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

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Business development

Collaborations, partnerships & alliances

Collaboration agreement: Phio & Glycostem

Phio Pharmaceuticals (MA, USA; www.phiopharma.com) has entered into a research collaboration with Glycostem Therapeutics (The Netherlands; www.glycostem.com) to explore the potential synergies of using Phio's self-delivering RNAi technology, sd-rxRNA[®], in combination with Glycostem's proprietary natural killer cell (NK cell) generation technology, oNKord[®], to develop cellular immunotherapies for cancer treatment with enhanced efficacy and/or safety [1].

License agreement: Gilead & MaxCyte

Gilead's Kite Pharma (CA, USA; www.kitepharma.com) has expanded its chimeric antigen receptor T (CAR-T) agreement with MaxCyte (MD, USA; www.maxcyte.com) [2]. The revised deal gives Kite the chance to apply MaxCyte's transfection technology to up to ten targets. Kite first struck a deal to use MaxCyte's technology, dubbed Flow Electroporation, in November 2018. Now, Kite has significantly expanded the deal by securing the right to use the technology in the nonviral engineering of CAR-T therapies against up to ten targets. MaxCyte granted Kite nonexclusive access to the technology in return for a financial package featuring development and approval milestones. MaxCyte is working on its own CAR-T candidates while licensing its technology to other companies. For its in-house pipeline, MaxCyte has used the technology to create autologous CAR-Ts using human mRNA.

License agreement: NantKwest & ProMab

NantKwest (CA, USA; www.nantkwest.com), a clinical-stage NK cell-based therapeutics company, and ProMab Biotechnologies (CA, USA; www.promab.com) have announced the establishment of a worldwide license to a B-cell maturation antigen-targeted antibody sequence for multiple myeloma along with an option for up to five undisclosed targeting sequences for exclusive use in the development of CAR-based NK-cell therapies [3].

License agreement: Sana & Harvard

Sana Biotechnology (WA, USA; <http://sana.com>) has executed a license agreement with Harvard's Office of Technology Development (MA, USA; <http://otd.harvard.edu>) [4]. Harvard's foundational technology consists of methods for producing hypoinmunogenic stem cells, which can be differentiated into any cell type and then transplanted into a patient without triggering immune rejection. The hypoinmunogenic stem cells are derived from human pluripotent stem cells that have been genetically engineered to appear benign to, effectively hiding

from, the immune system. To achieve this outcome, the inventors modified the cells' genomes to reduce the activity of genes that produce proteins that can provoke the transplant recipient's immune system, and to increase the activity of genes that produce tolerogenic factors that signal 'friend' not 'foe'. In addition to the platform technology, which is exclusively licensed to Sana within the field of therapeutics, the license agreement grants Sana nonexclusive access to Harvard technology for performing high-efficiency, *ex vivo* genome editing.

Manufacturing agreement: TCR² & Catapult

TCR Therapeutics (MA, USA; www.tcr2.com) has selected the advanced therapy medicinal products ecosystem in the UK to establish a site for global manufacturing systems and capabilities [5]. TCR will work with Cell and Gene Therapy Catapult (CGT Catapult; UK; <https://ct.catapult.org.uk>) at their Stevenage manufacturing center to produce its novel T cell receptor (TCR) therapies based on the company's proprietary TCR Fusion Construct, TRuC™, T cells. TRuC T cells specifically recognize and kill cancer cells by harnessing the entire TCR signaling complex independent of human leukocyte antigen. In preclinical studies, TRuC T cells have demonstrated superior antitumor activity compared with CAR-T cells, while exhibiting lower levels of cytokine release. The company's lead TRuC T cell product candidate, TC-210, is currently being studied in a Phase I/II clinical trial to treat patients with mesothelin-positive non-small-cell lung cancer, ovarian cancer, malignant pleural/peritoneal mesothelioma, and cholangiocarcinoma. TCR Therapeutics is the first US company to establish manufacturing operations at the CGT Catapult manufacturing center in Stevenage, which was opened in April 2018 backed by more than US\$78 (£60) million of UK government investment as part of the Industrial Strategy Challenge Fund.

Marketing agreement: Avita & COSMOTEC

Avita Medical (CA, USA; www.avitamemedical.com) has set an agreement with COSMOTEC (Japan, <http://cosmotec.com/english/>), an M3 Group company (<https://corporate.m3.com/en/>), to market and distribute the RECELL® Autologous Cell Harvesting Device for the treatment of burns and other wounds in Japan [6]. In addition, COSMOTEC filed on a Japan's Pharmaceuticals and Medical Devices Act application for approval to market the RECELL System in Japan. Japan is the second largest healthcare market in the world with >6000 patients with severe burns treated in hospitals each year.

Achievements

STEMCELL Technologies

STEMCELL Technologies (BC, Canada; www.stemcells.com) has been selected as a winner of Canada's Best Managed Companies program for 2019. Canada's Best Managed Companies is the country's leading business awards program, recognizing excellence in the management abilities and practices of Canadian owned and managed companies with revenues over C\$15 million [7]. STEMCELL Technologies is Canada's largest biotechnology company, privately owned. It currently employs more than 1200 individuals with >40 languages spoken across the company and a >50% female workforce at all levels. The company provides high-quality scientific tools and services to 22 countries directly, and >100 countries via distributors. Focused on long-term growth, STEMCELL reinvests all profits into the company; the goal is to see global sales of over C\$1 billion and 5000 employees by 2029.

Launching new products, services...

bluebird

bluebird bio (MA, USA; www.bluebirdbio.com) has officially opened its first wholly owned manufacturing facility in Durham (NC, USA), which will produce lentiviral vector for the company's investigational gene and cell therapies, including bb2121 and bb21217 for the treatment of multiple myeloma and potentially ZYNTEGLO™, autologous CD34⁺ cells encoding β -globin gene (formerly known as LentiGlobin™) for the treatment of transfusion-dependent β -thalassemia and sickle cell disease [8].

NanoSurface

NanoSurface Biomedical (WA, USA; www.nanosurfacebio.com) has launched the NanoSurface Car(ina)™ platform for highly predictive preclinical drug screening, using structurally matured human-induced pluripotent stem cell-derived heart tissues [9].

Clinical trials

Mesenchymal stromal/stem cells

BrainStorm

BrainStorm Cell Therapeutics (NY, USA; www.brainstorm-cell.com) has announced that the first patient has been enrolled in its Phase II open-label, multicenter study of repeated intrathecal administration of autologous mesenchymal stromal/stem cells (MSC)-neurotrophic factor (NTF) cells in participants with progressive multiple sclerosis (www.clinicaltrials.gov; ID: NCT03799718) [10]. Autologous MSC-NTF cells, NurOwn[®], are produced from autologous, bone marrow-derived MSCs, which have been expanded and differentiated *ex vivo*. MSCs are converted into MSC-NTF cells by growing them under patented conditions, which induce the cells to secrete high levels of neurotrophic factors. Autologous MSC-NTF cells can effectively deliver multiple NTFs and immunomodulatory cytokines directly to the site of damage to elicit a desired biological effect and ultimately slow or stabilize disease progression.

Pluristem

Pluristem (Israel; www.pluristem.com) has fully enrolled the second cohort of six patients in its ongoing Phase I clinical study evaluating PLX-R18 for the treatment of incomplete hematopoietic recovery following hematopoietic stem cell transplantation (HTCS), and has received Data and Safety Monitoring Board approval to continue to the final cohort of the study (www.clinicaltrials.gov; ID: NCT03002519) [11]. Results from the first two cohorts demonstrate PLX-R18 is safe and well tolerated, with early signals of efficacy in improving blood counts. The third and final cohort will be comprised of 15 patients who will receive two administrations of four million PLX-R18 cells/kg, 1 week apart, considered as the target dose for these patients. PLX-R18 cell therapy for the treatment of incomplete hematopoietic recovery following HTCS was granted Orphan Drug Designation by the US FDA.

Hematopoietic stem cells

Rocket

Rocket Pharmaceuticals (NY, USA; www.rocketpharma.com) has announced that the first patient has been dosed in the open-label, Phase I clinical trial of RP-L102, the company's self-inactivating lentiviral vector-based gene therapy for the treatment of Fanconi anemia [12]. The *ex vivo* administration process begins with the removal and isolation of hematopoietic stem cells using a CD34⁺ selection process. Autologous genetically modified CD34⁺ enriched hematopoietic cells (fresh or cryopreserved) are infused back into patients to restore function. RPL102 is currently being studied in a Phase I/II clinical trial in the EU with an Investigational Medicinal Product Dossier in place with the Spanish Agency for Medicines and Health Products. RP-L102 is also being studied in a Phase I clinical trial in the USA under the company's Investigational New Drug (IND) application for RPL102 that utilizes 'Process B', which incorporates higher cell doses, transduction enhancers and commercial-grade vector and cell processing. RP-L102 has been granted Orphan Drug, Fast Track and Regenerative Medicine Advanced Therapy designations for the treatment of Fanconi anemia type A in the USA and Advanced Therapy Medicinal Product classification and Orphan Drug Designation in Europe.

Regulations, approvals, acquisitions...

Japan

On 1 March 2019, Japan's Ministry of Education, Culture, Sports, Science and Technology deregulated human-animal chimeric embryo research for the production of human organs in animals. The Ministry of Education, Culture, Sports, Science and Technology's newly released guidelines effectively approved the production of human-animal chimeras, or chimeric individuals [13].

Green light

bluebird

bluebird bio (MA, USA; www.bluebirdbio.com) has announced that the Committee for Medicinal Products for Human Use of the EMA adopted a positive opinion recommending conditional marketing authorization for ZYNTGLO, a gene therapy for patients 12 years and older with transfusion-dependent β -thalassemia who do not have a β/β genotype, for whom hematopoietic stem cell transplantation is appropriate but a human leukocyte

antigen-matched-related HSC donor is not available [14]. ZYNTEGLO, formerly referred to as LentiGlobin for transfusion-dependent β -thalassemia, will be the first gene therapy to treat this disease.

CARsgen

CARsgen Therapeutics (China; www.carsgen.com), a clinical-stage company committed to developing CAR-T cell therapies for cancer, has announced that one of its leading drug candidates, CT053 fully human B-cell maturation antigen-CAR-T cell for the treatment of patients suffering from relapsed/refractory multiple myeloma, has received IND clearance from the National Medical Products Administration (China; www.emergobyul.com/resources/china/china-food-drug-administration) [15].

Rubius

Rubius Therapeutics (MA, USA; www.rubiustx.com) has announced that FDA has cleared the company's IND application for RTX-134, an allogeneic, off-the-shelf cellular therapy for the potential treatment of patients with phenylketonuria [16]. RTX-134 is a Red Cell Therapeutic™ product candidate that is genetically engineered to express the enzyme phenylalanine ammonia lyase inside the cell. RTX-134 is designed to circulate in the blood stream and degrade toxic levels of phenylalanine, which accumulate due to a deficiency in the phenylalanine hydroxylase enzyme. Compared with current therapeutic interventions, RTX-134 may have a more sustained treatment effect given the 120-day circulating time of red blood cells and may have a lower incidence of immune-driven adverse events, including the formation of neutralizing antibodies to the therapeutic enzyme, which often results in a reduction in efficacy. As a result, RTX-134 may provide a more efficacious and convenient treatment option to patients. The Phase Ib clinical trial is expected to be the first-ever clinical investigation of genetically engineered red blood cells. The company plans to begin enrollment during the second quarter of 2019, with initial clinical data expected during the second half of 2019.

Acquisitions

Xenetic

Xenetic Biosciences (MA, USA; www.xeneticbio.com) has announced its agreement to acquire the novel CAR-T platform technology, called 'XCART', a proximity-based screening platform capable of identifying CAR constructs, which can target patient-specific tumor neoantigens, with a demonstrated proof of mechanism in B-cell non-Hodgkin lymphomas [17]. The XCART technology, developed by The Scripps Research Institute (CA, USA; www.scripps.edu) in collaboration with the Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry (Russia; www.ibch.ru/en), is believed to have the potential to significantly enhance the safety and efficacy of cell therapy for B-cell lymphomas by generating patient- and tumor-specific CAR-T cells. Essentially, the XCART screening platform is the inverse of a typical CAR-T screening protocol wherein libraries of highly specific antibody domains are screened against a given target. In the case of XCART screening, the target is itself an antibody domain, and hence highly specific by its nature. The XCART technology creates the possibility of personalized treatment of lymphomas utilizing a CAR with an antigen-binding domain, which should only recognize, and only be recognized by, the unique B cell receptor of a particular patient's B-cell lymphoma.

Capital market & finances

AgeX

AgeX Therapeutics (CA, USA; www.agexinc.com), a biotechnology company focused on innovative therapeutics for human aging, has received US\$4.5 million from the exercise of AgeX common stock warrants [18]. Warrant holders purchased a total of 1,800,000 shares of AgeX common stock through the exercise of warrants at an exercise price of US\$2.50 per share. The warrants were issued to investors by AgeX during 2018. Any warrants that were not exercised have expired.

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