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Shaping immunity against infectious diseases with multivalent DNA vaccines

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Abstract

Immunization has dramatically transformed human and animal health. Since its earliest days, vaccination has served as a fundamental strategy for infectious disease prevention, providing population-level coverage for childhood diseases and seasonal infections, and serving as a rapid response to pandemic pathogens. Yet, there is continued circulation of endemic, emerging, and reemerging pathogens for which there are no licensed prophylactic measures. The successes of nucleic acid technologies during the COVID-19 pandemic, exemplified in the first two licensed mRNA vaccines [1] and the first DNA vaccine receiving emergency use authorization for human use [2], are reinvigorating vaccine development to tackle this urgent unmet need.

The inherent stability of DNA offers advantageous features such as thermostability and extended shelf life. These characteristics are pivotal for transport and storage in resource-constrained environments, like low and middle-income countries. Furthermore, the ability to encode large transgenes and well-established modular assembly pipelines are key attributes of DNA-based platforms. This versatility extends to combination strategies of individual DNA vaccines as a multivalent drug product. Multivalent synthetic DNA vaccines are therefore emerging as part of the exciting nucleic acid-based vaccine landscape as a strategy to induce robust and durable immunity in diverse global populations.

MULTIVALENT VACCINES & CHALLENGES

Many of the most successful vaccines are multivalent, including the MMR, DTaP/Tdap, seasonal influenza, pneumococcal conjugate, HPV, and several recommended vaccines, including COVID-19 vaccines and recently licensed respiratory syncytial virus vaccines [3]. Such vaccines provide single formulation coverage against multiple serotypes, strains, and, in some cases, related and unrelated pathogens. Co-administration of multivalent vaccines and combination vaccines can reduce the number of total vaccines and overall injections, improving the likelihood of uptake [4,5].

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However, along with the many traditional vaccine development challenges, multivalent vaccines face additional barriers, including achieving desired broad protective immunity at the preclinical and early Phase 1 clinical research stages and demonstrating sufficient non-inferiority data to support licensure [6,7]. Particular care must be taken to minimize interference between vaccine components, including competing immunodominance profiles that would result in a significant reduction in effectiveness compared to the individual licensed products.

From both efficacy and immunology perspectives, the strengths of multivalent vaccines lie in targeting complex pathogens, where single-antigen targeting may not provide sufficient protection. Multivalent vaccines can induce broadly protective immunity and mitigate the rapid evolution that leads to pathogen escape. Here, synthetic DNA vaccines have the potential to rise to the many challenges faced by multivalent vaccine development.

MULTIVALENT DNA VACCINES: A STRATEGY FOR INDUCING BROAD PROTECTIVE IMMUNITY

Synthetic multivalent DNA vaccines are rapidly progressing through preclinical studies, and early to late-stage clinical trials as both preventative and therapeutic vaccines targeting infectious diseases including HPV, HIV-1, chikungunya, dengue, influenza, Ebola, SARS-CoV-2, hantaan/puumala virus, cytomegalovirus and others [8–10]. Synthetic DNA vaccines, typically given via intradermal or intramuscular injection, historically struggled with poor immunogenicity in humans due to challenges with DNA delivery into the cell nucleus. Recent advancements in delivery methods like needle-free jet injection and electroporation have improved nuclear delivery. These methods, paired with synthetic gene design enhancements such as codon optimization for better mammalian cell expression, RNA structure analysis, and structural engineering, have resulted in improved *in vivo* DNA expression and enhanced immune responses (reviewed in [8,11]). Synthetic DNA vaccines stimulate both humoral and cellular immunity. Combining them with gene-encoded adjuvants broadens antibody responses, activates $CD4^+$ and $CD8^+$ T cell subsets, and establishes memory immune responses.

Synthetic DNA vaccine platforms continue to develop as strategies to respond to emerging and re-emerging human pathogens, zoonoses, and potential pandemic diseases. They offer flexibility in engineering, allowing single DNA vaccines to express multiple antigens, and combine multiple DNAs into one formulation. It is possible to incorporate multiple surface proteins to induce antibody responses and internal proteins to shape cellular immunity, offering potential approaches to address pathogen escape and redundancy mechanisms using rational design approaches. Synthetic DNA candidates can be designed to dissect immunological mechanisms related to individual vaccine components, including titration of vaccine antigens and to study induction of broad immunity against similar and divergent pathogens.

FUTURE PROSPECTS FOR MULTIVALENT DNA VACCINES

The future of vaccine development hinges on cross-disciplinary science. As metrics for vaccine-associated protection against infectious diseases evolve, fostering collaborative research among teams with diverse biological, manufacturing, and clinical expertise is essential to advancing DNA vaccines and other platforms. Rather than solely pursuing sterilizing immunity, vaccine development should encompass a range of infection control strategies, including reducing pathogenesis, limiting transmission, and aiming to prevent hospitalization while minimizing morbidity and mortality.

The landscape of synthetic DNA vaccines is evolving. Different synthetic DNA forms including antibiotic-free plasmid systems, minicircles, and closed linear DNA forms continue to advance, and there is renewed excitement about rapid amplification technologies. Although cGMP plasmid DNA manufacturing pipelines are established, additional process development and regulatory pathways are necessary for clinical evaluation of different DNA forms. Improvements in formulation and delivery have the potential to further enhance DNA vaccine immunogenicity. Innovative approaches like highly engineered synthetic DNA nanomedicines, epitope strings, and gene-encoded adjuvants show promise, particularly for expansion of germinal centers, focusing of cytotoxic $CD8^+$ T cell responses, and establishment of durable memory. Further research to understand correlates of protection associated with DNA vaccines and multivalent combinations will be important.

In addition to their utility for global vaccines, multivalent DNA vaccines have the potential to be expanded as personalized medicine strategies against chronic infections and for control of antimicrobial resistant pathogens in diseases like cystic fibrosis. Similar strategies are being evaluated preclinically and in human trials as cancer immunotherapy (reviewed in [12]). Furthermore, while DNA vaccines have previously been approved for use in animals, multivalent combinations have potential to further reduce cost and improve broad protective immunity. In conclusion, multivalent DNA vaccine development holds tremendous promise to expand vaccine effectiveness and delivery and to complement One Health strategies.

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Biography

AMI PATEL is an Assistant Professor in The Wistar Institute Vaccine & Immunotherapy Center in Philadelphia, Pennsylvania, USA. She holds a BSc in Microbiology and

Immunology from McGill University, an MSc in Medical Microbiology from the London School of Hygiene & Tropical Medicine, and a PhD in Medical Microbiology from the University of Manitoba. She received postdoctoral training at the San Raffaele Telethon Institute for Gene Therapy, Milan, Italy, the University of Pennsylvania, and The Wistar Institute. Patel is developing gene-encoded biologics, specifically non-viral DNA vectors, for vaccine and immunotherapy against emerging infectious diseases, with the goal of understanding cellular and immune mechanisms that contribute to protection versus pathogenesis. Patel's most recent studies include DNA vaccine development against ebolavirus, MERS-CoV, SARS-CoV-2, and DNA-encoded antibodies against multiple viral and bacterial pathogens. Her scientific advances in these areas include: 1) short and long-term study of DNA vaccine candidates in mice and macaques; and 2) sequence engineering and *in vivo* delivery developments to the rapidly advancing field of nucleic acid gene-encoded antibodies, specifically DNA-encoded antibodies.

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