1st International Workshop on
Inflammation and Immunity

You Give Me Fever

Current Topics in Inflammation

May 14-15, 2009
General Hospital Vienna, Austria
Big Lecture Hall, Kliniken am Südgarten

Inflammation and its Regulation

Inflammation and Cancer

Inflammation and Autoimmunity

Inflammation and Novel Therapies

Program & Abstracts

Organized by the students of the IAI PhD program of the MUW

FWF

PHD-PROGRAM
INFLAMMATION AND IMMUNITY

MEDICAL UNIVERSITY OF VIENNA

The organizing committee would like to thank the following sponsors for their generous support:

The paper for printing of this abstract booklet was kindly provided by sappi.

acknowledgements

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TABLE OF CONTENTS

The PhD and MD/PhD Program Inflammation and Immunity (IAI) aims at revealing novel mechanisms controlling the development and function of immune cells in health and disease and train excellent young researchers with a new qualification profile in basic, translational and clinical research. The IAI PhD program is closely linked to two Special Research Programs (SFB-F18 and SFB-F23) funded by the Austrian Science Fund (FWF) and several Austrian (GEN-AU, CDL) and European (NoE, RTN, Strep) networks.

Our overall scientific objective is to understand the detailed events and molecular mechanisms associated with inflammatory and immunological diseases. Genes, molecules, isolated cells and tissues as well as whole organisms are all being exploited as model systems. Thereby mouse immunologists will closely interact with human immunologists and establish a close interaction between basic and clinical science. We provide synergistic expertise in the fields of molecular biology, cell biology, mouse genetics, immunology, allergology, infectiology and immunopharmacology, also at the translational level. The major critical advantage of working in this interactive network will be the transfer of molecular observations made in vitro to the clinical treatment of immune and inflammatory diseases in patients. Access to patient material will be provided by the clinical research groups present within the IAI program. This interface between basic and clinical research is of particular importance for the success of the IAI PhD program.

The IAI PhD Program will concentrate its research efforts in the following four areas:

* Basic aspects of Immunity
* Inflammatory diseases
* Infectiology and Vaccinology
* Allergy, Hypersensitivity and Transplantation

Our scientific goals will be implemented by a state-of-the art career development plan which includes comprehensive educational training in the field of IAI, special lectures on career awareness, collaborative programs with international universities and research institutions, exchange of research tools and technologies, teaching and special scientific workshops. This will offer IAI PhD students all the prerequisites for a future successful career in academia, industry or any field of health care.

http://www.meduniwien.ac.at/phd-iai/
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Greeting from the IAI PhD Students

In 2007 the Medical University of Vienna launched its new PhD program “Inflammation and Immunity” (IAI), centered around training young researchers, with the goal of ascertaining novel aspects and mechanisms involved in immunological and inflammatory diseases. With support from the Austrian Science Fund (FWF) as well as the Medical University of Vienna, students are given the opportunity to work closely with experts in their chosen field of interest in a state-of-the-art laboratory environment. By enabling a synergistic network within the disciplines of immunology, cancer research, vaccinology, allergology and transplantation the aim is to create a tight bond between basic research and its clinical potentials.

While within the program, we students are given the privilege of designing and organizing an annual workshop. As all our research projects involve investigating different aspects of tissue inflammation this workshop will focus on providing us with the current state-of-affairs in inflammation. We have arranged a very diverse and impressive consortium of multinational experts in the field of inflammation that will hopefully entice stimulating discussions by their exchange of data and ideas.

With this, we would like to welcome you to the IAI’s 1st International Workshop on Inflammation and Immunity entitled “You Give Me Fever - Current Topics in Inflammation”. We are looking forward to informative talks and lively discussions and hope it will be a successful and memorable workshop. Welcome to Vienna and enjoy your stay in the Austrian capital.

The organizing committee

Welcome to the 1st International Workshop of the Doctoral Program Inflammation and Immunity (IAI)

"You Give Me Fever: Current Topics in Inflammation"

About two years ago the Doctoral Program “Inflammation and Immunity“ (IAI) has been implemented as an educational excellence platform in basic medical research at the Medical University of Vienna (MUW). Since then the MUW as a major European Center of biomedical research and education provides the infrastructure for students from all over the world. Meanwhile 18 internationally recruited PhD students from 8 countries have been accepted into the IAI program and they are conducting their research in the laboratories of the 8 Principal Investigators (PI) that are part of the IAI PhD program. All the PIs hold positions as professors or associated professors and are affiliated with six different Departments of the MUW. Our aim is to strengthen the research interactions and to extend our collaborative network beyond laboratory walls and different research disciplines, as well as language gaps and cultural differences. This workshop is part of our endeavor.

The topic chosen by our students for the 1st international workshop is Inflammation. The research in this area is of worldwide medical need and has potential to accelerate the process from basic discoveries to new therapeutic strategies leading to prevention, diagnosis and treatment of various diseases including cancer, rheumatoid arthritis and psoriasis, just to name a few. The students have invited internationally well-known experts and world leading scientists in the field and we are looking forward to an active exchange of opinions, stimulating discussions and exciting scientific interactions for the next two days.

In the name of all PIs I would like to thank the students for putting together such an exciting program and to all the speakers for accepting the invitation and traveling to Vienna to make this event possible. I wish all the IAI students and all participants of the workshop two exciting days.

Finally, we would like to express our gratitude towards the Austrian Science Fund (FWF) and the MUW for financing and supporting our PhD program and to all companies for co-sponsoring this workshop.

Maria Sibilia (IAI PhD program coordinator)

and
all PIs of the program:
Barbara Bohle, Wilfried Ellmeier, Franz X. Heinz, Georg Stingl, Herbert Strobl, Rudi Valenta, Thomas Wekerle

"You Give Me Fever: Current Topics in Inflammation"

Thursday, May 14, 2009

08:30 – 09:00 Registration

09:00 – 09:15 Welcome

OPENING LECTURE

Chair: Maria Sibilia

09:15 – 10:00 **Inflammatory and neoplastic skin diseases: New insights – new therapies**
Georg Stingl

SESSION I: INFLAMMATION AND ITS REGULATION

Chair: Véronique Schulten, Afitap Derya Köprülü

10:00 – 10:45 **Bones and fever regulation**
Josef Penninger

11:00 – 11:15 *Coffee Break*

11:15 – 12:00 **Interferons and Stats in infection, inflammation and the onset of adaptive immunity**
Thomas Decker

12:15 – 13:00 **Chemokine patterning by glycosaminoglycans and interceptors: Chemokinese phrase and fable *in vivo***
Antal Rot

13:15 – 14:30 *Lunch Break (poster session: IAI-PhD students and speakers)*

SESSION II: INFLAMMATION AND CANCER

Chair: Barbara Drobits, Oksana Vratskikh

14:30 – 15:15 **Molecular mechanisms linking inflammation & cancer**
Florian R. Greten

15:30 – 16:15 **AP-1 (Fos/Jun) in inflammation and cancer development**
Erwin F. Wagner

16:30 – 16:45 *Coffee Break*

16:45 – 17:30 **Friends or Foes - tumor promoting or tumor eliminating types of inflammation**
Martin Oft

Friday, May 15, 2009

08:30 – 09:00 Registration

SESSION III: INFLAMMATION AND AUTOIMMMUNITY

Chair: Anastasia Abramova, Thomas Bauer

09:00 – 09:45 **TAM receptor tegulation of the innate immune response**
Greg Lemke

10:00 – 10:15 *Coffee Break*

10:15 – 11:00 **CD4+ T cells in the inflamed CNS**
Steve Anderton

11:15 – 12:00 **Skin inflammation:**
A gene to function and therapy perspective
Frank Nestle

12:15 – 13:30 *Lunch Break*

SESSION IV: INFLAMMATION AND NOVEL THERAPIES

Chair: Katarzyna Niespodziana, Haley Ramsey

13:30 – 14:15 **Alarming the immune system:**
About novel adjuvants and skin-delivery in vaccine development
Alexander von Gabain

14:30 – 15:15 **Antibody therapeutics: Optimisation for purpose**
Roy Jefferis

15:30 – 16:15 **A paradigm for biological therapy:**
Bench to bedside translation of targeted anti-TNF therapy
Ravinder N. Maini

16:30 – 16:45 *Coffee Break*

PANEL DISCUSSION

Chair: Maria Sibilia, Georg Stingl

16:45 – 17:45 Greg Lemke, Raviner N. Maini, Martin Oft, Antal Rot

17:45 – 18:00 Closing Remarks

INFLAMMATORY AND NEOPLASTIC SKIN DISEASES: NEW INSIGHTS – NEW THERAPIES

Georg Stingl

Department of Dermatology, Division of Immunology, Allergy and Infectious Diseases
Medical University of Vienna, Vienna, Austria

The skin, the outermost layer of the body, is built in a way that allows it to protect the integrity of the host and, at the same time, to serve as bridge and communication site between inside and outside. This barrier function of the skin has a physical, a chemical, and an immunological component. Upon receipt of a danger signal or under certain pathological conditions, the skin is quickly populated by cells of the innate and adaptive immune system which, by the production of different types of mediators, give rise to inflammation and, as a consequence, to tissue damage and repair.

Research efforts in the last decade have provided insights into the pathogenesis of the most common inflammatory skin diseases which, at least in the case of psoriasis, have provided the basis for entirely novel treatment strategies that, in the meantime, have revolutionized our therapeutic armamentarium.

The opposite situation is true in skin cancer. Not only do cancer cells proliferate per se in an uninhibited fashion, but they are also not constrained by appropriate host defense mechanisms. We now have immunostimulatory compounds available that, upon topical application, induce tissue inflammation and endow immunocytes with cytodestructive effector functions that can contribute to cancer regression and perhaps also to the elimination of virus-infected cells.

This etiology- and pathogenesis-based approach to drug development will certainly result in the increased production of therapeutic tools of high efficacy as well as good tolerability that are tailored to the needs of the individualized patient.

BONES AND FEVER REGULATION

Josef Penninger

IMBA, Institute for Molecular Biotechnology of the Austrian Academy of Sciences, Vienna, Austria

RANKL and its receptor RANK are the key regulators of osteoclastogenesis also involved in lymph node formation and development of thymic epithelial cells. Moreover, new medicine based on RANKL inhibition is on the verge of wide-spread human use making it paramount to identify potential additional functions for RANKL. I will discuss the discovery of RANKL, the basic principles of RANKL/RANK function in bone metabolism and report a novel RANKL-RANK function in the brain

INTERFERONS AND STATS IN INFECTION, INFLAMMATION AND THE ONSET OF ADAPTIVE IMMUNITY

Thomas Decker

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Interferons (IFN) are cytokines with profound effects on host immune responses to pathogens. They can be classified into three distinct types, based on structural criteria and their interaction with distinct cell surface receptors. Type I IFN has been identified as antiviral cytokines, but they are produced in response to all pathogens and have widespread effects on both innate and adaptive immunity. IFN transmit their impact on cells largely through Jak-Stat signal transduction. In case of type I IFN this leads to the tyrosine phosphorylation and activation of Stat1 and Stat2 and the formation of a transcription factor termed ISGF3. In viral infections ISGF3 is essential for innate defence. In bacterial infections its role is less clear.

My group studies the impact of type I IFN and Stats on the innate immune response to an intracellular bacterial pathogen, Listeria monocytogenes. Unlike viral infections, production of type I IFN weakens host immunity to L. monocytogenes. We will present cells and mechanisms involved in type I IFN synthesis and show data suggesting how Stat target genes may weaken host immunity. Furthermore we will describe how ISGF3 interacts with other infection-regulated transcription factors to induce transcription of common target genes. Finally we will present data showing that type I IFN and Stats control the activity of dendritic cells and contribute to the onset of antigen-specific, T cell-mediated immunity.

CHEMOKINE PATTERNING BY GLYCOSAMINOGLYCANS AND INTERCEPTORS: CHEMOKINESE PHRASE AND FABLE IN VIVO

Antal Rot

MRC Centre for Immune Regulation, Institute of Biomedical Research, University of Birmingham, England

Leukocyte movement into distinct extravascular compartments is a hallmark of inflammation. Chemokines, structurally and functionally homologous chemotactic cytokines, mediate leukocyte emigration from blood and, subsequently, direct their locomotion within tissues. These processes are triggered by chemokines signaling through one of the multiple cognate G-protein-coupled receptors on leukocytes. Apart from chemokines, leukocyte emigration also requires the involvement of leukocyte and endothelial cell adhesion molecules. Although initially most chemokines are secreted, ultimately they seldom act in solution but are immobilized within microanatomical domains of their salient activities, including vascular endothelium. Hence, the in vivo action of chemokines depends on their specific interactions with “auxiliary” molecules, sulfated sugars of the glycosaminoglycan family and “non-signaling” chemokine receptors called “interceptors”, in particular. Glycosaminoglycans are abundantly expressed by the vascular endothelial cells and are present on the luminal endothelial cell surface. Here they efficiently immobilize chemokines and present them to the adherent leukocytes in conjunction with the tips of their luminal microvilli. However, in order to appear within their presentation sites on the luminal endothelial cell surface, tissue-derived chemokines have to cross the endothelial cell barrier. For inflammatory chemokines this is accomplished by their unidirectional active transport involving the Duffy antigen, an interceptor expressed by venular endothelial cells. Conversely, other chemokine interceptors, D6 in particular, may act as scavenging decoys and are involved in focal clearance of chemokines within tissues. Currently chemokine interceptors comprise, apart from the Duffy antigen and D6, also CXCR7 (RDC1) and CCR11 (CCX-CKR). Mapping their tissue and cell expression in health and disease and defining the scope of their cellular activities should elucidate how these molecules contribute to the chemokine activities in vivo. Remarkably, irrespective of the outcome of chemokine interactions with their interceptors, being either transport or elimination, interceptor activities lead to the establishment of characteristic chemokine patterns at the blood-tissue interface or within tissues. Such spatial chemokine patterns in the form of either step or continuous gradients are required to induce leukocyte emigration from blood and may be necessary to direct leukocyte migration within tissues, respectively. Thus, gradients of chemokines are established not (only) by their passive diffusion, as has been always postulated, but actively through chemokine interactions with interceptors. This activity of interceptors allows for correct phrasing of chemokine-encoded messages leading to their presentation to leukocytes in “comprehensible” and “meaningful” form and tailored to various pathophysiological situations.

MOLECULAR MECHANISMS LINKING INFLAMMATION & CANCER

Florian R. Greten

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A causal link between inflammation and cancer has been suspected for a long time but only over the recent years some of the underlying molecular mechanisms have been deciphered. One of the main signaling pathways responsible for linking inflammation and cancer is the classical NF-kB activation pathway (1). NF-kB has a dual role by either regulating directly the survival of tumorigenic cells or indirectly in immune cells by controlling the transcription of a variety of pro-inflammatory cytokines, which can act in a paracrine manner to stimulate growth of initiated cells (2). One of these NF-kB regulated pro-inflammatory cytokines is IL-6 and we speculated that gp130-mediated activation of Stat3 could be responsible for the pro-proliferative effects of IL-6. Using loss-of-function and gain-of-function mouse models in an inflammation-associated tumor model, we could demonstrate that IL-6 family cytokines indeed control Stat3 induced transcription of a variety of genes important for cell survival and proliferation of tumorigenic cells (3). Thus, Stat3 and NF-kB comprise the central signaling nodes in inflammation-associated cancers.

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AP-1 (FOS/JUN) IN INFLAMMATION AND CANCER DEVELOPMENT

Erwin F. Wagner

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The analysis of the molecular factors determining cell survival or death in response to inflammatory stimuli is essential for understanding the pathogenesis of inflammatory diseases including liver and skin cancer and for identifying novel therapeutic approaches.

In hepatitis and liver cancer, but also during liver regeneration, the expression of Jun/AP-1 is critically important. Using genetically modified alleles, we analyzed the Jun upstream kinase JNK and p38 as well as the p53/TNFα pathway in liver inflammation and cancer. Jun N-terminal kinase (JNK) is a major mediator of cytokine-induced cell death, whereas Jun functions as a survival gene in the Concanavalin A (ConA) model of TNFα-dependent hepatitis(1). The functions of JNK1/2, p38α and Jun were investigated during liver cancer development using the chemical-induced carcinogenesis model (2). Mice with liver-specific deletion of p38α show enhanced tumor development, whereas increased proliferation of *p38*α-deficient hepatocytes and tumor cells was suppressed by inactivation of JNK1 or c-Jun (3,4). These data demonstrate that while p38α MAPK suppresses liver cancer development, JNK1 plays an oncogenic role. The impact on therapeutic applications as well as the expression of components of this pathway in human hepatocellular carcinomas will be discussed.

In the second part I will illustrate how the mouse skin/epidermis has become an important model to study the regulation and function of Fos and Jun subunits in physiological and disease processes. We investigated the consequences of constitutive and inducible epidermal deletion of both Jun and JunB proteins during development and in adult mice (5). Mice lacking Jun and JunB in epidermal cells die at post-natal day 1 with a phenotype similar to cachexia. Recent molecular analyses demonstrating that the mutant pups die from a TNFα-dependent disease will be discussed, which contrasts to the psoriasis-like phenotype, when employing an inducible, epidermal knock-out strategy (5). Overall, these data demonstrate that the stress-responsive AP-1 proteins are general regulators of innate inflammation control in the skin.

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FRIENDS OR FOES - TUMOR PROMOTING OR TUMOR ELIMINATING TYPES OF INFLAMMATION

Martin Oft

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Chronic inflammation is epidemiologically associated with the cancer incidence in humans. Inflammation also promotes tumor development in mouse models of human cancer. This tumor associated inflammation has in its elements much in common with the deregulation of the immune system observed in immune mediated inflammatory diseases. Inflammatory cytokines such as Interleukin 23, TNFα, IL-6 and IL-1 are highly expressed in human cancer, in particular at later stages of tumor progression. Human cytotoxic T cells specific to oncogenes and onco-fetal antigens are present in human cancer patients but does not protect from tumor progression. The presence of T cells in the tumor tissue however correlates with a favorable prognosis for the patient. Yet, tumor infiltrating T cells frequently fail to express activation markers associated with immune surveillance and MHC molecules are expressed at a low level in tumor cells and tumor infiltrating dendritic cells. The immunological recognition of tumor antigens or the expansion of antigen specific T cell at large might therefore not be as profoundly impaired in tumor patients as the correct polarization and the effector function of tumor infiltrating T cells.

Mouse models of human cancer have recently shed some light on the molecular regulations for this association of tumors with inflammation and a rationale how inflammation fuels tumor progression. Mice deficient in IL-23, a cytokine essential for auto-inflammatory diseases, are also resistant to tumor induction by carcinogens. The absence of IL-23 signaling not only suppresses the infiltration of inflammatory macrophages and angiogenesis, but also increases the infiltration of cytotoxic CD8+ T cells and their activity in situ. Tumor infiltrating T cells isolated from IL23R deficient are highly activated. Surprisingly, short term neutralization of IL-23 repolarizes the deregulated tumor immunity, increasing the infiltration and activity of CD8 T cells.

We will present further data how the modulation of other pro-inflammatory cytokines can induce both: the inhibition of tumor associated inflammation and the recovery of cytotoxic T cell responses.

TAM RECEPTOR REGULATION OF THE INNATE IMMUNE RESPONSE

Greg Lemke

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Pathogen encounter by dendritic cells (DCs) and macrophages triggers a rapid inflammatory response that is essential to combating infection. However, this response must be tightly regulated, since unrestrained Toll-like receptor (TLR) and cytokine receptor signaling generates a chronic inflammatory milieu that often leads to autoimmunity. We have found that the TAM receptor tyrosine kinases - Tyro3, Axl, and Mer - broadly inhibit both TLR and TLR-induced cytokine receptor cascades (1,2). Remarkably, TAM inhibition of inflammation is transduced through an essential stimulator of inflammation - the type I interferon receptor (IFNAR) and its associated transcription factor STAT1. TLR induction of IFNAR-STAT1 signaling up-regulates components of the TAM system, which in turn usurp the IFNAR-STAT1 cassette to induce the cytokine and TLR suppressors SOCS1 and SOCS3. These results illuminate a self-regulating cycle of inflammation, in which the obligatory, cytokine-dependent activation of TAM signaling hijacks a pro-inflammatory pathway to provide an intrinsic feedback inhibitor of both TLR- and cytokine-driven immune responses. They have important implications for both TAM regulation of viral infection and the use of TAM-based therapies in concert with type I IFN treatment of autoimmune disease.

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CD4+ T CELLS IN THE INFLAMED CNS

Steve Anderton

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University of Edinburgh, Edinburgh, Scotland, UK

The inflammatory phase of multiple sclerosis (MS) appears to be driven autoimmune assault on CNS myelin. The mouse model, experimental autoimmune encephalomyelitis (EAE), can be induced by immunization with a variety of myelin autoantigens, and bears several of the immunopathological hallmarks of MS (1). EAE is used widely as the primary pre-clinical model for the development of new disease-modifying MS drugs. EAE is driven by CD4+ T cells (which can transfer disease upon passive-transfer to non-immunized hosts). Beyond this fact, it is remarkable that we still do not understand the basic natural history of this disease in terms of what do the autoaggressive T cells need to produce to drive the CNS inflammation and how do those models that show natural recovery from disease achieve this? Historically, EAE was viewed as the prototypic Th1-driven disease, mediated by T cells that produce IFN-γ (1). However, gene knockout studies have led to a recent revision of this paradigm, with some now believing the Th17 cells are the chief encephalitogenic cells (2-6).

Our interest was initially sparked by the natural recovery from EAE displayed by some models. Was this in any way immune-mediated? We showed that the recovery phase correlates absolutely with a striking increase in the frequency of CD4+foxp3+ T regulatory cells (Tregs) specifically within the inflamed CNS (7). These cells were highly activated compared to their counterparts from the periphery, were rapidly proliferating, were highly suppressive in vitro and could provide a degree protection against EAE when transferred to naïve hosts (7, 8). Importantly, mice that had been depleted of Tregs failed to recover from EAE (7, 9). We developed an in vitro readout of suppressive function for these CNS-derived Tregs and found that they could strongly inhibit IFN-γ production by CNS effector T cells, but did not inhibit the low-level production of IL-17 by these cells (8). This led us to compare the pathogenic potential of myelin-reactive Th1 versus Th17 populations; the prediction being that Th17 cells would transfer chronic disease because they could not be suppressed by Tregs within the CNS. Surprisingly, only Th1 cells could access the non-inflamed CNS to establish the EAE lesion. Th17 cells on their own were not pathogenic (10). More recent work has been exploring this difference in an attempt to identify the key T cell derived factors required for the initiation of EAE. We have also been exploring the therapeutic potential of Tregs, and our observations on this will be discussed.

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SKIN INFLAMMATION: A GENE TO FUNCTION AND THERAPY PERSPECTIVE

Frank O. Nestle

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To identify genes relevant to disease pathogenesis we performed a genome-wide association study in Psoriasis, one of the most common chronic inflammatory disorders. We detected a highly significant association between psoriasis and genetic markers in the interleukin-23 receptor (IL-23R) gene on chromosome 1p31, a finding replicated in an independent dataset. The most significantly associated polymorphism results in an amino acid substitution (Arg381Gln) located in the IL-23R cytoplasmic domain. The same variant has recently been implicated in the pathogenesis of inflammatory bowel disease, supporting a critical role of IL-23 signaling in epithelial inflammation. Functional dissection of the IL-23 pathway using immunosuppressed mice grafted with psoriatic skin revealed a key role for the IL-23 pathways in the disease process. These data provide genetic and functional evidence for a crucial role of the IL-23 pathway in cutaneous inflammation and lay the foundation for new treatment strategies in psoriasis and potentially other chronic epithelial inflammatory disorders.

ALARMING THE IMMUNE SYSTEM: ABOUT NOVEL ADJUVANTS AND SKIN-DELIVERY IN VACCINE DEVELOPMENT

Alexander von Gabain

Intercell AG, Campus Vienna Biocenter 6, Vienna, Austria

Infectious diseases remain one of the greatest global challenges for both the developed and the less developed parts of the world. Vaccines are the most promising hope to control infections worldwide. However, induction of protective immunity often fails due to a lack of immunogenicity of vaccine antigens, in the absence of proper adjuvants. Furthermore, traditional injectable vaccines are often not sufficiently targeting the frontline of innate immunity. These shortcomings concern all kind of vaccines; the improvement of existing ones, the development of novel ones, but also the launch of therapeutic ones.

Adjuvants have recently been recognized as means to overcome some difficulties to potentate existing vaccines, but also to design novel vaccines, including therapeutic vaccines. At this stage only Alum and MF59 are in use as adjuvants in registered products. Lately, a new generation of adjuvants is moving forward that target the so-called Toll-like receptors of antigen-presenting cells (APCs) that kick in also the cellular arm of the immune system, e.g. T_{H1}-driven immunity.

On the other hand, also new delivery technologies have the potential to facilitate the efficacy of existing vaccines and to enable novel vaccines by the virtue to depose the antigens at sites where the concentration of APCs is the highest; e. g. in the epidermis. A novel skin patch delivery technology has been developed and demonstrated to facilitate the efficacy of a “panflu” vaccine upon injection, but also to enable the development of an ETEC vaccine against traveler diarrhea. Thus, patch-derived skin delivery provides a tool to reduce the number of needle injections, but also to improve the adjuvantation of vaccines.

I will discuss novel adjuvant and skin delivery technologies in context with the design of novel prophylactic and therapeutic vaccines against infectious diseases, like TB, ETEC-mediated diarrhea and HCV.

ANTIBODY THERAPEUTICS: OPTIMISATION FOR PURPOSE

Roy Jefferis

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Recombinant monoclonal antibodies (rMAbs) are exemplars of translational medicine; both in terms of clinical benefit delivered and revenue generated within the biopharmaceutical industry. Additionally, it is estimated that ~ 30 % of new drugs likely to be licensed during the next decade will be based on antibody products. However, the demand for the manufacture of metric tonnes of product results in high “cost of goods” (CoG) that can limit their availability, due to the strain it puts on national and private health budgets. This can result in rigid patient selection and/or differences in drug availability.

To date all licensed antibodies have been based on the IgG class of immunoglobulins. This class predominates in blood and equilibrates with the extra-vascular space. The formation IgG/antigen complexes activate a wide range of effector functions resulting in the killing, removal and destruction of pathogens, i.e. inflammatory cascades. Humans express four subclasses of IgG and each subclass exhibits a unique profile of effector functions, therefore, the choice of IgG subclass is a vital decision point when developing an rMAb.

Uniquely, glycosylation within the IgG-Fc is essential to the expression of effector activities. The manufacture of rMAbs requires, ideally, complete fidelity with the natural glycoprotein form; however, this is not achieved with the Chinese hamster ovary (CHO) cell line; the predominant vehicle for rMAb production The presentation will explore the relative attributes of natural IgG antibody proteins and new rMAb variants resulting from protein and/or glycosylation engineering and novel production platforms that could contribute to lowering the CoG.

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A PARADIGM FOR BIOLOGICAL THERAPY: BENCH TO BEDSIDE TRANSLATION OF TARGETED ANTI-TNF THERAPY

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In the 1980's emerging recombinant DNA and monoclonal antibody technology stimulated a shift in the molecular concepts of pathogenesis and development of biological targeted therapies for rheumatoid arthritis (RA). During this period, at the Kennedy Institute of Rheumatology, London, Feldmann and I, together with our talented research team, initiated laboratory investigations into the role of cytokines in RA.

In studies on tissues from joints of patients' ex-vivo, we demonstrated expression of a number of pro-inflammatory cytokines and their inhibitors at sites of inflammatory and structural damage. When cells obtained from similar diseased tissues were cultured in vitro, it was found that the production of cytokines was dysregulated, pointing to endogenous cellular ligand-receptor interactions. Whilst the chronic over production of cytokines provided interesting insight into pathogenesis of disease, the known pleiotropy and redundancy of their action suggested that therapeutic targeting of a single cytokine would prove ineffective.

In further experiments designed to examine the possibility of inter-connectivity in cytokine production, the addition of a specific neutralising antibody to TNFα in the in vitro tissue culture model described above, demonstrated the inhibition of IL-1, IL-6 and GM-CSF synthesis. This surprising finding established the concept that TNFα was of pivotal importance in driving the inflammatory mechanism at the chronic stage of the disease.

Meanwhile, in the early 1990s, Centocor Inc had developed cA2, a mouse x human chimaeric anti-TNFα specific neutralising antibody, subsequently known as infliximab (Remicade®), for the treatment of septic shock, and agreed to support a proof concept study in standard drug-recalcitrant RA. Between 1992 and 1994 we demonstrated impressive therapeutic efficacy with excellent tolerability in observational and placebo-controlled trials. Continuing studies established pharmacokinetics, and an efficacy threshold, and the need for repeated therapy.

Subsequently, based on animal model studies demonstrating synergy of combination of monoclonal antibodies to TNF and T cells, we designed randomised clinical trials which demonstrated superior effectiveness of infliximab when added to the 'gold standard' drug methotrexate (MTX) for long term suppression of disease activity and structural damage of joints. The co-therapy approach was verified by others for 2 additional anti-TNF biological drugs, etanercept and adalimumab, and is now the regimen commonly used in clinical practice.

Our further studies have focused on the biological effects of TNF blockade in patients. These have demonstrated inhibition of production of pro-inflammatory cytokines, reduction in chemokine and adhesion molecule expression and angiogenesis, associated with blockade of leukocyte trafficking, restoration of haematological and immunological parameters and inhibition of cartilage and bone damage.

Today, 3 biological inhibitors of TNF have advanced the treatment of aggressive RA. Excellent response is observed, including disease remission, especially in patients with intervention early in the disease course. Adverse events including the incidence of serious infections remain a concern and mandate careful

selection and monitoring of patients. Long-term benefit in 50-60% has been observed and over 1 million patients have been exposed to anti-TNF biological drugs; however, high cost limits access.

Anti-TNF therapy is now a well established option for aggressive RA and over 1 million patients have been exposed to anti-TNF biologicals with long-term benefit in 50-60%. Excellent responses are seen especially in patients with intervention early in the disease course. Adverse events including the incidence of serious infections remain a concern and mandate careful selection and monitoring of patients considered suitable for this important therapeutic development.

Our work has stimulated the successful development of anti-TNF therapy for other inflammatory rheumatic diseases, inflammatory bowel disease and psoriasis. New targeted biological therapies for rheumatoid patients unresponsive to TNF-blockade and for other autoimmune diseases have now emerged and more are in the pipe-line.

References

(1) *Feldmann, M. Maini RN.* (2001). Anti-TNF alpha therapy of rheumatoid arthritis: what have we learned? Annu Rev Immunol 19:163-96.
(2) *Maini RN, Feldmann M*. (2002). How does infliximab work in rheumatoid arthritis? Arthritis Res. 4 suppl 2: S22-8
(3) *Feldmann M, Maini RN.* (2003). TNF defined as a therapeutic target for rheumatoid arthritis and other autoimmune diseases. Nature Med; 9: 1245-1250
(4) *Feldmann M, Maini SRN.* (2008). Role of cytokines in rheumatoid arthritis: an education in pathopysiology and therapeutics. Immunol Rev. 223:7-19

Registration

Registration will take place at the registration desk, which is located in the admission area at Level 6 of the Kliniken am Südgarten. Registration is open from 8:30 to 9:00 and during breaks. Admission to all scientific sessions is free.

Language

Official workshop language is English.

Congress Venue

Big Lecture Hall, Kliniken am Südgarten
General Hospital of Vienna
Währinger Gürtel 18-20
1090 Vienna, Austria

Workshop Secretariat

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Access to the Venue