This abstract book is dedicated to Dr. Jal Minocher Metha

Dr. Jal Minocher Metha was vice-chairman and director of the Serum Institute of India Limited (SIL) and Hon. President of the Poona District Leprosy Committee.

Dr. Metha was instrumental in the development of vaccines that helped to fight bacterial and viral diseases in less developed countries with the accreditation of the WHO.

Dr. Metha was actively involved with leprosy eradication programs in the country for more than 30 years and was a strong proponent for the development of a leprosy vaccine.

Dr. Metha's outstanding philanthropic efforts have inter alia been awarded with the Padma Bhusan price for scientific medical research and social work in leprosy in 1982.

Dr. Metha's work in leprosy related medical research and his engagement for social relief and rehabilitation of leprosy patients during his tenure of more than 40 years of voluntary and honorary service, can not be highly enough appreciated.

Dr. Metha died on October 13, 2001.

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Panel Discussion

Novel Vaccines Against Infectious Diseases – Developed Countries meet Developing Countries

April 14 – 17, 2005, Semmering, Austria

Welcome

Alexander von Gabain/Intercell/Austria

Two years ago, in April 2003, we organized a first international vaccine conference of that type, under the title "The Future of Vaccines - Cancer Meets Infectious Diseases". The conference was well attended by scientists, vaccine developers, but also by representatives from the investors' communities. We have been asked by many participants to repeat a similar type of interdisciplinary vaccine conference at the same location, however, with another focus. This year's topic regards novel vaccines against infectious diseases with unmet need that threaten people in both developed and developing countries.

The recent Tsunami has killed more than 200.000 people within several hours. The gigantic tragedy has raised our awareness how fragile human life is on our blue planet in the light of natural disasters. The killer wave, as horrible as it has been, may seem benign if compared to the death toll caused year by year by infectious diseases. Year after year the life of every fourth human being on earth is terminated by microbial infections, causing 13 million deaths in developing countries only, thereof six million children. Of the three killer microbes, HIV, Plasmodium vivax and Mycobacterium tuberculosis, the latter one alone accounts for the death of two to three million people each year. For a long time, TB seemed to be manageable with antibiotics, at least in the rich part of the world. Today, the disease is aggressively returning to developed countries where only librettos of classical operas and novels of the world literature have kept alive the memory of a threat that falsely is perceived as history. Furthermore, rapidly spreading microbes in hospitals and communities that are resistant to all known current antibiotic or chemotherapy treatments, novel emerging pathogens and bioterrorism have led to the notion that high living standard per se does not provide a safe barrier against the threat to be killed or irreversibly damaged by infectious diseases believed to be prevalent in developed countries only. In addition during the last few decades evidence has been gathered that important diseases, originally not assigned to infectious agents, may induce disability or are associated with (and may be caused by) pathogens. Microbial infections are related to autoimmune diseases, viral infections associated with important neurodegenerative diseases and some pathogens (Human papilloma virus, hepatitis B and C viruses and Helicobacter) are mentioned as causes of cancer. Not enough, the yearly flu epidemics, including

the related bird flu outbreaks, keep us reminded that the human family is under the constant risk that an influenza pandemic, as seen 1918, causing more than 20 million deaths can strike any time again.

In the control of infectious diseases, vaccination is arguably the most successful medical intervention that during the last 100 years has become a mandatory part of many countries' health care programs and shown to become an effective instrument. Vaccines are important products in modern society as they contribute hugely to public health, in preventing common diseases that in the past led to an even higher mortality in the general population than today, especially in children. Global vaccination programs have yielded impressive results; for example about 25 years ago, the WHO has been able to declare small pox to be defeated. Nevertheless, many vaccines used today in humans are based on outdated technologies, do not have the wanted efficacy, unacceptable side affects or are difficult to deliver to populations in areas with inferior medical infrastructure. Furthermore, development of novel vaccines is not progressing with the speed one would have hoped for and expected from the rapid advancement made in understanding of the scientific foundation of infectious diseases and of the immune system, from the recovered strength and growth of the established vaccine industries, from the rapidly increasing biotech scene, from the mounting engagement of nongovernmental organizations and from the impressive devotion of fortunes to vaccine programs, as exemplified by the Gate foundation. In contrast, the development of novel vaccines has never had a better scientific basis than today which has been largely facilitated by the recombinant DNA technology emerging about 30 years ago and provided the tools to establish the following facts:

» Improved understanding of the pathogens' life cycle und their interaction with their hosts;

» The importance of innate immunity and particularly the role of the antigen presenting cells that recognize microbes and help to instruct the adaptive immune response;

» T-cell immunity is equally important as B-cell immunity for mounting a proper protection against microbes;

» The materialization of defined and potent adjuvants that activate the pathways of the innate immune system through specific receptors, leading to an optimal adaptive immune response;

» Genome-based technologies have become available that have facilitated the identification of pathogen-specific B- and T-cell antigens that protect against the underpinning infection

» Novel vector systems have been developed that efficiently deliver antigens to the target cells.

The present conference is aiming to focus on novel vaccines directed against five major groups of pathogens, namely Flavi viruses, HIV, Influenza viruses, Mycobacterium tuberculosis and Streptococcus pneumonia that create a global threat for both the developed and developing countries and therefore should lead to concerted efforts of academic scientists dealing with the target microbes and related vaccine developments, professional vaccine developers from the pharma and biotech industries, representatives from the investors' community, but also from non-profit and non-governmental organizations that are engaged in the vaccine arena.

The conference (as the preceding one) has been organized by the Vienna Vaccine association that has been gaining the support of numerous private and public sponsors from all over the world to whom I would like to express my deep gratitude for their generous donations. I also would like to thank my colleagues of the conference' scientific advisory board for helping me and the organizational team with their unique expertise and networks of distinct contacts, Emilio Emini, Franz-Xaver Heinz, Steffan Kaufmann, Stafan Normark, Gerald Sadoff, Sir John Skehel and my local co-organizer, Thomas Decker. My gratitude goes also to Max Birnstiel, Hamilton Smith and Hans Tuppy for accepting the invitation to become patrons of the conference and thereby providing their outstanding names to the goals of our event. Finally, I would like to acknowledge the never-ending efforts and competent support of the local organizational team, Barbara Strutz-Grell, Kerstin von Gabain, Lucia Malfent, Martina Thyringer and Katharina Wieser.

The Tsunami wave of last December has reminded mankind that natural catastrophes do not necessarily distinguish between inhabitants from developed and developing countries. We therefore hope that participants and invited speakers will apply this notion to the challenge of infectious diseases and become productive to discuss progress and ways to develop and to distribute novel vaccines for all humans wherever the live on our blue planet.

Conference Program

Thursday, April 14, 2005

Registration, Welcome and Keynote Lecture

12:00-15:00	Registration
15:00-15:10	Alexander von Gabain/Intercell/Austria: *"Welcome"*
15:10-15:50	Stanley Cohen/Stanford University/USA: *"From recombinant DNA to a better understanding of host-parasite relationship"*
15:50-16:00	Break

Microbial Pathogens
Chair: Staffan Normark

16:00-16:30	Elaine Tuomanen/St. Jude Children's Research Hospital/Memphis/USA: *"Molecular mechanisms of pneumococcal invasion"*
16:30-17:00	Stefan H. E. Kaufman/Max-Planck Institute for Infection Biology/Berlin/Germany: *"Understanding the natural immune response to tuberculosis as basis for rational vaccine design"*
17:00-17:30	Franz Xaver Heinz/Department of Virology/Medical University of Vienna/Austria: *"Flaviviruses"*
17:30-17:40	Break
17:40-18:10	John Oxford/Department of Medical Microbiology and Retroscreen Virology/St Bartholomew's and the Royal London, Queen Mary, School of Medicine and Dentistry/University of London/UK: *"Digging in the Past of the Spanish Influenza Virus"*
18:10-18:40	Robert Gallo/Institute of Human Virology/University of Maryland/USA: *"Synopsis of HIV Biology especially as it may relate to vaccine development"*

Special Promotion

18:40-18:55	Matthias Frisch/Vienna Business Agency/Vienna: "Biotechnology in Vienna"

Dinner and Social Program

19:30	Dinner
20:30	Get-Together

Friday, April 15, 2005

Adaptive Immunity
Chair: Thomas Decker

08:30-09:00 Michael Neuberger/Medical Research Council Laboratory of Molecular Biology/Cambridge/UK: *"B-Cell Immunity"*

09:00-09:30 Rafi Ahmed/Emory Vaccine Center, Emory University School of Medicine, Atlanta/USA: *"The Development of Antigen-Specific T-Cells and Memory T-Cells"*

Pneumococcal Vaccines
Chair: Hamilton Smith

09:30-09:55 Ester Nagy/Intercell/Austria: *"From "antigenome" to vaccine candidates: a novel validated antigen identification approach leading to conserved protective pneumococcal proteins"*

09:55-10:20 Cécile Neyt/GSK/UK: *"Pneumococcal conjugate and protein vaccines."*

10:20-10:50 Break

Flavirial Vaccines
Chair: Franz X. Heinz

10:50-11:15 Michael Buschle/Intercell/UK: *"A next generation vaccine, IC-51(JE-PIV) against Japanese Encephalitis Virus that is immunogenic and safe"*

11:15-11:40 Alexander Khromykh/Sir Albert Sakzewski Virus Research Centre/Royal Children's Hospital, and Clinical Medical Virology Centre/University of Queensland/Brisbane/Australia: *"Kunjin (West Nile) virus-based vaccines"*

11:40-12:10 Break

12:10-12:35 Farshad Guirakhoo/Acambis/Cambridge/UK: *"ChimeriVax flavivirus vaccines"*

12:35-13:00 Christian Mandl/Clinical Institute for Virology/Medical University of Vienna/Austria: *"Capsid deletion mutants for the development of new flavivirus vaccines"*

13:00-14:30 Lunch

Influenza Vaccines
Chair: Hans Tuppy

14:30-14:55 Peter Palese/Mount Sinai School of Medicine/New York/USA: *"Biology of Influenza Virus"*

14:55-15:20 John Skehel/National Institute for Medical Research/London/UK: *"Immune recognition of influenza virus haemagglutinin"*

15:20-15:45 David Burt/ID Biomedical Corporation/Canada: *"An Intranasal Subunit Vaccine against Influenza"*

15:45-16:10 Jaap Goudsmit/Crucell/Netherlands: *"Next Generation Vaccines against Pandemic and Epidemic Influenza: PER.C6® as cell substrate"*

16:10-16:40 Break

HIV Vaccines
Chair: Robert Gallo

16:40-17:05 Bruce Walker/Massachusetts General Hospital/Aids Research Centre/Charlestown/USA: *"Immune Control and Immune Failure in HIV infection"*

17:05-17:30 David Watkins/University of Wisconsin Medical School/Madison/USA: *"Elite Controllers and Vaccine Studies in the SIV-Infected Indian"*

17:30-17:55 Dennis Burton/The Scripps Research Institute/La Jolla/USA: *"Neutralizing Antibodies and HIV Vaccine Design"*

17:55-18:20 Emilio Emini/International Aids Vaccine Initiative/New York/USA: *"The Promise and Challenge of HIV-1 Vaccine Development"*

Dinner and Social Program

19:30 Dinner and Social Program

Saturday, April 16, 2005

Innate Immunity
Chair: Elaine Tuomanen

09:30-10:00 Bruce Beutler/The Scripps Research Institute/La Jolla/USA: *"Deciphering innate immune response pathways using germline mutagenesis."*

10:00-10:30 Michel Nussenzweig/Rockefeller University New York/USA: *"Dendritic cell based approaches for vaccine development"*

10:30-11:00 Break

TB Vaccines
Chair: Max Birnstiel

11:00-11:25 William R. Jacobs/Albert Einstein College of Medicine and Howard Hughes Medical Institute/New York/USA: *"Pathogenesis of Mycobacterium Tuberculosis"*

11:25-11:50 Mark Doherty/Staten Serum Institute/Denmark: *"A Fusion Protein Subunit Approach towards a Vaccine*

11:50-12:15 Mark Alderson/Corixa/Seattle/USA: *"Subunit Approach towards a Novel Vaccine"*

12:15-13:30 Lunch

Panel Discussion "Novel vaccines for the world - how to streamline efforts of academia, biotech, vc, politics and charitable trusts?"

13:30-13:40 Alexander von Gabain/Intercell/Austria

13:40-13:50 Martin Friede/WHO Headquarters/Geneve/Switzerland

13:50-14:00 Jacques-Francois Martin/GAVI-The Vaccine Fund/France

14:00-14:10 Jerald Sadoff/Aeras Foundation/USA

14:10-14:20 Thomas Szucs/BB Biotech/Switzerland

14:20-14:30 David Cyranosky/Nature/Japan

14:30-14:40 Karen Bernstein/Biocentury Publications

14:40-14:50 Break

14:50-15:50 Discussion

Dinner and Social Program

19:00 Gala Dinner

Keynote Lecture

From recombinant DNA to a better understanding of host-parasite relationship
Stanley Cohen/Stanford University/USA

Infection and propagation of intracellular parasites and bacterial pathogens, as well as of viruses, require not only the expression of genes carried by the microorganism, but also of host cell genes that encode functions needed by the pathogen (Cellular Genes for Pathogen Propagation/Pathogenicity; CGPPs). Our lab has developed novel methods for discovering mammalian CGPPs, using a strategy of homozygous gene inactivation in cell culture, together with phenotype-based screens to isolate clones resistant to pathogen effects. This approach has identified genes and proteins required for the propagation of medically and agriculturally important viral pathogens, and for the lethality for anthrax and other toxins. Biological insights and potential therapeutic approaches that have resulted from these findings will be described.

By Stanley N. Cohen and Kwoh-Ting Li, Professor of Genetics and Professor of Medicine Stanford University

Notes

Microbial Pathogens

Molecular mechanisms of pneumococcal invasion

Elaine Tuomanen/St. Jude Children's Research Hospital/Memphis/USA

The pneumococcal surface engineers complex interactions with human cells that result in attachment, invasion, inflammation, and death of either the bacteria or the host cell or both. Of these interactions, colonization of the nasopharynx and sustained bacteremia are the minimal requirements for targets of a comprehensive vaccine. The architecture of the surface is constructed by noncovalent adducts of choline binding proteins to the cell wall, a process regulated by phase variation, two component systems, proteases, etc. These proteins and choline itself interact with the receptors for sIgA or platelet activating factor during adherence and invasion from the mucosa to the bloodstream. The choline binding proteins also manipulate innate host defenses and promote bacterial survival in vivo. NMR studies of one choline binding protein, CbpA, has revealed a novel structure and allowed assignment of functions to regions of this adhesin. Such regions are suitable for second generation vaccines. Elaboration of pneumolysin and hydrogen peroxide also contribute to host cell death by organ-specific cellular responses but have not added to vaccine efficacy. In vivo gene expression studies and comparative genomic hybridization have identified unanticipated virulence determinants that may be excellent future vaccine candidates. Their roles in various unusual clinical syndromes of pneumococcal disease expand our understanding of processes driving the course of infection.

Notes

Understanding the natural immune response to tuberculosis as basis for rational vaccine design

Stefan H. E. Kaufman/Max-Planck Institute for Infection Biology/Berlin/Germany

The available vaccine against tuberculosis, BCG, protects newborns from miliary tuberculosis, but fails to prevent the most prevalent form of disease, pulmonary tuberculosis in adults. Thus, Mycobacterium tuberculosis can be controlled (though not eradicated) by the immune response induced by natural infection. Acquired immunity against tuberculosis is a T cell-dependent phenomenon. The T cell system comprises distinct populations. CD4 T cells are undoubtedly of central importance for acquired resistance against tuberculosis. Antigens of M. tuberculosis also have access to MHC class I processing, probably through cross-priming. In addition, unconventional T cells also seem to participate in immunity against tuberculosis. Subunit vaccination strategies are based on the assumption that one or few antigens suffice for an efficient immune response. Hence, the identification of protective antigens represents an essential prerequisite for the success of this type of vaccines. Subunit vaccines come in two forms: Protein/adjuvant formulations or naked DNA constructs. Viable attenuated vaccines are based on the assumption that multiple antigens are required for efficacious protection. Two major strategies are being pursued: Knockout mutants of M. tuberculosis and improved recombinant BCG vaccines. Taking advantage of our increasing knowledge about the immune response to M. tuberculosis will clearly facilitate rational design of novel vaccines against one of the most frightening threats in the world, tuberculosis.

Notes

Flaviviruses

Franz Xaver Heinz/Medical University of Vienna/Austria

The genus flavivirus in the family flaviviridae comprises more than 70 distinct viruses many of which are arthropod-borne and transmitted to their vertebrate hosts by mosquitoes or ticks. Flaviviruses have enormous impact as disease agents world-wide and the most important human pathogens are yellow fever, dengue, Japanese encephalitis, West Nile, and tick-borne encephalitis viruses. Because of the specific requirements and constraints of their natural ecological cycles these viruses have a characteristic geographical distribution. Such endemic regions can be quite stable, as is the case with tick-borne encephalitis virus, but flaviviruses have also the potential to invade completely new territories, as exemplified by the importation of yellow fever to the Americas through the slave trade and the recent emergence of West Nile virus in North America. Human vaccines are in use against yellow fever (live attenuated), Japanese encephalitis and tick-borne encephalitis (both inactivated whole virus).

Flaviviruses are small enveloped positive-stranded RNA viruses that contain three proteins, designated C (capsid), M (membrane), and E (envelope). The E protein is the major constituent at the virion surface and mediates both receptor-binding and membrane fusion after uptake by receptor-mediated endocytosis. In mature virions this protein exists as an antiparallel homodimer and its atomic structure has the characteristic features of a class II viral fusion protein. Flaviviruses posses the fastest and most efficient fusion machinery of all enveloped viruses analyzed to date. The features of the E protein post-fusion structure suggest mechanistic similarities between class I and class II-mediated membrane fusion, despite the fundamentally different structures of the fusion proteins involved.

Antigenically all flaviviruses are related, as revealed by cross-reactivities in hemagglutination inhibition and enzyme immunoassays. Cross-neutralization, however, is only observed between members of more closely related viruses that are grouped into so-called serocomplexes. Studies with neutralization-escape variants and specifically engineered mutants have revealed that all three domains (I,II, and III) of the E protein contain antigenic sites involved in virus neutralization, whereas the dominant flavivirus cross-reactive epitope (not involved in virus neutralization) is located at the junction between domains I and III in the E protein dimer.

Notes

Digging in the Past of the Spanish Influenza Virus

John Oxford/University of London/UK

The worldwide pandemic of influenza virus in the autumn of 1918 was preceded by smaller outbreaks in confined army camps as early as 1917 in France and Germany and the UK and also summer attacks in 1918 itself. The epicentre of the 1917 early outbreak was Etaples which housed the notorious British Army training and hospital camp. Present in the camp and surrounds were 100,000 young soldiers, pigs, chicken, geese and ducks. Many of the soldiers had been gassed with a variety of 22 or so chemicals in the battle of the Somme. We have now a tentative identification of the first case in 1917, a young west county farmer boy soldier.

A combination of exhumations amd pathology archived lung samples are the data base for studies of the genetic antigenic and biological nature of the virus. Antigenic analysis of the HA places the virus in the H1N1 sub type whereas nucleotide sequence analysis of the HA show at least two receptor binding variants. X-ray crystallography studies of HA also indicate a unique hybrid receptor binding site region and the virus may have had an ability to bind both to avian and human cells. Finally a complete phylogenetic analysis of the pandemic virus will require comparative samples from the preceding years and post 1919: we have now located such archived lung samples.

Notes

Synopsis of HIV Biology especially as it may relate to vaccine development
Robert Gallo/Institute of Human Virology/University of Maryland/USA

The HIV genome contains all of the usual genes of any retrovirus (animals and humans) encoding structural proteins (gag, pol, env), and several others. These include the nuclear-functioning-RNA transcribing and exporting regulatory genes (tat and rev) for which functionally similar homologues (tax and rex) were known in the leukemia causing human retrovirus HTLV-1, as well as several additional genes supportive of HIV infection even of resting cells. One of these (vpr) is a requisite component of the pre-integration complex. Also Vpr, as well as other HIV genes, encode protein which contribute to immune impairment and, therefore, viral success by causing harm to the infected cell. For Vpr this is by causing nuclear herniation. By other gene products (env, tat and especially nef) it is mainly through producing T-cell activation which favor HIV replication and ultimately death of some of the infected CD4 T cells. Additionally, the HIV genome contains a gene (vif) whose protein product inactivates APOBEC3G, the RNA editing cytidine deaminase, which when unimpaired fosters RNA mutations of infecting viruses and thereby handicaps their replication.

HIV belongs to a special category of retroviruses (Lenti) which were known in certain ungulates and usually distinguished by their larger genome, greater carbohydrate content, capacity to infect resting cells (usually macrophages), and causing non-neoplastic disease. Though HIV also has these properties it differs from its animal counterparts in being (like HTLV-1 & 2) highly tropic for CD4+ T cells.

Viruses often have redundant mechanisms for their survival. For instance, HTLV-1 infects people chiefly by transmission of the DNA provirus in cells and not as free virons. Thus, HTLV-1 has multiple mechanisms for promoting the number of infected T cells (therefore, the amount of DNA proviruses). In contrast like most viruses, the survival of HIV depends upon viron number and avoidance of the immune system. It achieves this by redundancy in mechanisms which promote T-cell activation, extreme genomic variation, variable sites of viral DNA integration (ensuring variation in expression and giving rise not only to cells with high expression and causing cell death but also to cells with low level viral expression and escape from immune detection), and impairment of the immune response. The latter is through suppression or death not only of many infected CD4+ T cells, but importantly (and often a neglected topic) also of uninfected T cells. We (and others) have evidence that impairment of uninfected cells is mediated by extracellular gp120, extracellular Tat, and over-produced IFN-α.

Recently, much has been learned about the initiation of HIV infection, especially regarding the two receptor concept: CD4 binding and chemokine receptors (CCR5 and CXCR4) acting as co-receptor or in reality as the true receptor. CCR5 is of particular interest because (1) the vast majority of infections are with HIV variants that use CCR5; (2) many infections involve only CCR5 using HIV variants; (3) activating CCR5 expression correlates with rapid clinical progression; (4) the newest and most promising drugs against HIV target CCR5; and (5) conceptually any preventive vaccine with a serious chance of success will have to block HIV entry, and a main approach may involve gp120 binding to this receptor.

In my view since HIV is a retrovirus a preventive vaccine will have to approach, if not achieve, sterilizing immunity. To do this will require the development of high titer, broadly reactive, and sustainable neutralizing antibodies. One such approach will be highlighted.

Notes

Adaptive Immunity

B-Cell Immunity

Michael Neuberger/Medical Research Council Laboratory of Molecular Biology/Cambridge/UK

Novel proteins have been elaborated over evolutionary time by an iterative alternation of mutation and selection. In a similar way, the humoral immune system also uses an iterative alternation of mutation and selection to generate novel antibodies that display a high affinity for their cognate antigen – but this is achieved in a matter of a days. Such antibodies play a critical role in mediating protective immunity to many types of infection.

Gene rearrangement is used to produce a primary repertoire of antibodies. On entering the body, antigen triggers the clonal expansion of those B lymphocytes that express a cognate antibody, albeit one of low affinity. Rapid and specific affinity maturation is then achieved by subjecting the immunoglobulin genes in the rapidly expanding B cells to a period of intense mutation. The intensity of this mutational assault is tolerated because it is targeted specifically to the immunoglobulin genes, causing relatively little damage to other loci. Antigen-mediated selection then allows the preferential expansion of those mutants expressing antibodies displaying improved binding characteristics.

Two types of mutational processes underpin the production of specific antibodies. Targeted gene rearrangement (mediated by the RAG recombinase) allows the production of the primary repertoire of low affinity IgM antibodies. Followinga ntigen encounter, targeted deamination of deoxycytidine to deoxyuridine (mediated by the AID deaminase) allows the maturation of these primary IgM antibodies into secondary response, high affinity IgG antibodies. Regarding the selection processes, these need to allow both the initiation of the immune response when antibody/antigen affinities are very low as well as the maturation of the response when antibody/antigen affinities can be very high. Aspects of current thinking about both the mutational processes and the selection processes will be reviewed in the hope that these might provide some insight into vaccination strategies.

Notes

The Development of Antigen-Specific T-Cells and Memory T-Cells

Rafi Ahmed/Emory Vaccine Center, Emory University School of Medicine, Atlanta/USA

Abstract not received in time for print

Notes

Pneumococcal Vaccines

From "antigenome" to vaccine candidates: a novel validated antigen identification approach leading to conserved protective pneumococcal proteins
Ester Nagy/Intercell/Austria

The currently available pneumococcal polysaccharide-based vaccines, although highly efficacious in protecting against invasive diseases, provide only partial coverage for a fraction of the more than 90 different serotypes causing human infections. Thus, there is a need to develop novel vaccines containing protective antigens that are conserved in all serotypes.

We have developed an antigen discovery technology that combines the advantages of full genome coverage and serological antigen identification by using comprehensive small-fragment genomic surface display libraries and antibodies from humans exposed to and/or diseased by pathogenic microorganisms. This method, named antigenome technology has been applied to a dozen different bacteria and identified several hundred antigens. Our approach has also become productive in the identification of antigenic proteins of Streptococcus pneumoniae (Pneumococcus). In order to identify vaccine candidates, antigens were first characterized in a series of in vitro assays (opsonophagocytic killing, surface staining, ELISA with human sera, gene distribution in clinical isolates), and then tested for protection in a murine lethality/sepsis model of pneumococcal diseases. This approach identified highly conserved novel vaccine candidate antigens that induce high level of antibodies in humans during pneumococcal infections and colonization. Further characterization of the protective antigens by investigating their role in bacterial growth, in in vivo survival and in virulence strengthens their potency in pneumococcal vaccine development.

References:
(1) Etz H, Minh D, Henics T, Dryla A, Winkler B, et al. Proc. Natl. Acad. Sci. USA, 99, 6573-78 (2002)
(2) Nagy E, Henics T, von Gabain A, & Meinke A. Genomics, Proteomics and Vaccines, ed. G. Grandi 233-239 (2004)
(3) Meinke A, Henics T, Hanner M, Minh D & Nagy E. Vaccine, in press (2005)

Markus Hanner, Carmen Giefing, Beatrice Senn, Andreas Meinke and Eszter Nagy

Notes

Pneumococcal conjugate and protein vaccines

Cécile Neyt/GSK/UK

GSK's development of a pediatric pneumococcal vaccine aims at a multivalent conjugate beyond the currently licensed 7V conjugate in order to address the global medical need. The carrier protein used is ProteinD, a surface outer membrane protein from nontypable Haemophilus influenzae, that could potentially extend the otitis media coverage,and in addition to the > 7V pneumococcal conjugate could help to avoid serotype and/or etiological replacement. In adults and the elderly, there is a high unmet medical need for an improved pneumococcal vaccine to prevent pneumococcal bacteremia and pneumonia. The shortcomings of the 23V polysaccharide vaccine (PPV) are widely recognized.Improvements may include both conjugated polysaccharides and pneumococcal proteins. Conjugates are expected to induce improved anti-PS responses compared to PPV such as increased antibody response rates to PS, improved persistence and maintenance or renewal of immune memory. Protein antigens may extend coverage to non-vaccine-serotypes and potentially induce immune responses that can act in synergy with anti-polysaccharide immunity. Antigen discovery of pneumococcal proteins was performed by genome mining and preclinical evaluation.Variability analysis was conducted on strains covering the major MLST- and serotypes.

Notes

Flavirial Vaccines

A next generation vaccine, IC-51(JE-PIV) against Japanese Encephalitis Virus that is immunogenic and safe

Michael Buschle/Intercell/UK

A next generation vaccine, IC-51(JE-PIV), against Japanese Encephalitis Virus (JEV) has been developed. It is derived from the attenuated SA14-14-2 strain, grown on Vero cells , purified and formalin inactivated. The vaccine was originally developed by Walter Reed Army Institute of Research (WRAIR).

The vaccine completed successfully the phase 2 trial and is currently planned for pivotal phase 3 clinical trial.

The phase 2 study evaluated not only dosage amounts but also frequency in a randomized, open-label, one center, dose finding trial. Different schedules were compared with the currently licensed JE-VAX® JEV vaccine given in the recommended three dose schedule. The Phase 2 study showed that the IC-51(JE-PIV) is safe and induced good neutralizing antibody responses against JEV at less doses compared to JE-VAX. Safety and tolerability evaluation was a secondary objective of this trial. Safety was excellent and no serious adverse reactions related to the vaccine were observed after the cumulative administration of 164 injections.

The future development of the vaccine has been reviewed by the FDA in our last meeting with the agency in 2004. The vaccine for the phase 3 clinical study and future shall be produced in a state-of-the-art facility under GMP standards. The phase 3 clinical study proposes to study the safety and immunogenicity in a total of 3000 subjects. A convenient vaccine dosage and frequency was identified (from the previous studies) for the upcoming Phase 3 clinical evaluations.

In sum, data from phase 2 suggest an excellent profile of IC-51(JE-PIV) in terms of safety, tolerability, immunogenicity and convenience of dosing. Therefore this vaccine may be the next generation JEV vaccine.

*By Shailesh Dewasthaly, Erich Tauber and Michael Buschle**

Notes

Kunjin (West Nile) virus-based vaccines

Alexander Khromykh /University of Queensland/Brisbane/Australia

Kunjin virus, recently reclassified as the subtype of West Nile virus, is a naturally attenuated Australian flavivirus which in contrast to its very close relative, New York 99 strain of West Nile virus, does not cause an overt disease in humans and animals. We have been studying Kunjin virus for many years and more recently have initiated applications of Kunjin virus-based vectors for the development of anti-viral and anti-cancer vaccines. We have generated the first flavivirus replicons based on Kunjin virus and applied them for the development of vaccines against HIV and Ebola viruses as well as vaccines and therapeutics against cancers. Kunjin replicon vectors have proven to be highly efficient in induction of protective CD8 T cell and antibody responses against model viral and tumour challenges in mice (1, 2) and studies are currently planned for testing their efficacy in non-human primates. As a result of successful development of Kunjin replicon vectors a start-up biotech company, Replikun Biotech, has been recently formed to commercialize the technology. In addition to the replicon system we have been developing a vaccine against New York 99 strain of West Nile virus using an infectious Kunjin virus cDNA (3). We have recently identified a mutation in one of the Kunjin proteins leading to increased production of IFN-α/β (4) and have demonstrated that this mutation resulted in attenuation of Kunjin virus replication in mice without loosing its protective efficacy against challenge with New York 99 strain.

1.Anraku, I., T. J. Harvey, R. Linedale, J. Gardner, D. Harrich, A. Suhrbier, and A. A. Khromykh. 2002. Kunjin virus replicon vaccine vectors induce protective CD8+ T-cell immunity. J Virol 76:3791-9.

3.Harvey, T. J., I. Anraku, R. Linedale, D. Harrich, J. Mackenzie, A. Suhrbier, and A.A. Khromykh. 2003. Kunjin replicon vectors for human immunodeficiency virus vaccine development. J. Virol. 77:7796-7803.

3.Hall, R. A., D. J. Nisbet, K. B. Pham, A. T. Pyke, G. A. Smith, and A. A. Khromykh. 2003. DNA vaccine coding for the full-length infectious Kunjin virus RNA protects mice against the New York strain of West Nile virus. Proc Natl Acad Sci USA 100:10460-4.

4.Liu, W. J., H.B. Shen, X.J. Wang, H. Huang, and A.A. Khromykh. 2004. Analysis of adaptive mutations in Kunjin virus replicon RNA reveals a novel role for the flavivirus nonstructural protein NS2A in inhibition of beta interferon promoter-driven transcription. J. Virol. 78:12225-12235.

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Notes

ChimeriVax flavivirus vaccines

Farshad Guirakhoo/Acambis/Cambridge/UK

ChimeriVax™ technology utilizes yellow fever (YF) 17 D virus as a vector for delivery of the genes encoding the pre-membrane (prM) and envelope (E) proteins of other flaviviruses (e.g. dengue, Japanese encephalitis, West Nile) as vaccines. YF 17D vaccine was first used for human immunization in 1936, and over the following 60 years, 400 million people received the vaccine, with a strong record of safety and efficacy.

The principal focus of vaccine development is safety, since it cannot be determined without empirical testing whether the chimeras have altered phenotypic or virulence characteristics. In the case of the dengue constructs, wild-type prME genes were inserted into the YF 17D infectious clone, since evidence from empirically-derived live dengue vaccines suggested that the NS and not the prME genes controlled attenuation of these candidates. In the case of the encephalitis vaccines against Japanese encephalitis and West Nile, the prME genes contained mutations with desired attenuation phenotype. It is noteworthy that the chimerization phenomenon itself appears to also play a role in attenuation, since the chimeric viruses are less virulent than either of the donor strains used in the construction.

Extensive preclinical testing of the candidate vaccines has been conducted in mosquitoes, mice, hamsters, birds, horses and monkeys. These studies, many of which are now published have shown the ChimeriVax™ vaccine candidates to be significantly safer with respect to neurovirulence than commercial YF 17D. Preclinical studies of immunogenicity and protective activity of the chimeric viruses have been carried out, principally in monkeys. These studies have shown that a single inoculation results in a brisk neutralizing antibody response, high titers of antibody, and solid protection against lethal challenge with wild-type virus.

Clinical trials have now been conducted using chimeric vaccines against dengue, Japanese encephalitis, and West Nile. The data showed that a single inoculation results in seroconversion of nearly 100% of subjects. The levels of neutralizing antibody were similar to those in controls who receive YF vaccine and lasted for at least 12 months (the longest time evaluated to date). Viremia occurred during the first week, which was of low magnitude and duration, and did not exceed that induced by YF 17D. Side effects were minimal and resembled those to YF 17D. There was no interference with chimeric vaccination by prior YF immunity.

In summary, YF 17D vectored chimeric vaccines against heterologous flaviviruses are a promising approach to the rationale development of new vaccines.

By F Guirakhoo & TP Monath

Notes

Capsid deletion mutants for the development of new flavivirus vaccines

Christian Mandl/Clinical Institute for Virology/Medical University of Vienna/Austria

Flaviviruses consist of only three structural proteins, the two surface proteins prM/M and E, and the basic, alpha-helical capsid protein C. Together with the viral genome, a plus-stranded RNA molecule of approximately 11 kb length, multiple copies of protein C form the nucleocapsid which is engulfed by the viral membrane carrying the two surface proteins. Protein C is derived from the most amino-terminal portion of the polyprotein which is the only translation product of the RNA genome and which gets co- and post-translationally cleaved into the individual mature viral proteins. Using an infectious cDNA clone of tick-borne encephalitis virus, a human pathogenic flavivirus that is endemic in parts of Europe and Asia, various deletion mutations were introduced into the capsid protein. The analysis of viral mutants carrying various deletions ranging in size from a single amino acid residue to over 60 residues revealed that:

i. Deletions of only a few amino acid residues were well-tolerated and gave rise to viral progeny with a phenotype similar to wild-type virus.

ii. Larger deletions of up to approximately 20 residues also gave rise to viable viruses which, however, exhibited reduced growth properties and were significantly attenuated and immunogenic in adult mice.

iii. Mutants with still larger deletions up to approximately 30 residues and removing most or all of a flavivirus-conserved internal hydrophobic region were viable only in the presence of resuscitating mutations which arose spontaneously in a region of protein C downstream from the original deletion and increased the hydrophobicity of the protein.

iv. Deletions removing approximately two thirds of the entire protein generated self-replicating replicons. By means of additional genetic modifications these replicons could be manipulated to produce and export non-infectious subviral particles from transfected cells.

The data thus indicated a remarkable structural and functional flexibility of protein C and laid the ground for two new approaches towards flavivirus vaccine development, i.e. the directed construction of attenuated vaccine strains and particle-producing replicons. Potential advantages of this approach include the simplicity of mutant constructions and apparent safety features deriving from the fact that reversions of deletion mutants to the wild-type sequence are impossible and no heterologous sequence elements are needed.

Notes

Influenza Vaccines

Biology of Influenza Virus

Peter Palese/Mount Sinai School of Medicine/New York/USA

Influenza remains an important disease in humans and animals. In contrast to measles, smallpox and poliomyelitis, influenza is caused by viruses which undergo continuous antigenic change and which possess an animal reservoir. Thus, new epidemics and pandemics are likely to occur in the future, and eradication of the disease would be difficult to achieve. Although it is not clear whether a new pandemic is imminent, it would be prudent to take into account the lessons we have learned from studying different human and animal influenza viruses. Specifically, reconstruction of the genes of the 1918 pandemic virus and studies on their contribution to virulence will be important steps toward understanding the biological capabilities of this lethal virus. The availability of new antiviral drugs and the development of superior vaccines will provide us with better approaches to control influenza and to have a positive impact on its disease load.

Notes

Immune recognition of influenza virus haemagglutinin

John Skehel/National Institute for Medical Research/London/UK

The influenza virus membrane glycoprotein, haemagglutinin (HA) is the target of infectivity neutralizing antibodies. As a consequence it varies in antigenicity with passage, following transfer into the human population from an avian influenza reservoir. Structural analysis of mutant HAs and HA-monoclonal antibody complexes indicate the molecular basis and consequences of variation, particularly in relation to the mechanism of neutralization by inhibition of receptor binding. The contribution of this information to influenza surveillance and vaccination strategies will be considered, together with its relevance to other virus immunogenes.

Notes

An Intranasal Subunit Vaccine against Influenza

David Burt/ID Biomedical Corporation/Canada

FluINsure™ is an intranasal influenza subunit vaccine comprising split flu antigens and a Proteosome™-based adjuvant - outer membrane proteins of Neiserria meningitidis, which are known to activate APC's by interacting with TLR-2.

In mouse studies nasal Proteosome-Flu formulations induced serum hemagglutination inhibition (HI) and virus neutralization activity, significant virus-specific IgA in nasal and lung fluids and protection against lethal flu challenge. No treatment related clinical or histopathological findings were observed. Importantly, no inflammatory lesions or vaccine components were detected in the brain or olfactory bulbs of nasally immunized mice.

Eight human clinical trials performed in over 1,800 healthy adults with Proteosome-Flu vaccines have been completed. The vaccines were consistently safe and well-tolerated. In subjects with prior serum reciprocal HI titers < 40 for the immunizing antigens 50-80% showed four-fold rises, titers ≥ 40, or both against H1N1 and H3N2 antigens after immunization with any regimen; B antigens gave more variable results. Significant increases in nasal secretory IgA were observed against all three flu strains following both single and two-dose regimens. In two experimental challenge studies 153 healthy adults were given one (30 μg HA) or two (15 or 30 μg HA) intranasal doses of a monovalent Proteosome-H3N2 formulation and subsequently challenged with a homologous virus. Two-dose regimens showed 100% efficacy against febrile illness with laboratory confirmation of influenza infection and 84% efficacy against any illness with laboratory confirmation (both $p < 0.001$). The one-dose regimen showed 65% ($p = 0.07$) and 48% ($p = 0.044$) efficacy against these same endpoints. In a 1,349 subject field study healthy adults were given placebo or a trivalent FluINsure vaccine at either 30 μg as a single dose or 15 μg as two doses. The efficacy of one- and two-dose regimens was indistinguishable; overall efficacy was 84% against febrile illness with laboratory confirmation of influenza infection in a year marked by a poor match between the vaccine antigen and dominant circulating virus.

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Notes

Next Generation Vaccines against Pandemic and Epidemic Influenza: PER.C6® as cell substrate

Jaap Goudsmit/Crucell/Netherlands

The global demand for more and better influenza vaccines is growing. The increasing threat of a human pandemic, - due to the spreading of avian influenza in Asia (H5N1)-, requires even more agility of vaccine production and delivery than the epidemic vaccine. World-wide pandemic vaccine efforts focus on H5 and H7 viruses and epidemic vaccine efforts have to deal with variation in the H3N2 influenza A strains as well as the growth properties of the Influenza B strains.

All of these issues are related to both vaccine production and delivery as well as to the level of protection, in other ways the vaccine design.

The PER.C6® cell substrate deals primarily with the first set of challenges and less with the second.

PER.C6® is a cell line derived from primary human retina cells immortalized by the E1 gene of adenovirus 5. A Biologics Master File deposited at the FDA documents the derivation, the characteristics and the safety of the PER.C6 cell line. Merck produces its Ad5-based HIV vaccine, currently in Phase II proof of concept studies in the US, the Caribbean and South America on PER.C6®; both the pandemic and the epidemic cell-based Influenza vaccine programs of Sanofi Pasteur are based on PER.C6®. The PER.C6®-based clinical pandemic influenza programs are supported by the EU (Flupan) and the US government (RFP CDC).

The PER.C6® safety is based on the absence of advantageous agents and tumorigenicity. PER.C6® is uniquely suitable for transfection, a requirement for reverse genetics. Pandemic influenza strains, such as H5N1 and H7N1 replicate to high titers on PER.C6® as do epidemic strains such as the Fuijan family of H3N2 strains and influenza B strains. High yields of HA are obtained from PER.C6® cultures infected with pandemic and epidemic influenza strains as evidenced by classical measures as well as new assays like HPLC and FACS. Finally we have shown good immunogenicity of PER.C6®-derived HA of pandemic and epidemic strains and we are in the process of setting up pandemic lethal challenge models for H6N1, H7N7 and H9N2 to test efficacy and quantitative immune correlates for PER.C6-based pandemic vaccines.

Notes

HIV Vaccines

Immune Control and Immune Failure in HIV infection

Bruce Walker/Massachusetts General Hospital/Aids Research Centre/Charlestown/USA

Most current HIV vaccine strategies are predicated on an ability to induce immune responses that will contain infection rather than prevent infection. Such an approach is supported by data from persons who control infection after more than 25 years, suggesting that long term containment may be possible.

Emerging data suggest a combination of host and viral genetic factors, together with adaptive host cellular immune responses, that contribute to containment. Early loss of CCR5+CD4+ cells specific for HIV, viral evolution leading to CD8 T cell escape, dysfunction of CD8 T cells, and changes in viral fitness all contribute to loss of control. Despite these differences, data to be presented from population studies as well as studies in genetically identical adult twins infected at the same time with the same virus indicate that there is significant predictability in the adaptive immune responses to HIV, as well as constraints on mutations that arise within targeted epitopes. These data indicate that it is possible to define the not only the viruses being transmitted, but also to predict the earliest mutations that the virus will acquire under immune selection pressure, offering new strategies to deal with viral sequence diversity in vaccine development.

Notes

Elite Controllers and Vaccine Studies in the SIV-Infected Indian

David Watkins/University of Wisconsin Medical School/Madison/USA

Rare HIV-infected humans and simian immunodeficiency virus (SIV)-infected macaques control viral replication and exhibit unusually good clinical outcomes. The reasons for this control are poorly understood. Typical plasma setpoint levels of SIVmac239 in Indian rhesus macaques are 1 million copies/mL, and half of the animals die within a year post-infection. We have now followed viral replication in 161 Indian rhesus macaques, all infected with SIVmac239.

Eleven animals controlled replication of this highly pathogenic isolate to <500 copies/mL. Strikingly, all but four of these macaques express the Mamu-B*17 molecule, and this molecule binds an SIV-derived peptide recognized by immunodominant CD8+ T lymphocytes. To determine the mechanism of control, we are investigating the cellular immune responses, viral escape, and viral fitness in these controllers. Understanding these immune responses will be useful in designing vaccine regimens.

Notes

Neutralizing Antibodies and HIV Vaccine Design

Dennis Burton/The Scripps Research Institute/La Jolla/USA

There is now a widespread consensus that a successful HIV vaccine will need to include a component that elicits broadly neutralizing antibodies. The spike envelope proteins of HIV-1 incorporate many features that appear to have been selected to avoid broadly neutralizing antibody responses. These include a very highly glycosylated envelope protein, the presence of variable immunodominant loops and recessed or completely hidden conserved receptor binding sites. Nevertheless certain weaknesses in the envelope-spiked trimer are revealed by a small panel of broadly neutralizing human monoclonal antibodies. The possible exploitation of these apparent weaknesses in HIV vaccine design will be discussed.

Notes

The Promise and Challenge of HIV-1 Vaccine Development

Emilio Emini/International Aids Vaccine Initiative/New York/USA

With an estimated 14,000 new HIV-1 infections occurring every day, the development of an effective HIV-1/AIDS vaccine is imperative. Unfortunately, 20 years after the identification of the virus, the goal remains elusive. These years have witnessed remarkable advances in knowledge of the virus, of its pathogenesis and of the host's immune response to the infection. There have also been noted advances in fundamental understanding of the molecular and cellular workings of the human immune system. This knowledge has shown us how HIV-1 effectively thwarts the efforts of the immune system to eliminate the infection, and how difficult it may be to develop a vaccine that can prevent the infection. Yet, in spite of the formidable challenge, clear pathways exist for continued research.

Ideally, a vaccine to prevent the infection will elicit both antiviral neutralizing antibodies as well as specific antiviral cellular immune responses. However, the structure of the viral surface glycoprotein is such that it is largely protected from the effect of antibodies, and those glycoprotein determinants that are potentially exposed to antibodies are genetically highly diverse. Efforts to isolate and define human monoclonal antibodies that are potent and effective against diverse isolates of the virus have been frustrating. Nonetheless, continued and detailed study of the surface glycoprotein's structure does suggest that the virus exposes potentially conserved determinants during the infection process. The current challenge is the design of potential vaccine immunogens that can mimic these determinants and possibly elicit broadly reactive virus-neutralizing antibodies.

On the other hand, the effectiveness of the cellular immune response in controlling the persistent virus infection is increasingly appreciated. A growing body of genetic and functional data suggests that control of virus replication in an infected individual is largely the result of the host cellular immune response against virus-infected cells. In fact, the levels of replicating virus manifest during the initial acute infection and during the subsequent persistent infection appear to be established early in the infection and likely represent a balance between an effective antiviral cellular immune response and the virus' mediation of immune dysfunction. Accordingly, a vaccine that "primes" the cellular response, so that upon infection with the virus this balance favors antiviral cellular immunity, will result in an infection characterized by lowered virus loads. The consequence will be a lessened likelihood of virus transmission by the infected individual as well as substantially slower disease progression. A number of vaccine vector systems are currently undergoing human clinical study for safety and immunogenicity. To date, the most promising appear to be those based on the use of replication-defective

adenoviruses. Studies are also ongoing to define the most effective viral targets of the cellular response with a focus on identifying functionally important conserved or minimally variable targets. The next several years will witness increased efforts to better understand the nature of the most likely effective cellular responses as well as the development of novel vaccine vectors that can efficiently elicit these responses in humans. The uncertainties are still substantial, but continued study is critically important given the necessity imposed by the continuing pandemic.

Notes

Innate Immunity

Deciphering innate immune response pathways using germline mutagenesis

Bruce Beutler/The Scripps Research Institute/La Jolla/USA

An inherited system of immune responses is particularly susceptible to analysis using classical genetic methods. A spontaneous mutation in TLR4 (encoding the now well-know P712H substitution in C3H/HeJ mice) first disclosed that Toll-like receptors were sensors of conserved molecules of microbial origin[1]. The introduction of germline mutations at random, the identification of novel phenovariants, and the positional cloning of the causal mutations has revealed several other key proteins within this system of innate immune receptors. The method is particularly effective when used to study conditional mutations, which become apparent only with the stress of infection or a quasi-infectious stimulus. A novel adapter protein, now known as TRIF, was first identified as a signaling adapter for TLRs 3 and 4 using ENU mutagenesis, which created the Lps2 phenovariant[2]. Mutations of TRIF and TLR9 (Lps2 and CpG1) first revealed the viral sensing function of the intracellular TLRs[2,3]. CD36 was identified as an important co-factor for signal transduction from the TLR2/6 heterodimer when its gene was modified by the oblivious mutation[4]. And the 3d mutation has revealed a new and important component of TLR3, 7, and 9 signaling, also required for effective presentation of exogenous antigens (Tabeta, et al., submitted, and Hoebe, et al., submitted). Other mutations (pococurante and lackadaisical) have shed light on the structure and function of the adapter protein MyD88, on connectors in that link MyD88-independent and MyD88-dependent signaling pathways (feckless), and on the function of CD14 in MyD88-independent signaling (heedless). Using a very broad approach to the identification of innate immune signaling proteins, we are attempting to identify novel proteins that confer non-redundant resistance to mouse cytomegalovirus (MCMV) infection. Hundreds of proteins seem to be required for C57BL/6 mice to cope with this pathogen. The MCMV resistome probably represents a large portion of the universal resistome, given the degenerate character of the innate immune response as a whole.

Reference List

1. Poltorak,A. et al. Defective LPS signaling in C3H/HeJ and C57BL/10ScCr mice: mutations in Tlr4 gene. Science 282, 2085-2088 (1998).
2. Hoebe,K. et al. Identification of Lps2 as a key transducer of MyD88-independent TIR signaling. Nature 424, 743-748 (2003).
3. Tabeta,K. et al. Toll-like receptors 9 and 3 as essential components of innate immune defense against mouse cytomegalovirus infection. Proc. Natl Acad. Sci. U.S.A 101, 3516-3521 (2004).
4. Hoebe,K. et al. CD36 is a sensor of diacylglycerides. Nature 433, 523-527 (2005).

Notes

Dendritic cell based approaches for vaccine development

Michel Nussenzweig/Rockefeller University New York/USA

Abstract not received in time for print

Notes

TB Vaccines

Pathogenesis of Mycobacterium Tuberculosis

William R. Jacobs/Albert Einstein College of Medicine and Howard Hughes Medical Institute/New York/USA

Abstract not received in time for print

Notes

A Fusion Protein Subunit Approach towards a Vaccine

Mark Doherty/Staten Serum Institute/Denmark

The search for a new and improved vaccine against Tuberculosis (TB) is currently a very active field of research which in the last 10 years has benefited tremendously from advances in Genomics, Proteomics and Transcriptomics. The completed M. tuberculosis genome sequence and progress in molecular biology and computer science have hugely accelerated the pace of antigen discovery, resulting in the identification of a large number of antigens with potential in TB vaccines. This has given us not only a large panel of antigens from which to choose potential vaccine candidates, but allows us to begin to develop "customized" vaccines with purposes beyond merely boosting immunogenicity. The second great advance has been in our understanding of antigen-presenting cell activation in the course of natural infection, which has given us a number of new potential adjuvants that combine efficacy and safety. Together these advances have brought us to the last phase of the project– putting the most relevant molecules back together as fusion molecules and cocktails. This requires carefully monitoring aspects as immunodominance, recognition in different populations as well as vaccine manufacturing. This presentation will summarize the steps that have gone into selecting the components for the subunit vaccine now entering clinical trials, as well as discussing the potential for "second generation" vaccines built on a rapidly evolving technology platform.

Notes

Subunit Approach towards a Novel Vaccine

Mark Alderson/Corixa/Seattle/USA

The identification of mycobacterial antigens that preferentially activate T-cells to proliferate and secrete IFN-γ is critical to the development of subunit vaccines against tuberculosis. We have prioritized a subset of antigens for vaccine development that were initially identified in the context of the host response to infection in healthy PPD+ humans and C57BL/6 mice. Our lead construct, Mtb72F, comprises three components coding for a 72kDa poly-protein that induces protective immunity in mouse, guinea pig, rabbit and macaque models of tuberculosis. We are also investigating more recently discovered mycobacterial antigens that have been shown to induce protective immunity as a way of potentially improving upon the protection offered by Mtb72F. In addition to identification of appropriate antigens, the selection of optimal adjuvants and delivery systems is crucial to the success of subunit-based vaccines. In this regard, we have investigated antigen delivered in the form of DNA, recombinant adenovirus, or as protein formulated in two proprietary (GlaxoSmithKline) adjuvant systems, AS01B and AS02A. Recent studies have also investigated intranasal vaccination using synthetic toll-like receptor 4 agonists as mucosal adjuvants. The outcome of the immune response was found to be greatly influenced by the way in which antigen is delivered. The different vaccine formulations resulted in both qualitative and quantitative differences in immune responses elicited that did not necessarily correlate strongly with protection from challenge with M. tuberculosis. The culmination of these studies is an ongoing Phase 1 clinical trial assessing the safety and immunogenicity of an Mtb72F-based vaccine in normal healthy volunteers.

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Notes

Panel Discussion

Novel vaccines for the world - how to streamline efforts of academia, biotech, venture capital, politics and charitable trusts?

Participants: Karen Bernstein (Biocentury), David Cyranoski (Nature), Martin Friede (WHO), Thomas Szucs (BBBiotech), Jacques-Francois Martin (GAVI - The Vaccine Fund), Jerald Sadoff (Global Aeras TB Foundation) and Alexander von Gabain, Chair (Intercell AG)

Infectious diseases remain the worldwide greatest health threat to human beings and one of the major impediments to overcome the unacceptable economical misbalance between developed and developing countries. Vaccination is arguably the most successful medical intervention and is with no doubt the most cost-efficient investment to keep known and novel emerging infectious diseases under control, but also predicted pandemic threats. The defeat of infectious diseases by the virtue of vaccination, as exemplified by the eradication of small pox, could clearly free resources for improved life conditions of all human beings on earth, provided the global vaccine gap could be closed.

In the present panel journalists from leading scientific and biotech journals, vaccine experts from renowned nonprofit organizations, private foundations and industry, but also investors from the life science arena will discuss problems and their perspective solutions, regarding the development of novel vaccines needed for both developed and developing parts of the world. The discussion will try to analyze strength and weakness of vaccine development when academic and industrial approaches are compared. The panel will also touch the economical, financial, regulatory and manufacturing restrictions that may impede the development of novel vaccines. The participants will try to sketch a path how novel products may have to be moved forward such that they will sell in developed countries and eventually in the high price segment of less developed countries, but at the same time will meet the requirements to be distributed to populations unable to pay for vaccines. Particularly, the question will be addressed whether there may be optimal ways how biotech investors, vaccine industries, nonprofit organizations, charitable trusts and politics could partner up in creating a "win-win situation" for all involved parties: Extermination and prevention of the worldwide most threatening infectious diseases in both developed and developing countries, need incentives for the vaccine industry and their investors to drive novel vaccines forward, but also sufficient efforts to provide non-profit organizations with resources and strategies to optimally leverage novel vaccines to their clients.

The Kyoto treaty set up to control the global warming has shown that politicians, economists and scientist are able to reach a sound, but also disputed and ultimately expensive, agreement, if mankind seems to be endangered. The threat, the devastation and the economical damage of worldwide insufficiently controlled infectious diseases is much better documented and less controversial among the scientific community, than the cause of the climate change and the implemented counteractions. Consequently, a meeting held by leading economists, including three Nobel Prize laureates, last May in Copenhagen, prioritized the worldwide fight against major infectious diseases higher than too hastily decided measures against climate changes. Such a recommendation may encourage the decision makers of our world to call for Kyoto-like vaccine treaty that would provide enough resources to master the global threat and burden of infectious diseases. The panel may discuss such a vision.

Notes

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