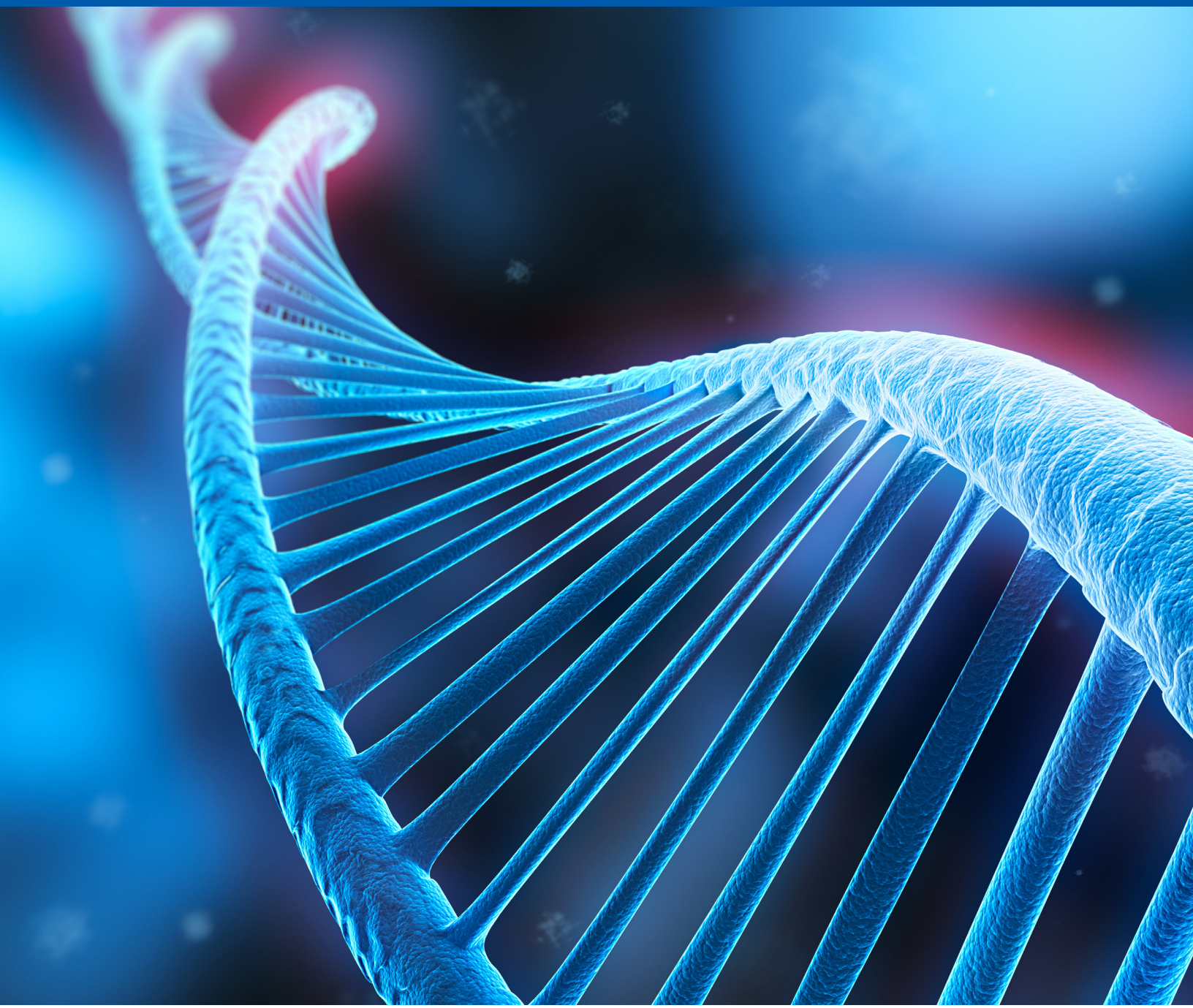
Cracking the code: Transformative role of pDNA in Advanced Modalities



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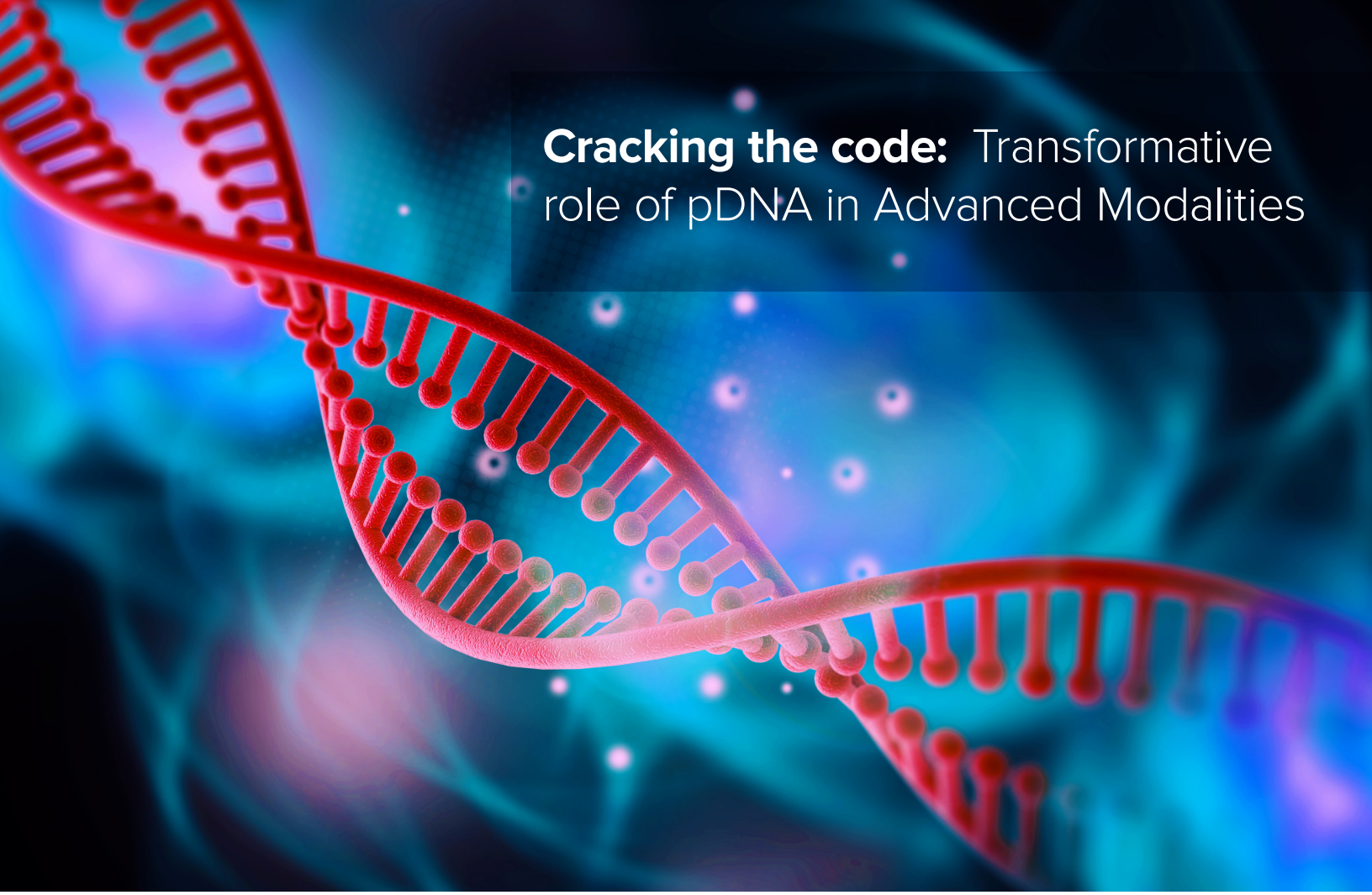


Cracking the code: Transformative role of pDNA in Advanced Modalities

CONTENTS:

Introduction

Pharmaceutical companies of all sizes have prioritized biologics development for their potential to deliver more precise, and effective treatments. Annual sales for new modalities (excluding messenger RNA products) have reached $20 billion in the last few years[1] alone. Since 2017, the FDA has already approved 27 cell and gene therapy products, with many more on the horizon.[2]

Cell therapies and gene-engineered cell therapies are fundamentally “living drugs” that can heal and replace damaged tissues or diseased organs.

Gene therapy is a technique that modifies a person’s genes to treat or cure disease. Gene therapies use several mechanisms to modify genes. These include the following:

- Replacing a disease-causing gene with a healthy copy of the gene
- Inactivating a disease-causing gene that is not functioning properly
- Introducing a new or modified gene into the body to help treat a disease.

These have the potential to provide curative therapies to a range of diseases that currently have no cure. This includes blood disorders, cancer, auto immune diseases, and metabolic disorders.[3]

What is pDNA?

Plasmids, also called pDNA, are circular molecules of DNA found naturally occurring in bacteria. They replicate independently (episomal) from the bacterial genomic DNA, a property that makes them ideally suited as a vector for genetic engineering. pDNA ranges in size from 1.5 to about 120 kilo-base pairs (kbp).

How do biologics developers use pDNA?

pDNA is relatively stable, simple to produce and cost-effective, which makes it useful for a range of applications.[4] pDNA was initially used in academic settings. Over time, biopharma began using pDNA for a wide range of therapies, including certain types of biologic therapies and vaccines.

Biologics: pDNA is used in the production of therapeutic proteins. It also serves as a starting material for gene therapies and gene-enabled cell therapies.

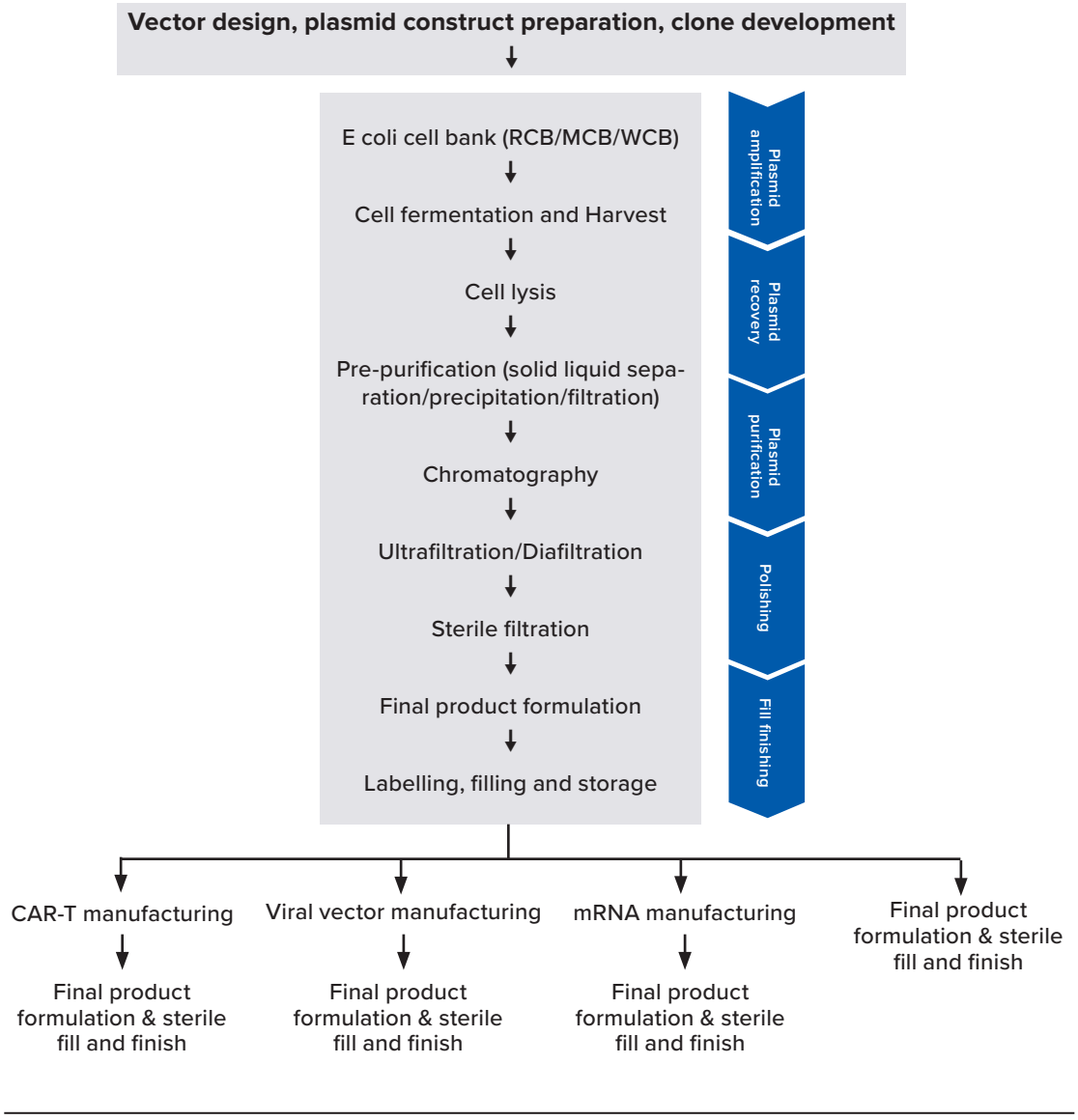
Plasmids contain the instructions for the synthesis of the viral vector and the gene of interest (the gene to correct the missing or defective gene).

In the case of CAR-T cell therapies, the pDNA contains the gene for chimeric antigen receptor (CAR). The CAR can bind to a target protein on the cancer cells. T cells modified with the CAR antigen thus locate and kill cancer cells that contain the target protein.

Vaccines. pDNA can be used as a precursor for manufacturing mRNA vaccines or used directly for making vaccines. For example, the COVID-19 Pfizer and Moderna vaccines, which billions of people received worldwide, use mRNA. Here, the sequence for the COVID-19 spike protein is used to create the plasmid construct and later manufactured as pDNA.

In the case of pDNA vaccine, the Central Drugs Standard Control Organization (CDSCO), which is the national regulatory authority for drug approvals in India, granted emergency approval to a pDNA vaccine developed by Zydus Cadila.[3] It is the world's first pDNA vaccine for humans to receive approval, with more on the horizon.[5]

The figure below depicts the manufacturing workflow for pDNA production across various therapies.



Manufacturing workflow for pDNA production for various therapies

pDNA market forecast

According to Precedence Research, the global pDNA manufacturing market size is expected to grow from about $446 million in 2022 to $2.1 billion by 2030—a compound annual growth rate (CAGR) of 21.7%.[5] The research firm attributes strong projected growth to increasing development of biologics, including gene therapies that use adeno-associated viral vectors for delivery.[6]

The mRNA therapeutics market is also poised for strong growth—a CAGR of about 13% between 2022 and 2030 according to the same research firm. COVID-19 vaccines and cancer therapies are fueling this growth.[7]

pDNA supply and demand

With more clinical development and rising commercial activity, CDMOs have seen a spike in demand for specialized cell and gene therapy manufacturing capabilities as well as for pDNA production. Currently, this demand is outweighing capacity, leading to a bottleneck in production.

Manufacturers that offer plasmid production have long wait lists. Select manufacturers are expanding their capabilities; however, building these facilities takes time.

What to look for in a pDNA engineering and manufacturing partner

Organizations who need pDNA for manufacturing biologics must choose a partner with the resources, expertise and facilities to manufacture pDNA of the desired quality and efficiency.

Because of the inherent risks involved in pDNA production and biologics manufacturing, it's important to choose a CDMO carefully. Here are a few characteristics to look for in a CDMO partner.

- **Therapeutic area expertise.** Look for CDMOs with experience in microbial bacterial and biologics manufacturing, as well as comprehensive scientific expertise. Since pDNA is primarily produced in E-coli, expertise and infrastructure in microbial manufacturing are key factors to consider while choosing a CDMO. Syngene has a proven track record in providing end-to-end solution in biologics manufacturing processes, including pDNA production with high purity and yield. The infrastructure

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and trained scientists have been serving multiple clients from all across the globe in diverse product classes such as peptides, proteins, monoclonal antibodies, plasmid DNA and mRNA.

- **Development and manufacturing capabilities:** Look for a CDMO with strong experience in microbial fermentation and platform process. Syngene offers cost-effective high-quality pDNA, including research grade, GMP-like grade and GMP grade pDNA. Its full-scope production capabilities make it a suitable choice for most research, development and GMP needs.
- **Cost-effective processes:** Biologics sponsors face ongoing pressure to lower the cost of development. Partnering with a CDMO with efficient processes keeps costs from spiraling beyond client budgets.
  Syngene not only has efficient processes in place, it has also implemented automation and digitization initiatives for inventory management resulting in optimized inventory and lower costs. The company also has the advantage of being headquartered in India, which is fast emerging as a biologics and biosimilar hub. According to the Association of Biotechnology Led Enterprises, India's biologics market will grow at a compound annual growth rate (CAGR) of 22% to hit $12 billion by 2025. This is for reasons of cost-effectiveness and availability of skilled workforce.
- **Commitment to compliance:** Strict adherence to regulatory and technical requirements is essential when developing biologics. Look for CDMOs with all applicable ISO, GMP and GLP certifications. In addition to GMP manufacturing and a GLP-certified labs, Syngene has a 100% successful track record in FDA and EMA regulatory inspections, as well as no reported data breaches in its 30 years of operation. It is proud to be ISO/IEC 27001 certified.[8]
- **Quality-first philosophy:** A CDMO for pDNA-derived products must focus on quality throughout the product's lifecycle. Look for a CDMO partner with a Quality Management System (QMS) that covers the full lifecycle of production facilities and equipment, laboratory control, manufacturing and packaging/labeling.

Syngene integrates quality into all work practices. Individual quality teams ensure compliance with GLP and GMP requirements. Ongoing investment in infrastructure and innovation reinforce the company's high standards.

Organizations who need pDNA for manufacturing biologics must choose a partner with the resources, expertise and facilities to manufacture pDNA of the desired quality and efficiency.

In 2021, the company expanded its biomanufacturing capacity to include a new microbial cGMP facility and an expanded mammalian cell manufacturing facility for more comprehensive chemistry, manufacturing and control (CMC) development solutions. The microbial facility has two fermenters of 200 litres and 500 litres capacity, allowing Syngene to offer higher-capacity pDNA offer higher capacity pDNA manufacturing.

Conclusion

pDNA is a critical component of many advanced and emerging therapies, including cell and gene therapies and vaccines. Since quality of the pDNA is critical to the success of biologics programs, biologics organizations must make decisions around pDNA design early in the development process. To ensure these fragile products move through development to commercial release without a hitch, look for a CDMO partner with a strong track record in quality, compliance, cost and delivery.

To know more about how to accelerate your pDNA projects, talk to Syngene experts.

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