COMMERCIAL INSIGHT: FEB 2018

Commercial insight: cell and gene therapy

Providing a critical overview of the sector's commercial developments – M&As, licensing agreements & collaborations, financial results, IPOs and clinical/regulatory updates, with commentary from our Expert Contributors.

Celularity made a splash this past month with the announcement of a $250 million series A round that will take the company well into development with an unusually broad pipeline of both allogeneic and autologous products at various stages of development, including CAR-T cells, placental stem cell-based immunotherapy products and market-ready regenerative medicine assets. We're in an era of significant financings, both venture-led and public. The Celularity series A was similar in size to that of BlueRock Therapeutics, which posted its first venture round of $225 million back in December 2017. Like the BlueRock series A, which included Bayer, Celularity garnered support from bluechip companies, including Celgene, to cast itself into the field. Celularity perhaps stands alone in the cell therapy world as a company developing products for oncology, autoimmune disease and degenerative disease, all under one roof. While the company's first financing round is certainly large, it is commensurate with the depth of the portfolio it will bring through clinical development.

This month sees plenty of good news from clinical trials, with Abeona Therapeutics, REGENXBIO, GenSight Biologics and Mesoblast all releasing positive study progress reports. REGENXBIO and GenSight both have locally delivered AAVs in early development for eye conditions, but whereas GenSight's treatment targets the very rare Leber's Hereditary Optic Neuropathy, REGENXBIO has gone for the much more common (but less well-defined from a genetic perspective) wet AMD. Turning to collaborations, Kite Pharma has placed a $150 million bet on Sangamo's zinc finger nuclease (ZFN) technology as its preferred gene editing tool, in the hope that this will lead to new cell-based therapies in oncology. Whether ZFNs will prove better than the alternative approaches of TALENs and CRISPR remains to be seen, but the deal shows that Kite wants gene-editing tools at its disposal and is a vote of confidence for the ZFN approach.

GENE THERAPY
Richard Philipson
Chief Medical Officer,
Trizell Ltd, UK

CELL THERAPY
Mark Curtis
Financial Portfolio Manager,
Emerging Technologies
Lonza AG
Switzerland

POSITIVE SAFETY LONG-TERM SAFETY PROFILE FROM AAV MEDIATED GS010

Paris-based Gensight Biologics has published detailed results from the Phase 1/2 trial of their gene therapy candidate for Leber Hereditary Optic Neuropathy (LHON). The primary endpoint of the study was the assessment of the safety and tolerability of GS010 – with no serious adverse events reported over the 96 weeks following intravitreal injection. The significant results draw attention towards the Phase 3 trials of the AAV mediated therapy – RESCUE and REVERSE. Topline data are expected from these later this year.

These latest results were published in the journal of the American Academy of Ophthalmology. One the study's investigators, Catherine Vignal, commented,

"This first-ever scientific publication of clinical data with GS010 is a major step forward for patients afflicted with LHON – a blinding disease affecting those in the prime of their life. If these promising results are confirmed in the ongoing Phase 3 studies, GS010 would offer a meaningful and life changing therapy for those so afflicted and become the standard of care for LHON."

TWO US PATENTS ISSUED TO CELLECTIS FOR T-CELL EDITING

Cellectis has been issued two US patents concerning methods for the preparation of genetically engineered T cells. The patents – US 9,855,297 and US 9,890,393 – are invented by senior Cellectis personnel, Dr André Choulika, Chairman & CEO; Dr Philippe Duchateau, Chief Scientific Officer; and Dr Laurent Poirot, Head of Early Discovery.

US 9,855,297 outlines a method of genetically modifying and expanding T cells for immunotherapy purposes. The gene editing is mediated by an RNA-guided endonuclease that is guided towards cleaving DNA in the T-cell genome. The RNA-guided endonuclease in this instance is Cas9. US 9,890,393, details a similar process, with the exception of the RNA-guided endonuclease comprising the amino acid sequence set forth in SEQ ID NO:1 or SEQ ID NO:2.

Based on CRISPR technology, the patents will be made available for licensing by Cellectis for companies looking into the use of CRISPR in T cells. There is scope, for example, in the use of the patented technology for the modification of CAR T cells, an emerging group of therapies.

CEO and inventor André Choulika commented,

"Cellectis is a pioneering gene editing company that has always been keen to be at the forefront of all gene editing technologies. We have been the first to explore the potential of CRISPR in its early days in various applications, including therapeutics and plants. These early findings ultimately led to the grant of this set of new patents. As such, these patents only reinforce Cellectis' leadership position in the gene editing industry."

DOI: 10.18609/cgti.2018.019

OPTIMISTIC UPDATES FROM ABEONA'S MPS III GENE THERAPY TRIAL

New results from the ongoing Phase 1/2 trial of ABO-102 for the treatment of Sanfilippo syndrome (MPS III) have been released by Abeona therapeutics. The positive results include reduction of up to 94.9% in heparan sulfate, a hallmark indicator of MPS III. Cognitive and behavioral stabilization and improvement have also been observed in the ten patients who have been dosed in the current cohort.

The orphan product and rare pediatric disease designated therapy administers a corrective copy of the MPS III gene in a single intravenous injection. No serious adverse events relating to the therapy have been observed to date, pointing towards a positive safety profile.

Principal investigator Kevin Flanigan commented,

"MPS IIIA is a profound and deadly lysosomal storage disease with no approved treatments available. The encouraging clinical data reported today provide strong additional support for a whole-body treatment approach involving intravenous delivery of an AAV to drive expression of the SGSH enzyme in all organs of the body, with an emphasis on expression in the central nervous system. We are especially pleased to see sustained decreases in CSF heparan sulfate in all subjects post-injection, along with positive signals of neurocognitive activity in Cohorts 1 and 2."

Abeona Therapeutics continues to release encouraging data from its ongoing Phase 1/2 clinical trial in MPS IIIA (Sanfilippo syndrome), a neuropathic lysosomal storage disease caused by deficiency in N-sulfoglucosamine sulfohydrolase (SGSH). ABO-102 is a self-complementary AAV-9 carrying the human SGSH gene, which is given as a single intravenous administration. In a mouse model of MPS IIIA, intravenous delivery of the human SGSH gene resulted in both CNS and widespread somatic restoration of SGSH activity, clearance of CNS and somatic glycosaminoglycan storage, improved behavior performance and significantly extended survival. These promising animal data appear to be translating to favorable outcomes in patients treated to date, with rapid and sustained reductions in urine and CSF heparan sulfate (which shows pathological accumulation in MPS IIIA) and neurocognitive benefits. Longer-term functional benefits are still to be demonstrated, but data up to 1 year post-treatment certainly give cause for optimism. –Richard Philipson

FIRST GLIOBLASTOMA PATIENT DOSED IN NANTKWEST NK TRIAL

NantKwest have dosed the first patient in a Phase 1 trial of their gliobastoma targeting therapy HER2.taNK. Based on the company's proprietary Natural Killer (NK) cell-based platform, the therapy incorporates chimeric antigen receptors (CARs) for the specific targeting of the human epidermal growth factor receptor 2 (HER2), which is overexpressed in many glioblastoma and other solid tumor cases.

The first of approximately 30 enrolled subjects, the patient has been treated in a trial being undertaken in Germany at the Frankfurt University Hospital. A parallel Phase 1 study is also being conducted in the US, both with the aims of assessing the safety and tolerability of the treatment.

A novel aspect of the trial sees the company incorporate GPS Cancer™ for the monitoring of molecular alterations in patients' cancer. The state of that art biomarker analysis tool is provided by affiliate NantHealth, and will provide vital information to the study team, enabling the enhancement of patient care.

The DIMENSION study is being administered to patients with advanced solid tumor malignancies in a number of combinations. Four levels of dose escalations are currently planned, with 20 patients to be enrolled in each arm. The other ongoing trials of FATE-NK100 are VOYAGE and APOLLO, which are treating myelogenous leukemia and ovarian cancer, respectively.

PRIMARY ENDPOINT FOR MESOBLAST'S AGVHD STEM CELL THERAPY ACHIEVED IN PHASE 3

Mesoblast's pediatric Phase 3 trial of MSC-100-IV for acute graft-versus-host cell disease (aGvHD) has achieved its primary endpoint. The cell-based therapy leverages allogeneic mesenchymal stem cells for children with aGvHD that has been unresponsive to initial steroid therapy.

The primary endpoint that has been successfully met is the significant overall response rate of 69% at day 28 post treatment. This contrasts with the historical 45% used as a control. The survival rates at day 100 were also found to be significantly improved, with 22% mortality versus 70% mortality previously. Full results from the trial were announced at the annual scientific meetings of the Center for International Blood & Marrow Transplant Research (CIBMTR) and the American Society of Blood and Marrow Transplantation (ASBMT).

The often-fatal condition of aGvHD frequently occurs in patients who have undergone a bone marrow transplant. There are currently no treatments for refractory aGvHD, hence these latest results from Mesoblast are an encouraging

DOI: 10.18609/cgti.2018.019

step forward. The company hopes that the fast track designated therapy, marketed as remestemcel-L, will be filed for approval following completion of the ongoing Phase 3 trial from which these latest results have arisen.

Chief Executive Silviu Itescu stated:

"These are tremendous results that show the potential of our cell therapies to make a substantial difference in the treatment of patients with serious and life threatening diseases. They are a testament to the capabilities and expertise of the entire clinical, regulatory and manufacturing teams at Mesoblast."

MESOBLAST HITS PRIMARY ENDPOINT IN GVHD

Mesoblast was successful in hitting its primary endpoint in a Phase 3 study of its mesenchymal stromal cell technology, remestemcel-L, in children with steriod refractory GVHD. Children treated with the therapy showed a day 28 overall response rate of 69%, compared to 45% in historical controls. Positive readouts with MSCs, and similar adult progenitor cells, have been few and far between over the last two decades, but Mesoblast has shown a great deal of conviction in bringing its products to market. The results of its Phase 3 study in GVHD will no doubt reinforce the company's drive. A Phase 3 readout in congestive heart failure is around the corner. –Mark Curtis

Mesoblast may be on track to achieve a landmark approval in the USA for its cell-based treatment for acute graft-versus-host disease (GVHD). Remestemcel-L is an allogeneic, mesenchymal lineage adult stem cell product, which is already approved in Japan as TEMCELL®. The product has had a long journey, beginning in 2008 when it established an expanded access program in the USA, which then led to a single arm Phase 3 study in children with steroid-refractory acute GVHD. The results of the Phase 3 study look impressive, with an overall response rate at 28 days of 69%, comparing favorably to a typical historical rate of approximately 45%, and 78% survival at the key 100 day time point. Acute GVHD is a notoriously difficult area in which to develop new treatments – patients are very sick and receiving multiple other concomitant treatments, so the company has done well to get as far as it has with a treatment that has the potential to be life saving. –Richard Philipson

ALDEVRON RELEASES OFF THE SHELF HELPER PLASMID FOR AAVS

Fargo headquartered Aldevron has released an off the shelf help plasmid for AAVs, pXX6-80 as pALD-X80. The contract manufacturing company has announced the immediate availability of the plasmid, which is intended to alleviate some of the costs of AAV manufacturing. It is also conducive to the meeting of regulatory requirements.

The off the shelf nature of the plasmid product avoids the regulatory issues associated with older plasmid helpers which contain antibiotic sequences, and the cost of manufacturing a custom plasmid line.

Aldevron CEO Michael Chambers stated,

"Gene therapy has experienced tremendous growth over the last year with the approval of multiple products that dramatically improve life. We are honored to serve this industry and our clients who are achieving these breakthroughs."

FIRST PATIENT TREATED IN THIRD FATE-NK100 CLINICAL TRIAL

The first patient has been dosed in the third trial of Fate Therapeutic's FATE-NK100, a cancer therapy that is administered combinatorially alongside the common monoclonal antibodies trastuzumab or cetuximab. The trial, DIMENSION, is investigating the safety and maximum dose of the therapy.

FATE-NK100 is an NK-based therapy that both boosts the often deficient, dysfunctional NK cells of a patient, as the first line of defense against cancer; and has been found to mediate the effects of monoclonal antibody therapy. This occurs when the NK cells are able to recognize and kill antibody coated tumor cells via a mechanism called antibody-dependent cellular cytotoxicity (ADCC).

The DIMENSION study is being administered to patients with advanced solid tumor malignancies in a number of combinations. Four levels of dose escalations are currently planned, with 20 patients to be enrolled in each arm. The other ongoing trials of FATE-NK100 are VOYAGE and APOLLO, which are treating myelogenous leukemia and ovarian cancer, respectively.

THIRD COHORT DOSED IN REGENXBIO'S WET AMD GENE THERAPY TRIAL

The third cohort of patients in RGENEXBIO's Phase 1 trial of RGX-314 has been completed. Based on the company's proprietary NAV® AAV8 platform, the therapy aims to treat Wet AMD – a

DOI: 10.18609/cgti.2018.019

condition which affects vision and is characterized by the formation of leaky blood vessels.

RGX-314 targets Wet AMD by encoding an antibody fragment that inhibits vascular endothelial growth factor (anti-VEGF). This prevents the formation of leaky blood vessels that result in the loss of vision through retinal fluid accumulation.

The Phase 1 trial from which this latest update has come is a dose escalation study being carried out across six centers in the USA. The latest cohort has enrolled six patients with the aim of assessing safety and tolerability.

"We are excited about the progress that we have made in the clinical development of our lead product candidate, RGX-314. Completing enrollment of the third cohort in the Phase 1 clinical trial brings us one step closer toward delivering on the promise of a one-time treatment with rapid and sustained therapeutic effects for patients with wet AMD, one of the largest indications for which gene therapy is being developed," said Stephen Yoo, Chief Medical Officer."

END OF TRIAL RESULTS OPEN DOOR FOR PHASE 3 OF BIOCANCELL'S BC-819

Clinically significant data has been announced at the completion of the BioCanCell's Phase 2 trial of Bladder cancer gene therapy BC-819 in combination with BCG. The therapy selectively activates a diptheria toxin in response to the presence of the H19, which is expressed in adult cancer cells. BC-819 has been fast track designated by the FDA.

The trial enrolled 38 patients, 95% of whom reached 3 months post-treatment without progression or reoccurrence; at 24 months this was 54%. Of the three serious adverse events that occurred during the total 24 months of the trial, none were deemed related to the therapy.

CEO Fran Haluska commented,

"We are pleased with the results of the trial as it demonstrates the feasibility of administering BC-819 and BCG together. We intend to use data from this study as the basis for the conduct of our pivotal Phase 3 study of BC-819 and BCG, which we plan to initiate under an SPA later in 2018."

AEVITAS AND UNIVERSITY OF MASSACHUSETTS ENTER AAV RESEARCH AGREEMENT

Aevitas Therapeutics and the University of Massachusetts medical school have entered an agreement of sponsored research into the construct of AAV technologies for gene therapy.

The company has also formed a scientific advisory board with Dr Gaungping Gao, whose lab the research will be carried out with, as its first member. Dr Gao is a veteran

of AAV serotype research and development. He is currently a professor of microbiology and physiological situations, as well as holding senior positions at the American Society of Gene & Cell Therapy, the Li Weibo Institute for Rare Diseases Research, and the Horae Gene Therapy Center & Viral Vector Core.

Aevitas is a subsidiary of Fortress Biotech, whose CEO Lindsay Rosenwald commented,

"Dr Gao is a world-renowned AAV gene therapy researcher who has made significant contributions to the development of safer and more effective AAV-based treatments. We look forward to leveraging his expertise as part of Aevitas' newly formed scientific advisory board, and through the research agreement with UMass Medical School, which will enable Aevitas to advance potentially lifelong treatments for complement-mediated diseases toward the clinic."

KITE TO LEVERAGE SANGAMO'S ZFN TECHNOLOGY IN $150 MILLION DEAL

Gilead company Kite and Sangamo have closed a deal that will see Kite using Sangamo's zinc finger nuclease (ZFN) platform for gene editing new cancer therapies. The agreement's terms include a $150 million upfront payment to Sangamo, with a further potential for $3.01 billion as a result of products that have leveraged the ZFN technology.

Gilead CEO John Milligan commented,

"The emergence of gene editing as a tool to edit immune cells holds promise in the development of therapies with potentially improved safety, efficacy and efficiency. We believe Sangamo's zinc finger nucleases provide the optimal gene editing platform, and we look forward to working with Sangamo to accelerate our efforts to develop next-generation autologous cell therapies, as well as allogeneic treatments that can be accessed more conveniently in the hospital setting for people living with cancer."

CELULARITY RAISES $250 MILLION FOR PLACENTAL-BASED TREATMENTS

The formation of Celularity has been announced alongside $250 million in initial funding contributions. The company, which leverages placental cells and tissues for therapeutic use, currently has five clinical stage candidates, which are being assessed for use against cancer, degenerative and immunological diseases. With a portfolio of 800 patents, and ownership of the world's only placental repositray, Celularity is built upon the pillars of Cell Therapy, Functional Regeneration and Biosourcing.

This round of funding was secured from numerous sources, notably Celegene, United Therapeutics and Sorrento Therapeutics amongst others. Made up of

DOI: 10.18609/cgti.2018.019

industry veterans including Bill Marris, previously CEO of Google Ventures; John Sculley, formerly of Pepsi-Cola and Apple; and Andrew von EschenBach, former FDA commissioner, the company's board is headed up by founder and CEO Robert Hariri.

CEO Hariri commented,

"My goal is to make it so the next generation grows up in a world where cancer is managed just like the common cold, and the body's natural regenerative engine remains empowered throughout our lives. Celularity is a new biotechnology company model founded to harness the placenta as a platform for discovery and therapeutics, ultimately with a goal of amplifying the body's ability to fight disease, restore function and extend the healthy lifespan. It is my vision that the cellular medicines we derive from the placenta will lead to abundant and affordable treatments."

GENE THERAPY STARTUP GENERATION BIO BAGS $100 MILLION IN SERIES B FINANCING

Generation Bio, the Atlas venture-backed biotechnology company has announced that it has raised US$100 million in Series B financing.

Headquartered in Cambridge, Massachusetts, Generation Bio's therapies are based on its proprietary GeneWave™ technology, which is aimed to deliver durable, high levels of gene expression and can be titrated to effect and re-dosed to sustain impact over a lifetime.

The fundraising campaign was led by Fidelity Management & Research Company, with Invus, Deerfield Management Company, Casdin Capital, Foresite Capital and Leerink Partners' Affiliates.

The Series B follows the $25 million Series A financing in the beginning of the year. The company will use the funds to move its first two therapeutic candidates targeting the liver through Investigational New Drug (IND) enabling studies, and to advance additional programs targeting genetic diseases of the retina, central nervous system and lungs.

The GeneWave technology is based on the discovery made by Dr Robert Kotin, Generation Bio's scientific founder and Head of Discovery. Dr Kotin discovered an alternate mode of non-viral gene transfer, known as closed-ended DNA (ceDNA), which has the unique ability to translocate to the nucleus without the use of a viral capsid. Once in the nucleus, ceDNA forms stable, non-integrating episomes resulting in high levels of long-term gene expression.

Using lipid nanoparticles to intravenously deliver ceDNA to the liver, the company intends to treat genetic diseases of the liver itself or to transform the liver into a living 'biofactory' for expressing systemic proteins to treat a wide variety of genetic diseases.

Dr Geoff McDonough, president and CEO of Generation Bio, commented:

"We are delighted to have the support of this group of experts, long-term investors who share our vision to create a generation of people living unaffected by genetic disease. This will be a critically important year for us as we develop the GeneWave platform and work towards our first development candidates to address rare diseases of the liver. The round will also support the development of approaches to deliver ceDNA to other tissues such as the eye, the central nervous system and the lungs."

CIRM GRANTS FATE THERAPEUTICS $4 MILLION TO ADVANCE FT516

Fate Therapeutics has received $4 million for the advancement of investigatory NK therapy FT516 to clinical trials. The grant was awarded by the California Institute for Regenerative Medicine (CIRM) due to the large scale, cost effective and safety potential that the NK approach has as a cancer immunotherapy.

FT516 expresses a novel version of the CD16 receptor that is down regulated in many cancer patients but is vital for the NK response to cancer. Preclinical studies have demonstrated the therapy's persistent anti-tumor activities both in vitro and in vivo. FT516 is set to be developed for a portfolio of tumors, and a range of both monotherapy and combinatorial applications. The NK cells used in the therapy are derived from induced pluripotent stem cells (iPSC) via the company's proprietary platform.

Fate CEO Scott Wolchko commented,

"FT516 has the potential to address a significant unmet need for more efficacious treatments across multiple solid-tumor types by restoring a patient's immune cell function and enhancing the therapeutic effect of monoclonal antibody therapy. We are honored that CIRM has recognized the potential therapeutic value of FT516 as well as the unique advantages of using clonal master iPSC lines to manufacture a well characterized, uniformly engineered cell product in large batches for off-the-shelf use."

FATE THERAPEUTICS MAKING GROUND IN NK CELLS

The NK cell clinical landscape is really heating up. Fate Therapeutics announced news on progress with two of its NK-based programs. The company received $4 million from CIRM to fund early development of FT516, an iPS-derived, allogeneic NK cell product engineered to be targeted to the CD16 receptor. The company also treated its first patient with FATE-NK100, an NK cell product that is also off-the-shelf, being developed for solid tumors. NantKwest is developing T-cell products engineered to express NK receptors. In the future, it will be interesting to see whether the NK receptor, paired with the cell killing activity of the T cell, is more or less potent in abolishing cancer than engineering NK cells themselves. –Mark Curtis

DOI: 10.18609/cgti.2018.019