Precision BioSciences
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Therapeutic genome editing

Precision BioSciences is harnessing its next-generation genome editing platform, ARCUS, to develop a pipeline of cell-based immunotherapies for cancer and autoimmune disease, as well as gene therapies for rare genetic disorders. The company is looking for uniquely suited partners to aid in these efforts.

Precision BioSciences is a genome editing company dedicated to solving fundamental therapeutic challenges by means of its proprietary, next-generation genome editing platform ARCUS (Latin for 'bow', to symbolize the platform's flexibility and accuracy). The platform, which is derived from a natural gene editing system called a homing endonuclease, affords maximal target specificity, easy delivery, and broad applicability.

Precision enjoys a dominant intellectual property position in the space, setting the company apart from others developing programmable-nuclease-based genome editing technologies.

Precision is now seeking to establish collaborations with other players interested in developing therapeutic solutions for some of the most pressing needs in oncology, autoimmune disease, and rare genetic disorders.

ARCUS

ARCUS is a next-generation genome editing platform exhibiting a broad range of *in vivo* and *ex vivo* editing capabilities, unparalleled target specificity, and optimal delivery dynamics (**Fig. 1**). The backbone of the ARCUS technology is the ARC Nuclease, a fully synthetic enzyme derived from the natural homing endonuclease I-*Cre*I.

Homing endonucleases represent one of four types of genome editing technologies currently under commercial development; the other three are ZFNs (zinc-finger nucleases), TALENs (transcription-activator-like effector nucleases), and CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats with the Cas9 endonuclease).

Homing endonucleases are unique in their ability to specifically recognize very long DNA sequences (12–40 base pairs), statistically reducing the number of homologous target sites on the human genome to one. Because they were evolved to edit natural genomes, homing endonucleases have specialist mechanisms for recognizing and cutting DNA that eliminate off-target effects that could be toxic to the cell. Hence, the ARCUS platform is exquisitely specific. Moreover, binding of the endonuclease to its target generates a double-strand DNA break that triggers the cell's DNA repair pathways and stimulates homologous recombination machinery at levels of efficiency not seen with older editing approaches.

The ARC endonuclease is small in size and is encoded by a single gene. This makes it easy to deliver to cells. And, importantly, ARCUS is much more programmable than previous homing-endonuclease-based gene editing technologies. ARCUS reagents can be developed that recognize extremely diverse DNA sequences for maximum utility against genes associated with disease.

Figure 1: Precision BioSciences is harnessing its genome editing platform, ARCUS, to develop cell-based immunotherapies and gene therapies.

"The ARCUS editing platform is now allowing Precision to take editing into therapeutic areas not considered realistic with prior genome editing technologies," said Matthew Kane, Precision's CEO.

Off-the-shelf CARs and TCRs

Cancer immunotherapy has emerged as a leading therapeutic strategy for certain types of tumors. Existing approaches rely largely on the *ex vivo* genetic engineering of a patient's T cells to express a tumor-specific chimeric antigen receptor (CAR) or a recombinant T cell receptor (rTCR) and the reintroduction of the engineered cells back into the patient. Although the technology has been highly successful on an individual-patient level, wider implementation has been hampered by the challenge of developing CAR/rTCR T cells for use in patients who lack sufficient numbers of high-quality T cells.

To overcome this challenge, Precision is applying its ARCUS technology to develop T cell therapies derived from healthy donors to enable consistent, scalable manufacturing more comparable to traditional biopharmaceuticals.

Precision's approach involves the use of ARCUS endonucleases to alter multiple aspects of T cell biology. Most important, ARCUS is used to turn donor-derived cells into universal T cells that can persist in an unrelated patient without inducing graft-versus-host disease. Additional gene edits can be used in some instances to make the cells resistant to checkpoint inhibition or immunosuppressant drugs to enhance cell survival in suppressive environments such as a solid tumor. A particularly attractive advantage of the Precision T cell platform is the ability to target the insertion of CAR/rTCR-encoding transgenes into a defined location in the genome. Unlike traditional approaches using viral vectors that integrate more or less randomly into the genome, the Precision platform enables the generation of genetically identical cells that express the CAR/rTCR at consistent levels. Thus, the resulting cell formulation is highly homogeneous and performs consistently across individuals.

In the first quarter of 2016, Precision entered into a global agreement with Shire (Baxalta) to codevelop CAR T cell therapies for up to six individual targets. The first program is expected to enter clinical studies in late 2017 or early 2018.

Rare genetic diseases

ARCUS is an ideal platform for the treatment of rare diseases caused by genetic defects. The combination of exquisite specificity and high rates of homology-directed DNA repair makes ARCUS safe for direct use in patients and capable of correcting gene defects in a high-enough percentage of cells to improve prognosis. This approach is superior to traditional gene therapies—such as vector-based gene addition or short interfering RNA—in that it permanently corrects a gene defect at the chromosomal DNA level.

ARCUS affords a versatile tool capable of inserting a missing gene into the genome, removing a disease-causing gene, excising a repeated DNA segment associated with disease, or fixing the 'spelling' of an incorrectly coded gene. Precision is using these different approaches to overcome genetic diseases in multiple tissues, including eye, central nervous system, and liver. Programs under development include retinitis pigmentosa, Friedreich's ataxia, and hemophilia A.

Partnering ARCUS

The recently announced global partnership with Shire (Baxalta) represents Precision's first foray into the collaborative landscape of biopharma. The company is now looking to in-license technologies that will further enable Precision's therapeutic programs in genetic and autoimmune disease and in oncology.

According to Michael Dombeck, Precision's VP of business development, "Precision is particularly interested to speak with prospective partners that may hold promising tissue-delivery and cell-manufacturing technologies that could further enhance our product development efforts."

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