

Scientific challenges and opportunities in developing novel vaccines for the emerging and developing markets

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Sonali Kochhar

Clinical Research & Drug Development Specialist; PATH; New Delhi, Delhi India

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Vaccines have had a major role in enhancing the quality of life and increasing life expectancy. Despite these successes and the development of new vaccine technologies, there remain multiple infectious diseases including AIDS, malaria and tuberculosis that require effective prophylactic vaccines. New and traditional technologies have a role in the development and delivery of the new vaccine candidates. The scientific challenges, opportunities and funding models for developing vaccines for low resource settings are highlighted here.

Introduction

The 13th World Vaccines Congress was held in Lyon, France on October 16th-18th 2012. In the session on New Technologies in Emerging Markets, the scientific challenges and opportunities in developing novel vaccines for the emerging and developing markets was discussed by Dr. Danilo Casimiro, Director Vaccines Discovery, Merck Research Laboratories, USA.

New Vaccine Targets

There are numerous new vaccine targets which exist in different patient populations. These include:

- **Pediatric** – Group A streptococcal meningitis (ACYW,B), pediatric combinations, respiratory syncytial virus and parainfluenza virus (RSV/PIV), enterovirus 71 (EV71).
- **Adolescent** – Chlamydia trachomatis, cytomegalovirus, herpes simplex virus (HSV), epstein-barr virus (EBV).
- **Adults** – Pneumococcus, cancer, improved influenza, alzheimer's disease, anti-cholesterol, Staphylococcus Aureus.
- **Elderly/others populations** – Bacterial diarrheas, universal influenza, clostridium difficile, chikungunya, HIV, tuberculosis, malaria.

These potential vaccines are against pathogens which cause significant clinical risk but are difficult targets for vaccine development (e.g., HIV, malaria, TB, RSV, HSV, group A Streptococcus).¹⁻³

Emerging Trends and Challenges in Vaccine Research and Development

These include:

- **Challenging vaccine targets and patient populations** – There are numerous emerging/re-emerging infectious diseases and a globally aging population (the percentage of the global population greater than 60 y is anticipated to be greater than 25% by 2030 as per a recent WHO ad hoc consultation on Aging and Immunization).
- **Expanding global business and diversified business models** – There is expanded access and delivery of vaccines, new pharmaceutical companies are entering the vaccine field, there is completion from emerging world vaccine manufacturers and developers which drive down the prices of vaccines and Public Private Partnerships are now involved in vaccine development [e.g., Product Development Partnerships (PDPs) e.g., PATH], with funding by the Gates Foundation.

Enabling Technologies and R&D Models for Vaccine Development

Examples of these include:

- **Protein expression systems** – An increasing number of cell substrates are becoming available for heterologous protein expression for human vaccine development which would lead of a decreased cost.⁴
- **Novel technology** – Examples include *Pichia* strains engineered to express selected human glycosylation molecules (Merck-GlycoFi), plant production of vaccines (Medicago, Fraunhofer have developed a tobacco plant based H5N1 flu vaccine), glyco-engineered *E. coli* (GlycoVaxyn is a biopharmaceutical company

Correspondence to: Sonali Kochhar; Email: skochhar@path.org
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utilizing its proprietary recombinant DNA technology to develop and manufacture the next-generation of bioconjugate vaccines).

- **Adjuvants** – These are helpful to increase the response rates and magnitude of the immune responses, simplify the immunization regimen, improve the vaccine response in immunologically impaired populations, improve the durability of the protective efficacy of vaccines, modify immune responses and enhance the quality of functional antibodies.⁵ Many novel adjuvants target Toll-like receptors (TLRs)⁶ [e.g., GSK Adjuvant System (AS)] but some have less defined mechanisms of action e.g., Saponins, Complete Freund's Adjuvant (CFA01).

However, current US trends in the licensure of new products containing novel adjuvants indicate continuing challenges to vaccine developers.

- **Vaccine presentation/delivery** – There are numerous innovative Vaccine Delivery devices. Some examples include- Needle free devices (including those developed by Bioject), Microneedle devices (e.g developed by Nanopass⁸), Patches (e.g developed by Vaxxas and IOMAI) and Intradermal injections (used for the Influenza vaccine by Sanofi Pasteur).⁷

- **Partnership models in infectious diseases** – There is funding available for vaccine development from: (1) Private Foundations and PDP (Product Development Partnerships) for diseases of Global Health, Neglected Diseases, Other Diseases of Poverty and Eradication Programs (e.g., Polio).⁸ Examples include the Bill and Melinda Gates Foundation, Wellcome Trust, PDPs (PATH, Aeras, Dengue Vaccine Initiative, etc), European Union [Framework Programme (FP), European Vaccine Initiative (EVI) and Tuberculosis Vaccine Initiative (TBVI)]; and (2) US Federal Funding is available for Translational Medicine, Vaccine Clinical Trials (Vaccine Trial Units), New Vaccine Technologies, Emerging Infectious Diseases, Bioterrorism and Infectious Diseases relevant to the military deployment. This is from the National Institute of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID), Defense Advanced Research Projects Agency (DARPA) and the Biomedical Advanced R&D Authority.

Novel Vaccine Programs

Examples of novel vaccine programs include those for mosquito-borne human viral diseases, diseases of poverty e.g., HIV and Malaria and Public-Private Partnerships in Vaccine R&D.

Mosquito-Borne Human Viral Diseases

Examples of Mosquito-Borne Human Viral Diseases include

- **Flaviviruses:** e.g., Dengue, Yellow Fever, Japanese Encephalitis, West Nile virus.
- **Alphaviruses:** e.g., Chikungunya, Ross River fever virus, Venezuelan Equine Encephalitis virus, Eastern Equine Encephalitis virus, Western Equine Encephalitis virus.

The Dengue and Chikungunya vaccine development are discussed below.

Dengue Vaccine

Dengue is a highly endemic disease transmitted by the *Aedes aegypti* mosquito. An approximately 2.5 billion population is at risk and it leads to approx. 50 million cases and 15,000 deaths per year throughout the tropics and subtropics. It is caused by any one of 4 related viruses which are transmitted by mosquitoes.^{9,10} There are no preventative vaccines or antiviral therapies that are currently available.

The Dengue vaccines under development include those from

- **Sanofi Pasteur** (ChimeriVax) in Phase III development. It is a live attenuated chimeric virus based on Yellow Fever (YF17D) backbone. Its strengths include decades of experience, established infrastructure to support Phase III trials and demonstrated safety and immunogenicity in Phase II trials. Its weaknesses include recent lack of efficacy against DEN 2 in a Phase II trial in Thailand and the dosing schedule of 3 doses at 6 mo interval required for tetravalent immunity is not ideal for endemic regions or travelers.

- **NIH Partners:** Butantan, Biological E in Phase 1 development. This is tetravalent live attenuated viruses with molecularly defined mutations including deletions in 3'UTR and chimeras using the DEN4 backbone. Extensive preclinical and clinical testing of each vaccine virus has been done to identify the best candidates and there is a strong partnership with Johns Hopkins for clinical studies. The weakness includes the same basic approach as ChimeriVax and the NIH partnering strategy which is non-exclusive with various partners.

- **Inviragen** in Phase I development. These are tetravalent live attenuated viruses, which are chimeras using the DEN2 PDK53 backbone. It is supported by NIH/CDC and access to endemic areas will be via Duke/NUS. The weakness is that this is the same approach as ChimeriVax.

- **Merck /HBI** in Phase I development. This is a tetravalent recombinant env subunit vaccine. There is a native antigen, shorter dosing schedule compared with live attenuated vaccines, no prM protein hence a lower risk of enhancement by anti-prM antibodies and a safety profile which is well suited to travelers. The weakness is the potential need for a novel adjuvant.

- **GSK, WRAIR and FioCruz (Brazil)** in preclinical development. This is a purified inactivated virus (PIV) adjuvanted with the GSK adjuvant systems. There is no viral interference, a shorter dosing schedule compared with live attenuated vaccines and a safety profile well suited to travelers. The weakness is the need for a novel adjuvant, low yields/high cost of goods and the formalin inactivation of the virus will destroy epitopes, which could result in increased risk of Dengue Hemorrhagic Fever.

Recombinant Subunit Dengue Vaccines

Recombinant subunit dengue vaccines (e.g., the Merck/HBI vaccine),¹¹ have the advantages of:

- Shorter dosing schedule compared with live attenuated virus vaccines. They could be easily integrated into the existing vaccination schedules.
- Non-replicating vaccine, hence the safety profile would allow administration to infants, elderly, pregnant women and immunocompromised subjects.

- The balance of immunogenicity of the four vaccine components is more easily adjusted and there is the relative ease of changing components of the multivalent vaccine compared with the live virus approaches.
- There is no prM (the DEN-2 PDK-53 structural gene) present in the vaccine formulation. This could possibly reduce the risk of adverse events associated with anti-prM antibodies.¹²

Merck's Dengue Vaccine

This is against Dengue 1, 2, 3 and 4. The antigen is the Envelope (E) proteins of Dengue 1, 2, 3, and 4 produced in *Drosophila* S2 cells. The adjuvant used is Saponin (Iscomatrix). The vaccine is in Phase I trials and the protection is mediated by neutralizing antibodies to all 4 types.

Merck's HIV Vaccine

Merck has a long history of developing antivirals and vaccines against HIV-1. The recombinant Adeno 5 (rAd5) competent HIV-1 vaccine (1999–2007) showed lack of efficacy in the Phase IIb STEP trial. There are multiple vector approaches in pre-clinical and clinical stages. These include:

- HIV Env gp41 fusion intermediate mimetics with highly conserved sequences. This has the potential for broad neutralizing activity and inhibition of dendritic cell mediated HIV-1 trans-infection in the acute phase.¹³
- Production of HIV Env proteins using Merck's glycoengineered *Pichia* strains.

Merck's Malaria Vaccine Program

This program (2010-present) is a collaboration between Malaria Vaccine Initiative (MVI) (the funding partner, responsible for project oversight and management), the NYU Langone Medical Centre (responsible for in vivo studies and biological assays) and Merck (responsible for antigen design, antigen production and carrier conjugation and formulation).

The circumsporozoite protein (CSP) has been recognized as a potential target in the development of vaccines focused on the

earlier stages of malaria infection. This approach targets a region of CSP important to a critical function of the protein. By blocking this function, it is hoped that invasion of the parasite into the liver, an essential step in causing malaria, can be prevented. CSP has already been shown to have protective efficacy in the field, in RTS,S, the most advanced malaria vaccine candidate.¹⁴

MSD-Wellcome Trust Hilleman Laboratories

This leverages on the basic research innovations in academia, government, non-governmental organizations and the industry. It builds on Merck's experience in vaccine bioprocess, formulation and analytics and Wellcome's experience in biomedical research for global health. It provides a flexible approach to the management of late development, manufacturing and marketing/sales.

The lab is expected to establish linkages among discovery, development and delivery experts. Merck and external scientists would work on the target leads, they would be transitioned to the Hilleman Labs for early development (lead – Phase I) and to multi-national Pharmaceutical manufacturers and low cost manufacturers for late stage development (Phase II – Filing), large scale manufacturing, marketing and distribution.

Conclusion

Vaccines have had and continue to have a huge positive impact on human health and economic development, but there are still many unmet public health threats posed by infectious diseases. Both new and traditional technologies have roles for developing new vaccine candidates and there are numerous vaccines in research and development that utilize these approaches. Recent models for partnerships in the fight against global diseases like HIV, TB, Malaria and Dengue not only provide sustained engagement of private and public sectors but also enable the development and delivery of innovative approaches in vaccine R&D.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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