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

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Business development

Collaborations, partnerships & alliances

Co-development agreement: Phio & Carisma

Phio Pharmaceuticals (MA, USA; www.phiopharma.com), a biotechnology company developing the next generation of immuno-oncology therapeutics based on its proprietary self-delivering RNAi (sd-rxRNA[®]) therapeutic platform, has entered into a research collaboration with Carisma Therapeutics (PA, USA; www.carismatx.com) to evaluate the potential of Phio's self-delivering RNAi compounds to synergistically modify Carisma's chimeric antigen receptor (CAR) macrophages [1]. Silencing of key genes using sd-rxRNA compounds may enhance the immune function of these cells as a novel adoptive cell therapy for use in cancer treatment.

Collaboration agreement: Allogene & Stanford

Allogene Therapeutics (CA, USA; www.allogene.com), a clinical-stage biotechnology company pioneering the development of allogeneic CAR T (AlloCAR T[™]) therapies for cancer, has entered into a research collaboration agreement with Stanford University (CA, USA; www.stanford.edu) to investigate a novel nucleic acid delivery system developed by Stanford researchers to more effectively, safely and flexibly deliver intracellular RNA or DNA into lymphocytes, including T cells [2]. Allogene intends to explore the use of this technology to advance the field of AlloCAR T therapy. The charge-altering releasable transporter system developed by Stanford researchers is designed to resolve several challenges associated with existing physical, viral and nanoparticle nucleic acid delivery methods [3–6]. During the research collaboration, Stanford researchers will design and optimize tools and reagents for *ex vivo* cell engineering for Allogene to evaluate in terms of efficiency, cell viability, cytotoxicity and functional cell performance.

Collaboration agreement: Gamida Cell & CIBMTR

Gamida Cell (Israel; www.gamida-cell.com) and the Center for International Blood and Marrow Transplant Research (CIBMTR[®]) have entered into a research agreement to collect and analyze health outcomes data in patients with hematologic malignancies who receive an allogeneic hematopoietic stem cell transplant from various donor sources [7]. The newly launched observational study by the CIBMTR and Gamida Cell will include both retrospective and prospective data contemporaneous to the international, randomized, Phase III study of omidubicel (formerly known as NiCord[®]), Gamida Cell's investigational advanced cell therapy designed to enhance the life-

saving benefits of bone marrow transplant. Topline data from the ongoing Phase III study is anticipated in the first half of 2020, and initial data from the multi-year observational study is anticipated next year. Omidubisel has not yet been approved for marketing in the USA or any other jurisdiction.

Omidubisel is the first bone marrow transplant product to receive Breakthrough Therapy Designation from the US FDA and has also received Orphan Drug Designation (ODD) in the USA and EU. In a Phase I/II clinical study, omidubisel demonstrated rapid and durable time to engraftment and was generally well-tolerated. A Phase III study evaluating omidubisel in patients with leukemia and lymphoma is ongoing in the USA, Europe and Asia (<https://clinicaltrials.gov>; ID: NCT02730299). Omidubisel is also being evaluated in a Phase I/II clinical study in patients with severe aplastic anemia (<https://clinicaltrials.gov>; ID: NCT03173937). The aplastic anemia IND application is currently filed with the FDA under the brand name CordIn[®], which is the same investigational development candidate as omidubisel.

The CIBMTR is a research collaboration between the National Marrow Donor Program[®] (NMDP)/Be The Match[®] and the Medical College of Wisconsin. Through a close partnership with Be The Match BioTherapies[®], a subsidiary of NMDP/Be The Match, the organizations offer end-to-end solutions for cell and gene therapy developers, including cell sourcing and collection, clinical trial services, supply chain and logistics, manufacturing and commercialization support and outcomes management. The CIBMTR collaborates with the global scientific community to advance hematopoietic cell transplantation and cellular therapy worldwide to increase survival and enrich quality of life for patients. The CIBMTR facilitates critical observational and interventional research through scientific and statistical expertise, a large network of transplant centers, and a unique and extensive clinical outcomes database.

Launching new products, services...

Fate Therapeutics

Fate Therapeutics (CA, USA; <https://fatetherapeutics.com>), a clinical-stage biopharmaceutical company dedicated to the development of programmed cellular immunotherapies for cancer and immune disorders, has opened its current Good Manufacturing Process (cGMP) compliant manufacturing facility for the clinical production of its off-the-shelf natural killer (NK) cell and CAR T-cell product candidates [8]. The company's cGMP facility, located in San Diego, California, is custom designed for the manufacture of off-the-shelf allogeneic cell products using clonal master induced pluripotent stem cell (iPSC) lines as a starting cell source. The new state-of-the-art facility has been commissioned and qualified, and the Company has been issued a drug manufacturing license by the State of California, Department of Health Services, Food and Drug Branch.

Achievements

Autolus

Autolus (UK; www.autolus.com) a clinical-stage biopharmaceutical company developing next-generation programmed T cell therapies, has published both preclinical results and clinical data from the ongoing Phase I CARPALL trial of AUTO1, demonstrating the potential of the company's novel CAR T therapy targeting CD19 in development for the treatment of pediatric acute lymphoblastic leukemia (ALL) [9,10]. They report that AUTO1, or CAT CAR T cells (CAT CAR T), utilizes a binder with a fast off rate and showed both increased proliferation/cytotoxicity *in vitro* and enhanced proliferative capacity and antitumor activity when compared with FMC63 CAR T therapies *in vivo* in xenogeneic model of ALL. CARPALL (<https://clinicaltrials.gov>; ID: NCT02443831) is a multi-center, nonrandomized, open label Phase I clinical trial of heavily pretreated patients under age 24 with high risk and relapsed CD19⁺ ALL. Enrolled patients had a median age of 9 years with a median of four lines of prior treatment. 17 patients were enrolled, and 14 patients received an infusion of CAR T cells. In the Phase I clinical trial, 86% (n = 14) of recurrent/refractory pediatric ALL patients achieved molecular complete remission after a single dose, with a median duration of remission of 7.4 months and no severe cytokine release syndrome (CRS; $\geq$ grade 3 or 4), in this relapsed and/or refractory patient population. This dataset confirms that AUTO 1 induces no severe CRS (grade 3–5). Nine patients experienced grade 1 CRS, and four patients experienced grade 2 CRS. No patients required tocilizumab or steroids.

Rocket

Rocket Pharmaceuticals (NY, USA; www.rocketpharma.com) has published long-term data from the ongoing Phase I/II trial of RP-L102, the company's lentiviral vector-based gene therapy for Fanconi Anemia [11,12]. The data

included in the manuscript are from the first four patients treated with RP-L102 in the Phase I/II FANCOLEN-I trial that utilized first-generation 'Process A' without the use of any conditioning regimen. Follow-up for each of the initial four patients was 18–30 months from administration of RP-L102. Progressive increases in the total number of corrected leukocytes were observed shortly after the initial administration of RP-L102 in all treated patients. Favorable safety profile with no serious adverse events associated with infusion of the investigational product in these initial four patients.

Sinogene

Sinogene (China; <https://sinogene.org>) has announced a commercial cloning of a cat for US\$ 35,000 [13,14]. To clone the cat, Sinogene scientists collected skin cells from the British short hair, which had died of a urinary tract disease. They used the cells, along with eggs harvested from other cats, to generate 40 cloned embryos. Scientists then inserted the embryos into four surrogate cats. The process produced three pregnancies over the course of about 7 months, two of which ended in miscarriage. Sinogene has offered pet-cloning services since 2015 and has cloned 40 dogs so far, each at \$53,000 a pup. China has no laws against animal cruelty and critics argue that cloning animals is inefficient, inhumane, and may have unintended consequences when the cloned creatures begin contributing to the gene pool. In particular, the use of surrogate animals raises ethical questions. Sinogene is currently attempting to clone a horse and eventually aims to clone endangered animals, such as pandas and the South China tiger. Cloning an endangered animal would require experiments on interspecies cloning, but no scientist has so far successfully cloned a cross species animal due to technological barriers.

Clinical trials

Pluripotent stem cells

Kadimacell

Kadimastem (Israel; www.kadimacell.com), a clinical stage cell therapy company, has announced promising interim results of cohort A of its Phase I/IIa clinical trial for the treatment of patients with Amyotrophic Lateral Sclerosis (ALS), a devastating motor neuron disease (<https://clinicaltrials.gov>; ID: NCT03482050) [15]. The primary objective of the trial is to evaluate the safety of injecting AstroRx®, an 'off-the-shelf' clinical-grade human embryonic stem cell-derived astrocyte cell product, developed and manufactured by the company, into the spinal cord fluid of ALS patients. A secondary objective of the trial includes preliminary efficacy.

An interim analysis to explore possible efficacy was initiated and conducted after all five patients in cohort A completed 3 months post-treatment visits. No serious adverse events nor dose-limiting toxicities were reported, and statistically significant preliminary efficacy was observed.

The five patients included in cohort A received the lowest dose of AstroRx (100 × 10⁶ cells).

Preliminary efficacy assessment was based on ALS Functional Rating Scale – Revised (ALS-FRS-R), the gold standard criteria to assess ALS progression by monitoring patient muscle functions over time. During the 3 months pretreatment period, the ALS-FRS-R decreased at an average rate of (-0.87) per month. This rate of decrease is similar to that reported in the scientific literature. The average ALS-FRS-R change in the 3 months post-treatment was (+0.26) per month.

These results demonstrate a statistically significant difference between the slope in the pretreatment period and the slope in the first 3 months post-treatment period ($p = 0.0023$). This indicates that the progression of the disease was reduced in the first post-treatment period compared with the pretreatment period. Preliminary and interim results of Cohort A will be presented at the prestigious annual NEALS meeting to be held in Florida, USA, at the beginning of October 2019. Final results of cohort A (total 6 months post-treatment period) are expected by year end 2019.

Following the recommendation of the trial's independent Data & Safety Monitoring Board and the approval of the Israeli Ministry of Health, all five patients of cohort B who will receive a higher dose of AstroRx cells (250 × 10⁶) were recruited. Results of cohort B are expected in Q3, 2020.

T cells

Avalon

Avalon GloboCare (NJ, USA; www.avalon-globocare.com), a developer of cell-based technologies and therapeutics, has initiated its first-in-human, Phase I clinical trial of CD19 CAR-T candidate, AVA-001, in China. The clinical trial will interrogate the treatment of relapsed/refractory B-cell malignancies, including B-cell lymphoblastic leukemia

and non-Hodgkin's lymphoma [16]. CAR-T cells are engineered to express a CAR that recognizes a specific cancer surface target to attack. Unlike traditional small molecule or biologic treatments, the autologous CAR-T therapies are specifically manufactured for each individual patient. AVA-001 was designed to provide a more powerful, personalized CAR delivery mechanism. Co-developed with China Immunotech (China; www.cn-immunotech.com), AVA-001 is considered to be a second-generation CAR-T using the 4-1BB (CD137), a costimulatory signaling pathway, which exhibited strong anticancer activity during the preclinical study. It is also expected to feature a shorter bio-manufacturing time. The production process starts with the extraction of T cells from an individual patient, which are then converted into CAR-T cells that are specifically targeted to recognize and destroy cancer cells. The company anticipates AVA-001 will entail a shortened bio-production cycle, which could potentially empower the clinicians to provide accelerated treatment to patients with hematologic malignancies. Avalon is expected to recruit 20 patients for clinical safety and efficacy monitoring and assessment (<https://clinicaltrials.gov>; ID: NCT03952923).

Celyad

Celyad (Belgium; www.celyad.com), a clinical-stage biopharmaceutical company focused on the development of CAR-T cell-based therapies, has announced the successful administration of CYAD-01 produced with the OptimAb manufacturing process to a patient enrolled in cohort 3 (300 million cells) of the Phase I DEPLETHINK trial (<https://clinicaltrials.gov>; ID: NCT03466320) [17]. CYAD-01 is an investigational CAR-T therapy in which a patient's T cells are engineered to express a CAR based on NKG2D, a receptor expressed on NK cells that binds to eight stress-induced ligands expressed on tumor cells. The OptimAb manufacturing process utilizes a shortened cell culture and incorporates a selective PI3K inhibitor. This results in a product that is enriched for T cells with a memory-like phenotype. Preclinical data demonstrate that CYAD-01 produced using the OptimAb manufacturing process drives improved antitumor activity in an aggressive acute myeloid leukemia (AML) model compared with CYAD-01 produced with the previous mAb manufacturing process. In October 2018, Celyad initiated the DEPLETHINK Phase I trial. The open-label, dose-escalation trial will evaluate a single infusion of CYAD-01 for the treatment of relapsed/refractory AML and myelodysplastic syndromes following preconditioning chemotherapy (cyclophosphamide [300 mg/m²] and fludarabine [30 mg/m²]). The trial will evaluate three dose levels of CYAD-01 including 100 million, 300 million and 1 billion cells per infusion, respectively. The primary end point of the trial is safety and secondary end points include clinical activity and pharmacokinetics.

Other

Mallinckrodt

Mallinckrodt (UK; www.mallinckrodt.com) has announced positive top-line results from its pivotal Phase III clinical trial of its investigational StrataGraft regenerative tissue (<https://clinicaltrials.gov>; ID: NCT03005106) [18]. The study, which met both primary end points, evaluated the efficacy and safety of a single application of StrataGraft in the treatment of deep partial-thickness thermal burns. Each study participant served as his or her own control. On average, 4% of the area of StrataGraft-treated sites required autografting by 3 months. By design, 100% of the area of control-treated sites was autografted and an additional 2% of the area required subsequent autografting by 3 months. This resulted in a 98% reduction in the area requiring autograft in the StrataGraft-treated sites compared with the control-treated sites ($p < 0.0001$). In addition, 83% of burn wounds treated with StrataGraft tissue alone achieved durable wound closure at the treatment site at 3 months postplacement (95% CI: 74.4–91.8%, meeting the predefined threshold of statistical significance). As a reference, 86% of the burn wounds treated with a single application of autograft achieved durable wound closure at 3 months postplacement (95% CI: 77.8–94.0%). Based on the positive Phase III data, Mallinckrodt plans to submit a Biologics License Application for StrataGraft tissue to the FDA in the first half of 2020.

StrataGraft tissue is an investigational product, and its safety and effectiveness have not yet been established by the FDA.

Neuralstem

Neuralstem (MD, USA; www.neuralstem.com), a biopharmaceutical company focused on developing novel treatments for nervous system diseases, has completed subject enrollment in its Phase II clinical trial of NSI-566 for the treatment of chronic ischemic stroke [19]. NSI-566, a spinal cord-derived neural stem cell line, is Neuralstem's lead stem cell therapy candidate and has also been evaluated in China in clinical trials for patients with ALS and chronic

spinal cord injury. The double-blind, placebo-controlled study enrolled 22 subjects that were randomized to one of two groups: a treatment group that received intracerebral administration of 72 million human neural stem cells or a sham surgery group. Subjects enrolled in the study were to have sustained chronic motor deficits due to an ischemic stroke 4–24 months prior to enrollment and will be evaluated for measures of efficacy for 12 months after surgery and measures of safety for an additional 48 months.

Regulations, approvals, acquisitions...

Green light

Adaptimmune

Adaptimmune Therapeutics (UK; www.adaptimmune.com), a T-cell therapy company, has announced that the FDA has granted ODD to SPEAR T-cells targeting MAGE-A4 (Adaptimmune's ADP-A2M4 program) for the treatment of soft tissue sarcomas [20]. Adaptimmune's ADP-A2M4 (MAGE-A4) SPEAR T-cell therapy is directed to a member of the MAGE family of cancer testis antigens expressed in a number of solid tumor cell types. The MAGE-A4 antigen is among the most commonly expressed cancer testis antigens. Adaptimmune is evaluating its affinity-enhanced SPEAR T-cells in synovial sarcoma and MRCLS in three trials: the recently initiated Phase II trial SPEARHEAD-1 in sarcoma; a radiation sub-study to enhance antitumor activity; and the ongoing pilot trial. Both the radiation sub-study and pilot trial include sarcoma as well as multiple other solid tumor indications. Adaptimmune is also evaluating a next-generation SPEAR T-cell (ADP-A2M4CD8) in sarcoma as well as other solid tumor indications in the SURPASS trial.

Avita

AVITA Medical (Australia; www.avitamedical.com), a regenerative medicine company focused on the development and commercialization of innovative therapies leveraging the healing properties of a patient's own skin, has announced that the FDA has approved the company's investigational device exemption application to conduct a pivotal trial evaluating the safety and effectiveness of the RECELL[®] Autologous Cell Harvesting Device (RECELL[®] System) in combination with meshed autografting for the treatment of acute full-thickness skin defects, such as degloving (a type of injury where the skin is ripped from the underlying tissue), crush wounds (a break in the external surface of the body), abrasions, lacerations and surgical wounds [21]. AVITA Medical will initiate a prospective, multi-center, randomized controlled study to compare the clinical performance of conventional skin grafting with and without the use of the RECELL System on acute nonburn full-thickness skin defects. Each patient will have a control wound treated with conventional skin grafting and a wound treated with expanded skin grafting in combination with the RECELL System. The study's two primary effectiveness end points are:

- Incidence of healing by 8 weeks post-treatment;
- Donor skin sparing, evaluated by comparing the ratios of donor skin required to treat the wounds.

Healing will be evaluated by a qualified clinician blinded to the treatment allocation. Additional long-term safety and effectiveness data collected over the course of the 52-week study will include blinded evaluation of scar outcomes and patient treatment preference.

CARsgen

CARsgen Therapeutics (China; www.carsgen.com), a clinical-stage biopharmaceutical company, has announced that the FDA has granted ODD to its investigational CAR-T-cell therapy fully human anti-B cell maturation antigen (autologous CAR T cells; ct053) for the treatment of multiple myeloma [22]. CARsgen has also received PRiority Medicines eligibility from the European Medicines Agency (EMA) [23]. Both ODD and PRiority Medicines eligibility were based on clinical data from an ongoing CT053 B cell maturation antigen CAR-T Phase I study in China. As of 30 June 2019, 21 out of 24 myeloma patients (87.5%) who received a median of 4.5 prior lines of myeloma therapy showed objective response. 19 out of 24 patients (79.2%) achieved complete response. There was no grade 3 or higher CRS. The duration of response data will be reported at a future date.

Fate Therapeutics

Fate Therapeutics (CA, USA; <https://fatetherapeutics.com>), a clinical-stage biopharmaceutical company dedicated to the development of programmed cellular immunotherapies for cancer and immune disorders, has announced

that the FDA has cleared the company's Investigational New Drug (IND) application for FT596, the company's first off-the-shelf CAR NK cell cancer immunotherapy which targets multiple tumor-associated antigens [24]. FT596 is derived from a clonal master iPSC line engineered with three functional modalities designed to optimize antitumor activity: a proprietary CAR targeting B-cell antigen CD19; a novel high-affinity 158V, noncleavable CD16 (hnCD16) Fc receptor; and an IL-15 receptor fusion. The company plans to initiate clinical investigation of FT596 as a monotherapy and in combination with CD20-directed monoclonal antibodies for the treatment of B-cell lymphoma and chronic lymphocytic leukemia.

FT596, which is the first cellular immunotherapy engineered with three active antitumor components cleared for clinical investigation by the FDA, is uniquely designed to overcome CD19 antigen escape. In addition to a proprietary CAR targeting CD19, FT596 expresses a novel hnCD16 Fc receptor that has been modified to augment antibody-dependent cellular cytotoxicity, enabling coincident targeting of CD19 and additional antigens such as CD20. FT596 also expresses IL-15 receptor fusion, a potent cytokine complex that promotes survival, proliferation and trans-activation of NK cells and CD8 T cells without the need for systemic cytokine support. Together, these features of FT596 are intended to maximize potency and minimize toxicity in treated patients.

FT596 is the third off-the-shelf, iPSC-derived NK cell product candidate from the company's proprietary iPSC product platform cleared for clinical investigation by the FDA in less than 1 year. The company is conducting first-in-human clinical trials of FT516, an off-the-shelf NK cell cancer immunotherapy engineered to express hnCD16, for the treatment of AML and B-cell lymphoma, and FT500, an off-the-shelf NK cell cancer immunotherapy, for the treatment of advanced solid tumors.

Novartis

Novartis' (Switzerland; www.novartis.com) Kymriah (tisagenlecleucel) has received routine reimbursement for all eligible UK patients on the NHS, following appraisal from the Scottish Medicines Consortium. The SMC approved the CAR-T therapy for use in adult patients with relapsed or refractory diffuse large B-cell lymphoma, who have not responded to two or more prior treatments [25]. The cost of Kymriah is US\$ 345,000 (£282,000) per patient at full list price, but the level of discount offered to the NHS has not been disclosed. Novartis' CAR-T rival from Gilead, Yescarta, has a UK list price of nearly US\$ 367,000 (£300,000) per patient.

Precision

Precision BioSciences (NC, USA; www.precisionbiosciences.com), a genome editing company, has announced the FDA has accepted its IND application for PBCAR20A, the company's second off-the-shelf CAR T-cell therapy program [26]. PBCAR20A is an allogeneic anti-CD20 CAR T therapy candidate in development for the treatment of non-Hodgkin lymphoma, chronic lymphocytic leukemia and small lymphocytic lymphoma. The company plans to initiate a Phase I/IIa clinical trial in the fourth quarter of 2019, with initial data expected in 2020 (<https://clinicaltrials.gov>; ID: NCT04030195). The study will include patients with non-Hodgkin lymphoma, of which a subset will have the diagnosis of mantle cell lymphoma. Precision BioSciences has received ODD for mantle cell lymphoma and plans to pursue this indication.

SanBio

The SanBio Group (CA, USA; <https://sanbio.com>) has announced that the FDA has granted Regenerative Medicine Advanced Therapy Designation for SB623 cell therapy for the treatment of chronic neurological motor deficits secondary to traumatic brain injury [27]. The designation is based on clinical results of SB623 including the Phase II Study of Modified Stem Cells in Traumatic Brain Injury trial (<https://clinicaltrials.gov>; ID: NCT02416492). Study of Modified Stem Cells in Traumatic Brain Injury was 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 neurological motor deficits secondary to traumatic brain injury. In this study, SB623 cells were implanted directly around the site of brain injury. SB623 is a proprietary, cell-based 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.

Red light

Abeona

Abeona Therapeutics Inc. (TX, USA; www.abeonatherapeutics.com) has recently received a clinical hold letter from the FDA clarifying that the FDA will not provide approval for the company to begin its planned Phase III clinical trial for EB-101 until it submits to the FDA additional data points on transport stability of EB-101 to clinical sites [28]. EB-101 is an investigational, autologous, gene-corrected cell therapy poised to enter late-stage development for the treatment of recessive dystrophic epidermolysis bullosa, a rare connective tissue disorder without an approved therapy. Treatment with EB-101 involves using gene transfer to deliver COL7A1 genes into a patient's own keratinocytes and transplanting them back to the patient to enable normal Type VII collagen expression and facilitate wound healing. In the USA, Abeona holds regenerative medicine advanced therapy, breakthrough therapy and rare pediatric designations for EB-101 and ODD in both the USA and EU.

Google

Google (CA, USA; www.google.com) has announced a new Healthcare and Medicines policy to prohibit advertising for unproven or experimental medical techniques such as most stem cell therapy, cellular (nonstem) therapy and gene therapy [29,30]. This new policy will prohibit ads selling treatments that have no established biomedical or scientific basis. The new policy also includes treatments that are rooted in basic scientific findings and preliminary clinical experience, but currently have insufficient formal clinical testing to justify widespread clinical use.

Acquisitions

Autolus & PPF

Investment group PPF (Czech Republic; www.ppf.eu) has acquired a 19.2% stake in biopharmaceutical firm Autolus (UK; www.autolus.com), a clinical-stage biopharmaceutical company developing next-generation programmed T cell therapies, making it the company's biggest shareholder [31]. PPF did not disclose the price of the acquisition, made through share purchases on the NASDAQ. Autolus had a market capitalization of US\$ 607 million at time of the acquisition, though its shares have lost 60% so far this year.

Castle Creek & Fibrocell

Fibrocell Science (PA, USA; www.fibrocell.com), a cell and gene therapy company focused on transformational autologous cell-based therapies for skin and connective tissue diseases, has reached an agreement to be acquired by Castle Creek Pharmaceutical Holdings, the parent company of Castle Creek Pharmaceuticals (NJ, USA; www.castlecreekpharma.com) [32]. Castle Creek Pharmaceutical Holdings, a privately held holding company that holds and invests in companies in the orphan dermatology space, will acquire Fibrocell for a total consideration of approximately US\$ 63.3 million, including repayment of debt and other financial instruments, in cash. Fibrocell common stockholders will receive all-cash consideration of US\$ 3.00 per share. This offer represents a 63% premium to Fibrocell's 30-day volume weighted average price as of 11 September 2019. The transaction was approved by the Boards of Directors of both companies and is expected to close in the fourth quarter of 2019.

Fibrocell's portfolio includes FCX-007, an investigational, late-stage stage gene therapy product candidate for the treatment of recessive dystrophic epidermolysis bullosa, 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. A Phase III trial was initiated recently, and if successful, a Biologics License Application filing is expected in 2021. For Phase I and II, see: <https://clinicaltrials.gov>; ID: NCT02810951.

Generex & ALTuCELL

Generex Biotechnology Corporation (FL, USA; www.generex.com) has signed a binding letter of intent to partner with ALTuCELL (NY, USA; <https://altucell.com>), a privately held biotechnology company. ALTuCELL's proprietary technology overcomes the major barriers to transplantation by a novel strategy utilizing patented micro-encapsulation technology, enabling a transplantable, cell-based therapy that avoids detection and rejection by the immune system [33].

NanoSurface & Silene

NanoSurface Biomedical (WA, USA; www.nanosurfacebio.com), a provider of biomimetic cell-based assay platforms and services, has acquired Silene Biotech (WA, USA; www.silenebiotech.com) a company focused on stem cell banking and services [34]. This acquisition expands NanoSurface's capabilities in developing human stem cell-based platforms and technologies to accelerate the development of new drugs. Under the agreement, NanoSurface has acquired Silene's IP, cGMP laboratory facilities, and its research, development and operations teams. NanoSurface will also continue to maintain Silene's ongoing cell banking operations and Silene's existing customer relationships.

Vertex & Semma

Vertex Pharmaceuticals (MA, USA; www.vrtx.com) has entered into a definitive agreement under which Vertex will acquire Semma Therapeutics (MA, USA; www.semma-tx.com), a privately held biotechnology company pioneering the use of stem cell-derived human islets as a potentially curative treatment for Type 1 diabetes, for US\$950 million in cash [35]. Semma has demonstrated a differentiated approach to treat Type 1 diabetes, a serious disease affecting over 1 million people in the USA alone. Semma has made two major scientific advances: the ability to produce large quantities of functional human pancreatic beta cells that restore insulin secretion and ameliorate hypoglycemia in animal models and a novel device that encapsulates and protects these cells from the immune system, enabling durable implantation without the need for ongoing immunosuppressive therapy.

Capital market & finances*Avita*

AVITA Medical (Australia; www.avitamedical.com), a regenerative medicine company with a technology platform positioned to address unmet medical needs in therapeutic skin restoration, announced that its American Depositary Shares (ADSs) have been approved to list on the Nasdaq Capital Market [36]. Trading began on 1 October 2019, under the ticker symbol 'RCEL'.

Celyad

Celyad (Belgium; www.celyad.com), a clinical-stage biopharmaceutical company focused on the development of CAR-T cell-based therapies, has closed a global offering of 2,000,000 ordinary shares comprised of 1,675,000 ordinary shares in the form of ADSs offered in the USA, Canada and certain countries outside of Europe at a price per ADS of US\$ 10.00 and 325,000 ordinary shares in Europe and certain countries outside of the USA and Canada in a concurrent private placement at a price per share of €9.08 [37]. Each ADS represents the right to receive one ordinary share. The gross proceeds to Celyad from the global offering amounted to approximately US\$ 20.0 million (€18.2 million), before deducting underwriting discounts and commissions and estimated offering expenses. In connection with the global offering, Celyad has granted the underwriters a 30-day option to purchase up to an additional 300,000 ordinary shares, which may be in the form of ADSs, on the same terms and conditions.

Fate Therapeutics

Fate Therapeutics (CA, USA; <https://fatetherapeutics.com>), a clinical-stage biopharmaceutical company dedicated to the development of programmed cellular immunotherapies for cancer and immune disorders, has closed an underwritten public offering of 9,890,000 shares of its common stock, which included 1,290,000 shares that were issued pursuant to the full exercise of the underwriters' option to purchase additional shares, at a public offering price of US\$ 17.50 per share [38]. Aggregate gross proceeds from this offering, including exercise of the option, were approximately US\$ 173.1 million, prior to deducting underwriting discounts and commissions and estimated offering expenses. Fate Therapeutics intends to use the net proceeds from the offering to fund clinical trials and nonclinical studies, the manufacture of its clinical product candidates, the expansion of its cGMP compliant manufacturing operations, the conduct of preclinical research and development and for general corporate purposes.

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