the effects on the reactor performance of the gas space hourly velocity, reactor temperature, pressure difference, sweeping gas flow rate, and inlet flow rate composition have been deeply assessed.
Is intermediate radiation dose escalation with concurrent chemotherapy for stage III non-small-cell lung cancer beneficial? A multi-institutional propensity score matched analysis.


Purpose: The clinical benefits and risks of dose escalation (DE) for stage III non-small-cell lung cancer (NSCLC) remain uncertain despite the results from Radiation Therapy Oncology Group (RTOG) protocol 0617. There is significant heterogeneity of practice, with many clinicians prescribing intermediate dose levels between the 0617 study arms of 60 and 74 Gy. This study investigated whether this strategy is associated with any survival benefits/risks by analyzing a large multi-institutional database. Methods and Materials: An individual patient database of stage III NSCLC patients treated with radical intent concurrent chemoradiation therapy was created (13 institutions, n=1274 patients). Patients were divided into 2 groups based on tumor Biological Effective Dose

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at 10 Gy (BED 10); those receiving standard dose (SD; n=552), consisting of 72 Gy ≤ BED 10 < 76.8 Gy [eg 60-64 Gy/30-32 fractions (fr), and those receiving intermediate dose (ID; n=497), consisting of 76.8Gy < BED 10 < 100.8 Gy (eg >64 Gy/32 fr and <74 Gy/37 fr), with lower-dose patients (n=225) excluded from consideration. Patients were then matched using propensity scores, leading to 2 matched groups of 196 patients. Outcomes were compared using various statistics including interquartile range (IQR), Kaplan-Meier curves, and adjusted Cox regression analysis. Results: Matched groups were found to be balanced except for N stage (more N3 disease in SD), median treatment year (SD in 2003; ID in 2007), platinum and taxane chemotheraphy (SD in 28%; ID in 39%), and median follow-up (SD were 89 months; ID were 40 months). Median dose fractionation was 60 Gy/30 fr in SD (BED 10 IQR: 72.0-75.5 Gy) and 66 Gy/33 fr (BED 10 IQR: 78.6-79.2 Gy) in ID. Survival curves for SD and ID matched cohorts were statistically similar (P=.27); however, a nonstatistically significant trend toward better survival for ID was observed after 15 months (median survival SD: 19.3 months; ID: 21.0 months). There was an increase in grades III to V lung toxicity associated with ID (13.0% vs 4.9%, respectively). Conclusions: No significant overall survival benefits were found with intermediate DE; however, more grade III or greater lung toxicity was observed. The separation of survival curves after 15 months of follow-up suggests that a small overall survival improvement associated with intermediate DE cannot be excluded.


Currently, androgen deprivation therapy (ADT) has a well-defined role when administered together with radiotherapy (RT): neo-adjuvant and concurrent combination for intermediate risk-disease and adjuvant therapy for high risk disease. Evidence of this association was generated by randomized trials designed and led approximately 30 years ago; thus the question which arises is how relevant and portable are those data in our current clinical practice? In the present review, we examine the pitfalls of these published randomized controlled trials, their relevance to present daily clinics, where high-dose external beam RT or brachytherapy is applied, as well as the adoption of ADT in patients with concomitant cardiovascular disorders.


Background: Radio-chemotherapy is one of the steps of multidisciplinary management in locally advanced pancreatic cancer. The Epidermal Growth Factor Receptor (EGFR) plays an important role in the disease pathway. The purpose of this prospective study is to evaluate the feasibility and the efficacy of radiotherapy in combination with gemcitabine and EGFR targeting therapy for patients with locally advanced disease. Materials and methods: From November 2008 through January 2012, 34 patients were included in this study. In all cases an accurate pre-treatment staging including CT scan, Endoscopic Ultra-Sonography (EUS), 18F - fluorodeoxyglucose (18F-FDG) PET-CT and laparoscopy with peritoneal washing was performed. External beam radiation was delivered with a total dose of 50.4 Gy (1.8 Gy per fraction). Patients were treated using 3D-conformal radiotherapy, and the clinical target volume was the primary tumor and involved lymph nodes. Gemcitabine 300 mg/m2 and Cetuximab were given weekly during radiation therapy. Results: Ten patients (29.4 %) were excluded from the protocol because of the evidence of metastatic disease at the pre-treatment staging. Three patients refused radiochemotherapy. Twenty-one patients completed the therapy protocol. During the combined therapy grade 3-4 toxicities observed were only hematological (leukopenia 47.8 %, thrombocytopenia 4.8 %, elevated gamma-GT 23.8 %, elevated alkaline phosphatase 4.8 %). Non-hematological toxicity grade 3-4 was never reported. Post-treatment workup showed partial response in five patients (24 %), stable disease in 11 patients (52 %) and disease progression in 5 patients (24 %). Two-year Local Control was 49 % (median, 18.6 months), 2-year Metastases Free Survival was 24 % (median, 10.8 months). One and two-year Overall Survival were 66 % and 28 % respectively, with a median survival time of 15.3 months. Conclusions: The combination of cetuximab and gemcitabine with concurrent radiation therapy provides a feasible and well tolerated treatment for locally advanced pancreatic cancer. Patients’ selection is crucial in order to treat patients appropriately.
TISSUE ENGINEERING & CHEMISTRY FOR ENGINEERING

Head:
M. Trombetta

Faculty: F. Basoli, A. Rainer

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.

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 represents 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.
Mecheri B., De Porcellinis D., Campana P.T., Rainer A., Trombetta M., Marietta A., Oliveira O.N. Jr., Licoccia S.

Tuning structural changes in glucose oxidase for enzyme fuel cell applications.


Stabilization and electrical contacting of redox enzymes with electrodes are fundamental requirements for bioelectronics devices, including biosensors and enzyme fuel cells (EFCs). In this study, we show increased glucose oxidase (GOx) stability by immobilization with Nafion. The immobilization process affected GOx conformation but was not detrimental to its activity, which was maintained for more than 120 days. The GOx/Nafion system was interfaced to a carbon cloth electrode and assembled in a prototypal EFC fed with glucose. Polarization and power density curves demonstrated that GOx/Nafion system was able to generate power, exploiting a Nafion-assisted electron transfer process to the electrode. Our findings are consistent with the onset of pH-dependent conformational equilibrium for the enzyme secondary structure and its active site. Significantly, the protective effect exerted by Nafion on the enzyme structure may be tuned by varying parameters such as the pH to fabricate durable EFCs with good electrocatalytic performance.

Giannitelli SM, Mozetic P, Trombetta M, Rainer A.

Combined additive manufacturing approaches in tissue engineering.


Advances introduced by additive manufacturing (AM) have significantly improved the control over the microarchitecture of scaffolds for tissue engineering. This has led to the flourishing of research works addressing the optimization of AM scaffolds microarchitecture to optimally trade-off between conflicting requirements (e.g. mechanical stiffness and porosity level). A fascinating trend concerns the integration of AM with other scaffold fabrication methods (i.e. “combined” AM), leading to hybrid architectures with complementary structural features. Although this innovative approach is still at its beginning, significant results have been achieved in terms of improved biological response to the scaffold, especially targeting the regeneration of complex tissues. This review paper reports the state of the art in the field of combined AM, posing the accent on recent trends, challenges, and future perspectives.

Gori M., Trombetta M., Santini D., Rainer A.

Tissue engineering and microRNAs: future perspectives in regenerative medicine.


Introduction: Tissue engineering is a growing area of biomedical research, holding great promise for a broad range of potential applications in the field of regenerative medicine. In recent decades, multiple tissue engineering strategies have been adopted to mimic and improve specific biological functions of tissues and organs, including biomimetic materials, drug-releasing scaffolds, stem cells, and dynamic culture systems. MicroRNAs (miRNAs), noncoding small RNAs that negatively regulate the expression of downstream target miRNAs, are considered a novel class of molecular targets and therapeutics that may play an important role in tissue engineering. Areas covered: Herein, we highlight the latest achievements in regenerative medicine, focusing on the role of miRNAs as key modulators of gene expression, stem cell self-renewal, proliferation and differentiation, and eventually in driving cell fate decisions. Finally, we will discuss the contribution of miRNAs in regulating the rearrangement of the tissue microenvironment and angiogenesis, and the range of strategies for miRNA delivery into target cells and tissues. Expert opinion: Manipulation of miRNAs is an alternative approach and an attractive strategy for controlling several aspects of tissue engineering, although some issues concerning their in vivo effects and optimal delivery methods still remain uncovered.
UROLOGY

Head:
G. Muto

Faculty: M. Buscarini
Other Personnel: E. Altobelli, R. Papalia

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.

High-intensity focused ultrasound (HIFU) for the treatment of prostate cancer in a prospective trial with long-term follow-up. Favourable outcome of HIFU was shown to be associated with careful patient selection, with low- to intermediate-risk disease being the ideal case.

Studies on development of nomograms predicting disease-free and cancer-specific survival after radical cystectomy providing optimal oncologic outcome prediction.

Studies on risk assessment of stone formation in stapled orthotopic ileal neobladder demonstrating that stone formation was comparable to that reported in the literature for completely hand-sewn ileal reservoirs. The only variable independently predictive of stone formation was intermittent self-catheterization.

A study on the role of Narrow Band Imaging in Management of Urothelial Carcinoma showing that NBI increases the detection of urothelial carcinoma in the bladder and upper tract, including flat high-grade lesions such as carcinoma-in-situ that are a diagnostic challenge under white light. NBI also appears to improve the quality of transurethral resection and thereby reduce the frequency of tumor recurrence.

A study on Axl receptor tyrosine kinase as a potential therapeutic target in renal cell carcinoma.
Most important publications

Mearini L., D’Urso L., Collura D., Nunzi E., Muto G., Porena M.

High-intensity focused ultrasound for the treatment of prostate cancer: A prospective trial with long-term follow-up.

Objective: High-intensity focused ultrasound (HIFU) is a minimally invasive treatment for prostate cancer. Data from the literature show promising oncological outcomes with a favourable side-effect profile. The aim of this study was to re-evaluate and bring up to date the follow-up of a previously published, prospective trial on HIFU as the primary treatment for prostate cancer. Materials and Methods: Between 2004 and 2007, 163 consecutive men with T1-T3aN0M0 prostate cancer underwent HIFU with the Sonablate 500. Follow-up included prostate-specific antigen (PSA) tests every 3 months after treatment and a random prostate biopsy at 6 months. Failure was defined according to positive findings at the 6 month biopsy and biochemical failure was defined according to the Phoenix criteria. Biochemical-free survival, metastasis-free survival and cancer-specific survival were calculated by Kaplan-Meier curves. Results: Median follow-up was 72.0 months. Of the 160 evaluable patients, 104 (65%) were biochemically disease free; in low- to intermediate-risk disease, on Kaplan-Meier analysis the 8 year biochemical-non-evidence of disease (bNED), metastasis-free survival and cancer-specific survival rates were 69.6%, 81.3%, 100% and 40.5%, 60.6%, 100%, respectively. A PSA nadir below 0.40 ng/ml and risk stratification below 0.40 ng/ml and risk stratification were associated with an increased risk of stone formation. A PSA nadir below 0.40 ng/ml and risk stratification were associated with an increased risk of stone formation. Results: At a median follow-up of 41 months (IQR 16-58) neobladder stone formation occurred in 41 patients (9.2%). All of these patients successfully underwent endoscopic stone lithotripsy with 34 as outpatient procedures. On univariable Cox analysis only female gender (p = 0.001, HR 3.29, 95% CI 1.59-6.83) and intermittent self-catheterization (p <0.001, HR 15.2, 95% CI 5.87-39.5) were associated with an increased risk of stone formation. On multivariable analysis the only independent predictor of stone formation was intermittent self-catheterization (p = 0.001, HR 8.98, 95%CI 2.59-31.1). Conclusions: In our series of stapled orthotopic ileal neobladders the rate of stone formation was comparable to that reported in the literature for completely hand-sewn ileal reservoirs. The only variable independently predictive of stone formation was intermittent self-catheterization.

Ferriero M., Guaglianone S., Papalia R., Muto GL., Gallucci M., Simone G.

Risk assessment of stone formation in stapled orthotopic ileal neobladder.

Purpose: The increasing trend of performing radical cystectomy with a minimally invasive approach has made stapled neobladders an attractive alternative to hand-sewn pouches. To date, data on the incidence and clinical impact of stone formation in long surviving neobladder cases are scarce. We report a long-term, single-center experience of stapled orthotopic ileal neobladder and identify predictors of stone formation. Materials and Methods: From May 2001 to October 2012, 445 consecutive patients (388 male, 57 female) underwent radical cystectomy and stapled orthotopic ileal neobladder. Univariable and multivariable analyses were performed to identify independent predictors of an increased risk of stone formation. Results: At a median follow-up of 41 months (IQR 16-58) neobladder stone formation occurred in 41 patients (9.2%). All of these patients successfully underwent endoscopic stone lithotripsy with 34 as outpatient procedures. On univariable Cox analysis only female gender (p = 0.001, HR 3.29, 95% CI 1.59-6.83) and intermittent self-catheterization (p <0.001, HR 15.2, 95% CI 5.87-39.5) were associated with an increased risk of stone formation. On multivariable analysis the only independent predictor of stone formation was intermittent self-catheterization (p = 0.001, HR 8.98, 95% CI 2.59-31.1). Conclusions: In our series of stapled orthotopic ileal neobladders the rate of stone formation was comparable to that reported in the literature for completely hand-sewn ileal reservoirs. The only variable independently predictive of stone formation was intermittent self-catheterization.


Development and external validation of nomograms predicting disease-free and cancer-specific survival after radical cystectomy.

Purpose: To develop two nomograms predicting disease-free survival (DFS) and cancer-specific survival (CSS) and to externally validate them in multiple series. Methods: Prospectively collected data from a single-centre series of 818 consecutive patients who underwent RC and PfNND were used to build the nomogram. External validation was performed in 3,173 patients from 7 centres worldwide. Time to recurrence and to cancer-specific death were addressed with univariable and multivariable analyses. Nomograms were built to predict 2-, 5- and 8-year DFS and CSS probabilities. Predictive accuracy was quantified using the concordance index. Results: Age, pathologic T stage, lymph node density and extent of PfNND were independent predictors of DFS and CSS (p <0.05). Discrimination accuracies for DFS and CSS at 2, 5 and 8 years were 0.81, 0.8, 0.79 and 0.82, 0.81, 0.8, respectively, with a slight overestimation at calibration plots beyond 24 months. In the external series, predictive accuracies for DFS and CSS at 2, 5 and 8 years were 0.83, 0.82, 0.82 and 0.85, 0.85, 0.83 for European centres; 0.73, 0.72, 0.71 and 0.80, 0.74, 0.68 for African series; 0.76, 0.74, 0.71 and 0.79, 0.76, 0.73 for American series. Conclusions: These nomograms developed from a contemporary series are simple clinical tools and provide optimal oncologic outcome prediction in all external cohorts.
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.

**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:

- Clamp the aorta horizontally, flush to the renal arteries, without mobilizing the endograft
- Open the sac and clamp the iliac branches by soft jaw external clamps close to the aortic bifurcation
- 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
- Clear the thrombus and oversaw the lumbar arteries
- 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 safe proximal anastomosis, double reinforced by the internal endograft and the external felt, without removing the suprarenal stent
- 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.

Matrix metalloproteinases and risk stratification in patients undergoing surgical revascularisation for critical limb ischaemia.


Critical limb ischaemia (CLI) is the most advanced form of peripheral artery disease (PAD) and it is often associated ith foot gangrene, which may lead to major amputation of lower limbs, and also with a higher risk of death due to fatal cardiovascular events. Matrix metalloproteinases (MMPs) seem to be involved in atherosclerosis, PAD and CLI. Aim of this study was to evaluate variations in MMP serum levels in patients with CLI (groups I and II) with respect to control group (group III). We documented significantly higher serum MMPs levels (P < 0.01) in patients with CLI (groups I and II) with respect to control group (group III). Finally, five patients with CLI (17.2%) showed poor outcomes (major amputations or death), and enzyme-linked immunosorbent assay (ELISA) test showed very high levels of MMP-1 and MMP-8. MMP serum levels seem to be able to predict the clinical outcomes of patients with CLI.

Spinelli F., Pipitò N., Martelli E., Benedetto F., De Caridi G., Spinelli D., Stilo F.

Endo first is not appropriate in some patients with critical limb ischemia because “bridges are burned”.


Background: The aims of this study were to determine the effect of failed prior endovascular treatment (EV) on early and midterm outcomes of subsequent lower extremity open surgical (OS) bypass. Methods: Patients undergoing infrainguinal bypass for critical limb ischemia (CLI) from January 2008 to December 2011 were retrospectively reviewed. The results after first-line bypass and bypass after failure of EV treatment were compared. A total of 213 patients (65.25% men; average age, 73.30 years) underwent bypass. OS patients were then divided into 2 groups: group 1 consisted of 138 patients who underwent primary OS for CLI without prior EV (control group) and group 2 consisted of 75 patients who had OS after a failed attempt at elective EV for peripheral vascular disease. Of the 213 bypass performed, 34% had a prior infrainguinal failed EV. The primary study end points were early and 1-year major amputations and graft occlusion. The secondary outcomes included early and 1-year mortality and the level of distal revascularization. Results: Secondary patency and limb salvage rates were significantly better in group 1 up to 1 year (99% vs. 86%, P < 0.001 at 1 month and 95% vs. 76%, P < 0.05 at 12 months, respectively). Conclusions: Previous failed EV should be predictive of poor outcome in patients undergoing distal OS for CLI.
The Virology Research Unit is involved in both basic and clinical virology. The 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.

The specific SNPs that are currently under study are:
- rs12979860, rs8099917, ss46945590 TT/delta G SNPs in Interferon lamda III-IV region mainly involved in host's innate immune response to infectious diseases. - rs738409 SNP in the Patatin-like phospholipase domain-containing protein 3 (PNPLA3) also known as adiponutrine that has been demonstrated to be a predictive marker of clinical progression in Non-Alcoholic fatty liver disease (NAFLD) patients
- rs116928232 SNP in the exon 8 of the Lysosomal acid lipase that has been associated with fatty metabolic dysfunctions.

The Unit is also involved in the comparison and validation of molecular methods applied for persistent viral infection (CMV, HCV, EBV and parvovirus infections).

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

The Virology Unit is also in close collaboration with the Department of Molecular Medicine -Virology section- “Sapienza” University of Rome and AIFA/EMA Institution.
Most important publications


In this review, we will revise the epidemiology pointing to HCV as an infection of the elderly, the evidences that HCV harms the health of the aged patient more than that of the young one, and the available experiences of HCV treatment in the elderly with the “old” IFN-based regimens and with the newer DAA drugs. We will conclude that the availability of IFN-free regimens should prompt us to change our mind and consider a significantly larger number of possible candidates among elderly patients, who would take significant advantage from viral eradication.


Human hepatitis A virus (HAV) is the major cause of acute hepatitis throughout the world and causes substantial morbidity in both developed and developing countries. HAV is transmitted mainly via a faecal-oral route, but indirect transmission is also possible as HAV can survive in water. Numerous waterborne epidemics have been observed following consumption of contaminated drinking water, food produce watered with untreated water or shellfish. In developing countries sanitary and hygienic conditions are usually scarce and low economic status, high crowding and inadequate water treatment contribute to a high endemicity pattern. This short paper describes a case of acute HAV infection in a 20-year-old man involved in a two-week medical workcamp in St. Damien Hospital of Ambanja, North Madagascar.
GRANTS FROM COMPETITIVE CALLS
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.

CIPRNET Critical Infrastructure Preparedness and Resilience Research Network
Url: https://www.ciprnet.eu
Coordinator: Fraunhofer (DE)
Partner: Campus Bio-Medico University of Rome (Research Unit of Automation and Control Theory), ENEA, TNO (NL), JRC (EU), UIC (FR), CEA (FR), Deltares (NL), University of Cyprus (CY), University of Technology and Life Sciences (PL), University of British Columbia (CA)
Funded under: FP7-SEC-2012
End: 01/03/2016
Contacts: Roberto Setola (r.setola@unicampus.it), Research Unit of Automation and Control Theory

The Critical Infrastructure Preparedness and Resilience Research Network or 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. By integrating resources of the CIPRNet partners acquired in more than 60 EU co-funded research projects, CIPRNet will create new advanced capabilities for its stakeholders. A key technology for the new capabilities will be modelling, simulation and analysis for CIP. CIPRNet builds a longlasting virtual centre of shared and integrated knowledge and expertise in CIP. This virtual centre shall provide durable support from research to end users. It will form the foundation for the European Infrastructures Simulation & Analysis Centre (EISAC) by 2020.

COMETHY: Compact Multifuel-Energy to Hydrogen Converter
Url: http://www.comethy.enea.it/project.php
Coordinator: ENEA
Partners: Processi Innovativi S.r.l., Acktar Ltd, Technion - Israel Institute Of Technology, Fraunhofer
Institute, University of Salerno, Centre for Research and Technology Hellas, Aristotelio Panepistimio Thessalonikis, Sapienza University, Stichting Energieonderzoek Centrum Nederland, Gkn Sinter Metals Engineering Gmbh, Campus Bio-Medico University of Rome (Research Unit of Chemical-

Physical Fundamentals of Chemical Engineering)

Funded under: FCH-JU-2010-1

End: 30/06/2015

Contacts: Luigi Marrelli (l.marrelli@unicampus.it), Research Unit of Chemical – Phisics Fundamentals of Chemistry Engineering

CoMETHy aims at the intensification of hydrogen production processes, developing an innovative compact and modular steam reformer to convert reformable fuels (natural gas, biogas, bioethanol, etc.) to pure hydrogen, adaptable to several heat sources (solar, biomass, fossil, etc.) depending on the locally available energy mix. The main role of UCBM is characterization of the structured foam as suitable support material.

EU-AIMS: European Autism Interventions – A Multicentre Study for Developing New Medica-
tions

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, Universitaet 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.

Structures

Url: http://www.structures-project.eu/

Coordinator: I.D.S. – Ingegneria dei Sistemi S.P.A.

Partners: Campus Bio-Medico University of Rome (Research Unit of Automation and Control Theory), Ecole Polytechnique Federale de Lausanne (EPFL), Haute Ecole Specialisee de Suisse Occidentale (HES-SO), University of York (UoY), Montena Technology SA (Montena), Helmut Schmidt Universitat der Bundeswehr Hamburg (HSU), Gottfried Wilhelm Leibniz Universitaet Hannover (LUH), Bergische Universitaet Wuppertal (BUW), Rheinmetall Waffe Munition GMBH (RWM), Universiteit Twente (UT), Istituto Superiore Mario Boella sulle tecnologie dell’informazione e delle telecomunicazioni (ISMB), Navigate Consortium Consorzio (NAVI)

Funded under: FP7-SEC-2011

End: 31/10/2015

Contacts: Roberto Setola (r.setola@unicampus.it), Research Unit of Automation and Control Theory

Strategies for the improvement of critical infrastructure resilience to electromagnetic Attacks – aims at analysing possible effects of electromagnetic (e.m.) attacks, and in particular of IEMI (intentional electromagnetic interference) on a set of critical infrastructures (energy systems, ICT
systems, transportation etc), at assessing their impact for our defence and economic security, at identifying innovative awareness and protection strategies and at providing a picture for the policy makers on the possible consequences of an electromagnetic attack. UCBM is in charge of providing methodologies and guidelines to evaluate infrastructure robustness against IEMI.

**ASKLEPIOS: Actions on food Supplements, False genuine (not) food exhibition, e-Learning platform, action on Pesticides, operation “In Our Sites” and JAD**

*Coordinator:* Carabinieri Headquarters for Healthcare
*Partner:* Campus Bio-Medico University of Rome (Research Unit of Tissue Engineering and Chemistry for Engineering), Studiare Sviluppo srl (IT), Italian National Institute of Health, Department of Therapeutic Research and Medicine Evaluation (IT), Italian Ministry of Health (IT), Confederazione Nazionale Coldiretti (IT), The Netherlands Food and Consumer Product Safety Authority (NL), Wageningen University & Research Centre (NL), Belgian Customs and Excise (BE)

*Funded under:* EU Commission-EUROPOOL for the EMPACT activities under the OAP Counterfeit Goods

*End:* 31/12/2016

*Contacts:* Marcella Trombetta (m.trombetta@unicampus.it), Research Unit of Tissue Engineering and Chemistry for Engineering

ASKLEPIOS aims at supporting awareness and exchange of best practices, improving data gathering and intelligence sharing, and providing strategic support for current or proposed operational activities. The project is carried out in the framework of Operational Activity 4.10 “BACCUS Class: an e-learning platform for training law enforcement officers to combat food crime” of the Europol project. Prof. Marcella Trombetta is the Scientific Coordinator of the project.

**RISING - indoor localization and building maintenance using radio frequency Identification and inertial Navigation**

*Coordinator:* Università Campus Bio-Medico di Roma
*Partners:* Tecnun - Universidad De Navarra, School of Engineering (TECNUN), Department of Engineering, Università degli Studi di Roma Tre (UNIROMA3)

*Funding under:* FP7 ERA-NET SAF-RA (INAIL, OSALAN)

*End:* 2016

*Contacts:* Roberto Setola (r.setola@unicampus.it), Research Unit of Automation and Control Theory

The RISING (indoor localization and building maintenance using radio frequency Identification and inertial Navigation) project is devoted to support on field operators during emergencies with a system for situational awareness and personal indoor positioning. The RISING solution is based on the integration of the RFID (Radio Frequency Identification) technology with an inertial navigation system. A set of RFID tags, conveniently pre-installed in the working environment, store information about their absolute position and information about the neighbor hazards and resources (type, location, etc.). This information are retrieved on-the-fly by rescuers equipped with RFID readers and displayed on his/her smart devices (i.e., a rugged tablet) to allow on-field situational awareness. In standard operating conditions, the RISING solution can also support the maintenance operators activities (plants preservation, trials, refueling, etc.).

**ITALIAN MINISTRY OF EDUCATION, UNIVERSITY AND RESEARCH (MIUR)**

National Operative Programme (Programma operativo Nazionale - PON) for Research and Competitiveness 2007-2013

**VIRTUALAB:** Advanced systems of biomedical mechatronics, diagnosis and medical therapy based on virtual and augmented reality, microelectronics and laboratories at high throughput

*Coordinator:* MASMEC S.p.A.
Cyclic nucleotides in biotic stress signalling in plant
Coordinator: University of Milan

Bioartificial materials and biomimetic scaffolds for a stem cells-based therapy for myocardial regeneration
Coordinate: Politecnico di Torino

PRIN (Research Projects of National Interest) 2010-2011
Biomechatronic hand prostheses endowed with bio-inspired tactile perception, bi-directional neural interfaces and distributed sensori-motor control
Coordinator: Eugenio Guglielmelli – Research Unit of Biomedical Robotics and Biomicrosystems (UCBM)

The interplay between glucose metabolism and the bone for cardio-metabolic characterization of a young population of obese subjects
Coordinator: Paolo Pozzilli – Research Unit of Endocrinology and Diabetes (UCBM)

Engineering physiologically and pathologically relevant organ Models for the INvestigation of age related Diseases (MIND)
Coordinator: Politecnico di Torino

Root growth control: a systems biology approach
Coordinator: Sapienza University

Emerging role of the endocannabinoid signalling in neuropsychiatric disorders
Coordinator: University of Insubria Varese-Como

Functional connectivity and neuroplasticity in physiological and pathological aging
Coordinator: Catholic University of the Sacred Heart
Partners: Research Unit of Neurology, Neurophysiology and Neurobiology (UCBM), University of Foggia, National Research Council, University of Milan, Sapienza University, University of Chieti-Pescara

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”

ITALIAN MINISTRY OF HEALTH - FINALISED RESEARCH

GR Ordinary 2009
NEurocontrolled MEchatronic prostheSIS (NEMESIS)
Coordinator: IRCCS San Raffaele Pisana
Partners: Research Unit of Biomedical Robotics and Biomicroystems (UCBM), Scuola Superiore Sant’Anna di Studi Universitari e di Perfezionamento, University of Cagliari, Catholic University of the Sacred Heart

GR Ordinary 2010
Towards intervertebral disc regeneration: mesenchymal stem/stromal cells with a novel bioactive hydrogel based approach
Coordinator: Gianluca Vadalà, Research Unit of Ortopaedics and Trauma Surgery (UCBM)
Partners: Research Unit of Ortopaedics and Trauma Surgery (UCBM); Research Unit of Hematology, Stem Cell Transplantation, Transfusion Medicine and Cellular Therapy (UCBM); Research Unit of Tissue Engineering and Chemistry for Engineering (UCBM); Cell Factory, Foundation IRCCS Cà Granda Ospedale Maggiore Policlinico; University of Padova – Department of Animal Medicine, Production and Health, AO Research Institute, Davos (Switzerland).

Early detection and treatment of recurrent, chemotherapy-resistant ovarian cancer stem cells by CPE peptide complexed superparamagnetic iron oxide nanoparticles (CPE-SPIONs)
Coordinator: Fondazione IRCCS Istituto Nazionale dei Tumori
Partners: Research Unit of Ginecology and Obstetrics (UCBM); Yale University, School of Medicine, New Haven, CT.

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 Pathology and Clinical Microbiology (UCBM), Istituto Superiore di Sanità, University of Roma “Tor Vergata”

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 Pathology and Clinical Microbiology (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

**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

**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 Pathology and Microbiology (UCBM), Research Unit of Tissue Engineering and Chemistry for Engineering (UCBM), Istituto Superiore di Sanità, National Research Council

**ITALIAN MINISTRY OF HEALTH**

**NATIONAL CENTRE FOR DISEASE PREVENTION AND CONTROL 2012**

Italian Network for early detection of Autism Spectrum Disorders  
**Coordinator:** Istituto Superiore di Sanità  
**Partners:** Research Unit of Neuropsychiatry and Neurogenetics (UCBM), Istituto Superiore di Sanità, IRCCS Stella Maris, Institute of Clinical Physiology National Research Council, IRCCS Bambino Gesù, IRCCS MEDEA, Sicily Region

**ITALIAN MINISTRY OF ECONOMIC DEVELOPMENT**

**NOVEL TECHNOLOGIES FOR MADE IN ITALY “INDUSTRIA 2015”**

DAHMS - *Distributed Architecture home modular multifunctional systems*.  
**Coordinator:** Hitachi Systems CBT S.p.A.  
**Partners:** UCBM (Research Unit of Electronics for Sensor Systems, Research Unit of Geriatrics, Research Unit of Biomedical Robotics and Biomicrosystems, Research Unit of Computer Systems and Bioinformatics, Research Unit of Food and Nutrition Science), Das S.r.l., Delta Software S.r.l., Iselqui Technology S.r.l., Pentronics S.r.l., Virtual Italian Parks S.r.l., ZP Engineering S.r.l., Istituto Superiore Mario Boella, Istituto Superiore di Sanità, Agenzia Internazionale per la Prevenzione della Cecità sezione italiana ONLUS, RadioLabs, University of Roma “Tor Vergata”, Telecom Italia S.p.A., ST Microeletronics S.r.l.

**LAZIO REGIONAL AUTHORITY**

**CO-RESEARCH**

CIA - Comprehension via Intelligent Awareness  
**Coordinator:** RESI Informatica S.p.A.  
**Partner:** Research Unit of Automatics (UCBM)

SIM – Multimedia Integration Development  
**Coordinator:** Proge-Software S.r.l.  
**Partner:** Research Unit of Automatics (UCBM), Research Unit of Orthopaedic and Trauma Surgery (UCBM)
NEUROHAND – Active upper limb prosthesis with neural and bidirectional control
Coordinator: Ortopedia Italia S.r.l.
Partners: Research Unit of Biomedical Robotics and Biomicrosystems (UCBM), Research Unit of Physical Medicine and Rehabilitation, San Raffaele S.p.A.

Modular lower limb orthoses for facilitating motor learning of gait patterns in children and adults with neurological disorders
Coordinator: ITOP Officine Ortopediche S.p.A.
Partner: Research Unit of Biomedical Robotics and Biomicrosystems (UCBM), Research Unit of Physical and Rehabilitation Medicine (UCBM)

TIPITEC – Novel technologies for food Italian products
Coordinator: Research Unit of Food Science and Nutrition (UCBM)
Partners: Research Unit of Electronics for Sensor Systems (UCBM), University Roma Tre, University of Roma “Tor Vergata”, Sapienza University, Catholic University of the Sacred Heart

OTHER GRANTS

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 Neurosciences (UCBM)

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 Jugendkrankenhaus 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 Hospital of Pittsburgh, University of South Florida, Robarts Research Institute, Canada

Cells-on-chip models for the development of integrated therapies based on immunotherapy targeting macrophage polarization: overcoming the resistance of the tumor stem compartment to conventional therapies in non-small cell lung cancer
Funding Body: Fondazione Guido Berlucchi
Partners: Research Unit of Oncology (UCBM), Research Unit of Tissue Engineering and Chemistry for Engineering (UCBM), CNR-IFN Laboratory of Micro and Nanofabrication

KOSMOMED - Telemedicine satellite services for Healthcare professional network
Funding Body: ESA – European Space Agency
Partners: Research Unit of Electronics for Sensor Systems (UCBM), Kell S.r.l.; Medtronic; OpenSky; CNIT, Vascular Surgery Division, Department of Surgery, Surgical Specialties and Organ Transplantation “Paride Stefanini”, “Umberto I" Polyclinic of Rome, Consorzio Ferrara Ricerche, Sapienza University

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

Understanding the interplay between cancer stem cells and immune system: an innovative on-chip approach
Funding Body: Italian Ministry of Foreign Affairs and International Cooperation, Italia-USA Scientific and Technological Cooperation
Coordinator: Daniele Santini – Research Unit of Oncology (UCBM)
Partners: Research Unit of Tissue Engineering and Chemistry for Engineering (UCBM), Molecular Foundry - Lawrence Berkeley National Laboratories California, USA

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

Antioxidant rich - food supplements for the protection against cosmic radiations - PAPARD
Funding Body: ASI – Italian Space Agency
Coordinator: Sapienza University
Partner: Research Unit of Food Science and Nutrition (UCBM), Research Unit of Diagnostic Imaging (UCBM), University of Florence

Studies Relevant to the Discovery and Development of Antigen Specific Therapies for Human Type 1 Diabetes RFA (Innovative Grant mechanism)
Funding Body: JDRF (Juvenile Diabetes Research Foundation)
Partner: Research Unit of Endocrinology and Diabetes (UCBM)
UNIVERSITY STRATEGIC 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. The thirteen projects submitted have been evaluated by external evaluators having recognized expertise and research background on the topics addressed by each specific project.

Three multidisciplinary projects lasting 2 years, coordinated by young researchers (under 40 years) have been funded (total funding: 500 KEuro) and started in April 2015 as described below.

Evaluation of bone strength and WNT pathway in obese patients

*Pl:* Dr. Nicola Napola, Research Unit of Endocrinology and Diabetes

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

Accumulating evidences suggest that obesity is detrimental to bone health despite potential positive effects of mechanical loading conferred by increased body weight. The main objective of this project is to investigate how obesity may impair bone health and to explore the potential key role of Wnt pathway. To this aim women elderly obese and control subjects who underwent surgery for standard hip arthroplasty were enrolled. Blood, bone, muscle and adipose tissue samples have been processed for Elisa, gene/protein expression and immunohistochemistry analysis. Data so far collected support our hypothesis that WNT is differently modulated in obesity and that mechanical loading on the skeleton of obese subjects downregulates sclerostin expression and facilitate local activation of WNT canonical pathway. Our data showed higher TNF$\alpha$ expression in both muscle and adipose tissue, together with lower Adiponectin in the obese. Further analyses obtained from more samples may provide novel insights in the relationship between obesity and bone health.

Data are represented as mean ± SEM. SOST/Sclerostin and Wnt5a expression in bone (A and B). SOST expression decreased in obese (Ob), compared to normal weight (N.W). N.W versus Ob had a p value= 0.063. Wnt5a expression presented a p value 0.05 in N.W. TNF expression in adipose tissue (C). WNT10b expression in muscle (D).
Smart surgical platform for the transpedicular delivery of advanced regenerative therapies into the intervertebral disc space

*P.I.:* 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 to develop tools for the delivery of ATMPs to the intervertebral disc (IVD) through the transpedicular approach, and to select biomaterials for closing the transpedicular tunnel and biological therapeutic products for IVD degeneration treatment.

During the first year the detailed design of the submodules of the START-Disc surgical platform was carried out, in particular: i) the design of the longitudinal ultrasonic driller for deep hole into the vertebra for transpedicular access; ii) a mechanical support composed by a Cartesian stage and a 2 Dof planar double parallelogram for orienting the surgical tools; iii) a redundant system to monitor the manual advancement of the ultrasonic drill and iv) a delivery system was designed able to deliver the ATMPs in the IVD space monitoring the IVD pressure. A suitable biomaterial was chosen to be used in the sealing procedure. Each of these submodules has been analyzed in order to plan a proper exploitation strategy.

*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

GUT2.0 project aims at developing an advanced in vitro model of the human gut, purposely designed as a platform for predictive human safety testing. There is an increasing need for novel in vitro models for toxicology, able to overcome the limitations of both animal testing and conventional in vitro cell models. As a major advancement in the field, the establishment of microfluidics-based models, known as “cells-on-chip”, represents an ideal and emerging tool. This approach, coupling co-culture protocols and microfluidic technologies, provides a high degree of control over the experimental parameters and exploits the power of modern microscopy tools, often not applicable during in vivo experiments. GUT2.0 will develop a stretchable cell culture platform (Intestine Microfluidic Device – IMD) recapitulating the main functions of the human intestine in terms of epithelial barrier function, interaction with the microflora, and smooth muscle contractility. The IMD will be validated against ‘gold standards’ for in vitro toxicology, for a measurable determination of performance improvement. Another key issue will be represented by the tight integration of the physical IMD platform with in silico modeling tools, for a consistent data analysis and extraction of toxicological data. First-year results include: the establishment of fully functioning prototypes of the IMD; the characterization of the IMD biophysics; the optimization of cell (co-)culture protocols. Validation activities of the IMD against in vitro 2D models (transwell inserts) and ex vivo human intestine tissue are ongoing.

Experimental setup for IMD actuation/monitoring (A) and vector plot of membrane displacement under actuation (B).
THE UNIVERSITY THIRD MISSION: IMPACT 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. 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. In this framework, UCBM has an operational headquarter in Puglia Region, in Bari mechatronic district where research activities in biomedical fields in collaboration with local enterprises and research centres are carried out; in particular research projects funded by Puglia Region and Italian Ministry of Education, University and Research are carried out in collaboration with MASMEC BIOMED, a division of MASMEC SpA. 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), Research Unit of Physical and Rehabilitation Medicine (UCBM), Research Unit of Orthopaedics and Trauma Surgery (UCBM), Research Unit of Neurology, Neurophysiology, Neurobiology (UCBM)

PONTE (Progetto Ospedale Nel TErritorio): Hospital in Territory

*Client:* Hospital “Ospedale Civile di Legnano”
*Contractor:* Research Unit of Geriatrics (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)

Research and development of innovative biological medicines in oncology: production of pegylated monoclonal antibody fragments and miRNAs for therapeutic and / or diagnostic purpose

*Client:* IRCCS Casa Sollievo della Sofferenza
*Contractor:* Research Unit of Genetic Pathology (UCBM)

GEPIKID

*Client:* National Institutes of Health
*Contractor:* Research Unit of Genetic Pathology (UCBM)

Development of a sensor for the microbiological qualitative and quantitative monitoring of ultra-pure water
Support for the technical contents of the web portal www.oil-gasportal.com

Small animal scanner prototyping for Magnetic Particle Imaging and synthesis of the better iron oxide nanoparticles to use as in vivo tracers

Development of a software package to detect the optimum set-up of acoustic prostheses

Liquid chromatography tandem mass spectrometry platforms to develop analytical protocols for drugs and metabolites in biologic fluids

Profiling new chemical entities towards the endocannabinoid system

Valorization and characterization of olive oil and analysis of the proto-diet in the “Colline Joniche” area

Technical-economical assessment of a carbon-driven power plant

Design of an experimental set-up for the monitoring of Extra-Vergin Olive Oil extraction processes using chemical sensors

A sensorial system for the evaluation of innovative food cooking methods

Situation Awareness” in complex Scenario” inside the NCS (Network-centric Cognitive System) project funding by the Italian Ministry of Defence under Piano Nazionale Ricerca Militare – PNRM n° 2009.40

Guideline for the Development Governance Procedures for Cyber Security of Social Networks

Development of a medical device for the early detection of exacerbation in COPD patients
A multicenter prospective randomized placebo-controlled double blind study to evaluate the effectiveness of low-frequency pulsed 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 and Neurobiology (UCBM)

“I care about myself”. Self-care experiences from the perspective of the people with COPD

Client: IPASVI, Rome
Contractor: Research Unit of Nursing Sciences (UCBM)

Development and psychometric testing of a measure of cancer patients’ perception of care dependency

Client: IPASVI Rome
Contractor: Research Unit of Nursing Sciences (UCBM)

Clinical trials

In 2015 45 contracts have been signed with large pharmaceutical companies and research networks for the development of clinical trials with a total funding of 1.7 MEuro. The Research Units mainly involved in these activities were Oncology, Endocrinology and Diabetes, Gastroenterology, Cardiovascular Science, Internal Medicine and Hepatology, Neurology, Neurophysiology, Neurobiology. The close synergy with principal investigators and continuous monitoring of the activities allowed increasing revenues of more than 70% with respect to 2014.

Moreover, UCBM in 2015 promoted 23 Investigator Initiated Trials (IIT).

Clinical trials performed in 2015 were mainly Phase 2 and some Phase 3 and 4 studies. One of the main objectives is to increase the number of Phase 1 clinical trial as well as to increase clinical trials for the validation of medical devices exploiting the close collaboration between the Engineering and Medicine and Surgery Departments.

Research exploitation

Patent portfolio

- Sodium 2-Mercaptoethane Sulfonate for use in the treatment of lumbar pain (IT1402161, EP2629768, WO2012052888); Inventors: F.E. Agrò, M. Carassiti, V. Denaro, A.C. Di Martino
- System for the estimation of cardiac output (IT1408989, EP20787878, WO2013084159); Inventors: M. Carassiti, S. Cecchini, E. Schena, S. Silvestri
- Apparatus and method for videorhinohygrometric (vri) measures (EP2010054, US9138168); Inventors: F. Salvinelli, R. Setola, M. Casale, P. Soda, V. Cusimano
- Locomotion device for endoscopic applications and related methods (IT1397408, US9131833); Inventors: D. Accoto, S. Passanisi
- Device and method for controlled adhesion upon moist substrate (IT1409811; EP2806817, US 20140353158, WO2013111076); Inventors: D. Accoto, C. Esposito, M. T. Francomano
- Device for mixing platelet-rich plasma with polymer solution (IT2014RM00190); Inventors: V. Denaro, R. Papalia, G. Vadala, A. Sudano, D. Accoto
- Upper limb movement therapy device (IT1388838); Inventors: D. Accoto, E. Cecchini, E. Guglielmelli, M. Orsini, F. Torchiani L. Zollo
UCBM spin-off companies

In 2015 two spin-off companies, namely ICAN Robotics srl and JUMPO srl, have been accredited by UCBM. The spin-off companies activities are related to robot-assisted rehabilitation and wearable sensors for human behavior monitoring. In particular, ICAN Robotics (www.icanrobotics.com) develops robotic technologies for rehabilitation and physical assistance of people with neurological, orthopedic or ageing-induced disorders; JUMPO develops novel technologies for fitness based on wearable sensors, but also other fields of application can be envisaged for Jumpo technology such as physical and rehabilitation medicine.

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 2015 is reported.

Rome, 23 January 2015

Bioimaging and near-infrared mediated cancer cell killing

“Surgical protocol Photo-Driven Upconversion Nanodevices as Theranostics: Bioimaging and Near-infrared Mediated Cancer Cell Killing”

Discussant: Professor Timothy T.Y. Tan, School of Chemical and Biomedical Engineering Nanyang Technological University Singapore.

Seminar promoted by the Plastic Surgery Unit, Campus Bio-Medico University Hospital.
Rome, 24 January 2015

5th Congress on The use of new technologies in diabetes
With the participation of professor Paolo Pozzilli, Endocrinology and Diabetes Unit, Campus Bio-Medico University of Rome.

Rome, 26 January 2015

Hepatocellular carcinoma
Seminar promoted by the Integrated Unity for the treatment of the Hepatocellular carcinoma, Campus Bio-Medico University Hospital in collaboration with the “Team for the minimally invasive treatment”.

Rome, 5 February 2015

Treatment of the corporeal profile alterations after bariatric surgery

Rome, 6 February 2015

New trends in prosthetic shoulder surgery
With the participation of professor Vincenzo Denaro and Francesco Franceschi, MD. Orthopaedic and Trauma Surgery Campus Bio-Medico University of Rome.

Rome, 25 February 2015

Perampanel: Molecular profile
Discussant: Elisabetta Grillo, EISAI Medical Affairs Manager
Seminar promoted by the Neurology Unit, Campus Bio-Medico University of Rome.

Rome, 26 February 2015

Lecture on palpebral ptosis
Discussant: Prof. Carlos Alberto Alfonso Ferreira, Federal University of Sao Paulo, Department of ophthalmology Sector of oculoplastic surgery
Seminar promoted by the Plastic Surgery Unit, Campus Bio-Medico University of Rome.

Rome, 27 February 2015

Neuro-rehabilitation seminars
Promoted by the Postgraduate School of Physical Medicine and Rehabilitation, Campus Bio-Medico University of Rome, in collaboration with Tor Vergata University, Sapienza University, and Verona University.

Rome, 27 February 2015

Agriculture-Food-Environment: building a relation for a sustainable development
As part of the Environment Week: Environmental culture for the protection of people and of human society.
Discussants: Andrea Sonnino, ENEA; Laura De Gara, Campus Bio-Medico University, Rome; Maria Gemma Grillotti, Campus Bio-Medico University Rome; Pasquale De Muro, Roma Tre University, Rome; Rossana Alloni, Campus Bio-Medico University, Rome; Nicolò Della Chiesa, Institute for University Cooperation Onlus; Giovanni De Paoli, ENEA; Marco Stefanoni, ENEA; Luigi Rossi, FIDAF.

Rome, 2 March 2015

Drug interactions in epilepsy: a roundtable
Discussants: Mario Tombini, Campus Bio-Medico University, Rome; Andrea Romigi Tor Vergata University; Caterina Cerminara, Tor Vergata University; Alessandra Morano Umberto I University Hospital; Domenica Battaglia, Catholic University of the Sacred Heart, Rome; Marina Trivisano, Ospedale Pediatrico Bambino Gesù; Giovanni Assenza, Gabriella Colicchio Catholic University of the Sacred Heart, Rome
With the participation of Prof. Meir Bialer, The Hebrew University of Jerusalem, Israel.
Promoted by the Neurology Unit, Campus Bio-Medico University of Rome, sponsored by the
Italian League Against Epilepsy.

Rome, 20 March 2015
Genomic epidemiology of bacterial pathogens: from cutting edge research to routine clinical practice
Discussant: Professor Marco Salemi, Associate Professor Department of Pathology, Immunology
and Laboratory Medicine College of Medicine, University of Florida, Gainesville.
Promoted by the Clinical Pathology and Microbiology Unit, Campus Bio-Medico University of Rome.

Rome, 25 March 2015
Chiari malformation: current therapeutic options
With the participation of Professo Domenico D’Avella, Head of the Postgraduate School in
Neurosurgery Padova University.
Seminar promoted by the following Campus Bio-Medico University Units: the Orthopaedics Unit,
the Anatomical Pathology Unit, the Physical Medicine and Rehabilitation Unit, and the Neurology Unit.

Rome, 26 March 2015
Optimal security investments for critical infrastructure systems
Discussant: Maria Paola Scaparra, Director of the MSc in Management Science and Business
Analytics at Business School, University of Kent, UK.
Seminar promoted by the Automation and Control Unit, Campus Bio-Medico University of Rome,
as part of the European project CIPRNet.

Rome, 18 April 2015
Concert “Spicchi di Luna inCanto”
Concert in support of autism research conducted by the Campus Bio-Medico University of Rome.
With the Iuvenilis Orchestra, S. Cecilia School of Music and the “Grande Coro” Rome.

Rome, 1 July 2015
Control of the upper limb prosthesis with invasive neural interfaces
Seminar organized as part of the Research Week 2015 by INAIL - the national institute for
insurance against accidents at work - and Campus Bio-Medico University of Rome.

Rome, 2 July 2015
Research Week 2015
Organized by the Centre for Integrated Research (CIR), Campus Bio-Medico University of Rome.

Rome, 3 July 2015
Workshop FAST: Ideas for a virtual lab of interdisciplinary research
Seminar organized by the Institute of Philosophy of Scientific and Technological Practice (FAST)
as part of the Research Week 2015.

Rome, 16 July 2015
Enhanced recovery after surgery (ERAS)
Discussant: Prof. Mustapha Adham, Edouard Herriot Hospital, Lyon (France); Sara Emerenziani,
MD Gastroenterology Unit, Campus Bio-Medico University of Rome.
Seminar organized by the General Surgery Unit, Campus Bio-Medico University of Rome.

Rome, 21 July 2015
Making connections: new toles for Netrin-1 and DCC regulating myelination, synaptogenesis,
and plasticity
Discussant: Dr. Timothy E. Kennedy, Ph.D., Dept of Neurology and Neurosurgery Montreal
Neurological Institute McGill University Montreal, Quebec, Canada.
Seminar organized by the Developmental Neuroscience Unit, Campus Bio-Medico University of Rome.

Rome, 22 July 2015
Towards genomic epidemiology of emerging bacterial pathogens
Discussant: Prof. Marco Salemi, Associate Professor, Department of Pathology, Immunology and Laboratory Medicine, College of Medicine, University of Florida, Gainesville, USA.

Rome, 17 September 2015
Mitigating obstructive sleep apnea and snoring by optimizing breathing patterns through an external device
Discussants: Dr. Andre Michalak, MD - Dr. Nicholas Michalak - Dr. Luca Giani
Seminar promoted by the Neurology Unit, Campus Bio-Medico University of Rome.

Rome, 23 September 2015
Updates on the medical and surgical treatment of endometriosis
Discussants: prof. Felice Petraglia Head of the Gynaecology and Obstetrics Department, Siena University
Seminar promoted by the Gynaecology and Obstetrics Unit, Campus Bio-Medico University of Rome.

Rome, 10 October 2015
Congenital vascular diseases: from diagnosis to management of rare vascular diseases
Discussants: Prof. Paolo Persichetti, Head of the Plastic Surgery and Dermatology Department, Campus Bio-Medico University Hospital, Prof. Cosmoferuccio De Stefano, Head Foundatione Alessandra Bisceglia ONLUS
Seminar promoted by the Plastic Surgery and Dermatology Unit, Campus Bio-Medico University of Rome.

Rome, 12 October 2015
CIPRNet Lecture: Secure estimation for wireless control under denial-of-service attacks
Discussants: Gabriella Fiore, Department of Information Engineering, Computer Science and Mathematics, L’Aquila University.

Rome, 13 October 2015
5° Workshop Tipitec: Quiet as a mouse? The word to technology
Seminar promoted by the Food Science and Nutrition Unit, Campus Bio-Medico University of Rome.

Rome, 14 October 2015
“Antioxidants, reality or myth?”
Workshop promoted as part of the Expo events
Discussant: Professor Laura De Gara, Food Science and Nutrition Unit, Campus Bio-Medico University of Rome.

Rome, 20 October 2015
Workshop: The risks associated with IEMI threats (Intentional ElectRomegnetic Interference): the results of the European Project STRUCTURES

Rome, 29 October 2015
6° Workshop Tipitec: In the garden of science technology bears fruit
Seminar promoted by the Food Science and Nutrition Unit, Campus Bio-Medico University of Rome.

Rome, 5 November 2015
Multimodal investigation of focal epilepsy combining EEG with MEG, fMRI and fNIRS
Seminar promoted by the Neurology Unit, Campus Bio-Medico University of Rome.
Rome, 19 November 2015
“From the Expo events to the Jubilee: security management”

Rome, 28 November 2015
2nd Update in osteometabolismo field
With the participation of: professor Paolo Pozzilli, Dr. Silvia Manfrini, Dr. Nicola Napoli, Dr. Andrea Palermo, Dr. Rocky Strollo, Endocrinology and Diabetes Unit, professor Vincenzo Denaro, Orthopaedics Unit, Campus Bio-Medico University of Rome.
Other participants: professor Daniele Diacinti – Rome, Dr. Stefania Falcone – Rome, Dr. Alberto Falcetti – Firenze, Dr. Daria Maggi – Rome, professor Silvia Migliaccio – Rome, professor Salvatore Minisola - Rome, Dr. Salvatore Monti – Rome, Dr. Assunta Santonati – Rome, Dr. Fabio Vescini – Udine, Dr. Sebastiano Vottari – Rome, Dr. Michele Zini - Reggio Emilia

Rome, 10 December 2015
Workshop: New technologies in biomedicine
With the participation of: professor Daniele Santini, dr. Francesco Pantano, Oncology Unit, professor Marcella Trombetta, professor Alberto Rainer Tissue Engineering & Chemistry for Engineering Unit, Campus Bio-Medico University of Rome.

Rome, 14 December 2015
Installation and testing of a magnetic resonance imaging system
With the participation of: Ing. Luciano Mirarchi, Siemens Healthcare
Seminar organized by the Measurements and Biomedical Instrumentation Unit, Campus Bio-Medico University of Rome.

Rome, 15 December 2015
Nutrition workshop: Communication in food products between international and European regulations
With the participation of: professor Laura De Gara, Food Science and Nutrition Unit, Campus Bio-Medico University of Rome, Paolo Patruno, Deputy Secretary General Citravi (Liaison Centre for the Meat Processing Industry in the EU) Chiara Di Stefano, Policy Advisor European Affairs, Ferrero.
Organized by the Food Science and Nutrition Unit, Campus Bio-Medico University of Rome.
National collaborations

AB Analitica srl, Italy
Altec S.p.A., Italy
Animal Facility Centre, University of Rome Tor Vergata, Italy
ASRIS Onlus, Cagliari, Italy
Autentica Srl, Italy
Azienda Ospedaliero-Universitaria Pisana, Italy
Biological Science Department and Interdepartmental Centre for Stem Cell Research, Milan University, Italy
Bio-Ker srl (Multimedica SpA group), Italy
Biomechanics Institute, S. Anna School of Advanced Studies, Italy
Cagliari University, Italy
Carabinieri Headquarters for Healthcare, Italy
Catholic University of the Sacred Heart, Italy
CEBR Centre of Excellence for Biomedical Research, University of Genova, Italy
Cell Factory, Foundation IRCCS Cà Granda Ospedale Maggiore Policlinico, Italy
Confederazione Nazionale Coldiretti, Italy
Consorzio Ferrara Ricerche, Italy
Das S.r.l., Italy
Delta Software S.r.l., Italy
Department of Anatomy, Catholic University of the Sacred Heart, Italy
Department of Animal Medicine, Production and Health, University of Padova, Italy
Department of Astronautics, Electrical and Energetics Engineering, Sapienza University, Italy
Department of Clinical Sciences and Experimental Medicine, Sapienza University, Italy
Department of Information and Electrical Engineering, University of L’Aquila, Italy
Department of Molecular Medicine - Virology Section, Sapienza University, Italy
Department of Neurosurgery, University of Padova, Italy
Department of Pathology, Catholic University of the Sacred Heart, Italy
Department of Pathology, Sapienza University, Italy
Department of Public Health, Section of Hygiene, Catholic University of the Sacred Heart, Italy
Department of Therapeutic Research and Medicine Evaluation, Italian National Institute of Health, Italy
Elettronika S.r.l., Italy
ENEA, Italy
Eureka S.r.l., Italy
FIRMA - Forum Interdisciplinare per la Ricerca sulle Malattie Autoimmuni, Italy
Foro Italico University of Rome, Italy
Gal Colline Joniche a r.l., Italy
Gala Spa, Italy
G. B. Bietti Foundation for Study and Research in Ophthalmology, Italy
GIRRC - Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale, Italy
Guido Berlucchi Foundation, Italy
Hitachi Systems CBT S.p.A., Italy
Hospital “Ospedale Civile di Legnano”, Italy
Humanitas Research Hospital, Italy
IASI Institute for Systems Analysis and Computer Science (CNR), Italy
ICRANet, Italy
I.D.S. Corporation, S.P.A, Italy
INAIL - Prosthetic centre, Italy
Institute for Microelectronics and Microsystems, National Research Council (CNR), Italy
Institute of Clinical Physiology, National Research Council, Italy
Institute of Cognitive Sciences and Technologies, National Research Council (CNR), Italy
Institute of Legal Medicine, Catholic University of the Sacred Heart, Italy
International Centre for Relativistic Astrophysics Network (ICRANet), Italy
International School for Advanced Studies (SISSA), Italy
IPASVI, Italy
IRCCS Bambino Gesù, Italy
IRCCS Cancer Institute “Giovanni Paolo II”, Italy
IRCCS Casa Sollievo della Sofferenza, Italy
IRCCS MEDEA, Italy
IRCCS Istituto Nazionale dei Tumori, Italy
IRCCS Regina Elena (IFO-IRE), Italy
IRCCS San Raffaele Pisana, Italy
IRCCS Stella Maris, Italy
Iselqui Technology S.r.l., Italy
Italian Association for the Study of the Liver (AISF), Italy
Italian Society of Internal Medicine, Italy
Italian Space Agency, Italy
ITOP Officine Ortopediche S.p.A., Italy
Kell S.r.l., Italy
Kinetics Technology KT, Italy
Laboratori Informatica Applicata (L.I.A.), Italy
Laboratory of Micro and Nanofabrication (CNR-IFN), Italy
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<th>Organization</th>
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International collaborations

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B&J Adaptaciones, Spain
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International Journal of Medical Biotechnology & Genetics (Associate Editor)
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PHD COURSES AND XXVIII CYCLE
(2013-2015) THESSES
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 carried out and completed within three years of study.

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**Ph.D in BIOENGINEERING AND BIOSCIENCES**

Duration: 3 years
Coordinator: Professor 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, the other to Science and food technology and nutrition. The 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 training in biomedicine, with other basic and applied 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, enabling technologies and systems for conceiving and developing novel medical devices, new approaches and understandings in medical and biological research; study systems and medical devices, medical and biological research, development of bioinspired medical and non-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 technology for the study of nutritional parameters and their impact in the prevention of diseases? Experimental protocols and procedures applied to clinical nutrition.
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 doctors 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

‘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

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### Tuesday 30 June 2015 – Aula Magna Trapezio

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<th>Time</th>
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| 9:30 a.m. - 10:00 a.m. | Welcome and Introduction  
Felice Barela, President  
Andrea Onetti Muda, Rector  
Paolo Sormani, General Manager of the University  
Simonetta Filippi, Pro-Rector for Education  
Eugenio Guglielmelli, Vice-rector for Research |
| 10:00 a.m. - 10:30 a.m. | Interdisciplinary training of young researchers  
Simonetta Filippi, Pro-Rector for Education |
| 11:00 a.m. - 1:00 p.m.* | Identity, mission and cultural project of the Campus Bio-Medico University of Rome  
Rossana Alloni, Campus Bio-Medico University Hospital |
| 2:00 p.m. - 6:00 p.m. | Short course: Radioisotopes and safety in the Lab  
Fabrizio Cichocki, Fismeco s.r.l.  
Pietro Luigi Indovina, Fismeco s.r.l.  
Leo Poggi, Prevention, Protection and Environment Office |

*parallel session EXPO/TIPITEC, Aula Magna PRABB

Welcome Lunch

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Campus Bio-Medico University of Rome / 2015 Research Yearbook

Tuesday 30 June 2015 – Aula Magna Trapezio
Ph.D dissertations defended in 2015
(*Link to full text dissertations: http://ilithia.unicampus.it/ilithia/Default.asp)

Impairment of human colonic smooth muscle contractility: role of microbiota modulation
Ph.D student: Annamaria Altomare  
Supervisor: Michele Cicala

Background: Several gastrointestinal (GI) tract disorders, such as acute enteritis, inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS), are associated with non-specific alterations.
of GI motility. We recently demonstrated the protective effect of inulin on LPS-induced damage of colonic smooth muscle in an ex vivo experimental model, which seems to be related to presence of oxidative stress.

AIMS: 1. To test whether exposure of the human colonic mucosa to pathogenic LPS may affect muscle cell contractility and to examine possible mechanisms responsible for the alterations in muscle contraction. 2. To evaluate the protective role of a prebiotic (Lactobacillus Rhamnosus GG) and a probiotic (INULIN) against LPS-induced oxidative stress.

Materials and Methods: Human colonic mucosa and submucosa, obtained from disease-free margins of resected segments for cancer, were sealed between two chambers containing Krebs solution, with the luminal side of the mucosa overlayed with 5 ml of Krebs (CONTROL), or 100 µg/mL LPS solution (LPS), or 100 µg/mL LPS +100 mg/mL inulin Fructafit IQ (LPS+INU). The biological system was kept oxygenated for 30 min at 37°C. Protein oxidation was evaluated in the colonic mucosa by measuring carbonyl group content using the dinitrophenylhydrazine and measuring the formed complex by spectrophotometric analysis. Total antioxidant capability of fructans, with different degrees of polymerization (DP – 8–125), was analysed by the TEAC method and compared with the antioxidant activity of simple sugars forming fructan polymers (glucose, fructose and sucrose). iTRAQ based analysis was used to separate and compare the total soluble proteomes from human colonic mucosa and submucosa treated. Each sample was labelled by one of four reagents of the iTRAQ 4-plex and then combined into one aliquote. Proteomic analysis was performed on colonic mucosa following CONTROL, LPS or LPS+INU exposure.

Results: All the tested fructans showed greater antioxidant capability than sucrose, glucose and fructose. The antioxidant activity of IQ was not affected by treatments at high temperature, as well as by pH changes and exposure to digestive enzymes. By measuring inulin in the model undenatants, we found that inulin did not cross the colonic mucosa layers. When the colonic mucosa was exposed to LPS+INU, the amount of the colonic mucosa carbonyl groups was reduced of about 60% compared to LPS exposed mucosa. The ROS protecting effects of inulin was also discussed on the light of the results obtained by proteomic analysis. Interestingly, Inulin is able to restore the level of some important proteins, involved in the inflammation processes, that are decreased following LPS exposure: High Mobility Group proteins, that mediate the transcription of Prdx genes protecting cells from oxidative stress; Tryptases, that have been implicated as mediators in inflammatory disorders; Glutathione S-transferases (GSTs), that are a superfamily of detoxification enzymes, which play an important role in the protection of tissues against potentially harmful compounds.

Conclusions: Inulin protects the human colon mucosa from LPS-induced oxidative stress. Our preliminary data suggest that the beneficial effects of inulin on the health of the host could be related, not only to its bifidogenic action, but also to its antioxidant properties.
Rome, 90 autopsies were performed and three samples of pancreatic tissue were taken (head, body and tail) for each case. In order to quantify beta-cell presence in tissue samples, standard immunohistochemical staining was employed, and semi-quantitative and quantitative methods were used. Results: The majority of islets and insulin in the homogenized tissue are found in the tail of the pancreas. Since the large majority of pancreatic cancers are detected in the head and body of the gland, our data, although limited by the small sample size, seem to suggest that irrespective of diabetes and associated factors, insulin “per se” should not be considered as a promoting factor for pancreatic cancer. Conclusion: We demonstrate that insulin assay in homogenized pancreatic tissue and insulin immunohistochemical staining from cadaver donors after a few hours of death are feasible, despite the known fact that this organ is exposed, more than others, to the local autolytic action of enzymes. The technique has proved to be reproducible and useful to achieve semiquantitative results. We conclude that it is unlikely that insulin may promote pancreatic cancer.

**Rem (risk of endometrial malignancy): elaborazione di un nuovo score predittivo di rischio del tumore dell’endometrio**

**Ph.D student:** Stella Capriglione  
**Supervisor:** Roberto Angioli  

**Purpose:** It is often difficult to distinguish a benign endometrial disease from a malignancy and tools to help the physician are needed to triage patients into high and low risk of endometrial cancer. The purpose of this study was to obtain a predictive model to assess the risk of endometrial malignancy (REM) in women with ultrasound endometrial abnormalities.  

**Experimental Design:** Women, between ages 45 to 80 years, diagnosed through ultrasound with endometrial abnormalities and scheduled to have surgery were enrolled on a prospective study at the Department of Gynaecologic Oncology of Campus Bio-Medico, University of Rome. Preoperative clinical, ultrasound and laboratory characteristics were taken into account. Logistic regression algorithm was used to categorize patients into low- and high-risk groups for endometrial cancer.  

**Results:** A total of 675 patients were considered for the analysis: 88 with endometrial cancer and 587 with benign endometrial disease. We divided the patients into two groups: training set (TS) and verification set (VS). Preoperative age, symptom, HE4 levels, and ultrasound endometrial thickness were found statistically significant, and were included into a multivariate logistic regression model to determine the probability to have endometrial cancer. In the TS, REM reported 93.3% sensitivity and 97.1% specificity (positive predictive value (PPV), 0.83; negative predictive value (NPV), 0.98; AUC, 0.95; 95% confidence interval (CI), 0.908–0.984). In the VS, REM reported 89.3% sensitivity and 95.4% specificity (PPV, 0.73; NPV, 0.98; AUC, 0.919; 95% CI, 0.829–0.970).  

**Conclusions:** Our data support the use of REM to triage patients into low- and high-risk groups for endometrial cancer, even if an external validation of the model is needed.

**Multiscale modelling to unravel the interplay between morphogen gradients and zonation in the root meristem of a.thaliana.**

**Ph.D student:** Micol De Ruvo  
**Supervisor:** Luisa Di Paola  

An intriguing challenge in developmental biology is to understand how organ development is spatially coordinated to form well-structured, patterned complex organisms in a reproducible way. In multicellular organisms, pattern formation is related to the graded distribution and activity of signaling molecules called morphogens: dividing cells exposed to particular concentration thresholds of a morphogen follow a developmental path of cell differentiation, which results in spatio-temporal patterns. Formation, positioning and maintenance of the boundaries between
these cell compartments are essential for the correct outcome of the patterning events. The development of animals and plants is based on a similar logic. Both in animal and plant development, a gradient of cell differentiation arises from stem cell niches, where local signals from an organizer coordinate the balance between self-renewal and the generation of daughter cells that differentiate into new tissues. However, in animals, at the completion of development, self-renewal and differentiation is strictly localized to very few stem cells. In contrast, plant post-embryonic development is maintained throughout the plant lifespan by the activity of root meristems, where stem cells are localized and the transition from cell division to cell differentiation is orchestrated to generate distinct developmental zones. In the model plant Arabidopsis thaliana, advanced molecular, genetic and genomic tools are available and root development is arguably the most tractable system. A key role for plant hormones in Arabidopsis root development is well established. Specifically, the phyto hormone auxin acts as a morphogen, as its asymmetric distribution within tissues sets positional information that guides cell-type specification, thus patterning and growth. Auxin peculiar carrier-mediated polar transport gives rise to a concentration gradient along the root longitudinal axis, which shapes developmental zones: stem cell niche, division zone and differentiation zone. The formation of an auxin maximum in the stem cell niche is essential to maintain stem cell function. At the boundary between the zones (transition boundary) auxin divisional activity is counteracted by the phyto hormone cytokinin, and their dynamic crosstalk is necessary to balance cell division over cell differentiation, in order to set a stable meristem size. Molecular genetic approaches have identified many of the key signals components underlying auxin and cytokinin interaction in the Arabidopsis root, providing qualitative but not quantitative insights into the activity of cytokinin on auxin distribution. Moreover, there are no tools available to make auxin gradients directly visible in living tissues. In order to explain the observed cell-type specific auxin distribution and how cytokinin shapes auxin gradients, I thus adopted a systems biology approach, integrating experimental evidence with mathematical and computational modelling. This approach enables a simplified and formal description of the biological mechanisms at different scales (molecular, subcellular, cellular and supracellular) and allows for theoretical assumptions that could guide future experiments, whose results can feedback into the model. In recent years, several modeling approaches have provided a good qualitative description of auxin transport, but the link between physico-chemical and biological descriptors is still missing and none of the proposed mechanisms unveils the developmental cues that drive the emergence of meristem zonation at the cellular level. During my PhD project, I dissected the problem both by theoretical and computational tools. Mathematical modelling is essential to define explicitly the relationship between physical entities attempting to find an analytical solution to the problem. On the other hand, computational modelling is advantageous in that it provides numerical solution to complex problems through the implementation of powerful algorithms. Therefore, I first developed a one-dimensional analytical and theoretical description based on physico-chemical laws, in order to provide a straightforward condition for auxin maximum formation and a framework for a quantitative assessment. Within this framework, I linked microscopic (cell-based) description to macroscopic (organ-scale) dynamics through a derived auxin diffusivity parameter and through reaction terms. The derivation of a cell-specific equivalent diffusivity allows for a direct link both between parameters and between discrete and continuous formalisms: in the limit of a continuous description, I was able to derive a linear diffusion equation, where all transport components are embedded within the equivalent diffusivity parameter. I was eventually able to estimate an average value for the equivalent diffusion coefficient. Extending the analysis to the organ scale I provided further conditions for the “reflux fountain” of auxin in the meristem. As an ultimate goal, I envision that this formalism could be used as a tool for the estimation of parameters given sensor-derived auxin maps. Moving forward, to investigate the cell-specific interplay between auxin and cytokinin and its effect on meristem size, I developed a two-dimensional computational model combined with a genetic approach. I integrated experimentally derived parameters into a spatial model at cellular resolution that simulates auxin transport within a layout resembling root geometries,
This two-dimensional model provides a mechanistic understanding on how the shape of the auxin graded distribution in the root depends on the hormone cytokinin, which controls both auxin transport and local auxin degradation. The model predicts, as an emerging property, that the dual input of cytokinin results in an auxin minimum at the transition zone. This auxin minimum acts as a positional signal to trigger the transition between dividing and differentiating cells, thereby setting a boundary to control meristem size and root growth.

Gluten intolerances and nutritional quality of einkorn wheat (Triticum monococcum)

**Ph.D student:** Gloria Gazzelloni  
**Supervisor:** Maria Grazia D’Egidio

Einkorn (Triticum monococcumssp monococcum) is a diploid wheat species tolerant to various biotic and abiotic stresses, capable of providing a cost-effective production even in absence of fertile soils. Recent studies show that the einkorn grain is characterized by high content of biologically active compounds such as tocols, carotenoids and fructo-oligosaccharides (FOS) and by the presence of prolamine with reduced toxicity for celiac patients. In this thesis work, the prolamins extracted from S. Pastore and Bolero common wheat varieties, have been digested with pepsin and trypsin and have been administered to human leukemia cells K562 (S) causing their complete agglutination at a concentration of ≥73 mg/L. The same effect has been found with prolamins extracted from three genotypes of einkorn wheat (ID 1636, ID 358 and Monlis) free of 7-gliadins. On the contrary, the prolamins obtained from einkorn cvs Hammurabi and ID331, both expressing 1ω-gliadins, have not been able to agglutinate K562 cells (S) even at concentrations ≥4000 mg/L. Moreover, the cultivation in vitro of small intestine mucosa from 5 celiac patients, exposed to prolamins extracted from common wheat cv. Bolero and einkorn wheat cvs Monlis and ID 358 have incorporated bromodeoxyuridine (BrdU) in a high percentage (≥30%) in the epithelial cells of the crypts; percentage significantly higher than that of untreated cells (14.4%) or of those cells exposed to the prolamins of einkorn cv. Hammurabi (14.2%). The stimulation of cell proliferation has returned to baseline (14.0%) when 10 µg/mL of 9-mer peptide QQPQRQPQPF have been added to the prolamins from common wheat cv. Bolero. Two-dimensional electrophoretic separations A-PAGE x SDS-PAGE identified 12-13 1ω-gliadins in cv. Hammurabi and a single 1ω-gliadin (1ω-331) at low apparent molecular weight (45 kDa) in cv. ID 331. The 1ω-gliadins of einkorn cv. Hammurabi belong to four families with different molecular weight (from 60 to 50 kDa), each consisting of 2 or 3 proteins, in addition to a small gliadin (1ω-331H) similar to the above-mentioned 1ω-331. Immunoblotting test, with specific antibodies developed in rabbit, allowed to ascribe six of 12-13 1ω-gliadins present in cv. Hammurabi to three gene families (in nucleotide sequence known to bind and peptide 9-mer QQPQRQPQPF to gliadin-331 and w-331H). The peptide was also found in 1ω-gliadin homologous to the 1ω-331 in other 19 accessions of einkorn wheat among the 48 analyzed. The analysis of the MALDI spectrum has showed that 1ω-331 is actually composed of two polypeptides, one of them has an amino acid sequence corresponding to the nucleotide sequence of the 1ω-21gliadin protein. The experimental cultivation of einkorn cvs Monlis, Hammurabi and ID331 in Rome and Sardegna in two cultivation systems (organic and conventional) has confirmed the high protein content, carotenoids and high antioxidant capacity compared to common (cv. Blasco) and durum (cv. Simeto) wheat. Moreover the farinographic and alveographic analysis showed that the einkorn doughs have values of alveographic W (11-52 Jx10-4) far from optimal values for the purposes of the bakery (W ≥180 Jx10-4). Among the three genotypes the variety Monlis, devoid of 1ω-gliadins, gave the best results from a technological point of view, whereas the variety Hammurabi, with several 1ω-gliadin components, showed poorer visco-elastic properties. The rheological parameters of ID 331, containing the sole 1ω-331, are similar to those of Monlis. In conclusion, it was obtained experimental evidences that the reduced toxicity of prolamins of einkorn cvs Hammurabi and ID331 is associated with the presence of the 1ω-gliadin peptides and in particular with the «protective» QQPQRQPQPF peptide present in 1ω-331 and 1ω-
331H gliadins. This peptide shows the insertion of the dipeptide sequence RP in QQPQQPF which is very common in the ω-gliadins of wheat and it has the same «protective» effect of QQPQDAVQPF and QQPQRQPPQPF peptides already described in the literature, respectively in durum wheat and rye. On the other hand, the absence of ω-gliadins was associated with a higher quality of gluten in Monlis than in Hammurabi. The variety ID 331 containing the ω-331 protein as the only ω-gliadin component puts together an acceptable bread making quality with a reduced toxicity to the intestinal mucosa of celiac individuals.

A swallowable smart pill for drug delivery into the gastrointestinal tract

Ph.D student: Rosa Goffredo
Supervisor: Eugenio Guglielmelli

Gastrointestinal system diseases are the most common cause of mortality and hospitalization (21.7 million 2010 in USA (2010)) in developed countries and, due to demographic changes, are still on the rise. Different pathologies are specific for every tract of the gastrointestinal system, from the esophagus to the bowel. In particular, chronic inflammatory diseases are widespread and require long lasting therapies. A new frontier in treatment of chronic diseases is represented by localized therapies that can bring benefits in terms of quantity of medication delivered and costs of the treatment. In recent years, technologies in medical robotics and micromechatronics are steadily growing and are capable of producing safe enough solutions to be applied in medicine. In fact, it is possible to find robots that help in several subdomains such as surgery, diagnosis and therapy. In addition, the development of Micro-Electro-Mechanical Systems (MEMS) technology permits the miniaturization of robots to use them in a less invasive way. In particular, untethered endoscopic tools have been developed and commercialized in order to reduce discomfort to the patients. To date, it has been shown that endoscopic capsules can provide more cost effective solutions than wired endoscopes for the same performance. As an example, capsule endoscopes overcome problems of insertion and intubation. Furthermore, capsules can navigate deeply into the small intestine that usually is a dead zone for wired endoscopes. Despite capsule endoscopes are widespread, new tools are to be developed for drug delivery and biopsy in order to implement therapeutic and intervention properties on the capsule. Focusing on therapeutic properties, capsules for drug delivery provide the possibility to improve the treatment of chronic gastrointestinal diseases. Major advantages that the use of capsule for drug delivery can bring are i) localized therapy, with a consequent reduction of drug doses and reduced side effects compared to systemic administration, ii) costs reduction, thanks to significantly reduced drug doses and iii) shortened hospitalization periods for patients. These advantages confer to capsules for therapeutic action a dominant role in new medical treatments, in particular for local drug delivery. The aim of this thesis is to investigate how to develop an autonomous micromechatronic system and how therapeutic functionalities can be embedded on a swallowable capsule. To this aim the following main topics have been addressed: 1. Design and fabrication of an autonomous smart pill, considering environmental requirements and biocompatibility. 2. Integration of micro-electronics on-board for autonomous navigation and sensors to monitor physiological conditions of the gastrointestinal tract and trigger the activation of the drug delivery system. 3. Development of an active drug delivery system to be integrated on a swallowable capsule. To these purposes, special attention has been given to: - the environment requirements in term of size, materials biocompatibility and power supply. - The development of a sensing system capable of triggering the activation of the drug delivery system. - The development of an effective drug delivery system capable of delivering a controlled desired amount of drug thanks to a custom made drug delivery pump sensorized with a novel strain sensor. In the thesis micromechatronics design principles and their specific application to medicine are detailed together with features of smart pills. Analyzing the state of the art, requirements and open challenges in the field of smart pills are pointed out, so the architecture of the system developed and the design of the capsule is described considering bio-
compatibility and size issues (topic 1). Then the sensing system (topic 2) is described. The use of impedance measurement in medical practice and the advantages of using impedance as a medical index for pathological alterations of gastrointestinal tissue properties are explored. The developed of the impedance sensor is then tested and results are presented. Then the development of the drug delivery system (topic 3) is presented. The design and fabrication of the custom made drug delivery system are presented together with its performances. As for local drug delivery a volume of 50 µl is required, a custom made electrolytic micro pump has been designed and integrated on board. The pump for drug release is sensorized with a novel strain sensor and different solutions for the sensorization are presented and discussed. The sensorization of the membrane is functional to the control of the volume of drug released. One major advantage of the use of a strain sensor is the resulting versatility of the system: the smart pill can be used to deliver different types of drugs, not being influenced by the viscosity of the medication, neither by external conditions (e.g. gastric fluids pressure). Finally, a swallowable smart pill has been designed and developed, its sensor system for lesion localization has been developed and tested and a novel drug delivery system, a novel drug delivery system has been developed and sensorized for the monitoring of the drug released.

**Advanced theoretical modelling and fluid-structure interaction analysis of patient-specific cardiovascular haemodynamics.**

**Ph.D student:** Maria Giuseppina Chiara Nestola  
**Supervisor:** Simonetta Filippi

Cardiovascular diseases are the most common cause of morbidity and mortality in the developed countries. Understanding the main mechanisms responsible for the onset and the subsequent development of these pathologies is essential in providing accurate and reliable representations of the physiological and pathological flow conditions in the cardiovascular system. Recent progress in medical imaging and geometry reconstruction techniques allowed scientists to obtain accurate descriptions of a vascular compartment of a specific individual. Nevertheless, despite the significant amount of biological data available, the translation of these data into more effective therapies, surgical planning and optimization of medical devices represents a very important issue. In this regard, computational models of the cardiovascular system have the potential to deliver a concrete aid in diagnosis and therapy in health-care. Indeed, numerical simulations of blood flow and the mechanical response of blood vessels may help both biomedical engineers and medical doctors to better characterize the patient conditions and increase the confidence of the estimate. This thesis focuses in this direction, by producing several novel outcomes. The first contribution consists in a deep investigation into the role of haemodynamics in the development of abdominal aortic aneurysms (AAAs) and the deposition of an intraluminal thrombus in the aneurysm sac. Indeed, several in vivo and in vitro observations suggested that non-physiological Wall Shear Stress (WSS, i.e. the tangential force per unit area exerted by blood on the arterial wall) might regulate the expression of an inflammatory, hypertrophic and thrombotic state. WSS signal may exhibit complex spatiotemporal patterns and the best way to extract quantitative synthetic information on the clinical risk is still an open question. Nevertheless, there is a recurring need to provide medical doctors with haemodynamic risk indicators/predictors supporting the decision-making protocol. In this dissertation, two novel synthetic risk predictors based on the Three-Band Decomposition (TBD) analysis are introduced and tested by performing geometrical multiscale fluid-structure interaction simulations in both idealized and patient-specific scenarios. In particular, the preliminary WSS analysis carried out using axially symmetric geometries suggests that the averaging operations involved in the definition of the risk indices commonly adopted in the Literature may induce a low level of information with respect to the complexity of the WSS spatiotemporal distribution. In this regard, the obtained results demonstrate that the TBD analysis can highlight the significant features of the shear stress and its role in the development of AAAs.
Moreover, the two novel risk predictors related to the TBD analysis improve the risk assessment for both thrombus deposition and bulge expansion in the aneurysms models. The results obtained in such simplified geometries are confirmed by accurate numerical simulations performed for patient-specific models of both a healthy abdominal aorta and an abdominal aortic aneurysm. In particular, as expected, the healthy scenario does not show a significant risk pattern. On the contrary, in the patient-specific AAA model, a good agreement is found between the sites of platelets deposition, computed by performing a particle tracking, and the risk information provided by the two TBD-based risk predictors. The results also show good agreement with clinical data, thus confirming the ability of the TBD analysis and the associated risk indices to give access to the risk information related to the thrombus development. The second novel outcome of this dissertation is to compare the biomechanical performances of the stented and the stentless biological prostheses used for the replacement of the aortic valve. In particular, a stented prosthesis consists of a porcine aortic valve or bovine pericardial tissue leaflets mounted on a rigid frame surrounded by a synthetic sewing ring. The stentless biological prosthesis is obtained from the stented one by eliminating any rigid support. In particular, the Sorin Freedom SOLO stentless prostheses require a minimal surgical implantation technique with a single suture running around the three sinuses of Valsalva. In this dissertation, a finite element analysis based on the fluid-structure interaction between the blood and the surrounding aortic wall is carried out. To this aim, three patient-specific aortic root geometries have been reconstructed and for each of these, the stented, the stentless, and the native (healthy) configurations have been drawn. The obtained results reveal that the stentless prosthesis leads the aortic root to recover a more physiological dynamics with respect to the stented one, both in term of displacement magnitude and von Mises stresses. Finally, the third novel contribution of this thesis concerns more analytical aspects related to the role of the spatial variations of WSS in the development of vascular pathologies. Indeed, experimental studies demonstrated that the spatial gradient of Wall Shear Stress (WSSG) may promote inflammatory processes in the arterial wall of the blood vessels. In the Literature, the WSSG has been defined as the directional derivative of the WSS. However, by using the rigid frame formalism, one can show that the geometrically correct definition must involve the evaluation of the intrinsic derivative. The relevant differences found between the two definitions, by adopting analytical and numerical estimates, support the necessity to re-evaluate the past considerations on the WSSG in the Literature, specifically on the haemodynamic risk.

Antioxidant compounds in durum wheat: study of genetic, environmental and technological influencing factors for the development of pasta with high nutritional and healthy potential.

Ph.D student: Daniela Martini
Supervisor: Maria Grazia D’Egidio

Aim of the research activity performed during the PhD was to investigate the effects of genetic, environmental (crop year and growing area) and technological factors (both traditional and innovative) on the occurrence of antioxidant compounds and on the total antioxidant activity in durum wheat and pasta. The researches were mainly focused on the occurrence of phenolic acids (PAs), analyzed by RP-HPLC on a semi-micro separation scale. PAs represent the most common form of phenolic compounds in durum wheat whole grain as soluble free, soluble conjugated and as insoluble bound forms acids. Total phenolic compounds, yellow colored pigments and total antioxidant capacity were also investigated. Results showed that crop year, genotype, growing area and their interactions significantly affected the content of antioxidant compounds and total antioxidant capacity of durum wheat, although to different extents. Regarding the technological processes, traditional milling and pasta-making negatively influence the content of antioxidant compounds and antioxidant activity, while innovative processes like the debranning appeared to be a valuable way for reaching the level representing the best compromise between nutritional, technological, sensory and hygienic-sanitary aspects. The last part of the research activity was devoted to develop durum wheat pasta with high nutritional, hygienic-sanitary and sensory quality.
by using durum wheat debranning, and to explore the bioavailability of phenolic compounds when the pasta samples were consumed. The development of innovative pasta obtained by using debranned products demonstrated that this process can be useful to preserve the occurrence of antioxidant compounds with a low impact on the technological quality and a relatively high bioavailability of phenolic compounds. In conclusion, the research activity performed during the PhD demonstrated that, besides environmental and genetic factors, innovative technological processes can be usefully applied to obtain high quality pasta which can help the consumers to increase their daily intake of fiber and many other bioactive compounds.

Prefrontal functions in multiple sclerosis patients without cognitive impairment: a neuropsychophysiological approach

Ph.D student: Simone Migliore
Supervisor: Fabrizio Vernieri

Main aim of this PhD thesis was to assess the prefrontal functioning in Multiple Sclerosis (MS) Patients without cognitive impairment. For this purpose three research protocols were carried out:

1. translation, cross-culturally adaptation and validation of the Italian version of the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS), the most sensitive and comprehensive battery available for MS cognitive assessment;
2. exploring the executive functions in MS patients without cognitive impairment compared to healthy controls (HC) by means of a task-switching paradigm;
3. assessment of the emotional processing in MS patients without cognitive impairment by means of psychophysiological approach and International Affective Picture System (IAPS), a set of pictures designed to study emotions recognition and widely used in psychological research.

The main results of each research project were the following:

1. PRELIMINARY STUDY: VALIDITY OF THE MACFIMS IN THE ITALIAN POPULATION. Cognitive dysfunction involves 40-65% of MS patients. It can be detected in all MS phenotypes since early stages of the disease and it tends to progress over time. MACFIMS has been proved to be the most sensitive and comprehensive battery available for MS cognitive assessment in English population. In Italy the MACFIMS applicability is limited in everyday clinical practice since the overall validity of this battery in the MS Italian population has never been demonstrated. One hundred and thirty patients with clinically diagnosed MS and 60 HCs matched by sex, age and education were enrolled. Our data confirmed the group differences between MS patients and HCs in cognitive performance as assessed by the MACFIMS. Overall, with respect to the Relapsing group, the Progressive one had lower performances in every test considered. The rate of cognitive impairment (CI) tended to increase both with disease duration and with physical disability. According to previous literature, more than half of MS patients (70.8 %) exhibit CI (at least two tests failed); out of them 18.5% were mildly, 10% were moderately, and 42.3% were severely compromised. The cognitive functions mostly affected were visual memory and information processing speed/executive functions. Considering the number of cognitive domains impaired, we found that 57.7% of MS patients showed at least two domains compromised (out of them 20.0% mildly, 16.9% moderately and 20.8% severely impaired). This classification may be more specific to identify MS patients with a clear cognitive impairment; in fact, patients with two tests failed in the same domain are not considered CI ‘multi-domain’. In evaluating the Principal Component Analysis (PCA), we identified four components: visual–spatial memory/processing speed; working memory; executive functions; verbal memory. Our study is the first to validate the Italian version of the MACFIMS.

2. A TASK SWITCHING PROTOCOL TO ASSESS EXECUTIVE FUNCTIONING IN MS PATIENTS WITHOUT COGNITIVE IMPAIRMENT. Impaired executive functioning can occur since early stages of MS; this pattern was correlated with changes in fronto-subcortical fiber tracts. A specific method for assessing executive functions is the task-switching paradigm, that examines the...
processes shifting from one task to another; the subjects complete a set of task, engaging operations that must be performed in an alternating or repeating sequence. Twenty-four MS patients without cognitive impairment and 25 HC (paired for age, sex and education) were enrolled. MACFIMS battery was administered to exclude subjects with cognitive impairment. Participants were asked to complete two different tasks in rapid and random sequence, so that the task may change from one trial to the subsequent (switch trial), or may be repeated (repetition trial). A significant difference between MS patients and HC was found: analyses on switch and repetition trials showed that the MS patients performed significantly worse just in switch trials. Moreover, a significant increase in Reaction Times (RT) in MS groups shifting from one task to another was observed. No differences were observed in RT related to the disengagement from the previously executed task. This study suggests a primary engagement of executive functions in MS patients without cognitive impairment, mainly depending by the functional integrity of the prefrontal cortex.

3. EMOTIONAL PROCESSING IN MULTIPLE SCLEROSIS: A PSYCHOPHYSIOLOGICAL STUDY.
Recent studies showed that MS can influence the emotions perception, both in behavioral terms and in neuronal activity. In order to examine the emotional processing, most of these studies considered emotional stimuli mediated by facial expressions. The aim of our study is to evaluate the emotional processing of complex stimuli in MS patients without cognitive impairment through a psychophysiological approach (Event Related Potential - ERP - and Skin Conductance - SC). Twenty-four MS patients without cognitive impairment and 23 HC (paired for age, sex and education) were enrolled. MACFIMS battery was administered to exclude subjects with cognitive impairment. Results showed differences between groups: patients exhibited higher SC response than HC when an emotional trigger was presented. Similarly, for the neurophysiological activity, patients showed higher latency of the P200 component on CZ (a component associated with attentional processes to emotional stimuli) than HC. No difference in behavioral response was found. Overall, our studies showed that detecting an early executive functions impairment (cognitive and behavioral/emotional one) with specific testing could be useful for a prompt enrolment of MS patients into adequate rehabilitation protocols.

DNA methylation signature in type 1 diabetes.
Ph.D student: Mary Anh Ngoc Dang
Supervisor: David Leslie
Type 1 diabetes is an autoimmune disease due to the interaction of genetic and non-genetic factors, leading to an immune response against insulin secreting islet cells. Concordance rates for type 1 diabetes in monzygotic twins vary widely and no single environmental factor has been shown to cause the disease. Therefore, epigenetics has been suggested to play a role in diabetes aetiology. Preliminary results identified DNA methylation changes in CD14+ monocytes from childhood-onset type 1 diabetes which antedated the disease. Following on from this work, this present study was carried out to investigate whole genome DNA methylation profiles in CD14+CD16-monocytes, CD4+ T cells, CD19+ B cells and buccal cells from 24 monozygotic twin pairs discordant for type 1 diabetes. DNA methylation was profiled using Illumina Infinium HumanMethylation450K BeadChip and analysed using the ChAMP pipeline. Bisulfite sequencing was also carried out on CD4+ cells from four monozygotic twin pairs also discordant for type 1 diabetes. Through bioinformatics analyses, 258 celltype specific differentially-methylated positions were identified from the 450K BeadChip and 125 differentially-methylated regions from bisulfite sequencing. DNA methylation was also shown to be stable, as similar methylation differences found in the preliminary study, were again detected in the same twin pairs sampled years later. As DNA methylation is a stable marker, it could be used as a biomarker. β-cell death in diabetes releases DNA with unmethylated CpG sites in the insulin promoter region into the blood circulation. To detect these differences, an assay was also developed testing serum samples from monozygotic
twin pairs. The data presented provided comprehensive DNA methylation profiles in type 1 diabetes from this discovery cohort. The methylation signature found will then be validated in diabetic, pre-diabetic and control singletons. This in turn will provide data for later functional analyses to identify genes associated with type 1 diabetes risk.

On inertial sensing of motion: validation, calibration and tracking with wearable devices in robotics and biomedical applications

Ph.D student: Luca Ricci
Supervisor: Domenico Formica

The class of inertial sensors have undergone a revolution in the last decades. From the technological standpoint, this transformation has brought a dramatic reduction in both size and cost after the advent of micromachined electro–mechanical system (MEMS) technology. From an application standpoint, they have spread out from the traditional aeronautical and naval fields (i.e. inertial navigation systems) to a plethora of new and different areas, e.g. automotive, robotics and clinical to name a few. Nowadays, inertial sensors are available on the market as system on chip (SoC) that are small enough to be unobtrusively attached to any system, including the human body, and their presence in consumer products has become a commonplace (e.g. in smartphones) virtually electing them as a top player in the upcoming wearables era. However, miniaturized inertial sensors come with inherent limitations that are mainly found in the reduced performance in terms of noise. Besides, the more recently introduced applications are still far from being mature (e.g. human motion capture). As a consequence, there is a number of open challenges related to the use of this evolved technology and that spans from signal processing and sensor fusion of noisy measurements to the improvement of existing algorithms and expansion to unexplored areas of application. The main objective of this work is to improve the state of the art with respect to some of these challenges. First, the dissertation examines the problem of establishing accuracy in measuring orientation for current inertial sensor fusion algorithms. A methodology based on the use of a robotic manipulator is presented and confidence intervals of static and dynamic performance are established. Then, the thesis discusses the problems of calibration and motion tracking with inertial sensors in two different contexts of application, i.e. ground mobile robotics and biomedical research. Regarding robotics, the setup explored in this thesis consisted of an omnidirectional wheeled platform, equipped with an inertial sensor and wheel encoders, intended to be navigated in a industrial setting. While this class of robots has superior mobility characteristics, difficulties related to their autonomous navigation prevent their widespread use in the research and industry. To overcome this limitation, a number of sensor fusion problems are presented and a solution proposed in order to self calibrate the platform and ameliorate accuracy of the navigation through robustness, e.g. against wheel slippage. Regarding the biomedical application, inertial sensors were used to reconstruct the motion of children (6-7 years old) in a daily life scenario. To this purpose, a novel calibration procedure and algorithms are introduced to improve accuracy over state of the art methods. The outcome of this research will permit the investigation of motor disorders at an earlier stage of development than is currently possible (e.g. for the case of autism spectrum disorder).

Effects of multiple dietary supplements on cardiometabolic health.

Ph.D student: Andreea Soare
Supervisor: Luigi Fontana

Introduction: Dietary supplements are widely used for health purposes. However, little is known about the metabolic and cardiovascular effects of combinations of popular over-the-counter supplements, each of which has been shown to have anti-oxidant and/or anti-inflammatory properties in cell culture or animal studies. Hypothesis: The main hypothesis of this PhD was that I think it
might be possible, by combining a large number of supplements/phytochemicals that have complementary, additive and/or synergistic effects, to duplicate to a large extent the anti-oxidant and/or anti-inflammatory properties in humans. Specific aims - To evaluate the effect of the supplements on markers of aging process as endothelial function and arterial stiffness, on processes involved in mediating aging and risk factors for diseases that mediate secondary aging, on markers of inflammation and oxidative-stress.

Methods: This study was a 6-month randomized, single-blind controlled trial, in which 56 non-obese (BMI 21.0-29.9 kg/m2) men and women, aged 38 to 55 yr, were assigned to a dietary supplement (SUP) group or control (CON) group, with a 6-month follow-up. The SUP group took 10 dietary supplements each day (100 mg of resveratrol, 650 mg of quercetin, 500 mg of acetyl-l-carnitine, 600 mg of lipoic acid, 900 mg of curcumin, 1 g of sesamin, a complex of 800 mg each of green, black, and white tea extract, 250 mg of pomegranate extract, and 1.7 g of cinnamon bark extract, and 1.0 g fish oil). Both the SUP and CON groups took a daily multivitamin/mineral supplement. The main outcome measures were arterial stiffness, endothelial function, biomarkers of inflammation and oxidative stress, and cardiometabolic risk factors.

Results - Twenty-four weeks of daily supplementation with 10 dietary supplements did not affect arterial stiffness or endothelial function in nonobese individuals. These compounds also did not alter body fat measured by DEXA, blood pressure, plasma lipids, glucose, insulin, IGF-1, and markers of inflammation and oxidative stress. Conclusions: Supplementation with a combination of popular dietary supplements has no cardiovascular or metabolic effects in non-obese relatively healthy individuals.

Interfacing the peripheral nervous system: towards the development of a bidirectional neural communication.

Ph.D student: Francesco Maria Petrini
Supervisor: Silvestro Micera

The human hand executes incredibly sophisticated tasks as the result of the synergistic interplay between motor and sensory functionalities. The hand loss is a life changing physiological and psychological trauma, which degrades significantly every day activities of people. The ideal prosthesis should restore sensory and motor capabilities to amputees. Current available devices, however, provide users with a restricted gamma of movements and without sensory feedback and, as a consequence, are often abandoned. In the last 20 years, the fascinating possibility to access the human peripheral nervous system, for the development of natural and effortless man-machine interfaces, has been proposed. However, presently, there is a gap between the proofs-of-concept that have been shown and reliable and efficient assistive bidirectional devices. Main reason for it is a limited basic understanding both about: i) the nature of the efferent peripheral signals that could be used as the signal triggering the actuation of a neuroprosthesis, and ii) about the effects of the afferent neural stimulation, and the way to use it in a sophisticated manner. Present thesis is aiming to advance the basic knowledge and to introduce novel findings into the bidirectional neuroprosthesis implementation. Indeed it presents novel strategies for decoding subjects’ voluntary motor intention from efferent fibers firing recordings, and for restoring sensory feedback in amputees by stimulating the afferent fibers in optimal way to transmit the effective sensory feedback to the brain. The design of these algorithms has been inspired by the natural mechanisms by which the peripheral nervous system drives hand movements and the physiological sensations coming from interaction with objects and their manipulation neuroprosthetics, peripheral nerve interfaces, motor control, sensory feedback restoration, efferent recording, afferent stimulation.

New tools for a technology-aided assessment of newborns’ oral-motor behavior

Ph.D student: Eleonora Tamilia
Supervisor: Eugenio Gugliemelli
Thanks to technology advances, the survival of high-risk newborns is increasing, and there is a rising concern about the potential problems that this population may encounter. As a result, both medical and research communities are calling for new and more reliable tools to support health care professional in assessing the newborn’s neuro-motor status, his readiness for discharge and planning for subsequent care. The newborn’s oral-motor behavior during feeding is the earliest window in which care providers and parents can view and assess the well-being of the infant. One of the major developmental milestones of high-risk newborns in fact is the attainment of adequate Nutritive Sucking (NS) skills for feeding: they often show oral-motor dyscoordination and are unable to suck and feed orally. This is why the importance of monitoring newborns’ oral-motor activity has been acknowledged over the years, and the need for reliable instruments has been recently stressed. Over the last decades significant advances occurred in the technology-assisted monitoring of NS disorders in newborns, however there are no accepted standards for their implementation in clinical practice, and so no objective tool is regularly and widely used. The goal of this PhD thesis was to provide new tools for a technology-aided assessment of newborns’ oral-motor behavior during feeding. The first objective has been to overcome the technological challenges emerging from the state of the art, designing a hardware platform that was suitable for a wide and regular application in both clinical (pre-discharge) and domestic (post-discharge) setting: i) A low-cost device for monitoring sucking pressures has been designed and developed in order to be easily integrated on a typical feeding bottle: the measuring system has been experimentally validated in laboratory and then tested collecting data on newborns during the routine clinical practice. ii) Two novel methods for the ecological estimation of nutrient consumption during bottle-feeding have been proposed and two low-cost sensor-based modules have been developed and experimentally validated in laboratory. iii) Given the importance of oral-respiratory coordination during NS, a sensing non-invasive solution capable of monitoring the temporal breathing pattern has been designed and developed with a completely non-invasive approach, in order to be easily embeddable on a common feeding bottle. Its laboratory validation fosters its successful application, and further work is needed to test and validate the system on newborns.

The second objective of this thesis has been to develop an automated analysis system capable of quantitatively assessing oral feeding ability, in order to help clinicians in routine clinical monitoring and decision-making. The increasing need for an objective assessment tool indeed makes also increasingly important to establish quantitative and reliable measures for a proper analysis of oral-motor function. A software system to systematically treat and analyze sucking pressure data has been developed: proper algorithms for automatic segmentation and features extraction have been proposed and tested for the analysis of different experimental data. Besides, a series of measures of motor control and variability in coordination has been introduced for the analysis of oral-motor function, and the results from their analysis seemed to indicate their useful contribution to the quantitative assessment of NS skills. Experimental data have been analyzed to investigate the suitability of the assessment system to the evaluation of the newborn’s maturational course, as well as to quantify the deviation from a typical behavior. The results obtained are promising and further work is now dedicated to the collection of a larger longitudinal set of data from both high-risk and healthy infants, in order to support the reported findings and also define normative data.

Prognostic role of objective response in patients affected by hepatocellular carcinoma after loco-regional treatment: comparison between EASL and mRECIST criteria

Ph.D student: Marianna Silletta
Supervisor: Bruno Vincenzi

Background: The European Association for the Study of the Liver (EASL) criteria and the modified Response Evaluation Criteria in Solid Tumors (mRECIST) are currently utilized to evaluate radiological response in patients affected by HCC and treated with loco-regional procedures. Several studies analysed the usefulness of these methods in predicting survival but there are not
definitive data. Aim: To perform a systematic review of studies evaluating mRECIST and EASL criteria validity in predictive radiological response in HCC undergoing loco-regional therapies and their validity in predicting survival. Methods: A comprehensive search of the literature was performed in electronic databases EMBASE, MEDLINE, COCHRANE LIBRARY, ASCO conferences and EASL conferences from March 2000 to June 10, 2014. Our search strategy included terms for HCC, mRECIST, and EASL, loco-regional procedures included transarterial embolization (TAE), transarterial chemoembolization (TACE) and cryoablation. Inter-method agreement between EASL and mRECIST was evaluated using the k coefficient. For each criteria, overall survival was calculated in responders vs. non-responders patients, considering all target lesions response. Results: Among 18 initially selected publications, 7 reports were considered eligible. All studies were published as full-text articles. 1357 patients were included. Kappa coefficient, available or calculated, showed an high concordance (that is k value >0.8) in the evaluation of response between EASL and mRECIST criteria. The two methods were in agreement in defining the kind of response in 1286 patients, that is 94.77% (kappa index 0.928, 95%, CI 0.912-0.944). Proportion of responders according to mRECIST and EASL criteria was 62.4% and 61.3%, respectively. HR for overall survival (responders versus non responders) according to EASL and mRECIST was 0.39 (95% confidence interval 0.26 – 0.61, p<0.0001) and 0.38 (95% confidence interval 0.24 – 0.61, p<0.0001), respectively. Conclusion: In this literature-based meta-analysis, mRECIST and EASL criteria showed high concordance in HCC patients treated with loco-regional treatments. Objective response according to both methods confirmed a strong prognostic relation in terms of overall survival. This prognostic value appears to be very similar between the two criteria.
AWARDS

*Scientific Exhibit Award of Excellence 2015, American Academy of Orthopaedic Surgeons.*


*Best Poster Presentation 2015 of the International Society for Limb Sparing (ISOLS), Orlando, USA.*

**Giulia Leanza**

"Best Oral Communication" Società Italiana dell’Osteoporosi, del Metabolismo Minerale e delle Malattie dello Scheletro (SIOMMMS).

**Carlo Massaroni**

2015 International Travel Grant, International Society of Biomechanics (ISB), "MoCBA: Motion Capture for Breathing Assessment".

**Gabriele Oliva**

Finalist within the CIPRNet young and CRITIS Awards at the 10th International Conference on Critical Information Infrastructures Security, Berlin, Germany, October 5-7, 2015.

**Alberto Rainer**


**Raffaele Rocco**

2015 ESTS - Young Investigators Award.

**Rocky Strollo**

Grant by Juvenile Diabetes Research Foundation (JDRF),
Grant by European Foundation for the Study of Diabetes (EFSD),
Grant by Società Italiana dell’Osteoporosi, del Metabolismo Minerale e delle Malattie dello Scheletro (SIOMMMS).

**Eleonora Tamilia, Domenico Formica, Anna Maria Visco, Alberto Scainia, Fabrizio Taffoni**


**Gianluca Vadalà, Luca La Verde, M.A. Rosa, Vincenzo Denaro**

Best Poster Presentation, Italian Society of Ortopaedic and Traumatology (SIOT) 100th Annual Meeting, Rome.

**2015 RESEARCH PAPERS AWARDED AS “UCBM PAPER OF THE MONTH”**

**October**


*Prognostic significance of K-Ras mutation rate in metastatic colorectal cancer patients.*

November
Ranieri F., Ferraccioli M., Stampanoni Bassi M., Musumeci G., Di Lazzaro V., Gainotti G., Marra C.
Familiarity for famous faces and names is not equally subtended by the right and left temporal poles. Evidence from an rTMS study.

December
Carotti S., Vespasiani-Gentilucci U., Perrone G., Picardi A., Morini S.
Portal inflammation during NAFLD is frequent and associated with the early phases of putative hepatic progenitor cell activation.
2015 PUBLICATIONS FULL LIST
PUBLICATIONS

Articles


A large-scale genetic analysis reveals a strong contribution of the HLA class II region to giant cell arteritis susceptibility.


Reply to J. Magalon et al.


Sambataro D., Sambataro G., Zaccara E., Maglione W., Vitali C., Del Papa N.

Tumoral calcinosis of the spine in the course of systemic sclerosis: report of a new case and review of the literature.


Zardi E.M., Ghittoni G., Maggiora D., Viera F.T., Di Matteo F., Rossi S.

Portal hypertensive gastropathy in cirrhotics without varices: a case-control study.


The involvement of T regulatory lymphocytes in a cohort of lupus nephritis patients: a pilot study.


Immune mediated myopathy following long-term statin therapy.


Sambataro D., Sambataro G., Zaccara E., Maglione W., Del Papa N.

A die-hard giant capillary.


Clinical comparison of QUANTA Flash dsDNA chemiluminescent immunoassay with four current assays for...
the detection of anti-dsDNA autoantibodies.
J Immunol Res. 2015; 2015:
902821. PubMed PMID:
25759849. IF 2,934

Soriano A., Shoenfeld Y.
Haemophagocytic lymphohistiocytosis: from diagnostic challenges to predictive possibilities.

Soriano A., Nesher G., Shoenfeld Y.
Predicting post-vaccination autoimmunity: who might be at risk?

Soriano A.
New therapeutic approaches to anti-neutrophil cytoplastic antibody-associated vasculitides: looking at tomorrow.
## AUTOMATION AND CONTROL THEORY

**Head:** R. Setola

### PUBLICATIONS

**Articles**

- **Oliva G., Panzieri S., Pascucci F., Setola R.**
  - *Sensor networks localization: extending trilateration via shadow edges.*
  - IEEE Trans Autom Control. 2015; 60(10): 2752-2755. DOI: 10.1109/TAC.2015.2404253. IF 2.779

- **De Cillis F., De Simio F., Guido F., Incalzi R.A., Setola R.**
  - *Distributed data clustering via opinion dynamics.*
  - Int J Distrib Sens N. 2015; N 753102. DOI: 10.1155/2015/753102. IF 0.665

- **Carpentieri A., Cozzoli E., Scimica M., Bonanno E., Sarandanelli AM., Gambacurta A.**
  - *Fall-detection solution for mobile platforms using accelerometer and gyroscope data.*

### Books & book chapters

- **Setola R., Sforza A., Vittorini V., Pragliola C.**
  - *Railway infrastructure security.*

## BIOCHEMISTRY AND MOLECULAR BIOLOGY

**Head:** M. Maccarrone

### PUBLICATIONS

**Articles**

  - *A potent systemically active N-Acylethanolamine acid amidase inhibitor that suppresses inflammation and human macrophage activation.*

- **Oliva G., La Manna D., Fagiolini A., Setola R.**
  - *Differential of human neuroblastoma cells toward the osteogenic lineage by mTOR inhibitor.*

  - *Global changes in DNA methylation in Alzheimer’s disease peripheral blood mononuclear cells.*

- **Carpentieri A., Cozzoli E., Scimica M., Bonanno E., Sarandanelli AM., Gambacurta A.**
  - *Downstream effects of endocannabinoid on blood cells: implications for health and disease.*

- **Fanali C., Rocco A., D’Orazio G., Dugo L., Mondello L., Aturki Z.**
  - *Determination of key flavonoid aglycones by means of nano-LC for the analysis of dietary supplements and food matrices.*

- **Gabrielli M., Battista N., Rignani L., Prada I., Antonucci F., Cantone L., Matteoli M., Maccarrone M., Verderio C.**
  - *Active endocannabinoids are...*
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secreted on extracellular membrane vesicles.

Maccarrone M.
Endocannabinoid signaling in female reproductive events: a potential therapeutic target?

Cifani C., Micioni Di Bonaventura M.V., Pucci M., Giusepponi M.E., Romano A., Di Francesco A., Maccarrone M., D’Addario C.
Regulation of hypothalamic neuropeptides gene expression in diet induced obesity resistant rats: possible targets for obesity prediction?

Chiurchiù V., Battistini L., Maccarrone M.
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Chiurchiù V., Lanuti M., De Bardi M., Battistini L., Maccarrone M.
The differential characterization of GPR55 receptor in human peripheral blood reveals a distinctive expression in monocytes and NK cells and a proinflammatory role in these innate cells.

The possible role of glutathione-S-transferase activity in diabetic nephropathy.

Chiurchiù V., Leuti A., Maccarrone M.
Cannabinoid signaling and neuroinflammatory diseases: a melting pot for the regulation of brain immune responses.

Extravirgin olive oil up-regulates CB1 tumor suppressor gene in human colon cancer cells and in rat colon via epigenetic mechanisms.

Gasperi V., Evangelista D., Oddi S., Florenzano F., Chiurchiù V., Aviglino L., Catani M.V., Maccarrone M.
Regulation of inflammation and proliferation of human bladder carcinoma cells by type-1 and type-2 cannabinoid receptors.

Screening of volatile compounds composition of white truffle during storage by GCxGC-(FID/MS) and gas sensor array analyses.

Epigenetic and proteomic expression changes promoted by eating addictive-like behavior.

Chakrabarti B., Persico A., Battista N., Maccarrone M.
Endocannabinoid signaling in autism.

Cormio A., Cormio G., Musico C., Sardanelli AM.[altra affiliation], Gasparre G, Gadaleta MN.
Mitochondrial changes in endometrial carcinoma: possible role in tumor diagnosis and prognosis (review).
PUBLICATIONS

Zollo L., Lopez E., Spedaliere L., Aracil N.G., Guglielmelli E.
Identification of dynamic parameters for robots with elastic joints.
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Sparaci L., Formica D., Lasorsa F.R., Mazzone L., Valeri G., Vicari S.

Zollo L., Zaccheddu N., Ciancio A.L., Morrone M., Bravi M., Santacaterina F., Laineri Milazzo M., Guglielmelli E., Sterzi S.
Comparative analysis and quantitative evaluation of ankle-foot orthoses for foot drop in chronic hemiparetic patients.
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Goffredo R., Accoto D., Guglielmelli E.
Swallowable smart pills for local drug delivery: present status and future perspectives.

BIOMEDICAL ROBOTICS AND BIOMICROSYSTEMS

Head: E. Guglielmelli

PUBLICATIONS

Articles

Zollo L., Lopez E., Spedaliere L., Aracil N.G., Guglielmelli E.
Identification of dynamic parameters for robots with elastic joints.
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Sparaci L., Formica D., Lasorsa F.R., Mazzone L., Valeri G., Vicari S.

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Maccarrone M., Bab I., Biró T., Cabral G.A., Dey S.K., Di Marzo V., Konje J.C., Kunos G., Mechoulam R., Pacher P., Sharkey K.A., Zimmer A.
Endocannabinoid signaling at the periphery: 50 years after THC.
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The effect of macrobiotic Ma-Pi 2 diet on systemic inflammation in patients with type 2 diabetes: a post hoc analysis of the MADIAB trial.

Conference Proceedings

Mozetic P., Bisogno T., Di Marzo V., Maccarrone M., Trombetta M., Rainer A.
Release of N-acylethanolamines by biomaterials of clinical relevance.

Books & book chapters

Battista N., Bari M., Maccarrone M.
Endocannabinoids and reproductive events in health and disease.
ISBN: 978-3-319-20824-4
Tagliabue M., Ciancio A.L., Brochier T., Eskiizmirliler S., Maier M.A.
Differences between kinematic synergies and muscle synergies during two-digit grasping.

Bellagamba F., Addessi E., Focaroli V., Pecora G., Maggiorelli V., Pace B., Paglieri F.
False belief understanding and “cool” inhibitory control in 3-and 4-years-old Italian children.

Guglielmelli E., Micera S., Migliavacca F., Pedotti A.
Moving along: in biomechanics, rehabilitation engineering, and movement analysis, Italian researchers are making great strides.

Guglielmelli E.
Quest for robots, quest for jobs.
IEEE Robot Autom Mag. 2015 Mar 1; 22(1):4. DOI: 10.1109/MRA.2015.2397572. IF 2,413

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Robots don’t pray [from the Editor’s desk].
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Navigating the new RAS publications landscape
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Guglielmelli E.
On research reproducibility: an interview with Gianluca Setti [Turning Point].
IEEE Robot Autom Mag. 2015 Sep 1; 22(3): 192-191. DOI: 10.1109/MRA.2015.2485492. IF 2,143

Guglielmelli E.
The future of automation [Turning Point].
IEEE Robot Autom Mag. 2015 Jun; 22(2): 120. DOI: 10.1109/MRA.2015.2424814. IF 2,413

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Feedforward neural network for force coding of an MRI-compatible tactile sensor array based on fiber Bragg grating.

Upper-limb kinematic reconstruction during stroke robot-aided therapy.

Ciocchetti M., Massaroni C., Saccomandi P., Caponero M.A., Polimadei A., Formica D., Schena E.
Smart textile based on fiber Bragg grating sensors for respiratory monitoring: design and preliminary trials.

Biomechanical and neural changes evaluation induced by prolonged use of non-stable footwear: a systematic review.

Focaroli V., Taffoni F., Iverson J.M.
Abilità di pianificazione motoria nei bambini a sviluppo tipico e con Disturbo dello Spettro Autistico.
Psicologia clinica dello sviluppo. 2015; 1:3-26. DOI: 10.14497/97 737
Conference Proceedings

Goffredo R., Accoto D., Santonico M., Pennazza G., Guglielmelli E.
A smart pill for drug delivery with sensing capabilities.

A bio-inspired force control for cyclic manipulation of prosthetic hands.

Caparelli C., Carpino G., Brunetti G., Larizza P., Guglielmelli E.
A preliminary health technology assessment of a guidance system for interventional radiology.

Development and preliminary testing of an instrumented object for force analysis during grasping.

Tamilia E., Formica D., Visco A.M., Scaini A., Taffoni F.
An automated system for quantitative analysis of newborns’ oral-motor behavior and coordination during bottle feeding.

Goffredo R., Ferrone A., Maloilo L., Pecora A., Accoto D.
A miniaturized electrolytic pump sensorized with a strain gauge based on thermoplastic nanocomposite for drug delivery systems.

A sensorial platform for mozzarella cheese characterization and authentication.

Books & book chapters

Accoto D., Laschi C., Guglielmelli E.


Patti G., Cavallari I. Patients with atrial fibrillation and CHA2DS2-VASc score 1: “To anticoagulate or not to anticoagulate? That is the question!”. Heart Rhythm. 2015 Dec; 12(12): 2515-20. PubMed PMID: 26188249. IF 5,076


CHEMICAL-PHYSICS FUNDAMENTALS IN CHEMICAL ENGINEERING

Head: V. Piemonte

PUBLICATIONS

Articles


De Falco M., Salladini A., Palo E., Iaquaniello G. Pd-alloy membrane reactor for natural gas steam refor-

ming: an innovative process design for the capture of CO2. Ind Eng Chem Res. 2015 Jul 15; 54 (27): 6950-6958. DOI: 10.1021/acs.iecr.5b01141. IF 2,587

Books & book chapters


Conference proceedings
Annesini M.C., Augelletti R., De Falco M., Frattari S., Gironi F., Murmura M.A. Production and purification of hydrogen-methane mixtures utilized in internal com-
bustion engines. 7th International Conference on Sustainable Planning and Development. DOI: 10.2495/SDP150461 ISBN 978-88-45649-24-1


CLINICAL PATHOLOGY AND MICROBIOLOGY

Head: S. Angeletti

PUBLICATIONS

Articles

Angeletti S., Spoto S., Fogolari M., Cortigiani M., Fioravanti M., De Florio L., Curcio B., Cavalleri D., Costantino S., Dicuonzo G.

Diagnostic and prognostic role of procalcitonin (PCT) and MR-pro-Adrenomedullin (MR-proADM) in bacterial infections.


Molecular epidemiology and phylogenetic analysis of hepatitis B virus in a group of migrants in Italy.


Gherardi G., Creti R., Pompilio A., Di Bonaventura G.

An overview of various typing methods for clinical epidemiology of the emerging pathogen Stenotrophomonas maltophilia.


Could β-hemolytic, group B enterococcus faecalis be mistaken for streptococcus agalactiae?


Procalcitonin, MR-proadrenomedullin, and cytokines measurement in sepsis diagnosis: advantages from test combination.

Dis Markers. 2015; 2015: 951532 PubMed PMID:26635427. IF 1,562

Gherardi G., Petrelli D., Di Luca M.C., Pimentel de Araujo F., Bernaschi P., Repetto A., Bellesi J., Vitali L.A.

Decline in macrolide resistance rates among Streptococcus pyogenes causing pharyngitis in children isolated in Italy.


Vratnica Z., Zehender G., Ebranati E., Sorrentino C., D’Ovidio C., Pompilio A., Crocetta V., Gherardi G., Carnevale A., Di Bonaventura G.

Fatal sepsis by Klebsiella pneumoniae in a patient with systemic lupus erythematosus: the importance of postmortem microbiological examination for the ex post diagnosis of infection.


Angeletti S., De Cesari S., Hart JG., Urbano M., Vitali MA., Fragliasso F., Dicuonzo G.

Laboratory automation and intra-laboratory turnaround time: experience at the University Hospital Campus Bio-Medico of Rome.


Giovanetti M., Grifoni A., Lo Presti A., Cella E., Montesano C., Zehender G., Ciccaglione AR., Ciccaglioni AR., Ciccaglioni AR.

Amino acid mutations in Ebola virus glycoprotein of the 2014 epidemic.


Vratnica Z., Zehender G., Ebranati E., Sorrentino C., D’Ovidio C., Pompilio A., Crocetta V., Gherardi G., Carnevale A., Di Bonaventura G.

Hepatitis B virus genotype and subgenotype prevalence and distribution in Montenegro.


Angeletti S., Lo Presti A., Cella
E., Dicuonzo G., Crea F., Palazzotti B., Dedej E., Ciccozzi M., De Florio L.

Matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS) and Bayesian phylogenetic analysis to characterize Candida clinical isolates.


Rhodotorula mucilaginosa skin infection in a patient treated with sorafenib.


Ciccozzi M., Cella E., Giovannetti M., Lo Presti A., Ciccglione A.R., Bon I., Gallo P., Musumeci M., Bonetti M., Picardi A., Riva E., Mottini G.

Hepatitis A virus in a medical setting in Madagascar: a lesson for public health.


MALDI-TOF mass spectrometry and blakpc gene phylogenetic analysis of an outbreak of carbapenem-resistant K. pneumoniae strains.


Angeletti S., Dicuonzo G., Avola A., Crea F., Dedej E., Vailati F., Farina C., De Florio L.


Azarian T., Lo Presti A., Giovannetti M., Cella E., Rife B., Lai A., Zehender G., Ciccozzi M., Salemi M.


The effect of macrobiotic Ma-Pi diet on systemic inflammation in patients with type 2 diabetes: a post hoc analysis of the MADIAB trial.


Piombo M., Chiarello D., Corbetto M., Di Pino G., Dicuonzo G., Angeletti S., Riva E., De Florio L., Capone F., Di Lazzaro V.

Cronobacter sakazakii DNA detection in cerebrospinal fluid of a patient with amyotrophic lateral sclerosis mimic syndrome.


**COMPUTER SYSTEMS AND BIOINFORMATICS**

Head: G. Iannello

**PUBLICATIONS**

**Articles**


Label-free near-infrared reflectance microscopy as a complimentary tool for two-photon fluorescence brain imaging.


Fiscon G., Paci P., Iannello G.

MONSTER v1.1: a tool to extract and search for RNA non-branching structures.


Fiscon G., Paci P., Colombo T., Iannello G.
A new procedure to analyze RNA non-branching structures.
Curr Bioinform. 2015; 10(3): 242-258. DOI: 10.2174/157489309666140820224651 IF 0,921

Quantitative neuroanatomy of all Purkinje cells with light sheet microscopy and high-throughput image analysis.

Cacace F., Germani A., Manes C.
A new approach to design interval observers for linear systems.
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Cacace F., Conte F., Germani A.
Filtering continuous-time linear systems with time-varying measurement delay.
IEEE T Automat Contr. 2015 May; 60(5): 1368-1373. DOI: 10.1109/TAC.2014.2357138 IF 2,779

A versatile clearing agent for multi-modal brain imaging.

Multidimensional approach to Solanaceae’s nutritional and gustative aspects.
Sensors- Basel 2015; 319: 177-182. DOI: 10.1007/978-3-319-09617-9_31. IF 2,245

Conference Proceedings


Borreo A., Onofri L., Soda P.

Bria A., Iannello G., Peng H.
An open-source VAA3D plugin for real-time 3D visualization of terabyte-sized volumetric images.

Cacace F., Conte F., Germani A., Palombo G.
A new method for the simultaneous estimation of state and delay in time delay systems.

Cacace F., Germani A., Manes C.
A state observer for nonlinear systems with large and variable measurement delays.

Books & book chapters

Cacace F., Germani A., Manes C.
State estimation and control of nonlinear systems with large and variable measurement delays.
DEVELOPMENTAL NEUROSCIENCE

Head: F. Keller

PUBLICATIONS

Articles
Bellagamba F., Addessi E., Focaroli V., Pecora G., Maggiorelli V., Pace B., Paglieri F.
False belief understanding and “cool” inhibitory control in 3-and 4-years-old Italian children.

Balzamino B.O., Esposito G., Marino R., Keller F., Micera A.
NGF expression in Reelin-deprived retinal cells: a potential neuroprotective effect.

Focaroli V., Taffoni F., Iverson J.M.
Abilità di pianificazione motora nei bambini a sviluppo tipico e con Disturbo dello Spettro Autistico.
Psicologia clinica dello sviluppo. 2015;1:3-26. DOI: 10.1449/79737

DIAGNOSTIC IMAGING

Head: B. Beomonte Zobel

PUBLICATIONS

Articles
Liguori C., Pitocco F., Di Giampietro I., De Vivo A.E., Schena E., Giurazza F., Sorrentino F., Zobel B.B.
Magnetic resonance comparison of left-right heart volumetric and functional parameters in thalassemia major and thalassemia intermedia patients.

Annibali O., Chiodi F., Sarlo C., Cortes M., Quaranta-Leoni F.M., Quattrocchi C., Bianchi A., Bonini S., Avvisati G.
Rituximab as single agent in primary MALT Lymphoma of the ocular adnexa.

A phase I feasibility study of multi-modality imaging assessing rapid expansion of marrow fat and decreased bone mineral density in cancer patients.

Percutaneous long bone cementoplasty for palliation of malignant lesions of the limbs: a systematic review.

Cone-Beam Computed Tomography (CBCT) versus CT in lung ablation procedure: which is faster?


Single-centre experience with percutaneous cryoablation of breast cancer in 23 consecutive non-surgical patients.


Epicentral disruption of structural connectivity in Alzheimer's disease.


Dakanalis A., Carrà G., Calogero R., Zanetti M.A., Gaudio S., Caccialanza R., Riva G., Clerici M.

Testing the cognitive-behavioural maintenance models across DSM-5 bulimic-type eating disorder diagnostic groups: a multi-centre study.


Interventional radiologist’s perspective on the management of bone metastatic disease.


Temperature monitoring during microwave ablation in ex vivo porcine livers.


Riva G., Santino G., Dakanalis A.

The neuropsychology of self-objectification.

Eur Psychol. 2015; 20(1): 34-43. DOI: 10.1027/1016-9040/a000190. IF 1,778


Visualization of myocardial infarction by post-mortem single-organ coronary computed tomography: a feasibility study.


Serinelli S., Panebianco V., Martino M., Battisti S., Rodacci K., Marinelli E., Zaccagna F., Semelka R.C., Tomei E.


Int J Legal Med. 2015 May; 129(3): 609-17. PubMed PMID: 25721414. IF 2,714

Quattrocchi C.C., Mallio C.A., Errante Y., Cirimele V., Carideo L., Ax A., Zobel B.B.

Gadodiamide and dentate nucleus T1 hyperintensity in patients with meningioma evaluated by multiple follow-up contrast-enhanced magnetic resonance examinations with no systemic interval therapy.


Altamura C., Ventriglia M., Martiní M.G., Montesano D., Errante Y., Piscitelli F., Scrascia F., Quattrocchi C., Palazzo P., Seccia S., Vernieri F., Di Marzo V.

Elevation of plasma 2-arachidonoylglycerol levels in Alzheimer’s disease patients as a potential protective mechanism against neurodegenerative decline.


Vecchio F., Miraglia F., Curcio G., Altavilla R., Scrascia F., Giambattistelli F., Quattrocchi C.C., Bramanti P., Vernieri F.,
Rossini P.M.

*Cortical brain connectivity evaluated by graph theory in dementia: a correlation study between functional and structural data.*


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*CT angiography and magnetic resonance angiography findings after surgical and interventional radiology treatment of peripheral arterial obstructive disease.*


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Re T.J., Scarciolla L., Takahashi E., Specchio N., Bernardi B., Longo D.

*Magnetic resonance fiber tracking in a neonate with hemimegalencephaly.*


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Lanza E., Palussiere J., Buy X., Grasso R.F., Beomonte Zobel B., Poretti D., Pedicini V., Balzarini L., Cazzato R.L.

*Percutaneous image-guided cryoablation of breast cancer: a systematic review.*


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Allegretti G., Saccomandi P., Giurazza F., Caponero M.A., Frauenfelder G., Di Matteo F.M., Beomonte Zobel B., Silvestri S., Schena E.

*Magnetic resonance-based thermometry during laser ablation on ex-vivo swine pancreas and liver.*


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Marano M., Vespasiani Gentiliucci U., Altamura C., Siotto M., Squitti R., Buccossi S., Quintiliani L., Migliore S., Greco F., Scarciolla L., Quattrocchi C.C., Picardi A., Vernieri F.

*Altered metal metabolism in patients with HCV-related cirrhosis and hepatic encephalopathy.*


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Schena E., Saccomandi P., Piccolo M., Massaroni C., Silvestri S., Piccolo C.L., Frauenfelder G., Giurazza F., Beomonte Zobel B.

*MRI-thermometry on ex vivo swine liver: preliminary trials to assess the sensitivity of two sequences.*


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Schena E., Fani F., Saccomandi P., Massaroni C., Silvestri S., Piccolo C.L., Frauenfelder G., Giurazza F., Beomonte Zobel B.

*MRI-thermometry on ex vivo swine liver: preliminary trials to assess the sensitivity of two sequences.*

**DIGESTIVE ENDOSCOPY**

Head: F.M. Di Matteo

**PUBLICATIONS**

**Articles**

Zardi E.M., Ghittoni G., Margiotta D., Viera F.T., Di Matteo F., Rossi S.

*Portal hypertensive gastropathy in cirrhosis without varices: a case-control study.*


Allegretti G., Saccomandi P., Giurazza F., Caponero M.A., Frauenfelder G., Di Matteo F.M., Beomonte Zobel B., Silvestri S., Schena E.

*Magnetic resonance-based thermometry during laser ablation on ex-vivo swine pancreas and liver.*


Saccomandi P., Schena E., Massaroni C., Di Matteo FM., Silvestri S.

*Goniometric measurement for the estimation of anisotropy coefficient of human and animal pancreas.*


**Conference Proceedings**

**DRUG SCIENCES**

Head: G. Minotti

**PUBLICATIONS**

**Articles**

Salvatorelli E., Menna P., Cantalupo E., Chello M., Covino E., Wolf F.I., Minotti G.

*The concomitant management of cancer therapy and cardiac therapy.*


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Minotti G., Graziani G., Delogu G.

*Editorial.*


**ELECTRONICS FOR SENSOR SYSTEMS**

Head: G. Pennazza

**PUBLICATIONS**

**Articles**


*Exhaled breath analysis by electronic nose in respiratory diseases.*


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*Screening of volatile compounds composition of white truffle during storage by GCxGC-(FID/MS) and gas*
sensor array analyses.
LWT-Food Sci Technol. 2015 Mar; 60(2): 905-913. DOI: 10.1016/j.lwt. 2014.09.054 IF 3.516
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The lung cancer breath signature: a comparative analysis of exhaled breath and air sampled from inside the lungs.
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Marchetti E., Tecco S., Santonico M., Vernile C., Ciccarelli D., Tarantino E., Marzo G., Pennazza G.
Multi-sensor approach for the monitoring of halitosis treatment via Lactobacillus brevis (CD2) – containing lozenges – a randomized, double-blind placebo-controlled clinical trial.
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Santonico M., Grasso S., Genova F., Zompanti A., Parente F.R., Pennazza G.
Unmasking of olive oil adulteration via a multi-sensor platform.
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Comorbidity modulates non invasive ventilation-induced changes in breath print of obstructive sleep apnea syndrome patients.

Conference proceedings
Goffredo R., Accoto D., Santonico M., Pennazza G., Guglielmelli E.
A smart pill for drug delivery with sensing capabilities.
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Ferri G., Parente F.R., Stornelli V., D’Amico A., Pennazza G., Santonico M.
A standard CMOS technology fully-analog differential capacitance sensor front-end.

Books & book chapters
Multidimensional approach to Solanaceae’s nutritional and gustative aspects.
ENDOCRINOLOGY AND DIABETES

Head: P. Pozzilli

PUBLICATIONS

Articles
Barchetta I., Guglielmi C., Bertocchini L., Calella D., Manfrini S., Secchi C., Pozzilli P., Calvallo M.G.
Therapy with proton pump inhibitors in patients with type 2 diabetes is independently associated with improved glycemic control.

Rationale, design, and baseline characteristics in Evaluation of LIXisenatide in Acute Coronary Syndrome, a long-term cardiovascular end point trial of lixisenatide versus placebo.

Insulin secretion in patients with latent autoimmune diabetes (LADA): half way between type 1 and type 2 diabetes: action LADA 9.

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FOOD SCIENCE AND NUTRITION

Head: L. De Gara

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GENERAL SURGERY

Head: R. Coppola

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**GENETIC PATHOLOGY**

**Head:** V.M. Fazio

**PUBLICATIONS**

**Articles**

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**GERIATRICS**

Head: R. Antonelli Incalzi

**PUBLICATIONS**

**Articles**

Laudisio A., Marzetti E., Franceschi F., Bernabei R., Zuccalà G.

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**Re: “Diagnosis of osteomyelitis with an indolent course”**

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**2015 Publications full list**

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Pedone C., Lelli D.

Books & book chapters
Antonelli Incalzi R., Scichilone N. (Eds.)
Bisogna pensare anche alla Co morbilità. Il paziente con BPCO e tumore polmonare

GYNAECOLOGY AND OBSTETRICS
Head: R. Angioli

PUBLICATIONS

Articles
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against Advanced Glycation End Products (AGEs) in diabetic cardiovascular disease.

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HEMATOLOGY, STEM CELL TRANSPLANTATION, TRANSFUSION MEDICINE AND CELLULAR THERAPY

Head: G. Avvisati

PUBLICATIONS

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HYGIENE, PUBLIC HEALTH AND STATISTICS

Head: T. Petitti

PUBLICATIONS

Articles


Books & book chapters

Norman GR., Streiner DL.[ ed. it. a cura di Capelli G., D’Abramo G.; traduzione di Capelli G., Federico B., Petitti T.] Biostatistica: quello che avreste voluto sapere ...


INSTITUTE OF PHILOSOPHY OF SCIENTIFIC AND TECHNOLOGICAL PRACTICE (FAST)

Head: E. Covino

PUBLICATIONS

Articles


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Head: A. Picardi

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Head: S. Morini

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Head: A.M. Persico

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Head: V. Di Lazzaro

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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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Inventors: V. Denaro, R. Papalia, G. Vadalà, A. Sudano, D. Accoto

Title: Device for mixing platelet-rich plasma with polymer solution.
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Publication Number: IT2014RM00190

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Head: F. Salvinelli

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Applicant: Campus Bio-Medico University of Rome
Publication Number: US9138168

Inventors: Casale M., Lupo R., Salvinelli F.

Title: Device for delivery of an aerosol substance
Applicant: Brio srl
Publication Number: WO201505-2653
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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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Head: G. Muto

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Head: F. Spinelli

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Head: E. Riva

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