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

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Business development

Collaborations, partnerships & alliances

Codevelopment agreement: Allele & SCM Lifescience

Allele Biotechnology and Pharmaceuticals (CA, USA; www.allelebiotech.com) has announced a joint research and development agreement with SCM Lifescience (Korea; <http://www.scmlifescience.co.kr/en/>) for the development of diabetes therapies using pancreatic β cells derived from induced pluripotent stem cells (iPSCs) [1].

Codevelopment agreement: Bayer & Khloris

Leaps by Bayer, the investment arm of the global life sciences company Bayer (Germany; www.bayer.us), and Khloris Biosciences (CA, USA; www.khlorisbiosciences.com) have announced that they have joined forces to develop novel, first-in-class anticancer vaccines based on human iPSCs [2]. This technology has the potential to address one of today's biggest issues in human health: to prevent and cure cancer [3].

Collaboration agreement: Editas & Blue Rock

Editas Medicine (MA, USA; www.editasmedicine.com), a genome editing company, and BlueRock Therapeutics (MA, USA; www.bluerocktx.com), an engineered cell therapy company, have announced a strategic research collaboration and cross-licensing agreement to combine their respective genome editing and cell therapy technologies to discover, develop and manufacture novel engineered cell medicines [4].

Collaboration agreement: Fibrocell & Castle Creek

Fibrocell Science (PA, USA; www.fibrocell.com) has completed a collaboration agreement with Castle Creek Pharmaceuticals (NJ, USA; www.castlecreekpharma.com) to develop and commercialize Fibrocell's lead gene therapy candidate, FCX-007, for the treatment of recessive dystrophic epidermolysis bullosa, a rare, life-threatening genetic disorder diagnosed at infancy with no cure or treatment approved by the US FDA [5]. FCX-007 is a genetically modified autologous fibroblast that encodes the gene for COL7. By genetically modifying autologous fibroblasts *ex vivo* to produce COL7, culturing them and then treating wounds locally via injection, FCX-007 offers the potential to address the underlying cause of the disease by providing high levels of COL7 directly to the affected areas while avoiding systemic distribution.

Under the terms of the collaboration agreement, Castle Creek will receive an exclusive license to commercialize FCX-007 in the USA. Castle Creek will be responsible for all development and manufacturing expenses up to US\$ 20 million prior to the initial Biologics License Application (BLA) filing with US FDA. If development spending

exceeds \$20 million, Castle Creek will be responsible for 70% of the excess costs and Fibrocell will cover 30% of these additional expenses. Castle Creek will also be responsible for all commercialization activities for FCX-007. Fibrocell will maintain responsibility for clinical development, regulatory interactions and manufacturing of the product under a future supply agreement with Castle Creek.

Fibrocell will receive an upfront payment of US\$ 7.5 million, US\$ 2.5 million for the first patient enrolled in the Phase III clinical trial and US\$ 30 million upon BLA approval and commercial readiness. Fibrocell is also eligible to receive up to US\$ 75 million in sales milestones, consisting of US\$ 25 million when FCX-007 achieves US\$ 250 million in cumulative net sales and an additional US\$ 50 million upon attaining \$750 million in cumulative net sales. In addition, Castle Creek Pharmaceuticals will pay Fibrocell a 30% share of the gross profits from FCX-007 sales.

Fibrocell will retain sole ownership of the Rare Pediatric Disease Priority Review Voucher, which may be granted upon market approval of FCX-007. The Priority Review Voucher can be used to obtain priority review for a subsequent New Drug Application or BLA and can be sold to another entity.

Collaboration agreement: Organesis & Digilab

Organesis (MD, USA; www.organesis.com) has entered into a collaboration agreement with Digilab (MA, USA; www.digilabglobal.com) to develop a live cell printing process and systems designed to automate the production of 3D live cellular structures and tissues [6]. Under the agreement, Organesis will have the exclusive rights to codevelop the process and systems required for its therapeutic collaboration programs and to utilize, market and distribute the new cell printer systems and related products. The systems will incorporate Digilab's proprietary synQUAD liquid dispensing technology, offering both on-the-fly and drop-by-drop, non-contact, cell printing, while maintaining the viability of even the most delicate cells. This flexible technology enables control over critical dispensing parameters such as height of dispense and dispensing speed, which allows printing of both viscous solutions and fragile cells. The Digilab 3D printer is the premier 3D bio printer on the market today with a 95% or greater live cell viability. The industrial process capability to be codeveloped by Organesis and Digilab is designed to provide closed-loop systems and solutions for culturing and printing a variety of cells with the initial focus on liver and liver derived cells for autologous clinical applications for point-of-care processing services.

License agreement: ReNeuron & Fosun

ReNeuron Group (UK; www.reneuron.com) has signed an exclusive license agreement with Fosun Pharmaceutical Industrial Development (China; www.fosunpharma.com/en/about/about.html), for the development, manufacture and commercialization of ReNeuron's CTX and hRPC cell therapy programs in China [7]. ReNeuron will receive £6.0 million (US\$7.9 million) on entering into the agreement, up to £6.0 million (US\$7.9 million) in near-term operational milestones and up to £8.0 million (US\$10.5 million) in future regulatory milestone payments. In addition, postlaunch profit threshold milestone payments are due at a rate of 5% of annual net profits derived from the licensed products in the year the relevant net profit milestones are exceeded, leading to total estimated milestone payments of £80.0 million (US\$104.8 million) provided all milestones and profit thresholds are successfully met. ReNeuron will also receive tiered royalties at rates between 12 and 14% on sales of the licensed products in the Chinese market. The Company will be responsible for supplying CTX and hRPC cells to Fosun until technical transfer activities have been completed.

Achievements

XenoTherapeutics

XenoTherapeutics (NV, USA; www.xenotherapeutics.com), a regenerative medicine company specializing in xeno-transplantation, received the Burke/Yannas Award for Best Bioengineering Paper at the 51 conference of the American Burn Association for its research of Xeno-Skin™ [8]. Xeno-Skin is a biologically active, split-thickness, xenotransplantation skin product consisting of dermal and epidermal tissue layers containing vital porcine cells derived from Designated Pathogen 'humanized' source animals. The winning research demonstrated 30-day efficacy of Xeno-Skin on partial- and full-thickness burn wounds, equal to the duration of allograft comparators in preclinical trials. XenoTherapeutics is currently enrolling patients for a first-in-human trial of Xeno-Skin at Massachusetts General Hospital (www.clinicaltrials.gov; ID: NCT03695939).

Launching new products, services...

ACEA

ACEA Biosciences (CA, USA; www.aceabio.com), a part of Agilent (CA, USA; www.agilent.com) unveiled the new xCELLigence® RTCA ePacer [9]. Human induced pluripotent stem cell cardiomyocytes are increasingly being used as a human-relevant *in vitro* model system for drug discovery, safety pharmacology and cardiac disease research. While these cells 'fit for purpose' for a number of applications, their inherent immature phenotype has limited their applicability for many *in vitro* studies. The xCELLigence ePacer allows for a scalable, efficient and high throughput method for maturing human induced pluripotent stem cell cardiomyocytes *in vitro*. Moreover, the specially designed microelectronic plates (E-Plates) are compatible with other orthogonal readouts such as calcium and high content imaging.

Built upon the same groundbreaking technology of the xCELLigence RTCA Cardio and CardioECR systems, the xCELLigence RTCA ePacer uses electrical stimuli to precisely stimulate and pace cardiomyocytes cultured in E-Plates. With the pacing protocols on the ePacer, researchers can produce functionally mature cardiomyocytes within 1–3 weeks, depending on the cardiomyocyte types and the pacing protocol details.

Importantly, after pacing is performed, the ePacer software is able to generate metrics to verify the extent of maturity of the paced cardiomyocytes. These functionally matured cardiomyocytes have much improved responses to inotropic compounds and are more predictive of ion channel modulators. In addition, a number of relevant ion channels, structural proteins and sarcomeric proteins are upregulated in these paced and functionally mature cardiomyocytes.

Boehringer

Boehringer Ingelheim (Germany; www.boehringer-ingelheim.com) launches Arti-Cell® Forte in Europe for the reduction of mild to moderate recurrent lameness associated with nonseptic joint inflammation in horses [10]. Equine lameness is truly common and impacts horse performance as well as equine welfare. Current treatment is not satisfactory for all cases and there is a clear need for innovation and new treatment options. Hence, the significant interest in treatment beyond symptoms, namely combatting the underlying root cause. Arti-Cell Forte is a groundbreaking first-ever approved therapy, developed toward targeting lameness, utilizing specifically primed, chondrogenic induced stem cells. Arti-Cell Forte comes in an ultra-low frozen ready-to-use presentation.

Celularity

Celularity (NJ, USA; www.celularity.com), a clinical-stage cell therapeutics company developing allogeneic cellular therapies harnessed from human placentas, today announced the company has entered into a long-term lease agreement to develop a 145,000 square-foot advanced cell manufacturing and research facility in Florham Park, NJ, USA [11]. Celularity will relocate its corporate headquarters to the new facility when it opens in early 2020.

Tempo Biosciences

Tempo Bioscience (CA, USA; www.tempobioscience.com) has released new human iPSC derived products and affiliated cell-based services in the following categories [12]:

- Tempo-iSchwann human iPSC-derived Schwann cells;
- Tempo-iCardio human iPSC-derived cardiomyocytes;
- TempoiKidneyPod human iPSC-derived kidney proximal tubules and podocytes 3D spheroids;
- Tempo-iMono human iPSC-derived CD14⁺ monocytes;
- Tempo-iPhago human iPSC-derived phagocytes.

These five new products add to the already existing Tempo Bioscience product line and expand TempoStemBank-iPSC offerings:

- Neurons and glia in the central nervous system;
- Neurons in the peripheral nervous system;
- Keratinocytes and melanocytes in the skin;
- Hepatocytes in the liver;
- Retinal pigment epithelium cells in the eye.

TempoATP, TempoMito and TempoVol biosensors are live-cell reporters of cellular, mitochondrial and cytotoxicity functions. Tempo Bioscience is the sole manufacturer of human iPSC-derived cell models that are engineered using nonviral, nucleic acids-free, serum-free and feeder-free technologies. Tempo is committed to advancing technologies that focus on disease modeling and drug safety evaluations using advanced human iPSC-derived cell models in 2D and 3D. Tempo's patient-relevant cell models aim to improve drug efficacy evaluations and safety assessments during drug development.

Clinical trials

Mesenchymal stromal/stem cells

Athersys/HEALIOS

Athersys (OH, USA; www.athersys.com) has announced that its partner, HEALIOS K.K. (Japan; www.healios.co.jp/en/) has enrolled the first patient in its ONE-BRIDGE study in Japan, evaluating MultiStem[®] cell therapy treatment of patients who suffer from acute respiratory distress syndrome (www.clinicaltrials.gov; ID: NCT03807804) [13]. The clinical trial investigates the efficacy and safety of MultiStem therapy for patients with pneumonia-induced acute respiratory distress syndrome. This trial will enroll 30 patients with 20 subjects receiving the cell therapy treatment and standard of care and ten subjects receiving standard therapy alone. The primary end point will be the number of ventilator-free days – the days in which the patient was not on a ventilator in the 28 days following the treatment.

SanBio

The SanBio Group (Japan; <http://sanbio.com>) has announced that SB623 met its primary end point, with patients treated with SB623 achieving an average 8.7 point improvement from baseline in the Fugl-Meyer Motor Scale, versus 2.4 in the control group, at 24 weeks, in a Phase II trial of patients with chronic motor deficit from traumatic brain injury [14].

SB623 is an investigational product made from modified and cultured adult bone marrow-derived mesenchymal stem cells that undergo temporary genetic modification. Implantation of SB623 cells into injured nerve tissue in the brain is expected to trigger the brain's natural regenerative ability to recover lost motor functions.

STEMTRA is a 12-month, Phase II, randomized, double-blind, surgical sham-controlled, global trial evaluating the efficacy and safety of SB623 compared with sham surgery in patients with stable chronic motor deficits secondary to traumatic brain injury. In this study, SB623 cells were implanted directly around the site of brain injury.

To be eligible for this trial, patients (ages 18–75) must have been at least 12 months post-TBI and had a Glasgow Outcome Scale extended score of 3–6 (e.g., moderate or severe disability). Patients must also have been able to undergo all planned neurological assessments and had no seizures in prior 3 months. The primary end point was mean change from baseline in Fugl-Meyer Motor Scale score at 6 months. The STEMTRA trial enrolled 61 patients from 13 surgical and 18 assessment sites in the USA, Japan and Ukraine.

Hematopoietic stem cells

Orchard

Orchard Therapeutics (UK; www.orchard-tx.com) has announced that the first patient with Wiskott–Aldrich syndrome (WAS) has been dosed in an open label study designed to evaluate engraftment of the cryopreserved formulation of OTL-103, its *ex vivo* autologous hematopoietic stem cell gene therapy (www.clinicaltrials.gov; ID: NCT03837483) [15].

Pluripotent stem cells

ISCO

Cyto Therapeutics, a wholly owned subsidiary of International Stem Cell Corporation (ISCO; CA, USA; www.internationalstemcell.com) has completed subject enrollment in its Phase I clinical trial of human parthenogenetic neural stem cells ISC-hpNSC[®] for the treatment of Parkinson's disease (www.clinicaltrials.gov; ID: NCT02452723) [16]. This clinical trial, which involved 12 patients with Parkinson's disease, was conducted in collaboration with investigators from Royal Melbourne Hospital. The goal of this study is to assess the safety and incidence of treatment-emergent adverse events after intracerebral transplantation of 30, 50 and 70 million ISC-hpNSC cells into the substantia nigra and striatum of patients with Parkinson's disease. Thus far there have been no serious

adverse events related to the transplanted ISC-hpNSC, which is a very significant achievement due to the invasive nature of the transplantation procedure. ISC-hpNSC consists of a highly pure population of neural stem cells derived from human parthenogenetic stem cells. ISCO's core technology, parthenogenesis, results in the creation of pluripotent human stem cells from unfertilized oocytes. Human parthenogenetic stem cells avoid ethical issues associated with the use or destruction of viable human embryos.

T cells

Collectis

Collectis (France; www.collectis.com) has announced plans to open a Phase I clinical trial to evaluate UCARTCS1 – its first allogeneic CAR T-cell therapy for multiple myeloma patients – at several sites in the USA shortly after US FDA approved the company's Investigational New Drug (IND) application [17,18]. The trial, called MUNDI-01, will assess multiple doses of the therapy to determine its safety, cell expansion and persistence, as well as its clinical efficacy in people with multiple myeloma. After determining a recommended Phase II dose – the most effective and safest – patients will be invited to continue treatment in an expansion part, studying the safety and efficacy of the optimal dose. Plans for the study were approved by the US FDA in the form of an IND application accepted by the agency.

Traditionally, CAR T-cell therapies consist of a patient's own immune cells, which are harvested and modified in the lab to recognize cancer cells. These cells are then expanded to several million and injected back into the patient to fight the tumor. But while autologous CAR T-cell therapies have shown promise in multiple cancer types, researchers are not always able to collect enough cells from a patient to create the treatment. The development and expansion of CAR T-cells also requires time the person with multiple myeloma often does not have. To sidestep these problems, Collectis has been developing off-the-shelf CAR T-cell products for a variety of blood cancers. Rather than using the person's own cells, these therapies are developed using T-cells from healthy donors, modified to avoid damage to half the patient's tissues.

UCARTCS1 is designed to target the signaling lymphocyte activation molecule family member 7 (SLAMF7), a protein found at the surface of myeloma cells. But T cells also produce this molecule, which would cause the CAR T-cells to attack the patient's T-cells and the engineered donor cells. Collectis employed the TALEN gene editing technology to remove SLAMF7 and the T-cell receptor from the surface of the engineered T-cells. This is designed to have a lymphodepleting effect – meaning that it works to eliminate the patient's T-cells and create room for the engineered cells – while avoiding cross reaction.

Gracell

Gracell Biotechnologies (China; www.gracellbio.com) has developed FasT CAR-T, a revolutionary platform that shortens the manufacturing time of CAR-T treatments from 2 weeks to 1 day [19]. FasT CAR-T also lowers manufacturing costs to a fraction of previous CAR-T therapies, while showing higher potency of CD19-directed FasT CAR-T ('CD19-F-CAR-T') in B cell acute lymphoblastic leukemia (B-ALL) and non-Hodgkin lymphoma (NHL), both *in vitro* and *in vivo*. With a first-in-human clinical study of CD19-F-CAR-T ongoing, Gracell said early clinical results show the therapy is safe and significantly more potent (20- to 40-times) than conventionally manufactured CAR-T agents (C-CAR-T) for treating B-ALL (www.clinicaltrials.gov; ID: NCT03559439).

Precision

Precision BioSciences (NC, USA; www.precisionbiosciences.com), a genome editing company with a proprietary ARCUS[®] platform, has dosed the first patient in the Phase I/IIa clinical trial of PBCAR0191, its first gene-edited allogeneic anti-CD19 chimeric antigen receptor (CAR) T cell product candidate (www.clinicaltrials.gov; ID: NCT03666000) [20]. Precision is developing PBCAR0191 in collaboration with Servier (France; <http://servier.com>). This CAR T cell product candidate is being evaluated in adult patients with relapsed or refractory (R/R) NHL or R/R B-cell precursor acute lymphoblastic leukemia (B-ALL) as an off-the-shelf cell therapy. The first patient dosed in this trial is being treated for R/R NHL, and precision believes this is the first US-based clinical trial to evaluate an allogeneic CAR T therapy for NHL. This multicenter, open label study of PBCAR0191 is expected to enroll up to 80 patients and several dose levels of PBCAR0191 will be investigated.

TC BioPharm

TC BioPharm (UK; <http://www.tcbiopharm.com>), a developer of allogeneic CAR-T immuno-oncology products and gamma delta ($\gamma\delta$) T cell therapies, has initiated a Phase I clinical study of TCB002, an allogeneic cell therapy consisting of activated and expanded $\gamma\delta$ T cells (www.clinicaltrials.gov; ID: NCT03790072) [21]. The trial, for treatment of patients suffering from acute myeloid leukemia, is being conducted at the Institute of Hematology and Blood Transfusion (ÚHK; Czech Republic; www.uhkt.cz/ihbt). Patient recruitment commenced January 2019 following regulatory approval late 2018. Dose escalation is in progress, with completion of treatment imminent for the first patient cohort. Developed by TC BioPharm, TCB002 comprises $\gamma\delta$ T cells sourced from healthy donors, expanded and activated in large numbers before being purified and formulated for infusion into patients. The donors are selected based on criteria designed to ensure that the cells are potent killers of cancer cells and can be a more effective and consistent treatment compared with the patient's own cells. $\gamma\delta$ T cells are a subset of lymphocytes which have both innate and adaptive immune properties and represent an emerging therapeutic option for cancer and other diseases. Use of allogeneic $\gamma\delta$ T cells from healthy donor cell banks paves the way for development of superior drug products through screening and selection of the highest quality starting material, facilitating preparation of consistent batches capable of treating many patients.

Other*AVITA*

AVITA Medical (Australia; <https://avitamedical.com>) has announced interim results describing clinical outcomes for pediatric patients treated using the RECELL[®] System [22]. Patients enrolled in the Investigational Device Exemption Compassionate Use and Continued Access studies had mixed-depth and full-thickness (third-degree) burns, and were treated with the combination of Spray-On Skin[™] Cells prepared using the RECELL system and widely meshed autografts. Patients in the studies experienced excellent healing outcomes, with 98% of wounds healed 4 weeks after treatment. In this study of pediatric patients which included those with life-threatening thermal burn injuries, Spray-On Skin Cells prepared using the RECELL System (<http://recellsystem.com>) were applied in combination with widely meshed split-thickness autografts to achieve definitive closure using minimal donor skin. A total of 107 burn injuries were treated in the study, and 98% achieved definitive healing within 4 weeks of treatment. Importantly, for patients with greater than 50% total body surface area (TBSA) burns, treatment with the combination of spray-on skin cells and widely meshed split-thickness autografts achieved the same high rate of healing at 4 weeks as patients with smaller burns (burns equal to or less than 50% TBSA) treated with the same combination. In addition, in the study the donor sites on all patients were treated with spray-on skin cells, and 62.5% of the donor sites were healed within a week of treatment, and 100% were completely healed within 2 weeks of treatment.

Magenta

Magenta Therapeutics (MA, USA; www.magentatx.com) has dosed the first subjects in a Phase I study of MGTA-145 (www.clinicaltrials.gov; ID: NCT03932864) [23]. Magenta intends to develop MGTA-145 in autoimmune diseases, blood cancers and genetic diseases. More than 85% of the 65,000 transplants in the US and Europe each year use mobilized hematopoietic stem cells as a cell source. MGTA-145 is a biologic chemokine factor that Magenta is developing as a first-line therapy for stem cell mobilization. MGTA-145 is designed to enable single-day mobilization and collection of high numbers of stem cells without granulocyte-colony stimulating factor, the current standard of care. MGTA-145 works synergistically with plerixafor (trade name Mozobil), another stem cell mobilization product. The Phase I study will investigate the safety and tolerability of MGTA-145 alone and in combination with plerixafor in healthy volunteers and establish recommended Phase II doses. The study will also measure the number of hematopoietic stem cells in the blood after dosing with MGTA-145 alone and in combination with plerixafor.

MaaT Pharma

MaaT Pharma (France; www.maatpharma.com) has announced that the independent Data and Safety Monitoring Board recommended the continuation, without amendment, of the ongoing Phase II HERACLES study (www.clinicaltrials.gov; ID: NCT03359980) [24]. The HERACLES trial investigates the use of lead biotherapeutic MaaT013 in steroid-resistant, gastrointestinal-predominant, acute graft-versus-host disease after allogeneic Hematopoietic

stem-cell transplantation. The second review assessed the safety of MaaT013 after ten patients treated, reinforcing the absence of safety issues during the trial as confirmed after the first review. Enrollment of patients in the trial continues as planned with additional sites recently opened in Germany and Italy. As of today, a total of 13 patients have been treated in the protocol. MaaT013 is the first full-ecosystem, off-the-shelf, reproducible, enema formulation manufactured using MaaT Pharma's integrated Microbiome Restoration Biotherapeutic platform. The product has a stability of up to 24 months, and is characterized by a high diversity and consistent richness of microbial species derived from pooled healthy donors and manufactured at the company's centralized European cGMP production facility. MaaT013 has been granted Orphan Drug Designation by the US FDA and the EMA, and is already being administered in compassionate use.

Mallinckrodt/Stratatech

Mallinckrodt (UK; www.mallinckrodt.com) has announced that Stratatech, a Mallinckrodt company, has completed patient enrollment in its ongoing pivotal Phase III clinical trial of StrataGraft[®], an investigational regenerative skin tissue (www.clinicaltrials.gov; ID: NCT03005106) [25]. The multicenter study is evaluating the efficacy and safety of StrataGraft in the promotion of autologous skin regeneration of complex skin defects due to severe thermal burns that contain intact dermal elements (also known as deep partial-thickness burns). The safety and effectiveness of StrataGraft have not yet been established by the US FDA. Investigators enrolled 71 patients 18 years and older with 3–49% TBSA complex skin defects caused by thermal burns across 12 clinical sites. StrataGraft is an engineered, bilayer human skin substitute in development for patients with severe burns or other complex skin defects. Designed to mimic natural human skin with both inner dermis-like and outer epidermis-like layers, StrataGraft is being developed to be sutured, stapled or secured with an adhesive and initially provide coverage during the wound-healing process. StrataGraft tissues are cryopreserved in order to deliver viable cells upon application. StrataGraft regenerative skin tissue is produced using Near-Diploid Immortal Keratinocytes (NIKS[®]) cells and human dermal fibroblasts grown in accordance with Good Manufacturing Practice. StrataGraft tissue, as well as the NIKS cells and dermal fibroblasts, have been thoroughly characterized, helping to ensure consistent delivery of tissue that is virus free, nontumorigenic, and consistent genetically batch to batch. Funding and technical support for the development of StrataGraft regenerative skin tissue is being provided by the Biomedical Advanced Research and Development Authority.

Promethera

Promethera Biosciences (Belgium; www.promethera.com) has announced clinical data from the ongoing Phase IIa study of its lead product candidate HepaStem[®] in patients with acute-on-chronic liver failure or acute decompensation (AD) at high risk of developing acute-on-chronic liver failure (ACLF) [26].

Currently, liver transplant is the only rescue treatment for patients suffering of ACLF and to a lesser degree for AD patients. There are no other existing therapies that can rescue the end-stage-liver failure. Promethera is developing HepaStem as an alternative to transplant; it consists of liver stem cells that are obtained from ethically donated healthy human organs and expanded in GMP culture conditions. These liver stem cells migrate through the blood and reach the liver, where they settle and support the tissue regeneration function.

In the trial, HepaStem cells have been infused intravenously in single or repeated infusions in multiple ascending doses in patients to assess the tolerability and the safety profile of the treatment. The trial recruited a total of 19 patients with a mean CLIF-ACLF score of 50 (12 patients) and a mean CLIF-AD score of 54 (seven patients) – both parameters used as a disease severity score and predict the 28-day mortality.

With two repeated doses at 0.5 million cells per kilogram of bodyweight and one infusion of 1 million cells per kilogram of bodyweight, no adverse events related to HepaStem occurred and no clinically significant changes were shown in platelet count, fibrinogen levels and coagulation factors following HepaStem infusion. In addition to this positive safety profile, the study has been showing trends in efficacy with improvement in three indicators of liver disease severity; model for end stage liver disease score, Child–Pugh score and bilirubin levels, at day 28 and up to 3 months after treatment initiation.

ReNeuron

ReNeuron Group (UK; www.reneuron.com) has updated positive preliminary data in the Company's ongoing Phase I/IIa clinical trial of its human retinal progenitor cell (hRPC) therapy candidate in the blindness-causing disease, retinitis pigmentosa (www.clinicaltrials.gov; ID: NCT02464436) [27]. All three subjects in the first cohort

of the Phase IIa element of the study have demonstrated a sustained and further improvement in vision compared with their pretreatment baseline. At most recent follow-up, subjects in the study showed a meaningful improvement from baseline in visual acuity of + 23 letters in the treated eye. The untreated control eyes did not show meaningful improvement (mean change from baseline of + 5 letters, range - 2 to + 12 letters). An improvement of + 23 letters is equivalent to reading an additional four lines of letters on the Early Treatment Diabetic Retinopathy Study eye chart, the standardized eye chart used to measure visual acuity in clinical trials. An improvement of at least + 15 letters from baseline on the Early Treatment Diabetic Retinopathy Study chart is considered to be clinically meaningful by the US FDA, as stated in their recent guidance on gene therapy for retinal disorders.

Rexgenero

Rexgenero (UK; www.rexgenero.com) has presented an update on its two Phase III SALAMANDER trials being conducted across Europe for its lead development program REX-001 to treat critical limb ischaemia in patients with diabetes (www.clinicaltrials.gov; ID: NCT03111238 and NCT03174522) [28]. REX-001 consists of bone marrow-derived autologous white blood cells and has shown efficacy in 80% of patients in Phase II and I/II studies. Rexgenero is planning to treat 138 patients in two Phase III SALAMANDER trials. Total 12 of the 25 planned trial sites are now open and treating patients in Spain, Austria, Portugal, Poland, Czech Republic and Hungary, with additional hospitals expected to be initiated by the end of the year in three additional countries.

Sernova

Sernova (ON, Canada; www.sernova.com) has announced the first Cell Pouch™ transplant of insulin-producing cells in its US Phase I/II clinical trial evaluating the safety and efficacy of the Cell Pouch for clinical islet transplantation in Type 1 diabetes (www.clinicaltrials.gov; ID: NCT03513939) [29]. The approved protocol is a Phase I/II nonrandomized, unblinded, single arm, company-sponsored trial, where diabetic subjects with hypoglycemia unawareness enroll into the study under informed consent. Participants are then implanted with Cell Pouches. Following the development of vascularized tissue chambers within the Cell Pouch, subjects are then stabilized on immunosuppression, and a dose of purified islets, under strict release criteria, is transplanted into the Cell Pouch. A sentinel pouch will be removed for an early assessment of the islet transplant. Subjects will be followed for additional safety and efficacy measures for approximately 6 months. At this point, a decision will be made with regards to the transplant of a second islet dose with subsequent safety and efficacy follow-up. Patients will then be further followed for 1 year. The primary objective of the study is to demonstrate the safety and tolerability of islet transplantation into the Cell Pouch. The secondary objective is to assess efficacy through a series of defined measures.

Regulations, approvals, acquisitions...

Green light

Autolus

Autolus Therapeutics (UK; www.autolus.com) has announced that the US FDA has granted orphan drug designation to autologous enriched T cells genetically modified with a retroviral vector to express two CARs targeting CD19 and CD22 (AUTO3) for the treatment of acute lymphoblastic leukemia (ALL) [30]. AUTO3 is a programmed T-cell therapy containing two independent CARs targeting CD19 and CD22 that have each been independently optimized for single target activity. By simultaneously targeting two B cell antigens, AUTO3 is designed to minimize relapse due to single antigen loss in patients with B cell malignancies. AUTO3 is currently being tested in pediatric ALL in the AMELIA clinical trial (www.ClinicalTrials.gov; ID: NCT03289455) and in diffuse large B-cell lymphoma in the ALEXANDER clinical trial (www.ClinicalTrials.gov; ID: NCT03287817).

AVROBIO

AVROBIO (MA, USA; www.avrobio.com) has announced that the US FDA has cleared the company's IND application for AVR-RD-01, its gene therapy candidate for the treatment of Fabry disease [31]. The company now expects to move forward on two key initiatives in its Fabry clinical program: the incorporation of AVROBIO's plato™ platform into its FAB-201 Phase II trial, and the dosing of patients at clinical sites in the USA. The plato platform consists of a state-of-the-art four-plasmid vector system, automation of a closed cell manufacturing process and a conditioning regimen that utilizes therapeutic drug monitoring. AVROBIO's lentiviral-based gene therapies

employ hematopoietic stem cells that are collected from the patient and then modified with a lentiviral vector to insert a functional copy of the gene that is defective in the target disease.

CRISPR Therapeutics & Vertex

CRISPR Therapeutics (Switzerland; www.crisprtx.com) and Vertex Pharmaceuticals (MA, USA; www.vrtx.com) have announced that the US FDA has granted Fast Track Designation for CTX001 for the treatment of transfusion-dependent β thalassemia [32]. CTX001 is an investigational, autologous, gene-edited hematopoietic stem cell therapy for patients suffering from severe hemoglobinopathies. CTX001 represents the first treatment to emerge from the joint research program. CRISPR Therapeutics and Vertex will jointly develop and commercialize CTX001 and equally share all research and development costs and profits worldwide.

ExCellThera

ExCellThera (QC, Canada; <http://excellthera.com>) has announced that the US FDA has granted regenerative medicine advanced therapy designation to its lead technology, ECT-001, in the treatment of hematologic malignancies [33]. The granted regenerative medicine advanced therapy designation is based on strong data from Phase I/II clinical trials using ECT-001 to expand stem and immune cells for the treatment of blood cancers. The ECT-001 technology is a combination of a small molecule, UM171, and an optimized culture system. The technology, capable of expanding the number of stem and immune cells exponentially in as little as 7 days, is used in novel curative cord blood transplant therapies for patients with blood cancers, allowing rapid engraftment, greatly reduced incidence of transplant-related mortality, low risk of chronic graft-versus-host disease and low risk of relapse, resulting in better outcomes for patients.

Incysus

Incysus Therapeutics (NY, USA; www.incysus.com), a biopharmaceutical company focused on delivering an innovative $\gamma\delta$ T-cell immunotherapy for the treatment of cancers, has announced that the US FDA has approved the IND application for the clinical study of a genetically modified $\gamma\delta$ T cell in combination with chemotherapy for the treatment of patients with newly diagnosed glioblastoma [34]. This approval will allow Incysus to initiate a first-in-human Phase I clinical trial of gene-modified $\gamma\delta$ T cells for cancer immunotherapy. Incysus' drug resistant immunotherapy (DRI) technology allows the simultaneous combination of standard-of-care chemotherapy with activated $\gamma\delta$ T cells that are genetically engineered to resist chemotherapy-induced cell death, allowing these T cells to attack the tumor at the time that it is most vulnerable. This combination allows the chemotherapy to maximally shrink chemo-sensitive tumor cells while disrupting the immunosuppressive tumor microenvironment. Additionally, by preserving immune cell function during a chemotherapy challenge, DRI can drive synergies by upregulating immune activating markers on the tumor surface to significantly increase tumor immunogenicity.

Janssen

The Janssen Pharmaceutical Companies (Belgium; www.janssen.com) of Johnson & Johnson has announced that the European Medicines Agency has granted a PRIME (PRiority MEDicines) designation for the company's investigational B-cell maturation antigen (BCMA) CAR T-cell (CAR-T) therapy, JNJ-68284528 (JNJ-4528) [35].

MolMed

MolMed (Italy; www.molmed.com) has announced that the Italian Medicines Agency (AIFA; www.aifa.gov.it/en/node/4111) has approved a first-in-human clinical trial testing MolMed's investigational CAR T-cell product, CD44v6, for the treatment of acute myeloid leukemia and multiple myeloma [36]. The Phase I/II trial will be conducted at two clinical centers in Italy and three additional sites in Spain, Germany and the Czech Republic. MolMed's investigational therapy, on the other hand, is intended to target CD44v6, a surface receptor present in some blood cancers, such as multiple myeloma and leukemia, as well as in several solid cancers, including breast, lung and colon cancers. In addition, researchers included two other features in their product, one that allows them to select only the modified T-cells for injection and tracing in the patient, and another that kills the T-cells when they are overactive and safety concerns exist.

SunBio

The SanBio Group (CA, USA; <http://sanbio.com>) has announced that Advanced Therapy Medicinal Product classification has been granted for SB623 for the treatment of patients with motor deficits arising from acquired brain injury, including traumatic brain injury, ischemic stroke and hemorrhagic stroke [37]. SB623 is an investigational product made from modified and cultured adult bone marrow-derived mesenchymal stem cells that undergo temporary genetic modification. Implantation of SB623 cells into injured nerve tissue in the brain is expected to trigger the brain's natural regenerative ability to recover lost motor functions.

In unrelated press release, the company has announced that SB623 has received the Sakigake Designation for innovative medical products from the Ministry of Health, Labour and Welfare of Japan (MHLW; Japan; www.mhlw.go.jp/english/) [38].

Capital market & finances*Autolus*

Autolus Therapeutics (UK; www.autolus.com) has closed underwritten public offering in the US of 4,830,000 American Depositary Shares (ADSs) representing 4,830,000 ordinary shares, at a public offering price of US\$24.00 per ADS, which includes an additional 630,000 ADSs issued upon the exercise in full of the underwriters' option to purchase additional ADSs [39]. Aggregate net proceeds to Autolus, after underwriting discounts but before estimated offering expenses, were US\$109.0 million. All of the ADSs were offered by Autolus.

Poseida

Poseida Therapeutics (CA, USA; www.poseida.com) has closed a Series C financing round, raising US\$ 142 million led by a US\$ 75 million equity investment from Novartis Pharma (Switzerland; www.novartis.com) [40]. The company's CAR-T product candidates are manufactured with Poseida's nonviral piggyBac® DNA Modification System, resulting in a high percentage of stem cell memory T cells. Stem cell memory T cells are the only T cell that is self-renewing and long-lived, potentially resulting in product candidates that are more efficacious, less toxic and more durable. Poseida is currently developing the following CAR-T product candidates:

- P-BCMA-101 is an autologous CAR-T therapy for the treatment of relapsed/refractory multiple myeloma; currently, enrolling patients for a Phase II registrational trial with initial dosing expected in the first half of P-PSMA-101 is an autologous CAR-T product candidate targeting PSMA-specific cancer cells in castrate resistant prostate cancer, with filing of an IND anticipated in the second half of 2019;
- P-BCMA-ALLO1 is an allogeneic, or universal donor, CAR-T product candidate, manufactured using Poseida's proprietary Cas-CLOVER™ site specific gene editing system, and is being developed as a treatment for relapsed/refractory multiple myeloma, with an IND filing anticipated by late 2019 or early 2020;
- P-MUC1C-101 is an autologous CAR-T product candidate in late-stage preclinical development for numerous solid tumor indications, including ovarian, breast, lung, colorectal, pancreatic and renal cancers, with filing of an IND anticipated in 2020

Poseida plans to broadly advance its current CAR-T programs and emerging pipeline programs, including gene therapies for orphan genetic diseases.

Precision

Precision BioSciences (NC, USA; www.precisionbiosciences.com), a genome editing company, has closed its initial public offering of 9,085,000 shares of common stock, which includes the full exercise of the underwriters' option to purchase 1,185,000 additional shares of common stock, at a public offering price of US\$16.00 per share [41]. The total gross proceeds to Precision were approximately US\$145.4 million, before deducting underwriting discounts and commissions and expenses payable by Precision. All of the shares were sold by Precision.

Rocket

Rocket Pharmaceuticals (NY, USA; www.rocketpharma.com) has announced that the California Institute for Regenerative Medicine (CIRM) has awarded Rocket a US\$ 6.5 mil CLIN2 grant award to support the clinical development of gene therapy for leukocyte adhesion deficiency-I (LAD-I) [42]. Rocket's IND for RP-L201 was accepted by the US FDA in November 2018. Proceeds from the grant will help fund clinical trial costs as well as

manufactured drug product for Phase I/II patients enrolled in the US clinical sites. The trial will evaluate the safety and efficacy of the infusion of autologous hematopoietic stem cells transduced with a lentiviral vector encoding the *ITGB2* gene.

Severe LAD-I is a rare, autosomal recessive pediatric disease caused by a mutation of the *ITGB2* gene that encodes for the β -2 integrin component CD18. CD18 is a key protein that facilitates leukocyte adhesion and extravasation from blood vessels to combat infections. As a result, children with severe LAD-I are often affected immediately after birth. During infancy, they suffer from recurrent life-threatening bacterial infections that respond poorly to antibiotics and require frequent hospitalizations. Children who survive infancy experience recurrent severe infections including pneumonia, gingival ulcers, necrotic skin ulcers and septicemia. Without a successful bone marrow transplant, mortality in patients with severe LAD-I is 60–75% prior to the age of 2 and survival beyond the age of 5 is exceedingly rare. The unmet medical need for patients with severe LAD-I is therefore significant.

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