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

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Business development

Collaborations, partnerships & alliances

Codevelopment & license agreement: Avalon & Arbele

Avalon GloboCare (NJ, USA; <http://avalon-globocare.com>) and its wholly owned subsidiary, Avactis Biosciences, have entered into a joint venture and exclusive license agreement with Arbele Ltd (Hong Kong; www.arbele.org) to codevelop next generation, transposon-based chimeric antigen receptor (CAR)-T and CAR-natural killer cellular therapies. These unique CAR vector constructs are nonvirally engineered, possessing multiple therapeutic targets as well as unique 'safety-switch' mechanisms. Based on Avalon's extensive hospital network for cellular therapy, together with the company's established GMP bioproduction facility in China (Epicon Biotech), this joint venture allows Avalon to accelerate the clinical development of more efficacious and safer CAR-T/CAR-natural killer therapies, such as those developed by Arbele.

Collaboration agreement: Gamida & Be The Match

Gamida Cell (Israel; www.gamida-cell.com) and Be The Match BioTherapies®, a subsidiary of the National Marrow Donor Program®/Be The Match® (MN, USA; <https://bethematchclinical.org>) offering integrated platforms and software to manage the collection and delivery of cellular therapies, have announced a strategic collaboration to improve outcomes for patients undergoing allogeneic bone marrow hematopoietic stem cell transplantation. The collaboration supports NiCord®, Gamida Cell's investigational cell therapy, which has the potential to serve as a universal bone marrow donor source for patients with hematologic malignancies or blood cancers and bone marrow failure disorders requiring bone marrow transplantation. Under the terms of the collaboration agreement, Gamida Cell and Be The Match BioTherapies will explore opportunities to work together across Gamida Cell's ongoing clinical development program for NiCord, including the Phase III clinical study in patients with high-risk blood cancers. Be The Match BioTherapies has an extensive history of involvement in the delivery of cord blood units for transplant and broad access to cord blood banks globally. The collaboration is expected to leverage a wide range of Be The Match BioTherapies' research assets and services, including the Be The Match Registry®, the largest in the world with more than 20 million potential donors, as well as personalized case management and logistics services.

Collaboration agreement: GE Healthcare & G-CON Manufacturing

GE Healthcare (IL, USA; www.gehealthcare.com) has begun working with G-CON Manufacturing (TX, USA; www.gconbio.com), makers of prefabricated cleanrooms, to offer a combined and deployable platform for early stage manufacturing of cell therapies and viral vectors. The G-CON will provide modular cleanroom infrastructure

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for GE's clinical and commercial production platforms to help simplify the manufacturing process. The end goal is for drug developers and manufacturers to be able to purchase their own full production lines and cleanroom environments, which can be housed within an 'off-the-shelf' warehouse-like building.

Collaboration agreements: Takeda & Memorial Sloan Kettering Cancer Center/Takeda & Noile

Takeda (Japan; www.takeda.com) has announced new research collaborations in immuno-oncology, an area of key strategic focus for the company. Through these collaborations, Takeda seeks to accelerate the discovery of next-generation cancer immunotherapies, including novel cell therapy approaches that may provide important opportunities for addressing the needs of patients with hard-to-treat cancers.

Takeda will collaborate with Memorial Sloan–Kettering Cancer Center (NY, USA; www.mskcc.org) to discover and develop novel CAR-T products for the treatment of multiple myeloma, acute myeloid leukemia and additional solid tumor indications. The broad, multifaceted collaboration will be coled by CAR-T therapy pioneer Michel Sadelain, Director of the Center for Cell Engineering at MSK and scientific founder of Juno Therapeutics.

Takeda exercised an option under its existing research collaboration with Noile-Immune Biotech (Japan; www.noile-immune.com/english/), which originated in September 2017. Due to the success of the collaboration, Takeda exclusively licensed NIB-102 and NIB-103 platforms for the treatment of various solid tumor indications and will codevelop these CAR-T cell therapies with Noile utilizing the company's proprietary 'Prime' (proliferation inducing and migration enhancing) CAR-T platform. The company plans to gain regulatory approval for human testing of NIB-102 by the end of this year.

Collaboration & license agreement: Adaptive & Genentech

Adaptive Biotechnologies (WA, USA; www.adaptivebiotech.com) has announced that it will enter into a worldwide collaboration and license agreement with Genentech (CA, USA; www.gene.com), a member of the Roche Group (Switzerland; www.roche.com), to develop, manufacture and commercialize novel neoantigen directed T-cell therapies for the treatment of a broad range of cancers. The collaboration will combine Genentech's global cancer immunotherapy research and development leadership with Adaptive's proprietary T-cell receptor discovery and immune profiling platform (TruTCR™) to accelerate a transformational new treatment paradigm of tailoring cellular therapy for each patient's individual cancer.

License agreement: bluebird & Inhibrx

The bluebird bio (MA, USA; www.bluebirdbio.com) and Inhibrx (CA, USA; www.inhibrx.com) have announced that they have entered into an exclusive license agreement to research, develop and commercialize CAR T-cell therapies using Inhibrx's proprietary single domain antibody platform to multiple cancer targets. The small size of single domain antibodies may enable the generation of more complex CAR-T cell products such as those designed to combine additional functions into a single CAR molecule or recognize multiple tumor antigens simultaneously.

License agreement: Stem Cell Medicine & Tel Aviv University

Stem Cell Medicine (Israel; www.stemcell-medicine.com), a biotechnology company developing new therapies for neurological indications, including mesenchymal stem cells (MSCs), has licensed an exosome-based technology for the treatment of neurodegenerative and neuropsychiatric indications, specifically, autism spectrum disorder. The treatment is based on exosomes from adult MSCs that are administered intranasally. The technology was licensed from Ramot, the business engagement center at Tel Aviv University (<http://ramot.org>).

License agreement: Stem Cell Medicine & Tel Aviv University

Thyas (Japan; <http://thyas.co.jp/en>) has signed a licensing agreement with iPS Academia Japan (<http://ips-cell.net/en/>), a technology licensing organization of induced pluripotent stem cell (iPSC)-related patents from Kyoto University. Under the agreement, Thyas obtains exclusive rights on patents related to production and use of iPSC-derived T cells, and nonexclusive rights on the patents related to iPSC generation, for development and commercialization of autologous immunotherapy of cancers and infectious diseases. Thyas will pay ongoing licensing fees to iPS-AJ. Financial terms of the agreement have not been disclosed. Thyas is a start-up biotechnology company from Center for iPSC Research and Application, Kyoto University, Japan, and supported by Kyoto University Innovation Capital, a wholly owned investment firm of the university.

Partnership agreement: GE Healthcare & Vanderbilt

GE Healthcare (IL, USA; www.gehealthcare.com) and Vanderbilt University Medical Center (TE, USA; <https://www.mc.vanderbilt.edu>) have announced a 5-year partnership to enable safer and more precise cancer immunotherapies. They will collaborate on methods to improve productivity, efficiency and cost of stem cell transplant processing operations by automating processes, digitizing workflows, improving throughput and industrializing operations.

Partnership agreement: Ngene & New York Stem Cell Foundation

The New York Stem Cell Foundation (NYSCF; NY, USA; <https://nyscf.org>) Research Institute has announced a partnership with Ngene Therapeutics to develop new disease treatments that leverage human stem cell research and novel gene editing techniques. The NYSCF will serve as a key partner to Ngene in stem cell derivation and differentiation toward the generation of high-quality cell lines for disease research and of clinical-grade, GMP cell lines for cell-based therapies.

Ngene, a newly founded joint venture between the gene editing company ToolGen (Korea; www.toolgene.com) and the biomedical company nSAGE (Korea), is dedicated to creating novel and effective gene editing-based stem cell therapies for acute alcoholic hepatitis, various neuroinflammatory indications and other diseases. The NYSCF Research Institute is a pioneer and acknowledged leader in stem cell technology, having developed the NYSCF Global Stem Cell Array, the premier automated robotic platform for reprogramming adult cells into iPSCs. In 2018, NYSCF began a collaboration with ToolGen and nSAGE that integrates gene editing and stem cell technologies to develop new treatments, and its partnership with Ngene represents a continuation of this work.

New products & services being launched*Frequency*

Frequency Therapeutics (MA, USA; www.frequencytx.com), a clinical-stage biotechnology company creating a new class of drugs based on small molecule stimulation of dormant stem cells within the body, which they refer to as progenitor cell activation, has closed a US\$42 million Series B financing, which brings the total capital raised by the company to US\$87 million.

Generex

Generex Biotechnology (ON, Canada; www.generex.com) has announced that its subsidiary Olaregen Therapeutix will launch three doses of US FDA 510K-Cleared Excellagen, the company's wound conforming gel matrix that is designated as a cellular- and tissue-based product for wound healing. The 0.5 and 0.8 cc syringes will be utilized to treat smaller wounds such as diabetic foot ulcers, venous stasis ulcers and pressure ulcers, and in patients who have undergone Mohs surgery for removal of cancerous tissue. The 3 cc syringe has been developed for larger wounds that are most frequently seen in emergency departments, operating rooms and surgical suites. Excellagen has a designated reimbursement code in the Healthcare Common Procedure Coding System, with a unique Q Code designation 4149 referred to as a skin substitute.

FUJIFILM Cellular Dynamics

FUJIFILM Cellular Dynamics (FCDI; WI, USA; <https://fujifilmcdi.com>), a US subsidiary of Fujifilm Corporation (Japan; www.fujifilm.com), is establishing a new cGMP-compliant production facility with an investment of about US\$ 21 million in order to enhance its production of human iPSCs for cell therapy. The facility is scheduled to begin operations during fiscal year ending March 2020. The FCDI will use the iPSCs produced at this facility to accelerate development of its regenerative medicine products. In addition, by also conducting contract development and manufacturing of iPSCs and iPSC-derived differentiated cells, it will expand its business and scale to the industrial stage.

Sana Biotechnology

Sana Biotechnology (WA, USA; <http://sana.com>), a new company focused on creating and delivering engineered cells as medicines for patients, announced its launch on 4 January 2019. The company is building critical core capabilities around:

- Making cells at scale *ex vivo* to replace any damaged or missing cells in the body;
- *In vivo* delivery to specific cell types of any payload – including DNA, RNA and proteins to reprogram cells;

- Immunology expertise to hide allogeneic cells (cells from a donor) or delivery vehicles from the immune system so that the body does not reject or eliminate them;
- Controllable gene and protein expression systems;
- Scaled, cost-efficient manufacturing solutions;
- Discovery and development of new technologies that will enable the ultimate breadth of application of cell and gene engineering.

STEMCELL Technologies

STEMCELL Technologies (BC, Canada; www.stecell.com) has released mTeSR™ Plus, an enhanced version of mTeSR1, the most widely published feeder-free human pluripotent stem cell (hPSC) maintenance medium. The new medium has undergone successful β -testing with several members of the Stem Cell COREdinates group and has completed rigorous in-house validation testing. Designed to promote a more consistent cell culture environment through sustained medium pH and stabilized components including FGF2, mTeSR Plus prevents the rapid onset of acidosis. This helps avoid conditions that have been associated with DNA damage, genomic instability and growth arrest in hPSCs. The stabilization enhancements allow for greater hPSC expansion rates, enhanced culture morphology and truly versatile feeding schedules including the option to skip weekends.

TC BioPharm

The TC BioPharm (TCB; UK; www.tcbiopharm.com), a developer of CAR-T immuno-oncology products, including gamma delta T ($\gamma\Delta T$) cell therapies, has completed formulation of its first allogeneic GDT cell banks. The T-cell banks provide TCB with core technology to develop a deep portfolio of next-generation CAR-T products directed against a wide variety of different cancer types, both hematological and solid tumors. The project was supported by funding from the European Union's Horizon 2020 Research and Innovation program via a €4 million grant. The GDT cell banks are collected and stored from healthy donors, providing a source for TCB to manufacture next-generation 'off-the-shelf' GDT cell therapies for future clinical product development. Using allogeneic material from healthy donors offers several advantages over conventional autologous CAR-T therapies, which uses the patient's own cells to treat their tumor, as TCB's proprietary allogeneic CAR-T cells are not prone to 'on-target, off-tumor' toxicities. Additionally, a larger population of cancer patients can be treated with a single reproducible product, 'campaign-manufactured' in bulk to keep costs lower, consequently increasing accessibility and reducing financial burden for healthcare systems.

Clinical trials

Asterias

Asterias Biotherapeutics (CA, USA; <https://asteriasbiotherapeutics.com>) has provided top-line 12 months data from the company's Phase I/IIa SCiStar study designed to evaluate the safety and potential efficacy of oligodendrocyte progenitor cells (OPC1) in the treatment of severe cervical spinal cord injury. All 25 subjects from the SCiStar study have now completed 12-month of follow-up as part of the study's protocol. The company also held a Type B meeting with the US FDA late last year where US FDA agreed with the company's plan to initiate a randomized, controlled Phase II study to further evaluate the safety and efficacy of OPC1.

The SCiStar trial is an open-label, single-arm trial testing three sequential escalating doses of OPC1 administered in 25 subjects with subacute motor complete (AIS-A or AIS-B) cervical (C-4–C-7) spinal cord injury. These individuals have essentially lost all movement below their injury site and experience severe paralysis of the upper and lower limbs. The AIS-A subjects have lost all motor and sensory function below their injury site, while AIS-B subjects have lost all motor function but may have retained some minimal sensory function below their injury site. The OPC1 is administered 21–42 days postinjury. The SCiStar study consists of five cohorts: in cohort 1, three AIS-A patients have received 2 million OPC1 cells; in cohort 2, six AIS-A patients have received 10 million OPC1 cells; in cohort 3, one AIS-A patient has received 10 million and five of them 20 million OPC1 cells; in cohort 4, six AIS-B patients have received 10 million OPC1 cells; in cohort 5, one AIS-B patient has received 10 million and three of them 20 million OPC1 cells.

Key findings at 12 months for the SCiStar study subjects:

- Positive safety profile – MRI scans at 12 months postinjection of OPC1 has shown no evidence of adverse changes in any of the 25 SCiStar study subjects treated with OPC1;

- Cell engraftment – all three SCiStar subjects in cohort 1 and 95% (21/22) of SCiStar subjects in cohorts 2–5 have MRI scans at 12 months consistent with the formation of a tissue matrix at the injury site, which is an encouraging evidence that OPC1 cells have engrafted at the injury site and helped to prevent cavitation. Cavitation is a destructive process that occurs within the spinal cord following spinal cord injuries, and typically results in permanent loss of motor and sensory function. Additionally, a patient with cavitation can develop a condition known as syringomyelia, which results in additional neurological and functional damage to the patient and can result in chronic pain;
- Improved motor function – at 12 months, 95% (21/22) of SCiStar study subjects who were administered either 10 or 20 million cells of OPC1 (cohorts 2–5) recovered at least one motor level on at least one side. At 12 months, 32% (7/22) of these subjects recovered two or more motor levels on at least one side. At 12 months, the average improvement in upper extremity motor score as measured by the International Standards for Neurological Classification of Spinal Cord Injury scale for cohort 2–5 subjects was 8.9 points. No subjects saw decreased motor function following administration of OPC1 and subjects consistently retained the motor function recovery seen through 6 months or saw further motor function recovery from 6 to 12 months.

Additional information on the Phase I/IIa trial, including trial sites, can be found at www.clinicaltrials.gov, using identifier NCT02302157, and at the SCiStar Study Website (www.SCiStar-study.com).

Athersys

Athersys (OH, USA; www.athersys.com) has announced summary results from its exploratory clinical study of the intravenous administration of MultiStem[®] cell therapy to treat patients who are suffering from acute respiratory distress syndrome. The study results provide further confirmation of tolerability and a favorable safety profile associated with MultiStem treatment. Importantly, MultiStem treatment was associated with lower mortality (25% in the treated vs 40% in the placebo group) and a greater number of ventilator-free and intensive care unit free days in the first month following diagnosis (10.3 in the treated vs 8.1 days in the placebo group). Furthermore, analysis of initial biomarker data reflects lower levels of inflammatory markers/cytokines following MultiStem treatment, an expected mechanism of action in this patient population. Patients in the exploratory study were evaluated through 28 days for the primary clinical assessment and will be further assessed through a 1-year follow-up period.

Cellular Biomedicine Group

Cellular Biomedicine Group (China; www.cellbiomedgroup.com) has announced the initiation of patient recruitment to support the study of C-CAR088, anti-B-cell maturation antigen (BCMA) CAR-T therapy, targeting relapsed and refractory multiple myeloma in China (www.clinicaltrials.gov; ID: NCT03815383 and NCT03751293). This Phase I clinical study will enroll 22 patients to evaluate the safety and efficacy of C-CAR088 in patients with relapsed and/or refractory multiple myeloma.

InGeneron

InGeneron (TX, USA; <http://ingeneron.com>) has enrolled the first patients in two new feasibility studies evaluating InGeneron's regenerative cell therapy as a way to treat facet joint syndrome, a major cause of chronic back pain and wrist osteoarthritis. The primary goal of the randomized controlled trials is to demonstrate the safety of the company's autologous point-of-care cell therapy in treating these indications. The US FDA has granted approval of these studies, and patient enrollment has begun. The two new indications complement the company's lead program in rotator cuff tendinopathy and build upon InGeneron's focus of developing regenerative cell therapies in musculoskeletal indications. InGeneron's therapeutic approach involves isolating these cells from patients' own adipose tissue through a minimally invasive liposuction procedure, processing them with the company's proprietary technology, and injecting the processed cells in the site of the patient's injury. Each feasibility study will involve the enrollment of 40 patients and includes a group that receives the cell therapy treatment and a control group that receives a corticosteroid injection. The use of corticosteroids is a current standard of care in the treatment of these indications. Patients enrolled in the studies will be monitored through follow-up visits for 52 weeks following the intervention.

Regulations, approvals, acquisitions

US FDA

In anticipation of a surge of IND applications for cell and gene therapies in the next few years, US FDA and CBER have announced plans to issue new guidance to advance their development. The US FDA intends to release multiple clinical guidance on different areas of products being actively developed, they said, including guidance on developing gene therapies for inherited blood disorders like hemophilia. It also plans to issue guidance clarifying how the accelerated approval pathway may be used when a gene therapy treatment's target is an underlying monogenetic change that causes a serious disorder not addressed by available therapy. In such cases, the gene therapy might offer the potential to alter or cure the underlying genetic defect that gives rise to, and causes the advance of, a disease.

Green light

Allogene

Allogene Therapeutics (CA, USA; www.allogene.com), a clinical-stage biotechnology company developing allogeneic CAR-T (AlloCAR T™) therapies for cancer, in collaboration with its development partner Servier (France; www.servier.com), has announced that the US FDA has cleared Allogene's investigational new drug (IND) application for anti-CD19 ALLO-501 iCAR T therapy in patients with relapsed/refractory non-Hodgkin lymphoma (NHL). Allogene is the sponsor of the ALLO-501 program. The Phase I portion of the study is designed to assess the safety and tolerability at increasing dose levels of ALLO-501 in the most common NHL subtypes of relapsed/refractory diffuse large B-cell lymphoma (DLBCL) or follicular lymphoma (FL). ALLO-501 will be administered following lymphodepletion with fludarabine/cyclophosphamide (Flu/Cy) and ALLO-647, Allogene's proprietary anti-CD52 monoclonal antibody. The ALPHA Phase I trial will treat up to 24 patients and is on track for initiation in the first half of 2019.

Cellular Biomedicine Group

Cellular Biomedicine Group (CBMG; China; www.cellbiomedgroup.com) has announced that its off-the-shelf human allogeneic adipose-derived mesenchymal progenitor cell AlloJoin® therapy for knee osteoarthritis (KOA) has been approved as the first stem cell KOA drug application in China for a Phase II clinical trial. China's National Medical Products Administration (www.nmpa.gov.cn; formerly the China FDA) clarified cell therapy regulations in December 2017 whereby all cell therapies are being treated as new drug application/IND. Following a 60-day period of priority review of CBMG's IND application for AlloJoin® for KOA, CBMG's IND application has become the first stem cell drug application to be approved by the China Center for Drug Evaluation for a Phase II KOA clinical trial since the Regulation's release. Center for Drug Evaluation is a part of National Medical Products Administration.

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 sickle cell disease. The CTX001 is an investigational *ex vivo* CRISPR gene-edited therapy for patients suffering from β -thalassemia or sickle cell disease in which a patient's hematopoietic stem cells are engineered to produce high levels of fetal hemoglobin (HbF; hemoglobin F) in red blood cells. HbF is a form of the oxygen carrying hemoglobin that is naturally present at birth and is then replaced by the adult form of hemoglobin. The elevation of HbF by CTX001 has the potential to alleviate transfusion requirements for β -thalassemia patients and painful and debilitating sickle crises for sickle cell patients. The CTX001 is being developed under a codevelopment and co-commercialization agreement between CRISPR Therapeutics and Vertex.

Japan

Japan has approved a stem cell treatment for spinal cord injuries using MSCs extracted from a patient's bone marrow. This is the first stem cell therapy for this kind of injury to receive government approval for sale to patients. According to the report in *Nature* [1], the cells are injected intravenously, which carries a risk of dangerous blood clots in the lungs, making it hard to justify unless they are proven to offer a benefit. In this particular case, there is insufficient evidence that the treatment works.

StemCyte

StemCyte (CA, USA; www.stemcyte.com) has announced that the US FDA approved its Phase II IND application for Allogeneic HLA-matched Umbilical Cord Blood Mononuclear Stem Cells MC001 for the treatment of spinal cord injury. The MC001 has already been shown to be efficacious, safe and well tolerated in a Phase II trial in China.

Mergers & acquisitions*ProKidney & inRegen*

ProKidney has announced the acquisition of inRegen (CA, USA; www.inregen.com) and its affiliate, Twin City Bio (NC, USA; www.twincitybio.com). ProKidney has been initially capitalized with US\$75 million to finance the purchase of inRegen and Twin City Bio and to fund the clinical development of inRegen's Renal Advanced Cell Therapy (ReACT). ReACT is an autologous cell therapy in which a small amount of the patient's own kidney cells is extracted via a conventional biopsy, these cells (including a high proportion of the SIX2 progenitor cell population) are expanded in the lab over 4–6 weeks and then reimplanted into the patient's diseased kidney. The goal of ReACT is to harnesses the body's intrinsic ability to repair damaged kidney tissues and restore them to native-like organs and tissues. If successful, ReACT has the potential to stabilize or improve renal function in patients with chronic kidney disease and delay or eliminate the need for dialysis and organ transplantation. ReACT is currently in multicenter Phase II clinical trials for the treatment of moderate to severe diabetic kidney disease (<https://reactstudy.com>). The Phase II clinical trials are based on a successful Phase I clinical trial, in which some of the first patients to be injected have been followed for over 4 years and remain dialysis free. The Phase I trial demonstrated that ReACT was well tolerated by patients with moderate to severe diabetic kidney disease. The ongoing Phase II program utilizes a newly developed percutaneous injection method that is conducted using conscious sedation. The new method has allowed minimally invasive methods to enhance the safety profile and provide equivalent or better efficacy than was seen in Phase I.

Capital market & finances*Poseida*

Poseida Therapeutics (CA, USA; <https://poseida.com>), the clinical-stage biopharma firm developing autologous CAR-T therapies for treating blood cancers and solid tumors, has filed a preliminary prospectus for a US\$115M Initial Public Offer. Lead candidate is Phase II-ready P-BCMA-101 therapy for multiple myeloma.

Promethera

Promethera Biosciences (Belgium; www.promethera.com), an innovator in cell-based liver therapeutics, has announced a strategic investment of US\$11.3 (EUR10) million by ITOCHU Corporation (Japan; www.itochu.co.jp), business conglomerate with global presence and networks with annual revenues of more than US\$50 billion. The ITOCHU is the first lead investor in Promethera's Series D round, which the company expects to close in Q1 2019.

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