

UNIVERSITA CAMPUS BIO-MEDICO DI ROMA



RESEARCH YEARBOOK 2016

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Foreword

Dear Stakeholder,

this Yearbook provides you an overview of Research at Campus Bio-Medico University of Rome (UCBM). It presents our research policies and strategies, and it reports specifically about the main facts, projects, scientific and innovation outputs produced by our institution in the 2016 calendar year.

Starting from this edition, the Yearbook is available in digital version only.

In line with past editions, the contents of this 2016 Research Yearbook have been selected and developed having in mind three main goals, namely:

• Dissemination and Promotion. The Yearbook aims at providing to all those interested in UCBM Research a comprehensive digest of the main ongoing research projects, and a simplified directory of the expertise. scientific equipment, technological facilities and services, research units and other organisational structures available in our university. We expect that all our stakeholders (e.g. students, researchers, experts and decision-makers from companies and from public and private institutions), will be able to easily retrieve from this document the 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. Extended information on our research activities can be retrieved on the research section of our official website http://www.unicampus.it/eng/research/;

- Accountability. This Yearbook is also intended to provide our main sponsors and external supporters a direct 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 and innovation capabilities;
- Self-assessment. The facts and data briefly presented in this Yearbook are fully instrumental in providing a clear set of internal and external benchmarks to our research community, to stimulate continuous improvement of our performance and of the quality of our research work. The Yearbook also includes a brief description of the internal quality assurance policies.

Overall, the 2016 research facts and figures clearly confirm that UCBM Research stands at the same level, both in qualitative and quantitative terms, of the top Italian universities: about 70% of our publications appeared on journals belonging to the first quartile (Q1) of the Scopus/Scimago international periodicals ranking; 17 % of Faculty members are now included in the Top Italian Scientists community; and a success rate of 12% has been reached on European Commission competitive calls.

Significant results were also obtained by the National Agency for the Evaluation of the University and Research system (ANVUR) 2016 analysis: UCBM ranks 2nd in the area of Biological Sciences, 10th in the area Medical Sciences, and 4th both in the areas of Chemical Sciences and of Industrial and Information Engineering, among all Italian Universities.

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 Academic 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 the visit to our University by an independent evaluation committee appointed by ANVUR gave positive results on the research quality indicators required for the accreditation of our university, and also very important inputs for consolidating and further improving our internal research quality assurance processes and procedures.

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, Head of the Graphics and Editing Services, and Antonella Benvenuto, Head of the Grant Office, for the hard work in the preparation of this document.

We do hope that you will enjoy this 2016 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 the mailbox of our Integrated Research Center (CIR), that is cir@unicampus.it

Eugenio Guglielmelli Pro-Rector for Research

Campus Bio-Medico

Chancellor Campus Bio-Medico

Andrea Onetti Muda

Campus Bio-Medico Campus Bio-Medico University of Rome University of Rome



On the cover

Proresolving lipid mediators resolvin D1, resolvin D2, and maresin 1 are critical in modulating T cell responses.



Resolvins and maresins have been recently discovered as *Specialized Pro-resolving lipid mediators* (SPMs), naturally produced from omega-3 fatty acids with the aim of terminating and resolving acute inflammation, thus preventing the spread of inflammation and its chronicization. Indeed, it is now widely accepted that uncontrolled inflammation or failure to resolve it is integral to many human diseases, including neurodegenerative, cardiovascular and autoimmune disorders.

Here, we have found that specific SPMs, in particular Resolvin D1, Resolvin D2 and Maresin 1, can control the balance between potentially pathogenic and tolerance-promoting human white blood cells (T lymphocytes), a balance that is often disrupted during chronic inflammation and autoimmune disorders. SPMs reduced the production of certain specific inflammatory mediators, termed "cytokines", by inflammatory T lymphocytes, and more importantly prevented the differentiation of highly pathogenic cells (called Th1 and Th17) and their ability to release inflammatory mediators. Interestingly, mice unable to produce these omega-3-derived lipid mediators showed greater inflammatory responses, which were reversed when fed a dietary supplementation of omega-3 precursor or when administered *in vivo* with specific resolvins.

Overall, our study not only proved the mechanism whereby a diet rich in omega-3 fatty acids is important for prevention of chronic inflammatory diseases, but also showed that SPMs may prove effective as potent anti-inflammatory agents by targeting key cells responsible for triggering chronic inflammation or autoimmunity. The results of this study now provide the groundwork to potentially use SPMs as new therapeutic strategies for the treatment of human chronic inflammatory and autoimmune diseases.





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2016 Research Facts and Figures

2016 Research Facts and Figures

2016 Research Facts and Figures

The research activities carried out in 2016 at the Campus Bio-Medico University of Rome have produced important outputs in terms of scientific publications, research projects, clinical trials and patents. Notably, the number of scientific publications, as shown in the Figures below, has grown over the past five years and has confirmed in 2016 a level, both in qualitative and quantitative terms, comparable to that of the best Italian universities, in relation to the size of the University and to the number of faculty members. In particular, number of publications, impact factor (I.F.) and normalized impact factor (N.I.F.) have increased respectively of 23%, 15% and 15% in the last five years.



Figure 1 - *Number of publications with I.F., total I.F. and total N.I.F. in the last five years*

As shown in Figure 2 the number of publications per faculty member is about 4 and increased by 10% with respect to 2012; the number of faculty members increased of 12% in the last five years as shown in Figure 3.







Figure 4 shows the overall scientific production in 2016 in terms of number of publications, Impact Factor (IF) and Normalized Impact Factor (NIF) for each of the 49 Research Units of the University.

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

Average of 4 publications with Impact Factor per faculty member in 2016. From the last data available from ANVUR that assesses the Italian University and Research system [Rapporto biennale sullo stato del sistema universitario e della ricerca – sintesi", ANVUR 2016.] the total average scientific productivity (not only publications with I.F.) of Italian public researchers in the period 2011-2014 is about 3,7, and the value drastically decreases to 0,6 publications/researcher if private Research Centers are also considered. The UCBM value of average number of publications for researcher



Figure 4 - Number of publications, Impact Factor (I.F.) and Normalized Impact Factor (I.F.N.I.F.) per Research Unit

I.F.

is also greater than that of the most of the countries analysed by ANVUR, such as China, South Korea, Germany, Russia and Spain; while UK, The Netherlands, France and Switzerland show greater values;

- 17 % of faculty members (21 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)
- 67% publications in the first quartile (Q1) according to SCImago ranking, which includes the top 25% journals in each subject category.

In 2016, 77 research projects, including clinical trials, were funded. The following figure illustrates the number of projects presented on competitive calls during the period 2014-2016.



Figure 5 - Projects presented on competitive calls (2014-2016)

During the last three years, the participation to competitive calls at University level has increased by 64%, raising from 80 projects presented during 2014 to 131 submitted throughout 2016.



The Figure above represents the projects approved per year of participation.

As for research projects submitted under European Commission competitive calls in 2016 a success rate of 12% has been reached with respect to a success rate of 5% in 2015.

In particular, the project "RESPINE", in which the Research Unit of Orthopaedic and Trauma Surgery is partner, has been granted, in the framework of Horizon2020 programme.

Moreover the ERC – Starting Grant "RESHAPE" won by Dr. Giovanni Di Pino started in September 1st 2016. Among the national projects it is worth mentioning 3 projects approved under the MIUR-PRIN programme, of which 2 coordinated by UCBM, that represent a success rate for UCBM of 9% against a national success rate of 6,8% on average.

The main funding bodies of 2016 ongoing projects were: European Commission, the National Institute for Insurance against Accidents at Work (INAIL), Italian Ministry of Education, University and Research, Italian Ministry of Health, Italian Ministry of Economic Development, Italian Space Agency, European Space Agency, Lazio Regional Authority as well as several business companies which have been supporting commissioned research and clinical trials; 41 internal clinical trials were also started.

As regards the activities related to exploitation of research results, in 2016 1 European patent has been granted. 3 applications for Italian patents, co-owned with other Universities and Research Centers, with INAIL and with a private company were filed and 1 patent has been entered in the national phase.

As of 31st December 2016 patent portfolio owned or co-owned by the University includes 20 families of patents (with a total of 48 patents, 34 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.



Evaluation of Research Quality (VQR 2011-2014)

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

With more than 130 participant organizations, almost 65,000 contributors, and 118,000 research products having been evaluated, the VQR is by far the most important and comprehensive research evaluation exercise ever attempted in Italy. For the period 2011-2014, the VQR has ranked UCBM second in the area of Biological Sciences among all Italian universities. UCBM was ranked fourth in other two areas, namely Chemical Sciences and Industrial and Information Engineering Areas, and UCBM was ranked tenth in the area of Medical Sciences. The VQR Report also shows that, as regards the single scientific disciplinary sectors, UCBM gained the first place (out of twenty-three universities) in Orthopaedics sector and the second place (out of thirty-two universities) in Neurology sector. Moreover, UCBM has been ranked third in Computer Systems, Diagnostic Imaging and Pathology sectors, out of fity-three, thirty-seven and thirty-four universities respectively. These results are based on the very good UCBM performance as measured by the specific indicators used for this ANVUR assessment: UCBM stands well above the average performance of all other universities in terms of scientific products classified of "excellent" or "good" quality.

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

Area	Overall ranking	Dimensional range ranking	% of publications in excellent and good levels
Area 03 Chemical Sciences	4° out of 56	4° out of 35	100%
Area 05 Biological Sciences	2° out of 62	2° out of 31	95,24%
Area 06 Medical Sciences	10° out of 52	8° out of 21	75,40%
Area 09 Industrial and Information Engineering	4° out of 63	4° out of 43	81,25%

Research Organization and Services

Research Organization and Services

Centre for Integrated Research

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

The figure below schematically shows CIR organization.

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 guidning 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



Figure 7 - Organization of the Centre for Integrated Research

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. results. The Research Administrative Area includes the following offices: Grant Office and Technology Transfer Office, Project Financial Management and Reporting Office and Clinical Trials Office. Activities of the offices are described below.

Grant Office

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

At the same time, the Office organizes seminars, workshops and informative events on competitive calls announcements.

The Office also provides technical-scientific support to activities of the Academic Research Scientific Committee.

Technology and Transfer Office

The Technology Transfer Office assists UCBM researchers in finding and assessing the best strategy to protect intellectual property and valorize research results, it manages the University patent portfolio in strict synergy with inventors, and promotes research results to SME and companies with the aim to exploit research activities through licensing of patents and implementation of joint research projects.

Furthermore the Office supports the promotion of joint laboratories with industries and spin-off research processes as well as incubation and acceleration of spin-off companies. Finally, it organizes seminars and workshops on technology transfer research issues.

Project Financial Management and Reporting Office

The Project Financial Management and Reporting Office assists the Research Units in the daily administrative management of the research projects.

It guarantees the proper post-award management of all grants, research contracts and clinical trials, analytical accounting management of research projects, expense analysis and monitoring. It also takes care of the projects periodic financial reports according to national and international regulations. Furthermore, it assists Research Units in the accounting administrative auditing of projects carried out by external auditing companies.

The office manages also the Unique Code Project a distinctive code for the identification of the project (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.

The Library

The Library mission is to provide comprehensive resources and services in support of the research, teaching, and learning needs. To fulfil this mission, the Library is committed to acquire, deliver and integrate information to support excellence in research, in education, and in patient care. The focus is to build broad print and e-resources collections, including access to specific databases and striving to make electronic content easily accessible to all users. The concrete support given to research activities, with reference to the scientific productivity, deals with the use of research evaluation metrics and its application to the analysis of research systems. Specifically it assists single users, departments or research units in the recovery of bibliometric indicators, such as the Impact Factor and the normalized Impact Factor, as well as the citation index data from Web of Science and Scopus.

Document supply service

The Library operates an advanced system for handling users' requests of documentation. The service allows registered users to request items, which are not available in the University Library. The service is accessible also off-campus, upon registration through the online form available on the Library website.

Doctoral dissertations theses repository

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

Contacts

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Pro-Rector for Research

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Academic Research Board

Andrea Onetti Muda - *Chancellor* Paolo Sormani - *General Manager of the University* Eugenio Guglielmelli - *Pro-Rector for Research* Gianfilippo Capriotti - *Head of Research Administrative Area*

Academic Research Scientific Committee

Eugenio Guglielmelli - Pro-Rector for Research

Marcella Trombetta - Research Coordinator of the Department of Engineering

Giorgio Minotti - Past Research Coordinator of the Department of Medicine and Surgery (until October 31, 2016)

Vincenzo Di Lazzaro - *Research Coordinator of the Department of Medicine and Surgery (from November 1, 2016)*

Research Administrative Area

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Ethics Committee

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

Members of the Ethics Committee

President Claudio Buoni

Alessandro Calisti, pediatrician

Fiorella Gurrieri, genetist

Giovanni Marino, local medicine representative

Giuseppe V. La Spina, *clinician*

Gemma Berta, voluntary work representative

Modesto D'Aprile, clinician

Paolo Pozzilli, biostatistician

Giorgio Minotti, pharmacologist

Giovanni Sironi, pharmacist

Domenica Tassielli, pharmacist, biomedical devices expert

Valentina Pepe, pharmacist

Lorenzo Cammelli, Hospital Administrator

Giuseppe La Monaca, legal matters expert

Maddalena Pennacchini, bioethics expert

Daniela Tartaglini, healthcare professions representative

Sara Emerenziani, *nutrition expert*

Salvatore Sciuto, clinical engineer

Francesco Di Matteo, clinical expert in diagnostic procedures and invasive techniques

Research Units

overview and main 2016 scientific outputs

Allergology, Immunology, Rheumatology



Head A. Afeltra

Faculty D.P.E. Margiotta

Other Personnel M. Lo Vullo, B. Marigliano, L. Navarini, A. Rigon, G. Sambataro, A. Soriano, M. Vadacca, E.M. Zardi

Description	Main research activities	Main collaborations
The unit's research interests con- cern epidemiology, pathogene- sis, diagnosis and therapy of the systemic autoimmune diseases. The most important research topi- cs are Systemic Lupus Erythema- tosus and Inflammatory Arthritis. The unit's research methodology is based on the integration of clini- cal tools, diagnostic imaging (mu- scoloskeletal Itrasonography and 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; Lipid mediators and Systemic Lupus Erythematosus; New bone formation and p40 inhibition; Biology, flow cytometry. 	 Forum Interdisciplina Ricerca sulle Malatt muni, (FIRMA); Gruppo Italiano di Reumatologia Clinic mentale (GIRRCS); Laboratory of Tissu stasis and Disease (letal Biology and E Research Center (Leuven; Rheumatology Day Gaetano Pini Institute The Zabludowicz (Autoimmune Diseas Medical Center, Israe Unit of Microbiology, Borramae Magnital

- m Interdisciplinare per la ca sulle Malattie Autoim-
 - (FIRMA); po Italiano di Ricerca in natologia Clinica e Speri-
 - tale (GIRRCS); pratory of Tissue Homeois and Disease (THD), Ske-Biology and Engineering arch Center (SBE), KU
 - en; imatology Day Hospital,
 - tano Pini Institute, Milan;
 - Zabludowicz Center for pimmune Diseases, Sheba ical Center, Israel:
 - of Microbiology, San Carlo Borromeo Hospital, Milan;
 - Unit of Rheumatology, Spedali Civili Brescia.

Most important publications

Margiotta D.P., Navarini L., Vadacca M., Lo Vullo M., Pignataro F., Basta F., Afeltra A.

The IL33/ST2 axis in Sjogren syndrome in relation to disease activity.

Eur Rev Med Pharmacol Sci. 2016 Apr;20(7):1295-9. PubMed PMID: 27097949. IF 1,575

Objective: Primary Sjogren's syndrome (pSS) is a systemic autoimmune disorder characterized by infiltration of the exocrine glands leading to secretory insufficiency. Despite the progress made in understanding the pathogenesis of the SS, many aspects remain to be clarified. Interleukin-33 (IL33) is a recently discovered cytokine, belonging to IL-1 superfamily. IL33 and its soluble receptor ST2 were implied in a number of immune and in autoimmune diseases pathogenesis. In this work, we analyzed expression of IL33 and ST2 in Siogren's syndrome.

Patients and methods: Serum IL-33 and soluble ST2 were analyzed using commercial ELISA kit in 15 pSS, 9 patients with Systemic Lupus Erythematosus and 9 controls.

Results: We found significant hyperexpression of sST2 in sera of SS patients and SLE patients compared to healthy subjects (p =0.04 and p = 0.07, respectively). In pSS, sST2 levels in pSS positively correlated with activity index SSDAI (r = 0.662, p = 0.007). In SLE, we found positive correlation between ST2 and SLEDAI 2K (r = 0.685, p = 0.04). Circulating levels of IL-33 were detectable in 2 of 15 SS patients, in 2 SLE patients and in 1 of control subjects.

Conclusions: We found a hyperexpression of sST2 in pSS and SLE patients with a possible immune modulatory role, because of a substantial suppression of circulating IL33. In our pSS and SLE cohort, sST2 levels were in correlation with disease activity indices.

Margiotta D., Navarini L., Vadacca M., Basta F., Lo Vullo M., Pignataro F., Zardi E.M., Afeltra A.

Relationship between leptin and regulatory T cells in systemic lupus erythematosus: preliminary results.

Eur Rev Med Pharmacol Sci.2016;20(4):636-41. PubMed PMID: 26957264. IF 1,575

Objective: Crescent literature data demonstrated a role of adipokines in immune responses, particularly leptin is involved in wide spectrum of pro-inflammatory functions. Several evidences suggested that leptin is able to inhibit T regulatory cells proliferation and function in vitro models. In the present study, we investigate the relationship between leptin and circulating T regulatory cells (Treas) in patients affected by systemic lupus erythematosus (SLE).

Patients and methods: 13 SLE patients and 11 healthy controls were enrolled. Metabolic syndrome and cardiovascular parameters were evaluated. Serum leptin levels were detected by commercial ELISA kit and circulating regulatory T cells were determined by FACS analysis as CD4+CD25highFOP3+ lymphocytes.

Results: Metabolic syndrome, defined by ATPIII criteria, was more prevalent in SLE compared to controls (38.4% vs. 0%, p = 0.04). as well as arterial hypertension (38.4% vs. 0%, p = 0.04). We did not find significant differences in mean leptin levels among SLE and controls $(13.13 \pm 1.51 \text{ ng/ml vs}, 9.48 \pm 8.67 \text{ ng/ml}, p = 0.6)$. Mean Treas percentage of total CD4 were 1.27 ± 0.9 in SLE vs. 2.8 ± 1.2 in healthy controls (p = 0.001). We found a negative correlation between leptin levels and Tregs percentage of total CD4 in SLE patients (r = 0.4, p = 0.01).

Conclusions: Our results suggest a role of leptin in the regulation of circulating T regulatory cells amount in human SLE.

Anesthesia, Intensive Care and Pain Management

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

Description

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

- Difficult airway management in Operating Theatre and ICU
- Tracheal intubation: advanced techniques
- · Research on Extraglottic devices and oxygenation rescue techniques
- Forces and pressures during direct and video laryngoscopy
- · Mechanical ventilation in Operating Theatre and ICU
- Pain therapy
- Loco-Regional Anesthesia

The AIC&PM Research Unit focuses its activities on:

Main research activities

- Anesthesia Loco-Regional anesthesia te-
- chniques Airway management in Emergency and Elective scenarios
- Airway management devices and innovations
- Cardiac anesthesia and drugs Obesity and perioperative sa-
- fety
- Pain management in perioperative medicine
- Multimodal care in pancreatic Surgery
- "in vitro" airway management

Most important publications

Carassiti M., Mattei A., Pizzo C.M., Vallone N., Saccomandi P., Schena E.

Bronchial blockers under pressure: in vitro model and ex vivo model. Br J Anaesth. 2016 Sep;117 Suppl 1:i92-i96. PubMed PMID: 27307290. IF 5,616

Pressures (Pe) exerted by bronchial blockers on the inner wall of the bronchi may cause mucosal ischaemia.

Our aims were as follows: (i) to compare the intracuff pressure (Pi) and Pe exerted by commercially available bronchial blockers in an in vitro and an ex vivo model; (ii) to investigate the influence of both the inflated intracuff volume and cuff diameter on Pe; and (iii) to estimate the minimal sealing volume (VSmin) and the corresponding Pe for each bronchial blocker studied.

Methods: The Pe exerted by seven commercial bronchial blockers was measured at different inflation volumes using a custom-designed system using in vitro and ex vivo animal models with two internal diameters (12 and 15 mm).

Results: In the same conditions, Pi was significantly lower than Pe (P<0.05), and Pe was higher in the in vitro model than in the ex vivo model. The Pe increased with the inflated volume, with use of the small-diameter model (P<0.05). Ex vivo models needed a higher minimal sealing volume than the in vitro models, and this volume increased with the diameter (e.g. the VSmin at a positive

strategies simulation to improve patients safety

- Intensive therapy
- Colistine theraputical targets in clostridium difficile infection during patient ultrafiltration
- Cardiac output monitoring innovations in mechanically
- Advanced pain control strategies in ICU
- Ecocardiography in post car-
- dio-surgical patients in ICU
- Pain Management
- FBSS (Patents development)
- · Post herpetic pain and neuro-
- biological modifications

pressure of 25 cm H2O required a Pe ranging from 12 to 78 mm Hg on the 15 mm ex vivo model and from 66 to 110 mm Hg on the 12 mm ex vivo model).

Conclusions: The Pi cannot be used to approximate Pe. The diameter of the model, the inflated volume, and the bronchial blocker design all influence Pe. A pressure higher than the critical ischaemic threshold (i.e. 25 mm Hg) was needed to prevent air leak around the cuff in the in vitro and ex vivo models.

Agrò F.E., Vennari M

The videolaryngoscopes are now the first choice to see around the corner. Minerva Anestesiol. 2016 Dec;82(12):1247-1249. PubMed PMID: 27654626. IF 2,036

Difficulty in the airway management is a crucial issue in anesthesia concerning operators' skills and experience, patients history and physical characteristics as well as circumstantial factors.

For a long period, the standard of care in assuring the airway has been tracheal intubation (TI) performed by direct laryngoscopy (DL) with Macintosh laryngoscope. At the same time, the search for a better glottic view and a more effective manoeuvre led to the use of innovative methods to assure the airway. In the last 20 years the development of videotechnologies and airway devices introduced in the clinical practice videolaryngoscopy, even to images displayed on smartphones.

Following the publication of the first experience with a videolaryngoscope (Glidescope®),1an historical and still open debate appeared about the clinical value of videolaryngoscopy and literature largely discussed its role in the airway management practice. In our opinion, operator's skills are crucial in the management of the airway: while the use of DL and extraglottic devices is part of clinical routine, other devices and technique such as fiberscope (predicted difficulties), videolaryngoscopes (unpredicted difficulties) and cricotyrotomy ("cannot ventilate cannot intubate" cases) need a specific and periodic training, because they are less frequently needed in the routinely practice. On the other, hand the best device does not exist in an objective perspective especially in case of unpredicted difficulties.It is a subjective choice depending on each operator's experience and training skills: the better known and the more used in routine clinical practice is the best device!

Petrini F., Di Giacinto I., Cataldo R., Esposito C., Pavoni V., Donato P., Trolio A., Merli G., Sorbello M., Pelosi P; Obesity Task Force for the SIAARTI Airway Management Study Group.

Perioperative and periprocedural airway management and respiratory safety for the obese patient: 2016 SIAARTI Consensus.

Minerva Anestesiol. 2016 Dec;82(12):1314-1335. PubMed PMID: 27759743. IF 2.036

Proper management of obese patients requires a team vision and appropriate behaviors by all health care providers in hospital. Specialist competencies are fundamental, as are specific clinical pathways and good clinical practices designed to deal with patients whose Body Mass Index (BMI) is ≥30 kg/m2. Standards of care for bariatric and non-bariatric surgery and for the critical care management of this population exist but are not well defined nor clearly followed in every hospital. Thus, every anesthesiologist is likely to deal with this challenging population. Obesity is a multisystem, chronic, proinflammatory disorder. Unfortunately, many countries are facing a marked increase in the obese population, defined as "globesity". Obesity presents an added risk in hospital, leading health care organizations to call for action to avoid adverse events and preventable complications. Periprocedural assessment and critical care strategies designed specifically for obese patients are crucial for reducing morbidity and mortality during surgery and in emergency settings, critical care and other particular settings (e.g., obstetrics). Specific care is needed for airway management, as are proactive strategies to reduce the risk of cardiovascular, endocrine, metabolic and infective complications; any effort can be fruitful, including special attention to the science of human factors. The Italian Society of Anesthesia, Analgesia, Resuscitation and Intensive Care (SIAARTI) organized a consensus project involving other national scientific societies to increase risk awareness, define the best multidisciplinary approach for treating obese patients in election and emergency, and enable every hospital to provide appropriate levels of care and good clinical practices. The Obesity Project Task Force, a section of the SIAARTI Airway Management Study Group, used a formal consensus process to identify a series of notes, alerts and statements, to be adopted as bundles, to define appropriate clinical pathways for hospitalized obese patients. The consensus, approved by the Task Force and endorsed by several European scientific societies actively operating in this field, is presented herein.

ventilated patients

Automation and Control Theory



Head R. Setola

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

Description

Main research activities

Main collaborations

The Unit of Automation and Control Theory aims at modeling, analyzing and controlling complex dynamic systems, ranging from biological and healthcare systems to industrial and home automation systems and Critical Infrastructures.

A particular emphasis is posed on the security issues underlying such complex systems, with the aim to develop robust, flexible and effective solutions. The activities of the Unit are focused on the development of innovative and strong multi-disciplinary methodologies, tools and technologies. Among others, the Unit provided both theoretical and applicative contributions in the fields of: security of industrial and home automation, optimization, financial modeling in healthcare sector, indoor localization, critical infrastructure protection and innovative desture-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 and industrial partners.

The unit has contributed to international projects, collaborations and trials:

- RISING (SAF€RA): development of innovative tools to localize first responders in indoor scenarios.
- CIPRNET (H2020): network of excellence on Critical Infrastructure protection and decision support systems for operators and managers. POSTE ITALIANE: tools and methodologies to identify phishing attempts.
- BNL: data analytics for the security and efficiency assessment of the crisis operators in the control room.
- STS: clinical trials on a gesture recognition interface to be used to access and manipulate patients' information in the surgery room.
- HEALTHCARE: modelling of the cost of patient hospitalization to measure and improve the consumption of hospital resources.

The Unit has established and strengthened the cooperation with several prestigious institutions; among others:

- Fraunhofer-Gesellschaft zur Förderung der angewandten Forschung e.V., Germany;
- ENEA Research Center, Italy;
- European Union;
- International Association of Insurance Supervisors (IAIS), Basel, Switzerland;
- European Commission, Joint Research Centre, Belgium;
- National Research Council (CNR), Italy:
- The Netherlands Organization for Applied Scientific Research (TNO), The Netherlands;
- San Camillo Forlanini Hospital, Italy;
- The Worldwide Railway Organization (UIC), France;
- University of British Columbia, Canada;
- University of Cyprus, Cyprus.

Most important publications

Papi M., Pontecorvi L., Setola R.

A new model for the length of stay of hospital patients. Health Care Manag Sci. 2016 Mar; 19(1):58-65. PubMed PMID: 25070138

Hospital Length of Stay (LoS) is a valid proxy to estimate the consumption of hospital resources. Average LoS, however, can be misleading if the underlying distribution is not symmetric. This paper uses routinely collected data of an Italian hospital patients from different departments over a period of 5 years. This will be the basis for a running example illustrating the alternative models of patients length of stay. The models includes a new density model called Hypergamma. The paper concludes by summarizing these various modelling techniques and highlighting the use of a risk measure in bed planning.

Oliva G., Setola R., Hadjicostis C. N.

Distributed finite-time calculation of node eccentricities, graph radius and graph diameter. Systems & Control Letters. 2016; 92: 20-27. DOI: 10.1016/j.sysconle.2016.02.015 IF 1,908

The distributed calculation of node eccentricities, graph radius and graph diameter are fundamental steps to tune network protocols or to execute distributed algorithms, which typically depend on these parameters. Most existing methods deal with undirected topologies and have high memory and/or bandwidth requirements. In this paper, we develop a distributed algorithm to solve this problem that takes advantage of the robustness and versatility of the max-consensus algorithm, and has low computational, memory and bandwidth requirements. Moreover, the agents communicate by broadcasting messages to their (out-) neighbors without requiring any knowledge on them or needing point-to-point communication capability.

Oliva G., Setola R., Panzieri S.

Critical clusters in interdependent economic sectors: a data-driven spectral clustering analysis. *Eur Phys J.-Spec Top. 2016;25(10): 1929-1944. DOI: 10.1140/epjst/e2015-50321-0. IF 1,417*

In this paper we develop a data-driven hierarchical clustering methodology to group the economic sectors of a country in order to highlight strongly coupled groups that are weakly coupled with other groups. Specifically, we consider an input-output representation of the coupling among the sectors and we interpret the relation among sectors as a directed graph; then we recursively apply the spectral clustering methodology over the graph, without a priori information on the number of groups that have to be obtained. We validate the proposed methodology considering a case study for Italy in the years from 1995 to 2011.

Biochemistry and Molecular Biology



Head M. Maccarrone

Faculty V. Chiurchiù, L. Dugo Other Personnel T. Bisogno, A. Leuti, A.M. Sardanelli

Description

The Research Unit has a long and widely recognized experience in chemistry, biochemistry, molecular biology, pharmacology and epigenetics of lipid signaling, that is interrogated under different disease conditions (most notably, neurodegenerative disorders [Alzheimer's disease 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 (i.e. resolvins and maresins), through their specific receptor

targets. In addition, metabolism of these ω -3 and ω -6 polyunsaturated fatty acid derivatives through multiple biosynthetic and degradative routes is studied by means of radiometric assays, in order to disclose the impact of metabolic regulation on the biological activity of these compounds. The effect of bioactive food components on lipid signaling is an additional focus of the Research Unit.

Main research activities

In collaboration with Prof. Charles Serhan (Brigham and Women's Hospital, Harvard Medical School, Boston) and with Prof. Anders Jacobsson (University of Stockholm), the group reported that resolvins and maresins, molecules produced in the body naturally from certain omega-3 fatty acids, regulate both in vitro and in vivo subsets of white blood cells that play a central role in immune processes and inflammation. These newly discovered lipid mediators, by targeting the balance between pathogenic Th1/Th17 and tolerogenic Treg cells, are part of a new class of molecules that may be useful for treating chronic inflammatory and autoimmune diseases.

Main collaborations

- Brigham and Women's Hospital, Harvard Medical School, USA
- University of Stockholm, Sweden

Most important publications

Chiurchiù V., Rapino C., Talamonti E., Leuti A., Lanuti M., Gueniche A., Jourdain R., Breton L., Maccarrone M.

Anandamide suppresses proinflammatory T cell responses in vitro through type-1 cannabinoid receptor-mediated mTOR inhibition in human keratinocytes.

J Immunol. 2016 Nov 1; 197(9):3545-3553. PubMed PMID: 27694494. IF 4,985

The endocannabinoid system comprises cannabinoid receptors 1 and 2 (CB1 and CB2), their endogenous ligands, anandamide (AEA) and 2-arachidonoylglycerol, and metabolic enzymes of these ligands. The endocannabinoid system has recently been implicated in the regulation of various pathophysiological processes of the skin that include immune competence and/or tolerance of keratinocytes, the disruption of which might promote the development of skin diseases. Recent evidence showed that CB1 in keratinocytes limits the secretion of proinflammatory chemokines, suggesting that this receptor might also regulate T cell dependent inflammatory diseases of the skin. In this article, we sought to investigate the cytokine profile of IFN- γ -activated keratinocytes, and found that CB1 activation by AEA suppressed production and release of signature TH1- and TH17-polarizing cytokines, IL-12 and IL-23, respectively. We also set

up co-cultures between a conditioned medium of treated keratinocytes and naive T cells to disclose the molecular details that regulate the activation of highly proinflammatory TH1 and TH17 cells. AEA-treated keratinocytes showed reduced an induction of IFN-γ-producing TH1 and IL-17-producing TH17 cells, and these effects were reverted by pharmacological inhibition of CB1. Further analyses identified mammalian target of rapamycin as a proinflammatory signalling pathway regulated by CB1, able to promote either IL-12 and IL-23 release from keratinocytes or TH1 and TH17 polarization. Taken together, these findings demonstrate that AEA suppresses highly pathogenic T cell subsets through CB1-mediated mammalian target of rapamycin inhibition in human keratinocytes. Thus, it can be speculated that the latter pathway might be beneficial to the physiological function of the skin, and can be targeted toward inflammation-related skin diseases, the cuff in the in vitro and ex vivo models.

Chiurchiù V., Leuti A., Dalli J., Jacobsson A., Battistini L., *Maccarrone M., *Serhan C.N. *Equally senior authors

Proresolving lipid mediators resolvin D1, resolvin D2, and maresin 1 are critical in modulating T cell responses.

Sci Transl Med. 2016 Aug 24;8(353):353ra111. PubMed PMID: 27559094. IF 16,264

Resolution of inflammation is a finely regulated process mediated by specialized proresolving lipid mediators (SPMs), including docosahexaenoic acid (DHA)–derived resolvins and maresins. The immunomodulatory role of SPMs in adaptive immune cells is of interest. We report that D-series resolvins (resolvin D1 and resolvin D2) and maresin 1modulate adaptive immune responses in human peripheral blood lymphocytes. These lipid mediators reduce cytokine production by activated CD8+ T cells and CD4+ T helper 1 (TH1) and TH17 cells but do not modulate T cell inhibitory receptors or abrogate their capacity to proliferate. Moreover, these SPMs prevented naïve CD4+ T cell differentiation into TH1 andTH17 by down-regulating their signature transcription factors, T-bet and Rorc, in a mechanism mediated by the GPR32 and ALX/FPR2 receptors; they concomitantly enhanced de novo generation and function of Foxp3+ regulatory T (Treg) cells via the GPR32 receptor. These results were also supported in vivo in a mouse deficient for DHA synthesis (ElovI2–/–) that showed an increase in TH1/TH17 cells and a decrease in Treg cells compared to wild-type mice. Additionally, either DHA supplementation in ElovI2–/– mice or in vivo administration of resolvin D1 significantly reduced cytokine production upon specific stimulation of T cells. These findings demonstrate actions of specific SPMs on adaptive immunity and provide a new avenue for SPM-based approaches to modulate chronic inflammation.

Mukhopadhyay P., Baggelaar M., Erdelyi K., Cao Z., Cinar R., Fezza F., Ignatowska-Janlowska B., Wilkerson J., van Gils N., Hansen T., Ruben M., Soethoudt M., Heitman L., Kunos G., *Maccarrone M., *Lichtman A., *Pacher P., *Van der Stelt M. *Equally senior authors

The novel, orally available and peripherally restricted selective cannabinoid CB2 receptor agonist LEI-101 prevents cisplatin-induced nephrotoxicity.

Br J Pharmacol. 2016 Feb;173(3):446-58. PubMed PMID: 26398481. IF 5,259

Here, we have characterized 3-cyclopropyl-1-(4-(6-((1,1-dioxidothiomorpholino)methyl)-5-fluoropyridin-2-yl)benzyl) imidazolidine-2,4-dione hydrochloride (LEI-101) as a novel, peripherally restricted cannabinoid CB2 receptor agonist, using both in vitro and in vivo models. We investigated the effects of LEI-101 on binding and functional activity. We assessed its in vitro and in vivo selectivity. Efficacy of LEI-101 was determined in a mouse model of cisplatin-induced nephrotoxicity. LEI-101 behaved as a partial agonist at CB2 receptors using β -arrestin and GTP_YS assays and was ~100-fold selective in CB2 /CB1 receptor-binding assays. It did not display any activity on endocannabinoid hydrolases and nor did it react with serine hydrolases in an activity-based protein profiling assay. In mice, LEI-101 had excellent oral bioavailability reaching high concentrations in the kidney and liver with minimal penetration into the brain. LEI-101 up to a dose of 60 mg·kg(-1) (p.o.) did not exert any CNS-mediated effects in the tetrad assay, in mice. LEI-101 (p.o. or i.p.) at 3 or 10 mg·kg(-1) dose-dependently prevented kidney dysfunction and/or morphological damage induced by cisplatin in mice. These protective effects were associated with improved renal histopathology, attenuated oxidative stress and inflammation in the kidney. These effects were absent in CB2 receptor knockout mice. These results indicate that LEI-101 is a selective, largely peripherally restricted, orally available CB2 receptor agonist with therapeutic potential in diseases that are associated with inflammation and/or oxidative stress, including kidney disease.

Research Units: overview and main 2016 scientific outputs

Head E. Guglielmelli



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

Other Personnel A. Alessi, R. Barone, A.L. Ciancio, G. Carpino, F. Cordella, A. Dellacasa Bellingegni, C. Gentile, E. Gruppioni, C. Lauretti, E. Noce, I. Portaccio, R. Romeo, M. Rossini, F. Salvadori, F. Scotto di Luzio, D. Simonetti, N.L. Tagliamonte, S. Valentini

Description

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

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

Main research areas are:

 Rehabilitation and assistive technologies: upper-limb and lower-limb therapy robots, motor and functional assessment, behavioral analysis, technical aids for independent living and work reintegration, assistive robots, upper limb prostheses, man-machine interfaces;

- Surgical Robotics: mechatronic tools for urological applications, haptic interfaces and biofeedback, master-slave robotic systems, teleoperated control;
- **Biomicrosystems:** miniaturized sensors, invasive neural micro-interfaces, microfluidic platforms;
- Neuroengineering and Neurodevelopmental Engineering: study of neuro-muscular disorders and gestures in developing children (also with autism), human behavior analysis and design of mechatronic components during neurodevelopment.

- Main research activities
- PPR2 funded by the National Institute for Insurance against
- Accidents at Work, 2014-2017
- AIDE funded by EC-H2020\ ICT 22 - 2014-2017
- PD-meter funded by the Ministry of Health, 2014-2017
- START-DISC University Strategic Project, 2015-2017

Most important publications

Oddo C.M., Raspopovic S., Artoni F., Mazzoni A., Spigler G., Petrini F., Giambattistelli F., Vecchio F., Miraglia F., Zollo L., Di Pino G., Camboni D., Carrozza M.C., Guglielmelli E., Rossini P.M., Faraguna U., Micera S.

Intraneural stimulation elicits discrimination of textural features by artificial fingertip in intact and amputee humans.

eLife. 2016 Mar 8;5:e09148. PubMed PMID: 26952132. IF 8,303

Restoration of touch after hand amputation is a desirable feature of ideal prostheses. Here, we show that texture discrimination can be artificially provided in human subjects by implementing a euromorphic real-time mechano-neuro-transduction (MNT), which emulates to some extent the firing dynamics of SA1 cutaneous afferents. The MNT process was used to modulate the temporal pattern of electrical spikes delivered to the human median nerve via percutaneous microstimulation in four intact subjects and via implanted intrafascicular stimulation in one transradial amputee. Both approaches allowed the subjects to reliably discriminate spatial coarseness of surfaces as confirmed also by a hybrid neural model of the median nerve. Moreover, MNT-evoked EEG activity showed physiologically plausible responses that were superimposable in time and topography to the ones elicited by a natural mechanical tactile stimulation. These findings can open up novel opportunities for sensory restoration in the next generation of neuro-prosthetic hands.

Ciancio A.L., Cordella F., Barone R., Romeo R.A., Bellin- gegni A.D., Sacchetti R., Davalli A., Di Pino G., Ranieri F., Di Lazzaro V., Guglielmelli E., Zollo L.

Control of prosthetic hands via the peripheral nervous system.

Front Neurosci. 2016 Apr 8;10:116. PubMed PMID: 27092041. IF 3,398

This paper intends to provide a critical review of the literature on the technological issues on control and sensorization of hand prostheses interfacing with the Peripheral Nervous System (i.e., PNS), and their experimental validation on amputees. The study opens with an in-depth analysis of control solutions and sensorization features of research and commercially available prosthetic hands. Pros and cons of adopted technologies, signal processing techniques and motion control solutions are investigated. Special emphasis is then dedicated to the recent studies on the restoration of tactile perception in amputees through neural interfaces. The paper finally proposes a number of suggestions for designing the prosthetic system able to re-establish a bidirectional communication with the PNS and foster the prosthesis natural control.

Badesa F. J., Morales R., Garcia-Aracil N. M., Sabater J. M., Zollo L., Papaleo E., Guglielmelli E.

Dynamic adaptive system for robot-assisted motion rehabilitation.

IEEE Systems J. 2016;10(3):984-991. DOI: 10.1109/JSYST.2014.2318594. IF 2,114

This paper presents a dynamic adaptive system for administration of robot-assisted therapy. The main novelty of the proposed approach is to close patient in the loop and use multisensory data (such as motion, forces, voice, muscle activity, heart rate, and skin conductance) to adaptively and dynamically change the complexity of the therapy and real-time displays of an immersive virtual reality system in accordance with specific patient requirements. The proposed rehabilitation system can be considered as a complex system that is composed of the following subsystems: data acquisition, multimodal human-machine interface, and adaptable control system. This paper shows the description of the developed fuzzy controller used as the core of the adaptable control subsystem. Finally, experimental results with ten subjects are reported to show the performance of the proposed solution.

Cardiovascular Science



Head G. Di Sciascio

Faculty G. Patti

Other Personnel M.C. Bono, V. Calabrese, P. Gallo, C. Goffredo, F. Mangiacapra, S. Mega, R. Melfi, M. Miglionico, A. Nusca, D. Ricciardi, E. Ricottini, G. Salvati

Description

Main research activities

Main collaborations

The Cardiovascular Science Research Unit comprises clinical cardiologists, interventional cardiologists, expert cardiologists in echocardiography and electrophysiology. Our Unit is involved in several national and international multicentre clinical trials, mainly focusing on new devices for percutaneous coronary intervention and new drugs for management of patients with cardiovascular diseases. Moreover, we performed and are performing several prospective experimental studies among a wide range of settings such as interventional pharmacology, glycaemic variability assessment, biological markers and cardiac electrophysiology.

Main research achievements:
Two randomized studies investigating the off-target effects of antiplatelet drugs in patients with coronary artery disease (CLOTILDIA and PROMICRO-2) have been finalized and the results have been published in major journals in the field of Cardiology.

- The randomized RIVENDEL study, investigating the effects of Ivabradine on vascular endothelial function, has been finalized and published.
- Stemming from the collaboration with the Cardiovascular Research Center Aalst, a study on the role of asymmetric dimethylarginine (ADMA) in contributing the extent and functional severity of coronary artery disease has been finalized and published.

Ongoing research projects:

- Impact of glycaemic variability assessed by a glucose continuous monitoring on platelet reactivity.
- Effects of Ranolazine on glycemic control in diabetic patients.
- Prospective evaluation of drug-eluting balloon versus drug eluting stent in PCI.
- Impact of micro-RNA evaluation on cardiac resynchronization therapy outcome.

Our Unit collaborates with several other Italian and international universities and research institutions:

- Cardiovascular Research Center Aalst, Belgium;
- Harvard Clinical Research Institute, Boston, USA;
- Technical University of Eindhoven, The Netherlands;
- Virginia Commonwealth Univer-
- sity, USA.

Most important publications

Mangiacapra F., Panaioli E., Colaiori I., Ricottini E., Lauria Pantano A., Pozzilli P., Barbato E., Di Sciascio. G.

Clopidogrel versus ticagrelor for antiplatelet maintenance in diabetic patients treated with percutaneous coronary intervention: results of the CLOTILDIA Study (Clopidogrel High Dose Versus Ticagrelor for Antiplatelet Maintenance in Diabetic Patients).

Circulation. 2016 Sep 13;134(11):835-7. PubMed PMID: 27619717. IF 17,202

This is a single-center, prospective, randomized, open label, cross-over study, comparing the effects of ticagrelor and high-dose clopidogrel on brachial artery reactivity and platelet reactivity in patients with type-2 diabetes mellitus (T2DM) treated with elective percutaneous coronary intervention.

Both flow-mediated dilation and nitroglycerin-mediated dilation values were significantly higher with ticagrelor compared with high-dose clopidogrel. After ticagrelor treatment, the incidence of endothelial dysfunction was lower compared with high-dose clopidogrel. Ticagrelor also resulted in significantly lower platelet reactivity and higher platelet inhibition.

These findings may provide the rationale for using ticagrelor in stable patients at high risk, such as diabetics.

Mangiacapra F., Di Gioia G., Pellicano M., Di Serafino L., Bressi E., Peace A.J., Bartunek J., Wijns W., De Bruyne B., Barbato E.

Effects of Prasugrel versus Clopidogrel on coronary microvascular function in patients undergoing elective PCI.

J Am Coll Cardiol. 2016 Jul 12;68(2):235-7. PubMed PMID: 27386781. IF 17,759

In this randomized study, we compared the effects of prasugrel and clopidogrel on coronary microcirculation in patients undergoing elective percutaneous coronary intervention (PCI). At baseline and post-PCI, we assessed the index of microvascular resistance (IMR) in the treated artery; high sensitive troponin T (Hs-TnT) was measured at before and 24 hours after PCI. Post-PCI IMR was significantly lower in the prasugrel as compared with clopidogrel group. Hs-TnT increased post-PCI in both groups, though less markedly in patients pretreated with prasugrel compared with clopidogrel.

Unlike with clopidogrel, prasugrel pretreatment prevents from PCI-related microvascular impairment and myocardial damage in patients with stable coronary artery disease.

Mangiacapra F., Conte M., Demartini C., Muller O., Delrue L., Dierickx K., Di Sciascio G., Trimarco B., De Bruyne B., Wijns W., Bartunek J., Barbato E.

Relationship of asymmetric dimethylarginine (ADMA) with extent and functional severity of coronary atherosclerosis.

Int J Cardiol. 2016 Oct 1;220:629-33. PubMed PMID: 27391005. IF 4,638

In patients with suspected coronary artery disease (CAD), we assessed the correlation of serum ADMA levels with extent and functional significance of coronary atherosclerosis. Angiographic CAD severity was evaluated by Bogaty score, whereas functional significance was assessed by fractional flow reserve (FFR). We observed across tertiles of ADMA levels increasingly higher extent of CAD. Patients with FFR \leq 0.80 in at least one vessel had significantly higher ADMA levels compared with patients without functionally significant CAD. Serum ADMA levels were independent predictors of abnormal FFR after adjustment for extent score. Serum ADMA levels are independent predictors of coronary atherosclerosis extent and functional significance of CAD.

Research Units: overview and main 2016 scientific outputs

Chemical-Physics Fundamentals in Chemical Engineering



Head V. Piemonte

Faculty L. Di Paola Other Personnel L. Marrelli

Description

Main research activities

Main collaborations

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.

- CHO cell growth optimization bioreactors modelling (in collaboration with Menarini Biotech, Pomezia, Italy).
 Energy storage tanks for CSP
- plants with molten salts. Modelling and optimization (In collaboration with the Italian National Agency for New Technologies, Energy and Sustainable Development - ENEA, Casaccia Research Centre, Rome, Italy).
- Bioartificial Liver optimization (in collaboration with Piaggio Research Centre, University of Pisa, Italy).
- Transport phenomena in the artificial and bioartificial organs (In collaboration with Umberto I University Hospital, Italy).
- Computational Biochemistry: proteins as networks (in collaboration with National Institute of Health, Italy).

Most important publications

Prisciandaro M., Capocelli M., Piemonte V., Barba D.

Process analysis applied to water reuse for a "closed water cycle" approach. *Chemical Engineering J. 2016;304:602-608. DOI: 10.1016/j.cej.2016.06.134. IF 5,310*

The reuse of wastewater is a key factor in a closed water cycle approach, in which wastewater is treated and then reused. This approach is both mandatory for the development of dry areas and necessary for the sustainability of industrialized countries in terms of environmental impacts and resource preservation. Although there are some virtuous examples of water reuse projects in the world,

 Italian National Agency for New Technologies, Energy and Sustainable Development, Casaccia Research Centre (ENEA), Italy:

- Menarini Biotech, Italy;
- National Institute of Health, Italy;
- Piaggio Research Centre, University of Pisa, Italy;
- Umberto I University Hospital, Italy.

there is still much to be done, especially in terms of incentives and economic viability. Aim of the present paper is to give thermodynamic and engineering elements in order to develop an economic incentive to promote wastewater reuse and to adopt the closed water cycle approach. At this scope a techno-economic analysis of the civil wastewater depuration and reverse osmosis treatment of the secondary effluent is presented, by using the typical approach of the chemical engineering. The cost of the treated water in relation to the fundamental parameters of the plant is calculated together with an "energy based" incentive, evaluated through the efficiency of the state-of-the-art desalination process. This last can make a reuse project economically feasible on the basis of rigorous thermodynamic considerations. These latter give a universal character to the incentive calculation and also reward the process optimization towards the goal of lowering the carbon emissions. The validity of the proposed method is evaluated through the analysis of three wastewater treatment and reuse projects at different scale. The results show how it is possible to obtain a positive Earnings Before Interests and Taxes (EBIT) for plant productivity above the 200 m3/day, by including the proposed incentive in the Business Plan of the integrated plant of Water Treatment and Reuse.

Annesini M. C., Tomei M. C., Piemonte V., Daugulis A. J.

Xenobiotic removal from wastewater in a two-phase partitioning bioreactor: Process modelling and identification of operational strategies.

Chemical Engineering J. 2016;296:428-436. DOI: 10.1016/j.cej.2016.03.123. IF 5,310

This paper proposes a dynamic model simulating the performance of a fed batch system operated as solid-liquid two-phase partitioning bioreactor, with polymer beads as the sequestering phase, applied to the removal of xenobiotic compounds from concentrated aqueous streams, in which substrate inhibition is significant. The model takes into account substrate mass transfer into, and within, the solid particles. Outputs of the models are xenobiotic concentrations in the liquid and solid phases and the concentration profile within the solid polymer beads. Sensitivity analyses have been performed on the influent concentration and on the main operating parameters, which can be modified to control the process performance (i.e. polymer/feed ratio, reaction and loading times). With an inhibitory substrate, the selected duration of the reaction period exhibits a critical value which determines the transition from high to low efficiency of the bioreactor. Application examples are provided for a target compound, 4-nitrophenol, previously investigated in TPPBs with an immiscible organic solvent, while Hytrel 8206 has been considered as the polymer partitioning phase. The proposed model has been shown to be a powerful tool to predict suitable operating conditions for TPPB systems treating inhibitory substrates.

Piemonte V., Di Paola L., laquaniello G., Prisciandaro M.

Biodiesel production from microalgae: ionic liquid process simulation.

J Clean Prod. 2016; 111: 62-68. DOI: 10.1016/j.jclepro.2015.07.089. IF 4,959

The industrial scale production of biodiesel, the most common biofuel, requires innovative solutions to become more and more competitive with a reduced environmental impact. Microalgae are the most promising feedstock for biodiesel production since they are grown on non-arable areas and reduce the greenhouse gas emissions as well. The oil extraction is the competitiveness bottleneck, largely impacting the overall process cost. Oil extraction using ionic liquids is considered a promising technique, which has the chance to become a benchmark for large scale applications. In this paper a novel process simulation of ionic liquid operation is developed, implemented by Aspen Hysys V7.3®. The chosen ionic liquid is Butyl-3-methylimidazolium chloride, a green solvent; since it is a non-conventional compound, a method to compute its properties through a thermodynamic model is provided. Moreover, a process scheme has been set up and simulated, composed of a lysis reactor, in which the ionic liquid is added for oil extraction, and a three phase separator, with recycle lines and several heat exchangers for heat recovery. Mass and energy balances have been carried out. The main results allowed to calculate the recovered oil as a function of the ionic liquid to dry biomass weight ratio (with assuming a bio-oil extraction yield of 100) and as expected, the bio-oil recovery yield increased at decreasing temperature. However, a complete recovery is not feasible, due to the physical constraints in the thermodynamic model hypotheses. Albeit some simplifying hypotheses for the thermodynamic properties, the novelty of this work is that it reports results of a process simulation, providing indication for industrial technological implementation coming from a professional tool for process simulation and control

Clinical Pathology and Microbiology



Head S. Angeletti

Faculty G. Gherardi

Other Personnel F. Antonelli, M. Ciccozzi, A. Conti, M. De Cesaris, L. De Florio, G. Dicuonzo, M. Fogolari

External Members E. Cella, M. Giovannetti

Description

Main research activities

The research unit is actively enrolled in the field of molecular evolution of microorganisms causing important epidemic worldwide and in the field of antimicrobial resistance. Furthermore, the activity of the research unit is focused on the evaluation of the role of rapid diagnostic bio-markers in the diagnosis and prognosis of bacterial and viral infections.

In the year 2016, the most important activities developed by the research unit have been in the areas of infectious disease and antibiotic resistance. At this aim, a close collaboration with of the University Hospital Campus Bio-Medico of Rome has been strengthened. Furthermore, the research unit established a scientific agreement with the Auxilium Society managing the CARA Centre of Castelnuovo di Porto in Rome for migrants and refugees. By this agreement, a protocol for migrants microbiological surveillance was developed and results of the surveillance reported in many important symposium such as "Diritto alla Salute delle popolazioni migranti" 7 novembre 2016, Sala della regina, Montecitorio; "Salute e migarzione: curare le popolazioni oltre I confine", 12-16 Dicembre 2016, Lampedusa and "La vulnerabilità dell'umano: la sfida delle popolazioni fragili alla sanità pubblica, presso Aula

conferenze PRABB dell'università Campus Bio-Medico di Roma. 28 Novembre 2016. Furthermore, the results of the microbiological surveillance have been object of some publication on international peer-reviewed scientific journals. Other important agreement have been signed with the Public Health Institute of Montenegro (Podgorica), the Public Institute of Bulgaria (Sofia) and with the Department of Pathology and Laboratory medicine of the University of Florida, Gaineville, USA. By these agreements, several scientific publications on international and peer-reviewed journals have been published and new scientific collaborations are ongoing.

Main collaborations

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

Most important publications

Angeletti S., Presti A.L., Cella E., Fogolari M., De Florio L., Dedej E., Blasi A., Milano T., Pascarella S., Incalzi R.A., Coppola R., Dicuonzo G., Ciccozzi M.

Klebsiella pneumoniae blaKPC-3 nosocomial epidemic: Bayesian and evolutionary analysis. Infect Genet Evol. 2016 Dec;46:85-93. PubMed PMID: 27815135. IF 2,591

K. pneumoniae isolates carrying blaKPC-3 gene were collected to perform Bayesian phylogenetic and selective pressure analysis and to apply homology modeling to the KPC-3 protein. A dataset of 44 blakpc-3 gene sequences from clinical isolates of K. pneumoniae was used for Bayesian phylogenetic, selective pressure analysis and homology modeling. The mean evolutionary rate for blakpc-3 gene was 2.67×10-3 substitution/site/year (95% HPD: 3.4×10-4-5.59×10-3). The root of the Bayesian tree dated back to the year 2011 (95% HPD: 2007-2012). Two main clades (I and II) were identified. The population dynamics analysis showed an exponential growth from 2011 to 2013 and the reaching of a plateau. The phylogeographic reconstruction showed that the root of the tree had a probable common ancestor in the general surgery ward. Selective pressure analysis revealed twelve positively selected sites. Structural analysis of KPC-3 protein predicted that the amino acid mutations are destabilizing for the protein and could alter the substrate specificity. Phylogenetic analysis and homology modeling of blaKPC-3 gene could represent a useful tool to follow KPC spread in nosocomial setting and to evidence amino acid substitutions altering the substrate specificity.

Angeletti S., Ceccarelli G., Vita S., Dicuonzo G., Lopalco M., Dedej E., Blasi A., Antonelli F., Conti A., De Cesaris M., Farchi F., Lo Presti A., Ciccozzi M., Sanitary Bureau of Asylum Seekers Center of Castelnuovo di Porto.

Unusual microorganisms and antimicrobial resistances in a group of Syrian migrants: sentinel surveillance data from an asylum seekers centre in Italy.

Travel Med Infect Dis. 2016 Mar-Apr;14(2):115-22. PubMed PMID: 26987764. IF 2,192

Background: Three years of civil war in Syria have caused death and increase of communicable diseases. The suffering population has been forced to migrate creating a fertile condition for epidemic spread of infection within the refugee camps. **Methods:** Forty-eight Syrian migrants, upon their arrival in Italy, were accommodated at the asylum seekers centre of Castelnuovo di Porto. They received a physical examination and were subjected to microbiological surveillance by blood, rectal, pharyngeal and nasal swabs collection and delivering to the Clinical Pathology and Microbiology Laboratory of the Campus Bio-Medico University of Rome. **Results:** All refugees resulted negative for HBV, HCV and HIV infections. In swabs a large number of unusual gram-negative bacteria species were isolated, such as Pseudomonas putida, Pseudomonas monteilii, Pseudomonas fulva, Pseudomonas moselii, Aeromonas veronii, Aeromonas caviae, Aeromonas hydrophila, Acinteobacter guilloviae, Acinteobacter lowffii; Acinetobacter johnsonii; Acinteobacter tjernbergae; Pantoea agglomerans; Pantoea calida. Among isolates, strains resistant to carbapenems, ESBL producers and methicillin resistant were found. **Conclusions:** The microbiological surveillance performed represents a useful action to understand refugees health status and to trace unusual microorganisms movement even carriers of antimicrobial resistance during migrants traveling.

Angeletti S., Ciccozzi M., Fogolari M., Spoto S., Lo Presti A., Costantino S., Dicuonzo G.

Procalcitonin and MR-proAdrenomedullin combined score in the diagnosis and prognosis of systemic and localized bacterial infections.

J Infect. 2016 Mar;72(3):395-8. PubMed PMID: 26723912. IF 4,382

Computer Systems and Bioinformatics



Head G. lannello

Faculty P. Soda, L. Vollero, F. Cacace

Other Personnel L. Acciai, P. Afferni, E. Cordelli, M. Merone, S. Petrichella, R. Valenti **External Members** A. Bria

Description

Main collaborations

The Computer Science and Bioinformaics (CoSBI) Research Unit is 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, Internet of Things (IoT) systems, applications and protocols, and modeling dynamic stochastic systems. More specifically, the Unit is working on:

- 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.
- Computer-aided diagnosis systems for automatic analysis of Indirect Immunofluorescence (IIF) images.
- Support Decision Systems for clinical applications, such as Chronic obstructive pulmonary disease (COPD) telemonitoring and prediction of diabetes complications.
- Algorithms for the analysis of EEG and EEG-TMS signals, and of fRMI images.
- Methods for time series forecasting, with applications big data analytics and social network analysis.
- Pattern recognition and machine learning methods to handle imbalance datasets.
- Bioinformatics tools for long non-coding RNAs analysis.
- Estimation methods for mathematical models of biological systems.

- The European Non-linear Spectroscopy Laboratory for the development tools for processing ultra terabyte images.
- Peng's Group at Allen Institute for Brain Science for joint development of tools for visualization of ultra terabyte images.
- The Gerontology Unit for developing a system to detect risk conditions for BPCO patients.
- The Neurology Unit for the identification of conditions and biomarkers of the Alzheimer's disease.
- The Robotic Unit, for developing a system for robotic tele-rehabilitation of the upper limb.
- The Immunology Unit for developing a CAD system to classify ANA samples in IIF.
- The Catholic University of the Sacred Heart for developing new strategies for type 1 diabetes mellitus monitoring and treatment.
- The Department of Information and Electrical Engineering of L'Aquila for developing new approaches for estimators and filters of uncertain dynamical systems and systems with delayed measurements.
- Pechenizkiy's Group at Eindhoven University of Technology, Department of Computer Science, for joint research on social network analysis.
- Prof. Zhang's Group at School of Computer and Information Engineering, Henan University, for joint research on pattern recognition and machine learning methods to handle imbalance datasets.

Most important publications

Bria A., Iannello G., Onofri L., Peng H.

TeraFly: real-time three-dimensional visualization and annotation of terabytes of multidimensional volumetric images.

Nat Methods. 2016 Mar;13(3):192-4. PubMed PMID: 26914202. IF 25,328

New sample preparation and high-throughput light-sheet microscopy techniques are increasingly capable of generating multidimensional (3D and higher) images easily exceeding the tera-byte size. Existing tools allow only 2D slice-based rendering of 3D image stacks and a free, open-source and cross-platform software tool for true 3D visualization and 3D annotation of very large multidimensional volumes is highly desired. To fill this gap, we have developed TeraFly software for interactive 3D visualization of terabytes of 3D and 4D (3D spatial information plus color) images, as well as 5D (4D plus time) image series, with subsecond response times from both local and remote data sources.

Ferreri F., Vecchio F., Vollero L., Guerra A., Petrichella S., Ponzo D., Määtta S., Mervaala E., Könönen M., Ursini F., Pasqualetti P., Iannello G., Rossini P.M., Di Lazzaro V.

Sensorimotor cortex excitability and connectivity in Alzheimer's disease: A TMS-EEG Co-registration study.

Hum Brain Mapp. 2016 Jun;37(6):2083-96. PubMed PMID: 26945686. IF 4,962

To investigate the neurophysiological hallmarks of motor cortex functionality in early AD we combined transcranial magnetic stimulation (TMS) with electroencephalography (EEG). We demonstrated that in mild AD the sensorimotor system is hyperexcitable, despite the lack of clinically evident motor manifestations. This phenomenon causes a stronger response to stimulation in a specific time window, possibly due to locally acting reinforcing circuits, while network activity and connectivity is reduced. These changes could be interpreted as a compensatory mechanism allowing for the preservation of sensorimotor programming and execution over a long period of time, regardless of the disease's progression.

Cacace F., Conte F., Germani A.

Memoryless approach to the LQ and LQG problems with variable input delay.

IEEE Trans Autom Control. 2016; 61(1):216-221. DOI: 10.1109/TAC.2015.2427611. IF 2,777

We study the LQ and LQG problems for linear time invariant systems with a single time-varying input delay and instantaneous (memoryless) state feedback. We prove that in the deterministic case a memoryless state feedback can be in general optimal only up to a certain delay, for which we provide a sufficient, and sometimes strict, bound. Moreover, we show that this memoryless control is optimal also in the case of time-varying delays and that the quadratic cost functional has the same value as in the case without delay. Finally, we prove that the cost functional is bounded also in the stochastic case for the same delay interval as in the deterministic case, but with a larger cost than the delay-less LQG solution.

Developmental Neuroscience



Head F. Keller

Other Personnel V. Focaroli, R. Marino

Description

Main research activities

Main collaborations

- The Developmental Neuroscience unit investigates developmental mechanisms at the molecular, cellular and systemic levels, both in animal models and in human infants. One major focus of the lab has been the interaction between reelin, a protein of the extracellular matrix and environmental factors, in particular gonadal hormones, during brain development. The reelin gene is a candidate gene for autism, a pervasive developmental disorders that is more frequent in males. The other major focus of the lab is the role of motor development and other embodied functions for development of cognitive functions and mental processes. Specifically, we are investigating early motor signs of autism risk in high-risk babies, who have an older sibling affected by this disorder. A new research focus of the lab is the investigation of embodied music perception in children.
- Motor development in siblings who are at high risk for autism;
 Novel behavioural tests of music perception in young children.
- Dr. Alessandra Micera, G. B. Bietti Foundation for Study and Research in Ophthalmology, Italy (interaction between NGF and reelin in the mouse retina);
- Dr. Nicola Di Stefano, Istituto FAST; Dr. Fabrizio Taffoni, Lab of Biomedical Robotics, UCBM (music perception in young children);
- Prof. Jana M. Iverson, University of Pittsburgh (motor development in siblings who are at high risk for autism).

Most important publications

Focaroli V., Taffoni F., Parsons S.M., Keller F., Iverson J.M.

Performance of motor sequences in children at heightened vs. low risk for ASD: a longitudinal study from 18 to 36 months of age.

Front Psychol. 2016 May 13;7:724. PubMed PMID: 27242630. IF 2,463

Recent research shows that motor difficulties are a prominent component of the behavioral profile of autism spectrum disorder (ASD) and are also apparent from early in development in infants who have an older sibling with ASD (High Risk; HR). Delays have been reported for HR infants who do and who do not receive an eventual diagnosis of ASD. A growing body of prospective studies has focused on the emergence of early motor skills primarily during the first year of life. To date, however, relatively little work has examined motor skills in the second and third years. Thus, the present research was designed to investigate motor performance in object transport tasks longitudinally in HR and LR (Low Risk) children between the ages of 18 and 36 months. Participants (15 HR children and 14 LR children) were observed at 18, 24, and 36 months. Children completed two motor tasks, the Ball Task and the Block Task, each of which included two conditions that varied in terms of the precision demands of the goal action. Kinematic data were acquired via two magneto inertial sensors worn on each wrist. In the Block Task, HR children reached more slowly (i.e., mean acceleration was lower) compared to LR children. This finding is in line with growing evidence of early delays in fine motor skills in HR children and suggests that vulnerabilities in motor performance may persist into the preschool years in children at risk for ASD.

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

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

Psychology of Music. 2016; 0305735616681205. DOI: 10.1177/0305735616681205. IF 2,010

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

Diagnostic Imaging



Head B. Beomonte Zobel Faculty R.F. Grasso, C.C. Quattrocchi

Other Personnel Y. Errante, S. Gaudio, F. Giurazza, C. A. Mallio

Description

Main research activities

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 2016, are in the following sectors:

- Contrast media, evaluating in vivo brain Gadolinium deposition from currently used contrast agents and being part of the European Gadolinium retention evaluation Consortium (E-GREC).
- Interventional Radiology, evaluating the technique of endovascular occlusion of pulmonary arteriovenous malformations; analyzing errors in cancer ablation procedures; analyzing a case of percutaneous radiofrequency ablation of a bleeding pseudoaneurysm during CT-guided renal cancer treatment.
- Neuroimaging, evaluating MRI diffusion, white-matter hyperintensities, and cognitive function in Alzheimer's disease and vascular dementia; cortical changes following brainstem injury in patients with "Locked-in Syndrome; differential diagnosis of brainstem lesions in children.
- Oncologic imaging, assessing clinical and radiological features driving patient selection for antiangiogenic therapy in non-small cell lung cancer (NSCLC).

Most important publications

Beomonte Zobel B., Quattrocchi C.C., Errante Y., Grasso R.F.

Gadolinium-based contrast agents: did we miss something in the last 25 years? Radiol Med. 2016 Jun;121(6):478-81. PubMed PMID: 26706453. IF 1,523

In the last 24 months, several clinical and experimental studies, suggested first and demonstrated later, a progressive concentration of Gadolinium in the brain of normal renal function patients, following repeated injections of some of the commercially approved Gadolinium-Based Contrast Agents. Although, till now, Gadolinium brain deposits have not been associated to any kind of neurological signs or symptoms, they oblige the radiology community to modify the actual approach in using Gadolinium contrast media in daily practice, to reduce unknown possible risks for patients.

Gridelli C., Camerini A., Pappagallo G., Pennella A., Anzidei M., Bellomi M., Buosi R., Grasso R.F.

Clinical and radiological features driving patient selection for antiangiogenic therapy in non-small cell lung cancer (NSCLC).

Cancer Imaging. 2016 Dec 28;16(1):44. PubMed PMID: 28031049. IF 1,470

Background: The use of antiangiogenic therapy in non-small cell lung cancer (NSCLC) requires evaluation of patient characteristics in order to avoid potential safety issues, particularly pulmonary haemorrhage (PH). The aim of this consensus was to identify important criteria for the selection of patients with NSCLC who would benefit from antiangiogenic therapy.

Methods: Radiologists and oncologists were selected for the expert panel. The nominal group technique (NGT) and the Delphi questionnaire were used for consensus generation. The NGT consisted of four steps, the result of which was used to set the Delphi questionnaire. A final report was generated based on the opinions of the experts from the panel.

RESULTS: An extremely important prerequisite for the evaluation of an antiangiogenic therapeutic approach in patients with NSCLC was thorough clinical and radiological analysis of the relationships between tumour and vascular or anatomical structures. The panel identified major parameters to be considered before the use of antiangiogenic treatment, collectively agreeing on the relevance of tumour cavitation, vascular infiltration, endobronchial growth and thromboembolism for chest tumour sites, and of the presence of aneurysms, extra-thoracic bleeding, brain metastases or thrombi for extra-thoracic sites. Moreover, a structured report containing information not only on the tumour but also on the general vascular status is essential to guide the treatment choice. The experts agreed that tumour localization in the absence of vessel infiltration, cavitation, and the use of antiplatelet therapy are relevant parameters to be assessed, but their presence should not necessarily exclude a patient from receiving antiangiogenic therapy.

CONCLUSION: Close co-operation between oncologists and radiologists is essential for ensuring therapeutic appropriateness in the NSCLC setting. Neither antiplatelet therapy nor tumour localisation are to be considered as contraindications to antiangiogenic treatment.

Corvino F., Silvestre M., Cervo A., Giurazza F., Corvino A., Maglione F.

Endovascular occlusion of pulmonary arteriovenous malformations with the ArtVentive Endoluminal Occlusion System[™].

Diagn Interv Radiol. 2016 Sep-Oct;22(5):463-5. PubMed PMID: 27559714. IF 1,406

Pulmonary arteriovenous malformations (PAVMs) are vascular anomalies of the lung and carry the risk of cerebral thromboembolism, brain abscess, or pulmonary hemorrhage. We describe a 64-year-old male with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome) who presented with a five-year history of progressive effort dyspnea and a PAVM in the right upper lobe successfully treated by transcatheter embolization of feeding arteries using a new occlusion device, the ArtVentive Endoluminal Occlusion SystemTM.

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Research Units: overview and main 2016 scientific outputs

Drug Sciences



Head G. Minotti Faculty E. Salvatorelli

Other Personnel P. Menna

Description

Main research activities

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.

Zamorano J.L., Lancellotti P., Rodriguez Muñoz D., Aboyans V., Asteggiano R., Galderisi M., Habib G., Lenihan D.J., Lip G.Y., Lyon A.R., Lopez Fernandez T., Mohty D., Piepoli M.F., Tamargo J., Torbicki A., Suter T.M.; Authors/Task Force Members.; ESCCommittee for Practice Guidelines (CPG) [Minotti G.]

use of anthracycline-like drugs. Preliminary data in laboratory animals showed that pixantrone was active, primarily in hematologic malignancies, but caused significantly less cardiotoxicity than doxorubicin or mitoxantrone. Pixantrone was cardiac tolerable also in animals pretreated with doxorubicin, which anticipated a therapeutic niche for pixantrone to treat patients with a history of prior exposure to anthracyclines. This is the case for patients with refractory/relapsed NHL. Pixantrone clinical development, regulatory ap-

proval, and penetration in clinical practice were nonetheless laborious if not similar to a rocky road. Structural and nominal similarities with mitoxantrone and anthracyclines may have caused a negative influence, possibly leading to a general perception that pixantrone

is a "me-too" anthracycline. Recent insights suggest this is not the case. Pixantrone shows pharmacological and toxicological me-

chanisms of action that are difficult to reconcile with anthracycline-like drugs. Pixantrone is a new drug with its own characteristics. For example, pixantrone causes mis-segregation of genomic material in cancer cells and inhibits formation of toxic anthracycline metabolites in cardiac cells. Understanding the differences between pixantrone and anthracyclines or mitoxantrone may help one to appreciate how it worked in the phase 3 study that led to its approval in Europe and how it might work in many more patients in everyday clinical practice, were it properly perceived as a drug with its own characteristics and therapeutic potential. The road is rocky

2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC).

Eur Heart J.2016 Sep 21;37(36):2768-2801. Erratum in: Eur Heart J. 2016 Dec 24; PubMed PMID: 27567406. IF 15,064

Most important publications

Menna P., Salvatorelli E., Minotti G.

Rethinking drugs from chemistry to therapeutic opportunities: Pixantrone beyond Anthracyclines. *Chem Res Toxicol. 2016 Aug 15;29(8):1270-8. PubMed PMID: 27420111. IF 3,025*

Pixantrone (6,9-bis[(2-aminoethyl)amino]benzo[g]isoquinoline-5,10-dione) has been approved by the European Medicines Agency for the treatment of refractory or relapsed non-Hodgkin's lymphoma (NHL). It is popularly referred to as a novel aza-anthracenedione, and as such it is grouped with anthracycline-like drugs. Preclinical development of pixantrone was in fact tailored to retain the same antitumor activity as that of anthracyclines or other anthracenediones while also avoiding cardiotoxicity that dose-limits clinical Vincenzi B., Armento G., Spalato Ceruso M., Catania G., Leakos M., Santini D., Minotti G., Tonini G.

Drug-induced hepatotoxicity in cancer patients – implication for treatment.

Expert Opin Drug Saf. 2016 Sep;15(9):1219-38. PubMed PMID: 27232067. IF 2,896

but not a dead-end.

Introduction: All anticancer drugs can cause idiosyncratic liver injury. Therefore, hepatoprotective agents assume particular importance to preserve liver function. Hepatic injury represents 10% of cases of acute hepatitis in adults; drug-related damage is still misjudged because of relative clinical underestimation and difficult differential diagnosis. Chemotherapeutic agents can produce liver toxicity through different pathways, resulting in different categories of liver injuries, but these drugs are not homogeneously hepatotoxic. Frequently, anticancer-induced hepatotoxicity is idiosyncratic and influenced by multiple factors.

Areas Covered: The aim of this paper is to perform a review of the literature regarding anticancer-induced liver toxicity. We described hepatotoxicity mechanisms of principal anticancer agents and respective dose reductions. Furthermore, we reviewed studies on hepatoprotectors and their optimal use. Tiopronin, magnesium isoglycyrrhizinate and S-Adenosylmethionine (AdoMet) demonstrated, in some small studies, a potential hepatoprotective activity.

Expert Opinion: Actually, in the literature only small experiences are reported. Even though hepatoprotective agents seem to be useful in the oncologic setting, the lack of well-designed prospective Phase III randomized controlled trials is a major limit in the introduction of hepatoprotectors in cancer patients and these kind of studies are warranted to support their use and to give further recommendations for the clinical practice.

Electrical Engineering



Head M. Parise

Description

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.

Main research activities

- 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.

Exact EM field excited by a short horizontal wire antenna lying on a conducting soil. *AEU-Int J Electron Commun. 2016;70(5):676-680. DOI: 10.1016/j.aeue.2016.02.004. IF 0,786*

To date, only under restrictive assumptions can we derive closed-form expressions for the fields generated by an electrically small horizontal wire antenna situated on a planar conducting soil. Such assumptions limit the validity of the derived formulas to specified frequency ranges, or to the case of highly-conducting material media. The purpose of this work is to relax all the constraints underlying the derivation of the previously published solutions to this half-space problem, and develop an analytical technique that allows to reduce the integral representations for the field components generated by the dipole source to a well-known elementary contour integral, whose evaluation is straightforward. Numerical results are presented to show the advantages of the obtained explicit formulas, which are valid regardless of the operating frequency, over the previous solutions.

Parise M.

Efficient computation of the surface fields of a horizontal magnetic dipole located at the air-ground interface.

Int J Numer Model-Electron Netw Device Fields.2016; 29(4):653–664. DOI: 10.1002/jnm.2120. IF 0,515

In this paper, the classic problem of determining the fields of a vertically oriented current-carrying small circular-loop antenna located near a plane air—earth boundary is revisited. It is well known that the Sommerfeld integrals describing the field components generated by the loop source cannot be exactly evaluated and that their numerical integration is made difficult by the presence of highly oscillatory terms in the integrands. Here, for both source and observation points on the interface, a rigorous method is developed that allows analytical integration of the Sommerfeld integrals, providing fast-convergent series representations for the surface fields. The obtained formulas permit to overcome all the drawbacks of the previously published approximate solutions to this problem, and to avoid the necessity of using purely numerical approaches when high computational accuracy is required. At the same time, the proposed series representations constitute an analytical benchmark for numerical procedures employed to solve electromagnetic boundary value problems, with applications in antenna design and close-to-the-surface communication.

Parise M.

Quasi-static vertical magnetic field of a large horizontal circular loop located at the earth's surface. *PIER Letters 2016; 62:29-34. DOI: 10.2528/PIERL16053003*

In this work, an analytical expression is derived for the radial distribution of the quasi-static vertical magnetic field of a current-carrying large circular loop placed on a homogeneous earth. The obtained expression results from applying a rigorous procedure, which leads to cast the Hankel transform describing the vertical magnetic field component into a form consisting of two elliptic integrals and a fast-convergent sum of spherical Hankel functions. The derived solution ensures the same degree of accuracy as the finite difference time domain method, but, as a purely analytical formula, has the advantage of requiring less computational time. Numerical results are presented to illustrate the validity of the developed formulation.

Electronics for Sensor Systems



Head G. Pennazza

Faculty: M. Santonico

Other Personnel S. Grasso, F.R. Parente, A. Zompanti

tific journals.

Description

Main research activities

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.

BIONOTE has been daily used in different wards of the polyclinic for many studies based on the analysis of biological fluids: exhaled breath, urine, exudate, pleural fluid. Three of these studies about lung cancer, hepatic diseases and lower limb ulcers have been published in international scien-

KOSMOMED project on telemedicine (financed by the European Space Agency) has achieved important results, which have been presented in ECSAT, the ESA facility in the Harwell Campus in Oxfordshire (UK).

Two patents involving ESS unit have been licensed in 2016: System For Characterisation Of Pure And Ultrapure Water (EP3001193); Device For Sampling Food Products (EP2962098).

 Academic Medical Center (AMC), Amsterdam:

Main collaborations

- Biomedical Department of Internal and Specialistic Medicine, University of Palermo, Italy;
- Coldiretti, Italy;
- Department of Industrial and Information Engineering and Economics, University of L'Aquila
- Division of Thoracic Surgery, Department of Thoracic Surgery and Oncology, National Cancer Institute, Pascale Foundation, IRCCS, Naples;
- Institute of Biomedicine and Molecular Immunology, National Research Council (CNR), Italy;
- Puretech srl, Italy;
- Tor Vergata Policlinic, Rome, Italy;
- Unit of Authenticity and Novel Food, Wageningen University, Netherland.

samples in solution in term of diagnostic accuracy and of feasibility when applied to the study of lower-limb ulcers, where the biological sample consists of ulcer's exudate. To this scope, BIONOTE's liquid sensors have been tested in a single-center pilot study. A total number of 30 clinical parameters have been collected for the medical characterization of each patient. A data fusion of the clinical parameters and of the BIONOTE data have been successful in discriminating ulcers evolution. In particular, the correct discrimination percentage between the ulcer analyzed at the first and at the second clinical evaluation (after therapy) was of 75%, 90% and 97.5% when based on clinical data, BIONOTE data and data fusion respectively. The consistency of BIONOTE ability in ulcer monitoring has been also confirmed by a good sensor's prediction ability with respect to three key-parameters: Leg Ulcer Measurement Tool (LUMT), peripheral oxygen saturation of haemoglobin (SpO2), Transcutaneous oxygen pressure (TcPO2)..

De Vincentis A., Pennazza G., Santonico M., Vespasiani-Gentilucci U., Galati G., Gallo P., Vernile C., Pedone C., Antonelli Incalzi R., Picardi A.

Breath-print analysis by e-nose for classifying and monitoring chronic liver disease: a proof-of-concept study.

Sci Rep. 2016 May 5;6:25337. PubMed PMID: 27145718. IF 5,228

Since the liver plays a key metabolic role, volatile organic compounds in the exhaled breath might change with type and severity of chronic liver disease (CLD). In this study we analysed breath-prints (BPs) of 65 patients with liver cirrhosis (LC), 39 with non-cirrhotic CLD (NC-CLD) and 56 healthy controls by the e-nose. Distinctive BPs characterized LC, NC-CLD and healthy controls, and, among LC patients, the different Child-Pugh classes (sensitivity 86.2% and specificity 98.2% for CLD vs healthy controls, and 87.5% and 69.2% for LC vs NC-CLD). Moreover, the area under the BP profile, derived from radar plot representation of BPs, showed an area under the ROC curve of 0.84 (95% Cl 0.76–0.91) for CLD, of 0.76 (95% Cl 0.66–0.85) for LC, and of 0.70 (95% Cl 0.55–0.81) for decompensated LC. By applying the cut-off values of 862 and 812, LC and decompensated LC could be predicted with high accuracy (PPV 96.6% and 88.5%, respectively). These results are proof-of-concept that the e-nose could be a valid non-invasive instrument for characterizing CLD and monitoring hepatic function over time. The observed classificatory properties might be further improved by refining stage-specific breath-prints and considering the impact of comorbidities in a larger series of patients.

Rocco R., Incalzi R.A., Pennazza G., Santonico M., Pedone C., Bartoli I.R., Vernile C., Mangiameli G., La Rocca A., De Luca G., Rocco G., Crucitti P.

BIONOTE e-nose technology may reduce false positives in lung cancer screening programmes.

Eur J Cardiothorac Surg. 2016 Apr;49(4):1112-7; discussion 1117. PubMed PMID: 26385981. IF 2,803

Objectives: Breath composition may be suggestive of different conditions. E-nose technology has been used to profile volatile organic compounds (VOCs) pattern in the breath of patients compared with that of healthy individuals. BIOsensor-based multisensorial system for mimicking NOse, Tongue and Eyes (BIONOTE) technology differs from Cyranose® based on a set of separate transduction features. On the basis of our previously published experience, we investigated the discriminating ability of BIONOTE in a high-risk population enrolled in a lung cancer screening programme. Methods: One hundred individuals were selected for BIONOTE based on the attribution to the high-risk category (i.e. age, smoking status, chronic obstructive pulmonary disease status) of the University Campus Bio-Medico lung screening programme. We used a measure chain consisting of (i) a device named Pneumopipe (EU patent: EP2641537 (A1):2013-09-25) able to catch exhaled breath by an individual normally breathing into it and collect the exhalate onto an adsorbing cartridge; (ii) an apparatus for thermal desorption of the cartridge into the sensors chamber and (iii) a gas sensor array which is part of a sensorial platform named BIONOTE for the VOCs mixture analysis. Partial least square (PLS) has been used to build up the model, with Leave-One-Out cross-validation criterion.

Results: The overall sensitivity and specificity were 86 and 95%, respectively, delineating a substantial difference between patients and healthy individuals. Conclusions: Our preliminary data show that BIONOTE technology may be used to reduce false-positive rates resulting from lung cancer screening with low-dose computed tomography in a cost-effective fashion. The model will be tested on a larger number of patients to confirm the reliability of these results.

Most important publications

Santonico M., Frezzotti E., Incalzi R. A., Pedone C., Lelli D., Zompanti A., Grasso S., Pennazza G.

Non-invasive monitoring of lower-limb ulcers via exudate fingerprinting using BIONOTE. Sensors and Actuators B: Chemical. 2016; 232: 68-74. DOI: 10.1016/j.snb.2016.03.101. IF 4,758

Liquid fingerprinting represents a non-invasive and easy method for diagnostic and screening medical tests. BIONOTE is a sensor system including voltammetric liquid sensors consisting of screen printed electrodes controlled by a high stable electronic interface. Bacterial colonization of lower-limb ulcers gives a huge production of volatile and semi volatile compounds which could modify the electrochemical pattern of ulcer's exudate. The main goal of this study was to test the electrochemical fingerprinting of biological

Endocrinology and Diabetes

Head P. Pozzilli



Faculty S. Manfrini, N. Napoli

Other Personnel S.I. Briganti, I. Cavallari, G. De Feudis, R. Del Toro, A. Di Mauro, S. Fallucca, E. Fioriti, V. Greto, C. Guglielmi, A. Lauria, G. Leanza, E. Maddaloni, D. Maggi, A.R. Maurizi, A. Naciu, A. Palermo, A. Piccoli, A. Soare, R. Strollo, G. Tabacco, D. Tuccinardi, C. Vinci, S. Pieralice

Lab Technician L. Valente Scientific Secretary S. Miglietta, M. Delfonso Secretary A. Suppa

Description

Main research activities

Main collaborations

- Over the years, the research activity related to endocrine and metabolic diseases has expanded significantly placing the Area of Endocrinology, University Campus Bio-Medico 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 diabetes, obesity and in post-menopause;
- Early diagnosis of thyroid cancer (microbiopsy and RAMAN technology);
- Extraskeletal effects of vitamin D; risk of fracture in T1D and T2D.

Main results:

- Discovery of 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 se-
- condary hypoparathyroidism;
- Macrobiotic diet in treatment of diabetes and obesity.

Most important publications

Palermo A., Mangiameli G., Tabacco G., Longo F., Pedone C., Briganti S.I., Maggi D., Vescini F., Naciu A., Lauria Pantano A., Napoli N., Angeletti S., Pozzilli P., Crucitti P., Manfrini S.

PTH(1-34) for the primary prevention of postthyroidectomy hypocalcemia: the THYPOS Trial. *J Clin Endocrinol Metab. 2016 Nov;101(11):4039-4045. PubMed PMID: 27525532. IF 1,994*

Context: There are no studies evaluating teriparatide for prevention of post-thyroidectomy hypocalcemia. **Objective:** Our objective was to evaluate whether teriparatide can prevent postsurgical hypocalcemia and shorten the hospitalization in subjects at high risk of hypocalcemia following thyroid surgery. **Design:** This was a prospective phase II randomized open-label trial.

- Biochemistry Area, University Campus Bio-Medico, Rome, Italy;
- Centre for Diabetes & Metabolic Medicine, St. Bartholomew's and The London School of Medicine, Queen Mary's College, London, UK;
- Department of Clinical Sciences and Experimental Medicine, Sapienza University, Italy;
- University of Harvard, Boston, USA;
- Washington University in St. Louis, USA.

Setting: This trial was set on a surgical ward. **Patients:** Twenty-six subjects (six males, 20 females) with intact PTH lower than10 pg/ml 4 hours after thyroidectomy were included. **Intervention:** Subjects were randomized (1:1) to receive SC administration of 20 mcg of teriparatide every 12 hours until the discharge (treatment group) or to follow standard clinical care (control group). **Main outcome measure:** Adjusted serum calcium, duration of hospitalization, and calcium/calcitriol supplementation were measured. Results: Overall, the incidence of hypocalcemia was 3/13 in treatment group and 11/13 in the control group (P = .006). Treated patients had a lower risk of ypocalcemia than controls (relative risk, 0.26 [95% confidence interval, 0.09-0.723)]). The median duration of hospitalization was 3 days (interquartile range, 1) in control subjects and 2 days (interquartile range, 0) in treated subjects (P = .012). One month after discharge, 10/13 subjects in the treatment group had stopped calcium carbonate supplements, while only 5/13 in the control group had discontinued calcium. The ANOVA for repeated measures showed a significant difference in calcium supplements between groups at 1-month visit (P = .04) as well as a significant difference between discharge and 1-month visit in the treatment group (P for interaction time group = .04).

Conclusions: Teriparatide may prevent postsurgical hypocalcemia, shorten the duration of hospitalization, and reduce the need for calcium and vitamin D supplementation after discharge in high risk subjects after thyroid surgery.

Amed S., Pozzilli P.

Diagnosis of diabetes type in children and young people: challenges and recommendations. *Lancet Diabetes Endocrinol. 2016 May;4(5):385-6. PubMed PMID: 27053420. IF 16.32*

Diabetes in childhood was previously almost always type 1 diabetes, but nowdays childhood diabetes is a complex diagnosis that often requires sophisticated investigations to accurately ascertain diabetes type. Although diabetes in children continues to mostly consist of autoimmune-mediated type 1 diabetes, increases in childhood obesity are driving increases in childhood-onset type 2 diabetes, and advances in molecular genetics have improved recognition of maturity onset diabetes of the young (MODY). This changing landscape requires clinicians to adapt their diagnostic approach to childhood diabetes to increase the likelihood of an accurate diagnosis of diabetes type and to provide the most appropriate and effective treatment. Improved access to sophisticated testing is necessary. Testing of patients for common antibodies is not sufficient and could potentially lead to misclassification of 5-10% of children with type 1 diabetes as type 2 diabetes. The goal is to ensure that young people with diabetes receive the right diagnosis so that they receive the most effective and least invasive therapy, to achieve the best health outcomes and quality of life for patients.

Maddaloni E., Cavallari I., De Pascalis M., Keenan H., Park K., Manfrini S., Buzzetti R., Patti G., Di Sciascio G., Pozzilli P.

Relation of body circumferences to cardiometabolic disease in overweight-obese subjects. *Am J Cardiol. 2016 Sep* 15;118(6):822-7. *PubMed PMID: 27457430. IF 3*,154

Body circumferences have been proposed as potential anthropometric measures for the assessment of cardiometabolic risk as they are independently associated with insulin resistance and diabetes. The aim of this study was to validate neck and wrist circumference and waist-to-hip ratio as practical markers of metabolic dysfunction and atherosclerosis; 120 subjects who underwent coronary angiography and carotid Doppler ultrasound were enrolled in this cross-sectional study. Exclusion criteria were history of diabetes, acute myocardial infarction, body mass index (BMI) <18.5 or \geq 45.0 kg/m(2). Metabolic dysfunction was ascertained by the calculation of visceral adiposity index (VAI) and by diagnosis of metabolic syndrome (MS). Advanced atherosclerotic disease was defined as \geq 70% coronary lumen and/or \geq 50% carotid lumen stenosis. No association between body circumferences and VAI or MS was found in subjects with BMI <25 kg/m(2). VAI was significantly related to waist-to-hip ratio (R(2) = 0.09, p = 0.008), neck (R(2) = 0.09, p = 0.007), and wrist circumferences (R(2) = 0.05, p = 0.041) in subjects with BMI \geq 25 kg/m(2). In overweight subjects, higher gender-specific tertiles of wrist circumference were independently associated with an increased risk of MS (odds ratio 2.57, 95% confidence interval 1.11 to 5.96, p = 0.028). VAI was independently associated with carotid intima-media thickness: β = 0.104, R(2) = 0.118, p = 0.003. Carotid intima-media thickness and MS, but not body circumferences, were associated with advanced atherosclerosis. In conclusion, these data indicate that anthropometric measurements, in particular wrist circumference, can be used as practical tools for assessment of metabolic risk in overweight-obese subjects but not as markers of advanced atherosclerosis.

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Research Units: overview and main 2016 scientific outputs

Food Science and Nutrition



Head L. De Gara

Faculty C. Fanali, V. Locato, M. Russo

Other Personnel S. Cimini, F. Orsini, V. Pasqualetti, W. Rizza, M. B. Ronci, G. Tripodo External Members P. Dugo, L. Mondello

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Main research activities

Main collaborations

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.

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

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

Most important publications

Hussain J., Chen J., Locato V., Sabetta W., Behera S., Cimini S., Griggio F., Martínez-Jaime S., Graf A., Bouneb M., Pachaiappan R., Fincato P., Blanco E., Costa A., De Gara L., Bellin D., de Pinto M.C., Vandelle E.

Constitutive cyclic GMP accumulation in Arabidopsis thaliana compromises systemic acquired resistance induced by an avirulent pathogen by modulating local signals. Sci Rep. 2016 Nov 4;6:36423. PubMed PMID: 27811978 IF 5,228

The infection of Arabidopsis thaliana plants with avirulent pathogens causes the accumulation of cGMP with a biphasic profile downstream of nitric oxide signalling. However, plant enzymes that modulate cGMP levels have yet to be identified, so we generated transgenic A. thaliana plants expressing the rat soluble guanylate cyclase (GC) to increase genetically the level of cGMP and to study the function of cGMP in plant defence responses. Once confirmed that cGMP levels were higher in the GC transgenic lines than in wild-type controls, the GC transgenic plants were then challenged with bacterial pathogens and their defence responses were characterized. Although local resistance was similar in the GC transgenic and wild-type lines, differences in the redox state suggested potential cross-talk between cGMP and the glutathione redox system. Furthermore, large-scale transcriptomic and proteomic analysis highlighted the significant modulation of both gene expression and protein abundance at the infection site, inhibiting the establishment of systemic acquired resistance. Our data indicate that cGMP plays a key role in local responses controlling the induction of systemic acquired resistance in plants challenged with avirulent pathogens.

Fanali C., Belluomo M.G., Cirilli M., Cristofori V., Zecchini M., Cacciola F., Russo M., Muleo R., Dugo L.

Antioxidant activity evaluation and HPLC-photodiode array/MS polyphenols analysis of pomegranate juice from selected Italian cultivars: a comparative study.

Electrophoresis. 2016 Jul;37(13):1947-55. PubMed PMID: 26814700. IF 2,482

Chemical composition of pomegranate juice can vary due to cultivar, area of cultivation, ripening, climate, and other variables. This study investigates the polyphenolic composition and antioxidant activity of juices obtained from six old Italian pomegranate cultivars. Fruit accessions physicochemical characteristics were determined. Total polyphenols content (TPC), anthocyanin content (TAC) and proanthocyanidin content (TPAC) were measured in the juice samples. Phenolic bioactive molecules were analyzed by HPLCphoto-diode array (PDA)/ESI-MS in all the pomegranate juices. In total, seven nonanthocyanidinic and six anthocyanidinic compounds were identified. The six anthocyanins were found in all juices although at different amounts. These results were correlated with antioxidant activity measured by three different chemical assays: 2,2 diphenyl-1-picrylhydrazyl (DPPH•) scavenging activity assay, Trolox equivalent antioxidant capacity (TEAC) method and ferric reducing-antioxidant power (FRAP) assay. Pomegranate juices obtained by six different varieties show variable polyphenolic content and antioxidant activity. The antioxidant capacity methods used have shown variable sensitivity, supporting the hypothesis that different methods for the assessment of antioxidant capacity of food compounds are indeed necessary, due to complexity of sample composition and assay chemical mechanism and sensitivity. Juices from Italian pomegranate show good levels of polyphenols content and antioxidant activity making them potential candidates for employment in the food industry.

Russo M., Arigò A., Calabrò M. L., Farnetti S., Mondello L., Dugo P.

Bergamot (Citrus bergamia Risso) as a source of nutraceuticals: limonoids and flavonoids.c J Funct Food. 2016;20:10–19. DOI: 10.1016/j.jff.2015.10.005. IF 3,973

Limonoids are human health promoters, and have many pharmacological properties: anticancer, antioxidant, antibacterial and antifungal. To the best of the authors' knowledge, there are no previous reports on the composition of limonoids in bergamot fruits, so the aim of this work was to characterize bergamot peel, pulp, seed and juice. Samples analysed showed the presence of both limonoids aglycones and glucosides. Limonoid aglycones are the most abundant in seeds and peels (70 and 80% of the total, respectively), while limonoid glucosides are the more abundant in juices and pulps (61 and 76% of the total, respectively). Moreover, a method to isolate pure limonoids from bergamot seeds and juice by means of a 2D-HPLC/PDA/MS preparative system is proposed. Pure molecules isolated were used to build calibration curves to quantify limonoids in real samples. Isolation of nutraceuticals from seeds and juices can represent an advantageous way to re-evaluate these by-products.

Gastroenterology



Head M. Cicala

Faculty S. Emerenziani, M.P.L. GuarinoOther Personnel A. Altomare, P. Balestrieri, M. Ribolsi, L.TrilloExternal Members R. Farrè (Leuven University, Belgium)

Description

Main research activities

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-impendance 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

Putignani L., Del Chierico F., Vernocchi P., Cicala M., Cucchiara S., Dallapiccola B.; Dysbiotrack Study Group.

Gut microbiota dysbiosis as risk and premorbid factors of IBD and IBS along the childhood-adulthood transition.

Inflamm Bowel Dis. 2016 Feb;22(2):487-504. PubMed PMID: 26588090. IF 4,358

Gastrointestinal disorders share pathogenic mechanisms, including genetic susceptibility, impaired gut barrier function, altered microbiota, and environmental triggers. Gut microbiota has been studied for inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS) in either children or adults, while modifiable gut microbiota features, acting as risk and premorbid factors along the childhood-adulthood transition, have not been thoroughly investigated so far. Tracking gut dysbiosis grading may help deciphering host phenotype-genotype associations and microbiota shifts. Dysbiosis-related indexes can represent novel laboratory and clinical medicine tools preventing or postponing the disease, finally interfering with its natural history.

Cocca S., Guarino M., Cicala M.

Asymptomatic parasitic illection in a Crohn's disease patient on anti-TNFa therapy: an alert for our patients?

J Crohns Colitis. 2016 Dec;10(12):1455-1456. PubMed PMID: 27208388. IF 6,585

It is known that parasitic infections are uncommon in Europe, with prevalence ranging between 0.01% to 10%.1 Human taeniasis is caused by three species of Taenia: asiatica, saginata, and solium: and generally occurs after consumption of raw or inadequately cooked beef. The patient may remain asymptomatic or with minor symptoms for a long period of time.2 Prevalence of parasitic infection in patients affected by inflammatory bowel diseases [IBD] has not been studied. We report a case of a 26-year-old Caucasian man with a recent diagnosis of ileal-colonic Crohn's disease [CD], treated with anti-tumour necrosis factor alpha [TNF α] therapy and presenting with an asymptomatic parasitic infection.

General Surgery



Head R. Coppola

Faculty R. Alloni, D. Borzomati, D. Caputo, M. Caricato, P. Crucitti, V. RipettiOther Personnel G. Capolupo, V. La Vaccara, S. Valeri

Description

The General Surgery Research Unit includes seven Academic Surgeons (one Full Professor, three Associate Professors and three Assistant Professors). In 2016, the research unit published 14 papers on English language international journals (IF: 46,738)

Main research activities

Research activities of the unit in 2016:

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).
- Prospective multicentric study on antibiotic prophylaxis in patients undergoing pancreaticoduodenectomy (promoted by R. Coppola, S. Valeri).
- Prognostic role of preoperative inflammatory markers for surgically resected pancreatic head cancer (promoted by R. Coppola, D. Caputo).
- The role of immunonutrition in patients undergoing pancreaticoduodenectomy for cancer (promoted by R. Coppola, R. Alloni, S. Valeri).
- New technologies for protein biomarkers discovery in pancreatic, prostate

moted by R. Coppola, D. Caputo).
Randomized Controlled Pilot Study Testing Use of Smartphone Technology for surgery patients undergoing pancreaticoduodenectomy (promoted by M. Cicala, R. Alloni, S. Valeri, S. Emerenziani, L. Trillo, C. Nuglio).
Induction chemotherapy with Folfiri-

nox followed by Radio-chemotherapy in locally advanced pancreas cancer (promoted by R. Coppola, L. Trodella, G. Tonini, S.Valeri, B. Vincenzi, M. Fiore).

 Prospective randomized trial on immunonutrition for patient candidate to surgery for cancer of the head of the pancreas (promoted by R. Coppola, M. Muscaritoli, S. Valeri, S. Emerenziani).

Colorectal surgery

- New technologies for colorectal adenocarcinoma protein biomarkers discovery: a pilot study (promoted by R. Coppola, D. Caputo).
 Impact of different types of cartridges for linear staplers in laparoscopic colorectal surgery: a prospective rando-
- lorectal surgery: a prospective randomized study (R. Coppola, D. Caputo, V. La Vaccara).
- Comprehensive multidisciplinary approach to colorectal cancer microenvironment (promoted by M. Caricato, G. Capolupo, V. La Vaccara, A. Crescenzi).
- Innovative technique for improving sensitivity of peritoneal washing cytology in gastric cancer (promoted by M. Caricato, G. Capolupo, V. la Vaccara, A. Crescenzi).

and breast cancer: a pilot study (pro- General surgery

- Parathyroid adenomas analysis by Raman spectroscopy (promoted by P. Crucitti, A. Palermo, S. Manfrini, A. Lauria Pantano) in collaboration with the Endocrinology Area and the department of Pathology of our hospital, together with CNR.
- e-NOSE/BIONOTE evaluation of the "breath print" for patients with a diagnosed lung cancer undergoing surgical resection (promoted by P. Crucitti, F. Longo, R. Antonelli Incalzi, G. Rocco) in collaboration with ECBM biomedical engineering.
- Low-dose CT scan lung cancer screening (promoted by P. Crucitti, F. Longo).

Main collaborations

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

Most important publications

Caputo D., Caricato M., Coppola A., La Vaccara V., Fiore M., Coppola R.

Neutrophil to lymphocyte ratio (NLR) and derived neutrophil to lymphocyte ratio (d-NLR) predict non-responders and postoperative complications in patients undergoing radical surgery after neo-adjuvant radio-chemotherapy for rectal adenocarcinoma.

Cancer Invest. 2016;34(9):440-451. DOI: 10.1080/07357907.2016.1229332. IF 2,231

In order to evaluate neutrophil-to-lymphocyte ratio (NLR) and derived neutrophil-to-lymphocyte ratio (d-NLR) in predicting response and complications in rectal cancer patients who underwent surgery after neo-adjuvant radio-chemotherapy, 87 patients were evaluated. Cutoffs before and after radio-chemotherapy were respectively 2.8 and 3.8 for NLR, and 1.4 and 2.3 for d-NLR. They were analyzed in relation to clinical and pathological outcomes. Patients with preoperative NLR and d-NLR higher than cutoffs had significantly higher rates of tumor regression grade response (TRG 4) and postoperative complications. Elevated NLR and d-NLR after radio-chemotherapy are associated with worse pathological and clinical outcome.

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

Microscopic residual tumor after pancreaticoduodenectomy: is standardization of pathological examination worthwhile?

Pancreas. 2016 May-Jun;45(5):748-54. PubMed PMID: 26495787. IF 2,738

Objectives: R1 resection rate after pancreaticoduodenectomy (PD) for cancer is highly variable. The aim of this study was to verify if a standardized histopathological work-up of the specimen affects the rate of R1 resection after PD for cancer.

Methods: Two groups of specimens were managed with (standardized method [SM] group) or without (non-standardized method [NSM] group) a SM of histopathological work-up. Each group included 50 cases of PD for periampullary cancer. Differences in terms of R1 resection rate between the 2 groups were evaluated. Correlation between R1 status and local recurrence was also evaluated. **Results:** The cohort of 100 patients consisted of 66 pancreatic ductal adenocarcinoma, 15 cholangiocarcinoma, and 19 ampullary cancer. The R1 resection rate resulted statistically higher in the SM group (66% vs 10%). Local recurrence was more frequently related to R1 resection in the SM group (34.3% of cases) than in NSM group (20% of cases).

Conclusions: The use of the SM of pathological evaluation of the specimen after PD for cancer determines a significant increase of R1 resection. This remarkable difference seems to be due to the different definition of minimum clearance. The SM seems to better discriminate patients in terms of risk of local recurrence.

Adsay V., Mino-Kenudson M., Furukawa T., Basturk O., Zamboni G., Marchegiani G., Bassi C., Salvia R., Malleo G., Paiella S., Wolfgang C.L., Matthaei H., Offerhaus G.J., Adham M., Bruno M.J., Reid M.D., Krasinskas A., Klöppel G., Ohike N., Tajiri T., Jang K.T., Roa J.C., Allen P., Fernández-del Castillo C., Jang J.Y., Klimstra D.S., Hruban R.H.; Members of Verona Consensus Meeting, 2013 [Coppola R.]

Pathologic evaluation and reporting of intraductal papillary mucinous neoplasms of the pancreas and other tumoral intraepithelial neoplasms of pancreatobiliary tract: recommendations of Verona Consensus Meeting. *Ann Surg. 2016 Jan;263(1):162-77. PubMed PMID: 25775066. IF 8,569*

Background: There are no established guidelines for pathologic diagnosis/reporting of intraductal papillary mucinous neoplasms (IPMNs). **Design:** An international multidisciplinary group, brought together by the Verona Pancreas Group in Italy-2013, was tasked to devise recommendations. **Results:** (1) Crucial to rule out invasive carcinoma with extensive (if not complete) sampling. (2) Invasive component is to be documented in a full synoptic report including its size, type, grade, and stage. (3) The term minimally invasive should be avoided; instead, invasion size with stage and substaging of T1 (1a, b, c; 0.5, >0.5-1, >1cm) is to be documented. (4) Largest diameter of the invasion, not the distance from the nearest duct, is to be used. (5) A category of indeterminate/(suspicious) for invasive component is to be documented separately. (8) Lesion size is to be correlated with imaging findings in cysts with rupture. (9) The main duct diameter and, if possible, its involvement are to be documented; however, it is not required to provide main versus branch duct classification in the resected tumor. (10) Subtyping as gastric/intestinal/pancreatobiliary/oncocytic/mixed is of value. (11) Frozen section is to be performed highly selectively, with appreciation of its shortcomings. (12) These principles also apply to other similar tumoral intraepithelial neoplasms (mucinous cystic neoplasms, intra-ampullary, and intra-biliary/cholecystic). **Conclusions:** These recommendations will ensure proper communication of salient tumor characteristics to the management teams, accurate comparison of data between analyses, and development of more effective management algorithms.

Geriatrics

Head R. Antonelli Incalzi

Faculty C. Pedone, S. Scarlata

Other Personnel N. Bettoni, I. Chiarella, L. Cortese, L. Costanzo, C. Di Gioia, A. Ferrini, P. Finamore, D. Fontana, F. Galdi, G. Giannunzio, R. Giua, A. Laudisio, D. Lelli, M. Ludovisi, L. Moro, C. Rivera, D. Spitaleri, A. Zito

External Members S. Ricci, I. Rossi Bartoli

Description

Main research activities

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

The lines of research currently ongoing are:

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

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

The study of frailty and sarcopenia showed that in older women a reduction of cortical bone mineral density is associated with subsequent cognitive impairment. We also showed that masticatory problems are associated with increased mortality. Finally, we showed that the different operational definitions of frailty are equivalent in predicting incident disability. With respect to respiratory diseases, we showed that the new reference standards for lung function are not better than the older ones in stratifying the mortality risk in people with COPD. Furthermore, we demonstrated the effects of an innovative vibro-tactile device in patients with sleep apnea. Santonico M., Frezzotti E., Incalzi R. A., Pedone C., Lelli D., Zompanti A., Grasso S., Pennazza G.

Are performance measures necessary to predict loss of independence in elderly people?

Background: The frailty phenotype (FP) requires the administration of performance tests not always feasible in clinical practice.

Furthermore, the discriminative capacity of the instrument has been rarely investigated. Methods: Frailty was defined by the presence

of \geq 3 criteria of the FP, or having \geq 2 criteria of an anamnestic FP (AFP), not including gait speed and handgrip strength. **Results:** For incident disability, FP showed sensitivity = .194, specificity = .963, PPV = .400, and NPV = .903. **Conclusions:** Both FP and

AFP showed low sensitivity in identifying older people who would die or develop disability, but they could well discriminate people who

Pedone C., Costanzo L., Cesari M., Bandinelli S., Ferrucci L., Antonelli Incalzi R.

J Gerontol A Biol Sci Med Sci. 2016 Jan;71(1):84-9. PubMed PMID: 26273019. IF 5,476

Most important publications

would not experience adverse outcomes.

Non-invasive monitoring of lower-limb ulcers via exudate fingerprinting using BIONOTE. Sensors and Actuators B: Chemical. 2016; 232: 68-74. DOI: 10.1016/j.snb.2016.03.101. IF 4,758

The main goal of this study was to test the electrochemical fingerprinting of biological samples in solution in term of diagnostic accuracy and of feasibility when applied to the study of the exudate from lower-limb ulcers. The correct discrimination between the ulcers analyzed at the first and at the second clinical evaluation (after therapy) was of 75%, 90% and 97.5% when based on clinical data, BIONOTE data and data fusion respectively. The consistency of BIONOTE ability in ulcer monitoring has been confirmed by a good sensor's prediction ability with respect to three key-parameters: Leg Ulcer Measurement Tool, peripheral oxygen saturation of hemoglobin, Transcutaneous oxygen pressure.

Laudisio A., Gemma A., Fontana D.O., Rivera C., Bandinelli S., Ferrucci L., Incalzi R.A.

Self-reported masticatory dysfunction and mortality in community dwelling elderly adults: a 9-year follow-up.

J Am Geriatr Soc. 2016 Dec;64(12):2503-2510. PubMed PMID: 27889908. IF 3,842

Objectives: To evaluate the association between masticatory dysfunction (MD) and mortality in older adults. **Measurements:** Cox regression was used to assess the association between self-reported MD and 9-year all-cause mortality. This association was also evaluated after stratifying according to use of dentures. **Results:** 35% of participants reported MD that was associated with higher mortality (RR: 1.23, 95% Cl: 1.02-1.48) after adjusting for potential confounders. Uncorrected edentulism was associated with the greatest risk of mortality (RR: 2.10, 95% Cl: 1.07-4.14). **Conclusion:** Self-reported MD is associated with all-cause mortality in community-dwelling elderly adults.

Gynaecology and Obstetrics



Head R. Angioli

Faculty F. Plotti

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

Description

Main research activities

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

Most important publications

Zhao S., Bellone S., Lopez S., Thakral D., Schwab C., English D.P., Black J., Cocco E., Choi J., Zammataro L., Predolini F., Bonazzoli E., Bi M., Buza N., Hui P., Wong S., Abu-Khalaf M., Ravaggi A., Bignotti E., Bandiera E., Romani C., Todeschini P., Tassi R., Zanotti L., Odicino F., Pecorelli S., Donzelli C., Ardighieri L., Facchetti F., Falchetti M., Silasi D.A., Ratner E., Azodi M., Schwartz P.E., Mane S., Angioli R., Terranova C., Quick C.M., Edraki B., Bilgüvar K., Lee M., Choi M., Stiegler A.L., BoggonT.J., Schlessinger J., Lifton R.P., Santin A.D.

Mutational landscape of uterine and ovarian carcinosarcomas implicates histone genes in epithelial-mesenchymal transition.

Proc Natl Acad Sci U S A. 2016 Oct 25;113(43):12238-12243. PubMed PMID: 27791010. IF 9,423

Carcinosarcomas (CSs) of the uterus and ovary are highly aggressive neoplasms containing both carcinomatous and sarcomatous elements. We analyzed the mutational landscape of 68 uterine and ovarian CSs by whole-exome sequencing. We also performed multiregion whole-exome sequencing comprising two carcinoma and sarcoma samples from six tumors to resolve their evolutionary histories. The results demonstrated that carcinomatous and sarcomatous elements derive from a common precursor having mutations typical of carcinomas. In addition to mutations in cancer genes previously identified in uterine and ovarian carcinomas such as TP53,

PIK3CA, PPP2R1A, KRAS, PTEN, CHD4, and BCOR, we found an excess of mutations in genes encoding histone H2A and H2B, as well as significant amplification of the segment of chromosome 6p harboring the histone gene cluster containing these genes. We also found frequent deletions of the genes TP53 and MBD3 (a member with CHD4 of the nucleosome remodeling deacetylase complex) and frequent amplification of chromosome segments containing the genes PIK3CA, TERT, and MYC Stable transgenic expression of H2A and H2B in a uterine serous carcinoma cell line demonstrated that mutant, but not wild-type, histones increased expression of markers of epithelial-mesenchymal transition (EMT) as well as tumor migratory and invasive properties, suggesting a role in sarcomatous transformation. Comparison of the phylogenetic relationships of carcinomatous and sarcomatous elements of the same tumors demonstrated separate lineages leading to these two components. These findings define the genetic landscape of CSs and suggest therapeutic targets for these highly aggressive neoplasms.

Angioli R., Lopez S., Aloisi A., Terranova C., De Cicco C., Scaletta G., Capriglione S., Miranda A., Luvero D., Ricciardi R., Montera R., Plotti F.

Ten years of HPV vaccines: State of art and controversies.

Crit Rev Oncol Hematol. 2016 Jun;102:65-72. PubMed PMID: 27066937. IF 5,039

The human papillomavirus (HPV) represents one of the most common sexually transmitted infections and it has been related to cervical cancer. The HPV vaccines prevent infection with certain species of HPV associated with the development of cervical cancer or genital warts. We carried out a PubMed search up to 2015 evaluating all randomized studies published in literature. This review discusses the current status of HPVs vaccines on the global market, efficacy, safety profiles, controversies and future vaccine developments. Three HPVs vaccines are currently on the global market: bivalent, quadrivalent and ninevalent. Bivalent and quadrivalent vaccines can protect against almost 70% of cervical HPV-related cancerous and precancerous conditions and the ninevalent vaccine, instead, provides a protection against almost 90%. The use of vaccinations raised several controversies in the last years and, currently, is not possible to establish which type of vaccine is most effective, however all of them are safe.

Cocco E., Lopez S., Black J., Bellone S., Bonazzoli E., Predolini F., Ferrari F., Schwab C.L., Menderes G., Zammataro L., Buza N., Hui P., Wong S., Zhao S., Bai Y., Rimm D.L., Ratner E., Litkouhi B., Silasi D.A., Azodi M., Schwartz P.E., Santin A.D.

Dual CCNE1/PIK3CA targeting is synergistic in CCNE1-amplified/PIK3CA-mutated uterine serous carcinomas in vitro and in vivo.

Br J Cancer. 2016 Jul 26;115(3):303-11. PubMed PMID: 27351214. IF 5,569

Background: Clinical options for patients harbouring advanced/recurrent uterine serous carcinoma (USC), an aggressive variant of endometrial tumour, are very limited. Next-generation sequencing (NGS) data recently demonstrated that cyclin E1 (CCNE1) gene amplification and pik3ca driver mutations are common in USC and may therefore represent ideal therapeutic targets.

Methods: Cyclin E1 expression was evaluated by immunohistochemistry (IHC) on 95 USCs. The efficacy of the cyclin-dependent kinase 2/9 inhibitor CYC065 was assessed on multiple primary USC cell lines with or without CCNE1 amplification. Cell-cycle analyses and knockdown experiments were performed to assess CYC065 targeting specificity. Finally, the in vitro and in vivo activity of CYC065, Taselisib (a PIK3CA inhibitor) and their combinations was tested on USC xenografts derived from CCNE1-amplified/pik3ca-mutated USCs.

Results: We found that 89.5% of the USCs expressed CCNE1. CYC065 blocked cells in the G1 phase of the cell cycle and inhibited cell growth specifically in CCNE1-overexpressing USCs. Cyclin E1 knockdown conferred increased resistance to CYC065, whereas CYC065 treatment of xenografts derived from CCNE1-amplified USCs significantly reduced tumour growth. The combination of CYC065 and Taselisib demonstrated synergistic effect in vitro and was significantly more effective than single-agent treatment in decreasing tumour growth in xenografts of CCNE1-amplified/pik3ca-mutated USCs.

Conclusions: Dual CCNE1/PIK3CA blockade may represent a novel therapeutic option for USC patients harbouring recurrent CC-NE1-amplified/pi3kca-mutated tumours.

Research Units: overview and main 2016 scientific outputs

Heart Surgery



Head E. Covino Faculty M. Chello

External Members F. Nappi, C. Spadaccio

Description

Main research activities

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 2016 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.

Most important publications

Spadaccio C., Mozetic P., Nappi F., Nenna A., Sutherland F., Trombetta M., Chello M., Rainer A.

Cells and extracellular matrix interplay in cardiac valve disease: because age matters. *Basic Res Cardiol. 2016 Mar;111(2):16. PubMed PMID: 26830603. IF 6,008*

Despite the satisfactory hemodynamic outcome and disappearance of mitral regurgitation after mitral repair surgery, this non-physiological situation results in a redistribution of forces within the mitral apparatus with an increased stress on the leaflets. The valvular interstitial cells actively respond to biomechanical changes, switching their phenotype and producing different patterns of extracellular matrix proteins. This biological event translates to changes in the anatomical and mechanical properties of the leaflets, leading to an increased stiffening and calcification. These concepts find a clinical reflex in the long-term thickening and calcification of the leaflets after repair, and in the leaflets remodeling phenomena described in chronically dilated ventricles. To respect the physiological movement and dynamics of the leaflets is mandatory, and a potential pharmacological modulation of the biological processes to ameliorate long-term results is hypothesized.

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

Predictive factors of long-term results following valve repair in ischemic mitral valve prolapse. *Int J Cardiol. 2016 Feb 1;204:218-28. PubMed PMID: 26681541. IF 4,638*

This study aims to describe a cohort of patients with ischemic mitral regurgitation over a long-term follow up, analyzing survival, reoperation and predictive factors of surgical outcomes. Our cohort was followed up until April 2015, with a mean follow up of 7 ± 3 years. Cardiac-related deaths occurred in 26 patients, with a mean survival of 114.2 months, including eight patients with in-hospital mortality. Reoperation was performed in 14 patients, due to valve repair failure. Twenty-six patients experienced moderate-to-severe mitral regurgitation. An index quantifying the stress on the annulus imparted by annuloplasty was elaborated and predicted endpoints. Perioperative parameters describing geometric features of left ventricle, valvular and subvalvular components should be considered to provide a tailored approach for mitral valve repair, or to opt for immediate replacement in case of unfavorable geometry.

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

Papillary muscle approximation versus restrictive annuloplasty alone for severe ischemic mitral regurgitation.

J Am Coll Cardiol. 2016 May 24;67(20):2334-46. PubMed PMID: 27199056. IF 17,759

Guidelines recommend surgery for patients with severe ischemic mitral regurgitation (MR). This study sought to investigate the benefit of papillary muscle surgery on long-term clinical outcomes of patients with ischemic MR. The primary endpoint was change in left ventricular end-diastolic diameter (LVEDD) after 5 years, measured as the absolute difference from baseline, which was evaluated by paired Student t tests. Secondary endpoints included changes in echocardiographic parameters, overall mortality, the composite cardiac endpoint (major adverse cardiac and cerebrovascular events [MACCE]), and quality of life (QOL) during the 5-year follow-up. Compared with RA only, PMA exerted a long-term beneficial effect on left ventricular remodeling and more effectively restored the mitral valve geometric configuration in ischemic MR, which improved long-term cardiac outcomes, but did not produce differences in overall mortality and QOL.
Hematology, Stem Cell Transplantation, Transfusion Medicine and Cellular Therapy



Head G. Avvisati

Faculty M.C. Tirindelli, O. Annibali

Other Personnel D. Armiento, M. Becilli, P.P. Berti, E. Cerchiara, E. Circhetta, M. De Muro, M. Di Cerbo, S. Ferraro, B. Giannetti, C. Gregorj, F. Landi, A.M. Morgia, C. Nobile, A. Pagano, C. Sarlo, A. Scardocci, S. Spurio, V. Tomarchio

Description

Main research activities

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 cel-Is (HSC) transplantation and, in collaboration with the Urology unit, has a leading national position in the treatment of severe resistant hemorrhagic cvstitis which may appear in these patients. In addition, the unit participate in several clinical Trials, proposed by the following cooperative Group: FIL (Fondazione Italiana Linfomi), IELSG (International Extranodal Lymphoma Study Group), GIMEMA (Gruppo Italiano Malattie Ematologiche dell'Adulto). Moreover, in cooperation with the 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, is conducting a study dealing with CMV reactivation in HSC transplanted patients.

The Unit collaborates with Research Unit of Computer Systems and Bioinformatics of this University to develop a mobile App for monitoring of side effects during treatment with kinase inhibitors in chronic lymphoproliferative diseases. In addition, the unit collaborate with the unit of Anatomical Pathology for the study of PD-1/PD-L1 axis in lymphoproliferative diseases.

Most important publications

Crescenzi A., Annibali O., Bianchi A., Pagano A., Donati M., Grifoni A., Avvisati G.

PD-1/PD-L1 expression in extra-medullary lesions of multiple myeloma. Leuk Res. 2016 Oct;49:98-101. PubMed PMID: 27619200. IF 2,606

Multiple myeloma patients may develop extraosseous involvement in the course of the disease making prognosis very poor and new drugs clearly needed. The PD-1/PD-L1 axis has emerged as a master immune checkpoint in antitumor responses and recent studies investigated the role of PD-L1 in multiple myeloma cells; no data however are still available about PD-L1 expression in extramedullary localizations. We demonstrate PD-L1 expression in 4/12 cases of extraosseous myeloma suggesting that these lesions represent a specialized microenvironment. We found presence of PD-1+ infiltrating lymphocytes in all observed cases supporting the relevance of PD-1/PD-L1 checkpoint in extramedullary myeloma. We also investigated the correlation in PD1/PD-L1 staining between marrow staining and EMP lesions.

Cicconi L., Divona M., Ciardi C., Ottone T., Ferrantini A., Lavorgna S., Alfonso V., Paoloni F., Piciocchi A., Avvisati G., Ferrara F., Di Bona E., Albano F., Breccia M., Cerqui E., Sborgia M., Kropp M.G., Santoro A., Levis A., Sica S., Amadori S., Voso M.T., Mandelli F., Lo-Coco F.

PML-RARa kinetics and impact of FLT3-ITD mutations in newly diagnosed acute promyelocytic leukaemia treated with ATRA and ATO or ATRA and chemotherapy. Leukemia. 2016 Oct;30(10):1987-1992. PubMed PMID: 27133819. IF 12,104

The APL0406 study showed that arsenic trioxide (ATO) and all-trans retinoic acid (ATRA) are not inferior to standard ATRA and chemotherapy (CHT) in newly diagnosed, low-intermediaterisk acute promyelocytic leukaemia (APL). We analysed the kinetics of promyelocytic leukaemia-retinoic acid receptor- α (PML-RAR α) transcripts by real-time quantitative PCR (RQ-PCR) in bone marrow samples from 184 patients and assessed the prognostic impact of fms-related tyrosine kinase 3-internal tandem duplication (FLT3-ITD) in 159 patients enrolled in this trial in Italy. After induction therapy, the reduction of PML-RAR α transcripts was significantly greater in patients receiving ATRA-CHT as compared with those treated with ATRA-ATO (3.4 vs 2.9 logs; P=0.0182). Conversely, at the end of consolidation, a greater log reduction of PML-RAR α transcripts was detected in the ATRA-ATO as compared with the ATRA-CHT group (6.3 vs 5.3 logs; P=0.0024). FLT3-ITD mutations had no significant impact on either event-free survival (EFS) or cumulative incidence of relapse in patients receiving ATRA-ATO, whereas a trend for inferior EFS was observed in FLT3-ITD-positive patients receiving ATRA-CHT. Our study shows at the molecular level that ATRA-ATO exerts at least equal and probably superior antileukaemic efficacy compared with ATRA-CHT in low-intermediaterisk APL. The data also suggest that ATRA-ATO may abrogate the negative prognostic impact of FLT3-ITD.

Annibali O., Sabatino F., Mantelli F., Olimpieri O.M., Bonini S., Avvisati G.

Mucosa-associated lymphoid tissue (MALT)-type lymphoma of ocular adnexa. Biology and treatment.

Crit Rev Oncol Hematol. 2016 Apr;100:37-45. PubMed PMID: 26857986. IF 5,039

Over the last decades, we have witnessed an increase in the incidence of primary ocular adnexa lymphomas (POALs) probably because advances in imaging techniques have enabled precise biopsies of the tumors. The ocular tissue biopsy, before the initiation of the appropriate treatment, is mandatory and necessary for a correct diagnosis of POALs by the use of immunophenotyping and a correct molecular classification. Only in a minority of cases the ocular adnexa are secondarily affected by a systemic disease. Among the POALs, the most common is the primary extra nodal lymphoma of MALT-type (POAML). POAML is rarely symptomatic in the early phase of the disease. As a consequence, often we see a delay in ophthalmic consultations and diagnosis. The clinical manifestations are heterogeneous and its management requires a multidisciplinary approach involving ophthalmologists, hematologists and radiotherapists.

Hygiene, Public Health and Statistics



Head T. Petitti Other Personnel A. lanni

Description

Main research activities and collaborations

Main research interests include:

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

In 2016 collaborations with internal research groups at the Campus Bio-Medico University of Rome (General Surgery, Pediatrics, Digestive Endoscopy, Respiratory Pathophysiology, Medical Imaging, Nursing Science) as well as National and European research institutions (National Cancer Institute - IRCCS "Fondazione G. Pascale" - Naples; Department of Public Health, Section of Hygiene, Catholic University of the Sacred Heart – Rome; Hôpital de Hautepierre, Strasbourg) were initiated. As part of these collaborations there are ongoing scientific studies that have produced results published in national and international journals in 2016 and are currently being published.

Most important publications

Nenna A., Spadaccio C., Prestipino F., Lusini M., Sutherland F.W., Beattie G.W., Petitti T., Nappi F., Chello M.

Effect of preoperative aspirin replacement with enoxaparin in patients undergoing primary isolated on-pump coronary artery bypass grafting.

Am J Cardiol. 2016 Feb 15;117(4):563-70. PubMed PMID: 26721653. IF 3,154

Management of preoperative antiplatelet therapy in coronary artery bypass grafting (CABG) is variable among surgeons: guidelines collide with prejudices because replacement of aspirin with low-molecular-weight heparin is still performed because of a presumed minor bleeding risk. This study aims to analyze postoperative bleedings and complications in patients scheduled for elective primary isolated on-pump CABG, depending on preoperative aspirin treatment or its replacement with enoxaparin. In this cohort study, we propensity score matched 200 patients in whom aspirin was stopped at least 5 days before CABG and replaced with enoxaparin and 200 patients who continued aspirin therapy until the day before surgery. Postoperative bleedings and complications were monitored during hospitalization. Among patients who continued aspirin treatment, mean overall bleeding was 701.0 \pm 334.6 ml, whereas in the matched enoxaparin group, it was significantly greater (882.6 \pm 64.6 ml, p value <0.001); this was associated with reduced postoperative complications, lower values of postoperative C-reactive protein in aspirin takers, and a presumed protective effect for statins. After propensity score adjustment, aspirin treatment carried a protective effect against major postoperative bleeding (odds ratio 0.312, p = 0.001). In conclusion, postoperative bleeding is reduced in patients who continued aspirin, likely due to a reduction in postoperative inflammation. The practice of empirically discontinuing aspirin and replacing it with enoxaparin before CABG should be abandoned. Patients with coronary artery disease referred to CABG should continue antiplatelet medications until the surgical procedure. Those results might be extended to patients under oral anticoagulant therapy requiring CABG.

Rocco G., Petitti T., Martucci N., Piccirillo M.C., LA Rocca A., LA Manna C., DE Luca G., Morabito A., Chirico A., Franco R., Accardo R., Normanno N., Botti G., Lodato S., Ciliberto G., Pedicini T., Giordano A.

Survival after surgical treatment of lung cancer arising in the population exposed to illegal dumping of toxic waste in the Land of Fires ('Terra dei Fuochi') of Southern Italy. Anticancer Res. 2016 May;36(5):2119-24. PubMed PMID: 27127112. IF 1,895

Aim: Terra dei Fuochi (TdF), the so-called 'Land of Fires' in Southern Italy, is an agricultural territory characterized by illegal dumping of toxic waste known to occur since the 1980s. It is unknown whether prognosis of patients developing cancer and living in that area may differ compared to those living in areas not exposed to this specific type of pollution. We retrospectively analyzed the 5-year survival rates of patients originating from the TdF diagnosed with lung cancer compared to patients from other areas.

Materials and Methods: Patients consecutively operated on for non-small cell lung cancer (NSCLC) between November 2004 and April 2013 at the Division of Thoracic Surgery of the National Cancer Institute of Naples were eligible. The study outcome was overall survival (OS). In addition, the TdF and non-TdF groups were compared through propensity score matching (PSM).

Results: Overall, 439 patients with resectable NSCLC were operated on, 123 (28%) from the TdF and 316 (72%) from other referral centers of our catchment area. There were 301 males and 138 females; the median age of the entire surgical population was 65 years (range=25-83) years. Apart from a different prevalence of hypertension and underweight patients, preoperative factors were evenly distributed between the two groups. At univariate analysis, OS was not different between the TdF and non TdF group (median 72 and 68 months, respectively; p=0.75 log-rank test). Multivariable analysis confirmed that living in the TdF area had no prognostic impact (hazard ratio=1.05; 95% confidence interval=0.70-1.57; p=0.78) on OS. PSM confirmed no statistically significant difference of OS (hazard ratio=1.01, 95% confidence interval=0.67-1.52; p=0.93).

Conclusions: Following surgery for lung cancer, TdF and non-TdF surgical candidates had similar long-term survival. Originating from the TdF does not seem to be associated with worse outcomes after surgical treatment of patients with lung cancer.

Mangiameli G., Arame A., Boussaud V., Petitti T., Rivera C., Pricopi C., Badia A., Achouh P., Legras A., Guillemain R., Riquet M., Cholley B., Sermet I., Le Pimpec Barthes F.

Lung transplantation in childhood and adolescence: unicentric 14-year experience with sex matching as the main prognosticator.

Eur J Cardiothorac Surg. 2016 Mar;49(3):810-7. PubMed PMID: 26188011. IF 2,803

Objectives: Lung transplantation (LTx) is an accepted therapy for selected infants, children and adolescents with end-stage lung and pulmonary vascular disease. It remains a challenge for a selected group of patients. In 2011, the number of paediatric lung transplantations (PLTxs) worldwide was 107. In France, a total of 131 PLTxs have been performed since 2000 (data from ABM: Agence de biomédecine), 65 of which were conducted at our institution.

Methods: All patients under 18 (4.8-17.11) years of age matching inclusion and exclusion criteria, who underwent LTx at our institution were included in this study (n = 58). We analysed the outcomes of these patients in terms of survival rates, controlling for indications for transplantations and surgical procedures. Secondary outcomes were analysis of surgical and medical complications and identification of prognostic factors in the field of LTx in these categories of ages.

Results: The 30-day mortality rate was 10%. Kaplan-Meier survival rates at 1 month, 1, 3, 5 and 10 years were 90, 81, 66, 60 and 57%, respectively; the median survival was 91 months. Reduced-size transplantation was performed in 33% of double-lung transplantation (DLTx) patients without negatively impacting survival. In our series, female sex, the presence of a sex mismatching and, in particular, the occurrence of a male donor to a female recipient (F/M group) have been poor prognostic factors after PLTx.

Onclusions: The overall survival after PLTx was encouraging (57% at 10 years). A PLTx should be offered to the small number of patients with end-stage pulmonary disease. The limited number of paediatric donor organs can be overcome by using reduced-size organs without a survival disadvantage to the patients. In our series, male sex and sex matching seemed to be positive predictive prognostic factors after PLTx but further studies are required to confirm these results and to also clarify the role of age of donor, time of cold ischaemia and body mass index in PLTx.

Institute of Philosophy of Scientific and Technological Practice (FAST)

Head E. Covino



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

Other Personnel S. Anzilotti, L. Campanozzi, N. Di Stefano, F. Keller, G. Ghilardi, M. Maioni, I. Malagrinò, A. Marchetti, G. Mottini, J. Nixon, P. Pellegrino, M. Pennacchini, L. Riva, M.T. Russo, C. Sartea

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

Description

Main research activities

The main thematic areas where it grows the FAST's research are: Bioethics Clinical, History of science, Forensic science and bio-law, the Philosophy of biology, Anthropology, Human ecology, Aesthetics and Neuroscience, Social psychology and Social medicine.

Luca Borghi

- History of the stethoscope in Italy in the first decades after its invention;
- Charles West, father of British paediatrics.

Marta Bertolaso

Participation in funded projects:

- Contemporary issues in metaphysics of biological sciences;
- The unity of the human being: from embryonic development to the generation of habits;
- Models and inferences in science. Logical, epistemological, and cognitive aspects;
- Evolving embodied habitats: living the environment;
- Self-on-a-chip: a study of embodiment in innovative 3D cell-culture models;
- "In silico medicine" and ethics: training and research program;
- MeTA-Es: It mainly deals with scientific and philosophical issues related with the ontology and epistemology of living beings and of the organismic development, cancer's experimental models, explanatory and causal issues in bio-medical sciences, the relevance of the domestic environment for health and the

elderly care (cfr. www.biotechnopractice.org).

Giovani Mottini

 In 2016, we carried out epidemiological researches in less developed countries in order to highlight the main health problems and perform a task of advocacy in the scientific community for better-focused medical interventions.

Laura Campanozzi

• The role and the concept of intuition in clinical reasoning.

Maria Teresa Russo

- International Research Group SARX (Grup de Recerca en Antropologia de la Corporalitat) Grup de Recerca Emergent (Grupo de Investigación Emergente reconocido por la Generalitat de Catalunya), Universitat Internacional de Catalunya (Member);
- European Project "Tempus RUMI" (Réseau des Universités Marocaines pour l'enseignement Inclusif) (2013-2016). N° project-544154-TEMPUS-1-2013-1-BE-TEMPUS-SMGR (Scientific Coordinator).

Most important publications

Riva M.A., Borghi L., Pagni F.

The first recorded use of microscopy in medicine: Pope Innocent XII's autopsy report. Lancet. 2016 Aug 6;388(10044):559. PubMed PMID: 27511777. IF 44,002

In the history of medicine, the discovery and the use of the microscope in clinical practice and biomedical research was a revolutionary achievement. The cultural shift from the traditional macroscopic necroscopy to a microscopic and ultrastructural perspective was essential for the development of modern pathology and for recognising physiopathological mechanisms of several diseases. Physicians started to use the microscope during the 17th century, but they initially limited its use to anatomical, and not pathological, studies. The first recorded use of microscopy in medicine was in 1700 for Pope Innocent XII's autopsy.

Ghilardi G., Morini S.

Hidden curriculum in medical education: the master's virtues. *MEDIC 2016; 24(1):37-45.*

This article addresses the hidden curriculum topic under the lens of the teacher and scholar relationship. This analysis is carried out within the framework of "virtue ethics", with a specific attention to the virtue of the charity for intellect. We develop the analogy between two distinct but strictly related fields: epistemology and pedagogy, by comparing tacit Knowledge and Hidden curriculum. Therefore, we analyse the topic of the master connected with the ideal of school, examined in its practical dimension that is "to create a school". The study ends with an exposition of virtues required in order to accomplish daily duties in university and in medical practice, pointing out the tight connection between the role of professor and the ways to practice this duty.

Tambone V., Ghilardi G.

An ethical evaluation methodology for clinical cases.

Persona y Bioética 2016; 20(1): 48-61. DOI: 10.5294/PEBI.2016.20.1.5

In the present article, we introduce an ethical evaluation methodology for clinical cases. Although rejecting proceduralism as a system, we develop a procedure that eventually could be formalized as a flow chart to help carry out an ethical evaluation for clinical cases. We clarify the elements that constitute an ethical evaluation aim (patient's health), integration (action interconnections), and how the action is performed. We leave aside the aspect of intentions, focusing on the object of a medical action, arguing that the internal aim of a clinical action carries a moral value per se. Our evaluation system takes into account only objects and circumstances and their intrinsic morality, since we are dealing with the evaluation of a clinical case, and not with a personal and complete clinical action.

Internal Medicine and Hepatology



Head A. Picardi

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

Description

Our Unit is involved in both spontaneous investigation projects on liver iniury, inflammation and fibrogenesis and in collaborative studies - coordinated by scientific societies (Italian Society of Internal Medicine (SIMI) and the Italian Association for the Study of the Liver (AISF). We are also involved in Other important collaborations are set two clinical trials on new drugs for the treatment of thrombocytopenia and for the treatment of liver steatosis. Main collaborations are set with other Units from our University and from the University of Navarra, Spain. Specifically, with the Units of Human Anatomy and of Clinical Pathology we have advan-

ced in the knowledge of the mechanisms of activation. maintenance and progression of portal inflammation in chronic liver disease. All those processes may involve and activate the compartment of liver staminal cells that are implied in hepato-carcinogenesis. with the Area of Geriatrics, of Oncology and with the Unit of Electronics for sensor Systems of the Faculty of Engineering.

Some clinical investigations have been initiated in the non-invasive evaluation of liver fibrosis through transient elastometry.

Main research activities

Our most relevant research results have been reached in two fields of chronic liver disease. The first is the characterization of some genetic polymorphisms implied in the pathogenesis of fatty liver disease and in cirrhosis (PNPLA3 and LIPA). The second is a proof of concept for the characterization of patients with liver cirrhosis of different stages by electronic nose.

Most important publications

Nenna A., Spadaccio C., Prestipino F., Lusini M., Sutherland F.W., Beattie G.W., Petitti T., Nappi F., Chello M.

Effect of preoperative aspirin replacement with enoxaparin in patients undergoing primary isolated on-pump coronary artery bypass grafting.

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Management of preoperative antiplatelet therapy in coronary artery bypass grafting (CABG) is variable among surgeons: guidelines collide with prejudices because replacement of aspirin with low-molecular-weight heparin is still performed because of a presumed minor bleeding risk. This study aims to analyze postoperative bleedings and complications in patients scheduled for elective primary isolated on-pump CABG, depending on preoperative aspirin treatment or its replacement with enoxaparin. In this cohort study, we propensity score matched 200 patients in whom aspirin was stopped at least 5 days before CABG and replaced with enoxaparin and 200 patients who continued aspirin therapy until the day before surgery. Postoperative bleedings and complications were monitored during hospitalization. Among patients who continued aspirin treatment, mean overall bleeding was 701.0 \pm 334.6 ml, whereas in the matched enoxaparin group, it was significantly greater (882.6 \pm 64.6 ml, p value <0.001); this was associated with reduced postoperative complications, lower values of postoperative C-reactive protein in aspirin takers, and a presumed protective effect for statins. After propensity score adjustment, aspirin treatment carried a protective effect against major postoperative bleeding (odds ratio 0.312, p = 0.001). In conclusion, postoperative bleeding is reduced in patients who continued aspirin, likely due to a reduction in postoperative inflammation. The practice of empirically discontinuing aspirin and replacing it with enoxaparin before CABG should be abandoned. Patients with coronary artery disease referred to CABG should continue antiplatelet medications until the surgical procedure. Those results might be extended to patients under oral anticoagulant therapy requiring CABG. The first recorded use of microscopy in medicine was in 1700 for Pope Innocent XII's autopsy.

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Conclusions: The overall survival after PLTx was encouraging (57% at 10 years). A PLTx should be offered to the small number of patients with end-stage pulmonary disease. The limited number of paediatric donor organs can be overcome by using reduced-size organs without a survival disadvantage to the patients. In our series, male sex and sex matching seemed to be positive predictive prognostic factors after PLTx but further studies are required to confirm these results and to also clarify the role of age of donor, time of cold ischaemia and body mass index in PLTx.

Measurements and Biomedical Instrumentation



Head S. Silvestri

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

Description

Main research activities

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

The research activity has been focused on innovative methods to obtain a temperature map of organs by means of magnetic resonance imaging, innovative MRcompatible optical fibre sensors for force measurement and experimental estimation of optical properties of neuroendocrine pancreatic tumor and other organs for modelling laser absorption during interstitial ablation therapy.

A research project has been funded by the Italian Ministry of University and Scientific Research: "Mechanical measurements for the musculoskeletal apparatus: novel and standardizable methodologies for metrological assessment of measurement systems". A research project has been funded by Campus Bio-Medico University of Rome: "Evaluation of bone strength and Wnt pathway in obese patients".

Most important publications

Saccomandi P., Larocca E.S., Rendina V., Schena E., D'Ambrosio R., Crescenzi A., Di Matteo F.M., Silvestri S.

Estimation of optical properties of neuroendocrine pancreas tumor with double-integrating-sphere system and inverse Monte Carlo model.

Lasers Med Sci. 2016 Aug;31(6):1041-50. PubMed PMID: 27147075. IF 2,461

The investigation of laser-tissue interaction is crucial for diagnostics and therapeutics. In particular, the estimation of tissue optical properties allows developing predictive models for defining organ-specific treatment planning tool. With regard to laser ablation (LA), optical properties are among the main responsible for the therapy efficacy, as they globally affect the heating process of the tissue, due to its capability to absorb and scatter laser energy. The recent introduction of LA for pancreatic tumor treatment in clinical studies has fostered the need to assess the laser-pancreas interaction and hence to find its optical properties in the wavelength of interest. This work aims at estimating optical properties (i.e., absorption, µa, scattering, µs, anisotropy, g, coefficients) of neuroendocrine pancreas tumor at 1064 nm. Experiments were performed using two popular sample storage methods; the optical properties of frozen and paraffin-embedded neuroendocrine tumor of the pancreas are estimated by employing a double-integrating-sphere system and

Research Units: overview and main 2016 scientific outputs

inverse Monte Carlo algorithm. Results show that paraffin-embedded tissue is characterized by absorption and scattering coefficients significantly higher than frozen samples (μ a of 56 cm-1 vs 0.9 cm-1, μ s of 539 cm-1 vs 130 cm-1, respectively). Simulations show that such different optical features strongly influence the pancreas temperature distribution during LA. This result may affect the prediction of therapeutic outcome. Therefore, the choice of the appropriate preparation technique of samples for optical property estimation is crucial for the performances of the mathematical models, which predict LA thermal outcome on the tissue and lead the selection of optimal LA settings.

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

Feasibility assessment of magnetic resonance-thermometry on pancreas undergoing laser ablation: sensitivity analysis of three sequences.

Measurement. 2016; 80: 21-28. DOI: 10.1016/j.measurement.2015.11.013. IF 1,742

Laser ablation (LA) is a minimally invasive technique for the treatment of tumors as an alternative to surgical resection. The light absorbed by tissue is converted into heat, and causes irreversible cell damage when temperatures higher than 60 °C are reached. The knowledge in real time of temperature may be particularly beneficial for adjusting laser settings applied during treatment and to be notified in real time about its end-point. As a consequence, several techniques for temperature monitoring within the tissue have been investigated along the last decades. In the field of LA, particularly attractive are non-invasive methods. Among these techniques, thermometry based on the analysis of Magnetic Resonance Imaging (MR-thermometry) has gaining large acceptance in this field. MR-thermometry allows estimating the temperature variation thanks to the thermal dependence of several MRI parameters, among others the most promising are T1 relaxation time, and proton resonance frequency shift. The aim of this study is to assess the sensitivity of MRI thermometry using three T1-weighted sequences (i.e., Inversion Recovery Turbo-FLASH, IRTF, Saturation Recovery Turbo-FLASH, SRTF, and FLASH) using an 1.5-T MR scanner on healthy swine pancreases undergoing LA. The reference temperature was measured by MRI-compatible fiber optic sensors (fiber Bragg grating sensors). The sensitivity of the proposed techniques was estimated and compared. The thermal sensitivity of the three sequences was -1.47 \pm 0.08 °C-1, -0.95 \pm 0.05 °C-1, and -0.56 \pm 0.04 °C-1 for IRTF, SRTF and FLASH, respectively. Results show that the proposed technique may be adequate for temperature monitoring during LA.

Massaroni C., Schena E., Saccomandi P., Silvestri S.

A novel tool and procedure for in-situ volumetric calibration of motion capture systems for breathing analysis.

IEEE 38th Annual International Conference of the Engineering in Medicine and Biology Society (EMBC). Orlando (Florida, USA)16-20 Aug. 2016. DOI: 10.1109/EMBC.2016.7592045. ISBN: 978-1-4577-0219-8

Optical motion capture systems are widely used in biomechanics although have not been significantly explored for measuring volumes and volume variations yet. The aim of this study was to propose and test a completely novel procedure for the calibration of motion capture systems for the breathing analysis in terms of volume measurements, by the use of a tool consisting in an ad-hoc designed in-situ calibration device (CD) and two algorithms for calibration. Both the calibration tool and the calibration procedure performed in the range 0-2780mL on an Optoelectronic Plethysmography (OEP) system are presented. The CD delivered known volume Δ VCD) variations to the OEP; the two algorithms performed the calibration by the comparison between Δ VCD and OEP recorded volume Δ VOEP), in both static and dynamic conditions. Discrimination threshold, accuracy, precision and repeatability for the volume variation measurements have been evaluated, as well as the calibration curve of the OEP. OEP volume threshold of ±8.92mL was assessed; the volume measurement accuracy was always better than 6.0% of measured volume, and a volume repeatability of ±2.7mL was found. Lastly, the calibration curve was assessed to be Δ VOEP= 0.962 Δ Vcd. Results demonstrate that the proposed calibration procedure can be useful to provide an in-situ accurate calibration of motion capture systems in the volume analysis, to optimize the hardware and the software of the available system for volume measurement as well as to establish the motion capture system appropriateness, in terms of technical suitability and data quality.

Microscopic and Ultrastructural Anatomy



Head S. Morini

Faculty S. Carotti, F. Zalfa Other Personnel F. Cimini, M. Francesconi, V. Panasiti, M. Zingariello

Description

Main research activities

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

The histological features of liver tissue, the biochemical serological parameters and the genetic signatures were investigated in order to identify factors connecting liver inflammation and fibrosis during non-tumoral liver diseases.

Histo-morphology, cellular and molecular biology techniques were applied to the study of the intracellular pathways regulating, proliferation and aggressiveness of melanoma in collaboration with Prof. C Bagni (Università di Roma "Tor Vergata" and University of Lausanne, Switzerland) and Prof. JC Marine (Catholic University of Leuven, Belgium). Histo-morphology and molecular approaches were applied also to the study of liver cancers (HCC and ICC), at both cellular and tissue level, in collaboration with Prof. MA Avila (Gene Therapy & Hepatology, University of Navarra, Pamplona, Spain).

Most important publications

Barchetta I., Del Ben M., Angelico F., Di Martino M., Fraioli A., La Torre G., Saulle R., Perri L., Morini S., Tiberti C., Bertoccini L., Cimini F.A., Panimolle F., Catalano C., Baroni M.G., Cavallo M.G.

No effects of oral vitamin D supplementation on non-alcoholic fatty liver disease in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial. BMC Med. 2016 Jun 29;14:92. PubMed PMID: 27353492 IF 8,005

Background: Non-alcoholic fatty liver disease (NAFLD) is the most common hepatic disorder worldwide, reaching prevalence up to 90 % in obese patients with type 2 diabetes (T2D), and representing an independent risk factor for cardiovascular mortality. Furthermore, the coexistence of T2D and NAFLD leads to higher incidence of diabetes' complications and additive detrimental liver outcomes. The existence of a close association between NAFLD and hypovitaminosis D, along with the anti-inflammatory and insulin-sensitizing properties of vitamin D, have been largely described, but vitamin D effects on hepatic fat content have never been tested in a randomized controlled trial. We assessed the efficacy and safety of 24-week oral high-dose vitamin D supplementation in T2D patients with NAFLD.

Methods: This randomized, double-blind, placebo-controlled trial was carried out at the Diabetes Centre of Sapienza University, Rome, Italy, to assess oral treatment with cholecalciferol (2000 IU/day) or placebo in T2D patients with NAFLD. The primary endpoint was reduction of hepatic fat fraction (HFF) measured by magnetic resonance; as hepatic outcomes, we also investigated changes in serum transaminases, CK18-M30, N-terminal Procollagen III Propeptide (P3NP) levels, and Fatty Liver Index (FLI). Secondary endpoints were improvement in metabolic (fasting glycaemia, HbA1c, lipids, HOMA-IR, HOMA-β, ADIPO-IR, body fat distribution) and cardiovascular (ankle-brachial index, intima-media thickness, flow-mediated dilatation) parameters from baseline to end of treatment. **Results:** Sixty-five patients were randomized, 26 (cholecalciferol) and 29 (placebo) subjects completed the study. 25(OH) vitamin D significantly increased in the active treated group (48.15 \pm 23.7 to 89.80 \pm 23.6 nmol/L, P < 0.001); however, no group differences were found in HFF, transaminases, CK18-M30, P3NP levels or FLI after 24 weeks. Vitamin D neither changed the metabolic profile nor the cardiovascular parameters.

Conclusions: Oral high-dose vitamin D supplementation over 24 weeks did not improve hepatic steatosis or metabolic/cardiovascular parameters in T2D patients with NAFLD. Studies with a longer intervention period are warranted for exploring the effect of long time exposure to vitamin D.

Segreto F., Carotti S., Tosi D., Pendolino A.L., Marangi G.F., Morini S., Persichetti P.

Toll-like receptor 4 expression in human breast implant capsules: localization and correlation with estrogen receptors.

Plast Reconstr Surg. 2016 Mar;137(3):792-8. PubMed PMID: IF 3,087

Background: Capsular contracture is the most common complication following breast augmentation and reconstruction. Myofibroblasts, which are specialized fibroblasts with contractile activity, are involved in its pathogenesis. Toll-like receptor 4 stimulation in fibroblasts induces transcription of genes involved in extracellular matrix remodeling and tissue repair; furthermore, it enhances sensitivity to transforming growth factor- β 1 and promotes transition to myofibroblasts. 17 β -Estradiol, by binding to its main receptors, α and/or β , increases the expression of toll-like receptor 4 and the production of proinflammatory mediators by macrophages; moreover, it promotes extracellular matrix production and myofibroblasts contraction and differentiation. The aim of the study was to investigate the expression of toll-like receptor 4 in breast implant capsules and its relationship with estrogen receptors.

Methods: The study enrolled 30 women who underwent expander removal following breast reconstruction. Specimens were stained with hematoxylin and eosin, Masson trichrome, immunohistochemistry, and immunofluorescence for toll-like receptor 4, α -smooth muscle actin (a marker of myofibroblasts), estrogen receptor- α , and estrogen receptor- β .

Results: Toll-like receptor 4 was expressed by fibroblasts and myofibroblasts of capsular tissue. Its expression positively correlated with estrogen receptor- β expression (p = 0.012). A positive correlation was found between estrogen receptor- β and α -smooth muscle actin expression (p = 0.037).

Conclusions: This study demonstrates the expression of toll-like receptor 4 in myofibroblasts of capsular tissue and its correlation with estrogen receptor- β positivity. Activation of toll-like receptor 4 and estrogen receptor- β , and their interplay, may be involved in myofibroblast differentiation and in the profibrotic pathogenic process underlying capsular contracture.

Spangrude G.J., Lewandowski D., Martelli F., Marra M., Zingariello M., Sancillo L., Rana R.A., Migliaccio A.R.

P-selectin sustains extramedullary hematopoiesis in the Gata1 low model of myelofibrosis. *Stem Cells. 2016 Jan;34(1):67-82. PubMed PMID: 26439305. IF 5,902*

Splenomegaly is a major manifestation of primary myelofibrosis (PMF) contributing to clinical symptoms and hematologic abnormalities. The spleen from PMF patients contains increased numbers of hematopoietic stem cells (HSC) and megakaryocytes (MK). These MK express high levels of P-selectin (P-sel) that, by triggering neutrophil emperipolesis, may cause TGF- β release and disease progression. This hypothesis was tested by deleting the P-sel gene in the myelofibrosis mouse model carrying the hypomorphic Gata1 (low) mutation that induces megakaryocyte abnormalities that recapitulate those observed in PMF. P-sel(null) Gata1 (low) mice survived splenectomy and lived 3 months longer than P-sel(WT) Gata1 (low) littermates and expressed limited fibrosis and osteo-sclerosis in the marrow or splenomegaly. Furthermore, deletion of P-sel disrupted megakaryocyte/neutrophil interactions in spleen, reduced TGF- β content, and corrected the HSC distribution that in Gata1 (low) mice, as in PMF patients, is abnormally expanded in spleen. Conversely, pharmacological inhibition of TGF- β reduced P-sel expression in MK and corrected HSC distribution. Spleens, but not marrow, of Gata1 (low) mice contained numerous cKIT(pos) activated fibrocytes, probably of dendritic cell origin, whose membrane protrusions interacted with MK establishing niches hosting immature cKIT(pos) hematopoietic cells. These activated fibrocytes were not detected in spleens from P-sel(null) Gata1 (low) or TGF- β -inhibited Gata1 (low) littermates and were observed in spleen, but not in marrow, from PMF patients. Therefore, in Gata1 (low) mice, and possibly in PMF, abnormal P-sel expression in MK may mediate the pathological cell interactions that increase TGF- β content in MK and favor establishment of a microenvironment that supports myelofibrosis-related HSC in spleen.

Molecular Medicine and Biotechnology

Head V.M. Fazio

Other Personnel M. Dabrowska, S. Virga External Members M. Costantini, L. Loiacono, M.L. Poeta

Main research 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 oncohemathology.

Wang J., Papanicolau-Sengos A., Chintala S., Wei L., Liu B., Hu Q., Miles K.M., Conroy J.M., Glenn S.T., Costantini M., Magi-Galluzzi C., Signoretti S., Choueiri T., Gallucci M., Sentinelli S., Fazio V.M., Poeta M.L., Liu S., Morrison C., Pili R.

Collecting duct carcinoma of the kidney is associated with CDKN2A deletion and SLC family gene up-regulation.

Oncotarget. 2016 May 24;7(21):29901-15. PubMed PMID: 27144525. IF 5,008

The genetic landscape and molecular features of collecting duct carcinoma (CDC) of the kidney remain largely unknown. Herein, we performed whole exome sequencing (WES) and transcriptome sequencing (RNASeq) on 7 CDC samples (CDC1 -7). Among the 7 samples, 4 samples with matched non-tumor tissue were used for copy number analysis by SNP array data. No recurrent somatic SNVs were observed except for MLL, which was found to be mutated (p.V297I and p.F407C) in 2 samples. We identified somatic SNVs in 14 other cancer census genes including: ATM, CREBBP, PRDM1, CBFB, FBXW7, IKZF1, KDR, KRAS, NACA, NF2, NUP98, SS18, TP53, and ZNF521. SNP array data identified a CDKN2A homozygous deletion in 3 samples and SNV analysis showed a non-sense mutation of the CDKN2A gene with unknown somatic status. To estimate the recurrent rate of CDKN2A abnormalities, we performed FISH screening of additional samples and confirmed the frequent loss (62.5%) of CDKN2A expression. Since cisplatin based therapy is the common treatment option for CDC, we investigated the expression of solute carrier (SLC) family transporters and found 45% alteration. In addition, SLC7A11 (cystine transporter, xCT), a cisplatin resistance associated gene, was found to be overexpressed in 4 out of 5 (80%) cases of CDC tumors tested, as compared to matched non-tumor tissue. In summary, our study provides a comprehensive genomic analysis of CDC and identifies potential pathways suitable for targeted therapies.

Most important publications

De Robertis M., Loiacono L., Fusilli C., Poeta M.L., Mazza T., Sanchez M., Marchionni L., Signori E., Lamorte G., Vescovi A.L., Garcia-Foncillas J., Fazio V.M.

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

Clin Cancer Res. 2016. Epub 2016 Jul 11. DOI: 10.1158/1078-0432.CCR-16-0709. PubMed PMID: 27401248. IF 8,738

Purpose: EphA2 receptor is involved in multiple cross-talks with other cellular networks, including EGFR, FAK, and VEGF pathways, with which it collaborates to stimulate cell migration, invasion, and metastasis. Colorectal cancer (CRC) EphA2 overexpression has also been correlated to stem-like properties of cells and tumor malignancy. We investigated the molecular cross-talk and miRNAs modulation of the EphA2 and EGFR pathways. We also explored the role of EphA2/EGFR pathway mediators as prognostic factors or predictors of cetuximab benefit in patients with CRC.

Experimental design: Gene expression analysis was performed in EphA2high cells isolated from CRC of the AOM/DSS murine model by FACS-assisted procedures. Six independent cohorts of patients were stratified by EphA2 expression to determine the potential prognostic role of a EphA2/EGFR signature and its effect on cetuximab treatment response.

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

Conclusions: These results suggest that EphA2/Efna1/Egfr genes, linked to a possible control by miR-200a and miR-26b, could be proposed as novel CRC prognostic biomarkers. Moreover, EphA2 could be linked to a mechanism of resistance to cetuximab alternative to KRAS mutations.

Santini G., Mores N., Shohreh R., Valente S., Dabrowska M., Trové A., Zini G., Cattani P., Fuso L., Mautone A., Mondino C., Pagliari G., Sala A., Folco G., Aiello M., Pisi R., Chetta A., Losi M., Clini E., Ciabattoni G., Montuschi P.

Exhaled and non-exhaled non-invasive markers for assessment of respiratory Inflammation in patients with stable COPD and healthy smokers.

J Breath Res. 2016 Jan 27;10(1):017102. PubMed PMID: 26814886. IF 4,177

We aimed at comparing exhaled and non-exhaled non-invasive markers of respiratory inflammation in patients with chronic obstructive pulmonary disease (COPD) and healthy subjects and define their relationships with smoking habit. Forty-eight patients with stable COPD who were ex-smokers, 17 patients with stable COPD who were current smokers, 12 healthy current smokers and 12 healthy ex-smokers were included in a cross-sectional, observational study. Inflammatory outcomes, including prostaglandin (PG) E2 and 15-F2t-isoprostane (15-F2t-IsoP) concentrations in exhaled breath condensate (EBC) and sputum supernatants, fraction of exhaled nitric oxide (FENO) and sputum cell counts, and functional (spirometry) outcomes were measured. Sputum PGE2 was elevated in both groups of smokers compared with ex-smokers with COPD (P = 0.0029) versus healthy subjects: P < 0.03), whereas EBC PGE2 was elevated in current (P = 0.0065) and ex-smokers with COPD (P = 0.0029) versus healthy ex-smokers. EBC 15-F2t-IsoP, a marker of oxidative stress, was increased in current and ex-smoker groups (COPD: P < 0.01; healthy subjects: P < 0.02) versus healthy ex-smokers. FENO was elevated in both smoker groups (COPD: P < 0.001 for both). These data suggest that the biological meaning of these inflammatory markers depends on type of marker and biological matrix in which is measured. An approach combining different types of outcomes can be used for assessing respiratory inflammation in patients with COPD. Large studies are required to establish the clinical utility of this strategy.

Molecular Neurosciences



Head M. D'Amelio

Other Personnel A. Nobili, F. Sciarra

External Members L. La Barbera, V. Cavallucci, M.C. Dell'Acqua

Description

Main collaborations

The Molecular Neurosciences Unit focuses on neurodegenerative diseases and other neuropsychiatric conditions by means of the application of biologic techniques. We have a particular interest in the pathogenesis of *B*-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:

- Center of Excellence for Biomedical Research, Université Libre de Bruxelles;
- National Research Council (CNR), Italy;
- Roma Tre University, Italy;
- Sapienza University, Italy;
- University of Genova, Italy;
- University of Perugia, Italy.

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.

Most important publications

Costa C., Parnetti L., D'Amelio M., Tozzi A., Tantucci M., Romigi A., Siliquini S., Cavallucci V., Di Filippo M., Mazzocchetti P., Liguori C., Nobili A., Eusebi P., Mercuri N. B., Calabresi P.

Epilepsy, amyloid- β , and D1 dopamine receptors: a possible pathogenetic link?

Neurobiol Aging. 2016 Dec;48:161-171. PubMed PMID: 27701029. IF 5,153

Experimental and clinical observations indicate that amyloid- β 1-42 (A β 1-42) peptide not only represents a major actor in neurodegenerative mechanisms but also induce hyperexcitation in individual neurons and neural circuits. In this abnormal excitability, possibly leading to seizures, the D1 dopamine (DA) receptors may play a role. Cerebrospinal fluid levels of A β 1-42 were measured in patients with late-onset epilepsy of unknown etiology. Moreover, the effect of amyloid peptide on the hippocampal epileptic threshold and synaptic plasticity and its link to D1 receptor function were tested in experimental mouse model of cerebral amyloidosis and in acute model of A β 1-42-induced neurotoxicity. Among 272 evaluated epileptic patients, aged >55 years, 35 suffered from late-onset epilepsy of unknown etiology. In these subjects, cerebrospinal fluid A β 1-42 levels were measured. The effects of A β 1-42, amyloid oligomers, and D1 receptor modulation on epileptic threshold were analyzed by electrophysiological recordings in the dentate gyrus of mice hippocampal slices. We found that $A\beta$ 1-42 levels were significantly decreased in cerebrospinal fluid of patients with late-onset epilepsy of unknown etiology with respect to controls suggesting the cerebral deposition of this peptide in these patients. $A\beta$ 1-42 enhanced epileptic activity in mice through a mechanism involving increased surface expression of D1 receptor, and this effect was mimicked by D1 receptor stimulation and blocked by SCH 23390, a D1 receptor antagonist. $A\beta$ 1-42 may contribute to the pathophysiology of late-onset epilepsy of unknown origin. Our preclinical findings indicate that the D1 receptor is involved in mediating the epileptic effects of $A\beta$ 1-42. This novel link between $A\beta$ 1-42 and D1 receptor signaling might represent a potential therapeutic target.

Laricchiuta D., Cavallucci V., Cutuli D., De Bartolo P., Caporali P., Foti F., Finke C., D'Amelio M., Manto M., Petrosini L.

Effects of anti-NMDA antibodies on functional recovery and synaptic rearrangement following hemicerebellectomy.

Neuromolecular Med. 2016 Jun;18(2):190-202. PubMed PMID: 27027521. IF 3,692

The compensation that follows cerebellar lesions is based on synaptic modifications in many cortical and subcortical regions, although its cellular mechanisms are still unclear. Changes in glutamatergic receptor expression may represent the synaptic basis of the compensated state. We analyzed in rats the involvement of glutamatergic system of the cerebello-frontal network in the compensation following a right hemicerebellectomy. We evaluated motor performances, spatial competencies and molecular correlates in compensated hemicerebellectomized rats which in the frontal cortex contralateral to the hemicerebellectomy side received injections of anti-NMDA antibodies from patients affected by anti-NMDA encephalitis. In the compensated hemicerebellectomized rats, the frontal injections of anti-NMDA antibodies elicited a marked decompensation state characterized by slight worsening of the motor symptoms as well as severe impairment of spatial mnesic and procedural performances. Conversely, in the sham-operated group the frontal injections of anti-NMDA antibodies elicited slight motor and spatial impairment. The molecular analyses indicated that cerebellar compensatory processes were related to a relevant rearrangement of glutamatergic synapses (NMDA and AMPA receptors and other glutamatergic components) along the entire cortico-cerebellar network. The long-term maintenance of the rearranged glutamatergic activity plays a crucial role in the maintenance of recovered function.

Krashia P., Ledonne A., Nobili A., Cordella A., Errico F., Usiello A., D'Amelio M., Mercuri N. B., Guatteo E., Carunchio I.

Persistent elevation of D-Aspartate enhances NMDA receptor-mediated responses in mouse substantia nigra pars compacta dopamine neurons.

Neuropharmacology. 2016 Apr;103:69-78. PubMed PMID: 26707656. IF 4,936

Dopamine neurons in the substantia nigra pars compacta regulate not only motor but also cognitive functions. NMDA receptors play a crucial role in modulating the activity of these cells. Considering that the amino-acid D-Aspartate has been recently shown to be an endogenous NMDA receptor agonist, the aim of the present study was to examine the effects of D-Aspartate on the functional properties of nigral dopamine neurons. We compared the electrophysiological actions of D-Aspartate in control and D-aspartate oxidase gene (Ddo(-/-)) knock-out mice that show a concomitant increase in brain D-Aspartate levels, improved synaptic plasticity and cognition. Finally, we analyzed the effects of L-Aspartate, a known dopamine neuron endogenous agonist in control and Ddo(-/-) mice. We show that D- and L-Aspartate excite dopamine neurons by activating NMDA, AMPA and metabotropic glutamate receptors. Ddo deletion did not alter the intrinsic properties or dopamine sensitivity of dopamine neurons. However, NMDA-induced currents were enhanced and membrane levels of the NMDA receptor GluN1 and GluN2A subunits were increased. Inhibition of excitatory amino-acid transporters caused a marked potentiation of D-Aspartate, but not L-Aspartate currents, in Ddo(-/-) neurons. This is the first study to show the actions of D-Aspartate on midbrain dopamine neurons, activating not only NMDA but also non-NMDA receptors. Our data suggest that dopamine neurons, under conditions of high D-Aspartate levels, build a protective uptake mechanism to compensate for increased NMDA receptor numbers and cell hyper-excitation, which could prevent the consequent hyper-dopaminergia in target zones that can lead to neuronal degeneration, motor and cognitive alterations.

Molecular Psychiatry and Neurogenetics



Head A.M. Persico

Other Personnel G. Barbieri, C. Brogna, M. Canali, C. Cannizzaro, A. Costa, S. Gabriele, C. Lintas, C. Picinelli, I.S. Piras, R. Sacco, P. Tomaiuolo, M. Verdecchia

Description

Main research activities

Main collaborations

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 gPCR (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 neurop-

sychiatric disorders (ECNP).

- Biological Science Department and Interdepartmental Centre for Stem Cell Research Milano University, Italy;
- Brain Centre Rudolf Magnu, The Netherlands;
- Department of Translational Neuroscience, University Medical Centre Utrecht, The Netherlands;
- Institute of Psychiatry, King's College London, UK;
- Neurotoxicology & Neuroendocrine Department Istituto Superiore di Sanità, Italy;
- Proteomics Laboratory, Tuscia University, Viterbo, Italy;
- Psychology Department Sapienza University, Italy.

Most important publications

Loth E., Spooren W., Ham L.M., Isaac M.B., Auriche-Benichou C., Banaschewski T., Baron-Cohen S., Broich K., Bölte S., Bourgeron T., Charman T., Collier D., de Andres-Trelles F., Durston S., Ecker C., Elferink A., Haberkamp M., Hemmings R., Johnson M.H., Jones E.J., Khwaja O.S., Lenton S., Mason L., Mantua V., Meyer-Lindenberg A., Lombardo M.V., O'Dwyer L., Okamoto K., Pandina G.J., Pani L., Persico A.M., Simonoff E., Tauscher-Wisniewski S., Llinares-Garcia J., Vamvakas S., Williams S., Buitelaar J.K., Murphy D.G.

Identification and validation of biomarkers for autism spectrum disorders.

Nat Rev Drug Discov. 2016 Jan; 15(1):70-3. PubMed PMID: 26718285. IF 47, 120

Di Giorgio E., Frasnelli E., Salva RO., Scattoni M.L., Puopolo M., Tosoni D., NIDA-Network., Simion F., Vallortigara G., Apicella F., Gagliano A., Guzzetta A., Molteni M., Persico A., Pioggia G., Valeri G., Vicari S.

Difference in visual social predispositions between newborns at low- and high-risk for autism. Sci Rep. 2016 May 20;6:26395. PubMed PMID: 27198160. IF 5,228

Some key behavioural traits of Autism Spectrum Disorders (ASD) have been hypothesized to be due to impairments in the early activation of subcortical orienting mechanisms, which in typical development bias newborns to orient to relevant social visual stimuli. A challenge to testing this hypothesis is that autism is usually not diagnosed until a child is at least 3 years old. Here, we circumvented this difficulty by studying for the very first time, the predispositions to pay attention to social stimuli in newborns with a high familial risk of autism. Results showed that visual preferences to social stimuli strikingly differed between high-risk and low-risk newborns. Significant predictors for high-risk newborns with familial risk for ASD, allowing for a prospective approach to the emergence of autism in early infancy.

Gevi F., Zolla L., Gabriele S., Persico A.M.

Urinary metabolomics of young Italian autistic children supports abnormal tryptophan and purine metabolism.

Mol Autism. 2016 Nov 24;7:47. PubMed PMID: 27904735. IF 4,961

Background: Autism spectrum disorder (ASD) is still diagnosed through behavioral observation, due to a lack of laboratory biomarkers, which could greatly aid clinicians in providing earlier and more reliable diagnoses. Metabolomics on human biofluids provides a sensitive tool to identify metabolite profiles potentially usable as biomarkers for ASD. Initial metabolomic studies, analyzing urines and plasma of ASD and control individuals, suggested that autistic patients may share some metabolic abnormalities, despite several inconsistencies stemming from differences in technology, ethnicity, age range, and definition of "control" status.

Methods: ASD-specific urinary metabolomic patterns were explored at an early age in 30 ASD children and 30 matched controls (age range 2-7, M:F = 22:8) using hydrophilic interaction chromatography (HILIC)-UHPLC and mass spectrometry, a highly sensitive, accurate, and unbiased approach. Metabolites were then subjected to multivariate statistical analysis and grouped by metabolic pathway. **Results:** Urinary metabolites displaying the largest differences between young ASD and control children belonged to the tryptophan and purine metabolic pathways. Also, vitamin B6, riboflavin, phenylalanine-tyrosine-tryptophan biosynthesis, pantothenate and CoA, and pyrimidine metabolism differed significantly. ASD children preferentially transform tryptophan into xanthurenic acid and quinolinic acid (two catabolites of the kynurenine pathway), at the expense of kynurenic acid and especially of melatonin. Also, the gut microbiome contributes to altered tryptophan metabolism, yielding increased levels of indolyl 3-acetic acid and indolyl lactate.

Conclusions: The metabolic pathways most distinctive of young Italian autistic children largely overlap with those found in rodent models of ASD following maternal immune activation or genetic manipulations. These results are consistent with the proposal of a purine-driven cell danger response, accompanied by overproduction of epileptogenic and excitotoxic quinolinic acid, large reductions in melatonin synthesis, and gut dysbiosis. These metabolic abnormalities could underlie several comorbidities frequently associated to ASD, such as seizures, sleep disorders, and gastrointestinal symptoms, and could contribute to autism severity. Their diagnostic sensitivity, disease-specificity, and interethnic variability will merit further investigation.

Neurology, Neurophysiology, Neurobiology

Head V. Di Lazzaro

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

Other Personnel C. Altamura, R. Altavilla, F. Assenza, G. Assenza, N. Brunelli, F. Capone, A. Cascio Rizzo, G. Cecchi, C. Costa, L. Di Biase, A. Di Santo, E. Falato, A. Fallacara, L. Florio, A. Guerra, J. Lanzone, M. Marano, M. Paolucci, A. Pepe, F. Ranieri, L. Ricci, M. Ulivi, F. Ursini

Description

Main collaborations

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).

Development of innovative methods of neuromodulation to promote recovery in patients with chronic stroke. Non-invasive brain stimulation of the human cerebral cortex using transcranial alternating current stimulation to selectively modulate cortical GABAergic and Cholinergic circuits. Use of non-invasive brain stimulation to explore functional changes of cerebral cortex after stroke and the role of these changes in recovery.

Most important publications

Guerra A., Pogosyan A., Nowak M., Tan H., Ferreri F., Di Lazzaro V., Brown P.

Phase dependency of the human primary motor cortex and cholinergic inhibition cancelation during beta tACS.

Cereb Cortex. 2016 Oct;26(10):3977-90. PubMed PMID: 27522077. IF 8,285

The human motor cortex has a tendency to resonant activity at about 20 Hz so stimulation should more readily entrain neuronal populations at this frequency. We investigated whether and how different interneuronal circuits contribute to such resonance by using transcranial magnetic stimulation (TMS) during transcranial alternating current stimulation (tACS) at motor (20 Hz) and a nonmotor resonance frequency (7 Hz). We tested different TMS interneuronal protocols and triggered TMS pulses at different tACS phases. The effect of cholinergic short-latency afferent inhibition (SAI) was abolished by 20 Hz tACS, linking cortical beta activity to sensorimotor integration. However, this effect occurred regardless of the tACS phase. In contrast, 20 Hz tACS selectively modulated MEP size accor-

ding to the phase of tACS during single pulse, GABAAergic short-interval intracortical inhibition (SICI) and glutamatergic intracortical facilitation (ICF). For SICI this phase effect was more marked during 20 Hz stimulation. Phase modulation of SICI also depended on whether or not spontaneous beta activity occurred at ~20 Hz, supporting an interaction effect between tACS and underlying circuit resonances. The present study provides in vivo evidence linking cortical beta activity to sensorimotor integration, and for beta oscillations in motor cortex being promoted by resonance in GABAAergic interneuronal circuits.

Di Lazzaro V., Capone F., Di Pino G., Pellegrino G., Florio L., Zollo L., Simonetti D., Ranieri F., Brunelli N., Corbetto M., Miccinilli S., Bravi M., Milighetti S., Guglielmelli E., Sterzi S.

Combining robotic training and non-invasive brain stimulation in severe upper limb-impaired chronic stroke patients.

Front Neurosci, 2016 Mar 8:10:88. PubMed PMID: 27013950. IF 3.398

Previous studies suggested that both robot-assisted rehabilitation and non-invasive brain stimulation can produce a slight improvement in severe chronic stroke patients. It is still unknown whether their combination can produce synergistic and more consistent improvements. Safety and efficacy of this combination has been assessed within a proof-of-principle, double-blinded, semi-randomized, sham-controlled trial. Inhibitory continuous Theta Burst Stimulation (cTBS) was delivered on the affected hemisphere, in order to improve the response to the following robot-assisted therapy via a homeostatic increase of learning capacity. Twenty severe upper limb-impaired chronic stroke patients were randomized to robot-assisted therapy associated with real or sham cTBS, delivered for 10 working days. Eight real and nine sham patients completed the study. Change in Fugl-Meyer was chosen as primary outcome, while changes in several quantitative indicators of motor performance extracted by the robot as secondary outcomes. The treatment was well-tolerated by the patients and there were no adverse events. All patients achieved a small, but significant, Fugl-Meyer improvement (about 5%). The difference between the real and the sham cTBS groups was not significant. Among several secondary end points, only the Success Rate (percentage of targets reached by the patient) improved more in the real than in the sham cTBS group. This study shows that a short intensive robot-assisted rehabilitation produces a slight improvement in severe upper-limb impaired, even years after the stroke. The association with homeostatic metaplasticity-promoting non-invasive brain stimulation does not augment the clinical gain in patients with severe stroke.

Thiis V.N., Brachmann J., Morillo C.A., PassmanR.S., Sanna T., Bernstein R.A., Diener H.C., Di Lazzaro V., Rymer M.M., Hogge L., Rogers T.B., Ziegler P.D., Assar M.D.

Predictors for atrial fibrillation detection after cryptogenic stroke: results from CRYSTAL AF.

Neurology. 2016 Jan 19;86(3):261-9. PubMed PMID: 26683642. IF 8,166

Objective: We assessed predictors of atrial fibrillation (AF) in cryptogenic stroke (CS) or transient ischemic attack (TIA) patients who received an insertable cardiac monitor (ICM).

Methods: We studied patients with CS/TIA who were randomized to ICM within the CRYSTAL AF study. We assessed whether age, sex, race, body mass index, type and severity of index ischemic event, CHADS2 score, PR interval, and presence of diabetes, hypertension, congestive heart failure, or patent foramen ovale and premature atrial contractions predicted AF development within the initial 12 and 36 months of follow-up using Cox proportional hazards models.

Results: Among 221 patients randomized to ICM (age 61.6 ± 11.4 years, 64% male), AF episodes were detected in 29 patients within 12 months and 42 patients at 36 months. Significant univariate predictors of AF at 12 months included age (hazard ratio [HR] per decade 2.0 [95% confidence interval 1.4-2.8], p = 0.002), CHADS2 score (HR 1.9 per one point [1.3-2.8], p = 0.008), PR interval (HR 1.3 per 10 milliseconds [1.2-1.4], p < 0.0001), premature atrial contractions (HR 3.9 for >123 vs 0 [1.3-12.0], p = 0.009 across quartiles), and diabetes (HR 2.3 [1.0-5.2], p < 0.05). In multivariate analysis, age (HR per decade 1.9 [1.3-2.8], p = 0.0009) and PR interval (HR 1.3 [1.2-1.4], p < 0.0001) remained significant and together yielded an area under the receiver operating characteristic curve of 0.78 (0.70-0.85). The same predictors were found at 36 months.

Conclusion: Increasing age and a prolonged PR interval at enrollment were independently associated with an increased AF incidence in CS patients. However, they offered only moderate predictive ability in determining which CS patients had AF detected by the ICM.

Neurophysiology and Neuroengineering of Human-Technology Interaction



Head G. Di Pino

Faculty D. Formica Other Personnel A. Mioli, A. Noccaro, S. Summa, J. Tosi

Description

Main collaborations

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

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

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

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

Its multidisciplinary flavor favors direct applications on the healthy subjects and patients. The Unit is newborn.

- Main activities of 2016 were focused on:
- the second phase "preclinical" of a project that sees the development of an automated device to monitor Parkinson Disease motor state and @ Home patient monitoring;
- the activities useful to prepare the clinical validation of a close loop neurally-interfaced hand prosthesis;
- the background analysis for the development of technological platforms to induce, evaluate and foster prosthesis embodiment;
- the design and development of Hardware and Software Systems of virtual and augmented reality, and of cognitive studies that integrate VR-AR stimuli, external stimulations (e.g. tDCS, TMS) and the recording and processing of biological signals (EEG, fMRI, EMG).

Most important publications

overall recoverability.

Taffoni F., Tamilia E., Giorgino M., Morbidoni G., Rosi A., Scaini A., Formica D.

Neurorehabil Neural Repair. 2016 Jan:30(1):3-8. PubMed PMID: 25896987. IF 4.035

Di Pino G., Pellegrino G., Capone F., Assenza G., Florio L., Falato E., Lotti F., Di Lazzaro V.

carriers do not differ in terms of absolute ability to recover from stroke, but they do differ on the way they recover.

A novel system to study the coordination of sucking and breathing in newborns during bottle feeding. IEEE Sens J. 2016;16(23):8589-8596. DOI: 10.1109/JSEN.2016.2613889. IF 1,889

Val66Met BDNF polymorphism implies a different way to recover from stroke rather than a worse

In search for individualized predictors of stroke recovery, the Val66Met polymorphism of the brain-derived neurotrophic factor (BDNF) is attracting great interest. The dominant thought is in favor of a worse recovery in Met carriers. Conversely, we suggest that Met

Current clinical practice lacks of quantitative tools for the assessment of nutritive sucking and its coordination with breathing. This paper aimed to fill this gap by integrating a module for neonatal breathing monitoring with a system for the measurement of sucking during bottle feeding. We designed a new in-house flow meter, based on two commercial transistors, and tested in laboratory to assess its static response and dynamic characteristics. We integrated the flow meter into a new electronic architecture for an easy integration of this module with our system for nutritive sucking assessment. Finally, we collected preliminary data from preterm and a term newborn population.

Ricci L., Taffoni F., Formica D.

On the orientation error of IMU: investigating static and dynamic accuracy targeting human motion. *PLoS One. 2016 Sep 9;11(9):e0161940. PubMed PMID: 27612100. IF 3,057*

The accuracy in orientation tracking attainable by using inertial measurement units (IMU) when measuring human motion is still an open issue. This study presents a systematic quantification of the accuracy under static conditions and typical human dynamics, simulated by means of a robotic arm. Two sensor fusion algorithms, from the classes of stochastic and complementary methods, are considered. The proposed protocol implements controlled and repeatable conditions and validates accuracy for an extensive set of dynamic movements. Reported results emphasize critical issues associated with this technology and provide a baseline level of performance for the human motion related application.

Nonlinear Physics and Mathematical Modeling



Head S. Filippi

Faculty C. Cherubini, L. Chiodo, A. Gizzi Other Personnel A. Loppini

Description

Main collaborations

The nonlinear physics and mathematical modeling research Unit investigates different problems belonging to Physics, Mathematics, Engineering, Biology and Medicine. Theoretical, analytical and numerical tools are applied to investigate complex dynamics underlying biological systems as well as astrophysics and classical and quantum field theories, with particular attention to fluid dynamics, nonlinear solid mechanics, condensed matter physics and stellar and black hole dynamics. Regarding biophysics, research activities focus on animal and human physiopathology of cardiac, intestine, neural, endocrine systems through the derivation and solution of mathematical models calibrated on experiments. To this aim, advanced tools of numerical calculus, atomistic simulations, biomedical imaging as well as data analysis are implemented with the aim of obtaining predictive information regarding complex systems. The Unit moreover extends its skills through national and international networks of collaborations.

In 2016 the research Unit has continued its long-lasting collaboration with the International Center for Relativistic Astrophysics Network (ICRANet) being awarded of an 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. In the framework of a new scientific agreement between UCBM and the Italian Institute for Technology (IIT), the group is working at a neuroscience project focused on computational and experimental investigation of physiological neural networks. Most important publications

Cherubini C., Filippi S.

The Hamiltonian field theory of the Von Mises wave equation: analytical and computational issues. *Commun Comput Phys. 2016; 19(3):758-769. DOI: 10.4208/cicp.101114.140715a. IF 1,778*

The Von Mises quasi-linear second order wave equation, which completely describes an irrotational, compressible and barotropic classical perfect fluid, can be derived from a nontrivial least action principle for the velocity scalar potential only. In this article, the classical Hamiltonian field theory specifically associated to such an equation is developed in the polytropic case and numerically verified in a simplified situation. The existence of such a mathematical structure suggests new theoretical schemes possibly useful for performing numerical integrations of fluid dynamical equations.

Yong Z., Trevisanutto P.E., Chiodo L., Santoso I., Barman A.R., Asmara T.C., Dhar S., Kotlov A., Terentjevs A., Della Sala F., Olevano V., Rübhausen M., Venkatesan T., Rusydi, A.

Emerging giant resonant exciton induced by Ta substitution in anatase TiO 2: a tunable correlation effect.

Physical Review B. 2016; 93(20): 205118. DOI: 10.1103/PhysRevB.93.205118. IF 3,718

Titanium dioxide (TiO2) has rich physical properties with potential implications for both fundamental physics and new applications. Tuning its optical properties is usually done via doping and/or nanoengineering. Within a combination of an innovative experimental technique, high-energy optical conductivity, and state-of-the-art ab initio electronic structure calculations, we report an emerging, novel resonant exciton in the deep ultraviolet region of the optical response, related to correlation effects. Our results shed light on a new optical phenomenon in anatase TiO2 films and on the possibility of tuning electronic properties by Ta substitution.

Pandolfi A., Gizzi A., Vasta M.

Coupled electro-mechanical models of fiber-distributed active tissues. *J Biomech. 2016 Aug 16;49(12):2436- 44. PubMed PMID: 26916512. IF 2,431*

A constitutive model for stochastically distributed fiber reinforced tissues is discussed, where the active behavior of the fibers depends on the relative orientation of the electric field. Examples of passive and active behaviors predicted by the model in terms of response to biaxial testing are presented, and comparisons with passive experimental data are provided.

Nursing Science



Head M.G. De Marinis

Faculty M. Matarese, M. Piredda, D. Tartaglini

Description

Main collaborations

The Unit investigates topics within clinical, pedagogical and organizational areas using quantitative and qualitative methods. Clinical areas include mainly palliative care, geriatric and cancer nursing. Palliative care topics include nursing care dependence, pressure ulcers, care for adolescents who lose a parent and place of death. Geriatric topics include self-care (of elderly living at home and of elderly with chronic diseases), nutrition, quality of life and continuity of care. 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 Alberto Sordi Foundation are the following:

- The concept of Self-care for home-dwelling older people;
- Self-care for the promotion.

Most important publications

Piredda M., Biagioli V., Giannarelli D., Incletoli D., Grieco F., Carassiti M., De Marinis M.G.

Improving cancer patients' knowledge about totally implantable access port: a randomized controlled trial.

Support Care Cancer. 2016 Feb;24(2):833-41. PubMed PMID: 26201750. IF 2,535

Purpose: Providing patients with written information about totally implantable access ports (TIAP) is recommended during the pre-implantation period to reduce anxiety and to help recalling information. No study tested the effectiveness of information about TIAP neither with oral communication nor with booklets. This study aimed at evaluating the effectiveness of an information booklet, alone or together with answers to clarification questions, both in improving patients' short and long time knowledge about TIAP and in decreasing patients' physiological indicators of anxiety immediately after TIAP implantation.

Methods: Randomized controlled trial with three parallel groups: group A (n=34) receiving only the booklet, group B (n=34) receiving

the booklet with answers to clarification questions, group C (n=37) receiving routine care.

Results: After 3 months, pair comparisons revealed a significant improvement in knowledge of TIAP in each group (p<.001), together with a significant difference in group C compared with group A (p<.001) and B (p<.001), similar to each other. Physiological indicators of anxiety decreased in the intervention groups compared to control group immediately after TIAP implantation.

Conclusions: The interventions provided resulted effective in decreasing patients' physiological indicators of anxiety immediately after TIAP implantation and improving patients' knowledge about TIAP at 3 months. Adding answers to clarification questions to the booklet was not more effective than the booklet alone. A well-designed booklet with attention both to scientific content and to communication.

Piredda M., Bartiromo C., Capuzzo M.T., Matarese M., De Marinis M.G.

Nursing care dependence in the experiences of advanced cancer inpatients.

Eur J Oncol Nurs.2016 Feb;20:125-32. PubMed PMID: 26174067. IF 1,618

Purpose: Increasing burden of cancer in Europe and socio-demographic trends imply that more cancer patients will face high levels of dependency. Care dependency is often perceived as a distressing expe- rience by cancer patients who are concerned about becoming a burden to others. The experience of care dependence has been scarcely investigated in advanced cancer patients, especially in the hospital setting. This study aimed at describing advanced cancer patients' experiences of care dependence in hospital and of the factors perceived by them as contributing to decrease or increase this dependence.

Methods: The study used a descriptive phenomenological approach based on Husserl's (1913) life world perspective. Data collection and analysis followed Giorgi's (1997) five basic methodological steps. Data were gathered by semi-structured interviews with thirteen advanced cancer adult inpatients of a teaching hospital. The interviews were audio-recorded and the recordings transcribed word for word. **Results:** Three themes emerged: 'dependency discovers new meanings of life', 'active coping with de- pendency' and 'the care cures the dependent person'. The essential meaning of care dependency was the possibility to become aware of being a person as both an object and subject of care.

Conclusion: Dependence appears as an experience with strong relational connotations, which enable patients to see differently their life, themselves, the world and others. Dependency is revealed as a natural experience, only partly in accordance with previous studies. Deeper insight into the meaning patients attach to care dependency can enable nurses to better meet the patient's needs, e.g. by improving caring relationships with patients.

Biagioli V., Piredda M., Mauroni M.R., Alvaro R., De Marinis M.G.

The lived experience of patients in protective isolation during their hospital stay for allogeneic haematopoietic stem cell transplantation.

Eur J Oncol Nurs. 2016 Oct;24:79-86. PubMed PMID: 27697280. IF 1,618

Purpose: Patients undergoing allogeneic haematopoietic stem cell transplantation (HSCT) usually receive hospital care in protective isolation until full neutrophil recovery. Although the aim of protective isolation is to benefit patients' health by preventing risks of infection, it could have severe psychological implications. The aim of this study was to explore the lived experiences of protective isolation in adult patients who had been treated with allogeneic HSCT.

Method: A descriptive phenomenological inquiry based on Giorgi's approach was conducted in a university hospital in Italy. Ten patients (7 female and 3 male, age range 28e66), who had undergone allogeneic HSCT to treat a haematological malignancy, were interviewed about their hospital stay in protective isolation.

Results: A general meaning structure was identified as being isolated to achieve transformation. The revelatory themes were as follows: (1) the special place for transformation, (2) the experience of embodied transformation, and (3) light and shade from inside and outside. Participants experienced a transformation of themselves, of their relationships with loved ones, and of the environment. **Conclusions:** Since patients may live the experience of being treated with allogeneic HSCT in protective isolation as a transformation process, health-care providers should monitor the psychosocial implications of the isolation practice.

Oncology

Head G. Tonini



Faculty D. Santini, B. Vincenzi

Other Personnel G. Armento, M.C. Cursano, L. D'Onofrio, D. De Lisi, E. Dell'Aquila, C. Della Pepa, M. Fioramonti, I. Fioroni, A.M. Frezza, C. Grilli, M. Imperatori, M. Iuliani, A. La Cesa, E. Marrucci, C. Mazzara, F. Pantano, R. Ratta, G. Ribelli, E. Rossi, M. Russano, M. Silletta, M. Spalato Ceruso, C. Spoto, M. Stellato, L. Stumbo, O. Venditti, V. Virzì, A. Zoccoli **| Data manager** T. Grassani, C. Potestà

Description

Main research activities

Main collaborations

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

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

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

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

- Department of Surgery, Oncology and Gastroenterology, University of Padova, IOV-IRCCS, Italy;
- National Institute of Health and Medical Research (INSERM), France;
- Osteoncology and Rare Tumors Center, IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST), Italy.

Most important publications

Santini D., Tonini G.

Treatment of advanced renal-cell carcinoma.

N Engl J Med. 2016 Mar 3;374(9):888-9. PubMed PMID: 26962913. IF 59,558

In our laboratory, we have explored the potential direct role of cabozantinib in bone using a totally human model of primary osteoclasts and osteoblasts. In brief, we found that noncytotoxic doses of cabozantinib had a significant inhibitory effect on osteoclast activity; moreover, cabozantinib induced in mature osteoblasts a significant decrease in the expression of receptor activator of nuclear factor kappa-B ligand (RANKL) and a concomitant up-regulation of osteoprotegerin levels. Data regarding skeletal-specific end points in the study by Motzer et al. could provide further evidence of a double antiresorptive and antitumoral effect of cabozantinib against the vicious cycle of bone metastases that occur in almost 35% of patients with advanced renal-cell carcinoma.

Vincenzi B., Fioroni I., Pantano F., Angeletti S., Dicuonzo G., Zoccoli A., Santini D., Tonini G.

Procalcitonin as diagnostic marker of infection in solid tumors patients with fever. *Sci Rep. 2016 Jun 17;6:28090. PubMed PMID: 27312877. IF 5,228*

Procalcitonin (PCT) seems to be the most promising infection marker. We aimed to define the potential role of PCT as an earlier diagnostic marker in patients with fever and solid tumor. This retrospective study enrolled 431 patients. A statistically significant difference in PCT levels between patients with positive and negative HE was observed (P < 0.0001). Moreover comparing PCT values in patients with positive and negative HE, we obtain in the positive HE subpopulation an AUC of 0.7 and a cut-off of 1.52 ng/dL reached high sensitivity (61.6%) and specificity (70.1%). Using this last cut-off, instead of the normal reference value, we achieve a risk reduction to overestimate an infection status of 23.4%. We support the clinic usefulness of serum PCT dosage in febrile advanced solid tumor patients. A PCT cut-off of 1.52 ng/dL could be helpful in the management of the antibiotic therapy preventing delays of oncologic treatments.

Santini D., Santoni M., Conti A., Procopio G., Verzoni E., Galli L., di Lorenzo G., De Giorgi U., De Lisi D., Nicodemo M., Maruzzo M., Massari F., Buti S., Altobelli E., Biasco E., Ricotta R., Porta C., Vincenzi B., Papalia R., Marchetti P., Burattini L., Berardi R., Muto G., Montironi R., Cascinu S., Tonini G.

Risk of recurrence and conditional survival in complete responders treated with TKIs plus or less locoregional therapies for metastatic renal cell carcinoma.

Oncotarget. 2016 May 31;7(22):33381-90. PubMed PMID: 27027342. IF 5,008

We retrospectively analyzed the risk of recurrence and conditional Disease-Free Survival (cDFS) in 63 patients with complete remission during treatment with tirosin kinase inhibitor (TKI), alone or with local treatment in metastatic renal cell carcinoma. 37% patients achieve CR with TKI alone, while 63% with additional loco-regional treatments. 49% patients recurred after CR, with a median Disease free survival of 28.2 months. Patients treated with multimodal approaches present lower rate of recurrence (40% vs 61%) and longer Disease free survival compared to patient treated with TKI alone (16.5 vs 41.9 months, p=0.039). Furthermore the rate of recurrence was higher in patients with brain (88%), pancreatic (71%) and bone metastasis (50%). Patients who continued TKI therapy after complete response had a longer disease free survival than patients who stopped therapy, although the difference was not significant (42.1 vs 25.1 months, p=0.254). 2y-cDFS was better in patients treated with multimodal treatment and who continued TKIs than the other patient arms. The prognostic value of CR depends on the site where was obtained and how was obtained (with or without locoregional treatment). Cessation of TKI should be carefully considered in complete responder patients.

Ophthalmology



Head S. Bonini

Description

Main research activities

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.

Most important publications

Annibali O., Sabatino F., Mantelli F., Olimpieri O.M., Bonini S., Avvisati G.

Mucosa-associated lymphoid tissue (MALT)-type lymphoma of ocular adnexa. Biology and treatment.

Crit Rev Oncol Hematol. 2016 Apr;100:37-45. PubMed PMID: 26857986. IF 5,039

Over the last decades, we have witnessed an increase in the incidence of primary ocular adnexa lymphomas (POALs) probably because advances in imaging techniques have enabled precise biopsies of the tumors. The ocular tissue biopsy, before the initiation of the appropriate treatment, is mandatory and necessary for a correct diagnosis of POALs by the use of immunophenotyping and a correct molecular classification. Only in a minority of cases the ocular adnexa are secondarily affected by a systemic disease. Among the POALs, the most common is the primary extra nodal lymphoma of MALT-type (POAML). POAML is rarely symptomatic in the early phase of the disease. As a consequence, often we see a delay in ophthalmic consultations and diagnosis. The clinical manifestations are heterogeneous and its management requires a multidisciplinary approach involving ophthalmologists, hematologists and radiotherapists.

Mantelli F., Moretti C., Macchi I., Massaro-Giordano G., Cozzupoli G.M., Lambiase A., Bonini S.

Effects of sex hormones on ocular surface epithelia: lessons learned from polycystic ovary syndrome.

J Cell Physiol. 2016 May;231(5):971-5. PubMed PMID: 26491950. IF 4,155

Polycystic ovary syndrome (PCOS) is the most common endocrine abnormality in women of reproductive age. Although its clinical consequences have been known for a long time to extend beyond the reproductive system, with type-2 diabetes and obesity being the most common, the involvement of the ocular surface in PCOS has been described only more recently. The ocular surface is a morphofunctional unit comprising eyelid margin, tear film, cornea, and conjunctiva. Increasing evidence indicates that these structures are under a sex hormone control and relevant diseases such as ocular allergy and dry eye are often caused by alterations in circulating or local steroid hormones levels. Novel treatments targeting sex hormone receptors on ocular surface epithelial cells are also being developed. In this review we aim to describe the current knowledge on the effects of sex hormones at the ocular surface, with a special focus on the effects of androgen.

Micera A., Balzamino B.O., Di Zazzo A., Biamonte F., Sica G., Bonini S.

Toll-like receptors and tissue remodeling: the pro/cons recent findings. *J Cell Physiol. 2016 Mar;231(3):531-44. PubMed PMID: 26248215. IF 4,155*

The Toll-like Receptor (TLR) family ensures prompt response towards pathogens, protecting the host against infections, and guarantees a realistic balance between protective and detrimental activities. Multiple regulating mechanisms characterize TLR activity that is not limited to innate and adaptive antimicrobial immune responses, as observed in the inflammatory (either infective, allergic, or autoimmune) responses associated with tissue remodeling. Following the insult and the arise of inflammatory response, tissue remodeling takes place and might develop in fibrosis, depending on microenvironment as a result of imbalanced fibroblasts (FBs) and myofibroblasts (myoFBs) activation/survival. The process is driven by an epithelial-fibroblast-immune cell cross-talk. While the main FB function is the matrix metabolism for tissue homeostasis or repair, the myoFB differentiation represents a crucial step in attempting repair of injury. FBs/myoFBs provide more than structural support at site of injury, synthesizing and/or reacting to different cytokines, growth factors, neuromediators and soluble/lipid mediators. TLR-bearing FBs/myoFBs might contribute at the innate immune level, providing a second line of protection/defense as well as being a target/effector cell of tissue remodeling. TLRs might also interfere with acute inflammation as well as with established fibrosis, triggering structural/functional changes in agreement with the genetic background, the site of lesion, the entity of associated infection, the poor blood circulation or the pharmacological treatments, all together strictly influencing tissue repair/remodeling process. This review will focus on the recent findings on TLRs at launch and long-lasting tissue remodeling process, that strongly suggest TLRs as optional targets for future therapies.

Orthopaedic and Trauma Surgery

Head R. Papalia



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

Other Personnel E. Albo, C. Amato, A. Berton, F. Buschini, F. Cancilleri, V. Candela, M. Ciuffreda, V. Denaro, G. De Angelis, L. Diaz, G. Di Giacomo, A. Di Martino, A. Guarnieri, A. Lamberti, A. La Notte, F. Lotti, G. Marineo, M. Paciotti, A. Palumbo, N. Papapietro, S. Petrillo, G. Rizzello, F. Russo, G. Salvatore, F. Spiezia, A. Tecame, G. Vadalà, S. Vasta, B. Zampogna

Description

Main research activities

Main collaborations

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 Orthopeadic where basic and preclinical researches are performed. Two full time biologist with cell and molecular biology expertise as well as histology work in the laboratory. Preclinical studies have been carried out for several years at the Animal Facility of Tor Vergata University of Rome and in collaboration with the Veterinary Hospital at University of Padua.

- 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;
- Finite element analysis of the metastatic spine to evaluate the risk of fracture and the role of preventive vertebroplasty;
- Translational computational analysis to optimize surgical treatment for patellar instability;
- Development of a computer model to study shoulder instability;
- Management of early osteoarthritis of the knee with new hydrogel hyaluronan-based formulations;
- Conservative treatment of meniscal lesions with intraarticular injections of hyaluronic acid.

- AO Research Institute, Davos, Switzerland;
- Bambino Gesù Italian Pediatric Research Hospital, Italy;
- Beth Israel Deaconess Medical Center, Center for Advanced Orthopedic Studies, Harvard Medical School teaching hospital, USA;
- Centre for Sports and Exercise Medicine, Mile End Hospital, UK;
- Clinica Città Di Parma, Italy;
- Clínica do Dragão Espregueira-Mendes Sports Centre, Portugal;
- Department of Neurosurgery, Uni-
- versity of Padova, Italy; • Division of Sports Medicine Duke,
- Duke University, Sports Medicine Centre, USA
- Humanitas Research Hospital, Italy;
 Orthopaedic Biomechanics Laboratory, Mayo Clinic Rochester, USA;
- Sports Medicine and Shoulder Service, Departement Of Motion Analysis
- Hospital for Special Surgery, USA;
 University of Pittsburgh Medical Center (UPMC), USA.

Most important publications

Papalia R., Diaz Balzani L., Torre G., Tirindelli M.C., Nobile C., Maffulli N., Denaro V.

Intraoperative application Platelet rich fibrin, postoperative injections OF PRP or microfracture only for osteochondral lesions of the knee: a five-year retrospective evaluation.

J Biol Regul Homeost Agents. 2016 Oct-Dec;30(4 Suppl 1):41-49. PubMed PMID: 28002899. IF 1,546

Cartilage lesions are the most common cause of chronic knee pain. Micro-fracturing is reliable, effective, easy to perform and inexpensive. We propose a novel approach to cartilage lesions where microfractures are performed contextually to intra-operative or post-operative administration of platelet concentrates. We retrospectively evaluate 48 patients divided in 3 groups. Group 1: 15 patients underwent microfractures and intraoperative administration of PRF (PRF group); group 2: 16 microfractures and postoperative injections of PRP (PRP group); group 3: 17 patients with isolated microfractures (Microfractures group). Clinical scores (IKDC, VAS pain) were administered at 2 and 5 years postoperative and MRI was performed to evaluate the lesions of patients according to the MOCART criteria (2006). Patients treated with platelet concentrates achieved better clinical results compared to patients treated with microfracture only. The PRF group showed better results than the PRP group at 2 years, with loss of significance at 5 years. At MOCART score, PRF group obtained better results earlier than the other two groups.

Vadalà G., Di Martino A., Russo F., Tirindelli M.C., De Felice L., Agostini F., Papalia R., Denaro V.

Autologous bone marrow concentrate combined with platelet-rich plasma enhance bone allograft potential to induce spinal fusion.

J Biol Regul Homeost Agents. 2016 Oct-Dec;30(4 Suppl 1):165-172. PubMed PMID: 28002915. IF 1,546

Bone marrow cells concentrate (BMCs) is a source of osteoprogenitor cells and platelet-rich plasma (PRP) is a source of growth factors. The objective of the study was to determine whether BMC and PRP could increase the potential of bone allograft to induce posterolateral-lumbar spinal fusion compared to the bone allograft alone. A prospective nonrandomized radiographic study has been conduced on 10 patients with posterolateral instrumented fusion for degenerative lumbar disease with 1-year follow-up using CT scan. A fresh frozen bone allograft alone and bone allograft with a mixture of autologous BMC and PRP blended with thrombin were apposed in the right and left posterolateral side, respectively. CT showed good right fusion masses (allograft alone) in 4 patients and poor in 6; good left masses (BMC and PRP plus allograft) in 9 patients and poor in 1. The differences detected between right-side and left-side masses show an advantage in adding BMC and PRP to the bone allograft to increase spinal fusion rate.

Longo U.G., Berton A., Denaro L., Salvatore G., Denaro V.

Development of the Italian version of the modified Japanese orthopaedic association score (mJOA-IT): cross-cultural adaptation, reliability, validity and responsiveness.

Eur Spine J. 2016 Sep;25(9):2952-7. PubMed PMID: 26961972. IF 2,132

The modified Japanese orthopaedic association scale (mJOA) is considered one of the most appropriate outcome measures for the assessment of cervical spondylotic myelopathy (CSM). The mJOA-IT was developed following a forward-backward translation procedure. Psychometric properties were assessed. The mJOA-IT proved to be a reliable outcome measure for CSM. It was associated with the Nurick scale while it was not associated with NDI, SF-36 and SF-36 components. The mJOA-IT was also responsive (d = 0.867). This form is recommended to be used for clinical and research purposes in Italy, to promote the global standardisation of assessment tools and to compare studies on CSM worldwide.

Otolaryngology



Head F. Salvinelli

Faculty M. Casale

Other Personnel V. Frari

Description

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

Main research activities

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

the end of our study selection process, 25 relevant publications were included, three of them regarding gingivitis, 13 of them relating to chronic periodontitis, seven of them relating to dental surgery, including implant and sinus lift procedures, and the remaining three articles describing oral ulcers. Not only does topical administration of HA play a pivotal key role in the postoperative care of patients undergoing dental procedures, but positive results were also generally observed in all patients with chronic inflammatory gingival and periodontal disease and in patients with oral ulcers.

Casale M., Vella P., Moffa A., Oliveto G., Sabatino L., Grimaldi V., Ferrara P., Salvinelli F.

Hyaluronic acid and upper airway inflammation in pediatric population: a systematic review. *Int J Pediatr Otorhinolaryngol. 2016 Jun;85:22-6. PubMed PMID: 27240491. IF 1,125*

Background: Inflammatory disease of upper airway in pediatric population represents a social problem for both the pharmaco-economic impact and a burden for the family. To date, the use of topical therapies represents a significant therapeutic progress because they are able to reduce mucosal inflammation and improve tissue healing. Topical Hyaluronic Acid (HA) is a promising molecule that has been recently proposed as adjuvant treatment in the inflammatory disease of the upper aerodigestive tract (UADT) infections. **Aims:** The aim of our work was to review the published literature regarding all the potential therapeutic effects of HA in the inflammatory disease of upper airway in pediatric population and evaluate the effectiveness of HA, alone or in combination, in children affected by cystic fibrosis.

Methods: Relevant published studies about use of HA in UADT in pediatrics were searched in Pubmed, Google Scholar, Ovid using various keywords with no limit for the year of publication. Studies based on the use of HA with nasal packing and with invasive administration of HA were excluded.

Results: At the end of our selection process, four publications have been included: one of them in children with recurrent upper respiratory tract infections, one of them in children with bacterial acute rhinopharyngitis, two of them in children affected by cystic fibrosis. **Conclusions:** Topical administration of HA plays a pivotal role in all the children suffering from UADT inflammatory disease, and positive results are generally observed in children with cystic fibrosis.

Casale M., Sabatino L., Moffa A., Capuano F., Luccarelli V., Vitali M., Ribolsi M., Cicala M., Salvinelli F.

Breathing training on lower esophageal sphincter as a complementary treatment of gastroesophageal reflux disease (GERD): a systematic review.

Eur Rev Med Pharmacol Sci. 2016 Nov;20(21):4547-4552. PubMed PMID: 27874942. IF 1,575

Objective: Gastroesophageal reflux disease (GERD) represents one of the most common gastrointestinal disorders, but is still a challenge to cure. Proton pump inhibitors (PPIs) are currently the GERD's standard treatment, although not successful in all patients; some concerns have been raised regarding their long term consumption. Recently, some studies showed the benefits of inspiratory muscle training in increasing the lower esophageal sphincter pressure in patients affected by GERD, thereby reducing their symptoms. **Materials and methods:** Relevant published studies were searched in Pubmed, Google Scholar, Ovid or Medical Subject Headings using the following keywords: "GERD" and physiotherapy", "GERD" and "exercise", "GERD" and "breathing", "GERD and "training".

Results: At the end of our selection process, four publications have been included for systematic review. All of them were prospective controlled studies, mainly based on the training of the diaphragm muscle. GERD symptoms, pH-manometry values and PPIs usage were assessed.

Conclusions: Among the non-surgical, non-pharmacological treatment modalities, the breathing training on diaphragm could play an important role in selected patients to manage the symptoms of GERD.

Most important publications

Casale M., Moffa A., Vella P., Sabatino L., Capuano F., Salvinelli B., Lopez M.A., Carinci F., Salvinelli F.

Hyaluronic acid: perspectives in dentistry. A systematic review.

Int J Immunopathol Pharmacol. 2016 Dec;29(4):572-582. PubMed PMID:27280412. IF 1,470

To date, topical therapies guarantee a better delivery of high concentrations of pharmacologic agents to the soft periodontal tissue, gingiva, and periodontal ligament as well as to the hard tissue such as alveolar bone and cementum. Topical hyaluronic acid (HA) has recently been recognized as an adjuvant treatment for chronic inflammatory disease in addition to its use to improve healing after dental procedures. The aim of our work was to systematically review the published literature about potential effects of HA as an adjuvant treatment for chronic inflammatory disease, in addition to its use to improve healing after common dental procedures. Relevant published studies were found in PubMed, Google Scholar, and Ovid using a combined keyword search or medical subject headings. At

Research Units: overview and main 2016 scientific outputs

Pathology



Head A. Onetti Muda

Faculty G. Perrone, C. Rabitti Other Personnel M. Amato, G. Deda, M. Donati, G. Nicolò, S. Ferrari

Main research activities

Research topics:

Description

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

- ded by
- 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 mutodiagnostic tool for cancer;
- Morphologic bone changes related to metabolic diseases.
- Funded projects: • Clinical trial PAM50 PROSIGNA-
- Principal Investigator: Perrone; Fun-

- ded 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.

Main collaborations

- Medical Oncology Department, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain;
- Bambino Gesù Hospital, Pathologic Anatomy, IRCCS - Rome, Italy.

been fully clarified. We aimed to evaluate the HER2 status concordance between primary gastric cancer and corresponding distant metastasis. HER2 status was evaluated by IHC (immunohistochemistry) and/or FISH (fluorescence in situ hybridization) in 41 patients in primary gastric cancer and in paired metastasis. HER2 was assessed according scoring criteria applied in clinical approach. HER2 positivity was found in 14,6 % primary tumors and in 24,4% corresponding metastasis. HER2 concordance rate between primary and metastasis was 80,5 % (K-value = 0,388). Eight/41 (19,5 %) cases resulted discordant: 6 patients with metastatic HER2 positive lesions were found HER2 negative in primary cancers while 2 patient HER2 positive in primary lesion showed a negative conversion in metastasis. Our results showed a good concordance in terms of HER2 status between primary and metastatic lesions, as well as in biopsy and surgical removed specimens. However, the higher rate of HER2 positive status found in metastatic lesions underlined the importance of HER2 assessment in all samples obtained from different sites of gastric cancer disease.

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

Microscopic residual tumor after pancreaticoduodenectomy: is standardization of pathological examination worthwhile?

Pancreas. 2016 May-Jun;45(5):748-54. PubMed PMID: 26495787. IF 2,738

Objectives: R1 resection rate after pancreaticoduodenectomy (PD) for cancer is highly variable. The aim of this study was to verify if a standardized histopathological work-up of the specimen affects the rate of R1 resection after PD for cancer.

Methods: Two groups of specimens were managed with (standardized method [SM] group) or without (non-standardized method [NSM] group) a SM of histopathological work-up. Each group included 50 cases of PD for periampullary cancer. Differences in terms of R1 resection rate between the 2 groups were evaluated. Correlation between R1 status and local recurrence was also evaluated. **Results:** The cohort of 100 patients consisted of 66 pancreatic ductal adenocarcinoma, 15 cholangiocarcinoma, and 19 ampullary cancer. The R1 resection rate resulted statistically higher in the SM group (66% vs 10%). Local recurrence was more frequently related to R1 resection in the SM group (34.3% of cases) than in NSM group (20% of cases).

Conclusions: The use of the SM of pathological evaluation of the specimen after PD for cancer determines a significant increase of R1 resection. This remarkable difference seems to be due to the different definition of minimum clearance. The SM seems to better discriminate patients in terms of risk of local recurrence.

Rau J.V., Graziani V., Fosca M., Taffon C., Rocchia M., Crucitti P., Pozzilli P., Onetti Muda A., Caricato M., Crescenzi A.

RAMAN spectroscopy imaging improves the diagnosis of papillary thyroid carcinoma. *Sci Rep. 2016 Oct* 11:6:35117. *PubMed PMID:* 27725756. *IF* 5.228

GCI Rep. 2016 Oct 11;6:35117. PubMed PMID: 27725756. IF 5,228

Recent investigations strongly suggest that Raman spectroscopy (RS) can be used as a clinical tool in cancer diagnosis to improve diagnostic accuracy. In this study, we evaluated the efficiency of Raman imaging microscopy to discriminate between healthy and neoplastic thyroid tissue, by analyzing main variants of Papillary Thyroid Carcinoma (PTC), the most common type of thyroid cancer. We performed Raman imaging of large tissue areas (from $100 \times 100 \,\mu\text{m2}$ up to $1 \times 1 \,\text{m2}$), collecting 38 maps containing about 9000 Raman spectra. Multivariate statistical methods, including Linear Discriminant Analysis (LDA), were applied to translate Raman spectra differences between healthy and PTC tissues into diagnostically useful information for a reliable tissue classification. Our study is the first demonstration of specific biochemical features of the PTC profile, characterized by significant presence of carotenoids with respect to the healthy tissue. Moreover, this is the first evidence of Raman spectra differentiation between classical and follicular variant of PTC, discriminated by LDA with high efficiency. The combined histological and Raman microscopy analyses allow clear-cut integration of morphological and biochemical observations, with dramatic improvement of efficiency and reliability in the differential diagnosis of neoplastic thyroid nodules, paving the way to integrative findings for tumorigenesis and novel therapeutic strategies.

Most important publications

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

HER2 status in gastric cancer: comparison between primary and distant metastatic disease. Pathol Oncol Res. 2016 DOI: 10.1007/s12253-016-0082-5. Epub 2016 Jun 30. 27363700. IF 1,940

HER2 (human epidermal growth factor receptor-2) assessment in histological samples of gastric cancer is essential to determine which patients might benefit from trastuzumab therapy. HER2 is often evaluated in primary tumor even if trastuzumab therapy is used to treat metastatic disease. However, the exact relationship in terms of HER2 status between primary and metastatic tumors has not

Physical and Rehabilitation Medicine



Head S. Sterzi

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

Description

Main research activities

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

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

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

- Bambino Gesù Italian Pediatric Research Hospital, Italy;
- Burke Hospital, USA;

Main collaborations

- INAIL Prosthesis Center, Italy;
- San Raffaele Foundation IRC-CS, Italy;
- Santa Lucia Foundation IRCCS, Italy;
- Thoracic Surgery Unit of the University Hospital A. Gemelli.
 - Italy.

Most important publications

Morrone M., Miccinilli S., Bravi M., Paolucci T., Melgari J.M., Salomone G., Picelli A., Spadini E., Ranavolo A., Saraceni V.M., DI Lazzaro V., Sterzi S.

Perceptive rehabilitation and trunk posture alignment in patients with Parkinson disease: a single blind randomized controlled trial.

Eur J Phys Rehabil Med. 2016 Dec;52(6):799-809. PubMed PMID: 27171537. IF 2,063

AIM: To evaluate whether a perceptive rehabilitation treatment could be more effective than a conventional physical therapy program in improving postural control and gait pattern in patients with Parkinson Disease. **DESIGN:** Single blind, randomized controlled trial. **POPULATION:** Twenty outpatients affected by idiopathic Parkinson Disease. **METHODS:** Recruited patients were divided into two groups: the first one underwent individual treatment with Surfaces for Perceptive Rehabilitation (Su-Per) and the second one received conventional group physical therapy treatment. **RESULTS:** No significant differences were found for gait parameters (cadence, gait speed and stride length) within Su-Per group and between groups. **CONCLUSIONS:** Perceptive training may help patients affected by Parkinson Disease into restoring a correct midline perception and to improve postural control.

Sterzi S., Giordani L., Morrone M., Lena E., Magrone G., Scarpini C., Milighetti S., Pellicciari L., Bravi M., Panni I., Ljoka C., Bressi F., Foti C.

The efficacy and safety of a combination of glucosamine hydrochloride, chondroitin sulfate and bio-curcumin with exercise in the treatment of knee osteoarthritis: a randomized, double-blind, placebo-controlled study.

Eur J Phys Rehabil Med. 2016 Jun;52(3):321-30. PubMed PMID: 26937646. IF 2,063

AIM: to assess efficacy and safety of CartiJoint Forte combined with physical therapy in treating subjects with knee OA. **DESIGN:** A multicenter, prospective, randomized, double blind, placebo-controlled clinical trial. **POPULATION:** Fifty-three patients were randomly assigned to an experimental group (N=26) or a control group (N=27). **METHODS:** The two groups both received 20 sessions of physical therapy during the course of the trial. Primary outcome was pain intensity, measured using the Visual Analogue Scale (VAS). **RE-SULTS:** VAS at rest was found to be reduced between T0 and T1, as well as between T0 and T2. VAS at motion revealed a significant "group × time-check" interaction, with increasing effect of time on VAS reduction in the experimental group at 8 weeks. **CONCLU-SION:** CartiJoint Forte, added to physical therapy, may ameliorate pain and help to improve algofunctional score in knee OA patients.

Miccinilli S., Morrone M., Bastianini F., Molinari M., Scivoletto G., Silvestri S., Ranieri F., Sterzi S.

Optoelectronic plethysmography to evaluate the effect of posture on breathing kinematics in spinal cord injury: a cross sectional study.

Eur J Phys Rehabil Med. 2016 Feb;52(1):36-47. PubMed PMID: 25900344. IF 2,063

AIM: To evaluate the effect of posture (sitting and supine) on respiratory kinematics in chronic spinal cord injured patients using optoelectronic plethysmography. **DESIGN:** Cross-sectional study. **POPULATION:** Twenty chronic spinal cord injured patients and twenty healthy subjects matched for gender, age and smoking habits. **METHODS:** All subjects underwent optoelectronic evaluation. Compartmental volumes and respiratory functional parameters were analyzed by means of analysis of variance. Post-hoc comparisons by means of t-tests were performed to analyze differences within and between study groups. **RESULTS:** Supine position increases vital capacity and forced expiratory volume in the first second. **CONCLUSION:** Optoelectronic plethysmography measurements showed that even if in supine position there is an improvement in respiratory functional parameters, the respiratory kinematics of the chest wall is disadvantaged.

Research Units: overview and main 2016 scientific outputs

Plastic Surgery and Dermatology



Head P. Persichetti

Faculty C. Dianzani, G.F. Marangi, S. Tenna

Other Personnel A. Aveta, B. Brunetti, B. Cagli, A. Cogliandro, V. Panasiti, S. Santoro, P. Simone, V. Toto

Description

Fields of interests and research:

- · Reconstructive surgery following neoplasms, malformations or trauma of:
- head and neck upper and lower limb
- thorax
- abdomen berineum
- 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 mammaplasty)

Most important publications

- Abdomen (abdominoplasty, lipo-
- Upper and lower limb (thigh lift, brachioplasty, liposuction)
- Filler Botulinum toxin

suction)

- · Application of regenerative medici-
- ne in skin reniuvenation · Application of regenerative medicine in the treatment of acne scars
- Lasers treatment of: Hemangiomas
- Scars
- Cutaneous lesions
- Photoaging
- Hypertrichosis

Main research activities

- · Application of regenerative medicine in treatment of atrophic acne scars: nanofat plus PRP infiltration and fractional CO2 laser resurfacing
- The use of PRP in breast implant capsule contracture.
- · Treatment of venous ulcers with different combinations of fat graft and platelet rich plasma: a prospective comparative evaluation

- Quality of life in patients affected by breast cancer treated with reconstructive procedures: application of the BREAST-Q questionnaire
- Evaluation of the postero-medial scar brachioplasty technique associated to lipo-aspiration in the post-bariatric arm remodeling.
- · Platelet-rich plasma in breast implant capsule contracture.
- IPL in the treatment of posterior blepharitis.
- The use of regenerative devices in chronic wounds: a prospective randomized control trial
- · Bioelectrochemical sensor to detect antibiotic-resistant Pseudomonas Aeruginosa
- · Evaluation of the periprosthetic breast capsule in patients subjected to breast reconstruction with tissue expanders with different surfaces.

Main collaborations

- · Department of Plastic and Reconstructive Surgery, Kansai Medical University, Japan;
- Singapore Centre for Environmental Life Sciences Engineering, Nanyang Technological University, Singapore,

Segreto F., Carotti S., Tosi D., Pendolino A.L., Marangi G.F., Morini S., Persichetti P.

Toll-like receptor 4 expression in human breast implant capsules; localization and correlation with estrogen receptors.

Plast Reconstr Surg. 2016 Mar; 137(3):792-8. PubMed PMID: 26910659. IF 3,087

Background: Capsular contracture is the most common complication following breast augmentation and reconstruction. Myofibroblasts, which are specialized fibroblasts with contractile activity, are involved in its pathogenesis. Toll-like receptor 4 stimulation in fibroblasts induces transcription of genes involved in extracellular matrix remodeling and tissue repair; furthermore, it enhances sensitivity to transforming growth factor- β 1 and promotes transition to myofibroblasts. 17 β -Estradiol, by binding to its main receptors, α and/or B, increases the expression of toll-like receptor 4 and the production of proinflammatory mediators by macrophages; moreover,

it promotes extracellular matrix production and myofibroblasts contraction and differentiation. The aim of the study was to investigate the expression of toll-like receptor 4 in breast implant capsules and its relationship with estrogen receptors. Methods: The study enrolled 30 women who underwent expander removal following breast reconstruction. Specimens were stained with hematoxylin and eosin, Masson trichrome, immunohistochemistry, and immunofluorescence for toll-like receptor 4, a-smooth muscle actin (a marker of myofibroblasts), estrogen receptor-a, and estrogen receptor-B. Results: Toll-like receptor 4 was expressed by fibroblasts and myofibroblasts of capsular tissue. Its expression positively correlated with estrogen receptor- β expression (p = 0.012). A positive correlation was found between estrogen receptor- β and α -smooth muscle actin expression (p = 0.037). **Conclusions:** This study demonstrates the expression of toll-like receptor 4 in myofibroblasts of capsular tissue and its correlation with estrogen receptor-B positivity. Activation of toll-like receptor 4 and estrogen receptor- β , and their interplay, may be involved in myofibroblast differentiation and in the profibrotic pathogenic process underlying capsular contracture.

Brunetti B., Tenna S., Aveta A., Poccia I., Segreto F., Cerbone V., Persichetti P.

Posterior trunk reconstruction with the dorsal intercostal artery perforator based flap: Clinical experience on 20 consecutive oncological cases.

Microsurgery. 2016 Oct;36(7):546-551. PubMed PMID: 25821103. IF 2,054

Background: Few studies in the recent literature have investigated the reliability of dorsal intercostal artery perforator (DICAP) flap in posterior trunk reconstruction. The purpose of this report is to describe our clinical experience with the use of DICAP flaps in a cohort of oncological patients. Patients and methods: Twenty patients underwent posterior trunk reconstruction with DICAP based flaps. Patients age ranged from 45 to 76 years. All defects resulted from skin cancer ablation. Defect sizes ranged from 4×4 to 6×8 cm. The flaps were mobilized in V-Y or propeller fashion. The flaps were islanded on 1 (12 cases), 2 (6 cases), or 3 (2 cases) perforators. Donor sites were always closed primarily.

Results: Eleven V-Y advancement flaps were performed; one of these was converted to a perforator-plus peninsular flap design. which retained an additional source of blood supply from the opposite skin bridge. Nine flaps were mobilized in propeller fashion. Flap dimensions ranged from 4×6 to 6×14 cm. Mean operative time was 70 min. One V-Y flap complicated with marginal necrosis that healed with no need for reintervention. All the other flaps survived uneventfully. No other complications were observed at recipient and donor sites. Follow-up ranged from 3 months to 2 years. All the patients were satisfied with the surgical outcome. Conclusions: DICAP based flaps proved to be a reliable option to resurface posterior trunk defects following oncological resection, allowing to achieve like-with-like reconstruction with excellent contour and minimal donor-site morbidity.

Cogliandro A., Persichetti P., Ghilardi G., Moss T.P., Barone M., Piccinocchi G., Ricci G., Vitali M., Giuliani A., Tambone V.

How to assess appearance distress and motivation in plastic surgery candidates: Italian validation of Derriford Appearance Scale 59 (DAS 59).

Eur Rev Med Pharmacol Sci. 2016 Sep;20(18):3732-3737. PubMed PMID: 27735048. IF 1,575

Objective: The Derriford Appearance Scale (DAS) 59 was specifically designed to measure psychosocial adjustment in patients with appearance problems. Previous studies using the DAS59 have proven it to be a reliable method of assessing the appearance-related quality of life after plastic surgery procedures. The aim of this study was to develop a valid and reliable Italian version of the DAS59. Patients and Methods: The first Italian translation of this guestionnaire was conducted according to the DAS59 protocol that was designed by the original authors of the questionnaire. Eight hundred patients participated in this study and filled out three questionnaires (DAS59, General Health Questionnaire (GHQ)12 and Beck's Depression Inventory (BDI)-II). There were 400 adult patients with a history of previous plastic surgeries and 400 adult patients without any personal history of previous plastic surgery procedures. A total of 50 patients were selected randomly for test-retest analysis.

Results: The overall internal consistency was excellent ($\alpha = 0.95$) and equal to that of the original article that first described the scale. There was a good correlation between all the items. Domains demonstrated good internal consistency (Cronbach's alpha) and correlation within themselves. The construct validity of the Italian DAS59 was assessed under convergent validity that confirmed the correlation with scales related to other psychological conditions. GHQ12 showed relevant correlation with DAS59, while BDI-II did not. Conclusions: A valid and reliable Italian DAS59 version was developed that can be used for research and clinical assessment of patients with appearance problems and concerns, especially before and after plastic surgery procedures.

Research Units: overview and main 2016 scientific outputs

Process Engineering



Head M. De Falco

Faculty M. Capocelli

Other Personnel D. Barba, A. Germanà, N. Greco, G. Iaquaniello, R. Pizzi

Description

Main research activities

- 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.

Main collaborations

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

Most important publications

De Falco M., Capocelli M., Centi G.

Dimethyl ether production from CO2 rich feedstocks in a one-step process: Thermodynamic evaluation and reactor simulation.

Chemical Engineering J. 2016;294:400-409. DOI: 10.1016/j.cej.2016.03.009. IF 5,310

The dimethyl ether (DME) direct production from CO2-rich feedstock has been evaluated from thermodynamic and fixed bed reactor simulation perspectives, in order to evaluate the potentialities of using CO2 as reagent in one-step DME synthesis. The thermody-

namic model has been applied to perform a detailed sensitive analysis of DME synthesis process at temperature within the range 200-275 °C, pressures of 20-70 bar and inlet composition of H2/C0 = 1-3 and C02/C0 = 0-2.5. The results show a stringent thermodynamics threshold in DME yield (DME yield < 30%), when the C02/C0 ratio is greater than 2 in the fed to the synthesis reactor. The results have been confirmed by the kinetic mathematical model and reactor simulation, which includes chemical reactions, heat transfer and pressure drop along the fixed bed reactor. The performed simulations point out the role of cooling fluid temperature and reactor pressure. Furthermore, the kinetic modeling, in agreement with the thermodynamic approach, evidences the negative effect of water formed during C02 conversion and further steps. The proposed thermodynamic and kinetic insight states that water removal during C02 conversion, for example by hydrophilic membrane, is a mandatory element to enable industrial production of DME in the framework of C02 valorization.

Prisciandaro M., Capocelli M., Piemonte V., Barba D.

Process analysis applied to water reuse for a "closed water cycle" approach. *Chemical Engineering J. 2016;304:602-608. DOI: 10.1016/j.cej.2016.06.134. IF 5,310*

The reuse of wastewater is a key factor in a closed water cycle approach, in which wastewater is treated and then reused. This approach is both mandatory for the development of dry areas and necessary for the sustainability of industrialized countries in terms of environmental impacts and resource preservation. Although there are some virtuous examples of water reuse projects in the world, there is still much to be done, especially in terms of incentives and economic viability. Aim of the present paper is to give thermodynamic and engineering elements in order to develop an economic incentive to promote wastewater reuse and to adopt the closed water cycle approach. At this scope a techno-economic analysis of the civil wastewater depuration and reverse osmosis treatment of the secondary effluent is presented, by using the typical approach of the chemical engineering. The cost of the treated water in relation to the fundamental parameters of the plant is calculated together with an "energy based" incentive, evaluated through the efficiency of the state-of-the-art desalination process. This last can make a reuse project economically feasible on the basis of rigorous thermo-dynamic considerations. These latter give a universal character to the incentive calculation and also reward the process optimization towards the goal of lowering the carbon emissions. The validity of the proposed method is evaluated through the analysis of three wastewater treatment and reuse projects at different scale. The results show how it is possible to obtain a positive Earnings Before Interests and Taxes (EBIT) for plant productivity above the 200 m3/day, by including the proposed incentive in the Business Plan of the integrated plant of Water Treatment and Reuse.

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

Performance analysis of an innovative PCM-based device for cold storage in the civil air conditioning. Energy and Buildings 2016;122:1-10. DOI: 10.1016/j.enbuild.2016.04.016. IF 2,973

An innovative solution to store cold energy for civil application based on phase change materials (PCM) is presented and evaluated. The storage tank is thought to be installed in a traditional chiller-fan coil system to shave the electricity peak loads required by the users, thus allowing a better management of the electricity grids (by avoiding the summer peaks for air conditioning) and a significant energy saving thanks to the improvement of the chiller Coefficient of Performance (COP).

A 5 kWh prototype has been tested to prove the technological feasibility and has been simulated by a physical-mathematical model based on the energy balance and heat exchanging equations. The model, once validated against experimental data, has been implemented to assess the technology behavior changing operating parameters as the filling ratio, the initial temperature of the PCM and the charging power.

The optimization of the heat exchanging configuration can lead to a minimum loading time of 54 min for the 5 kWh storage tank (charging power of 5.7 kW). Globally, the mathematical simulations confirmed the capability of the system to operate at high charging/ discharging power, thus making it optimal for the integration in a chiller-fan coil system with the "peak shaving" logic.

Radiation Oncology



Head S. Ramella

Faculty R.M. D'Angelillo

Other Personnel A. Carnevale, A. Di Donato, M. Fiore, B. Floreno, C. Greco, E. Ippolito, A. Iurato, P. Matteucci, E. Molfese, C.G. Rinaldi, S. Silipigni, L. Trodella, L.E. Trodella

Most important publications

Meert A.P., Noël J.L., Gamarra F.; Thoracic Oncology HERMES Task Force [Ramella S.]

The thoracic oncology specialist: curriculum recommendations in thoracic oncology training. *Eur Respir J. 2016 Sep;48(3):628-31. PubMed PMID: 27581409. IF 8,332*

The HERMES (Harmonising Education in Respiratory Medicine for European Specialists) project is funded by the European Respiratory Society and has the declared aims of harmonising education in thoracic medicine, recognising diplomas and certificates of qualification, and improving mobility for medical specialists across the EU. This takes into account Directive 2013/55/EU of the European Parliament and of the Council. HERMES is working towards the development of harmonised and structured programmes for education across respiratory specialities to ensure that the best care is delivered for those suffering from respiratory diseases.

Description

Main research activities

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

The main results in lung cancer have been obtained by a multi institutional and international experience on predictive mortality for locally advanced disease. The international collaboration resulted also in the development of the European curriculum recommendations for training in thoracic oncology, a multidisciplinary project involving radiation oncology, medical oncology, pneumology and thoracic surgery. The main project on the same topic was the adaptive approach during chemoradiation.

In prostate cancer, a national project on the adjuvant role of radiation therapy has been conducted. New research protocols have started on the castration resistant patients and in intermediate risk patients. A new project to investigate the cardiotoxicity in hormonal patients has been proposed by our group in a CNR observational study closed in 2016.

Multidisplinary treatment protocols in gastrointestinal cancer are ongoing, exploring the intensification of the integrated approach in pancreatic patients and the reduced toxicity in rectal cancer. Scorsetti M., Leo F., Trama A., D'Angelillo R., Serpico D., Macerelli M., Zucali P., Gatta G., Garassino M.C.

Thymoma and thymic carcinomas.

Crit Rev Oncol Hematol.2016 Mar;99:332-50. PubMed PMID: 26818050. IF 5,039

Thymomas and thymic carcinomas are rare tumours of the mediastinum.

Histological classification is based on rate of non-malignant-appearing thymic epithelial cells and proportions of lymphocytes, while staging system concerns localisation of the involved areas. Surgery is the mainstay of treatment with a 10-year survival of 80%, 78%, 75%, and 42% for stages I, II, III and IV. Radiotherapy has a role in selected cases and platinum-based chemotherapy remains the standard of care for patients with advanced disease. A multimodality approach would be advisable when surgery is not recommended. Since molecular aberrations are poorly understood and targeted therapies are yet being studied. In this review, we describe key aspects of clinical management.

Arcangeli S, Ramella S, De Bari B, Franco P, Alongi F, D'Angelillo RM.

A cast of shadow on adjuvant radiotherapy for prostate cancer: A critical review based on a methodological perspective.

Crit Rev Oncol Hematol. 2016 Jan;97:322-7 PubMed PMID: 26455883. IF 5,039

This is a critical review focusing on the applicability in clinical daily practice of data from three randomized controlled trials (RCTs): SWOG 8794, EORTC 22911, and ARO/AUO 96-02.

An analytical framework, based on the identified population, interventions, comparators, and outcomes (PICO) was used to refine the search of the evidence from the three large randomized trials regarding the use of radiation therapy after prostatectomy as adjuvant therapy (ART).

ART has a high level of evidence due to three RCTs with at least 10-year follow-up recording a benefit in biochemical PFS, but its penetrance in present daily clinics should be reconsidered. While the benefit of ART or SRT is eagerly expected from ongoing randomized trials, a dynamic risk-stratified approach should drive the decisions making process.

Research Units: overview and main 2016 scientific outputs

Tissue Engineering & Chemistry for Engineering



Head M. Trombetta

Faculty F. Basoli, A. Rainer

Other Personnel F. Abbruzzese, M. Costantini, S.M. Giannitelli, M. Gori

es the application of an organ-on-chip

model in the field of predictive safety.

The approach proposed by the present

method represents a significant advan-

ce in the field of in vitro models, as we

foresee to recapitulate, within the 'chip'

footprint, a multicellular gut environment.

This approach re- presents an increased

level of complexity if compared with the

in vitro toxicological models for the in-

testine. Hence, its development should

provide the necessary degree of interplay among different cell populations for a ro-

Prof. Marcella Trombetta is National Co-

ordinator 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 sy-

stem interaction". The project aims to

develop advanced models for the in vitro

study of cellular interactions, taking ad-

vantage from 3D co-culture technologies

within microfluidic devices. In particular,

bust safety testing model.

Description

Main research activities

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

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

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

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

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

Prof. Marcella Trombetta is Scientific Coordinator and Leader of the Operational Activity 4.10 "BACCUS Class: an e-learning platform for training law enforcement officers to combat food crime" of the Europol project coordinated by Carabinieri NAS "ASKLEPIOS-Actions on food Supplements, fake genuine (not) food exhibition, e-LEarning platform, action on Pesticides, operation "In Our Sites" and JAD" funded by EU Commission- Europol for the EMPACT activities under the OAP Counterfeit Goods. Prof. Marcella Trombetta is partner of the project CIPR-Net, Critical Infrastructure Research and Resilience Network Co-funded by EU FP7. CIPRNet establishes a Network of Excellence in Critical Infrastructure Protection

(CIP). CIPRNet performs research and development that addresses a wide range of stakeholders including (multi)national emergency management, critical infrastructure operators, policy makers, and the society. cer-related death globally, requiring an early diagnosis of NAFLD as a potential risk factor. However, the molecular mechanisms underlying NAFLD are still under investigation. So far, many in vitro studies on NAFLD have been hampered by the limitations of 2D culture systems, in which cells rapidly lose tissue-specific functions. The present liver-on-a-chip approach aims at filling the gap between conventional in vitro models, often scarcely predictive of in vivo conditions, and animal models, potentially biased by their xenogeneic nature.

HepG2 cells were cultured into a microfluidically perfused device under free fatty acid (FFA) supplementation, namely palmitic and oleic acid, for 24h and 48h. The device mimicked the endothelial-parenchymal interface of a liver sinusoid, allowing the diffusion of nutrients and removal of waste products similar to the hepatic microvasculature. Assessment of intracellular lipid accumulation, cell viability/cyto-toxicity and oxidative stress due to the FFA overload, was performed by high-content analysis methodologies using fluorescence-based functional probes.

The chip enables gradual and lower intracellular lipid accumulation, higher hepatic cell viability and minimal oxidative stress in microfluidic dynamic vs. 2D static cultures, thus mimicking the chronic condition of steatosis observed in vivo more closely.

Overall, the liver-on-a-chip system provides a suitable culture microenvironment, representing a more reliable model compared to 2D cultures for investigating NAFLD pathogenesis. Hence, our system is amongst the first in vitro models of human NAFLD developed within a microfluidic device in a sinusoid-like fashion, endowing a more permissive tissue-like microenvironment for long-term culture of hepatic cells than conventional 2D static cultures.

Costantini M., Colosi C., Mozetic P., Jaroszewicz J., Tosato A., Rainer A., Trombetta M., Święszkowski W., Dentini M., Barbetta A.

Correlation between porous texture and cell seeding efficiency of gas foaming and microfluidic foaming scaffolds.

Mater Sci Eng C Mater Biol Appl. 2016 May;62:668-77. PubMed PMID: 26952471. IF 3,420

In the design of scaffolds for tissue engineering applications, morphological parameters such as pore size, shape, and interconnectivity, as well as transport properties, should always be tailored in view of their clinical application. In this work, we demonstrate that a regular and ordered porous texture is fundamental to achieve an even cell distribution within the scaffold under perfusion seeding. To prove our hypothesis, two sets of alginate scaffolds were fabricated using two different technological approaches of the same method: gas-in-liquid foam templating. In the first one, foam was obtained by insufflating argon in a solution of alginate and a surfactant under stirring. In the second one, foam was generated inside a flow-focusing microfluidic device under highly controlled and reproducible conditions. As a result, in the former case the derived scaffold (GF) was characterized by polydispersed pores and interconnects, while in the latter (μ FL), the porous structure was highly regular both with respect to the spatial arrangement of pores and interconnects and their monodispersity. Cell seeding within perfusion bioreactors of the two scaffolds revealed that cell population inside μ FL scaffolds was quantitatively higher than in GF. Furthermore, seeding efficiency data for μ FL samples were characterized by a lower standard deviation, indicating higher reproducibility among replicates. Finally, these results were validated by simulation of local flow velocity (CFD) inside the scaffolds proving that μ FL was around one order of magnitude more permeable than GF.

Spadaccio C., Mozetic P., Nappi F., Nenna A., Sutherland F., Trombetta M., Chello M., Rainer A.

Cells and extracellular matrix interplay in cardiac valve disease: because age matters. *Basic Res Cardiol. 2016 Mar;111(2):16. PubMed PMID: 26830603. IF 6,008*

Cardiovascular aging is a physiological process affecting all components of the heart. Despite the interest and experimental effort lavished on aging of cardiac cells, increasing evidence is pointing at the pivotal role of extracellular matrix (ECM) in cardiac aging. Structural and molecular changes in ECM composition during aging are at the root of significant functional modifications at the level of cardiac valve apparatus. Indeed, calcification or myxomatous degeneration of cardiac valves and their functional impairment can all be explained in light of age-related ECM alterations and the reciprocal interplay between altered ECM and cellular elements populating the leaflet, namely valvular interstitial cells and valvular endothelial cells, is additionally affecting valve function with striking reflexes on the clinical scenario. The initial experimental findings on this argument are underlining the need for a more comprehensive understanding on the biological mechanisms underlying ECM aging and remodeling as potentially constituting a pharmacological therapeutic target or a basis to improve existing prosthetic devices and treatment options. Given the lack of systematic knowledge on this topic, this review will focus on the ECM changes that occur during aging and on their clinical translational relevance and implications in the bedside scenario.

Most important publications

Gori M., Simonelli M.C., Giannitelli S.M., Businaro L., Trombetta M., Rainer A.

Investigating nonalcoholic fatty liver disease in a liver-on-a-chip microfluidic device. PLoS One. 2016 Jul 20;11(7):e0159729. PubMed PMID: 27438262. IF 3,057

Nonalcoholic fatty liver disease (NAFLD) is a chronic liver disease worldwide, ranging from simple steatosis to nonalcoholic steatohepatitis, which may progress to cirrhosis, eventually leading to hepatocellular carcinoma (HCC). HCC ranks as the third highest cause of can-

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Urology



Head G. Muto

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

Description

The research unit of urology is mainly focused on clinical research. Minimally invasive surgery, modern source of energy in the treatment of BPH and bladder cancers urinary diversions with sexual function preservation are the main field of interest. 2016 research involved:

Main research activities

- Molecular mechanisms responsible for bone homing and destruction in metastatic prostatic cancer.
- Pros-IT CNR: an observational, prospective, multicenter study providing information on patients' quality of life and its variations over time in relation to the treatments received for the prostate cancer.

for cT1 renal tumors.

- Risk of recurrence and conditional Disease-Free Survival in patients with complete remission during treatment with tirosin kinase inhibitor alone or with local treatment in metastatic renal cell carcinoma.
- An European study demonstrating that that Metabolic syndrome is associated with an increased risk of high-grade and advanced prostate cancer.
- Evaluation of the impact of hospital volume on the use of PN

Most important publications

De Nunzio C., Simone G., Brassetti A., Mastroianni R., Collura D., Muto G., Gallucci M., Tubaro A.

Metabolic syndrome is associated with advanced prostate cancer in patients treated with radical retropubic prostatectomy: results from a multicentre prospective study.

BMC Cancer. 2016 Jul 7;16:407. PubMed PMID: 27386844. IF 3,265

Background: Prostate cancer (PCa) is the most common non-skin cancer in USA and the second leading cause of cancer death in Western Countries. Despite the high mortality associated with PCa, the only established risk factors are age, race and family history. A possible association between metabolic syndrome (MetS) and PCa was firstly described in 2004 and several subsequent studies in biopsy cohorts have shown conflicting results. Aim of our multicentre prospective study was to investigate the association between MetS and PCa in men undergoing radical prostatectomy (RP).

Methods: From January 2012 to June 2015, 349 consecutive men undergoing RP for PCa at three centres in Italy were enrolled into a prospective database. Body Mass Index (BMI) as well as waist circumference was measured before RP. Blood samples were also collected and tested for total PSA, fasting glucose, triglycerides and HDLs. Blood pressure was also recorded. We evaluated the association between MetS, defined according to Adult Treatment Panel III, PCa stage (advanced stage defined as $pT \ge 3$ or N1) and grade (high grade defined as Gleason Score $\ge 4 + 3$) using logistic regression analyses.

Results: Median age and preoperative PSA levels were 66 years (IQR: 61-69) and 7 ng/ml (IQR: 5-10), respectively. Median BMI was 26.12 kg/m(2) (IQR 24-29) with 56 (16 %) obese (BMI \ge 30 kg/m(2)) patients and 87 (25 %) patients with MetS. At pathological evaluation, advanced PCa and high-grade disease were present in 126 (36 %) and 145 (41.5 %) patients, respectively. MetS was significantly associated with advanced PCa (45/87, 51 % vs 81/262, 31 %; p=0.008) and high-grade disease (47/87, 54 % vs 98/262, 37 %; p=0.001). On multivariable analysis, MetS was an independent predictor of pathological stage \ge pT3a or N1 (OR:

2.227; CI: 1.273-3.893; p = 0.005) and Gleason score $\ge 4 + 3$ (OR: 2.007, CI: 1.175-3.428; p = 0.011). **Conclusions:** We firstly demonstrated in a European radical retropubic prostatectomy cohort study that MetS is associated with an

increased risk of high-grade and advanced prostate cancer. Further studies with long term follow-up should evaluate the impact of Mets on PCa survival.

Simone G., De Nunzio C., Ferriero M., Cindolo L., Brookman-May S., Papalia R., Sperduti I., Collura D., Leonardo C., Anceschi U., Tuderti G., Misuraca L., Dalpiaz O., Hatzl S., Lodde M., Trenti E., Pastore A.L., Palleschi G., Lotrecchiano G., Salzano L., Carbone A., De Cobelli O., Tubaro A., Schips L., Zigeuner R., Tostain J., May M., Guaglianone S., Muto G., Gallucci M.

Trends in the use of partial nephrectomy for cT1 renal tumors: analysis of a 10-yr European multicenter dataset.

Eur J Surg Oncol. 2016 Nov;42(11):1729-1735. PubMed PMID: 27106494. IF 2,94

Aim: Although extensively addressed in US registries, the utilization rate of Partial Nephrectomy has been poorly addressed in European settings. Our aim is to evaluate the impact of hospital volume on the use of PN for cT1 renal tumors.

Methods: 2526 patients with cT1N0M0 renal tumors treated with either PN or radical nephrectomy at 10 European centres in the last decade were included in the analysis. Joinpoint regression analysis was used to identify significant changes over time in linear slope of the trend for each center. The correlation between yearly caseload and the slopes was assessed with the non-parametric Spearman test. Coincident pairwise tests and regression analyses were used to generate and compare the trends of high-volume (HV), mid-volume (MV) and low-volume (LV) groups.

Results: Yearly caseload was significantly associated with increased use of PN (R = 0.69, p = 0.028). The utilization rate of PN was stable at LV centres (p = 0.67, p = 0.7, p = 0.76, for cT1, cT1a, and cT1b tumors, respectively), while increased significantly at MV (p = 0.002, 0.0005 and 0.007, respectively) and HV centers (all p < 0.0001). Regression analysis confirmed the trends for HV and MV as significantly different from those observed in LV centres (all p \leq 0.002) and highlighted significant differences also between MV and HV centres (all p \leq 0.03).

Conclusions: We confirmed the association between caseload and the use of PN for cT1 tumors. Our findings suggest that a minimum caseload might turn the tide also in LV centres while a selective referral to HV centers for cT1b tumors should be considered.

Santini D., Santoni M., Conti A., Procopio G., Verzoni E., Galli L., di Lorenzo G., De Giorgi U., De Lisi D., Nicodemo M., Maruzzo M., Massari F., Buti S., Altobelli E., Biasco E., Ricotta R., Porta C., Vincenzi B., Papalia R., Marchetti P., Burattini L., Berardi R., Muto G., Montironi R., Cascinu S., Tonini G.

Risk of recurrence and conditional survival in complete responders treated with TKIs plus or less locoregional therapies for metastatic renal cell carcinoma.

Oncotarget. 2016 May 31;7(22):33381-90. PubMed PMID: 27027342. IF 5,008

Purpose: We retrospectively analyzed the risk of recurrence and conditional Disease-Free Survival (cDFS) in 63 patients with complete remission during treatment with tirosin kinase inhibitor (TKI), alone or with local treatment in metastatic renal cell carcinoma. **Results:** 37% patients achieve CR with TKI alone, while 63% with additional loco-regional treatments. 49% patients recurred after CR, with a median Disease free survival of 28.2 months. Patients treated with multimodal approaches present lower rate of recurrence (40% vs 61%) and longer Disease free survival compared to patient treated with TKI alone (16.5 vs 41.9 months, p=0.039). Furthermore the rate of recurrence was higher in patients with brain (88%), pancreatic (71%) and bone metastasis (50%). Patients who continued TKI therapy after complete response had a longer disease free survival than patients who stopped therapy, although the difference was not significant (42.1 vs 25.1 months, p=0.254). 2y-cDFS was better in patients treated with multimodal treatment and who continued TKIs than the other patient arms.

Conclusions: The prognostic value of CR depends on the site where was obtained and how was obtained (with or without locoregional treatment). Cessation of TKI should be carefully considered in complete responder patients.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, 0.83, 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.

Faculty F. Stilo

Vascular Surgery



Head F. Spinelli

Other Personnel E. Martelli

Description

struction after tumor resection is one

Decision making impacts on survi-

We already showed that the Endova-

scular technique and open bypass are

complementary in treatment of CLI.

as these apply to different patterns of

disease. While the majority of patien-

ts 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

of our specific interest.

Main research activities

val in Critical Limb Ischemia.

EVAR: How to make open conversion after supra renal grafts a safe operation. Our interests focus on all the aspects EV treatment of endoleaks is not

the value of this approach

of arterial surgery, from the carotid always possible, and an open conartery endarterectomy/bypass for version is occasionally needed. In the prevention of cerebral ischemia, case of suprarenal grafts this can be down to the plantar revascularizaa hazardous procedure. Following the tion for limb salvage, through all the principle of minimally invasive laparotomic aneurysm repair, we propose a diseases of the aorta. When endotechnique to make open conversion vascular treatment is the best choisafer, avoiding the removal of the ce for the patient, it strictly follows whole suprarenal graft. This is based the Instructions For Use from the on the following principles: manufacturer. Large vessels recon-

1. Clamp the aorta horizontally, flush to the renal arteries, without mobilizing the endograft.

2. Open the sac and clamp the iliac branches by soft jaw external clamps close to the aortic bifurcation.

3. Divide the graft 5 to 10 millimetres below the proximal clamp, and divide the iliac branches inside the sac as distal as possible. The metallic struts can be sectioned by a steel wire cutter. Remove the central part of the graft, leaving the aortic and iliac stumps in place.

- 4. Clear the thrombus and oversaw the lumbar arteries.
- 5. Pass a teflon felt band around the aorta near the proximal clamp and implant a new bifurcation graft by sawing the residual inner endograft, the native aortic wall and the external teflon band altogether in order to obtain a firm and safe proximal anastomosis, double reinforced by the internal endograft and the exter-

nal felt, without removing the suprarenal stent.

- 6. Anastomose the iliacs to the residual iliac endografts and close the sac.
- By avoiding the need to gain distal control, a mini laparotomy is fully adequate, and the patient can benefit of this less invasive technique.
- In the last two years we treated eleven patients without complications, a mean blood loss of 380 ml, and a mean post- operative hospital stay of 5 davs.

Restenosis after CEA: carotid graft versus CAS.

Restenosis after CEA is currently treated by CAS. Late reports have shown suboptimal late results.

We already reported our series of carotid restenosis treated by a carotid vein graft in patients with a long life expectancy. We have updated our series with the late controls favoring this option versus CAS.

Endovascular and Open treatment of aortic embolism causing distal disease.

Critical limb ischemia due to aortic athero embolism is not as rare as it is currently believed. This is an insidious disease and If unrecognized can be at the origin of failures of treatment and bad outcomes. An endovascular aortic coverage, coupled with a femoral to popliteal or tibial graft seems to be a durable solution. We reviewed our series of such hybrid procedures, and described the diagnostic workout, technique and results.

Most important publications

Karim S., Lucas V., Verma A., Girgrah N., Ramee S., Castriota F., Micari A., Roscitano G., Spinelli F., Gafoor S., Haseeb A., Khan A., Franke J., Matic P., Reinartz M., Bertog S., Vaskelyte L., Hofmann I., Sievert H.

How should I treat Budd-Chiari syndrome after liver transplantation with inferior vena cava occlusion? EuroIntervention. 2016 May 17;12(1):124-8. PubMed PMID: 27173874. IF 3,863

Virology



Head E. Riva Other Personnel L. Piccioni

Description

quencing analysis.

Main research activities

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 PyroseThe specific SNPs that have been under study mainly included rs12979860, rs8099917, ss46945590 TT/ delta G SNPs in Interferon lamda III-IV region. These SNP are involved in host's innate immunity and in the treatment response in chronic infectious diseases. Also rs738409 SNP in the Patatin-like phospholipase domain-containing protein 3 (PNPLA3) and rs116928232 SNP in the exon 8 of the Lysosomal acid lipase have been investigated.

The Unit has been also involved in the comparison and validation of molecular methods applied for persistent virus (CMV, HCV, EBV and parvovirus).

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.

Most important publications

Mengarelli A., Annibali O., Pimpinelli F., Riva E., Gumenyuk S., Renzi D., Cerchiara E., Piccioni L., Palombi F., Pisani F., Romano A., Spadea A., Papa E., Cordone I., Canfora M., Arcese W., Ensoli F., Marchesi F.

Prospective surveillance vs clinically driven approach for CMV reactivation after autologous stem cell transplant.

J Infect. 2016 Feb;72(2):265-8. PubMed PMID: 26687516. IF 4,382

The paper describes the comparison between a prospective surveillance strategy with pre-emptive therapy and a clinically driven approach of CMV reactivation in patients with hematologic malignancies who had undergone an autologous stem cell transplant (ASCT). Two different strategies for CMV infection diagnosis were adopted: a clinically driven approach, in which the CMV DNAemia was investigated by plasma polymerase-chain-reaction (PCR) only on clinical suspicion of infection, and a prospective surveillance strategy, in which PCR was performed weekly in all patients regardless of clinical suspicion for at least 5 weeks after transplant. As expected, post-transplant CMV reactivations were significantly more frequent in patients who underwent a prospective surveillance (31.4% vs 11.4%, P = 0.032), with a high rate of asymptomatic infections (15, 55.6%). However, a similar incidence of end-organ disease was observed between the cohorts (7.4% vs 7.1% of reactivated patients). The mortality rate among patients with post-transplant CMV reactivation and the global transplant-related mortality were similar between the two groups. Despite limitations due to the non-randomized design of the study, our data suggest that a prospective surveillance of post-transplant CMV reactivation doesn't have a clear clinical advantage when compared with a clinically driven strategy in lymphoma and myeloma patients undergoing ASCT also in the era of novel agents (monoclonal antibodies, proteasome inhibitors, immunomodulators.

Mazzuti L., Lozzi M.A., Riva E., Maida P., Falasca F., Antonelli G., Turriziani O.

Evaluation of performances of VERSANT HCV RNA 1.0 assay (kPCR) and Roche COBAS AmpliPrep/ COBAS TaqMan HCV test v2.0 at low level viremia.

Eur J Phys Rehabil Med. 2016 Jun;52(3):321-30. PubMed PMID: 26937646. IF 2,063

The study addressed the concordance between low level HCV values obtained using the VERSANT HCV RNA 1.0 Assay (kPCR) and COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0. The correlation between the values obtained by the two RT-PCR assays for samples with quantifiable HCV RNA levels revealed that viral load measured by kPCR significantly correlated with that of the CAP/ CTM (R=0.644, P<0.0001). The results show a good concordance (n=126/144, 87%); discordant results were mainly observed in the assessment of values below the lower limit of detection of the assays. These variations may have an impact on clinical decisions for patients on HCV triple therapy or interferon-free regimens. It is therefore, recommended to monitor individual patients with the same test throughout treatment.

Vespasiani-Gentilucci U., Gallo P., Piemonte F., Riva E., Porcari A., Vorini F., Tozzi G., Piccioni L., Galati G., De Vincentis A., Carotti S., Morini S., D'Amico J., Angeletti S., Pedone C., Picardi A.

Lysosomal acid lipase activity is reduced both in cryptogenic cirrhosis and in cirrhosis of known etiology.

PLoS One. 2016 May 24;11(5):e0156113. PubMed PMID: 27219619. IF 3,057

Liver cirrhosis is characterized by a severe acquired reduction of LAL-activity, the precise causes and consequences of which need to be further addressed. DBS-determined lysosomal enzyme activities seem to be affected by white blood cell and platelet counts, and the specificity of these tests can be reduced when applied to determined populations, such as cirrhotics.



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 (I.zollo@unicampus.it), Research Unit of Biomedical Robotics and Biomicrosystems

The AIDE project has the ambition to strongly contribute to the improvement of the usertechnology 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, Tissue Engineering & Chemistry for Engineering), 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.

EU-AIMS

European Autism Interventions – A Multicentre Study for Developing New Medications

Url: http://www.eu-aims.eu/ Coordinator: Roche Partners: King's College London, Central Institute

of Mental Health Mannheim, Radboud University, Cambridge University, deCODE Genetics, University

Medical Centre, Universität Basel, Institut Pasteur, GABO:mi, Max-Planck Institute of Experimental Medicine, European Molecular, Biology Laboratory, NeuroSearch, Karolinska Institutet, Eli Lilly and Company Ltd., Janssen, Pharmaceutica, Institut de Recherches Servier, Vifor Pharma, Birkbeck College, Institute of Education, Campus Bio-Medico University of Rome (Research Unit of Molecular Psychiatry and Neurogenetics), Autism Speaks, Pfizer, CEA, Universität Ulm

Funded under: Innovative Medicine Initiatives End: 31/03/2017

Contacts: Antonio Persico (a.persico@unicampus.it)

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

ASKLEPIOS

Actions on food supplements, fake 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 & Chemistry for Engineering), Studiare Sviluppo srl (IT), Italian National Institute of Health, 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: Campus Bio-Medico University of Rome

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: 30/06/2016

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.).

RESHAPE

Restoring the Self with Embodiable Hand Prostheses

Principal Investigator: Dr. Giovanni Di Pino, Campus Bio-Medico University of Rome

Funding under: ERC-StG-2015 - ERC Starting Grant

End: 31/08/2021

Contacts: Giovanni Di Pino (g.dipino@unicampus.it), Research Unit of Neurophysiology and Neuroengineering of Human-Technology Interaction

RESHAPE aims to study prosthesis embodiment, identify what makes a hand prosthesis easily embodiable, and test non-invasive brain stimulation to facilitate the embodiment.

The first of three phases develops the enabling technology and defines the embodiment protocol.

The following phase evaluates thirty myoelectric-prosthesis users and the first of two amputees implanted with peripheral neural electrodes, for functional ability, prosthesis embodiment and acceptability and for phantom limb pain (PLP), before and after neuromodulation.

In the last phase, a neuro-controlled prosthesis is optimized in line with the specifications defined in the previous phase and tested in the second implanted amputee.

Patients are stimulated with a homeostatic plasticity-based rTMS either on premotor cortex or on intraparietal sulcus. A robot-aided TMS compensates head-coil relative displacement, allowing the subject to operate the prosthesis during the stimulation.

RESPINE

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

Coordinator: Centre Hospitalier Universitaire Montpellier

Partners: Campus Bio-Medico University of Rome, Universidad De Navarra, Universidad De Valladolid, Univercell-Biosolutions, National University Of Ireland, Galway, Citospin S.L., Institut De Terapia Regenerativa Tisular SI, Assistance Publique - Hôpitaux De Paris, Centre Hospitalier Universitaire De Nantes, Centre National De La Recherche Scientifique (CNRS), Ecrin European Clinical Research Infrastructure Network, Bg Klinikum Bergmannstrost Halle Ggmbh, Universite De Montpellier **Funding under:** H2020-SC1-2016-RTD **End:** 31/12/2020

Contacts: Gianluca Vadalà (g.vadala@unicampus.it), Research Unit of Orthopaedic and Trauma Surgery

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

ITALIAN MINISTRY OF EDUCATION, UNIVERSITY AND RESEARCH

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) **Partners:** Research Unit of Tissue Engineering and Chemistry for Engineering (UCBM), Research Unit of Measurements and Biomedical Instrumentation (UCBM), Research Unit of Computer Systems and Bioinformatics (UCBM), Research Unit of Orthopaedic and Trauma Surgery (UCBM), Research Unit of Neurology, Neurophysiology, Neurobiology (UCBM), Polytechnic University of Milan, University of Cagliari, Sant'Anna School of Advanced Studies, National Research Council, International School for Advanced Studies Trieste

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)

Partners: University of Verona, Polytechnic University of Marche, Sapienza University, University of Chieti-Pescara, University of Brescia, "Foro Italico" University of Rome

Engineering physiologically and pathologically relevant organ Models for the INvestigation of age related Diseases (MIND)

Coordinator: Politecnico di Torino

Partners: Research Unit of Heart Surgery (UCBM), Research Unit of Tissue Engineering and Chemistry for Engineering (UCBM), University of Pisa, University of Genova, Polytechnic University of Milan, University of Calabria, University of Cagliari, University of Bologna, Polytechnic, University of Marche, University of Turin, National Research Council

Root growth control: a systems biology approach

Coordinator: Sapienza University

Partners: Research Unit of Chemical-Physical Fundamentals of Chemical Engineering (UCBM), National Research Council, University of Udine, University of Milan

Emerging role of the endocannabinoid signalling in neuropsychiatric disorders

Coordinator: University of Insubria Varese-Como **Partners:** Research Unit of Biochemistry and Molecular Biology (UCBM), University of Cagliari, Sapienza University, National Research Council, University of Teramo, University of Foggia e University of Rome "Tor Vergata"

Functional connectivity and neuroplasticity in physiological and pathological aging

Coordinator: Catholic University of the Sacred Heart

Partners: Research Unit of Neurology, Neurophysiology, 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"

PRIN (Research Projects of National Interest) 2015

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

Coordinator: Università di Milano

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

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

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

Pancreatic $\beta\mbox{-cell}$ identity, glucose sensing and the control of insulin secretion

Coordinator: Paolo Pozzilli - Research Unit of endocrinology and diabetes

Partners: Università degli Studi di Verona, Università degli Studi di Catania, Università degli Studi di Parma, Università degli Studi di Roma "La Sapienza, Università Cattolica del Sacro Cuore, Università degli Studi di Siena, Università di PISA, Università degli Studi di Roma "Tor Vergata", Libera Università "Vita Salute S. Raffaele" Milano

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 Biomicrosytems (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 Obstretics (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 Clinical Pathology and 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 Diabe-

tes (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

RF - Network Project 2013

Italian autism spectrum disorders network: filling the gaps in the National Health Care System

Coordinator: Istituto Superiore di Sanità **Partners:** Research Unit of Molecular Psychiatry and Neurogenetics (UCBM), IRCCS Eugenio Medea – Associazione La Nostra Famiglia, Fondazione Stella Maris, Bambino Gesù

RF Industrial Co-Financing 2013

Extremely low frequency magnetic field (ELF-MF) stimulation as a neuroprotective treatment in acute ischemic stroke

Coordinator: UCBM

Partners: Research Unit of Neurology, Neurophysiology, Neurobiology (UCBM), IGEA S.p.A.

GR Ordinary 2013

Cerebellar-cortical circuits in Autism Spectrum Disorders: new perspectives for treatment implementation.

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

ITALIAN MINISTRY OF ECONOMIC DEVE-LOPMENT

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

LAZIO REGIONAL AUTHORITY

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

OTHER GRANTS

A novel approach to identify COPD phenotypes, forecast clinical course and plan the therapeutic strategy

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

Evaluation of corneal innervation as a new tool to detect autonomic neuropathy in diabetes

Funding Body: Fondazione Roma Coordinator: Research Unit of Endocrinology and Diabetes (UCBM) Partner: Research Unit of Ophthalmology, Sapienza

University.

Reaching, posture, object exploration, and language in high and low risk infants

Funding Body: National Institutes of Health Coordinator: University of Pittsburgh, USA Partners: Research Unit of Developmental Neuroscience (UCBM)

Research Projects

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

Antioxidant rich – food supplements for the protection against cosmic radiations – PAPARD

Funding Body: ASI – Italian Space Agency Coordinator: Sapienza University Partners: Research Unit of Food Science and Nutrition (UCBM), Research Unit of Diagnostic Imaging (UCBM), University of Florence

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

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

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.I.; 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

Hearth Remote monitoring - COR

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

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)

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

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

In Silico Medicine: Research and Training Program

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

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

Funding Body: EFSD (European Foundation for the Study of Diabetes), JDRF and Lilly **Partner:** Research Unit of Endocrinology and Diabetes (UCBM)

PI: Rocky Strollo (Endocrinology and Diabetes, UCBM); CoPI: Ahuva Nissim (Queen Mary University of London); CoPI: Paolo Pozzilli (Endocrinology and Diabetes, UCBM)

Evaluation of bone fragility in type 1 diabetes

Funding Body: SIOMMMS (Societá Italiana dell'Osteoporosi, del Metabolismo Minerale e delle Malattie dello Scheletro)

Partner: Research Unit of Endocrinology and Diabetes (UCBM)

PI (Young investigator): Rocky Strollo Supervisor: Nicola Napoli (Endocrinology and Diabetes, UCBM)

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

Funding Body: GILEAD Health Program **Partner:** Research Unit of Hematology, Stem Cell Transplantation, Transfusion Medicine And Cellular Therapy (UCBM)

PI: Dr. Ombretta Annibali

Other Research Units involved: Research Unit of Computer Systems and Bioinformatics (UCBM)

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

Funding Body: Iscra-Cineca HPC **Partner:** Research Unit of Nonlinear Physics and Mathematical Modeling

A full atomistic computational study of the ion permeation in the human alpha7 nicotinic receptor. Acronym (IONLGIC)

Funding Body: Iscra-Cineca HPC Computational grant

Partner: Research Unit of Nonlinear Physics and Mathematical Modeling

A full atomistic computational study of the active and inactive states of the human $\alpha7$ nicotinic receptor

Funding Body: ICHEC-Irish Centre for High-End Computing HPC Computational grant **Partner:** Research Unit of Nonlinear Physics and Mathematical Modeling A competitive call has been launched in 2014 with the aims of enhancing the capabilities of UCBM Research Units to oversee and participate in the HORIZON 2020 European research programme, promoting synergy and collaboration between the Engineering and Medicine and Surgery Departments as well as promoting young researchers.

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

Gene expression analysis in bone showed that obe-

se subjects present a lower expression of SOST

and Wnt5A genes. In the adipose tissue, we found

a higher GSK3B, TNFa at and a trend for higher IL6

and IL8 in obese than healthy subjects: as expected

adiponectin expression was more than 50% lower

in obese than lean subjects. Gene expression at the

muscle revealed a significantly lower SFRP expres-

sion and a trend for lower WNT5A, GSK3B and Wn-

The information so far collected confirms our

hypothesis that WNT pathway is differently modula-

ted in obese. According to our data, mechanical load

on the skeleton in obese individuals down-regulates

sclerostin expression in osteocytes likely activating

Wnt canonical pathway. This may explain high BMD

t10B (more than 50%) in obese vs lean ones.

The results of the 2nd year of activity of the projects are described below.

Evaluation of bone strength and WNT pathway in obese patients

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

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

The overall aim of this project is to evaluate the role of Wnt pathway and inflammation on bone strength in obese patients. According to protocol, elderly patients undergoing hip arthroplasty have been recruited. During surgery, bone, muscle and fat specimens have been collected and used for histomorphometry, biochemical tests and biomechanical analysis.





Figure 9 - START-Disc surgical platform: left) intraoperative set-up; right) ultrasonic driller

Smart surgical platform for the transpedicular delivery of advanced regenerative therapies into the intervertebral disc space

PI: Prof. Rocco Papalia, Research Unit of Orthopaedic and Trauma Surgery

Other Research Units involved: Biomedical Robotics and Biomicrosystems, Neurology, Neurophysiology, Neurobiology

The START-Disc goals are to develop a smart surgical platform 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 second year, the submodules of the START-Disc surgical platform have been developed, in particular: i) a mechanical support (MS) with 5 Dof for positioning and orienting the surgical tools, able to be interfaced with common surgical tables; ii) an ultrasonic driller for deep hole into the vertebras preserving the soft tissues; iii) a rotary drill to characterize the mechanical impedance of bone tissues and to implement a first monitoring system of the manual advancement of the drill and iv) a pressure sensor for intraoperative measuring the IVD pressure during the ATMPs delivery, based on the measurement of circumferential displacement of PVC tube in which flow the repairing biomaterial. The MS has been analyzed in order to plan a proper exploitation strategy.

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

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

The project "GUT2.0 - A multi-cellular 'gut-on-chip' technology for predictive human safety testing: an integrated experimental and modeling approach" aims to develop a microfluidic model of the intestine barrier as an in vitro model for predictive safety testing. The outcomes of the second year include the establishment of the microfluidic platform with multiaxial stretching capability. Activities have regarded i) the computationally informed design of the chip optimized geometry; ii) the device microfabrication via soft-lithographic techniques; and iii) the experimental validation of the device prototypes. The device has been used for the establishment of an on-chip functional enterocyte layer, and the optimization of the cell culture protocol is ongoing. The project has successfully set up different in vitro and ex vivo models of the intestine barrier based on cell lines, intestine mucosa biopsies, and colonic explants, to be used as a benchmark for the biological validation of the on-chip intestine barrier model. A computational framework for the analysis of the in vitro data toward an in silico predictive safety testing is under development.



Figure 10 - Comparison between the in silico modeled (on the left) and the experimentally obtained (on the right) multiaxial stretching of the chip.

Grant Program on Embodiment

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

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

PI: Marta Bertolaso

Other Research Units involved: Tissue Engineering and Chemistry for Engineering, Nonlinear Phisycs and Mathematical Modeling, Oncology

Cells-on-chip are in vitro models of biological microenvironments that combine co-culture protocols and microfluidic technologies: they consist in interconnected compartments linked through a microfluidic circulatory system. They allow a high degree of control over the experimental parameters, and the use of modern microscopy. The Campus Bio-Medico University of Rome hosts an interdisciplinary consortium working on cell chips for several research projects. The consortium is formed by: a Tissue Engineering Unit, a Translational Oncology Unit and a Non-linear Physics and Mathematical Modelling Unit. The experimental part of the project is building an on-chip model of tumor interaction with different immune cell populations. This innovative experimental model raises issues of several kinds; technical and methodological, theoretical, epistemological and philosophical. On these questions, the scientific units collaborate with a Unit of Philosophy of Scientific and Technological Practice and Philosophy of Biology to determine the quality of the new model as a proof of concept not only for the study of cancer and tissue organization, but also for the consideration of cell chips as dynamic embodied selves ("selves-on-chips").

Music: embodiment in action (MEDIA)

PI: Nicola Di Stefano

Other Research Units involved: Research Unit of Biomedical Robotics and Biomicrosystems, Research Unit of Neurophysiology and Neuroengineering of Human-Technology Interaction

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

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

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

PI: Maddalena Pennacchini

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

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

The project is organized into four phases:

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

- P2: Implementation of a training program for patients and caregivers. Under this phase, a group of selected patients undergo a training process. Each patient/caregiver is instructed in using the App and is informed on the information that the App collects and distributes. Moreover, a set of preliminary data is collected as paper form surveys, in order to build up a baseline for successive data analysis
- **P3:** Remote Monitoring of patients and caregivers, that consists in the collection of data from patients and caregivers. The users employ their mobile App to periodically compile surveys and to submit their data to the physician of the project. The physician interacts with a specific patient/caregiver as soon as he provides new data. Collected data is anonymized and stored in a database.
- P4: Data Analysis. All the data are analyzed and the impact of the proposed approach is evaluated. Other actions related to the dissemination of results and the definition of new projects are performed.



Impact of Research on Society

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

The activities are mainly devoted to strengthen competitiveness by promoting process and product innovation and by networking with local SMEs and National and International companies with a twofold aim: placement of students and exploitation of the research activities of the Research Units of Engineering and Medicine and Surgery Departments. In this context the project "INTESE - Innovation and Technology transfer to support exploitation of research results" funded by Lazio Regional Authority is worth a mention. The main objectives of the project consist in developing collaborations with local companies of process and product innovation by exploiting competencies and technologies developed by UCBM Research Units and staff mobility so fostering a mutual beneficial approach to create a critical mass of competencies and resources.

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

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

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

COMMISSIONED RESEARCH

PPR2 Project

Control of upper-limb prosthesis with neural invasive interfaces

Client: INAIL-Centro per la Sperimentazione ed Applicazione di Protesi e Presidi Ortopedici di Vigorso di Budrio (BO)

Contractor: Research Unit of Biomedical Robotics and Biomicrosystems (UCBM),

Other Research Units involved: Research Unit of Physical and Rehabilitation Medicine (UCBM), Research Unit of Orthopaedic and Trauma Surgery (UCBM), Research Unit of Neurology, Neurophysiology, Neurobiology (UCBM)

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)

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

Client: Puretech S.r.l. Contractor: Research Unit of Electronics for Sensor Systems (UCBM)

Support for the technical contents of the web portal www.oil-gasportal.com

Client: Serintel S.r.l. Contractor: Research Unit of Process Engineering (UCBM)

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

Client: Eureka S.r.l.

Contractor: Research Unit of Drug Sciences (UCBM)

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

Client: Department of Agricultural and Environmental Science, University of Bari **Contractor:** Research Unit of Electronics for Sensor Systems (UCBM)

A sensorial system for the evaluation of innovative food cooking methods

Client: Autentica Srl Contractor: Research Unit of Electronics for Sensor Systems (UCBM)

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

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

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, 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 Sicence (UCBM)

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

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

Determination of polyphenols in hazelnut kernels and their derived food products

Client: Soremartec Italia s.r.l. - FERRERO Group Contractor: Research Unit of Food Science and Nutrition (UCBM)

Endocannabinoid biomarkers in inflammatory bowel disease of pets

Client: Vetagro SpA Contractor: Research Unit of Biochemistry and Molecular Biology (UCBM)

Production of a manual on insulin infusion pump

Client: Medtronic International Trading Sarl Contractor: Research Unit of Endocrinology and Diabetes (UCBM)

Blood lysosomal acid lipase activity in patients with non-alcoholic fatty liver disease

Client: Alexion Pharma Contractor: Research Unit of Internal Medicine and Hepatology (UCBM)

Evaluation of the in vitro effects of caertain target compounds on an experimental model of epilepsy

Client: Phytecs, Inc. Contractor: Research Unit of Biochemistry and Molecular Biology (UCBM)

Total laboratory automation: advantages in preanalytical, analytical and post analytical process

Client: Siemens Healthcare S.r.I Contractor: Research Unit Clinical Pathology and Microbiology

IEEE Editorial Services Agreement

Client: The Institute of Electrical and Electronics Engineers, Incorporated ("IEEE") **Contractor:** Research Unit of Biomedical Robotics and Biomicrosystems (UCBM)

Assessment of neonatal oro-motor performance during bottle feeding

Client: Artsana S.p.A.

Contractor: Research Unit of Biomedical Robotics and Biomicrosystems (UCBM),

Other partners involved: "Santa Maria Goretti" Hospital

LCA perspective to assess the environmental impact of a PCM-based device for cold storage in the civil air conditioning

Client: Upgrading Services SpA Contractor: Research Unit of Chemical – Physics Fundamentals in Chemical Engineering (UCBM)

STS – Surgery Touchless System

Client: Proge Software srl Contractor: Research Unit of Automation and Control Theory (UCBM)

Brand Protection on Marketplace

Client: Poste Italiane SpA **Contractor:** Research Unit of Automation and Control Theory (UCBM)

Optimization of Control Room resources

Client: Banca Nazionale del Lavoro Contractor: Research Unit of Automation and Control Theory (UCBM)

CLINICAL TRIALS

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During the year 2016, 139 studies have been approved by the independent Ethics Committee of the UCBM. 76 (54,7%) and 63 (45,3%) of these projects were interventional or observational studies, respectively. The distribution of studies among the different Research Units (at least 5 studies per Unit) is summarized in Figure 1. The very majority of the interventional trials is of Phase 2 or 3. UCBM is actively working for being soon fully compliant with the legal requirements for conducting Phase 1 studies.



Figure 11 - Number of studies approved in 2016 and distribution according to Research Units UCBM

UCBM promoted 48 of the new studies approved in 2016 (34,5 % of the total). On the other side, 49 projects were promoted by not-for-profit institutions / research networks, and 42 projects were sponsored by Companies (pharmaceutical or developing medical devices) (Figure 2). Globally speaking, around 200 studies were ongoing in UCBM during 2016.



Figure 12 - Percentages of studies promoted by Industry, UCBM or Others among those approved in 2016

Quality and efficiency for clinical research

A major objective for UCBM is to achieve increasingly efficient clinical research, and in compliance with the highest quality standards. One significant change for clinical research in the context of UCBM is the entry into force, in December 2016, of new internal rules for examination and approval of the research projects. The aim of this regulation is to make more rapid the institutional evaluation of new studies, but at the same time ensuring that projects are analyzed from an ethical and scientific point of view, but considering their effective feasibility and sustainability as well. The contents of this regulation are available at http://www.unicampus.it/ documents/ricerca/UCBM dr 195 regolamento sperimentazioni cliniche.pdf. According to this procedure. essential documents for new clinical studies have to be submitted to the Clinical Trials Office (Ufficio Sperimentazioni Cliniche - USPC). The specific tasks of the USPC in this context include

- a preliminary evaluation of the local feasibility of the study, by considering composition of the study team, effective recruitment potential, adequacy of premises and equipments, tracking performance etc.
- an economic analysis to assess sustainability for the University Hospital
- in case of studies not promoted by UCBM, compliance of the insurance policy and definition of the financial agreement with the Sponsor (when needed)
- in case of studies promoted by UCBM, scientific and methodological support for definition of the study protocol, and management of the research.

The preliminary assessment by USPC is performed by considering the opinion of the various skills and competencies involved in conducting clinical research in the context of Campus Bio-Medico University Hospital (namely, representatives of the clinicians, nurses, Pharmacy, Health Direction of the Hospital, and the Academic Research Board).

Following this first step, the final approval for the study is issued by the independent Ethics Committee of the Campus Bio-Medico University of Rome. To have an Ethics Committee which acts within UCBM is a particular strength for the Institution, both from a cultural and procedural point of view. The Ethics Committee of UCBM passed the selection made some years ago by the National and Regional Health Authorities, and which reduced by about two-thirds the number of Ethics

Committees operating in Italy.

The USPC and the Ethics Committee work in close synergy to create a path as accurate and quick as possible to authorize the conduct of clinical trials.

More generally, the USPC is responsible for the system of quality of clinical research in UCBM, with the aim of achieving and / or maintaining standards comparable with those of the leading international research centers, and complying with existing regulations on clinical trials. In this perspective, the USPC acts in cooperation with the governing bodies of the University Hospital in order to ensure continuing training in Good Clinical Practice (GCP) for Principal Investigators and their staff, and therefore organizing courses chaired by qualified Quality Assurance experts. In addition, the Office deals with conditions required under current regulations in respect of the national Health Authorities (Italian Ministry of Health, Italian Medicines Agency etc.). Moreover, it assists the Institution in the dialogue and interaction with industrial Sponsors throughout the development of the study, and it is responsible for monitoring and managing any deviations from the study procedures and / or malfunctions of the research system. Finally, and specifically for not-for-profit studies promoted by UCBM, USPC provides advice to Investigators on the definition of study design, management of the study (including experimental drug, in cooperation with the Hospital Pharmacy), and reporting of the results.
RESEARCH EXPLOITATION

Patent portfolio owned/co-owned by UCBM

- 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, WO2013084159, EP20120815801); Inventors: M. Carassiti, S. Cecchini, E. Schena, S. Silvestri.
- Apparatus and method for videorhinohygrometric (vri) measures (EP2010054, US2009221927); Inventors: F. Salvinelli, R. Setola, M. Casale, P. Soda, V. Cusimano.
- Anti-sleep glasses (EP2729922, US2014303690, CN103534739, WO2012160205); Inventors: F.E. Agrò; F. Agrò; G. Agrò; L. Agrò
- Device for sampling food products (IT0001416505, EP2962098, WO2014132185); Inventors: G. Pennazza, M. Santonico, A. Zompanti, M. Dachà, A. D'Amico.
- Locomotion device for endoscopic applications and related methods (IT1397408, US20130324796); 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.
- A sampling device for the ocular surface based on imprinting (IT102015000008750, WO2016147122); Inventors: A. Micera, L. Zollo, B. Balzamino, I. Ghezzi, R. Sgrulletta. Co-owner: Fondazione G. B. Bietti.
- Device for mixing platelet-rich plasma with polymer solution (IT2014RM00190); Inventors: V. Denaro, R.Papalia, G. Vadalà, A. Sudano, D. Accoto
- Upper limb movement therapy device (IT1388838); Inventors: D. Accoto, E. Cecchini, E. Guglielmelli, M. Orsini, F. Torchiani, L. Zollo.
- Robotic device for assistance and rehabilitation of lower limbs (IT1414072, EP2906172,

US2015272809, SG11201502765W, CA2887671, CN104812352, IL238211, MX2015004478, KR20150077439, WO2014057410); Inventors: D. Accoto, G. Carpino, M. Di Palo, S. Galzerano, E. Guglielmelli, F. Sergi, N. L. Tagliamonte.

- A bioactive material for the regeneration of cartilage and process for the obtainement thereof (IT1411615, WO2013IB54372); Inventors: M. Centola, V. Denaro, A. Marsano, I. Martini, A. Rainer, M. Trombetta, G. Vadalà. Co-owner: Universitatsspital Basel.
- Porous material for cytoinclusion, process for the obtaining thereof an its use. (IT102016000111352); Inventors: A. Crescenzi, M. Trombetta, C. Taffon, A.Rainer, P. Mozetic, M. Costantini, A. Santoro. Co-owner: UCS Diagnostic srl
- Diagnostic method of pancreas cancer based on the determination of mutations of K-RAS gene (IT0001417084); Inventors: A. Onetti Muda, G. Perrone.
- Method for the fabrication of cell-laden constructs based on thermosensitive hydrogels (IT102015000020718, PCT IT/2016/000142); Inventors: V. Chiono, P. Mozetic, S. M. Giannitelli, A. Rainer, M.Trombetta, M. Boffito, E. Gioffredi, S. Sartori. Co-owner: Politecnico di Torino.
- Method for measuring slippage between surfaces (IT102016000105302); Inventors: R. Romeo, L. Zollo, E. Guglielmelli. Co-owner: INAIL
- Method for positioning the units of an array of tactile sensors for obtaining a hyper spatial acuity and processing method thereof (IT102016000076248); Inventors: C.Oddo, R. Romeo, L. Zollo, L. Beccai, E. Guglielmelli, M. Chiara Carrozza. Co-owners: Scuola Superiore Sant'Anna, Istituto Italiano di Tecnologia.
- Haptic interface module (IT1399399); Inventors: D. Accoto, E. Cecchini, E. Guglielmelli.
- Pneumopipe Auxiliary device for collection and sampling of exhaled air (EP2641537); Inventors: G. Pennazza, M. Santonico, A. D'Amico, R. Antonelli Incalzi, M. Petriaggi.
- Coronary shunt positioner (IT1410043); Inventors: E. Covino. Co-owner: Assut Europe SpA

UCBM spin-off companies

Two spin-off companies, namely ICAN Robotics srl and JUMPO srl, are accredited by UCBM. The spinoff companies activities are related to robot-assisted rehabilitation and wearable sensors for human behavior monitoring.

ICAN Robotics (www.icanrobotics.com) is an innovative start-up company, founded in September 2014, active in the field of biomedical robotics, developing technologies for rehabilitation and physical assistance for patients with neurological, orthopedic or age-induced conditions.

The company complies with the strictest quality requirements for the development of safe and effective biomedical systems (quality system certified both ISO 9001 and ISO 13485). ICan robotics develops innovative and user-friendly products, which can be used not only in healthcare facilities, but also at patients' abodes, for the benefit of the quality of life of patients and their caregivers.

The first product by ICan robotics is the ICone (Figure 13), an adaptive system for the intensive rehabilitation of neurological patients with upper limb disabilities, e.g. caused by a stroke. The ICone proposes engaging exercises to stimulate the voluntary coordination of shoulder and elbow segments. ICone is an all-inone system, compact and portable, the only one with robotic capabilities cleared for use at patient's home.



Figure 13 - The ICone system

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 2016 is reported.

Rome, February 11 2016

Cleft lip palate: framing the clinical and surgical treatment

Discussant: Dr. Mario Zama, Director U.O.C. Plastic Surgery and Maxillofacial, Bambino Gesù Italian Pediatric Research Hospital.

Seminar promoted by the Plastic, Reconstructive and Cosmetic Surgery Unit, Campus Bio-Medico University Rome.

Rome, February 17 2016

Overview of image guided minimal invasive surgery

Discussant: Professor Haim Azhari, Department of Biomedical Engineering, TECHNION - Israel Institute of Technology.

Rome, March 4 2016

Quo Vadis, Science? Lunchtime Meetings on the emerging orientations of scientific research.

"The fall of reductionist dogmas and the rise of systemic paradigms"

Rome, March 4 2016 Distal myopathies

Discussant: Professor. Margherita Milone, Director of Neuronuscular Medicine Fellowship, Department of Neurology and Associate Professor of Neurology, Mayo Clinic, Rochester, Minnesota. Seminar promoted by the Neurology, Neurophysiology, Neurobiology Unit, Campus Bio-Medico University of Rome.

Rome, March 15 2016

Molecular importance of metals in nutrition

Discussant: Professor. Enrico Dainese, Faculty of Biosciences and Technology Agro-Food and Environmental, Teramo University.

Seminar promoted by the Food Science and Nutrition Research Unit, Campus Bio-Medico University of Rome.

Rome, March 24 2016

Craniosynostosis and Cranio-Facial

Discussant: Dr. Mario Zama, Director U.O.C. Plastic Surgery and Maxillofacial, Bambino Gesù Italian Pediatric Research Hospital.

Seminar promoted by the Plastic, Reconstructive and Cosmetic Surgery Unit, Campus Bio-Medico University of Rome.

Rome, March 31 2016 Embryology of the face

Discussant: Professor. Cosmoferruccio De Stefano, Head Foundatione Alessandra Bisceglia ONLUS. Seminar promoted by the Plastic, Reconstructive and Cosmetic Surgery Unit, Campus Bio-Medico University of Rome.

Rome, April 5 2016

Modelling solutions to 21st Century healthcare challenges

Discussant: Sean McGinty, University of Glasgow.

Rome, April 6 2016

Application of the ketogenic diet in headaches: the rediscovery of an ancient therapy

Discussant: Dr. Cherubino Di Lorenzo, IRCCS "Regina Elena", Italy. Seminar promoted by the Food Science and Nutrition Research Unit, Campus Bio-Medico University of Rome.

Rome, April 11 2016 Elements of bioreactor design for tissue engine-

ering Biomedical Engineering Seminar promoted by the Departmental Faculty of Engineering.

Rome, April 2016

Neural reorganization patterns driving motor recovery after stroke: one year follow-up study Discussant: Dr. Carmelo Chisari, Laboratory "Analysis and Processing of Engines Disorders", U.O. Neurorehabilitation - Department of Neurosciences University Hospital Pisana.

Seminar promoted by the Neurology Unit, Campus Bio-Medico University of Rome.

Rome, April 15 2016

Quo Vadis, Science? Lunchtime Meetings on the emerging orientations of scientific research.

"The fading interface between natural and artificial. New kinds of robustness for robotic systems" Seminar promoted by Institute of Philosophy of Scientific and Technological Practice.

Rome, April 21 2016

Entropion and Ectropion

Discussant: Professor. Carlos Alberto Alfonso Ferreira, Department of Ophthalmology Federal University of Sao Paulo, Brasil.

Seminar promoted by the Plastic, Reconstructive and Cosmetic Surgery Unit, Campus Bio-Medico University of Rome.

Rome, April 27 2016

Innovative topics related to microbiology of food Discussants: Dr. Dario De Medici, Dr.ssa Elisabetta Suffredini, Dr.ssa Monica Gianfranceschi, Department of Veterinary Public Health and Food Safety, National Institute of Health, Italy. Seminar promoted by the Food Science and Nutrition Unit, Campus Bio-Medico University of Rome.

For a global governance of the new migration

Discussant: Professor Andrea Riggio, Professor of Geography, University of Cassino and Lazio Meridionale. Seminar promoted by the Food Science and Nutrition Unit, Campus Bio-Medico University of Rome.

Rome, May 6 2016

A Mitochondrial etiology of metabolic and degenerative disease

Discussant: Professor Douglas C. Wallace, Center for Mitochondrial and Epigenomic Medicine, Children's Hospital of Philadelphia and Department of Pathology and Laboratory Medicine, University of Pennsylvania, USA. Seminar promoted by the Food Science and Nutrition Unit, Campus Bio-Medico University of Rome.

Rome, May 16 2016

Motor control, learning and plasticity in Parkinson's disease

Discussant: Professor. M. Felice Ghilardi, The Sophie Davis School for Biomedical Education, City University of New York.

Seminar promoted by the Neurology, Neurophysiology, Neurobiology Unit, Campus Bio-Medico University of Rome.

Rome, May 17 2016

The preservation techniques of fertility in patients with neoplastic diseases

Discussant: Dr. Maria Vita Ciccarone, San Carlo di Nancy Hospital and Head Association Gemme Dormienti ON-LUS.

Seminar promoted by the Hematology Unit, Campus Bio-Medico University of Rome.

Rome, May 19 2016

Presentation of the 2016 Call of Ministry of Health: Ricerca Finalizzata e Giovani Ricercatori

Speakers from the Ministry of Health give advice and tips on the preparation of proposals.

Rome, 20 May 2016

The diseases on the border of psychiatry and neurology

Seminar of Neurology promoted Medical School and by the Postgraduate School of Neurology, Campus Bio-Medico University of Rome and by the Postgraduate School of Psychiatry, Tor Vergata University.

Rome, May 24 2016

Current strategies to optimize results and avoid complications in prosthetic breast reconstruction (PBR)

Alternatives to acellular dermal matrices (ADMs) in prosthetic breast reconstruction (PBR)

Discussant: Dr. Horacio F. Mayer, Sub Chief Plastic Surgery Service Italian Hospital of Buenos Aires, Editor-in-Chief European Journal of Plastic Surgery, Springer Verlag Heidelberg.

Seminars promoted by the Plastic, Reconstructive and Cosmetic Surgery Unit, Campus Bio-Medico University of Rome.

Rome, May 25 2016

Innovation: from project to market. The experience of ICan robotics

Discussant: Maria Teresa Francomano, Chief Operating Officer ICan Robotics.

Seminar organized by the Department of Engineering, Campus Bio-Medico University, Rome.

Rome, May 26 2016

Human body: does mechanics matter? The paradigm of the multiscale hierarchical mechanics in soft tissues

Discussant: Professor. Giuseppe Vairo, Tor Vergata University, Department of Civil and Informatic Engineering (DICII).

Rome, May 27 2016

"Quo vadis science?" - Lunchtime meeting on the emerging orientations of scientific research "Where is medicine going? The case for in silico medicine and critical thinking"

Seminar promoted by Institute of Philosophy of Scientific and Technological Practice.

Rome, June 3 2016

Neurostimulation to augment the function in physiopathology: from brain plasticity to clinical practice

Discussant: Professor. Cyril Schneider, Professor of Neurophysiology, Laval Huniversity, Québec City, Department of Rehabilitation and Faculty of Medicine. Seminar promoted by the Neurology, Neurophysiology, Neurobiology Unit, Campus Bio-Medico University of Rome.

Rome, December 20 2016

Rome, December 202016

of Rome.

Osvaldo Cruz Foundation - Bahia.

Genomics and new commons

ZIBRA: Real-time analysis on ZIKA virus in Brazil

Discussant: Daniele Manzella, Arizona State University.

Seminar promoted by the Food Science and Nutri-

tion Research Unit, Campus Bio-Medico University

Rome, June 8 2016

Inhibition of bacterial respiration and applications to bioelectrochemical sensors

Discussant: Dr. Enrico Marsili, Principal Scientist Singapore Centre on Environmental Life Science Engineering (SCELSE), School of Chemical and Biomedical Engineering (SCBE), Nanyang Technological University, Singapore.

Seminars promoted by the Plastic, Reconstructive and Cosmetic Surgery Unit, Campus Bio-Medico University of Rome.

Rome, June 23 2016

NGS Technologies applied to molecular diagnostics in oncology

Discussant: Professor Ettore Capoluongo, Unit of Clinical Molecular Biology, Agostino Gemelli Polyclinic, Catholic University of the Sacred Heart, Rome. Seminar promoted by the Laboratory of Pathology and Clinical Genetics, Campus Bio-Medico University of Rome.

Rome, July 1 2016

Movement neuro-mechanics: interfacing, modelling and control

Discussant: Massimo Sartori, Institute of Neurorehabilitation Systems, Bernstein Focus Neurotechnology Göttingen, University Medical Center Göttingen, Germany.

Seminar promoted by the Biomedical Robotics and Biomicrosystems Research Unit.

Rome, July 4-8 2016 Research Week 2016

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

Rome, July 11 2016

Understanding the role of mitochondria in muscular dystrophy

Discussant: Alessia Angelin, PhD, The Children's Hospital of Philadelphia.

Rome, July 14 2016

Development of low-impedance interface for the rehabilitation of patients with balance disorders Discussant: Carlo Tiseo, Robotic Research Centre, School of Mechanical & Aerospace Engineering, Nanyang Technological University, Singapore. Seminar promoted by the Biomedical Robotics and Biomicrosystems Research Unit.

Rome, July 27 2016

Materials modelling in biomedical engineering Lecture organized by Dr. Michael Sutcliffe, Coordinator of Departmental Bioengineering Research Theme and Responsible of Biomechanics Group, University of Cambridge.

Rome, September 16 2016 Applications of non-invasive brain stimulation in obsessive compulsive disorder

Discussant: Professor. Antonio Mantovani, MD, PhD, Assistant Professor of Psychiatry, Department of Physiology, Pharmacology & Neuroscience, CUNY School of Medicine, City College of New York. Seminar promoted by the Neurology, Neurophysiology, Neurobiology Unit, Campus Bio-Medico University of Rome.

Rome, September 16 2016 Machine-Assisted Chemical Processes and the Future of Chemistry

Discussants: Claudio Battilocchio, Homerton College Research Associate Innovative Technology Centre for ACS and Professor. Steven V. Ley group, Department of Chemistry, University of Cambridge.

Rome, October 7 2016

"Quo vadis science?" - Lunchtime meeting on the emerging orientations of scientific research "Critical thinking in scientific research: Critical thinking applied to research in the medical device industry" Seminar promoted by Institute of Philosophy of Scientific and Technological Practice

Rome, November 23 2016 Effects on muscle regeneration of bioactive components of food-borne

Discussant: Dr. Laura Teodori, Director of Research, Laboratory of Diagnostic and Metrology, FSN-TEC-FIS-DIM, ENEA.

Seminar promoted by the Food Science and Nutrition Research Unit, Campus Bio-Medico University of Rome.

Rome, November 25 2016

"Quo vadis science?" - Lunchtime meeting on

the emerging orientations of scientific research

"Certainty and uncertainty: Critical thinking in modeling complex systems" Seminar promoted by Institute of Philosophy of Scientific and Technological Practice.

Rome, November 28 2016

Multiple sclerosis: present and future Discussant: Chiara Ricella, MD, PhD, Medical Science Liaison, Biogen Italia S.r.l. Seminar promoted by the Neurology, Neurophysiology, Neurobiology Research Unit, Campus Bio-Medi-

Rome, December 5 2016

co University of Rome.

CIPRNet Lecture: Dynamical robustness to synchronization of complex networks: methods and applications to electrical infrastructures Discussant: Professor. Mattia Frasca, Research Associate, University of Catania.

Rome, December 14 2016

'Computational neurorehabilitation': from the modelling of neuromotor recovery to the personalized rehabilitation

Discussant: Vittorio Sanguineti, Department of Informatic, Bioengineering, Robotics e Systems Engineering (DIBRIS), Genova University. Seminar promoted by the Biomedical Robotics and Biomicrosystems Research Unit.

Rome, December 15 2016

Exploiting response variability to probe sensorimotor function

Discussant: John Rothwell, Professor of Human Neurophysiology, UCL, Institute of Neurology, London, UK.

Rome, December 19 2016

Neuroscience and Rehabilitation: translational research and technological innovation in clinical practice

Discussants: Dr. Marco Molinari, Director U.O.C. Neurorehabilitation, Fondazione Santa Lucia IRCCS, Roma;

Ing. Nevio Luigi Tagliamonte, Laboratory of Robotics Neurorehabilitation, Laboratory of Rehabilitation of Spinal Cord Injury, Santa Lucia Foundation IRCCS, Rome.



Research Agreements and Collaborations

National agreements and collaborations

Altec S.p.A., Italy Artsana S.p.A., Italy ASRIS ONLUS Cagliari, Italy Autentica Srl, Italy Bambino Gesù Paediatric Hospital, Italy Banca Nazionale del Lavoro, Italy Carabinieri Headquarters for Healthcare, Italy Catholic University of the Sacred Heart, Italy Cell Factory, Foundation IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy CNIT - Consorzio Nazionale Interuniversitario per le Telecomunicazioni, Italy Confederazione Nazionale Coldiretti, Italv Consorzio Ferrara Ricerche, Italy Elesta S.r.l., Italy ENEA. Italv Eureka S.r.l., Italv Fondazione IRCCS Istituto Nazionale dei Tumori, Italy "Foro Italico" University of Rome, Italy ICRA - International Center for Relativistic Astrophysics, Italy IGEA S.p.A. International School for Advanced Studies Trieste, Italy IPASVI, Italy IRCCS Eugenio Medea – Associazione La Nostra Famiglia, Italy IRCCS Fondazione Santa Lucia, Italy IRCCS Fondazione Stella Maris, Italy IRCCS Regina Elena (IFO-IRE), Italy IRCCS San Raffaele Pisana, Italy Italian Ministry of Health, Italy Italian National Institute of Health. Department of Therapeutic Research and Medicine Evaluation, Italy Kell S.r.I., Italy Medtronic International Trading Sarl, Italy

National Research Council (CNR), Italy

Network Future in Research (Consorzio Futuro in Ricerca), Italy OpenSky, Italy "Paride Stefanini", "Umberto I" Polyclinic of Rome, Italy Pfizer Italia S.r.l., Italv Politecnico di Torino, Italy Polytechnic University of Marche, Italy Polytechnic University of Milan, Italy Poste Italiane SpA, Italy Proge Software srl, Italy Puretech S.r.I., Italy Sant'Anna School of Advanced Studies, Italy Sapienza University, Rome, Italy Selex ES SpA, Italy Serintel S.r.I., Italy Siemens Healthcare S.r.l. Italv SOREMARTEC ITALIA S.r.l., Italy Studiare Sviluppo S.r.l., Italy University "Roma Tre", Italy University of Bari, Italy University of Bologna, Italy University of Brescia, Italy University of Cagliari, Italy University of Calabria, Italy University of Catania, Italy University of Chieti-Pescara, Italy University of Florence, Italy University of Foggia, Italy University of Genova, Italy University of Insubria Varese-Como, Italy University of Milan, Italy University of Padova, Italy University of Parma, Italy University of Pisa, Italy University of Rome "Tor Vergata", Italy University of Siena, Italy University of Teramo, Italy

University of Turin, Italy University of Udine, Italy University of Verona, Italy Upgrading Services SpA, Italy Vascular Surgery Division, Department of Surgery, Surgical Specialties and Organ Transplantation "Paride Stefanini", "Umberto I" Polyclinic of Rome, Italy Vetagro SpA, Italy Vita-Salute San Raffaele University, Italy

International agreements and collaborations

Alexion Pharma, USA AO Research Institute Davos, Switzerland Assistance Publique - Hôpitaux De Paris, France Autism Speaks, USA B&J Adaptaciones, Spain Belgian Customs and Excise, Belgium Bg Klinikum Bergmannstrost Halle Ggmbh, Germany Birkbeck College, United Kingdom Cambridge University, United Kingdom CEA. France Cedar Foundation, USA Central Institute of Mental Health Mannheim, Germany Centre Hospitalier de Luxembourg, Luxembourg Centre Hospitalier Universitaire De Nantes, France Centre Hospitalier Universitaire Montpellier, France Centre National De La Recherche Scientifique (CNRS). France Charles University Prague, Czech Republic Children's Hospital of Pittsburgh, USA Citospin S.L., Spain Commissariat à l'Energie Atomique et aux Energies Alternatives (Neurospin/CEA), France deCODE Genetics, Iceland Deltares. The Netherlands ECRIN - European Clinical Research Infrastructure Network, France Eli Lilly and Company Ltd., United Kingdom Erasmus MC Sophia Rotterdam, The Netherlands European Commission, Joint Research Centre, Bel-

aium European Molecular Biology Laboratory, Germany F. Hoffmann-La Roche Ltd., Switzerland Fraunhofer-Gesellschaft zur Förderung der angewandten Forschung e.V., Germany GABO:mi, Germany Hospital Clinico San Carlos Madrid, Spain Hospital de Cruces University of Pais Vasco, Spain Institut de Recherches Servier, France Institut De Terapia Regenerativa Tisular SI, Spain Institut Pasteur, France Institute of Education, United Kingdom Janssen Pharmaceutica, Belgium Karolinska Institutet, Sweden Kinder und Jugendkrankenhaus Auf der Bult Hannover, Germany King's College London, United Kingdom Linkoping University, Sweden Max-Planck Institute of Experimental Medicine, Germany National University of Ireland, Galway, Ireland NeuroSearch. Denmark Phytecs Inc., USA Radboud University. The Netherlands Robarts Research Institute, Canada Sommelweis University Budapest, Hungary The Children's Hospital at Westmead NSW, Australia The Institute of Electrical and Electronics Engineers, Incorporated (IEEE), Belgium The National Institute for Health and Welfare Helsinki. Finland The Netherlands Food and Consumer Product Safety Authority, The Netherlands TNO, The Netherlands Union des Industries Chimiques (UIC), France Univercell-Biosolutions, France Universidad De Navarra, School of Engineering (TEC-NUN), Spain Universidad De Valladolid, Spain Universidad Miguel Hernández, Spain

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Editorial board membership

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Antonelli Incalzi R.	Advances in Respiratory Medicine Aging Clinical and Experimental Research Italian Journal of Medicine (Section editor) Journal of Frailty and Aging
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Beomonte Zobel B.	Applied Radiation and Isotopes
Bertolaso Marta	Bioethics Update Current Bioinformatics Filosofia e saperi. Sconfinamenti tra saperi umanistici e scienze della vita/ Crossing borders between humanities and life sciences Medic - Metodologia didattica e innovazione clinica Medicina e Storia Rivista per la Filosofia Scienze e Ricerche
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Casale M.	Austin Otolaryngology Dataset Papers in Medicine Global Journal of Otolaryngology
Chello M.	Journal of Geriatric Cardiology World Journal of Cardiology World Journal of Hypertension World Journal of Surgical Procedures World Journal of Translational Medicine
Chiodo L.	Thin Solid Films, Frontiers in Materials
Cicala M.	Frontiers in Neuroscience

Coppola R.	International Journal of Surgery International Journal of Surgery Case Reports International Journal of Surgery Open International Journal of Surgery Protocol
D'Amelio M.	Neuromolecular Medicine Molecular Neurobiology Scientific Reports (Neuroscience Section)
Di Lazzaro V.	Behavioural Neurology Brain Stimulation Case Reports in Medicine Neurology Research International
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Dugo P.	Advisory Board di Flavour and Fragrance Journal
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Longo U.G	American Journal of Stem Cells BMC musculoskeletal disorder

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Silvestri S.	The Open Biomedical Engineering Journal
Spinelli F.	Italian Journal of Vascular and Endoovascular Surgery Inernational Angiology Journal of Infection and Public Health Diseases
Sterzi S.	European Journal of Physical and Rehabilitation Medicine

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Ph.D Courses

The Campus Bio-Medico University of Rome offers Ph.D courses to students motivated to gain autonomy and rigor in scientific research. Courses aim to provide doctoral students a scientific culture, methodological tools and advanced technical skills, thereby contributing to the growth of research and scholarship in Italy and internationally.

The primary purpose of PhD study is the preparation and presentation of a substantial piece of original research designed to be completed within three years of study. Full text Ph.D dissertations are deposited in the open access repository ILITHIA. The repository is indexed in OpenDOAR, an authoritative worldwide directory of academic open access repositories. Link: http://ilithia.unicampus.it/ilithia/Default.asp

Authors hold copyright of dissertation in accordance with current legislation (Law 633/1941) and subsequent amendments and additions. The dissertations present in the University repository are a guarantee for the author, certifying and dating intellectual property. The repository helps to ensure a high level of visibility of Ph.D dissertations increasing significantly their impact, for the benefiting of both researchers and Campus Bio-Medico University itself.

PH.D IN INTEGRATED BIOMEDICAL SCIENCES AND BIOETHICS

Duration 3 years

Coordinator Prof. Paolo Pozzilli

Students enrolled

XXIX Cycle (2013/2014): A.C. Amisi, F. Ausania, B. Brunetti, R.L. Cazzato, L. Florio, V.L. Greto, D. Grieco, M. Maioni, N.J. Palathara, E. Rossi, S. Saracini, L. Stumbo, D. Tuccinardi

XXX Cycle (2014/2015): R. Altavilla, A. Piccoli, V. La Vaccara, G. Leanza, G. Ribelli, L. Riva, C. Vinci, A. Soriano

XXXI Cycle (2015/2016): A. Aveta, E. Dell'Aquila, A. Di Mauro, P. Finamore, A. Grasso, E. Maddaloni, A. Pezzuto, V. Toto

XXXII Cycle (2016/2017): G. Armento, I. Cavallari, L. Costanzo, L. Di Biase, I. Giovannoni, A. Mioli, S. Santoro, F. Segreto, A. Sisto

Learning outcomes

The structure of the Ph.D in Integrated Biomedical Sciences and Bioethics is designed to produce graduates who have a thorough knowledge of the literature and comprehensive understanding of scientific methods and techniques applicable to their own research. This particular Ph.D focuses its attention in integration of the broader fields of biomedical research with a more philosophical approach which include further study in anthropology, ethics, aesthetics, epistemology, and bioethics.

Research fields

- The Ph.D in Integrated Biomedical Sciences and Bioethics is divided in various tracks:
- Endocrinology: MED/13, MED/09, MED/08, BIO/10, MED/16, MED/18
- Bioethics: MED/43, BIO/14, MED/26, BIO/16
- Osteo-Oncology Pathology: MED/06, MED/04, BIO/10, MED/15, MED/40, MED/16
- Aging Sciences and of Tissue Regeneration: MED/09, MED/19, MED/26, MED/15

PH.D IN BIOENGINEERING AND BIOSCIENCES

Duration 3 years

Coordinator Prof. Giulio lannello

Students enrolled

XXIX Cycle (2013/2014): P. Balestrieri, R. Barone, E. Lisi, C. Massaroni, M. Morrone, L.M. Montoni, M. Morrone, R.A. Romeo, M.B. Ronci, D. Simonetti, A. Zompanti

XXX Cycle (2014/2015): B.O. Balzamino, A. Della Casa Bellingegni, F. Giurazza, E. Noce, F. Orsini, F. Sciarra, G. Tripodo, S. Valentini

XXXI Cycle (2015/2016): L. Acciai, E. Cordelli, M.C. De Maggio, E. Galassi, C. Lauretti, D. Lelli, I. Portaccio, P. Tomaiuolo, J. Tosi

XXXII Cycle (2016/2017): S. Cocca, C. Gentile, E. Gruppioni, M. Langone, M. Menci, A. Noccaro, F. Scotto Di Luzio, R. Sicilia, A. Vilmercati

Learning outcomes

The structure of the Ph.D in Bioengineering and Biosciences is designed to produce graduates with rigorous research and analytical skills, who are exceptionally well-equipped to carry out research in academic, industry, or government positions. The program is divided in two tracks: one oriented to biomedical engineering applications the other to Science and food technology and nutrition.

Ph.D program allows graduates to:

- develop new methods, instruments and systems, for biomedical engineering and for food sciences and nutrition;
- describe, plan, coordinate and carry out research programs developing technical and medical-biological skills;
- integrate traditional formation in the biomedicine, with knowledge such as maths and technology which can face the increasing complexity of "bioinspired" research fields.

Research fields

The main fields of study are:

- **Bioengineering:** study, design and development of new methods, systems and medical devices, medical and biological research, development of bioinspired medical technologies;
- Material science and nanotechnology: study, development and testing of materials for industrial applications with a particular consideration to medical and food applications;
- Modelling: study and use of complex systems models for applications in biology and medicine;
- Food chemistry and plant physiology: study and development of new knowledge and protocols for the characterization of bioactive molecules and their metabolism. Use of new technologies for the nutritional enhancement of traditional and innovative foods;
- Nutrition: use of advanced technological for the study of nutritional parameters and their impact in the prevention of diseases; Experimentation protocols and procedures applied to clinical nutrition.

Graduate School – shared education platform

The Coordinating Board for Ph.D programs, formed by Doctoral program Coordinators and supported by the Centre for Integrated Research, in the academic year 2013/14 created a training event called 'Graduate School – a shared education platform'. Its goal was to offer a training course in Scientific Research, cutting across individual Degree Programs, to investigate issues of common interest.

The event is organized with a series of short lectures that address specific issues identified by Doctoral program Coordinators.

Monday July 4 th 2016	09:30-10:00	Welcome and Introduction Felice Barela, <i>President</i> Andrea Onetti Muda, <i>Rector</i> Paolo Sormani, <i>General Manager of the University</i>
	10:00–10:15	Presentation of "School 2016" Eugenio Guglielmelli, <i>Pro-Rector for Research</i> Giulio lannello, <i>Coordinator of the Ph.D in Bioengineering and Bioscience</i> Paolo Pozzilli, <i>Coordinator of the Ph.D in Integrated Biomedical Sciences and Bioethics</i>
	10:15-13:00	 Workshop "In silico medicine" Introduction: What is new for the Clinical Trials, Marta Bertolaso, <i>FAST</i> New perspectives in interdisciplinary research - the VPH experience (Virtual Physiological Human), Christian Cherubini, <i>Non Linear Physics and Mathematical Models Research Unit</i> An example: Organs On A Chip, Alberto Rainer, <i>Tissue Engineering and Chemistry for Engineering Research Unit</i> and Daniele Santini, <i>Oncology Research Unit</i> Experimental Systems: Epistemological and Philosophical Issues, Annamaria Dieli, <i>Tor Vergata University</i> and Marta Bertolaso, <i>FAST</i> Emerging Ethical Issues, Ilaria Malagrinò, <i>FAST</i> In Silico Medicine and the European Research Programs, Marta Bertolaso, <i>FAST</i>
	Welcome Lunch	
	14:30-15:30	The identity, mission and cultural project of Campus Bio-Medico University of Rome Simonetta Filippi, <i>Pro-Rector for Education</i>
	15:30-17:00	The experience abroad of a Ph.D student: opportunities and mistakes not to make Nicola Napoli, <i>Endocrinology and Diabetes Research Unit</i> Francesco Basoli, <i>Tissue Engineering & Chemistry for Engineering Research Unit</i>
Tuesday July 5th 2016	08:30-13:00	Research Day
	Lunch	
	14:30-15:30	How to disseminate research Communication Area UCBM
	15:30-16:30	The protection of intellectual property Elisabetta Papa, , Italian Patents Society
	16:30-17:30	The activities of the Italian Camp Foundation for the exploitation of research Marco Martellucci, Italian Camp Foundation
	18:30	Cocktail for the students on the Trapezio Terrace

esday July 6 th 2016 - T8 class	09:30-10:00	The added value of an international Ph.D in relation to job placement Paolo Pozzilli, Coordinator of the Ph.D in Integrated Biomedical Sciences and Bioethics
	10:00-10:45	Why undertake a biomedical research path Francesco Giorgino, <i>Delegate to Research, Bari University</i>
	10:45-11:00	Meeting with Giuliano Poletti, <i>Minister of Labor and Social Policy</i> "The Ph.D student: a resource for the labor market and the country's competitiveness"
	Coffee Break	
	11:30-13:00	Workshop "Advanced models for in vitro drug screening and toxicology" QSAR models and read-across strategies for predictive safety testing, Serena Manganelli, <i>Mario</i> <i>Negri Institute</i> Cellular and molecular basis of intestinal permeability, Ricard Farré Marti, <i>Katholic University of Leuven</i> New generation in vitro models for cardiac diseases, Giancarlo Forte, <i>Director of Center for Tran-</i> <i>slational Medicine, FNUSA-ICRC</i>
/edn	Lunch	
3	14:00-16:00	Challenges in whole-brain imaging: from optics to image analysis Ludovico Silvestri, CNR-Institute National of Optics
	16:00-18:00	Laboratory of image analysis Giulio Iannello, Paolo Soda and Luca Vollero, <i>Computer Systems and Bioinformatics Research Unit</i>
3 class	09:30-11:00	Introduction to Biostatistics Massimo Ciccozzi, National Institute of Health
116 - T	Coffee Break	
uly 7 th 20'	11:30-13:00	Biostatistics Laboratory - Part 1 Massimo Ciccozzi, National Institute of Health
sday .	Lunch	
Thur	14:00-18:00	Biostatistics Laboratory - Part 2 Massimo Ciccozzi, National Institute of Health
	09:30-11:00	Bioengineering and Soft Robotics Cecilia Laschi, Delegate to Research, Sant'Anna School of Advanced Studies, Pisa
	Coffee Break	
)16	11:30-13:00	Learning from nature how to build Plantoids and other bio-inspired systems Barbara Mazzolai, Director of Center of di Micro-biorobotics, Italian Institute of Technology (IIT), Pisa
3th 2(Lunch	
Friday July 8	14:30-14:45	Intermediate geriatric care as a pillar for integrated care: practice and research perspectives Marco Inzitari, Autonoma University of Barcelona, Barcelona, Spain
	14:45–15:00	New Horizons in human physical performance tests Gianluca Padula, <i>University of Lodz, Poland</i>
	15:00-16:30	How to write a scientific article Giorgio Pennazza, Electronics for Sensor Systems Research Unit Claudio Pedone, Geriatrics Unit Discussion contributions sent from Ph.D students of XXIX cicle
	16:30-17:00	Final reflections and conclusions

Ph.D dissertations defended in 2016

*Link to full text dissertations: http://ilithia.unicampus.it/ilithia/Default.asp

SUBSTRATE ENGINEERING TO CONTROL CELL BEHAVIOUR

Ph.D student Franca Abbruzzese Tutor Marcella Trombetta

The topographic study of nano and micro-surfaces assumes considerable importance in Tissue Engineering. It allows, in fact, to obtain information on the interaction of cells with substrates that mimic the micro-architectural features of the extracellular matrix (ECM) of the native tissue of interest. In this way it is possible to develop biomaterials having biophysical (topography, mechanical properties) and biochemical (oxygen tension, surfacecoating) characteristics, which is able to replace in vitro complex biological systems. The aim of this PhD thesis is to study the influence of differently engineered substrates obtained through two well-established soft-lithographic techniques (ReplicaMolding (REM) and Micro-Contact Printing (mCP)) on the behaviour of several cell types (tenocytes, tendon-derived stem cells and bone marrow stromal cells). The REM technique was used for the fabrication of polydimethylsiloxane (PDMS) substrates with different stiffness obtained modifying the ratio between pre-polymer and curing agent (5:1 and 10:1 w/w). Cell culture has allowed to study the role of the different topographical features on cell morphology, proliferation, migration and production of collagen (type I and type III). The second technique (m;CP) was used to obtain protein (type I collagen and poly-L-lysine) patterns both on polypropylene substrates and on polycaprolactone (PCL) 3D scaffolds obtained by electrospinning. PDMS molds with different relief structures were fabricated by REM technique and used to print the protein islands. The influence of substrate topography on cell morphology, proliferation, and preservation of cell stemness was analyzed.

DESIGN AND CONTROL OF A DEXTEROUS UPPER-LIMB PROSTHETIC SYSTEM

Ph.D student Roberto Barone Tutor Loredana Zollo

The human hand is considered as the highest example of dexterous system capable of interacting with different objects and adapting its manipulation abilities to them. The control of poliarticulated prosthetic hands represents one important research challenge, typically aiming at replicating the manipulation capabilities of the natural hand. The success of grasping and manipulation tasks of commercial prosthetic hands is mainly related to amputee visual feedback since they are not provided either with tactile sensors or with sophisticated control. As a consequence, slippage and object falls often occur. Another important issue to consider is the preshaping of the hand, in fact it is very important to avoid injuries for the amputees giving them a prosthetic wrist. Literature studies highlight the importance of the active pronosupination and passive flexion-extension for an upper limb amputee. This thesis wants to address the specific issue of enhancing grasping and manipulation capabilities of existing prosthetic hands, by changing the control strategy and designing a new prosthetic wrist. For this purpose it proposes a multilevel control based on two distinct levels: a high and a low level. The low level control is a parallel force-position control and directly communicate with the actuators of the prosthetic hand while the high level could be a policy search learning algorithm or an actor-critic reinforcement learning (RL) combined with central pattern generators. With the RL as high level, it was carried out the control of a commercial biomechatronic hand (the IH2 hand) including the main features of recent poliarticulated prosthetic hands. The training phase of the hand was performed in simulation, the parallel force/position control was tested in simulation whereas preliminary tests were performed on the real IH2 hand. The results obtained in simulation and on the real hand provide an important evidence of the applicability of the bio-inspired neural control to real biomechatronic hand with the typical features of a hand prosthesis. With the policy search learning algorithm as high level, the control has been tested on an anthropomorphic robotic hand with prosthetic features (the IH2 hand) equipped with force sensors. Bi-digital and tri-digital grasping tasks with and without slip information have been carried out. The KUKA-LWR has been employed to perturb the grasp stability inducing controlled slip events. The acquired data demonstrate that the proposed control has the potential to adapt to changes in the environment and guarantees grasp stability, by avoiding object fall thanks to prompt slippage event detection. For what concerns the wrist, an active prono-supination and passive flexionextension modules are designed in order to avoid compensatory movements during grasps. The main intention of this thesis is to develop the control strategies and the mechanical design of the wrist previously described. A wrist/hand combined control is proposed and preliminary tests on the prono-supination module have been carried out.

INTUITION IN MEDICINE: A THEORETICAL AND PRACTICAL FRAMEWORK TO IMPROVE CLINICAL REASONING

Ph.D student Laura Leondina Campanozzi Tutor Giampaolo Ghilardi

BACKGROUND Clinical reasoning is a skill that could be improved as long as we know what it does entail. Nowadays, a fresh wave of scientism is taking place in clinical methodology, mainly as a consequence of both the success of Evidence Based Medicine (EBM) and the critical debate derived since its inception. The lack of due attention paid to the role of intuition in medicine is just one among the others different signs of this situation. Specifically, it is not possible to justify rationally a framework of clinical intuition if we support an epistemological approach that univocally exploits the measurable aspects of medical cognition. In this respect, an adequate epistemology of clinical reasoning must also account for intuition as one of the factors determining the quality of the diagnostic process, even if it goes beyond a merely quantitative research approach.

OBJECTIVES The aim of this study was to address the role and the concept of intuition in diagnostic clinical reasoning from the epistemological point of view, not being either universally recognized or systematically investigated. We extended the understanding of clinical intuition by gaining insight into its theoretical underpinnings consistent with its complex nature and importance in medical practice. The present research attempted to fill a gap between the practice and the theory of clinical intuition, ridding it of the prevailing uncritical perceptions and ambiguity, so as to favor the appropriate use of this essential cognitive skill. Based on the framework proposed, an educational approach was discussed in order to highlight those conditions than can foster the trigger of effective intuition in medicine.

MATERIALS & METHODS The study was organized in three main sections. The first part provides an overview of clinical reasoning by focusing on the epistemological value of the realism for an adequate approach to the topic of medical cognition. The second section investigates the intuitive dimension of clinical reasoning moving from the philosophical ground to the proper medical one. Drawing upon both Popper's methodological tradition and the dual-process theory of cognition, we pointed out the unavoidable and precious nature of hypotheses formulated by the physician, as well as their intrinsic intuitive dimension. We reviewed literature on both perspectives in order to outline a first conceptualization of intuition by showing its strengths and flaws. Finally, the third section provides a theoretical framework to understand clinical intuition by addressing the nature, the object and the process of this cognitive tool, through a description of some emblematic case studies in medicine. The Platonic tradition, also revisited by the epistemology of Michael Polanyi, was integrated with the Aristotelian-Thomistic one, for a broader and realistic picture of intuition in medicine.

RESULTS Focusing and clarifying those philosophical underpinnings useful to highlight this phenomenon and

its close link with diagnostic hypothesis generation, a definition of clinical intuition took shape as an intellectual and a-logical faculty, distinct from the sensorial one, that arises suddenly with an immediate awareness of its content and without a step-by-step process.

We spoke of "essential intuition" to denote the tendency to acquire the essence or formal cause of the clinical case investigated that specifies it from the others, although we have widely pointed out that intuitive outcome cannot be qualified apodictically.

The intuitive experience usually occurs through a recognition of analogies, seeing traces in the current clinical situation that recall to mind regularities already known but applied elsewhere. The recognition of a pattern by intuition can be unconscious or not, as well as quick or less than the time, as a consequence of a network of conditions. This suggested that intuition is not a unitary construct and led us to identify two main intuitive modes that can take place in clinical setting from an epistemological point of view: ordinary and extraordinary. The theoretical framework emerged from this study provided a first step to address an educational approach regarding a range of factors that can influences the genesis, immediacy and accuracy of clinical intuition. We described this not marginal aspect by proposing the term "ecology of intuition" to refer to internal and external conditions of the subject that affect its arising.

Broader qualitative phenomenological studies of clinical intuition are required to promote an increased awareness of its tacit aspects and to gather useful data to establish more informed and focused training paths to improve intuitive skill.

INSULIN AND ITS POTENTIAL ROLE IN PANCREATIC CANCER: HISTO-MORPHOLOGICAL AND IMMUNE-HISTOCHEMICAL STUDY ON POST MORTEM PANCREATIC MATERIAL

Ph.D student Gabriella Teresa Capolupo Tutor Marco Caricato

Introduction: Several studies suggest that correlation exists between diabetes and different types of cancer. However the temporal association between diabetes and pancreatic cancer is controversial. Some evidence suggests the hypothesis that insulin can promote neoplastic transformation, cancer growth and progression of this neoplasia. The aim of this work was to investigate the relationship between insulin and pancreatic cancer, acquiring new data on insulin detected in pancreatic tissue by dosing insulin concentrations directly in samples of human pancreas. Materials and methods: In the period from January 2012 to November 2015, in collaboration with the Pathology Service and the Geriatric Surgery Unit at "Università Campus Bio-Medico" and the Institute of Human Anatomy at the "Università Cattolica del Sacro Cuore" of 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-guantitative and guantitative 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.

TRANSCRANIAL MAGNETIC STIMULATION IN STROKE

Ph.D student Fioravante Capone **Tutor** Vincenzo Di Lazzaro

Aim of the present study is to evaluate the possible applications of transcranial magnetic stimulation (TMS) in stroke patients. It is organized in three sections. In the first part (Study 1), we have evaluated the neuroprotective effect of extremely low-frequency magnetic fields (ELF-MF) in acute ischemic stroke. In the second part (Study 2), we have evaluated the association of repetitive TMS and robotic rehabilitation to promote motor recovery in patient with chronic ischemic stroke. In the last part (Study 3 and 4), TMS was used to study the mechanisms of plasticity and to obtain prognostic information about recovery after stroke. Taken together, our data demonstrate that TMS is a non-invasive technique that can be used in the management of stroke patients, both in acute and in chronic phase.

POLY-METHYIL-METACRYLATE DOES NOT PROVIDE SIGNIFICANT REINFORCEMENT TO A CADAVERIC DIAPHYSEAL MODEL UNDERGOING BENDING STRESS

Ph.D student Roberto Luigi Cazzato Tutor Giuseppe Tonini

Aim: To test the consolidative properties of two different consolidative intra-medullary (IM) techniques (osteoplasty and Kirshener-augmented osteoplasty) in a diaphyseal cadaveric model undergoing three point bending test. Materiale and methods: Thirty different human cadaveric tibia specimens were randomly and equally assigned to receive no IM consolidation (Group 1), osteoplasty (Group 2), or Kirshener-augmented osteoplasty (Group 3). All specimens were subsequently tested on a dedicated servohydraulic machine with a three-point bending test. Fracture load and Young's module were obtained for each tested specimen. In the end, fracture occurrence and its morphology both to bone and to IM consolidative material were evaluated. Results: The median quantity of PMMA injected was 18 ml for group 2 (p25-p50; 15-21) and 19 ml for group 3 (p25-p50; 17-21). In terms of fracture load, no significant difference was found when comparing group 1 and 2 (z =-0.793; P = 0.4295), group 1 and 3 (z = -0.944; P = 0.3472), and group 2 and 3 (z = -0.454; P = 0.6501). Neither, Young's module differed significantly when comparing group 1 and 2 (z = 0.121; P = 0.9044), group 1 and 3 (z = 0.338; P = 0.7278), and group 2 and 3 (z = 0.148; P = 0.8807). The most common type of bone was B0 (14/30, 46.6%) and A2 (8/30, 26.6%). Fractures to the IM material occurred in 4 cases (4/30, 13.3%) and were always consistent with PMMA fracture. Conclusions: PMMA does not confer any consolidative advantage to dyaphisis undergoing bending stresses as compared to non-PMMA augumented dyaphisys.

MODULATION BY EXTRAVIRGIN OLIVE OIL ON THE ENDOCANNABINOID SYSTEM IN CO-LORECTAL CANCER

Ph.D student Antonio Costa

Tutor Mauro Maccarrone

Extravirgin olive oil (EVOO) represents the typical lipid source of the Mediterranean diet, an eating habit pattern that has been associated with a significant reduction of cancer risk. Diet is the more studied environmental factor in epigenetics, and many evidences suggest dysregulation of epigenetic pathways in cancer. The aim of our study was to investigate the effects of EVOO and its phenolic compounds on endocannabinoid system (ECS) gene expression via epigenetic regulation in both human colon cancer cells (Caco-2) and rats exposed to short and long-term dietary EVOO. We observed a selective and transient up-regulation of CNR1 gene – encoding

for type 1 cannabinoid receptor (CB₁) – that was evoked by exposure of Caco-2 cells to EVOO (100ppm), its phenolic extracts (OPE, 50µm) or authentic hydroxytyrosol (HT, 50µm) for 24h. None of the other major elements of the ECS (CB₂, GPR55 and TRPV1 receptors; and NAPE-PLD, DAGL, FAAH, and MAGL enzymes) was affected at any time point. The stimulatory effect of OPE and HT on CB₁ expression was inversely correlated to DNA methylation at CNR1 promoter and was associated with reduced proliferation of Caco-2 cells. Interestingly, CNR1 gene was less expressed in Caco-2 cells when compared to normal colon mucosa cells, and again this effect was associated with higher level of DNA methylation at CNR1. Moreover, in agreement with the in vitro studies, we also observed a remarkable (-4 fold) and selective increase in CB₁ expression in the colon of rats receiving dietary EVOO supplementation for 10 days. Consistently, CpG methylation of rats Cnr1 promoter, miR23a and miR-301a, previously shown to be involved in the pathogenesis of colorectal cancer and predicted to target CB₁ mRNA, was reduced after EVOO administration down to -50% of controls. Taken together our findings demonstrating CB₁ gene expression modulation by EVOO or its phenolic compounds via epigenetic mechanism, both in vitro and in vivo, may provide a new therapeutic avenue for treatment and/ or prevention of colon cancer.

INERTIAL SENSING FOR HUMAN ACTIVITY RECOGNITION AND PERSONAL INDOOR LOCA-LIZATION

Ph.D student Francesca De Cillis **Tutor** Roberto Setola

In the last few years, the interest in tracking people's habits and behaviors found even more interest among the scientific and industrial community. Monitoring people conditions, understanding their necessities and demands represent key values in a wide variety of fields. Nevertheless, healthcare, assistance and safety are possibly the fields that most actively leverage the knowledge gained from the analysis of the human behaviour. For these reasons, the automatic recognition of human physical activities, commonly referred to as Human Activity Recognition (HAR), has emerged as a key research area in the fields of human-computer interaction, mobile and ubiquitous computing. Depending on the specific application domain, the inference of human behaviour could be assessed in different ways; however, the revolution that have undergone the class of inertial sensors in the last decades, has elected on-body inertial sensing to be the most prevalent monitoring technology in the HAR field. Integrating accelerometers, gyroscopes and compasses, the inertial sensor is able to measure physical quantities thus tracking body motion, in principle, without restrictions. Despite the proven research interest among the topic, on-body inertial sensors HAR applications are still far from being mature. There is indeed a number of open challenges that spans from signal processing and sensor fusion to the improvement of existing algorithms and expansion to unexplored application areas. The objective of this work consists into improving the current state of the art in the inertial-based HAR field. As the first research focus, the dissertation examines the current state of the art in the field of HAR systems for gait assessment. Walking represents one of the most important daily activity and has significant influence on the quality of life. At the same time, it represents the function at the basis of several HAR application fields (healthcare, safety & security, sport and entertainment). In this context, we presents a pervasive solution for gait patterns classification that uses data retrieved from a waist-mounted inertial sensor. The proposed algorithm has been conceived to operate continuously for long term applications. In contrast to classic approaches that use a large number of features and sophisticated reasoners, our solution is able to assess 4 different gait patterns (standing, level walking, stair ascending and descending) by using only 3 features and a light classifier. A leading HAR application field strongly related to the gait assessment is the personal Indoor Localization and Positioning (ILP) field. Tracking the pose of a user moving into indoor environments may indeed be useful in several contexts (special population care, key building management, retail industry, etc.), but is definitively crucial in case of emergencies. Given this demand, the second goal of this work is devoted to illustrate the HIPS, an hybrid indoor positioning

system. Integrating inertial navigation and exteroceptive sensors, the HIPS is able to overcome typical limitations arising from the individual implementation of a single approach, providing a user position estimate with a room-level accuracy. Apart from tracking human conditions, detecting anomalous behaviour represents another key-research area in the HAR field. Concerning healthcare, a typical example of such applications is represented by fall detection systems. Falls can potentially cause severe physical injuries and can reduce the independence of older individuals through dramatic psychological consequences. These findings called for the development of pervasive and easy-to-use assistive devices for fall detection. The third and last goal of this work is indeed devoted to illustrating the FALLEN, an algorithm that uses accelerometer and gyroscope data retrieved from a waist-mounted inertial sensor for detecting falls. Integrating acceleration and gyroscope data, FALLEN enables to overcome the limitations of classic approaches and allows differentiating falls from typical daily activities, increasing the overall system's accuracy without affecting the computational load.

CYBER-PHYSICAL SECURITY OF SCADA SYSTEMS AGAINST PHYSICAL FAULTS, CYBER THREATS AND GENERIC MALICIOUS ATTACKS

Ph.D student Estefania Etcheves Miciolino Tutor Roberto Setola

As Critical Infrastructures are becoming more complex and vital for modern societies, their management, monitoring and protection becomes of paramount importance, specially in safety-critical situations. Several studies are being carried out in the last years, having the objective of enhancing the security level and highlighting any vulnerability of these. It is clear that tests cannot be performed directly on real infrastructures due to security and safety issues, hence the development of realistic emulated environments becomes essential. Moreover, the scientific community has often considered and studied separately the cyber and physical domains constituting these complex systems, whilst it is essential to consider the overall environments, for example analyzing how cyber events may affect the operative condition of the physical infrastructure, as well as how anomalies in the physical dimension may generate a critical situation with respect to the Industrial Control Systems' monitoring architecture. Having this problem in mind, a wide study on Industrial Control Systems is carried out, analyzing their constituting components, evolution and vulnerabilities. It is then followed by an analysis of the state-of-the-art on the diagnosis of physical faults and an overview of the cyber threats that these systems face. Making good use of these studies and being aware of the security concerns of cyber-physical systems, an innovative testbed reproducing the operation of a water infrastructure has been developed. In the designed system it is possible to introduce several types of physical faults and/or cyber anomalies, as well as to implement different configurations in order to test several scenarios and control strategies. The testbed is here described in detail, and its effectiveness regarding cyber-physical concerns is illustrated via several experimental tests.

VALUTAZIONE DELL'EFFETTO ANTITUMORALE DI CABOZANTINIB SULL'OSTEOSARCOMA E SUL MICROAMBIENTE OSSEO

Ph.D student Marco Fioramonti Tutor Bruno Vincenzi

Osteosarcoma (OS) is the most common primary malignant tumor of bone. Thanks to its high heterogeneity and to survival signals from bone microenvironment, OS can resist to current standard treatments and for this reason, novel therapies are needed. Literature data assert that c-MET oncogene, a tyrosine-kinase receptor, plays a crucial role in OS initiation and progression. In the present study, we aimed to evaluate the effect of c-MET inhibitor cabozantinib (CBZ) on OS both directly and through its action on bone microenvironment. We

tested different doses of CBZ on in vitro models of OS alone or in co-culture with bone cells in order to reproduce OS-tumor microenvironment interactions. We demonstrated that CBZ is able to decrease proliferation and migration of OS cells, inhibiting ERK and AKT signalling pathways. As a consequence, OS cells activate autophagic process. Furthermore, CBZ leads to a further inhibition of the proliferation of OS cells expressing receptor activator of nuclear factor ?B (RANK), thanks to its effect on bone microenvironment, where it causes an overproduction of osteoprotegerin and a decrease of production of RANK ligand by osteoblasts. Overall, our data demonstrate that CBZ might represent a new potential treatment against OS, affecting both OS cells and their microenvironment. In this scenario, RANK expression in OS cells could represent a predictive factor of better response to CBZ treatment.

THE EFFECT OF WEIGHT GAIN IN METABOLICALLY NORMAL OR ABNORMAL OBESE SUBJECTS

Ph.D student Gemma Fraterrigo Tutor Samuel Klein

Obesity is associated with insulin resistance and increased intrahepatic triglyceride (IHTG) content, both of which are risk factors for diabetes and cardiovascular disease. However, a subset of obese people does not develop these metabolic complications. Weight gain is associated with the development and worsening of nonalcoholic fatty liver disease (NAFLD), but the mechanisms responsible for this association are not know. Here, we tested the hypothesis that people defined by IHTG content and insulin sensitivity as "metabolically normal obese" (MNO), but not those defined as "metabolically abnormal obese" (MAO), are protected from the adverse metabolic effects of weight gain. An increased number of macrophages in adipose tissue is associated with insulin resistance and metabolic dysfunction in obese people. However, little is known about other immune cells in adipose tissue from obese people, and whether they contribute to insulin resistance. In an effort to investigate the underlying differences between MNO and MAO, we investigated the characteristics of T cells in adipose tissue from MAO subjects, MNO subjects, and lean subjects. Body composition, multiorgan insulin sensitivity, VLDL apolipoprotein B100 (apoB100) kinetics, and global transcriptional profile in adipose tissue were evaluated before and after moderate (\sim 6%) weight gain in MNO (n = 12) and MAO (n = 8) subjects with a mean BMI of 36 ± 4 kg/m2 who were matched for BMI and fat mass. Imaging and stable isotope tracers techniques were combined to evaluate the effect of moderate weight gain in 27 obese people on intrahepatic triglyceride (IHTG) content and hepatic lipid metabolism in order to elucidate the mechanisms responsible for weight-gain induced IHTG accumulation. Plasma cytokine concentrations and subcutaneous adipose tissue CD4+ T-cell populations were assessed in 9 lean, 12 MNO, and 13 MAO subjects. Skeletal muscle and liver samples were collected from 19 additional obese patients undergoing bariatric surgery to determine the presence of cytokine receptors Although the increase in body weight and fat mass was the same in both groups, hepatic, skeletal muscle, and adipose tissue insulin sensitivity deteriorate, and VLDL apoB100 concentrations and secretion rates increased in MAO, but not MNO, subjects. Moreover, biological pathways and genes associated with adipose tissue lipogenesis increased in MNO, but not MAO, subjects. Also, our results demonstrate that weight gain causes an imbalance between hepatic availability and disposal of fatty acid by increasing de novo lipogenesis, reducing fatty acid oxidation, and by inadequately increasing VLDL secretion. Adipose tissue from MAO subjects had 3- to 10-fold increasese in numbers of CD4+ T cells that produce interleukin (IL)-22 and IL-17 (a T-helper [Th] 17 and Th22 phyenotype) compared with MNO and lean subjects. MAO subjects also had increased plasma concentrations of IL-22 and IL-6. Receptors for IL-17 and IL-22 were expressed in human liver and skeletal muscle samples. II-17 and II-22 inhibited uptake of glucose in skeletal muscle isolate from rats and reduced insulin sensitivity in cultured human hepatocytes. These data demonstrate that MNO people are resistant, whereas MAO people are predisposed, to the adverse metabolic effects of moderate weight gain and that increased adipose tissue capacity for lipogenesis might help protect

MNO people from weight gain—induced metabolic dysfunction. Weight gain causes and imbalance between hepatic availability and disposal of fatty acid which are likely responsible for increased IHTG accumulation. Adipose tissue from MAO people contains increased numbers of Th17 and Th22 cells, which produce cytokines that cause metabolic dysfunction in liver and muscle in vitro. Additional studies are needed to determine whether such alterations in adipose tissue T cells contribute to the pathogenesis of insulin resistance in obese people.

INNOVATIVE SENSORS FOR FOOD QUALITY MONITORING WITH A NON-DESTRUCTIVE APPROACH

Ph.D student Francesco Genova **Tutor** Giorgio Pennazza

Nowadays, sensors are becoming more and more important in life sciences. Both in biomedical fields where the need of a continuous monitoring of body parameters is a desired characteristic and in food industry, where checking the quality of the rough materials is now a fundamental requirement. Nevertheless, different environments require specific sensing techniques. Agri-food sensors are requested to control and certify food safety, quality and convenience; furthermore, as the agri-food processes are highly variable, the sensors require the capability to handle this variability. Sensor fundamental requirements are often the disposability of the sensing element, indeed risk of contamination between different samples are typical characteristics of food science sensors. They should be characterized by a fast and reliable response, for example in quality control tests. This PhD thesis dealt with the use and optimization "on field" of a sensor platform consisting of gas and liquid sensors for qualitative assessment of food by fingerprinting. This platform is named BIONOTE. Sensor responses have been validated by means of a multidisciplinary experimental procedure consisting on data correlation with specific biochemical parameters. The innovation given by this technology is represented the utilization of a non-destructive tool for on-line monitoring of food quality as an alternative rapid and accurate method for routine analysis. Thus the thesis want to introduce a new device able to perform real-time, sensitive and possibly label free detection of target analytes or foods by exploiting the different sensing properties given by the use of different transducers and a unique chemical interactive material, the anthocyanin. A brief introduction to the state of the art of the technologies used in food analysis is reported in the first Chapter. In Chapter 2 a description of the BIONOTE platform is given. Then, applications on filed of the BIONOTE potentiality are described and results are presented and discussed. Finally conclusions are drawn.

IMMUNOMODULATORY ROLE OF OMEGA 3 POLYUNSATURATED FATTY ACID-DERIVED PRO-RESOLVING LIPID MEDIATORS ON CELL-MEDIATED ADAPTIVE IMMUNITY

Ph.D student Alessandro Leuti Tutor Mauro Maccarone

Inflammation represents a crucial physiological process mounted by immune system to react to tissue damage and pathogens. Acute inflammation, which is usually the quickest immune reaction to occur upon the insurgence of an infection, is a widely conserved mechanism that is triggered and regulated mostly by cells of the innate immunity (i.e. dendritic cells, monocyte/macrophages, neutrophils and NK cells) and is meant to be the first line of defense against microbes. Since innate immune cells only recognize a relatively limited number of pathogen-associated molecular patterns, higher efficiency requires the action of the specialized cells of the adaptive immune system (i.e. T and B lymphocytes), which potentiate innate functions. Acute inflammation can have two main outcomes: on one hand, prolonged immune reactions can lead to chronic inflammation, which involves the concerted action of macrophages and lymphocytes; on the other hand, inflammation can

undergo resolution with complete return to tissue homeostasis. Resolution of inflammation is a pivotal process that is meant to actively quench phlogistic signals. Even though this mechanism has been thought for a long time to act in a passive way, in recent years it has been unequivocally established that it is instead a finely regulated and active process, governed by a new class of lipid mediators, which are synthesized by essential polyunsaturated fatty acids such as arachidonic acid (AA), eicosapentaenoic acid (EPA) and docosahexanenoic acid (DHA). These molecules, which have been termed pro-resolving lipid mediators (SPMs), orchestrate self-limitation of inflammation mostly by acting on innate immune cells; even though a growing number of works are starting to suggest that SPMs might also act on adaptive immunity, our current knowledge of the immunoregulatory actions exerted by SPMs on chronic inflammation and its main effectors, the lymphocytes, is still very scarce. Thus, we investigated the immunomodulatory effect of crucial DHA-derived bioactive lipids such as RvD1, RvD2 and Maresin 1 on pivotal populations of cell-mediated adaptive immunity, i.e. CD4+ and CD8+ cells, as well as the most important T lymphocyte subsets (TH1, TH2, TH17 and iTreg). In order to achieve this goal we analyzed immune functions by means of polychromatic flow cytometry alongside with well-established molecular biology and biochemistry techniques such as gRT-PCR, western blot and ELISA assays. We found that DHA-derived SPMs strongly inhibit the production of pro-inflammatory cytokines (i.e. IFN-?, TNF-a and IL-17) in circulating CD4+ and CD8+ lymphocytes, and reduced the production of IL-2, a pivotal lymphocyte mitogen, without inducing apoptosis or necrosis. In order to further characterize the complete spectrum of immunoresolving actions elicited by DHA-derived SPMs, we assayed their ability to modulate de novo generation of T helper cells (TH1, TH2 and TH17) and induced regulatory T cells (iTreg) from naïve T cell precursors. RvD1, RvD2 and MaR1 were able to reduce intracellular production and release of TH1 and TH17 signature cytokines (IFN-? and IL-17 respectively), as well as inhibiting the expression of their pivotal transcription factors (T-bet and RORc), without affecting in any way TH2 function. On the other hand they enhanced the immunoregulatory properties of iTreg cells by enhancing the expression of their key transcription factor Foxp3, while boosting the release of the anti-inflammatory cytokine IL-10 and the expression of their immunosuppressive receptor CTLA-4. These effects were mediated by the two well-known SPMs receptors, GPR32 and ALX/FPR2. The direct evidence of a role for SPMs in modulating cell-mediated immunity holds huge importance in that it unveils a new level of regulation that the immune system may use to balance inflammatory responses, and considerably improve our knowledge of the vast network of bioactive lipids that regulate inflammatory processes. This could be crucial in theorizing possible future therapeutic approaches for many T cell-dependent chronic inflammatory diseases.

EMERGENT DYNAMICS OF ELECTRICALLY COUPLED BETA-CELLS: IMPLICATIONS FOR PHYSIOPATHOLOGY OF THE ENDOCRINE PANCREAS

Ph.D student Alessandro Loppini Tutor Simonetta Filippi

More than 40 years of research studies on the endocrine beta-cells have enlightened most of the fundamental mechanisms involved in insulin secretion in rodents, with a vast published literature that confirms our knowledge of the electrophysiology of these cells, based on both experiments and mathematical models. Although, much more remains to be understood, with particular regards to the loss of beta-cell functionality in pathologies such as diabetes. Among the mechanisms involved in the normal regulation of insulin secretion in mouse islets, gap junction electrical coupling was shown to be an essential aspect in beta-cell endocrine function. Intercellular communications induced by such coupling represent in fact an efficient way through which cells can synchronise their intrinsically heterogeneous activity, homogenising pancreatic islets response to glucose stimuli, improving glucose responsiveness, and giving rise to a global pulsatile insulin release, which is more effective than a constant insulin supply. Therefore in this scenario, the pancreatic islet is a complex structure where beta-cells explicate their function through communication. It is also proven that the loss of

direct electrical coupling in rodents leads to an altered beta-cells function, characterised by impaired glucose tolerance and insulin secretion. Interestingly, in this case, the resulting pattern of hormone release resembles those observed in diabetic patients, thus suggesting that the beneficial effect of electrical coupling may be compromised or lost in diabetic islets. In confirmation of that, recently published studies show altered expressions of the protein forming junctional channels in in-vitro environments resembling diabetic inflammatory condition, and an increase resistance to cytotoxic compounds in the case of electrically coupled beta-cells. Moreover such metabolic disorders can have dramatic effects on the islet architecture itself and alter intercellular communication by topological modification of the islet, which are very likely to occur especially in autoimmune forms of diabetes, where beta-cells are progressively killed by an intra-islet infiltrate of immune cells. Such evidence requires investigating deeply gap junction properties between beta-cells, extending the knowledge accumulated on rodents to the less studied human case. Concerning this, published literature have shown interesting aspects regarding the human islet. In fact, in common with rodents, also in humans are expressed proteins forming gap junctional channels, and moreover, functional tight junctions have been observed by histological studies. Furthermore, an even more intriguing fact is that human islet architecture is completely different compared to the mouse islet. Therefore, it is reasonable to think that gap junction channels not only have a role in homogenising and synchronising the response of human beta-cells, but it can also be hypothesised that such a different topology of the islet have a considerable effect on cells emergent activity and could imply significant functional differences respect to the rodent case. Unfortunately, the human beta-cell electrophysiology has been analysed only recently, and electrical coupling between human beta-cel-Is remains a largely unexplored topic. Therefore, in this dissertation a mathematical modelling approach is adopted to investigate gap junction coupling effect on the emergent dynamics of beta-cell populations, trying to analyse the collective behaviour of coupled cell clusters in-silico. Different electrophysiological models are used in this framework to reproduce the dynamics of both mouse and human beta-cells. Specifically, based on a mouse electrophysiological model, two studies here presented are focused on the analysis of the emergent electrical activity of coupled cell populations, and its robustness upon operating conditions, such as the cluster topology, the stimulatory glucose concentration, and the intrinsic biological noise. Finally, a third study based on a mathematical model fine-tuned on human electrophysiology attempts to estimate and analyse gap junction coupling between human beta-cells, validating obtained results against the few available experimental studies. This dissertation contains new results outlined in the following. At first, a study of compact beta-cell clusters shows that a coherent dynamics characterises beta-cells in mouse islets. This robust dynamical state ensures a long-range correlated cellular activity, and it is strictly dependent on both glucose stimulation level and cluster size. The beta-cell cluster is able to switch from coherent to uncorrelated dynamics resembling phase transition and critical phenomena observed in other physical systems. It is worth noting that a similar regulation of the dynamics around a critical point is a feature of other biological networks, such as neuronal networks. At second, a study concerning the topological effects on the emergent dynamics shows that the beta-cells in mouse islets can be viewed as a fully coupled functional unit while the human islet seems to be characterised by functionally distinct modules of beta-cells. This substantial difference is mainly due to the percolated network architecture underlying beta-cells arrangement in human islets, which induces a complex pattern of intercellular synchronisations. It is important to note that such pattern shows scale-free similarity features characteristic of the percolated cluster resembling the human beta-cell arrangement, not observed in the compact mouse architectures. Finally, the third study represents to the best of our knowledge the first attempt to estimate gap junction conductance between human beta-cells. Results obtained are surprisingly in agreement with the reported values of the junctional conductance between mouse beta-cells. The analyses of small coupled populations of human beta-cells show moreover that the estimated strength of coupling can substantially alter the emergent dynamics, and consequently the insulin release.

PhD Courses and XXIX cycle theses (2014-2016)

THE CATEGORY OF RELATIONSHIP IN THE EXPERIENCE OF PREGNANCY. FOR THE HER-MENEUTIC OF HUMAN PROCREATION

Ph.D student Ilaria Malagrinò Tutor Maria Teresa Russo

I think that my existing research expertise will contribute to the research project and the research team both from a methodological and conceptual point of view.

Indeed, for my PhD thesis (program) I've worked on the intimate relationship between foetus and maternal organisms in order to find a proper category to signify its nature. After an analysis of biological, biochemical, physiological, psychological evidence on maternal-foetal relationship, a first step of my research was characterized by the study of the different descriptions and categorizations of this relationship. So, I've analyzed the concepts of symbiosis, parasitism, absolute or unconditional hospitality, attachment, dialogue and communication, found in biological, philosophical and psychological literature on this topic. The inadequacy of these categories to grasp the intimate nature of 'in-between', focusing only one side of the relationship or forgetting the role of both the actors, and the lack of systemic research, seemed to me the logical consequence of an insufficient hermeneutical reflection on gestation.

For this reason, the second step of my research has been characterized by the inquiry on the theoretical meaning of pregnancy. This study has led me to an analysis of the philosophical reflections on this topic of Irigaray, Kristeva, Young and Edmée Mottini-Coulon. Despite the differences between the authors, I thought interesting their common definition of pregnancy as a dynamic process that has its expression in the body. A body that is particular, dialectical, and ambivalent in its dual unity and in its subjective anatomy. Every symptom or growth equates to an identity movement, a mutual dance between two selves. For this reason, pregnancy appears in the texts of these feminists thinkers as an actualizing of being. However, their attempts to articulate an alternative ways of conceptualising the pregnant organism, stressing the need to reconceptualise the relationship between self and body, result in fragmentary references that along with criticism of essentialism prevent a philosophical systematization about pregnancy. Hence the need of a further deepening justified by the consideration that such work could be read in perspective but also retrospectively.

The analysis of the pregnancy's categories would help to shed direct light on an experience ignored by speculative thought, but, at the same time, would allow further study and reflection on the human structure and condition. So, in the third stage of my research, I've tried to analyze pregnancy as contradictory body experience in the light of the phenomenological reflection of Michel Henry on the living and lived body and in the fourth, I've tried to test how Ricoeur's notion of 'Oneself as Another' could fit with the problem of personal identity, its persistence and its relationally dynamic structure.

Finally, according to the biological and psychological literature, in a fifth step I've proposed to categorize the nature of the relationship between mother and foetus as recognition, applying to pregnancy what Ricouer's says in 'Parcours de la reconnaissance'. In particular, I thought the use of the plural 'parcours' instead the singular form of this term is very interesting, because it embodies a series of conceptual meanings which authorize an analogical and not univocal use of this expression. Furthermore, it seemed to me that this term could show the relationship, the 'in-between', at the same time, containing a clear reference to the subjects involved in it.

NEW PERSPECTIVES, MANAGEMENT AND PROBLEMS ASSOCIATED WITH THYROID CANCER TREATMENT

Ph.D student Giuseppe Mangiameli Tutor Anna Crescenzi

In the first part of this Phd thesis we investigated the role of Raman spectroscopy (RS) in thyroid cancer dia-

gnosis; in the second part we report the results of PTH (1-34) treatment to prevent hypocalcemia in subjects at high risk of post-surgical hypocalcemia after thyroidectomy. Raman spectroscopy (RS) is a non-invasive optical label-free tool increasingly used to get molecular fingerprints of biological tissues. It is able to provide bioanalytical information on any biomolecule with high specificity. Technological advances over the last decade have created a new and faster Raman imaging microscope instrument, providing morphological tissue investigation of large areas coupled with point-by-point spectral analysis of biochemical composition. This option is important not only for discrimination between healthy and pathological tissues. The reported results have demonstrated the feasibility and reproducibility of RS to discriminate normal thyroid tissue from PTC, and between classical and follicular variants of PTC, on the basis of their biochemical fingerprints. Based on the experimental results obtained in this work, we can attest the significant carotenoids presence in the PTC tissues with respect to the healthy tissue, in which their absence or minimal and localized presence was detected. To our knowledge, this is the first experimental evidence of carotenoids presence in the neoplastic thyroid tissue. Several future perspectives can derive from these preliminary results: 1. the development of a RS optical biopsy system to investigate thyroid tissue alterations. 2. The development of intraoperative technology which may able to classify cell populations in real time, making it an ideal guide for surgical resection and decision making. In the second section of this Phd thesis we report the results of Monocentric Prospective Phase II Randomized Open Label Trial (Teriparatide for HYpocalcemia in POst-surgical Subjects: Thypos Trial). The objective of this trial was to evaluate whether teriparatide can prevent postsurgical hypocalcemia and shorten the hospitalization in subjects at high risk of hypocalcemia following thyroid surgery. Twenty-six subjects (six males, 20 females) with intact PTH lower than 10 pg/ml 4 hours after thyroidectomy were included and then they randomized (1:1) to receive SC administration of 20 mcg of teriparatide every 12 hours until the discharge (treatment group) or to follow standard clinical care (control group). The obtained results allow us to conclude that Teriparatide may prevent postsurgical hypocalcemia and shorten the duration of hospitalization.

SURGICAL TREATMENT OF THE GIANT CELL TUMOR (GCT): CONTROL OF LOCAL RECURRENCE AND FUNCTIONAL OUTCOMES

Ph.D student Gianluca Marineo Tutor Alberto Di Martino

Background Giant cell tumor (GCT) of bone is a primary tumor that commonly occurs in the epiphyses of long bones, and most frequently in the distal epyphises of the femur [1-3]. GCT is a benign bone tumor, even though it has local aggressivenes, and it can metastatize to the lungs with nodules having the same histologic features of the primary tumor. Cells in the tumor belong to one of two cell lines: stromal spindle cells, and multinucleated giant cells [5]. The giant cells are a population present in a reactive way to the production of local growth factors, and are responsible for bone resorption and osteolysis of the TCG [2,4]. The histology only serves to make the diagnosis: however the grading cannot predict the behavior of the lesion, and has not prognostic significance. Lesions are classified according to Campanacci et al. Surgery is the gold standard in the treatment of GCT [1,3]: Curettage, with intralesional margins, is carried out in all stage 1 lesions, in most of stage 2 and rarely in lesions with stage 3. After curettage, patients typically have a better functional outcome, but are exposed to an increased rate of local relapse. In the case that curettage is not technically possible for the altered mechanical properties of the bone or because of the soft tissues invasion, segmental resection followed by modular or composite prosthetic implants, (or by grafting and plating in the distal radius) [15]. After curettage of the lesion, the filling of the void can be performed by bone allograf or bone cement, which also has a local adjuvant action. The aim of the current study is to quantify the overall function, and incidence of local recurrence after surgery for TCG depending on the kind of surgery and the material used to fill the local void, by retrospectively analyzing the cohort of patients managed at the Rizzoli Institute of Bologna from 1990-2013. Materials and Methods The clinical and follow-up data included the charts of 412 patients operated on for GCT of the extremities, followed for at least two year follow-up. 412 patients, of which 216 females and 196 males. The detected average age was 34 years; 101 cases were located upper limb, lower limb 311. Stage 2 and 3 account for the majority of cases, with only 6 cases of stage 1. Curettage was performed with opening of a wide enough window to display the entire tumor cavity, removal of the tumor by means of curettes and use of high-speed milling cutter. Filling the cavity after curettage was performed by bone cement in 108 patients, by cement and subchondral graft in 78, and bone grafts alone in 55; in 4 patients the void was left unfilled. Resection was performed In 159 cases, with wide margins in 140 cases, marginal in 5 and focally intralesional in 14 cases. In these patients, the reconstruction was with osteoarticular graft in 60 cases, modular prosthesis in 58 case, composite implants in 16 cases. It was not carried out no reconstruction in 25 cases localized to the proximal fibula or distal ulna. Functional evaluation was performed by Muscoskeletal Tumor Society Score. Results The overall recurrence rate was 17.5%; in particular, it reached 20.4% after curettage and 13.2% after resection and reconstruction. Local relapse after curettage was observed significantly less in patients whose void is filled by bone cement. Local relapse after curettage was observed significantly less in patients whose void is filled by bone cement. Comparing the functional results according to the scale of MSTS Enneking, patients treated with curettage or resection had a mean score of 92.7±13.2 for the former and 85.4±15.6 for the latter. The ANOVA test showed a significant difference between the type of surgery and the remaining functional outcome (Welch test, p = 0.00003) bringing the best values of about 10% in curettage compared to resection.

NEW DIAGNOSTIC AND THERAPEUTIC ASPECTS OF SUBCLINICAL AND CLINICAL FORMS OF PARATHYROID GLAND DISEASES

Ph.D student Andrea Palermo Tutor Paolo Pozzilli

1. RESEARCH QUESTION Can alendronate and vitamin D improve the bone mineral density in patients with normocalcemic primary hyperparathyroidism? ABSTRACT Introduction: normocalcemic primary hyperparathyroidism (NPHPT) is defined by normal serum calcium and consistently elevated PTH levels after ruling out the causes of secondary hyperparathyroidism. It is likely that subjects with NPHPT may develop kidney and bone disease. As no data on the pharmacological treatment of NPHPT are available, we aimed to investigate the effects of alendronate and cholecalciferol on both BMD and bone biochemical markers in postmenopausal women with NPHPT. Safety of vitamin D was evaluated as secondary endpoint. Methods and design: the study was a prospective open label randomized trial comparing 15 postmenopausal women with NPHPT (PMW-NPHPT), treated with oral alendronate plus cholecalciferol (treated group) and 15 PMW-NPHPT treated only with cholecalciferol (control group). Blood samples were obtained at baseline and after 3, 6, and 12 months. Bone turnover markers (BTM) were measured at baseline, 3, and 6 months, respectively. BMD was assessed at baseline and after 12 months. Results: after 1 year of treatment, BMD increased significantly at the lumbar, femoral neck, and hip level in the treated group, but not in the control group (p = 0.001). No differences were found between or within groups in serum calcium, PTH, and urinary calcium levels. BTM significantly decreased in the treated group but not in the control group, at 3 and 6 months (p < 0.001), respectively. No cases of hypercalcemia or hypercalciuria were detected during the study. Conclusion: the results of this study indicate that alendronate/cholecalciferol may increase BMD in postmenopausal women with NPHPT. Alendronate/cholecalciferol or vitamin D alone does not affect serum or urinary calcium. 2. RESEARCH QUE-**STION** What is the prevalence and the metabolic bone profile of the normocalcaemic hypoparathyroidism? ABSTRACT Introduction: there are no consistent data on the prevalence and bone status of normocalcaemic hypoparathyroidism (NHYPO) as defined by normal adjusted calcium and low PTH level. Our aim was to determine the prevalence and the metabolic bone profile of NHYPO in older women, assessing its evolution over time. The second objective was to evaluate the prevalence of other calcium metabolic disorders. Methods and

design: the Osteoporosis and Ultrasound Study (OPUS) is a 6-yr prospective study of fracture-related factors. A total of 2419 older women (age 55-79 yrs) and 258 younger women (age 30-40 yrs) participated. Complete follow-up data were available in 1416 subjects. After calculating the adjusted calcium according to James' formula, we identified 'abnormal' calcium and PTH using Mahalanobis distances and allocated older women into different pathological categories using reference intervals from the healthy young women. Results: we identified 57 subjects with NHYPO (2.4%). These women had lower than expected bone turnover as assessed by bone alkaline phosphatase (-14.5%, 95% CI: -26.2 to -3.0, P = 0.007), CTX (-66.3%, 95% CI: -74.0 to -56.4, P <0.001) and osteocalcin (-36.8%, 95% CI: -45.6 to -26.6, P <0.001). After 6 years, of the 35 NHYPO subjects with follow-up data, none developed overt hypoparathyroidism and only 15 (0.6%) subjects had persistent evidence of NHYPO. We also identified 86 subjects (3.6%) affected by hyperparathyroid hypercalcaemia. Conclusion: this is the first large population-based study to investigate NHYPO in older women. NHYPO is fairly common, not always persistent and is characterized by low bone turnover. 3. RESEARCH QUESTION Can PTH(1-34) treatment restore the calcium and phosphate balance and improve the quality of life in adult subjects with post-operative hypoparathyroidism? ABSTRACT Introduction: conventional therapy for hypoparathyroidism consists of calcium and calcitriol, but sometimes normal serum calcium cannot be maintained. and/or this approach might lead to nephrocalcinosis, nephrolithiasis, or renal insufficiency. The objective of the study was to investigate the effects of 6 months of PTH(1-34) treatment in adult subjects with postoperative hypoparathyroidism and to evaluate quality-of-life changes. Methods and design: this is an Italian multicentric 2-year prospective, open-label study that has included 42 subjects with surgical hypoparathyroidism (90% females, age range 34-77 y). The intervention included a twice-daily PTH(1-34) 20 mcg sc injection. At baseline and after 6 months of PTH(1-34) treatment, calcium and vitamin D supplementation requirements, serum calcium, phosphate, creatinine, alkaline phosphatase, uric acid, and 24-hour urinary calcium excretion were evaluated. Quality of life was evaluated by the Rand 36-Item Short Form Health Survey covering eight domains of physical and mental health. Results: the mean serum calcium levels significantly increased from baseline to 15 days $(7.6 \pm 0.6 \text{ ys } 9.1 \pm 0.9 \text{ mg/dL}, P < .001)$ and remained stable until the end of the observational period. despite a significant reduction in calcium and vitamin D supplementation. Phosphate levels gradually decreased from baseline to the sixth month (P = .005 for the trend), whereas the alkaline phosphatase increased (P <.001). Data from the Rand 36-Item Short Form Health Survey showed a significant improvement in the mean scores of all eight domains (P <.001). Conclusion: this is the largest study that demonstrates the effectiveness of PTH(1-34) in the treatment of adult patients with postsurgical hypoparathyroidism, and it shows that PTH(1-34) may improve the mental and physical health in hypoparathyroid subjects. 4. RESEARCH QUESTION Can PTH(1-34) prevent the onset of hypocalcemia and shorten the duration of hospitalization in subjects with high risk of post-surgical after thyroidectomy? ABSTRACT Introduction: subjects undergoing thyroidectomy may experience severe hypocalcemia often requiring extended hospitalization with increased healthcare costs. Up to now, there are no studies evaluating the use of teriparatide for prevention of postoperative hypocalcemia. The objectives of this study are to evaluate whether teriparatide can prevent post-surgical hypocalcemia and shorten the hospitalization in subjects at high risk of hypocalcemia following thyroid surgery. Methods and design; this is a prospective Phase II Randomized Open Label Trial conducted in the Surgical ward of the Campus Bio-Medico University of Rome. 26 subjects (6 males, 20 females, mean age 53.4, SD 17.0) with iPTH <10 pg/ml 4 hours after thyroidectomy have been enrolled. Subjects have been randomized (1:1) to receive subcutaneous administration of 20 mcg of teriparatide every 12 hours until the discharge (treatment group) or to follow the standard clinical care (control group). The Main Outcome Measure were Adjusted serum calcium, duration of hospitalization, calcium/calcitriol supplementation. Results: treated patients had a lower risk of hypocalcemia than controls [RR 0.26 (95% CI:0.09- 0.723)]. The median duration of hospitalization was 3 days (IQR:1) in control subjects and 2 days (IQR:0) in treated subjects (P = 0.012). One month after discharge, 10 out of 13 subjects in the treatment group had stopped calcium carbonate supplements, while only 5/13 in the control group had discontinued calcium. The ANOVA for repeated measures showed a significant difference in calcium supplements between groups at one month visit (P = 0.04) as well as a significant difference between discharge and one month visit in the treatment group (P for interaction time group = 0.04). Conclu-

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sions: our findings suggest that Teriparatide may prevent post-surgical hypocalcemia, shorten the duration of hospitalization and reduce the need for calcium and vitamin D supplementation after discharge in high risk subjects after thyroid surgery.

SIGNAL PROCESSING TECHNIQUES AND BRAIN IMAGING IN TMS EEG SIGNALS

Ph.D student Sara Petrichella Tutor Luca Vollero

TMS allows to give a control input into specific target nodes in a complex network, characterize the dynamics, capture the responses physiologically via EEG and ultimally relate those to the behaviour (e.g. muscle twitch) as shown in the study VI. The study I can be considered an example of asymmetric hyperexcitability, accessed by TMS mapping technique, that could represent a mechanism of brain functional plasticity in a chronic disorder, such as congenital hydrocephalus. The study II presented suggest that in Alzheimer's Disease (AD) and Subcortical Ischemic Vascular Dementia (SIVD) the motor cortex is functionally rearranged and its excitability is enhanced, supporting the idea that cortical hyperexcitability can promote cortical plasticity. In the study III by using EEG-TMS co-registration, was clearly demonstrated that the sensorimotor system in mild AD is strongly hyperexcitable and could be preliminary interpreted as a compensatory mechanism allowing the preservation of sensorimotor programming and execution over a long period despite disease progression. The study IV confirms the hypothesis that bidirectional neural interface could be of primary interest to redirect cortical areas deprived of their original function because of amputation toward restorative neuroplasticity. In the study V the results suggest that a multimodal approach is helpful for advanced study of the characteristics of excitability and connectivity morpho/functional physiological and pathological aging. Indeed, it allows identifying anomalies in the connections between different brain areas of being possibly causative mechanisms involved in the pathogenesis of Alzheimer's disease. From the study VI clearly emerge that EEG co-registrated with TMS is a unique toolbox to evaluate not only the connectivity between areas as results of an inductive procedure but actually to measure -for the first time- the strength of connections existing between the dynamically activated areas. This is crucial to guarantee innovative paradigms of rehabilitation in stroke patients and amputees.

QUANTITATIVE METHODS FOR HOSPITAL PLANNING AND CONTROL

Ph.D student Luca Pontecorvi Tutor Marco Papi

The provision of hospital resources, such as beds, operating theatres and nurses, is a matter of considerable public and political concern and has been the subject of widespread debate. The political element of healthcare emphasises the need for objective methods and tools to inform the debate and provide a better foundation for decision-making. An appreciation of the dynamics governing a hospital system, and the flow of patients through it, point towards the need for sophisticated capacity models reflecting the complexity, uncertainty, variability and limited resources. A common current practice is to plan and manage hospital capacities through a simple deterministic models using average patient flows, average needs, average length-of-stay, average duration of surgical operations etc. Average analysis can be misleading since the underlying distribution is not symmetric. To overcome such limit it is described the probability distribution of some of the most important proxies for measuring the consumption of hospital resources such as discharge rate, admission rate, number of hospitalized patients, and Length of Stay (LoS). While model proposed to describe the LoS is an innovative generalization of models previously applied in this area, the model for the description of the discharge and admission rate is borrowed from the financial mathematics. It is assumed that exist an analogy between the default of a financial institution and discharge of a patient. This approach come up with a simple and closed-form formula for the distribution function of the discharge rate and the admission rate. Moreover some risk metrics, used

in financial mathematics, are applied in order to analysis the tail of the distributions. In order to investigate the activities of the hospital departments, a deterministic analysis of numeric indicators is performed. Among the common measured clinical parameters, a robust metrics, characterizing the constituent entities and the best opportunity tools for the characterization of the results, have been identified. Using this approach is provided an application in the evolution of the department. Particularly, the attention is focused on the evolving of the medical team. Deterministic approached turns out to be not suitable for the development of decision support tools, mathematically speaking, a hospital corresponds to a complex stochastic system so that the common deterministic approach for planning and managing the system can be expected to be inadequate. Hence it is also provided a methodological approach to optimize the hospital resource allocation based on stochastic dynamic programming (SDP). SDP approach is well-positioned to model these types of problems because of the explicitly sequential nature of the decision policies they produce. The aim is to reduce the probability of having a number of patients different from a fixed level over a define interval of time. It is shown that the optimal policy proposed performs better than an empirical policy. In modern societies, the cost of healthcare are increasing year by year. The requirement is to cut costs without diminishing the quality of care. One solution is to increase efficiency; hospital need to plan their operations to use available resources in an optimal fashion. In order to analysed the relation between LoS, risk score, and costs, Real Option Approach (ROA) is applied. Physician has the right but not the obligation to discharge a patent if some efficiency conditions are not verified. In according financial yield curve models, a cost function is estimated and the results are compared whit value obtain from ROA. It is also proposed an application of the Lotka-Volterra model and an extension of the Heston model. The thesis has the following outline: Chapter 1 presents an introduction to healthcare systems and briefly discusses sources of fund and issues affecting healthcare quality and costs. It also highlights the importance of using quantitative models to analyse different healthcare delivery strategies and optimize costs. Chapter 2 focuses on healthcare financing systems in different countries and describes different methods of paying for healthcare providers. The strengths and weaknesses of the discussed methods are also pointed out. Chapter 3 introduces a generic framework for healthcare planning. This framework, encompassing 4 hierarchical levels of control and four managerial areas, is used to identify external and internal environmental characteristics affecting the organization of healthcare systems. Chapter 4 provides an overview of the main mathematical theories used in subsequent chapters. These include stochastic differential equations, real option analysis, option pricing and Poisson processes. Chapter 5 introduces a statistical model to describe the length of stay of hospital patients. The proposed model overcomes some of the limitations of previous models by using a Phase-Type Gamma distribution which is able to capture the data characteristics in a more accurate way. The model is tested on a case study based on the Campus Bio-Medico hospital database. Chapter 6 introduces some quality indicators as a tool to evaluate health systems performance and quality. A dynamic stochastic optimization model is then proposed to optimize hospital bed occupancy. Three different models to describe patient discharge probabilities are also proposed and then used to evaluate the optimal policies. Chapter 7 introduces three financial-like models to describe the variable costs associated with patient hospitalization: a Nelson-Siegel model; a Black-Scholes model and a Cox-Ingersoll-Ross model. The second part of the dissertation, Chapters 8 and 9, tackles different problems that the student has investigated during his doctoral studies and which are not related to healthcare system planning. Specifically, Chapter 8 describes a model to optimize the consumption of financial inspection resources for tax evasion by analysing the interaction between prevention/control activities and illegal behaviours. Chapter 9 proposes a new stochastic volatility model for the calibration of option prices.

CALORIE RESTRICTION AND THE MEDITERRANEAN DIETS: A PILOT-STUDY ON THE APU-LIAN AND SICILIAN PROTOTYPICAL MEDITERRANEAN DIETS

Ph.D student Wanda Rizza **Tutor** Raffaele Antonelli Incalzi

The present PhD thesis collects the work of my three years Doctoral degree in Human Food and Nutrition Sciences, which I started at Washington University in Saint Louis (MO, USA) in 2013, and continued at Campus Bio-Medico University of Rome (Italy), from February 2014 to December 2015. In the first chapter, I present the main subjects studied during the first year of PhD program, thoroughly exploring their features and systematic applications: Calorie restriction and a number of related topics, such as Intermittent Fasting and Calorie Restriction Mimetics. In fact, throughout the year spent at the Washington University in St Louis, I worked with professor Luigi Fontana, who has been studying Calorie Restriction (CR) for as many as twenty years, and currently leads as the Principal Investigator (PI) of a clinical research team at the Division of Geriatrics and Nutritional Sciences and Center for Human Nutrition, Washington University School of Medicine, Within this context, I took part in three different clinical studies, two of which are currently still ongoing, and I learnt for the first time how clinical research really works, quickly developing a true passion for it. Thanks to this experience, I could write and see published my first two papers: one regarded the role of CR in promoting healthy longevity, and the other presented the latest data on long-term CR in enhancing cellular quality-control processes in human skeletal muscle. I am still now very passionate about this theme, thence I have chosen to thoroughly discuss it in this chapter, to illustrate both the state of the art and the future perspectives of such a debated topic. In the second chapter, I expose an overview of the literature regarding the features of the Mediterranean Diet (MD). More specifically, I first present the original MD model, then I compare it with four other dietary patterns - basing such evaluation on the available scientific data -, and afterwards I illustrate the latest evidences on the MD's role in preventing multifactorial diseases and promoting longevity. Finally, this section also aims at introducing my own PhD project, which is fully described in the third and last chapter of my dissertation. In this chapter, I describe the pilot study I performed between March 2014 and October 2015, within two different areas of Southern Italy. This study was realized thanks to the Campus Bio-Medico University, and particularly to professor Raffaele Antonelli Incalzi, who first exposed to me the idea of investigating the evolution of the MD by characterising the past dietary pattern of a delimited Mediterranean area, in order to better understand whether the diet was more respondent to the MD original model six to seven decades ago than it is today, as well as if the current diet can be considered 'Mediterranean' in its real sense. To investigate this hypothesis, we performed the "Prototypical Mediterranean Diet study" within two selected and geographically delimited areas of Southern Italy, by comparing the diet adopted sixty to seventy years ago (Prototypical Mediterranean Diet, PMD) with the contemporary one (Contemporary Mediterranean Diet, CMD). More specifically, we first collected guali-guantitative data on both the PMDs and the CMDs by singularly interviewing the 208 recruited subjects; we then analyzed the macronutrients and micronutrients intakes for both groups and carried out the gualitative characterization of the two PMDs; lastly, we verified to which extent both the PMDs and the CMDs fitted the recommendations of two well recognized international guidelines, the Italian dietary recommendations (LARN) and the USDA dietary guidelines.

INDIVIDUALIZED TREATMENT OF PATIENTS WITH ADVANCED NSCLC: POTENTIAL AP-PLICATION FOR CIRCULATING TUMOUR CELLS (CTCS) MOLECULAR AND PHENOTYPICAL PROFILING

Ph.D student Elisabetta Rossi Tutor Daniele Santini

NSCLC is a major cause of cancer-related death in both men and women globally. Despite recent advances in early tumour detection, surgical treatment, radio-chemotherapy, and targeted therapy, the NSCLC-related high mortality rate remains a daunting challenge. The therapeutic choice is driven by the molecular/genetic assessment of the primary tumour as determined at diagnosis. This practice needs to be integrated with other methods for real time tumour mutational screening. Indeed, a body of evidence is emerging that the feasibility of new tools for monitoring the malignancy throughout the continuum of care may offer major benefits to the patients. Since predictive biomarkers are lacking so far, CTC assays have gained interest to assist clinicians in patient management. Recent experiences demonstrated that CTC detection could help improve the diagnosis and predict a prognosis in patients with non-small cell lung cancer (NSCLC). However, EpCAM positive CTCs are less frequently detected in NSCLC patients compared to other epithelial tumours. In NSCLC, CTCs show a different cytokeratin (CK) pattern and a lower expression of full-length Epithelial Cell Adhesion Molecule (EpCAM) compared to other carcinomas. Indeed, 80% of patients were CTC-positive by the EpCAM-independent ISET compared to only 23% by standard CellSearch assay. The primary aim of the Project is to determine the percentage of CTC-positive patients, and the total CTC numbers in advanced NSCLC at baseline, before starting treatment. We questioned whether we could detect a higher number of CTCs by implementing the standard CellSearch assay. Secondary aim is to evaluate if CTCs count modifications are an early predictor of response to treatment. The exploratory aim is set and applying the molecular and phenotypic profiling of CTCs, in order to verify if these data could be relevant to manage patient therapy. We then investigated in some selected NSCLC patients, the potential of the combined use of CTCs and cfDNA assays as a dynamic indicator of treatment efficacy. We evaluated 189 patients, enrolled from December 2012 to June 2016 in trial no. NCT02407327 (http://www.clinicaltrials.gov). To address these aims we determined the percentage of CTC-positive patients and total CTC number in our cohort using standard assay (SA) and an expanded assay (EA) that was set to tailoring the cytokeratin panel for NSCLC. We demonstrated that the presence of tumour cells was associated with a poor prognosis leading to the definition of a cut-off value (=1 cell) in metastatic NSCLC with standard assay (SA) and with expanded assay (EA), we showed a better predictive value concern STP. The CTCs level variation during the treatment predict a good response to therapy, and the phenotype and molecular characterization of CTCs is feasible using different methods with several degrees of in depth investigation. All data collected provides useful information about disease evolution. We compared, where possible, the EGFR mutational status of the NSCLC primary tumour and that of the CTC and cfDNA collected at baseline and after the first line of treatment, and found consistent results in all the analysed samples. Our data suggests a potential complementary use of Circulating Tumour Cells and cfDNA in solid Tumours concerning molecular information. To indicate that in the circulating compartment we could find a window to survey the disease evolution, the relationship between subpopulation of cancer cells, the therapy response and the host relationship. This evidence documents and confirms the great impact that the detections and the characterization of CTCs, with malignant proprieties, could have in tailored medicine if this biomarker will be inserted in the decisional tree used in the clinical management of patients.

Impact of Research on Society

EVALUATION OF ANTIOXIDANT CAPACITY IN HYPOXEMIC PATIENTS THROUGH BAP TEST AND ANALYSIS OF ERYTHROCYTE MEMBRANES

Ph.D student Francesca Flavia Rossi **Tutor** Chiara Fanali

Hypoxia is a condition that is determined at the cellular and tissue level, where there are present low levels of oxygen due to inadequate distribution. Hypoxemia instead is defined as oxygen deficiency in the blood. The objective of this study was to evaluate the levels of biological antioxidant capacity using a standardized method of analysis in plasma and through an experimental method that uses advanced erythrocyte membranes. It has been suggested that patients suffering from hypoxemia may be more fully subjected to oxidative stress, compared to a control sample consisting of healthy subjects with the characteristics that will be indicated later, and a third sample of subjects in geriatric patients not hypoxemic. Subjects and Methods: We enrolled 88 patients belonging to the Day Hospital and the department for acute geriatrics, and to the blood transfusion center of the Campus Bio-Medico. The first group consisted of 31 hypoxemic subjects, suffering from respiratory failure. The second group consists of 30 subjects in geriatric patients not hypoxemic, suffering from varying degrees of functional impairment, poly-pathological. Finally, the third group consisting of 27 healthy subjects, referred to as the control group. an experimental "in vitro" model for the analysis of samples of erythrocyte membranes was applied in the following ways: comparison of magnitude of the erythrocyte membranes induced damage as a result of photooxidation on samples collected from the study subjects - comparison with respect to a group of elderly patients normal-ossiemici - comparing them to a group of healthy patients younger than 60 years. Results and Discussion: A comparative assessment of the three groups, as regards the analysis of erythrocyte membranes, are not observed statistically significant differences. Specifically, an inter-group comparison was made: between patients belonging to group "hypoxemic" and the "control" group is not observed statistical significance, in fact the value of P value is equal to 0.95. The same can be said both in the comparison between "controls" and "geriatric not hypoxemic" and between "hypoxemic" and not "hypoxemic", also in this case in fact, the P value is not indicative of statistical significance with values of 0.26, respectively, and 0.18. Comparative analysis of the three groups, inherent in the BAP test, there was a significant difference between patients' hypoxaemic "and" controls "with P value equal to 0.0018 and among geriatric patients and healthy controls with no hypoxaemic value of P value <0.0001 So in geriatric patients has resulted in a lower antioxidant capacity of plasma from donors; this in relation to the fact that they are subjected to greater oxidative stress, in relation to the aging condition and hypoxemia On the contrary, in the comparison between hypoxemic patients and not hypoxemic, in geriatric age, has not revealed a statistically significant with a value P value equal 0.69. In conclusion, the resulting data are relevant with regard to the use of the BAP test as an evaluation of the anti-oxidant capacity test in elderly patients; appear also no significant data emerged in relation to the analysis of erythrocyte membranes.

ADVANCED MICROFLUIDIC DEVICES MIMICKING THE DYNAMIC AND 3D PHYSIOLOGICAL MICROENVIRONMENT FOR DIAGNOSTIC APPLICATIONS

Ph.D student Maria Chiara Simonelli Tutor Marcella Trombetta

Despite a recognized value in nowadays research, conventional two-dimensional (2D) cell cultures still fail to provide accurate prediction of tissue functions and behavior in vivo. In fact, cells grown on flat tissue culture substrates can differ considerably in their morphology, cell-cell and cell-matrix interactions, and differentiation from those growing in more physiological 3D environments. On the other hand, animal models may not adequately reproduce several features of human tumors, drug therapeutic responses, and autoimmune diseases. Recent advances in tissue engineering and biomedical technologies aim for the integration of biology with the

spatial positioning capabilities allowed by microfabrication techniques. Physiological environments provided by extracellular matrices can be reproduced, besides the development of tissues, organs and tumors, paving the way to the so-called organ-on-chip technology. Microfluidic devices are generally fabricated as polydimethylsiloxane (PDMS) replicas of a lithographically obtained master. They allow a precise control on cells and tissue microenvironment, thus enabling the exposure of cells to medium flow. These aspects led to advanced systems, faithfully reproducing physiologically relevant conditions. Furthermore, the additional ability of these models lays in the chance of manufacturing optically transparent platforms, which might be observed in real time under the microscope, allowing a high-throughput imaging analysis. This thesis work highlights the power of these complex microengineered systems. In a first example, a "NAFLD-on-chip" device, exploiting a sinusoid-like geometry with a microchannel array to simulate the endothelial-like barrier, was used for high density 3D hepatocyte culture, with the aim to recapitulate the onset of nonalcoholic fatty liver disease. As a second example, a tumor-on-chip platform was developed to study the interaction between Cancer Stem Cell (CSCs) behavior with immune cells, in particular with Tumor-Associated Macrophages (TAMs). These models would accelerate and facilitate translational research to perform the screening of new therapies. In this sense, in vitro 3D models provide a bridge on the gap between traditional cell culture and animal models.

DESIGN, REALIZATION AND TESTING OF A MULTI-SENSORY DEVICE FOR FOOD AND ME-DICAL APPLICATIONS

Ph.D student Alessandro Zompanti **Tutor** Giorgio Pennazza

In most cases analyses on gas and liquid samples are performed using several sensors arranged in multi-dimensional systems (array of sensors) or in network systems (sensors systems expressly distributed on a special area), according to the specific application. Sensors array are intended to mimic the working principles of the human senses: advancements made in the field of electronic miniaturization, power consumption reduction and data analysis techniques make possible the realization of these new technologies. Measuring devices implementing sensors array are used both in the medical applications fields, because of their minimally invasive approach for the patients, and in the food industry field because of their non-destructive approach towards the food samples. This PhD research activity is focused on the design, realization and test of a novel multi-sensory system for medical and food applications.

EFFECT OF COCOA POLYPHENOLIC EXTRACT ON MACROPHAGE POLARIZATION

Ph.D student Maria Giovanna Belluomo Tutor Laura Dugo

Polyphenols-rich cocoa has many beneficial effects on human health, such as anti-inflammatory effects. Macrophages function as control switches of the immune system, maintaining the balance between pro- and anti-inflammatory activities. We investigated the hypothesis that cocoa polyphenol extract may affect macrophage pro-inflammatory phenotype M1 by favoring an alternative M2 anti-inflammatory state on macrophages deriving from THP-1 cells. Chemical composition, total phenolic content and antioxidant capacity of cocoa polyphenols extracted from roasted cocoa beans were determined.THP-1 cellswere activated with both LPS and INF-? for M1 or with IL-4 for M2 stimulations. Specific cytokines were quantified. Cellular metabolism, through mitochondrial oxygen consumption, and ATP levels were evaluated. In this work it was shown that cocoa polyphenolic extract attenuated in vitro inflammation showing a significantly decreased macrophage response to M1 activation, demonstrated by a significantly lowered secretion of pro-inflammatory cytokines. Moreover, treatment of M1 macrophages with cocoa polyphenols influences macrophage metabolism by

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promoting oxidative pathways led to a significant increase of O2 consumption by mitochondrial complexes and a higher production of ATP through oxidative phosphorylation. In conclusion cocoa polyphenolic extract suppresses inflammation in M1 phenotype and influences macrophage metabolism by promoting oxidative pathways and M2 polarization of active macrophages.

PREOPERATIVE MULTIMODAL REHABILITATION IN PANCREATIC AND PERIAMPULLARY TUMOR SURGERY: PRELIMINARY RESULTS OF A RANDOMIZED CLINICAL TRIAL

Ph.D student Fabio Ausania Tutor Giuiseppe Tonini

HAEMOSTASIS AFTER LAPAROSCOPIC REMOVAL OF ENDOMETRIOTIC CYSTS: COMPARI-SON BETWEEN BIPOLAR COAGULATION AND FLOSEAL: A PROSPECTIVE STUDY

Ph.D student Patrizio Damiani

Tutor Roberto Angioli

EEG-TMS TECHNIQUE: IMPROVEMENT OF EEG DATA ANALYSIS BY REMOVING ARTI-FACTS AND CLINICAL APPLICATIONS IN HEALTHY SUBJECTS AND IN ACUTE CEREBRO-VASCULAR DISEASE

Ph.D student Federica Giambattistelli Tutor Fabrizio Vernieri

THE CARE IN TIME: "TEMPUS FUGIT"

Ph.D student Lucia Giuliani **Tutor** Vittoradolfo Tambone

NATURAL HISTORY OF BONE METASTASES IN PATIENTS WITH NON-SMALL CELL LUNG CANCER: A MULTICENTER RETROSPECTIVE STUDY

Ph.D student Angela La Notte

Tutor Alberto Di Martino

EVALUATION OF NUTRITIONAL STATUS, PHYSICAL PERFORMANCE INDICES AND AN-TIOXIDANT CAPACITY IN A GERIATRIC POPULATION

Ph.D student Eleonora Nunziata Tutor Chiara Fanali

NATURAL HISTORY OF BONE METASTASES FROM PRIMARY TUMORS OF THE BILIARY TRACT: MULTICENTRIC RETROSPECTIVE ANALYSIS

Ph.D student: Nicola Papapietro Tutor Daniele Santini

PROGNOSTIC VALUE OF REMOTE ISCHEMIC PRECONDITIONING CORONARY IN ELDERLY PATIENTS IN CARDIAC REHABILITATION

Ph.D student Elpidio Santillo Tutor Raffaele Antonelli Incalzi

THE RESIDENT AND COLONIZING MICROBIOTA OF BILE

Ph.D student Genoveffa Francesca Sapia Tutor Giordano Dicuonzo

STUDY OF SUSCEPTIBILITY TO OXIDATIVE STRESS OF ERYTHROCYTE PURIFIED MEM-BRANES IN PEOPLE WITH ALZHEIMER'S DISEASE

Ph.D student Francesco Maria Serino Tutor Raffaele Antonelli Incalzi

ATHEROSCLEROSIS AND OSTEOPOROSIS INDUCED BY AROMATASE INHIBITORS IN WO-MEN WITH HISTORY OF BREAST CANCER: AN EXPERIMENTAL CLINICAL TRIAL

Ph.D student Chiara Spoto Tutor Francesco Pantano

STUDY OF THE MECHANISMS INVOLVED IN ROS SCAVENGING IN TWO VARIETIES OF RICE (ORYZA SATIVA SSP. JAPONICA) WITH DIFFERENT SALINE STRESS SENSITIVITY

Ph.D student Maria Beatrice Ronci Tutor Vittoria Locato

MODULATION OF BRAIN PLASTICITY FOR UPPER LIMB MOTOR RECOVERY IN ISCHEMIC STROKE

Ph.D student Lucia Florio Tutor Vincenzo Di Lazzaro



Awards

Alessandra Berton

1st level Grant - Italian Society of Orthopedics and Traumatology (SIOT) Fellowship SIGASCOT - Federation of Orthopaedic Trainees in Europe Summer School

Valerio Chiurchiù

"Best scientific contribution" 2016 Human & Translational Immunology Conference.

Marcello De Falco

"First Paper Award" International Conference on Material Science and Engineering Technology 2016 (ICMSET 2016), October 14-16, Phuket (Thailand).

Laura De Gara

Pavoncella Award for Female Creativity, 5th edition: Scientific Research

Giovanni Di Pino

"2016 Italia Giovane" Award

Alessio Gizzi

GNFM-INdAM, Visiting Professor Project Grant 2016.

Mauro Maccarrone

"2016 Mechoulam Award" by the International Cannabinoid Research Society.

Marco Miglionico, Annunziata Nusca

"GISE Fellow" at the Congress of the Italian Society of Invasive Cardiology (GISE).

Giovanni Muto, Emanuela Altobelli, Maurizio Buscarini, Rocco Papalia

Best video on Thuvep at the 2016 Annual Congress of the Italian Society of Urology

Nicola Napoli

2016 "lan T Boyle Award" by the European Calcified Tissue Society (ECTS)

Emiliano Noce, Loredana Zollo, Angelo Davalli, Rinaldo Sacchetti, Eugenio Guglielmelli.

Young Researcher" Award at the V Conference of the

GNB (National Group of Bioengineering), June 20-22, Napoli.

"Relationship between neural and muscular recordings during hand control".

Gabriele Oliva

"Domenico Razzé" prize for the best PhD thesis in the field of Critical Infrastructure Protection.

Matteo Paolucci, Claudia Altamura, Riccardo Altavilla and Fabrizio Vernieri

Best Poster at the National Congress of the Italian Society for the Study of Headaches

Paolo Pozzilli

Awarded at the 9° World Congress for Prevention of diabetes and its complications.

Fabrizio Russo

2nd level Grant - Italian Society of Orthopedics and Traumatology (SIOT).

Francesco Spinelli

Ippocrate Award for Surgery

Eleonora Tamilia

PhD dissertation Award "Alberto Mazzoldi", XXXV School of the National Group of Bioengineering, September 26/29, Bressanone. "New tools for a technology-aided assessment of newborns' oral-motor behavior"

A. Sicilia, Lucio Trodella, Michele Fiore, Luca Eolo Trodella, Aurelia Iurato, Carlo Greco, Barnaba Floreno, M. Miele, P. Trecca, A. Carnevale, S. Ramella, R.M. D'Angelillo

"Best oral communcation" XXVI National Congress of the Italian Association of Radiation Oncology (AIRO)".

Gianluca Vadalà

Best Paper Award at the International Spine Week Appointed European representative of the International Society for the Study of the Lumbar Spine.

2016 Research Papers Awarded by the Department of Medicine and Surgery as "UCBM Paper of the Month"

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Head A. Afeltra

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Head F.E. Agrò

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Head R. Setola

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Head M. Maccarrone

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BIOMEDICAL ROBOTICS AND BIOMICROSY-STEMS

Head E. Guglielmelli

Articles

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Head R. Antonelli Incalzi

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Head R. Angioli

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HEART SURGERY

Head E. Covino

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HEMATOLOGY, STEM CELL TRANSPLAN-TATION, TRANSFUSION MEDICINE AND CELLULAR THERAPY

Head G. Avvisati

Articles

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MICROSCOPIC AND ULTRASTRUCTURAL ANATOMY

Head S. Morini

Articles

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Head V.M. Fazio

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Head A.M. Persico

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Head V. Di Lazzaro

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Head G. Di Pino

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Head S. Filippi

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Head F. Spinelli

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