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VIRAL VECTORS, VACCINES – A NEW ERA OF COLLABORATIVE DESIGN

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As healthcare professionals begin to administer COVID-19 vaccinations across the globe, the conversation about vector-based treatments has expanded. Viral vectors are relatively new to the industry and even newer to the market, having only been developed 20 years ago, but their value has become more apparent as pharmaceutical technologies and capabilities have evolved.

Viral vectors contain a safe virus carrier that transports extraneous gene information into the vaccinated organism, causing immunological reactions or enabling integration of desired genes into the cells for therapeutic purposes.

In addition to prophylactic vaccines for disease prevention, viral vectors can also be used for gene therapy treatments. Here, specific genes are introduced into cells for expression of specific therapeutic proteins. However, the diversity of viral vectors, along with their newness, means many drug manufacturers still do not have the means to scale up their production.

More often than with most traditional biologics, companies must turn to CDMOs to bring vector-based products to market. So, it is important that they know how to assess a CDMO's capabilities for helping them achieve their goals. It is just as important that CDMOs know how to learn from their clients.

EQUIPMENT, EXPERTISE, AND EXPENSE: THE SPECIAL NEEDS OF VIRAL VECTOR PRODUCTS

Developers face many hurdles in taking a vector-based treatment from lab to market, but access to the necessary facilities and equipment is perhaps among the highest. Companies seeking to produce vector-based therapies require access to cell lines, cell characterization and analysis resources, cell propagation in cell factories (large, plastic single-use systems with up to 25,000 cm^2 of surface area each), and fermenting systems, which may contain thousands of liters of cell suspension medium or cells prone on a carrier surface. Companies scaling up viral vectors need expertise about how systems and equipment affect the product, so they know how best to set up systems for optimal yields and potency as well as safety.

The standard equipment for producing vaccines when vectors first emerged 20 years ago was stainless steel, which does not provide the flexibility necessary for scaling up vector-based products. So, most of the equipment is specially designed for these purposes, and therefore it is much more expensive. Single-use technology (SUT) affords greater flexibility in general but also often fails to meet the scale and standards for producing viral vectors. The SUT equipment that does work for vectors is expensive. Such SUT equipment also must be fully characterized, which not only increases costs but can create dependency on specific types of SUT equipment, and problems if it suddenly becomes unavailable. Changing it could result in different behavior within the product or the storage vials, affecting purity, potency, and/or safety. Unexpected changes may cause supply shortages for the product and require additional comparability studies.

When characterizing cell lines, developers must ensure that they contain no indigenous or adventitious viruses, no tumorigenicity, and no potential to cause harm in patients. They also require access to all historical information about the viral vector as a starting material. Vectors must be functional and carry no microbiological or viral contamination and be tested for genetic stability. The manufacturing equipment must be capable of reliable, reproducible performance at a high degree of accuracy.

Viruses and vectors require specialized fermentation processes. Fermentation and purification steps also tend to adversely affect virus propagation, often lowering yields and raising costs. Specific equipment is required for purification and concentration of the viruses up to the rigorous regulatory and industry standards. Viruses, as a complex of proteins, carbohydrates, and lipids, often require stabilization and maintenance in their stable form, usually through freeze-drying or liquid frozen storage. Such processes require aseptic conditions. If possible, sterile filtration before filling may be used. Even the final manufacturing processes – visual inspection, labelling, and packaging – can be demanding if the viral vectors are not stable at ambient temperatures and exposure to light.

UNDERSTANDING VIRAL VECTORS IS VITAL TO MODERN PROGRESS

While the speed of COVID-19 vaccines' emergence seems remarkable, it is on par with the standard rate of development; the science behind the vaccines now on the market began about 10 years ago. It is not that researchers lacked knowledge about viruses like SARS-CoV-2 (COVID-19) then, but new tools like next-generation sequencing of viral genomes and bioinformatics provide insights into function and structure of emerging viruses within days after their detection. New technologies like artificial gene synthesis, construction of viral vectors, and mRNA technologies accelerated development of these vaccines.

In traditional vaccines, the viruses are attenuated or inactivated and then injected to create a desired immune response. However, these vaccine strains often contain, on their surface or in their genome, proteins and genome sequencers that can suppress or modify the immune response in an undesirable direction.

Viral vectors, on the other hand, are now well-known to be safe in humans. They are usually deleted to limit replication in human cells and to shut down immunosuppressive viral genes.

Viral backbones like Modified Vaccinia Virus Ankara or certain human adenoviruses enter human cells, initiate replication of their genome, and express the introduced target protein. The replication of the vector is interrupted due to missing viral gene elements. Some viral vector pro teins are generated and act as immune-stimulating agents. Such interactions induce and enhance immunological responses to the desired protein.

Viral vectors also provide more options for eliciting a specific reaction. For example, one vector might cause the immune system to produce more neutralizing antibodies, whereas a different vector could boost cellular defense mechanisms like cytotoxic T cells that will recognize and destroy virus-infected cells.

Conversely, viral vectors may also be designed for transfer of specific genes into cells to complement missing genes for gene therapy. In such cases, vectors with low immunogenicity, like adeno associated viruses, are used. They should assure that the complementary genes produce missing proteins for reconstitution of the normal cell metabolism.

Current knowledge of viral vector applications emerged from setbacks as much as successes. These lessons are also a result of IDT Biologika's collaboration with partners and customers around the world. IDT Biologika has worked since 1997 to help numerous companies and academic institutions develop vector-based products for diseases such as smallpox and Ebola – which are now licensed and being used successfully in West Africa.

These successes, though, also came from lessons learned through unsuccessful efforts. In 2001, for example, IDT partnered with a university to create a malaria vaccine. Despite years of clinical development, testing – both of vectors and protein components – and trials, there is still no product on the market for malaria treatment. However, the concepts that emerged are among the most reliable yet and have influenced the design of productive treatments for other diseases.

Partnerships invite and sometimes even force new ideas to emerge in short order, propelling a struggling product to success or bringing certain diseases into a new light. For example, an immunologist may have a comprehensive understanding of tumor-induced diseases and autoimmune responses, but if collaboration is not prioritized, they might not discover the link between their work and the infectious disease space. Viral vectors could hold the key to treating diseases like tuberculosis, which is less common today but could re-emerge should the bacteria become more resistant to available antibiotics.

GOOD PARTNERSHIPS EMPHASIZE LEARNING AND MUTUAL IMPROVEMENT

Since viral vectors first entered the industry, IDT Biologika has been making room for the science and companies who want to explore it with us. Handling live organisms is a considerable challenge, and viruses especially, as they are notorious for their ability to adapt to their environments. For two decades, IDT has learned from our collaborations with corporate and university partners how to design and improve the specialized spaces and systems necessary to manufacture and scale up these products.

These spaces work for us as well as our clients. IDT is now in the process of developing a vector-based COVID-19 vaccine, using a vector that has been proven safe in humans for nearly 20 years, with low reactogenicity in children, cancer patients, or immunosuppressed patients. This model also is likely to reduce many of the side effects that are common with current vaccines and may lengthen the periods of primary immunity and vaccine-induced immunity.

Because of the steps we have taken within our company and with our partners, we have been able to expand our capability and capacity for developing and scaling up vector-based therapies with great success. IDT can help clients bring viral vectors in vials all the way to fully developed and approved pharmaceutical products. As we have pursued new projects and new avenues of discovery, we have designed and integrated analytical processes and testing that meet both cGMP and U.S. and EU Pharmacopoeia standards.

Our teams also can provide guidance and support for process characterization. For instance, we can sequence a microorganism within days and obtain complete information about the sequence, such as how much a virus changes the genome when grown in suboptimal conditions, or whether it loses the genes of interest. Another challenge companies may face, especially as production of COVID vaccines accelerates, is the availability of raw starting materials. IDT has the resources to produce most raw and starting materials on-site, eliminating much of the reliance on third-party suppliers, except for items like salts and amino acids.

IDT has been expanding its facilities for more than two decades, to meet our own needs as well as the production needs of our clients. This expansion includes a new site in Rockville, Maryland, USA, as well as new drug substance manufacturing and fill-finish lines at our Germany site. Our new, high-speed fill-finish vial line is specially designed for viral vector-based vaccines and gene therapy products. This line allows for sterile aseptic filling on one side of the line and separation of operators from the live agent on the other and provides finished products in vials.

CONCLUSION

Viral vectors have a name in the industry now more than ever, and their potential applications are still largely unexplored. While complex and often difficult to manage, these products can be developed and produced successfully to the great benefit of patients across the globe. Specialized equipment, materials, capabilities, and expertise are necessary, and it helps to have a partner that provides all of these as we continue to pursue new horizons in this space. What is even more critical to success, however, is a spirit of collaboration and a willingness for developers, manufacturers, researchers, and CDMOs to learn together and build upon their shared experience to advance this exciting science.

ABOUT THE AUTHOR

Dr. Andreas Neubert has more than 30 years of experience in vaccine development and manufacturing. He worked for more than 15 years on R&D projects for different viral vaccines. He received extensive training on Vaccine Manufacturing, Gene Technology, and Current Good Manufacturing Practice for Biological and Biotechnology derived Pharmaceutical Products. He is the Chief Science Officer of IDT Biologika and has an excellent knowledge in modern vaccines technologies, quality control, and analytical characterization of vaccines according to European and FDA cGMP regulations. He is an appointed guest lecturer at University Halle/Saale for GMP in Pharmaceutical Biotechnology and lecturer for several national and international training courses in GMP and vaccinology. He is a member of the national Society for Virology and the Parental Drug Association. He is the author or co-author of over 20 scientific publications and meeting abstracts.

ABOUT THE COMPANY

IDT Biologika is an international leader in contract development and manufacture of vaccines, viral vectors, and biologics. IDT Biologika is a full-service CDMO providing end-to-end services for viral vaccines and viral vectors and have supported clients in developing and manufacturing some of the leading human vaccines in use today against infectious diseases and viruses around the world, including COVID vaccines.
IDT Biologika offers biologics development and manufacturing to support clinical to commercial scale drug substance and drug product manufacturing capabilities in Europe (Germany) and North America (Rockville, Maryland). These locations support our fully integrated services and are cGMP and up to BLS2-compliant, with approvals from the FDA, EMA, and ANVISA.