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Vaccines Summit-2021

September 20-22, 2021 | Online Meeting

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Scientific Sessions

The Evolution of Vaccinology

Stanley Plotkin
Consultant and Emeritus Professor of the University of Pennsylvania, Vaxconsult, LLP

"Vaccines have evolved over the centuries, moving from inactivated and attenuated vaccines to isolated protein and polysaccharides, to virus-like particles, vectored proteins and nucleic acids coded for proteins. The future of vaccination is brighter than ever, but certain unknowns remain."

Exciting progress with malaria vaccines

Adrian V. S. Hill
Director of the Jenner Institute and the Lakshmi Mittal & Family Professor of Vaccinology at Oxford University

Biography:

Since the 1990s he has developed a leading malaria vaccine programme, spanning over 60 clinical trials in Europe and Africa, with one vaccine now showing high level efficacy and in late stage development. This programme has introduced and validated particularly immunogenic vaccine technologies including chimpanzee adenoviral vectors and virus-like particles in saponin adjuvants.

In 2005 he founded the Jenner Institute at Oxford University, now the largest academic vaccine centre globally with clinical-stage vaccine programmes against sixteen diseases, including malaria, HIV, TB, COVID-19, MERS and emerging pathogens and cancer.

In 2020, with many others at the Institute, he helped develop a new chimpanzee adenoviral vector-based COVID-19 vaccine to licensure and large-scale manufacture in less than a year.

Synthetic DNA Approaches for Immunization and Immunotherapy

David Weiner
Wistar Institute Professor & WW Smith Chair in Cancer Research,
Director Vaccine & Immunotherapy Center,
Executive Vice President of the Wistar Institute,
Professor Emeritus University of Pennsylvania School of Medicine, Philadelphia PA

Synthetic DNA is an important platform for generation of vaccines and immunotherapy approaches which are being developed to target cancers and infectious disease. In collaboration we have advanced vaccines for MERS, Ebola, and SARS-Cov2 (currently in Phase III trials) as well as for cancer immunotherapy. We have reported that these vaccines generate both humoral and diverse cellular immunity in a temperature stable, translatable platform. We have been focusing on the development of next generation immunogens as well as biologics which assemble in vivo. We will present studies of DNA launched self assembling antigens as a novel tool for infectious disease. We will also discuss synthetic DNA as a tool for immunotherapy of difficult targets.

Study of Adaptive Responses to SARS CoV2

Alessandro Sette
Professor and Member, Infectious Disease and Vaccine Center, La Jolla Institute for Immunology

We will review our studies in the course of the last year, starting from the prediction of potential targets and the demonstration of immune responses in early convalescents. Subsequent studies analyzed correlates of immunity in the acute phase of disease, and highlighted the phenomenon of crossreactivity between SARS CoV2 and common cold coronaviruses at the level of T cell recognition. The most recent studies characterized the duration of immune responses following natural infection, definition of the epitope repertoire for SARS CoV2 reactive T cells, and analyzed the impact of variant-associated mutations on T cell recognition

mRNA-1273: A Summary of Current Data and a View to the Future

Jacqueline Miller
Senior Vice President, Therapeutic Area Head, Infectious Diseases, Moderna

Biography:

Dr. Jacqueline Miller is currently the SVP, Therapeutic Area Head for Infectious Diseases at Moderna, and leads the Development teams for Vaccines. She received her M.D. from Northwestern University and trained in pediatrics at Children's Hospital of Philadelphia. She later joined Merck Research Laboratories in vaccine clinical development, and subsequently joined GSK to lead meningococcal vaccine development, eventually becoming Head of Clinical Research and Development for US Vaccines. During her time at previous companies, she contributed to the licensure of 5 novel vaccines. In 2020, she joined Moderna to help achieve Emergency Use Authorization for its COVID-19 vaccine, and is happy to have the opportunity to discuss that experience and the future of COVID-19 vaccine development at the Vaccine Summit 2021.

Mitigating Future Pandemics: New Threats and Strategies to Consider

Gregory C. Gray, MD, MPH, FIDSA
Professor, Duke Infectious Diseases, Duke Global Health Institute, Nicholas School of the Environment
Duke University
Durham, NC 27710 USA

Objectives:

1) To review future respiratory virus pandemic threats

2) To present a One Health/global health strategy for novel respiratory virus pathogen detection, characterization, and mitigation

3) To present the discovery of a novel canine-like alphacoronavirus infection in a human pneumonia patient.

Abstract:

Our current pre-pandemic pathogen surveillance strategies failed to detect both the 2009 and 2019 pandemic viruses. It seems clear that the world's current virological and immunological strategies to detect pre-pandemic pathogens are not working. In this presentation, Professor Gray will review the need for conducting surveillance for novel respiratory virus pandemic threats and current strategies for detecting them. He will also present a One Health-oriented surveillance strategy and argue that it would be more successful if more widely employed. Professor Gray and his teams have recently used this One Health strategy in detecting respiratory virus cross-species spillover events between various animal species as well as between humans and animals. Most recently this work has included the detection, culture, and full genome assembly of a novel canine-like alphacoronavirus in a human pneumonia patient in Malaysia. This virus may represent the 8th known human coronavirus and a new pandemic threat.

COVID-19: Developing a Vaccine During a Pandemic

Dan Barouch
Director, Center for Virology and Vaccine Research, Beth Israel Deaconess Medical Center

Dr. Dan Barouch received his Ph.D. in immunology from Oxford University and his M.D. from Harvard Medical School. He is currently the William Bosworth Castle Professor of Medicine and Professor of Immunology at Harvard Medical School, Director of the Center for Virology and Vaccine Research at Beth Israel Deaconess Medical Center, a member of the Ragon Institute of MGH, MIT, and Harvard, and part of the Bill & Melinda Gates Foundation Collaboration for AIDS Vaccine Discovery. His laboratory focuses on studying the immunology and virology of HIV-1 infection and developing novel vaccine and eradication strategies. His group has also applied their vaccine expertise to preclinical and clinical studies of other infectious diseases of global significance, including Zika virus, tuberculosis, and most recently SARS-CoV-2. His recent work contributed to the development of the single-shot Johnson & Johnson COVID-19 vaccine, which is now being rolled out in the United States and throughout the world. He was elected to the National Academy of Medicine in 2020.

PfSPZ vaccines: From concept to proof of principle to genetically attenuated late arresting replication competent PfSPZ vaccine manufactured in bioreactors for use in malaria elimination campaigns.

Stephen L. Hoffman, MD
Sanaria Inc., Rockville, MD 20878 USA

Our goal is the development and commercialization of *Plasmodium falciparum* (Pf) sporozoite (SPZ) vaccines for the prevention of malaria in individuals and the elimination of malaria in entire geographic regions using vaccines that prevent infection and thereby prevent clinical disease and transmission. This challenging goal has required a multi-stage development process. The first-generation vaccine is the radiation-attenuated, early arresting, non-replicating PfSPZ Vaccine reported to provide 100% protection against Pf infection by homologous controlled human malaria infection (CHMI) at 3 weeks after last dose in 2013 and 46% to 57% % protection against Pf infection by field exposure in adults in Mali and Burkina Faso for 6 to 18 months after last dose of vaccine in 2017 to 2021. This vaccine is now moving to Phase III assessment in 2022 to support marketing authorization. The second-generation vaccine is the chemo-attenuated, replication competent PfSPZ-CVac reported to provide 100% protection against Pf infection by homologous CHMI at 10 weeks after last dose in 2017 and 100% protection against Pf infection by heterologous CHMI at 12 weeks after last dose in 2021 at at less than 25% of the dose needed for the radiation-attenuated vaccine; a field trial in Mali is in progress. This vaccine has provided the best protection, by far, of any malaria vaccine against CHMI. However, because it must be administered with an antimalarial drug to prevent malaria, it has limitations. The next-generation PfSPZ vaccine will be a genetically attenuated, late arresting replication competent (LARC) PfSPZ vaccine that will not require an anti-malarial drug. This vaccine will enter clinical trials in 2022 and based on animal studies is expected to be as potent as PfSPZ-CVac but without PfSPZ-CVac's tolerability and safety concerns. All of these PfSPZ vaccines are manufactured in mosquitoes. However, we are now moving to finalization of the manufacturing process in bioreactors without mosquitoes and anticipate transitioning rapidly to a bioreactor manufactured PfSPZ-LARC vaccine that will have optimal tolerability, safety, and potency with significantly reduced cost of goods. The data supporting each step and future plans will be presented.

Vaccine, a cornerstone in immunotherapy for cancer; more than a T cell priming tool

Samir N. Khleif
Director, Jeannie and Tony Loop Immuno-Oncology Research Laboratory, Lombardi Comprehensive Cancer Center

Biography:

As an immunologist and immune therapist, his interest has been in developing novel immune therapeutics, cancer vaccines and delineating the mechanisms of resistance to immunotherapy. His research program is translational tumor immunology focused on understanding mechanisms through which the immune system and cancer cells interact and how to overcome tumor tolerance in developing therapeutic approaches.

Development of Novel T cell Targeting Vaccines

Daniel F. Hoft, MD, PhD
Saint Louis University School of Medicine & Center for Vaccine development

Traditionally, vaccines focus on inducing protective antibody. However, T cells can provide both direct and indirect protection by: 1) recognition and elimination of infected cells, 2) cytokine-mediated activation of antimicrobial properties, and 3) helper effects for B cell responses. We have focused on 2 novel T cell targeting vaccine strategies. First, conventional αβTCR+ T cells are being targeted for development of universal influenza vaccines. Both CD4+ T cells reactive with promiscuous HLA-DR-restricted epitope clusters, and CD8+ T cells restricted by all six major supertypes of HLA class I, are being targeted. Proof-of-concept studies have demonstrated feasibility of this approach in HLA transgenic mice. We are currently confirming high population coverage of our CD4 epitopes, completing identification of CD8 epitopes for all 6 HLA class I supertypes, and developing optimal delivery formats for our T cell targeting universal influenza vaccines. Second, we have demonstrated that human γδ T cells can inhibit intracellular replication of *Mycobacterium tuberculosis* (Mtb), a unique antigen from Mtb activates $\gamma_9\delta_2$TCR+ protective T cells, and immunization of nonhuman primates with our novel antigen can protect against pulmonary Mtb challenge. We currently are focused on identifying the biologically active core of our novel antigen, understanding the mechanisms for how Mtb-specific γδ T cells recognize antigen and provide protection, and the development of adjuvants that can enhance in vivo differentiation and expansion of γδ T cells. Our work indicates that we and others will be successful in harnessing the power of T cells for novel and powerful vaccine strategies.

Immune correlates of protection and activation of immune cells after the challenge: From Ebola to COVID-19

Alexander Bukreyev
Departments of Pathology and Microbiology & Immunology, Galveston National Laboratory, University of Texas Medical Branch

While significant progress has been made with Ebola virus (EBOV) vaccine measures, the immune correlates of vaccine-mediated protection remain uncertain. Five mucosal vaccine vectors based on human and avian paramyxoviruses provided non-human primates with varying degrees of protection, despite expressing the same EBOV glycoprotein (GP) immunogen. Each vaccine produced antibody responses which differed in Fc-mediated functions, isotype composition and in magnitude and coverage towards GP and its conformational and linear epitopes. Differences in the degree of protection and comprehensive characterization of the response afforded the opportunity to identify which features and functions were elevated in survivors and could therefore serve as vaccine correlates of protection. Pairwise network correlation analysis of 139 immune and vaccine-related parameters was performed to demonstrate relationships with survival. Total GP-specific antibodies measured by biolayer interferometry, but not neutralizing, IgG or IgA titers, correlated with survival. Fc-mediated functions and the amount of receptor-binding domain antibodies were associated with improved survival outcomes alluding to the protective mechanisms of these vaccines. Therefore, functional qualities of the antibody response, particularly Fc-mediated effects and GP specificity, and not just its magnitude, appear central to vaccine-induced protection against EBOV. The heterogeneity of the response profile between the vaccines indicates that each vaccine likely exhibits its own protective signature and the requirements for an efficacious EBOV vaccine are complex.

Development of Next Generation UB-612 Vaccine

Farshad Guirakhoo, PhD
CSO, Vaxxinity

In this talk we discuss the immunogenicity and efficacy of the first multitope protein-peptide vaccine against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). UB-612 consists of eight components rationally designed for induction of potently neutralizing antibodies and broad T cell responses against SARS-CoV-2: the S1-RBD-sFc fusion protein, six synthetic peptides (one universal peptide and five SARS-CoV-2-derived peptides), a proprietary CpG TLR-9 agonist, and aluminum adjuvant. The vaccine candidate provides excellent S1-RBD binding and high neutralizing antibody responses, robust cellular responses, and a Th1-oriented response. In animal challenge studies, UB-612 vaccination reduced viral load and prevented development of disease in mouse and non-human primate challenge models. With a Phase 1 trial completed and phase 2 study ongoing involving ~4000 subjects in Taiwan and additional trials planned toward an Emergency Use Authorization approval/licensure worldwide, UB-612 is a highly promising and differentiated vaccine candidate for prevention of SARS-CoV-2 transmission and COVID-19 disease. In the view of emergence of Variants of Concerns (VOC), especially dominance of the Delta variant, we present our next generation data demonstrating improvement in immunogenicity of UB-612 to counter VOC.

Computational design of immune-focused SARS-CoV-2 nanoparticles

Daniel Kulp
Associate Professor, Vaccine & Immunotherapy Center
The Wistar Institute

SARS-CoV-2 vaccines may target epitopes which reduce durability or increase the potential for escape from vaccine-induced immunity. Using novel synthetic vaccinology, we developed rationally immune focused SARS-CoV-2 Spike-based vaccines. Glycans can be employed to alter antibody responses to infection and vaccines. Utilizing computational modeling and in vitro screening, we incorporated glycans into the Spike Receptor-Binding Domain (RBD) and assessed antigenic profiles. We developed glycan-coated RBD immunogens to elicit stronger neutralizing antibodies and engineered seven multivalent configurations. Advanced DNA delivery of engineered nanoparticle vaccines rapidly elicited potent neutralizing antibodies in guinea pigs, hamsters and multiple mouse models, including human ACE2 and human antibody repertoire transgenics. RBD nanoparticles induced high levels of cross-neutralizing antibodies against variants-of-concern that are durable beyond six months. Single, low dose immunization protected against death in a lethal SARS-CoV-2 challenge. Single-dose coronavirus vaccines via DNA-launched nanoparticles provide a platform for rapid clinical translation of novel, potent and durable coronavirus vaccines.

Development of a transmission blocking multivariant Covid-19 vaccine

Nikolai Petrovsky
Director of Endocrinology, Flinders University

The development of a safe and effective vaccine is a key requirement to overcoming the COVID-19 pandemic. Recombinant proteins represent the most reliable and safe vaccine approach but generally require a suitable adjuvant for robust and durable immunity. We used the SARS-CoV-2 genomic sequence and *in silico* structural modelling to design a recombinant spike protein vaccine (Covax-19™). A synthetic gene encoding the spike extracellular domain (ECD) was inserted into a baculovirus backbone to express the protein in insect cell cultures. The spike ECD was formulated with Advax-SM adjuvant and first tested for immunogenicity in C57BL/6 and BALB/c mice. The Advax-SM adjuvanted vaccine induced high titers of binding antibody against spike protein that were able to neutralise the original wildtype virus on which the vaccine was based as well as the variant B.1.1.7 lineage virus. The Covax-19 vaccine also induced potent spike-specific CD4+ and CD8+ memory T-cells with a dominant Th1 phenotype, and this was shown to be associated with cytotoxic T lymphocyte killing of spike labelled target cells *in vivo*. Ferrets immunised with Covax-19 vaccine intramuscularly twice 2 weeks apart made spike receptor binding domain (RBD) IgG and were protected against an intranasal challenge with SARS-CoV-2 virus 2 weeks after the second immunisation. Notably, ferrets that received two 25 or 50mg doses of Covax-19 vaccine had no detectable virus in their lungs or in nasal washes at day 3 post-challenge, suggesting the possibility that Covax-19 vaccine may in addition to protection against lung infection also have the potential to block virus transmission. Covax-19 vaccine is currently in advanced stage human clinical trials.

Pandemics unveil major shortcoming in contemporary vaccine design: Too little, too late….

Vanden Bossche G.
Coimeva Comm. Ven., Belgium

Current 'progress' in the vaccine field is largely based on new technologies such as those involved in novel manufacturing processes or in big data mining (-omics) enabling molecular analysis of immunorelevant genes and immune signalling pathways. However, much less progress has been made in our fundamental understanding of host-pathogen interactions and immune subversive mechanisms which pathogenic agents have evolved to escape natural mechanisms of host immune defence. As a result, selection of vaccinal antigens still largely relies on naturally induced immune responses that correlate with recovery from acute disease caused by specific pathogens. The immune responses these antigens induce are restricted by antigenic variability of the pathogen and/ or the immuno-genetic background of the host. Immune responses induced by contemporary vaccines are, therefore, prone to immune escape. Natural selection of immune escape variants is even more likely to occur when individuals exerting suboptimal immune pressure have a high chance of becoming exposed to circulating virus. Provided widespread immune selection pressure, these immune escape variants will even be able to adapt to the rising immune status of the vaccinated population. This already explains why classical vaccines fail to prevent variants from arising and further evolving when mass vaccination campaigns are conducted in populations that are continuously exposed to the circulating virus, a situation which typically occurs during a pandemic. Under these conditions, the effect of these vaccines is simply 'too little' and comes 'too late' to prevent evolving variants from circumventing vaccine-elicited immunity.

Keywords: immune evasion; natural selection; adaptation; mass vaccination; pandemic

Biography:

Dr. Vanden Bossche received his DVM from the University of Ghent, Belgium, and his PhD degree in Virology from the University of Hohenheim, Germany. He held adjunct faculty appointments at universities in Belgium and Germany. After his career in Academia, Geert joined several vaccine companies (GSK Biologicals, Novartis Vaccines, Solvay Biologicals) to serve various roles in vaccine R&D as well as in late vaccine development. Geert then moved on to join the Bill & Melinda Gates Foundation's Global Health Discovery team in Seattle (USA) as Senior Program Officer; he then worked with the Global Alliance for Vaccines and Immunization (GAVI) in Geneva as Senior Ebola Program Manager and subsequently joined the German Center for Infection Research in Cologne as Head of the Vaccine Development Office. Geert is now primarily serving as a Biotech/ Vaccine consultant while also conducting his own research on Natural Killer cell-based vaccines.

As a creative thinker, innovator, entrepreneur and visionary, Geert has been invited to speak at multiple international congresses. His work and supportive advice are driven by a relentless passion to translate scientific breakthrough findings into competitive solutions to emerging challenges in public and global health.

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Poster Presentations

A novel tool to enable multivalent vaccine development for influenza and coronavirus.

Scott Fu
Filed Application Scientist

Influenza and coronavirus pose unique challenges in vaccine development. Continuous antigenic drift requires new reagents and tools for analytical assessment and this challenge can represent a bottleneck in vaccine production and virus eradication. Improved characterization assays for identity, potency, and stability are needed to replace cumbersome and inefficient methods such as SRID and ELISA, which can cause increased development time and higher manufacturing costs. A lack of standardized assays and reagents also leads to a missed opportunity to compare results across manufacturing sites and products, and diminishes a coordinated global effort. InDevR seeks to eliminate these bottlenecks by providing a standardized, ready to use kit with reagents that are versatile for antigenic drift. The VaxArray® Portfolio offers a simple multiplex solution that is validated to ICH guidelines and is manufactured under ISO:13485 quality standards. The VaxArray system has been implemented for bioprocess improvement at several influenza and coronavirus vaccine manufacturing sites, and has already gained traction with FDA and Health Canada submissions.

A Bi-Antigen Recombinant Subunit SARS-CoV-2 Vaccine comprising S1 Subunit and N protein, expressed in Pichia pastoris: A Low-cost, Safe and Effective Candidate Designed for Developing Countries

Ganesh Kumraj*, **Jainendra Jain**, **Syed Ahmed**, **Davender Bhati**, **Sanket Shah** and **Piyali Majumder**
Techinvention Lifecare Pvt. Ltd, Mumbai, India.

SARS-CoV-2 Spike (S) Glycoprotein is directly recognized by the immune system, representative antigen for T-cell response and a key target for neutralizing antibodies. S1 subunit of S protein has RBD which binds to host ACE-2 receptors mediating attachment. RBD has multiple dominant neutralizing epitopes and targeted by neutralizing antibodies. N-terminal Domain within S1 is also a target for neutralizing antibodies. N protein is highly conserved, abundantly expressed during infection and a representative antigen for T-cell response. Both S1 and N protein induce stable immune responses and presents the idea of a bi-antigenic recombinant subunit SARS-CoV-2 vaccine. Pichia pastoris is one of the desirable expression platforms in recombinant technology to produce cost-effective product with high yield and easy to scale-up process. Furthermore, Pichia pastoris is a suitable host for high expression with several post-translational modifications and offers technology transfer options to developing countries. Therefore, we have developed a bi-antigenic recombinant subunit SARS-CoV-2 vaccine comprising S1 and N protein using Pichia pastoris as the platform technology. As SARS-CoV-2 continues to spread globally, there is an urgent need to develop accessible and low-cost vaccine for developing countries. Our technology addresses several challenges in vaccine design by providing economic and effective option for preventing SARS-CoV-2 infections in developing countries. The platform used to develop the technology has the advantage of not requiring dedicated or specialized facility making it an affordable option using existing manufacturing facilities without significant investments. Highly conserved N protein across coronavirus species makes it an attractive target for universal coronavirus vaccine.

Biography:

Dr. Ganesh Kumraj holds a Doctorate in Life Sciences from University of Rajasthan, India, and is a seasoned biotech professional. He has rich experience spanning 3 decades in the field of vaccines and biologicals. He has held reputed positions in a number of Indian Pharma companies and his expertise includes technology transfer, new product development, project design, manpower training, QMS implementation, etc. He has extensive knowledge of international standards and regulations for the pharma and biotech industry and is conversant with global working styles and patterns.

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Day 2: September 21, 2021

Scientific Sessions

Development of a versatile one-shot vaccine targeting platform

KAVISHNA Ranmali[1], CHEANG Nicholas[1], LAHOUD Mireille[2] and Sylvie ALONSO[1]*
[1]Infectious Diseases Translational Research Programme; Department of Microbiology&Immunology; Yong Loo Lin School of Medicine; National University of Singapore (Singapore).
[2]Monash Biomedicine Discovery Institute & Department of Biochemistry and Molecular Biology; Monash University (Australia).

As part of the arsenal available to fight infectious diseases, vaccines are an important weapon. The mRNA vaccine technology appears well suited to tackle a pandemic. They can be rapidly generated, they do not require culturing the pathogen, and they have proved to be scalable. Recent clinical trials and data available from populations vaccinated with COVID-19 mRNA vaccines have indicated that these vaccines are generally safe and protect against the severe forms of the disease.

Despite these fantastic achievements, mRNA vaccines still meet with some limitations. In addition to complex manufacturing processes, mRNA vaccines are not suitable for peptide vaccine candidates that are poorly immunogenic. Hence, it is critical to continue the research and development of alternative vaccine platforms.

In that context, we have been developing a novel and versatile vaccine platform that has the potential to confer rapid and sustained protective immunity upon a single shot of small amounts of antigen, including poorly immunogenic candidates. The antigen candidate is plugged to the heavy chains of an anti-Clec9A monoclonal antibody that targets a specific subpopulation of dendritic cells. I will present proof-of-concept data with two vaccine antigen candidates, namely M2e, the 23-amino acid long leading universal flu vaccine candidate; and the larger receptor-binding domain (RBD) from SARS-CoV2 Spike protein. A single administration of Clec9A-M2e and Clec9A-RBD constructs triggers rapid and prolonged protective antibody responses. Remarkably, the results support that this targeting strategy can overcome the poor immunogenicity of small vaccine antigen candidates (M2e) and can accommodate larger protein cargos (RBD).

Biography:

Dr Alonso graduated with a PhD degree in Molecular and Cellular Biology from the Universite Claude Bernard Lyon I (France), and pursued her postdoctoral training at Pasteur Institute of Lille (France) and Cornell University (NY, USA). She then joined National University of Singapore in 2004 where she established her research group. For the past 15 years, she and her team have been studying host-pathogen interactions and virulence mechanisms in a number of bacterial and viral diseases. She has also been developing vaccine delivery systems.

Vaccine Hesitancy: The Next Challenge in the Fight Against COVID-19

Amiel A. Dror[1,2], Netanel Eisenbach[1,2], Shahar Taiber[4], Nicole G. Morozov[4]*, Matti Mizrachi[1,2] Asaf Zigron[2,3], Samer Srouji [2,3] and **Eyal Sela[1,2]**
[1]Department of Otolaryngology, Head and Neck Surgery, Galilee Medical Center, Nahariya, Israel
[2]The Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel
[3]Oral and Maxillofacial Department, Galilee Medical Center, Nahariya, Israel
[4]Department of Human Molecular Genetics and Biochemistry, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Vaccine hesitancy remains a barrier to full population inoculation against highly infectious diseases. Coincident with the rapid developments of COVID-19 vaccines globally, concerns about the safety of such a vaccine could contribute to vaccine hesitancy. We analyzed 1941 anonymous questionnaires completed by healthcare workers and members of the general Israeli population, regarding acceptance of a potential COVID-19 vaccine. Our results indicate that healthcare staff involved in the care of COVID-19 positive patients, and individuals considering themselves at risk of disease, were more likely to self-report acquiescence to COVID-19 vaccination if and when available. In contrast, parents, nurses, and medical workers not caring for SARS-CoV-2 positive patients expressed higher levels of vaccine hesitancy. Interventional educational campaigns targeted towards populations at risk of vaccine hesitancy are therefore urgently needed to combat misinformation and avoid low inoculation rates

Ebola and SARS-CoV-2: CHO-based manufacturing provides high quality subunit-vaccine candidates and diagnostics

Paco Pino*, **Divor Kiseljak, Joeri Kint, Jason Mclellan, Jamie Triccas, Ronald Dijkman, Gerco den Hartog, François Spertini, Ahmed Bouzidi, Sunil David, Maria J. Wurm** and **Florian M. Wurm**
ExcellGene, Route de l'Ile-au-Bois 1A, 1870 Monthey, Switzerland

The recent pandemic has highlighted the need to target emerging and re-emerging viruses by efficient vaccine developments. Most antiviral vaccines work by inducing specific immune responses against the surface proteins of the virus, which are essential for entry into the host cell. The goal of any vaccination is the production of neutralizing antibodies as well as long-term memory responses in circulating immune cells. The surface proteins of enveloped viruses are usually heavily glycosylated, multimeric complexes, with inherent structural flexibility and instability. Frequently, they need to be processed to adopt their proper conformation. These properties make these proteins challenging to produce.

The recent COVID19 pandemic showed that current protein production technologies for such subunit protein antigens are insufficient to meet the global demand for these critical molecules. Using optimized Chinese Hamster Ovary based technologies, we developed scalable, GMP-compliant, chemically defined processes for production of Ebola GP1/2 and SARS-COV-2 Spike surface antigens. Within weeks we were able to produce grams quantities of fully active and stabilized Ebola GP1/2 and SARS-COV-2 Spike protein trimers. Vaccination with the Ebola GP/1 trimer induced sterilizing protection in mice. Similarly, the SARS-CoV-2 spike-trimer induced high antibody titers in mice and provided exceptional sensitivity and specificity in diagnostic tests. These observations highlight the potential of CHO cells for manufacturing of potent sub-unit vaccines at low cost and (very) large scale.

Intranasal mucosal vaccine mediated protection against SARS-CoV-2 transmission in rhesus macaques

Yongjun Sui[1]*, Jianping Li[1], Roushu Zhang[2], Sunaina Kiran Prabhu[2], Hanne Andersen[3], David Venzon[4], Anthony Cook[3], Renita Brown[3], Elyse Teow[3], Jason Velasco[3], Jack Greenhouse[3], Tammy Putman-Taylor[3], Tracey-Ann Campbell[3], Laurent Pessaint[3], Ian N. Moore[5], Laurel Lagenaur[1], Jim Talton[6], Matthew W. Breed[7], Josh Kramer[7], Kevin W. Bock[5], Mahnaz Minai[5], Bianca M. Nagata[5], Mark G. Lewis[3], Lai-Xi Wang[2] and **Jay A. Berzofsky[1]**

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[6]Alchem Laboratories, Alachua, FL 32615
[7]Laboratory Animal Sciences Program, Frederick National Laboratory for Cancer Research, Bethesda, MD 20892

An effective SARS-CoV-2 vaccine is urgently needed. While most vaccine strategies have focused on systemic immunization, here we compared the protective efficacy of two adjuvanted subunit vaccines with spike protein S1: an intramuscular (IM)-primed /boosted vaccine and an IM-primed/intranasal (IN)-boosted mucosal vaccine, in rhesus macaques. The IM-alum-only vaccine induced robust binding and neutralizing antibody and persistent cellular immunity systemically and mucosally, while IN boosting with nanoparticles including IL-15 and TLR agonists elicited weaker T-cell and antibody responses, but higher dimeric IgA and IFNα. Nevertheless, following SARS-CoV-2 challenge, neither group showed detectable subgenomic RNA in upper or lower respiratory tracts vs naïve controls, indicating full protection against viral replication. Though mucosal and systemic protective mechanisms may differ, results demonstrate both vaccines can protect against respiratory SARS-CoV-2 exposure. The mucosal vaccine, which was safe after multiple doses and can clear the input virus more efficiently in the nasal cavity, may act as a potent reinforcing boost for conventional systemic vaccines to provide overall better protection.

Preclinical Immunogenicity Characterization of ARCT-021 SARS-CoV-2 Vaccine

Sean M. Sullivan, Ph.D.
Executive Director
Arcturus Therapeutics, Inc., San Diego, CA

The self-transcribing and replicating RNA (STARR™) technology combined with Arcturus Therapeutics proprietary lipid nanoparticle (LNP) delivery technology has produced a safe and effective vaccine against SARS-CoV-2 virus. Mouse immunogenicity studies showed continuous increase in neutralizing antibody titers for up to 60 days after a single vaccination along with a strong Th1 cell mediated immune response. Lethal virus challenge studies using a human ACE2 transgenic mouse model yielded 100% protection after a single 2 µg RNA dose. T cell and B cell depletion studies with a sublethal virus challenge in the same transgenic mouse model showed complete protection after B cell depletion and no protection after T cell depletion. Rhesus macaque immunogenicity studies showed high neutralizing antibody titers after two prime injections 28 days apart. A further increase in neutralizing antibody titers were observed with a boost injection 120 days after the second prime injection. Non-human primate virus challenge studies showed significant reduction in bronchoalveolar virus genomes after single and double prime vaccinations. Preliminary preclinical results for second generation vaccines designed with improved anti-viral immunogenicity exhibited cross neutralization against alpha, beta, gamma and delta circulating viral variants in mice and non-human primates. The first generation vaccines are in late stage clinical trials and the second generation vaccines are planned for entry into the clinic.

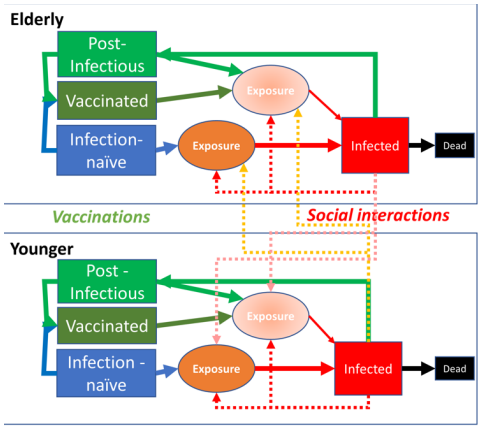
Personalized Vaccination Strategies for Covid-19 to minimize deaths and maximize benefit across different age strata despite limited vaccine supply

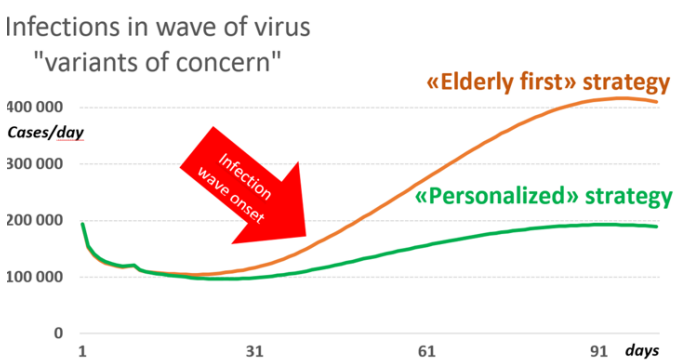
Patrick Hunziker
University Hospital Basel

Background: In the Covid-19 pandemic, new waves of Coronavirus "Variants of Concern" are currently observed in many countries and vaccination is one cornerstone of overcoming the pandemic. While many countries have chosen an "Elderly first, one dosage fits all" approach to vaccination, Swiss scientists have explored the impact of accelerated vaccination strategies on case load and deaths by applying the highly active mRNA vaccines in a personalized fashion.

Younger persons, through more frequent social activities, contribute largely to driving a pandemic wave, but they also show a stronger immune response to vaccination and have a low risk of death. This raises the possibility that using a lower vaccine dose in the younger may allow vaccinating a much larger number of people rapidly.

Aims: To explore whether trading individual vaccine efficacy for increased numbers of vaccinations by personalized vaccine dosing would help the world to overcome the pandemic faster.





Methods and Findings: A computer modelling study from the University Hospital of Basel and CLINAM Foundation, Switzerland, incorporated the coronavirus infection wave, a limited vaccine supply, age-dependent differences in social interaction, response to vaccination and disease risk, to predict evolution of waves of coronavirus infections and resulting deaths

If a personalized, age-matched vaccination dose is used instead of the vaccination strategy currently used in most countries, these data promise a significant shortening of the wave of infections and a marked reduction in deaths and infection counts.

Such a strategy can be immediately put into practice if backed by the regulatory body of a country and may be of particular value in countries that were not yet able to vaccinate a large proportion of their population because of limitations in vaccine availability or economic constraints.

Summary: *Personalized vaccine strategies minimize deaths and case numbers in a Coronavirus wave of "Variants of Concern" when vaccine supply is limited.*

Biography:

Patrick Hunziker has studied Medicine the University of Zurich, Switzerland. He received a doctoral decree based on thesis work in experimental immunology focusing on generation of polyclonal and monoclonal antibodies to specific epitopes from the University of Zurich in 1989 at the University Hospital in Zurich, Switzerland.

He earned specialist degrees in Internal Medicine, Cardiology and Intensive Care Medicine. As a fellow the Massachusetts General Hospital, Harvard Medical School, he worked on cardiac imaging in a joint project with the Massachusetts Institute of Technology, Cambridge. 2008 Patrick Hunziker became professor for Cardiology and Intensive Care Medicine at the University of Basel. His professional activities in Europe, the U.S., Africa and China gave him a broad insight into the needs for the medicine of the future in a variety of settings. Hunziker became involved in medical applications of Nanoscience in the late nineties and has been the pioneer physician in Nanomedicine in Switzerland since then. With improved prevention, diagnosis and cure of cardiovascular disease as his main research topic, he worked in the nanoscience fields of atomic force microscopy, nanoptics, micro/nanofluidics, nanomechanical sensors and polymer nanocarriers for targeting.

He is the co-founder of the European Society of Nanomedicine, cofounder of the European Foundation for Clinical Nanomedicine and co-initiator of the European Conference for Clinical Nanomedicine and is clinically active as deputy head of the Clinic for Intensive Care Medicine at the University Hospital Basel, Switzerland. After being founding president of the European Society for six years he was elected as President of the International Society for Nanomedicine, which is uniting members from all continents in the world and realizes regular Summer schools on Nanomedicine.

NIAID Preclinical Services Facilitate SARS-CoV-2 Vaccine Product Development by Standardizing the Microneutralization Assay for Phase III Vaccine Trials

Janet Lathey*, **Aparna Kolhekar**, **Nancy Ulbrandt** and **Larry Wolfraim**
DMID/NIAID/NIH, USA.

The Division of Microbiology and Infectious Diseases (DMID), part of the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH), supports extramural research to control and prevent diseases caused by human infectious agents except HIV. In addition to the direct funding of grants and contracts, DMID offers preclinical services (PCS) to support animal model development, development of novel therapeutics, vaccines, and diagnostic products for emerging infectious diseases like COVID-19. Using the PCS contract mechanism, DMID has funded the development of Human and Non-Human Primate (NHP) clinical and nonclinical assays and critical reagents for SARS-CoV-2 vaccine research. Microneutralization (MN) assays and Enzyme Linked Immunosorbent Assays (ELISAs) have been developed and bridged from humans to NHPs. Positive and negative controls with acceptance criteria have been established. Conditions for both assays have been optimized, qualified, and used in evaluation of Human and NHP studies. In addition, the MN assay was validated for use in Phase III vaccine trials. The MN assay was developed and validated with SARS-CoV-2 convalescent and vaccinee serum and has been used to evaluate thousands of samples from Phase III vaccine trials. This assay has also been calibrated to the WHO Standard for International Units. Both assays are available to perform testing at the contract site and will be used by NIAID and Biomedical Advanced Research and Development Authority (BARDA) to support the development of promising vaccine candidates.

Biography:

Janet Lathey, Ph.D., is a senior level virologist, immunologist, and translational scientist, specializing in vaccine development, measuring product effectiveness, and bioassay development. She is currently a Program Officer in the Vaccine Section of OBRRTR/DMID/NIAID/NIH. Dr. Lathey has previously worked at Emergent BioSolutions on Anthrax vaccine development and measuring effectiveness. At Sanofi Pasteur as part of the clinical immunology group she was involved in the evaluation of influenza vaccines, and at ZYCOS she developed clinical assays for a therapeutic HPV vaccine. Before moving into vaccines, Dr. Lathey developed and standardized assays for HIV with the AIDS Clinical Trials Group.

Nasal nanoparticulate vaccine for toxoplasmosis

Pr. Didier Betbeder
CEO,CSO VAXINANO, 1 place Verdun F-59045 Lille Cedex, France

Toxoplasmosis is a disease that results from infection with the Toxoplasma gondii parasite. Infection usually occurs by eating undercooked contaminated meat, exposure from infected cat feces, or mother-to-child transmission during pregnancy. Toxoplasmosis infects 2 billion of people and is responsible for abortion if the infection occurs during the pregnancy. Toxoplasmosis is lethal in immune-suppressed or immune-comprised patients and there is 350 million of people having ocular toxoplasmosis. There is no preventive treatment or vaccine against this parasite. A vaccine needs to develop an immune response able to block the parasite in the mucosa and to eliminate infected cells. Vaxinano develops the use of nanoparticles able to cross the mucus and deliver efficiently the antigens within the nasal mucosa therefore allowing to avoid the use of immunomodulators. In this presentation we will describe the interaction of starch nanoparticles with airway mucosa and their ability to deliver antigens within cells (1-4). Furthermore, their interest for a vaccine against T.gondii infection in different species including non human primates will be presented (5-7).

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Biography:

Pr. Didier BETBEDER has 30 years' experience in drug delivery using colloids, ranging from basic research to clinical studies. Working with the World Health Organisation he obtained his PhD in 1988 to treat sleeping sickness, before spending 2 years as a post-doctoral fellow at the University of Warwick (England). He was then engaged by BioEurope, a company specialising in biocatalysis, before joining Biovector Therapeutics (France) as Research director from 1992 – 2001. He was then Pr at the University of Artois and Lille 2 from 2001-2019. He founded Vaxinano in 2016 and joined Vaxinano as president and CSO in September 2019. His research focusing on the development of innovative nanoparticles based on polysaccharide and phospholipid assemblies for vaccines.

He developed from research to clinical development a technology based on polysaccharidic nanoparticles supporting a phospholipid bi-layer. Nasal vaccine formulations have been clinically trailed with BioChem Pharma (Canada), SmithKline Beecham (Belgium) and Chiron (Italy), and he has collaborated with RIBI Immunochem (US), Merck and Sanofi Pasteur. He has extensive experience in Nanomedicine, and in particular on prophylactic and therapeutic nanovaccines. He was president of the French control release society (GTRV) from 2004-08, board member of SFNano (French society of nanomedicine) and has over 100 international publications and 25 patents to his name. He is the founder of VAXINANO a company who is developing vaccines for human and animal health.

Distinct SARS-CoV-2 antibody reactivity patterns elicited by natural infection and mRNA Vaccination

Rafael Assis[1], Aarti Jain[1], Rie Nakajima[1], Algis Jasinskas[1], Saahir Kahn[2], Anton Palma[3], Daniel M. Parker[4], Anthony Chau[5], Joshua M. Obiero[1], Delia Tifrea[7], D. Huw Davies[1], Bruce Albala[4], Bernadette Boden-Albala[4], Sebastian Schubl[6] and **Philip L. Felgner[1]***
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[2]University of Southern California, Division of Infectious Diseases, Los Angeles, CA, USA
[3]University of California Irvine, Institute for Clinical & Translational Science
[4]University of California Irvine, Program in Public Health, Department of Population Health &Disease Prevention
[5]University of California Irvine, Dept. of Statistics
[6]University of California Irvine, School of Medicine, Department of Surgery
[7]University of California Irvine, School of Medicine

We analyzed data from two ongoing COVID-19 longitudinal serological surveys in Orange County, CA., between April 2020 and March 2021. A total of 8,476 finger stick blood specimens were collected before and after an intensive mRNA vaccination campaign. IgG levels were determined using a multiplex antigen microarray containing 10 SARS-CoV-2 antigens, 4 SARS, 3 MERS, 12 Common CoV, and 8 Influenza antigens. Twenty-six percent of 3,347 specimens from unvaccinated Orange County residents in December 2020 were SARS-CoV-2 seropositive; out of 852 seropositive individuals only 77 had symptoms and 9 sought medical care. The antibody response was predominantly against nucleocapsid (NP), full length spike and the spike S2 domain. Anti-receptor binding domain (RBD) reactivity was low and there was no cross-reactivity against SARS S1 or SARS RBD. A vaccination campaign at the University of California Irvine Medical Center (UCIMC) started on December 16, 2020 and 6,724 healthcare workers were vaccinated within 3 weeks. Seroprevalence increased from 13% at pre-vaccination in December to 79% post-vaccination in January, 93% in February and 99% in March. mRNA vaccination induced much higher antibody levels than natural exposure especially against the RBD domain and significant cross-reactivity against SARS RBD and S1 was also observed. Nucleocapsid protein antibodies can be used to distinguish individuals in a population of vaccinees to classify those who have been previously infected and those who have not, because nucleocapsid is not in the vaccine. Previously infected individuals developed higher antibody titers to the vaccine than those who were not previously exposed. Hospitalized patients in intensive care with severe disease reach significantly higher antibody levels then naturally exposed mild cases, but the severe cases don't reach antibody levels equivalent to the vaccine. These results indicate that mRNA vaccination rapidly induces a much stronger and broader antibody response than SARS-CoV-2 infection.

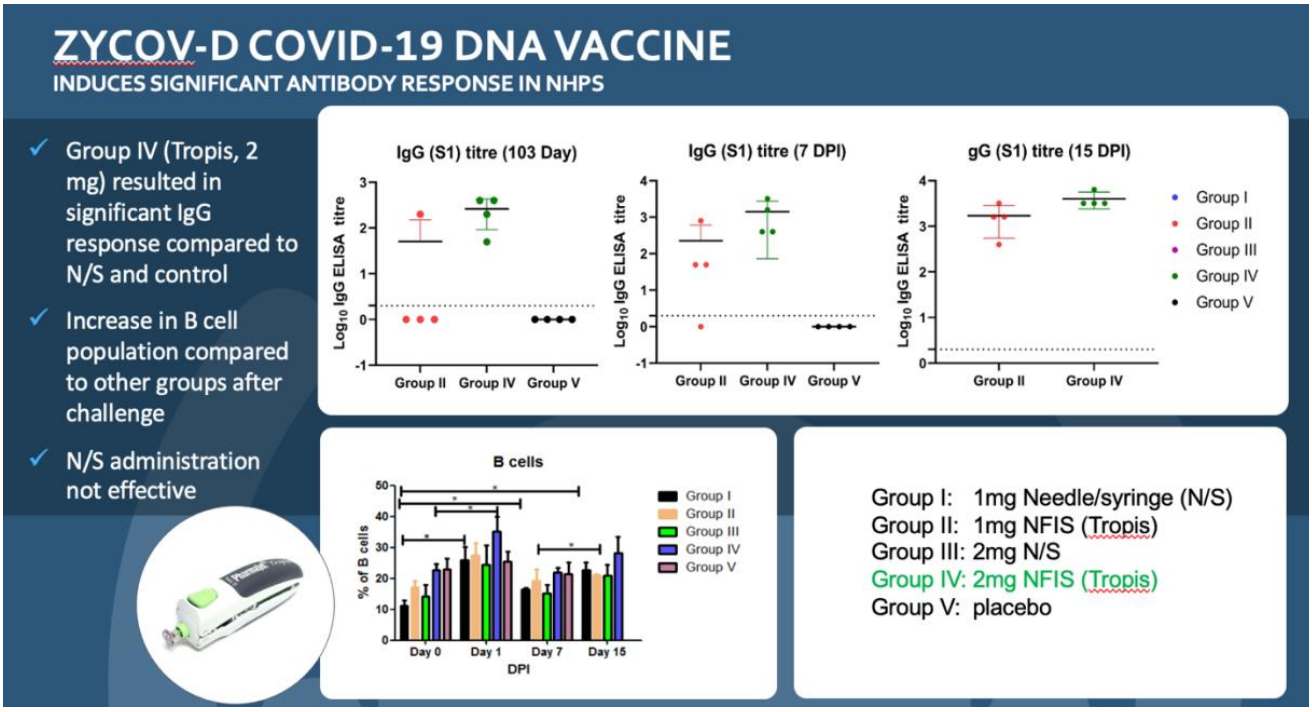
ZyCoV-D COVID-19 DNA Vaccine

Erin K Spiegel, PhD
PharmaJet, Inc.

The PharmaJet Stratis® and Tropis® Needle-free Injection Systems (NFIS) are commercialized, validated injection device systems with established manufacturing, safety, and effectiveness profiles for injection of various vaccines and therapeutics. The PharmaJet NFIS are being used in pharmaceutical development programs with over 70 different collaborators, heavily focused in the nucleic acid space. The PharmaJet Systems are especially effective at delivering nucleic acid-based vaccines and therapeutics (e.g. plasmid DNA and mRNA), and in many cases, have replaced the need for electroporation. Furthermore, the PharmaJet Systems are particularly well suited to improving vaccination programs around the world due to their portability, ease of use, cost-effectiveness, and high acceptability by users and patients.

Notably, the Tropis NFIS is an optimal platform for efficient intradermal delivery resulting in dose savings with comparable immunogenicity. We will describe highlights from our development activities with various collaborators using the PharmaJet NFIS for delivery of vaccines to prevent COVID-19. DNA based vaccines from SaudiVax and GeneOne have shown promise in preclinical studies, with enhanced immunogenicity of the vaccines using Tropis delivery into the skin. Additionally, USAMRIID demonstrated strong neutralizing antibody titers and protection from challenge in a hamster model with their DNA-based COVID-19 vaccine, and BioNet Asia is beginning a Phase I clinical trial in Australia following promising preclinical work with both intradermal and intramuscular needle-free administration.

Finally, the figure below shows that Tropis intradermal administration of a DNA based COVID-19 vaccine (ZyCoV-D, Cadila Healthcare) in NHPs resulted in 1) significant IgG response compared to needle and syringe and control groups and 2) an increase in B-cell populations after challenge (bioRxiv 2021.02.02.429480; Cadila Healthcare, India).



At this time, Phase III clinical trials evaluating efficacy of the ZyCoV-D vaccine have been completed and the vaccine is expected to be approved for use in India by summer of 2021.

Overall, PharmaJet has developed a robust portfolio of collaborators with pharmaceutical development programs that see numerous benefits as a result of needle-free administration. These activities, with a focus on our recent COVID-19 development programs, will be summarized in our presentation.

Characterization of antibody epitopes in SARS-CoV-2 natural infection and vaccination, and prediction of effects of mutations on immune response with Serum Epitope Repertoire Analysis (SERA).

John Shon
Serimmune, Inc.,

The humoral immune response to both natural infection and vaccination is critical in the development of and duration of immunity to SARS-CoV-2 and its various variants. It is clear that host immune responses vary in both natural infection and vaccination, although it is unclear what the clear correlates of protection are. Most serology platforms and approaches elucidate humoral response to whole antigen or sub-units of antigens to qualify and quantify antibody response. SERA uses a 10 billion member, random bacterial peptide display library coupled with next generation sequencing and bioinformatics to characterize the immune response in individuals at amino-acid resolution. This enables characterization of distinct profiles of epitopes associated with infection and vaccination, including disease severity, and also enables predictions of the effects of mutations on linear epitopes without altering the assay. We will review the application of this technology in elucidating epitopes associated with SARS-CoV-2 from several studies and also demonstrate its use in longitudinal monitoring of epitopes

Generation of a gp96-Based SARS-CoV-2 Vaccine (ZVX-60) to Induce Long-Lived Memory T-cell Responses Against COVID-19

Seavey MM[1], Natasa Strbo[2]*, Fisher E[2], Padula L[2], Podack K[2], O'Neill K[2], Jayaraman P[1], Jasuja R[1] and Wolf J[1]
[1]Heat Biologics, Inc., Morrisville, NC., USA
[2]University of Miami, Miller School of Medicine, Miami, FL., USA

The emergence of SARS-CoV-2 variants has highlighted the need for T-cell immunity against this deadly virus. Specifically, CD4+ T-helper responses are required for sufficient B-cell help for the generation of neutralizing antibodies, and CD8+ T-cells are required to clear virus-infected cells. Heat Biologics (Heat) has developed a next generation, cellular vaccine platform, that incorporates an antigen chaperone with natural adjuvant properties (secreted gp96-Ig) and combined it with a potent T-cell costimulator, OX40L, stably transfected and co-expressed in an allogeneic cell line, rendered replication incompetent for multiple immunizations. Heat's SARS-CoV-2 vaccine is based on Viagenpumatucel-L (HS-110) technology which had recent success in the clinic for NSCLC (NCT#02439450), and HS-130, currently in a phase 1 trial (NCT#04116710). Heat generated a gp96/OX40L-Ig, SARS-CoV-2 Spike protein overexpressing cell-based vaccine, (ZVX-60), for the induction of potent memory T-cell responses, and aid in the production of neutralizing antibodies. Heat's gp96based vaccine has shown efficacy and protection against multiple infectious agents including malaria, HIV/SIV and Zika virus in mice and primate models.

Given on a prime/boost schedule, ZVX-60, could induce significant effector memory, tissue resident memory, and virus specific CD8+ Tcells in the lungs and spleen. Induction of polyfunctional and polyclonal CD4+ and CD8+ Tcells secreting key antiviral cytokines (TNF-alpha, IFN-gamma, IL-2) in response to ex vivo challenge with S1 and S2 subunit Spike peptides demonstrated the ability of this vaccine to induce several different subsets required to fight COVID19 infection. Memory CD4+ and CD8+ Tcells could be detected out to 30 and 60days post immunization. ZVX-60 was also tested in mice expressing the human HLAA2 to determine if humanrelevant Tcells could be induced by vaccination. Polyepitope CD8+ Tcells were induced by vaccination against both the S1 and S2 Spike subunits with greater increases seen in the bronchoalveolar lavage (BAL) and the spleen.

Consistent with our previous findings, the gp96 cellbased vaccine strategy resulted in the preferential induction of CD8+ T cells systemically and in epithelial compartments. The increase in tissue resident memory Tcells was observed in the lungs. The addition of OX40L greatly increased CD4+ T-cell help resulting in a significant induction of IgG and IgM responses. Vaccination also increased the percent of CD69+ CXCR6+ tissue resident memory cells in the bronchial alveolar lavage fluid (BAL) of exposed mice in a dosedependent manner. Next steps include mouse and monkey SARS-CoV-2 challenge efficacy studies. ZVX-60 is currently undergoing cGMP manufacturing for clinical implementation. This is a first demonstration of the utility and versatility of our proprietary secreted gp96-Ig SARS-CoV-2 vaccine platform that can be rapidly engineered and customized based on other and future pathogen sequences.

Background Rates for Severe Cutaneous Reactions in the US: Contextual Support for Safety Assessment of Novel COVID-19 Vaccines

Diane Gubernot*, **Mikhail Menis** and **Manette Niu**
Epidemiologist/Health Scientist, Office of Biostatistics and Epidemiology/ABRA
Center for Biologics Evaluation and Research, US Food and Drug Administration

Post-vaccination skin reactions range from relatively minor dermatologic reactions due to nonspecific inflammation at the injection site to rare instances of severe delayed hypersensitivity reactions such as erythema multiform (EM), Stevens Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). We performed a literature search in PubMed (1990-present) on the background incidence of EM, SJS and TEN in the US population, and of post-vaccination EM, SJS, and TEN. The US background incidence rates per million for SJS ranged from 5.3 to 63, for TEN ranged from 0.4 to 5 and for SJS/TEN ranged from 0.8 to 12.35. Since these diagnostic conditions may overlap, some studies reported the rates for EM/SJS/TEN combined (range= 4.6 to 35.5 per million). The published literature, including studies of postmarket surveillance reports submitted to the FDA/CDC Vaccine Adverse Event Reporting System, describes post-vaccination EM, SJS, and/or TEN as rare occurrences. The vaccines most frequently associated with EM, SJS and/or TEN were MMR, DTaP, and varicella. The majority of the US vaccine reports of EM, SJS, SJS/TEN or TEN occurred in children within 30 days of vaccination. The reporting rate for varicella vaccine ranged 1 to 4 per million doses for EM and 0.1 to 0.5 per million doses for SJS; no cases of TEN were reported. This review provides a summary of background rates and other characteristics for severe skin manifestations in the general population and among vaccine recipients, which can be used in epidemiological studies and for the safety surveillance of COVID-19 vaccines and other biologics.

Incorporating the Novel Complement Peptide-Derived Immunostimulant CPDI-02 with Nanoscale Dosage Forms for Mucosal Vaccines

Joseph A. Vetro, PhD,
Department of Pharmaceutical Sciences, College of Pharmacy, University of Nebraska Medical Center, Omaha

CPDI-02 is a novel, second-generation decapeptide agonist of C5aR1 that selectively activates mononuclear phagocytes over neutrophils to potentiate innate and adaptive immune responses while minimizing neutrophil-mediated toxicity. Systemic immunization with CPDI-02 directly conjugated to chemical moieties, peptides, proteins, or inactivated pathogens generates humoral and cellular immune responses. We recently found that respiratory immunization with CPDI-02-conjugated CTL epitopes encapsulated in biodegradable nanoparticles or with whole protein immunogen encapsulated in biodegradable nanoparticles modified with surface-conjugated CPDI-02 generates long-term memory subsets of mucosal and systemic memory T-cells. The effects of CPDI-02 incorporation strategies on the generation of long-term humoral and cellular adaptive immune responses by a given encapsulated immunogen after respiratory immunization, however, have not been fully characterized. This talk will provide a brief overview of our current and future work toward identifying CPDI-02 incorporation strategies that potentially maximize the generation of required long-term protective adaptive immune responses by intranasal nanoscale dosage forms for peptide, protein, and mRNA vaccines.

Biography:

Dr. Joseph Anthoney Vetro received an undergraduate degree in Chemistry from the University of Nebraska at Omaha (UNO) and a Ph.D. in Biochemistry and Molecular Biology from the St. Louis University Health Sciences Center as an American Heart Association Predoctoral Fellow under Dr. Yie-Hwa Chang. He then completed postdoctoral training at the University of Kansas in the Department of Pharmaceutical Chemistry as an American Heart Association Postdoctoral Fellow under Dr. Russ Middaugh. From there, he joined the Department of Pharmaceutical Sciences at the University of Nebraska Medical Center (UNMC) as a Research Assistant Professor where he is currently an Associate Professor.

Cellular immune monitoring to support gene therapy trials including ELISPOT assays

Magdalena Tary-Lehmann
Cellular Technology Limited

Assessing immunogenicity of antigen specific responses is a challenge in the biopharmaceutical industry, as an increasing number of drugs/vaccines/ gene therapy trials aim to elicit a response from the cellular components (e.g., T, B cells) of the immune system in both the preclinical and clinical phases. Measurements of antibodies in bodily fluids (e.g., by ELISA) have provided robust and reproducible results for decades, and such assays have been validated for monitoring of B-cell immunity. In contrast, measuring T-cell immunity has proven to be more of a challenge, due to the need to test live cells in functional assays ex vivo. While T cells play a critical role reliable measurements of antigen-specific T cell responses ex-vivo remain seemingly problematic, as typically, T cells occur in very low frequencies in test samples, such as peripheral blood. Therefore, monitoring antigen-specific T cells and their effector functions is critical for the assessments of the efficacies of specific immune therapies. For this reason, assays such as ELISA and others should be complemented with a single cell assay such as ELISPOT. ELISPOT assays can be run in a reproducible fashion and be employed in a regulated environment using fresh or cryopreserved PBMC's from patients.

We CTL specialize in cell mediated immune monitoring (using ELISPOT, ELISA, micro-neutralization assays, etc.), standardization of procedures including separation and cryopreservation of functional PBMC from whole blood, instrumentation and materials. Our extensive contract laboratory services support many pharmaceutical studies (clinical and preclinical) from custom development to validation, and testing. Examples of such successful T and B cell monitoring will be presented.

Neutralizing Antibodies Against Coronaviruses

Pamela J. Bjorkman
Division of Biology and Biological Engineering, California Institute of Technology

The SARS-CoV-2 virus has caused a world-wide pandemic resulting in a massive loss of lives and detrimental effects on the economies of most countries. We are using single-particle cryo-electron microscopy (cryo-EM) to solve structures of infection- and vaccination-induced antibodies complexed with the spike trimer of SARS-CoV-2 in order to elucidate the structural correlates of antibody-based immune protection. Structural comparisons allowed us to classify antibodies against the receptor-binding domain (RBD) of spike trimer into categories. These classifications and structural analyses provide rules for assigning current and future human RBD-targeting antibodies into classes, evaluating avidity effects, and suggesting combinations for clinical use, and provide insight into immune responses against SARS-CoV-2. Our structural studies have also guided the development of a potential pan-betacoronavirus vaccine. The vaccine approach involves co-display of diverse sets of RBDs from SARS-like beta coronaviruses (sarbecoviruses) on nanoparticles (mosaic-RBD-nanoparticles) that results in increased breadth of neutralizing responses in mice compared with nanoparticles presenting only SARS-CoV-2 RBDs. This modular vaccine platform could provide protection from SARS-CoV-2 as well as potential future emergent coronaviruses that could cause pandemics.

Development of rapidly deployable and broadly effective COVID-19 vaccines

Louis D. Falo, Jr. MD, PhD
Chairman, Department of Dermatology, Univ. of Pittsburgh School of Medicine
Professor, Department of Bioengineering, Univ. of Pittsburgh Swanson School of Engineering
The Univ. of Pittsburgh Clinical and Translational Science Institute
The UPMC Hillman Cancer Center, and
The Univ. of Pittsburgh McGowan Institute for Regenerative Medicine

Development of rapidly deployable and broadly effective COVID-19 vaccines is critical to limit the devastating consequences of infection by this emerging pathogen, and several vaccine strategies are currently being developed. The skin is a rational and often overlooked target for vaccine delivery. It contains a rich population of antigen presenting and immune accessory cells capable of inducing a proinflammatory microenvironment favoring the induction of potent and durable adaptive immunity. Here we summarize potential advantages of skin-targeted immunization and our efforts to develop a skin-targeted vaccines using a dissolvable microneedle array delivery platform.

COVID-19 Vaccination and the Daily Cases, Hospitalizations and Death Rates: a Case Study of Tennessee in the United States

Ali Roghani
Division of Epidemiology - University of Utah

Background: The COVID-19 outbreak highlights the vulnerability to novel infections, and vaccination remains a foreseeable method to return to normal life. However, infrastructure is inadequate for the vaccination of the whole population immediately. Therefore, policies have adopted a strategy to vaccinate the elderly and vulnerable populations while delaying others.

Objective: This study uses the Tennessee official statistic to understand how age-specific vaccination strategies reduce daily cases, hospitalization, and death rate.

Method: The research used publicly available data of COVID-19, including vaccination rates, positive cases, hospitalizations, and death from the health department of Tennessee. This study targeted from the first date of vaccinations, December 17, 2020, to March 3, 2021. The rates were adjusted by data from U.S. Census Bureau (2019), and the age groups were stratified at ten-year intervals from the age of 21.

Results: The result shows that vaccination strategy can reduce the numbers of patients with COVID-19 in all age groups with lower hospitalization and death rates in older. The elderly had a 95% lower death rate from December to March, while no change in the death rate in other age groups. The hospitalization rate was reduced by 80% for people aged 80 or older, while people who were between 50 to 70 had almost the same hospitalization rate.

Conclusions: The study indicates that targeting older age groups for vaccination is the optimal way to avoid higher transmissions, reduce hospitalization and death rates.

Introduction: In December 2019, the severe respiratory coronavirus in Wuhan, China, has caused a coronavirus disease outbreak (COVID-19) [10]. In the next few weeks, COVID-19 became the main headline worldwide, and daily cases and deaths increased considerably [11]. As of the end of November 2020, more than 14 million infections and 279,000 deaths have been confirmed nationally, making the United States the highest number of cases in the world to date [12]. With more than 368,000, 4,500 daily cases and death, Tennessee has been identified as one of the hardest-hit states in the U.S. [12]. Vaccinations and social distancing are essential factors for the COVID-19 Prevention [13]. COVID-19 Vaccination rollout in Tennessee started on December 17, 2020, and by March 3, 13.3% of the population had already received mRNA vaccines such as the Pfizer BNT162b2 (Tozinameran) and the Moderna mRNA-1273 [1;2]. In addition to reduced interpersonal contact and physical distancing, vaccination programs positively influence controlling the virus's spread and reducing deaths [3]. While COVID cases and deaths had the highest rates in January 2021 in the U.S., manufacturers currently cannot cover the enormous demand. As the vaccine supply is limited, it is crucial to prioritize who gets the vaccine; therefore, groups at the highest risk of getting the virus or individuals who are seriously ill receive the vaccine first. Previous research showed that prioritizing younger populations will significantly impact reducing COVID-19 cases relative to prioritizing older age groups. However, prioritizing younger age groups is associated with the lowest reduction in COVID-19 mortality compared to other approaches [16]. Besides, Tennesseans are eligible for vaccines based solely on their age, and these age-based phases have run simultaneously with those at high-risk health conditions. This paper has modeled how the vaccination program in Tennessee is likely to change COVID-19-related daily cases, deaths, and hospitalization among adults.

Data: This study used publicly available data of COVID-19, including vaccination rates, positive cases, hospitalizations, and death from the health department of Tennessee in the state level. All data used in this study are available at https://www.tn.gov/health/cedep/ncov/data. The rates also were adjusted by data from U.S. Census Bureau (2019) [4].

Measures: This study started from the first date of vaccinations, December 17, 2020, to March 3, 2021. The health department of Tennessee provides statistics of first and second doses of vaccinations, cases, hospitalization, and death every day. The data were stratified based on ten-year intervals from the age of 21 to 81 and more.

Statistical Analysis: The methodology for generating a descriptive time series of vaccinations, daily cases, deaths, and hospitalizations involved two steps. The first was to convert aggregate data to daily data to create time series data. The second was to adjust data for each age group by the census data, including the percentage of Tennesseans who received vaccines, had COVID-19, hospitalized, and died. The goal is to produce a series of trends over consecutive time intervals to understand the changes in COVID-19 cases,

Contd..

hospitalizations, and death after the onset of vaccinations. The data were analyzed with the R programming language (version 3.5.2) (R Core Team 2018) [14].

Result: During the first 78 days of vaccination in Tennessee, there were 953,568 individuals vaccinated by the 1st dose, and 495,032 individuals received their 2nd dose. 18.2% and 30.3% of vaccines were for people of age 81+ and 71-80, respectively, which shows that half of the vaccination has been for those older than 71. Figure 1 indicates the percentage of those who received the first vaccine from December 17, 2020, to March 3, 2021. Individuals who had less than 70 had a higher vaccination rate before January; however, from January to March 3, 40%, 36% of 80+, and 71-80 have been vaccinated receptively, which shows most of the daily vaccines were used for these two age groups. Figure 2 shows that just 25% of Tennesseans who were older than 81 received the second vaccine dosage, while a small percentage of other age groups have been vaccinated. Although the age group of 71-80 had a very close rate of receiving the first vaccine dosage compared to the 81+ age group, they received the second dosage similar to other age groups.

Daily cases for all age groups decreased inevitably after the onset of vaccination to day 78 (Figure 3). Daily cases were decreased for younger from around 0.2% at the end of January to less than 0.05% at the end of the study period. This percentage was considerably higher for the older people in the study periods (from 0.1% to close to 0.01% daily cases). Before starting the vaccinations, older age groups were considerably had the highest hospitalization rates. Their hospitalizations decreased at the end of the study period from 0.010% of Tennessee's older population to 0.003%. There was no substantial change in other age groups' hospitalization rates, although, on some days, age groups of 51-60 and 61-70 had high hospitalization rates. From the middle of February, age groups of 70+ did not experience high hospitalization rates, and age groups of 51-60 had almost the highest rate of daily hospitalization. Lastly, the death rates of 71+ age groups decreased, while there was no change in death rates of other age groups during the study period. Although Tennesseans over 71 faced 0.015% of daily death by COVID at the end of 2020, this percentage decreased substantially to 0.003% at the end of the study period. The results show that the gap between the older and younger was high before starting vaccination, and after vaccination, the differences diminished, which indicates all age groups had the same death rates.

Discussion: The COVID-19 is still spreading in the United States, and the hospitalization and death rate are high. Vaccines offer great hope for better conditions, but an effective vaccination strategy is needed to stop the pandemic and restore people's everyday lives. Unfortunately, vaccine doses are being delivered slowly and sporadically, which means it is difficult for most people to be vaccinated right now, even if they are eligible. Based on the current policy, the high-risk groups such as first responders, the elderly, and individuals with high-risk health conditions should receive the vaccines first [5]. In this study, I used the Tennessee official statistic from the onset of COVID vaccination (17th of December 2021) to understand how age-specific vaccination strategies change daily cases, hospitalization, and death rate. The charts indicate that phase 1 of the vaccination strategy has reduced the numbers of patients in all age groups, with lower hospitalization and death rates for the elderly. The result demonstrates that more than half of vaccines were for more than 70 years old, and it was a practical approach in blocking the transmission in the elderly population and other age groups. COVID-19 daily cases of older groups decreased to 90 % from the end of 2020 by the end of February 2021. Also, less than half of vaccines were used for less than 70, and they had less than 80% lower daily cases at the end of the study period. Although this study cannot confirm the association between the onset of vaccination and the considerable reduction in Covid-19 transmission in younger age groups, the statistics indicate a significant decrease in daily cases among Tennesseans in all age groups. Moreover, 25% of people who were older than 81 received the vaccines, and around 10% of other age groups received the second dosage. However, this age group did not have better results than their counterparts in the 71-80 age group in hospitalizations and death rate. This study includes 78 days of vaccination statistics; thus, it is too early to conclude the second dosage's influence. Future studies should consist of a longer period to have more accurate results concerning the second dosage.

Vaccines lead to great hospitality and mortality reduction for older age groups in Tennessee. People who older than 80 had a 95% less death rate than in the middle of December. 71-80 age group death rate decreased during the study period; however, the 61-70 age groups had almost the same death rate from the middle of December to the end of February. The statistics show that there was no change in the death rate in other age groups. Tennessean's hospitalization of more than 80 years old were reduced to 80 % in the study period, while people between 50 to 70 had almost the same hospitalization. It is essential to know individuals who were between 51-60 had the highest hospitalization rates in Tennessee. Although the data cannot identify people with higher risk, the higher hospitalization rate among the younger population implies health system in Tennessee could not identify people at higher risk efficiently. A previous study shows that a significant proportion of the people who had two or more chronic conditions simultaneously

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are more likely to be hospitalized by SARS-CoV-2 [9]. Additionally, while health workers are placed at the highest risk groups, immunizing this population and supplying personal protective equipment will help increase the resiliency of the health system during the epidemic [17].

The findings should be considered in the context of several data limitations. I did not derive individual-level data to estimate hospitalization risks, mortality rate, and COVID-19 transmissions. Moreover, several studies [6; 7] indicate racial and ethnic disparity by health systems increases the risk of getting sick, hospitalized, and dying from COVID-19. Future studies should examine vaccination in different races by age group to estimate who should get the vaccine first. Additionally, the data does not include nonpharmaceutical public health control measures, which would be an essential indicator to control daily cases [8]. Although hospitalization, cases, and death statistics prior to the onset of vaccination could provide a more accurate picture regarding the changes by vaccination, the preliminary analysis showed the gaps between older and younger age groups were consistent before the vaccination onset up to the end of January. Since February, however, the gap between older and younger age groups has diminished considerably. The reason why there were no immediate changes after the vaccination onset could be due to two factors. First, the previous research showed that the effectiveness of vaccines takes a while to protect those who are vaccinated [15]. It has taken a more extended period to show the effectiveness of vaccination as just around 35 percent of the older age group were vaccinated at the end of February. Second, I was not able to distinguish the daily cases, hospitalization, and death rates of those who were vaccinated.

Conclusion: The vaccination was started at the beginning of a "3rd wave" in Tennessee, and by December, and January SARS-CoV2 positive cases and hospitalizations increased considerably. This work has concentrated on Tennessee's dynamics COVID-19. It concludes that the vaccine should be optimally targeted at the elderly in the first step, indicating that vaccination reduces daily cases for the whole population while reduces hospitalization and death rate in the older population. This study, consistent with the previous studies [8], shows mRNA Covid-19 vaccines have a protective effect for blocking transmission even after a single dose. This study also indicates that prioritizing the vaccination of the elderly is a practical approach for reducing the number of deaths and hospitalization.

Code Availability: The code to perform all analyses described in Methods and Usage Notes sections was written in R-3.6.2 and is publicly available at https://www.tn.gov/health/cedep/ncov/data.

Author Approval: All authors have seen and approved the manuscript.

Declaration of Conflicting Interests: The authors declare that there is no conflict of interest.

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Author Contributions: Ali Roghani designed the study and implemented methods and analyses.

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Expression of CRM_{197} and Other Vaccine Carrier Proteins in an Engineered *E. coli*

Andrew Lees*, Ph.D., Morgane Ollivault-Shiflett, MSc., and **Min-Ju Chang, Ph.D.**
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Conjugate vaccines consist of carbohydrates, peptides, or other poorly immunogenic antigens chemically linked to a carrier protein, which elicits T cell help. Conjugate vaccines have proven remarkably effective in preventing disease but are costly to develop and manufacture. Fina Biosolutions focuses on the research and development of conjugate vaccines. To facilitate availability and reduce the cost of CRM_{197} and other conjugate vaccine carrier proteins, we have developed a novel *E. coli* expression system, which we call the Gor/Met strain. Gor/Met *E. coli* has an oxidative cytoplasm. The strain can express disulfide-bonded proteins as intracellular, soluble, properly-folded proteins. In addition to the oxidative cytoplasm, the strain has been engineered to efficiently cleave the N-terminal methionine found on cytoplasmic *E. coli* proteins. To create the strain, we deleted the gor gene in BL21(DE3), resulting in an oxidative cytoplasm. The deleted gor gene was replaced with a methionine peptidase with the same promoter as the plasmid containing the recombinant protein gene so that peptidase is co-expressed when needed. Gor/Met achieves high cell densities, unlike other comparable strains, making it commercially viable for recombinant protein expression. Remarkably, Gor/Met can grow to >300g/L in fed-batch fermentation. We have initially used the Gor/Met strain to address the need for low-cost "carrier proteins," a critical requirement for affordable conjugate vaccines. Among the proteins expressed are CRM_{197} (EcoCRM®, 58.4 kDa), recombinant tetanus toxin heavy chain C (rTTHc, 52 kDa) and a genetically detoxified tetanus toxin, M8TT (a 150 kDa protein with 5 disulfide bonds). EcoCRM® is produced at ~ 2 g/L fermentation culture in the Gor/Met strain. rTTHc and 8MTT are produced at >0.5 g/L fermentation. FinaBio's EcoCRM® has been extensively compared to CRM_{197} obtained from multiple manufacturers (Hickey et al., J Pharm Sci. 107, 1806, 2018) and is being used for several conjugate vaccines in development targeting *S. pneumoniae, Group B Strep*, malaria and vaccines for drugs of abuse. Clinical grade EcoCRM® is available now. All three proteins were found by mass spec analysis to have extremely low levels of N-terminal methionine, showing that the amino acid was efficiently cleaved by the peptidase. This work shows the potential of the Gor/Met *E. coli* to be a commercially viable production strain for producing high yields of disulfide-bonded proteins with their native sequence. Each of the proteins was found to be a good carrier protein for peptides and polysaccharides. In addition to producing carrier proteins, the Gor/Met strain promises to be a useful new *E. coli* expression system for producing other disulfide bonded proteins.

Biography:

Andrew Lees is founder and scientific director of Fina Biosolutions LLC (Rockville, MD), a company focused on promoting affordable conjugate vaccines by making the technology available to emerging market vaccine manufacturers. Among his contributions in the field, Andrew developed an efficient linking chemistry which is widely used in conjugate vaccines, a class that includes vaccines for S. pneumoniae and meningococcal disease. The chemistry has helped to reduce the cost of these vaccines. Prior to starting Fina Biosolutions in 2006, he was Director of Vaccine Development at biotech companies Virion Systems (1993-1999) and Biosynexus (1999-2006). He was also an associate research professor at the Uniformed Services University (1993-1999). Andrew is an professor at the University of Maryland School of Medicine Center for Vaccine Development, the Uniformed Services University, Dept. of Medicine and the University of Toledo, Dept of Chemistry. He has over 70 publications and 25 patents, mainly in the area of conjugate vaccines. He received his BS in chemistry from Harvey Mudd College in chemistry (1976) and his Ph.D. in Biophysics from Johns Hopkins (1984). Honors include the Uniformed Services Meritorious Service Award, Harvey Mudd College Outstanding Alumni Award and is a Johns Hopkins University Outstanding Alumni. On graduating from Hopkins, he was on the cover of Baltimore Magazine as one of "84 people to watch in '84", due to his role as a leading Baltimore area magician.

Clinical Translation of a Liposome-based RBD vaccine for COVID-19

Wei-Chiao Huang
POP Biotechnologies

The emergence of coronavirus disease 2019 (COVID-2019) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has led to a global public health crisis. The receptor-binding domain (RBD) of the SARS-CoV-2 spike protein is a candidate vaccine antigen that binds human Angiotensin-converting enzyme 2 (ACE2), leading to virus entry. Nanoparticle-based vaccines have shown potential to enhance immune responses, especially for the RBD, which has hapten-like properties.

POP Biotechnologies reported the first peer-reviewed RBD nanoparticle vaccine based on cobalt porphyrin-phospholipid (CoPoP) technology [1]. This convert soluble RBD proteins into ~100 nm particles with simple mixing. The process is via stable insertion of polyhistidine-tagged antigens into the lipid bilayer resulting in spontaneous antigen-particle formation. In addition, similar to the clinical stage adjuvant AS01, the liposomes incorporate a monophosphoryl lipid A (a TLR4 agonist), and optionally QS-21 (an inflammasome activator) into the liposome phospholipid bilayer. This liposomal platform approach can make use of well-characterized recombinant antigens without any further protein engineering or chemical conjugation.

Our current data shows that RBD is exquisitely suited for the CoPoP approach. Upon mixing with CoPoP liposomes, RBD is rapidly converted into 100 nm particles. Following intramuscular (IM) immunization of mice with nanogram doses of RBD, RBD-particles induces orders of magnitude higher functional neutralizing antibodies compared to other adjuvants including alum, AS01-like liposomes, and ISA720. The potent immune response of the liposomal platform is due to converting the antigen into nanoparticles, which could mimic the nature of the virus itself, and could generate higher level of neutralizing antibodies.

Currently, the application of this next generation, particle-forming CoPoP technology for a COVID-19 vaccine has moved into human phase I/II clinical trials in South Korea with our partner, EuBiologics in their Eucorvac-19 vaccine.

[1]Huang et al., SARS-CoV-2 RBD Neutralizing Antibody Induction is Enhanced by Particulate Vaccination Advanced Materials doi:10.1002/adma.202005637.

Biography:

Dr. Wei-Chiao Huang is the Head of Vaccine Research and Development at POP Biotechnologies. She joined the company in 2018. Her present work is focused on the development and validation of liposomal vaccine adjuvants. She worked in malaria transmission-blocking vaccines in collaboration with the PATH Malaria Vaccine Initiative (PATH-MVI) and the Global Health Innovation Technology Fund (GHIT). She manages POP BIO's industry collaborations including that with Eubiologics. She has over five years of experience in vaccine development, antigen-liposomes conjugation and animal immunization. She is a co-inventor of the core POP BIO vaccine adjuvant technology.

SCIENTIA MEETINGS
Vaccines Summit-2021
September 20-22, 2021 | Online Meeting

A synthetic peptide CTL vaccine confers protection from SARS-CoV-2 challenge in rhesus macaques

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Background: Persistent transmission of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has given rise to a worldwide COVID-19 pandemic. Several vaccines, evoking protective spike antibody responses, conceived in early 2020, are currently being deployed in mass public health vaccination programs. Recent data suggests, however, that as sequence variation in the spike genome accumulates, some vaccines may lose efficacy. Using a previously validated vaccine platform, we tested the efficacy of a peptide-based vaccine targeting HLA Class I epitopes of the SARS-CoV-2 nucleocapsid protein. The nucleocapsid protein was selected based on its historically lower propensity for sequence variation and its previous identification as being a target of long lasting T cell immunity in recovered SARS-CoV-1 patients.

Method: Using a macaque model of SARS-CoV-2 infection, we administered room temperature stable biodegradable microspheres loaded with synthetic peptides and adjuvants to a cohort of four Rhesus macaques. Unvaccinated control and vaccinated macaques received 5.0 x 10^8 $TCID_{50}$ units of SARS-CoV-2, followed by measurements of viral load, serial chest x-radiography and sampling of peripheral blood and bronchiolar lavage (BAL) fluid. Gene expression in BAL cells was characterized using Nanostring technology.

Results: Vaccinated animals were free of pneumonia-like infiltrates that characterized SARS-CoV-2 challenged macaques and had lower viral loads relative to controls. Analysis of gene expression in BAL cells of vaccinated macaques relative to unvaccinated macaques revealed unique signatures associated with the enhanced development an adaptive immune responses relative to controls. For example, following vaccination and viral challenge, we found up regulation of both Mamu MHC Class I and Class II genes in macaque BAL cells relative to unvaccinated, viral challenged macaques.

Conclusions: We demonstrate that a synthetic peptide vaccine based on known immunogenic HLA Class I bound CTL epitopes from the SARS-CoV-2 nucleocapsid protein provides protection against SARS-CoV-2 infection in nonhuman primates.

Keywords: SARS-CoV-2; animal model; macaque; vaccine; MHC Class I peptide; T-cell;

Novel next generation "universal" SARS CoV-2 vaccine (COVE-001)

Thomas Tillett
MBF Therapeutics

MBF Therapeutics' is developing a novel next generation "universal" SARS CoV-2 vaccine (COVE-001) that is designed to provide a universal vaccine with improved safety characteristics and greater consumer acceptance for the human health market. MBFT is utilizing ours proprietary T-Max™ platform to 'turbo charge' the immune response by identifying multiple core conserved viral antigens and formulating with proprietary immunomodulators to be effective against current and future variants. These will also be designed to elicit potent and durable memory T cells to provide long-term (years) of protection and sterilizing immunity. COVE-001 will be delivered employing CaptaVax™ nanoparticles, MBFT's proprietary biodegradable, inert non-viral delivery system that enhances intranasal antigen uptake in mucosal tissues where they are delivered to specialized immune cells (Antigen Presenting Cells) that elicit cellular immune responses. Intranasal delivery builds an immunological barrier to pathogen entry at the initial site of infection. Finally these will enhance consumer acceptance by:

- Ease of administration through needleless intranasal administration
- One dose given every several years to provide durable, cross-protective, T-cell immunity
- Fewer side effects from low-reactivity vaccine components.

Substantial impact of post-vaccination contacts on cumulative infections during viral epidemics

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The National Institutes of Health, The National Library of Medicine

Background: The start of 2021 was marked by the initiation of a global vaccination campaign against the novel coronavirus SARS-CoV-2. Formulating an optimal distribution strategy under social and economic constraints is challenging. Optimal distribution is additionally constrained by the potential emergence of vaccine resistance. Analogous to chronic low-dose antibiotic exposure, recently inoculated individuals who are not yet immune play an outsized role in the emergence of resistance. Classical epidemiological modelling is well suited to explore how the behavior of the inoculated population impacts the total number of infections over the entirety of an epidemic.

Methods: A deterministic model of epidemic evolution is analyzed, with seven compartments defined by their relationship to the emergence of vaccine-resistant mutants and representing three susceptible populations, three infected populations, and one recovered population. This minimally computationally intensive design enables simulation of epidemics across a broad parameter space. The results are used to identify conditions minimizing the cumulative number of infections.

Results: When an escape variant is only modestly less infectious than the originating strain within a naïve population, there exists an optimal rate of vaccine distribution. Exceeding this rate increases the cumulative number of infections due to vaccine escape. Analysis of the model also demonstrates that inoculated individuals play a major role in the mitigation or exacerbation of vaccine-resistant outbreaks. Modulating the rate of host–host contact for the inoculated population by less than an order of magnitude can alter the cumulative number of infections by more than 20%.

Conclusions: Mathematical modeling shows that optimization of the vaccination rate and limiting post-vaccination contacts can perceptibly affect the course of an epidemic. The consideration of limitations on post-vaccination contacts remains relevant for the entire duration of any vaccination campaign including the current status of SARS-CoV-2 vaccination. DOI: https://doi.org/10.12688/f1000research.52341.1

Mucosal vaccine approaches to elicit tissue resident memory (TRM) cells against respiratory pathogens

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Tissue resident memory (TRM) cells are thought to be important in providing lung mucosal immunity to pathogens, however, the elicitation of these cells for vaccine purposes has yet to be refined. We have identified K. pneumoniae antigen/adjuvant combinations that elicit Th1 and Th17 cells in the lung as well as K. pneumoniae specific mucosal IgA and IgG. Vaccine-elicited lung CD4+ T-cells homed to the lung and were protective in an adoptive transfer experiments. Vaccine-elicited cells provided lung and systemic immunity independent of polysaccharide serotype. However immunity was dependent on the Th17 cell transcription factor STAT3 as we as well as IL-17R signaling in adventitial fibroblasts. Importantly, Th17 cells showed reduced plasticity and relative resistance to the immunosuppressant FK506 when compared to Th1 cells. Thus, these cells were able to confer protection in the setting of transplant immunosuppression. These data demonstrate a novel vaccine strategy that elicits lung TRM cells and achieves serotype independent immunity to K. pneumoniae even in the setting of calcineurin therapy for transplantation.

Maternal Immunization for Protection of Neonates from RSV

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Respiratory syncytial virus (RSV) is a significant human pathogen severely impacting neonates and young children, but no vaccine is licensed to protect this vulnerable population. Furthermore, direct vaccination of neonates is potentially unsafe and possibly ineffective. Maternal vaccination may be the best and safest approach to neonate protection through the passive transfer of maternal neutralizing antibodies *in utero* to the fetus after maternal immunization. We have reported that immunization of pregnant cotton rats, a surrogate model for human maternal immunization, with novel RSV virus-like particle (VLP) vaccine candidates containing stabilized pre-fusion RSV F and G proteins provide significant levels of protection of offspring of immunized dams from RSV challenge. Extending these studies, we assessed the durability of those protective responses in dams, the durability of protection in offspring, and the transfer of that protection to offspring of two consecutive pregnancies without a second boost immunization. Confirming our previous reports, four weeks after birth, offspring of the first pregnancy were significantly protected from RSV replication in lungs and nasal tissues after RSV challenge. However, the overall protection of offspring of the second pregnancy was considerably reduced. This decline in protection occurred even though the levels of total anti-pre-F IgG and neutralizing antibody titers in dams remained at similar and high levels before and after the second pregnancy. The results are consistent with an evolution of antibody properties in dams to populations less efficiently transferred to offspring or inefficient placental transfer of antibodies in elderly animals.

Development of a vaccine to prevent or reduce Epstein-Barr virus diseases

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Epstein-Barr virus (EBV) infects 90% of adults worldwide and is the predominant cause of infectious mononucleosis. The virus is associated with numerous B cell malignancies, such as Hodgkin lymphoma and Burkitt lymphoma, as well as epithelial cell cancers such as nasopharyngeal carcinoma and gastric carcinoma. At present, no vaccines are licensed to prevent EBV disease or infection. We have developed two approaches for EBV vaccines. First, we produced recombinant nanoparticles expressing EBV gp350, the most abundant viral protein and the primary target for neutralizing antibodies in human plasma that prevent infection of B cells. Second, we produced recombinant nanoparticles expressing EBV gH/gL/gp42, which are key components of the viral fusion apparatus and key targets for neutralizing antibodies in human plasma that prevent infection of epithelial cells and B cells. Immunization of mice and nonhuman primates with these vaccines induced high titers of neutralizing antibodies. Vaccinating mice with combined gp350 and gH/gL/gp42 nanoparticles induced markedly higher neutralizing titers to prevent infection of epithelial cells and slightly higher neutralizing titers to prevent infection of B cells than immunization with EBV gp350 nanoparticles alone. Thus, a combined gp350 and gH/gL/gp42 nanoparticles vaccine may be effective in reducing or preventing EBV diseases and plans are underway to test these vaccines in clinical trials.

Vaccines Summit-2021

September 20-22, 2021 | Online Meeting

Day 3: September 22, 2021

Scientific Sessions

RelCovax™, a second-generation multivalent SARS-CoV-2 vaccine candidate designed to meet global vaccination demands

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Reliance Life Sciences, part of the Reliance Group of Companies in India, has developed a uniquely constructed, low-cost, easily manufactured SARS-CoV-2 vaccine candidate that has been specifically developed to enable global access, especially to low and medium cost countries, to safe and effective protection from SARS-CoV-2 infection and COVID-19 disease. The product employs well-established traditional recombinant protein manufacturing processes together with mature, potent adjuvant technology to yield a multi-antigen subunit vaccine. A 223 amino acid Spike receptor binding domain (RBD) subunit antigen is manufactured and purified from CHO cell fermentation, and a 419 amino acid nucleocapsid subunit antigen is produced using *E. coli*-based fermentation. These two antigens are then formulated with adjuvants in sodium phosphate buffer to yield a simple and well-defined final drug product. Immunogenicity analysis (both antibody and cellular responses) were performed using a wide range of antigen and adjuvant formulations in a murine model to select the final formulation parameters, and SARS-CoV-2 studies were performed using the well-established golden hamster model. The resulting product candidate is now being manufactured under GMP conditions. Rigorous pharmacology, toxicology, and chemistry/manufacturing/controls analyses including stability studies have been completed, and a common technical document (IND) is currently under review by the Central Drugs Standard Control Organisation (CDSCO) under Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India. Initial Phase 1 prime/boost dose ranging studies focused on selecting the final dose, as well as demonstrating immunogenicity and safety of RelCovax™ will begin enrollment during Fall 2021.

Development of an inactivated SARS-CoV-2 vaccine candidate BBV152 and its response towards variant of concern

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Indian Council of Medical Research-National Institute of Virology, Pune and Bharat Biotech Pvt Ltd, Hyderabad have developed and assessed the immunogenicity and protective efficacy of an inactivated SARS-CoV-2 vaccine formulated with Toll-like receptor 7/8 agonist molecule adsorbed to alum (Algel-IMDG) in Rhesus macaques and hamster model. After demonstration of safety, immunogenicity and protection in animal models, vaccine candidate BBV152 was successfully evaluated in Phase I/II/III (NCT04471519) clinical trials in India and was granted Emergency Use Authorisation by Indian regulators. BBV152 is currently being used in mass immunization programme of India. Data from these study substantiates the immunogenicity and protective efficacy of BBV152. The overall efficacy against symptomatic disease is 77·8% in the Phase III clinical trial. Efficacy for severe symptomatic COVID-19 is 93.4% and against asymptomatic COVID-19 is 63·6%. Against the Delta Variant of Concern (B.1.617.2), BBV152 conferred 65·2% protection. Further sera of COVID-19 naïve vaccinated individuals, COVID-19 recovered fully immunized individuals and breakthrough cases were evaluated for its response toward neutralization of B.1, Alpha, Beta, Delta and Delta AY.1 variants . BBV152 vaccine induced sera generated detectable neutralizing antibody titers to all VoCs with modest reductions in titers when comparing the variant strain to the prototype strain.

Biography:

Dr. Pragya D Yadav, M.Sc., PhD

I am in-charge of Biosafety level-4 laboratory, Asia's first state of art facility to handle deadly pathogens at ICMR-NIV, Pune.

As the head of BSL-4 I have been instrumental in establishing standard work practices and biosafety procedures preparing for outbreak investigations. Through nationwide Serosurvey of bats, ticks, domestic animals and ticks and human discovered the presence of highly pathogenic CCHF, Nipah, Hantan and SARS viruses in India. I have extensively worked on disease-causing viruses of public health importance like KFD, Zika, Yellow fever, Ebola, Lassa, Marburg, Dengue, Chikungunya, Bunyaviruses and Nairobi Sheep Disease. I have developed diagnostic tests for CCHF, Nipah, SARS-COV-2 and KFD viruses and transfer of technology to industry has had a major impact in monitoring the diseases in India.

The most significant contribution in the ongoing COVID-19 pandemic was to isolate the SARS-CoV-2 virus and all its variants. My studies on the development and demonstrating the efficacy of Covaxin are unparalleled contribution in the field of vaccinology. I have contributed to the understanding of pathogenesis and transmissibility of the SARS-CoV-2 variants by carrying out Hamster studies which have enhanced the knowledge in the scientific community of the world.

Cancer Vaccines Are Back: this time to Stay

Pirouz Daftarian PhD
Senior Manager IO and Vaccines at MBL International
Director of Scientific Engagement at CrownBio, JSR Life Sciences.

Today, scalable novel vaccines platforms such as synthetic RNA platforms, self-amplifying RNA, (small circular) DNA plasmid, (neo)epitope / peptide based vaccines, and vector-based vaccines, as well as, novel delivery platforms, for examples protamine, dendrimers, microbiome and various cationic lipid formulations, are in pipelines or have reached more than 1000 clinical trials.

There is an urgent need for rapid, accurate, and high throughput methods for immunomonitoring of this huge vaccine engines in preclinical and in clinical setting. These immunomonitoring methods and models should include in vivo models as well as in vitro models to expedite the accurate proof of concept, the R&D all the way to populate the INDs to get the vaccines to human.

We have devised immune monitoring platforms and products at MBLI and have been conducting studies to assess potency of vaccines and immunomodulatory agents at CrownBio. T cells mounted by natural infection, vaccines or antigen exposure may be detected in periphery (1-3% of clonotypes circulate in the periphery), or splenocytes of mice. However, for accurate and quantitative analysis of peptide specific CD4+ or CD8+ T cells there is a major bottleneck, the generation of MHC tetramers for each different peptide / MHC allele. Here, I present 2 new platforms for rapid, high-quality creation of custom Class I and Class II MHC tetramers in laboratories in a few hours with QuickSwitch™, a proprietary technology for exchanging peptides on an MHC tetramer. To show the impact of this this platform for immune monitoring, I will also present QuickSwitch generated tetramers for SARS-CoV-2 Delta variant. This reagent allows simple and direct detection of T cells that react with Delta variant.

The platform comes with internal controls, and a peptide exchange factor. Any peptide of interest may be assessed first for its ability to occupy the groove, thereby gathering binding affinity information for the MHC/peptide complex of MHC, and yet results in the creation of your custom MHC tetramer ready to use- all in one day. This platform is used for purposes such as epitope discovery, neoantigen vaccine research, verification of T cell staining using the new peptide specific tetramer, and more.

The Language of Vaccine Confidence: Lessons from the COVID-19 Vaccine Rollout

Mark R. Miller
Vice President of Communications, de Beaumont Foundation

The rollout of the COVID-19 vaccines in the United States has offered insights that will be relevant for ongoing communication about vaccines – and for health communication in general. The question is whether the health field will learn from these lessons and improve the way they communicate about other health issues. In particular, the words we use matter and can literally save lives.

Political polarization and disinformation have complicated the U.S. rollout, especially since the COVID-19 vaccines were developed during the Trump Administration but rolled out at the beginning of the Biden Administration. Mark Miller, a former White House official during the Clinton Administration, has been coordinating and analyzing original polling and focus groups conducted on behalf of the de Beaumont Foundation – with a particular focus on the political divide that has threatened both vaccine uptake and adherence to public health guidance like masking and distancing. See polling and focus group results and messaging tools at www.ChangingtheCOVIDConversation.org.

Leveraging his professional expertise in communications, health, and politics, Mr. Miller will bring these issues to life, offer practical tips, and humanize them with personal stories.

This session will provide an overview of polling that reveals insights into how Americans perceive COVID-19 and the COVID-19 vaccines. For example, in early August we found that 81% of unvaccinated parents believe that vaccines for diseases like measles and mumps are safe for children, but only 60% believe the COVID-19 vaccines are safe for children. That tells us that calling unvaccinated people "anti-vaxxers" is inaccurate and unproductive. What's needed is not education about the safety of vaccines in general, but about the COVID-19 vaccines in particular.

With a focus on identifying language that works in building vaccine confidence, our research has covered how personal experiences with COVID-19 (having it or knowing people who have had severe cases or died) have shaped perceptions, which messengers are most trusted, how family members and peers influence attitudes, and how values like personal liberty factor into decisions about vaccination and COVID-19 protocols. This research has been used by federal officials, governors, mayors, and members of Congress, as well as state and local health departments, medical associations, and education leaders. Attendees will leave with practical insights from a non-clinical

What will audience learn from your presentation?

Most public health and medical professionals do not have formal training in communication, especially not in crisis situations, politically sensitive environments, and high-profile health incidents like pandemics.

- Attendees will learn new research and communication insights from a non-medical communications expert with decades of experience in high-pressure environments.
- Attendees will take a way new knowledge about words and language that works – and doesn't work – when communicating about vaccines and other health issues.
- Attendees will learn about the role that opinion polling and focus groups can play in shaping a regional, national, or international response – but also in informing the day-to-day work of health professionals.

Biography:

Mark Miller has decades of senior experience in communication, health, philanthropy, and politics – with a focus on solving problems and improving lives. He has worked at the White House, two charitable foundations, a top 10 children's hospital, and *The Washington Post*. Currently, as vice president of communications for the de Beaumont Foundation, Mark creates practical solutions to help public health professionals improve the health of communities nationwide. In response to the COVID-19 pandemic, he helped create the Public Health Communications Collaborative and is a founding member of the Society for Health Communication. See LinkedIn bio for more detail.

Recent related publications:

"Language Choice About COVID-19 Vaccines Can Save Lives," *Journal of Communication in Healthcare*, April 2021

"Changing the COVID-19 Conversation: It's About Language," *JAMA Health Forum*, Feb. 10, 2021

A modeling path through epidemiology, virology, and immunology to SARS-CoV-2 vaccine composition decisions

Jim Koopman*, **Carl Simon**, **Wayne Getz** and **Richard Salters**
Developing Theory that Serves Public Health

The pace of new mutations that increase SARS-CoV-2 transmissibility and escape natural and vaccine stimulated immunity is increasing. Several disciplines have developed informative new methods that should inform decisions regarding what mutations should be included in vaccines. But neither Epidemiology, Virology, Immunology, nor complex systems modeling of the pandemic can provide quantifiable assurance of good decisions on their own. We propose an approach that helps these disciplines provide input in a manner that minimizes the unknowns affecting a decision and clarifies more of the unknowns. The key elements of the needed model are parameters for 1) escape mutations that act only during reinfections or vaccination breakthrough infections, 2) transmission increasing mutations, 3) multiplicative joint effect mutations where one mutation creates conditions where another has greater effects such as mutations in the NTD opening up the RBD, 4) additive joint effects between other pairs of mutations, 5) Antibody Dependent Enhancement mutations that allow for antibody mediated cell entry of virus. Immunology and Virology provide the theoretical basis for making these parameters correspond to specific immune responses to specific epitopes. The key to integrating the different disciplines is a Decision Robustness and Identifiability Analysis DRIA strategy that helps insure that the model is not making assumptions that if realistically relaxed would change a decision or is not overfitted to data in a manner that allows for different decisions that could also fit the data. This approach allows for choosing combinations of mutations to maximize immune effects and minimize further mutations. This should be more effective that a strategy that chooses a variant for a new vaccine as is done for influenza.

Prevention of Covid-19 Transmission Beyond the Needle: DCOY101, a novel antiviral fusion peptide-based prophylactic nasal spray.

Barbara Hibner*, **Peter Marschel***, **Frederick E. Pierce II*** and **Shahin Gharakhanian****
*Research & Development Program Team,
**Scientific Advisory Board,
DECOY Therapeutics, CAMBRIDGE MA, USA

Introduction: Covid-19 is a global health crisis with specific local features. This pandemic has revealed the complexities of global infection control involving age-driven infection patterns, levels of awareness, high viral variations, changes to vaccine immune response over time, social media, the heterogeneity of social responses and medical co-morbidities. A "one-size-fits-all" approach has proven insufficient. Vaccines are the backbone, but gap analysis points to the need for additional agents. Methods/Results: We are developing a broad antiviral bioconjugate platform. Our lead candidate is a novel antiviral fusion peptide-based prophylactic nasal spray. DCOY101, a 41 amino acid heptad repeat C-based peptide, has been engineered to enhance half-life and target respiratory tissue. (1) DCOY101 lipopeptide inhibited S-mediated SARS-CoV-2 fusion (IC50=10nM/IC90~100nM) in 293T cells expressing ACE2 (mBio, 2020; 11:e01935). (2) DCOY101 inhibited live virus in monolayer Vero E6 cultures via a plaque neutralization assay (IC50=6nM). (3) DCOY101 enabled a 4-log reduction in viral load in a human airway epithelial ex vivo model. (4) DCOY101 is equipotent vs alpha, beta and gamma variants in a pseudotype assay. (5) Based on a close analogue, POC nasal drops QDx4 days demonstrated prophylaxis in a validated ferret transmission model, preventing infection in treated ferrets (0/6 infected) co-housed with a maximally infected ferret. All mock treated animals (6/6) became infected (de Vries RD et al., Science 2021, 371: 1379-1382).

Conclusion: Multiple prophylactic and population-friendly approaches are required to control Covid-19. DCOY101 can complement vaccines with advantages in manufacturing, self-administration, shelf life and no requirement for a cold supply chain.

Biography:

- Barbara HIBNER, PhD, is the Co-founder, Chief Scientific Officer and SVP R&D at DECOY Therapeutics. She has 25 years of leadership experience in pharma and biotech relative to new drug discovery. Past positions held: Bayer, Chiron, Millennium Pharmaceuticals, and Takeda Pharmaceuticals.
- Shahin GHARAKHANIAN, MD [Pharmaceutical Medicine & Infectious Diseases]. Chair, Scientific Advisory Board, DECOY Therapeutics. Expertise: Clinical Development of Drugs and Vaccines. R&D track record: Allergy Immunotherapy, Covid-19, Flu, chronic HBV, HIV, Tuberculosis.

Customer Case Studies of Rapid Vaccine Analysis for Corona, Influenza, and more.

Scott Fu
Filed Application Scientist

Vaccine analysis has typically relied on techniques that were designed years ago and take time to execute. Influenza is a classic example with the use of SRID and subjective HA/HAI. Here we present the case studies of adoption of the VaxArray® Platform, a novel microarray platform to quantify both antigens and antibodies in a variety of samples across the vaccine development process. Rapid assessment and high sensitivity enable detection of target protein from crude in-process samples, from low dose vaccines such as those administered by microneedle, and from adjuvanted drug product. Simultaneous measurement of multiple antigens, from bioprocess to DS to DP, will be presented. Examples will include vaccines targeting influenza, COVID, and measles/rubella.

Patient specific dendritic cell vaccines as cancer immunotherapy

Robert O. Dillman, M.D.
AIVITA Biomedical, Inc. Irvine, CA. USA.

AIVITA Biomedical Inc. is manufacturing patient-specific anti-cancer vaccines (DC-ATA) consisting of autologous dendritic cells (DC) loaded with autologous tumor antigens (ATA) derived from short term-cell cultures of tumor-initiating cells. Clinical trials with first-generation DC-ATA demonstrated minimal toxicity and encouraging overall survival results in patients with metastatic melanoma and metastatic renal cell cancer. Accrual to a clinical trial in newly-diagnosed glioblastoma has completed enrollment. Trials are ongoing in newly-diagnosed advanced ovarian cancer, and in combination with anti-PD-1 in metastatic melanoma. The product evolution and clinical results will be discussed.

Agnostic Cancer Vaccine: Synergistic Interaction of Oxaliplatin and Oncolytic Virus

J. Milburn Jessup, MD FACS
Research Scientist
Washington DC Veterans Affairs Medical Center

Immunogenic cell death is a form of necroptosis caused by viruses, select cytotoxic agents and radiation that causes the release of tumor antigens in association with eat me and take me signals that promote innate immunity as well as cross-prime adaptive immune responses to the tumor. The advantage of this approach is that it is agnostic to the specific tumor antigen and stimulates the host to determine what may be important as an immune response. Our approach in preclinical colorectal carcinoma involves the synergistic interaction of Oxaliplatin with a conditional replicating chimeric adenovirus that induces cell-mediated immunity to tumor antigens to control tumor growth after a single injection. Our data indicate that the combination of agents is better than either alone and causes partial responses in 90% of large murine tumors with a complete response in 20%. This results in significant improvement in overall survival. Data will be presented to support the synergistic action of the two agents as well as the nature of the immunogens targeted by this agnostic immunization.

An Env-Gag VLP mRNA vaccine induces broad-spectrum neutralization and protects macaques from heterologous tier-2 SHIV infection

Peng Zhang[1], Elisabeth Narayanan[2], Shilei Ding[3], Yaroslav Tsybovsky[5], Richard Koup[4], Johnathan Misamore[7], John R. Mascola[4], Andrea Carfi[2], Andres Finzi[3], Anthony S. Fauci[1] and **Paolo Lusso[1]***

[1]Laboratory of Immunoregulation, [4]Vaccine Research Center, and [6]Laboratory of Molecular Microbiology, NIAID, NIH, Bethesda, MD; [2]Moderna Inc., Cambridge, MA; [3]Université de Montréal, Canada; [5]Advanced Technology Research Facility, NCI, NIH, Frederick, MD; [7]Bioqual Inc., Rockville, MD (USA).

Recent advances in mRNA technology have enabled the development of mRNA vaccines for Covid-19 and other infectious diseases. In 2017, we designed an HIV-1 mRNA vaccine characterized by: *i)* use of membrane-bound, native-like envelope (Env) trimers; *ii)* co-formulation of HIV-1 Env and SIV Gag mRNAs to induce the production of virus-like particles (VLPs); *iii)* priming with germline antibody-engaging Env to recruit unmutated precursors of broadly neutralizing antibodies (bNAbs); and *iv)* focusing on shared bNAb epitopes by repeated boosting with mixed heterologous Envs of different clades. Immunized animals rapidly developed autologous neutralizing antibodies and eventually, after the third heterologous boost, broad tier-2 neutralizing antibodies, albeit at low titers. Robust anti-Env $CD4^+$ T-cell responses were also induced. Vaccinated animals were protected from repeated low-dose rectal challenges with a heterologous difficult-to-neutralized tier-2 simian-human immunodeficiency virus (SHIV AD8). Protection was correlated with the presence of antibodies to the CD4-binding site. Thus, a Gag-Env VLP mRNA platform represents a promising approach for the development of an HIV-1 vaccine.

Efficacy of an epithelial stem cell-based AIDS vaccine to induce immune responses and control transmission

Marie-Claire Gauduin, Ph.D.
Texas Biomedical Research Institute, and The Southwest National Research Center, Texas, USA

A vaccine that restricts viral replication at mucosal portal of entry may help controlling HIV infection. We have used epithelial stem cells as permanent source of viral antigens and their differentiated offspring as antigen-producing presenting cells. We developed a SIV single cycle vaccine under the control of the involucrin promoter (pINV-SIVsc), which was tested for its ability to drive SIV expression in terminally differentiated epithelial cells, induce mucosal immune response, and protection against SIV challenge. Eight female macaques were immunized (1 dose, epidermic, atraumatic) at week 0 and monitored over time for specific immune responses in blood, mucosal secretions, and various lymphoid/non-lymphoid tissues. As expected, the evaluation of vaccine-antigen expression profiles by immunohistofluorescence showed that vaccine antigens were produced in the upper layer of vaginal epithelia up to three months after vaccination with pINV-SIVsc. SIVenv was also detected via anti-gp120 immunoPET/CT scans in the uterus and vagina from a vaccinated monkey at multiple weeks after vaccination. Strong mucosal antibody responses and specific CD8+ T cells expressing a4ß7 were detected within 2-weeks post-vaccine. While no pINV-SIVsc replication was demonstrated, two independent experiments confirmed that vaginal immunization elicits durable antigen expression from terminally differentiated keratinocyte-specific promoter in female macaques. Animals were challenged at weeks 12 or 24 using repeated doses of SIV. Eight additional macaques served as unvaccinated SIV-infected controls. As expected, all unvaccinated SIV-infected controls had high viremia and significant CD4+ T cells reduction in the gut; However, we demonstrated significant delay in viral acquisition and lower viremia with 2-3 logs reduction at viral peak, 4-5 logs-reduction at set-point, to undetectable viremia by week 20 post-SIV. In addition, robust SIV-specific T cell responses were detected in blood, LN and mucosa of all vaccinated animals. We demonstrated a positive correlation between the generation of mucosal and systemic T cell responses and control of viremia as well as inverse associations between viremia and post-challenge vaginal antibody responses. All vaccinated animals manifested durable, aviremic control of infection with SIV for 2 years when CD8-depletion was performed. The dramatic fall in viremia coincided with the recovery of T lymphocytes in blood and significant increase of both systemic IgG and SIV-specific CD8+ T cells of all animals. The study demonstrated the efficacy of epithelial stem cell-based vaccine to serve as antigen delivery system and generate specific mucosal immune responses leading to significant delay in infection and rapid control of viremia to undetectable.

SCIENTIA MEETINGS
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September 20-22, 2021 | Online Meeting

Innate cell markers that predict anti-HIV neutralizing antibody titers in vaccinated macaques

Matthieu Van Tilbeurgh[1], Pauline Maisonnasse[1]*, Jean-Louis Palgen[1], Monica Tolazzi[2], Yoann Aldon[3], Nathalie Dereuddre-Bosquet[1], Mariangela Cavarelli[1], Anne-Sophie Beignon[1], Ernesto Marcos-Lopez[1], Anne-Sophie Gallouet[1], Gabriel Ozorowski[4], Andrew B. Ward[4], Ilja Bontjer[5], Paul F. McKay[3], Robin J. Shattock[3], Gabriella Scarlatti[2], Rogier W. Sanders[5,6] and **Roger Le Grand[1]**

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Keywords: Mass-cytometry, SOSIP protein, vaccine signatures, predictive markers.

Given the time and resources invested in clinical trials, innovative early risk prediction methods are needed to decrease late-stage failure in vaccine development. Using a three steps clustering approach, we analyzed blood myeloid cells of cynomolgus macaques before and 24 hours after each immunization by mass-cytometry. Three groups of cynomolgus macaques (n=6) were immunized three times (week 0, 8 and 24) with 20 µg of recombinant HIV Env glycoprotein trimer (ConM SOSIP.v7) either by intramuscular injection (IM) of the ConM SOSIP.v7 adjuvanted with monophosphoryl lipid A (MPLA) or squalene emulsion (SQ), or subcutaneous injection (SC) of the ConM SOSIP.v7 adjuvanted with MPLA. Unique vaccine signatures were identified based on the surface expression of HLA-DR, CD39, CD86, CD11b, CD45, CD64, CD14, CD32, CD11c, CD1c, FcεRI, and CADM1. By combining these markers, we identified early innate cell responses that predict IgG binding, neutralizing antibody (nAb) responses and FcγRIIIa engagement induced in ConM SOSIP.v7 immunized cynomolgus macaques. Our results demonstrate that monitoring immune signatures during early vaccine development could assist in identifying biomarkers that predict vaccine immunogenicity.

Biography:

I am a PhD student at the Commissariat à l'Energie Atomique et aux énergies alternatives (CEA) in Fontenay-aux-Roses (France), after receiving a Masters degree in Immunology from The Phillippe Maupas University of Tours (France). My research aim is to define signatures and biomarkers of human immunodeficiency virus (HIV) and yellow fever virus (YFV) vaccines responses in Cynomolgus macaques, using mass-cytometry. Currently, I am elucidating the importance of CD4+ve T cell responses in generating the long-term memory induced by the YF-17D vaccine.

Harnessing public B cell responses with pathwa-amplifying vaccines

Daniel Lingwood
The Ragon Institute of MGH, MIT and Harvard

The human antibody repertoire endows for low titer but genetically reproducible antibody responses engaging functionally conserved targets on pathogens like influenza virus. Using a vaccine model in which antibodies develop from human-like B cell receptor (BCR) repertoires, we demonstrate that such 'public' targeting arises via non-conventional antigen recognition, where germline-endowed contact enables selective vaccine-amplification of antibodies targeting invariant microbial features.

OVX836, NP-based universal influenza vaccine candidate: Results of Phase 2A Clinical Trial

Leroux-Roels I.[1], **Tourneur J.**[2], **Leroux-Roels G.**[1], **Guyon-Gellin D.**[2], **Le Vert A.**[2*], **Nicolas F.**[2] and **Willems P.**[2]
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Introduction: Cellular immunity to well-conserved influenza nucleoprotein (NP) is associated with protection against influenza disease, providing strong rationale for NP-based influenza universal vaccine. OVX836 is an unadjuvanted recombinant vaccine composed of the NP sequence of Influenza A virus fused to Oligodom®, OSIVAX's proprietary pro-immunogenic tag. We have previously shown that OVX836 induces NP-specific CD4+, CD8+ T-cell and IgG responses in mice, protects mice and ferrets from challenges with multiple strains of influenza, and is safe and immunogenic in humans (Phase 1 trial).

Method: Randomized, double-blind, reference-controlled Phase 2a study evaluating immunogenicity and safety of one intramuscular dose of OVX836 at 90µg and 180µg in healthy 18-65 year-old subjects, compared to Influvac TetraTM, quadrivalent seasonal influenza sub-unit vaccine

Result: Immunogenicity: Primary immunogenicity endpoint achieved (superiority of OVX836 over Influvac Tetra in terms of change Day1-Day8 of NP-specific T-cell IFN-γ activity by ELISPOT): median D8/D1 ratio 1.83, 1.93 and 1.03 for OVX836 90µg, OVX836 180µg, Influvac Tetra, respectively (overall difference; p=0.0006). Data support higher immunogenicity for 180µg than 90µg dose: (i) on D8 and D29 and for NP-specific CD4 T-cell responses, OVX836 180µg was significantly different from OVX836 90µg (p=0.0406 and p=0.0353, respectively); (ii) for total T-cells and humoral (anti-NP IgG) response, there was a trend for a dose-effect at D8 and D29. Safety: Both dosages of OVX836 are safe and well-tolerated, comparable to Influvac Tetra. Low incidence of "severe" events, similar to Influvac Tetra and no dose-limiting effects even for the 180µg dose. Efficacy: Observed numbers of Influenza-Like Illnesses (ILIs) occurring during influenza season as of 14 days post-vaccination were 8, 2 and 3 in OVX836 90µg, OVX836 180µg and Influvac Tetra groups respectively, suggesting a potential protective effect of OVX836 at 180µg.

Conclusion: OVX836 was immunogenic with 180µg being superior to 90µg, while both doses were safe and well-tolerated at. A signal for efficacy was observed at the 180 µg dose.

ALFQ: A Potent Adjuvant for a peptide vaccine

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Liposomes composed of closed shells of phospholipid bilayers were originally introduced in the 1960s as models of plasma membranes of cells. They have since evolved as versatile platforms for carrying and targeting payloads of drugs (such as mRNA), antigens, or adjuvants for development of novel vaccines. Recent advances in liposomal formulations have produced increased immunogenic potency, together with safety, for new types of human vaccines, including vaccines to malaria, HIV-1, shingles, tuberculosis, covid-19, and others. Army Liposome Formulation (ALF) carries monophosphoryl lipid A (MPLA) as an adjuvant, and ALFQ comprises ALF plus QS21 saponin as a second adjuvant. ALF and ALFQ contain saturated fatty acyl chains in neutral and anionic phospholipids, and cholesterol (43% for ALF; and >50% for ALFQ). ALF and ALFQ each have been utilized as a safe and potent adjuvant in numerous human clinical trials with different types of proteins as antigens.

Small poorly immunogenic molecules such as individual peptides or haptens have often been conjugated to large carrier schlepper proteins that carry T helper cell epitopes to affect an immune response. However, previous results have also suggested that ALF-type adjuvants could induce immune responses to certain types of unconjugated peptides. Here we examined the possibility of inducing both binding and neutralizing immune responses to multiple strains of type A influenza virus by creating an unconjugated composite peptide chain containing several different conserved peptides as antigens, together with a T helper epitope, and with ALFQ as the adjuvant. When compared with the composite peptide conjugated to CRM197 as a protein carrier, the unconjugated composite peptide displayed broadly neutralizing immunogenicities in mice that were equal to, and sometimes superior to, the conjugated composite peptide. The results suggest that when combined with ALFQ as a powerful adjuvant, certain types of unconjugated synthetic peptides might serve effectively as antigens. This could lead to inexpensive and easy-to-manufacture conserved antigenic peptide structures that could induce immune responses to multiple viral strains, and which could be readily employed to respond to emergence of new viral variants.

Recent reference (open access): Sei CJ, Rao M, Schuman RF, Daum LT, Matyas GR, Rikhi N, Muema K, Anderson A, Jobe O, Kroscher KA, Alving CR, Fischer GW. Conserved Influenza Hemagglutinin, Neuraminidase and Matrix Peptides Adjuvanted with ALFQ Induce Broadly Neutralizing Antibodies. Vaccines (Basel). 2021 Jun 25;9(7):698. doi: 10.3390/vaccines9070698. PMID: 34202178; PMCID: PMC8310080.

Vaccination with a lymph node targeted Amphiphile-CpG adjuvant promotes potent cellular and humoral immunity to SARS-CoV-2 protein subunit antigens

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The ongoing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic highlights the need for development of effective vaccine adjuvants which can promote potent protective immunity with balanced humoral and cellular responses. Here, we evaluated a lymph node targeted CpG DNA TLR-9 agonist, AMP-CpG, to promote immunity directed against an admixed SARS-CoV-2 Spike-2 receptor binding domain protein in mice and non-human primates. AMP-CpG uses diacyl lipid Amphiphile (AMP) modification to efficiently target lymph nodes, where innate and adaptive immune responses are coordinated. Comparator vaccination with alum and unmodified CpG were included to assess immune response induction of a lymph node targeted adjuvant relative to either a depot forming or systemically distributed adjuvant. Compared to alum and unmodified CpG, immunization with AMP-CpG induced >25-fold higher antigen-specific T cells in the peripheral blood that produced multiple T helper 1 (TH1) cytokines, trafficked into lung parenchyma, exhibited potent killing of antigen-positive targets in vivo, and were maintained for >5 months after vaccination. Antibody responses favored TH1 isotypes (IgG2c and IgG3) and potently neutralized Spike-2-ACE2 receptor binding, with titers 265-fold higher than natural convalescent patient COVID-19 responses. Vaccination with 10-fold reduced antigen dose maintained T cell and antibody responses which were also preserved in immunosenescent aged mice. Vaccine responses were highly cross-reactive to SARS-CoV-2 variants of concern. Vaccination in Rhesus macaques induced rapid antigen-specific serum IgG with potent neutralizing activity exceeding levels observed in convalescent human samples. Polyfunctional cytokine producing CD8 and CD4 T cells were also elicited. These results suggest that efficient delivery of AMP-CpG to the lymph nodes enables potent and coordinated activation of balanced cellular and humoral immunity and can be applied for rapid development of prophylactic or therapeutic vaccine candidates targeting a variety of disease-specific antigens.

Building biomanufacturing capabilities in the kingdom of Saudi Arabia via government entities consortium

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As part of Vision 2030, the Kingdom of Saudi Arabia (KSA) is undergoing immense changes in its technology and manufacturing landscape, diversifying the economy by allocating resources in distinct domains to expand Saudi research, development and manufacturing in many sectors, including healthcare and life sciences. According a recent survey conducted by the Saudi Ministry of Industry, the biopharmaceutical market value was reported at $8.2 Bn, showing “Oral Solids” is the largest sector and “Biologics/ Biosimilars” is the fastest-growing.

The vast majority of the market is supplied by imported goods, with some multinationals facilitating domestic manufacturing by gradually moving manufacturing into the Kingdom. Vision 2030 envisions Saudi participation throughout the pharmaceutical value chain: distribution, fill finish, API/BDS manufacture and research and development. Saudi Arabia is establishing a “biopharma ecosystem” through a successful model involving joint efforts from government institutes, R&D facilities, and the private sector. Through its institutional and industrial arms, the government is providing the needed infrastructure for future international collaboration via the National Vaccine and Biomanufacturing Center (NVBC). The Center will be the cornerstone for developing monoclonal antibody (mAb), vaccine and biosimilar treatment products to be developed and manufactured in Saudi Arabia. Programs such as the NVBC, a planned BioPark and continuing private and multinational investment will enable Saudi Arabia move into the leadership of the domestically developed and manufactured biopharmaceuticals in the MENA Region and beyond.

The government is investigating ways to build this successful consortium. A survey of the major Saudi research-based institutions (government and universities) to identify and classify promising is the first step toward this goal. This requires analysis of the overall capabilities of the institutes and expert evaluation of the strengths of each program the development status of their leading candidates and possible funding or collaborative activities. The establishment of NVBC enables the government to focus their activities on the expansion of a domestic biopharmaceutical industry to produce essential biologics, including vaccines, biosimilars, and advanced therapies. NVBC, as the lead institution within the Kingdom, offers an opportunity for international collaboration under the government umbrella support and incentive programs.

Short-term blockade of BCG induced IL-10 sustains long term protection against Mycobacterium tuberculosis infection in mice

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Tuberculosis (TB) is one of the deadliest infectious diseases affecting 1/4th global population. BCG immunization is one of the best resources available to control the TB related deaths worldwide, however BCG fails to provide a long term protection and gradually loses its efficacy. We have shown that Interleukin-10 (IL-10) plays a critical role in TB disease progression and blockade of IL-10 signaling during the early phase of Mycobacterium tuberculosis (M.tb) infection results in enhanced protection in mice. BCG immunization induces early IL-10 production in the lungs. We hypothesized that blockade of IL-10 signaling during BCG vaccination would increase the magnitude of protection against M.tb challenge. Mice co-immunized with a single dose of anti-IL-10R1antibody with BCG showed an early protection at day 30 and sustained this protection with a significant reduction(1.5log) in M.tb lung CFU(Colony forming unit) until day 330, whereas BCG- control group lost the protection by day-60 post M.tb challenge. This reduced bacterial burden and lung pathology was associated with increased survival. BCG/anti-IL-10R1 immunized mice showed significant increase in central memory markers and reduced pro-inflammatory cytokines TNF-α, IL-12, IL-17 and IFN-γ at day 49 post immunization and also at day 30 and 60 post challenge. Our findings demonstrate that using IL-10 blockade via a single dose of anti-IL-10R1 antibody at the time of BCG vaccination is a promising approach that can be translated to the human studies as ideal candidate vaccine to provide long term protection against M.tb infection.

MVX01: A global, serotype-independent, pneumococcal protein fusion vaccine candidate

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Matrivax

Matrivax is developing MVX01, a novel serotype-independent pneumolysin (PLY) toxoid-Choline binding protein A (CbpA) fusion protein vaccine candidate to prevent disease caused by *Streptococcus pneumoniae* infection. Current pneumococcal Polysaccharide Conjugate Vaccines (PCVs), ranging in valencies from 7 to 20, only protect against the serotypes represented in the vaccine formulation, yet more than 100 serotypes exist.

Matrivax is developing MVX01 as a standalone vaccine or a complement to PCVs. In preclinical murine studies, MVX01 elicited functional antibodies that neutralized the cytolytic activity of PLY and prevented CbpA mediated adhesion of *S. pneumoniae* to human lung epithelial cells. Moreover, MVX01 conferred protection from lethal intranasal (IN) infection from 3 *S. pneumoniae* serotypes. More extensive murine protective efficacy studies were performed with the PLY toxoid portion of MVX01 (PLY-DM) whereby immunization with PLY-DM conferred protection from 17 of 20 serotypes (85% efficacy) that included both Prevnar 13® (PCV13) and emerging serotypes. Further, in these studies PLY-DM vaccination conferred superior protection than PCV13 alone and a combination of PLY-DM and PCV13 conferred the highest level of protection. PLY-DM and MVX01 were evaluated in bridging studies and elicited comparable anti-PLY IgG antibody titers and protective efficacy. MVX01 was successfully evaluated in a rabbit toxicology study and is a Phase 1 clinical candidate.

A highly immunogenic UVC-inactivated Sabin-based polio vaccine

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Although highly effective, flaws in the two current polio vaccines (oral polio vaccine, OPV, and inactivated polio vaccine, IPV) have become serious concerns as polio eradication has progressed. OPV (live Sabin strains) can revert to pathogenic forms in vaccinated individuals and cause disease in the unvaccinated or immune-compromised (i.e., vaccine-associated poliomyelitis). IPV cannot replicate in the patient but is manufactured using large quantities of pathogenic virus, which constitutes biohazard and biosecurity risks. These types of limitations have led to a call by the Global Polio Eradication Initiative and others for the development of updated polio vaccines. Current chemical methods of virus inactivation using formalin are slow, while others such as ionizing radiation and UVC exposure are known to destroy critical protective epitopes. In an effort to generate a "next-generation" polio vaccine, we further developed our system to produce a candidate that we have named *Ultra*IPV. The platform technology uses a protective antioxidant complex during irradiation which increases the quantity and quality of immunogenic neutralizing epitopes retained throughout. Here we investigate the ability of the new method to protect epitopes in Polio Virus 1, 2 and 3 Sabin strains during UVC exposure. We show that UVC routinely inactivates Sabin strains of PV-1, 2 and 3 within 30 seconds. Importantly, the UVC-inactivated viruses stimulate potent neutralizing antibody responses in Wistar rats providing functional evidence that critical epitopes are retained. UVC inactivated polioviruses generated with the technology also had an extremely high level of neutralizing activity per µg as determined by mass spectroscopy. Freeze-thaw stability studies indicate that equivalent neutralizing activity is retained following -40°C storage. We believe this vaccine production method solves or eliminates numerous problems with current Polio vaccines.

Biography:

Dr. Stephen Dollery has spent several years studying viruses including HSV, KSHV and more recently Polioviruses. He recently moved to Biological Mimetics, Inc. from the Laboratory of Viral Diseases at the US NIH. At Biological Mimetics, Inc. he researches and develops several platform-based technologies spearheading several projects that span a diverse set of microbes, while maintaining an interest in basic science.

Inactivated bacterial vaccine candidates against *Acinetobacter baumannii*

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Acinetobacter baumannii is a bacterial pathogen that is often multidrug-resistant (MDR) and causes a range of life-threatening illnesses, including pneumonia, septicemia, and wound infections. *A. baumannii* can be found in soil samples leading to wound infections and has been associated with hospital-acquired infections, especially for immune compromised patients on ventilators or recovering from surgery. Some antibiotic treatments can reduce mortality if treatment begins early enough, but mortality rates often exceed 50%. Although several prophylactic strategies have been assessed, no vaccine candidates have advanced to clinical trials or have been approved.

In this poster, we discuss our efforts to produce inactivated vaccine candidates from a variety of planktonic and biofilm cultures of the highly pathogenic *A. baumannii* strain, AB5075. The bacteria was propagated using a large number of culture techniques and media to identify a panel of five cultures that demonstrated a wide variety of distinct protein profiles. Replicative activity was extinguished by exposure to 10 kGy gamma radiation in the presence of a complex composed of manganous (Mn^{2+}) ions, a decapeptide, and orthophosphate. Mn^{2+} antioxidants that prevent hydroxylation and carbonylation of irradiated proteins. The complex was adapted from the radiation-resistant *Deinococcus radiodurans* and has been shown to protect the exterior protein epitopes whilc allowing nucleic acid to be destroyed.

Mice were immunized and boosted twice with 1.0×10^7 irradiated bacterial cells and then challenged intranasally with live AB5075 using two mouse models. Planktonic cultures grown for 16 h in rich media and biofilm cultures grown in static cultures underneath minimal (M9) media stimulated immunity that led to 80-100% protection.

Biography:

Gregory J. Tobin is the President and CEO of Biological Mimetics, Inc. a vaccine design biotech company. Dr. Tobin's work focuses on developing novel vaccine strategies to overcome evolution and other methods by which pathogens evade host immunity. Current projects include the development of improved vaccines against A. baumannii, MRSA, polio, influenza, and human rhinovirus.

Cold-Chain Elimination and Needle-free Administration of Vaccines Upon the Application of Thin Film Freezing Technology

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Vaccination is a critically important and effective tool in the prevention of emerging and re-emerging infectious diseases. Almost all vaccines are recommended by WHO to be transported and stored at 2°C to 8°C. Messenger RNA (mRNA) COVID-19 vaccines must be transported and stored frozen (e.g. -20oC or -80oC), which imposes severe logistical barriers to storage, distribution, and final administration to patients. Thin Film Freezing (TFF) technology is an innovative freezing technology that can be applied to convert liquid vaccines to a more stable dry powder form to potentially eliminate the cold-chain and allow for needle-free administration (e.g., inhalation, nasal). In a recent study, TFF technology was applied to a liquid norovirus vaccine from Takeda. The vaccine powder was stable for 8 weeks at 40 oC, 75% relative humidity, without significant changes in its physicochemical properties, or a loss of antigen potency. The TFF platform has also been successful in converting many other vaccines to dry powders, including FDA-approved human vaccines (e.g., Merck's Gardasil, Sanofi's Fluzone, GSK's Engerix B and SHINGRIX), a veterinary tetanus toxoid vaccine, as well as human vaccines currently under clinical development (e.g., virus-based EBOV or COVID-19 vaccine candidates, plasmid DNA-based and mRNALNP- based vaccines). Due to excellent aerosol properties, the TFF vaccine dry powders can be directly aerosolized into the lungs or the nasal cavity. In addition, intranasal immunization of rats with an adjuvanted TFF vaccine dry powder has better storage stability and induces specific antibodies not only in the serum samples, but also in nasal and lung mucosal secretions, whereas injectable administration of the liquid vaccine only induces specific antibodies in the serum samples. In summary, the TFF technology platform provides a potential solution to eliminate cold-chain requirements of vaccines, and it also provides the public the potential of needle-free vaccination.

Disclaimers: Cui and Williams are co-inventors on IP related to the studies. The University of Texas System has licensed this IP to TFF Pharmaceuticals, Inc. Williams owns equity in and consults for TFF Pharmaceuticals, Inc. Moon, Sahakijpijarn and Xu consult for TFF Pharmaceuticals, Inc.

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Per oral immunization with nanoparticle vaccines induces protective immunity against genital *Chlamydia* challenge

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Sexually transmitted infections (STIs) represent a major health challenge worldwide, with more than 1 million new infections acquired daily. In the US, *Chlamydia* continues to be a leading cause of STIs, with 1.7 million cases of approximately 2.3 million STIs reported in 2017. Chlamydial infections in women may result in cervicitis, salpingitis, pelvic inflammatory disease, causing infertility or life-threatening ectopic pregnancy. In spite of efforts, no effective vaccine against *Chlamydia* has been licensed for use to date. Chlamydial infections are acquired mucosally. Thus, an effective vaccine that induces mucosal and systemic immunity would be ideal. However, the female reproductive tract (FRT) mucosa is a poor site for immunization. Using the murine model of infection with *C. muridarum* we show that per-oral (PO) immunization with chlamydial major outer membrane protein (MOMP) supported within a telodendrimer nanolipoprotein particle (MOMP-tNLP) induces mucosal and systemic humoral immune response. Moreover, PO immunization significantly lowers *Chlamydia* burden the uteri, ovaries and oviducts, reduces hydrosalpinx pathology, and enhances *Chlamydia* clearance from the FRT. We propose that following their priming in the gut-associated lymphoid tissue, B cells are subsequently recruited to the FRT where they serve as a source of *Chlamydia*-neutralizing secreted antibodies. Therefore, PO rather than per-vaginal immunization is more effective for inducing protection against genital *Chlamydia* challenge. These findings will add to our understanding of mucosal immunology and the role of the gut in regulating immunity in the FRT. Ultimately, this work will be important for developing PO vaccines against *Chlamydia* and other sexually transmitted pathogens.

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