

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.



GENE THERAPY: The race to get the first product approved in hemophilia continues apace, as both Shire and uniQure release positive news this month, albeit in different types of the condition. It's a crowded space – competitors include Biomarin, Dimension Therapeutics, Sangamo Biosciences and Spark Therapeutics. Biomarin leads the field in hemophilia A with a product already in Phase 1/2, so Shire has some catching up to do following the announcement of its IND submission for SHP654. In hemophilia B, uniQure presented clinical data showing that patients may be eligible for treatment with AMY-060 even when they have pre-existing neutralising antibodies; however, the news is somewhat tarnished by the announcement that Chiesi has withdrawn from an agreement to co-develop the treatment, citing “changes in strategic priorities”.



GENE THERAPY
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CELL THERAPY: The cell and gene therapy industry is inching closer to approvals in major markets for the world's first CART therapies. Both Novartis and Kite have BLAs submitted in the USA for pediatric acute lymphoblastic leukemia (ALL) and relapsed or refractory non-Hodgkin lymphoma (NHL),

respectively. In July, Kite Pharma became the first company to submit a Marketing Authorization Application to the EMA for a CART product (axi-cabtagene ciloleucel). While the first indications being targeted by Novartis and Kite are different, there will be overlap in patient populations in the future. It will be interesting to see how the company's position their products as approvals are granted following the first set of indications and what the dynamics of market uptake will look like. The latter will be driven by reimbursement, though prospects are strong in both cases.



APPROVAL FOR COHORT 3 ENROLLMENT IN BIOTIME'S DRY-AMD CELL THERAPY TRIAL

The independent group of medical experts: the Data Safety Monitoring Board (DSMB) which is monitoring biotech BioTime's Phase I/IIa OpRegen® clinical trial, has authorized the Company to move forward with enrollment for cohort 3. This follows data from the first two cohorts that supported the treatment of Dry Age-Related Macular Degeneration (Dry-AMD) with the cell therapy.

Dry-AMD is the leading cause of blindness in people over 60. It is caused by loss or dysfunction of the layer of retinal pigment epithelial (RPE) cells generally in the macula - the region of the eye responsible for the sharp, central vision that is utilized in facial recognition and activities such as reading and driving. RPE cells support light detecting photoreceptor cells that are vital for vision. To combat this degradation of the RPE layer, OpRegen® injects a suspension of RPE cells subretinally. A proprietary process that drives the differentiation of human pluripotent stem cells is used to generate high purity OpRegen® RPE cells; an allogeneic, off-the-shelf product

that is hoped to require just a single procedure.

Cohort 1 and 2 studies of the Fast Track designated therapy demonstrated that the transplanted OpRegen cells remained in place at the one year follow up, and uniquely in an area of the scar that was completely depleted of RPE. There was also possible evidence of a biological response with some areas appearing to show structural improvement. Cohort 3 will focus on optimizing the cell concentration and volume prior to the treatment of an earlier stage of the disease in cohort 4. Patients will be enrolled at the company's existing sites in Israel and a further two sites in the US with treatment aiming for completion by the end of 2017.

One of the trial's lead ophthalmologists, Richard McDonald commented, "Our team is enthusiastic about the early data showing a positive response from the implanted cells. The DSMB's approval is an important milestone. We look forward to enrolling our first patient in the trial as this is a debilitating disease."



FDA RECOMMENDS ACCELERATING ABEONA'S EB-101 INTO PHASE 3

The FDA has recommended that Abeona Therapeutics advance their gene-corrected skin graft candidate EB-101 to a pivotal Phase 3 trial. The acceleration of the EB-101 program was recommended by the FDA at a recent Type-C meeting.

EB-101 is an autologous, *ex vivo* therapy for the treatment of the genetic skin disorder recessive dystrophic epidermolysis bullosa (RDEB). Also known as butterfly syndrome, RDEB carries devastating symptoms including chronic blistering, open wounds and joint contractures. The condition can ultimately shorten a patient's lifespan. Patients with RDEB lack functional type VII collagen owing to mutations in the gene *COL7A1* that produces C7 collagen and is the main component of anchoring fibrils that stabilize the skin onto the basement membrane.

EB-101 addresses the underlying cause of RDEB by inserting *COL7A1* into a patient's own skin cells. Data from the Phase 1/2 trials

of the therapy has demonstrated more than 50% significant wound healing for more than 2 years post administration. These results have supported the orphan designations that the therapy has received from both the FDA and European Medicines Agency.

"The FDA guidance is an important milestone in our clinical development plan for EB-101, and we are pleased to be moving forward into a registrational Phase 3 clinical study in 2018. Abeona is committed to advancing innovative gene therapies that address the unmet needs of patients suffering with dystrophic epidermolysis bullosa, a devastating rare skin disease. We are grateful that the FDA has recognized EB-101 as a rare disease product that addresses the underlying disease pathology to offer significant therapeutic benefit for RDEB patients, and we look forward to the collective work ahead in advancing this therapy," commented Abeona CEO Timothy J Miller.



Abeona Therapeutics remains on track for a 2018 Phase 3 start in RDEB. Its product, EB-101, is manufactured from autologous keratinocytes, transduced with the gene *COL7A1* and grown *ex vivo* to form a skin patch, which can then be applied to an open wound. Data from an earlier Phase 1/2 study indicating improved wound healing rates compared to historical data, although the number of patients treated was very small ($n = 6$). The outcome of a recent Type C Meeting with FDA appears to have been positive, with a recommendation to proceed to a pivotal Phase 3 trial, but details of the meeting are sketchy, and it remains to be seen whether any future application for approval will rely on supportive natural history data in RDEB. Nevertheless, the company is ahead of its competitor Fibrocell, which is developing a lentivirus-based approach, where transduced fibroblasts are injected directly into the papillary dermis of blisters and wounds. – Richard Philipson



NEW DATA FROM UNIQUIRE EXPANDS POTENTIAL PATIENT FIELD

uniQure has presented new data that suggests that the presence of pre-existing anti-AAV5 neutralizing antibodies (NABs) is not a factor in the efficacy of their hemophilia B gene therapy AMT-060. This would mean that patients with pre-existing NABs would not necessarily be excluded from treatment, as has been the case to date.

AMT-060 is a gene therapy in which AAV5-mediated gene transfer of Factor IX (FIX) is used to correct the underlying cause of the condition. Data from patients in uniQure's ongoing Phase 1/2 trial who were retrospectively found to have anti-AAV5 NABs but all presented increases in FIX activity, together with results from testing in

non-human primates, led researchers to their latest conclusion that AAV5 can successfully mediate gene transfer in the presence of NABs. Further to this, none of the patients who tested positive for NAB titers, experienced over time elevations in liver enzymes post-gene transfer, FIX activity loss or clinically relevant T-cell responses to the capsid.

"This development potentially expands the applicability of AAV5 gene therapies to nearly all hemophilia B patients. We believe these factors contribute to making AAV5 a potential best-in-class vector for delivering gene therapies more effectively and safely to a greater portion of patients in need of treatment," commented CEO Matthew Kapusta.



DURABLE COMPLETE RESPONSES IN PHASE I TRIAL OF NANTKWEST'S ANK CELL THERAPY

News from a trial of NantKwest's aNK cell therapy platform in relapsed hematological malignancies was successful enough for the cell therapy to warrant further clinical investigation. The aNK cell therapy platform is being developed as an allogeneic, off-the-shelf therapy that harnesses the power of, and enhances, natural killer cells to directly target and kill cancer cells.

Results from the Phase 1 trial carried out in Canada demonstrated continuing evidence of safety and efficacy, with an overall response rate of 42% and no evidence of grade 3

or 4 adverse events. Of note, two out of the 12 patients in the safety study with relapsed Hodgkin's lymphoma and multiple myeloma, demonstrated durable complete response with single agent aNK therapy, and remain free of disease to date, 10 years and 2 years, respectively.

"Consistent with previous studies, Dr. Keating's clinical trial results, reporting a 42% overall response rate, provide additional clinical validation of the unique potential to deliver long-term remissions with limited toxicity using the company's novel NK cell therapy.

Our aNK cell therapy is currently in an ongoing Phase 2 clinical study in Merkel cell carcinoma and represent a critical, foundational component

in the company's recently launched NANT Cancer Vaccine clinical trial program," stated CEO Patrick Soon-Shiong.



EXPERT PICK

NantKwest reported positive data from a long running clinical study in Canada, showing that some lymphoma and multiple myeloma patients treated with unmodified NK cells had durable, complete responses. One patient has been in remission for 2 years while a second is disease free 10 years after treatment. The study investigated NantKwest's first generation allogeneic NK cell platform (aNK), which it has expanded on in recent years to produce NK cells engineered with antibodies and CARs. – Mark Curtis



COMPLETION OF ENROLMENT IN GENSIGHT'S PHASE 3 TRIAL OF LHON THERAPY

Gensight has completed enrolment for their Phase 3 trial of GS010, a gene therapy for the treatment of Leber's hereditary optic nerve neuropathy (LHON). Titled RESCUE, the study will investigate the efficacy of GS010 as the primary endpoint, and secondary endpoints will include factors such as quality of life scales, bio-dissemination and the time course of immune response. Results from the trial are expected in the third quarter of 2018 from 36 patients in seven centers in both the USA and Europe.

GS010 addresses the mitochondrial genetic basis of LHON (the G11778A mutation in the mitochondrial *ND4* gene) by leveraging a mitochondrial targeting sequence (MTS) proprietary technology platform. This uses an adeno-associated viral (AAV) vector to transfer the correct gene to the cell; once the

functional protein is expressed it is shuttled to the mitochondria via specific nucleotide sequences.

"The completion of enrollment in our RESCUE Phase 3 Study of GS010 is a significant accomplishment for GenSight and for the LHON Community. We have now completed enrollment in both of our ongoing Phase 3 studies and look forward to reporting data in the first half of 2018," commented CEO Bernard Gilly.

Dr Mark Moster, an investigator in the study, added, "We are very excited to be part of the RESCUE and REVERSE trials with GS010. Safety and pharmacodynamics results seen in the Phase 1/2 study are particularly encouraging, and if confirmed in these Phase 3 trials, GS010 could be a potentially transformative treatment for LHON, and a fantastic hope for patients and their families."

EXPERT
PICK

The announcement that GenSight Biologics has completed enrolment of its second Phase 3 study in LHON takes the company one step closer to a possible first approved gene therapy treatment for this devastating eye condition.

GS010 uses an AAV2 vector, containing the human wild-type mitochondrial *ND4* gene, combined with its proprietary mitochondrial targeting sequence technology, which permits missing mitochondrial proteins to be shuttled into the mitochondrion, enabling restoration of mitochondrial function. Both Phase 3 trials use a sham injection design, where one eye receives active treatment and the other a control injection, although interestingly only REVERSE requires both eyes to be affected at entry into the study. Idebenone, an anti-oxidant treatment, was approved for LHON in 2015 by EMA, although the approval under 'exceptional circumstances' requires the manufacturer, Santhera Pharmaceuticals, to conduct additional studies on the long-term effects and safety of the treatment, and to establish and maintain a registry of LHON patients treated with its therapy. – Richard Philipson

PRIME DESIGNATION FOR TOCAGEN'S
COMBINATORIAL GLIOMA THERAPY

The European Medicines Agency (EMA) has granted cancer selective gene therapy company Tocagen PRIME (PRiority MEdicines) designation for Toca 511 (vocimagene amiretrorepvec). The therapy is designed for the treatment of patients with high-grade glioma (HGG).

Toca 511 is an injectable retroviral replicating vector (RRV) that encodes a prodrug activator enzyme, cytosine deaminase (CD). Derived from yeast, CD does not naturally occur in humans. This is administered in combination with Toca FC, an investigational small molecule that is converted into the anticancer drug 5-FU in CD producing cells. This combination therapy is intended to directly kill cancer cells and immune-suppressive myeloid cells, resulting in activation of the immune system against cancer.

The EMA's decision was based on Phase 1 data that included complete

or partial tumor shrinkage in patients treated with Toca 511 and Toca FC. Earlier this year, these data also resulted in the combination therapy gaining Breakthrough Designation from the FDA.

Under PRIME designation, drug developers receive enhanced interaction and early dialogue with the goal of optimizing development plans and accelerating evaluation so medicines can reach patients earlier. As such, CEO Marty Duvall commented, "The EMA's granting of PRIME designation for Toca 511 underscores the urgent need for new treatments for high-grade glioma, one of the deadliest cancers. We are committed to working closely with the EMA to expedite the advancement of our product candidate, and bringing a potentially transformative treatment option for high-grade glioma to European patients and physicians as quickly as possible."



CAPRICOR RECEIVES RARE PEDIATRIC DISEASE DESIGNATION FOR DMD CARDIAC STEM CELL THERAPY

Capricor Therapeutics has received a Rare Pediatric Disease Designation for their stem cell therapy candidate, CAP-1002. Intended for treatment of Duchenne muscular dystrophy (DMD), CAP-1002 targets the heart – the ultimate cause of death for DMD patients. The designation can serve to expedite the review process for the treatment via a Priority Review Voucher worth millions of dollars.

CAP-1002 infuses cardiac stem cells from a healthy donor into the heart via the coronary arteries. Capricor is trialing the treatment in a Phase 1/2 study – the HOPE trial – that has enrolled 25 patients with DMD associated heart disease. At 6 months post-treatment, all patients were reported to have improved heart and arm function of a significant level. No patient has discontinued treatment, and the approach has been well-tolerated to date. A 12-month update from the

trial is expected later this year and the company also plans to initiate randomized double-blind, placebo-controlled clinical trial of intravenous, repeat-dose CAP-1002 in boys and young men with DMD in the second half of this year, subject to regulatory approval.

CEO Linda Marbán commented, “The Rare Pediatric Disease Designation adds to our previous Orphan Drug Designation for CAP-1002 for the treatment of Duchenne muscular dystrophy, which together underscore the urgent need for treatment options for this devastating rare disease as well as provide Capricor with certain incentives for their development.”

The Priority Review Voucher gained as part of the designation gives the company the option to shorten the review process by 4 months, or raise capital by selling it to a big pharma company – a common move for smaller biotechs.



UNANIMOUS FDA SUPPORT SIGNALS APPROVAL ON THE HORIZON FOR NOVARTIS'S CAR T THERAPY

In what looks to be the last leg of the chimeric antigen receptor T cell (CAR T) race to approval, Novartis has won the unanimous support of the FDA's advisory panel with a 10–0 vote. This sets the timer for the Swiss giant's CTL019 therapy to win FDA approval by October this month. News of the vote saw

the company's share price spike by 1.5% on the day.

CTL019 engineers autologous T cells to treat children with B-cell acute lymphoblastic leukemia. In trialing, the therapy achieved an 83% remission rate that far exceeds the current course of treatment for the cancer. Novartis's team were

quizzed on safety concerns by the advisory committee with questions covering neurotoxicity, cytokine release syndrome, the risk of secondary malignancies and the safety implications of the low proportion of CAR-positive T cells in some batches.

Autologous therapies present considerable logistical challenges, the tackling of which will be critical to the successful rollout of CTL019 once approval is secured. The company is prepping for approximately 30 sites to administer the therapy initially, with eventual expansion into more locations if this goes well. With a risk mitigation strategy in

place that will establish a 15-year post-approval patient registry, doctors will also be provided with a management algorithm to help spot and control toxicities. Furthermore, administration of CTL019 will be staggered to further mitigate safety incidences.

Close on the heels of Novartis is Kite Pharma whose own CAR T therapy is due for a final FDA decision by the end of November this year. Kite's CEO celebrated Novartis' news as a win for the future of CAR T therapies, and both Kite and fellow CAR developer Juno experienced hikes in share price along with Novartis of between 0.5 and 1.1%.



IND APPLICATION SUBMITTED FOR SHIRE'S HEMOPHILIA A GENE THERAPY

Massachusetts-based biotech company, Shire, has submitted an investigational new drug (IND) application to the FDA concerning SHP654, a gene therapy for the treatment of hemophilia A.

SHP654 bypasses the traditional factor-based treatment route by inducing liver cells into producing their own source of the blood clotting factor VIII (FVIII), the genetic deficiency of which characterises hemophilia A. The therapy involves the delivery of a codon-optimized, B-domain deleted *FVIII* (*BDD-FVIII*) gene via a recombinant adeno-associated virus serotype 8 (rAAV8) vector.

Clearing the IND application give Shire the go ahead to administer the therapy in humans. The company plans to initiate a global multi-center study evaluating safety and dosage, given the desired IND

outcome. Ultimately, the company aims to bring the therapy to the worldwide market for the long-term treatment of hemophilia A through sustained FVIII expression.

Medical Director Paul Monahan commented, "Shire is leveraging decades of scientific leadership in hemophilia to advance research in gene therapy for this community. Drawing from our rich heritage, Shire is well equipped to sustainably support the development of gene therapies that aim to advance current standards of care and minimize the burden of this disease. SHP654 uses a proprietary technology platform designed to produce sustained levels of factor similar to the natural mechanisms of the body. Our goal with gene therapy for hemophilia is to uphold the highest standards for safety and efficacy."



4D TO COLLABORATE WITH FOUNDATION FIGHTING BLINDNESS ON AAV MEDIATED GENE THERAPIES



4D Molecular Therapeutics (4DMT) has partnered with the Foundation Fighting Blindness (FFB), a non-governmental source of research and funding for inherited retinal degradations. Under the agreement, 4DMT, a leader in adeno-associated virus (AAV) gene therapy vector discovery and product development, will provide access to its proprietary vector technology and manufacturing capabilities. Meanwhile FFB will identify potential collaborators, provide expertise and fund approved projects. 4DMT will retain all patent and commercial rights to its proprietary AAV vector variants whilst all programs under the collaboration will require approval by both parties.

“We are very impressed with 4D’s vector evolution approach, the company’s product pipeline

and manufacturing expertise. The potential is great for developing a number of gene therapeutics that could treat those affected by retinitis pigmentosa and allied conditions using a simple intravitreal injection approach,” said Patricia Zilliox, Chief Drug Development Officer at the FFB.

“We are extremely excited by this collaboration with FFB, a globally-recognized leader in the effort to cure blindness due to inherited retinal degenerations. FFB has tremendous expertise identifying the best retinal research as well as an outstanding network of funded investigators and companies with whom we hope to collaborate to develop a portfolio of products that will benefit those affected with retinal degenerative diseases,” added David Kirn, CEO of 4DMT.



CELLECTIS GRANTED PATENT FOR CRISPR USE IN T CELLS

Biopharmaceutical company Cellectis has been granted a patent for the invention of using RNA-guided endonucleases, such as Cas9 or Cpf1 for the genetic engineering of T cells by the European Patent Office.

Patent EP3004337 claims a method for genetically modifying T cells by introduction into the cells and/or expression in the cells of at least an RNA endonuclease and specific guide RNA, which directs

the endonuclease to at least one locus in the T cell. The endonuclease is expressed from transfected mRNA; the RNA guide is expressed as a transcript from a DNA vector. This is followed by the expansion of the resulting cells *in vitro*. Cellectis will make this patent available for licensing to companies that are willing to use this technology in T cells.

“We have been the first to explore the potential of CRISPR in its early days in various applications,

including therapeutics and food, and these early findings ultimately led to the grant of this new patent. While Cellectis has selected TALEN® as the most robust and adaptable technology for human therapeutic use and for the Company's product pipeline, our team does sometimes use CRISPR-based nucleases for T-cell research, as it is

a less expensive option and convenient for gene discovery purposes. As such, this patent only further reinforces Cellectis' leadership position in the gene editing industry, with more patents coming down the pike for the Company in the near future," commented André Choulika, CEO and co-inventor of the patent.



ONES TO WATCH

Collectis, which is pioneering the field of allogeneic T-cell immunotherapy with its UCART platform, already has a broad suite of technologies for editing the genome. The company added to its IP portfolio this past month, after being granted a patent by the European Patent Office, describing the use of guide RNA and RNA endonucleases for editing DNA. The company is decidedly biased to TALENs for editing purposes, but says it will use the technology in house for discovery projects, and also out-license the technology to developers interested in carrying out gene editing in T cells.

– Mark Curtis



UNIQUIRE REACQUIRES HEMOPHILIA B GENE THERAPY RIGHTS FROM CHIESI

A shift in rights over the hemophilia B gene therapy, AMT-060, has seen uniQure re-acquire the full rights to the development and commercialization of the candidate. Subsequently, AMT-060 is being dropped by Italian healthcare group Chiesi Farmaceutici who held rights to the therapy in Europe and other select territories. Finally, the move signals the termination of the co-development and licensing agreement between the two companies.

AMT-060 is comprised of an adeno-associated virus (AAV) carrying the Factor IX gene, which is mutated in hemophilia B patients. This year the therapy has been granted a breakthrough designation in the

USA, and PRIME status in Europe. uniQure will now be solely responsible for the therapy, including \$3 million of expenses incurred this year, which would have been split with Chiesi under the previous deal. The company is confident however that this will not impact their cash guidance; the expectation is that funds will be available to run operations well into 2019.

A statement by uniQure CEO Matthew Kapusta said, "We are very pleased to reach an agreement with Chiesi to acquire back European and other territorial rights to our lead gene therapy program in hemophilia B. By regaining unencumbered, global rights to a

late-stage program that has demonstrated significant clinical benefit for patients with hemophilia B, we believe uniQure is better positioned to accelerate the global clinical development plan, maximize shareholder return on our pipeline and

take advantage of new potential opportunities related to the program. We are grateful for the substantial investments that Chiesi has made in AMT-060, and we have been fortunate to have them as a collaboration partner over the years.”



OXFORD BIOMEDICA TO SUPPLY LENTIVIRAL VECTORS FOR NOVARTIS' CAR T PRODUCT

Oxford Biomedica has closed on a lucrative deal with Novartis for the commercial supply of the lentiviral vectors for Novartis' upcoming blockbuster CAR T therapy, CTL019. Oxford stands to gain up to \$100 million over three years for its services, with \$10 million being paid upfront. Jefferies analysts figure Novartis could earn between \$84 million and \$97 million a year if CTL019 hits peak sales of at least \$1 billion a year.

The lentiviral vector is a key component in the manufacturing

process of the personalised leukaemia drug. The therapy requires that autologous, cryopreserved blood by shipped to a facility where it is reprogrammed genetically – this is mediated by the lentiviral vector – and then manufactured in the lab before being shipped back to the patient for infusion.

Oxford CEO John Dawson stated, ‘The new deal with Novartis will strengthen the group's balance sheet immediately and will support the group's continued growth over the next 3 years.’



SPARK UNDER FDA REVIEW FOR POTENTIAL FIRST US GENE THERAPY

Spark Therapeutics has submitted the Biologics License Application (BLA) for what could be the USA's first gene therapy to reach market. The FDA has begun the review of Luxturna (voretigene neparovec) and is expected to reach a verdict on the retinal disease therapy by January 2018.

Luxturna is intended to treat the as yet untreatable condition

RPE65-mediated inherited retinal dystrophy, an inherited retinal disease (IRD). RPE-65-mediated IRD eventually progresses to blindness with prior symptoms including decreased light sensitivity during childhood or early adulthood, and involuntary back-and-forth eye movements. Caused by a biallelic mutation in the *RPE65* gene, Luxturna aims to correct the mutation

and has performed significantly against a placebo in trial. The recent BLA is supported by Phase 3 data that showed bilateral multi-luminance mobility testing (MLMT) scores of 1.8 in comparison in patients treated with Luxturna, compared with a mean change of 0.2 in the control group.

If Spark is successful in taking their gene therapy to market, they face considerable hurdles in the successful commercialization of

Luxturna. Earlier this year UniQure/Chiesi's €1 million-per-treatment gene therapy candidate Glybera was withdrawn from the EU market, having been the only gene therapy to receive EU approval to commercialize thus far. The withdrawal was due to a lack of demand; a cautionary tale for the gene therapy industry, particularly companies such as Spark who are set to reach the BLA approval milestone in coming months.