Shape Therapeutics
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Taking gene therapy to the next level

Shape Therapeutics is developing next-generation gene-therapy technologies that harness the power of artificial intelligence and RNA editing to repair disease-causing mutations.

Current gene therapies fall short on many fronts: the risk of introducing harmful genetic alterations, the lack of tissue-specific delivery systems, along with high manufacturing costs, all mean that very few patients are likely to benefit from these therapies.

The preclinical-stage biotech company Shape Therapeutics (ShapeTX), based in Seattle, Washington, is using artificial intelligence and machine learning to develop RNA-based therapies that are easy to manufacture and can be delivered to specific tissues by using engineered adeno-associated viruses (AAVs).

Francois Vigneault, co-founder and CEO of ShapeTX, has long been fascinated by the smallest of biological entities: viruses. "I rely a lot on first-principle thinking, so I was immediately attracted to the simplicity and power of viruses," he said.

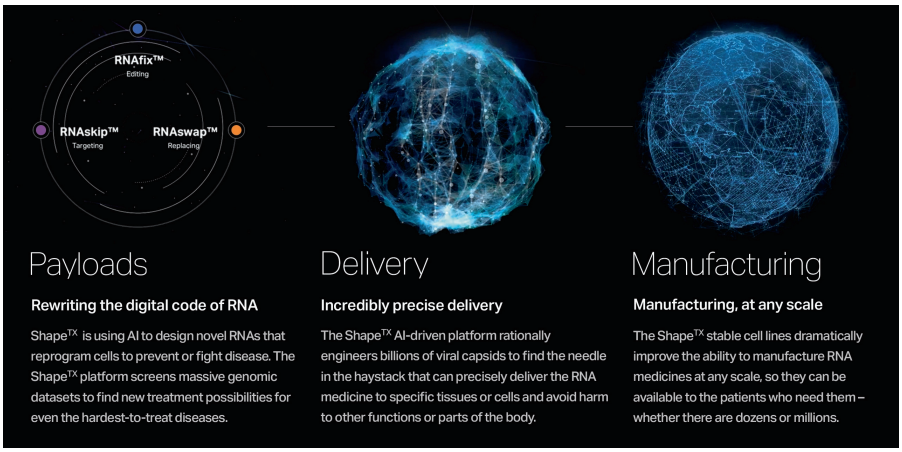
After 10 years as a maritime warfare officer in the Royal Canadian Navy, Vigneault pursued a career in biosciences. He worked in George Church's laboratory at Harvard Medical School developing cutting-edge genomic technologies. Together, Vigneault and Church co-founded the startup company AbVitro, which pioneered high-throughput single-cell sequencing to advance therapies for cancer, and for autoimmune and infectious diseases.

AbVitro was acquired by Juno Therapeutics in January 2016 (now part of Bristol Myers Squibb). Not long afterwards, Vigneault and his colleague from the Church lab Prashant Mali, along with John Suliman, co-founded ShapeTX to develop new RNA-targeted therapies for some of the world's most challenging diseases. "Our goal is to transform patients' lives by combining large datasets, artificial intelligence and programmable RNA," Vigneault said.

The COVID-19 pandemic and the successful use of RNA vaccines against SARS-CoV-2 has boosted research into RNA therapeutics. Unlike DNA-based gene therapies, which cause permanent genetic changes in a cell's nucleus, RNA therapies carry out their activity in the cytoplasm and are more easily manipulated, without the same risk of unintended genetic effects.

When comparing the two approaches, Vigneault uses an analogy: "If you have a computer problem, you don't go changing the hardware, you install a software update. It's the same when trying to fix a genetic problem. Rather than fix it at source (DNA editing), you can upload a patch (RNA editing), which is less complex, more efficient and carries less risk."

> **ShapeTX is already working in partnership with Roche to advance RNA-editing therapies**



ShapeTX's three key areas of work. RNA editing tools, tissue-specific AAVs and manufacturing technology (end-to-end approach). AAV, adeno-associated viruses; AI, artificial intelligence.

New RNA tools to fix disease

ShapeTX uses a guide RNA that can recruit the cell's own adenosine deaminase acting on RNA (ADAR) enzymes to edit a precise location on a target RNA. ADARs can correct guanine-to-adenine (G-to-A) mutations, which are the cause of numerous rare diseases and have been linked with larger genetic disorders, including Parkinson's disease and Alzheimer's disease.

The ShapeTX RNA-editing technology has been used to treat a mouse model of Hurler syndrome—the most severe form of the lysosomal storage disease mucopolysaccharidosis type 1—and Duchenne muscular dystrophy[1,2].

"Our goal is to provide just the RNA as the software update, without the need for a large protein system like CRISPR relies on, which could be recognized by the immune system as foreign and trigger immunogenicity," Vigneault explained.

Delivery and manufacturing solutions

In addition to building an arsenal of programmable RNA tools with broad applicability across a wide range of therapeutic areas, ShapeTX is making disruptive changes to improve the delivery and manufacture of gene therapies.

"99% of the viruses and liposomes that are currently used to deliver gene therapies end up in the liver, where they can cause toxicity," said Vigneault. Researchers at ShapeTX have developed a platform to generate viral vectors that target specific tissues. So far, they have generated AAVs that specifically target the central nervous system and muscle tissue in non-human primates, enabling more-efficient delivery of therapies for brain diseases and muscle disorders, respectively.

Scaling up manufacturing for gene therapies is a major bottleneck for clinical trials. The supply of most gene therapies under development still relies on processes created in the 1970s, requiring huge reactors to produce tiny amounts of product, Vigneault explained. "We've re-invented the cells that go into the reactor so they produce a much higher amount and higher quality of product, drastically reducing the cost of treatment."

ShapeTX has generated stable cell lines for AAV production that outperform standard transient expression methods. The company is planning to build a good manufacturing practice (GMP) facility that can be used by other companies to manufacture their own gene therapies.

ShapeTX is already working in partnership with Roche to advance RNA-editing therapies for Alzheimer's disease, Parkinson's disease and other rare disorders, and is eager to establish further collaborations to realize the full potential of its platform technologies. "We see all companies as potential collaborators, not competitors. We want to work with them to get safe and effective treatments to patients faster and at an accessible price point," Vigneault said.

1. Katrekar, D. et al. *Nat. Methods* **16**, 239–242 (2019).
2. Katrekar, D. et al. *Nat. Biotechnol.* **40**, 938–945 (2022).

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