1st Freiburg,Germany - Mendoza, Argentina Symposium on Translational Medicine

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Submitted: 23. April 2018
Published: 24. May 2018
Volume: 5
Issue: 5

Affiliation: Facultad de Ciencias Médicas Universidad Nacional de Cuyo, Argentina

Languages: English
Keywords: Cancer, Cardiovascular and Neurological Maladies
DOI: 10.17160/josha.5.5.423

1st Freiburg - Mendoza Symposium on Translational Medicine

Cancer, Cardiovascular and Neurological Maladies

Monday, 5th of March 2018

Location: UNCuyo, Seminars Room IHEM - Faculty of Medical Sciences, Centro Universitario, Parque General San Martín, Mendoza

Sponsors: German Honorary Consulate in Mendoza, BioThera-Roland Mertelsmann Stiftung, UNCuyo, ELEA-Phoenix and Pfizer Laboratories

5 de Marzo: Seminars Room IHEM - Faculty of Medical Sciences

09.00 **Opening:** Dean of the Faculty of Medical Sciences Prof. Dr. Pedro Eliseo Esteves, Rector of the National University of Cuyo , Ing. Agr. Daniel Pizzi and Prof. Dr.Dr.h.c.mult. Roland Mertelsmann, Albert-Ludwigs- University of Freiburg.

Session 1: Cancer and Leukemia //Facilitator: Dr. Alejandra Mampel

09.30 **Towards a personalized medicine in breast cancer: contributions and proposals from Mendoza, Argentina**
Prof. Dr. Laura Vargas
Facultad de Ciencias Médicas Universidad Nacional de Cuyo, IMBECU-CONICET

10.00 **The Darwinian View of Cancer: Chances and Challenges**
Prof. Dr.Dr.h.c.mult. Roland Mertelsmann
Albert Ludwigs University of Freiburg

10.30 **Engineered Biointerfaces through Tailormade Surface-attached Polymer Networks – From to new diagnostic tools to implantable materials**
Prof. Dr. Jürgen Rühe
Albert Ludwigs University of Freiburg

11.00 **Coffee break**

Session 2: Cardiovascular Diseases and High Altitude Research//Facilitator: Prof. Dr. Borner

11.30 **Cardiovascular research: from the heart to the people, and back**

Prof. Dr. Emiliano Diez
Instituto de Fisiología, Facultad de Ciencias Médicas
Universidad Nacional de Cuyo, IMBECU-CONICET

12.00 **Myocardial triggers involved in the activation of remote ischaemic preconditioning**
Prof. Dr. Ricardo J. Gelpi
Instituto de Fisiopatologia Cardiovascular, Facultad de Medicina, Universidad de Buenos Aires, Argentina

12.30 **High altitude medicine – chances and challenges**
Dr. Birke Ahlfeld
Center for Intensive Care, Lucerne Cantonal Hospital (LUKS), Switzerland

13.00 **Lunch**

Session 3: Neurological Diseases // Facilitator: Prof. Dr. Fabián Cremaschi

14.30 **Are we all addicts? A neurobiological perspective on compulsive behaviour**
Prof. Dr. Sean Patterson
Instituto de Fisiología, Facultad de Ciencias Médicas
Universidad Nacional de Cuyo, IHEM-CONIET

15.00 **Metabolomics in neurological diseases and asphyxia: status, chances and challenges**
Prof. Dr. Hans-Peter Deigner
Dean of the Faculty of Medical and Life Sciences University
Furtwangen

15.30 **Coffee break**

Session 4: Immunity, Inflammation and Environment // Facilitator: Prof. Dr. Mertelsmann

16.00 **Mechanisms of intracellular pathogen survival: playing a strategic game with autophagy**
Prof. Dr. María Isabel Colombo
Área de biología molecular, Facultad de Ciencias Médicas
Universidad Nacional de Cuyo, IHEM- CONICET

16.30 **New insights into the molecular mechanisms and treatment of Aspergillosis in immunocompromised patients**
Prof. Dr. Dr. h.c. Christoph Borner
Director International Master of Biomedical Sciences (IMBS)
Institute of Molecular Medicine, Albert Ludwigs University of Freiburg

17.00 **What´s the point of justice in health research?** PhD student
Felicitas Holzer (UBA/Paris-Sorbonne, CONICET)

17.30 **"Synchronizing" the Argentine and German Systems of higher education: Chances and Challenges**
Dr. Wolfgang Zimmermann, BioThera Roland Mertelsmann Foudation

18.15 **Closing:** Dean of the Faculty of Medical Sciences Prof. Dr. Pedro Eliseo Esteves, Authorities of the National University of Cuyo and Prof. Dr.Dr.h.c. Roland Mertelsmann, Albert-Ludwigs- University of Freiburg.

Tuesday, 6th of March 2018 - CILINDROS UNCUYO (CICUNC)

BRIEF COMUNICATIONS – YOUNG RESEARCHERS OF THE UNIVERSIDAD NACIONAL DE CUYO AND IMBS

SESION I - Cilindro Central // Facilitators Dr. Alejandra Mampel – Dr. Laura Vargas

09.00 **EPIDEMIOLOGY OF INVASIVE DISEASES CAUSED BY *Streptococcus agalactiae***

Bárbara Soledad ARIAS; *Universidad Nacional de Buenos Aires*

09.15 **HOST CELL-*Trypanosoma cruzi* INTERACTION: NOVEL ASPECTS FOCUSED ON MEMBRANE BIOPHYSICS AND microRNAS**

Dr. Juan CUETO; Instituto de Fisiología - Facultad de Ciencias Médicas de la Universidad Nacional de Cuyo. *Instituto de Histología y Embriología de Mendoza (IHEM-CONICET).*

09.30 **COPPER INDUCED TOXICITY AND THE PROTECTIVE ROLE OF GLUTATHIONE: IMPLICATION OF IMPAIRED PROTEIN FOLDING RATHER THAN OXIDATIVE STRESS**

Christian SAPORITO-MAGRINA¸ *Facultad de Farmacia y Bioquímica de la Universidad de Buenos Aires. Institute of Molecular Medicine and Cell Research, Faculty of Medicine, Albert Ludwigs University of Freiburg*.

09.45 **A FRESHWATER SNAIL AS AN EXPERIMENTAL MODEL TO EXPLORE PHYSIOLOGICAL RESPONSES TO ENVIRONMENTAL STRESS: HYPOMETABOLISM AND XENOBIOTICS**

Maximiliano GIRAUD-BILLOUD; *Instituto de Fisiología de la Facultad de Ciencias Médicas Universidad Nacional de Cuyo. Instituto de Histología y Embriología de Mendoza (IHEM-CONICET)*

10.00 **mRNA EXPRESSION OF THE PROLACTIN RECEPTOR ISOFORMS IN AUTOIMMUNITY**

Dr. Juan Pablo MACKERN-OBERTI, *Instituto de Fisiología de la Facultad de Ciencias Médicas Universidad Nacional de Cuyo. Instituto de Medicina y Biología Experimental de Cuyo (IMBECU-CONICET)*

10.15 **PIGMENT EPITHELIUM-DERIVED FACTOR (PEDF) EXPRESSION IN THE REPRODUCTIVE TRACT OF MALE RATS IS REGULATED BY ANDROGENS**

Dr. María de los Ángeles MONCLUS. *Área de Histología y Embriología de la Facultad de Ciencias Médicas de la Universidad Nacional de Cuyo. Instituto de Histología y Embriología de Mendoza (IHEM-CONICET).*

10.30 **P38 REGULATE LUNG COLONIZATION IN METASTASIS ASSAY**

Dr. Sebastian REAL. *Instituto de Fisiología de la Facultad de Ciencias Médicas Universidad Nacional de Cuyo. Instituto de Histología y Embriología de Mendoza (IHEM-CONICET).*

10.45 ***Chlamydia trachomatis*: PATHOGEN-HOST CELL INTERPLAY**

Mariano ALONSO BIVOU; *Área Química Biológica de la Facultad de Ciencias Médicas de la Universidad Nacional de Cuyo. Instituto de Histología y Embriología de Mendoza (IHEM-CONICET)*

SESION II - Cilindro Sur // Facilitators Dr. Emiliano Diez – Dr. Armando Damiani

09.00 **VASCULAR INFLAMMATION ON METABOLIC SYNDROME MODEL**

Dr. Nicolás RENNA; *Área de Fisiología Patológica de la Facultad de Ciencias Médicas de la Universidad Nacional de Cuyo. Instituto de Medicina y Biología Experimental de Cuyo (IMBECU-CONICET)*

09.15 **CARDIOVASCULAR DISEASES AND DIABETES: EFFECT OF OXIDATIVE STRESS, INFLAMMATION AND ANGIOGENESIS ON THE VASCULAR WALL**

Dr. María Isabel QUESADA**;** *Área Química Biológica de la Facultad de Ciencias Médicas de la Universidad Nacional de Cuyo. Instituto de Medicina y Biología Experimental de Cuyo (IMBECU-CONICET)*

09.30 **CARDIAC ACTIONS OF C-TYPE NATRIURETIC PEPTIDE IN EXPERIMENTAL ARTERIAL HYPERTENSION**

Estefania PRENTKI SANTOS; *Instituto de Química y Metabolismo del Fármaco, Facultad de Farmacia y Bioquímica de la Universidad de Buenos Aires (UBA-CONICET). Institute of Physiology, Universität Würzburg*

09.45 **GALECTIN 1 PROMOTES TUMOR CELL MIGRATION BY ENHANCING NA^+/H^+ EXCHANGER ISOFORM 1 (NHE1) ACTIVITY**

Dr. Victoria BOCANEGRA*, Área de Fisiopatología – Facultad de Ciencias Médicas – Universidad Nacional de Cuyo. Instituto de Medicina y Biología Experimental de Cuyo (IMBECU-CONICET).*

10.00 **Hsp70 ROLE ON MIGRATION AND CYTOSKELETON MODULATION AS AN EFFECT OF LOSARTAN IN PROXIMAL TUBULE CELLS (PTC) FROM SPONTANEOUSLY HYPERTENSIVE RATS (SHR)**

Dr. Victoria COSTANTINO, *Área de Fisiopatología – Facultad de Ciencias Médicas – Universidad Nacional de Cuyo. Instituto de Medicina y Biología Experimental de Cuyo (IMBECU-CONICET)*

10.15 **ACTIVATED COAGULATION AT HIGH ALTITUDE**

Dr. Sebastián DONATO; *Hospital José Néstor Lencinas, Mendoza, Argentina*

10.30 **RESPIRATORY DISORDERS IN PEOPLE ASCENDING THE SUMMIT OF ACONCAGUA (6962 MSNM)**

Dr. Birke AHLFELD, *Center for Intensive Care, Lucerne Cantonal Hospital (LUKS), Switzerland.*

10.45 **ESTABLISHMENT OF A LABORATORY OF VIROLOGY AT THE FACULTY OF MEDICAL SCIENCES FOR RESEARCH AND DIAGNOSIS OF IMPORTANT VIRAL PATHOGENS**

Dr. Armando DAMIANI; *Área Química Biológica de la Facultad de Ciencias Médicas de la Universidad Nacional de Cuyo; Instituto de Medicina y Biología Experimental de Cuyo IMBECU-CONICET.*

Superior Council Room - Universidad Nacional de Cuyo

11:00 Assembly of directors of IMBS program and authorities of the Faculty of Medical Sciences and both Universities to evaluate cooperation.

13.00- 14.00 **Lunch (CICUNC)**

OPENING SPEECH Symposium Freiburg Mendoza

This is a very special day for our School of Medicine and for the Universidad Nacional de Cuyo. We are very pleased to inaugurate this, the first Mendoza-Freiburg Symposium on Translational Medicine.

The initiative for organizing this symposium arose a few months ago, during the visit of Professors Borner and Mettersmann. It was supported by the German Consulate of Mendoza, particularly by Mr. Andres Vollmer. He, the faculty and the young researchers who compose our team showed their excitement about the symposium through their active engagement with its organization.

Dear guests, we are very thankful and gladly acknowledge your interest, passion and strong vocation in venturing beyond the European scientific environment. While our Medical School is just sixty-eight years old, it is widely recognized in our country as a public institution with high standards for the education of physicians, nurses and health technologists.

As an example of our fruitful past, I wish to mention the research project conducted in the early fifties by Professor Héctor Perinetti and Professor John Stanbury, from the Harvard Medical School. The outcome of this collaboration was the eradication, in a few years, of endemic goiter in Mendoza and later in the whole country, through the addition of iodine to table salt. This was, perhaps, our first experience in translational medicine, although of course, this particular expression was unknown at that time!

Another well known of our professors of physiology was Juan Carlos Fasciolo, from the research group led by Professor Bernardo Houssay, the latter our first Nobel laureate in Medicine and Physiology. Professor Fasciolo was a member of the Argentine team which discovered the renin-angiotensin system, in parallel with the American team led by Irving Page. Professor Fasciolo was a well-known researcher in arterial hypertension.

In the sixties, our department of Cardiology was visited by the Crawford Mission from Stockholm. As a result, several of our cardiac surgeons received an advanced training.

Twenty years ago, with collaboration of the Harvard Medical School, we were able to accomplish a substantial, innovative change in our medical curriculum, which was ground-breaking in Argentina and has since been imitated by several medical schools of our country. The major features of this curricular innovation were: problem-based learning strategies, integration of subjects and contents, and training in patient-physician communication skills starting in the first semester of the career.

Right now, we are receiving you all with the clear aim of establishing a continuous exchange of scientific knowledge on translational medicine, and hopefully also of initiating a joint academic pathway for training the next generation of German and Argentine clinical researchers.

However, we should acknowledge that for decades our country has been suffering from social, political and economic unresolved issues, which inevitably have had an impact on health care. Just to mention a few examples, more than half of our children and teenagers are growing in poverty, there is a lack of equality in the access to the healthcare system, and there are huge disparities in the geographical distribution of physicians. Primary care physicians are few, particularly in small towns and places away from the academic centers. Also, there is a paucity of physicians interested in research and more particularly in clinical investigation.

These and other standing problems, like the shortage of nurses, compel us to continuously improve our curricula of studies and to do all we can to improve the current scenario.

For the solution of the problems affecting health care and quality of life of our people, we should recognize the outstanding importance of an output of scientifically sound physicians, with a deep concern for the patients, respectful to one another, able to work as a team and deeply conscious of their role as leaders for healthcare improvement.

We are very proud to let you know that four years ago, our students created by themselves a scientific association for promoting research activities during the whole career. They have organized meetings and requested the help of our established researchers to share their experiences and to become actively engaged in their research projects.

You may wonder, "Why are we as Faculty so strongly convinced of the significance of our approach to medical education?" It is because we ourselves have learned from our mentors who are active in biomedical research that advances in science are slow and nonlinear and are often started by observing something unusual or unexpected. Discovery demands not just curiosity but a passion for clarity and the will to perform hard work, features that take time to be developed. Students should achieve what Louis Pasteur called *"a prepared mind"* to detect and pursue opportunities for new discoveries.

Actively engaging them in research during the formative years is probably the best way to pass on to the students the role of science in allowing advances in the understanding, prevention, and treatment of disease.

Considering the elusive and provisional nature of scientific knowledge, we need to emphasize that our textbooks are painfully incomplete and that the current concepts represent only a temporary phase of understanding. They are not the final word but just a transient stop. Hence the need for continuous study and

analysis after graduation. To paraphrase the protagonist of Bertold Brecht's *Life of Galileo*, *"the goal of science is not to open the door to everlasting wisdom, but rather to close the doors to everlasting ignorance."*

Another important and urgent task that we have is to identify the faculty members who can model a genuine passion for the acquisition of new knowledge, in order to be selected, recruited and rewarded for their talents.

Those educators will transmit to their students not just bare passion, but also critical thinking skills. At a lab, or in a clinical Ward, the critical review of new publications should be encouraged and practiced throughout all the years of medical formation.

In an era characterized by the erosion of our time for reflection, we as medical educators should insist in staying focused on the rigorous path of reason, guiding our students in the search for the truth, as it was instilled in us by our own best mentors, some of whom I mentioned at the beginning of this introductory talk.

For all the reasons stated above, we are pleased to open this symposium, which will surely strengthen our students and faculty in their enthusiastic effort to meet the challenges of the best medical education. Moreover, I am confident that we will be able to integrate our faculties with the aim of accomplishing the call of science for the generation of knowledge and its translation into an improved health for our communities.

Pedro Eliseo Esteves

Dekan der Med. Fakultaet (UNCuyo)

Prof. Dr. Emiliano R. Diez

Instituto de Fisiología, Facultad de Ciencias Médicas

Universidad Nacional de Cuyo.

Cardiovascular research: from the heart to the people and back.

Cardiovascular translational research is a multidirectional continuum in a network of knowledge. Before, we called this type of research "bench-to-bedside", translating knowledge from the basic sciences into new clinical treatments. Current translational networks involve basic research, pre-clinical research, clinical research, clinical implementation, and public health. Translation is a type of communication between people who speak different languages (disciplines). In the cardiovascular field, it involves interdisciplinary work between biologists, engineers, pharmacologists, physicians, cardiologist, epidemiologists, economists, and politicians among other professionals. Identification and engagement of stakeholders are critical aspects of good translational projects. However, the interlocutors have different aims. For example, the objective of basic researchers is to improve general understanding, pre-clinical researchers look for safety and efficiency, clinical researchers seek the appropriate patients to benefit and care, scientific societies agree in the implementation and politician interact with the people to improve their health. Good intentions are not free of problems or mistakes. The success rate of the cardiovascular research is insufficient. Lack of gender considerations and the complexities of lifestyles are hardly addressed in cardiovascular oriented research. The production of new device, drugs or biological therapies is extremely slow and inefficient. The rate of new information becomes a big data problem which is worsened by personal privacy issues. We could learn from previous mistakes and increase the successful experience of cardiovascular translational science. More people should engage these renewed promising approaches to deliver better science for better lives.

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Are we all addicts? A neurobiological perspective on compulsive behavior.

Drug addiction, we are told, is perhaps the worst medical problem of the modern world. It is disconcerting, then, to realize that we still do not have a clear definition of what constitutes addiction. Here I will address the question from the broader perspective of compulsive behaviors. Compulsive behavior exists in every part of life. We go to work, even if we hate our jobs. We overindulge in food or drink, while we talk about losing weight. We text our online contacts, even though a family member is sitting next to us - perhaps doing the same thing. Is there a central mechanism that can explain all this?

A fundamental mechanism that underlies all our behaviors is the preference encoded in differences in the release of the neurotransmitter dopamine within the brain circuit known as the basal ganglia. This circuit is involved in all voluntary actions, including the compulsive actions that characterize addictions. Thus, we are left with a conundrum - do all our actions have the possibility of becoming addictive? How is it that we have lived with addictive substances including the most potent drugs for millennia while widespread drug addiction has been only an occasional event?

There is clearly an epidemic of drug abuse in Western countries that requires a deeper analysis than has yet been applied. The model of drug addiction as a disease is tempting for many pragmatic reasons but may be leading us down the wrong path.

Roland Mertelsmann

Department of Medicine I

Oncology, Hematology, and Stem Cell Transplantation

Freiburg University Medical Center, Germany

A Darwinian View of Cancer: Chances and Challenges

Cancer is an acquired genetic disease of clonal origin. Carcinogenesis and its subsequent development follow the principles of evolution, starting with a single cell with stem cell properties and a proliferative advantage, leading to clonal expansion, clonal evolution and subsequent demise by killing the host: “Evolution gone awry”.

Evolution can be divided into three essential steps: 1. “Chance” or random movement of molecules allows structures to interact. 2. Molecular affinity, “Necessity” (J. Monod, Chance and Necessity: Essay on the Natural Philosophy of Modern Biology, 1970), leads to a new structure providing novel properties and function. The 3rd step of the evolutionary processes, for which I would propose the term “Synclipse”, occurs, if the new constellation provides a biochemical and biological survival advantage, “survival of the fittest”, in a given environmental singularity.

The initial event, in the context of germ line predisposing mutations/polymorphisms, reflects the cellular reaction to environmental factors: microenvironment, chemicals, radiation, viruses by altering epigenetic gene regulation. These genes of importance for proliferation, apoptosis and differentiation, are thus more prone to mutations, and after further evolution a malignant phenotype is acquired. The development of these new molecular structures and functions follow the principles of evolution outlined above. These genetic alterations are the basis for the pathophysiological alterations of the malignant phenotype and are also potential targets for therapeutic strategies. The genetic analysis, whole exon and whole genome sequencing, identify the genetic alterations in specific genes that frequently code for proteins targeted by small synthetic molecules. Re-sequencing in different metastases and during the clinical course has demonstrated the ongoing evolution of cancer cells. Cancer is a „moving target“requiring iterative adaptation of therapeutic strategies.

Felicitas Holzer, MSc, MPhil

Ph.D. student Sorbonne University and University of Buenos Aires

Justice in international health research

Abstract

Recently, there has been a substantial debate about the ethics of international health research[1] in low and middle-income countries (LMICs). Over the past decade, the amount of research sponsored or carried out by foreign entities has increased substantially (Department of Health and Humans Services 2001, London and Zollman 2010). The driving force of this increase are significant costs savings that go along with a significant bargaining power for foreign sponsors when research is exported to LMIC communities (London and Zollman 2010). The ethics of *international* health research is a subcategory of the ethics of health research and usually refers to research studies conducted in LMICs that are externally sponsored by organizations from high-income countries.

Host countries of LMICs often lack strong domestic health research systems and health care systems (Pratt and Loff 2011, Emanuel 2000). Also, they lack a substantial social investment in scientific research. As a result, the research agenda is frequently set by foreign sponsors (London and Zollman 2010). Due to the imbalanced relation of health resources between researchers and sponsors on the one side, and the governments of host countries and representatives of the host communities on the other side, many commentators have raised awareness for considerations of justice in international health research. International guidelines, most notably in the CIOMS guidelines (CIOMS-WHO 2016) and the Declaration of Helsinki (WMA 2013), have increasingly defined additional obligations of justice towards communities in LMICs in international health research.

Presenting the case of outsourced research trials in Latin America, my aim is to open the debate on the general aims of research, such as the generation of socially valuable knowledge and scientific progress, as well as to discuss fairness considerations and benefit sharing in the context of such trials.

[1] Synonymously used for international clinical, biomedical and pharmacological research, including studies devoted to investigate the prevention and treatment of disease (mostly on humans), genetic and environmental factors related to disease and health, as well as physical, chemical, and functional mechanisms of life processes and disease.

Dr. Wolfgang Zimmermann, Freiburg

"Synchronizing" the Argentine and German Systems of higher education:

Chances and Challenges

1. Higher Education in Germany Germany has state and state-accredited institutions of higher education which are mainly divided into universities, universities of applied sciences, and colleges of art and music. The majority of higher education institutions are financed by the state and therefore fall under its regulatory control. However, there are also higher education institutions run by the Churches, and by private institutions that are officially recognized by the state. The German research structure/system consists of two pillars: research conducted at universities and research conducted at research institutions outside of universities. Tradition and basis of German Universities is „the unity and freedom of teaching and research". The model based on the ideas of Wilhelm von Humboldt (1810), research is one of the fundamental tasks of universities, includes also the liberty of research and teaching. It is the opposite of the Napoleonic model of universities. The Humboldtian model of higher education (German: Humboldtisches Bildungsideal) is a concept of academic education that emerged in the early 19th century and whose core idea is a holistic combination of research and studies. It integrates the arts and sciences with research to achieve both comprehensive general learning and cultural knowledge, and it is still followed today.

2. Higher Education in Argentina The Argentine higher education system is based, since its conception during the colonial period, on the old and dogmatic Spanish higher education system, which is basically a Continental education system (opposed to the Anglo-Saxon Model). The 'Napoleonic' system of higher education was adopted by Spain. A historic event took place in the Reforma Universitaria de 1918, a highly-popular series of reforms that took place in the oldest university of the Country, the Universidad de Córdoba that finally paved the way to the modernization of the Argentinian higher university systems as it is known nowadays. Since its foundation, it was focused on the teaching of Professions offering Professional degrees.

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Metabolomics in neurological diseases and asphyxia: status, chances and challenges

Metabolomics data are key to the elucidation of pathobiochemical mechanisms and an integral part of disease-related omics analyses. They further offer opportunities for diagnosis, prognosis and therapy control in numerous- including neurodegenerative diseases.

This paper provides an overview on recent developments in metabolomics in Alzheimer's disease, Multiple sclerosis (MS) and asphyxia of neonates. Recent publications report a good match of a brain metabolite signature with plasma data in Alzheimer's patients and indicate a disturbed glucose- as well as glutamate-glutamine metabolism in MS patients. In CSF samples of MS patient's metabolic changes were found to be disease stage dependent. In asphyctic neonates asphyxia was found to be reflected by characteristic plasma metabolite signatures involving *e.g.* Krebs-cycle metabolites. Metabolite quantification thus offers numerous opportunities in characterizing and prognosing above mentioned neurodegenerative diseases.

Birke Ahlfeldt
Dr. med. Kantonsspital Luzern

High altitude medicine- Chances and challenges

High altitude medicine is an evolving topic, not only in healthy people ascending into high altitude (e.g. mountaineering/hiking, residing at higher altitudes…), as high-altitude environments become more accessible. Hostile and extreme environment, climate, accessibility of care delivery and limited resources represent challenges of high altitude medicine. Medical conditions appearing in high altitude include hypothermia, trauma, and, most importantly, the consequences of hypobaric hypoxia which affects the respiratory, cardiovascular, neuroendocrine and renal system. Human bodies react with acclimatization when ascending, which offers interesting insights into physiology of hypoxemia. Critically ill patients clinically present with similar clinical features caused by hypoxemia. Currently, clinical therapy of hypoxemia focuses on global hypoxemia and oxygen delivery while researchers only started to unravel cellular pathomechanisms of regional hypoxia and oxygen utilization. New technologies to improve clinical care on an individualized level and further studies on pathomechanisms and therapies designed to treat hypoxia on a cellular level may not only be beneficial to create risk-profiles for and predict altitude sickness but may also contribute to a better understanding of cellular hypoxia in clinical settings.

Jürgen Rühe
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Engineered Biointerfaces through Tailormade Surface-attached Polymer Networks – From to new diagnostic tools to implantable materials

Abstract

Surface-attached polymer networks can tailor the surface properties of a material precisely to the specific needs laid out by medical applications and to create a favorable interaction of the artificial material with the biological system. However, chemical tools are needed, which allow for the attachment of polymer molecules to the device surfaces to ensure sufficient stability of the coating. Our approach for such surface architectures is based on polymers bearing photochemically or thermally reactive groups. Upon activation these groups attach to neighboring C,H-groups via C,H insertion crosslinking (CHic). Surface-attached polymer networks can be generated through this process and deposited on different substrate materials ranging from biomaterials, polymers to glass or metal surfaces.

These specifically designed surfaces can be used for a variety of biomedical applications. We use such coatings in blood contacting environments in the context of ventricular assist devices and for the reduction of scar formation after a glaucoma treatment. If further functional groups are incorporated, such layers can also take on an active role in the interaction with a biomedical environment and can be used to increase the sensitivity of biochips for DNA, RNA and protein or cell analysis. In the latter case we use such systems for the capture and analysis of circulating tumor cells (CTC). Additionally, we describe the development of new biochips which allow e.g. a diagnosis of HPV infections or the detection of mastitis in milk samples. In many cases the combination of a bioinert background and very specific probes are key to allow for a precise and reliable analysis especially in real serum samples.

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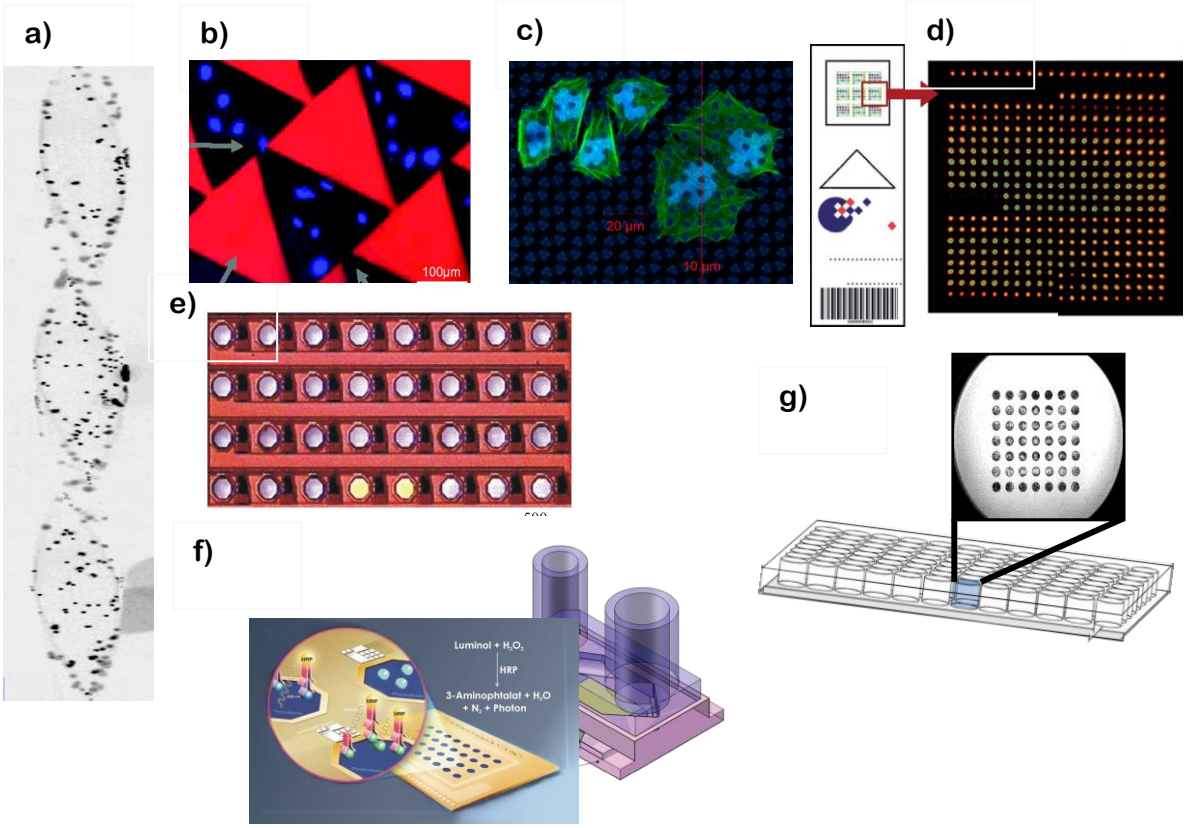

Fig. 1: Selected images of tailor-made biomaterials for the control of cellular adhesion a) medical wire for the capture of circulating tumor cell b) spatial control of cell adhesion c) nulear deformation of SaO2 cells on microstructured surfaces and bioanalytical devices d) DNA biochips e) and f) CMOS based chips for pneumoccae detection g) microarray in a well plate)

Facultad de Ciencias Médicas

Universidad Nacional de Cuyo

I Simposio de Medicina Traslacional

Libro de resúmenes

Mendoza, Argentina

5 y 6 de marzo de 2018

Editores académicos

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RESPIRATORY DESORDERS IN PEOPLE ASCENDING THE SUMMIT OF ACONCAGUA (6962 msnm)

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Following the ascent of 3 guides and 5 participants during the 1st field training course in Mountain Medicine (Aconcagua Provincial Park, Argentina) run by AAMPA in February 2016, overnight sleep was investigated. In total forty-six, polygraphs were performed using a portable equipment (ApneaLink™ Plus, ResMed, Australia) that allows a continuous three channel recording: measurement of thoracic effort, nasal flow, heart rate and oxyhemoglobin saturation. To access the response to high altitude eight studies were done in Mendoza (700 masl), three in Penitentes (2650 masl), eight in Las Cuevas (3150 masl) and all the others inside Aconcagua´s Provincial Park (Confluencia (3400 masl, n=8); Plaza de Mulas Base Camp- (4300 masl, n=8); Camp 1 (5000 masl, n=4); Camp 2 (5400 masl, n=4) and back in Plaza de Mulas (n=3)) during the expedition to the summit. In addition, blood samples were obtained for each subject before and after the course, moreover, levels of salivary cortisol were collected twice daily and permanent body temperature was recorded to evaluate the circadian rhythm, and daily assessment of AMS symptoms was performed using the Lake Louise Score (LLS). This study aims to investigate sleep at high altitude to evaluate its impact on the process of acclimatization.

Chlamydia trachomatis: PATHOGEN-HOST CELL INTERPLAY

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Chlamydia trachomatis (*Ct*) is the most prevalent sexually-transmitted bacterium worldwide. It completes its entire life cycle within human cells, inside of a modified vacuole termed inclusion. As an obligate intracellular pathogen, Ct has evolved multiple strategies to bind to, invade and parasite the host cell. In our laboratory, we aim to describe the interaction of the bacterium and the host from various approaches and scales. We have studied the manipulation of intracellular trafficking pathways executed by the bacterium to, conveniently, prevent its degradation, create a favorable niche for replication and evade the immune defense. In this way, we have reported the active recruitment of several Rab proteins and their effectors (Rab14, FIP2, Rab39a, Rab39b) to the membrane inclusion, a process that results in the acquisition of nutrients essential for growth and replication. Moreover, we study the modulation of signaling pathways (Akt, PKC) during the course of infection that may play a role in the development of Ct. To further complete the study of Ct life cycle in our team, we have described how galectin-1 enhanced its attachment to cervical epithelial cells to promote entry and invasion. A thorough understanding of the epidemiology and biology of Ct is crucial for the improvement of therapeutic strategies. For the former, we have dedicated efforts for the development of diagnostic tools of Ct and other sexually-transmitted pathogens; and for the latter, our laboratory has established a murine model of infection of Ct for *in vivo* assays of new therapeutic targets.

EPIDEMIOLOGY OF INVASIVE DISEASES CAUSED BY *Streptococcus agalactiae*

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Recently, our research group conducted a "National Multicentre Study of *Streptococcus agalactiae* invasive infections" that included 87 healthcare centers of 32 cities of Argentina. In the context of this epidemiological study we recovered a collection of invasive isolates; most of them from adults with different underlying medical conditions and the others from neonatal sepsis (Early Onset Disease – EOD, and Late Onset Disease - LOD). We have finished the phenotypic analysis, including serotyping, antibiotic resistance profile and clinical data. During the last year, we have developed a collaborative project with the research group leader by Prof. Henneke, at the Centre for Chronic Immunodeficiency from the University of Freiburg. This group investigates receptor-mediated mechanisms underlying cellular innate immunity against bacteria, specifical commensals of the skin (staphylococci) and respiratory/ intestinal tract (GBS) at the beginning of life in humans and mice. Currently, this working group carries out a variety of methods, including infection models in mice, *in vitro* models and clinical studies. This collaborative work allowed the development of new techniques as well as an important interchange of experience. We proposed to study the survival of invasive strains of GBS from EOD, in phagocytic cells. In this context, we evaluated if the survival to phagocytosis is associated with the capsular variant of each serotype. It will be useful to have a first estimation of this possible association. Afterward, we have started a second project together in order to describe the virulence of invasive isolates of GBS, specifically those strains belonging to the worldwide spread clonal complex 17.

GALECTIN 1 PROMOTES TUMOR CELL MIGRATION BY ENHANCING NA^+/H^+ EXCHANGER ISOFORM 1 (NHE1) ACTIVITY

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Tumor cells evade immune responses and shape local and systemic microenvironments establishing a distinctive cellular phenotype. Galectin 1 (Gal1), a glycan-binding protein, controls tumor progression by modulating tumor immunity and migration through binding to specific glycan structures of cell surface receptors. In solid tumors, NHE1 favors cancer progression through pH modulation. We aimed to elucidate the role of Gal1 on NHE1 regulation in murine melanoma cells and its role in tumor cell migration. To determine NHE1 activity we used a BCECF-AM flow cytometry kinetics assay. We observed increased NHE1 activity in melanoma cells in comparison to a non-tumorigenic cell line. To evaluate Gal1 participation in NHE1 hyperactivity, cells were treated with a NHE1 inhibitor (Eipa), recombinant Gal1 (rGal1) or were silenced for Gal1 (shGal1). We observed diminished NHE1 activity after Eipa treatment with similar results obtained after shGal1 silencing. Notably, rGal1 treatment augmented NHE1 activity, reverting the Eipa-dependent inhibition of NHE1. Accordingly, Gal1 immunoprecipitated with NHE1, suggesting that Gal1 could interact with NHE1 and control pH-dependent regulation by this antiporter. To further address the biological relevance of NHE1/Gal1 interaction, we evaluated migration of shGal1 melanoma cells. Both Gal1 signaling or NHE-1 inhibition impaired B16 cell migration. In contrast, exposure to rGal1 restored tumor migration under both conditions. These results suggest a possible role for Gal1 in modulating tumor cell behavior via NHE1 activation. Understanding the mechanisms through which the acidic microenvironment could shape tumor cell phenotype could help improve anticancer therapies.

Hsp70 ROLE ON MIGRATION AND CYTOSKELETON MODULATION AS AN EFFECT OF LOSARTAN IN PROXIMAL TUBULE CELLS (PTC) FROM SPONTANEOUSLY HYPERTENSIVE RATS (SHR)

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Angiotensin II (AII)/AT_1 receptor effects are dependent on reactive oxygen species (ROS) production. AII induces renal injury through NADPH oxidase-dependent ROS generation. ROS function as signaling molecules contributing to migration, differentiation, and cytoskeletal remodeling. Previously, we identified Hsp70 and CHIP as Nox4-interacting proteins, mediating ubiquitination and proteasomal degradation of Nox4 included within Losartan antioxidant effect on SHR PTC. Here, we evaluate Losartan (L) effect on migration, actin cytoskeletal organization and junctional-related protein in SHR PTC. Primary culture of PTC from SHR rats was stimulated with AII, treated with L or untreated (C). Live Cell Time-lapse Microscopy showed that L induces decreased cell displacement and slowed down cellular rate movement compared to C and AII PTC. Also, the cells remained attached and did not change their morphology compared to C and AII PTC. Immunofluorescence shows actin filaments highly organized in L treated cells compared to C and AII treated cells. Furthermore, L increased the cortical E-cadherin levels. When the Hsp72 expression was silenced, L treated cells showed velocity and displacement values like C PTC. In addition, L was unable to stabilize the cytoskeleton showing an increase in misaligned actin filaments and decreased cortical E-cadherin. Western Blot showed L increased vinculin and E-cadherin and decreased Nox4, p-ERK and p-p38 levels related to AII and C. Also, L decreased Rac1 and RhoA levels in membrane fractions, this effect was reversed in Hsp70 silenced cells. In conclusion, Losartan AT_1R blockage induces actin cytoskeleton stabilization and cell migration reduction. Moreover, through Hsp72 protein knockdown, we demonstrate that the chaperone is required for the cytoskeletal integrity modulation within the effect of L in PTC from SHR. A protective role of L could be suggested avoiding tubular cell detachment and stabilizing cell junctions.

HOST CELL-*Trypanosoma cruzi* INTERACTION: NOVEL ASPECTS FOCUSED ON MEMBRANE BIOPHYSICS AND microRNAs

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Trypanosoma cruzi is the causative parasite of Chagas disease. This life-threatening illness was confined to Latin America but demographic factors have determined its occurrence in non-endemic regions. As an obligate intracellular parasite, *T. cruzi* resides transiently in a host-cell membrane-bounded vacuole, known as parasitophorous vacuole (PV). To entirely surround a particle as large as a trypanosome (10-15 µm long), different organelles contribute with the membrane. Our previous research project has contributed significantly to the notion that the major membrane donor organelles to the PV formation are lysosomes, recycling/early endosomes and plasma membrane. During the course of these studies, we started being interested in two intriguing aspects that nowadays drive our research: The influence of host cell membrane tension in the invasion process and the host regulatory mechanisms that drive gene expression changes during infection. Plasma membrane tension influence cell processes ranging from vesicle trafficking to signal transduction pathways. Interestingly, we have observed that recently internalized parasites are highly motile and can protrude from the cell early after the invasion, stretching the plasma membrane out from the inside. This suggests that host cell plasma membrane could be subjected to strong mechanical forces. Simultaneously, *T. cruzi* invasion specifically modulates host cell gene expression to subvert the metabolic machinery for its own benefit. Now we have evidence that this could be conducted by a post-transcriptional gene regulatory mechanism mediated by microRNAs. Through these novel approaches, we hope to reveal unknown aspects of the biology of *T. cruzi* and the host cell interaction and find new non-serological biomarkers for Chagas disease diagnosis.

ESTABLISHMENT OF A LABORATORY OF VIROLOGY AT THE FACULTY OF MEDICAL SCIENCES FOR RESEARCH AND DIAGNOSIS OF IMPORTANT VIRAL PATHOGENS

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Infectious diseases caused by viruses are of great public health significance with human herpes viruses as the leading cause of human viral disease, second only to influenza and cold viruses. Moreover, the recent emergence and re-emergence of viral infections transmitted by vectors—Zika, chikungunya, dengue, West Nile, yellow fever and others—is a cause for international concern. In this regard, the establishment of a Laboratory of Virology with a role in diagnosis, monitoring, and research at the Faculty of Medical Sciences is critical.

As a first step towards the establishment of such laboratory, research in the field of virology was initiated last year. The construction of mutant variants of human herpesvirus type 2 (HSV-2), the most common cause of genital herpes, are under development. Such mutant viruses will be characterized *in vitro* and *in vivo* for potential use as vaccine candidates.

ACTIVATED COAGULATION AT HIGH ALTITUDE

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Both coagulation and fibrinolytic activity are involved in the genesis of High Altitude Pulmonary Edema. Many studies were performed at altitudes higher than 5000masl, but only a few were done at lower altitudes. Being D-dimer (DD) a very sensitive activation of coagulation marker, our investigation goal was to measure DD and other hematological and haemostatic parameters in a group of climbers (13 subjects , 6 women and 7 men) on a 3 day expedition in Puente del Inca, Mendoza, Argentina, reaching 3500 masl and sleeping at 2800 masl. Blood tests were done before and immediately after climbing, considering those conditions that could change the samples quality. DD (chemiluminescence), automatic cell blood count, C-reactive protein (CRP) (immunonephelometric) and fibrinogen (Clauss Method) were measured. Male´s results were compared to female´s and represented as mean values, standard deviation. Comparison between the two groups was done using the Mann Whitney U-test. The climbers did not show any symptoms of acute mountain sickness AMS. There was a significant elevation of DD pre: 219,8±136,03; range: 82,4-613,5; post: 609,89±918,57; range: 203,9-3586,8 ng/ml; $p<0.01$. There were no changes in platelet count, CRP or fibrinogen. Highest values of DD were observed in women. The elevation of DD concentration may show that there is coagulation activity at moderate altitudes in a group of Argentinian mountaineers without symptoms of AMS. Ingestion of oral contraceptive and/or hormonal changes may be reasons for higher values of DD in women.

A FRESHWATER SNAIL AS AN EXPERIMENTAL MODEL TO EXPLORE PHYSIOLOGICAL RESPONSES TO ENVIRONMENTAL STRESS: HYPOMETABOLISM AND XENOBIOTICS

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Many animals show different physiological responses to overcome the consequences of harsh environmental conditions such as extreme temperatures or shortage of oxygen, food or water. The freshwater snail *Pomacea canaliculata* is a successful invasive species that show physiological responses which may protect it from water shortage (during estivation) or low temperatures (during hibernation). These two hypometabolic states (and the arousal from them) imply imbalances between oxyradical production and antioxidant defenses. A particular feature of this species is the occurrence of a tissue system that stores uric acid as intracellular crystalloids and as renal urinary concretions. The stored uric acid seems to prepare the snail against the oxidative stress of arousal reoxygenation, as part of the 'preparation for oxidative stress' strategy, since this purine is used as an antioxidant. Comparative physiological studies of the mechanisms involved in tissue protection during hypometabolic states (and arousal) may provide answers to medical problems such as organ transplantation, myocardial infarction or wound healing. Furthermore, we proposed other applications of *P. canaliculata* focusing on the growth of the female phallic structures in response to environmental pollutants. Ampullariidae are unique among gastropods in that females show rudimentary phallic structures as those of mammals and these structures grow in response to organotin compounds (used in paints and in agriculture) and other agrochemical compounds. This masculinizing effect of contaminants and their possible deleterious effects on reproduction may be used as bioindicators of freshwater pollution, if the studies are made with snails from a laboratory cultured strain, under controlled conditions and with females of known age.

mRNA EXPRESSION OF THE PROLACTIN RECEPTOR ISOFORMS IN AUTOIMMUNITY

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Autoimmune diseases are heterogeneous and difficult to treat pathologies. Immune cells can be modulated by several endocrine mediators such as adrenaline, cortisol, and prolactin. In the case of prolactin, it is known that liver cells express several isoforms including a long isoform (PRL-RL) that signals via STAT5 and JAK molecules and a short isoform (PRL-RS) that signals only via JAK molecule. Although it is known that immune cells express the PRL-RL, it is not known whether immune cells express short isoforms. The aim of this work was to evaluate whether murine and human immune cells (from healthy and lupus) express the prolactin receptor short and long isoforms. To this end, C57BL/6 mice were euthanized, the spleen was harvested. Blood samples from healthy donors were harvested and red blood cells were lysed. RNA from murine spleen and human blood leukocytes were obtained following Trizol reagent protocol instructions. Then cDNAs were synthesized with the subsequently PCR amplification. PCR products were visualized by agarose gel electrophoresis. We found that both murine and human leukocytes express mRNA PRL-RL. In addition, we also found that both murine and human leukocytes express the mRNA PRL-RS. Furthermore, spleen cells and PBMCs from lupus mice and patients displayed higher expression of mRNA PRL-RL form suggesting lupus cells are more sensible to prolactin. In conclusion, these results demonstrated that immune cells express both prolactin receptor isoforms and lupus immune cells displayed a differential expression. To our knowledge, this is the first report that showed human leukocytes express PRL-RS.

PIGMENT EPITHELIUM-DERIVED FACTOR (PEDF) EXPRESSION IN THE REPRODUCTIVE TRACT OF MALE RATS IS REGULATED BY ANDROGENS

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Pigment epithelium-derived factor (PEDF) expression has been described in many organs as showing neurotrophic, anti-angiogenic, anti-apoptotic, anti-inflammatory, anti-oxidant and pro-cellular survival properties. However, references to its activity in the murine male reproductive system are scarce, except in the regulation of sperm conjugation in rat epididymis. We aimed to characterize the expression of PEDF in the male reproductive tract of Wistar rats and explore their hormonal regulation using immunohistochemistry, semi-quantitative RT-PCR and Flutamide administration. We found that PEDF is expressed in the epididymis, prostate and seminal vesicles, but notably not in the testes. These findings differ from those described in humans and primate's testes, where PEDF expression has been detected in peritubular cells. Immunofluorescence staining indicated the presence of PEDF over the surface of sperm inside the epididymal lumen. Androgen dependence of PEDF expression, evaluated by Flutamide administration, diminished along the male reproductive tract. This decrease in expression was reversed after 30 days without Flutamide administration. The epididymis is an essential organ in sperm maturation-storage. The role of PEDF in this physiological process has not been fully elucidated. Considering that in other systems PEDF has anti-apoptotic, anti-oxidants and pro-cell survival properties, its expression along the epididymis may be related to the protection of spermatozoa while they are stored.

CARDIAC ACTIONS OF C-TYPE NATRIURETIC PEPTIDE IN EXPERIMENTAL ARTERIAL HYPERTENSION

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In the heart C-type, natriuretic peptide (CNP) is mainly released by the endothelium and, also in lower levels, by cardiac myocytes and fibroblasts. Its actions are mediated by a guanylyl cyclase B (GC-B) receptor, which produces cGMP upon CNP binding and is expressed in different myocardial cells, including myocytes and fibroblasts. Administration of synthetic CNP greatly prevents cardiac hypertrophy and fibrosis in spontaneously hypertensive rats (SHR) and in mice with experimental cardiac pressure-overload by Angiotensin II (Ang II) infusion. To dissect the fibroblasts actions of endogenous local CNP *in vivo*, we generated and validated a new genetic model with induced fibroblast-specific deletion of GC-B (iFibro GC-B KO) in adult mice using the Cre/LoxP system. After proper crossings, an effective reduction of GC-B was achieved at a genomic, protein and functional level. We then studied the impact of this deletion on hypertensive heart disease infusing Ang II via osmotic minipumps. Ang II infusion resulted in an increase of left ventricular (LV) afterload by means of elevated aortic and intraventricular pressures in iFibro GC-B KO and control mice. Also, a marked cardiac hypertrophy and interstitial fibrosis were observed by means of morphometric analysis and increased levels of specific molecular markers, brain natriuretic peptide (BNP) for hypertrophy and collagen I for fibrosis, in both genotypes. However, the global contractile function was preserved in all cases. Though GC-B deletion in fibroblasts did not alter the blood pressure levels or the hypertrophy induced by Ang II, it significantly worsened the fibrotic response situating the CNP/GC-B endogenous system in cardiac fibroblasts as a key mediator of tissue fibrosis *in vivo*.

CARDIOVASCULAR DISEASES AND DIABETES: EFFECT OF OXIDATIVE STRESS, INFLAMMATION AND ANGIOGENESIS ON THE VASCULAR WALL

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The Vascular Biology laboratory develops activities related to the study of Oxidative Stress associated with cardiovascular diseases and Diabetes. We study the relationships between biological oxidations, hypercholesterolemia, insulin resistance and atherosclerosis. We studied the participation of the arterial wall, from the endothelium, the intima-media layer, the adventitia, to the perivascular adipose tissue, in the establishment and development of atherosclerosis, with emphasis on the inflammatory and angiogenic proteins involved in the process. Regarding oxidative stress, our aim is to study the regulation and expression of the NADPH oxidase system found in the arterial wall considered as the main system capable of generating oxidative stress in the vessel. For our studies, we use cell cultures and animal models of hypercholesterolemia (Apolipoprotein E-deficient mice (ApoE - / -), or Diabetes (chronic fructose administration). Different natural compounds (autochthonous plants), Nox small molecule inhibitors and drugs (sensitizers to Insulin and formulations with nanoparticles) are tested in order to find possible therapeutic compounds that decrease the production of Reactive Oxygen Species, improve endothelial function, reduce inflammation or avoid atheroma plaque vulnerability.

P38 REGULATE LUNG COLONIZATION IN METASTASIS ASSAY

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Cells from primary tumors need to go through several steps to become fully metastatic. During this process, cancer cells acquire the ability to invade, migrate across the surrounding tissue, enter into the circulation and colonize distant organs. The p38 MAPK signaling pathway plays important roles in the ability of the cells to integrate externals signals and to elaborate appropriated responses. The participation of p38 in several *in vitro* processes associated with cancer progression has been widely reported, but there is no clear information about the real role of p38 in metastasis ***in vivo***. In the present study, we show that cancer cells require p38 MAPK expression to metastasize the lung of immunocompetent animals, in experimental metastasis assay. Using shRNA against p38 in Lewis Lung Carcinoma Cells, we deeply explore the whole mechanism of metastasis, and we found that p38 is not required to the process of anoikis, extravasation, adhesion, invasion neither tumor formation ability. In contrast, we found that cells with low expression of p38 have problems in colonizing the lung parenchyma of Black 6 mice, as they show less tumor burden in colonization assays. This colonization problem seems to be immune-dependent, as we found no differences when we inject this cell in immunodeficient mice (Nude). We conclude that p38 MAPK in cancer cells is required to form the initial niche in the lung parenchyma, leading to problems to colonize the lung and metastasize.

VASCULAR INFLAMMATION ON METABOLIC SYNDROME MODEL

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The laboratory of cardiovascular physiopathology works to discover the pathological mechanisms involved in vascular remodeling and atherosclerosis. The central axis of our research is vascular inflammation. For this, we work on a pathological experimental model of metabolic syndrome that is formed from the administration of 10% fructose in drinking water, ad libitum, to Wistar Kyoto (WKY) or spontaneously hypertensive rats (SHR). This model allows the study of the initial phase of atherosclerosis: vascular remodeling, in the presence of normo-cholesterolemia, allowing the results to be independent of those caused by the accumulation and oxidation of LDL. In this experimental model, in the last 20 years, we have demonstrated: hypertension, hyperinsulinism and insulin resistance with cardiovascular remodeling. At the vascular level, there is a 1- migration and change of phenotype of the vascular smooth muscle cells, 2- activation of eNOS and NADP (H) oxidase with, consequent decrease in the bioavailability of NO, 3- lipid peroxidation and activation, 4- and, by multiple intracellular pathways, NF-kB and AP-1, initial promoters of inflammatory response. Also, we have demonstrated the central role of renin-angiotensin-aldosterone system and cytokines such as MCP-1, Leptin, and IL-6. All mechanisms were evaluated by the pharmacological blockade. The expression of AT-1, AT-2, MAS-1 receptors was demonstrated. As well, endothelial repair has been studied from the expression of CD133 and VEGFR2 at the endothelial level, which is completely diminished in the experimental mode and in the presence of inflammatory markers. In our latest trials, we have evaluated the central role of the IL-6 alpha receptor in the activation of the vascular inflammatory microenvironment.

COPPER INDUCED TOXICITY AND THE PROTECTIVE ROLE OF GLUTATHIONE: IMPLICATION OF IMPAIRED PROTEIN FOLDING RATHER THAN OXIDATIVE STRESS

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The accumulation of copper (Cu) ions which take place in Wilson Disease (WD) leads to cellular damage and ensuing cell death. While Cu ions may induce oxidative stress, its direct involvement in cell death is uncertain since no antioxidant therapy has resulted effectively in the treatment of WD. Here we show through microarray studies that BEAS-2B cells exposure to a lethal concentration of Cu(II) of 800 uM for up to 24 h induced a strong heat shock response but no antioxidant response. While an enhanced production of oxidants was observed, the intracellular antioxidant GSH was not oxidized previous to the onset of cell death and the GSH precursor NAC did not protect the cells. Nonetheless, GSH protected the cells although independently of its reduced -SH group. Cu(II) in vitro was able to induce protein aggregation and this was effectively prevented by both GSH and GSSG. Interestingly, cell death was potentiated in SV40MEFs incubated with Cu(II) and the pro-aggregating metal Zn(II), while the incubation of Cu(II) with the pro-oxidizing metal Fe(II) did not potentiate cell death. In conclusion, intracellular Cu accumulation results toxic due to direct metal interaction with proteins which impairs proteostasis while oxidative stress does not drive cell death. Additionally, the major antioxidant GSH is a protective agent, independently of its reduced -SH group and acting as a chelating agent rather than an antioxidant. Altogether, these results explain why antioxidant therapies did not result effectively in the treatment of WD.