

Commercial insight: cell and gene therapy

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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: Juno fortified its bid to become the global cell-based immunotherapy company by creating a joint venture with WuXi AppTec in China. The new company, JW Biotechnologies, will be based out of Shanghai and owned 50/50 by the two parties. WuXi is a dominant player in China's R&D, manufacturing, and contract services industries. As part of the deal the new company will have access to licensing candidates from Juno's CAR and TCR pipeline for marketing in China. In return, Juno will receive upfront payments, milestones, and royalties. This is the first significant deal we have seen that brings cell-based immunotherapy to the Chinese market and will further strengthen Juno's balance sheet over the long-term. Juno also announced that Celgene will exercise its option to market Juno's CD19 product outside of North America and China, for which Juno received a payment of \$50 million.



GENE THERAPY
Alan Boyd
CEO, Boyds, UK



CELL THERAPY
Mark Curtis
Analyst,
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GENE THERAPY: Upscaling the manufacture of gene-based therapies and, in particular cell-based therapies, as they approach commercialisation has

been problematic for several products in recent times. Therefore it is good to see that companies and academic groups are establishing closer collaborations to help resolve some of the problems that occur. The move by GE Ventures and the Mayo Clinic to establish a new entity that will focus on manufacturing is therefore a step in the right direction. Only time will tell if this more collaborative approach will bring the expected benefits, but at least it's worth a try.



FDA ACCEPTS ADAPTIMMUNE'S IND APPLICATION

Adaptimmune Therapeutics have revealed that the US Food and Drug Administration (FDA) has accepted an investigational new drug (IND) application for the company's genetically modified T-cells expressing affinity enhanced T-cell receptors specific for alpha fetoprotein (AFP), found to be highly expressed in 30% of hepatocellular carcinomas (HCC). This new therapy aims to be a viable solution for patients with locally advanced or metastatic HCC.

The IND will allow Adaptimmune to begin an open label Phase I study to ascertain the safety and

efficacy of its therapeutic candidate. Up to 30 subjects are expected to be enrolled with a primary objective of evaluating safety and tolerability in subjects with AFP-positive HCC.

"Hepatocellular carcinoma is one of the most common and deadly types of cancer in the world and it represents a significant unmet medical need, as there is a dearth of effective therapies for advanced disease. We are pleased to initiate clinical evaluation of our AFP T-cell therapeutic candidate in this patient population," said Rafael Amado, CMO of Adaptimmune.



BIOMARIN REPORTS ENCOURAGING GENE THERAPY DATA

BioMarin have released new data from a midstage study, which saw an elevation in Factor VIII rates following administration of the hemophilia A gene therapy.

A total of 8 patients were tested in the Phase I/II study using the experimental gene therapy, BMN 270. The therapy makes use of an adeno-associated virus as a vector to deliver a functional copy of the Factor VIII

gene, which hemophilia A patients lack but require to prevent excessive bleeding. A single infusion to the patient's own cells should, in theory, provide a long lasting effect.

The patients, with severe hemophilia A, were given a single dose of BMN 270. Of these, two high-dose patients saw their Factor VIII levels elevate above 50%, with five out of six patients displaying levels above 5%.

“We are encouraged by this early data on BMN 270 and the trend we are seeing in increasing Factor VIII levels over time. BMN 270 could have the potential to reduce and possibly eliminate the need for infusions of Factor VIII,” said Hank Fuchs, CMO at BioMarin.

Although the results seem promising, some issues regarding safety did arise, as alanine aminotransferase liver enzyme levels did elevate in some patients resulting in the need to administer corticosteroid therapy. BMN 270 has been granted orphan drug designation in Europe from the FDA.



CALADRIUS REACHES AGREEMENT WITH JAPANESE PMDA

Cell therapy company, Caladrius Biosciences, Inc., have announced that the Japanese Pharmaceutical and Medical Devices Agency’s (PMDA) have granted the company a pass, following review of the Clinical Trial Notification for a pivotal Phase 2 clinical trial for CLBS12, a CD34 cell therapy for critical limb ischemia (CLI). As such, the company will now be able to proceed with the trial.

A total of 35 patients will be enrolled in the study which will be a prospective, randomized, controlled, multicenter study in patients with no-option CLI, conducted in Japan. The randomized patients will be dosed with autologous G-CSF-mobilized peripheral blood-derived CD34⁺ cells (CLBS12) via an intramuscular injection.

“We are pleased that our interactions with the PMDA have led to the design of a relatively small and, we believe, low risk trial that could significantly advance CLBS12 and the Company’s CD34 asset. We look forward to achieving a partnership to enable the launch of this pivotal Phase 2 trial in Japan. CLI is just the entry-point to explore the broader applicability of the CD34 platform therapy, which could potentially be effective in the treatment of chronic heart failure or dilated cardiomyopathy,” said David J. Mazzo, CEO of Caladrius.



CHMP ISSUES POSITIVE OPINION FOR GSK’S STRIMVELIS

The Committee for Medicinal Products for Human Use (CHMP) have issues a positive opinion for Strimvelis™, GSK’s gene therapy treatment for adenosine deaminase deficiency which causes severe combined immunodeficiency (ADA-SCID).

The stem cell gene therapy is created from a patient’s own cells which is then used to correct the disease. If approved, the treatment will be available for patients with ADA-SCID who have no suitable human leukocyte antigen

(HLA) matching stem cell donors available.

The gene therapy was originally developed by Ospedale San Raffaele and Fondazione Telethon, Italy and was brought forward by GSK through a strategic collaboration. GSK had collaborated with biotech, MolMed S.p.A, who applied their expertise to optimize, standardize and characterize the manufacturing process that had been suitable for clinical trials. The new process is now reported to be robust and suitable for commercial supply.

“This positive opinion is a major milestone in GSK’s commitment to the development of innovative, transformative medicines. If approved, Strimvelis will become the first corrective *ex-vivo* gene therapy for children to achieve regulatory approval anywhere in the world. With our shared mission and complementary expertise we believe this collaboration will continue to deliver much needed new medicines for patients with rare genetic diseases.”
- Martin Andrews, Head of the Rare Disease Unit at GSK.



EXPERT PICK

It is good news that Strimvelis, GSK’s gene therapy for the treatment of adenosine deaminase deficiency which causes the severe condition of ADA-SCID in children has received a positive opinion for approval from the CHMP at the EMA. This will make it the third gene-based therapy to receive approval

or to be recommended for approval in Europe following on from Glybera (UniQure) and T-Vec (Amgen). Strimvelis will be the first corrective *ex-vivo* gene therapy utilizing the patient’s own stem cells as the carrier, to receive regulatory approval anywhere in the world. This is a landmark decision, as it shows that this method of delivery and administration of the gene product is acceptable to the Regulators. Given the three gene therapies that have now been reviewed and approved in the EU, we now have examples of a direct gene therapy replacement product in the form of Glybera, a combination gene therapy/oncolytic virus in the form of T-Vec and an *ex-vivo* gene therapy/stem cell combination product as Strimvelis. I think the future for gene therapy products is now looking much brighter given this progress and has laid the foundation that gene-based products are a reality as prescription medicines - **Alan Boyd**.



BLUEBIRD BIO SET TO REVEAL IMMUNE-ONCOLOGY & GENE THERAPY DATA

Bluebird bio, Inc., have announced that they will holding a total of 10 presentations at the *American Society of Gene & Cell Therapy 19th Annual Meeting*, being held on the 4–7th May in Washington, DC, USA They are set to present data from their clinical, preclinical, and research and manufacturing programs.

The academic collaborators of bluebird will give two of the presentation and will highlight data that has been previously presented from bluebird’s ongoing clinical trials. Interim data from the Phase 2/3 Starbeam Study of their candidate gene therapy, using a lentiviral (Lenti-D) vector to treat cerebral

adrenoleukodystrophy, will be presented by David Williams, Chief of Hematology/Oncology at Boston Children's Hospital. Marina Cavazzana, Hospital Necker, University Paris Descartes, will be presenting data from the HGB-205 study of LentiGlobin in patients with severe sickle cell disease and those with transfusion-dependent β -thalassemia.

"As bluebird continues to build a differentiated T cell oncology franchise, we are excited to present three oncology abstracts that highlight our work on the next generation

of technology for T cell-based immunotherapy – including methods of generating T cells with sustained anti-tumor activity, small-molecule regulated chimeric antigen receptors (CARs) and genome editing to generate improved CAR T cells. From our hematopoietic stem cell programs, we will also share updates in five presentations covering improvements in scalable manufacturing, transduction efficiency and assay development – critical areas for making gene therapy available to more patients." – Philip Gregory, CSO, Bluebird Bio.



The announcement this past week that bluebird bio will be presenting a total of 10 presentations at the ASGCT meeting is interesting and does demonstrate the progress that the company has made recently. The presentations are set to cover the company's research, manufacturing, pre-clinical and clinical activities across the range of the therapeutic

indications that they are working on. Clearly the devil is in the detail that will have been presented at the congress and it will be useful to see this reviewed and considered over the coming weeks. Watch this space! – Alan Boyd.



NIH HALTS WORK BY KITE'S COLLABORATOR

Kite Pharma's collaborator at the National Cancer Institute, Steven Rosenberg has had his work halted by the NIH. Production at two separate facilities have been shut down, one of which included cell therapies Dr Rosenberg is working on, after inspections revealed that their work did not comply with quality and safety regulations.

The NIH released a statement regarding the matter, "There is no evidence that any patients have been harmed, but a rigorous clinical

review will be undertaken. NIH will not enroll new patients in affected trials until the issues are resolved."

A fungal infection was discovered in vials of albumin last summer at certain facilities, manufactured for the NIH Clinical Center. Uncovering this lead to further inspections which eventually resulted in this action, although no details were provided on what was discovered to warrant the suspension.

Rosenberg has contributed pivotal work for Kite's development of



re-engineered T cells to fight cancer. Currently, Kite is in a race with Juno, Novartis and other biotechs

that are currently trying to deliver the cell therapy for patients.



CELGENE BUYS INTO CAR-T COLLABORATION WITH JUNO

Celgene have made a \$50 million payment to Juno to take up an option on their CAR-T effort. The deal will provide development and commercialization rights for the CD19 program in Europe and other territories outside China and North America.

Celgene are already at the forefront of CAR T therapies, having previously struck a \$1 billion deal with Juno, giving them a leading role.

Juno currently has three therapies in development that target the CD19 receptor: JCAR015 currently undergoing a Phase II trial for adults with relapsed/refractory acute lymphoblastic leukemia (ALL); JCAR017 is currently in two Phase I trials, one in pediatric patients with ALL and another in patients with non-Hodgkin

lymphoma (NHL); JCAR014 is in a Phase I trial in adult ALL, NHL, and chronic lymphocytic leukemia. In addition JCAR014 is also part of a combination trial with durvalumab, AstraZeneca's PD-L1 immune checkpoint inhibitor.

"Celgene's development and commercial expertise, particularly in hematologic malignancies, make them our ideal partner and will accelerate our global development capabilities for patients with ALL, CLL, and NHL. The long-term collaboration with Celgene is an important component of our plan to develop our engineered T cell platform rapidly and effectively for the benefit of patients around the world, and we are encouraged by the progress we are making together," said Hans Bishop, Juno's President and CEO.



INTREXON ANNOUNCES COLLABORATION FOR T1D

Intrexon has announced the formation of Intrexon T1D Partners, LLC. This new joint venture, with a number of external investors, will focus on developing antigen-specific immunotherapies for treating type 1 diabetes (T1D).

T1D is most known for the autoimmune destruction of beta cells, responsible for producing insulin, in the pancreas. As a result, blood

and urine glucose levels are elevated, bringing on a range of complications.

This new venture will set out to create a simple pill for T1D patients that's will put a stop to the autoimmune-induced damage. This will hopefully be applicable for both early stage patients, that are not insulin dependent yet and for some late stage patients to prevent the external administration of insulin.

“Clinical translation of antigen-specific therapies to date has been insufficient to halt T1D in high-at risk individuals or new-onset patients, in part due to degradation of immunomodulatory molecules, non-specificity, and inconsistent delivery to gastro-intestinal mucosa. ActoBiotics biotherapeutics can mediate the transport and targeted delivery of therapeutic proteins directly to

the gut mucosal tissue, enabling the uptake and presentation of intact antigens to the Gut-Associated Lymphoid Tissue (GALT), the preferred site for induction of local and peripheral antigen-specific immune tolerance. We believe this is a promising approach that will provide a disease-modifying therapy for T1D patients,” said Samuel Broder, SVP, Head of Intrexon’s Health Sector.



EXPERT PICK

There’s been no shortage of innovation in the diabetes space in recent years. Companies like Sernova and ViaCyte are taking a regenerative medicine approach with PSC-derived pancreatic progenitors and beta cells to deliver insulin to patients. More recently, T regulatory cells (Tregs) have come under the spotlight as a means to delay the formation and onset of type 1 diabetes (T1D). Caladrius is in mid-stage development investigating Tregs in early-stage T1D patients. Intrexon added a novel technology to the mix this past month and announced it will deploy its Actobiotics platform, via Intrexon T1D Partners, for the treatment of T1D. Actobiotics are orally available bacteria engineered to secrete therapeutic proteins directly to the gut mucosa. In this instance, Intrexon is engineering *Lactococcus* to express the auto-antigens GAD-65 and IL-10, which was shown in preclinical studies to mediate the activation of suppressive Tregs and reduce inflammation in the pancreas. Intrexon will own 50% of the new venture along with a syndicate of investors, including White Rock Capital Partners – **Mark Curtis**.



NANTBIOSCIENCE & NANTKWEST PARTNER WITH NATIONAL CANCER INSTITUTE

The announcement came from NantBioScience this month detailing a new Cooperative Research and Development Agreement (CRADA) with the National Cancer Institute (NCI). The establishment of this partnership will push the development of recombinant natural killer (NK) cells and monoclonal antibodies as monotherapies and combination cancer immunotherapies.

The companies will be collaborating with Dr Jeffrey Schlom,

Chief of the Laboratory of Tumor Immunology and Biology, from the NCI, and Dr James Gulley, Chief of the Genitourinary Malignancies Branch, also from the NCI. The teams will focus expanding the pre-clinical and clinical development of recombinant NK cells and monoclonal antibodies.

“This CRADA is a significant milestone in our goal to develop novel combination immunotherapies for cancer patients. We are pleased that

Dr. Schlom and Dr. Gulley and their cancer immunotherapy teams have partnered with NantBioScience and NantKwest to carry out these pioneering studies. This partnership explores and will hopefully verify that a multi-targeted approach to employing immunotherapies will lead to a substantial benefit for patients with a range of cancers and cancer stages,” said Patrick Soon-Shiong, CEO of NantBioScience and NantKwest.



ONES TO WATCH

The National Cancer Institute has been a rich source of technology for Kite Pharma, the latter of which formed a CRADA with the NCI back in 2012 to develop CAR and TCR products. NantKwest has decided it will also tap into the expertise of the NCI and NIH through a CRADA to investigate engineered NK cells, alone, and in combination with vaccines, immune modulators, and monoclonal antibodies, for a variety of cancer indications. The collaboration will greatly expedite the development of NK cell combinatorial approaches for treating cancer, and potentially bring NK cells forward as a competitor to the more popular CAR and TCR approach using T cells – *Mark Curtis*.

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GE & MAYO ANNOUNCE GENE THERAPY VENTURE

GE Ventures and Mayo Clinic have launched a new joint venture that will accelerate the development of new gene therapies.

The companies will jointly launch Vitruvian Networks, Inc., as a new platform that will provide easy access to cell and gene therapies using advanced software and manufacturing services. The new system will provide data analytics to therapy producers, easing the way therapists will treat patients, by providing faster and more accurate treatments for patients.

The project was initially conceived as a means of producing autologous cell that will be used to treat blood cancers, but evolved into a system that will provide advanced assistance to therapists and patients to treat blood cancer.

The company will be assisted by Mayo for cell therapy processes and clinical results in developed

personalized therapies and will use GE's cell therapy business to derive better outcomes.

“Merging GE's operational excellence with emerging cell and gene therapies will enable faster, more effective and safer treatments for patients. Mayo Clinic is a key leader in patient treatment delivery in cancer care and regenerative medicine, so we are honored to have incubated this solution in joint partnership.” said Sue Siegel, CEO, GE Ventures.

“We are excited that Vitruvian Networks will further drive standardization of the industry, increase scalability and bring forward the realization of critical therapeutic potential to address the unmet needs of patients around the world,” commented Andre Terzic, director of the Mayo Clinic Center for Regenerative Medicine.



PLURISTEM ENTERS INTO AGREEMENT WITH TES HOLDINGS

The agreement was established with a goal of allowing Pluristem to acquire a key patent in Japan to cover the treatment of ischemic diseases with placental cell therapy. The patent will cover the use of placenta-derived mesenchymal stem cells capable of producing VEGF, a signalling protein that promotes blood vessel growth which is essential for repairing damage in ischemic tissue in the heart, brain or skeletal muscle.

“Placenta-derived cell therapies may significantly improve the health and wellbeing of millions of people who suffer from ischemic disease. We are pleased that Pluristem, which is a leading player in the world’s regenerative medicine space, has licensed this patent because their unique experience with

placental cell therapies make them optimally positioned to use knowledge developed at the University of Tokyo which demonstrates Japan’s strong capabilities in this space. We hope that this cooperation will advance the regenerative medicine industry and benefit the people with unmet medical needs,” commented Akio Hayashi, President of TES Holdings.

“Placenta-derived cell therapies may significantly improve the health and wellbeing of millions of people who suffer from ischemic disease.” - Akio Hayashi, TES Holdings



NEW COMPANY ANNOUNCED BY JUNO THERAPEUTICS & WUXI APPTEC

A new company, JW Biotechnology (Shanghai) Co., Ltd, will be established to further the development of novel cell-based cancer immunotherapies in China. The company will make use of Juno’s CAR and T cell receptor technologies in combination with WuXi’s R&D, manufacturing platform and local expertise will be used to develop novel cell-based immunotherapies for patients with hematologic and solid organ cancers. James Li, has been appointed as CEO of JW Biotechnology (Shanghai) Co., Ltd.

“JW Biotechnology will leverage Juno’s expertise in cell therapy technologies and WuXi AppTec’s excellence in contract services, and collaborate broadly with Chinese medical communities and government regulators to develop cell therapies that will deliver cutting-edge cancer treatments to Chinese patients. These novel technologies offer a unique opportunity that holds the potential to save lives while transforming the treatment of cancer,” said Dr Li.



GENSIGHT BACKS OUT OF IPO OFFERING

Gene therapy specialists, GenSight Biologics, have postponed their plans to go public after having already downsized earlier expectations.

Having already scaled down their initial \$100 million IPO to \$65 million, the company have decided to abandon these plans. The company has however had more luck with venture capital funding, having already closed a \$36 million Series B financing round, which will be used to fund trials for their lead product, GS010, which is being developed as a potential treatment for Leber's Hereditary Optic Neuropathy (LHON).

The therapy will work by repairing a faulty gene that leads to LHON, through the use of a viral

vector to deliver a corrective copy of the gene. A Phase III trial is already under way, with results expected to be released next year, but additional funding will still be required to cover the costs of the late-stage study program. The treatment has already received orphan status in the U.S. and Europe. The disease affects roughly 4000 people in the U.S. with 100 new cases added to the pool of LHON patients every year.

GenSight is developing an additional gene therapy, GS030, for retinitis pigmentosa. Viral vectors will be used to introduce DNA that will increase the production of a photosensitive protein that will partially restore a patient's vision.



GADETA TO ADVANCE NOVEL CANCER IMMUNOTHERAPIES TO THE CLINIC

The Dutch start-up, Gadeta B.V., who specialises in the discovery and development of novel immunotherapies based on gamma delta ($\gamma\delta$) T cell receptors announced the completion of a Series A financing.

The 7 million euro Series A financing was led by Baxalta Ventures and Medicxi Ventures. Gadeta's technology platform is based on work by Prof. Jürgen Kuball, who made ground breaking discoveries studying the role of $\gamma\delta$ T cell receptors and their ability to differentiate between hematological and solid tumor cells based on metabolic differences. Kuball is the co-founder and

chief scientific officer of Gadeta. He also chairs the section of applied & tumor-immunology within the laboratory of translational immunology at the University Medical Center Utrecht.

"Supported by the Series A financing, we're excited to accelerate our programs and rapidly advance them to the clinic. With its unique ability to target the metabolic changes in tumor cells, the strong therapeutic potential of our platform holds tremendous promise for the treatment of hematological and solid tumors," commented Mark de Boer, co-founder and CEO of Gadeta.