Industry updates from the field of stem cell research and regenerative medicine in August 2019

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Latest developments in the field of stem cell research and regenerative medicine compiled from publicly available information and press releases from nonacademic institutions in August 2019.

First draft submitted: 12 September 2019; Accepted for publication: 16 October 2019; Published online: 8 November 2019

Keywords: industry • regenerative medicine • stem cells

Business development

Collaborations, partnerships & alliances

Codevelopment agreement: Adaptimmune & Noile-Immune

Adaptimmune Therapeutics (UK, www.adaptimmune.com) and Noile-Immune Biotech (Japan, www.noile-immune.com/english/home), biotechnology companies focusing on the development of innovative cancer immunotherapies, have announced that they will codevelop next-generation Specific Peptide Enhanced Affinity Receptor (SPEAR) T-cell products, incorporating Noile-Immune's Proliferation Inducing and Migration Enhancing (PRIME) technology, based upon coexpression of IL-7 and CCL19 [1]. The PRIME technology, which is already being investigated for augmentation of chimeric antigen receptor T (CAR-T)-cell activity, will be investigated with Adaptimmune's SPEAR T cells, as part of Adaptimmune's next-generation programs. Adaptimmune will have exclusive rights to develop and commercialize resulting products on a worldwide basis. Adaptimmune will make an upfront cash payment and milestone payments to Noile-Immune of up to US\$312 million across all programs. Noile-Immune is also entitled to receive mid-single digit royalties on net sales of resulting products. The companies plan to gain regulatory approval for human testing of the first target program by 2021.

Collaboration agreement: Immatics & Celgene

Immatics Biotechnologies (Germany; www.immatics.com), a clinical-stage biopharmaceutical company active in the discovery and development of T-cell redirecting cancer immunotherapies, and Celgene Corporation (NJ, USA; www.celgene.com) have entered into a strategic collaboration and option agreement to develop novel adoptive cell therapies targeting multiple cancers [2]. Celgene secures exclusive options to three Immatics T-cell receptor-engineered T-cell therapy (TCR-T) targets, whereas Immatics will receive US\$75 million upfront payment and may be eligible for future opt-in exercise, milestone and royalty payments.

Immatics may develop TCR-T programs against solid tumor targets discovered with Immatics' XPRESIDENT technology. Programs would utilize proprietary T-cell receptors (TCRs) identified by Immatics' XCEPTOR[®] TCR discovery and engineering platform.

If Immatics develops programs against the TCR-T targets, Immatics will be responsible for the development and validation of these programs through lead candidate stage, at which time Celgene may exercise opt-in rights and assume sole responsibility for further worldwide development, manufacturing and commercialization of the

TCR-T-cell therapies. Immatics would have certain early stage codevelopment rights or cofunding rights for selected TCR-T-cell therapies arising from the collaboration.

Service agreement: iBio & Lung Biotechnology

iBio (NY, USA; www.ibioinc.com) has entered into a Master Services Agreement with Lung Biotechnology (MD, USA; <https://lungbiotechnology.com>), a subsidiary of United Therapeutics Corporation (MD, USA; www.unither.com), to produce recombinant human collagen (rhCollagen)-based bioink for 3D-bioprinted organ transplants [3]. iBio will collaborate with Lung Biotechnology to scale-up production of rhCollagen in tobacco plants using iBio's FastPharming™ System. The FastPharming System combines plant protein expression, automated hydroponics and glycan-engineering technologies to rapidly deliver gram quantities of high-quality biologics for research or further manufacturing. Under the Master Services Agreement, the initial work to be performed by iBio involves the development of a scalable purification process for rhCollagen tailored to the biofabrication of lung scaffolds that United Therapeutics licensed from CollPlant Biotechnologies (Israel; www.collplant.com), as well as cGMP supply of the material for clinical trials. Anticipating the need for commercial quantities of rhCollagen-based bioinks, iBio envisions additional projects focused upon process optimization and capacity expansion, the latter of which will employ iBio's Factory Solutions capabilities.

Clinical trials

T-cells

Eureka Therapeutics

Eureka Therapeutics (CA, USA; www.eurekatherapeutics.com), a clinical stage biopharmaceutical company developing novel T-cell therapies that harness the evolutionary power of the immune system, has initiated a Phase I/II, multicenter, open-label, dose-escalating, clinical trial of ET140202 ARTEMIS™ T-cell therapy in advanced hepatocellular carcinoma (<https://clinicaltrials.gov>; ID: NCT03998033) at City of Hope (CA, USA; www.cityofhope.org) [4]. ET140202 utilizes Eureka's proprietary ARTEMIS antibody TCR platform engineered with a proprietary human TCR-mimic antibody to target an α -fetoprotein-peptide/human leukocyte antigen-A2 complex on hepatocellular carcinoma cancer cells. Data presented in September 2018 from Eureka's ongoing proof-of-concept first-in-human study of ET140202 in China (<https://clinicaltrials.gov>; ID: NCT03965546) demonstrated a favorable safety profile with no observed cytokine release syndrome or drug-related neurotoxicity. The patients who are selected for the clinical trial have metastatic or locally advanced, inoperable liver cancer and have progressed or have not been able to tolerate at least one line of treatment for their disease. The clinical trial tests for safety and proper dosing levels. If the initial study participants react favorably, the trial will move into drug efficacy testing.

NKMax America

NKMax America (CA, USA; <https://nkmaxamerica.com>), a biotechnology company harnessing the power of the body's immune system through the development of natural killer cell therapies, has dosed the first subject in study SNK01-US01, a Phase I clinical trial evaluating SNK, an *ex vivo*-expanded autologous natural killer cell therapeutic, in patients with pathologically confirmed solid cancer refractory to conventional therapy (<https://clinicaltrials.gov>; ID: NCT03941262) [5].

Precigen

Precigen (MD, USA; www.precigen.com), a wholly owned subsidiary of Intrexon Corporation (MD, USA; www.dna.com) and a biopharmaceutical company specializing in the development of innovative gene and cellular therapies, has announced that the first patient has been dosed with Precigen's PRGN-3005, a first-in-class investigational therapy using Precigen's UltraCAR-T™ therapeutic platform [6]. PRGN-3005 UltraCAR-T is an autologous CAR-T-cell therapy manufactured using nonviral gene delivery and is under investigation for the treatment of patients with advanced, recurrent platinum resistant ovarian, fallopian tube or primary peritoneal cancer (<https://clinicaltrials.gov>; ID: NCT03907527). PRGN-3005 utilizes Precigen's transformative UltraCAR-T therapeutic platform, which eliminates *ex vivo* expansion and reduces manufacturing time to allow for rapid next day administration of UltraCAR-T cells following nonviral gene transfer. PRGN-3005 UltraCAR-T is a multigenic CAR-T-cell investigational therapy utilizing Precigen's advanced nonviral gene-delivery system to coexpress a CAR, membrane-bound IL-15 and a kill switch for better precision and control.

Other

DiscGenics

DiscGenics (UT, USA; www.discgenics.com), a clinical-stage biotechnology company focused on developing regenerative cell-based therapies that alleviate pain and restore function in patients with degenerative diseases of the spine, has announced that the first patients have been treated in its Japanese safety study, a clinical trial of IDCT for mild-to-moderate degenerative disc disease (<https://clinicaltrials.gov>; ID: NCT03955315) [7]. IDCT is a homologous, allogeneic, injectable cell therapy that utilizes biomedically engineered progenitor cells, known as ‘Discogenic cells’ that have been derived from intervertebral disc tissue. This prospective, randomized, double-blinded, sham-controlled study is designed to evaluate the safety and preliminary efficacy of IDCT at two dosage levels in subjects with single-level, symptomatic lumbar degenerative disc disease, a major cause of chronic low back pain.

StemCells

StemCells (CA, USA) used the company’s proprietary allogeneic central nervous system (CNS) stem cells (HuCNS-SC) to treat four boys with Pelizaeus–Merzbacher Disease, an X-linked leukodystrophy (<https://clinicaltrials.gov>; ID: NCT01005004). Subsequently, all subjects were followed for an additional 4 years in a separate follow-up study to evaluate safety, neurologic function, MRI data and immunologic response [8]. The neurosurgical procedure, immunosuppression and HuCNS-SC transplantation were well-tolerated and all four subjects were alive at the conclusion of the study period, 5 years post-transplant. Although there was no evidence of tumor development or other long-term adverse clinical effects of stem cell transplantation, two of four subjects developed donor-specific human leukocyte antigen alloantibodies, demonstrating that neural stem cells can elicit an adaptive immune response.

Regulations, approvals & acquisitions

Green light

MustangBio

MustangBio (NY, USA; www.mustangbio.com), a clinical-stage biopharmaceutical company focused on translating today’s medical breakthroughs in cell and gene therapies into potential cures for hematologic cancers, solid tumors and rare genetic diseases, has announced that the US FDA has approved the Company’s Investigational New Drug application to initiate a multicenter Phase I/II clinical trial of MB-102 (CD123 CAR T) in acute myeloid leukemia, blastic plasmacytoid dendritic cell neoplasm and high-risk myelodysplastic syndrome [9].

MB-102 is a CAR-T-cell therapy that is produced by engineering patient T cells to recognize and eliminate CD123-expressing tumors. CD123 is widely expressed on bone marrow cells of patients with myelodysplastic syndrome and hematologic malignancies, including in 75–89% of acute myeloid leukemia patients and over 90% in blastic plasmacytoid dendritic cell neoplasm patients. MB-102 has shown promising response rates in early small populations of these patients in an investigator-sponsored Phase I clinical trial being conducted by City of Hope, where the CAR-T-cell therapy was also developed.

In a separate press release, MustangBio has announced that City of Hope (www.cityofhope.org) has received a US\$9.28 million grant from the California Institute for Regenerative Medicine to fund an ongoing Phase I clinical trial of MB-103 (HER2-specific CAR-T cells) for the treatment of HER2-positive breast cancer with brain metastases (<https://clinicaltrials.gov>; ID: NCT03696030) [10]. City of Hope patents covering the HER2 CAR were licensed to MustangBio in 2017.

MustangBio and St Jude Children’s Research Hospital (TN, USA; www.stjude.org) have announced that MB-107, a lentiviral gene therapy for the treatment of X-linked severe combined immunodeficiency, also known as bubble boy disease, has been granted the Regenerative Medicine Advanced Therapy designation by the US FDA [11]. MustangBio licensed MB-107 from St Jude in August 2018. MB-107 is currently being assessed in two Phase I/II clinical trials for XSCID: the first, in newly diagnosed infants under the age of two (<https://clinicaltrials.gov>; ID: NCT01512888) and the second, in patients over the age of two who have received prior hematopoietic stem cell transplantation (<https://clinicaltrials.gov>; ID: NCT01306019).

Acquisitions

Bayer & BlueRock

Bayer AG (Germany; www.bayer.com) and BlueRock Therapeutics (MA, USA; <https://bluerocktx.com>) have announced an agreement under which Bayer will fully acquire BlueRock Therapeutics, a privately held US-headquartered biotechnology company focused on developing engineered cell therapies in the fields of neurology, cardiology and immunology, using a proprietary-induced pluripotent stem cell platform [12]. Following a 2016 joint venture with Versant Ventures (CA, USA; www.versantventures.com) to establish BlueRock Therapeutics, Bayer will acquire the remaining stake for approximately US\$240 million in cash to be paid upfront at closing and an additional US\$360 million payable upon achievement of predefined development milestones. With Bayer currently holding 40.8% stake, the investment corresponds to a total company value of BlueRock Therapeutics of approximately US\$1 billion. With this transaction, Bayer will own full rights to BlueRock Therapeutics' CELL+GENE™ platform, including a broad intellectual property portfolio and associated technology platform including proprietary-induced pluripotent stem cell technology, gene engineering and cell differentiation capabilities. In addition to its current focus, BlueRock Therapeutics' platform brings the opportunity to extend to other therapeutic areas beyond the current development programs. To preserve the entrepreneurial culture as an essential pillar for nurturing successful innovation, BlueRock Therapeutics' will remain an independent company operating on an arm's length basis.

Capital market & finances

Centers for Medicare & Medicaid Services

The US Centers for Medicare and Medicaid Services has finalized a decision to cover expensive cancer cell therapies sold by Gilead Sciences (CA, USA; www.gilead.com) and Novartis (Switzerland; www.novartis.com) [13]. The Centers for Medicare and Medicaid Services, which runs Medicare – the federal government's health plan for Americans 65 years and older – said it will cover the US FDA-approved therapies when provided in healthcare facilities that have programs in place to track patient outcomes. The nationwide decision clears up 'a lot of confusion' about coverage and will help patients get access to the novel therapies, known as CAR-T.

Lineage Cell Therapeutics

Lineage Cell Therapeutics (CA, USA; www.lineagecell.com), a clinical-stage biotechnology company developing novel cell therapies, has announced that it has been awarded a new US\$670,621 Small Business Innovation Research grant to advance its Vision Restoration Program, generating 3D human retinal tissue derived from pluripotent cells [14]. Lineage's Vision Restoration Program aims to address a wide range of severe retinal degenerative conditions including retinitis pigmentosa, advanced forms of age-related macular degeneration and ocular trauma. The program and its award are distinct from OpRegen, the Company's clinical-stage cell therapy program, which features the subretinal delivery of retinal pigment epithelium cells for the treatment of dry age-related macular degeneration.

Financial & competing interests disclosure

Dusko Ilic has received an honorarium from Future Science Group for the contribution of this work. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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