Commercial insight: cell and gene therapy

MAR 2016

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.

CELL THERAPY: **The news item that really stood out this past month was Vericel's topline results from its Phase 2b study of Ixmyelocel-T in patients with advanced heart failure due to ischemic dilated cardiomyopathy. The company announced that the study hit its primary endpoint, reducing patient deaths, hospitalizations, and unexpected ER visits by 37%. Adult stem cell platforms have historically had challenges in the clinic; many failing to demonstrate potency despite peppering a diverse range of indications. This has certainly been the case with Aastrom, which, even though formed in 1989, didn't have an approved product on the market until it purchased Sanofi's regenerative medicine business in 2014 for $6.5 million. The company finally got the results it was looking for with its autologous bone marrow-derived cell therapy, which saw the stock price double and made it the second adult stem cell company in less than a year to report on positive topline results. Last August TiGenix met its primary endpoint in a Phase 3 study evaluating allogeneic adipose-derived stem cells in patients with Crohn's disease. To the credit of industry, it has found strength through adversity.**

GENE THERAPY
Alan Boyd
CEO, Boyds, UK

CELL THERAPY
Mark Curtis
Associate, CCRM, Canada

Rahul Sarugaser
VP, Corp. Dev., Hemostemix, Canada

GENE THERAPY: Two announcements caught my eye this month; the first was from GSK and their tie up with Miltenyi Biotec to help with the industrialisation of their cell and gene therapy programmes; whilst the second was from Cobra Biologics and there collaboration with the Centre for Process Innovation to focus on the development of an industrial manufacturing platform for AAV production. They caught my eye because both were collaborations relating to manufacturing programmes. Scale up of the manufacture of gene therapy and increasing the yields produced has always been an issue with gene therapies. So to help solve these problems, rather than trying to sort them all out using in house expertise, clearly these two companies have now turned to outside companies for assistance. I think this will happen more in the future, as in the long run it can only save time and money – so good moves by both companies.

FDA ACCEPTS BLA FILING FROM VERICEL

Vericel Corporation, a developer of cell therapies, have announced the acceptance of a Biologics License Application (BLA) by the FDA for their investigational product MACI (matrix applied characterized autologous cultured chondrocytes). MACI is a third generation autologous chondrocyte implant that utilizes cultured chondrocytes embedded on a resorbable collagen membrane. If approved, the implant will be used as a treatment for symptomatic cartilage defects of the knee.

"The FDA's acceptance of the MACI BLA for review represents another important milestone toward our goal of providing a new treatment option for the repair of symptomatic cartilage defects of the knee in adult patients," said David Recker, CMO of Vericel.

In other news, Vericel also announced positive results from their Phase 2b ixCELL-DCM clinical trial, a multicenter, randomized, double-blind, placebo-controlled Phase 2b study. The study was designed to determine the safety and efficacy of ixmyelocel-T, a patient-specific, multicellular therapy used to treat patients with advanced heart failure caused by ischemic dilated cardiomyopathy (DCM). The therapy is generated using the patient's bone marrow using Vericel's proprietary technology to increase mesenchymal stromal cell populations needed to repair damaged tissue.

The primary endpoint of the trial was reached, which saw a reduction in deaths or cardiovascular related hospitalisations during the 12 months post ixmyelocel-T treatment. The FDA has granted ixmyelocel-T orphan product designation as a treatment for DCM.

"The results of the ixCELL-DCM study, which we believe is the largest randomized cell therapy trial to treat congestive heart failure completed to date, demonstrated a statistically significant and clinically meaningful reduction in cardiac events in patients who received treatment with ixmyelocel-T compared to placebo," said Recker.

DOI: 10.18609/cgti.2016.018

BENITEC'S ddRNAi THERAPY SHOWS PROMISE

Benitec Biopharma Ltd, has announced the successful demonstration of their DNA-directed RNA interference (ddRNAi) therapy, BB-HB-331, which specifically targets the hepatitis B virus (HBV).

Following a single administration, a durable suppression of HBV *in vivo* was observed. This approach attempts to combine gene silencing with the potential long durability of a gene therapy. BB-HB-331 consists of an AAV8 capsid and recombinant DNA expressing three short hairpin RNAs that specifically targets and inhibits HBV RNA expressed in conserved regions spanning several phenotypes.

The *in vivo* studies were carried out in mice whose liver cells were replaced with human hepatocytes, making them more susceptible to HBV infection. Once infected, the mice were treated with BB-HB-331. Key findings of the experiment are as follows: reduced serum HBV DNA, a reduction of intracellular liver HBV DNA by 94.9%, suppression of serum antigens (HBsAg and HBeAg), and decreased levels of viral RNA and cDNA. The experiment was able to validate previous *in vitro* studies of BB-HB-331.

"These results demonstrate the utility of an approach that combines RNAi with gene therapy to treat HBV. In addition to these encouraging results, we note that the HBV serum DNA and antigen levels continued to drop through the pre-determined conclusion of the study, and may not have reached their lowest levels. As previously communicated, Hep B represents a significant commercial opportunity and we will continue to apply key learnings from our clinical stage hepatitis C program to advance the Hep B program towards the clinic." – David Suhy, Benitec's CSO

EXPERT PICK

One of the main problems in using iRNA as a potential therapy is the delivery of the product to the location where it is needed. This month there are announcements from both Benitec and UniQure that show that they might have a solution to this problem by using gene therapies with transgenes that express the inhibitory RNA. With the Benitec product they are using a DNA-directed RNA interference therapy which specifically targets the hepatitis B virus, whilst UniQure are using expression cassette-optimized artificial microRNAs to treat Huntington's disease. The data presented from both companies is *in vivo* data from mouse models but the results show that significant silencing is occurring. This is an important step forward for this treatment modality and it will be interesting to see if these effects are carried forward into patients with the respective diseases - ***Alan Boyd.***

NEW TECHNOLOGY FROM MESOBLAST TO TREAT TYPE 1 DIABETES

Mesoblast Limited have exclusively licensed patented technology originally developed at Harvard Medical School which can be used to modify mesenchymal lineage adult stem cells (MLCs).This process of *ex vivo* fucosylation, which adds fucose to the cell's surface receptors, allows MLCs to be recognized and bound by cells lining the blood vessels of inflamed tissues, giving the MLCs enhanced homing properties.

Preclinical studies have demonstrated that modified MLCs are able to successfully induce a durable reversal of Type 1 diabetes (T1D). The enhanced targeting technology was able to increase the number of MLCs that could reach the inflamed pancreas in autoimmune diabetic mice by three-fold.

"The hypothesis was that inflammation that destroys pancreatic islet cells could be controlled by selectively targeting the pancreas with anti-inflammatory mesenchymal lineage cells. The realization was that this new clinical approach essentially cured mice of Type 1 diabetes," explained Robert Sackstein, Professor of Medicine at Harvard Medical School.

UNIQURE REVEALS PROOF OF CONCEPT FOR GENE THERAPY FOR HUNTINGTON'S DISEASE

Human gene therapy developer, uniQure, have released new preclinical data that supports its gene therapy program for Huntington's disease.

uniQure's gene therapy, AMT-130, is delivered as a one-time dose to the CNS to silence the Huntington gene (*HTT*), delivered via an AAV5 vector. The study describing the preclinical study was published in *Molecular Therapy – Nucleic Acids*.

The paper describes several approaches that were used to silence the HTT gene using expression cassette-optimized artificial microRNAs (miHTTs). Using uniQure's baculovirus-based manufacturing platform, several miHTTs constructs were incorporated into an AAV5 vector before being administered to a humanized mouse model. Results displayed a strong silencing of mutant *HTT* and complete silencing of *HTT in vitro* and *in vivo*.

"We are excited by the results of this study, and believe this degree of knock-down of mutant Huntingtin protein, if duplicated in our ongoing non-human primate safety toxicology studies and future human clinical trials, could significantly alter the course of the disease," said Charles W Richard, Senior Vice President, R&D Neuroscience at uniQure.

DOI: 10.18609/cgti.2016.018

BLUEBIRD BIO TO PRESENT DATA FROM PHASE 2/3 STUDY FOR CALD

Bluebird bio, have announced that they will present data from their ongoing Phase 2/3 Starbeam study at the *American Academy of Neurology* (AAN) *2016 Annual Meeting*, which is being held from 15 to 21 April 2016 in Vancouver, Canada.

Their candidate gene therapy has been developed with a lentiviral (Lenti-D) vector and will be administered as a potential treatment for cerebral adrenoleukodystrophy (CALD), a neurodegenerative disease affecting young males that can be fatal if untreated. The only current therapy that has proven affective are allogeneic hematopoietic stem cell (HSC) transplants but is not without risks. These involve graft rejection and transplant mortality. The product candidate is made up of the patient's own HSCs which should alleviate the issues associated with current treatment methods.

The Starbeam Study is designed to assess the safety and efficacy of the gene therapy in young males, up to the age of 17, diagnosed with CALD. The onset of CALD is brought on by the absence of a crucial protein required to break down very long chain fatty acids, which builds up in the CNS and results in the neurodegeneration associated with the disease. The therapy involves the transplantation of a patient's own modified stem cells carrying a functional copy of the gene encoding the protein that breaks down the fatty acids. The primary efficacy endpoint of this study will be the proportion of patients that have no major functional disabilities 24 months after infusion.

ALL EYES ON BLUEBIRD

Bluebird bio have announced that the interim data from their ongoing Phase 2/3 Starbeam Study, which involves patients with cerebral adrenoleukodystrophy, will be presented at the forthcoming meeting of the American Academy of Neurology. A snapshot of the results was given in the announcement that stated they were encouraged by the safety profile and the radiographic and neurologic results from the 17 patients treated with their Lenti-D product that had now had a median follow up time of 9 months. For the full results we will have to wait till the 20th April when the presentation is given but at this stage the results do look promising; but with the primary endpoint of the study being the proportion of patients with no major functional disabilities at 24 months post infusion, it's a case of 'watch this space' - *Mark Curtis & Rahul Sarugaser.*

KITE ANNOUNCES CLINICAL COLLABORATION

Kite Pharma has entered into a clinical trial collaboration with Genentech to ascertain the safety and efficacy of KTE-C19, an investigational immunotherapy, in combination with atezolizumab in patients with refractory, aggressive non-Hodgkin lymphoma (NHL).

KTE-C19 uses a patient's genetically modified T-cells to express a CAR that specifically targets the CD19 antigen, typically found on the surface of B cell lymphomas and leukemias. Atezolizumab is a monoclonal antibody which specifically and competitively binds to the protein PD-L1, a tumor receptor which functions as a T-cell inhibitor. A combined use of the two could boost the therapeutic effects of KTE-C19 as the inhibition of PD-L1 can extend the activity and effects mediated by the T-cell immunotherapy.

"KTE-C19 is currently in four pivotal studies and early clinical findings have shown a potential for breakthrough efficacy in refractory, aggressive NHL and other B cell malignancies. The scientific rationale for combining KTE-C19 and atezolizumab in refractory, aggressive NHL is compelling, and could potentially lead to opportunities to advance this combination in other indications." – Arie Belldegrun, Chairman, President and CEO of Kite.

ADURO ANNOUNCES FIRST PATIENT DOSED IN CLINICAL TRIAL

Aduro Biotech have revealed that the first patient has been dosed in their clinical study, SEASCAPE (Study of Epacadostat and CRS-207 in Adults with Platinum Resistant Ovarian Cancer), a phase 1/2 clinical study to assess the safety, efficacy and tolerability of CRS-207 in combination with Incyte Corporation's epacadostat for ovarian cancer.

CRS-207 is based on the LADD platform, Aduro's proprietary platform of live-attenuated double-deleted *Listeria monocytogenes* strains that have been engineered to induce a potent innate immune response and to express tumor-associated antigens to induce tumor-specific T cell-mediated immunity. Epacadostat is an inhibitor of indoleamine 2,3-dioxygenase 1 (IDO1), an immunosuppressive enzyme that prevents tumor detection from the immune system.

"By combining two immuno-oncology therapies which we believe have synergistic mechanisms of action, we and Incyte look forward to potentially advancing new treatment options for patients with ovarian cancer that could result in more effective therapy than either therapy alone," said Stephen T Isaacs, Chairman, President and CEO of Aduro.

SEASCAPE, co-funded by Aduro and Incyte, has been designed to determine the recommended dose levels for CRS-207 and epacadostat. Aduro will enrol up to 40 patients with platinum-resistant ovarian, fallopian or peritoneal cancers for the phase 1 study and up to 86 patients in phase 2.

DOI: 10.18609/cgti.2016.018

FIRST PATIENT TREATED IN CALADRIUS' PHASE 2 TRIAL

Caladrius Biosciences have announced that the first subject has been treated in The Sanford Project: T-Rex Study, a phase 2 clinical trial for the T-regulatory (Treg) cell-based therapy (CLBS03), Caladrius' candidate for the treatment of recent-onset T1D. Tregs regulate immune activity by moderating T effector cell activity which, in the case of T1D, uncontrollably attack insulin-producing pancreatic beta cells.

The trial will evaluate the safety and efficacy of CLBS03, with 111 subjects aged between 12 and 17 expected to enrol. The subjects will be randomly split into three groups: high dose, low dose and placebo. Evaluation will occur over the course of 2 years, with key endpoints being the standard medical and regulatory endpoints for a typical T1D trial.

"The initiation of enrolment of this trial marks an important milestone for our investigational type 1 diabetes program and moves this program into the clinical development stage," said David J Mazzo, CEO of Caladrius.

GSK PARTNERS WITH MILTENYI BIOTEC

GlaxoSmithKline has announced their collaboration with German company, Miltenyi Biotec in what is seen as a move to integrate greater automation and technology into GSK's cell and gene therapy manufacturing capabilities

The announcement comes as part of an effort to develop new therapies to treat cancers and rare diseases. These therapies require the extraction of endogenous cells from the body, genetically altering them and then reintroducing them back into the patients system to either replace/correct faulty genes or to harness the immune system to target and kill cancer cells. This new collaboration aims to overcome the constraints presented when attempting to scale up these processes for manufacturing.

"Cell based gene therapies are living treatments, unique to individual patients and complex to manufacture. We see tremendous potential for the cell and gene therapy platform we are building within GSK, however the complexity of current manufacturing processes limits their use to local treatment of small patient populations," said Patrick Vallance, GSK's president of Pharmaceuticals R&D

As part of this strategic collaboration, GSK will incorporate Miltenyi's automation and high-tech processing technology into their cell and gene therapy manufacturing processes. If successful, costs could be significantly reduced and the speed at which these therapies are developed vastly increased.

"Working with Miltenyi Biotec, our vision is to transform current technology so that we can expand the possibilities for cell and gene therapy treatment to wider patient populations with broader geographical reach."

CALADRIUS SUBSIDIARY PCT ANNOUNCES COLLABORATION WITH HITACHI CHEMICAL

Caladrius subsidiary, PCT LLC, has entered into a global collaboration with Hitachi Chemical Co., a Japanese company that specializes in developing innovative products that includes systems for healthcare and life sciences in global markets.

The deal will include licensing, development and equity components. Hitachi has purchased 19.9% equity interest in PCT for $19.4 million with Caladrius retaining the remainder. In addition, the companies plan to explore the idea of establishing a joint venture in Europe.

"This partnership with Hitachi Chemical underscores the value of PCT's expertise in cell therapy manufacturing and process development and will allow for the acceleration of our vision to create a global commercial enterprise with deep engineering expertise. Moreover, Hitachi Chemical's investment in PCT shows its confidence in the growth of the cell therapy field as the field continues to shift towards Phase 2 and Phase 3 trials and into commercial distribution as regulatory approvals are obtained," said Robert Preti, President of PCT.

EXPERT PICK

The PCT collaboration with Hitachi is yet another deal fueling the regenerative medicine market in Japan. The collaboration not only sees Hitachi take a 20% equity stake in PCT (valuing the company at around $100 million) but gives the company access to PCT's manufacturing technology and know-how for certain Asian jurisdictions for an upfront and additional milestones and royalties. There are currently just under 600 clinical studies underway investigating regenerative medicine products, about 70 of which are in late-stage. As this pipeline matures competition around cell therapy manufacturing will intensify in anticipation of commercial products. PCT's deal with Hitachi follows a similar deal Lonza made last year with Nikon that provided Nikon with access to Lonza's technology, facilities designs, and consulting services in order to establishing a manufacturing footprint in Japan. Hitachi and PCT are also exploring potential for a partnership in Europe - ***Mark Curtis & Rahul Sarugaser.***

SPARK THERAPEUTICS ACQUIRES GENABLE TECHNOLOGIES

Developers of novel gene therapies for the treatment of dominant genetic diseases, Genable, have been acquired by Spark Therapeutics.

The Ireland-based company, Genable, who have collaborated with Spark since 2014, will be a wholly owned subsidiary of Spark. Through the acquisition, Spark acquires Genable's lead gene therapy product, RhoNova™, for the treatment of rhodopsin (RHO)-linked autosomal dominant retinitis pigmentosa (adRP), an inherited form of blindness.

DOI: 10.18609/cgti.2016.018

Annette Clancy, Chair of the Board of Directors of Genable highlighted the benefits Spark will provide in the development of their lead product, "We are delighted that this transaction with Spark Therapeutics Inc. will ensure the expedient clinical development of RhoNova™ for the treatment of autosomal dominant rhodopsin linked retinitis pigmentosa (RHO-adRP), a leading cause of inherited blindness. The unanimous recommendation of the Board was that Spark Therapeutics, world leaders in AAV gene therapies, has the relevant resources and expertise to maximise the chance of success for RhoNova™ and deliver its benefit for patients."

"Spark Therapeutics, a global leader in AAV-based gene therapy, has collaborated with Genable since 2014 in the development of RhoNova™, our Product has and will continue to greatly benefit from Spark's knowledge and technology platform" added Prof. Jane Farrar, co-founder and CSO of Genable.

CELLECTIS ANNOUNCES IMMUNOTHERAPY PARTNERSHIP

Cellectis has entered into a research collaboration and license agreement with MabQuest, a biotech that specializes in the development of antibody-based therapeutics. The agreement will drive the development of a new class of antibodies that target PD-1, a cell surface receptor expressed on T cells. The new antibodies being developed will enhance T cell activity through a new mechanism to speed up cell recovery following exhaustion. These differ from current antibodies targeting PD-1 as they act to disrupt the interaction between PD-1 and its ligand found on tumors, PD-L1 and instead will act via a whole new mechanism.

MabQuest has granted an exclusive rights option to Cellectis, that once exercised, will grant Cellectis worldwide exclusive rights over the family of PD-1 antibodies developed under the collaboration.

"...[this] is a tremendous opportunity for MabQuest to move into clinical development with this new class of anti-PD-1 mAbs. This collaboration will also boost MabQuest's discovery program to develop additional antibody-based strategies to modulate the host immune system," said Giuseppe Pantaleo, President of MabQuest.

It's well established now that tackling solid tumors with CAR/TCR products will require combinatorial approaches. Almost all of the leading Pharma companies have placed their bets and forged deals with the leading cell-based immunotherapy companies. Notable collaborations include Cellectis/Pfizer, Kite/Genentech (Roche), OncoSec/Merck, Adaptimmune/GSK, and Juno/MedImmune (AstraZeneca). Driving these collaborations is the pairing of CAR/TCR products with checkpoint inhibitors, primarily anti-PD-1 and anti-PD-L1, in attempt to boost immunogenicity of tumor cells. Cellectis' deal with MabQuest is interesting because it involves a new class of PD-1 antagonist, that unlike the majority that are in development, does not target PD-1–PD-L1 interaction. Paired with the company's UCART product this would be a very unique combination indeed - *Mark Curtis & Rahul Sarugaser.*

ARGOS THERAPEUTICS ANNOUNCES $60M FINANCING

Argos Therapeutics, immuno-oncology specialists, have announced a sale of up to $60 million in common stock for a securities purchase agreement. The proceeds from the initial closing will allow the company to fund their expenses into the third quarter of 2016 and should the remaining closings occur, the funds gathered will fund their operations into the second quarter of 2017. This falls in line with when the company will expect to have obtained the final data from a phase 3 trial of their autologous immunotherapy, AGS-003, for the treatment of metastatic renal cell carcinoma.

STEMCELLS INC. ANNOUNCING CLOSING OF PUBLIC OFFERING

StemCells, Inc., have announced that they have closed their offering of common stock and warrants, selling a total of 26,667,000 shares of common stock at a public offering price of $8 million.

"This transaction was structured to include short-term warrants, which provide the potential for the Company to receive approximately $4 million in additional capital over the next two years. This is a critical timeframe for the Company as we expect to have final results from our ongoing Pathway study in the fourth quarter of 2017," said Greg Schiffman, CFO of StemCells, Inc.

The Pathway study is a phase 2 proof-of-concept trial in cervical spinal cord injury which makes use of the company's HuCNS-SC platform technology, a highly purified composition of human neural stem cells.

LION BIOTECHNOLOGIES NAMES NEW CSO

Michael T Lotze, MD, has been named as chief scientific officer and vice president of research at Lion Biotechnologies. Dr Lotze brings over 35 years of clinical experience, having treated over 100 patients with gene therapy at the University of Pittsburgh and was involved in initiating the first approved gene therapy protocols at the NIH.

"Michael's deep expertise in immuno-oncology, combined with his extensive clinical experience, will be an asset to Lion as we continue advancing our clinical programs and developing our tumor-infiltrating lymphocyte technologies in various cancer indications, both alone and in combination with other therapeutic agents," said Elma Hawkins, Lion's president and CEO.

DOI: 10.18609/cgti.2016.018

EXECUTIVE VICE PRESIDENT, TECHNICAL OPERATIONS APPOINTED AT KITE PHARMA

Tim Moore has been appointed as executive vice president, technical operations. Mr. Moore has over 30 years of experience in industry. His main role will be having responsibility for: product development, manufacturing, supply chain, quality assurance, and end-to-end process optimization for Kite's T cell product candidates.

"Tim has directly contributed to the design and management of one of the most reliable, efficient and skilled biopharmaceutical manufacturing operations in the world. We are pleased to welcome Tim Moore and the deep, global experience he brings in biopharmaceutical production to Kite," said Arie Belldegrun, Chairman, President, and CEO of Kite.