VACCINES - THE KEY PARADIGM FOR THE 21st CENTURY'S HEALTH CARE STRATEGY

5th Semmering Vaccine Symposium

April 28–30, 2011
Hotel Schloss Weikersdorf, Baden/Vienna
www.viennavaccines.com

Organized by:
Alexander von Gabain and Thomas Decker

Scientific Advisory Board:
Franz-Xaver Heinz, Hans Wigzell, Rafi Ahmed, Thomas Decker and Noel Barrett.

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The Semmering Symposium 2011 is held under the auspice of the Royal Swedish Academy of Engineering Sciences, IVA, and co-sponsored by The Elsevier journal *Vaccine*, Intercell AG, CureVac GmbH and Bank of America Merrill Lynch

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About Vienna Vaccines

Vienna Vaccines is an independent non-profit organization devoted to building worldwide vaccine networks.
Through the Semmering Symposium, held every second year, the organization has succeeded in establishing an interactive forum for leaders within the vaccine arena.
Vienna Vaccines is entirely funded by sponsorship and the registration fees for the symposia.

Welcome

Alexander VON GABAIN

Vienna Vaccines,
Chairman

Vienna Vaccines is delighted to welcome all participants and contributors to the 5th Semmering Vaccine Symposium in the wonderful historical health spa resort of the City of Baden in the outskirts of Vienna. The special character of the Semmering Vaccine Symposia arises from its mission to network leaders in basic research, vaccine industries, financial institutions and public or private institutions engaged in the vaccine area. The public outreach of this symposium series is increased by discussion of social, political and economical implications of vaccine development, alongside aspects of research and development. The symposia invite specialized and general journalists and interested laymen to participate in this discourse. The Semmering Vaccine Symposia thus weighs the need for vaccines as pillars of present day and future public health against their social and political acceptance and their economic feasibility.

The special format of this meeting ensures that results and interpretations presented by invited experts are challenged and discussed by a panel of similarly qualified colleagues. With this procedure we hope to stimulate an intensive debate that will include all meeting participants and thereby to intensify our effort to provide open questions with a maximal input from all vaccine-related areas.

My deep gratitude goes to all the financial sponsors and supporters, particularly in a time when resources are extremely restricted. I also would like to thank the SAB members, especially my long-term University colleague and friend, Prof. Thomas Decker. I am indebted to the Symposium management, Anna Bolin and Barbara Strutz-Grell, for their extremely competent and professional organisation of the current Symposium and their devoted team, Johannes Fuchs, Vera Schwartz, Martina Thyringer, Lina von Obernitz and Nina Waibel.

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FRIDAY, APRIL 29

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In memoriam Jürg Tschopp

Jürg TSCHOPP †
University of Lausanne,
Lausanne, Switzerland

"Our death is not an end if we can live on in our children and the younger generation. For they are us, our bodies are only wilted leaves on the tree of life."

~Albert Einstein

The organizers deeply regret the loss of Jurg Tschopp who sadly passed away on March 22, 2011. He will be dearly missed in the scientific community, but the overwhelming impact of his work will remain.

Jürg Tschopp received his PhD in biophysics at the University of Basel in 1979. He then joined the group of Müller-Eberhard at the Scripps Clinic in La Jolla.
In 1982, he was appointed assistant professor at the Department of Biochemistry of the University of Lausanne, where he was promoted to the rank of full professor in 1989.
Since 2003 he was deputy-director of the Department of Biochemistry. His recent research focused on signaling pathways that control apoptosis and innate immunity.

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OPENING SESSION

key note lecture

Martin SCHUURMANS

Chairman Governing Board of
the EIT – European Institute
of Innovation and Technology

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EIT: Create ecosystems that nurture new business creation for Europe

THE SPEAKER

Martin SCHUURMANS

Chairman Governing Board of the EIT – European Institute of Innovation and Technology

Dr. Schuurmans (1946, PhD TU/Eindhoven in 1971) spent the first 20 years of his professional life as a scientist. He joined Philips in 1968 to later become the head of experimental and theoretical physics in the Philips Research Laboratories, Eindhoven, Netherlands. He was professor of Solid State Physics at TU/Delft between 1985-1991.

In 1991 he went into Research and Innovation management. 1991-1994 he headed the solid state research at Philips Laboratories in Briarcliff, NY, USA. 1995-2000 he was Chairman of the Philips Research Laboratory in Eindhoven and Vice-Chairman of Philips Research world-wide. He has helped prepare the High Tech Campus of Eindhoven promoting open innovation and he has established the Philips Research Laboratory in Shanghai, China. From 2000-2002 he was CEO of the global Philips Industrial Technology Centre.

From 2002 until retirement from Philips in 2005 he was a member of the board of Philips Health Care (Boston, USA) responsible for Innovation and Industry and has established the Philips-Neusoft JV for Medical Equipment in Shenyang, China.

In 2005 he has founded the Sino-Dutch Biomedical School of Information Engineering (BMIE) in Shenyang, China; 2006/7 he lived in China and was BMIE's dean. As of 2008 he is chairman of EIT.

ABSTRACT

World-wide the race is on to create eco-systems that nurture the next superstar company (nytimes.com/dealbook). In such a place public and private enterprise heavily overlap. Europe has chosen to develop EIT, the European Institute of Innovation and Technology, for that purpose. EIT's knowledge innovation communities consist of networks of eco-systems (co-location centers) where excellent education, research and business activities are in close proximity. This should foster innovation in terms of new products and services for existing companies, new business creation and new company creation and lead to entrepreneurially developed people. EIT added value and challenges will be described.

SESSION I

badly needed novel vaccines

Chair:

Alexander VON GABAIN

MFPL University of Vienna,
Chair SAB Intercell,
Vienna, Austria

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Flaviviruses

THE SPEAKER

Franz Xaver HEINZ

University of Vienna,
Institute of Virology,
Vienna, Austria

Franz X. Heinz was born in 1949 and did his PhD in Virology at the University of Vienna. Early in his scientific career, he designed new technologies for the development of a highly purified vaccine against tick-borne encephalitis virus that is now in widespread use in Europe. From 1987 to 1993 Franz X. Heinz was a member of the WHO steering committee for the development of dengue and Japanese encephalitis vaccines and from 1989 to 1996 he was a Guest Professor of Virology at the University of Graz. In 1999 he became Full Professor of Virology at the Medical University of Vienna and since 2004 he is the director of the Department of Virology, Medical University of Vienna. Currently Franz X. Heinz is a member of the National Academy of Germany and a core member of the European Academy of Microbiology, as well as a member of the scientific boards of the Robert-Koch institute in Berlin, the Bernhard Nocht Institute for Tropical Medicine in Hamburg, and the Vienna-based biopharmaceutical company Intercell. His major research achievements and interests are in the area of flaviviruses, including vaccine development, molecular antigenic structure, molecular mechanisms of virus entry and viral epidemiology.

ABSTRACT

Flaviviruses have a significant impact as human disease agents in different parts of the world and the potential of emerging in previously non-endemic regions. The most important human pathogenic flaviviruses are yellow fever virus, dengue virus (serotypes 1 to 4), Japanese encephalitis virus, West Nile virus, and tick-borne encephalitis virus. Effective human vaccines are in use for the prophylaxis of Yellow fever (live attenuated), Japanese encephalitis (live attenuated and inactivated whole virus), and tick-borne encephalitis (inactivated whole virus). Although dengue is the most important flavivirus with respect to global disease incidence, the use of vaccines has so far been hampered by the potential risk of immune enhancement, proposed to be responsible for a higher frequency of severe forms of disease (dengue hemorrhagic fever and dengue shock syndrome) in secondary infections with different dengue virus serotypes and in children born to seropositive mothers. Currently, several kinds of dengue vaccines have reached an advanced stage of development, including live attenuated, whole inactivated virus and subunit vaccines. For avoiding the risk of immune-enhancement, all of these approaches aim at the simultaneous induction of a solid protective immunity against each of the four dengue virus serotypes.

Structurally, flaviviruses are among the best-studied enveloped viruses. The structure of the most important immunogen, the envelope protein E, has been determined to atomic resolution by X-ray crystallography, and the architecture of virus particles has been resolved by cryo-electron microscopy. Through the combination of structural and immunological investigations, we have gained a detailed understanding of the effects of antibody-binding to the virus and its different antigenic subsets. This includes the definition of virus neutralization and antibody-mediated enhancement (ADE) of infectivity at a molecular level. The latter phenomenon is of special relevance for dengue vaccines, since it has been proposed to play an important role in the immunopathology of severe forms of dengue virus infections. The current picture of the molecular antigenic structure of flaviviruses will be presented in the context of its biological significance for vaccine development.

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C. difficile

THE SPEAKER

Ginamarie FOGLIA

Sanofi Pasteur, Inc.
Swiftwater, USA

Ginamarie Foglia, DO, MPH, FACP is a Director of Clinical Development at Sanofi Pasteur Inc., and a board-certified internist and infectious disease specialist, medical epidemiologist, and associate professor. Dr. Foglia received her doctoral degree from the University of Medicine and Dentistry of New Jersey and her Masters of Public Health from Yale University, and completed an Infectious Disease/Public Health Fellowship at the Centers for Disease Control and Prevention in Georgia.
Prior to joining Sanofi Pasteur, Dr. Foglia was the Medical Director of Infectious Disease Consulting and Infection Control at Pocono Medical Center in Pennsylvania. She also served with the United States Army Medical Corps from 2000–2005, attaining the rank of Lieutenant Colonel. During her military service, Dr. Foglia initially worked as Principal Investigator at the Walter Reed Army Institute of Research and Associate Professor at the Uniformed Services University of Health Sciences in Maryland. From 2002–2005 she was based in Kenya, where she led the U.S. Military HIV/AIDS program, jointly sponsored by the National Institutes of Health and the Department of Defense (DoD), conducting vaccine research, international surveillance, and infrastructure development. During this period, she was also appointed as the DoD representative for the Presidential Emergency Plan for AIDS relief in Kenya, and served as advisor to the Kenyan Ministry of Health and the US Embassy. Dr. Foglia has published several manuscripts and has presented at many international conferences.

ABSTRACT

Clostridium difficile has become the most frequent hospital-acquired infection in the North America and the EU. However, active surveillance is currently patchy and the disease burden remains under-reported and under-estimated, although *C.difficile associated diarrhea* (CDI) is clearly present worldwide and disease awareness is increasing. In the US, EU, and CAN, CDI is no longer just a nosocomial disease and also has been reported with increasing frequency in the community. The emergence and spread of hypervirulent strains (such as BI/NAP1/027) has increased morbidity and mortality associated with CDI. Current treatment options are sub-optimal. Of the patients treated for CDI, 20% relapse and 65% of those experiencing a second relapse go on to become chronic cases. However, there is an association between increased serum levels of IgG antibody against toxin A and asymptomatic carriage of *C. difficile*. Phase I data for sanofi pasteur's *C. difficile* vaccine candidate - which is being developed for the prevention of primary disease - showed an immune response above the threshold associated with protection. The target population are adults at risk of CDI, such as adults with planned hospitalization, long-term care/nursing home residents, adults with co-morbidities requiring frequent and/or prolonged antibiotic use.

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TB Program

THE SPEAKER

Peter Lawætt ANDERSEN

Statens Serum Institut,
Copenhagen, Denmark

Prof. Peter Lawætz Andersen is Vice President of Vaccine Research and Development at Statens Serum Institut (SSI). Prior to this he was director of Infectious Disease Immunology (1997-2002) and the Tuberculosis Research Unit (1991-1997) both at SSI. Prof. Andersen has since 2006 been Adjunct Professor at Copenhagen University.
In his current position at the SSI, he is responsible for the overall coordination of vaccine research and development, covering activities from early research and to clinical development.
Prof. Andersen's research has been focused on the identification and characterisation of antigens, immune mechanisms and vaccine delivery systems that mediate protection against various pathogens and his main scientific interest has been immunity to intracellular pathogens such as Mycobacterium tuberculosis and Clamydia trachomatis. Prof. Andersen has pioneered work both on novel diagnostic assays (the IGRA assays), novel TB vaccines (H1/H4/H56) and the CAF series of liposomal adjuvants.
Prof. Andersen is the coordinator of several multidisciplinary research consortia including the international Center for Nano-Vaccines and the Gates Grand Challenge 12 Consortium. He has served on a number of committees to advise and co-ordinate strategies for vaccine and diagnostic development and has organized and chaired numerous international meetings. Prof. Andersen has more than 250 publications, within the field of infection, immunity and vaccine research in peer-reviewed journals and is the inventor of more than 20 novel patents within the vaccine field.

ABSTRACT

The leading novel TB vaccines in clinical trials are all designed as prophylactic vaccines for pre-infection administration and are either based on purified antigen in adjuvant or delivered in viral vectors systems such as Adenovirus or MVA. One promising approach has been to combine selected molecules into polyprotein antigens with improved immunogenicity and efficacy. Two antigens from the ESX family of important T cell antigens (ESAT6 and TB10.4) have been fused to the Ag85B antigen and form the basis for the H1 and H4 molecule. These molecules administered in the adjuvant IC31 or CAF01 are now in clinical trials and the first data on safety and immunogenicity are very promising with very robust and long lived T cell responses. Subunit vaccines can be used to boost BCG immunity either administered together (Tandem administration), shortly after BCG (early boost) or in adolescence when BCG immunity starts to wane (Late boost). A late BCG boost would frequently be administrated postexposure to latently infected individuals. To address this complication we have developed a multistage vaccine strategy designed to prevent the reactivation of latent TB by either pre- or post-exposure administration. We have combined the early secreted antigens Ag85B and ESAT6 with the Rv2660c latency-associated antigen. Rv2660c is stably expressed in late stages of infection in the mouse model of TB infection, a stage that was characterized by markedly reduced overall transcription levels of most other genes tested. H56 is the first vaccine with activity both when administered before (preventive) and after Tuberculosis infection (post-infection). H56/IC31 has just entered clinical trials in South Africa.

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Challenges and opportunities in HIV vaccine development

THE SPEAKER

Wayne C. KOFF

International AIDS Vaccine Initiative, New York, USA

Dr. Wayne Koff serves as Chief Scientific Officer and Senior Vice President of Research and Development (R&D) at the International AIDS Vaccine Initiative, where he oversees IAVI's R&D programs focused on the development of a safe and effective AIDS vaccine. These programs include the Neutralizing Antibody, Control of HIV/Live Attenuated, and Vector Discovery consortia focused on HIV vaccine discovery, a global network of laboratories focused on AIDS vaccine discovery and development, a product development infrastructure that has successfully advanced multiple DNA and viral vector based HIV vaccine candidates to clinical trials, and a network of partnerships in the developing world which collectively have undertaken Phase I/II safety and immunogenicity trials, and clinical research studies to expedite AIDS vaccine development. Prior to joining IAVI, Dr. Koff led the NIH AIDS vaccine program (1987-1992), establishing preclinical and clinical trials infrastructure, and served as Vice President, Vaccine Development at United Biomedical, Inc., (1992-1998) where he led the team which conducted the first clinical trials of AIDS vaccines in the developing world.

ABSTRACT

During the past few years, there has been incremental progress towards the development of a safe and effective HIV vaccine. These advances have included: the first demonstration of protection against HIV in human efficacy trials, identification of new and potentially more vulnerable targets on HIV for vaccine designs to elicit broadly neutralizing antibodies, and demonstration of control of infection in rhesus monkeys immunized with novel viral vector based immunogens. Our laboratories at IAVI, together with our collaborators, have focused on the challenges associated with designing effective vaccine candidates to elicit broadly neutralizing antibodies and cellular immune responses against HIV. Our immunogen design efforts to elicit broadly neutralizing antibodies have included: 1) screening of HIV+ subjects to identify the subset with broad and potent HIV-specific neutralizing antibodies; 2) identification of monoclonal antibodies (mAbs) from such subjects and determining, at the molecular level, the target binding sites on HIV of such mAbs; and 3) designing and screening immunogens to mimic the binding sites of the mAbs with the goal of eliciting broadly neutralizing antibodies. These efforts, have led to the identification of several HIV+ "elite neutralizers", new broad and potent monoclonal antibodies against HIV, and the screening of the first generation of candidate immunogens. Our efforts to design immunogens capable of controlling HIV infection have focused on the development of replicating viral vector based immunogens, due in large part to the failure of non-replicating vectors to provide any benefit with respect to control of HIV infection e.g. suppression of viral load, in human efficacy trials. Our aim is to mimic the efficacy conferred by live-attenuated SIV with vectors safe for human use. The selection and prioritization of vectors is based on our current hypotheses for why live-attenuated SIV outperforms other vaccine strategies regarding prevention and control of SIV. These hypotheses include the persistent replication of the vector, targeting the gut-associated lymphoid tissues where SIV and HIV establish a beach-head early post-infection, and finally the potential need to target the vector directly to CD4+ CCR5+ cells. Human efficacy trials of novel vaccine candidates, the advancement of replicating viral vector based candidates to clinical trials, and continued progress towards identification of immunogens that elicit broadly neutralizing antibodies, will likely be included in future.

THE CHALLENGER

Michael PFLEIDERER
Paul Ehrlich Institut,
Langen, Germany

Michael Pfleiderer is a biologist holding a Ph.D. in molecular virology.
Since 1998 he is at the Paul-Ehrlich-Institut, German Federal Institute for Vaccines and Biomedicines.
On the European level Dr. Pfleiderer is a member of the Biologics Working Party (BWP) of the Committee for Medicinal Products for Human Use (CHMP) at the European Medicines Agency (EMA) in London.
For their Vaccine Working Party (VWP), Dr. Pfleiderer was re-elected as Chairman by CHMP.
For EMA Dr. Pfleiderer was chairing the pandemic Task Force (ETF) coordinating regulatory and scientific issues related to the recent influenza pandemic.

STATEMENT

The majority of human infectious diseases can currently not be prevented by vaccination nor are there sufficient therapeutic options for treatment of infections. In many cases these deficiencies will have no major consequences since a considerable part of infectious agents causes only low burden of disease at least in a healthy population. In numerous other cases, however, pathogenicity and wide spread endemicity pose enormous health risks to an exposed population. The most prominent reason why no acceptable vaccines are yet available against such pathogens is that our scientific understanding is insufficient in order to translate from massive health risks to safe and effective vaccines. Nevertheless, many promising projects are currently part of the research portfolios of industry as well as academia. Out of numerous other projects four particularly interesting cases will be presented and discussed in this section. Each of them addresses a different gap of knowledge illustrating why a vaccines can't be delivered on command. Dengue vaccines are good examples on how concerns on disease enhancement through vaccination of individuals with pre-existing immunity currently hampers straightforward vaccine development. It also lines out how time consuming and cumbersome scientific steps taken to adequately respond to these concerns actually are.Nosocomial infections, e.g. caused by Clostridium difficile but also by many other microbial pathogens pose an extreme risk to hospitalized patients and demonstrate scientific challenges to be overcome before efficient vaccines and effective vaccination strategies can be developed for high risk groups in a high risk environment. Tuberculosis as one of the major burdens of disease of humanity requires particularly precise scientific knowledge about host pathogen interaction in order to target a vaccine specific immune response against vulnerable structures of the pathogen ensuring robust and long lasting protection. Finally, decades of HIV vaccine research currently confronts us with some of the limitations of vaccine research and development against a class of viral pathogens being highly variable and, in addition, able to integrate into the human genome, thus being inaccessible to any antiviral immune response. Collectively, these examples are representative for the complexity of vaccine development. They also illustrate that infectious diseases for which no or only insufficient vaccine options are available will require enormous scientific and financial input. It might be discussed how globally available research funds and industries' expertise in product development might better be converted into joint efforts in order to faster overcome major public health threats.

Challenge Panel

THE CHALLENGER

Andrew BAUM

Morgan Stanley & Co. International Limited, London, UK

Andrew joined Morgan Stanley in April 1997. Andrew has been the top ranked European Pharmaceutical Analyst in the Extel Poll for the last three years. He heads the pan-European pharmaceutical team. Andrew and his team consistently rank in the top three teams in external EU and Global investor polls (Institutional Investor, Greenwich and Reuters). He benefits from a deep strategic insight of the global healthcare value chain, as well as broad network of contacts throughout the industry. In 2004, Andrew was one of the earliest commentators to highlight to investors the deep structural deficiencies of the historic operating structure and the need to evolve towards a radically different model (Pharma 2.0).

Andrew is widely sought after to share his insights with the most senior levels of management within the healthcare industry. He regularly lectures for a number of prestigious organisations including The Institute of Comparative Law, The World Vaccine Congress as well as occasional presentations to some of the leading management consultancies.

Before joining the firm, Andrew was a UK pharmaceutical and biotechnology analyst at Salomon Brothers. From 1994 to 1996, he was a practicing physician at the Royal National Orthopaedic Radcliffe Hospital in Oxford (the medical centre of Oxford University) where he completed his residency.

Andrew is a member of the American Heart Association, American Society of Oncology and the DIA. He is also a Fellow of the Royal Society of Medicine.

Andrew holds an MA in Physiological Sciences and an MD from Oxford University.

STATEMENT

Its never looked so good. A financial perspective. The relative ROI (return on investment) of vaccine development for the Pharmaceutical industry has never looked so attractive. Declining periods of exclusivity for therapeutics, especially small molecules, combined with increasing payor sensitivity, has severely diminished the potential returns on therapeutics small molecule agents so prolific in the last two decades. A therapeutic vaccine's key economic merits vs. therapeutics are (i) the high barriers to western generic entry (ii) generally favourable pharmacoeconomic analysis in developed markets (iii) commercial opportunities in emerging markets.

The recent advances in vaccine technology, and a more constructive regulatory environment excite us. The approval of novel adjuvants and the emergence of technologies such as reverse genomics and therapeutic vaccines provide upside to street estimates for vaccines. On the reimbursement side, governments and NGO's are increasingly minded to fund novel vaccine development and access at acceptable prices premiums, recognising the high unmet medical need and strong societal impact that comes from a successful vaccine. The rising tide of enforcement and product liability suits against therapeutics, again favour the relative attractiveness of vaccines vs. therapeutics.

But there are risks. Patient preference is a fragile dynamic as demonstrated by the recent MMR scare and the anti- HPV backlash. Sponsors need extreme care in patient and physician education to achieve financial and business goals. On the regulatory angle, it is likely wrong to expect that the low historic clinical attrition rates for vaccine programs can be applied to vaccines against novel future targets. We expect future attrition rates to be higher than the historic average (we note HIV, Herpes Simplex, TD). Multinationals must expect pricing pressure from domestic vaccine manufactures in emerging markets. Finally, we see potential risks when pharmaceutical executives run vaccine businesses insufficiently sensitive to the complexities of vaccine development, manufacture and marketing.

Successful vaccine investment by multinational requires experienced vaccine executives who understand the exquisite long time lines of vaccine development and commercialisation. Investors continue to under-appreciate the value of novel developing world vaccines such as Dengue and TB. Multinationals needs to improve the understanding of their current and potential investors on the availability of alternate capital pools to fund access (NGO, Governments, low cost/ high volume).

SESSION II

what vaccinologists expect from immunologists

Chair:

Thomas DECKER

Max F. Perutz Laboratories,
Vienna, Austria

vienna vaccines
NETWORKING EXCELLENCE

Role of TH17 in the pneumococcal immune response

THE SPEAKER

Richard MALLEY

Harvard Medical School,
Children's Hospital,
Boston, USA

Rick Malley, M.D., began his education at the Ecole Active Bilingue in Paris, France, getting his French Baccalaureate in 1982. He received his B.A. from Yale University and his M.D. from Tufts University in 1990. He pursued pediatric training at Children's Hospital Boston, where he also trained in both pediatric infectious diseases and emergency medicine. In 1997, a chance meeting with Dr. Porter Anderson led to his interest in the development of a species-specific pneumococcal vaccine for use in developing countries. Under Dr. Anderson's mentorship, he shifted his research to the development of novel vaccines against pneumococcus, leading to numerous scientific publications describing various aspects of pneumococcal pathogenesis and prevention, such as acquired and innate immunity, correlates of protection, and mechanisms of protection from nasopharyngeal colonization. Dr. Malley runs a research laboratory at Children's Hospital Boston, with funding from NIH and PATH, focusing on innate and acquired immune responses to pneumococci. Dr. Malley is the Kenneth McIntosh Chair in Pediatric Infectious Diseases at Children's Hospital Boston and an Associate Professor of Pediatrics at Harvard Medical School. In collaboration with PATH and the ongoing participation of Dr. Anderson, Dr. Malley is leading an international effort (consisting of researchers from Children's, Instituto Butantan, Brazil and the University of Goteborg, Sweden) for the development and manufacture of a whole-cell killed pneumococcal vaccine for use in developing countries. Approval from US FDA is being sought to begin Phase I trials in 2011 in the US. He also sits on the Scientific Advisory Board of Genocea Biosciences and has a scientific collaboration with their group, to identify broadly-conserved CD4+ T cells pneumococcal antigens against colonization and invasive disease.

ABSTRACT

There is ample evidence that anticapsular antibodies confer serotype-specific immunity to pneumococci. From both murine and human studies, it is very clear that anticapsular antibodies provide protection against invasive disease. For mucosal colonization or disease, there is compelling evidence that higher levels of antibodies directed against the capsule will provide significant protection as well. Similarly, it has also been shown that antibodies directed against noncapsular antibodies may also confer protection against pneumococcal infections.

At the same time, there are some interesting clues that antibodies may not be the only component of acquired immunity to this mucosal organism. First of all, children show reduced risk of invasive disease well before these anticapsular antibodies appear, suggesting the involvement of other mechanisms. HIV-infected adults are at significantly higher risk of pneumococcal disease. Recently, we also showed that in elderly patients with chronic obstructive pulmonary disease (COPD), higher levels of anticapsular or noncapsular antibodies directed against pneumococcus do not appear to provide increased protection against acquisition of a new strain of pneumococcus.

So what could some other protective factors be? Our laboratory has reported that immunization of mice with whole pneumococci confers CD4+ TH17 cell-dependent, antibody- and serotype-independent protection against colonization. We showed that this immunity, rather than preventing initiation of carriage, accelerates clearance over several days (as is seen in children as they get older) and is accompanied by neutrophilic infiltration of the nasopharyngeal mucosa. Adoptive transfer of immune CD4+ T cells conferred immunity to naïve RAG1-/- mice. A critical role of interleukin (IL)-17A was suggested by experiments using mice lacking the IL-17A receptor and correlative studies. Recent findings relating these data to humans, including COPD patients, will be presented. This line of investigation has led to a novel antigen discovery approach, aiming at the identification of TH17 pneumococcal antigens to pave the way for the discovery and development of a pneumococcal vaccine, in collaboration with Genocea Biosciences and PATH. As will be described in this presentation, the goal is to develop a vaccine that can provide T-cell mediated protection against nasopharyngeal colonization and B-cell mediated protection against pneumonia and invasive disease.

vienna vaccines
NETWORKING EXCELLENCE

Regulation of adaptive immunity by NK cells

THE SPEAKER

Giorgio TRINCHIERI

National Cancer Institute
at Frederick,
Frederick, USA

Giorgio Trinchieri received his M.D. from the University of Torino, Italy, in 1973. He was a member of the Basel Institute for Immunology (Basel, Switzerland) and an investigator at the Swiss Institute for Experimental Cancer Research (Epalanges sur Lausanne, Switzerland). From 1979 to 1999 he was at Wistar Institute in Philadelphia and became Hilary Koprowski Professor and Chairman of the Immunology Program. He was then Director of the Schering Plough Laboratory for Immunological Research in Dardilly, France, and an NIH Fogarty Scholar at the Laboratory for Parasitic Diseases, NIAID, before becoming director of the Cancer and Inflammation Program (CIP) and chief of the Laboratory of Experimental Immunology at NCI in August 2006. As CIP director, he oversees the operations of two major intramural laboratories that constitute the major immunologic component of the NCI inflammation and cancer initiative that seeks to partner NCI's expertise in inflammation and immunology with its cutting-edge cancer etiology and carcinogenesis program. He has been interested for many years in the interplay between inflammation/innate resistance and adaptive immunity, and in the role of pro-inflammatory cytokines and interferons in the regulation of haematopoiesis, innate resistance and immunity. In 1989, his group at the Wistar Institute discovered Interleukin-12 and its role in tumour immunity, infections and autoimmunity. His main focus of research is now the role of inflammation, innate resistance, and immunity in carcinogenesis, cancer progression, and prevention or destruction of cancer.

ABSTRACT

The generation of Th1 response depends on the interaction between innate resistance mechanisms, antigen-presenting cells, and T cells with humoral factors such as Interleukin-12 (IL-12) and other cytokines playing a major role in bridging innate and adaptive immunity. Different types of antigen-presenting cells (APCs) and dendritic cells (DCs) responds to different stimuli for IL-12 production and IL-12 production may be differentially regulated by interferon-g in different APCs. Natural Killer (NK) cells represent an important source of interferon-g during an innate response licensing certain DCs for IL-12 production and thus controlling the characteristic of the ensuing adaptive immune responses. In particular, the CD8a+ subset of DCs in response to various stimuli is very efficient in releasing IL-12 in the absence of interferon-g, other type of DCs and myeloid cells are strictly dependent on interferon-g. Experimental infection with *Toxoplasma gondii* represents a good model to dissect the role of different APCs, NK cells, and interferon-g in the generation of a Th1 adaptive immune response. Whereas in vivo and in vitro parasite extracts are very effective in inducing an interferon-g independent IL-12 production from CD8a+ DCs, during infection several other types of APCs are involved and NK cells play an important role in allowing the generation of a protective Th1 response by the Inteferon-g/IL-12 axis.

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NETWORKING EXCELLENCE

TLR ligands, cytokines, and the T cell response

THE SPEAKER

Jay A. BERZOFSKY

National Cancer Institute,
Bethesda, USA

Dr. Jay Berzofsky was appointed Chief of the new Vaccine Branch, Center for Cancer Research, National Cancer Institute, in 2003, after being Chief of the Molecular Immunogenetics and Vaccine Research Section, Metabolism Branch, National Cancer Institute, NIH, since 1987. He graduated Summa cum Laude from Harvard (1967), and received a Ph.D. and M.D. from Albert Einstein College of Medicine. After interning at Massachusetts General Hospital, he joined NIH in 1974. Dr. Berzofsky's research has focused on antigen processing and presentation by MHC molecules, the structure of antigenic determinants, cytokine and regulatory cell control of T cell function and avidity, and translation to the design of vaccines for AIDS, malaria, cancer, and viruses causing cancer. He has over 440 scientific publications. Dr. Berzofsky has received a number of awards, including the U.S. Public Health Service Superior Service Award, the 31st Michael Heidelberger Award, the McLaughlin Visiting Professorship, the Australasian Society for Immunology Visiting Lectureship, the Tadeusz J. Wiktor Memorial Lectureship, and the Herschel Zackheim Lectureship Award. He is past President of the American Society for Clinical Investigation, a member of the Association of American Physicans, and a Fellow of the American Association for the Advancement of Science, and was elected Distinguished Alumnus of the Year for 2007 by the Albert Einstein College of Medicine. He was also elected Chair of the Medical Sciences Section of the American Association for the Advancement of Science (AAAS) for 2007-2008. In 2008, he received the NIH Director's Award and the NCI Merit Award.

ABSTRACT

We have examined cytokines and synergistic combinations of toll-like receptor agonists as defined molecular adjuvants to improve not only the quantity, but perhaps more importantly, the quality of the T cell immune response to vaccines. In particular, we find that IL-15 as an adjuvant can select for higher avidity CD8+ T cells that are more effective at clearing virus infections and tumors, and can also substitute for CD4+ T cell help to induce long-lived memory CD8+ T cell responses. Translating this finding to humans, we found that induction of a primary in vitro CD8+ T cell response was dependent on CD4+ T cell help, but such help could be replaced with IL-15 in vitro, whereas IL-2 was less effective. IL-15 could also restore CD8+ T cell responses in vitro in blood lymphocytes from HIV-infected patients to levels found in healthy controls. We have also found two double combinations of TLR ligands that can synergistically increase the magnitude of CD8+ T cell response as measured by tetramer staining, as well as increase the activation of dendritic cells. However, only a triple combination of TLR ligands was sufficient to induce strong protection against a vaccinia virus challenge of mice, and this protection depended not on a further increase in T cell numbers, but rather an increase in their functional avidity. We translated these murine studies into a macaque study of these adjuvant combinations in a mucosal vaccine against SIVmac251 intrarectal challenge, and showed that the vaccine combined with both types of adjuvants was more protective than with either one alone. These adjuvants induced not only a more effective polyfunctional T cell adaptive immune response, but also innate immune protection as well, synergistically upregulating the viral restriction factor APOBEC3G. We are combining these approaches with ones to remove the negative regulatory "brakes" on the response. Therefore, a "push-pull" approach using molecular adjuvants to improve T cell quantity and quality to push the response, combined with blockade of negative regulation to pull the response, may allow for the development of a more effective vaccine against chronic viral infections or cancer.

vienna vaccines
NETWORKING EXCELLENCE

Different DCs - different functions

THE SPEAKER

Georg STINGL

General Hospital Vienna,
Vienna, Austria

Georg Stingl, MD (Co-Course Director) is Professor and Chairman, Division of Immunology, Allergy & Infectious Diseases, Department of Dermatology, University of Vienna Medical School, Vienna, Austria.
Dr. Stingl attended the University of Vienna Medical School, Vienna, Austria, earning his MD in 1973. He completed his Internship and Residency at the Department of Dermatology I., University of Vienna Medical School, Austria between1973-1976. This was followed by a period (1974-1976) of Immuno(dermato)logical research at the Immunology Institute, University of Vienna, under the guidance of Prof. Dr. Walter Knapp, M.D., and then by a Visiting fellowship (1977-1978) at the Dermatology Branch, National Cancer Institute, Bethesda, MD, U.S.A. In 1978, he joined the staff at the Department of Dermatology, University of Innsbruck Medical School (Chairman: Prof. Dr. Klaus Wolff): Establishment of an immunological laboratory. In 1980 he became Associate Professor -"venia legendi" for Dermatology and Venerology as well as Specialist (Facharzt) in Dermatology and Venerology. From 1981-1992, Dr. Stingl was Director of the Immunology program at Department of Dermatology I., University of Vienna Medical School (Chairman: Prof. Dr. Klaus Wolff) becoming Professor of Dermatology, and Chief of the Division of Cutaneous Immunobiology, Department of Dermatology I., Univ. of Vienna Medical School, Vienna, Austria in 1985. In 1992 he became Chairman, Division of Immunology, Allergy & Infectious Diseases, Department of Dermatology, University of Vienna Medical School, Vienna, Austria.
Dr. Stingl is the author of numerous publications in the fields of clinical and microscopic dermatology and venerology, immunodermatology, dermatological microbiology, allergology, photobiology, cellular and molecular immunology, cell biology, molecular biology, electron microscopy and pharmacology. Over the years, he has appeared as Guest Professor at several medical universities and Lecturer at conferences and symposia, meetings and societies. He is a member of numerous international academic institutes, and is on the Board of several societies, advisory panels, scientific journals and committees including the Austrian Academy of Sciences. During his career, Dr. Stingl has received many distinguished awards.

ABSTRACT

Dendritic cells(DC) were discovered during the 1970ies. They were soon recognized as professional antigen-presenting cells (APC) as defined by a cell's capacity to induce antigen-specific responses in naïve, resting T cells. While it was originally assumed that DC invariably stimulate productive T cell reactions, it is now clear that both the quantity and the quality of the T cell response depend on the type and maturation status of the DC. The latter is critically linked to the display of surface-bound MHC antigens and costimulatory molecules as well as to the type and magnitude of cytokines secreted by the DC. As a consequence, immature DC promote down-regulation of T cell responses whereas fully mature DC activate robust T cell proliferation and cytotoxicity.
It is also clear now that the DC family is much more complex than previously thought. Apart from remarkable differences between DC of humans and mice, there exists also an enormous DC heterogeneity within a given species. This is best exemplified by DC residing in normal and diseased human skin. Under homeostatic conditions, the epidermis and dermis are populated by Langerhans cells and dermal dendritic cells, respectively. Recent evidence suggests that, against the original belief, Langerhans cells are primarily concerned with down-regulating duties. Upon perturbance of the skin and the receipt of danger signals, "inflammatory-type" DC appear on the stage. These include myeloid (e.g. slan-DC) and plasmacytoid, interferon-g-producing DC. They not only function as APC but, surprisingly enough, can also acquire cytotoxic potential and, thus, be involved in anti-infectious and anti-cancer host responses. In fact, they are found in sizeable numbers in certain inflammatory skin diseases such as psoriasis and around regressor tumors. There exist a number of immunomodulatory drugs which can either abrogate (e.g. anti-TNF-αantibodies) or activate (e.g. imiquimod) these cells. We have recently observed that glucocorticosteroids can endow Langerhans cells to induce and expand regulatory T cells. This findings sheds new light on the mechanism(s) by which these hormones suppress immune as well as inflammatory tissue responses.

vienna vaccines
NETWORKING EXCELLENCE

Challenge Panel

THE CHALLENGER

Michael PRIDE

Pfizer Inc.,
Pearl River, New York, USA

Michael W. Pride, Ph.D. is a Director of Vaccine Research and Early Development at Pfizer's Pearl River, NY campus. Dr. Pride is responsible for the development and validation of diagnostic and multiplex serology assays for the successful advancement of various vaccine programs.

Dr. Pride received his doctoral degree in Experimental Pathology / Immunology from SUNY at Buffalo (Roswell Park Cancer Institute) and postdoctoral training at the University of Texas M.D. Anderson Cancer Center in the departments of Immunology and Clinical Immunology / Biological Therapy in which he studied the cellular immune response in patients administered an experimental therapeutic melanoma vaccine. He continued his training as a Research Fellow in the laboratory of Dr. Margaret L. Kripke working on the origins and characteristics of ultraviolet-B radiation-induced suppressor T lymphocytes.

In 1997, Michael moved to Wyeth-Ayerst Research (now Pfizer) in the Department of Viral Vaccine Immunology. During the following 14 years Michael has led research efforts in the areas of antigen discovery, establishment of assays to monitor cell mediated immune responses and most currently the development and validation of diagnostic and multiplex serology assays.

STATEMENT

Vaccinologists are primarily concerned with three factors: safety, efficacy and duration of protection. Immunologists generally tend to focus on a particular cell (i.e. T cell or DC) or type of response (innate / adaptive) and investigate ways on how to improve the quantity and/or quality of a particular cell phenotype/response for the purpose of enhancing/manipulating the immune system or response to a vaccine candidate. While there are numerous vaccines and adjutants that work extremely well in animal models, there are currently no clinical trials that have definitively demonstrated that a vaccine and or adjuvant has elicited a CMI response correlating with clinical efficacy.

With this in mind it is important to consider the following:

- What group will the vaccine / adjuvant target (infants, adolescents, adults, elderly).
- What functional assays will need to be developed in order to identify correlates of protection?
- How would reasonable clinical trials, with appropriate and defined endpoints, be designed (esp. in the absence of a correlate of protection).
- If regulatory pathways are going to be manipulated, how could one control or predetermine that you are not going to down or up regulate the overall immune system in a harmful manner.

THE CHALLENGER

Rino RAPPUOLI

Novartis Vaccines,
Siena, Italy

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.
He is member of European Molecular Biology Organization and foreign associate of the American National Academy of Sciences. He has published more than 450 works in peer-reviewed journals.
He introduced several novel scientific concepts, the names of which became popular. Examples are the concept that bacterial toxins can be detoxified by manipulation of their genes (genetic detoxification, 1987), the concept that microbes are better studied in the context of the cells they interact with instead of artificial laboratory conditions (cellular microbiology, 1996), the use of genomes to develop new vaccines (reverse vaccinology, 2000), the observation that the genome of a species (pangenome, 2005) is larger than the genome of an organism of the same species.
Several molecules he worked with became part of licensed vaccines. He characterized a molecule, CRM197, that today is the most widely used carrier for vaccines against H. influenzae, N. meningitidis and pneumococcus vaccines, and is used multiple times to vaccinate most children of the globe. Then he developed a vaccine against pertussis by engineering B. pertussis to produce a non toxic pertussis toxin antigen. This was the first rationally designed molecule approved for human use. Later he developed the first conjugate vaccine against meningococcus C that eliminated the disease in the UK in 2000. He pioneered the use of genomic information for vaccine development (reverse vaccinology). The first genome-derived vaccine against meningococcus B is now in Phase III clinical trials, several others are in earlier stages of development. Finally, in 1997 he obtained the regulatory approval for MF59, the first vaccine adjuvant approved for human use after the approval of aluminium salts in the 1920s. MF59 is now being used in many other experimental vaccines, the most advanced of which is a vaccine against pandemic influenza.

STATEMENT

Historically vaccines have been developed empirically, following the principles of Pasteur, to isolate, inactivate and inject the microorganisms that cause disease. Immunology has not contributed to the development of existing vaccines and some people say that sometimes it may have been an obstacle to vaccine development.
On the other hand, Immunology has made tremendous progress during the last few years and we believe we are getting close to the time when it will contribute to vaccine development.
In our session we have a few examples on this topic. The first is pneumococcus. Conjugate vaccines are extremely effective and we know they work by induction of opsonophagocytic antibodies (OPA) against the capsular antigen that kill the bacteria in an in vitro assay. OPA is accepted by regulatory agencies to license vaccines. The limit of conjugate vaccines is that they cover 7 or 10 or 13 of the over 90 serotypes present and therefore non-vaccine serotypes replace the present circulating serotypes making the vaccines obsolete. The solution would be a vaccine based on proteins present in all pneumococcus strains. These proteins exist and induce protection in the mouse model. However, with the exception of pili, they do not induce OPA. Our speaker today tells us that they induce Th17 immunity. Unfortunately, we do not know whether and how Th17 immunity kills bacteria and we do not have an in vitro assay that correlates with protection such as OPA. How are we going to convince regulatory agencies that Th17 is equivalent to protection?
The example of pneumococcus is similar to the one of Toxoplasma. Here Th1 response and Il12 are involved in protective immunity; however, no regulatory agency would license a vaccine based on these correlates.
In summary, Dendritic cells, NKT cells, CD4+, CD8+ Tcells, Th1, Th2, Th17 immunity, interferon gamma and other cytokine production, are new things that we can measure, but none of them so far correlates with protection. How are these concepts going to help vaccine development?

THE CHALLENGER

Thomas DECKER

Max F. Perutz Laboratories,
Vienna, Austria

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 theRockefeller 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

STATEMENT

A common denominator of the individual contributions to the session `what vaccinologists expect from immunologists´ is the problem how to direct immune responses towards a maximum of protection against a particular pathogen or against immune-related diseases such as cancer. Provided we know precisely what type of immune response is most adapted to a challenge with antigen, one of the key issues is how to address the population of DC best suited to activate and stimulate appropriate Th subpopulations. Work by Dr. Trinchieri shows that immuneregulatory cells such as NK cells must be considered as manipulators of DC maturation and activity. The challenge to stimulate a well-adapted immune response to a vaccine target is emphasized by the fact that a single type of immunity (e.g. Th1, Th2, Th17) alone may not provide sufficient effector mechanisms and protection as suggested by Dr. Malley's studies with Pneumococcus. For a vaccinologist it may therefore be necessary to find ways to produce a mixed immune response during which different Th subpopulations produce the correct set of humoral and cellular effector mechanisms. In addition, work by Dr. Stingl and Dr. Berzofsky emphasizes that activation of regulatory T cells and other immunesuppressive mechanisms must be considered as well. In my judgement there are three major issues for discussion. First, how large is the influence of the antigenic epitopes in a vaccine not only as determinants of immunogenicity, but also as regulators of the immune response type. Second, what ideas have emerged from recent work to target the correct population of antigen-presenting cells. Third, in how far are ligands of pattern recognition receptors, or combinations of such ligands in reference to Dr. Berzofsky's work, the solution to determining not only the efficacy of one effector mechanism, but to generate the appropriate combination of effector mechanisms for maximal protection.

SESSION III

about allergies, autoimmunity, microbes and vaccines

Chair:

Eszter NAGY

Arsanis GmbH,
Vienna, Austria

vienna vaccines
NETWORKING EXCELLENCE

Innate immune regulation of gut microbiota and potential therapeutic opportunities to treat metabolic disease and chronic infections

THE SPEAKER

Andrew T. GEWIRTZ

Emory University,
School of Medicine,
Atlanta, USA

Andrew Gewirtz, Ph.D. is currently an Associate professor of Pathology, Microbiology, and Immunology at Emory University School of Medicine, in Atlanta GA, USA. Dr. Gewirtz earned a B.S. in Physics in 1988 and Ph.D. in Biochemistry in 1996. From 1997-present, he has studied host-microbial interactions in the intestine in the context of infectious disease and chronic inflammatory diseases.
His research has revealed that the protein flagellin, which bacteria use to construct flagella that provide motility, serves as a major interface between the host and microbial world. Bacterial flagellin is recognized by 2 distinct components of the innate immune system, name TLR5 and NLRC4.
The host uses these proteins to keep commensal and pathogenic microbial communities in check. Alterations of gut microbial communities can result in inflammatory and/or metabolic diseases.
Dr. Gewirtz's research has been published in leading journals such as Science and JCI. Dr. Gewirtz serves on numerous editorial boards and review panels for various funding agencies.

ABSTRACT

The human intestine contains approximately 10^{14} (1-2 kg) of bacteria, collectively referred to as the gut microbiota, which is comprised of about 5000 distinct species. While the majority of these bacteria are not a threat to their host, the gut microbiota nonetheless contains numerous bacteria that can be viewed as opportunistic pathogens and often sporadically includes bacteria viewed as traditional pathogens in that they are capable of causing disease in healthy hosts. The ability of the intestine to keep the microbiota in-check is essential for human survival. We have observed that bacterial flagellin, which allows bacteria to achieve locomotion, is a central target by which the intestinal immune system protects itself from both pathogens and commensal microbes of the gut microbiota. Consequently, deletion of the flagellin receptor, TLR5, a component of the innate immune system that recognizes the bacterial protein flagellin impairs the ability of the intestine to rapidly squelch pathogenic challenges resulting in prolonged inflammation. Moreover, mice lacking TLR5 were prone to developing spontaneous colitis. However, altering the microbiotas of TLR5 mice in a manner designed to reduce their colitis caused TLR5-deficient mice to develop hallmark features of metabolic syndrome including hyperlipidemia, hypertension, insulin resistance, and increased adiposity. These metabolic changes correlated with alterations in the composition of the gut microbiota and, importantly, transfer of the gut microbiota from TLR5-deficient mice to wild-type germ-free mice conferred many features of metabolic syndrome to the recipients. These results support the emerging view that the gut microbiota plays a role in multiple chronic inflammatory diseases including both IBD and metabolic disease and suggest that manipulation of the microbiota may be one approach to combat these disorders. Lastly, recent work in our lab indicates that exogenous administration of TLR ligands may be an effective means of eliminating select members of the microbiota and thus, may be used as a novel approach to treat chronic infections.

vienna vaccines
NETWORKING EXCELLENCE

A vaccine for the treatment of grass pollen allergy based on hypoallergenic hybrid molecules

THE SPEAKER

Birgit LINHART

General Hospital Vienna,
Vienna, Austria

Birgit Linhart graduated as a biologist at the University of Vienna, Austria, working at the Department of Genetics and Microbiology on stress-signalling in plant cells.
She thereafter moved to the Medical University of Vienna, Department of Pathophysiology, Division of Immunopathology, to work on hybrid allergens for diagnosis and treatment of allergies for her Ph.D.
Since 2004 Birgit Linhart worked as a postdoc, and obtained an assistant position at the Medical University of Vienna in 2008. Her major research interests comprise the diagnosis and treatment of Type I allergies focussing on the generation of therapeutic and prophylactic allergy vaccines, which are based on allergen derivatives.
Due to this work Birgit Linhart is the author/co-author of six patent applications. Furthermore she is concerned with the development of animal models for studying the mechanisms underlying IgE responses to allergens.

ABSTRACT

More than 10% of the world population suffer from grass pollen allergy. Current allergy vaccines contain crude allergen extracts prepared from natural allergen sources, whereby their poor quality hampers the therapeutic success. Due to the knowledge of the disease eliciting molecules and their availability as recombinant proteins, vaccines can be produced, which are based on recombinant allergens. However, grass pollen represents a complex allergen source containing multiple allergens, some of them exhibiting very low immunogenicity. Furthermore, the application of 'wildtype' allergens which display anaphylactic activity could cause unwanted IgE-mediated side-effects in the course of immunotherapy.
We therefore developed a strategy for the generation of a grass pollen vaccine, which is based on the rearrangement of fragments derived from the four major timothy grass pollen allergens Phl p 1, Phl p 2, Phl p 5, and Phl p 6 in the form of hypoallergenic hybrid molecules. Codon-optimized synthetic genes encoding combinations of fragments derived from the four allergens were designed according to epitope mapping studies and structural data and subsequently expressed in *Escherichia coli*. Seventeen recombinant hybrid molecules were purified by affinity chromatography and evaluated regarding expression, purity and fold, solubility, and reduced allergenic activity. Two hypoallergenic hybrid molecules consisting of reassembled elements of the four grass pollen allergens were identified which upon immunization in different animal models induced IgG antibodies blocking allergic patients' IgE recognition of the grass pollen allergens. These hypoallergenic hybrid molecules represent safe and efficient vaccines for immunotherapy of grass pollen allergy.

vienna vaccines
NETWORKING EXCELLENCE

The Hygiene Hypothesis; Consequences for vaccine development

THE SPEAKER

Bengt BJÖRKSTÉN

Karolinska Institute,
Stockholm, Sweden

Bengt Björkstén is emeritus professor of Allergy Prevention and Paediatrics at the Karolinska Institutet, Stockholm, Sweden. He was the first director of the interdisciplinary Centre for Allergy Research, a network comprising over 100 senior and postdoctoral researchers.

He has served on the Council or as Committee Chairman in numerous scientific associations, including the American and the European Academy of Allergy and Clinical Immunology and as the President of the Nordic Paediatric Federation 1992–2000. He is the founding Editor-in chief of Pediatric Allergy and Immunology.

Research was initially focussed on paediatric immunology and infectious diseases and over the past 25 years it has mainly been related to clinical and experimental allergy, including long-term prospective studies on prediction and prevention of allergy and the interaction between environmental and genetic factors in the development of immune regulation, notably the role of the intestinal microbiota.

He has received several honours in Australia, Canada, Estonia, Finland, Germany, Israel, South Africa, Sweden and USA. Over the past 25 years, he has been invited as major speaker to numerous international meetings, including all major International Paediatric, Immunology, Clinical Immunology and Allergy congresses. He is the author of over 280 original papers, 120 book chapters and reviews and over 500 congress abstracts and various other publications.

ABSTRACT

The so called Hygiene Hypothesis (HH) is based on epidemiological, clinical and animal studies which, taken together, suggest that broad exposure to a wealth of microorganisms early in life are associated with protection against immune mediated diseases, particularly against allergies, but also conceivably against type-1 diabetes and Inflammatory Bowel Disease. The term “Hygiene Hypothesis” is misleading, however, as less diverse microbial exposure has little relationship with infections, nor with “hygiene” in the usual meaning of the word.

The postnatal maturation of the immune regulation is largely driven by exposure to microbes. Germ free animals manifest excessive immune responses when immunised and they do not develop normal immune regulation or oral tolerance. The maturation process is not necessarily associated with infection, however, as a diverse exposure to microbes is mostly due to commensal rather than pathogenic microorganisms.

Prospective studies from Estonia, with a low, and Sweden with a high prevalence of allergy, as well as type-1 diabetes, indicate that the regulatory mechanisms are established more rapidly after birth in Estonia, with a more traditional life style than in Scandinavia. There is also a close correlation globally between the prevalence of allergy and type-1 diabetes. A unifying link between the increase in both Th1-dependent autoimmune disease and Th2-linked atopic allergy would be a disturbed immune regulation involving T regulatory cells, rather than merely a shift towards Th2 immunity, as was originally thought to underlie the HH.

No one would seriously question the enormous gains in Public Health by improved hygiene and nobody would argue against vaccinations and advocate severe childhood infections merely to reduce the incidence of hay fever. A better term than HH would therefore be “Microbial Deprivation Hypothesis”, as this would point towards the possibility to prevent or perhaps even to treat, several immunologically mediated diseases with cocktails of non-pathogenic microorganisms and antigen mixtures derived from them. Vaccinations against potentially lethal infections remain a corner stone of public health.

vienna vaccines
NETWORKING EXCELLENCE

A diabetes vaccine

THE SPEAKER

Photo: Victor Brott

Elisabeth LINDNER

Diamyd Medicals,
Stockholm, Sweden

Elisabeth Lindner, MSc and MBA graduated with a Master in Biotechnology from the Royal Institute of Technology in 1982 and graduated with an MBA in International Marketing 1996 from Uppsala University.
The professional experience includes Biotech, Biopharma and Pharmaceutical companies such as Fermenta, Pharmacia Fine Chemicals, KabiGen, Kabi Biopharmaceuticals, KabiPharmacia, Pharmacia, Metcon Medicine, Octapharma and Diamyd Medical.
Lindner has had senior management positions in an international environment since the early nineties with reporting staff in Sweden, Italy and US. The focus area from start was Drug Substance development Biopharma and has geared more and more over to Drug Product development, manufacturing, clinical development and general management. Lindner is currently the President and CEO of the Diamyd Medical group, a Biopharmaceutical company listed on the NasdaqOMX Small cap list, with subsidiaries in Sweden and US.
Lindner joined Diamyd in April 2008 and the company has since then successfully taken its antigen-based diabetes therapy Diamyd® into Phase III trials in nine European countries and in the US. The Diamyd® therapy was recently licensed to Ortho-McNeil-Janssen Pharmaceuticals, a Johnson & Johnson company.
Diamyd Medical is also pursuing a clinical program against severe neuropathic pain.

ABSTRACT

Type 1 diabetes is an autoimmune disease characterized by a gradual autoimmune breakdown of the beta cell function resulting in a complete loss of endogenous insulin production leading to a loss of blood sugar control. Patients with Type 1 diabetes are dependent on frequent administration of exogenous insulin for life. Although insulin is a prerequisite for survival, it does not cure the underlying autoimmune disease and patients with diabetes suffer both short-term and long-term complications such as ketoacidosis, hypoglycemia, cardiovascular disease, retinopathy, nephropathy and neuropathy.
Diamyd Medical is developing an antigen-based therapy, Diamyd®, for the treatment of autoimmune diabetes.The active substance is Glutamic Acid Decarboxylase (GAD), a major auto-antigen in Type 1 diabetes, adsorbed on aluminium hydroxide. The hypothesized mechanism of action is that the treatment intervenes and modulates the autoimmune process and thereby preserves the residual beta cell function. During 2005 to 2007 a 30-month long Phase II study of Diamyd® was carried out, encompassing 70 children and adolescents between 10 and 18 years of age with newly diagnosed Type 1 diabetes. Significant long-term efficacy in slowing the loss of beta cell function, i.e. the body's own capacity to control blood sugar through insulin production, was demonstrated in patients who received Diamyd® compared to the patients that received placebo. The treatment consisted of two subcutaneous injections, one prime injection and one boost injection 30 days later, in a vaccine like regimen. Diamyd® is now being evaluated in two Phase III trials in Europe and the US.
The disease process starts long before the actual clinical symptoms of diabetes occur. Subjects at risk have genetic markers and gradually develop biomarkers of autoimmune diabetes prior to presenting with clinical symptoms. With a genetic predispositionalone the risk is approximately 5% to present with the disease. Interestingly, if a homozygotictwin presents with Type 1 diabetes the risk is 50% that the other twin will present as well. This means that unknown environmental factors are also involved. Currently four biomarkers are known, of which antibodies against GAD is the most prevalent at diagnosis, and patients with two or more biomarkers are at approximately 50% risk to present with the disease within five years.
There is increased interest in treating Type 2 diabetes, at the time of diagnosis or at the pre-diabetic stage with the aim of preventing progression of the disease and its micro- and macro vascular complications. Similarly, intervention at the earliest stages in the development of Type 1 diabetes could potentially delay disease progression and its complications.

THE CHALLENGER

Hans WIGZELL

Karolinska Institute,
Stockholm, Sweden

Hans Wigzell was the President of the Karolinska Institute 1995-2003 and the Chief Scientific Advisor to the Swedish government 1999-2007 and Professor at the Karolinska Institute, Sweden. He holds a doctorate in medicine and a doctorate in science from the Karolinska Institute.
Hans Wigzell is emeritus at Karolinska Institute, Sweden, and is active at the Department of Microbiology, Tumor and Cell Biology. Currently, he is Chairman of the Board of the Karolinska Development AB, and a member of the supervisory boards of Raysearch AB, Biovitrum AB, Epixis S.A., Probi AB, and Neodynamics AB.

STATEMENT

The immune system is a prisoner within our bodies. Changes in life style, social behaviour, diet, poverty etc can have profound consequences with regard to the capacity of the immune system to function in positive or negative ways. There is a global epidemic in allergic diseases strikingly linked to economic development. Bengt Björksten will talk about the striking collection of data indicating that changes in lifestyle particularly involving early childhood is a most important player in the epidemic. In particular, changes in the microbial flora in young children seem to be a most important factor in this regard. Allergic diseases nowadays constitute a major health care factor. Old fashioned allergy vaccines have suffered from dangers in causing anaphylactic reactions as well as being relatively poorly defined. Birgit Linhart will describe techniques to produce new safe hypoallergenic vaccines using molecular biological techniques to create hybrid molecules from several grass pollen allergens. Parallel to the allergic epidemic there is also a global obesity epidemic. The innate immune system is using special receptors for pathogen recognition and deletion of such receptors can have profound consequences for the well being of the individual. Andrew Gewirtz has studied bacterial flagellin and its specific receptor of the innate immune system, TLR5. Deleting the TLR5 gene resulted in grave inflammation of the colon of the animals whereas attempts to altering the microbial flora to reduce inflammation caused the animals to develop obesity and metabolic syndrome. Transfer of such gut flora to normal mice introduced metabolic disease in the recipient mice, adding still more weight that gut bacteria very likely play a role in the global obesity epidemic. In parallel to allergies certain autoimmune diseases like typ1 I diabetes are also on the rise suggesting that similar immunoregulatory consequences are underlying these groups of diseases. Various autoantigens from the beta cells of the pancreas are known to constitute targets in type I diabetes. Elisabeth Lindner will present data using one such autoantigen, the protein GAD, as an autovaccine in human type 1 diabetics. The date from phase II studies indicate that it seems possible to change the aggressive autoimmunity to a tolerant kind of immune response as exemplified by changes both with regard to specific immune reactivity and clinical progression.

Challenge Panel

THE CHALLENGER

Philippe MOINGEON

Stallergenes S.A.,
Antony Cedex, France

Philippe MOINGEON received his PhD in immunology from Paris XI University, and an MBA from Open University Business School (UK). He was formerly resident in Paris Hospitals (1981-1986), Assistant Professor at Harvard Medical School (Boston, USA, 1991-1994), Director for the cancer vaccine program (1994-1998) and General Secretary for Research and Development (1999-2003), at Aventis Pasteur.
Since 2003, he is currently Vice President for Research and Development at Stallergènes SA, a French biopharmaceutical company specialized in the development of allergy vaccines.

STATEMENT

This session covers a broad ground, encompassing topics as diverse as the interface between microbes and the immune system, or means to induce tolerance against allergens and autoantigens.
Specifically, Pr Bengt Björksten will discuss our current view of the hygiene hypothesis (or rather the microbial deprivation hypothesis), with the idea that a limited exposure to microbes can be held responsible for the increased prevalence of autoimmune diseases and allergies currently observed in developed countries. Pr Andrew Gewirtz is studying the interaction between microbiota and the innate immune system in the gut, through the engagement of TLR5 and NLRC4 receptors with flagellin and other pathogen-associated molecules. Those two presentations support the idea that immunologically-mediated diseases could conceivably by treated with non pathogenic micro organisms or molecules derived thereof.
Dr Elisabeth Lindner is currently leading a program aiming at the development of a therapeutic vaccine against type I diabetes, targeting the Glutamic Acid Decarboxylase (GAD) autoantigen. In parallel, Dr Birgit Linhart is developing second generation allergy vaccines based upon recombinant allergens, most particularly using modified molecules lacking any binding capacity for IgEs (ie hypoallergens), but nonetheless preserving a capacity to elicit anti-inflammatory IgG and T cell responses.
All those approaches, in one way, remind us of the yin and the yan of the immune system, in that immune homeostasis consists in a finely tuned balance between effector and regulatory mechanisms. This balance is affected by conditions in the natural environment, with for example a lower microbial exposure leading to a decrease in the induction of regulatory T cells, thus resulting in an increase in both Th1 and Th2 mediated pathologies. Our improved knowledge of the mechanisms through which pathogens are shaping the immune system can not only shed light of the physiopathology of numerous inflammatory diseases. It can also pave the ground for the design and development of innovative therapeutic vaccines against common allergies or autoimmune diseases.

SESSION IV

novel adjuvants - breakthroughs and setbacks, where will we end?

Chair:

Sefik S. ALKAN

Alkan Consulting LLC,
Basel, Switzerland

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NETWORKING EXCELLENCE

Adjuvants and innate immunity

THE SPEAKER

Hermann WAGNER

Technical University Munich,
München, Germany

Studies of Human Medicine (MD) and Human Biology (Ph-D) led Hermann Wagner first to Tübingen/Hamburg (Germany) and and then to Melbourne (Australia), in 1973 he joined Prof. P. Klein in Mainz (Institute of Medical Microbiology). In 1983 he moved to Ulm as chairmen of the Institute of Med. Microbiology and Immunology. In 1989 he moved to the Technical University Munich (TUM) as Head of the Dept. of Med. Microbiology, Immunology and Hygiene. Both in Ulm and at the TUM he has initiated and coordinated as speaker "Collaborative Research Programs" (Sonderforschungsbereiche) of the German Research Foundation (DFG). Honorary functions include President of the German Society of Immunology, and Dean of the Faculty of Medicine (TUM). He received a Doctor Honorary Degree (Dr. h.c.) of the University Würzburg, the "Order of Merit" of Bavaria and of the Federal Republic of Germany.
He is a member of the Bavarian Academy of Sciences, and the German Academy of Sciences-Leopoldina.

ABSTRACT

A rational development of novel vaccination strategies requires in addition to Antigen (Ag) "triggers" of the innate immune response in the form of adjuvant. These stimuli should not only enhance but also direct adaptive immune response into the direction aimed at, i.e. promotion of either Th-1, Th-2, Th-17 or Treg immunity. Promotion of Th-1 responses, for example can be achieved by synthetic ligands of Toll-like receptors (TLR's), a well studied case being the TLR9 ligand CpG-DNA known to drive in Dendritic Cells (DC's) robust Interleukin 12 synthesis via canonical NFκB signaling. In the mouse cross-linking of CpG-ODN's to rec. Ag further enhances immunogenicity of Ag's, yet in human only plasmacytoid (p) DC's express TLR9. While there is circumstantial evidence that TLR2 signaling promotes Th-2 responses, the biology of C-type lection receptors (CLR's) driven signaling comes at surprise. Ligands for Dectin 1, -2 or Mincle engage the tyrosine kinase SYK for CARD 9 activation – and such activated DC's promote Th-17 differentiation – and produce Interleukin 2. Interestingly CARD9 deficient mice succumb early after mycobacterial infection, while vaccination with synthetic Dectin 1 ligands plus rec. TBC protein effectively induces immune resistance. These examples underline our need to understand in detail the differential impact – and their respective cross-connection of pattern-recognitic receptor (PRR) driven signaling on the immunobiology of Antigen-presenting cells (APC's). This knowledge appears pre-condition to use in future custom-made adjuvants that enhance AND direct adaptive immunity.

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NETWORKING EXCELLENCE

TLR-4: From research to registered vaccines

THE SPEAKER

Ozzie BERGER

GlaxoSmithKline Biologicals,
Wavre, Belgium

Ozzie Berger is currently serving as Director of Regulatory Strategy in GSK Biologicals' Global Center for Adjuvants and Alternative Delivery Systems.
In August 2009, Ozzie transferred from GSK Biologicals' office in King of Prussia, PA to the headquarters in Wavre, Belgium, as part of a 2-year global assignment, in order to work with Nathalie Garcon in the newly created Adjuvant Center. Ozzie's main role is to define and develop effective regulatory strategies in support of GSK Biologicals' global programs for adjuvanted vaccines.

Before his move to Belgium, Ozzie was a Head in US Regulatory Affairs supporting GSK Biologicals' influenza vaccines franchise with oversight of 9 development programs and 2 commercial products.
Ozzie has 20 years of global regulatory and quality experience in the biopharmaceutical industry, mainly focused on vaccines. He joined GSK in January 2002 and before that he worked for seven years in CMC regulatory affairs at Merck, West Point, PA. Prior to that Ozzie worked at three start-up biotech companies within quality control, quality assurance and research roles. Ozzie received a Bachelor of Arts degree from Arcadia University in 1991.

ABSTRACT

Improved understanding of the important role of toll-like receptor (TLR) signalling in the induction of immune responses has led to increased interest in TLR agonists. 3-O-desacyl-4'-monophosphoryl lipid A (MPL) is to date the best characterised TLR agonist and the only one present in licensed human vaccines. MPL acts via TLR4 pathway, resulting in a transient enhanced production of cytokines and chemokines leading to the maturation and migration of APCs to the lymph nodes. GSK started research on adjuvant combinations more than 20 years ago to address the demanding needs of vaccines for challenging populations or pathogens. The first adjuvant combination containing a TLR agonist licensed for use in human vaccines is Adjuvant System AS04 which consists of MPL adsorbed onto a particulate form of aluminium salt. AS04 is used in a Hepatitis B vaccine *(Fendrix™)* and a human papillomavirus (HPV) 16/18 vaccine *(Cervarix®)*.

Preclinical studies revealed a superior adjuvant activity of AS04 *versus* aluminum salts alone. AS04 required the spatial and temporal co-localization of antigens and adjuvant. In the lymph nodes that drain the injection site, but not in other lymph nodes or the spleen, AS04 was shown to activate and increase the numbers of dendritic cells and monocytes. Altogether these data support a model where AS04 rapidly triggers a transient innate immune response that is spatially contained in the injection site and the draining lymph nodes leading to an enhanced activation of antigen presenting cells. Hence these findings on AS04 mode of action can explain the favorable safety profile and the robust adaptive response of the HPV 16/18 L1 VLP vaccine observed in clinical trials & practice.

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NETWORKING EXCELLENCE

MF59

THE SPEAKER

Derek O'HAGAN

Novartis Vaccines
and Diagnostics,
Cambridge, USA

Derek O'Hagan originally qualified as a pharmacist in the UK in 1984, before completing a PhD Thesis in 1988, on the use of biodegradable microparticles as vaccine delivery systems. After becoming a Lecturer in Drug Delivery and establishing a research group on vaccine delivery at the Department of Pharmaceutical Sciences, University of Nottingham, he moved to the US in 1993 to progress basic research into clinical evaluation. He joined Chiron corporation in 1995 and subsequently worked on several concepts that moved into clinical trials, including microparticles for the delivery of DNA vaccines and bioadhesive polymers for mucosal vaccine delivery. He also worked on the emulsion adjuvant MF59, which is included in a licensed flu vaccine. He is currently the Global Head of Vaccine Delivery Research for Novartis Vaccines, based in Cambridge, MA, and is responsible for formulation science and novel vaccine delivery research. He also leads a multi functional team responsible for research on vaccine adjuvants. He is the author of >120 original research publications, >60 chapters and reviews and is a named inventor on >50 filed patents. He was awarded the Conference Science medal of the Royal Pharmaceutical Society of Great Britain in 1997, and the Young Investigator Research Achievement Award of the Controlled Release Society in 1999.

ABSTRACT

The oil-in-water emulsion adjuvant MF59 has been included in licensed products for seasonal and pandemic influenza vaccines. It was originally licensed in a seasonal vaccine to be used in elderly adults, but has recently completed a field efficacy study in young children and showed significantly enhanced efficacy over an unadjuvanted seasonal vaccine. Moreover, it has been extensively evaluated for a range of other vaccine antigens and is generally more potent than the established adjuvant, Alum. Despite the extensive use of oil-in-water emulsions, including MF59, and their proven efficacy and safety in humans, their mechanism of action is only partially understood. We have found that MF59 activates innate immunity at the injection site in mice, including up regulation of cytokine and other genes involved in blood cell recruitment. In agreement with the modified local gene expression profiles, we could show that MF59 promoted a rapid infiltration of blood cells into the muscle. In addition, by using fluorescently labeled antigen we could demonstrate that MF59 promotes antigen uptake by several blood cell types and increases the transport of the antigen from the muscle to the draining lymph nodes. Recently, we have dissected the relative contribution of the various individual components of the MF59 emulsion to innate immune genes activation, antigen uptake, cell migration and adjuvant effect. We have also assessed the requirement of several innate immune-related genes including Nlrp3 inflammasome and MyD88 for MF59 adjuvant effects and local innate immune activation.

vienna vaccines
NETWORKING EXCELLENCE

Role of the inflammasome in adjuvanticity

THE SPEAKER

Veit HORNUNG

University Hospital,
University of Bonn,
Bonn, Germany

Prof. Veit Hornung received his M.D. from the University of Munich (Germany) in 2003, and subsequently undertook his postdoctoral training at both the University of Munich and the University of Massachusetts Medical School in Worcester (USA). In 2008 he joined the University of Bonn (Germany), as a full professor, where he established his current lab within the Institute of Clinical Chemistry and Clinical Pharmacology. Prof. Hornung's research focuses primarily on the recognition of nucleic acids by the innate immune system, with a major aim of identifying nucleic sensing pathways and their respective ligands that initiate antiviral immunity. In the course of his postdoctoral training, Prof. Hornung defined optimal RNA ligands for TLR7 and TLR8 and identified 5' triphosphate RNA as the ligand for the cytosolic RNA helicase RIG-I. More recently, Prof. Hornung has focused on the activation of the so-called inflammasome pathway, a cytosolic protein scaffold that triggers the autocatalytic cleavage of caspase-1, an important checkpoint in inflammation. Here, the novel DNA sensor AIM2 was identified, a receptor that plays an important role in antimicrobial defense against DNA viruses and cytosolic bacteria. Currently, efforts are being undertaken to target these nucleic acid sensors for the induction of adaptive immune responses using novel adjuvants.

ABSTRACT

The innate immune system relies on its capability to detect invading microbes, tissue damage or stress via evolutionarily conserved receptors. The nucleotide-binding domain leucine-rich repeat (NLRs) containing family of pattern recognition receptors includes several proteins that drive inflammation in response to a wide variety of molecular patterns. Especially the NLRs that participate in the formation of a molecular scaffold termed the 'inflammasome' have been intensively studied in past years. Inflammasome activation by multiple types of tissue damage or by pathogen associated signatures results in the autocatalytic cleavage of caspase-1 and ultimately leads to the processing and thus secretion of pro-inflammatory cytokines, most importantly interleukin IL-1β and IL-18. So far, several proteins have been described that can initiate the formation of inflammasome complexes: the NLR proteins NLRP1, NLRP3, NLRC4 and the PYHIN (pyrin and HIN200 domain–containing) protein AIM2. Up to now, only AIM2 has been shown to directly bind to its activating stimulus (double stranded DNA), whereas the NLR inflammasome proteins have not been established as bona fide receptors. Of all of the NLR Proteins, NLRP3 has attracted particular attention due to the fact that it seems to sense a large variety of stimuli of diverse physiochemical nature (e.g. ATP, pore forming toxins or crystalline material) and also because it plays a pivotal role in many inflammatory diseases. In addition, it has been shown that NLRP3 activation is required for the adjuvanticity of alum-based vaccines, yet these results remain controversial. Here, I will review the controversial molecular mechanisms that regulate NLRP3 signaling and highlight recent advancements in DNA sensing by the inflammasome receptor AIM2.

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NETWORKING EXCELLENCE

Neonatal immunization: which challenges for novel vaccines?

THE SPEAKER

Claire-Ann SIEGRIST

University of Geneva,
Geneva, Switzerland

Claire-Anne Siegrist is Professor of Vaccinology at the University of Geneva (Switzerland), in charge of infectious diseases and immunology at the University Hospitals of Geneva, Director of the Pediatric Department of the University of Geneva and head of the WHO collaborating Center for Neonatal Vaccinology.

After her MD graduation at the University of Geneva, she trained in Geneva and in the INSERM-CNRS Immunology Center of Marseille-Luminy, France, where she studied the mechanisms of antigen presentation to the immune system and obtained an Advanced Diploma (DEA) in Immunology. After her return to Geneva, Dr Siegrist continued her molecular and cellular immunology studies on the regulation of MHC molecules and their influence on immune responses. In 1994, Dr Siegrist initiated a new research group on Vaccinology and Neonatal Immunology, which was recognized in 1996 as a WHO Collaborating Center for Neonatal Vaccinology.
Prof. Siegrist was nominated as Professor of Vaccinology at the University of Geneva in 1999, at the Swiss Academy of Medicine in 2002 and in 2004 at the Swiss National Research Foundation. In 2005, she received the Bill Marshall Award from the European Society for Paediatric Infectious Diseases.
Professor Siegrist serves as an expert in Vaccinology on various national and international Advisory Committees.
She is the President of the Swiss Advisory Committee for Immunizations (CFV/EKIF) since 2004 and was nominated at the UK Joint Committee for Vaccination and Immunization (JCVI) in 2008 and at the WHO Strategic Advisory Group of Experts (SAGE) in 2010.
She has contributed to a large number of original scientific publications in the field of vaccine immunology, studying in particular the mechanisms of the maturation of early life vaccine responses, identifying strategies likely to enhance them and allowing a better understanding of the influence of maternal immunity on immune maturation.

ABSTRACT

The neonatal immune system was long considered as a “tolerizing” system and subsequently described as “immature” as compared to that of adults. Recent evidence allows concluding that it is – in contrast – perfectly adapted to the unique situation and challenges of an abrupt transition from pre- to post-natal life. To avoid potentially detrimental responses against maternal antigens or commensals, T cell responses which are readily elicited in early life are preferentially polarized towards CD4+ Th2 cells and away from CD4+ Th1/Th17 and CD8+ T cells. Importantly, antigen-specific adult-like CD4+ Th1/TH17 and CD8+ responses may be nevertheless be elicited by specific formulations / adjuvants. These formulations are characterized by their in vivo targeting / activation of only a small number of antigen-positive/adjuvant-positive DCs, thus avoiding the induction of anti-inflammatory / regulatory mechanisms. The exact function / contribution of early life regulatory T cells is still being investigated.

Neonatal B cell responses are also not “deficient” but preferentially polarized towards the induction of memory cells rather than of antibody-producing-cells. This is reflected by a progressive development of the number and size of Germinal Centers, an important question being the extent to which it may be modulated by novel vaccines. Another hallmark is the short persistence of vaccine-induced antibodies, resulting from the limited establishment of long-lived plasma cells in the early life bone marrow, where the production of the APRIL survival factor is limited. Thus, the likelihood of life-long antibody-mediated protection in the absence of boosting is somewhat remote. Interestingly, immune memory elicited in infancy may also not persist as long as that induced in mature hosts. Finally, early life responses are susceptible to vaccine interference, which may evolve as a major challenge as the number of infant vaccines continue to increase.

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Challenge Panel

THE CHALLENGER

Steven G. REED

IDRI – Infectious Disease Research Institute,
Seattle, USA

Steve Reed is Founder and CEO of Immune Design Corp., a Seattle based vaccine company, and Head of Research and Development of the Infectious Disease Research Institute, a global health not for profit biotech.

In 1994 Dr. Reed co-founded Corixa Corporation where he served as Chief Scientific Officer until leaving in 2004. He founded Dharma Therapeutics, a transdermal delivery company. His academic appointments include Adjunct Professor of Medicine at Cornell University Medical College and Research Professor of Pathobiology at the University of Washington.
He serves on several editorial review committees, has served as a member of the Tropical Medicine Review Board of the National Institutes of Health, and is a member of the Vaccine Development and Diagnostics Steering Committees of the World Health Organization.
Dr. Reed graduated from Whitman College in 1973, and received a PhD in Microbiology and Immunology from the University of Montana in 1979.

That year he was appointed as Scientist of the National Institute of Amazon Research in Manaus, Brazil, where he directed research on tropical diseases. Dr. Reed joined Cornell University Medical College in 1980 as Assistant Professor of Medicine, continuing to work in Brazil as manager of the Cornell-Bahia program in International Medicine. He joined the Seattle Biomedical Research Institute in 1984 where he worked until founding IDRI in 1993.
Dr. Reed's research interests have focused on the immunology of intracellular infections, and on the development of vaccines and diagnostics for both cancer and infectious diseases.
He has more than 220 original articles, several book chapters, and holds more than 100 issued patents for diagnostics, vaccines, and therapeutics of infectious diseases and cancer.

STATEMENT

Safe and effective adjuvants for prophylactic and therapeutic vaccine use are resulting from the identification and optimizing formulations of small molecules. Effectively engaging macrophages and dendritic cells (DC), leading to T cell responses is essential for developing a new generation of T cell vaccines (e.g. tuberculosis, malaria, HIV), as well as for improving the quality and duration of antibody responses (influenza, HPV, HIV, etc.). The most advanced approaches to new adjuvant development consist of using TLR ligands (TLRL), to provide synergism between the formulation and the TLRL. Using the crystal structure of the MD2 molecule of human TLR4, we have designed and optimized a new generation of ligands. Engagement of TLR4 may lead to activation of signaling pathways, or to inhibition of signaling pathways, depending in part on the molecular structure of the TLR ligand, and its interaction with MD2. Position, number, and length of acyl chains present in the TLR4L all influence responses by antigen-presenting cells (APC). Furthermore, varying these factors, e.g. acyl chain number may produce molecules active in mouse, but not human, APC.

We have characterized molecular signatures of human dendritic cell (DC) responses using novel TLR4L, alone or in combination, to design adjuvant potency and immune response quality.
The manner in which TLRL are formulated dramatically influences the nature of the immune response induced. We have developed formulations of our lead TLR4L, GLA, and have evaluated a variety of these, including oil/water emulsions, micellar, niosomal, and liposomal, in clinical trials and in a variety of preclinical models. When properly formulated, GLA, which was optimized for activity on human cells, but is also active in animal models, has the ability to focus the T cell to type I, to down regulate type 2 responses, induce CD8 T cells, and effectively enhance and broadened specific antibody responses, including mucosal immune responses. We have also shown that cells from elderly individuals strongly recognize GLA, producing cytokines in a manner qualitatively and quantitatively indistinguishable from cells from healthy adults. Thus, it appears that selective molecular synthesis and formulation may lead to a new generation of TLR4L- based adjuvants with improved qualities over natural products.

THE CHALLENGER

Martin FRIEDE

World Health Organization,
Geneva, Switzerland

Dr Martin Friede currently leads the technology transfer team within the department on innovation, information, evidence and research (IER) at the World Health Organization in Geneva, Switzerland. Prior to taking this position he was the WHO focal point for matters related to the development and use of adjuvants, as well as technologies to facilitate vaccine delivery such as needle-free systems, and vaccine stabilization methods.

Dr Friede created the WHO's Global Adjuvant Development Initiative to facilitate supply of adjuvants and know-how on vaccine formulation to public sector vaccine developers.
Prior to joining WHO Dr Friede held several positions in the vaccine industry. He received his PhD in biochemistry from the University of Cape Town in South Africa.

STATEMENT

Novel adjuvants –
breakthroughs and setbacks, where will we end?

The path to successful development of an adjuvanted vaccine is riddled with pitfalls, however none as difficult to overcome as the demonstration of safety to a level that satisfies not only the regulatory agencies, but the public in general. Vaccines are continuously being questioned with regards to safety, however in general this is from a small subset of the public. But when adjuvants are added, there is not only more vociferous public concern, but even some regulatory agencies are unsure of how much data is required before they can approve the vaccine.

For example, during the H1N1 pandemic, where the addition of oil-in-water adjuvants to pandemic vaccines enabled at least a doubling of the available vaccine supply, one of the biggest barriers to uptake of the vaccine was fear of the adjuvant. Extensive preclinical studies, clinical studies in a wide population range, and also data from millions of older adult recipients showing that vaccines containing these adjuvants are safe, was ignored, and unfounded hypothetical associations of the adjuvant entered mainstream communications. This perception could have disasterous public health consequences in the event of a more serious pandemic. These concerns that adjuvants can or could cause rare severe adverse events has also led to several candidate vaccines being abandoned, including for example a TLR-9 adjuvanted hepatitis B vaccine.

The concerns generally voiced are that adjuvants, through a non-specific immune stimulation, can trigger or exacerbate autoimmune responses, resulting in 'gulf war syndrome', multiple sclerosis, arthritis or other pathologies. Yet there is little scientific data to indicate that this can happen, and more data to support the contrary, that immune stimulation is safe. Unfortunately there are no accepted preclinical models for evaluating the risk of inducing autoimmunity, so proving that the adjuvant will not do this is somewhat of a challenge.

Several lessons have however been learnt from the past: Firstly, testing a novel adjuvant with a vaccine which does not really need the adjuvant, is risky. In case of an adverse event the regulators will veer on the side of caution since an effective vaccine already exists. For such vaccines, it is preferable to use an adjuvant with a history of safety. And secondly, once an adjuvant has been associated with adverse events, in the clinic or even in preclinical studies, it is rather difficult to rehabilitate a tarnished reputation.

In conclusion, for many vaccines it will be easier to use an existing adjuvant than to create new adjuvants, but for diseases where current adjuvants are inappropriate, the benefit afforded by the new vaccine needs to be visible and communicated.

THE CHALLENGER

Sefik S. ALKAN

Alkan Consulting LLC,
Basel, Switzerland

Dr. Sefik S. Alkan is a scientific executive with 30 years of accomplishments in drug discovery, management and proven leadership with top pharmaceutical companies. He has diverse experience across therapeutic areas such as Inflammation, Autoimmune Diseases, Allergy/Asthma, Oncology, and Vaccination. He received his PhD in Microbiology/Immunology at the Hacettepe University, Ankara, and studied immunochemistry (APC-T and T –B cell interactions using well defined synthetic antigens) at the University of California, San Francisco Medical Center. After becoming Professor of Immunology, in 1976 he joined Basel Institute of Immunology and worked on generation of antibody diversity, and human hybridomas. In the 1980's he started his career in the pharmaceutical industry starting with Ciba-Geigy later Novartis (-1998), HMR later Aventis (1998-2003). He then joined 3M Pharmaceuticals (2003-2007) to work on TLR agonists as immune modulators and vaccine adjuvants. In 2007 he joined Alba Therapeutics to work on regulation of epithelial tight junctions. He is currently an adjunct Professor at the UMDNJ, RWJ Medical School, Department of Molecular Genetics and Microbiology, New Jersey. In 2009 he moved to Switzerland and founded Alkan Consulting in Basel. He is the author of 160 publications and inventor/co-inventor in more than 58 issued patents.

STATEMENT

Can we really "relationally design" vaccines? Molecular engineering allows us to synthesize subunits of vaccines. We have now several novel synthetic adjuvants, and modern delivery methods. Thus, we can potentiate the desired immune response in some vaccines. However, we have not yet discovered all the *rules of induction of protective immune responses*. A well-coordinated collaboration of rapid *innate* and slow *adaptive* immune systems is a prerequisite for the success of vaccines. But also, successful design of a vaccine necessitates knowledge about the *invasion strategy* of each infectious agent. Only then can we induce appropriate B cell (antibody isotype) and T cell responses (TH1, TH2, Th9, TH17, Th22, T-regulatory cells, and T-killer cells etc) and NK cells. As the immune cells integrate a multitude of signals at a given time, these cell-subsets are induced in distinct conditions and can be reinforced or destabilized by other conditions. To this end, recent studies have used *systems biology* approaches to obtain a global picture of the immune responses to vaccination in humans. This method enabled researchers to identify early innate signatures that predict the immunogenicity of vaccines, as well as to discover potentially novel mechanisms of immune regulation. The new technologies and computational tools permit the comprehensive analysis of the interactions between all of the components of immunity over time. Thus, *systems biology* is expected to provide relevant and novel insights into the mechanisms of action of vaccines and thus to improve their design and effectiveness.

SESSION V

improving administration also for vaccines in the less developed world

Chair:

Maria Elena BOTTAZZI

The George Washington University,
Washington, USA

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Patch technology

THE SPEAKER

Larry ELLINGSWORTH

Intercell USA, Inc.,
Gaithersburg, USA

Dr. Ellingsworth directs Intercell's Patch Center of Excellence and leads technology development efforts at Intercell USA, Inc. (previously Iomai Corporation) with a focus on transcutaneous immunization. He has over 25 years of experience in research management in the pharmaceutical and biotechnology industries, including at Iomai Corp., Collagen Corp., Celtrix Pharmaceuticals, and Antex Biologics. Dr. Ellingsworth received his B.S. in Genetics from the University of California-Davis (UCD), an M.S. in Genetics from California State University, and a Ph.D. in Immunology from UCD.

ABSTRACT

Delivering effective and affordable vaccines to developing countries represents a significant challenge for the vaccine industry. Intercell is working with organizations such as PATH and AERAS Global Tuberculosis Foundation to further development of pneumococcal and tuberculosis vaccines. Moreover, the Company's first licensed vaccine, against Japanese Encephalitis virus, provides the potential to prevent a significant burden of disease in endemic areas throughout Asia. The development of vaccines for developing countries is hampered by the extreme conditions in which the vaccines will be distributed and administered. Intercell's vaccine patch technology, with its ease of administration and storage in a nitrogen-purged pouch, is expected to increase accessibility to vaccines among the world's poorest populations. Phase II and Phase III efficacy trials of the Traveler's Diarrhea Vaccine System were recently conducted. This patch system consists of two components: a single-use Skin Preparation System (SPS:Buffer), that is used to gently disrupt the stratum corneum (SC) prior to patch application, and a dry formulated patch containing heat-labile toxin from enterotoxigenic E. coli. Whilst the efficacy endpoints in these studies were not met they supported the continued investigation of the patch technology as a suitable route of immunization for other vaccine candidates; the pivotal studies confirmed that transcutaneous immunization (TCI) with the Traveler's Diarrhea Vaccine System induced reproducible levels of protective antibodies against the LT toxin resulting in a meaningful reduction of LT specific ETEC episodes. The potential to formulate other antigens, with or without an adjuvant, into a dry, stable, manufacturable patch configuration, and the ability to elicit immunity by TCI, form the basis of Intercell's TCI approach to develop more effective and easier to use vaccines for the future.

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Microneedle technology and its application to influenza vaccination by the intradermal route

THE SPEAKER

Martine DENIS

Sanofi Pasteur,
Marcy l'Etoile, France

Dr. Martine Denis, D.V.M., is Senior Director, Clinical Development at sanofi pasteur. Her responsibilities encompass the clinical development of sanofi pasteur influenza candidate vaccines. Before joining sanofi pasteur, she has been in charge of the coordination of new influenza vaccine development at GlaxoSmithKline Biologicals. Her previous professional experience includes positions such as the head of HIV Immunology, head of Clinical Immunology Viral Vaccines, and head of Preclinical Virology Herpes Viruses at GlaxoSmithKline Biologicals.

She also led the Vaccine Clinical Development activities at Henogen, a Belgian Biotechnology company. Dr. Denis has been a member of the faculty of Veterinary Medicine, Department of Immunology-Vaccinology at the University of Liège, Belgium. Over the past fifteen years, Dr. Denis contributed to a variety of virus vaccine projects at various stages of development from early research to post-marketing activities.

ABSTRACT

The intradermal route long has been known to be an efficient method of vaccination. However, in the previous absence of a system allowing for simple and reliable injection into the dermis, the intramuscular (IM) or subcutaneous routes generally have been preferred. Sanofi Pasteur recently launched the first influenza vaccines administered by the intradermal route, using the Becton Dickinson Soluvia™ microinjection system.

Intanza® 9µg, the vaccine indicated for subjects aged 18 to 59 years, illustrates the capacity of a vaccine administered by intradermal route to elicit, with less antigen, an immune response comparable to that induced by a conventional IM vaccine. Intanza® 15µg, the intradermal vaccine indicated for subjects aged 60 years and over, induces higher levels of antibodies than its intramuscular counterpart, and antibody levels as high as those induced by an MF59-adjuvanted influenza vaccine.

Despite anatomical differences and involvement of different antigen presenting cells following intradermal vs. deeper vaccine injection, the cellular and antibody responses induced by influenza vaccination display similar characteristics. In a clinical trial comparing the immunogenicity of a single administration of Intanza® 9µg or Vaxigrip® (15µg administered IM) the two vaccines induced a similar increase in antibody titers and frequency of vaccine-specific circulating B cells. As may be expected for split-virion inactivated vaccines, neither the ID nor the IM vaccine significantly affected the pre-vaccination levels of cellular immunity as measured by vaccine-specific cytokine-expressing CD3+CD8+ or CD3+CD8- lymphocytes. The pattern of in vitro cytokines secretion after antigen stimulation was also found to be similar in subjects who had received the intradermal or the IM vaccine.

In conclusion, the intradermal influenza vaccine allows for minimally invasive and convenient vaccination as compared to standard IM influenza vaccines. The primary benefit of the intradermal influenza vaccine is the induction of increased levels of functional serum antibodies compared to IM vaccination at an equivalent dose, or the induction of antibody responses similar to IM vaccines using less vaccine antigen.

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Enhancing vaccination outcomes with an ID jet injection device

THE SPEAKER

Michael ROYALS

PharmaJet, Golden, Colorado, USA

Dr. Royals was a 2005 founding member of PharmaJet and currently serves as Chief Science Officer. In that capacity he coordinates Global Public Health Initiatives that include: 1) planning and implementation of pre and post-market clinical studies; 2) coordinating with in-country immunization program stakeholders to ensure programmatic and user needs are reflected in the technology brought to the market; 3) analysis, development and execution of market introduction strategies, and 4) serves as the Primary Investigator on US Center's for Disease Control and National Institutes of Health product development contracts.

Prior to joining PharmaJet Dr. Royals established Bio-Logistics Preclinical, a company that provides medical device development services in support of 510(k) and PMA applications to the FDA. He received his Doctor of Veterinary Medicine Degree from Colorado State University in 1995.

ABSTRACT

PharmaJet, a company founded to serve global public health vaccination needs, recently brought to market a needle-free jet injector optimized to deliver 0.1ml fluid volumes to the skin. The path to market, including derivation of stakeholder requirements, engineering hurdles, planning discussions with National Regulatory Authorities and device marketing clearance activities are discussed. Preclinical activities revealed distinct performance differences between jet injection and needle-based delivery methods. These differences included injectate volume retained in the skin immediately after injection, kinetics of injectate arrival at the regional draining lymph nodes and dermal dispersion patterns of injectate. Studies to elucidate the immunological consequences of these differences are being evaluated. Results from five pre-clinical and three clinical studies using the ID device suggest good utility with killed viral, modified live viral and DNA vaccines. In 2010 and 2011 PharmaJet was awarded next-generation ID device development contracts by the US Centers for Disease Control. Contract progress will be discussed.

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PCPP-based microneedles

THE SPEAKER

Georg MUTWIRI

University of Saskatchewan, Saskatoon, Cananda

Dr. Mutwiri is a Professor in the School of Public Health and a Senior Scientist at the Vaccine and Infectious Disease Organization (VIDO)/International Vaccine Center, at the University of Saskatchewan.
Dr. Mutwiri achieved his D.V.M. from the University of Nairobi, Kenya, and a Ph.D. in Immunology from the University of Guelph, Canada. He later completed postdoctoral research training in mucosal immunology at the University of California in San Diego, USA. Dr. Mutwiri then joined the University of Saskatchewan, Canada in 1997.

Dr. Mutwiri has established an active, externally funded Research Program and has had numerous collaborations internationally. Current research activities in his laboratory include the discovery and development of vaccine adjuvants and delivery systems. He has published numerous papers in the area of vaccinology, and has over 70 publications in peer-reviewed international journals and book chapters.

ABSTRACT

Intradermal (ID) immunization using microneedles represents a potentially powerful technology which can enhance immune responses, provide antigen sparing and improve shelf-life of vaccines. However, macroneedles are not fully compatible with many vaccine adjuvants. In the present investigations we evaluated the polyphosphazene adjuvants, PCPP, with a microneedle-based ID immunization technology. When used as part of an ID delivery system for hepatitis B surface antigen, PCPP demonstrated superior adjuvant activity in pigs compared to intramuscular administration, and significant antigen sparing. It also accelerates the microneedle fabrication process and reduces its dependence on the use of surfactants. PCPP-coated microneedles have the potential to improve the efficacy of ID vaccination with a patch delivery system.

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Challenge Panel

THE CHALLENGER

Maria Elena BOTTAZZI

The George Washington University, Washington, USA

Dr. Bottazzi is Associate Professor and Vice-Chair for Administration of the Department of Microbiology, Immunology and Tropical Medicine (MITM) at The George Washington University (GW) in Washington, DC. Her major interests are translational research and vaccine development for neglected tropical diseases and the role of vaccines as control tools in international public health programs and initiatives.

Within MITM, Dr. Bottazzi is Co-Director of the GW Center for Neglected Infections of Poverty, which includes the Institute of Translational Research and Development. In addition, Dr. Bottazzi is Director for Product Development of the Human Hookworm Vaccine Initiative (a Product Development Public-Private Partnership of the Sabin Vaccine Institute). Dr. Bottazzi was recently appointed as Associate Co-Investigator at GW for the new Clinical and Translational Science Institute at Children's National Medical Center. Dr. Bottazzi is an Associate Editor for Public Library of Science (PLoS) Neglected Tropical Diseases Journal and is the author or co-author of multiple scientific and technical papers in molecular, cellular biology, immunoparasitology, and vaccine development and is the recipient of multiple extramural awards.

Dr. Bottazzi is a native of Tegucigalpa, Honduras, where she obtained a B.S. in Microbiology and Clinical Chemistry from the National Autonomous University of Honduras and her Ph.D. from the Molecular Pathology & Experimental Immunology Program at the University of Florida. After completing her post-doctoral training at University of Miami and University of Pennsylvania, Dr. Bottazzi relocated to GW. She has been on the faculty since 2001 and with Professor and Chair, Dr. Peter Hotez, she has established and manages one of the newest and most successful academic departments devoted to infectious disease problems in developing countries.

STATEMENT

The development and testing of novel vaccine delivery platforms and administration routes are critical to the development of vaccines targeting neglected tropical diseases (NTDs) or the so-called diseases of the poor. These platforms need to be evaluated at early stages of development because for these types of vaccines, resources are scarce and the interest of industry partners is rarely captured.

The challenge will be how to accelerate the development, testing and approval of these delivery technologies for their future application to NTD vaccines. The solution may be to link the testing of new vaccine delivery technologies to the development of second generation vaccines already approved and needed in the developing world (Hepatitis B, HPV). In this way, knowledge-based capacity will be transferred to developing countries that can then be used in the development of other vaccines.

Access to these technologies could be accomplished through linkages with Product Development Partnerships (PDPs), which could provide early assessment of alternate delivery platforms during the development of these new vaccines. Some PDPs such as Sabin Vaccine Development, IDRI and IVI are already collaborating with public sector vaccine manufacturers.

Several key factors need to be taken into consideration by vaccine developers:

1. Delivery technologies should be developed and tested in parallel with other platforms such as novel adjuvants to ensure compatibility.
2. Robust and adequate immunological and potency studies should be developed to gain understanding of the immunological consequences of utilizing novel delivery technologies.
3. National regulatory agencies and other stakeholders in developing countries should be engaged early in development to ensure that future needs, accessibility and delivery processes are addressed.
4. Market assessments should be performed to ensure introduction strategies are successful.
5. Appropriate funding mechanisms should be evaluated, since mechanisms such as AMCs and PRVs have not yet been successfully used for NTD vaccines.

Ultimately, the objective is to use these technologies to improve and induce a more efficacious immune response. This could lead to antigen and/or dose sparing, which ultimately would result in reductions in vaccine costs (e.g., production, delivery and distribution).

THE CHALLENGER

Andreas MEINKE

Intercell AG,
Vienna, Austria

Dr. Andreas Meinke graduated in Biology from the University of Freiburg, Germany and obtained his Ph.D. in 1992 from the University of Freiburg and the University of British Columbia in Vancouver, Canada. Subsequent to his work at the Department of Microbiology and Immunology at UBC, he joined the Department of Microbiology and Genetics, University Vienna, as an Assistant Professor.
In 1998, Dr. Meinke joined the newly founded biotech company Intercell AG, where he was instrumental for the development of the AIP technology that led to the development of several vaccines, currently in pre-clinical and clinical development. At Intercell, he held various positions and was appointed to head the Research Department in 2010.
During his career, Dr. Meinke has authored and co-authored more than 50 publications lectured in several University programs and filed more than 20 patents in the field of antigen discovery.

STATEMENT

Up to date, most vaccines are delivered to humans by intramuscular or subcutaneous injection using a syringe or by oral administration (e.g. Polio, Cholera, and Rotavirus). The intradermal (ID) route is so far only used for the administration of few marketed vaccines; BCG against tuberculosis, vaccines against rabies (e.g. Rabipur® and Verorab) and recently flu (Intanza®).
The renewed interest in intradermal or also (trans)cutaneous delivery has been spurred by the fact that the dermis and epidermis are particularly rich in APCs, rendering these sites ideal for the induction of a more efficient immune response with a potentially lower vaccine dose. Although numerous clinical trials have been reported with novel ID vaccines, the majority have been performed in only few indications (Rotavirus, Hepatitis B and Influenza).
As cost and availability are two of the main drivers for the supply of vaccines to the less developed world, the highest likelihood of success for the introduction of novel vaccines that are applied by intradermal immunization will be with those vaccines that are associated with high costs and/or limited availability. In addition, any vaccine that will strongly benefit from its intradermal delivery in regard to efficacy should be considered a promising candidate. Furthermore, delivery of vaccines via ID or cutaneous application will also reduce the risk of injuries and infection as caused by the use of needles and thereby improve their safety.
Nevertheless, there are a number of obstacles for the development of intradermal/cutaneous vaccines that have to be tackled prior to successful market entry. Most importantly, clinical evidence needs to be collected directly comparing the novel vaccine with the traditional vaccine at the same, but lower than currently applied dose. In order to induce efficient immune responses some vaccines will require the use of novel adjuvants, when Aluminium salts or oil-in-water adjuvants prove to be too reactogenic in combination with the respective antigen. And in addition, the costs associated with a novel ID vaccine as compared to a traditional vaccine need to be properly calculated, including not only costs for manufacturing, but all incremental costs relating to introduction of such vaccine to routine immunization.
A novel ID or cutaneous delivered vaccine that has overcome these hurdles will be of large benefit especially for less developed countries, protecting individuals from infectious diseases at a lower dose and price combined with a safer administration.

THE CHALLENGER

Christoph KLADE

Intercell AG,
Vienna, Austria

Dr. Klade is a biochemist and immunologist by training. He obtained his PhD from the University of Vienna and took further training in immunology at the Universities of Berkeley and Stanford, California. After university he has spent over sixteen productive years in industrial R&D in big pharma (Boehringer Ingelheim) and biotech (Intercell).
Major achievements include:

- setting up technology platforms for discovery of both B- and T-cell antigens
- bio-assay development & validation for measuring B- and T-cell mediated immune responses
- technical development of vaccine candidates from pre-clinical to licensure
- clinical trials phase 0-IV

After joining Intercell in 1999, Dr. Klade was involved in the discovery of Staphylococcus aureus antigens that are now in late stage clinical development. Next he set up a comprehensive T-cell epitope identification program and led Intercell´s pioneering therapeutic Hepatitis C vaccine approach.
Dr. Klade set up the Department of Clinical Immunology (responsible for all immunological monitoring of Intercell´s vaccine trials including T-cell and serology assays) and the Department of Technology Development (responsible for process and product development and industrialization from preclinical to commercialization). Both proved invaluable for the successful late-stage development of Intercell´s first product a prophylactic vaccine against Japanese Encephalitis that got U.S., European and Australian marketing approval early in 2009. 2008-2011 Dr. Klade served as Senior Vice President for Global Clinical Development at Intercell, overseeing and steering over 20 clinical trials (phase 0-IV) in 7 different indicatons.

STATEMENT

Vaccines have probably saved more lives than any other medical intervention. In that regard their availability and implementation in particular in early childhood immunization programs can be seen in line with basic needs like clean water and adequate nutrition, appropriate housing, hygiene and education.
Vaccine development has been greatly spurred in recent years. New technologies and even novel scientific disciplines like molecular biology / molecular immunology have made an impact. In parallel vaccine production capabilities have been constantly improving as exemplified by cell-culture derived vaccines with higher purity, improved reactogenicity profile and better economics.
Nevertheless significant issues remain especially for less developed countries.

a) scientific: for some of the most deadly diseases like AIDS or tuberculosis still no vaccines are on the horizon.
b) technical: many vaccines still require cold-chain distribution which still cannot be achieved in large parts of the world.
c) medical: traditional vaccines administered using steel needles all too often provoke needle sharing. Unfortunately, many examples of inadvertent spreading diseases by this practice exist. One of the saddest is probably the spread of Hepatitis C in Egypt (Frank et al. 2000, Lancet 355). Novel trans-dermal immunization strategies as discussed in this session, but also entirely different approaches like edible vaccines may prove to help overcoming such issues in future.
d) in addition economic (availability), political (recommendation, implementation), logistic (distribution) and sometimes even societal (acceptability) issues are hampering use of vaccines.

Only concerted action addressing all these issue will lead to full translation of the powerful benefits vaccines can bring to the world.

SESSION VI

quo vadis flu vaccines - learning from the H1N1 pandemic in the light of new technologies and established paradigms

Chair:

Geert VANDEN BOSSCHE

Bill & Melinda Gates Foundation,
Seattle, USA

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Signature features and health burden of the 2009 H1N1 pandemic and historic pandemics

THE SPEAKER

Lone SIMONSEN

The George Washington University, Washington, USA

Dr Simonsen is a research professor at the George Washington University, and holds an appointment with the RAPIDD infectious disease modeling network hosted at the Fogarty International Center, National Institutes of Health (NIH). She is also the president of SAGE Analytica, a consulting business in Bethesda, Maryland.
Dr. Simonsen holds a PhD in population genetics from University of Massachusetts, Amherst, and is an expert in infectious disease epidemiology, pandemic influenza, surveillance methodology, vaccine effectiveness and vaccine adverse events. Over the past two decades she has worked at the Centers for Disease Control and Prevention, the World Health Organization and the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health, and has published ~100 papers, book chapters, commentaries and letters. She is an editor of several journals, including Epidemics, Plos Currents Influenza and Plos Medicine. As a senior epidemiologist she advised the NIAID institute leadership on influenza, SARS, and vaccine issues, and assisted WHO with SARS and pandemic influenza response, before leaving the government in 2007 to pursue a career in academia and consulting in the private sector. Her current research focuses on signature features of elucidating the epidemiology of historic influenza pandemics, developing novel surveillance strategies for tracking the ongoing pandemic, modeling of burden of respiratory viruses, and evaluating benefits associated with vaccine programs (influenza, PCV7, rotavirus vaccines). Resently Dr. Simonsen served on an influenza expert panel for the Council of Foreign Relations in NY, presented on pandemic surveillance issues at the President's Council of Advisors on Science and Technology Policy in DC, on influenza vaccine benefits at a Lancet conference in Beijing, on signature features of historic influenza at a NIH-sponsored meeting in Copenhagen, and on pandemic surveillance strategies at Harvard School of Public Health.

ABSTRACT

The WHO was severely criticized of overdoing the public health response to the 2009 H1N1 pandemic. We review recent insights and lessons from past pandemic "signature pattenns" to put the contemporary experience in perspective.
Who is at risk of pandemic mortality? In contrast to seasonal influenza where >90% of deaths are of seniors, a key signature of historic pandemic influenza is the mortality shift towards younger ages. The severe 1918 pandemic and the 2009 pandemics are dramatic examples of this phenomenon, with 9 out of 10 pandemic deaths occurring among persons <65 years. The 1957 and 1968 pandemics featured a more moderate age shift.
How does one compare severity of pandemics? Because of the age shift, counting numbers of deaths is not an appropriate metric to compare the severity across pandemic and seasonal influenza periods. Instead, we used US mortality surveillance data to estimate Years of Life Lost (YLL), a metric that weighs a young person's death greater. In this "apples to apples" comparison, the 2009 pandemic caused as many as ~1.7 million YLL – similar to the 1968 pandemic.
Is the 2009 H1N1 pandemic over? Not necessarily. Historic pandemics are characterized by recurrent waves; the pandemic virus continued to circulate and dominate in the following 2-5 winter seasons before becoming established as a "seasonal" influenza virus. The 2010-2011 experience of the H1N1-pandemic virus was by many indicators more severe than the 2009 experience.
Can we be certain the worst is over? Not necessarily. The 1918 pandemic virus featured a relatively mild 1st wave several months before it went on to kill ~2% of the global population during 1918-20. Likewise, during the 1968 A/H3N2 pandemic the majority of deaths in Europe occurred during the second season of circulation (1969-70). For the 1889 pandemic, most deaths occurred during the 3rd wave with two years delay.
In a historic perspective, numerous uncertainties remain about the H1N1 pandemic that warrants continued vigilance, and continuing efforts to protect the population with vaccine and by other means. It is too early to talk about this pandemic in past tense.

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Novel influenza vaccines: how will they meet health needs

THE SPEAKER

Klaus STÖHR

Novartis Vaccines and Diagnostics,
Cambridge, USA

Before his current position as Vice-president and Head, Global Policy; Novartis Vaccines&Diagnostics, Klaus held various positions at Novartis after he joined the company in 2007:

- Vice-President and Global Head, Influenza Strategy Liaison and Key Account Management; NVD Oct 08–Aug10
- Vice-President and Global Head, Influenza Franchises, NVD Feb 07–Sep 08

Before joining Novartis, he worked at the World Organzation from 1992 to 2007 in various program in the following positions such as:

- Special Advisor on Influenza Pandemic Vaccine Development; WHO Initiative for Vaccine Research, Jan 06–Jan 07
- Head, WHO Global Influenza Programme, 01–Jan 06
- Coordinator, WHO SARS Aetiology and Diagnosis, WHO, Feb 03–July 03
- Scientist, Animal and Food related Public Health Risks, Department of Communicable Diseases, WHO, 1998–2001

Before joining WHO Klaus had worked initially as Scientist and later as Head of the Department of Infectious Diseases at the National Institute for Epidemiology and Infectious Disease Control in Animals, Germany since 1987.

Education and post-graduate training

- PhD (Dissertation on Epidemiology and Infectious Disease Control) 1984–1987
- Research Fellowship in Epidemiology and Infectious Disease Control, University of Leipzig, 1984–1987
- Thesis (Guidelines for investigations of infectious disease outbreaks), University Leipzig, 1983–1984

Publications

- > 60 scientific publications (since 1992)
- >180 invited presentations at international meetings (since 1992)

Academic Positions

- Honorary Professor, Freie University, Berlin 2007
- Consultant Professor Shantou Medical University; China 2001

Awards

- Included in the Scientific American' list of 50 research and policy leaders in 2005
- Award for Leadership in Health; Medical Science Center, Texas University, 2005
- Corresponding Member, European Society for Clinical Virology since November 2003

ABSTRACT

The key challenges in influenza immunization are to increase immunization coverage, offer improved vaccines for children and elderly (effectiveness; cross-reactivity), constrained pandemic production capacity and time pressure during the seasonal production race. Vaccine advancements can help address several of these challenges. However, one of the key obstacles remains low immunization coverage in high risk groups for which immunization is already recommended. Improvement here will require public health investments and commitment by national authorities into driving vaccine uptake in developed countries.

More than 15 companies of different size have pre-clinical or clinical with influenza vaccines development programs. Many of them develop new production platforms (cell, plant and bacterial expression; viral vectors; DNA) in the hope to combine production efficiencies (unit costs; time to market) with enhanced vaccine effectiveness. The latter has direct patient benefits. However, the former may only be relevant for pandemic preparedness and early begin of seasonal immunization unless reduced vaccine costs are used by health authorities directly to drive vaccine up-take. That remains to be seen.

Several ongoing efforts to increase vaccine efficacy are focusing on e.g. adjuvants and fusion proteins (and other TLR agonists). Others see new production platforms and rapid manufacturing ramp up as solution to improve efficacy (often through increasing antigen content) and time to seasonal vaccine market. New delivery systems (nasal, skin) in development have still to demonstrate improved vaccine efficacy for high risk groups. Antigen sparing achieved through this approach will have only patient benefit if reduced costs are reinvested into increasing immunization rates.

A universal vaccine protecting against various influenza subtypes and replacing seasonal immunization is not yet in sight.

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The antigenic evolution of influenza virus

THE SPEAKER

Derek SMITH

University of Cambridge,
Cambridge, UK

Derek Smith is Professor of Infectious Disease Informatics in the Zoology Department at Cambridge University. He is also a member of the Department of Virology at Erasmus Medical Center in The Netherlands, and is a Senior Research Fellow at the Fogarty International Center at the United States National Institutes of Health. He is a temporary advisor to the World Health Organization and is a member of its influenza vaccine strain selection committee.

He is also involved in vaccine strain selection for other human and non-human pathogens. His research is focused on how pathogens evolve, to what extent this evolution is predictable, and determining public and animal health measures against such ever-changing pathogens. He received a United States National Institutes of Health Director's Pioneer Award in 2005 for his work on Antigenic Cartography, a method that enables detailed study of pathogen evolution.

ABSTRACT

Thirty plus years of global influenza virus surveillance, in multiple species, provides a remarkable dataset for the study of influenza virus evolution. Because the purpose of much of this surveillance is vaccine strain selection, these data have been analyzed antigenically as well as genetically. I will describe the evolution of recent

A (H1N1) pandemic influenza viruses, as well as these viruses when they have circulated in humans and pigs over the last 70 years. In addition I will describe the evolution of swine and human seasonal influenza A(H3N2) viruses from the last influenza pandemic in 1968, and of ~13,000 influenza A(H3N2) viruses from six continents during 2002-2007. These studies of human influenza viruses will be contrasted with studies in other species, to show the importance of the coevolution of the virus and population-level immunity to the virus.

Finally, I will describe how the methods used to quantify and visualize the antigenic evolution of influenza viruses can also be applied to other pathogens.

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A cell culture flu vaccine

THE SPEAKER

Foto: Petra Spiola

Hartmut J. EHRLICH

Baxter Innovations GmbH,
Vienna, Austria

Dr. Hartmut Ehrlich is a physician with over 20 years experience in biopharmaceutical research and product development. He graduated from Medical School at the University of Giessen, Germany in 1985 and completed his Doctorate at the Clinical Research Unit for Blood Coagulation and Thrombosis of the Max-Planck-Foundation. Subsequently, he spent over 6 years in basic research and patient care at the Department of Medicine, Hematology-Oncology of Indiana University and the Lilly Laboratories for Clinical Research in Indianapolis, Indiana, the Department of Molecular Biology at the Central Laboratory of the Dutch Red Cross in Amsterdam, The Netherlands, and the Kerckhoff-Clinic of the Max-Planck-Foundation in Bad Nauheim, Germany. In 1991, Dr. Ehrlich joined Sandoz, now Novartis, and spent almost 4 years in clinical development as well as corporate project management in immunology-oncology in Nuremberg, Germany and Basel, Switzerland. Dr. Ehrlich joined Baxter in 1995 as Medical Director for its former Biotech business, and held several positions of increasing responsibility until September 2003 when he was named Vice President, Global Clinical R&D for the BioScience Division. In September of 2006, he was promoted to his current position, leading all R&D and Medical Affairs for BioScience.
During his career, Dr. Ehrlich has authored and co-authored well over 100 scientific publications and book chapters. He has been lecturing in several university programs in Austria and abroad, and he is on the Advisory Board for the Biotec MBA program at Danube University in Krems/Austria. Most importantly, he was associated with the successful development and licensure of numerous biotechnological products in the areas of hematology – oncology, immunology, critical care, hemophilia, vaccines and biosurgery.

ABSTRACT

Conventional methodologies used to manufacture influenza vaccines have a number of disadvantages. Public health authorities have been recommending for decades that alternative cell culture systems be developed that allow production of influenza vaccine using robust, well characterised manufacturing systems. The ideal substrate to produce biologicals has been defined as a continuous cell line which can be fully characterised with respect to absence of tumorogenicity and freedom from adventitious agents. We have developed a Vero cell culture platform which has been optimised for the development of a wide variety of candidate vaccines against emerging virus diseases and particularly influenza viruses.
Both seasonal and pandemic Vero cell derived influenza vaccines (VCIV) have been demonstrated to be well tolerated and immunogenic in a number of clinical studies. Generally, safety and immunogenicity studies are sufficient for the licensure of seasonal influenza vaccines. The induction of hemagglutinin (HA)-specific antibodies, as determined by the hemagglutination-inhibition (HI) assay, is a well established correlate of laboratory-confirmed efficacy and clinical effectiveness of egg-derived seasonal influenza vaccines.
In our studies, culture-confirmed influenza infection (CCII) and antigenic typing were used to provide a stringent assessment of the ability of a novel inactivated Vero cell-derived influenza vaccine (VCIV) to prevent seasonal influenza infection in healthy adults. Efficacy and immunogenicity data were then analyzed to investigate whether hemagglutination inhibition (HI) titer can be used as a correlate of VCIV-induced protection from seasonal influenza. In this study protective efficacy for antigenically-matched CCII was 78.5% and 71.5% for all laboratory confirmed infections. A reciprocal HI titer of ≥15 was found to provide a reliable correlate of CCIV-induced protection and there was no additional benefit with titers >30.
These data provide evidence that this novel VCIV is safe, immunogenic and efficacious and indicate that existing correlates of protection for seasonal influenza vaccines may also apply to VCIV.

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A simple approach to a flu vaccine

THE SPEAKER

Thomas HOFSTAETTER

VaxInnate,
Cranbury, USA

Dr. Hofstaetter is the President and Chief Executive Officer at VaxInnate, a biotechnology company pioneering breakthrough technology for developing novel vaccines and a member of the VaxInnate Board of Directors.
Prior to joining VaxInnate, Dr. Hofstaetter spent more than 30 years in leadership positions at research-based pharmaceutical companies. He held executive roles in research and development, as well as strategy and business development, during postings around the world, including the United States, Japan, France and his native Germany.
During his service at Wyeth from 2004 until the firm's acquisition by Pfizer in 2009, Dr. Hofstaetter was Senior Vice President of Corporate Business Development and a member of both the Wyeth Management Committee, and the Pharmaceuticals Management Team.
A biochemist by training, Dr. Hofstaetter holds a PhD in Molecular Biology, magna cum laude, and a Master of Science degree in Biochemistry from the University of Tuebingen in Germany.
Dr. Hofstaetter began his pharmaceutical industry career in 1978, when he joined Behringwerke AG in Marburg, Germany, as a research scientist, rising to become Head of Research and later General Manager of the Business Unit for Immunology and Oncology.
From 1991 through 1994 he served as General Manager of the Pharmaceuticals Unit of Hoechst Japan in Tokyo.
He moved to the United States in 1995 to become Senior Vice President of Business Development and Strategy for Hoechst Marion Roussel. From 1999 to 2004, Dr. Hofstaetter was Senior Vice President of Corporate Development at Aventis.

ABSTRACT

Established technologies to manufacture flu vaccines in either eggs or cell culture have serious shortcomings in terms of speed and productivity which limit their utility in responding to pandemic threats. Moreover, the currently approved vaccines show limited efficacy in core target groups like the elderly. This can only be improved by adding adjuvants which comes with its own issues and is still not approved in the US.
VaxInnate has developed a novel technology which offers a solution for these problems: Our vaccines consist of the globular head of the viral hemagglutinins fused genetically to proprietary variants of a potent stimulator of the innate immune system, the bacterial protein flagellin. These constructs can be expressed in E. coli which allows the production of hundreds of millions doses within a few months. Clinical trials with prototype seasonal and pandemic H1 vaccines have confirmed high immunogenicity at 1-2 ug doses combined with excellent tolerability up to at least 20 ug.

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Challenge Panel

THE CHALLENGER

John OXFORD

Queen Mary School of Medicine, London, UK

John Oxford is Professor of Virology at St Bartholomew's and the Royal London Hospital, Queen Mary's School of Medicine and Dentistry. He has co-authored two standard texts: 'Influenza, the Viruses and the Disease with Sir Charles Stuart-Harris and G.C. Schild and most recently 'Human Virology, a Text for Students of Medicine, Dentistry and Microbiology' now in its third edition, published by Oxford University Press. Professor Oxford has also published 250 scientific papers.

His research interest is the pathogenicity of influenza, in particular the 1918 Spanish Influenza strain, which he combines with conducting clinical trials using new influenza vaccines and antiviral drugs. This research has been featured on Science TV programmes recently in the UK, USA, Germany and Holland. He is Scientific Director of the college research virology company called Retroscreen Virology Ltd (www.retroscreen.com).

STATEMENT

The influenza A Swine H1N1 is a Darwinian creature of huge consequence scientifically and from the viewpoint of the community. Survival of the fittest implies dominance and this virus has displaced other influenza A viruses. Paradoxically, since the over 65's have natural immunity to the H1N1 family death rates from H1N1 have been low and moreover H3N2 viruses have been pushed aside.

From a community viewpoint the entirely new feature of the H1N1 pandemic has been the Justa position of "a virus with a name" alongside the desire of families who have lost children to the virus to past photos on facebook. Deaths in young children, although relatively few, have therefore had a huge impact in the community.

To my mind a huge effort is now required to extend vaccine to HCW's and to their families and to carers as well as covering the highly emotive group of paediatrics.

Scientifically there is recent progress with universal flu vaccines, encompassing constructs of M2, M1 and NP and also peptides designed for novel antigenic sites. At the centre of these discoveries is human quarantine itself involving big issues of informed consent and conduct to the highest standards of clinical practice.

THE CHALLENGER

Michael PERDUE

U.S. Department
of Health & Human Services,
Washington, USA

Dr. Michael Perdue joined the HHS' Biomedical Advanced Research and Development Authority (BARDA) in September 2007 as Deputy Director for the Influenza and Emerging Diseases Division. He became Director of the Division in March 2009. He received his Ph.D. in virology from the University of Mississippi Medical Center in Jackson and held postdoctoral appointments at Duke University and the University of Minnesota. He served on the faculty of the University of Kentucky Medical School where he performed National Institutes of Health-funded basic research on avian retroviruses, before joining the US Department of Agriculture. While with the USDA, he worked on avian influenza viruses in Athens, GA where, over a period of 15 years, he published scores of articles on various aspects of avian influenza virus molecular biology, molecular epidemiology and vaccine development. In 2001 he became Research Leader for USDA's Environmental Microbial Safety Laboratory in Beltsville, Maryland, where he led a research team and a 25-member staff. In September of 2004 Dr. Perdue joined the US Centers for Disease Control and Prevention in Atlanta and was seconded to the World Health Organization Headquarters in Geneva, Switzerland. Among other international liaison duties there he served as Team Leader for Avian Influenza at the Human/animal Interface. While with USDA, Dr. Perdue had been closely involved in the characterization of the first avian and human H5N1 influenza viruses that appeared in Hong Kong in 1997. He has followed the spread and characteristics of the diseases caused by the H5N1 viruses since then. In January of 2006 he served as 'Event Manager' for the WHO headquarters response to the human infections with H5N1 in Turkey and was a WHO spokesperson for avian influenza issues. As Deputy Director for the Influenza and Emerging Diseases Division, he also served as a Project Officer on cell culture based influenza vaccine development contracts and in a wide range of activities supporting the Pandemic Influenza Program. As Division Director now he oversees the program that includes more than 40 active federal contracts and grants.

STATEMENT

Three fundamental questions arise regarding the future of influenza vaccines: Do we need more, do we need them to be made faster, and do they need to be better? There are also basically three types of influenza vaccines: Seasonal, Pandemic and Pre-pandemic. This sets up a useful matrix[1] from which to discuss, plan, and work. For seasonal vaccines, our current status indicates that we do not need more – we are still throwing away tens of millions of doses each year. Likewise, the manufacturing pathways and processes for seasonal vaccines are now fixed, and under normal circumstances the seasonal vaccine is delivered on time. So we'd have to say that we don't need more seasonal vaccine, nor for it to be produced faster. While we could all agree on differing levels of positive responses for other cells in the matrix, unfortunately, the lack of need and urgency for seasonal vaccines may impinge on progress that could benefit the development and manufacturing of pre-pandemic and pandemic vaccines.

[1]*Influenza vaccine needs:*

VACCINE TYPE	MORE?	BETTER?	FASTER?
Seasonal	No	Yes	No
Pandemic	Mild-no; Severe-yes	Yes*	Yes
Pre-pandemic	Yes/No? (current policy-No)	Yes	Yes/No?

*The H1N1 pandemic vaccines were excellent.

The US (and other) government's decision to provide monovalent H1N1 vaccine for anyone who wanted it has been generally applauded as the right thing to do. This decision was supported by the available data, which showed that H1N1 vaccines were generally excellent vaccines. However, only licensed vaccine manufacturers were able to provide this vaccine and, in the US, only egg-grown vaccine was used. This session will cover existing and new technologies for influenza vaccines and the advantages and disadvantages of each. One major challenge is to identify ways to assist in the evaluation and accelerated development of newer vaccine technologies that can produce better influenza vaccines more quickly and hasten their advancement across the finish line. Regardless of the general consensus for addressing each cell in the matrix, this progress will provide additional options that can be used to save lives before and during the next pandemic.

SESSION VII

late breakers in vaccine development

Chair:

Gerd ZETTLMEISSL

Intercell AG,
Vienna, Austria

vienna vaccines
NETWORKING EXCELLENCE

T cell vaccines

THE SPEAKER

Jessica FLECHTNER

Genocea Biosciences, Inc.
Cambridge, USA

Jessica Baker Flechtner, Ph.D. is the Vice President of Research at Genocea Biosciences, Inc.
Dr. Flechtner established the company's functional laboratory, and is leading Genocea's research efforts to identify novel T cell antigens for inclusion in vaccines directed against a variety of infectious diseases. Prior to joining Genocea, Dr. Flechtner was an Immunology Consultant at Biovest International, where she guided the development of assays to evaluate the success of the company's autologous Follicular (Non-Hodgkin's) Lymphoma vaccine in patients. As a researcher at Mojave Therapeutics, Inc. and Antigenics Inc., which acquired Mojave's intellectual property, Dr. Flechtner developed protein and peptide-based vaccines and immunotherapies for cancer, infectious disease, autoimmunity and allergy. She is an inventor on ten pending or issued patents and has multiple peer-reviewed scientific publications.
Dr. Flechtner performed her post-doctoral work in the laboratory of Dr. Harvey Cantor at the Dana Farber Cancer Institute and Harvard Medical School. She holds a Ph.D. in Cellular Immunology and a B.S. in Animal Science from Cornell University, and is a member of the American Association of Immunologists and American Society for Microbiology.

ABSTRACT

Vaccines have had a major impact on the prevention of communicable diseases, including the eradication of smallpox and the near-eradication of polio. However, there remain a large number of pathogens that have been intractable to vaccine development. One of several explanations is that conventional methods by which vaccines are developed are not applicable to these pathogens; namely, the focus on antibody-mediated immunity. Many pathogens for which vaccines do not exist reside within human cells during some point of their replicative cycle within the host, thus being inaccessible to antibodies. It is at this stage that the cell-mediated arm of the immune system can be mobilized to prevent disease. To this end, the identification of the antigenic targets of T cells that can subsequently be used as components of candidate vaccines has gained importance. A method has been developed where CD4+ and CD8+ T cells from naturally exposed individuals can be screened against a proteomic library that contains every full-length protein predicted to be expressed by a pathogen and is individually arrayed in microtiter plates. By screening the library with T cells from multiple human donors from different ethnic backgrounds, protein antigens that are recognized by a broad human population are identified. Further segregation of identified antigens based on the clinical outcomes of the donors leads to the discovery of protein antigens that are correlated with natural immunity and protection, which can then be included in novel vaccine formulations. This technology has been successfully applied to four diverse pathogens: the obligate intracellular bacterium, *Chlamydia trachomatis*; the mucosal colonizing organism, *Streptococcus pneumoniae*; the neurotropic virus, Herpes Simplex Virus type-2; and the malaria-causing apicomplexan parasite, *Plasmodium falciparum*. Animal proof of concept for vaccine efficacy has been established in three of these targets. Taken together, these results indicate that using a comprehensive approach to limit the thousands of possible T cell antigens to those specifically associated with protection in a broad and ethnically diverse human population can be successfully applied for antigen discovery and the generation of novel T cell-based vaccines for previously intractable disease targets.

vienna vaccines
NETWORKING EXCELLENCE

Paradigm shift in discovery and production of glycoconjugate vaccines

THE SPEAKER

Michael WACKER

GlycoVaxyn AG,
Schlieren, Switzerland

Michael Wacker co-founded GlycoVaxyn in 2004 and acts as scientific director. In this role, he is responsible for research and preclinical product development. Michael did his PhD in microbiology at the Swiss Institute of Technology in Zurich (ETHZ) and as well as his post doctoral fellowship. During this time he invented the technology.

He is the author of several publications in international scientific journals, including Science and PNAS. In addition, he is inventor of numerous patent applications. He graduated in biochemistry from the ETH in Zurich.

GlycoVaxyn AG was founded in 2004 as a spin off of the Swiss Institute of Technology in Zurich (ETHZ). The company has licensed a technology which allows the in vivo synthesis of complex glycoconjugates in Escherichia coli. Glycoconjugates are constituted by a polysaccharide part covalently linked to a protein. This technology has potentially various therapeutic applications as polysaccharides/glycoproteins are ubiquitous in most living organism and have a number of important functions. The main focus is the generation of vaccine against bacterial diseases. The company has started to demonstrate the potential of the technology while applying its technique to the synthesis of bacterial antigen with the intension to use as vaccination tool. Its most advanced glycoconjugate vaccine is going to enter into human clinical trials in 2010. GlycoVaxyn is venture financed with Eur 25 millions invested to date. The investors are Sofinnova Partners (France), Index Ventures (Switzerland) and Edmond de Rothschild Investment Partners (France). The company is located outside Zurich and employs 34 highly qualified collaborators mainly in biological research and process development.

ABSTRACT

GlycoVaxyn AG, a leader in the development of innovative bioconjugate vaccines based on complex polysaccharide structures, is developing a multivalent *Shigella* conjugate vaccine. Conjugate vaccines are a safe and efficient way to increase human health. We have developed a proprietary technology that allows the synthesis of these complex immunogenic bioconjugates via a biological process in *E. coli*, resulting in a robust and reproducible process and yielding a highly defined product. The conjugation of an antigenic polysaccharide to a designer protein of choice occurs via an N-glycosidic linkage through an enzymatic process in *E. coli*. The conjugate vaccine is extracted afterwards from of *E. coli* and purified by chromatography.

Shigellosis is a severe diarrheal condition resulting from bacterial infection. Each year, 1 million people are estimated to die from Shigella infection and 580,000 cases of shigellosis are reported among travelers from industrialized countries. To obtain a broad protection against the disease, GlycoVaxyn is developing a multivalent vaccine against *S. flexneri* serotypes, *S. dysenteriae* and *S. sonnei*. The shigella vaccine consists of different Shigella polysaccharides conjugated to a protein carrier. A production process has been developed to extract the bioconjugate from *E. coli*. The *S. dysenteriae* O1 bioconjugate was tested in a single-blind, first in human study to evaluate safety, reactogenicity and immunogenicity at two doses, with or without adjuvant, in 40 healthy naïve volunteers. The candidate vaccine exhibited a good safety profile. No significant adverse reactions were observed at any of the vaccine dose levels. In addition, the results showed a robust immune response indicated by seroconversion in 80% of the volunteers. All vaccine dose levels tested elicited significant IgG as well as IgA antibody responses. This is the first time that a biologically synthesized conjugate vaccine has been tested in humans and is a first step towards the development of a multivalent Shigella vaccine.

vienna vaccines
NETWORKING EXCELLENCE

Sipuleucel-T: autologous cellular immunotherapy for prostate cancer

THE SPEAKER

Robert SIMS

Dendreon Corporation,
Seattle, USA

Dr. Sims is board certified in Hematology and Medical Oncology. He joined Dendreon in 2003 as Medical Director and was promoted to Senior Medical Director in 2007. Dendreon (Nasdaq: DNDN) has been dedicated to targeting cancer and transforming lives through the discovery and development of novel products like Provenge®, an active immunotherapy which was approved by the FDA in 2010 for the treatment of men with metastatic castrate resistant prostate cancer. Dr. Sims has been the Medical Monitor for all recent and current clinical trials at Dendreon.

Prior to joining Dendreon Dr. Sims was a practicing hematologist-oncologist in the Pacific Northwest. Dr. Sims received his M.D. degree at Oregon Health Sciences University, followed by internal medicine residency training at NYU Medical Center. He received his hematology-oncology fellowship training at Fox Chase Cancer Center in Philadelphia, PA. He is an author on over 20 publications.

ABSTRACT

Sipuleucel-T is an autologous cellular immunotherapy that has been shown to enhance overall survival (OS) of men with asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer (mCRPC) by 4.1 months (HR=0.775; P=0.032).

Sipuleucel-T is prepared by culturing peripheral blood mononuclear cells from leukaphereses obtained at Weeks 0, 2, and 4 with a recombinant fusion protein [prostatic acid phosphatase (PAP) and GM-CSF] *ex vivo*. Product parameters were evaluated by flow cytometry, including cumulative total nucleated cells (TNC), absolute CD54+ cells, and CD54 upregulation. Antigen presenting cells (APCs) and T cell activation-associated cytokines, T cell proliferation, IFN-γ ELISPOT and antibody responses were assessed in a subset of patients during and/or after treatment.

CD54 upregulation of APCs, antigen-specific T cell proliferation, type-1 cytokine secretion, and IFN-γ ELISPOTs were increased in the product at Weeks 2 and 4 compared to Week 0. Cellular and humoral responses to the recombinant protein and PAP were observed at Weeks 6, 14 and 26. Integrated analysis of patients treated with sipuleucel-T from three Phase 3 mCRPC studies (N=476) showed correlations between OS and cumulative CD54+ cells (P=0.016), TNC (P<0.001), and CD54 upregulation (P=0.002). In a subset of the largest study, evidence of correlations were observed between OS and antibody response at Week 6 (P=0.079), T cell proliferation at Week 14 (P=0.057), and ELISPOT at Week 26 (P=0.049).

Conclusion: Sipuleucel-T is the first FDA-approved autologous cellular immunotherapy for advanced prostate cancer. In a subset of patients, it has been shown to stimulate persistent cellular and humoral immune responses. Correlations between immune parameters and OS suggest that these may be candidate biomarkers for clinical activity.

vienna vaccines
NETWORKING EXCELLENCE

Advances in the development of vaccines against neglected tropical diseases

THE SPEAKER

Maria Elena BOTTAZZI

The George Washington University, Washington, USA

Dr. Bottazzi is Associate Professor and Vice-Chair for Administration of the Department of Microbiology, Immunology and Tropical Medicine (MITM) at The George Washington University (GW) in Washington, DC. Her major interests are translational research and vaccine development for neglected tropical diseases and the role of vaccines as control tools in international public health programs and initiatives.
Within MITM, Dr. Bottazzi is Co-Director of the GW Center for Neglected Infections of Poverty, which includes the Institute of Translational Research and Development. In addition, Dr. Bottazzi is Director for Product Development of the Human Hookworm Vaccine Initiative (a Product Development Public-Private Partnership of the Sabin Vaccine Institute). Dr. Bottazzi was recently appointed as Associate Co-Investigator at GW for the new Clinical and Translational Science Institute at Children's National Medical Center. Dr. Bottazzi is an Associate Editor for Public Library of Science (PLoS) Neglected Tropical Diseases Journal and is the author or co-author of multiple scientific and technical papers in molecular, cellular biology, immunoparasitology, and vaccine development and is the recipient of multiple extramural awards.
Dr. Bottazzi is a native of Tegucigalpa, Honduras, where she obtained a B.S. in Microbiology and Clinical Chemistry from the National Autonomous University of Honduras and her Ph.D. from the Molecular Pathology & Experimental Immunology Program at the University of Florida. After completing her post-doctoral training at University of Miami and University of Pennsylvania, Dr. Bottazzi relocated to GW. She has been on the faculty since 2001 and with Professor and Chair, Dr. Peter Hotez, she has established and manages one of the newest and most successful academic departments devoted to infectious disease problems in developing countries.

ABSTRACT

One of the major hurdles in the critical path for the development and testing of novel and translational discoveries is overcoming the so-called "valley of death", or the product development gap for taking a bench discovery to the point where it shows a clear path to the clinic. Sabin Vaccine Development is a product development-public private partnership (PD-PPP) founded to develop recombinant protein vaccines targeting neglected tropical diseases, a group of chronic, debilitating, and poverty-promoting infections (i.e. hookworm and schistosomiasis). Two major NTD vaccines have transitioned into the vaccine development critical path, a bivalent hookworm vaccine and a schistosomiasis vaccine. The Human Hookworm Vaccine program comprises on the development of antigens targeted to block hookworm anemia. The two lead candidate antigens include a glutathione S-transferase, *Necator americanus* (Na)-GST-1, which is known to be involved in hookworm heme detoxification and an aspartic protease, Na-APR-1, used by adult hookworms to degrade host hemoglobin after blood ingestion. The Schistosomiasis Vaccine Program comprises on the development of the lead candidate antigen, *Schistosoma mansoni* (Sm)-TSP-2 surface tetraspanin, a molecule that interferes with the critical functions of the schistosome tegument. Advances in the development of these two NTD vaccines will be presented including the pre-clinical criteria used for the rigorous selection of the candidate antigens such as the use of animal models to determine specific endpoints such as blood loss, worm burdens and fecal egg counts, the assessment of the immunoepidemiological profiles and the study of function/structure of each of the proteins. Data will also be presented of the early stage process development, analytical and biochemical characterization, technology transfer, cGMP manufacture and upcoming clinical development plans.

vienna vaccines
NETWORKING EXCELLENCE

Messenger RNA-based vaccines: a new approach to immunization

THE SPEAKER

Karl-Josef "Kajo" KALLEN

CureVac GmbH,
Tübingen, Germany

Kajo holds a MD from the RWTH Aachen, Germany, and a PhD in Cell Biology from University College London. He received his education in internal medicine and oncology at the I. Medizinische Klinik of Mainz University and is a board certified internist. Kajo has a strong basic science background in Biophysics, Cell Biology and Molecular Immunology and did a Habilitation in Biochemistry at the Christian-Albrechts University in Kiel. At Merck-Serono, Kajo was involved in the clinical development of cetuximab in Japan and after his promotion to Senior Medical Director was responsible for the global clinical development of the Cancer Immunotherapy portfolio of Merck-Serono. He is member of several international working groups that presently develop new paradigms for the clinical development of cancer vaccines and immunotherapies. He received extensive management education from MIT Sloan School of Management and London Business School.

ABSTRACT

Polynucleotide-based vaccine formats principally offer the possibility to vaccinate against any protein antigen, including targets that would be difficult or impossible to produce, e.g., seven-transmembrane spanning proteins. Ideally, the same production process could be used or be rapidly adapted to produce multiple vaccines against disparate targets. Such a nimble and flexible vaccine technology based on messenger RNA (mRNA) has been developed by CureVac.

CureVac's RNActive® vaccines are two-component vaccines: Component 1 is an mRNA optimized for efficient and stable antigen expression. Component 2, which stimulates Toll like receptor 7 (TLR7), is represented by the same mRNA complexed with the cationic peptide protamine. RNActive® vaccines induce balanced adaptive immune responses, i.e. B and T cell-mediated immunity, including effector and sustained memory responses. For example, RNActive® vaccines encoding typical influenza antigens protected against lethal homologous and heterologous challenges with different influenza A virus strains. Protection was persistent and could also be elicited by single dose vaccination. Furthermore, first clinical results from tumor immunotherapeutic studies indicate safety and biological activity in humans. Clinical-grade material could be rapidly produced within a few weeks from receipt of an antigen sequence by a highly scalable production process.

In summary, RNActive® vaccines represent a flexible and rapidly producible breakthrough technology that might be universally applicable for vaccination against protein antigens.

CONCLUDING PANEL DISCUSSION

need and acceptance of vaccines - how to deal with it

Chair:

Alexander VON GABAIN

MFPL of the University of Vienna,
Chair of the SAB of Intercell,
Vienna, Austria

Alexander VON GABAIN

MFPL of the University of Vienna, Chair of the SAB of Intercell, Vienna, Austria

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 the Karolinska Institute, Sweden, as well as an advisor to pharmaceutical and biotech companies. From 1992 to 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 successfully floated on the Vienna Stock Exchange in 2005. From 2005 to 2009 he was Member of the Executive Management Board and CSO of the Company. His research interests are in the fields of microbial gene expression, host-parasite interactions, and immunology. He has published more than 100 publications and book chapters and is holding numerous patents. He holds a professorship of Microbiology at the Max Perutz Laboratories, Vienna, and a foreign adjunct professorship at the Karolinska Institute, Stockholm. He is member of several professional organizations and serves on the boards of biotech enterprises, including TVM Capital, Munich. His achievements have been acknowledged by prestigious industrial awards and academic prizes and honourable memberships, including the Royal Swedish Academy of Engineering Sciences, IVA. In September 2008, he was appointed into the Governing Board of the European Institute of Technology (EIT).

The importance of vaccines for global health care and how to deal with fear

STATEMENT

Panel by Norman Baylor, Shan Lu, Stanley Plotkin, John Shiver, Fred Zepp, Thomas Szucs & Alexander von Gabain

Infectious diseases remain the worldwide greatest health threat and one of the major impediments to overcome the unacceptable economical misbalance between developed and developing countries. The threat, the devastation and the economical damage of worldwide insufficiently controlled infectious diseases is extremely well documented, as is the notion that vaccination is arguably the most successful medical intervention. Globally, vaccines are one of the few cost-effective interventions that result in population-level benefit across the age spectrum. It is with no doubt the most cost-efficient investment to keep known and novel emerging infectious diseases under control, but also predicted pandemic threats. No other medical countermeasures have been as effective in reducing or eliminating the incidence of infectious diseases, such as measles, mumps, rubella, smallpox, and diphtheria. Currently available, highly effective and safe vaccines have a still underused potential to meet a huge global burden of infectious diseases and to save further millions of lives, provided that vaccine developers and providers, charity funds, governmental and non-governmental organisation will be able to synergize in an optimal global fashion. The defeat and reduction of infectious diseases by the virtue of vaccination, could clearly free resources for improved life conditions for all humans on earth, provided the global vaccine gap could be closed.

Unfortunately, the undoubted gigantic benefit of vaccines for global health care is set off by the growing "anti-vaccine movement" which is largely rooted in fear, misinformation, and bad science, particularly in the developed part of the world. In those countries, the exposure of many citizens with life-threading infectious diseases is dramatically reduced, last not least due to the success of the childhood vaccine schedules and through the mediated herd protection. Thus, fundamental opponents of vaccination, often acting in a fashion of "charlatan camouflage", readily take advantage of peoples' legitimate concerns, lack of knowledge and understandable fears, with the consequence that they become principally opposed against vaccination: "The problem with current vaccine groups is that they are advocating for a problem that doesn't exist. Vaccines do not cause autism, diabetes or other developmental disorders or diseases." (Paul Offit). As a result some parents choose to withhold or draw out their children's vaccine schedule, leading to an increased period of time, when children are susceptible to certain diseases. Consequently, some childhood diseases, once mostly eradicated, are making a comeback, even in the developed part of the world and, as the consequence carry the negative debate and attitude into less developed and emerging countries. General public acceptance of vaccines is an enormous challenge for public health care systems. Multiple federal, state, and local entities have attempted to address this challenge through various outreach campaigns, programs, and incentives. In a time of elevated government distrust, transparency is critical. Thus, future generations of vaccinologists need to be globally oriented in both mindset and daily practice.

In the panel, we will try to discuss questions related to the global need for vaccines and the forces at work leading to the improvement of existing and to the development of novel vaccines, but also counteracting their optimal and worldwide usage.

THE PANELLIST

Stanley PLOTKIN

Consultant in Vaccinology,
Doylestown, USA

Dr. Stanley A. Plotkin is Emeritus Professor of the University of Pennsylvania, Adjunct Professor of the Johns Hopkins University and Executive Advisor to Sanofi Pasteur. Until 1991, he was Professor of Pediatrics and Microbiology at the University of Pennsylvania, Professor of Virology at the Wistar Institute and at the same time, Director of Infectious Diseases and Senior Physician at the Children's Hospital of Philadelphia. For seven years he was Medical and Scientific Director of Sanofi Pasteur, based at Marnes-la-Coquette, outside Paris. He is now consultant to a number of vaccine manufacturers and non-profit research organizations.

He is a member of the Institute of Medicine of the National Academy of Sciences and the French Academy of Medicine. His bibliography includes nearly 700 articles and he has edited several books including a textbook on vaccines. He developed the rubella vaccine now in standard use throughout the world, is codeveloper of the newly licensed pentavalent rotavirus vaccine, and has worked extensively on the development and application of other vaccines including anthrax, oral polio, rabies, varicella, and cytomegalovirus.

STATEMENT

Acceptance by the public of recommended vaccines has been a problem since the time of Jenner and is a complex phenomenon derived from a mixture of fears concerning safety, mistrust of authority, misinformation created by the media and the Internet, as well as strongly held religious and philosophical opinions. No longer is it possible to simply assume that the public will acquiesce to vaccine recommendations.

That being said, the majority of the public will accept vaccines when their importance is explained, and another segment will accept if their questions are answered. For the remainder, only legal remedies are available, which will vary with the culture of different countries, ranging from legal obligation as in the United States to ignoring the problem, as in some European countries.

Important factors in vaccine acceptance are the concepts of community and altruism. In Latin America, where the feeling of community is still prevalent, the idea that being vaccinated protects others as well as oneself creates an obligation that is important in maintaining high vaccine coverage. Of course, inordinate fear of a particular disease, as meningitis for example, is a driving force in all societies.

However, the crux of the problem in developed countries is how to deal with legitimate questions. Governments must do more to explain why a vaccine is recommended. Education of physicians and nurses is also paramount, especially where medical and nursing schools do a poor job of training about vaccines. Professional societies also have an important role. Literature that is straight forward, non-condescending and accurate must be made available to all parents and prospective vaccine recipients.

THE PANELLIST

Fred ZEPP

Johannes Gutenberg University,
Mainz, Germany

Professor Fred Zepp is currently Medical Director and Chairman of the Department of Pediatrics at the University Medicine, Johannes Gutenberg University Mainz, Germany. While working as a research fellow at the Department of Pediatrics, Prof. Zepp obtained his MD. Professor Zepp has held many professional posts including head of the Reference Laboratory for Cell-Mediated Immunity of Vaccines and head of the Vaccination Centre, both at the University Hospital, Johannes Gutenberg University Mainz. In addition, he was chairman of the Association for Pediatric Immunology and chairman of the Advisory Board of the Foundation 'Preventive Medicine in Pediatrics'. He also serves as a member of the German Vaccination Advisory Board (STIKO) since twelve years and in 2006 he became member of the Scientific Advisory Board of the German Medical Association. In 2009 he was appointed president of the German Society of Pediatrics and Adolescent medicine. Professor Zepp has contributed to over 100 research articles and reviews, particularly in the fields of cell-mediated immune response to vaccines, candidate vaccines, immune responses to acute respiratory tract infections in children, and the immune responses of newborns.

STATEMENT

The introduction of universal vaccination programs worldwide has led to an impressive reduction and control of many life-threatening infectious diseases over the past 50 years. While vaccines obviously have provided undisputable benefits, the effectiveness of new and existing programs strongly depends on trust and acceptance by the general public. In recent years maintenance of public vaccination programs was repeatedly challenged by concerns about safety and concerns about the rising costs of new innovative vaccine developments. While most health care providers as well as public health officials and epidemiologists state that these fears are unfounded, persisting unbalanced risk perception by the public undermines the effectiveness of vaccination programs.

Factors contributing include the increased media attention given to the theoretical risks associated with vaccination, the spread of anti-vaccination information via the internet and the disappearance of vaccine-preventable diseases. In addition the beliefs of some complementary and alternative medicine providers may contribute to the anti-vaccination movement. Finally, sub-optimal immunization rates are further influenced by inadequate political commitment, poor coordination between different levels of government and health care provision, general misconceptions about contraindications, difficulties with complex and changing immunization schedules and the 'busy lives' factor. Surprisingly even some scientists dispute potentially weakening effects vaccines might exert on the infant's immune system as well as unforeseen, long-term complications of vaccination, such as auto-immune diseases, cancers or neurological sequelae. In consequence a minority claims that the risks associated with infectious diseases in general are lower than the risks of complications caused by vaccines

To counteract this development and improve trust in public vaccination programs physicians and health educators must deal fully and respectfully with the vaccine safety concerns of parents and patients. Health-care workers, from general practitioners to midwives, need to keep up to date with developments in the debate and learn how to discuss, rather than dismiss, parents' fears. Moreover, health politicians as well as public health organizations need to increase their activities in educating an informing the general population. Vaccine coverage might also benefit by providing financial incentives for health care providers and direct measures like recall systems to encourage parents to immunize their children.

THE PANELLIST

John SHIVER

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

Dr. John Shiver is Vice President, Vaccines Discovery. He is responsible for the worldwide leadership of vaccine basic research for the Infectious Diseases Franchise leading the teams of scientists working to develop novel vaccines against a broad range of diseases, including HIV/AIDS, human papillomavirus, rotavirus, zoster, influenza and bacterial infections.

Dr. Shiver has gained international recognition in the scientific community for his leadership of Merck's novel HIV vaccine research program. He has led Merck's HIV-1 vaccine research team since 1992 playing an instrumental role in the development of vaccines based on gene delivery technologies and of quantitative immunological assays to measure T cell immune responses.

After graduating with a B.S. degree in Chemistry/Mathematics from Wofford College, Dr. Shiver received a Ph.D. in Physical Chemistry from the University of Florida, and completed a postdoctoral fellowship in Biophysics at Purdue University. He joined Merck in 1991 following four years as a Senior Staff Fellow in the Experimental Immunology Branch of the National Cancer Institute, National Institutes of Health. Dr. Shiver is an Editorial Board Member for the Journal of Virology and Drug Discovery Today: Disease Mechanisms. He is a member of the NIH HIV-1 Vaccine Testing Network Laboratory Science Advisory Committee and the Aeras Immunology Technical Advisory Group (a nonprofit group dedicated to the development of tuberculosis vaccines), and the External Steering Committee for the Emory University Vaccine Center. He is on the Executive Board of the International Society of Vaccines and the Scientific Advisory Board of the Seattle Biomedical Research Institute. He is also an Adjunct Professor at the University of Pennsylvania College of Medicine in Philadelphia.

Dr. Shiver is the author of more than 100 articles that have been published in leading scientific journals, including Science, Nature, Cell, and the Proceedings of the National Academy of Sciences. In addition, Dr. Shiver is a co-author of 24 awarded patents covering his contributions in the field of novel vaccine development.

STATEMENT

While substantial progress has been made to provide affordable, safe and effective vaccines to global populations, there still exist considerable opportunities for continued success against vaccine-preventable diseases. The obvious and very important successes have been achieved against poliovirus and small pox and there measles and other immunizations that are routine in developed nations are becoming more available as well. This trend should continue with the introduction of highly effective, safe vaccines against rotaviruses, pneumococcus, and HPV. The implementation of these vaccines to global populations will be facilitated by lower costs through greater manufacturing efficiency and achieving more thermostable formulations that reduce, or eliminate, the need for maintaining cold chain storage. Greater ease of administration, such as by oral, nasal, or needle-free patch delivery also facilitate broader usage of these products such as has been the case for the Sabin poliovirus vaccine.

THE PANELLIST

Thomas SZUCS

European Center
of Pharmaceutical Medicine,
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Thomas Szucs is Professor of Pharmaceutical Medicine and Director of The Insitute of Pharmaceutical Medicine/ European Center of Pharmaceutical Medicine at the University of Basel. He is also a Professor and part-time lecturer for Medical Economics at the University of Zurich. Previously he was Chief Medical Officer of Hirslanden Holding, the largest private hospital chain in Switzerland. From 1998 to 2001 he was head of the Department of Medical Economics, a joint venture of the University Hospital in Zurich and the Institute of Social and Preventive Medicine of the University of Zurich. Professor Szucs' former appointments include head of research and founder of the Center of Pharmacoeconomics of the University of Milan, head of the working group for Clinical Economics at the University of Munich, senior consultant at Arthur D. Little Inc and head of the Department of Health Economics at F. Hoffmann-La Roche Ltd. in Basel. He holds a medical degree from the University of Basel, a Masters in Business Administration from the University of St Gallen, Switzerland, a Master of Public Health degree from Harvard University, and is board certified in Pharmaceutical Medicine as well as in Prevention and Public Health. Recently, he has received a LL.M in International Business Law with a specialisation in Information- and Technology Law from the University of Zurich. He is also member of the editorial board of several scientific journals and has published more than 300 articles, book chapters and monographies. He has worked extensively in the field of pharmaceutical economics and epidemiology. In addition he is head of the Swiss Association of Health Economics. He serves on the board of various biotech companies and is chairman of BB Biotech, a large biotech investment company. Recently he has also been appointed as chairman of the largest Swiss health insurer.

STATEMENT

Vaccines are the most popular preventive intervention worldwide. The wide use of vaccination either in children or in selected populations at high risk has produced substantial achievements in the control of vaccine-preventable diseases. The economic importance of vaccines lies partly in the burden of disease that can be avoided and partly in the competition for resources between vaccines and other interventions. Interventions that produce both a health benefit and cost savings are inherently cost-effective. For some vaccines economic evaluations consisted of comparing the costs of vaccination with the savings in treatment costs. For all these vaccination strategies, monetary savings are attained together with improved health status, and the decision to vaccinate is straightforward. However, other (newer) vaccines that do not save costs produce health benefits. The decision to vaccinate depends now on the willingness of the society to pay for increased health benefits.

An instrument to assess the relative value of different immunization strategies is the economic evaluation, in which different vaccination strategies are being calculated and compared with a reference strategy, which is often the non-intervention strategy, i.e. no vaccination. Costs can be divided in medical costs related to the disease (medication, laboratory tests, consultations, hospitalizations) or to the vaccination (purchasing price of the vaccine, costs for administering the vaccine, treatment of side effects). Societal costs are indirectly related to the treatments and vaccination and are mainly costs of lost productivity due to disease.

Medicines differ from classical vaccines in at least three ways: firstly, there is a longer tradition of economic evaluations for vaccines than for medicines. Some of the earliest economic studies were carried out in the field of vaccines in the public health arena. Secondly, comparatively fewer central decision makers need to be convinced as compared to drugs. The reason for this being a more centralised process of recommending vaccines and vaccination policies. Thirdly, externalities are more relevant in the field of vaccines. Positive externalities are present in the case where herd immunity prevents the spread of the disease in the community.

For the investor, vaccination is a challenging area with potentially high returns, provided the companies are able to demonstrate a value case for patients, society and payors.

THE PANELLIST

Shan LU

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Dr. Shan Lu is a physician scientist, an academic vaccine researcher and a leader in the International Society for Vaccines.

Currently he is a professor in the Department of Medicine at the University of Massachusetts Medical School, USA and holds adjunct professor appointments at several leading Chinese academic biomedical institutions. In the last two decades, Dr. Lu has used the DNA vaccine approach to develop and optimize vaccines against HIV-1, bioterrorism (plague, smallpox, anthrax and botulinum) and emerging pathogens (SARS, seasonal and pandemic influenza, EV71 and C. diff), pathogens causing chronic infectious diseases (hepatitis viruses and h-CMV) and pathogens causing neglected infectious diseases including diarrhea. His research has focused on the immunogenicity of antigens and the optimization of protective antibody responses. His group developed and tested the first ever DNA prime-protein boost HIV vaccine in humans. Dr. Lu is a member of the Executive Board for the International Society for Vaccines (ISV) and served as a co-chair for the 2nd to 4th Annual Global Congresses organized by the International Society for Vaccines (ISV). He has been a member on US NIH vaccine grant review panels including serving as Chair for the selection of key biodefense vaccines for US national vaccine stockpiling. He serves on the review panels for China's National Natural Science Foundation grant applications, and is also an Executive Committee member of China AIDS Vaccine Initiative (CAVI).

STATEMENT

Globalization, digitization, and humanization of vaccinology

We are living in a smaller, better-connected and more individual-centered world. Vaccinology, which is still not considered a real science by many in the biomedical research circle, is faced with the challenges of satisfying the curiosity of newfound scientists eager to join the field and also addressing suspicions from consumers who are having doubts on the benefits associated with mass vaccination.

The existing models of vaccine R&D and distribution may no longer be sufficient to allow for the survival of the big vaccine companies let alone capture emerging opportunities that can bring vaccinology to new heights.

Paradoxically, with a greater proportion of the population now living in improved conditions in many developing countries, the demand for vaccines may not be increased proportionally.

The issues are: 1) What vaccines are needed and will their need changes based on times and geographical locations? 2) How to develop and distribute such vaccines, 3) Where will such a new system be established? and 4) Who should be in charge of such system and who should be the contributing partners? Future generations of vaccinologists need to be globally oriented in both mindset and daily practice.

The explosion of information in related fields, such as molecular biology, microbiology, immunology, infectious disease, and public health, prevents even the most knowledgeable vaccinologists claim that any particular vaccine has been developed according to the utmost standards put forth in theory, yet that is exactly what many critics (whether they wear *Regulatory* hats or not) are expected to request.

The credible and timely updated sources of information, most likely in the form of digital media with easy access and independent evaluation, will be critical to not only the general public but also to vaccine professionals. Zero tolerance of vaccine adverse events among the general population in combination with individualized medicine from the scientific community does not allow much room for error for future vaccines. Ethnic background, socioeconomic conditions, and nutritional status have become factors in the new equation of vaccine efficacy. Productive dialogues among vaccine developers, clinicians, and targeted populations rather than simple guidelines may be more effective in gaining the acceptance of vaccines.

In the first decade of the 21st century, we have witnessed an unprecedented interest in vaccinology. Pleasant surprises did happen with the licensing of new vaccines and approval of new applications to existing vaccines to expanded world population. The true visionary leaders in vaccinology need to capture the momentum and further promote the field to a healthy and sustainable growth.

THE PANELLIST

Norman BAYLOR

Food and Drug Administration,
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Dr. Norman W. Baylor received his PhD in molecular microbiology from the University of Kentucky. He spent three years as a postdoctoral fellow at the University of Virginia School of Medicine in the Department of Microbiology and Immunology working on influenza virus, and 3 years with the Program Resources Incorporated as a Senior Research Scientist at the National Cancer Institute-Frederick Cancer Research Facility working in the area of retrovirology.

Dr. Baylor joined the U.S. Food and Drug Administration in 1991 as a scientific reviewer in the Office of Vaccines Research and Review (OVRR), within the Center for Biologics Evaluation and Research (CBER) where he was actively involved in the licensure of the first acellular pertussis vaccine, varicella vaccine and several combination vaccines. Other positions held in OVRR include the Associate Director of Policy and later the Deputy Director. In 2004, Dr. Baylor was selected as the Director of OVRR where he is responsible for planning, developing and administering CBER's broad national and international programs and operational activities involving vaccines and related products. He oversees the activities of over 300 professional employees engaged in research and regulatory activities related to the development, manufacture, and testing of vaccines and related products. This entails managing OVRR's programs to review investigational new drug applications, biologics license applications and supplements, and performance of control testing of biological products.

Dr. Baylor also serves as FDA's liaison to CDC's Advisory Committee on Immunization Practices, the DHHS National Vaccine Advisory Committee, and most recently as a representative of the International Advisory Committee (IAC) to the Malaria Eradication Research Agenda (MalERA). Dr. Baylor also serves as an expert advisor to the World Health Organization on several global vaccine initiatives. He has been with the FDA for over 18 years.

STATEMENT

Vaccines are considered one of the most significant contributions to public health. No other medical countermeasures have been as effective in reducing or eliminating the incidence of infectious diseases such as measles, mumps, rubella, smallpox, and diphtheria. Globally, vaccines are one of the few cost-effective interventions that result in population-level benefit across the age spectrum. Unfortunately, the growing "anti-vaccine movement" is rooted largely in fear, misinformation, and bad science. According to Paul Offit, MD, Chief of Infectious Diseases at The Children's Hospital of Philadelphia and Professor of Pediatrics at the University of Pennsylvania School of Medicine, "The problem with current vaccine groups is that they are advocating for a problem that doesn't exist. Vaccines do not cause autism, diabetes or other developmental disorders or diseases." Some parents choose to withhold or draw out their children's vaccine schedule, leading to an increased period of time when children are susceptible to certain diseases. Consequently, some childhood diseases once mostly eradicated are making a comeback.

Public acceptance of vaccines is an enormous public health challenge. Multiple federal, state, and local entities have attempted to address this challenge through various outreach campaigns, programs, and incentives. In a time of elevated government distrust, transparency is critical. In February 2009, the potential adventitious agent, porcine circovirus 1 (PCV-1), was discovered in rotavirus vaccines. The US FDA quickly informed the public of the risks, carried out its own scientific investigation, and convened a public advisory meeting. Such deliberate and proactive actions will be instrumental in helping the public regain confidence in government authorities.

Media technology will play an important role in vaccine avocation efforts and the dissemination of information that demonstrates the safety and benefits of vaccines. Important objectives of the US National Vaccine Plan include 1) Evaluating new media (such as mobile technologies and social media) and utilizing it appropriately to reach target audiences with accurate and timely information about vaccines and 2) maintaining current, easily accessible, evidence-based online information on vaccine preventable diseases and vaccines, including benefits and risks and the basis of immunization recommendations.

Dissemination of sound science and education will help offset public rejection of vaccines, yet the enormity of this task should not be underestimated. Education efforts should seek to simplify complicated concepts into easy to understand language while emphasizing the benefits of vaccination versus the perceived risks. Ultimately, the public seeks quality information from a trustworthy source so healthcare providers should be prepared to effectively communicate with patients and allow parents and guardians to voice concerns.

POSTER SESSION

poster session abstracts

Wenji ZHANG | Florian ANDERL

WENJI ZHANG

Goal of ELISPOT proficiency accomplished: ELISPOT assays provide reproducible results among different laboratories for T-cell immune monitoring — even in hands of ELISPOT novices

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T cell monitoring remains challenging in tumor vaccine trials due to the necessity of testing live cells in functional assays, and the low frequencies of tumor antigen-specific T cells. Recent multi-center initiatives that aimed at harmonizing T cell assays have drawn attention to alarming- 30-, 20- and 150-fold inter-laboratory variations in test results for ELISPOT, ICS and tetramers, respectively (*Immunity*, 2009, 31: 527-528). The authors concluded: "The high degree in variability makes the comparison between any two labs become a game of chance". Puzzled and alarmed by this message, we undertook a similar effort for ELISPOT together with a European consortium, NEUCAPs. For our study, we required that all participants from the eleven reporting labs follow the same detailed protocol using one uniform platform, and that the study participants had never previously conducted an ELISPOT assay (the results of their first attempt were recorded for the study). While three of the labs failed with the basic logistics of the trial, eight detected the peptide-specific CD8+ T-cells in frequencies approximating the values established by the Reference Laboratory. These results show that ELISPOT can produce comparable, reliable data (even from untrained personnel) if a standardized platform for the assay and data analysis is followed. Since ELISPOT assays have been qualified and validated for regulated studies, they are ideal candidates for robust and reproducible monitoring of T-cell immunity in tumor vaccine trials.

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FLORIAN ANDERL

A new vaccination strategy against *Helicobacter pylori* infection through induction of gamma-glutamyltranspeptidase specific inhibitory antibodies

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As one of the most prevalent bacterial infections worldwide, *Helicobacter pylori (H.p.)* is affecting half of the worlds population, causing peptic ulcers and gastric cancer. Until now no human vaccination study was successful, although big efforts have been initiated to develop a vaccine against this pathogen. Thus, an approved vaccine for humans is still not in sight. It has to be figured out if the failure in human trials is due to the vaccine formulation - antigen and adjuvant composition, as well as the type of immunity induced – systemic or mucosal. Our group described a virulence factor of *H. pylori*, the H.p. gamma-glutmyltranspeptidase (HPgGT) that inhibits the proliferation of T-cells and thus prevents the generation of an effective immune response. We used HPgGT in an experimental mouse infection model for a novel vaccination approach. As HPgGT is a secreted protein, HPgGT specific T-cells can hardly target the pathogen. Therefore HPgGT was combined with outer membrane proteins to induce protective T-cell responses. With different vaccine designs we tested their capability to induce protection, revealing a need for mucosal immunization.

Notably, immunization with HPgGT induced a strong antibody response, which blocked its enzymatic activity, thereby counteracting the immunosuppressive activity of HPgGT. In infection experiments this vaccinations led to a substantial decrease of bacterial colonization in the stomach, making this novel "liberation vaccine" a promising candidate for a new immunization strategy.

Elizabeth NYEKO | Shumaila Nida HANIF

ELIZABETH NYEKO

Memory CD8 T Cell Response in Avian Influenza A (H5N1): Insights from a Convalescent H5N1 Cohort in Vietnam

Elizabeth Nyeko[1], Cameron Simmons[2], Annette Fox[3], Do Lien Anh Ha[2], Menno D. de Jong[2], Laurel L. Y. Lee[1], Nguyen Van Vinh Chau[2], Yanchun Peng[1], Vu T K Lien[4], Nguyen L K Hang[4], Le Thi Quynh Mai[4], Sarah L Rowland-Jones[1], Andrew McMichael[1], Peter Horby[2], Jeremy J. Farrar[2] and Tao Dong[1].

Antibodies are critical to the clearance of influenza, but with negligible antibody-mediated immunity to H5 surface protein in most human populations due to antigenic variation; a H5N1 pandemic would be catastrophic. H5N1 is a highly virulent strain of influenza virus that produces severe disease with a fatality rate of c.60%. It presents with an aggressive clinical course in humans resembling that of reconstructed 1918 H1N1 highly pathogenic influenza virus in macaques. Fortunately however, H5N1 remains incapable of sustained human-to-human transmission although it is likely the virus may evolve such capability in future by reassortion/ mutation. Convalescent plasma and manufactured antibodies are indicated to be beneficial in H5N1. However, while antibody response is not detected for days; the T cell response can be mounted within several hours and early viral suppression promotes survival. Evidence in mice and humans suggest influenza-specific CD8 T cells play a critical role in viral clearance, and that memory CD4 cells maintain this CD8 response. However, caveats remain in the understanding of the nature of a protective CD8 T Cell response in recovered H5N1 cases; and whether virus-specific CD8 T cells are indeed protective.

We investigated the dynamics and nature of the memory T cell response associated with good clinical outcome in our cohort of convalescent H5N1 subjects – we mapped H5N1 epitopes using overlapping peptides, determined HLA-restriction, CD4/CD8 phenotype, quantified H5N1-specific and cross reactive epitopes using tetramers, and are assessing the quality of the memory response, dissecting the kinetics and dynamics over a two year period, and ability to control virus infection *in vitro*.

The antigen-specific memory T cell response to overlapping synthetic peptides spanning the full proteome of influenza A/ VietNam/CL26/2005 (H5N1) provides a picture of functional immunity with CD4 and CD8 T cell memory to a range of H5N1 synthetic epitopes, with varying levels of immunodominance, directed not only to the more conserved NP and M regions, but also the more variable H5-HA. As such, the study provides insight into T cell vaccine strategies that may control infection with highly pathogenic H5N1 viruses.

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SHUMAILA NIDA HANIF

Cellular immune responses in mice induced by *M. tuberculosis* PE35-DNA vaccine construct

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PE35 gene of *Mycobacterium tuberculosis* is present in the region of difference (RD) 1 that is deleted in all vaccine strains of *Mycobacterium bovis* BCG. The aim of this study was to clone *PE35* DNA into a DNA vaccine plasmid with CMV promoter and interleukin-2 secretory signal and evaluate the recombinant plasmid for induction of antigen-specific cellular responses in mice. DNA corresponding to PE35 was PCR-amplified from the genomic DNA of *M. tuberculosis* H_{37}R-v, cloned into pGEMT-Easy vector and sub-cloned into the DNA vaccine vector pUMVC6. BALB/c mice were immunized with recombinant pUMVC6/PE35 and spleen cells were tested for T-helper (Th)1 (antigen-induced proliferation and secretion of IFN-γ, Th2-type IL-5) and anti-inflammatory (IL-10) cytokine responses to pure recombinant PE35 protein and its synthetic peptides. Mice immunized with the recombinant plasmid DNA (pUMVC6/PE35) showed positive Th1-type cellular responses to pure PE35, but not to an irrelevant antigen, i.e. PPE68. However, the vaccine construct did not induce antigen-specific Th2-type (IL-5) or anti-inflammatory (IL-10) reactivity to PE35. Testing with synthetic peptides showed that Th1-type cells recognizing various epitopes of PE35 were induced in mice immunized with pUMVC6/PE35 DNA. These results suggest that pUMVC6/PE35 may be useful as a safer vaccine candidate against TB.

Melinda HERBÁTH

Improved cellular uptake contributes significantly to the enhanced immunogenic properties of CpG-antigen conjugatess

Melinda Herbáth[1], Zsuzsanna Szekeres[2], Anna Erdei[1,2], József Prechl[2]

Effective subunit vaccine designs require safe but powerful strategies that ensure effective antigen uptake and proper activation of antigen presenting cells. CpG motifs that occur in bacterial and viral DNA and are the ligands of the pattern recognition receptor TLR9, are promising candidates for this role, as pathogen associated molecular patterns can be used to induce innate immune responses that promote adaptive immunity.

Our aim was to determine the effect of coupling a TLR9 agonist CpG oligodeoxynucleotide (ODN 1668) to the model antigen streptavidin (SA) on antigen uptake by and activation of APCs *in vitro*, and on the immune responses in mice *in vivo*. We used suboptimal doses of CpG ODN to avoid deleterious systemic reactions but to retain adjuvanticity.

We mixed CpG or coupled biotinylated CpG (CpGb) ODNs to SA and also studied the immunogenicity of the mixture of these two formulations (SA + CpG, SA-CpGb and SA-CpGb + CpG, respectively) compared to SA alone. We measured cell association and uptake of the complexes and activation of B and T cells and BMDCs by flow cytometry. We immunized mice with these formulations and studied the effect of TLR9 targeting with serological tests (ELISA, reverse protein array) and reverse ELISPOT assays. We performed RT PCR on the cell types mentioned above to determine TLR9 expression.

Biotin-mediated coupling of CpG ODNs to SA (SA-CpGb) resulted in enhanced association and uptake of streptavidin by APCs and T cells. In contrast to DCs and T cells, this uptake was not influenced by the presence of and 10- or 100-fold excess of free CpG ODN in B cells *in vitro*. We observed a much higher expression level of TLR9 in B cells than in DCs. The number of antigen specific antibody secreting cells were significantly higher in the draining lymph nodes when SA-CpGb complexes were administered compared to SA and SA-CpGb + CpG treatments. Our data suggest that competition between SA-CpGb complexes and free CpG can occur *in vivo*, as vaccinating SA-CpGb + CpG (in 1:1 ODN ratio) reduced the level of total antigen specific antibodies dramatically compared to the SA-CpGb treatment. The concentration of both antigen specific IgG1 and IgG2a antibodies were highest when SA-CpGb complexes were administered. The presence of free CpG (SA-CpGb + CpG) reduced the level of these antibodies.

These results imply that improved cellular uptake is at least as important in the enhancement of immunity against CpG coupled antigen, as the focused effect of the activatory ODN exerted on the target cells. We assume that the competition we observed occurs mainly on myeloid DCs *in vivo*, given that this cell type has a low TLR9 expression level compared to B cells. Our results can help find the best formulation of vaccine designs that contain CpG ODN as an adjuvant.

Our work is supported by an NKTH-OTKA grant (K68617).

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Vinay SAINI

VINAY SAINI

To compare the release of nitric-oxide after administration of HBsAg loaded Polymeric Lamellar Substrate Particles=PLSPs [PLGA (75:25)] and microspheres=Ms [PLGA(50:50)] in mice

Vinay Saini[1], P. K. Murthy[2], and Dharmveer Kohli[1]

Methods: Blank PLSPs and Ms were prepared using non-solvent induced precipitation method and double emulsion solvent evaporation method (W/O/W), respectively. HBsAg was adsorbed separately in PLSPs and Ms. These microparticles were characterized in- vitro for their size, polydispersity index (measured by photon correlation spectroscopy), shape (using scanning electron microscopy), percentage antigen adsorption-efficiency (using bicinchoninic acid protein estimation method).The antigen integrity (Sodium Dodecylsulphate- Polyacrylamide Gel Electrophoresis), in-vitro release were also evaluated. The immune-stimulating activities were studied following subcutaneous injection of PLSP-10 mcg HBsAg and Ms-10 mcg HBsAg in separate groups (single-dose on day 0) and compared with Plain-10 mcg HBsAg vaccines (two-doses on 0 and 15 days) in separate groups (Balb/c mice).The peritoneal macrophages isolated (after 30 days of primary immunization) aseptically from the animals and incubated in-vitro with HBsAg (5mcg /ml) or LPS (1mcg /ml). Nitric oxide (NO) in the culture supernatants was determined using Griess- reagent.

Results: The designed microparticles possessed an average size less then 10 micrometer, were efficient for phagocytosis. The nitric-oxide release was found more for PLSPs adsorbed antigen (single-dose) vaccine in comparison to two doses of plain antigen vaccine ($P<0.01$).Nitric-oxide release was also found more for PLSPs than that of Ms.

Discussions: The more angular form or macrostructure and more hydrophobocity of the PLSPs stimulate the activity of immune cells such as macrophages (due to an increased probability of tissue reaction) than that of smooth and spherical surface Ms. NO pathway is induced by IFN-γ or LPS and is known as classically activated macrophages (CAMF).These data support that NO may reduce the expression of Hepatitis B viral antigens in the cell, thereby can be used to diminish the severity of the immune -mediated liver diseases (after testing in large animal models).

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Christina SCHELLENBACHER

A novel human papillomavirus (HPV) vaccine (RG1-VLP) to protect against mucosal and cutaneous types

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Currently licensed bivalent (Cervarix; HPV16/18) or quadrivalent (Gardasil; HPV6/11/16/18) human papillomavirus (HPV) vaccines are based on virus-like particles (VLP), self-assembled from major capsid protein L1, that induce high-titer and type-restricted neutralizing antibodies. Prophylactic vaccination protects against ano-genital infection and disease by two most prevalent (HPV16/18) of the 15 high-risk (hr) genital-mucosal types with high-efficacy, yet cross-protection against non-vaccine hr HPV is limited. One (quadrivalent) vaccine also protects against genital warts caused by low-risk HPV6/11. Conversely, the minor capsid protein L2 contains type-common epitopes that induce low-titer neutralizing antisera and cross-protect against heterologous papillomavirus types in animal studies.

To augment L2 immunogenicity and provide broader cross-protection against heterologous HPV, we have generated an HPV16 VLP based vaccine (RG1-VLP) that displays a key cross-neutralization L2 epitope (RG1). By inserting the 20 amino-acid peptide RG1 into an immunogenic surface loop of HPV16 L1, the repetitive (360 times) display of L2 by the assembled particle induces broadly cross-neutralizing antisera to a number of high-risk and low-risk mucosal HPV without compromising type-restricted L1-specific immunity (Schellenbacher et al, J Virol, 2009).

Immunization with RG1-VLP using the human-applicable adjuvant alum-MPL (similar to AS04 used in Cervarix) induced broadly cross-neutralizing antibodies against hr mucosal HPV16/18/31/45/52/58, low-risk HPV6/11 and hr cutaneous HPV5 in both rabbits and mice. To evaluate the full spectrum of vaccine efficacy, neutralization assays were established based on novel pseudovirions, or infectious cutaneous HPV virions isolated from patients' skin warts. Antisera to RG1-VLP additionally cross-neutralized mucosal hr HPV26/33/35/39/68/56/59/68/73, mucosal low-risk HPV32, and cutaneous HPV2/27/3/76, but not HPV1/4. Using an experimental in-vivo genital challenge model, passive transfer of 20 microliter immune serum raised against RG1-VLP effectively protected mice against vaginal infection with pseudovirions of phylogenetically divergent mucosal hr HPV16/45/73/56/59.

This novel RG1-VLP HPV vaccine is a promising candidate to protect against a broad-spectrum of mucosal and cutaneous HPV infections and diseases.

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Annett HESSEL

Vectors based on Modified Vaccinia Ankara expressing influenza H5N1 hemagglutinin induce substantial cross-clade protective immunity

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Background: New highly pathogenic H5N1 influenza viruses are continuing to evolve with a potential threat for an influenza pandemic. So far, the H5N1 influenza viruses have not widely circulated in humans and therefore constitute a high risk for the non immune population. The aim of this study was to evaluate the cross-protective potential of the hemagglutinins of five H5N1 strains of divergent clades using a live attenuated modified vaccinia Ankara (MVA) vector vaccine.
Methodology/Principle Findings: The replication-deficient MVA virus was used to express influenza hemagglutinin (HA) proteins. Specifically, recombinant MVA viruses expressing the HA genes of the clade 1 virus A/Vietnam/1203/2004 (VN/1203), the clade 2.1.3 virus A/Indonesia/5/2005 (IN5/05), the clade 2.2 viruses A/turkey/Turkey/1/2005 (TT01/05) and A/chicken/Egypt/3/2006 (CE/06), and the clade 2.3.4 virus A/Anhui/1/2005 (AH1/05) were constructed. These experimental live vaccines were assessed in a lethal mouse model. Mice vaccinated with the VN/1203 hemagglutinin-expressing MVA induced excellent protection against all the above mentioned clades. Also mice vaccinated with the IN5/05 HA expressing MVA induced substantial protection against homologous and heterologous AH1/05 challenge. After vaccination with the CE/06 HA expressing MVA, mice were fully protected against clade 2.2 challenge and partially protected against challenge of other clades. Mice vaccinated with AH1/05 HA expressing MVA vectors were only partially protected against homologous andheterologous challenge. The live vaccines induced substantial amounts of neutralizing antibodies, mainly directed against the homologous challenge virus, and high levels of HA-specific IFN-γ secreting CD4 and CD8 T-cells against epitopes conserved among the H5 clades and subclades.
Conclusions/Significance: The highest level of cross-protection was induced by the HA derived from the VN/1203 strain, suggesting that pandemic H5 vaccines utilizing MVA vector technology, should be based on the VN/1203 hemagglutinin. Furthermore, the recombinant MVA-HA-VN, as characterized in the present study, would be a promising candidate for such a vaccine.

Yvonne HOFMEISTER

A Tick-Borne Encephalitis Virus Vaccine Based on the European Prototype Strain Induces Broadly Reactive Cross-Neutralizing Antibodies in Humans

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Background: The *Mammalian Tick-borne Virus Group* of the genus Flavivirus comprises a European-, Far Eastern- and Siberian *Tick-borne encephalitis virus* (TBEV) subtype. Previous studies demonstrate some degree of cross-neutralization between individual members of the subtypes, however, due to peculiarities of individual virus isolates as well as differences in the applied methods for analysis, it could not consistently be determined whether the neutralization capacity of e.g. vaccine-induced antibodies is equivalent across these antigenically distinct viruses. To circumvent these problems, hybrid viruses that encode the TBEV surface proteins (prME) for representative viruses within all subtypes, and *Omsk Hemorrhagic Fever Virus* (OHFV), were constructed in the genomic context of *West Nile Virus* (WNV). These viruses allow for the unbiased head-to-head comparison in neutralization assays as they exhibit the antigenic characteristics of the TBEV strains from which the surface proteins were derived from, but exhibit comparable Particle to Infectivity ratio and growth in cell culture.

Methods: Individual prM and E surface proteins derived from various TBEV strains, representative for all TBEV subtypes, were integrated in a WNV cDNA system, and the resulting hybrid viruses were characterized regarding growth and infectivity in cell culture. Serological comparability between a TBEV wildtype virus and the corresponding hybrid virus, which encodes for the same surface proteins was analyzed in Microneutralization Assay (µNT). µNT assays using all hybrid viruses were carried out using a subset of sera derived from a TBEV vaccine trial.

Results: Human sera derived from a TBEV vaccine trial were analyzed and revealed equivalent neutralizing antibody titers against European-, Far Eastern- and Siberian subtype viruses, indicating equally potent cross-protection against these TBEV strains, and a somewhat reduced but still protective neutralization capacity against more distantly related viruses like OHFV.

The vaccine is therefore expected to fully protect not only against the European but also against the Far Eastern and the Siberian TBEV subtypes, as well as, albeit less potently, the more distantly related OHFV.

Orlinger KK, Hofmeister Y, Fritz R, Holzer GW, Falkner FG, Unger B, Loew-Baselli A, Poellabauer E, Ehrlich HJ, Barrett NP, Kreil TR. A Tick-Borne Encephalitis Virus Vaccine Based on the European Prototype Strain Induces Broadly Reactive Cross-Neutralizing Antibodies in Humans. Journal of Infectious Diseases [2011], in press

Vibhuti SINGH | Severin ZINÖCKER

VIBHUTI SINGH

A cronic contact eczema mitigates alopecia areata through down-modulation of antigen specific T cell response and promotion of apoptosis

Vibhuti Singh, Margot Zoeller – Department of Tumor Cell Biology, University Hospital of Surgery, Heidelberg.

Alopecia Areata (AA) is an autoimmune disease affecting anagen stage hair follicles and is characterized by a peri and Intrafollicular infiltrate of CD4+ and CD8+ T cells. The most effective way of treating AA is by application of contact sensitizers like Diphencyprone or Squaric acid dibutyl easter (SADBE). This topical application is refreshed several months so that a mild form of a chronic eczema is persistently maintained. The mechanism underlying the curative effect of chronic contact eczema in AA is still unknown, recent studies in the C3H/ HeJ mouse model of AA provided evidence for a hindrance in APC migration as well as strong expansion of myeloid derived suppressor cells (MDSC) that hampered T cell proliferation and activation, the effect of latter was abolished by all trans retinoic acid which drives MDSC into differentiation. This confirmed a central role of MDSC in AA therapy. To prove weather the curative effect of SADBE treatment ,indeed, relies on MDSC induction we compared the effect of *in vivo* SADBE treatment with the effect of in vitro co- cultures of AA lymph node cells with MDSC derived from SADBE treated AA mice. SADBE as well as MDSC strongly interfered with AA LNC proliferation accompanied by weak down regulation of Zeta chain, and strongly impaired activation of Lck and Zap 70, and less pronounced the cjun and MAPK pathway. The strongest effect was seen in presence of AA skin lysate used as surrogate autoantigen, proliferation was also impaired in the presence of PMA plus Ionomycin indicating that SADBE / MDSC act at least partly independent of the TCR complex. Infact SADBE/ MDSC promoted activation of several proapoptotic molecules engaged in mitochondrial apoptotic pathway and interfered with activation of the antiapoptotic proteins Akt and with Bad phophorylation though less pronounced. The latter effects strongly correlated with TNFα secretion by MDSC and TNFRI expression in AA/DTH lymphocytes.
Taken together, SADBE treatment results in the expansion of MDSC which impair T cell activation and contribute to breaking autoimmune T cell apoptosis resistance via promoting activation of pro apoptotic proteins.

SEVERIN ZINÖCKER

Mycoplasma hyorhinis infection of Mesenchymal tromal Cells efficiently blocks the activation of T cells in vitro

Severin Zinöcker[1,2], Meng-Yu Wang[3], Peter Gaustad[4], Gunnar Kvalheim[5], Bent Rolstad[2], and John T. Vaage[1]

Background: Mesenchymal stromal cells (MSC) have important immunosuppressive functions and are currently under investigation for clinical treatement of autoimmune diseases and graft*versus*-host disease (GvHD) following allogeneic hematopoietic cell transplantation (alloHCT).
Methods: In an experimental animal model of alloHCT, we investigated the inhibitory effects of rat bone marrow-derived MSC on T cell proliferation both *in vitro* and as a cell therapy for GvHD *in vivo*.
Results: MSC initially showed surprisingly strong inhibition of in vitro mixed lymphocyte reactions. We later discovered that our primary MSC cultures had been involuntarily infected with the common cell culture contaminant *Mycoplasma hyorhinis*, and that infection increased the anti-proliferative effect of MSC dramatically. Inhibition could not be explained solely by the well-known ability of mycoplasmas to degrade tritiated thymidine, but likely was the result of rapid dissemination of *M. hyorhinis* in lymphocyte cultures. Furthermore, mycoplasma infection decreased the numbers interferon γ–producing T cells as well as natural T regulatory cells and accelerated cell death in stimulated lymphocytes. Despite these potent inhibitory effects on alloactivated T cells *in vitro*, preventive and therapeutic infusions of syngeneic or allogeneic mycoplasma-infected MSC could not protect rats against lethal GvHD *in vivo*.
Conclusions: MSC are efficient vectors of mycoplasma infection resulting in potent suppression of T cell proliferation, emphasizing the importance of cell culture monitoring for this contaminant.

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Se Jin IM and Yong bok SEO | Hong NAM KOONG

SE JIN IM & YONG BOK SEO

Recombinant IL-7 fused with nonlytic Fc augmented protection against heterologous virus challenge

Se Jin Im[1], Yong Bok Seo[1], Ki Seok Park[2] and Young Chul Sung[1,2]

The engagement of an adjuvant is one of the fascinating strategies for opposing influenza pandemics due to a dose-sparing effect and the cross-protection. We previously demonstrated that IL-7 fused with nonlytic Fc (hIL-7-mFcm) was superior to IL-7 and IL-7 fused with lytic Fc for the increase in antigen-specific T cell responses by DNA vaccination. Here, we examined the adjuvant effect of recombinant IL-7 fused with nonlytic Fc for influenza vaccine.
Codelivery of hIL-7-mFcm with seasonal flu vaccine achieved about 9-fold higher IgG titers and detectable hemagglutination-inhibition (HI) titers compared to vaccine alone. Furthermore, one out of six dose of adjuvanted vaccine still induced 2.3-fold higher IgG titers than vaccine alone in mice. In particular, a half-dose of adjuvanted vaccine also generated 4 to 10-fold higher IgG titers and HI titers as well as early considerable IgG responses in monkeys.
More interestingly, protection of mice from lethal challenge with antigenically distant influenza virus was significantly increased by codelivery of hIL-7-mFcm (82%) and even one out of six dose of adjuvanted vaccine was also more effective than vaccine alone (42% vs. 9%, $p<0.05$).
Additionally, we confirmed that the adjuvant effect of hIL-7-mFcm was mainly achieved via CD4+ cell-dependent mechanisms. Taken together, recombinant IL-7 fused with nonlytic Fc could be an attractive adjuvant to overcome limited influenza vaccine supply and unmatched sequences of HA protein for future pandemics.

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HONG NAM KOONG

CXCL11 as a vaccine adjuvant enhance type-1 T cell responses

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Chemokines have been reported to play important roles in eliciting adaptive immune responses by selectively attracting the innate cellular components to the site of antigen presentation. To investigate the effects of chemokine as an adjuvant on the adaptive immune responses induced by DNA vaccine, an OVA DNA vaccine was co-delivered with plasmid DNA encoding chemokine CXCL11. Our results indicated that co-delivery of CXCL11-expressing plasmid increased antigen-specific CD8+ T cell responses in terms of IFN-γ secretion more than 2.3 fold in mice immunized with OVA DNA vaccines. Furthermore CXCL11 increased the frequency of antigen-specific CD8+ T cell population, along with effector memory phenotype ($CD44^{hi}CD62L^{low}$) population. We also demonstrated that co-administration of CXCL11 and OVA can significantly augment anti-tumor effects in vivo. Our study revealed that CXCL11 enhances T cell responses via increasing both antigen-specific CD8+ T cell proliferation and anti-apoptotic activity.
In conclusion, our results suggest that CXCL11 might serve a promising DNA vaccine adjuvant for the development of effective DNA vaccines.

Claudia SOLDNER

Tailoring antibody responses by vaccination with VLP together with novel adjuvants

C. Soldner[1], T. Ebensen[2], C. J. Buchholz[3], C.A. Guzman[2], U. Kalinke[1]

Introduction: Previously, it has been shown that immunization of mice with virus-like particles (VLP) expressing the vesicular stomatitis virus glycoprotein (VLP-VSV) on the surface induce neutralizing T cell-independent IgM and T cell-dependent IgG antibody responses. In this study, this VLP-VSV immunization model was employed to analyze the influence of different adjuvants on the magnitude and quality of antibody responses. Pegylated α-Galactosylceramid (α-GalCerMPEG), a typical NKT-cell ligand and c-di-AMP a second messenger, modulating cell surface properties of microorganisms were investigated in this model.

Methods: Mice were immunized i.v. or i.n. with VLP-VSV together with different adjuvants. Every four days after immunization blood samples were drawn and analyzed for VSV neutralizing activity. To this end, serial serum dilutions were mixed with VSV, transferred onto Vero cells, and the reduction of numbers of plaques was determined. Serum dilutions reducing plaque numbers by 50% were taken as titer. For detection of IgG subclasses a VSV-specific ELISA was carried out. The in vivo protective capacity was determined by i.n. immunization and infection of mice, lacking the adaptor of cytosolic viral nucleic acid–recognition receptors RIG-I like helicases (CARDIF-/-). CARDIF-/- mice were pre-treated two times with VLP-VSV with or without an adjuvant and were challenged with 103pfu VSV i.n. . The survival of VSV infected mice was monitored over 16 days.

Results: The i.v. immunization with VLP-VSV in α-GalCerMPEG enhanced neutralizing IgG responses to a similar extent as the co-treatment with poly(I:C). Moreover, presence of α-GalCerMPEG promoted the switch to IgG2b, IgG2c, and IgG1 whereas poly(I:C) only elicited IgG2b and IgG2c. Other adjuvants such as c-di-AMP showed limited enhancement effects on neutralizing activity of serum IgGs after i.v. treatment whereas a massive increase of VSV-neutralizing IgG antibodies was induced after i.n. treatment. In an in vivo protection assay CARDIF-/- mice pre-treated with VLP-VSV in c-di-AMP survived a lethal dose VSV challenge, whereas CARDIF-/- mice immunized only with VLP-VSV died about day seven post infection.

Discussion: Since immunization with VLP-VSV alone did not confer protection in an in vivo assay, whereas co-administration of VLP-VSV together with α-GalCerMPEG prolonged survival, the question arose whether an adjuvant for human treatment can be found showing a similar protective effect. We observed after VLP-VSV administration in combination with poly(I:C) or α-GalCerMPEG subtle differences in IgG subclass distribution. These presented results suggest that the used experimental setting might be suitable as a preclinical test to determine adjuvant activities.

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By bus: Bus 360 departs at Doblhoffbrücke in Baden and arrives in front of the Opera in Central Vienna (approx. 50 min.)
By train: Trains depart regulary from Baden Railwaystation to Central Vienna

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