Eterna Therapeutics
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Harnessing the therapeutic potential of mRNA

Eterna Therapeutics is using state-of-the-art messenger RNA (mRNA) technology to develop cell and gene therapies for cancer and a wide range of other indications.

The recent success of COVID-19 mRNA vaccines has fuelled efforts in the development of mRNA vaccines against other pathogens and of therapeutics that use mRNA to repair or improve cell function.

The Massachusetts-based biotech company Eterna Therapeutics has in-licensed a patent-protected portfolio of mRNA technologies to express proteins that can modify the genome of living cells or proteins that can reprogram cells into other cell types (Fig. 1).

"Our aim is to use mRNA to encode cell-engineering proteins, including gene-editing and cell-reprogramming proteins, to directly repair damaged cells and restore lost function," said Matt Angel, a pioneer in mRNA technology, CEO and president of Eterna. As co-founder and CEO of Factor Bioscience Inc. and co-founder of Novellus Therapeutics and Exacis Biotherapeutics, Angel has a wealth of experience in mRNA, nucleic-acid delivery, gene-editing and cell-reprogramming technologies.

Manipulating protein expression with mRNAs has several advantages over DNA-based delivery systems. Inserting DNA encoding gene-editing proteins into cells carries the risk of genomic integration and leads to a relatively long exposure to gene-modifying proteins, which in turn increases the probability of off-target mutagenesis. In contrast, mRNAs remain in the cytoplasm, eliminating the risk of genomic integration, and their natural degradation pathway ensures only temporary activity.

"We believe that mRNA-based cell engineering is fundamentally safer than any other approach and we expect that our technologies, which are protected by over 100 patents in the United States, Europe and other major market countries, will be used in the most advanced cell-engineering therapies in medicine," Angel explained.

Gene-editing mRNAs for cancer immunotherapy

Eterna makes synthetic mRNAs that express gene-editing proteins capable of deactivating, inserting or replacing specific DNA sequences in living cells to repair disease-causing mutations and confer new functionality.

For example, Eterna's technologies can be applied to immune cells to develop next-generation immunotherapies. "Autologous chimeric antigen receptor (CAR) T cell therapies that genetically modify a patient's own immune system so it can recognize and target a specific protein on cancer cells have fundamentally changed the way we think about treating cancer," Angel said. However, these first-generation CAR-T products have some challenges and limitations. Not all patients are eligible for treatment and because of their patient-specific nature, the manufacturing process is lengthy and costly.

Eterna's mRNA cell engineering platform addresses cellular dysfunction

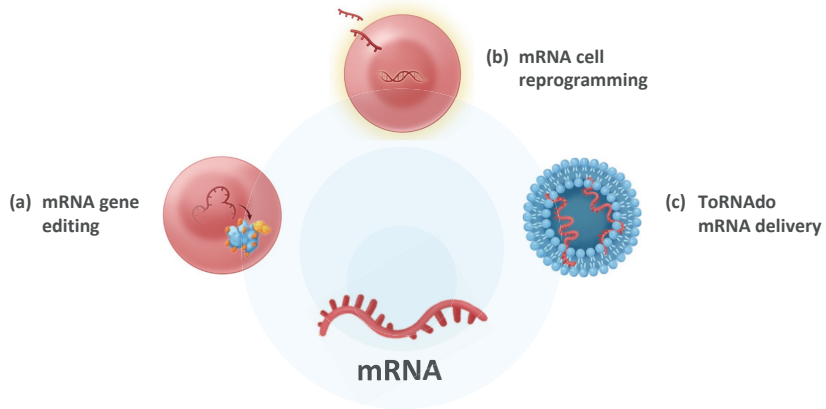

Fig. 1 | Eterna's mRNA cell-engineering platform. (**a**) Synthetic mRNA can express gene editing proteins to repair genetic damage and confer new functionality and (**b**) express reprogramming proteins that generate new cells. (**c**) The ToRNAdo mRNA delivery system enables in vivo repair of cellular dysfunction.

As a result, there has been great interest in generating allogeneic ('non-self'), universal 'off-the-shelf' CAR-T cell therapies. "We can use our mRNA to encode a gene-editing protein to engineer T cells from a healthy donor so they don't trigger a graft-versus-host type effect," Angel explained. "We can also use mRNA technology to insert a CAR that helps T cells find and kill cancer cells expressing the protein that the receptor is designed to bind."

By improving the efficacy and safety of these fundamental cell-engineering steps, Eterna's goal is to accelerate the development of allogeneic CAR-T cell therapies and make them accessible to more cancer patients.

Cell-reprogramming mRNAs for regenerative medicine

Eterna also makes synthetic mRNAs to express cell-reprogramming proteins and generate new cell types. "We can use our mRNA technology to re-write a cell's gene-expression program, enabling a somatic cell, such as a skin cell, to adopt a stem-cell state that can differentiate into any needed cell type," Angel said.

These induced pluripotent stem cells can be differentiated into tissue-specific cell types, such as nerve cells or heart cells, and transplanted into patients to replace cells affected by injury or disease without the risk of immune rejection. Eterna's cell-reprogramming RNAs can also be delivered in vivo to induce these and other kinds of phenotypic changes in cells in a patient's body[1].

A unique delivery system

To achieve their therapeutic effects, exogenous mRNA molecules must reach specific target cells and produce sufficient proteins of interest. Eterna has in-licensed a lipid nanoparticle-delivery system (ToRNAdo) that facilitates fusion with cell membranes and enables the efficient delivery of nucleic acids, including mRNA, in vivo to the brain, eye, skin and lung[2].

In addition, Eterna makes proprietary chemical and structural enhancements to mRNAs that regulate their degradation, effectively acting as built-in off switches.

Strategic partnerships

Eterna is working with strategic partners to realize the therapeutic potential of its powerful suite of technologies. In 2022, the company entered a research agreement with The University of Texas MD Anderson Cancer Center to evaluate its allogeneic cell therapies for the treatment of acute myeloid leukemia and solid tumors, and in February 2023, the company entered into an agreement with Lineage Cell Therapeutics to develop gene-edited iPSC therapies in neurology indications. "We can offer partners exclusive rights to technologies that have applications in the treatment of essentially every disease," Angel concluded.

1. McCarthy, S. et al. *Nucleic Acid Ther.* (in the press, 2023).
2. Kostas, F. et al. *Mol. Ther.* **28**, abstr. 1327 (2020).

CONTACT
Matt Angel, CEO
Eterna Therapeutics
Cambridge, MA, USA
Tel: +1-212-582-1199
Email: info@eternatx.com