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Reshaping the production of DNA-based therapies

Touchlight's DNA synthesis platform is ready to meet the growing demands of the genetic medicine industry.

The success of mRNA COVID-19 vaccines demonstrates that nucleic acid-based therapies are an effective and safe strategy for preventing SARS-CoV-2 infection. Although DNA or mRNA vaccines are easier to make than traditional vaccines, which require the production of live or attenuated viruses or viral proteins, generating massive quantities of the sequence of interest can be challenging.

Typically, DNA is produced in bacteria grown in large stainless steel fermenters, followed by complex purification methods. "The process is expensive, takes a long time and the resulting DNA contains unwanted bacterial sequences such as antibiotic resistance genes," said Helen Horton, Chief Research Officer at Touchlight and member of the UK government Vaccines Taskforce.

Touchlight, a privately owned UK-based company founded in 2007, has developed a rapid, scalable, easy to transfer, cell-free method to make unique DNA vectors, known as Doggybone DNA (dbDNA) (Fig. 1). Touchlight's dbDNA can be manufactured to good manufacturing practice (GMP) at multi-gram scale in a 5-day process. "Our linear, double-stranded DNA constructs can be produced much more rapidly than traditional plasmid DNA with simple, inexpensive benchtop equipment, which would allow developing nations to produce their own vaccines," Horton explained.

Touchlight has established a contract development and manufacturing organization (CDMO) that is currently deploying the dbDNA technology across a multitude of modalities within genetic medicine, including in viral vector manufacturing, genome editing and the production of nucleic acid medicines (mRNA and DNA).

The company is also investing in its own portfolio of products linked to its production process to drive proof-of-concept and validation of the technology in key genetic medicine markets. "There is a growing number of proof-of-concept studies in animals for a whole range of DNA-based therapies," Horton said, "and we are ideally placed to enable the rapid development of products into the clinic as we can easily up-scale production".

The COVID-19 pandemic has highlighted the urgent need for technologies such as dbDNA to solve issues with vaccine supply chains as well as to respond to new variants. "The possibility of producing gram quantities of DNA from emerging virus variants within days demonstrates how our platform can improve preparedness for the next pandemic," she added.

Realizing the potential of DNA vaccines

Historically, DNA vaccines have not provided robust antibody responses in humans, partly owing to difficulties in delivering them to the nucleus of antigen-presenting cells. However, they offer a number of advantages over mRNA vaccines, including the stimulation of both a strong cellular immune response by T cells as well the production of antibodies by B cells, and stability at room temperature, making them much easier to deploy in countries where the cold chain is difficult to maintain.

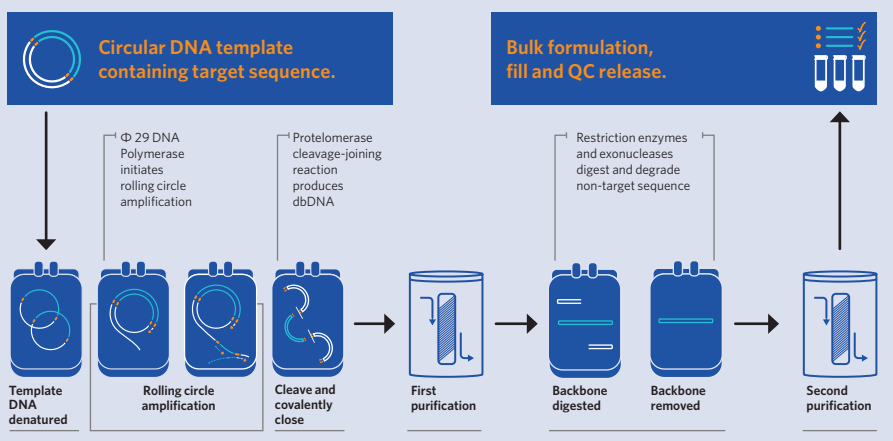

Fig. 1 | Touchlight's DNA synthesis platform. Manufacturing DNA vectors known as Doggybone DNA (dbDNA) in a rapid, scalable, easy to transfer and cell-free method.

Although no DNA vaccines have yet been licensed for humans, they are used in the veterinary arena to protect diverse species, including salmon, pigs, dogs and horses, against disease. Touchlight has recently partnered with Stonehaven Incubate to develop new vaccine solutions for aquaculture, and is exploring the use of DNA vaccine candidates for various animal health indications.

Several DNA vaccines are undergoing clinical trials for the treatment of cancer and for preventing SARS-CoV-2 infection. Zydus Cadila's plasmid DNA-based COVID-19 vaccine (ZyCoV-D) delivered via a needle-free injection system is now in phase 3 trials in India and could become the first DNA vaccine to be approved for humans.

"We are just starting to witness the potential of DNA in the vaccine field," Horton said. Touchlight's innovation team is working on developing new types of dbDNA that can target specific cells to enhance DNA immunogenicity, avoid the need for delivery devices and elicit an effective, long-lasting response.

Cancer Research UK has partnered with Touchlight to progress its DNA vaccine candidate for solid tumors (TGL-100) through phase 1/2 clinical trials in patients with head and neck squamous cell carcinoma. "The vaccine consists of dbDNA that encodes two cancer antigens found in more than 95% of head and neck cancers that are not human papillomavirus-driven, as well as at high rates in non-small cell lung cancer and other solid tumors," Horton explained.

Touchlight is also developing a novel DNA vaccine against SARS-CoV-2 that directs an immune response not just against the virus's spike protein, as current vaccines do, but also against other parts of the virus. This could stimulate a more robust response and confer broader protection against new variants. In addition, the company is exploring the use of different routes of administration. "Current vaccines are all delivered intramuscularly, which is known to elicit a systemic immune response; we are looking at simultaneous intradermal and intranasal administration to induce a strong mucosal immune response," Horton said.

dbDNA-based vaccines can be used to deliver more than one antigen, and, unlike viral vector-based vaccines, there is no risk of developing anti-vector immunity. Thus, they can be used to boost previously administered vaccines and used repeatedly, which is critical for therapeutic cancer vaccines that need to be administered every few weeks and seasonal influenza vaccines.

Touchlight is already collaborating with most major mRNA vaccine companies, and its latest fundraising round will enable it to triple its manufacturing capacity and produce up to 1 kg of GMP DNA per month from early 2022. "Our goal is to meet the growing demand for starting material in the manufacture of mRNA vaccines, whilst driving new or improved forms of potentially life-saving genetic medicines," Horton concluded.

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