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

Dusko Ilic^{*,1} & Mirjana Liovic²

¹Stem Cell Laboratories, Guy's Assisted Conception Unit, Department of Women & Children's Health, Faculty of Life Sciences & Medicine, King's College London, London, SE1 9RT, UK

²Medical Center for Molecular Biology, Faculty of Medicine, University of Ljubljana, 1000 Ljubljana, Slovenia

*Author for correspondence: dusko.ilic@kcl.ac.uk

Latest developments in the field of stem cell research and regenerative medicine compiled from publicly available information and press releases from nonacademic institutions in August 2020.

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Business development

Codevelopment agreement: NantKwest & ImmunityBio

NantKwest (CA, USA; www.nantkwest.com), a clinical stage, natural-killer (NK) cell-based therapeutics company, and ImmunityBio (CA, USA; www.immunitybio.com), a privately held immunotherapy company, have signed a definitive agreement to jointly develop, manufacture, market and commercialize therapeutics and vaccines for combating the COVID-19 pandemic [1]. Under the terms of the definitive agreement, the two companies agree to share equally the costs incurred after 21 August 2020 of development, manufacturing, marketing and commercialization of the products each is developing related to COVID-19. Should a product be commercialized successfully, the companies have agreed to a 60–40% split of net profits, with the larger share going to the company that developed the product. The agreement also details the structure of shared governance of the joint collaboration. The two product candidates currently in development under the agreement are a mesenchymal stromal/stem cell (MSC) therapeutic from NantKwest, whose goal is to reduce the time a critically ill patient spends on a ventilator; and a COVID-19 vaccine product from ImmunityBio, which is anticipated to soon enter into a Phase I clinical trial.

Codevelopment agreement: Vor & Metagenomi

Vor Biopharma (MA, USA; www.vorbiopharma.com), an oncology company pioneering engineered hematopoietic stem cells for the treatment of cancer and Metagenomi (CA, USA; <https://metagenomi.co>), a gene editing company discovering breakthrough systems for curing genetic disease, have announced that Vor will evaluate the potential use of Metagenomi's gene editing technology to develop engineered hematopoietic stem cell-based therapies for the treatment of blood cancers, such as acute myeloid leukemia [2]. The collaboration is nonexclusive and applies to preclinical research only. Further terms of the agreement are not being disclosed.

Collaboration agreement: Pluristem & ADSCC

Pluristem Therapeutics (Israel; www.pluristem.com) has signed a nonbinding Memorandum of Understanding with the Abu Dhabi Stem Cells Center (ADSCC; Abu Dhabi; www.adssc.ae/en-us/Pages/default.aspx), a specialist healthcare center focused on cell therapy and regenerative medicine [3]. The parties have agreed to exchange research results, share samples, join usage of equipment and testing and other essential activities related to advancing the treatment and research of cell therapies for a broad range of medical conditions, including COVID-19. ADSCC has been treating COVID-19 patients with stem cells sourced from the patient's blood, by returning the cells back

into the patient's lungs as a fine mist through a nebulizer, a machine that helps a patient breathe in medicine through a mask or mouthpiece. Pluristem has treated patients with its placental PLX-PAD allogenic product via compassionate use. The cells were administered as intramuscular injection.

Collaboration agreement: Viacyte & Gore

ViaCyte (CA, USA; www.viacyte.com), a clinical stage regenerative medicine company and Gore (DE, USA; www.gore.com), a global materials science company with expertise in medical device development and drug delivery technologies, have signed an agreement covering the next phase of their ongoing collaboration focused on the development of ViaCyte's Encaptra[®] Cell Delivery System enabled by proprietary Gore advanced material technologies [4]. The Encaptra System has the potential to negate the need for immunosuppression and is an important component of the PEC-Encap[™] product candidate (also known as VC-01) that ViaCyte is developing as a potential transformative therapy for patients with Type 1 diabetes. The biologically active component of the PEC-Encap product candidate is human embryonic stem cell derived pancreatic islet cell progenitors, called PEC-01[™] cells. These cells are contained within the Encaptra System and implanted in a patient subcutaneously. Once implanted and successfully engrafted, the PEC-01 cells mature into beta cells that secrete insulin in a regulated manner to control blood glucose levels. Other cells of the normal human islet are also produced. The Encaptra System serves to protect the PEC-01 cells from the host immune system thus eliminating the need for immune suppression drugs commonly used with other transplants. A critical enabling component of the Encaptra System that contains and protects the cells is a specifically designed semipermeable membrane that encapsulates the cells but allows for diffusion of oxygen and nutrients into the device and insulin and other hormones out of the device and into the circulation. This membrane also enables the formation of a vascular network on the surface of the device after implantation. Under the terms of the agreement, Gore will manufacture and supply a proprietary Gore membrane and the device component for use with ViaCyte's PEC-Encap product candidate. Should the membrane prove successful in the ongoing trial, Gore will assume the responsibility for manufacturing the Encaptra System incorporating the novel membrane technology for late stage clinical development and commercial use.

Launching new products & services

Kiadis

Kiadis Pharma (the Netherlands; www.kiadis.com), a clinical stage biopharmaceutical company developing innovative cell-based medicines for life-threatening diseases, has announced a new research program, K-NK-ID101, that will focus on the development of K-NK cells as a treatment for COVID-19 [5]. This new program marks the start of broader application of Kiadis' K-NK technology platform as a potential treatment, not only for cancer, but also for infectious diseases. In support of the K-NK-ID101 program, Kiadis has started collaborating with five premier Dutch institutions to study different antiviral mechanisms of Kiadis' K-NK cell therapy platform against SARS-CoV-2, the virus that caused the COVID-19 pandemic. The collaboration will study NK-cell biology in COVID-19 patients, the elimination of SARS-CoV-2 virus and virally infected cells by K-NK cells, and synergies between monoclonal antibodies, vaccines and K-NK cells. NK cells are the human immune system's first line of defense against tumor cells and infectious disease. Activity of K-NK cells has been demonstrated against cytomegalovirus and BK virus in the K-NK002 clinical trials, and against CNS and pulmonary fungal and bacterial agents in the K-NK003 clinical trials. COVID-19 breaks down NK cell immunity, and severe COVID-19 patients lack functional NK cells. K-NK-ID101 cells potentially have enhanced antiviral activity, while avoiding exacerbating needless inflammation, and therefore may be uniquely suited to repair this lack of functional NK cells. Since K-NK-ID101 cells can be manufactured at large scale and frozen down, they can be immediately and globally made available to patients. Also, the broad antiviral activity of K-NK cells could potentially serve as a universal countermeasure to fight future viral pandemics; Kiadis will learn more about the potential of the platform through research conducted through these collaborations.

Clinical trials

Pluripotent stem cells

Kadimastem

Kadimastem (Israel; www.kadimastem.com), a clinical-stage biotechnology company developing cell therapies for the treatment of severe debilitating diseases, announced that its lead product, AstroRx[®], showed a positive efficacy signal and a good safety profile in cohort B of the company's Phase I/IIa clinical trial in amyotrophic lateral sclerosis

(ALS) [6]. The primary objectives of the trial were safety evaluation and tolerability of a single administration of allogeneic astrocytes derived from human embryonic stem cells, administered in escalating doses. The secondary objective was to evaluate the efficacy, including ALS Functional Rating Scale-Revised, the gold standard scale to assess ALS progression by monitoring patient muscle functions over time. The data demonstrated a clinically meaningful signal and statistically significant decline in disease progression rate. Earlier this year, due to COVID-19, the Data Safety Monitoring Board of the Phase I/IIa clinical trial recommended to put additional cohorts on hold to ensure the safety and wellbeing of the patients. Considering the ongoing situation presented by COVID-19 in Israel, the uncertainty and setbacks imposed, the company decided to not pursue the additional cohorts of the current Phase I/IIa clinical trial.

Mesenchymal stromal/stem cells

Pluristem

Pluristem Therapeutics (Israel; www.pluristem.com) has announced that Germany's health regulatory agency, the Paul Ehrlich Institute, has cleared the company's Phase II clinical protocol for its study titled, 'A randomized, controlled, multicenter, parallel-group Phase II Study to evaluate the efficacy and safety of intramuscular injections of mesenchymal-like adherent stromal cells (called PLX-PAD) for the treatment of severe COVID-19' [7]. Forty patients hospitalized with severe cases of COVID-19 complicated by acute respiratory distress syndrome will be enrolled in the study. The primary efficacy end point of the study is the number of ventilator free days during the 28 days from day 1 to day 28 of the study. Safety and survival follow-up will be conducted at day 60, week 26 and week 52. In addition to this study in Germany, pluristem is currently conducting a Phase II COVID-19 trial in the US which will enroll 140 patients (<https://clinicaltrials.gov>; NCT04389450).

Pluristem

Pluristem Therapeutics (Israel; www.pluristem.com) has completed patient enrollment in its Phase I study evaluating PLX-R18 as a treatment for incomplete hematopoietic recovery following hematopoietic cell transplantation (HCT), in the US and in Israel (NCT03002519) [8].

Incomplete hematopoietic recovery poses a significant risk to HCT recipients who fail to respond to standard of care treatments, making them vulnerable to infections and bleeding. PLX-R18 may address the unmet need in this patient population by stimulating the regenerative potential of bone marrow where other treatments have proven ineffective. The US FDA has granted orphan drug designation to PLX-R18 in this indication.

The Phase I multicenter, open-label, three cohort dose-escalating study is evaluating the safety of intramuscular injections of PLX-R18 cells in 20 subjects, with incomplete hematopoietic recovery persisting for at least 3 months after HCT. The follow-up period is 12 months. Safety is the primary end point, with efficacy end points including changes in white blood cells, platelets counts, hemoglobin levels, changes in blood products requirements and changes in quality of life.

Hematopoietic stem cells

bluebird bio

bluebird bio (MA, USA; www.bluebirdbio.com) has announced updated results from the clinical development program for its investigational elivaldogene autotemcel (eli-cel, Lenti-D™) gene therapy in patients with cerebral adrenoleukodystrophy (CALD), including long-term results from the Phase II/III Starbeam study (ALD-102/LTF-304) and data from the Phase III ALD-104 study (NCT01896102 and NCT03852498, respectively) [9].

Eli-cel is a one-time investigational gene therapy designed to address the underlying genetic cause of CALD by adding functional copies of the *ABCD1* gene into a patient's own hematopoietic (blood) stem cells (HSCs) that have been transduced *ex vivo* with the Lenti-D lentiviral vector. The addition of a functional gene allows patients to produce the ALDP, which is thought to break down the toxic accumulation of very-long-chain fatty acids in the brain. There is no need for donor HSCs from another person, as is required for allogeneic HSC transplantation.

The ALD-102 study has completed enrollment. All reported data below are as of January 2020 and reflect a total population of 32 patients with a median follow-up time of 30.0 months (9.1–70.7 months). The primary efficacy end point in the study is the proportion of patients who are alive and free of major functional disabilities (MFDs) at month 24. Of those patients who have or would have reached month 24, 87% have met the primary end point and continue to be alive and MFD-free at more than 2 years of follow-up (n = 20/23). 14 patients have at least

4 years of follow-up, including ten patients who have reached at least their year 5 follow-up visit. The nine patients from ALD-102 that have not reached month 24 have shown no evidence of MFDs.

bluebird bio is currently enrolling patients for ALD-104, a Phase III study designed to assess the efficacy and safety of eli-cel in patients with CALD after myeloablative conditioning using busulfan and fludarabine, a different chemotherapy conditioning regimen than what is used in ALD-102 (busulfan and cyclophosphamide). The primary efficacy end point is the proportion of patients who are alive and free of MFDs at month 24, and the primary safety end point is the proportion of patients with neutrophil engraftment after eli-cel infusion. All reported data below are as of February 2020. In ALD-104, the 13 patients currently on study have a median of 6.1 months of follow-up to date (min–max: 2.2–10.3 months). All 13 patients achieved neutrophil engraftment and 12/13 evaluable patients had platelet engraftment (platelet engraftment pending in one patient as of data cut date).

No events of acute or chronic graft-versus-host-disease (GvHD) have been reported and there have been no reports of graft failure, graft rejection, cases of insertional oncogenesis or replication competent lentivirus.

The EMA accepted eli-cel gene therapy for the treatment of CALD into its Priorities Medicines scheme in July 2018, and previously granted orphan medicinal product designation to eli-cel. The US FDA granted eli-cel orphan drug status, rare pediatric disease designation, and breakthrough therapy designation for the treatment of CALD.

Other

MaaT Pharma

MaaT Pharma (France; www.maatpharma.com) has announced clinical data on the compassionate use of its lead full-ecosystem microbiome restoration biotherapeutic, MaaT013. The data included 11 patients that developed gastrointestinal, acute Graft-versus-host-disease, a severe condition where the transplant donor's immune cells attack the patient's tissues after receiving an allo-HSCT to treat their hematologic malignancies [10]. All patients showed some response to MaaT013, with five patients achieving a complete response and two having a very good partial response 28 days after first dosing.

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Regulations, approvals, acquisitions...

Green light

Calidi

Calidi Biotherapeutics (CA, USA; www.calidibio.com), a clinical-stage biotechnology company, announced today that the Investigational New Drug (IND) application submitted by its partner, Personalized Stem Cells (CA, USA; www.personalizedstemcells.com), has received FDA approval for the treatment of COVID-19 and pneumonia patients using stem cell therapy [11]. Calidi has partnered with PSC for over 2 years, most recently contributing the stem cell lines used to manufacture treatment for the upcoming first trial, 'CoronaStem 1', which will be conducted among 20 hospitalized COVID-19 patients in California.

Editas

Editas Medicine (MA, USA; www.editasmedicine.com), a genome editing company, has announced that the US FDA has granted rare pediatric disease designation for EDIT-301, an experimental, autologous cell medicine, being developed as a potentially best-in-class, durable medicine for sickle cell disease [12]. EDIT-301 is comprised of sickle patient CD34⁺ cells genetically modified using a highly specific and efficient CRISPR/Cas12a (also known as Cpf1) RNP to edit the HBG1/2 promoter region in the beta-globin locus. Red blood cells derived from EDIT-301 CD34⁺ cells demonstrate a sustained increase in fetal hemoglobin production, which has the potential to provide a durable treatment benefit for people living with sickle cell disease. The company plans to file an IND application for EDIT-301 by the end of 2020.

RenovaCare

RenovaCare (NJ, USA; www.renovacareinc.com), developer of patented technologies for spraying self-donated stem cells for the regeneration of skin and other organs and tissues, has announced that the US FDA conditionally approved the company's investigational device exemption application to conduct a clinical trial to evaluate the safety and feasibility of autologous skin stem cells rendered by its CellMist™ System from and applied topically with the SkinGun™ spray device for treatment of burn wounds [13].

The clinical trial protocol is an open-label single-arm clinical study that will enroll 14 human burn subjects with partial-thickness second- or third degree thermal burn wounds. The company expects to conduct the clinical study at multiple US burn centers.

Sentien

Sentien Biotechnologies (MA, USA; <https://sentienbiotech.com>), a clinical-stage biotechnology company developing novel approaches to cell therapy, has announced that the US FDA has approved the company's IND application for the evaluation of Sentien's lead asset, SBI-101, for the treatment of severe COVID-19 [14]. Approval of this IND allows Sentien to initiate a Phase $\frac{1}{2}$ study with a focus on COVID-19 patients suffering from both acute respiratory distress syndrome and acute kidney injury requiring renal replacement therapy. SBI-101 is a combination product that integrates allogeneic MSCs within an extracorporeal, blood-filtration device. MSCs are a unique source of therapeutic secreted factors that modulate the immune-mediated inflammatory response to acute organ injury. By keeping the MSCs confined within a blood-filtration device, SBI-101 enables controlled, dynamic and sustained delivery of MSC-secreted factors to the patient's blood, without the need for direct injection of the MSCs themselves. SBI-101 integrates into a standard blood circuit such as used with renal replacement therapy, thereby providing patients with both standard-of-care and MSC-mediated blood conditioning in a single session.

Capital market & finances

Applied StemCell

Applied StemCell (CA, USA; www.appliedstemcell.com) has been awarded close to US\$ 2.0 million US dollars in a Small Business Innovation Research grant from the NIH [15]. This fast track Phase I/II grant award will support Applied StemCell to advance and improve the efficiency of its proprietary TARGATT™ integrase technology for human gene therapies (referred to as the hTARGATT™). Applied StemCell's approach will take advantage of the site-specificity and large DNA insertion capability of the serine integrase, PhiC31 (ΦC31) and engineer it to insert exogenous DNA into a defined and safe harbor locus in the human genome. The scope of the grant will also cover an unbiased detection and characterization of potential off-target insertion sites to ensure safety of this platform for therapeutic gene editing. This study will provide useful insight into the applicability of the hTARGATT™ gene therapy platform and build the foundation for its use in gene therapy for potentially 10,000 monogenic human diseases.

Lineage cell

Lineage Cell Therapeutics (CA, USA; www.lineagecell.com) has received US\$ 24.6 million in cash from Juvenescence (UK; <https://juvenescence.ltd>), representing principal and interest due under a convertible promissory note [16]. The note was issued in August 2018 as partial payment for the sale by Lineage to Juvenescence of 14.4 million shares of common stock of AgeX Therapeutics (CA, USA; www.agexinc.com).

Financial & competing interests disclosure

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