Delivering the next generation of breakthrough genomic medicines

DANAHER

During the pandemic, several of Danaher Corporation's global science and technology companies pivoted to help scientists and drug developers analyse the SARS-CoV-2 virus and support the generation of new vaccines to combat COVID-19. Achievements include significant contributions to the research and development (R&D) of clinical diagnostics methods and tools for COVID-19, and support for the commercial development of the University of Oxford–AstraZeneca and Moderna vaccines. These accomplishments were founded on early investment and innovation in the genomic medicines space, aimed at providing genomic medicine developers the dedicated tools, services and expertise they need, at every scale and every stage, from the academic bench through to the industrial manufacturing facility and, finally, to the clinic (**Fig. 1**).

The past five years have witnessed United States Food and Drug Administration approval and commercial launch of 20 drug products in the genomic medicine space, including 6 viral vector gene modified cell therapies for cancer, 2 adeno-associated viral (AAV) vector therapies for rare genetic diseases, 3 small interfering RNA (siRNA) therapies, 4 antisense oligonucleotide (ASO) therapies, 3 adenovirus (Ad) vector-based vaccines, and 2 messenger RNA (mRNA) vaccines for COVID-19[1]. These drug approvals were enabled, in part, by decades of scientific and technological advancements in delivery platforms. These include the refinement of Ad vectors to improve their safety profile, the discovery of new AAV serotypes, the evolution of lipid nanoparticle (LNP) engineering, the discovery of CRISPR–Cas9, and the suite of chemical modifications for oligonucleotides that improve their resistance to nuclease degradation and safety in vivo.

Despite these advancements, the current toolbox of delivery technologies has major limitations. To deliver the next generation of breakthrough genomic medicines, the field will have to double down on cross-disciplinary R&D efforts focused on the development of new delivery technologies, hence this short feature will focus exclusively on delivery.

LIPID NANOPARTICLE DELIVERY: RIPE FOR INNOVATION

All of the approved mRNA vaccines for COVID-19 and one of the siRNA-based therapies use LNPs to deliver their cargo to the cells of interest. The successful mRNA vaccine efforts have spurred a new generation of innovation beyond infectious disease. For example, preliminary results from an ongoing trial have shown that a CRISPR–Cas9-based mRNA drug can be delivered into the body using LNPs to target the liver and reduce expression of the gene that causes transthyretin amyloidosis (ATTR)[2].

Despite these successes, LNP-enabled RNA medicine is a field ripe for innovation. For instance, the formulation of RNA payloads into LNPs is critical for efficacy because charged nucleic acids are unlikely to spontaneously cross the lipid bilayer of cell membranes into the cytoplasm where they are biologically active[3]. Currently, there are multiple methods for assembling LNPs that encapsulate nucleic acids. However, the resulting LNP drug products can vary in potency depending on the method used. And not all of these methods are scalable.

There is substantial opportunity for innovations to bridge the gap between manufacturing large volumes of a vaccine product and the smaller scale multi-product manufacturing better suited for cancer, rare disease and engineered cell therapy applications. With regards to drug targeting, LNP delivery into specific cell and tissue populations remains a challenge. Pre-clinical proof-of-concept studies suggest that there are novel LNP formulations that can go beyond liver and intramuscular applications. Yet, there remains a major need for clinical translation of these novel LNP formulations.

ADENO-ASSOCIATED VIRAL VECTORS: OPPORTUNITIES AND CHALLENGES

AAV-based therapies, by contrast, have shown the potential for serotype-dependent tissue specificity. To date, hundreds of AAV serotypes have been isolated from nature or synthetically designed in the lab, each with a unique physical capsid structure and biological attributes. AAV6, for example, is known to target skeletal muscle, AAV8 is a workhorse for liver-based applications, and AAV9 has been shown to cross the blood–brain barrier and enable delivery of a therapeutic payload to the central nervous system (CNS). Coupled with capsid engineering, transgene optimization and synthetic cell-specific promoter designs, AAVs can serve as an effective chassis for enabling the next generation of targeted tissue delivery[4].

Unlike LNPs, AAVs have encountered challenges in manufacturing scaleup and analytical characterization limiting their use to rare and orphan genetic diseases. Much of these challenges are a function of the physical complexity of an AAV virion and the cell line-based manufacturing systems. An aspirin molecule is composed of 21 atoms. A standard monoclonal-based biologic medicine is composed of 25,000 atoms. By contrast, a standard AAV drug product is composed of millions of atoms and is a heterogenous mixture of full and empty capsids. For a personalized viral vector gene modified cell therapy, like chimeric antigen receptor (CAR)-T cell therapy, the complexity increases by orders of magnitude. There is a significant need for new drug manufacturing and analytical workflows that enable the scaleup and characterization of AAV and viral vector-based therapies for clinical and commercial applications.

Challenges such as the elimination of host cell proteins and other potential contaminants, including adventitious viruses,

from the final drug product can be addressed using both traditional solutions applied in new ways, such as filters upstream in the production process, and novel technological approaches such as microflow liquid chromatography with tandem mass spectrometry (LC-MS/MS). In parallel, there is a need for fully integrated data capture, data mining, and informatics tools that can mine the full complexity of these manufacturing workflows and enable continuous process improvements. This could include the incorporation of in-line analytics based on new methods such as capillary isoelectric focusing (cIEF) for precisely determining the ratio of empty, full and partially filled AAV capsids, to quickly and accurately inform decisions and enable prompt and effective resolution.

NEXT-GENERATION DRUG DELIVERY

In the past few months, clinical holds and patient deaths in the AAV viral vector gene therapy space have shown the limitations of the current generation of delivery technologies. On a positive note, recent months have also witnessed significant pre-clinical activity and innovations in delivery approaches. For example, several recent reports have described the development and application of engineered DNA-free virus-like particles (eVLPs) that efficiently package and deliver base editor or Cas9 ribonucleoproteins within the context of in vivo gene editing applications[5]. Likewise, there have been significant innovations in the development of novel chemical, physical, polymer, peptide, exosome and protein-based delivery modalities[6].

The COVID-19 pandemic has highlighted the power of genomic medicine, wherein scientists were able to go from sequencing the genetic code of SARS-CoV-2 to a
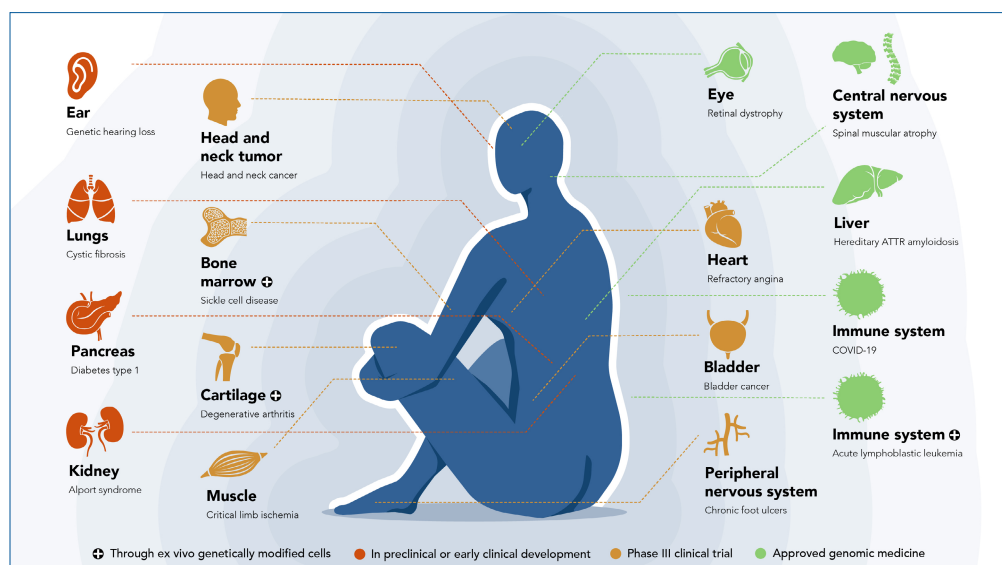

Figure 1. Unlocking the full potential of the genome. Genomic medicines are being developed to treat disease at several organ, tissue and cell targets.

functional vaccine with over 90% efficacy in less than a year. The rapid pace of development was enabled, in part, by decades of basic and translational research focused on developing and optimizing LNP technologies.

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To unleash the next generation of breakthrough medicines, we will need to improve upon the current generation of delivery technologies while simultaneously adding new tools to the delivery armamentarium. These types of efforts are going to require focused and dedicated cross-disciplinary initiatives that harness the best of chemistry, engineering, biology, computational informatics,

manufacturing, regulatory and drug development expertise.

With a view to supporting these initiatives, we at Danaher and our family of life science companies have expanded our commitment to the genomic medicine space by bringing on board new leaders who share a wealth of expertise and extensive experience in gene therapy, cell therapy and molecular oncology among other disciplines. In parallel, Danaher continues to invest in new innovations and partner with like-minded organizations in academia, government, the non-profit sector and industry to help advance the field. These are just a few of the ways that Danaher is contributing towards supporting the discovery and development of new genomic medicines for the patients who need them. Being part of the genomic medicine community enables us to deliver on our shared purpose of helping realize life's potential.

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The following companies are all life sciences companies of Danaher Corporation: DH Life Sciences, LLC, Precision NanoSystems, Inc; Pall Corporation; Aldevron; and Integrated DNA Technologies (IDT).