Industry updates from the field of stem cell research and regenerative medicine in March 2020

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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 2020.

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Business development

Collaboration agreement: Allovir & Baylor

AlloVir (MA, USA; www.allovir.com), a late-clinical stage T-cell immunotherapy company, has announced the expansion of its research and development collaboration with Baylor College of Medicine (TX, USA; www.bcm.edu) to include the discovery and development of allogeneic, off-the-shelf, virus-specific T-cell therapies to combat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19 [1]. With AlloVir's proprietary technology, in addition to targeting SARS-CoV-2, the investigational virus-specific T-cell therapy may also address other coronavirus (CoV) strains including SARS-CoV and Middle East respiratory syndrome-related (MERS-CoV) as well as the endemic CoVs that commonly afflict immunocompromised patients. AlloVir aims to develop a therapy for CoVs that can be used as a stand-alone treatment or incorporated into the company's multi-respiratory virus investigational therapy, ALVR106, which is designed to address other devastating and life-threatening community-acquired respiratory viruses.

AlloVir uses natural immune stimulant proteins called cytokines combined with nonharmful fragments of the virus to activate and expand naturally occurring cells against target viruses. These cells are then provided to immunocompromised patients in order to restore natural T cell immunity to prevent and/or treat associated viral infections and diseases. AlloVir has developed a proprietary manufacturing process that allows for a bank of virus-specific T cells to be developed from a small number of carefully chosen, healthy, virus-immune, third-party donors. AlloVir's virus-specific T-cells therapies do not require exact immunological matching to patients, allowing hundreds of patients to be treated with virus-specific T cells manufactured from a single donor. AlloVir's therapies can be stored in a frozen state and thus supplied rapidly and globally as an off-the-shelf therapy for patients suffering from, or at risk for, one or more viral infections and diseases.

Collaboration agreement: Avectas & Centre for Commercialization of Regenerative Medicine

Avectas (Ireland; www.avectas.com), a cell engineering technology business and Centre for Commercialization of Regenerative Medicine (CCRM; ON, Canada; www.ccrm.ca), a not-for-profit organization funded by the Government of Canada, the Province of Ontario and leading academic and industry partners to support the development of regenerative medicines and associated enabling technologies, with a specific focus on cell and gene therapy, have entered into a collaboration to accelerate the translation of Avectas' nonviral cell engineering platform Solupore[®] into the clinic [2]. Cell and gene therapies offer the potential to dramatically transform the treatment of diseases, including cancer, for millions of patients worldwide. However, a global viral vector shortfall could halt

progress in the industry as very few contract development and manufacturing organizations have the capabilities required to manufacture vectors that can deliver molecules to cells. Avectas developed Solupore to address an urgent need for an efficient, nonviral cell engineering solution to facilitate therapeutic development in the areas of immuno-oncology and gene editing. Solupore is designed for use with mRNA, DNA and proteins, including gene editing tools such as CRISPR. It achieves excellent engineering efficiencies for delivery of these payloads to primary T cells and natural killer (NK) cells for immuno-oncology and gene editing applications.

Collaboration agreement: Avectas & CCRM

Avectas (Ireland; www.avectas.com) has entered into a collaboration agreement with Vycellix (FL, USA; www.vycellix.com), a private, immuno-discovery, life science company working on the development of cell and gene-based therapies [3]. The companies will collaborate on the delivery of Vycellix's novel RNA immunomodulator VY-M using Avectas' cell engineering platform, Solupore.

License agreement: Oxford Biomedica & Juno

Oxford Biomedica (UK; www.oxb.com), a gene and cell therapy company, has signed a new license and clinical supply agreement (LSA) with Juno Therapeutics (WA, USA; www.junotherapeutics.com), a Bristol-Myers Squibb (NY, USA; www.bms.com) company [4]. The LSA grants Juno Therapeutics, a nonexclusive license to Oxford Biomedica's LentiVector[®] platform for its application in CAR-T and TCR-T programs in oncology and other indications and additionally puts in place a 5-year clinical supply agreement, which may be extended further. Under the terms of the LSA, Oxford Biomedica will receive an upfront payment of US\$10 million in cash and potentially up to US\$86 million upon achievement of certain development and regulatory milestones related to multiple products and indications. Oxford Biomedica is also entitled to receive up to US\$131 million in sales-based milestone payments and an undisclosed royalty on the net sales of products sold by Juno Therapeutics utilizing the LentiVector platform. Oxford Biomedica will also receive payments from process development and scale-up projects as well as relating to the good manufacturing practices (GMP) manufacture of lentiviral vectors for use in clinical trials. As part of the LSA, Juno Therapeutics will have access to Oxford Biomedica's new 7800 m² commercial manufacturing center OxBox, in Oxford, UK. Oxford Biomedica is already working on four undisclosed active projects, with Juno able to initiate additional projects in the future.

Launching new products & services

Century Therapeutics

Century Therapeutics (PA, USA; www.centurytx.com), developer of genetically engineered, universal induced pluripotent stem cell (iPSC)-derived immune effector cell products (NK, T, DC and macrophage) designed to specifically target hematologic and solid tumor cancers, has announced the opening of its Seattle, WA, USA-based Innovation Hub to develop next-generation product candidates that overcome barriers that have limited the effectiveness of cell therapies in solid tumor cancers [5]. The site will advance the company's novel iPSC science and allogeneic cell products by establishing expertise in data sciences and machine learning, synthetic biology, cancer biology and immuno-oncology.

Kuur Therapeutics

Kuur Therapeutics (TX, USA; www.kuurtx.com) has launched its new business in partnership with Baylor College of Medicine (TX, USA; www.bcm.edu) and Baylor's Center for Cell and Gene Therapy (TX, USA; www.bcm.edu/centers/cell-and-gene-therapy) [6]. The company will advance the work of its predecessor, Cell Medica, to develop anticancer therapies using its innovative chimeric antigen receptor NK T cell (CAR-NKT) therapy platform. IP Group, Baylor College of Medicine and Schroeder Adveq are investing to support two Phase I studies: GINAKIT 2 (autologous CAR-NKT cells in neuroblastoma) and ANCHOR (allogeneic CAR-NKT cells in CD19 malignancy). The ongoing GINAKIT2 study is now enrolling patients at the third dose level and the ANCHOR study IND has recently been approved by the US FDA, with first patient treatment expected in 1H 2020. The funding will also support the preclinical development of an allogeneic CAR-NKT product for treatment of hepatocellular carcinoma, ahead of an IND submission anticipated in 1H 2021. One of the challenges with allogeneic therapies is that infusing a patient with donor-derived lymphocytes can induce graft-versus-host disease, a potentially life-threatening condition in which the infused cells recognize the patient's tissues as foreign. The NKT cells used in Cell Medica's CAR-NKT platform have an invariant T cell receptor that does not distinguish between self- and

nonsell-tissues, making them unlikely to induce graft-versus-host disease when given to another person. Kuur's CAR-NKT cells are also engineered to secrete IL-15, to prolong persistence and enhance antitumor activity.

Achievements

NanoSurface Biomedical

NanoSurface Biomedical (WA, USA; www.nanosurfacebio.com) has executed an exclusive IP license agreement related to innovative heart-on-chip technology developed by researchers at the University of Washington (UW; WA, USA; www.washington.edu) [7]. An experimental system built from the same heart-on-chip technology was launched into space on Friday, 6 March 2020 at 11:50 p.m. EST aboard SpaceX's 20th resupply mission to the International Space Station (ISS) as part of the Tissue Chips in Space initiative conducted in partnership between the National Center for Advancing Translational Sciences and the ISS US National Laboratory (ISS National Lab). NanoSurface will commercialize the heart-on-chip platform for use by pharmaceutical companies in preclinical drug development. The heart-on-chip system will spend 30 days aboard the ISS as part of a series of experiments intended to study the effects of microgravity on human cells and tissues. The heart-on-chip platform uses 3D engineered cardiac tissues (3D ECTs) grown from human cardiomyocytes or beating heart cells, derived from iPSCs. As the 3D ECTs beat, researchers can measure the amount of force generated by each contraction and then evaluate how that force changes after treating the tissues with candidate drugs. The 3D ECTs can be made from cells from either healthy individuals or individuals with diseases, offering great promise in predictive preclinical testing of candidate drugs for safety and efficacy.

Clinical trials

Mesenchymal stromal/stem cells

Celltex

Celltex Therapeutics (TX, USA; <https://celltexbank.com>) has begun active discussions with the FDA regarding a study using mesenchymal-like cells (MSCs) against COVID-19-type symptoms [8].

Cellenkos

Cellenkos (TX, USA; www.cellenkosinc.com) has submitted a clinical development proposal to the Biomedical Advanced Research and Development Authority to start a Phase I/II clinical trial with CK0802 for treatment of COVID-19 mediated acute respiratory distress syndrome (ARDS) [9]. Cellenkos will leverage its clinical experience with CK0802 for other inflammatory disorders, including amyotrophic lateral sclerosis and fast-track development of CK0802 to treat respiratory complications caused by COVID-19 infection.

Lattice

Lattice Biologics (MO, USA; www.latticebiologics.com) has begun enrolling patients in its Phase I clinical trial to address safety and efficacy of its stem cell technology, AmnioBoost, for the treatment of SARS related to COVID-19 infection [10]. AmnioBoost is derived from amniotic fluid taken from nonrelated, healthy, living donors during a caesarian delivery. The baby is not harmed in any way. To be eligible for the US trial, individuals must have laboratory confirmed infection with COVID-19 and evidence of lung involvement requiring supplemental oxygen or mechanical ventilation. The study will not enroll individuals with mild symptoms or individuals who are asymptomatic. All potential patients will undergo a physical exam, participants will then be randomized into the investigational group or the placebo group. Individuals enrolled into the investigational group will receive ~ 5 million stem cells of AmnioBoost on the first day of enrollment and will receive another ~ 5 million stem cells on the second day of enrollment. Clinicians will monitor the patients' temperature, blood pressure, need for supplemental oxygen and other factors daily to determine daily scores based on a scale of clinical outcomes. In the initial stage of investigation, the clinicians will compare participant outcomes on the seventh day in both groups, to assess if AmnioBoost treatment has produced any clinical benefit. The study will be halted if there is no evidence of a treatment difference between AmnioBoost and placebo. Initial patient enrollment in the trial will be limited to ten patients and conducted in the Seattle area, WA, USA.

Mesoblast

Mesoblast (Australia; www.mesoblast.com) has announced that it plans to evaluate its allogeneic MSC product candidate remestemcel-L in patients with ARDS caused by COVID-19 in the USA, Australia, China and Europe [11].

The company is in active discussions with various government and regulatory authorities, medical institutions and pharmaceutical companies to implement these activities. Mortality in COVID-19 infected patients with the inflammatory lung condition ARDS is reported to approach 50% and is associated with older age, co-morbidities such as, diabetes, higher disease severity and elevated markers of inflammation [12]. Current therapeutic interventions do not appear to be improving in-hospital survival. Remestemcel-L has potential for use in the treatment of ARDS, which is the principal cause of death in COVID-19 infection. This is supported by recently published results from an investigator-initiated clinical study conducted in China which reported that allogeneic MSCs cured or significantly improved functional outcomes in all seven treated patients with severe COVID-19 pneumonia [13]. Additionally, in *post-hoc* analyses of a 60-patient randomized controlled study in chronic obstructive pulmonary disease, remestemcel-L infusions were well tolerated, significantly reduced inflammatory biomarkers and significantly improved pulmonary function in those patients with elevated inflammatory biomarkers. Since the same inflammatory biomarkers are also elevated in COVID-19, these data suggest that remestemcel-L could be useful in the treatment of patients with ARDS due to COVID-19.

Pluristem

Pluristem Therapeutics (Israel; www.pluristem.com) has signed a collaborative agreement with the BIH Center for Regenerative Therapy and the Berlin Center for Advanced Therapies at Charité University of Medicine Berlin to expand its existing framework and research agreement and conduct a joint project evaluating the therapeutic effects of Pluristem's patented PLX cell product candidates for potential treatment of the respiratory and inflammatory complications associated with the COVID-19 CoV [14]. PLX cells are allogeneic MSC that have immunomodulatory properties that induce the immune system's natural regulatory T cells and M2 macrophages and thus may prevent or reverse the dangerous overactivation of the immune system. Accordingly, PLX cells may potentially reduce the fatal symptoms of COVID-19 induced pneumonia and pneumonitis. Previous preclinical findings of PLX cells, revealed significant therapeutic effects in animal studies of pulmonary hypertension, lung fibrosis, acute kidney injury and gastrointestinal injury which are potential complications of the severe COVID-19 infection. Clinical data using PLX cells demonstrated the strong immunomodulatory potency of PLX cells in patients post major surgery. Taken together, PLX cells' potential capabilities with the safety profile observed from clinical trials involving hundreds of patients worldwide potentially position them as a therapy for mitigating the tissue-damaging effects of COVID-19.

Following the approval of the Israeli Ministry of Health, Pluristem has already dosed three patients in two different hospitals in Israel under a compassionate use program for the treatment of COVID-19 [15,16]. Pluristem expects to enroll additional patients in Israel in the coming days and anticipates providing updates on clinical outcomes once significant data has been gathered. All three treated patients are in a high-risk group based on age and pre-existing conditions, have been experiencing severe respiratory failure and intubation with a ventilator. Pluristem is closely following the medical condition of these patients in conjunction with the hospitals' medical professionals delivering the care.

Immune system cells

GEMoaB

GEMoaB (Germany; www.gemoab.com), a privately-owned biopharmaceutical company focused on the development of immunotherapies for hard-to-treat cancers, has apheresed the first patient in a Phase IA study with UniCAR-TCD123 (<https://clinicaltrials.gov>; ID:NCT04230265), the lead product candidate from its proprietary UniCAR cellular immunotherapy platform [17]. UniCAR has been designed to ensure excellent control over the universal CAR-T effector cell through a rapidly switchable on/off capability. This is combined with high flexibility to effectively target tumor antigens of choice by re-directing and activating CAR-T effector cells through soluble adapters termed 'targeting modules'. UniCAR-T-CD123 is investigated in late stage, relapsed/refractory acute leukemia expressing the CD123 antigen. The Phase IA study includes patients with CD123 positive relapsed/refractory acute myeloid leukemia post standard treatment as well as CD123 positive relapsed/refractory acute lymphoblastic leukemia post CD19-targeting therapies and will examine the feasibility, safety and potential efficacy of the combined application of a single dose of UniCAR-T and the continuous infusion of the CD123 specific targeting module TM123.

Standard CAR-T cells depend on the presence and direct binding of cancer antigens for activation and proliferation. An inherent key feature of the UniCAR platform is a rapidly switchable on/off mechanism (less than 4 h after interruption of targeting modules supply) enabled by the short pharmacokinetic half-life and fast internalization

of soluble adaptors termed targeting modules. These targeting modules provide the antigen-specificity to activate UniCAR gene-modified T cells (UniCAR-T) and consist of a highly flexible antigen-binding moiety, linked to a small peptide motif recognized by UniCAR-T.

NantKwest

NantKwest (CA, USA; www.nantkwest.com), a clinical-stage immunotherapy company focused on NK cells to treat cancer and infectious diseases, has announced dosing of the first patient in a Phase II trial for second- and third-line Merkel cell carcinoma (MCC), an aggressive type of skin cancer, in patients who are refractory to immune checkpoint inhibitors [18]. The trial will evaluate the company's first-in-class, off-the-shelf CD16-targeted NK (haNK) cells in combination with ImmunityBio's (CA, USA; <https://immunitybio.com>) IL-15 superagonist N-803 and Avelumab. Avelumab is a fully human monoclonal antibody targeting PDL1 developed by Merck (Germany; www.merck.com) and Pfizer (NY, USA; www.pfizer.com) as a pharmaceutical drug for use in immunotherapy, originally for the treatment of non-small-cell lung carcinoma. It has received orphan drug designation by the EMA for the treatment of gastric cancer in January 2017. The FDA approved it in March 2017 for MCC. The EMA approved it in September 2017 for the same indication. Patients with metastatic or locally advanced MCC have an extremely poor prognosis, with less than 20% of patients surviving longer than 5 years. Typically, these patients are treated with a range of drugs, including chemotherapy, which can result in significant side effects. Although new immune therapies have the potential to improve survival, MCC is still fatal for a majority of patients who have progressed on or after treatment with a checkpoint inhibitor and represents an unmet medical need. The single-arm study will involve 43 patients who failed all standard of care treatments for MCC, including checkpoint therapy (QUILT-3.063; <https://clinicaltrials.gov>; ID:NCT03853317). Clinical trial sites are currently being activated. In January 2020, NantKwest and ImmunityBio have announced a complete response in metastatic pancreatic cancer in the first patient to receive PD-L1 tumor-targeted NK cells (PDL1.t-haNK) combined with IL-15 superagonist N-803.

Other cell types

Avita

AVITA Medical (Australia; www.avitamedical.com), a regenerative medicine company with a technology platform positioned to address unmet medical needs in therapeutic skin restoration, has initiated a study for soft tissue reconstruction with the enrollment of the first patient at the AZ, USA [19]. This study will evaluate the safety and effectiveness of the RECELL[®] System when used as an adjunct to meshed autografts in patients undergoing reconstruction of skin defects not associated with a burn injury. The RECELL System (<https://recellsystem.com>) is used to prepare Spray-On Skin[™] Cells using a small amount of a patient's own skin, providing a new way to treat severe burns, while significantly reducing the amount of donor skin required. The RECELL System is designed to be used at the point of care alone or in combination with autografts depending on the depth of the burn injury.

The company also announced the initiation of a trial for the treatment of pediatric scald injuries with enrollment of the first patient at the Arizona Burn Center at Valleywise Medical Health Center in Phoenix, AZ [20]. This study seeks to demonstrate that treatment with the RECELL System of partial-thickness burn injuries within 72-h can safely and effectively increase the incidence of healing at the tenth day when compared with a standard wound dressing.

Regulations, approvals & acquisitions

Green light

AlloVir

AlloVir (MA, USA; www.allovir.com), a late-clinical stage allogeneic T-cell immunotherapy company, has been granted Orphan Drug Designation from the EMA for Viralym-M (ALVR105) as a potential treatment of viral diseases and infections in patients undergoing hematopoietic stem cell transplantation [21]. Viralym-M is the company's lead allogeneic, off-the-shelf, multivirus-specific T-cell therapy, being developed for the treatment and prevention of serious viral diseases caused by six commonly occurring, devastating viral pathogens in immunocompromised individuals: BK virus, cytomegalovirus, human herpes virus-6, Epstein Barr virus, adenovirus and John Cunningham (JC) virus. Viral diseases are a primary reason for poor outcomes in transplant patients, resulting in potentially devastating and life-threatening consequences. In addition to Orphan Drug Designation, Viralym-M has been granted PRIority MEdicines designation from the EMA and regenerative medicine advanced therapy designation from the FDA. Viralym-M is one of only seven investigational therapies, to date, to receive both PRI-

ority MEDicines and regenerative medicine advanced therapy designations from the EMA and FDA, respectively. AlloVir plans to initiate Phase III pivotal and Phase II proof-of-concept studies with Viralym-M in 2020 targeting six commonly occurring, devastating and life-threatening viral pathogens.

Arcellx

Arcellx (MD, USA; www.arcellx.com), a clinical-stage biopharmaceutical company devoted to developing immune cell therapies for cancer and other diseases, has announced that the FDA has granted Orphan Drug Designation to CART-ddBCMA, its engineered T-cell therapy utilizing a novel binding domain, for the treatment of patients with multiple myeloma (<https://clinicaltrials.gov>; ID: NCT04155749) [22]. Arcellx continues to enroll patients in its Phase I trial of CART-ddBCMA therapy for the treatment of relapsed and refractory multiple myeloma, the first in a series of clinical trials planned for the stepwise development of the Arcellx ARC-T + sparX cell therapy platform. This trial marks the first-in-human trial of the Arcellx binding domain, which the company plans to evaluate in future ARC-T + sparX trials.

AVROBIO

AVROBIO (MA, USA; www.avrobio.com), a clinical-stage gene therapy company, has announced that the FDA has granted orphan drug designation to the company's investigational gene therapy, AVR-RD-04, for the treatment of cystinosis [23]. The gene therapy consists of the patient's own hematopoietic stem cells, which are genetically modified to express cystinosin, the protein that is functionally deficient in people with cystinosis. A Phase I/II clinical trial to evaluate the safety and efficacy of the investigational gene therapy in patients with cystinosis is actively enrolling up to six participants and is funded by grants to the University of California, San Diego (UCSD; CA, USA; www.ucsd.edu) from the California Institute for Regenerative Medicine (CIRM; www.cirm.ca.gov) as well as the Cystinosis Research Foundation (CRF; CA, USA; www.cystinosisresearch.org).

ImStem

ImStem Biotechnology (CT, USA; www.imstem.com), a biopharmaceutical company pioneering the development of MSC derived from human embryonic stem cells through a proprietary method using a trophoblast intermediate stage (hence also known as T-MSC) for the treatment of neurological, autoimmune and rare orphan diseases, has received notification from the FDA that it has lifted the hold and cleared the investigational new drug application to evaluate IMS001 for the treatment of multiple sclerosis [24]. IMS001 was derived from the pluripotent cell line ESI-053 licensed from AgeX (CA, USA; www.agexinc.com).

Red light

Rubius

Rubius Therapeutics (MA, USA; www.rubiustx.com) has pulled the plug on its lead drug RTX-134 after its first use in a Phase Ib generated 'uninterpretable' data [25]. While there were no reported adverse events and RTX-134 administration was well tolerated, the results from the first patient were uninterpretable possibly due, in part, to the low dose of cells administered and the sensitivity of the flow cytometry assay used to detect circulating cells. The data capped off a series of setbacks for the phenylketonuria asset, leading Rubius to stop the trial and focus instead on its oncology and autoimmunity prospects. Without RTX-134 spearheading its pipeline, Rubius is left reliant on solid tumor cell therapy RTX-240 to provide early clinical validation of its platform. Red Cell Therapeutics are engineered to express biotherapeutic proteins within or on their cell surface to create highly selective, potent and allogeneic cellular medicines aimed at treating a range of diseases. They can potentially be used to kill tumors in cancer and regulate the immune system for the treatment of autoimmune diseases. The FDA recently cleared an investigational new drug of the candidate, which expresses 4-1BBL and IL-15TP, but Rubius is yet to dose a patient.

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