Changing the fate of cellular immunotherapy

Clinical-stage biopharmaceutical company Fate Therapeutics is creating first-in-class (re)programmed cellular immunotherapies for cancer and immune disorders. Preclinical and clinical development of the company’s product pipeline is driven by a determined pursuit of a new cell therapy paradigm and an expanding array of strategic partnerships to support its innovative mission.

The use of cells as therapeutic entities for the treatment of human diseases is rapidly expanding, and emerging results from clinical trials suggest that cellular immunotherapies hold tremendous opportunity for the treatment of cancer and immune disorders. However, current cellular immunotherapies often require the use of patient cells and logistically complex manufacturing steps, which can result in cells with suboptimal biological properties and therapeutic function.

Since its founding a decade ago, clinical-stage biopharmaceutical company Fate Therapeutics has pioneered approaches to cellular (re)programming of immune cells, including natural killer (NK) cells, T cells and CD34+ cells, based on the simple motto that “better cell therapies start with better cells.” These approaches have created a deep product portfolio of first-in-class cellular immunotherapies.

For certain product candidates, Fate uses ex vivo pharmacologic modulation to enhance the biological properties and therapeutic function of donor cells. These programmed cell products are then administered to the patient (Fig. 1). In other cases, the company uses human-induced pluripotent stem cells (iPSCs) to generate a master pluripotent cell line. Master pluripotent cell lines can be used to repeatedly create clonal populations of effector cells to enable off-the-shelf treatment of many thousands of patients (Fig. 2).

Using iPSCs, which are capable of unlimited self-renewal and differentiation potential into all cell types of the body, is a first-of-kind approach to cell therapy. Our master pluripotent cell lines serve as a backbone into which we can engineer targeting and functional elements, such as chimeric antigen receptors, and from which we can derive effector cells such as NK and T cells, said Scott Wolchko, president and CEO of Fate.

Fate is developing its first-in-class cellular immunotherapy programs through an expanding array of strategic collaborations, and in therapeutic indications where the unmet need is large and where regulatory agencies offer efficient and expedited development and review programs.

Immuno-oncology pipeline

**FATE-NK100** — Fate’s most advanced immuno-oncology product is FATE-NK100, a first-in-class cancer immunotherapy that uses programmed donor NK cells to treat patients.

NK cells have an innate ability to selectively identify and rapidly destroy abnormal cells, such as cancer or virally infected cells, through multiple cytotoxic mechanisms while leaving normal, healthy cells unharmed.

FATE-NK100 comprises a highly specialized and functionally distinct subset of NK cells, known as adaptive memory NK cells, that express the memory-like activating receptor NKG2C and the maturation marker CD57. The company has shown in preclinical studies that FATE-NK100 has enhanced effector function, long-term persistence and greater resistance to immune-checkpoint pathways compared to conventional NK cells used in the clinical setting today.

In February 2017, the US Food and Drug Administration (FDA) cleared an investigational new drug (IND) application for a phase 1 open-label, dose-escalation clinical trial of FATE-NK100, and the company is now sponsoring a first-in-human clinical trial at the Masonic Cancer Center, University of Minnesota for the treatment of relapsed/refractory acute myeloid leukemia.

**CD16 iPSC-derived NK (iNK) cell** — Fate’s lead iPSC-derived cancer immunotherapy is a targeted iNK cell product created from a master engineered pluripotent cell line that expresses a high-affinity, noncleavable CD16 (hnCD16) Fc receptor. NK cell activation through the CD16 receptor has been proven to play a major role in driving the antitumor efficacy of monoclonal antibodies for the treatment of breast, head and neck, colorectal and certain blood cancers.

The company’s proprietary hnCD16 Fc receptor incorporates two unique modifications designed to augment the receptor’s binding affinity to certain monoclonal antibodies and to block the shedding of CD16, which can inhibit NK cell activation. A single engineered iPSC expressing this hnCD16 Fc receptor was isolated, clonally expanded and differentiated via a highly efficient and reproducible proprietary process capable of producing over one million iNK cells from one iPSC.

Fate is developing its hnCD16-iNK cell product as an off-the-shelf cancer immunotherapy for the treatment of hematologic and solid tumors, both as a monotherapy and in combination with monoclonal antibodies.

**CAR iPSC-derived T (iT) cell** — Fate is developing targeted iT cell immunotherapies created from master engineered pluripotent cell lines that express chimeric antigen receptors (CARs). In September 2016, the company announced a partnership with Memorial Sloan Kettering Cancer Center (MSKCC) for the development of off-the-shelf iT cell products. Additionally, Fate launched a majority-owned subsidiary, Trinity Therapeutics, Inc., to focus exclusively on the advancement of off-the-shelf iT cell immunotherapies.

Immunoregulation pipeline

**ProTmune** — Allogeneic hematopoietic-cell transplantation (HCT) is potentially curative for many hematologic malignancies and rare genetic disorders, but life-threatening complications associated with the procedure are common, with up to 60% of patients developing acute graft-versus-host disease (GvHD) and 70% of patients experiencing at least one severe infection within the first 180 days after HCT. There are currently no approved therapies for the prevention of GvHD, giving rise to a significant unmet medical need.
Fate’s ProTmune is a programmed cellular immunotherapy consisting of a donor-sourced peripheral blood graft that is pharmacologically modulated ex vivo with two small molecules, FT1050 and FT4145, in a patient-protected process that enhances the biological properties and therapeutic function of the graft cells.

In June 2016, the FDA granted Fast Track designation to ProTmune for reduction of the incidence and severity of acute GVHD in patients undergoing allogeneic HCT. This was followed by FDA Orphan Drug Designation and European Commission Orphan Medicinal Product Designation for ProTmune in September and October 2016, respectively, covering allogeneic HCT for the treatment of a broad range of diseases.

ProTmune is undergoing clinical testing for use as a next-generation HCT graft. The company is conducting a multicenter phase 1/2 clinical trial of ProTmune in adult subjects with hematologic malignancies, the PROTECT study, to evaluate safety and tolerability and to assess the potential of ProTmune to prevent acute GVHD.

ToleraCyte – Autoimmune diseases arise from abnormal immune responses in which the body’s immune system attacks and damages its own tissues. Some of the most common autoimmune diseases include rheumatoid arthritis, type 1 diabetes, systemic lupus erythematosus, multiple sclerosis, inflammatory bowel disease, celiac disease and asthma. It is estimated that more than 23 million people in the United States alone suffer from autoimmune disorders, which makes it the third most common category of illness in the United States after cancer and heart disease.

ToleraCyte is a pharmacologically programmed CD34+ cell therapy with potent immunoregulatory properties. In preclinical studies, Fate has demonstrated that programmed CD34+ cells traffic to sites of T cell dysregulation and express powerful T cell regulatory factors, including PD-L1 and IDO1. The company is investigating the potential of programmed CD34+ cells to immunologically check autoimmune T cells and induce immune tolerance.

IPSC platform development
The discovery that the fate of fully differentiated human cells can be reprogrammed ex vivo to generate pluripotent stem cells through the expression of certain genes is one of the most remarkable scientific breakthroughs of the past decade. Further, the indefinite expansion of iPSCs in culture enables the creation of a potentially unlimited cell source for differentiation into specialized cell types for therapeutic application.

Fate has capitalized on iPSCs to create cell products that are well defined, are uniform in composition, are well defined, are uniform in composition, have a consistent and dose-dependent pharmacologic profile, and can be delivered off the shelf for the treatment of large numbers of patients. Fate has built a proprietary iPSC platform and is applying it to genetically engineer, single-cell isolate, characterize and select iPSCs for clonal expansion and cryopreservation as master pluripotent cell lines.

The company directs the fate of its master pluripotent cell lines to create cells of the immune system, including NK cells, T cells and CD34+ cells, and is advancing a pipeline of off-the-shelf iPSC-derived immunotherapies. Fate’s iPSC platform is supported by an intellectual property portfolio of over 60 issued patents and 90 pending patent applications.

Cellular therapy collaborations

University of Minnesota – In July 2015, Fate entered into a partnership with the University of Minnesota to research and develop its first-in-class adaptive memory NK cell product, FATE-NK100.

In preclinical studies assessing function across a broad range of hematologic and solid tumors, FATE-NK100 has shown enhanced antitumor activity, improved persistence, and increased resistance to immune-checkpoint pathways compared to NK cell therapies that are in clinical use today. Additionally, FATE-NK100 has been shown in preclinical models to significantly augment antibody-directed cellular cytotoxicity against cancer cells when coadministered with antigen-specific monoclonal antibodies to CD20, HER2 or EGFR.

In February 2017, Fate announced the expansion of its partnership with the University of Minnesota to initiate clinical translation of its off-the-shelf hCD16-iNK cell product. According to Jeffrey Miller, deputy director of the university’s Masonic Cancer Center, “Fate is at the forefront of a paradigm shift in cellular immunotherapy, pioneering the delivery of off-the-shelf cell products that are homogeneous, administered in multiple dosage regimens and complement current standard-of-care cancer treatments utilizing monoclonal antibodies and checkpoint inhibitors.”

MSKCC – Current cellular immunotherapies involve multi-step manufacturing processes that are logistically challenging and complex, and significant hurdles remain to ensure that patient-specific T cell immunotherapies can be efficiently and consistently manufactured, and safely and reliably delivered, at the scale necessary to support broad patient access and widespread commercialization.

In September 2016, Fate entered into a partnership with MSKCC for the development of off-the-shelf iT cell products using engineered iPSC lines. The three-year partnership is being led by Michel Sadelain, director of the Center for Cell Engineering at MSKCC and a pioneering scientist in the CAR-T cell cancer immunotherapy space. Together, Fate and MSKCC have amassed significant and complementary expertise to deliver off-the-shelf iT cell immunotherapies, including the engineering, selection, expansion and maintenance of pluripotent cells and the efficient generation of iT cells with enhanced safety profiles and effector functions.

Juno Therapeutics – In May 2015, Fate entered into a research collaboration with Juno to identify small-molecule modulators that enhance the biological properties and therapeutic function of engineered T cell immunotherapies. The strategic collaboration brings together Fate’s expertise in ex vivo pharmacologic modulation and Juno’s scientific and clinical leadership in engineered T cell product development. Under the collaboration, Fate seeks to identify small-molecule modulators of immune cells, and Juno is responsible for incorporating pharmacologic modulators into its development of engineered T cell immunotherapies.

Novel partnering opportunities
Fate seeks to share its cell-programming expertise with strategic partners for the development of first-in-class and best-in-class cell products. Fate believes it is uniquely positioned as the partner of choice to maximize the therapeutic potential of cell therapies through ex vivo pharmacologic modulation. Additionally, Fate is seeking to apply its industry-leading iPSC product platform with strategic partners to create master pluripotent cell lines and codevelop off-the-shelf cell products.