

4th BRIDGING THE GAP

International Workshop

Cell Communication in Health and Disease

February 15th-16th 2011 Vienna, Austria
General Hospital, Kliniken am Südgarten, Big Lecture Hall

Information & free registration:
www.phd-cchd.at/workshop



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Alessio Fasano (USA)

Tamás Freund (Hungary)

Hugh Perry (UK)

Yosef Yarden (Israel)

Yael Stern-Bach (Israel)

Sandra Pellegrini (France)

Ruth Murrell-Lagnado (UK)

Mieke Dewerchin (Belgium)

Veit Hornung (Germany)

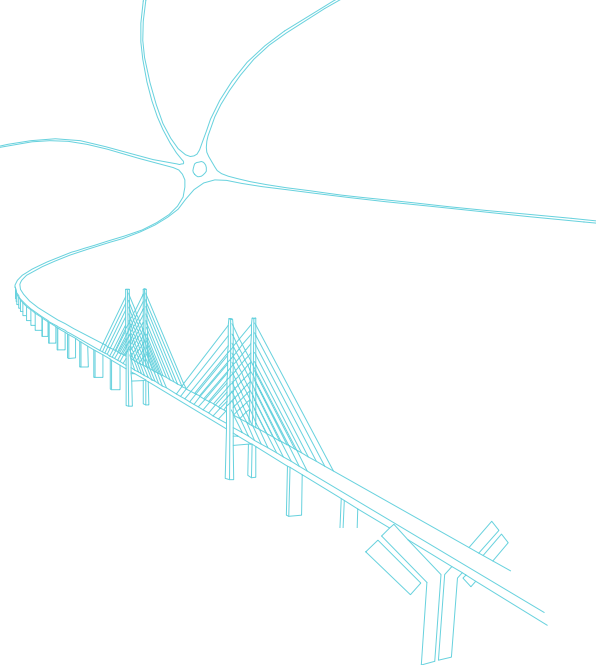
Jessica Hamerman (USA)

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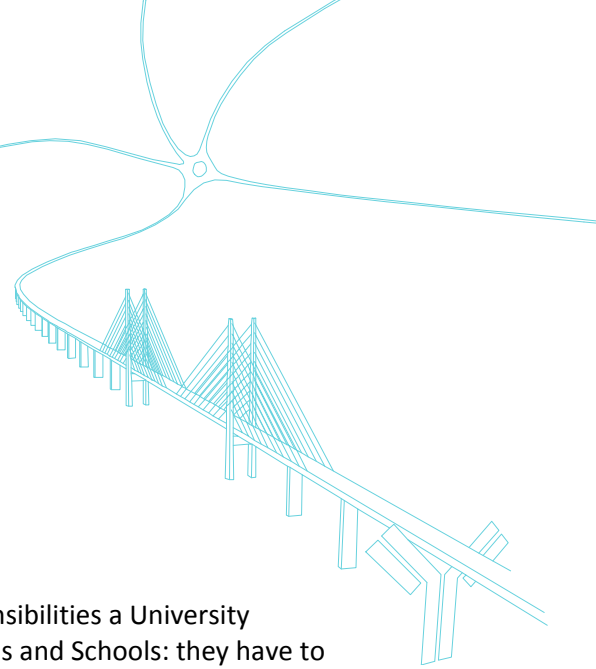
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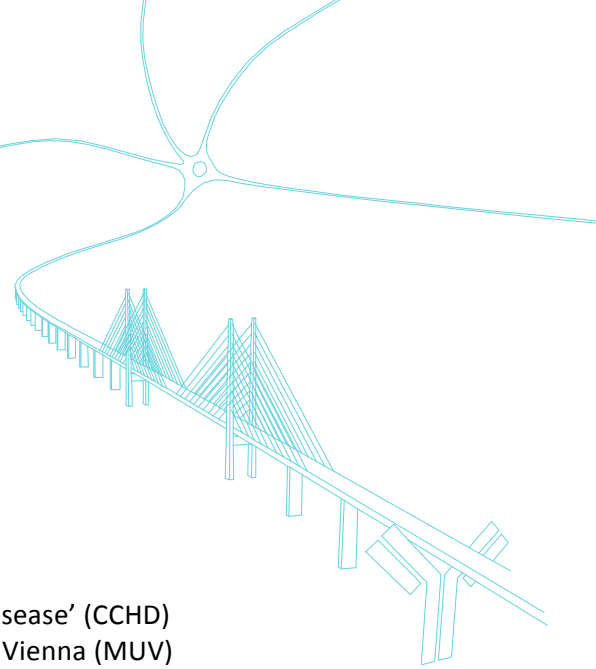


WELCOME MESSAGE

The training of young scientists is one of the most important responsibilities a University has to deal with. This is important especially for Medical Universities and Schools: they have to recruit scientists for basic research, but also scientists for translational as well as clinical research. Not only scientists focusing on basic research but also researchers in translational and applied medical science need a strong scientific background and an excellent training in both medical and life sciences as a basis for their future work. The doctoral program CCHD provides interdisciplinary education in four important research areas of the MUV: neurobiology, vascular biology, immunology, and inflammation research. Thus, the CCHD program includes groups from basic research departments (brain research, pharmacology, and vascular biology), from translational departments (immunology and pathology) and from clinical departments (endocrinology and metabolism). In this manner, CCHD represents a wide spectrum of research at the MUV.

As also so called “generic skills” should be trained in the CCHD course, the PhD students have to learn how to organize conferences. As a result, we are about to experience the 4th International Workshop on Cell Communication in Health and Disease themed “Bridging the Gap”. It reflects the motto of the CCHD program and attempts to familiarize the participants with the concept of the doctoral program. Therefore, both organization and realization of the workshop have a strong impact on the training outcomes of CCHD.

Rudolf Mallinger
Vice Rector for Studies and Teaching, MUV



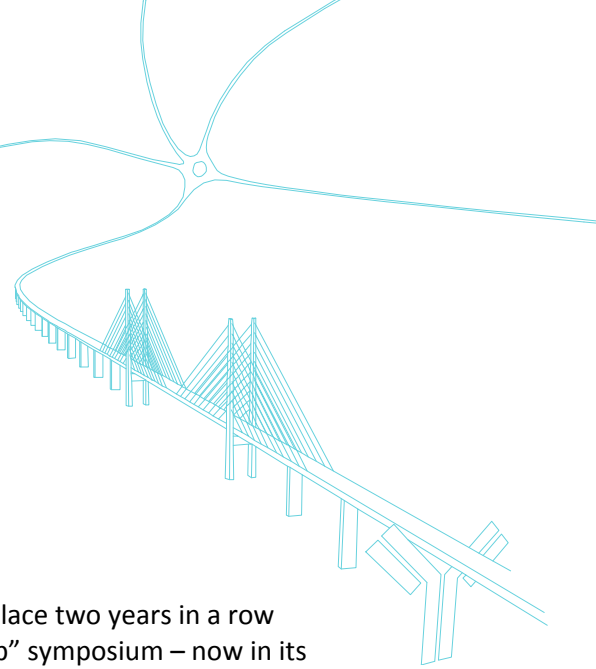
WELCOME MESSAGE

The doctoral training course 'Cell Communication in Health and Disease' (CCHD) was initiated by 12 scientists working at the Medical University of Vienna (MUV) or the Research Center for Molecular Medicine of the Austrian Academy of Sciences (CeMM) in spring 2005 in order to constitute a showcase of multidisciplinary doctoral education. Due to funding by the Austrian Science Fund (FWF), the MUV, and the CeMM after successful international peer review, this is the first 'Doktoratskolleg' set up at the MUV.

Since autumn 2006, CCHD provides highly talented and well educated students with challenging interrelated research projects that range from basic biomedical sciences, via applied to clinical sciences. To give these students the opportunity to acquaint themselves with intellectual and technical skills that can be employed in highly divergent areas, four research themes that deal with organ independent ubiquitous regulatory systems (neurobiology, vascular biology, immunology, and inflammation research) form the multidisciplinary frame work. By bringing PhD students who work in these heterogeneous fields together, they are prompted to learn not only about the scientific background of their own thesis projects, but also about other more unrelated biomedical research areas. The unifying theme of CCHD is the investigation of molecular elements involved in the communication within and between cells, whether in health or disease. However, the focus is not a single type of cell communication, such as synaptic transmission, interleukin signalling, or angiogenesis, but we rather aim at bridging the gap between different organ systems and between different paradigms of cellular communication.

Being in its fifth year, the 25 students of the CCHD program have the opportunity to organize this Fourth International Workshop of Cell Communication in Health and Disease. As in the previous workshops, its leitmotif is scientific multidisciplinary with emphasis in neurobiology, vascular biology, immunology, and inflammation research. The exciting program spans from the roles of growth factor receptors in tumorigenesis, via mechanisms of inflammation in brain and vessel diseases, to the role of endocannabinoids in anxiety and epilepsy. I would like to thank our student members for putting this impressive program together and I am very grateful to our guests for accepting the students' invitation in order to share not only their results and expertise, but also their experiences and views with us. I look forward to illuminative presentations, lively discussions and exchange of personal ideas and new concepts. I do hope that this will be a memorable event not only for the CCHD members, but also for all other participants, as it was in the previous four years.

Stefan Boehm
Coordinator of CCHD



WELCOME MESSAGE

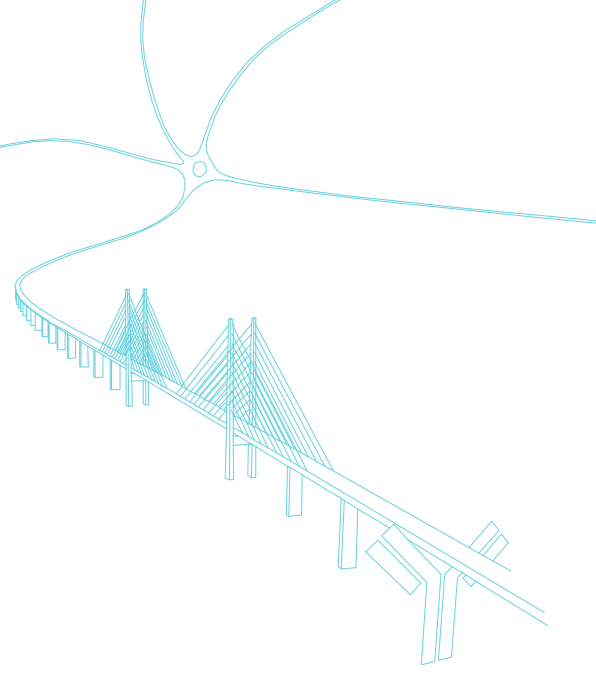
In Viennese society, a famous proverb claims that an event taking place two years in a row has become a tradition. This would mean that the “Bridging the Gap” symposium – now in its fourth year – has managed to associate itself with this sought-after status. We, this year’s organizers, cordially invite you to join us in further consolidating this workshop as a fix point in Vienna’s varied conference schedule.

“Cell Communication in Health and Disease” (CCHD) is a self contained Ph.D. program offered by the Medical University of Vienna and co-financed by the Austrian Science Fund (FWF). Its primary mission is to provide and combine state-of-the-art theoretical and practical education in the fields of neurobiology, vascular biology, immunology and inflammation research. Each year, the newly enrolled students are given the opportunity to organize an international workshop dealing with major issues in these fields.

In line with the interdisciplinary philosophy embraced by the CCHD agenda, we tried to establish a diverse program featuring international top researchers from Europe and overseas in today’s molecular-driven basic research. Within the following two days, they will present important developments in their fields and share with us the contributions they have made. We call on you, the audience, to actively take part in the scientific discussions scheduled between presentations. This will bring to life our motto of interdisciplinary knowledge seeking – in other words, “bridge the gap”.

Having said this, we hope you enjoy the selection of talks assorted for 2011. Also, do not hesitate to address us during the symposium to comment and give us your feedback.

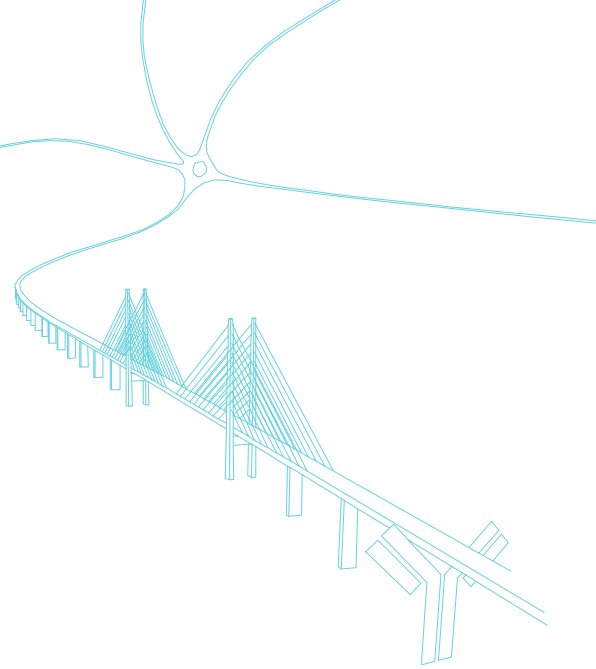
The Organizing CCHD Students’ Committee



PROGRAM

BRIDGING THE GAP 2011

DAY1, FEB 15th



Chairs of session

Program

Session I

8.30-9.00 Registration & Opening
of the 4th CCHD symposium

Hans Lassmann

9.00-10.00

SPEAKER 1: V Hugh Perry
Southampton, UK

The influence of systemic inflammation on the
brain in health and disease

10.00-10.30 Coffee break

Session II

Hannes Stockinger &
Giulio Superti-Furga

10.30-11.30

SPEAKER 2: Giuseppina Caligiuri
Paris, France

Role of CD31 in the control of inflammation and
atherothrombosis

11.30-12.30 SPEAKER 3: Alessio Fasano
Baltimore, USA

Zonulin, intestinal permeability, and
inflammation: Bridging the gap between innate
immunity and autoimmunity

12.30-13.30 Lunch

Session III

Brigitte Hantusch &
Harald Esterbauer

13.30-14.30

SPEAKER 4: Tatiana Petrova
Lausanne, Switzerland

Mechanisms of lymphatic vascular development
and remodeling

14.30-15.30 SPEAKER 5: Ruth Murrell-Lagnado
Cambridge, UK

Mechanisms contributing to the diversity of
purinergic receptor signalling

15.30-16.00 Coffee break

Session IV

Erika Jensen-Jarolim &
Thomas Klausberger

16.00-17.00

SPEAKER 6: Yosef Yarden
Rehovot, Israel

Oncogenic receptors for growth factors: Defective
cell communication offers opportunities for
cancer therapy

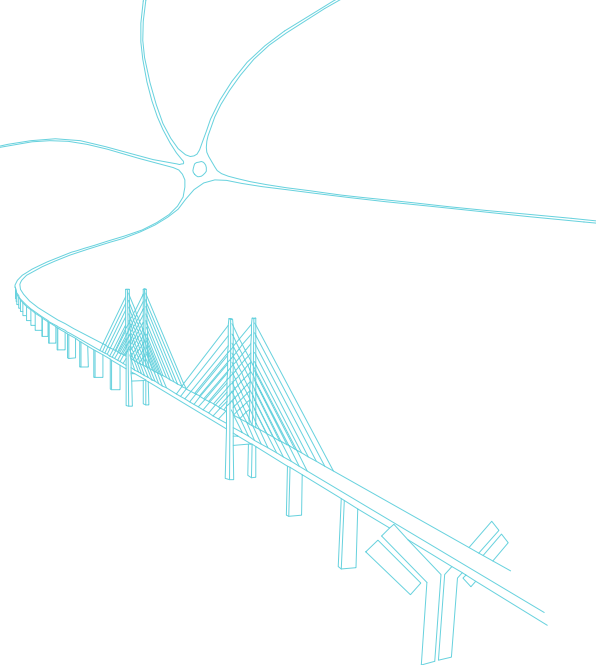
17.00-18.00 SPEAKER 7: Tamás F. Freund
Budapest, Hungary

Control of cortical inhibition and excitation by
endocannabinoids: Novel insights into anxiety
and epilepsy

19.30 Social event at Plachutta's
Grünspan

BRIDGING THE GAP 2011

DAY2, FEB 16th



Chairs of session

Program

Session V

Werner Sieghart	9.00-10.00	SPEAKER 8: Yael Stern-Bach Jerusalem, Israel	AMPA-type glutamate receptors and their accessory transmembrane proteins
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	10.00-10.30	Coffee break	
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Session VI

Sylvia Knapp & Stefan Boehm	10.30-11.30	SPEAKER 9: Sandra Pellegrini Paris, France	Type I IFN, a large cytokine family with pleiotropic activity in complex responses
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	11.30-12.30	SPEAKER 10: Mieke Dewerchin Leuven, Belgium	Functional genomics to study angiogenesis in health and disease
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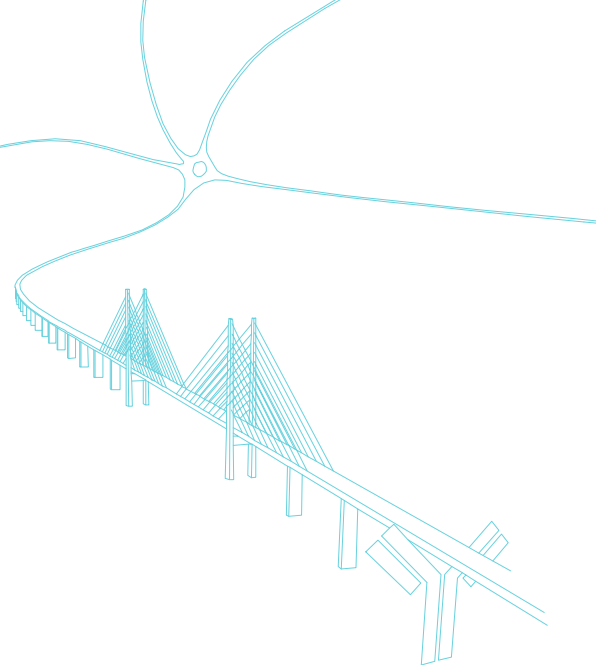
	12.30-13.30	Lunch	
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Session VII

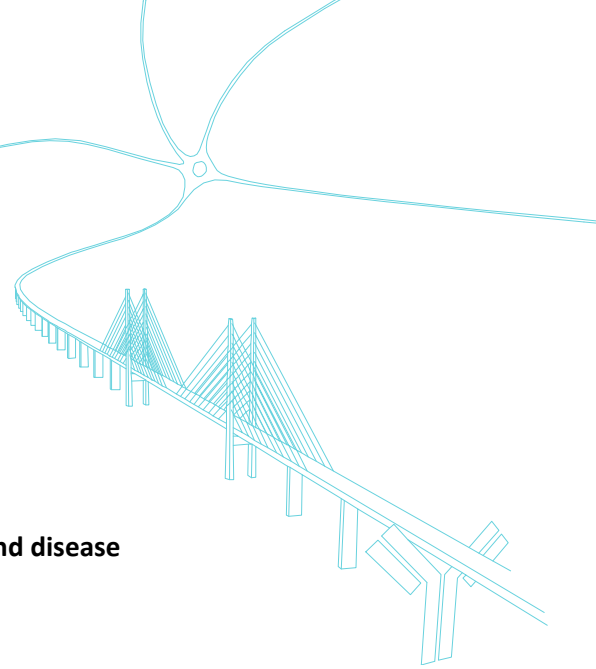
Sonja Sucic & Maximilian Zeyda	13.30-14.30	SPEAKER 11: Veit Hornung Bonn, Germany	Intracellular DNA recognition by the innate immune system
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	14.30-15.30	SPEAKER 12: Jessica Hamerman Seattle, USA	Regulation of inflammatory responses by ITAM signaling in macrophages
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	15.30-16.00	Closing of the 4th CCHD symposium	
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ABSTRACTS



The influence of systemic inflammation on the brain in health and disease

V Hugh Perry

School of Biological Sciences
University of Southampton, UK
v.h.perry@soton.ac.uk

We have all at one time or another experienced the consequences of a systemic infection that gives rise to fever, malaise, lethargy and depression, symptoms commonly referred to as sickness behaviour. We now know the humoral and cellular routes by which systemic inflammation communicates with the neurons of the brain and it is apparent that the resident macrophages of the brain, the microglia, play a part in this process. In the normal healthy brain the effects of a systemic infection are transient and reversible. However, in the diseased or aged brain the microglia are no longer constrained by the CNS microenvironment and take on an activated or “primed” phenotype. In animal models systemic inflammation communicates with these primed microglia leading to enhanced cytokine synthesis in the brain, which in turn leads to exaggerated sickness behaviour, neuronal degeneration and acceleration of neurodegenerative disease. Clinical studies show that common systemic infections and the associated inflammatory response may have a profound effect on patients with ongoing neurodegenerative disease.



Role of CD31 in the control of inflammation and atherothrombosis

Giuseppina Caligiuri

Institut national de la santé et de la recherche médicale (INSERM)

Paris, France

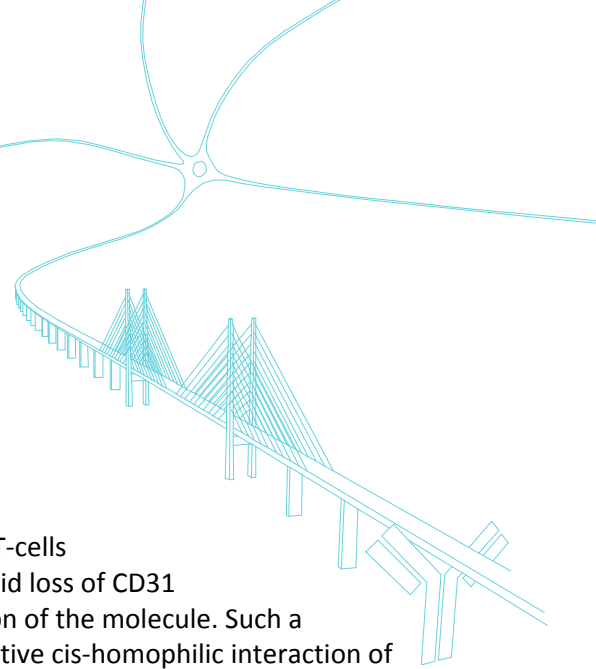
giuseppina.caligiuri@inserm.fr

Innate and adaptive immune responses play a major role in chronic inflammatory diseases such as rheumatoid arthritis, multiple sclerosis and atherothrombosis (atherosclerotic plaque thrombosis, aortic aneurysms dissection). Various putative immune target auto-antigens have been proposed as the key inflammatory triggers. However, these antigens are also detected in asymptomatic individuals. The only difference between asymptomatic and symptomatic patients is that the lymphocytes are abnormally activated in the latter. Indeed, the abnormal immuno-inflammatory responses observed in chronic inflammatory diseases, including atherothrombosis, could rather be due to a defect in the mechanisms of control of the systemic immune tolerance.

In this setting, CD31 (PECAM1) plays a first line role because this adhesive molecule functions as a homophilic immune inhibitory receptor, mutually preventing the activations of interacting cells regardless of their nature. Indeed, in the absence of CD31, the degree of innate and adaptive immune responses, platelet activation and aggregation, and dysfunction of the endothelial barrier are greatly enhanced.

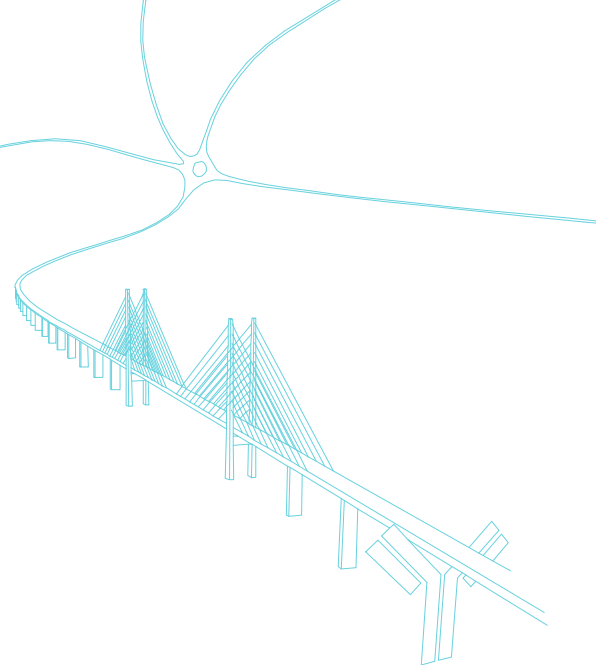
CD31 consists of a single chain molecule comprising 6 Ig-like extracellular domains numbered starting from the most membrane-distal one, a short transmembrane segment and a cytoplasmic tail containing two ImmunoTyrosine-based Inhibitory Motif (ITIM)s. Crosslinking of the membrane distal Ig-like domains of CD31 induces outside-in inhibitory signaling triggered by the phosphorylation of its ITIMs, and the recruitment and activation of SH2-containing phosphatases. All endothelial cells, platelets and leukocyte precursors are CD31 positive, but certain blood T cells are found to CD31 negative. We observed that lack of CD31 on lymphocytes lowers their activation threshold while the presence of CD31 confers regulatory properties, *in vitro*. Interestingly, we found that a reduced percentage of circulating CD31+ T cells is a hallmark of atherothrombosis in mice and patients while the overexpression of a fusion protein containing the whole extracellular CD31 sequence protects against the inflammatory response associated with experimental atherosclerosis and significantly prevents the progression of the disease.

The mechanical engagement of the distal CD31 domains is necessary for the protection conferred by the fusion protein, possibly because it drives the key event for CD31 signaling: the clusterization of CD31 molecules on the cell membrane with activating receptors able to phosphorylate CD31 ITIMs. Thus such a treatment cannot be proposed in established chronic inflammatory diseases, where activated lymphocytes are mainly CD31 negative.



Indeed, the most recent findings indicate that CD31 expression on T-cells dynamically changes with cell activation. We have shown that a rapid loss of CD31 upon T-cell stimulation is due to cleavage of the extracellular portion of the molecule. Such a cleavage disables the first trans-homophilic interaction but an effective cis-homophilic interaction of the truncated juxtamembrane CD31 domain 6 and the downstream ITIM signaling can be sustained with using a synthetic homotypic peptide of this region. The administration of this peptide prevents the pathologic immune responses associated with experimental atherothrombosis, rheumatoid arthritis and multiple sclerosis.

This discovery has opened novel and important clinical applications based on the detection of the truncated soluble CD31 in the plasma to evaluate the degree of ongoing immune system activation and on the therapeutic potential of the rescuing peptide in patients with chronic inflammatory diseases, such as rheumatoid arthritis, multiple sclerosis and atherothrombosis.



**Zonulin, intestinal permeability, and inflammation:
Bridging the gap between innate immunity and autoimmunity**

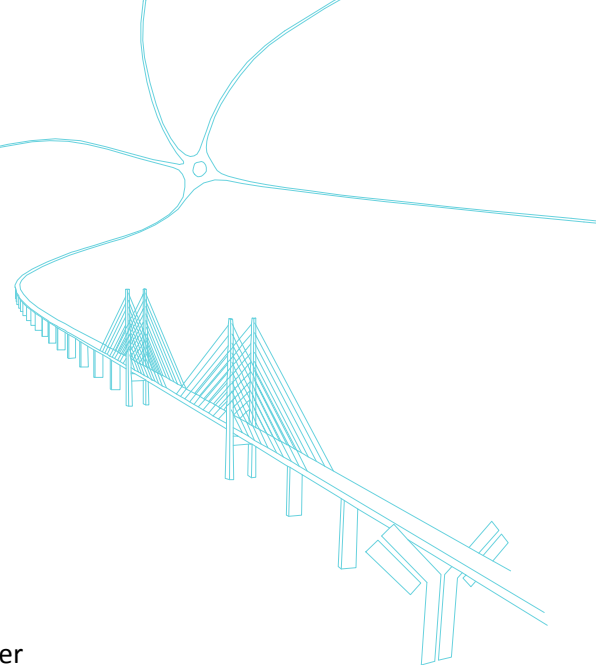
Alessio Fasano

Mucosal Biology Research Center and Center for Celiac Research
University of Maryland School of Medicine
Baltimore, MD U.S.A.
afasano@mbrc.umaryland.edu

The intestinal epithelium is the largest mucosal surface providing an interface between the external environment and the mammalian host. Its exquisite anatomical and functional arrangements and the finely-tuned coordination of digestive, absorptive, motility, neuroendocrine and immunological functions are testimonial of the complexity of the gastrointestinal system. Also pivotal is the regulation of molecular trafficking between the intestinal lumen and the submucosa via the paracellular space. Under physiological circumstances, this trafficking is safeguarded by the competency of intercellular tight junctions (TJ), structures whose physiological modulation is mediated, among others, by the TJ modulator zonulin. The structural and functional characteristics of intercellular TJ and the protean nature of the intestinal content suggest that the gut mucosa represent the “battlefield” where friends (i.e., nutrients and enteric microflora) and foes (i.e., pathogenic microorganisms and their toxins) need to be selectively recognized to reach an ideal balance between tolerance and immune response to non-self antigens. This balance is achieved by selective antigen trafficking through TJ and their sampling by the gut associated lymphoid tissue. If the tightly regulated trafficking of macromolecules is jeopardized, the excessive flow of non-self antigens in the intestinal submucosa can cause autoimmune disorders in genetically susceptible individuals.

Our data indicate that gliadin initiates intestinal permeability through a CXCR3-mediated, MyD88-dependent release of zonulin that enables paracellular translocation of gliadin and its subsequent interaction with macrophages within the intestinal submucosa. Gliadin interaction with macrophages triggers signalling through a TLR pathway, resulting in the establishment of a pro-inflammatory (Th1-type) cytokine milieu that causes an innate immune-mediated early mucosal damage that may lead to adaptive immune response targeting either the gut (celiac disease) or other organs (pancreas in type 1 diabetes).

This new paradigm subverts traditional theories underlying the development of autoimmunity, which are based on molecular mimicry and/or the bystander effect, and suggests that the autoimmune process can be arrested if the interplay between genes and environmental triggers is prevented by re-establishing intestinal barrier competency.

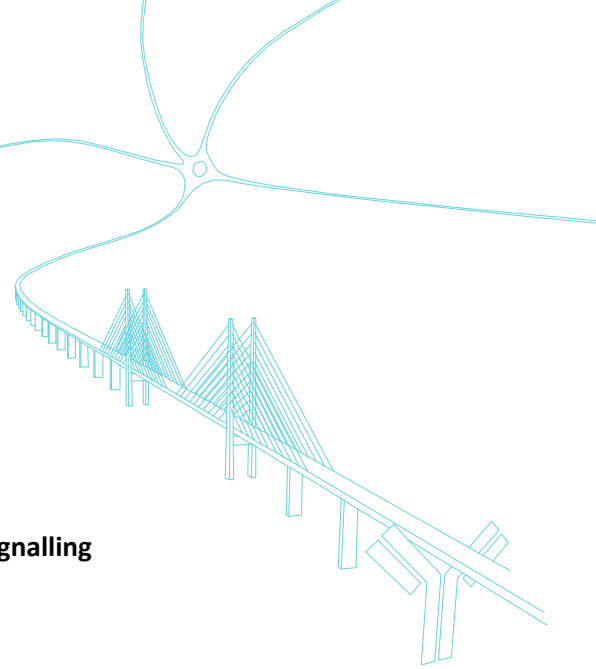


Mechanisms of lymphatic vascular development and remodeling

Tatiana V. Petrova

Division of Experimental Oncology, Multidisciplinary Oncology Center
University of Lausanne and CHUV
Epalinges, Switzerland
tatiana.petrova@unil.ch

The lymphatic vasculature forms a vessel network that drains interstitial fluid from tissues and returns it to the blood circulation. Lymphatic vasculature has also recently emerged as a prominent area in biomedical research because of its involvement in pathogenesis of several human diseases, such as solid tumour metastasis, inflammation and lymphedema. I will discuss the essential steps of lymphatic vascular development, such as lymphatic endothelial differentiation, sprouting and formation of mature lymphatic vascular network, and the role of transcription factor Foxc2 and calcineurin/NFAT in the regulation of the latter process.



Mechanisms contributing to the diversity of purinergic receptor signalling

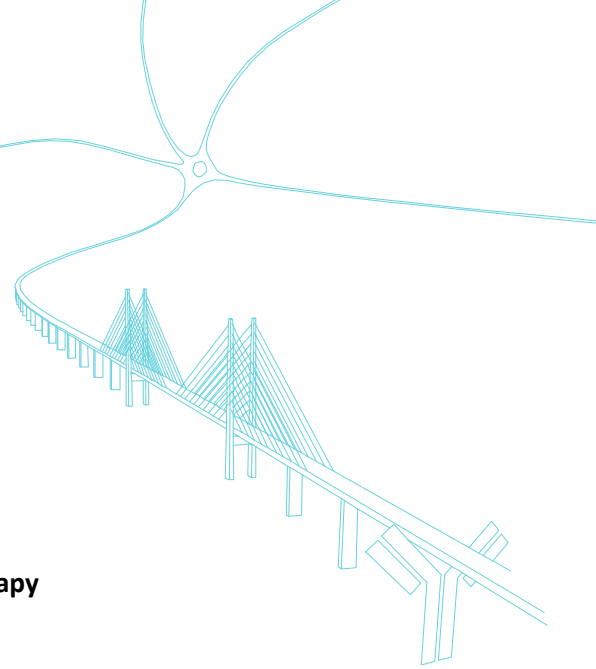
Ruth Murrell-Lagnado

Dept Pharmacology, University of Cambridge
Cambridge, UK
rdm1003@cam.ac.uk

Extracellular ATP is an important signalling molecule that controls numerous biological processes in the nervous, immune, endocrine, respiratory and cardiovascular systems. Its effects are mediated via cell surface P2 receptors of which there are two types: the G protein coupled P2Y receptors and the P2X receptors, which possess an integral cation channel that opens in response to ATP. All cells release ATP via mechanisms that include exocytosis, channel-mediated and cell lysis and release is increased following injury and in a number of disease states. ATP receptors therefore play an important role in many pathologies as well in health and are important therapeutic targets in pain and inflammation.

Seven members of the P2X family, sharing 35-50% amino acid identity, have been identified in vertebrates and these subunits show a widespread and overlapping distribution and are able to co-assemble as homo- and heterotrimeric receptors. Unrelated proteins such as nicotinic and 5-HT₃ receptors and the pannexin hemichannel also appear capable of associating with P2X receptors. The response of P2X receptors is further regulated by controlling the trafficking of receptors to the plasma membrane and intracellular compartments by the interaction between motifs in specific subtypes and additional accessory proteins pointing to potentially novel physiological roles.

In this seminar I will discuss the experimental basis for our understanding of how P2X receptor signalling is regulated at the level of the assembly of functional channel complexes, interactions between channels and mechanisms controlling receptor trafficking to and from the cell surface.

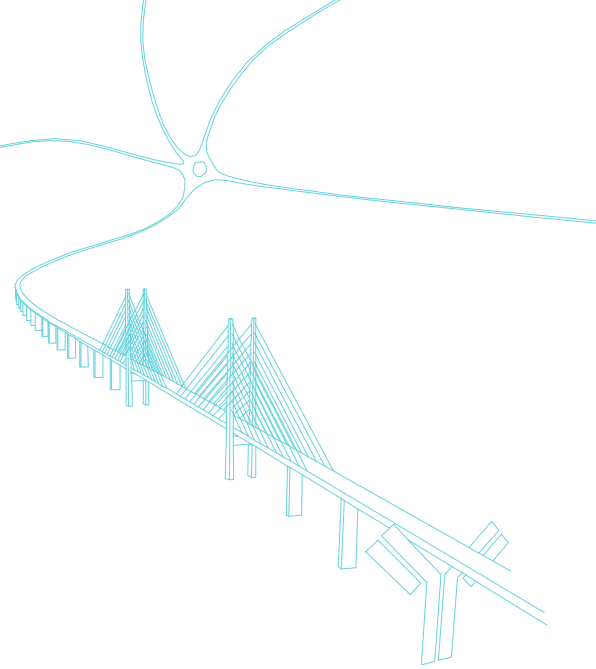


**Oncogenic receptors for growth factors:
Defective cell communication offers opportunities for cancer therapy**

Yosef Yarden

Department of Biological Regulation, the Weizmann Institute of Science
Rehovot, Israel
yosef.yarden@weizmann.ac.il

Human-made information relay systems invariably incorporate supervisory components, which are mirrored in biological systems by dense feedback and feedforward circuitries. This distributed configuration will be exemplified using cellular regulation by epidermal growth factors and receptor tyrosine kinases of the EGFR/ERBB family. Studies in invertebrates and in mammalian EGFR systems unveiled a web of activity-dependent regulatory loops, which fall into early and late groups. In the early phase, ubiquitylation and neddylation, which largely mediate receptor endocytosis, as well as primary and secondary (backward) phosphorylation, play major roles in immediate regulation of receptor signaling. On the other hand, late regulatory mechanisms of the network comprise newly-induced RNAs, microRNAs and proteins, which account for the specificity of the response to external stimuli. The dynamic behavior of the EGFR network and similar signaling systems identify feedback and feedforward loops as a computational core able to perform complex tasks, like digitalization of graded signals, filtration of noise, calculation of fold induction and fixation of output, which leads to stable phenotypes. Importantly, cancer and other diseases harness the regulatory mechanisms of the network by weakening negative feedback and enhancing positive feedback, thereby manipulating critical time constants of the network. My lecture will highlight several examples of defective feedback regulation in cancer, as well as opportunities they offer for therapy of solid tumors.



**Control of cortical inhibition and excitation by endocannabinoids:
Novel insights into anxiety and epilepsy**

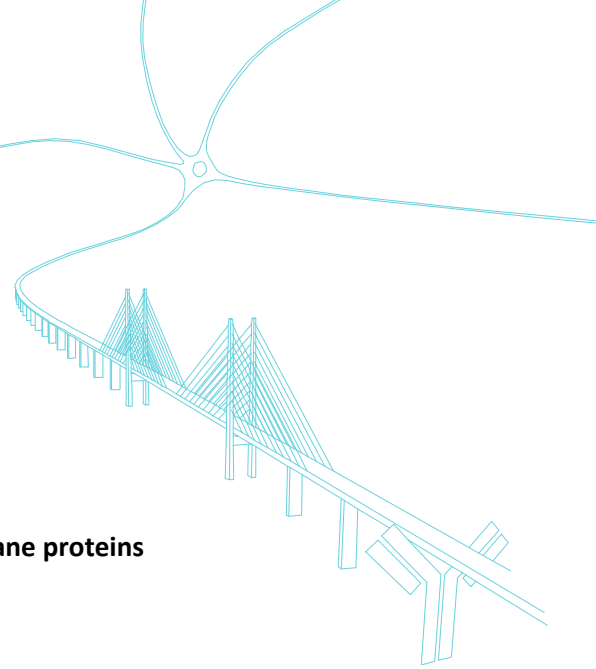
Tamás F. Freund

Institute of Experimental Medicine, Hungarian Academy of Sciences
Budapest, Hungary
freund@koki.hu

Endogenous cannabinoids are thought to be retrograde mediators in several forms of synaptic plasticity. Depolarization of hippocampal pyramidal cells, or a rise in intracellular calcium, evokes a CB₁ cannabinoid receptor-mediated short-term depression of GABA release from afferent inhibitory terminals (depolarization-induced suppression of inhibition; DSI). CB₁ receptors present on interneuron axons mediate both endo- and exogenous cannabinoid actions on cortical GABAergic transmission and associated cognitive functions or disfunctions. Most of the CB₁-modulated interneurons belong to the CCK-containing basket cells, which receive abundant subcortical input, and express several receptors – in addition to CB₁ – that are implicated in anxiety. These features enable CCK-positive interneurons to function as a fine-tuning device for cortical fast oscillations, mediating motivational and emotional impacts.

On the other hand, cannabinoids are known to suppress glutamatergic EPSCs as well, boutons forming asymmetrical synapses on pyramidal cell spines are equipped with presynaptic CB₁ receptors. In addition, diacylglycerol lipase alpha (DGL- α), the synthesizing enzyme of the endocannabinoid 2-arachidonoylglycerol (2-AG), is present in dendritic spines, postsynaptic to the CB₁-expressing terminals, thus confirming that 2-AG produced by DGL- α in spines may be involved in retrograde signaling at glutamatergic synapses. The specific location of DGL- α together with mGluR5 in the perisynaptic annulus raises the possibility that glutamate spillover could activate, via mGluR5, the synthesis and release of 2-AG, which may serve to reduce further glutamate release from the presynaptic terminals. Malfunctioning of this negative feed-back system may be involved in epileptogenesis, since a downregulation of CB₁ receptors on glutamatergic terminals is among the most profound molecular changes in lobectomy samples of human epileptic patients observed even before degeneration of CA1 pyramidal cells begins.

Thus, in the cerebral cortex, endocannabinoids are involved in the presynaptic regulation of both GABAergic and glutamatergic transmission, and malfunctioning of this control machinery is implicated in several brain disorders. Identification of the molecular architecture of this signaling system may shed light on its functional roles, and point to new drug targets in pharmacotherapy.

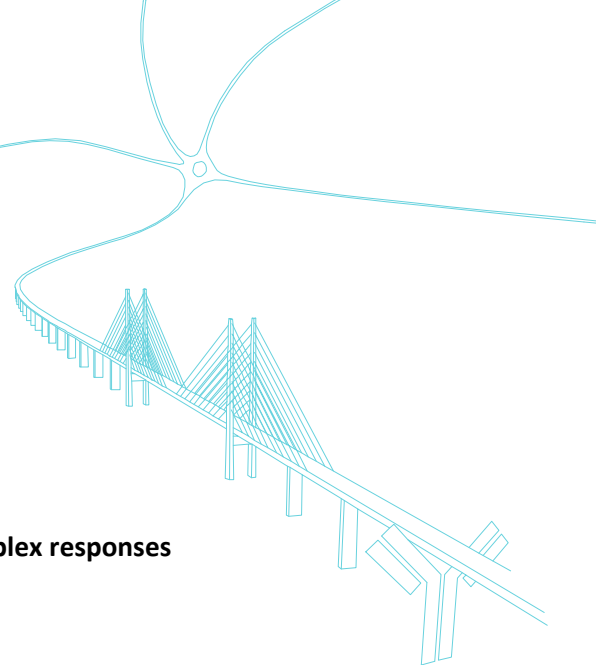


AMPA-type glutamate receptors and their accessory transmembrane proteins

Yael Stern-Bach

Department of Biochemistry & Molecular Biology, IMRIC
The Hebrew University-Hadassah Medical School
Jerusalem, Israel
yaelste@ekmd.huji.ac.il

AMPA-type glutamate receptors (AMPA) are of fundamental importance in the brain. They are responsible for the majority of fast excitatory synaptic transmission and their overactivation is potentially excitotoxic. AMPARs are implicated in synapse formation and stabilization, and regulation of AMPAR number and function is the principal mechanism underlying synaptic plasticity. Changes in AMPAR activity have been described in the pathology of numerous diseases, such as Alzheimer's disease, stroke and epilepsy. In addition to a wide variety of cytoplasmic proteins, which bind to the intracellular C-terminal domain of the receptor and regulate its synaptic insertion and retrieval, AMPARs also associate with several types of transmembrane proteins that regulate receptor properties at multiple levels and in opposing directions. These include the well established transmembrane AMPAR regulatory proteins (TARPs), the more recently identified CNIH2/3 of the cornichon family, CKAMP44 and SynDIG1, and the invertebrate Sol-1. The lecture will cover what is currently known on the molecular mechanisms of AMPAR regulation by these interactors, individually and combined. Besides providing fundamental insights into AMPAR function and regulation, a full understanding of these mechanisms may enable the creation of small peptides that either inhibit or mimic AMPAR regulation by a particular interactor, hence providing pharmaceutical tools for the treatment of brain pathologies where AMPARs are involved.

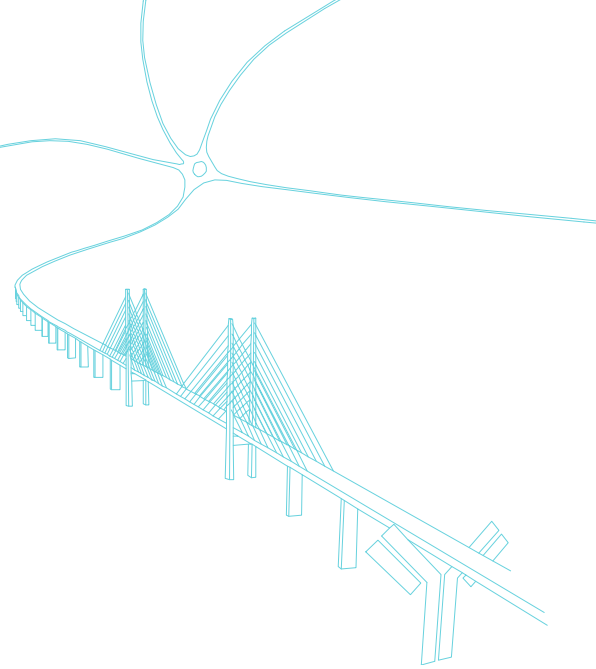


Type I IFN, a large cytokine family with pleiotropic activity in complex responses

Sandra Pellegrini

Cytokine Signaling Unit, Dept of Immunology, Institut Pasteur
Paris, France
pellegrini@pasteur.fr

Physiological and pathological modifications of the immune response are often driven or worsened by altered production and/or response to cytokines which can re-program cellular function and fate. Molecular understanding of cytokine signaling is therefore the basis for more rational and targeted medical intervention in immune response dysfunctions, whether infectious or autoimmune diseases, cancer, vaccination or transplantation. In the complex cytokine network, type I interferons (IFN α/β) form a large family (17 genes) regulating differentiation, function and homeostasis of immune cell lineages. IFN contribute to immediate defense against pathogens, development of adaptive immunity and protective antitumor responses. Unique features of type I IFN are an extreme pleiotropy and cell context-specific bioactivities. Two subtypes, IFN α 2 and IFN β , are widely used in the clinic and are the major treatments of chronic HCV infection and multiple sclerosis, respectively. Yet, the mechanism of their beneficial action remains ill defined. We have been interested in dissecting IFN α vs IFN β activities. In many cell lines, IFN β is remarkably more potent than IFN α in inhibiting cell growth and the molecular basis of this α/β differential will be discussed. We have studied a particular α/β 'differential' state whereby cells that are primed with either type I or the unrelated type III IFN (IFN λ or IL-28/29) become refractory to all IFN α subtypes but retain sensitivity to IFN β . Understanding the crosstalk between type I and type III IFNs is essential given the high incidence of resistance to IFN α therapy in treated HCV-infected patients and in view of developing new molecules to be used in clinical settings.

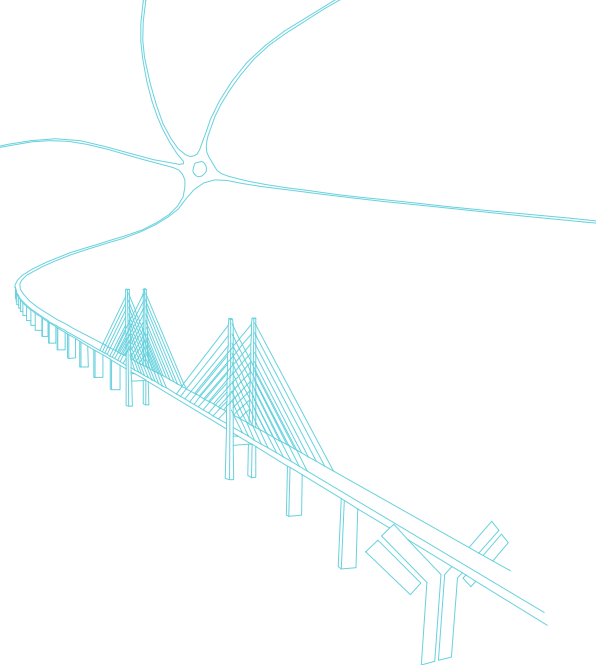


Functional genomics to study angiogenesis in health and disease

Mieke Dewerchin

Vesalius Research Center
VIB – KULeuven, Belgium
mieke.dewerchin@med.kuleuven.be

In vertebrates, blood vessels form an extensive network, which is spatially organized to optimize delivery of oxygen and nutrients to all cells throughout the body. During development, endothelial precursors differentiate and coalesce into tubes of a primary vascular plexus, a process called 'vasculogenesis'. This primitive network subsequently expands via angiogenesis (sprouting and branching of preexisting vessels) to give rise to a complex, hierarchical circuit. Over the past few decades, extensive research has greatly advanced our knowledge of blood vessel formation at a cellular and molecular level, and has already yielded pro- and anti-angiogenic therapies benefiting numerous patients. Indeed, many disorders are characterized by an imbalance in angiogenesis, which is either insufficient (such as in ischaemic heart and limb disease, stroke and delayed wound healing) or excessive (such as in cancer and ocular disease). Many of these disorders are major causes of morbidity and mortality. The lecture will give an overview of the major cellular and molecular processes involved in blood vessel formation in health and disease, with attention to experimental in vitro and in vivo models and genetic technologies employed, and will then further zoom in into some of the recently obtained novel insights.

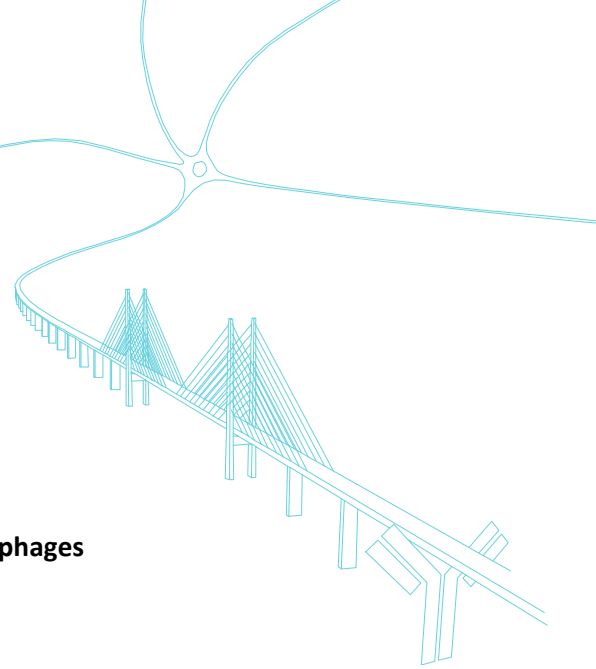


Intracellular DNA recognition by the innate immune system

Veit Hornung

Institute for Clinical Chemistry and Clinical Pharmacology
Unit for Clinical Biochemistry
University Hospital, University of Bonn
Bonn, Germany
veit.hornung@uni-bonn.de

A central function of our innate immune system is to sense microbial pathogens by the presence of their nucleic acid genomes or their transcriptional or replicative activity. In mammals, a receptor-based system is mainly responsible for the detection of these “non-self” nucleic acids. Tremendous progress has been made in the past years to identify host constituents that are required for this intricate task. With regard to the sensing of RNA genome based pathogens by our innate immune system, a picture is emerging that includes certain families of the toll-like receptor family (TLR3, TLR7, TLR8) and the RIG-I like helicases (RIG-I, MDA5 and LGP2). Genetic loss of function studies implicate that the absence of these pathways can lead to a complete lack of recognition of certain RNA viruses. At the same time, intracellular DNA can also trigger potent innate immune responses, yet the players in this field are less clear. We and another group recently identified a role for RNA polymerase III in the conversion of AT-rich DNA into an RNA ligand that is sensed by the RIG-I pathway. However, at the same time other sensing pathways must exist that additionally operate to sense non-self DNA in cytoplasm or maybe even in the nucleus. This redundancy of DNA sensing pathways has tremendously complicated the search for the yet elusive innate immune DNA receptor(s).



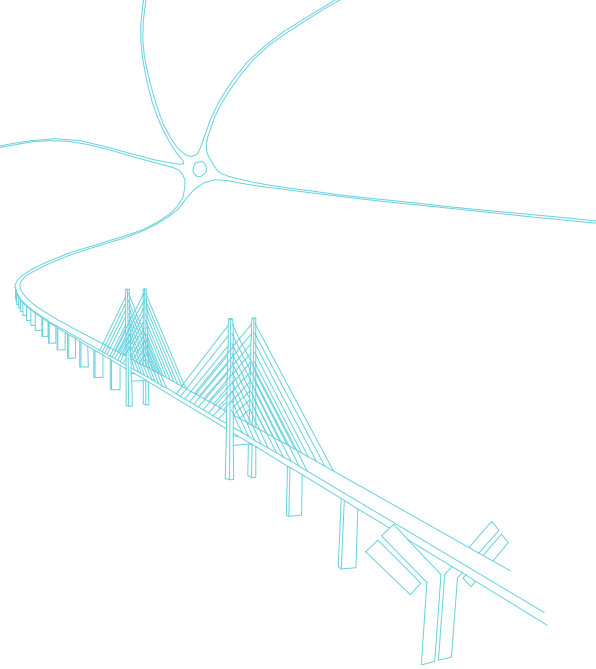
Regulation of inflammatory responses by ITAM signaling in macrophages

Jessica A. Hamerman

Immunology Program, Benaroya Research Institute, Seattle, WA
Department of Immunology, University of Washington, Seattle, WA
jhamerman@benaroyaresearch.org

Macrophages are situated throughout the body where they function to survey their surroundings for the presence of pathogens. In response to detection of pathogens, macrophages produce a variety of pro-inflammatory cytokines to initiate inflammation and protective immune responses. The activities of many of these pro-inflammatory cytokines, such as tumor necrosis factor (TNF), can be toxic to the host and therefore their production must be tightly regulated. Macrophages express receptors that are specific for pathogens, such as Toll-like receptors (TLRs), as well as a variety of receptors that sense the extracellular milieu, including Ig superfamily receptors, integrins and C-type lectins. Ligation of these receptors can modulate the production of pro-inflammatory cytokines by macrophages in response to TLR ligation by pathogens. Our laboratory studies a family of macrophage receptors that pair with adapters containing immunoreceptor tyrosine-based activation motifs (ITAMs) that have been implicated in both inhibition and activation of TLR-induced inflammatory responses. Here, I will discuss how ITAM signaling regulates inflammatory responses in macrophages.

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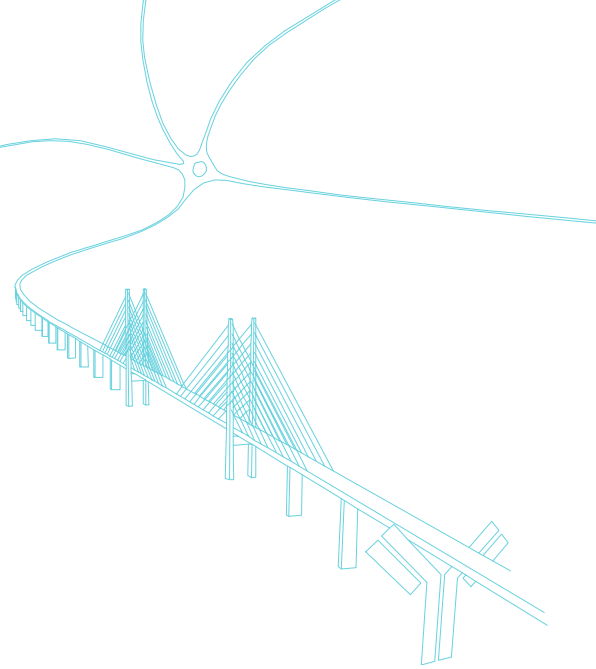
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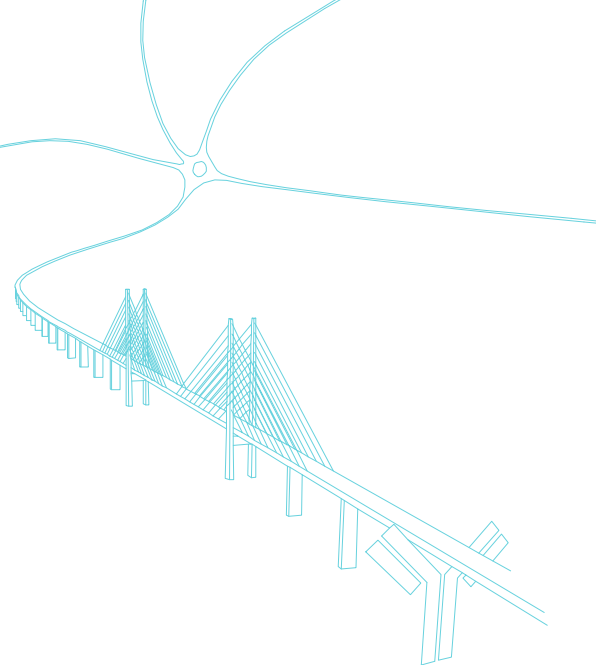


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Michael Lagler, Isabella Salzer, Philipp Schatzlmaier, Caroline Stremnitzer, Josef Singer, Marco Treven
Cornelia Schuh, Eva Hochbrugger, Josefine Lindroos, Gabriel Wagner, Carol-Ann Eberle, Riem Gawish

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carol-ann.eberle@meduniwien.ac.at

caroline.stremnitzer@meduniwien.ac.at

cornelia.schuh@meduniwien.ac.at

eva.hochbrugger@meduniwien.ac.at

gabriel.wagner@meduniwien.ac.at

isabella.salzer@meduniwien.ac.at

josefine.lindroos@meduniwien.ac.at

marco.treven@meduniwien.ac.at

michael.lagler@meduniwien.ac.at

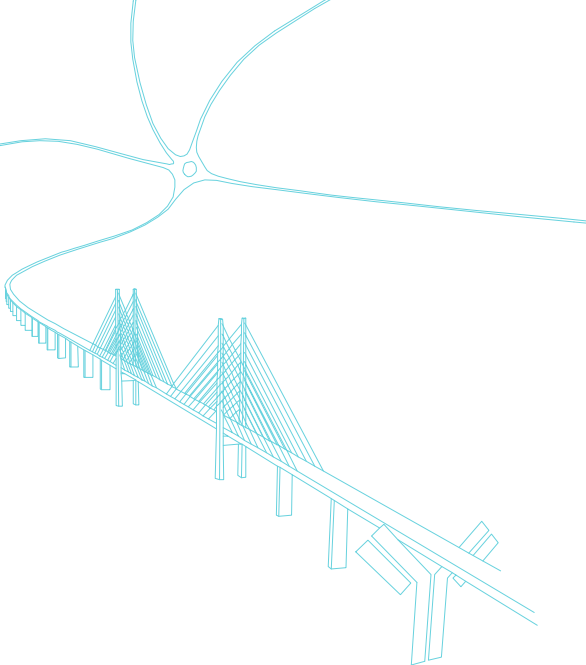
riem.gawish@meduniwien.ac.at

philipp.schatzmaier@meduniwien.ac.at

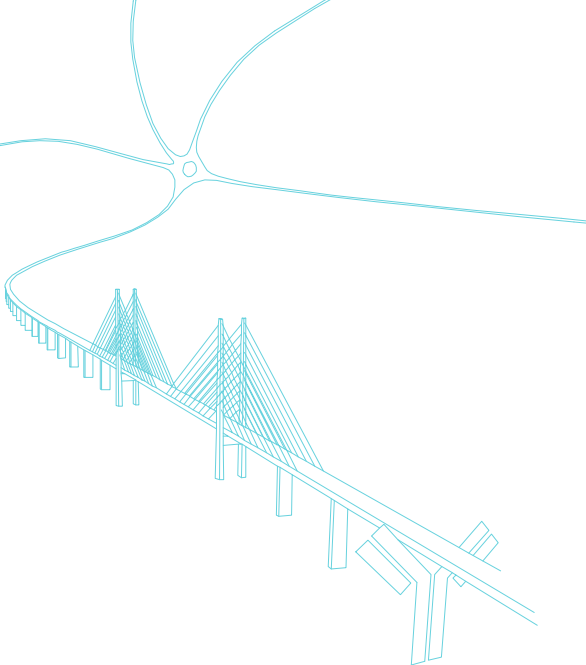
josef.singer@meduniwien.ac.at

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