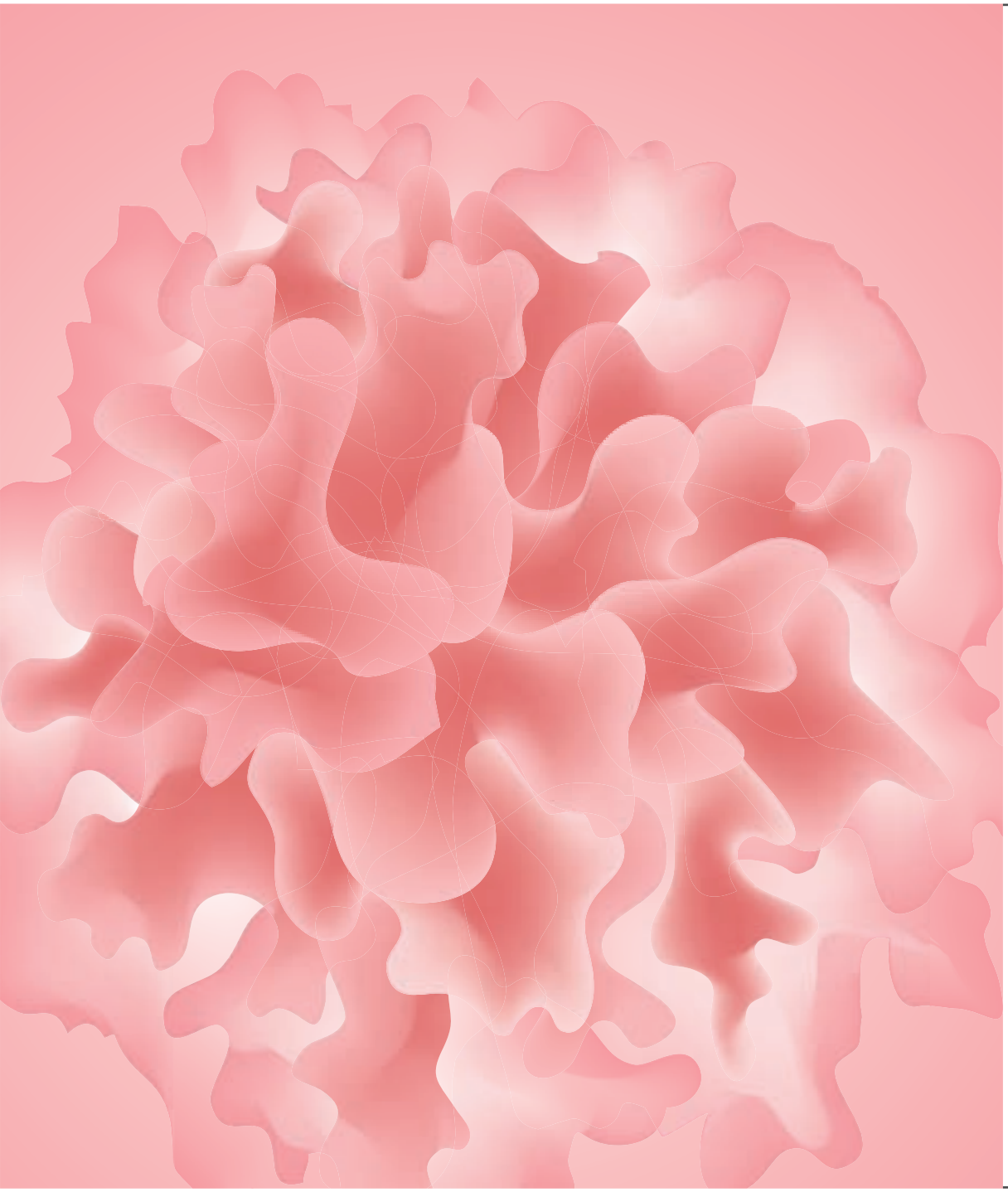
Vaccines in the light of immune therapy and therapeutic antibodies

4th Semmering Vaccine Symposium 2009



April 23–26, 2009

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About Vienna Vaccines

Vienna Vaccines is an independent non-pr ofit organization devoted to building worldwide Vaccine Networks.
Its goals are to support the cooperation between academia, governmental/non-governmental or ganizations, v accine industry and fi nancial institutions in the v accine arena and to present Austria as a country with a high potential in terms of healthcare and emphasize the significance of Vaccines.
Vienna Vaccines is entir ely funded b y sponsors and b y the participation fees for the symposium.

Welcome

Alexander VON GABAIN

Vienna Vaccines,
Chairman

Vienna Vaccines is delighted to welcome all participants and contributors to the fourth Semmering Vaccine Symposium in the wonderful health spa r esort of the City of Baden in the outskirts of Vienna. The previous three symposia were devoted to the following themes: "The Future of Vaccines – Cancer Meets Infectious Diseases" (2003), "No vel Vaccines against Infectious Diseases – Developed Countries meet Developing Countries" (2005) and "Challenges forVaccine Development: Medical Needs and Social Implications" (2007).

In the tradition of the previous events which were extremely well per ceived b y par ticipants and public opinion, w e ar e confident that w e will be able to maintain the unique spirit and atmosphere of this S ymposium series. Semmering has become an ackno wledged br and name, when it r egards to stimulate a constructiv e dialog betw een academia, v accine industries, financial institutions, public and private organizations engaged in the v accine arena, but also to include specialized and gener al journalists and inter ested laymen into this discourse.

Most conferences in the fi eld are either too lar ge in order to get opinion leaders and exper ts with differ ent backgr ound into constructive discussions. Other vaccine conferences and workshops are too specialized and often cope only with one disease tar get or a too narr ow selection of exper ts needed for the launch of novel vaccines.

Our symposia ar e filling this gap b y integrating, as many as possible, exper tise opinions into the pr ogram, but also b y building sustainable networks. Vienna Vaccines is an independent non-pr ofit or ganization dev oted to building global vaccine networks.

The goal of Vienna Vaccines is to initiate and to support contacts and cooper ations betw een all kind of key play ers and parties engaged in the v accine ar ena, but also to position Austria as a country with a high potential in terms of innovation and biomedical r esearch. Vienna Vaccines wants to spread knowledge, to illustr ate the r elevance of biotech for healthcare and to emphasiz e the signifi cance of v accines. The or ganization is entir ely funded b y sponsors and b y the fees of the conference participants.

At this place my deep gr atitude goes to all the fi nancial sponsors and suppor ters, par ticularly in a time when r esources are extr emely restricted. I also would like to thank the SAB members, especially my long-term University colleague and friend, Prof. Thomas Decker.

Last not least I am extremely indebted to the Symposium management, Nina Waibel and Barbara Strutz-Grell, for their extremely competent and pr ofessional or ganisation of the current Symposium and their devoted team, Johannes Fuchs, Kerstin v on G abain, L ea Kilchenmann, Astrid Meinl, Vera Schwarz and Martina Thyringer.

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Schedule

THURSDAY, APRIL 23

OPENING SESSION		
15:00–15:15	Alexander VON GABAIN	Welcome address
SESSION I: NEEDED VACCINES, CHAIR: PETER LACHMANN		
15:15–15:45	Michael PFLEIDERER	The registration pathway of novel vaccines – closing the gap between high tech and safety
15:45–16:15	Rino RAPPUOLI	Towards a MenB vaccine
16:15–16:45	John VEKEMANS	The RTS,S/AS malaria candidate vaccine: on the eve of Phase III
16:45–17:15	Jerald SADOFF	TB Vaccine Development
17:15–17:45	Martin FRIEDE	Developing vaccines for neglected diseases
	17:45–18:00 AFTERNOON BREAK	
	OPENING OF THE POSTER SESSION AND GET TOGETHER	
18:00	Opening of the poster session and aperitifs	
19:00	Dinner (Sponsored by Merrill Lynch)	

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MORNING SESSION, CHAIR: RINO RAPPUOLI		
8:30–09:00	Ulrich HEININGER	A risk/benefit analysis of vaccines
SESSION II: FINDING THE TARGET, CHAIR: ARMELLE PHALIPON		
09:00–09:30	Alessandro SETTE	Predicting vaccine antigens
09:30–10:00	Felix REY	Crystal structures the dengue virus envelope protein in complex with neutralizing antibody fragments
10:00–10:30	Adnane ACHOUR	Development of a novel generation of MHC class I-binding super-peptides for vaccines
	10:30–11:00 MORNING BREAK	
SESSION III: MICROBES, GENOMES, EVOLUTION AND MICROBIOMICS, CHAIR: THOMAS DECKER		
11:00–11:30	Antoine DANCHIN	Natural selection and immortality
11:30–12:00	Birgitta HENRIQUES-NORMARK	Epidemiology of Pneumococcus
12:00–12:30	Thomas MEYER	Vaccination against Helicobacter pylori and the targeting of host cell functionsas an immune-modulatory approach
12:30–13:00	Joël DORE	Human intestinal microbiomics in health and disease
	13:00–14:30 LUNCH BREAK	
SESSION IV: STUDY OF THE IMMUNE RESPONSE, CHAIR: ULRICH KALINKE		
14:30–15:00	Thomas DECKER	Type I interferons: innate cytokines and regulators of adaptive immunity
15:00–15:30	Claude LECLERC	Therapeutic vaccination against large established tumors by a new delivery system targeting dendritic cells
15:30–16:00	Adrian HAYDAY	The role of T-gamma and -delta cells
16:00–16:30	Reinhold FOERSTER	CCR7 as a key regulator for lymph node homeostasis
	16:30–19:00 AFTERNOON BREAK	
	AUSTRIAN EVENING	
19:00	Austrian Evening (Sponsored by Intercell AG)	

SATURDAY, APRIL 25

SESSION VA: MABS IN INFECTIOUS DISEASES, CHAIR: SERGE LEBECQUE		
08:30–09:00	Peter LACHMANN	Passive Immunisation against Infectious Disease – an old paradigm revisited
09:00–09:30	Arturo CASADEVALL	Anti-infective AB strategies
09:30–10:00	Eszter NAGY	Group B Streptococcus Prevention Strategy Based on Monoclonal Antibodies
	10:00–10:30 MORNING BREAK	
SESSION VB: MABS IN INFECTIOUS DISEASES, CHAIR: MICHAEL PFLEIDERER		
10:30–11:00	Fons UYTDEHAAG	Recognition of a highly conserved epitope across influenza virus subtypes by a influenza virus neutralizing human monoclonal antibody
11:00–11:30	Ulrich KALINKE	TGN1412: Lessons Learnt
11:30–12:00	James E. CROWE, Jr.	Human antibodies that neutralize pandemic influenza viruses
	12:00–13:30 LUNCH BREAK	
SESSION VI: THERAPEUTIC CANCER VACCINES, CHAIR: CLAUDE LECLERC		
13:30–14:00	Michael T. LOTZE	Damage Associated Molecular Pattern Molecules [DAMPs] Promote Immune Responses
14:00–14:30	Martin KAST	A new therapeutic vaccine induces lifelong protection from prostate cancer
14:30–15:00	Melvyn LITTLE	TandAbs for recruiting NK-cells and T-cells to kill tumor cells
	15:00–15:30 AFTERNOON BREAK	
SESSION VII: DIARREHAL DISEASES, CHAIR: ESZTER NAGY		
15:30–16:00	Gregory GLENN	The vaccine patch containing heat-labile toxin from Escherichia coli for protection against travelers' diarrhoea
16:00–16:30	Armelle PHALIPON	Towards a Shigella vaccine: dream or reality?
16:30–17:00	Florian SCHÖDEL	The Pentavalent Rotavirus Vaccine, RotaTeq™: From Development to Licensure and Beyond
CLOSING SESSION: THE NEED OF NEW VACCINES, CHAIR: GERD ZETTLMEISSL		
17:00–17:30	Jean STEPHENNE	The need of new vaccines
17:30–18:00	Alexander VON GABAIN	Closing remarks
	18:00–19:30 AFTERNOON BREAK	
	GALA EVENING	
19:30	Gala Dinner (Sponsored by Novartis)	

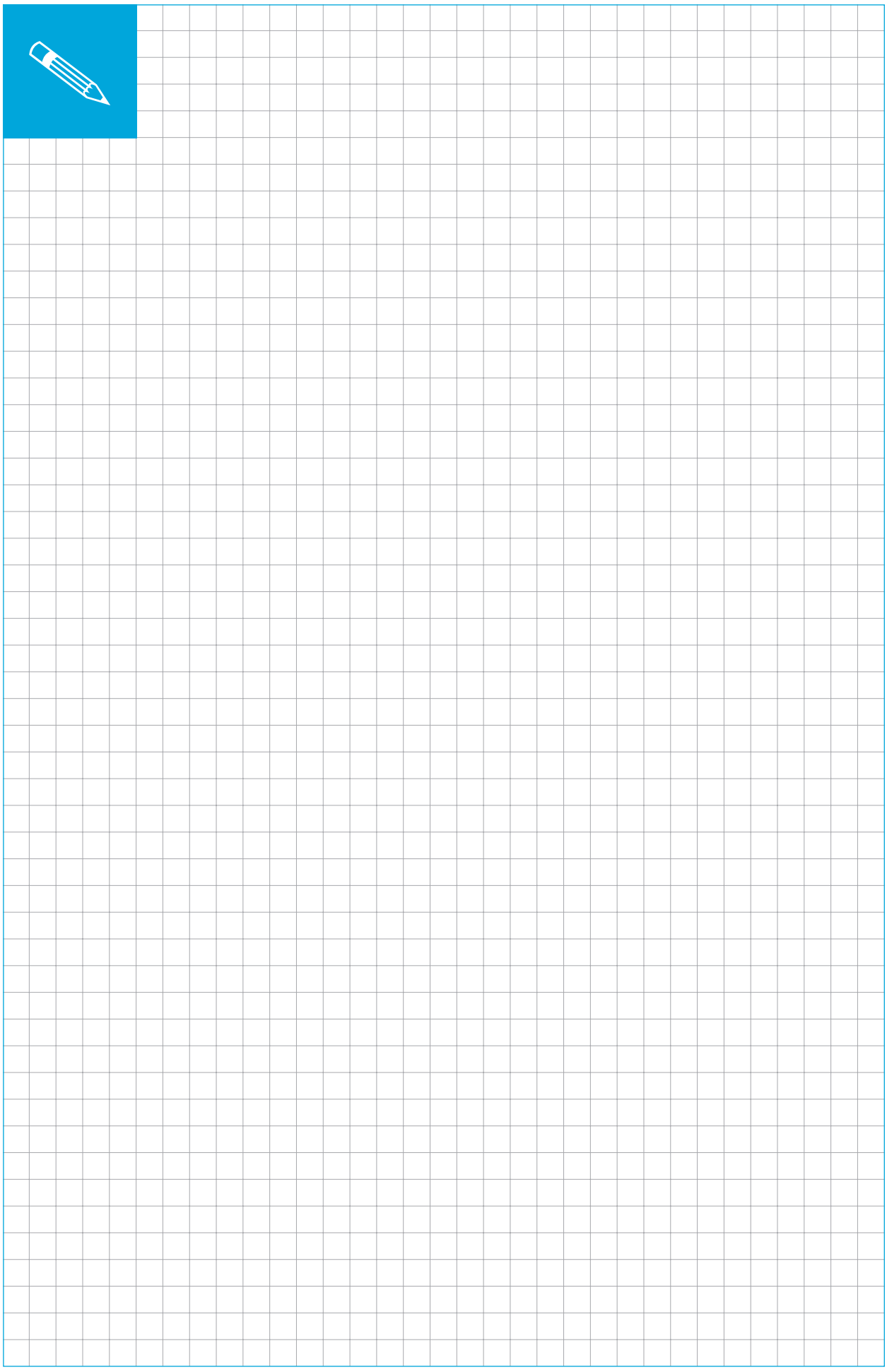
SESSION I

Needed vaccines

Chair:

Peter LACHMANN

Cambridge University,
Cambridge, United Kingdom



The registration pathway of novel vaccines – closing the gap between high tech and safety

THE SPEAKER

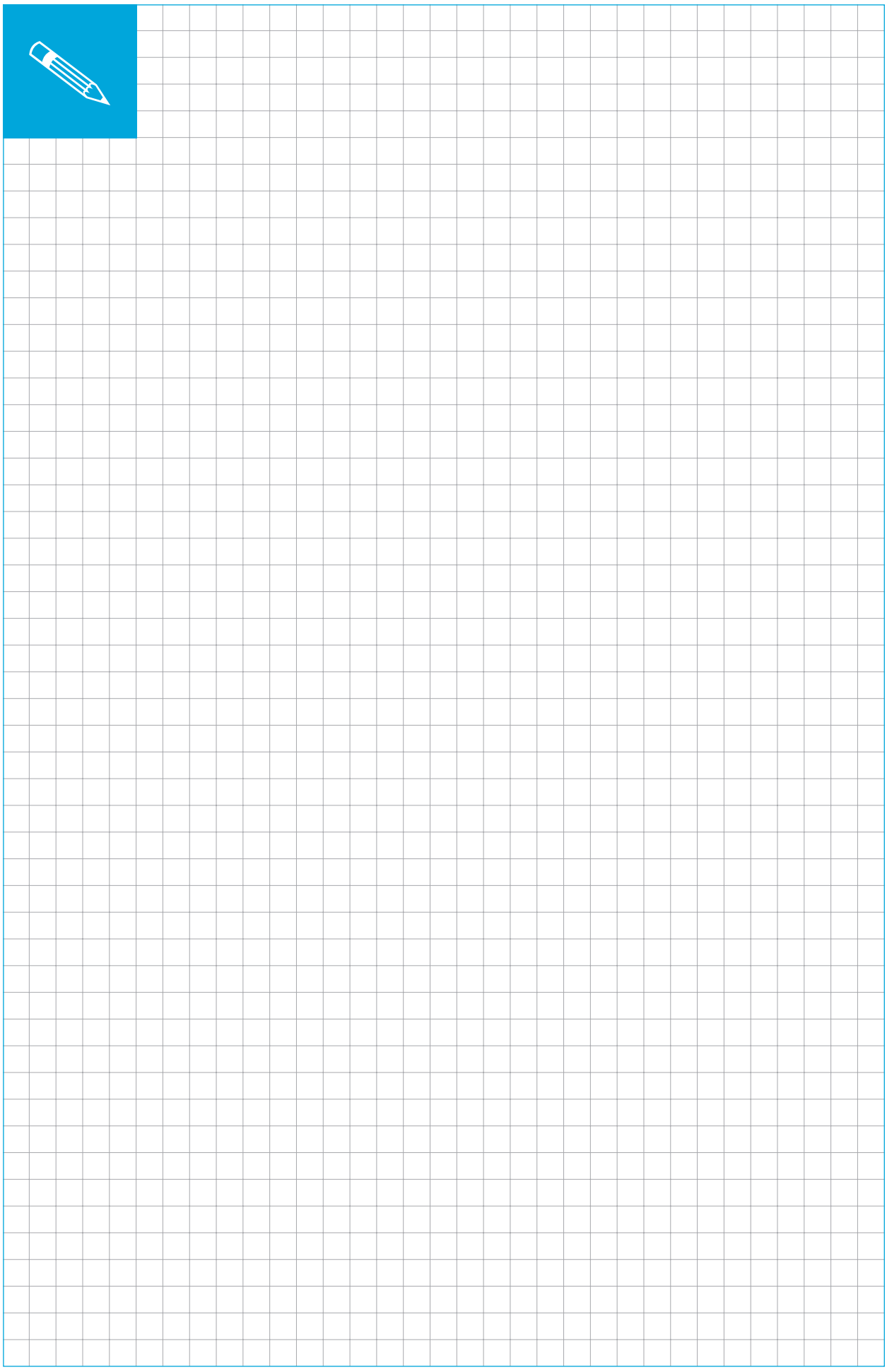
Michael Pfleiderer is a biologist and holds a Ph.D. in molecular virology. After his university career he worked in the molecular biology laboratories of IMMUNO AG, Vienna, Austria (now BAXTER), on various aspects of the production of recombinant medicinal products including vaccines.
Since 1998 he is at the Paul-Ehrlich-Institut, Federal Agency for Sera and Vaccines of Germany.
In his current position he is the Head of the Human Viral Vaccines Section and responsible for all issues related to vaccine licensing and regulation as well as for batch testing and release.
On a national level Dr. Pfleiderer is a member of a number of advisory boards, in particular with regard to issues related to pandemic influenza vaccines and pandemic preparedness planning.
On the European level Dr. Pfleiderer is a member nominated by Germany for the Biologics Working Party (BWP) of the Committee for Medicinal Products for Human Use (CHMP) at the European Medicines Agency (EMEA) in London, as well as for the BWP Influenza ad hoc Working Group whose chairman he is.
For their Vaccine Working Party (VWP), Dr. Pfleiderer was recently elected as Chairman by CHMP. Dr. Pfleiderer has significantly contributed to EMEA and WHO guidance on scientific and regulatory issues related to vaccines.
For WHO Dr. Pfleiderer is frequently acting as a temporary advisor. The European Centre for Disease Prevention and Control (ECDC) has nominated Dr. Pfleiderer as an expert for the newly established Scientific Expert Panel on Vaccines and Immunisation.
The Viral Vaccine Section Dr. Pfleiderer is heading at PEI has a leading function for many of the licensing applications for vaccines submitted so far to EMEA either as a Rapporteur, Co-Rapporteur or Peer Reviewer. Moreover, many scientific advices submitted to EMEA for vaccines have been assessed by the Viral Vaccine Section.
Finally, this section acts on behalf of Germany as the Reference Member State (RMS) for the European Union (EU) for a variety of vaccines mainly seasonal influenza vaccines.

Michael PFLEIDERER

Paul Ehrlich Institut, Langen, Germany

ABSTRACT

Submitting a Marketing Authorization Application to a competent authority is always the fi nal and consequently the most crucial milestone follo wing a complex series of ev ents ranging fr om labor atory dev elopment of a pr omising candidate v accine, pr oof of concept inv estigations, up to the early and late pharmaceutical and clinical dev elopment. Options chosen b y manufactur ers to ensur e that this fi nal step is completed successfully hav e signifi cantly changed over time. It is evident that mechanisms of gr anting a Marketing Authorizations hav e shifted almost completely fr om purely national pathways to principles that are accepted by all Member S tates of the E U and ev en beyond. Our curr ent regulatory system has ev olved fr om fi rst attempts dating back to the 1960-ies, aimed to harmoniz e legal and scientific principles for vaccine evaluation and licensing, to robust structures which are appreciated by both, manufacturers as well as r egulatory bodies. Bey ond the laws which set the scene, “the rules go verning medicinal pr oducts in E urope”, a plethora of scientific principles has been agr eed on in E urope and acr oss the Atlantic which help to av oid that div ergent scientifi c conclusions ar e dr awn in differ ent countries on one and the same vaccine. Considering the complexity and the impressive number of novel vaccines (and other medicinal products) that hav e been licensed in the r ecent past or which are under dev elopment, it is questionable whether such huge inv estments would hav e been made in the absence of options offering str aightforward and standar dized access to huge markets. Mor eover, roles of regulatory agencies, academia and industry and inter actions between them have fundamentally changed o ver time r esulting in the r eplacement of inappr opriate, inconsistent and contr adictory regulatory hur dles by scientific norms, standards, scientific advice options as w ell as pharmaco vigilance and risk management principles which ensur e continuous and r eliable evaluation of safety and efficacy of novel vaccines from early development to post marketing.
This presentation provides an o verview on the mechanisms of v accine ev aluation and licensing, defi nes r oles and r esponsibilities of parties involved and provides an outlook in the future development of the present regulatory system.



Towards a MenB vaccine

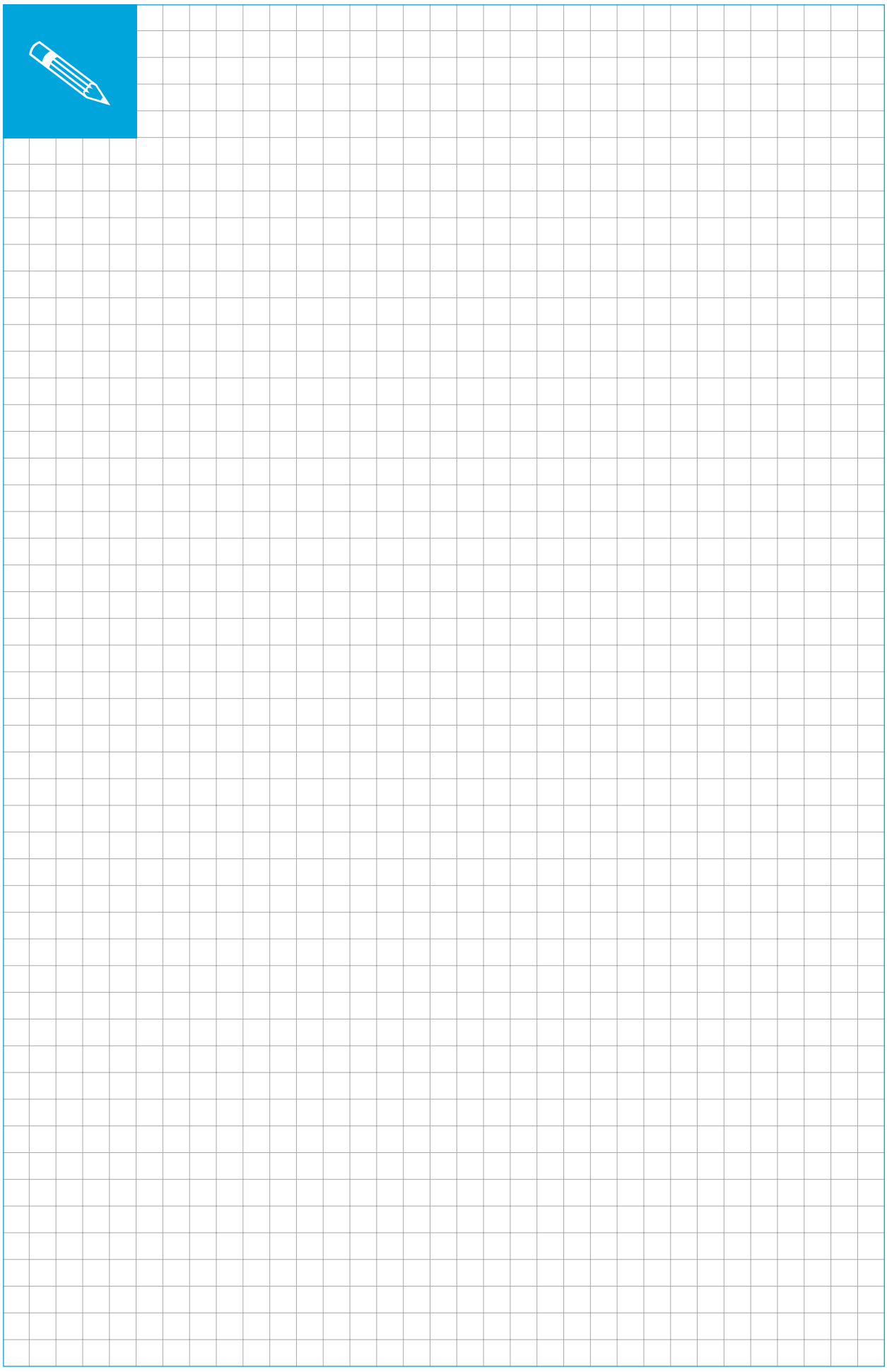
THE SPEAKER

Dr. Rino Rappuoli, PhD, is Global Head of Vaccines Research at Novartis Vaccines and Diagnostics, based in Siena, Italy. He earned his PhD in Biological Sciences at the University of Siena and has served as a visiting scientist at Rockefeller University in New York and Harvard Medical School in Boston.
Dr. Rappuoli is co-founder of the scientific field cellular microbiology, a discipline that merges cell biology and microbiology. He is an active member of numerous international associations, including the US National Academy of Sciences (NAS) and the European Molecular Biology Organization (EMBO), and has a publication record of more than 400 works. In 2005, he was awarded the Gold Medal by the Italian President for his contributions to public healthcare.
The main focus of Dr. Rappuoli's research has been bacterial pathogenesis. Areas of expertise include bacterial toxins and vaccines, mucosal vaccines Bordetella pertussis, Helicobacter pylori, Neisseria meningitidis and group B streptococcus. Dr. Rappuoli developed the first recombinant bacterial vaccine (against pertussis) and a conjugate vaccine against meningococcus C. Both products have been approved for human use. Currently, he is involved in the development of a vaccine against serogroup B meningococcus using a genome-based approach; the development of influenza vaccines produced in cell culture; and the development of vaccines against avian influenza.

Rino RAPPUOLI
Novartis Vaccines, Siena, Italy

ABSTRACT

The gram negative bacterium Neisseria meningitidis colonizes the upper respiratory tract of 10% of the human population. In rare cases, (with a frequency of approximately 1/100000 people), the bacterium ends up in the blood stream and causes sepsis; from the bloodstream it can cross the blood-brain barrier and cause meningitis. The disease which occurs mostly in infants, young children and adolescents, is dramatic and can lead to death (10-15% mortality), or to disability (20-25% of the cases). Some of the disabilities are quite severe such as loss of legs and hands.
Five different serotypes of the bacterium cause disease in humans, these are serotypes A,B, C, Y, W135. We have developed a vaccine against serotypes A,C, Y and W135 by conjugating the bacterial capsular polysaccharide to the carrier protein CRM197. The vaccine which induces protective levels of antibodies in adolescents and in infants has been successfully tested in phase 3 trials. Developing a vaccine against meningococcus B has been more challenging because the B capsular polysaccharide is identical to a human polysialic acid and is therefore a self antigen. After many unsuccessful attempts, a vaccine against meningococcus B has been designed using the genomic sequence of the bacterium to predict protective antigens. This new technology, named reverse vaccinology, allowed the development of a vaccine which in mice, adults and infants induces protective levels of antibodies against strains representative of the global population diversity of serogroup B meningococcus.



The RTS,S/AS malaria candidate vaccine: on the eve of Phase III

THE SPEAKER

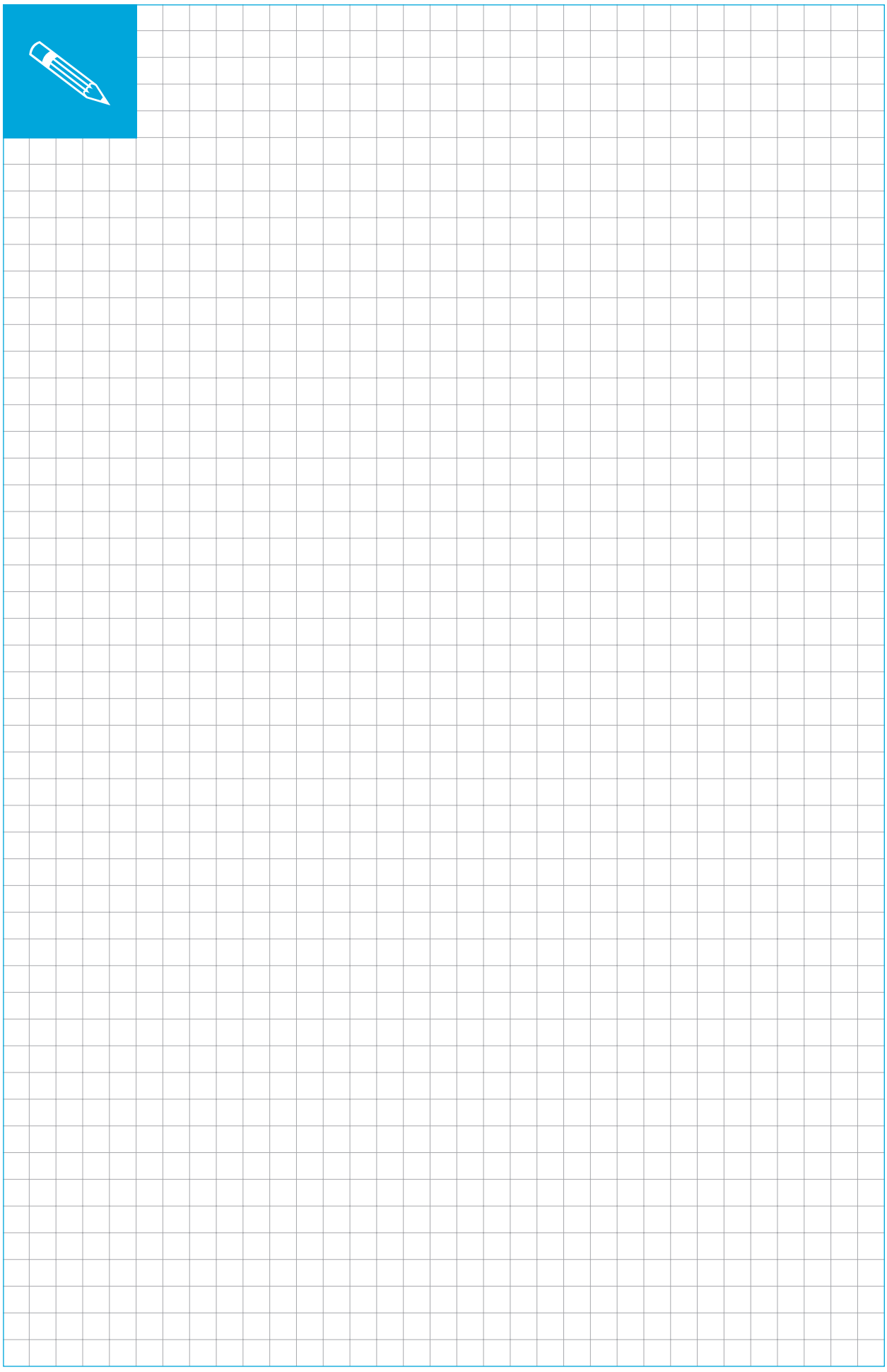
Johan Vekemans, MD, PhD, from Belgium, trained in pediatrics in Brussels, in tropical medicine in Antwerp and in immunology at the Paris Institut Pasteur. His main interests are clinical research in pediatric diseases of the tropics and vaccine development.
After having studied the impact of the maternal Trypanosoma cruzi infection on neonatal immunity in Bolivia (1996), he worked on the characterization of cellular immune responses to neonatal vaccines (1997-2000) and to tuberculosis candidate vaccine antigens (1998-2001). He was stationed at the Medical Research Council in The Gambia for 2 years, doing both laboratory based research and clinical pediatrics.
He joined GSK Biologicals in 2005 to work on the RTS,S malaria candidate vaccine development program governed by a public-private partnership with the Gates-funded PATH Malaria Vaccine Initiative. His input in this program pertains to study design, clinical care, vaccine safety review, malaria immunology, research centers assessment and development, capacity building, ethics of research in resource poor countries.

John VEKEMANS
GlaxoSmithKline Biologicals, Rixensart, Belgium

ABSTRACT

Added to the existing control measures, a malaria vaccine could gr eatly contribute to the fi ght against this terrible obstacle to global health and dev elopment. The R TS,S/AS malaria candidate vaccine, which contains the RTS,S antigen formulated with one of two Adjuv ant Systems (AS), ASo1 or ASo2, targets the pre-erythrocytic stage of the Plasmodium falciparum par asite. R TS,S/AS is being dev eloped b y GS K, through a public-priv ate par tnership with the P ATH Malaria Vaccine Initiativ e for administr ation to infants and childr en in malaria endemic r egions in sub-Sahar an Africa, ideally through the Expanded Program of Immunization (EPI).
Early studies of RTS,S/ASo2 demonstrated a promising safety profile, immunogenicity and the potential for partial protection against infection in malaria-naïve volunteers[1,2] and semi-immune Gambian adults.[3] Protection against clinical malaria and severe disease, lasting over 18 months was demonstrated in a proof-of-concept study in Mozambican children aged 1-4 years.[4,5] Subsequent trials have been undertaken to support the inclusion in E PI. When administered according to a staggered r egimen RTS,S/ASo2D conferr ed 66% pr otection against P. falciparum infection in Mozambican infants during a 3 months follo w-up period.[6] Concomitant administr ation with D,T,Pw and Hib antigens in a similar population found that the RTS,S/ASo2D vaccine had a good safety profile, did not interfer e with the immunological r esponses to the co-administered E PI antigens and demonstr ated 65% effi cacy against first infection with P. falciparum, during a 6 months post vaccination period.[7]
Preclinical studies and studies in adults suggested that the RTS,S/ASo1 formulation may provide higher immunogenicity and vaccine efficacy. This formulation was subsequently tested in children and demonstrated an efficacy against malaria of 53% amongst 809 childr en aged 5–17 months in K enya and Tanzania, over an average period of 8 months.[8]
These trials support the initiation of the Phase I II program, which is scheduled to start in early 2009.

[1]Stoute JA, et al. N EJM 1997;336:86-91. | [2]Kester KE, et al. J Infect Dis 2001;183:640-7. | [3]Bojang K A, et al. Lancet 2001;358:1927-34. | [4]Alonso PL, et al. Lancet 2004;364:1411-20. | [5]Alonso PL, et al. Lancet 2005;366:2012-8. | [6]Aponte J J, et al. Lancet 2007;370:1543-51. | [7]Abdulla S, et al. N EJM 2008;359:2533-44. | 8Bejon P, et al. NEJM 2008;359:2521-32.



TB Vaccine Development

THE SPEAKER

Jerald C. Sadoff became President and Chief Executive Officer of the Aeras Global TB Vaccine Foundation in June 2003. Dr. Sadoff has spent more than three decades developing vaccines for dozens of diseases, from chicken pox to malaria. He came to Aeras from Merck, where he was the Executive Director of Clinical Development of Vaccines. While at Merck, Dr. Sadoff led the efforts to develop and obtain licensure for eight licensed vaccines to prevent: hepatitis A, (VAQTA®); Haemophilus influenza type b (Liquid Pedvax™); 4-degree stable varicella vaccine (Varivax II®); a hepatitis B-Hib (Comvax™); the 6 valent Hep B, Hib, Polio, DTP (Hexavac™); Measles, Mumps, Rubella, Varicella (ProQuad®), and recently Zoster (Zostavax™) and rotavirus (Rotateq®).

Before joining Merck, Dr. Sadoff was Director, Division of Communicable Diseases and Immunology, at the Walter Reed Army Institute of Research, where he worked on vaccines against bacterial, viral and parasitic diseases, including sepsis, gonorrhea, cholera, shigella, dengue, HIV and malaria. He attained the rank of Colonel in the US Medical Corps. Throughout his career, he has chaired or served on over 20 national and international task forces, initiatives, consulting groups and advisory boards. Currently, he is Chair of the USAID Malaria Vaccine Scientific Consultants Group and Chair of the NIH/NIAID Oversight Task Force for Malaria. He serves on the NIAID AIDS Vaccine Research Working Group and the Scientific Advisory Board of the International AIDS Vaccine Initiative,

Jerald C. SADOFF

AERAS Global TB Vaccine Foundation, Rockville, Maryland, USA

the NIH Vaccine Research Center and Harvard HIV Vaccine IPCAVD. Over the last 30 years, he has authored some 300 articles, book chapters, and abstracts. Dr. Sadoff received his BA and MD from the University of Minnesota at Minneapolis.

Developing Vaccines For Neglected Diseases

THE SPEAKER

Martin Friede is the scientific officer responsible for vaccine delivery systems within the Initiative for Vaccine Research (IVR) at the World Health Organization in Geneva, Switzerland. In this position he is the WHO focal point for matters related to the development of technologies to improve vaccines including adjuvants, stabilization methods and alternative vaccine administration systems.
He established and leads the Global Adjuvant Development Initiative.
Prior to joining WHO Dr Friede held several positions in the vaccine industry: He was Vice President of Development for Apovia Inc. a Californian vaccine development company, prior to which he was responsible for vaccine formulation and vaccine delivery research at Smithkline Beecham Biologicals (now GlaxoSmithKline).
Martin Friede received his PhD in biochemistry from the University of Cape Town in South Africa.

Martin FRIEDE

World Health Organization, Geneva, Switzerland

ABSTRACT

There is little consensus on what constitutes a neglected disease, and given the significant existing research and development activities surrounding TB, malaria and HIV, for the purposes of this presentation we will focus on the neglected tropical diseases (NTDs) comprising of a group of bacterial and parasitic infections which exclusively infect the worlds poorest populations. These include the protozoal infections such as leishmaniasis, and trypanosomiasis; helminth infections such as hookworm and schistosomiasis; and bacterial infections such as leprosy and Buruli ulcer. While the direct mortality resulting from these infections is relatively low, these diseases result in chronic disability which affects the potential to learn and work and retains the populations in an impoverished environment. Since so little attention is paid to these diseases, it is fitting to call them ‚Neglected diseases', and since theses neglected diseases do not directly cause much mortality, it is difficult to attract the attention of policy-makers to these so that they are no longer neglected. However, by analysing the effect of the disease burden using DALYs, it becomes apparent that the combined effect of this disease family is comparable to that of heart disease and greater than malaria. Developing vaccines, therapies and other disease controls against these neglected diseases should therefore be a priority - and could lead to reduced morbidity from other diseases since infection with these also increases susceptibility to malaria and HIV.

For many of these infections therapeutic drugs exist, however the use of drugs is itself complicated by the cost of the drugs, poor efficacy of the drugs, frequent adverse events associated with the drugs, inadequate diagnostic procedures, emerging drug resistance, difficulty in ensuring patient compliance, and reinfection after treatment. The development of effective vaccines against these infections could very significantly reduce the disease burden, and avoid the challenges associated with drug therapy. For many of the NTDs prophylactic vaccination appears feasible. The genomes of many of the pathogens have been sequenced; candidate antigens have been identified, proof-of-concept demonstrated in preclinical models, and for several diseases including leishmaniasis, hookworm and schistosomiasis clinical trials are underway. The development of these vaccines, however, faces numerous challenges: the candidate recombinant antigens require adjuvants in order to induce protective immunity, and access to safe and effective adjuvants is a limiting factor; the target population is hard to reach and in hot climates, so the vaccine should be thermostable; proof-of-concept studies can be difficult to achieve, particularly on limited R&D budgets; the cost of the vaccine must be kept very low; and there is little financial incentive to invest in such vaccines. As an example we will describe the public-private-partnership development of a candidate leishmania vaccine based on the Leish 111f antigen combined with a novel adjuvant system.

MORNING SESSION

Chair:

Rino RAPPUOLI

Novartis Vaccines,
Siena, Italy

A Risk/Benefit Analysis of Vaccines

THE SPEAKER

Prof. Dr. Ulrich Heininger has been in charge of the Division of infectious diseases and vaccines at the University Children's Hospital in Basel, Switzerland, since 1998. Previously, he was working in the field of pediatric infectious diseases at the University of Erlangen, Germany. He has conducted several vaccine studies as study coordinator and principal investigator in the recent past. His clinical work is in the fields of general pediatrics and infectious diseases. He is also one of the founding members of „The Brighton Collaboration", an international collaboration of volunteers aiming at standardization of adverse events following immunization. In Switzerland, he is one of the 7 scientists running the INFOVAC-Ped service, a nationwide information network for vaccine related questions raised by physicians in private practice.
Prof. Heininger has been appointed to the German and Swiss National Immunization Recommendation Boards in 2001 and 2004, respectively; further, he has been a board member of the European Paediatric infectious Disease Society (ESPID) from 1999 to 2005. Furthermore, he serves on the editorial board of several journals, including Archives of Disease in Childhood, and has published more than 200 scientific publications in the field of paediatric infectious diseases and vaccines.

Ulrich HEININGER

University Children's Hospital (UKBB) Basel, Basel, Switzerland

ABSTRACT

Significant progress regarding hygiene, nutrition, and antimicrobial treatment as well as immunizations have lead to a significant decline of morbidity and mortality of infectious diseases in the recent past. Furthermore, immunizations are one of the most cost-effective tools for prevention. However, lack of perception of the substantial risks of complications associated with infectious diseases cause increasing doubts about the necessity of immunizations among some physicians and segments of the public today. This development is highly worrisome and needs to be adequately addressed by constantly informing physicians and the public about the risks of vaccine-preventable diseases, the efficiency, safety and benefits of available vaccines, as well as providing convincing arguments justifying current immunization recommendations. These activities are indispensable for successful implementation and continuation of current immunization programs.
Examples will illustrate how media reports can jeopardize immunization programmes and how extensive and labor intensive studies have been able to re-establish confidence in the respective vaccines.

SESSION II

Finding the target

Chair:

Armelle PHALIPON

Institut Pasteur,
Paris, France

Predicting vaccine antigens

THE SPEAKER

"New infectious agents originate all the time dating back to the plague in the siege of Athens in the 7th Century to the endemic flu in 1918 that killed 20 million people. For medical science, it's a perennial race between new infectious diseases coming up and society reacting to them, understanding them and ultimately defeating them." – Alessandro Sette, Ph.D.

Dr. Sette started at LIAI in 2002 as the Head of the Initiative for Emerging Diseases and Biodefense. In 2003 he became the Head of the Division of Translational Immunology. At LIAI, Dr. Sette's research focuses on the identification of epitopes, working to understand how vaccines should be constructed. The team's work is heavily focused on emerging disease threats or bioterror threats, such as SARS, arena viruses, smallpox and flu viruses. Dr. Sette's group is also leading an effort to bring a premier collaboration resource to the scientific community. The NIAID has awarded Dr. Sette a long-term contract to design and produce a national Immune Epitope Database (IEDB) to aide in the acceleration of vaccine-development on a global scale. Dr. Sette received his degree in Biological Sciences from the University of Roma, Laboratory of Pathology in 1984. In 1984, Dr. Sette was a Postdoctoral Fellow in the same laboratory. From 1986-1988, he joined The National Jewish Center for Immunology and Respiratory Medicine in Denver, in the USA as a post-doctoral fellow. In 2002, Dr. Sette was named Adjunct Professor in the Department of Experimental Medicine at the Scripps Research Institute, where he is also Scientific Director of the Rheumatic Diseases Core Center since 2004. In 2003 he was named Adjunct Professor in the department of Medicine at the University of California, San Diego. Dr. Sette is a member of numerous grant review panels and a reviewer for many scientific publications. He is also a member of the editorial advisory board for Immunogenetics, Human Immunology, Current Pharmaceutical Biotechnology, Current Drugs, and Tissue Antigens.

Alessandro SETTE

La Jolla Institute for Allergy and Immunology, San Diego, California, USA

ABSTRACT

Herein we illustrate approaches to the analysis of immune responses, taking vaccinia virus as a model system. We have systematically analyzed the targets of immune responses to VACV in humans, HLA transgenic mice, common murine strains and macaques, both at the level of class I and class II responses. In addition, the patterns of protein expression determined by proteomic analysis, and the viral mRNA expression patterns determined by tiling gene arrays have been considered.

To identify and characterize VACV-specific epitopes, we utilized bioinformatics prediction algorithms based on binding motifs, combined with T cell assays, such as ELISPOT and intracellular cytokine assays. To address questions regarding the regulation of immunodominance an analysis was performed based on all known epitopes and antigens identified so far, including factors such as time of antigen expression during viral replication cycle, functional category, and size.

We observed the CD4 and CD8+ T cell epitopes are not randomly distributed across the VACV proteome, some proteins are non-immunogenic, while others are frequently recognized across diverse MHC haplotypes. However the antigens recognized by CD4 versus CD8 cells tend to be different, suggesting that different variables dictate immunodominance for these two different cell types. Furthermore, it was observed that CD4 epitope tend to be derived from antigens recognized by antibody responses, and also abundantly expressed at the protein level, as detected by proteomic analysis. Conversely, CD8 epitopes tend to be derived form antigens whose mRNA is expressed in high amounts.

These results contribute to the understanding of immunodominance mechanisms and also help defining multi-epitope sets, useful for diagnostics development and vaccine evaluations.

Crystal structures the dengue virus envelope protein in complex with neutralizing antibody fragments

THE SPEAKER

Professional Interests
Structural virology, study of macromolecular assemblies, mechanistic biology, membrane fusion.

Education and Degrees
- Doctorat de l'Université de Paris XI (Orsay), 1988. Biochemistry.
- D.E.A. de Biochimie (master's degree) de l'Université de Paris XI (Orsay). 1984. Biochemistry
- „Licenciatura" (Master's degree) Instituto Balseiro, Bariloche, Argentina. 1981. Theoretical Physics.

Professional Experience and Positions
- 1983–1988 Pre-doctoral Fellow with Prof. Joël Janin, University of Paris-Sud, France.
- 1988–1995 Post-doctoral Fellow with Prof. Stephen C. Harrison, Harvard University, Boston USA.
- 1995–1999 Group Leader, CNRS „Laboratoire d'Enzymologie et Biochimie Structurales" Gif-sur-Yvette, France.
- 1999–2004 Director. Structural Molecular Virology Laboratory, CNRS/INRA, Gif-sur-Yvette, France.
- 2004–Present Director, Virology Department, Institut Pasteur, Paris.
- 2005–Present Director, Structural Virology Unit, Institut Pasteur, Paris.
- 2007–Present Director, CNRS URA 3015, Institut Pasteur, Paris.

Awards
- "Médaille d'argent" (CNRS award, 2004).
- EMBO membership (elected in 2005)

"Chaire Professorale Serono" (in 2006)
- Member of Academia Europaea (elected in 2008)

Felix REY
Institut Pasteur, Paris, France

ABSTRACT

Joseph Cockburn1, Erika Nav arro-Sanchez1, Carlos Kikuti1, Ana P. Goncalves2, Ching-Juh Lai2, Hugues Bedouelle3 and Félix A. Rey1

Epidemic dengue fever/dengue hemorrhagic fever (DF/DHF) is one of the most impor tant infectious diseases affecting tropical urban ar eas. Each y ear there ar e an estimated 50-100 million dengue infections, 500000 cases of DH F that must be hospitaliz ed and 20000-25000 deaths, mainly in children. Epidemic DF/DH F has an economic impact on the community of the same or der of magnitude as malaria and other impor tant infectious diseases. There ar e currently no vaccines nor antiviral drugs available for dengue viruses; the only effective way to pr event epidemic DF/DH F is contr ol of the mosquito vector.

The existence of four differ ent dengue viruses, termed dengue serotypes 1 to 4, together with antibody-dependent enhancement (ADE) of the infection, complicate the sear ch for an efficient and safe vaccine. The ADE effect is manifest when antibodies present in sub-neutralizing concentrations in the serum bind to circulating virions. Binding with a stoichiometry below that required for neutralization allows efficient entry into macrophages via Fc receptors, the infection of which is thought to aggr avate the disease outcome . Infection b y dengue virus of one ser otype usually leads to pr otection for life against that par ticular ser otype, but the same antibodies ar e needed at much higher concentr ation to neutr alize virions fr om differ ent ser otypes, r esulting in an incr eased risk of dev eloping a sev ere form of the disease in patients undergoing a secondary infection with a differ ent ser otype. Development of a safe v accine thus r equires car eful design of immunogens such that the risk of facilitating the infection of macrophages is reduced. We have embarked in structural studies to delineate the epitopes at the virus surface can result in. In this presentation, the structure of an antibody capable of neutr alizing all four ser otypes in complex with antigen fr om each of the four ser otypes will be pr esented, as well as a complex of an antibody specific for dengue serotype 4. The implications for understanding the mechanism of neutralization by these antibodies will be discussed in light of the development of an efficient anti dengue vaccine.

[1]Institut P asteur, Unité de Virologie S tructurale; 25 rue du Dr R oux, 75015 Paris, France | [2]Laboratory of Infectious Diseases, National Institute of Aller gy and Infectious Diseases, Bethesda, MD 20892 USA | [3]Institut Pasteur, Unité de Prévention et Thérapie moléculaires des Maladies humaines; 25 rue du Dr Roux, 75015 Paris, France

Development of a novel generation of MHC class I-binding super-peptides for vaccines

THE SPEAKER

Date of birth
June 6, 1967, Swedish citizen

Eucation
- 2007, Docent in Immunology, Karolinska Institutet
- 2001, Ph.D., Karolinska Institutet
- 1994, M.Sc., Royal Institute of Technology, Stockholm
- 1990, B.Sc., Umeå University, Sweden.

Academic position
2008-2014, Senior Research position 'Directed Tumor Therapy' awarded by the Swedish Research Council

Honors
- 2000, Jonas Söderquist Award to "Specially Talented Immunologist"
- 2004, Alex and Eva Wallströms Award
- 2005, "Teacher of the year", Biotechnology engineering, KTH
- 2005, Karolinska Institutet Research Foundation Young Investigator Award

Ph.D. and post doc supervision
- PhD supervision - main supervisor 3
- PhD supervision - co-supervisor 6
- Post doc supervision 6

Publications
41 original publications, 1 review.

Adnane ACHOUR
Karolinska Institutet, Stockholm, Sweden

ABSTRACT

MHC class I molecules play a crucial r ole in immune sur veillance b y selectiv ely binding to intr acellular peptides and presenting them at the cell surface to CD8+ T lymphocytes, including cytoto xic T lymphocytes, via the T cell r eceptors (TCRs). Each allelic form of an M HC class I molecule is capable of binding a diverse series of peptides, and this capacity, coupled with variations in the peptide binding specificities of the differ ent alleles, gener ates the br oad sampling of peptide epitopes necessary for a cellular immune function. R ecognition of peptides complexed to MHC molecules by TCRs is a critical event in initiation of an immune response.
The most common modifications that may improve binding to MHC and increase TCR response has until now been to complement the inter actions between the peptide and the M HC molecule. Many r esearch gr oups hav e designed enhanced binding peptides by substituting the observed anchor residues with those that ar e pr eferred b y the M HC molecule. Unfortunately this approach does not work well for most antigenic peptides.
In contr ast, w e hav e dev eloped alternativ e ideas to design a new family of alter ed peptide ligands (APL), based on the comparative analysis of sev eral crystal structur es and our knowledge of the subtle inter action betw een peptides and MHC class I molecules. Our analysis has r esulted in a no vel discovery whereby w e hav e assessed both structur ally and functionally that the modification of the same non-anchoring position within differ ent peptides allo ws for a higher binding affinity and stabilization capacity of peptides to multiple MHC molecules and r esults in enhanced immunogenicity .
The development of a new generation of super-peptides that mimic wild-type peptides will hav e clear implications for future dev elopment of no vel immunother apies and differ ent types of T-cell based vaccines against infections and cancer.

SESSION III

Microbes, genomes, evolution and microbiomics

Chair:

Thomas DECKER

Max F. Perutz Laboratories,
Vienna, Austria

Natural selection and immortality

THE SPEAKER

Trained as a mathematician, AD shifted to genetics in the early seventies. To understand the core of what life is, AD initiated the Bacillus subtilis genome project, completed in 1997. His genome analyses provide strong arguments to see living organisms as information traps.

AD published four books on the origin of life and the structure of genomes (The Delphic Boat, 2003). He created the HKU-Pasteur Research Centre in 2000 introducing genomics in Hong Kong. Member of the EMBO, he is the director of the Department Genomes and Genetics at the Institut Pasteur.

Antoine DANCHIN

Institut Pasteur,
Paris, France

ABSTRACT

Information is central to Biology, essentially via the genetic program and information transfers between the program embodied by nucleic acids and its expression. Physics witnesses a revolutionary shift of emphasis from the standard categories of Reality, matter, energy, space and time, to information as an authentic fifth category. In this context, I use comparative genomics to investigate the role of a concept that has often been considered as quite fuzzy, and which is at the centre of many heated controversies, Natural Selection. The role of this process is explored at the level of the separation between the process of reproduction, from the process of replication. Analysis of gene persistence in bacterial genomes permits identification of a core genome, the paleome, reminiscent of a scenario of the origin of life. The paleome, which is made of approximately 500 genes, comprises genes deemed essential, which code for the constructor and the replicator of the cell, supporting life. It also comprises a set of genes, often non essential, which code for enegy-dependent degradation functions, permitting reproduction of life.

I conjecture that Natural Selection is the process that makes room for accumulation of information, using energy to prevent degradation of informative entities. Making the parallel with the process of accumulation of information in the physical world, and which asks for erasing the memory to make room for novel information using energy to prevent destruction of functional entities, I remark that the commonplace observation that babies are born very young, suggests that the genes coding for degradative processes are used by ageing cells to make a young progeny, thereby trapping information in any available form. I further show that comparative genomics suggests that polyphosphate (a mineral) could play the role of the essential energy reservoir that is used in the process. A brief discussion about adaptive mutations shows that they could be the explicit manifestation of the process of accumulation of information, further suggesting that the process of cancer could be initiated in stem cells which acquire adaptive mutations leading to immortalisation.

Epidemiology of Pneumococcus

THE SPEAKER

Birgitta Henriques Normark is professor in medical microbial pathogenesis at the Department of Microbiology, Tumor and Cellbiology, Karolinska Institutet (KI), and Head physician at the Swedish Institute for Infectious Disease Control (SMI). She received her MD from KI in 1983, and her specialization in Clinical Bacteriology in 1994. During the 1980/90's she worked as a physician in Södertälje/Huddinge hospital in the Departments of Ear-Nose-and Throat diseases as well as in Infectious Diseases, and at the National Bacteriological Laboratory, which was reorganized to become SMI in 1993. She received her PhD in 2000 at KI in Infection Disease Control. In 2005 she got a research position at the Royal Academy of Sciences in Sweden in Clinical experimental research (50%), and in 2008 she got a research position from the Swedish Research Council in Clinical bacteriology (50%). She became associate professor in 2004 and professor in 2008 at KI. Her major research is on respiratory tract infections, focusing on infections caused by pneumococci and Group A streptococci. Her research ranges from the clinics and epidemiology to basic understanding of pathogenesis studying bacterial factors as well as host factors of importance for disease development. Also, resistance development, host-parasite interactions and vaccine development are targeted. She participates in several collaborative networks within Europe and has many national and international collaborators.

Birgitta HENRIQUES-NORMARK

Swedish Institute for Infectious Disease Control, Solna, Sweden

ABSTRACT

Streptococcus pneumoniae or pneumococci is a major cause of morbidity and mor tality world-wide. WHO estimates suggest that fatal pneumococcal infections contribute signifi - cantly to the annual global mortality rate attributed to respiratory disease. The fatality r ate is estimated to be about 1-2 million deaths ev ery year i e in the same r ange as for tuberculosis. Pneumococci are the major cause of otitis media, sinusitis and community-acquired pneumonia and are also a common cause of inv asive diseases such as septicaemia, a common complication of pneumonia, and meningitis. Even though being a devastating pathogen pneumococci ar e also common colonizers of the upper r espiratory tract and up to 60-70% of children attending day-care centres may harbour these bacteria in the nasopharynx without having a disease. A major question is how these bacteria sometimes cause severe diseases while they usually only colonize harmlessly. Antibiotic resistance has emerged among pneumococci to most antibiotics used, affecting tr eatment outcome. To study the epidemiology and spr ead of pneumococci w e use differ ent classical typing methods such as ser otyping as w ell as molecular techniques. Pneumococci can be divided into at least 91 ser otypes depending on their capsular polysaccharide structures, and an association between virulence and capsular type has been observed. The serotype distribution among severe invasive infections differs depending on time period and geogr aphic ar ea studied. To study genetic r elatedness between isolates we use molecular typing methods such as PFGE (pulsed fi eld gel electr ophoresis and the sequenced based method MLST (multi locus sequence typing). Licensed pneumococcal vaccines are based on a limited amount of the polysaccharide capsular structur es and expansion of non-vaccine types has been observed after vaccine introduction.

Vaccination against Helicobacter pylori and the targeting of host cell functions as an immune-modulatory approach

THE SPEAKER

Thomas F. Meyer studied Biology at Heidelberg University, Germany, and received his PhD (1979) with a project on in vitro DNA replication.
After having spent time at Cold Spring Harbor Laboratory (1980) and at the Public Research Institute, New York (1981) he joined the MPI for Medical Research in 1982 and became staff scientist at ZMBH (Centre for Molecular Biology of Heidelberg University) in 1983. In 1985 he moved to MPI for Biology in Tübingen where he became Director of the Department of Infection Biology (1990).

Since 1994, Thomas Meyer is co-founder of the Max Planck Institute for Infection Biology (MPIIB) and Director of the Molecular Biology Department. He holds professorships at the Charité University Medicine and the Humboldt University and is a member of EMBO and the German Academy of Naturalists Leopoldina.

Thomas F. MEYER

Max-Planck-Institut für Infektionsbiologie, Berlin, Germany

ABSTRACT

Immunity against H. pylori has only been obtained in animal models where protection depends on induction of T helper cells. In contrast, chronic infection in humans appears to specifically inhibit T cell responses via induction of regulatory T cells and direct inhibition of T cell activation. Although various vaccines have been tested in clinical trials, it remained unclear whether immunity against H. pylori exists in humans and whether vaccination is feasible. We tested live vaccines based on recombinant Salmonella Ty21a, the licensed typhoid fever vaccine, in volunteers subsequently challenged with H. pylori. Although the vaccines were not satisfactory, the studies revealed clearly that T cell reactivity against H. pylori antigens correlated with clearance or significant reduction of H. pylori burden.

Infection, generally, depends on specific molecular and cellular interactions of both pathogen and host. Moreover, the pathology of infections is usually a consequence of host cell responses rather than due to a direct assault of pathogen determinants, including toxins.
Therefore, we pursued the identification of host cell determinants with crucial functions in the infection process. Targeting such host cell determinants might provide a future means to treat infections. However, a variation of this approach might also lead to novel means facilitating immune modulation during the course of vaccination.

Human intestinal microbiomics in health and disease

THE SPEAKER

Dr. Joël Doré, research director, vice-director of the Research Unit of Ecology and Physiology of Digestive System at the INRA Centre of Jouy-en-Josas, is the head of the Molecular Ecology team (four scientists, four engineers, five technicians, three post-doctorate fellows, two PhD students). He has developed a growing interest in the field of molecular ecology as it offers the possibility to reconsider our culture-based understanding of microbial diversity within gut ecosystems. He developed all culture independent molecular methodologies aimed at reassessing the human intestinal microbiota on a phylogenetic basis. That includes direct molecular characterization of complex communities based on rDNA cloning and sequencing and species diversity profiling; in situ quantification and identification of micro-organisms. Since 2001, Joël Doré has been involved in the first Human Intestinal Metagenomics project in Europe, coordinated by Renaud Nalin (Libragen S.A.).

Joël DORÉ
INRA,
Paris, France

ABSTRACT

The past ten y ears hav e seen a complete r eassessment of the phylogenetic make-up of the dominant human intestinal microbiota based on cultur e independent molecular approaches. Essential no vel kno wledge was acquir ed indicating that :

- In healthy adults, mor e than 80% of bacterial phylotypes belong to 3 major phyla : Bacter oidetes, Firmicutes (Cl. leptum Cl. coccoides) and Actinobacteria (Bifidobacterium, Atopobium)
- more than 80% cloned rDN A sequences in adults (nearly 90 % in seniors) r epresent putative novel species, most of which will have so far eluded cultivation.
- The dominant human intestinal micr obiota is r esistant to modification over time, even over several years, and it is resilient upon erythr omycin or amo xicillin-clavulanic acid treatments.
- A limited number of species appear altogether more prevalent and more numerous, hence constituting a phylogenetic core, and potentially a functional cor e of the human intestinal ecosystem.
- Yet a large fraction (~2/3) of dominant bacterial phylotypes is subject-specific.
- It becomes possible to defi ne Eubiosis and in a few cases, specific disturbances of the dominant micr obiota can be associated with disease states; such as infl ammatory bowel diseases or obesity.

Specificities of the gut micr obiota in I BD could be outlined. On a phylogenetic standpoint, dominant bacterial species that ar e uncommon in healthy subjects could be obser ved in patients that presented a specific distortion in microbiota composition (dysbiosis). A metagenomics approach indicated a reduction in the proportion and in the biodiversity of the Clostridium leptum gr oup of the Firmicutes phylum in CD patients. In a clinical trial, the absence of detectable Faecalibacterium prausnitzii - a major member of the C. leptum gr oup and one of the most pr evalent bacterial species of the human gut micr obiota - was associated with a higher risk of postoperative recurrence of ileal CD. F. prausnitzii was further shown on cellular and animal models to exert anti-inflammatory properties. A proteomics appr oach further indicated the existence of secreted bacterial signatures in faecal proteomes of CD patients.

An integr ated micr obiomics appr oach appears pr omising to identify new tar gets and new str ategies, fr om bacterial strains to metabolites, for health-nutrition or therapeutic applications in immune and degener ative diseases. Potential and expressed functionalities and not only the phylogenetic structure of the micr obiota can no w be accounted for . The metagenomic characterization of the ecosystem will allow to build the r epertoire of genes of the human gut micr obiota, but also to explor e its conser ved set of genes and their expression in situ. Preliminary functional screenings further confirm the potential to inv estigate molecular signalling between the microbiome and human cells. This knowledge will in turn r epresent a po werful compar ative tool to quantitatively evaluate variability over time and space and to identify signatures of health or diseases.

SESSION IV

Study of the immune response

Chair:

Ulrich KALINKE

Twincore Centre of Experimental
and Clinical Infection Research,
Hannover, Germany

Type I interferons: innate cytokines and regulators of adaptive immunity

THE SPEAKER

Education and Positions held

- 1976-82 MSc in Biology, Albert-Ludwigs University, Freiburg, Germany
- 1986 PhD from the Albert-Ludwigs University of Freiburg, Germany
- 1986-87 Postdoctoral Fellow, Fraunhofer Institute for Molecular Biology, Hannover Germany
- 1987-90 Post-doctoral fellow at the Rockefeller University, New York, USA, Lab of J.E. Darnell
- 1990-93 Assistant professor and group leader, Department of Immunobiology. Fraunhofer Institute, Hannover, Germany
- 1992-93 Visiting professor at the Karolinska Institute, Stockholm
- Since 1993 Group leader and Professor of Immunobiology, Department of Microbiology, Immunobiology and Genetics, Max F. Perutz Laboratories, University of Vienna, Austria.

Date of birth: 04 March 1956
Place of birth: Tegernsee, Germany

Current position
Full Professor, Head of Dept. Microbiology and Immunobiology, Max F. Perutz Laboratories, University of Vienna

Thomas DECKER
Max F. Perutz Laboratories, Vienna, Austria

ABSTRACT

Synthesis of type I Interferons (IFN-I) is a hallmark of innate immune responses to both viral and nonviral pathogens. It results from the position of the IFN-I genes as endpoints of signalling pathways stimulated by plasma membrane, endosomal and cytoplasmic pattern recognition receptors. While originally identified as cytokines establishing innate resistance to viruses, a wealth of recent investigations established the impact of IFN-I on immunity to all classes of pathogens. This results from both cell-autonomous antimicrobial effects and from regulatory activities on cells that orchestrate adaptive immunity, including dendritic cells (DC) and T lymphocytes. We have investigated the impact of IFN-I on the development of antigen-specific cytolytic T cell (CTL) responses, stimulated by peptide and the immune adjuvant IC31TM. We will present results suggesting that IFN-I synthesis and signalling essentially contribute to the functional competence of DC for CTL activation. By contrast IFN-I signalling by CD8+ T cells was not required for the development of peptide-specific cytolytic activity. Together with findings in the recent literature our data suggest a variable and context-dependent input of IFN-I into CTL responses, reflecting the regulation of DC, T lymphocytes, or both.

Therapeutic vaccination against large established tumors by a new delivery system targeting dendritic cells

THE SPEAKER

Claude Leclerc, PhD, is Professor at the Pasteur Institute. She is the Head of Immune Regulation and Vaccinology in the Department of Immunology of the Pasteur Institute and the Director of U883 INSERM.
Claude Leclerc has worked in vaccinology for 35 years and has contributed to the development of synthetic adjuvants, synthetic peptidic vaccines and of several delivery systems. In particular, her laboratory has established the strong potential of CyaA, a safe and efficient delivery system targeting dendritic cells to elicit immune responses. Based on this vector, she has recently developed a therapeutic vaccine against cervical cancer under clinical development. She has recently developed two therapeutic vaccine candidates against melanoma and carcinoma, under pre-clinical development. Her lab has also contributed to the understanding of the role of dendritic cells in initiating and regulating immune responses and of the mechanisms responsible for the poor immune responses of neonates.
Claude Leclerc is the author of 250 publications and 20 patents.
Her laboratory at the Pasteur Institute is presently focused its activity on the understanding of the mechanisms that control the activation and regulation of T cell responses, in adult and neonates, and on the development of new strategies of vaccination against tumors and infections, such as HIV and tuberculosis.

Claude LECLERC

Institut Pasteur, Paris, France

ABSTRACT

Dendritic cells (DCs) ar e no w w ell r ecognized as the most potent professional APCs, with a unique capacity to inter act with naive T cells to initiate primary immune responses. Thus targeting DCs represents the main objective in designing new delivery systems for vaccine development. We have recently developed a new proteinic vector based on the adenylate cyclase (CyaA) from Bordetella pertussis. CyaA uses a unique mechanism of cell invasion in which the catalytic domain is delivered fr om cell surface dir ectly to the cytosol of tar get cells, through the cytoplasmatic membrane. We have shown that CyaA binds specifi cally to the CD11b/CD18 integrin expressed on DCs. Using the TC1 tumor model, an aggressively growing tumor cell line that expr esses the HPV16 E6 and E7 proteins, w e hav e demonstr ated that tar geting the HPV E7 antigen to dendritic cells using the CyaA vector is an efficient strategy to induce ther apeutic anti-tumor immune r espons-es. This therapeutic effect was demonstr ated by injection of the vaccine, CyaA-E7, to mice 10 days after the graft of tumor cells. However, the therapeutic efficacy of the vaccine is progressively lost as the tumor gr owth, r eaching a non-significant value if the vaccination is performed 25-30 days after the tumor graft.
The analysis of regulatory effector cells recruited as theTC1 tumor grows revealed an elevated percentage of CD25+FoxP3+ regulatory cells among CD4+ T cells in the tumor and, less markedly, in spleen and tumor draining lymph nodes. At late tumor stages, an incr ease of CD11b+G R1+ myeloid cells was also obser ved in spleen. Various tr eatment combinations were used to r estore the anti-tumor activity of the C yaA-E7 vaccine in large tumors-bearing mice.

The role of T-gamma and -delta cells

THE SPEAKER

Professor Adrian Hayday is a biochemistry graduate of Queens' College Cambridge. He obtained his Ph.D. in Tumour Virology in 1978 and undertook post-doctoral training at M.I.T., where he elucidated the nature of c-myc proto-oncogene activation in a distinct class of human Burkitt's lymphomas, and then contributed to the discovery of an unanticipated set of white blood cells known as gamma delta T cells. After 13 years on the Faculty at Yale University he returned to Guy's Hospital London in 1998, as Kay Glendinning Professor and Chair of Immunobiology at King's College. He has published over 160 papers, mostly in molecular immunology. His research focuses on identifying and understanding molecules that regulate the development and function of "unconventional T cells" a term he has popularised to describe large numbers of T-lymphocytes (including gamma delta cells) which do not recognise complexes of peptides and MHC. His group has shown that such cells compose a key tissue-associated immune surveillance response that can reduce susceptibility to carcinogenesis and inflammation. Recently, Professor Hayday has co-led clinical trials utilising gamma delta T cell activation in tumour immunotherapy. In 1997, Professor Hayday was awarded the William Clyde DeVane Medal, Yale College's highest honour for teaching and scholarship, and was elected Fellow of the Academy of Medical Sciences in 2002. He has advised several bodies, including the NIH, the American Cancer Society, the Howard Hughes Medical Institute; the Max Planck Institute; and the Wellcome Trust (2001-07) where he chaired the funding committee in Basic Immunology and Infectious Diseases (2004-07). He was elected General Secretary of the British Society of Immunology (2005), and awarded Honorary Fellowship of King's College (FKC) (2006).

Adrian HAYDAY

Kings College,
London, United Kingdom

ABSTRACT

It is now widely-accepted that adaptive immune responses, which are the key to antigen-specific vaccination, are initiated by cells of the innate response that are triggered by encounter with microbe-associated molecular patterns (MAMPs), such as peptidoglycans or certain nucleic acids. Thus, such moieties are being exploited as adjuvants in vaccine design. While this model adequately explains the respective roles of adaptive antigen specific lymphocytes and innate myeloid-lineage cells, such as dendritic cells, it omits mention of large numbers of "unconventional "lymphocytes whose phenotypes do not easily conform to either the adaptive or innate response. Such cells are typified by gamma delta T cells, and many express an activating receptor, NKG2D, that permits them to respond to ligands, such as MICA (human) and Rae-1 (mouse) that are expressed by stressed parenchymal cells. We have asked whether activation of NKG2D alone is sufficient to promote immune responses, independent of any involvement of MAMPs. To accomplish this, we have constructed a transgenic system in which Rae-1 may be activated by an "antibiotic switch" in the absence of any other stress. The results of these experiments, and their implications for vaccine design will be discussed. We shall also approach the issue of the unexplained diversity of NKG2D ligands and the polymorphism of MICA, and how this may relate to individual responses to vaccines. In sum, unconventional lymphocyte activation may profoundly affect the course of an immune response, implying the utility of exploiting such cells in vaccine design. In this regard, ongoing methods for the clinical manipulation of gamma delta T cells will also be presented.

CCR7 as a key regulator for lymph node homeostasis

THE SPEAKER

Reinhold Förster is Full Professor of Immunology and Head of the Institute of Immunology at Hannover Medical School. He studied Veterinary Medicine in Munich and Cambridge (UK) and graduated at the University of Munich in 1988 as a veterinary surgeon. In 1991, he obtained his doctorate in veterinary medicine summa cum laude with a dissertation in the laboratory of Prof. Anton Mayr on the role of pox viruses and pox virus protein on neutrophil function.
From 1991-1993, he stayed as a postdoctoral fellow in the laboratory of Prof. Ernst-Ludwig Winnacker at the GenCenter at Munich University starting his work on chemokines and their receptors.
From 1994 to 2000 he worked as a research associate at the Max-Delbrueck-Center for Molecular Medicine in Berlin.
He obtained his Habilitation in 1998 at the Free University of Berlin. In 2000, he was appointed Associate Professor (C3) at the University Clinic for Surgery of the University of Erlangen, and in 2001, he was appointed to his current position at MHH.

Research interest and achievements
Reinhold Forster has developed a deep interest in studying the role of chemokines in the functional organization lymphoid organ.
Using gene targeting in mice he has published fundamental papers regarding the function of chemokine receptors such as CXCR5, CCR9 and CCR7.
His current interests lie in the identification of molecular mechanisms that control the migration of immune cells to and their positioning within lymphoid organs.

In addition, he studies the role of sphingosine-1-phosphate receptors in lymphocyte homing and egress and addresses the role of steady state turnover of dendritic cells for the induction of peripheral tolerance.

Reinhold FOERSTER

Hannover Medical School, Hannover, Germany

A further research project focuses on the molecular cues that guide developing T cell through the characteristic microenvironments of the thymus and their impact on negative selection. Further on, in vivo imaging of immunological processes in lymphoid organs by means of 2-photon microscopy has been recently established in his lab and will fundamentally extent approaches used to study complex immune responses.

ABSTRACT

A key featur e of the immune system is its ability to induce protective immunity against pathogens while maintaining tolerance to wards self and innocuous envir onmental antigens. Recent evidence suggests that b y guiding cells to and within lymphoid or gans, CC-chemokine r eceptor 7 (CC R7) essentially contributes to both immunity and tolerance. This r eceptor is inv olved in or ganizing thymic ar chitecture and function, lymph-node homing of naiv e and r egulatory T cells via high endothelial v enules, as w ell as steady state and infl ammation-induced lymph-node-bound migr ation of dendritic cells via affer ent lymphatics. Her e, I will focus on the cellular and molecular mechanisms that enable CCR7 and its two ligands, CCL19 and CCL21, to contr ol lymph node T cell homeostasis at multiple lev els that affect the quality of adaptive immune responses.

SESSION V

mAbs in infectious diseases

Chair, Session Va:

Serge LEBECQUE

Humalys,
Lyon, France

Chair, Session Vb:

Michael PFLEIDERER

Paul Ehrlich Institut,
Langen, Germany

Passive Immunisation against Infectious Disease – an old paradigm revisited

THE SPEAKER

Sir Peter Lachmann trained in medicine at Cambridge (1950-1953) and University College Hospital (1953-1956) and obtained a PhD (1962) and ScD (1974) in Cambridge in immunology.

His principal research interests are:
The immunochemistry, biology and genetics of the complement system
Microbial immunology. Particular topics include microbial subversion of the innate immune response and immunisation, both active and passive.
Immunopathology, particularly in relation to systemic LE, to multiple sclerosis and to age-related macular degeneration
Insect sting allergy (also reflecting his interests as a bee-keeper)

He is emeritus Sheila Joan Smith Professor of Immunology in the University of Cambridge, a fellow of Christ's College and honorary fellow of Trinity College. He is also Scientific Adviser to the Federation of European Academies of Medicine.

He was the founder President of the UK Academy of Medical Sciences (1998-2002) and has served as its representative on the Inter Academy Medical Panel executive (2000 – 2006). He has been Biological secretary of the Royal Society (1993 –98) and President of the Royal College of Pathologists (1990-93); and served on UNESCO's international bioethics committee from 1993-98. In these capacities he has become involved with the ethical and policy aspects of medical science, particularly in connection with public health, vaccination, stem cells, transmissible spongiform encephalopathies and genetically modified food crops.

Peter LACHMANN
Cambridge University, Cambridge, United Kingdom

ABSTRACT

The use of antibodies both for the pr evention and for the treatment of infectious disease goes back to the earliest days of immunology. With the much impr oved safety of human immunoglobulins and intr oduction of monoclonal antibody technologies of inter est in " passive immunother apy" has been revived.
Antibody is both necessary and suffi cient to pr ovide "sterilising" immunity against viruses. Antivir al antibodies ar e therefore a major ar ea of inter est. Human immunoglobulins against hepatitis A and B, CMV , Varicella, RSV, Measles and Rabies ar e all appr oved for tr eatment in the U S. Their possible use against pandemic flu and other emerging virus diseases is also of interest.

Antibodies given by mouth can protect against enteric infections. Producing antibodies in food – milk and, par ticularly, eggs - using tr ansgenic technology has gr eat potential for prophylaxis, for example against enter otoxins. The r emarkable heat stability of the single chain camelid antibodies makes them very suitable for this purpose.

Anti-infective AB strategies

THE SPEAKER

Arturo Casadevall, MD, PhD is the Leo and Julia Forchheimer Professor of Microbiology & Immunology at the Albert Einstein College of Medicine of Yeshiva University in the Bronx, New York. He is Chairman of the Department of Microbiology and Immunology and served as Director of the Division of Infectious Diseases at the Montefiore Medical Center at the Albert Einstein College of Medicine from 2000-2006. Dr. Casadevall received both his MD and PhD (biochemistry) degrees from New York University in New York, New York. Subsequently, he completed internship and residency in internal medicine at Bellevue Hospital in New York, New York. Later he completed subspecialty training in Infectious Diseases at the Montefiore Medical Center and Albert Einstein College of Medicine. Dr. Casadevall major research interests are in fungal pathogenesis and the mechanism of antibody action. In the area of Biodefense Dr. Casadevall has an active research program to understand the mechanisms of antibody-mediated neutralization of Bacillus anthracis toxins. He has authored over 410 scientific papers. Dr. Casadevall was elected to membership in the American Society for Clinical Investigation, the American Academy of Physicians, and the American Academy of Microbiology. He was elected a fellow of the American Academy for the Advancement of Science and has received numerous honors including the Solomon A Berson Medical Alumni Achievement Award in Basic Science from the NYU School of Medicine, the Maxwell L. Littman Award (mycology award), the Rhoda Benham Award from Medical Mycology Society of America, and the Kass Lecture of the Infectious Disease Society of America.
Dr. Casadevall is an editor of Infection and Immunity and serves in the editorial board of the Journal of Clinical Investigation and the Journal of Experimental Medicine. He has served in numerous NIH committees including those that drafted the NIAID Strategic Plan and the Blue Ribbon Panel on Biodefense Research. He is currently a member of the National Science Advisory Board for Biosecurity and co-chairs the NIAID Board of Scientific counselors.

Arturo CASADEVALL

Albert Einstein College of Medicine, New York, USA

From 2000-2006 Dr. Casadevall was director of the Division of Infectious Diseases at AECOM-Montefiore and oversaw the expansion of its research program. He is highly regarded as a teacher and was elected to the Davidoff Society. Dr. Casadevall has organized numerous symposia and conference and was the Chair of the Program committee of the Infectious Disease Society of America in 2006. Dr. Casadevall has taken a national leadership role in postgraduate education and chairs the Career Development committee of the American Society of Microbiology.

ABSTRACT

Antibody therapy was the mainstay of antimicr obial therapy until supplanted b y antibiotics in the mid-20th century . At the time most antibody therapeutics were heterologous reagents that were expensive and had signifi cant toxicity. After being ignored for almost half a century antibody therapies are again being consider ed for many infectious diseases. Several dev elopments ar e r esponsible for this r enaissance in interest in antibody therapies. First, the increase in resistance has reduced the effectiveness of antimicrobial therapy. Second, antimicrobial therapy is often unsatisfactory in immunocompromised hosts where antibody therapy could contribute to host defense.Third, several new microbial diseases have been described for which there is no effective antimicrobial therapy. Fourth, there has been tremendous progress in antibody technologies that allow the generation of human reagents with remarkably low toxicity. This presentation will provide the historical backdrop for antibody-based therapies and discuss new approaches including radioimmunotherapy (RIT) for infectious diseases. R IT involves the attachment of a radionuclide to an antibody to make the molecule microbicidal. RIT is already used for the treatment of certain tumors and for metastatic imaging but its application to infectious diseases promises to be simpler and potentially mor e effective than in oncology.

Group B Streptococcus Prevention Strategy Based on Monoclonal Antibodies

THE SPEAKER

Eszter Nagy, MD, PhD, is VP of Pre-clinical Research & Development and member of the Management Committee at Intercell. She joined Intercell in 1999 among the first senior staff scientists and made fundamental contributions to the development of the genomic based antigen identification and validation technology currently used at Intercell for discovering bacterial vaccine candidate antigens. In 2004 she was appointed to co-ordinate pre-clinical research with the focus on Intercell's two major technologies (antigen discovery for bacterial pathogens, novel adjuvant/delivery system) and in 2005 became VP of pre-clinical R&D. Before Dr. Nagy joined the company, she worked in academic research in the fields of molecular biology, cellular immunology and cellular physiology at several institutions in the US, such as the Dartmouth College and Medical School (Hanover, NH) and Roswell Park Cancer Institute (Buffalo, NY, US). She completed her medical degree in Hungary (Univ. Med. School of Pecs) and obtained her PhD in molecular biology.
Eszter Nagy is publishing in the fields of anti-microbial immunity, bacterial pathogenesis and antigen discovery for vaccine development.
She is the holder of more than twenty patents in the field of vaccines and biotechnology.

Eszter NAGY
Intercell AG,
Vienna, Austria

ABSTRACT

Group B Strep (Streptococcus agalactiae) is one of the most important causes of life threatening infections, such as sepsis, meningitis and pneumonia in neonates (but also in immunocompromised and elderly). Although prenatal screening and the administration of intrapartum antibiotics for individuals at high risk have greatly reduced the incidence of early-onset invasive disease, late-onset disease incidences did not change. In addition, there is a fear supported with clinical observations that antibiotic prophylaxis may induce an increase in non-GBS sepsis in neonates. Currently, most alternative strategies aim at prophylactic active vaccination.
Our focus is to develop a passive immune therapy to prevent GBS infections in prematurely born, mainly before the 34th pregnancy week when placental transfer of antibodies from the mother is very low. In order to generate protective mAbs, first we identified conserved immunogenic surface proteins of GBS by the ANTIGENome technology using genomic surface display libraries of the pathogen and human serum and cervical IgG and IgA antibodies. Passive protection studies with rabbit hyperimmune sera selected a group of antigens that showed protection against a panel of nine different GBS strains in lethal sepsis models. Mouse mAbs generated against these antigens showed remarkable efficacy against certain strains. We identified a cocktail of mAbs that provided broad protection against multiple serotypes in a neonatal sepsis model. Depending on the antigen target, we observed different mode of action for the protective mAbs, including neutralization with Fab fragments. Thus, the protection by these antibodies does not solely rely on intact immune system that is very beneficial in premature neonates (or in immunocompromised and elderly).
Our proof-of-concept study with murine mAbs tested in this stringent and relevant efficacy model suggest that human application has a high likelihood of success to prevent life threatening GSB disease.

Recognition of a highly conserved epitope across influenza virus subtypes by a influenza virus neutralizing human monoclonal antibody

THE SPEAKER

In 1976 Fons UytdeHaag graduated in Veterinary Medicine with honor at the University of Utrecht, The Netherlands. He was awarded a NWO research fellowship and joined the research on the regulatory role of human T cells in the antibody response with Rudy Ballieux at the University Hospital, University of Utrecht, The Netherlands. He received his PhD with honor in 1980 from the University of Utrecht.
Fons Uytdehaag has been head of the Laboratory of Cellular Immunology at the National Institutes of Public Health (RIVM) in The Netherlands from 1980 to 1984. On sabbatical leave in 1984-1986 he joined Prof. Jacques Urbain at University of Brussels on a study of idiotype vaccination and Prof. Hidde Ploegh at Netherlands Cancer Institute, Amsterdam to study MHC class II restricted antigen processing and presentation of virus membrane glycoproteins. In 1986 he joined Prof. Albert Osterhaus at RIVM to become head of the Laboratory of Immunobiology working on HIV, FIV, FLV, CPV, rabies, measles, polio Phocid Distemper Virus, mechanisms of antigen presentation and idiotype vaccines. Together with Albert Osterhaus he moved to Erasmus University in Rotterdam to become associate Prof. Virology, Faculty of Medicine from 1993-1998.
In 1998 Fons UytdeHaag joined Introgene, a start-up biotech company in Leiden, The Netherlands. After the merger of Introgene with Ubisys from Utrecht, he became the Director Vaccine R&D of Crucell Holland BV. in Leiden, The Netherlands. At present he is Senior Director R&D Strategy Development at Crucell Holland BV
Fons UytdeHaag is author or co-author of more than 150 scientific publications and of many patents.

Fons UYTDEHAAG
Crucell,
Leiden, Netherlands

ABSTRACT

Fons UytdeHaag, R obert Friesen, Mandy Jongenelen, Mark Throsby, Jaap Goudsmit.
Crucell Holland BV, Leiden, The Netherlands

Influenza virus presents a persistent and significant threat to public health worldwide. Due to the high genetic variability of influenza virus careful matching of viral strains in a seasonal influenza vaccine to the predominant circulation strains, critical for the success of an infl uenza vaccine, provides many challenges. Thus seasonal infl uenza vaccines often pr ovide sub-optimal protection, as in 2007-2008. Nev ertheless, vaccination remains the most effective countermeasure against influenza, especially in the light of the incr easing resistance of influenza strains against neuraminidase inhibitors and amantadines. Apart from the mutations that rapidly and continuously accumulate in the infl uenza virus hemagglutinin (HA) from year to year, HAs can be shuffled from a pool of 16 HA subtypes of avian viruses to a human virus leading to a pandemic. Predicting the subtype of the next pandemic and the time it will arise is at present impossible.
A treatment or a v accine effective against infections caused by multiple influenza virus subtypes would take away the cumbersome annual strain selection procedure and lessen the threat of any emerging pandemic viruses.
Using phage display technology a human monoclonal antibody active against a br oad range of distinct infl uenza virus subtypes was developed. This antibody is able to prevent infection as well as, in contrast to neuraminidase inhibitors, to prevent and cure disease caused by multiple influenza virus subtypes in mice and ferr ets. The epitope identifi ed by this broadly neutralizing antibody may accelerate the design of improved infl uenza v accines and antibody-based ther apies to protect against infection caused b y multiple infl uenza virus subtypes.

TGN1412: Lessons Learnt

Ulrich KALINKE

Twincore Centre of Experimental and Clinical Infection Research, Hannover, Germany

THE SPEAKER

Prof. Dr. Ulrich Kalinke is Director of TWINCORE, Centre of Experimental and Clinical Infection Research where he is also heading the Division of Experimental Infection Research. After he studied Biology in Hannover, Germany, he did his Ph.D. at the German Cancer Research Centre, Heidelberg, where he studied peripheral T cell tolerance and the role of CD8 as a co-receptor in specific T cell recognition. For his postdoctoral time he moved to Zürich, Switzerland, where he worked in the laboratory of Nobel Laureate Rolf Zinkernagel. During that time he analyzed virus-neutralizing antibody responses. Then Prof. Kalinke was appointed as Staff Scientist and Leader of the "Anti-Viral Defense Group" at the European Molecular Biology Laboratory in Monterotondo near Rome, Italy. In that environment he focused on the analysis of innate immune responses induced upon virus infection. In 2002 he was appointed Head of Division of Immunology at the Paul-Ehrlich-Institut in Langen, Germany.
There he was responsible for all licensing aspects of monoclonal and polyclonal antibodies and of therapeutic vaccines. Furthermore, he pursued basic research on the interface between innate and adaptive immunity. During that time Prof. Kalinke became also involved in the field of regulatory research where he and his colleagues addressed issues such as challenges and opportunities of biosimilars and new developments in tumor vaccines. At his current position he is developing a translational infection research programme as a joint venture between the Helmholtz-Centre of Infection Research in Braunschweig and the Medical School Hannover.
In addition to undertaking basic and clinically associated research projects he helped to developed new teaching formats to distribute knowledge about regulatory issues relevant for clinical trial applications.
Currently he is holding a Guest Scientist Status at the Paul-Ehrlich-Institut to constitute a strong link between academia and a competent authority and to further develop regulatory research issues.

ABSTRACT

Superagonistic anti-CD28 antibodies such as TGN1412 activate T lymphocytes without triggering theTCR/CD3-complex. In rats and mice these r eagents induce pr eferential expansion of regulatory T cells and can be used for the treatment of autoimmune diseases. In March 2006, six healthy volunteers experienced serious adv erse r eactions during a fi rst-in-human clinical trial of the superagonistic anti-CD28 monoclonal antibody TGN1412. Preclinical studies did not provide any toxicity signals neither in in vitr o studies with human immune cells nor in in vivo studies using rodents or non-human primates. We addressed the question why TGN1412 induced serious adverse events in humans but not in non-human primates and other animal models. Sequence analysis revealed that the CD28 extracellular domains of humans and non-human primates, including TGN1412 binding sites, w ere completely conser ved. We dev eloped a fl ow cytometry-based method for the determination of r eceptor occupancy using primary T cells. That test showed that binding of TGN1412 to CD28 on human and non-human primate T cells was similar. Furthermore, FACS analysis indicated a compar able ratio of CD4+ vs. CD8+ T cells in blood samples of the two species. Interestingly, TGN1412 as w ell as a commer cially av ailable superagonistic anti-CD28 antibody induced sustained calcium flux in human naïve and memory CD4+ T cells, whereas Macaca derived T cells sho wed a r educed calcium fl ux into the cytosol. The calcium release was associated with the induction of pro-inflammatory cytokines, most notably IFN- and TNF- . Thus, our data suggest a molecular basis for the severe side effects caused by TGN1412 and impinge upon the relevance of non-human primates as pr eclinical models for reagents that are supposed to modify the function of human T cells. Latest r esults addressubg Fcg mediated effects will be discussed.

Human antibodies that neutralize pandemic influenza viruses

THE SPEAKER

Dr. Crowe is a viral immunologist and board-certified pediatric infectious diseases specialist at Vanderbilt University in Nashville, TN, USA. He is Professor of Pediatrics, Microbiology and Immunology, Ingram Professor of Cancer Research, Director of the Vanderbilt Vaccine Center, and Director of the Vanderbilt Alliance for Nanomedicine. He is Director of the Monoclonal Antibody and Biosensor Program of the SouthEast Regional Center for Excellence in Biodefense, USA. His laboratory has a broad portfolio of work in the area of microbial pathogenesis and immunity, with an aim to discovery of mechanisms important to development of new vaccines. The laboratory has working groups in three main areas: 1) Antiviral antibodies and B cells, 2) Virus-specific T cells, and 3) Cell biology of respiratory virus infection. The laboratory has ongoing work with influenza, respiratory syncytial virus (RSV), influenza viruses, human metapneumovirus, rotavirus, novel coronaviruses and vaccinia virus. The laboratory has significant commitments in the area of biodefense research. The group is also invested in early efforts in nanomedicine, a discipline in which technologies that operate at a very small scale are being developed for medical intervention. He was the recipient of investigator awards from the March of Dimes, American Society for Microbiology, Pediatric Infectious Diseases Society, and Society for Pediatric Research. He was the awarded the 2002 Judson Daland Prize of the American Philosophical Society, the 2005 Oswald Avery Award of the Infectious Diseases Society of America, the 2006 E. Mead Johnson Award for Excellence in Pediatrics, and the 2007 Outstanding Investigator Award, American Federation for Medical Research.

James E. CROWE, Jr.

Vanderbilt University, Nashville, Tennessee, USA

ABSTRACT

Investigation of the human antibody r esponse to pandemic influenza virus infection has been lar gely limited in the past to ser ologies (HAI and neutr alizing tests) with relatively little analysis of the B cell at the molecular lev el. Recent work has r ecovered the gene sequences of pandemic viruses of the 20th century, includung the 1918 pandemic virus. Little is known about human adaptive immunity to these viruses. We took advantage of the 1918 virus sequencing and the resultant production of recombinant 1918 haemagglutinin (HA) protein antigen to char acterize at the clonal lev el neutralizing antibodies induced by natural exposure of survivors to the 1918 pandemic virus. R emarkably, most sur vivors tested in their 10th decade of life had r are 1918-specific B cells cir culating. We isolated B cells from subjects and generated monoclonal antibodies that sho wed potent neutr alizing activity against 1918 virus. The antibody genes had an unusually high degree of somatic mutation, bound to the 1918 HA protein with high affinity, had ex ceptional virus-neutralizing potency and pr otected mice fr om lethal infection. These studies suggested survivors may be ex cellent sources of B cells fr om which we can obtain highly potent antivir al anibodies. In r ecent studies we have studied the human r esponse to other pandemic flu viruses of the 20th century, and to H5N1 v accination. The studies reveal interesting features of the molecular basis for influenza virus neutralization.

SESSION VI

Therapeutic cancer vaccines

Chair:

Claude LECLERC

Institut Pasteur,
Paris, France

Damage Associated Molecular Pattern Molecules [DAMPs] Promote Immune Responses

Michael T. LOTZE

University of Pittsburgh, Pittsburgh, Pennsylvania, USA

THE SPEAKER

Michael T. Lotze, MD is Professor of Surgery and Bioengineering; Vice Chair of Research within the Department of Surgery; Asst. Vice Chancellor in the six schools of the Health Sciences at Pitt; and Director of Strategic Partnerships within the University of Pittsburgh Cancer Institute as well as the Catalyst Program within the recently funded Clinical and Translational Research Institute. He has worked in the field of Immunology and clinical medicine for over 35 years and believes that a fundamental understanding of cancer biology and immunology is essential to making progress in Oncology. He received his M.D. and B. Med. Sciences from Northwestern University within the Honors Program in Medical Education. He is the co-inventor of 10 patents in dendritic cell vaccines and antigen discovery and serves as associate editor of the Journal of Immunotherapy. He has over 500 publications in peer reviewed journals and book chapters and has edited several texts including three editions of Current Cancer Therapy [with John Kirkwood], the Surgical Treatment of Advanced Cancer [with Joshua Rubin], and Cellular Immunology and the Immunotherapy of Cancer [with Olivera J. Finn]. He developed and edited the 4th Edition of the Cytokine Handbook [2003], the 1st edition of Measuring Immunity [2004], and both editions of Dendritic Cells [1998, 2002], with Dr. Angus Thomson as well as Cytokines and Cancer [2007] with Michael Caligiuri. His research focuses on the role of necrotic cell death and how it modifies immunity and the biology of inflammation and cancer as wells as cellular immunotherapy using cytokines, NK cells, and DCs. His academic career included surgical training at the University of Rochester as well as fellowships at the M.D. Anderson Institute and the National Cancer Institute. He was Senior Investigator in the Surgery Branch of the NCI from 1982-1990 and founding director and Chief of the Division of Surgical Oncology at Pitt from 1990-2000 as well as its training program in an SSO approved surgical oncology program. Until 2001 he served as Vice-President for Discovery Research in Inflammation and Oncology at SmithKline Beecham and Vice President of High Throughput Biology within Discovery Research in GlaxoSmithKline. He is past President of the International Society of Biologic Therapy of Cancer and currently also heads up the Federation of Clinical Immunology Societies Centers of Excellence, located at 51 sites world-wide.

ABSTRACT

Tumor progression in adults is associated with apoptotic inhibition, autophagy, increased necrosis and reactive inflammation. Aponecr otic cells r elease sev eral endogenous danger signals, which recruit and activate inflammatory cells. Necrosis, or Type III death, is distinguished largely morphologically from apoptotic [T ype I] and autophagic [T ype II] death, and has even been identified in protists. These distinctions have critical impor t not so much for the dying cell as for the nature of the subsequent host r esponse. High-mobility gr oup B 1 protein (HMGB1) is primarily a nuclear chromatin-binding protein released when cells die follo wing necrotic cell death and also secr eted by inflammatory cells, but sequester ed in the cells during apoptotic, autophagic or platinum-induced death. Histone H1, also a chr omatin-binding pr otein, conversely is not r eleased when cells die follo wing necr osis such as the setting of ischemia/r eperfusion injury. H MGB1 [but not histone H1] is r eleased follo wing deter gent lysis, but not r eleased b y UV irr adiation induced apoptosis, and moved into the cytosol during autophagy. We have evaluated human tumor cell lines, including lymphoma, leukemia, ovarian, melanoma and colon cancers by immunohistochemistry, western blot of nuclear and cytosolic fr actions, and nude mouse x enografts. H MGBI is not only r eleased b y necr otic tumor cells but also actively secreted. Stimuli which promote autophagic fl ux pr omotes tr anslocation to the cytosol. In vitro and in vivo, HMGBI is over-expressed in tumors and unlike normal cells, it is primarily extr anuclear, located within the cytoplasm. R eparative str omagenesis, angiogenesis, epithelial proliferation and altered host immune function b y HMGB1 thus may paradoxically promote tumor growth when released from dying tumor cells or lysed by activated NK cells or specific T-cells. The ability of HMGB1 to alter miRNA in DCs and other inflammatory cells is being ev aluated. The role of oxidation to eliminate DAMPs in the setting of chronic inflammatory conditions is also being assessed.

A new therapeutic vaccine induces lifelong protection from prostate cancer

Martin KAST

University of Southern California, Los Angeles, California, USA

THE SPEAKER

W. Martin Kast, PhD, was born in the Netherlands in 1958 and came to the USA in 1992 and 1994 to work in a biotech company and as a visiting professor, respectively and stayed in the USA from 1996 onwards, first at Loyola University Chicago and from 2003 onwards at the University of Southern California in Los Angeles, CA. He currently holds the Walter A. Richter Cancer Research Chair and is a Professor of Molecular Microbiology & Immunology and Obstetrics & Gynecology at the Norris Comprehensive Cancer Center of the University of Southern California in Los Angeles, CA. There he teaches medical and graduate students and leads a large research team. His research involves the design of therapeutic cancer vaccines including ones directed against human papilloma virus (HPV) and prostate cancer. Several of his therapeutic HPV vaccines have been or are currently tried out in national clinical trials and the Beckman Immune Monitoring Core that he directs performs the immune monitoring of the patients in these trials. He also studies the interaction of HPV with cells of the human immune system to find out how HPV escapes immune detection and how to reverse that. He has published over 220 articles and 50 book chapters and is the inventor on 14 patents in the medical field. He is a recipient of the Antoni van Leeuwenhoek research award and a career award from the Royal Netherlands Academy of Arts and Sciences. He has trained 46 graduate students and postdocs that are all having careers in science or medical research in a variety of countries. He has also recruited 11 faculty members to the institutions he has been or currently is affiliated to. He is an associate editor for several medical journals including Cancer Research and currently on the scientific advisory board of 9 biotechnology and pharmaceutical companies,

one of which he chairs. He has served on many study sections including NIH study sections and reviews for over 50 different scientific journals. His latest research on using therapeutic prostate cancer vaccines in the preventive setting is drawing massive international press acclaim. In his little spare time he is a movie actor.

ABSTRACT

T cell inducing v accines, based upon platforms of Venezuelan equine encephalitis virus r eplicons (VR P), attenuated recombinant v esicular stomatitis virus and naked DN A, all coding for the pr ostate cancer-associated antigens pr ostate stem cell antigen or six tr ansmembrane epithelial antigen of the pr ostate, w ere tested in homologous or heter ologous prime-boost regimens in prostate cancer prone TRAMP mice to assess immunogenicity lev els and anti-tumor immunity . When male mice w ere v accinated at an age of 8 w eeks, the age at which they hav e dev eloped pr ostate intr aepithelial neoplasia, all control vaccinated mice succumbed of prostate cancer within a year but of the DNA prime, VRP boosted mice 90% were alive at month 12 and 65% at month 18. This indicates that w e ar e able to induce lifelong pr otection against prostate cancer dev elopment in these mice. In another set of experiments the additional effect of androgen ablation on the prostate cancer vaccines' immunogenicity was analyzed and it was found that andr ogen ablation could augment the immunogenicity of these v accines but only when applied after immunization. A member of a new class of tumor antigens based on sperm fibrous sheet proteins was shown to be highly expressed on prostate cancer cells and not on normal prostate cells and could be par t of commer cially attr active new prostate cancer vaccines. The heterologous prime-boost strategy was also found to be absolutely superior when tested with another tumor antigen in rhesus macaques. In conclusion, the str ong in viv o anti-tumor r esponses in pr ostate cancer pr one mice and the unpr ecedented high cellular immune responses in non-human primates pr ovide strong justification for further development of the heterologous prime-boosting concept as a strategy for therapeutic and especially preventive anti-cancer vaccines.

TandAbs for recruiting NK-cells and T-cells to kill tumor cells

THE SPEAKER

After graduating as a chemist at the University of Wales in Bangor, I changed to the biochemistry department to work on enzymatic dehalogenation for a Ph.D. The first position of my research career was as a postdoc at the Max-Planck-Institute of Cell Biology in Wilhelmshaven in Germany studying the mechanism of action of steroid hormones. I then obtained a tenured position at the German Cancer Research Center (DKFZ) in Heidelberg to investigate the primary structure of microtubules. Our group was the first to determine the complete primary structure of tubulin. The structure and function of microtubules was the subject of my habilitation at the University of Heidelberg in 1985 and a year later I became an external Professor of Biochemistry in the Faculty of Biology.

In 1990 I was appointed head of the research group "Recombinant Antibodies" at the German Cancer Research Center. Our group was one of the first to develop technologies for generating and screening antibody libraries. We also developed novel antibody formats for treating disease, particularly cancer. I was a co-founder of the antibody biotech company Affitech (Oslo, Norway) in 1997 and the founder and CEO of Affimed Therapeutics in 2000 focusing on the development of recombinant antibody therapeutics. In 2002, I was co-founder of the annual "International Congress on Recombinant Antibodies". Affimed recently succeeded in obtaining substantial investments in 2007 and is now well-positioned to take its first product into clinical development.

Melvyn LITTLE

Affimed Therapeutics, Heidelberg, Germany

ABSTRACT

Tetravalent TandAbs comprised only of antibody variable domains have been created for the highly effective recruitment and activation of either NK cells or T cells to kill tumor cells. Three highly diverse libraries generated at Affimed have provided an excellent source of the human Ab components, particularly for the two antibodies that recruit immune cells. These are:

a) Humananti-FcγRIII (CD16) with (i) exclusive specificity for the A isoform on NK cells, that binds equally well to all alleles, (ii) high affinity, (iii) minimal inhibition by excess serum IgG.
b) A humanized anti-CD3 with high affinity for recruiting T cells.

TandAbs are quite stable and the two binding sites for each target provide a relatively low k_{off}. The molecular weight of about 105-110 kD is well above the size of app. 50kD for first pass renal clearance. Continuous infusions should therefore not be necessary. Furthermore, since TandAbs have no constant domains, there is less danger of extensive cross-linking with various immune effector cells. They are not glycosylated and can be produced in mammalian cells or bacteria. Examples will be shown that are being developed for the treatment of Non-Hodgkin´s Lymphoma, Hodgkin´s Lymphoma and solid tumors.

SESSION VII

Diarrehal diseases

Chair:

Eszter NAGY

Intercell AG,
Vienna, Austria

The vaccine patch containing heat-labile toxin from Escherichia coli for protection against travelers' diarrhoea

THE SPEAKER

Gregory Glenn is the Chief Scientific Officer of Intercell USA Inc., based in the Washington, D.C. area. He was the scientific founder of Iomai Corporation, and pioneered vaccine delivery technologies that target the skin. He is a recognized expert in vaccine delivery and adjuvant science, and has led a team developing transcutaneous immunization using a patch for over a decade, bringing the technology from fundamental preclinical observations to the conduct of over 34 human clinical trials and into late-stage product development.

He has had a longstanding interest in the pathophysiology and vaccine development for ETEC disease, and he has shepherded an ETEC vaccine patch from the earliest preclinical studies to a point of entering a pivotal commercial field trial evaluation as a vaccine for travelers this year. Dr. Glenn is a clinician and former pediatrician who conducted clinical and basic research at the Walter Reed Army Institute of Research in Washington, D.C. during the 1990s, and is currently an associate at the Johns Hopkins School of Public Health.

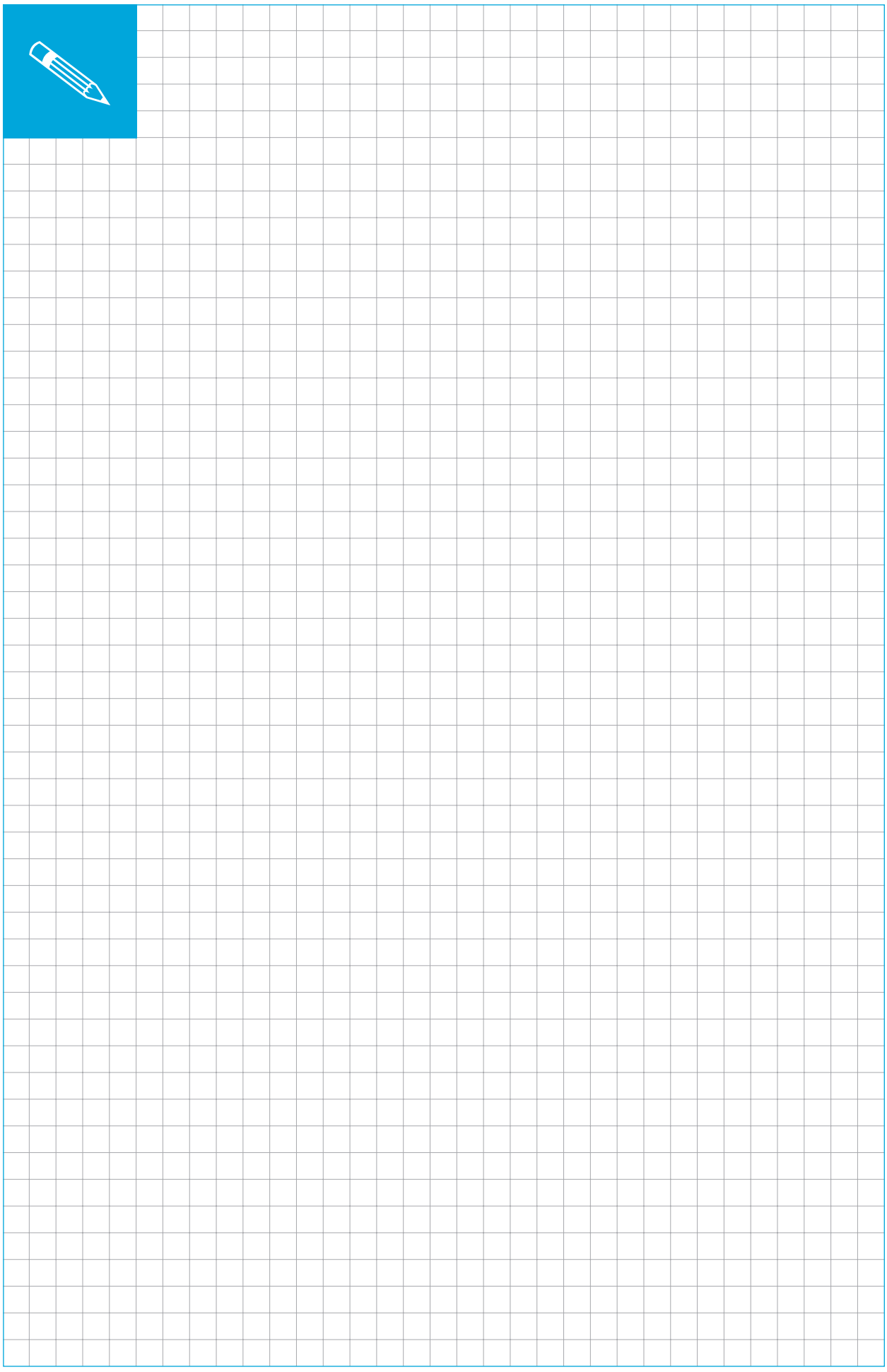
Gregory GLENN

Intercell USA Inc.,
Gaithersburg, Maryland, USA

ABSTRACT

Travelers' diarrhoea (TD) affects up to 50% of the 54 million travelers to endemic countries. Enterotoxigenic E. coli (ETEC) is the most frequent cause of all diarrhoea in travelers, resulting in 20-75 % of all TD cases. The illness caused by ETEC usually lasts from 3-5 days and ranges from mild diarrhoea without dehydration to severe cholera-like disease. Long-term sequelae of post-infectious irritable bowel syndrome are also seen in 10-30% of subjects contracting travelers' diarrhoea. In infants in the developing world, ETEC is also major cause of morbidity and mortality. A vaccine to prevent both the acute and chronic effects of travelers' diarrhoea would meet a major unmet medical need.

Intercell has developed a vaccine patch containing the antigen LT, a key pathogenic factor in ETEC disease. LT delivered in a patch to the skin immune system induces robust anti-LT immune responses that have been shown to protect against illness caused by travelers' diarrhoea. In a field trial in US travelers to Mexico and Guatemala, the vaccine demonstrated a 75% protective efficacy against moderate to severe diarrhoea and significantly reduced the duration and frequency of illness in those vaccinees who contracted travelers' diarrhoea (Lancet 371:2019-2025, 2008). The vaccine effects appear to extend beyond LT secreting ETEC, and replicate previous field trial using a toxin-based vaccine. The broad protective effects appear to be related to maintenance of the integrity of the innate mucosal barrier through neutralization of toxin-mediated effects that render humans susceptible via the common but sub-clincal exposure to toxin-producing organisms. Intercell has developed and optimized a novel vaccine patch delivery system in over 30 clinical trials, and preparations are underway to evaluate the LT patch in a large, pivotal field efficacy trial in Latin America.



Towards a Shigella vaccine: dream or reality?

THE SPEAKER

Armelle Phalipon leads the group working on adaptive immunity to Shigella infection and development of vaccine strategies in the Molecular Microbial Pathogenesis Unit directed by Professor Philippe Sansonetti. With more than 15 years of experience working on Shigella, she has deciphered the targets and effectors of the humoral response to infection and discovered two novel molecular mechanisms of secretory IgA-mediated protection at mucosal surfaces. She is currently studying the impact of Shigella-induced acute inflammation on the generation of adaptive immunity. Moreover, the direct targeting of cells of the adaptive immunity by Shigella virulence effectors is also investigated.

Dr. Phalipon has a long-standing interest in combining fundamental and applied research, as exemplified by her participation in the development of dipsticks for diagnosis of shigellosis in emergency conditions based on the use of monoclonal antibodies, generated by her, for fundamental research purposes. In addition, in collaboration with Dr. Laurence Mulard, she has developed an alternative approach to design subunit vaccines to Shigella infection, i.e. chemically defined glycoconjugate vaccines based on the use of protective carbohydrate epitopes of the polysaccharide moiety of lipopolysaccharide, the main protective Shigella antigen. Besides teaching activities at the national and international level, she is Co-Director of the first Vaccinology Course launched at the Pasteur Institute in 2008. Dr. Phalipon is also a member of the WHO Steering Committee for Diarrheoal Diseases.

Armelle PHALIPON

Institut Pasteur,
Paris, France

ABSTRACT

Shigellosis, an acute bloody diarrhea caused by the Gram negative entero-invasive Shigella spp, still represents a major public health burden in many developing countries. Children under the age of five are the main target of the disease, representing 69% of all episodes and 60% of all deaths. Even though recent surveys indicate a trend towards less mortality, morbidity remains a concern. S. dysenteriae type 1 (SD1) is associated with the most severe form of the disease and high mortality rate during epidemics. However, most of the deaths associated with shigellosis are attributable to the endemic form of the disease, most often caused by S. flexneri. Considering the still increasing number of multidrug-resistant Shigella isolates, the ineffectiveness of oral rehydration, and the severe acute complications observed in the pediatric population coupled to the slow and limited improvement in hygiene and water supply conditions in most of the developing countries, vaccination remains the most appropriate strategy to fight shigellosis. The major target would be the pediatric population of the developing world. However, such vaccine could also benefit to travelers to high risk areas, particularly those working or intervening in these areas such as members of NGOs, army personnel, etc. Following several decades of research, there is yet no vaccine available against shigellosis. Two approaches are clearly emerging: (i) live attenuated deletion mutants based on rational selection of genes that are key in the pathogenic process, and (ii) conjugated detoxified polysaccharide parenteral vaccines, or more recently, conjugated synthetic carbohydrate parenteral vaccines. Some of these approaches have already undergone phase I/II clinical trials with promising results. However, important issues have also emerged, particularly the discrepancy between colonization and immunogenic potential of live attenuated vaccine candidates depending upon the population concerned (i.e. nonendemic vs. endemic areas). Efforts are needed to definitely establish the proof of concept of these approaches, including clinical trials which should also soon explore the possibility to associate different serotypes in provide protection against the most predominant Shigella strains. More basic research is also required to explore the search for cross-protective protein antigens. Emphasis will be put on the strategies and vaccine candidates currently developed at the Pasteur Institute.

Most recent reviews:
Phalipon A., Mulard M. and P. J. Sansonetti. Microbes and Infection, 2008, 10, 1057-1062. | Levine M. M., Kotloff K. L., Barry E. M., Pasetti M. F., and M. B. Sztein. Nature Microbiology Review, 2007, 5, 540-553.

The Pentavalent Rotavirus Vaccine, RotaTeq™: From Development to Licensure and Beyond

THE SPEAKER

Florian Schödel is a Vice President in ID/Vaccines Clinical Research of Merck Research Laboratories, West Point, PA. He graduated in medicine at the Technical University, Munich, in 1983 and received a first doctoral degree (Dr. med.) in 1986 in Transplantation Immunology and a second degree (Dr. med. habil.) in Medical Microbiology and Hygiene in 1991 from the University of Munich. He is a faculty member at the University of Munich and an adjunct Professor of Research at the Biodesign Center of the Arizona State University. Florian's research at the Max-Planck Institute for Biochemistry, Scripps Clinic and Research Institute, the Walter-Reed-Army Institute Research and INSERM focused on hepatitis B, on approaches to the development of recombinant vectored vaccines against various disease such as malaria, hepB and typhoid fever and on the study of virus like particles as carriers for vaccine epitopes. Florian joined Merck Research Laboratories in November 1996 as Director Clinical Vaccine Research in Europe where he was responsible for vaccine clinical trials in Europe and for the clinical development of rotavirus, measles, mumps and rubella vaccines. He was the clinical liaison to a European joint venture (SP-MSD) for Merck and participated in the joint development of pediatric combination vaccines (leading to two European MAs). He oversees clinical vaccine development, which has led to several internationally licensed vaccines. He also contributes to clinical and analytical research development (serology and other assays).

Florian SCHÖDEL

Merck & Co. Inc.,
West Point, Pennsylvania, USA

ABSTRACT

Several rotavirus vaccines have been developed over the last decades. Initial approaches were based on the classical „Jennerian" approach and utilized simian and bovine rotavirus strains, which provided some cross-protection against human rotavirus strains but did not cause illness in infants and young children because of their species-specific tropism. Disappointingly, the demonstrated efficacy of these vaccines was not consistent across studies. Thus, human-animal reassortants containing an animal rotavirus backbone with human rotavirus surface G and/or P proteins were developed, which demonstrated more consistent efficacy than that observed with the non-reassortant rotavirus strains. Merck's rotavirus vaccine, RotaTeq®, contains 5 human-bovine reassortant rotaviruses consisting of a bovine (WC3) backbone with human rotavirus surface proteins representative of the most common G (G1, G2, G3, G4) or P (P1A[8]) types worldwide. Results of a large-scale Phase III clinical study, conducted in 11 countries worldwide, showed that 3 doses of RotaTeq™ were efficacious, immunogenic, and well tolerated with no increased clinical risk of intussusception. Using a validated clinical scoring system, RotaTeq™ was shown efficacious against rotavirus gastroenteritis of any severity (74%) and severe disease (98-100%). Reductions in rotavirus-associated hospitalizations and emergency department (ED) visits, for up to 2 years postvaccination, were 95% in Europe, 97% in the United States, and 90% in the Latin American/Caribbean regions. Robust postlicensure evaluation of the vaccine has confirmed the vaccine's excellent safety profile. The vaccine was recently shown to be 100% effective in routine use in the United States in reducing hospitalizations and emergency department visits and 96% effective in reducing physician visits. Additional studies in 6 different locations in the United States have shown 85-95% reduction in rotavirus-associated hospitalizations and/or emergency department visits in the first 2-2.5 years of routine use. A large study conducted using a national laboratory also showed 70% reduction in rotavirus positive lab tests between the pre and post-vaccine era. Clinical trials are currently ongoing by Merck and PATH, in collaboration with WHO and CDC, to evaluate the efficacy, immunogenicity, and safety of RotaTeq™ in Sub-Saharan Africa and Southeast Asia. In collaboration with IMPAACT, Merck will soon evaluate the safety and immunogenicity of RotaTeq™ in infants born to HIV-positive mothers. These activities mark an important step toward rotavirus vaccine introduction in the developing world, where the burden of disease is substantial.

CLOSING SESSION

The need of new vaccines

Chair:

Gerd ZETTLMEISSL

Intercell AG,
Vienna, Austria

The need of new vaccines

THE SPEAKER

Academic Qualifications

- Engineer in Chemistry and Bioindustries at the University of Gembloux (Belgium) in 1972.
- Special degree in Business and Administration at the University of Louvain-La-Neuve (Belgium) in 1980.

Experience

- One year (1973 - April 1974), as Engineer in a laboratory for analysis of food materials.
- 29 years (April 74 - today) in the Biological Division of SmithKline Beecham (Rixensart) in the following positions :
  - Technical and Scientific training.
  - Head of Bulk (bacterial and viral) vaccines production for 5 years.
  - Vaccine Production Manager from 1980 to June 1981.
  - Vaccine Plant Director (Human and Veterinarian) from July 1981 to May 1984.
  - Vaccine Plant and Human Vaccines Development Director from June 1984 to April 1986.
  - Vaccine Plant and Human Vaccine R&D Director from May 1986 to February 1988.
  - Vice President Human Vaccine Research and Development, and Production from March 1988 to January 1991.
  - Vice President and General Manager from January 1991.
  - Senior Vice President and General Manager from October 92

Present Position

- President and General Manager SB Biologicals from July 1998 (GlaxoSmithKline Biologicals since December 2000).
- President of the Board of Directors of GlaxoSmithKline Biologicals.
- Administrator of GlaxoSmithKline Biologicals
- Member of Pharmaceutical Operating Committee of GSK.
- President of the Board of Directors of BESIX
- Member of the Board of Directors of Fortis Bank
- Member of the Board of Directors of GBL
- Member of the Board of Directors of Henogen
- Member of the Board of Directors of IBA
- Member of the Board of Directors of Nanocyl
- Member of the Board of Directors of the FEB

Jean STEPHENNE

GlaxoSmithKline Biologicals, Wavre, Belgium

- President of „Union Wallonne des Entreprises“ from December 1997 to October 2000
- Founder of EVM (European Vaccines Manufacturing) and President from 1992-1995.
- Member of the International Association of Biological Standardization (IABS).
- Member of the European Society for Animal Cell Technology (ESACT).
- Manager of the Year (Trends-Tendances) in 1996 – Belgium
- Innovator of the year by the Business Week Magazine in 2005
- Doctor Honoris Causa by the University of Gembloux (Belgium) in 2006.

ABSTRACT

Advances in biotechnology and immunology are yielding exciting progress in the development of new biologics and vaccines, both for prevention and treatment. Yet in both in the developed and under developed world, we see a backlog of new vaccines waiting to be introduced, an „innovation pile up“. At the same time, we can see the arrival of many new products in the coming years. What is the „need for new vaccines“? Reviewing the state of the science and the vaccine and biologics pipeline, what lessons can we learn to accelerate the introduction and adoption of currently under-utilised and future vaccines?

Novel vaccines – entrepreneurial contributions and scientific challenges

THE SPEAKER

Chief Scientific Officer, Executive Board Member and founder of the Intercell AG
Alexander von Gabain obtained his Ph.D. in Genetics at the University of Heidelberg and held a post-doctorate position at the Stanford University. In the 1980s and 1990s he was a Professor at the University of Umeå and at the Karolinska Institute, Sweden as well as advisor to pharmaceutical and biotech companies. During 1992-1998 he was Chair of Microbiology at the University of Vienna at the Campus Vienna Biocenter, Austria. In 1998 he co-founded Intercell AG and led the company as CEO, until it was successful floated on the Vienna Stock Market in 2005. He is holding a professorship of Microbiology at the Max Perutz Laboratories, Vienna and a foreign adjunct professorship at the Karolinska Institute in Stockholm. He is member of several professional organizations and serves in the Supervisory Boards of biotech enterprises, including TVM Capital in Munich. Recently, he has been appointed into the founding Supervisory Board of the European Institute of Technology (EIT).

Alexander VON GABAIN
Intercell AG,
Vienna, Austria

ABSTRACT

Vaccination is arguably the most successful medical intervention which has become during the last century a mandatory part of many countries' health care programs and shown to be an effective instrument in the control of infectious diseases worldwide. Development and launch of novel vaccines has seen a turn around in the late 1980ies. This trend has been triggered by the appearance of novel pathogens, by the need to control the rebound of global infectious diseases and by the encouraging progress made in relevant scientific fields, but also in the arena of novel manufacturing technologies. The impressive comeback of vaccines is also due to the entrepreneurial spirit found in biotech companies, but also in established pharmaceutical industries. Both have formed, alongside with non-profit organizations and academic laboratories, sophisticated alliances that have facilitated the development of novel vaccines and expanded the spectrum of existing vaccines.

With the growing portfolio of worldwide registered and administered vaccines, but also with the intensified vaccination schedules starting with birth and ending in late life, the challenges are increasing: How to reduce, to best combine and to optimize the vaccines during all life stages, how to monitor their long-term protection, how to assure their efficacy in elderly, how to deal with the variability of human populations regarding differences in genetics, pathogen pre-exposure and colonization with normal microbial flora and, finally, how to deal with the variability of pathogens regarding their genetic plasticity and their already observed mechanisms to escape vaccines.

POSTER SESSION

Poster Session Abstracts

MICHAEL C. AICHINGER

Adjuvating the Adjuvant – KLK driven uptake of the TLR9 agonist ODN1a into dendritic cells

Michael C. Aichinger [1], Michael Ginzler [2], Julian Weghuber[3], Lars Zimmermann[3], Alexander von Gabain[2], Rudolf Schweyen[1] and Tamás Henics[1]

The cationic antimicrobial peptide, KLKLLLLLKLK (KLK) and the TLR9-agonist, oligo-dIC13 (ODN1a) function together as a potent vaccine adjuvant, termed IC31TM. While the membrane-interacting properties of KLK and the immuno-modulating capabilities of ODN1a had been characterized in detail, little was known of how these molecules function together on their primary target cells, the dendritic cells (DCs). Here we show that a KLK-based aggregate entraps ODN1a and associates at the surface of dendritic cells. KLK potentiates the uptake of ODN1a into distinct compartments of the peripheral cytoplasm, while the bulk of the peptide remains localized in the cell membrane vicinity. ODN1a co-localizes with early and late endosomes as well as the endoplasmic reticulum and TLR9 containing vesicles.
These data extends the understanding of the adjuvant effect of IC31™.

[1]Department of Genetics, Max F. Perutz Laboratories, Vienna, Austria | [2]INTERCELL AG, Vienna, Austria | [3]Biophysics Institute, Johannes Kepler University, Linz, Austria

M. E. CUENO

FEASIBILITY OF A PLANT-BASED VACCINE AGAINST HIV-1

M. E. Cueno [1,4], Y. Hibi[1], Katsuo Karamatsu[2,3], Yasuhiro Yasutomi[2,3], Antonio C. Laurena[4],Takashi Okamoto[1]

BACKGROUND: Plant-made vaccines have grown to be an ideal method for vaccine production due to its ability to induce mucosal immunity, relatively cheaper production cost and affordability. HIV-1 Tat plays a major role in HIV viral proliferation and in clinical progression to AIDS making it an ideal vaccine target. Previous attempts to express Tat in tomato, however, only induced humoral responses and certain physiological abnormalities were also observed in tomato. We naturalized Tat expression in tomato plant to lessen its toxic effects and tested for its immunogenic potential.
METHODS: Acodon-optimized Tat gene was synthesized and introduced into tomato plant through bombardment. Transgenic tomato lines were tested for Tat expression and the tomato extracts were introduced intradermally to mice. Immunogenic responses were observed through ELISA and ELISPOT. Concurrently, strategies were made to hinder the toxic effects of Tat on the tomato plant host.
RESULTS: Tat expression was observed in all transgenic tomato lines with noticeable abnormalities to the host regardless of developmental stage. Further analyses of this phenomenon reveal a novel association between Tat and tomato CKO. Interestingly, we found that the RGD and Arg-rich motifs of Tat have common functional use in the tomato explaining our observed abnormalities and substituting these regions easily avoided such abnormalities. Nevertheless, when extracts were obtained from the transgenic tomato lines and intradermally introduced to mice, both humoral and cellular responses were induced.
CONCLUSION: Though physiological abnormalities exists when Tat is expressed in tomato plant, it is still capable of inducing both humoral and cellular responses proving the feasibility of producing a plant-based vaccine for HIV provided appropriate mutations on Tat are made to avoid toxicity.

[1]Molecular and Cellular Biology Laboratory, Graduate School of Medical Sciences, Nagoya City University, Aichi 467-8601 JAPAN; | [2]Laboratory of Immunoregulation and Vaccine Research, Tsukuba Primate Research Center, National Institute of Biomedical Innovation, Tsukuba, Ibaraki 305-0843 JAPAN; | [3]Department of Immunooregulation, Mie University Graduate School of Medicine, Mie 514-8507 JAPAN; | [4]Biochemistry Laboratory, Institute of Plant Breeding, University of the Philippines Los Banos, Laguna 4031 PHILIPPINES

Mario FELDMAN

Bacterial Engineered Glycoproteins (BEGs): towards a novel generation of conjugate vaccines

Jeremy Iwashkiw, Yasuharu Watanabe, Amirreza Faridmoayer and Mario Feldman
Alberta Ingenuity Centre for Carbohydrate Sciences. Department of Biological Sciences. University of Alberta, Edmonton, AB, Canada. T6G 2E9. mfeldman@ualberta.ca

Diseases caused by pathogenic bacteria continue to be among the highest causes of mortality worldwide. The development of antibiotic resistance by pathogens is occurring at alarming rates. Therefore, alternative strategies for protection of public health are urgently needed, and one of the strategies is vaccination. Since many pathogenic bacteria are covered by polysaccharides, immune responses directed to these polysaccharides will prevent colonization and infection. However, purified polysaccharide vaccines produce a transient immune response. To generate long-term protection, bacterial polysaccharides must be covalently attached to an appropriate protein carrier. The efficacy of conjugating bacterial polysaccharides to proteins is best illustrated by the Haemophilus influenzae type b conjugate vaccine that has virtually eradicated this disease in immunized children. Presently, the production of these conjugate vaccines requires intricate synthetic chemistry for obtaining, activating, and attaching the polysaccharides to protein carriers. The polysaccharides are either purified from the pathogen, or synthetically produced. In most cases, polysaccharides are too complex to be obtained by simple chemical methods, which make this process economically inviable. In addition, extraction of the polysaccharides from the organisms requires large cultures of pathogenic bacteria, which constitutes a major health hazard. Furthermore, the removal of endotoxins from the polysaccharides is required. Finally, chemical attachment of the polysaccharide to the protein often results in large and heterogeneous clusters of conjugates, and considerable amount of toxic waste is generated during the conjugation process.
It has recently been established that bacteria are able to glycosylate proteins. The key enzymes in bacterial glycoprotein synthesis are the oligosaccharyltransferases responsible for the attachment of the carbohydrates to the proteins in vivo. The two most studied members of this family are PglB from Campylobacter jejuni, which is responsible for N-glycosylation of several proteins in this organism, and PglL, which participates in protein O-glycosylation in Neisseria menigitidis. We have previously shown that these enzymes are functional in Escherichia coli, and that they have the ability to transfer a variety of polysaccharides to protein carriers in vivo. The bacterial engineered glycoproteins (BEGs) that can be generated may constitute a new generation of conjugate vaccines, circumventing most of the disadvantages of the conventional chemical methods, significantly reducing costs, and improving the reproducibility of the conjugates obtained. In this work we obtained BEGs that target brucellosis and other bacterial infections. We also show that BEGs can elicit an IgG immune response, suggesting that they may be able to protect against these microorganisms.

Vaccination of Children in Bangladesh: A Data Analysis of the 2007 Bangladesh Demographic Health Survey

Mohammed Abul K alam, Institute of Epidemiology , Disease Control & Research, Mohakhali, Dhaka 1212, Bangladesh

Universal immunization of children less than one year of age against the six major v accine-preventable diseases (tuber - culosis, diphtheria, per tussis, tetanus, poliomy elitis, and measles) is one of the most cost effectiv e pr ograms to r e- duce infant and child morbidity and mor tality. The Expand- ed Program on Immunization (E PI) is a priority pr ogram for the go vernment of Bangladesh. It follo ws the international guidelines recommended by the World Health Or ganization (WHO). Accor ding to the guidelines, childr en ar e consid- ered fully immuniz ed when they hav e received one does of the vaccine against tuber culosis (BCG), three doses each of the vaccine against diphtheria, Pertussis and tetanus (DPT), three doses of polio v accine (excluding polio given at birth), and one dose of measles v accine. One does of B CG is giv en at bir th or at the fi rst contact with health workers; the DPT and polio v accines r equire thr ee doses at appr oximately 6, 10, and 14 w eeks of age; and measles v accine is given soon after 9 months of age. WHO recommends giving children all of these vaccines before their first birthday and recording the vaccinations on a vaccination card given to the parents.
The go vernment of Bangladesh established the r outine E PI program against six v accine pr eventable diseases in 1979. Efforts intensified after 1985 when Bangladesh committed it- self to reach universal immunization by 1990. In 2003 the na- tional EPI program incorporated the hepatitis B v accine with support from the Global Alliance for Vaccination and Immuni- zation (GAVI). The hepatitis B vaccine was initially distributed in seven districts and one city corporation and then gradually expanded to all districts of Bangladesh by October 2005. The hepatitis B v accine, which is not included in the calculation of full v accination co verage, is giv en in thr ee doses along with the doses of the DPT and polio vaccines.
The 2007 Bangladesh Demogr aphic Health Sur vey (B DHS) collected data on childhood v accinations for all sur viving children born during the fi ve-year period befor e the sur vey. Bangladesh, immunizations are routinely recorded on a vac- cination car d. For each child, mothers w ere asked whether they had the v accination card and, if so, to sho w the card to the interviewer. When the mother was able to show the vacci- nation card, the dates of v accinations were transferred from the card to the questionnaire. If the vaccination card was not available (or a vaccination was not recorded), mothers were asked to recall whether the child had received each vaccine. Vaccination car ds w ere seen for 58 per cent of childr en age 12-23 months. Childr en in urban ar eas ar e mor e likely than other childr en to be fully v accinated. Among divisions, the highest level of co verage is seen in Barisal (90 per cent) and the lowest in Sylhet (71 percent). Mother's education is posi- tively associated with children's likelihood of being fully vac- cinated: 93 per cent of childr en whose mothers completed secondary or higher education ar e fully v accinated, com- pared with 72 per cent of childr en whose mothers hav e no education. Childr en fr om households in the highest w ealth quintile are more likely to be fully vaccinated than children in the lowest quintile (88versus 80 percent).

Renate KASTNER | Elisabeth KERNBAUER

RENATE KASTNER

The protein tyrosine phosphatase cTP from L. monocytogenes contributes to virulence in epithelial cells and in an oral infection model

Renate Kastner, Didier Soulat, Elisabeth K ernbauer, Thomas Decker – Max F. Perutz Laboratories, University of Vienna, Dr. Bohr-Gasse 9/4, 1030 Vienna, Austria

The gram-positive pathogen L. monocytogenes is a facultative intracellular bacterium, which has the ability to sur vive and r eplicate within the cytosol of infected cells and then spread from cell to cell. F ollowing internalization or phagocytic uptake L. monocytogenes r apidly escapes fr om the phagolysosome and multiplies within the cytosol. R emarkably, although L. monocytogenes does not express any typical protein-tyrosine kinase, w e noted that its genome encodes a protein with str ong homology to conv entional protein tyrosine phosphatases (PTPs). To address the biological function of the listerial cTP, w e generated a ctp knock-out and compared its virulence to wild-type L. monocytogenes in macrophages and epithelial cells. In macr ophages, which are pr ofessional phagocytic cells, ther e is no differ ence in bacterial virulence and in the induction of an antimicr obioal response. Ho wever, in epithelial cells (CaCo-2) wher e the bacteria trigger their o wn uptake b y the adhesin internalin A, the ctp mutant shows defects in intracellular growth compared to wt L. monocytogenes. Additionally, we analyzed the cTP mutant str ain in an or al in viv o infection model, inv estigating the bacterial loads of spleen, liver and intestine. Most interestingly, w e could sho w that the cTP mutant is defective in colonization of orally infected mice. Together we could characterize the pr otein tyrosine phosphatase cTP as a new factor of Listeria monocytogenes virulence.

ELISABETH KERNBAUER

Modulation of the immune response to Listeria monocytogenes by Type I Interferons

E. Kernbauer, R. Kastner, S. Stockinger, T. Decker – Max F. Perutz laboratories, Vienna, Austria

Listeria monocytogenes is a gr am positiv e, facultativ e intracellular human pathogen which elicits type I Interfer on (IFN-I) production. IFN-Is are important cytokines in antiviral responses. Ho wever, in Listeria monocytogenes infections IFN-Is hav e adv erse effects. Mice lacking the I FN-I r eceptor (IFNAR) are more resistant to Listeria monocytogenes infection compared to wildtype mice. We identified the interferon producing cell in an infection model b y using v arious gene-targeted mice and accompanied these studies by in vitro cell culture models. We could show that a myeloid cell of splenic origin is r esponsible for the major par t of I FN-I pr oduction. Unexpectedly, the inv olvement of plasmacytoid dendritc cells (pDCs), Cd11c+ cells described to be pr oducers of v ast amounts of IFN-Is in viral infections, could be excluded. This notion is suppor ted b y two lines of evidence: i) is the I FN-I pr oduction dependent on TLR9, a typical pathway of I FN-I induction of pDCs, ii) Cd11c+ cells contribute to IFN-I production, as could be sho wn in a cell sor ting experiment. This experiment revealed a critical r ole of my eloid cells (Cd11b+) cells in the IFN-I production. The harmful effects for the host of I FN-Is w ere determined using v arious infection r outes. The analysis of bacterial loads of liv er, spleen and intestine showed a signifi cant decrease in I FNAR deficient mice compared to wildtype mice after different time points. The characterisation of the infection with r espect to the I FN-I response after oral delivery of the bacteria will be a future task using histology, cytokine analysis and infection of gene-targeted mice for the IFN-I synthesis pathway.

REINHARD KIRNBAUER

Chimeric L1/L2 Papillomavirus-like Particles (VLP) As Potential Broad-Spectrum HPV Vaccines

Kirnbauer R[1], Roden R[2], Schellenbacher C[1]

Papillomavirus-like particles (VLP) consisting of self-assembled L1 major capsid protein vaccines provide enduring, high-titer and type-restricted protective antibody responses. In contrast N-terminal peptides of L2 induce low-titer antisera that also cross-neutralize heterologous types. The aim was to more completely characterize neutralizing epitopes within N-terminal HPV16 L2 in the context of chimeric L1/L2VLP, and to improve L2-immunogenicity by surface-display on highly-ordered particles.

Overlapping peptides of HPV16 L2 were genetically engineered for repetitive expression by VLP surface loops. Chimeric proteins were baculovirus-expressed and gradient-purified. Two NZW rabbits were immunized in Freund's adjuvant with each native or SDS-denatured particles. Established immunogens were further administered using alum-MPL adjuvant and into Balb/c mice. Sera were analyzed by L2 peptide-ELISA and pseudovirion neutralization assays. The majority of recombinant proteins assembled into VLP. By L2 peptide-ELISA immune sera revealed titers up to 60,000 indicating immunogenic epitopes in surface-displayed L2 peptides. Sera to chimeras E, F and I neutralized homologous HPV16 with titers up to 1000, whereas antisera to 3 additional chimeras were non-neutralizing for HPV16. One of the chimeric VLP induced broadly neutralizing antisera to divergent high-risk HPV 16/18/31/45/52/58, low-risk HPV11 and beta-type HPV5, with titers ranging from 50 to 10,000. Alum/MPL adjuvanted immunogen induced a similar neutralization pattern, in both rabbit and mice, albeit less robust with 100-fold lower titer. Native VLP induced higher titers than denatured particles. Immunization with chimeric L1 VLP displaying L2 peptides in adjuvant applicable for human use can induce broad-spectrum antibody responses to mucosal high-risk, low-risk and beta papillomaviruses.

[1]Laboratory of Viral Oncology (LVO), DIAID, Dept. of Dermatology, Medical University Vienna (MUW), Austria; | [2]Pathology, Johns Hopkins University, Baltimore, USA

GEETY NABY

The development of a vaccine for Streptococcus using a C5a agonist (YSFKPMPLaR) as a molecular adjuvant

The complement factor C5a is a potent inflammatory molecule which has been shown to stimulate the humoral immune response leading to enhancement of antigen-specific antibody (Ab) production, via interaction with the C5a receptor. Our laboratories have developed a linear peptide C5a agonist (YSFKPMPLaR) termed EP54. We have shown previously that conjugating this compound to small antigenic peptides (e.g. MUC1 and nicotine), is able to create circulating antigen-specific Abs, demonstrating the molecular adjuvant capacity of this C5a agonist. This present study aimed to determine whether conjugation of this C5a agonist to Streptococcus J8 peptide (J8) would form Abs against Streptococcus in vivo, and that these Abs would be protective. In order to investigate this, we conjugated J8 to YSFKPMPLaR and injected this adjuvant (100µg; i.p.) into B10BR mice at days 1, 21 and 28. Mice were bled every 5 days and examined for Ab titres. We found that the conjugated peptide J8-YSFKPMPLaR produced specific Abs against J8, whereas the J8(control) did not produce any Abs. This Ab production occurred after 5 days of primary immunization and was highest at day 25. These results indicate that by conjugating a C5a agonist peptide to an antigen, and thereby targeting C5a receptor-expressing immune cells, we are able to produce Abs for normally non-immunogenic peptides. This study suggests that the use of such technology may be used for the future development of a human Streptococcus vaccine.

David PEJOSKI | Christina B. PLANITZER

DAVID PEJOSKI

Investigation of lipopeptide primed CD4+ T cell responses using an influenza A model

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The use of synthetic, CD4+ T cell epitope-based lipopeptide vaccines in contr olling infl uenza A virus was inv estigated. Three conser ved T-helper cell epitopes fr om infl uenza A virus w ere individually coupled to the lipid moiety S-[2,3 bis(palmitoyloxy)propyl]cysteine (P2C), which is a ligand for TLR-2 and then administer ed to BA LB/c mice b y the subcutaneous r oute. CD4+ T cells obtained fr om inoculated mice proliferated and pr oduced I FN-γ when exposed to peptide in vitr o. Mice challenged with virus one month after r eceiving lipopeptides mounted higher anti-infl uenza antibody responses and elicited better hemagglutination inhibiting Ab than control animals.
Mice inoculated with lipopeptide v accines also demonstrated significantly lower pulmonary viral titres when compared with contr ol animals follo wing challenge with liv e influenza virus. In conclusion, priming a CD4+ T cell population with influenza epitopes reduces the viral load indicating

CHRISTINA B. PLANITZER

West Nile Virus: In vitro Neutralization an In Vivo Protection of human IgG Subclasses

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Rationale: The 1999 intr oduction of WNV into the naiv e US population resulted a major arbo virus epidemic, with an estimated 2.8 million mostly asymptomatic infections in the US to date. Consequently, intravenous immune globulins (IVIG) that are produced from the plasma of thousands of U S donors contain v ariable degr ees of WNV-neutralizing antibodies. IVIG lots of higher WNV neutr alization titers hav e ev en been shown to be protective against lethal WNV infection in an animal model (CB Planitz er, J Modr of, TR Kreil, JID [2007] 196: 435). Understanding the molecular basis of the pr otection affor ded bay WNV infection, and pr ovide guidance for the development of a vaccine.

Methods: IVIG lots of high WNV-neutralizing capacity w ere separated by fractionated protein A affinity chromatography into IgG subclasses. The r esulting IgG 2, 2 and 3 fr actions were tested for in vitr o neutr alization capacity and in viv o protection in a mostly WNV challenge mouse model.
Results: At identical antibody pr otein concentr ations, the IgG1 fraction contained significantly higher in vitro WNV neutralization capacity than the other subclasses, or ev en the parent IVIG preparation. Even when diluted to identical WNV antibody neutralization titers for evaluation of in vivo protection, the IgG1 fraction was still significantly more protective.
Conclusions: After human WNV infection, neutr alizing antibodies ar e pr edominantly of IgG1 subclasses. At identical neutralization titers, IgG1 is also pr otective, possibly based on more effective adaptor functions with other compatments of the immune system. It might be desir able for a WNV vaccine to (also) effectively induce WNV neutralizing antibodies of the IgG1 subclasses.

IC31® Directly Stimulates Innate Immune Cells

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The fully synthetic adjuvant IC31® consists of an immunostimulatory oligodeoxynucleotide ODN1a and the peptide KLK. IC31® is characterized by a broad mechanism of action, as well as an excellent safety profile[1]. It is well established that ODN1a is acting via the TLR9/MyD88-dependent pathway of the innate immune system[2] and thus contributes to the activation of the more specific adaptive immune responses.
In these studies we explored the ability of IC31® to act directly on innate immune cells, namely NK cells. As comparator CpG, the best characterized TLR9 agonist and known stimulator of NK cells[3], was used. We observed an accumulation of CCR7^{+} cells being also positive for the NK-cell marker NK1.1 in the draining lymph nodes shortly after injection. This suggests that IC31® induces NK1.1 cell homing to the lymph nodes and thus might support NK-dendritic cell interaction in the lymph nodes, being an important feature for reciprocal activation and type 1 immune response induction[4]. Moreover, treatment of mice with IC31® induced an up-regulation of the early activation marker CD69 on NK1.1^{+} spleen and lymph node cells. Though significant, the upregulation of CD69 upon IC31® treatment was lower compared to CpG treatment, especially in the spleen cells on day 4, and on day 3 in the lymph node cells. Most interestingly, a remarkable induction of a CD69 ^{high}NK1.1^{low} cell population was seen, highlighting the possibility of direct stimulation of other lymphoid cells, e.g. B cells or T cells. This finding was further extended by in vitro stimulation of isolated spleen cells with IC31® that showed an up-regulated CD69 expression on CD19^{+} B cells after 6 hours of stimulation.
The direct activation of some innate immune cell types, such as NK cells, in addition to the well-documented stimulation of type 1 T cell responses, makes IC31® an even more attractive adjuvant for the development of therapeutic vaccines against cancer and chronic infections as well as for prophylactic immunization against intracellular pathogens, such as M. tuberculosis[5].

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Haleema SADIA

Tuberculosis : epidemiology,natural history and vaccine research

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Background: Tuberculosis is the second most common infectious disease worldwide. Tuberculosis is affecting one thir d of the world‘s population and ar ound 20 million people ar e active cases. This article will reviews the epidemiology, natural history,and modern vaccine research for tuberculosis.
Methods: We ex ecuted an extensiv e sear ch for ar ticles on the Tuberculosis epidemiology, natural history and vaccine research and reviewed their findings.
Results: TB is the leading cause of death among HIV positive people with a fatality of about 80%.Tuberculosis is caused by infection with Mycobacterium tuberculosis. Mode of spr ead is by aerosol droplets. It may cause systemic disease affecting many organs including spleen, gastrointestinal tract and brain,bones, joints and liver. If worldwide control of tuberculosis does not impr ove, millions of new cases and millions of deaths ar e expected in near futur e. The global bur den of tuberculosis is mainly because of poor contr ol in Southeast Asia, sub-Saharan Africa, and eastern E urope, and because of association of M tuberculosis and HIV co infection in some countries. There are many Vaccine Strategies for Tuberculosis:Live attenuated v accines like (B CG) which mimic natur al infection,and therefore provide the br oadest r ange of per tinent stimuli to the immune system. Ho wever, (BCG) efficacy in pr otecting against tuber culosis r emains contr oversial. A range of studies indicate an overall reduction of risk of TB by 50%. Efforts are going on to modify B CG or M. tuber culosis by recombinant DNA technology to make a new liv e attenuated vaccine. We can express a variety of antigens in B CG. If we become able to identify the critical immune tar gets of M. tuberculosis expressed in BCG, this will provide a better live attenuated vaccine. Second possibility to pr oduce a liv e attenuated M. tuberculosis vaccine would be to knock out the genes in M. tuber culosis which ar e required for virulence or for prolonged survival within macrophages. Effective peptide vaccine for tuber culosis can also be dev elop but for achieving this goal the specifi c antigens must be identifi ed first. Active research is going on to pr oduce nucleic acid, or DN A vaccine. DNA vaccine involves the use of either antigen encoding naked DNA in buffer solution, which has been proven to transect cells in viv o, or a vir al v ector coding for specifi c disease antigens. The possibility of using DN A vaccines is a promising alternative to BCG.
*Recommendations:*There is great need for active research in exploring various vaccines Strategies for Tuberculosis.

Polio Virus Vaccines: update on different types and modern research

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Background: Poliomyelitis, often called polio is an acute viral infectious disease caused by poliovirus. Polio was one of the most lethal childhood diseases of the 20th century. Polio epidemics have killed thousands of people; the disease has caused paralysis and death for much of human history.
Methods: We discussed different types of current polio vaccines and modern research in this field.
Results: Two polio vaccines are commonly used throughout the world for poliomyelitis. The first one was developed by Jonas Salk in 1952; it consists of an injected dose of inactivated poliovirus. The second was an oral vaccine developed by Albert Sabin. These two vaccines have eradicated polio from most countries of the world and reduced the worldwide incidence of polio from 350,000 cases in 1988 1300 cases in 2007. The Salk vaccine, or inactivated poliovirus vaccine (IPV), is based on three virulent reference strains, Mahoney (type 1 poliovirus), MEF-1 (type 2 poliovirus), and Saukett (type 3 poliovirus).These strains were grown in a type of monkey kidney tissue culture (Vero cell line), which are formalin inactivated. The injected Salk vaccine confers IgG-mediated immunity in the bloodstream, which prevents infection from progressing to viremia and protects the neurons. The Salk vaccine is 60 - 70% effective against PV1 (poliovirus type 1), over 90% effective against both PV2 and PV3.The duration of immunity induced by IPV is not known yet. Oral polio vaccine (OPV) is a live-attenuated vaccine, produced by the passage of the polio virus through non-human cells at a sub-physiological temperature, which causes spontaneous mutations in the viral genome. The attenuated poliovirus in the Sabin vaccine replicates in the gut, the primary site of infection and replication. OPV is superior in administration and there is no need for sterile syringes. OPV provide longer lasting immunity than the Salk vaccine. The virus used in the vaccine is shed in the stool and is able to spread to others within a community, resulting in protection against poliomyelitis even in individuals who have not been directly vaccinated against polio. The virus also has strict requirements for transport and storage, which are a problem in some hot or remote areas. A major concern about the oral polio vaccine (OPV) is its ability to revert to a form that can cause paralysis. Clinical disease, including paralysis, caused by this vaccine-derived poliovirus (VDPV) is indistinguishable from that caused by wild polioviruses. Outbreaks of vaccine-associated paralytic poliomyelitis (VAPP) have been reported in many countries of the world.
Conclusions: There is still need for active research in exploring various vaccines Strategies for Polio and to combat side effects associated with polio vaccination.

Margarita SMIDT | Zehra VISRAM

MARGARITA SMIDT

Moraxella catarrhalis and nontypeable Haemophilus influenzae iron-regulated proteins as potential vaccine candidates

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Otitis media (inflammation of the middle ear) is a very common disease of early childhood. Streptococcus pneumoniae, nontypeable Haemophilus influenzae (NTHi) and Moraxella catarrhalis are the three major pathogens causing otitis media. The burden of disease, and the increasing prevalence of antibiotic resistance in otitis media pathogens, warrant the development of vaccines. These studies focused on the identification of protein candidate vaccine antigens from NTHi and M. catarrhalis. The complete DNA genomes of NTHi and M. catarrhalis were fragmented, open reading frames were enriched by cloning in a frame-selection vector, and these peptide-coding DNA fragments were subcloned in a display vector for surface display in E. coli, using FhuA and LamB as scaffolds. The bacterial surface-display libraries were then screened using biotinylated human IgGs derived from patients as well as healthy individuals. Library clones selected by the human IgGs were validated by DNA sequencing, Western blotting, peptide ELISA and bioinformatic analysis. Analysis of the NTHi and M. catarrhalis membrane proteomes was performed in parallel, to guide selection of lead vaccine candidates. Of more than 150 antigens identified for both NTHi and M. catarrhalis, a number of proteins involved in iron acquisition have been identified. The level of expression of some M. catarrhalis proteins was influenced by the iron concentration in the medium. The role of iron-regulated candidate vaccine antigens in the bacterial lifecycle and pathogenesis is being characterized by the generation of gene deletion mutants. To explore the surface exposure of the candidate vaccine antigens, as well as the functionality of antibodies against the antigens, immune sera raised against recombinant proteins will be tested in flow cytometry as well as serum bactericidal assays.

ZEHRA VISRAM

Characterization of lead Streptococcus agalactiae antigens

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In spite of the introduction of preventive measures by screening of pregnant women and intrapartum antibiotic treatment, Streptococcus agalactiae Group B Streptococci (GBS) remains to be the leading cause of pneumonia, sepsis and meningitis in newborns.
Using Intercell's Antigen Identification Programme® six GBS antigens were identified that showed protection in a mouse sepsis model against multiple strains and serotypes either by active or passive immunization. In order to better understand the role of these antigens in GBS pathogenesis and aid the development of monoclonal antibody-based immune prophylaxis, we characterized these six proteins by generating gene deletion mutant strains. Four of the six proteins have been characterized before and implicated in adhesion and/or counteracting host responses, while the role of the two other candidates are enigmatic so far. Although no phenotype was observed for in vitro grown bacteria, all the mutants displayed a reduced virulence in mice when compared to the wild type strain.
By in vitro expression analysis we determined the conditions that allow us to examine the surface accessibility and functional antibody inducing capacity of the six lead candidate antigens. This was essential for the selection of murine mAbs that were tested to be efficacious in lethal mouse sepsis models and serve the basis for development of fully human mAbs.

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