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

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Business development

Collaborations, partnerships & alliances

Collaboration agreement: Adaptimmune & Alpine Immunosciences

Adaptimmune Therapeutics (UK; www.adaptimmune.com) and Alpine Immune Sciences (WA, USA; www.alpineimmunosciences.com) have announced a collaboration and license agreement to develop next-generation SPEAR T-cell products, which incorporate Alpine's secreted and transmembrane immunomodulatory protein (termed SIPTM and TIPTM) technology [1]. This collaboration will further enhance Adaptimmune's efforts to design and develop next-generation SPEAR T-cell therapies.

Collaboration agreement: StemoniX & National Center for Advancing Translational Sciences

StemoniX (MN, USA; www.stemonix.com) has entered into a Research Collaboration Agreement with the National Center for Advancing Translational Sciences (MD, USA; <https://ncats.nih.gov>) to screen a library of neuronal signaling and opioid compounds using electrophysiologically active neural 3D customized microOrgan model microBrain as part of the NIH HEAL (Helping to End Addiction Long-term) initiative, a trans-NIH effort to advance national priorities in addressing the opioid crisis through science [2].

Collaboration agreement: Tmunity & University of California San Francisco

Tmunity (PA, USA; www.tmunity.com) has entered into an exclusive licensing and research collaboration with the University of California San Francisco (UCSF, CA, USA; www.ucsf.edu) aimed at advancing novel engineered T-cell receptor therapies for rare and currently incurable pediatric conditions with high mortality rates [3]. Initially, research will focus on diffuse intrinsic pontine glioma (DIPG) and mutation K27M in the H3.3 histone. DIPG is a rare and highly aggressive brain stem tumor. Approximately 300 children in the USA are diagnosed with DIPG each year, with most diagnoses occurring between 5 and 9 years of age. Children with DIPG have a median overall survival of 9–10 months using currently available treatments that mainly manage symptoms and complications associated with the disease.

Manufacturing & collaboration agreement: ExCellThera & New York Blood Center

ExCellThera (QC, Canada; www.excellthera.com) has entered into a manufacturing and collaboration agreement with Comprehensive Cell Solutions (CCS), a division of New York Blood Center (NYBC, NY, USA; www.nybloodcenter.org) for the clinical grade production of ExCellThera's lead cell therapy product, ECT-001 [4]. The agreement

provides ExCellThera access to NYBC's cGMP clean room manufacturing facilities in New York for the production of ECT-001, to be used in clinical trials principally in the USA. 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 blood transplant therapies for patients with blood malignancies and other diseases, allowing more 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. The US FDA has granted ECT-001 orphan drug designation for the prevention of graft-versus-host disease and regenerative medicine advanced therapy designation in the treatment of hematologic malignancies.

Sponsored research & licensing agreement: Avalon & Massachusetts Institute of Technology

Avalon GloboCare (NJ, USA; www.avalon-globocare.com) has entered into a sponsored research and licensing agreement with Massachusetts Institute of Technology (MA, USA; www.mit.edu) to generate novel therapeutic targets for cellular therapy using artificial intelligence-enhanced protein design 'QTY Code' technology [5]. This breakthrough technology of 'QTY Code' greatly enhances the solubility of designer peptides and proteins, therefore expanding the repertoire of selected therapeutic targets against cancers and other diseases. Avalon will initiate R&D with Massachusetts Institute of Technology to design the next generation of therapeutics for cytokine release syndrome, T-cell leukemia, as well as novel methodology to re-engineer immune cells for cellular immunotherapy.

Achievements

Semma

Semma Therapeutics (MA, USA; www.semma-tx.com) has published the data demonstrating improvements in the production of insulin-producing β cells from stem cells [6,7]. Led by Harvard University researchers in collaboration with scientists from Semma, the study characterized the types of cells produced by the applicable cell differentiation methods and demonstrated biological and physical separation methods using cell surface marker ITGA1 (CD49a) and magnetic sorting to increase the purity of β cells in a sample of converted stem cells from 30 to 80%.

Launching new products, services...

Bayer

Bayer (Germany; www.bayer.com) is investing US\$150 million to build a cell culture facility in Berkeley, CA, USA [8]. The 40,000-square-foot site will support Bayer's pipeline of oncology and cardiology programs when it comes online late in 2021. Berkeley currently houses a recombinant factor VIII production plant that makes hemophilia A treatments. The Bayer Berkeley plant dates back to the 1970s and underwent a US\$100 million expansion in 2017 but was the subject of job cuts last year ahead of the planned transfer of production to Germany. The cell culture investment affirms Bayer's commitment to Berkeley, where it employs about 1100 people. Bayer considered eight locations around the world before deciding on Berkeley, in large part due to the biotech talent pool in the area.

Clinical trials

Mesenchymal stromal/stem cells

BioCardia

BioCardia® (CA, USA; www.biocardia.com) has announced positive results from a study of the company's Helix™ Biotherapeutic Delivery System for cell therapy used to treat patients early following acute myocardial infarction to prevent long-term heart failure [9]. The study was designed to determine if intramyocardial injection of autologous bone marrow-derived mononuclear cells using the Helix System 2–4 weeks after acute myocardial infarction is feasible, might block ventricular adverse remodeling and improve symptoms of heart failure. Nine patients were treated with cell therapy delivered intramyocardially with the Helix system, and these results were reviewed relative to 11 patients previously treated with the NOGA XP delivery system and a control group of 11 patients treated with optimal standard care. At 12 months, patients with Helix-delivered cell therapy experienced a 7.33% improvement in ejection fraction at 12 months ($p = 0.017$) compared with the control group. There was no 12-month data available for the NOGA system at 12 months. Helix patients also showed an improvement in New York Heart Association (NYHA) class of more than one class over control at 6 months (2.55 ± 0.1 vs 1.33 ± 0.1 , $p = 0.0078$),

which was greater than both the NOGA-treated and control groups. The Helix system is currently part of a US Phase III pivotal trial of our CardiAMP™ cell therapy used in patients with heart failure resulting from a heart attack (<https://clinicaltrials.gov>; ID: NCT02438306).

InGeneron

InGeneron (TX, USA; www.ingeneron.com) has enrolled the first patients in an FDA-approved study evaluating InGeneron's cell therapy as a way to treat partial thickness rotator cuff tears involving a partial tear in the supraspinatus tendon (<https://clinicaltrials.gov>; ID: NCT03752827) [10]. The primary goal of the double-blinded, multicenter trial is to demonstrate the effectiveness of the company's autologous point-of-care cell therapy in treating this indication. The trial plans to enroll 246 patients at up to 15 sites across the USA and is among the largest regenerative cell therapy studies in this indication to date. A partial rotator cuff tear is one of the most common orthopedic impairments of a person's shoulder and can be characterized by a degenerative and often chronic condition found in the supraspinatus tendon. The condition is estimated to affect >1 million patients in developed economies annually. InGeneron is investigating the use of autologous adipose-derived regenerative cells as an outpatient treatment to potentially provide patients with better options than currently available. InGeneron's therapeutic approach involves isolating regenerative cells from patients' own adipose tissue through a minimally invasive liposuction procedure, processing them with the company's proprietary technology, and injecting the isolated cells in the site of the patient's injury under ultrasound guidance. The pivotal study is double blinded, and will include a group of patients who receive 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 partial rotator cuff tears. Patients enrolled in the study will be monitored through follow-up visits for 48 weeks following the intervention.

Hematopoietic stem cells

Magenta

Magenta Therapeutics (MA, USA; www.magentatx.com) has presented Phase II clinical data on its cell therapy, MGTA-456, at the annual meeting of the American Academy of Neurology in Philadelphia, PA, USA [11]. MGTA-456 is a cell therapy designed to provide a high dose of hematopoietic stem cells that are well matched to the patient. The company plans to enroll 12 patients in the ongoing Phase II study in inherited metabolic disorders, which include cerebral adrenoleukodystrophy (cALD), Hurler syndrome, metachromatic leukodystrophy and globoid cell leukodystrophy (<https://clinicaltrials.gov>; ID: NCT03406962). The primary end point of the study is neutrophil engraftment after transplantation. The study is also collecting both short- and long-term disease-specific outcomes. Data from the first five evaluable patients transplanted with MGTA-456, a CD34⁺ Expanded Cell Therapy Product, show rapid engraftment in preliminary Phase II trial results.

Key results in patients with cALD:

- Both patients had stable neurological function scores, which remained unchanged between baseline and 6 months post-transplant, suggesting progress of the disease has been arrested;
- The Loes score, a method for quantifying the severity of brain abnormalities and atrophy found on MRI, also remained stable in both patients after 6 months;
- Both patients showed resolution of gadolinium enhancement on MRI, an indicator of brain inflammation, by 1 month post transplant, and the resolution persisted at 6 months. Durable resolution of gadolinium enhancement is correlated with long-term disease benefit in patients with cALD.

Key results in patients with Hurler syndrome:

- As previously reported, all three patients with Hurler syndrome achieved normal levels of blood leukocyte IDUA enzyme, the enzyme that is deficient in untreated patients with Hurler syndrome, by day 42 post transplant. This suggests that transplant with MGTA-456 is affecting the disease process in these patients;
- Normalization of blood leukocyte IDUA enzyme after transplant has been significantly associated with improvement in disease;
- Patients showed a marked decline in urine total glycosaminoglycan (GAG), the toxic metabolites implicated in disease, after transplant;

- Both of these findings are correlated with improved long-term disease outcomes.

Overall results:

- All five patients met the primary end point of neutrophil engraftment;
- MGTA-456 was well tolerated.

T cells

Celgene & bluebird

Celgene (NJ, USA; www.celgene.com) and bluebird bio (MA, USA; www.bluebirdbio.com) have published interim results from CRB-401, the ongoing Phase I study of bb2121 (<https://clinicaltrials.gov>; ID: NCT02658929), the companies' lead investigational B-cell maturation antigen (BCMA)-targeted chimeric antigen receptor (CAR) T-cell therapy candidate for patients with relapsed and refractory multiple myeloma [12,13]. As of the data cut-off date of 30 April 2018, manageable safety, and deep and durable responses were reported in the first 33 patients infused with bb2121 BCMA-targeted CAR T cells. Patients in the study were heavily pretreated, with a median of seven prior multiple myeloma treatment regimens (range: 3–23), which included prior treatment with immunomodulatory drugs, proteasome inhibitors and daratumumab in the majority of patients. All but one patient had previously received an autologous stem cell transplant. For the first 33 patients, the most common grade ≥ 3 events were hematologic toxicities, including neutropenia (85%), leukopenia (58%), anemia (45%) and thrombocytopenia (45%). Neurotoxicity all-grades occurred in 14 (42%) patients; 13 (39%) were grade ≤ 2 and one patient (3%) had grade 4 neurotoxicity, which resolved within 1 month. 25 (76%) patients experienced cytokine release syndrome; 23 (70%) were grade ≤ 2 events and two (6%) were grade 3 events; all events were reversible. Infection occurred in 14 (42%) patients; two were grade 3 (6%) and there were no grade 4 events. Peak CAR T cell expansion was higher in patients with cytokine release syndrome and CAR T cells remained detectable in the blood in 57% of patients at 6 months following infusion. Treatment with bb2121 resulted in an 85% objective response rate with 45% of patients achieving a complete response ($n = 15$) and an additional 27% of patients ($n = 9$) achieving a very good partial response to yield a greater than or equal to very good partial response rate of 73%. 16 responding patients were evaluable for assessment of minimal residual disease, and all tested minimal residual disease negative at one or more time points. Responses to bb2121 CAR T-cell infusion occurred early, with a median time to first partial response or better of 1 month (range: 0.5–3), and responses were durable, with a median duration of response of 10.9 months (95% CI: 7.2 to not estimable). Researchers observed that greater CAR T-cell expansion occurred in responding patients. Responses were observed independent of tumor or serum BCMA levels. Median progression-free survival among all 33 patients was 11.8 months (95% CI: 6.2–17.8). The published data from CRB-401 trial provide the foundation for advancing the development of bb2121, which is currently being assessed in multiple clinical studies across different patient populations within multiple myeloma. In November 2017, bb2121 was granted Breakthrough Therapy Designation (BTD) by the FDA and Priority Medicines (PRIME) eligibility by the EMA based on preliminary clinical data from the Phase I CRB-401 study. bb2121 is being developed as part of a co-development, co-promote and profit share agreement between Celgene and bluebird bio. Potential approval of bb2121 in the USA is anticipated in the second half of 2020. bb2121 is an investigational therapy; safety and efficacy have not yet been established. bb2121 has not been approved for use by any health authority.

Other

PolarityTE

PolarityTE (UT, USA; www.polarityte.com) has announced data from two pilot studies on the use of its SkinTE™ product, both showing successful closure of diabetic foot ulcers (DFUs) and venous stasis leg ulcers (VLU) within a 12-week period [14]. The cases involved patients with lower extremity chronic wounds that were difficult to treat or had failed to heal with standard dressing care and conventional treatments, using a single application of SkinTE. SkinTE is a human cellular and tissue-based product derived from a patient's own skin intended for the repair, reconstruction and replacement of skin tissue. The first study included wound closure rates for 11 DFU patients with Wagner 1 and Wagner 2 wounds. The second study included wound closure rates for five VLU patients. All patients had wounds resistant to standard dressing care. The chronic wounds in 10 of the 11 patients with DFUs and all five VLU patients demonstrated granulation, progressive epithelialization and closure within 12 weeks following a single application of SkinTE. The wounds remained closed, with no adverse reactions, during follow-up

visits at least 14 weeks post initial SkinTE application. One DFU patient required treatment due to a nonrelated infection stemming from prior hardware in their foot, which required removal of the product before wound closure was achieved. The studies are pilots for two multicenter, randomized controlled clinical trials evaluating SkinTE for DFUs and VLUs that the company previously announced (<https://clinicaltrials.gov>; ID: NCT03881254 and NCT03881267).

Promethera

Promethera Biosciences (Belgium; www.promethera.com) has announced the dosing of the first patient in a Phase IIa clinical study for the company's HepaStem development program in patients with late-stage nonalcoholic steatohepatitis [15]. The multicenter, open-label PANASH study will evaluate the safety and preliminary efficacy of Promethera's investigational drug HepaStem, a novel allogenic cell-based therapy for severe liver diseases, in patients with cirrhotic and precirrhotic nonalcoholic steatohepatitis (<https://clinicaltrials.gov>; ID: NCT03963921). The study will enroll a minimum of 24 patients via centers in eight European countries. The completion of the trial is expected for H1 2020.

Regulations, approvals, acquisitions...

Green light

Athersys

Athersys (OH, USA; www.athersys.com) has announced that its clinical program evaluating MultiStem[®] cell therapy for the treatment of acute respiratory distress syndrome has received Fast Track designation from the FDA [16]. This important designation is given to qualified investigational therapies that show promise in providing benefit to patients in areas of significant unmet medical need. Fast Track designation allows for an expedited regulatory review process after the clinical data are submitted to help speed development of promising therapies to the market in order to help patients in areas where current standard of care is limited. Multistem represents a unique 'off-the-shelf' mesenchymal stromal/stem cell-based product that can be manufactured in a scalable manner, may be stored for years in frozen form, and is administered without tissue matching or the need for immune suppression.

Fibrocell

Fibrocell Science (PA, USA; www.fibrocell.com), a gene therapy company focused on transformational autologous cell-based therapies for skin and connective tissue diseases, has announced that the FDA has granted the Regenerative Medicine Advanced Therapy (RMAT) designation to FCX-007, the Company's gene therapy candidate for the treatment of recessive dystrophic epidermolysis bullosa (RDEB) – a devastating, genetic skin disease with high mortality [17]. FCX-007 is Fibrocell's clinical stage, gene therapy product candidate for the treatment of RDEB, a congenital and progressive orphan skin disease caused by the deficiency of the protein COL7. 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. Fibrocell is developing FCX-007 in collaboration with Intrexon (MD, USA; www.dna.com). In addition, Fibrocell is working in collaboration with Castle Creek Pharmaceuticals (NJ, USA; www.castlecreekpharma.com) to develop and commercialize FCX-007 for the treatment of RDEB. Castle Creek is recognized for its innovation in drug development for rare skin diseases and its commitment to bringing novel therapies to those living with epidermolysis bullosa.

Novartis

A Japanese government panel has approved a price of 33.5 million yen (US\$305,800) for Novartis' (Switzerland; www.novartis.com) cancer treatment Kymriah [18]. The one-time, personalized therapy, which was approved in Japan in March, will be available in the country for young people with acute lymphoblastic leukemia and adult patients with diffuse large B-cell lymphoma (DLBCL). The CAR-T therapy, which Novartis believes could treat up to 216 Japanese patients a year, potentially generating annual sales of 7.2 billion yen (US\$65.7 million), has been hailed as a revolutionary, last-ditch hope for people whose cancer advanced after previous treatment.

Poseida

Poseida Therapeutics (CA, USA; www.poseida.com) has announced the FDA has granted orphan drug designation to PBCMA-101 for the treatment of relapsed and/or refractory multiple myeloma [19]. PBCMA-101 is an autologous CAR-T therapy developed using Poseida's piggyBac® platform technology. P-BCMA-101 is comprised of a high percentage of long-lived, self-renewing stem cell memory T cells targeting cancer cells expressing BCMA. Poseida's no-viral piggyBac DNA modification system results in CAR-T product candidates with a high percentage of stem cell memory T cells, the only T cell that is self renewing and long lived, leading to CAR-T products with improved efficacy, lower toxicity and potentially greater durability than earlier generation CAR-T therapies. Orphan drug designation is granted by the FDA Office of Orphan Products Development to drugs and biologics, which are intended for the treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the USA. Under the Orphan Drug Act, the FDA may provide grant funding toward clinical trial costs, tax advantages, FDA user-fee benefits and 7 years of market exclusivity in the USA following marketing approval by the FDA. Poseida has received grant funding from the California Institute for Regenerative Medicine (CA, USA; www.cirm.ca.gov) to support the clinical development of P-BCMA-101.

Pending*Mesoblast*

Mesoblast (Australia; www.mesoblast.com) has filed the first component of a rolling submission for a Biologics License Application (BLA) to the FDA for remestemcel-L in the treatment of children with steroid-refractory acute graft versus host disease, a life-threatening complication of an allogeneic bone marrow transplant [20]. The FDA has agreed to a rolling review of the BLA, which enables individual components to be submitted and reviewed on an ongoing basis rather than waiting for all sections to be completed. The rolling process will provide opportunity for ongoing communication, and during this process the company expects it will be able to adequately address any substantial matters raised by the FDA. Remestemcel-L has received Fast Track designation for acute graft versus host disease and under this designation Mesoblast intends to request a priority review once its BLA filing is completed and accepted by the FDA.

Capital market & finances*BioTime*

BioTime (CA, USA; www.biotimeinc.com) has been awarded a new R&D grant for 2019 up to 9 million Israeli New Shekels (approximately US\$2.5 million) from the Israel Innovation Authority (Israel; <https://innovationisrael.org.il/en/contentpage/israel-innovation-authority>) [21]. The grant provides funding for the continued development of OpRegen, the company's retinal pigment epithelium transplant therapy currently in Phase I/IIa development for the treatment of dry age-related macular degeneration, the leading cause of blindness in the developed world. To date, the Israel Innovation Authority has provided annual grants totaling approximately US\$15 million for the development of the OpRegen program.

Gilead & Kite

Gilead Sciences (CA, USA; www.gilead.com) has announced that Kite Pharma (CA, USA; www.kitepharma.com), the cancer-focused cell therapy company it acquired in 2017, will become a separate business unit [22]. Kite is mainly known for Yescarta, a CAR-T cell therapy currently approved to treat certain types of lymphoma. Gilead said first-quarter sales of Yescarta totaled US\$96 million, which was short of the average analyst estimate of US\$103 million.

Promethera

Promethera Biosciences (Belgium; www.promethera.com) has closed a €39.7 million (US\$45 million) Series D financing [23]. Proceeds from the financing will accelerate the company's ongoing HepaStem clinical program in acute-on-chronic liver failure and the launch of the company's first clinical trial in nonalcoholic steatohepatitis. In addition, the funding will be used for its manufacturing scale up, preclinical programs and overall operations of the company and the group.

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