

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.



This past month the FDA made progress in formalizing the development and commercialization of cell therapy and regenerative medicine products in the USA with the release of new guidance describing the regenerative medicine advanced therapy (RMAT) designation and how it relates to other regulatory support mechanisms. The RMAT, which is reserved for therapies that are intended to treat, modify, reverse or cure, serious conditions, will include all of the benefits of the existing breakthrough therapy designation and fast track designation, including discussions on surrogate endpoints. Companies seeking a RMAT designation will only need to show that a therapy has the potential to address an unmet medical need in order to receive support. The policies now in place will no doubt stimulate the development of novel regenerative medicine therapies. What will be critical now is the development of a reimbursement environment conducive to the uptake of these therapies as they make their way to market.



GENE THERAPY

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CELL THERAPY

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This month sees plenty of good news in the clinical development arena. Two companies have announced positive progress in their early clinical development programs: Ultragenyx has successfully completed the first cohort of three patients in its Phase 1 study in OTC deficiency, and Abeona has enrolled the first patient with MPS IIIA at its site in Spain, adding to already active sites in the USA and Australia. Ziopharm has released new data showing encouraging median overall survival in patients with recurrent glioblastoma treated with its IL-12-based gene therapy, and AveXis has achieved a notable milestone with the publication in the *New England Journal of Medicine* of positive clinical

data from its ongoing trial in spinal muscular atrophy. There's also an announcement from BioCanCell that clinical data on its lead product, BC-819, in development for non-muscle invasive bladder cancer, will be presented at the upcoming Genitourinary Cancers Symposium in February 2018.



14-DAY RESULTS RELEASED FROM FATE-NK100 PHASE 1 TRIAL

Fate therapeutics has announced top line data from its Phase 1 trial of natural killer (NK) cell therapy FATE-NK100. The therapy is being studied under the company's VOYAGE trial in patients with refractory or relapsed acute myelogenous leukemia (AML).

Initial results include a patient in the second dose cohort achieving a morphologic leukemia-free state (mLFS). This outcome followed a single infusion of the FATE-NK100 cells; at 14 days post-treatment the levels of these cells detected in peripheral blood stood at 3×10^4 . The first subject treated in the lower dose arm of the study achieved a 50% reduction in leukemic blasts by 14 days. At 76%, they had a particularly high incidence of FATE-NK100

cells in the peripheral blood. The final, and highest, dose cohort for the novel approach is currently enrolling.

Lead investigator Sarah Cooley commented,

"These are encouraging early data for FATE-NK100 in refractory and relapsed AML, especially in patients with such high leukemic blast burden in the marrow that have exhausted all therapeutic options. The disappearance of all cells with morphologic characteristics of leukemia validates the in vivo anti-leukemia activity of FATE-NK100. We look forward to continuing enrolment in the VOYAGE study and to dosing the first patient with FATE-NK100 in the APOLLO study for the treatment of women with recurrent ovarian cancer."



NEW & PROMISING DATA FROM AVExis's SMA GENE THERAPY

New data from AveXis's AAV vector-based gene therapy shows promise as the spinal muscular atrophy (SMA) drug improves on previous results from 8 months prior.

AveXis released this latest data in the New England Journal of Medicine, which details improvements in subjects' ability to speak and sit up unassisted. Of the 12 patients in the study, 11 are now able to speak – 3

up from the previous 8. Another two patients also gained the ability to sit unassisted bringing the total to 9 of the 12. The number of patients in the trial who do not need permanent ventilation is also encouraging. These are positive results from the company whose therapy would rival Biogen's Spinraza if it gains market approval.

Questions that remain to be answered for the company include:

firstly, how to price the therapy, particularly given Spinraza's substantial \$750,000 cost; and whether there is the possibility of the therapeutics effects fading and thus creating a need for readministration.

AveXis CEO Sean Nolan commented to investors,

"Both of the regulatory agencies have agreed that the... confirmatory trials for SMA Type 1 would be a single arm utilizing natural history as the control with relatively few patients, 15 or 20 in the USA and approximately 30 in EU. And they have each asked us to seek discussion with them to talk about accelerated approval or conditional approval."



EXPERT PICK

The publication of data from AveXis's ongoing trial in spinal muscular atrophy (SMA) provides a further boost to the field, which already has

one treatment approved for use in children with SMA. The observation that all 15 treated children in the study were alive and event-free at 20 months of age compares favourably with a rate of survival of 8% in a historical cohort. Clinical benefits were primarily observed in the higher dose cohort of 12 patients, who received a single IV administration of 2×10^{14} vg/kg of the AAV-based therapy. Of note, four patients experienced marked elevations of serum aminotransferase levels, but these were successfully treated with prednisolone. AveXis's scAAV9 gene therapy may be more attractive to patients and their families as it is potentially a one-off treatment, whereas Biogen's antisense oligonucleotide nusinersen (Spinraza) probably requires life-long repetitive intrathecal treatment. However, if the benefits of the gene therapy decline over time, the development of antibodies to the viral capsid will probably mean that further treatments cannot be given. Clearly, longer term follow-up is needed, but these results look very promising indeed.

– Richard Philipson



FDA PUBLISHES NEW DESIGNATION FOR REGENERATIVE MEDICINES

The FDA has combined the benefits of fast track and breakthrough designation in a new policy framework for the regenerative medicine industry. Named the Regenerative Medicine Advanced Therapy (RMAT)

designation, it will expedite the process for selected cell therapies to reach the market.

Four documents pertaining to the new framework have been published with three building on

existing texts under the 21st Century Cures Act. The RMAT draft device guidance is a new text and responses to it will be accepted for 90 days. Topics covered include clarifications on when cell and tissue-based products are exempt from established regulations; and the use of the terms ‘minimal manipulation’ and ‘homologous use’.

Investigational regenerative medicine therapies that treat, modify, reverse or cure serious conditions may apply for the new designation. To do so they must have produced preliminary evidence of efficacy with a single, open-label study of a

skin burn cell therapy cited by the FDA as an acceptable example.

FDA commissioner Scott Gottlieb outlined that another intention of the new designation is to inhibit the rise of non-legitimate cell therapies:

“Alongside all the promise, we’ve also seen products marketed that are dangerous and have harmed people. With the policy framework the FDA is announcing today, we’re adopting a risk-based and science-based approach that builds upon existing regulations to support innovative product development while clarifying the FDA’s authorities and enforcement priorities.”



CELLECTIS OPTIMIZES TALEN TARGETING FOR IMMUNOTHERAPY DEVELOPMENT

Cellectis has published a study in the journal *Molecular Therapy – Nucleic Acids* documenting the fine tuning of TAL nucleases (TALEN®), allowing more accurate targeting of the T-cell immunotherapy checkpoint PD1. This is a significant move for the company who are focused on the development of CAR T cell based immunotherapies where highly specific gene editing of the allogeneic products is a necessity.

In the study led by Drs Anne-Sophie Gautron and Alexandre Juillerat, specific nucleases were

designed by taking advantage of the exclusion capabilities of the Repeat Variable Diresidue (RVD). Replacing RVDs allowed for the optimal redesign of TALEN combinations by disrupting both TRAC and PDCD1 at specific locations. The approach also mitigated the occurrence of low frequency offsite processing.

The report concluded that,
“This development validated in human primary T cells will enable TALEN tools for gene editing to be applied more broadly and safely in basic research and disease treatment.”



ENCOURAGING RESULTS FROM BIOCELL'S PHASE 2 BLADDER CANCER TRIAL

BioCanCell has released supplementary final results from its trial of gene therapy BC-819 for

bladder cancer, which enhance the candidate’s safety and efficacy profile. At a median of 18 months

post-administration, patients in the trial had successfully surpassed the median reoccurrence and progression times for the condition, as well as presenting no serious adverse events.

BC-819 is an intravesical double stranded DNA plasmid, which expresses a lethal cellular toxin, derived from diphtheria, when taken up by malignant cells.

The trial from which this latest data has been derived enrolled 38 patients who were treated with a combination of BC-8219 and current treatment drug Bacillus

Calmette–Guérin (BCG). The trial assessed varying administration methods over a 6–12 week period. Detailed results obtained from the trial have been submitted for the 2018 Genitourinary Cancers Symposium Annual Meeting being held in February 2018.

BioCanCell 's CEO Frank Haluska commented,

"We are encouraged by the updated study results given the limited treatment options currently available for patients with non-muscle invasive bladder cancer (NMIBC), a serious area of unmet medical need."



ZIOPHARM REPORTS POSITIVE FOLLOW-UP DATA FROM BRAIN CANCER GENE THERAPY TRIAL

Ziopharm's brain cancer gene therapy candidate, Ad-RTS-hIL-12 plus veledimex, has reported positive survival and mechanism results from an ongoing study of the therapy in patients with recurrent glioblastoma (rGBM).

Ad-RTS-hIL-12 is a controlled human interleukin-12 (hIL-12) gene therapy that has been administered in subjects in combination with 20mg of veledimex. The 11.1-month follow-up data was presented by Ziopharm at the 22nd Annual Meeting and Education Day of the Society for Neuro-Oncology (SNO). The company highlighted positive progress that includes an improved median overall survival length of 12.5 months, with a particularly significant 100% survival rate in patients who also took low dose steroids. MRI scans of patients also found a decrease in the size of several of the tumor lesions. To date, no adverse events of drug-related deaths have occurred;

maintaining the safety profile of the therapy.

The latest results have also indicated mechanisms of action by which Ad-RTS-hIL-12 affects an immune system response to the tumors. Survival can now be correlated with the intra-tumor production of hIL-12 as well as the ratio of circulating killer CD8+ T cells to suppressor FOXP3+ T cells.

Lead author of the presentation, Dr Antonio Chiocca, commented,

"These new mechanistic data, especially taken together with the promising extension of patients' median overall survival, provide additional validation that controlling IL-12 can engage the body's own immune system safely to generate a T-cell response against rGBM. We are excited to see increasing evidence of a targeted, local immune response making brain tumors hot and illustrating how this immunotherapy contributes to patients' survival."



ULTRAGENYX DOSES FIRST OTC DEFICIENCY PATIENT IN PHASE 1/ 2 GENE THERAPY TRIAL

The first ornithine transcarbamylase (OTC) deficiency patient has been dosed in Ultragenyx's gene therapy trial targeting the condition. The Phase 1/ 2 study is investigating three patients in the first cohort, each will be treated with a single intravenous infusion of the orphan designated, AAV mediated gene therapy candidate DTX301.

Caused by a genetic defect in the liver enzyme, which detoxifies ammonia, OTC deficiency is a common urea cycle disorder. Patients in the study will therefore be assessed for changed in ureagenesis – the pathway by which ammonia is metabolised. Ammonia levels,

neurocognitive assessment, biomarkers and safety are indicators that will additionally be assessed. The first results from the trial are expected in early 2018. Pre-clinical studies have demonstrated a normalization of urinary orotic acid levels; a marker of ammonia metabolism.

A success in this gene therapy approach would alleviate the symptoms of ammonia accumulation, which include acute and chronic neurological effects. It would also eliminate the need for daily management drugs or liver transplant, which are the only current options for treatment.



The announcement of completion of dosing in the first cohort of three patients with ornithine transcarbamylase (OTC) deficiency brings some welcome good news for Ultragenyx.

The AAV8-based gene therapy (DTX301) was acquired by Ultragenyx following its recent merger with Dimension Therapeutics Inc., and provides the company with a further diversification of its pipeline, building on its existing portfolio of biologics and small molecules. The company took a knock earlier in the year with the release of news that a Phase 3 study evaluating aceneuramic acid extended release in patients with GNE myopathy did not meet its primary or key secondary endpoints, leading to the discontinuation of clinical development of the product. The development of DTX301 will be watched carefully by clinicians, regulators and patients alike; a previous trial in OTC deficiency led to the death of Jesse Gelsinger, who was 18 years old and healthy when he died in 1999 during a gene-therapy experiment. The current study still has two further dose cohorts to evaluate, but the news of completion of dosing in the first cohort gives cause for cautious optimism.

– Richard Philipson



FDA LIFTS 3-MONTH HOLD ON CELLECTIS' UCART123 TRIALS

The FDA has lifted their previously instated hold on the Phase 1 trial-ling of Cellectis' chimeric antigen receptor (CAR) T cell candidate for the treatment of acute myeloid leukemia (AML) – UCART123. The move comes 3 months after the hold, resulting from the death of a 78-year-old patient who experienced severe cytokine release syndrome, was ordered.

The FDA has specified conditions for the reinstatement of the trial. This includes a reduction in the dose level, a maximum subject

age of 65 for initial enrolments, a commitment to staggering treatment of patients, and extra screening parameters up to the day of infusion itself.

UCART123 is the first allogeneic CAR T product approved for trial-ling by the FDA. Genetically modified CAR T cells are engineered to target CD123 antigens that are characteristic of AML tumors. The investigational candidate has also been passed for trialing in blastic plasmacytoid dendritic cell neoplasm (BPDCN).



ABEONA ENROLS FIRST PATIENT IN SPAIN ARM OF MPS IIIA GENE THERAPY TRIAL

Abeona Therapeutics has dosed the first patient in its Phase 1/2 clinical trial of gene therapy ABO-102, which is designed to target the severe progressive disease Mucopolysaccharidosis type IIIA (MPS IIIA). The trial is being conducted in Spain and being managed by a local subsidiary established by Abeona to manage its European development programs.

Studies to date have confirmed that ABO-102 reaches the target tissues successfully following a single intravenous injection of an AAV vector carrying the corrective gene copy. The global trial assessing ABO-102 is also enrolling in Australia and the USA, with nine patients having completed dosing in these locations to date.

Juan Ruiz, CMO of Abeona, said of this latest news:

"We are pleased to initiate enrollment at our Spain clinical site for ABO-102. We remain encouraged by the improvements observed in clinically relevant biomarkers post-dosing of the gene therapy in the patients in Cohort 3 and the ongoing safety profile ABO-102 demonstrates. Developing a local company presence in Spain allows us to exercise closer supervision and further advance Abeona's gene therapy programs in Europe, as well as advance our relationships with the patient community. We are grateful to the many patient foundations and parents who have supported the research needed to advance a potential treatment for this devastating unmet medical need. We are also proud to collaborate with one of the leading clinical centers in Spain dealing with MPS IIIA patients."



LICENSING AGREEMENTS & COLLABORATIONS



NOVARTIS LEVERAGES HOMOLOGY'S AAV-MEDIATED GENE EDITING TECH

Novartis has licensed rights to the use of Homology's gene editing technology in a new deal between the Swiss giant and the company that it backed in a series B round earlier this year.

Novartis plans to use the technology – a novel way of Adeno-associated virus (AAV) vector-mediated gene editing by directed homologous recombination (AMEnDR) – to develop candidates for undisclosed ophthalmic and hemoglobinopathy diseases. Homology's AAV vectors have the capacity to initiate homologous recombination by which DNA letters can be changed via a more efficient and naturally occurring process than other existing vectors.

Whilst the details of the deal have not been released, Homology is confirmed to receive an upfront payment, equity investment, and cash for development programmes.

The company will also share US profits from the *in vivo* hemoglobinopathy with Novartis, and may be entitled to biobucks from eventual sales.

Lloyd Klickstein, head of translational medicines, new indications discovery unit at the Novartis Institutes for Biomedical Research, commented,

"With this collaboration, Novartis is adding another emerging technology to our cell and gene therapy toolbox. We believe Homology's technology has great potential for development of new therapies. These are early days in the exploration of genome editing technologies for therapeutic use. It's too early in our collaboration with Homology to discuss timelines, but we are acutely aware of the urgent needs of our patients and our hope is to develop these technologies rapidly to bring definitive new therapies to the clinic."



SYNPROMICS & UCL TO COLLABORATE ON GENE THERAPY FOR PARKINSON'S

Synpromics is to collaborate with University College London (UCL) to develop a gene therapy for Parkinson's disease. The partnership will focus on synthesizing central nervous system gene promoters, which will then be used by researchers at UCL to advance a gene therapy approach for the targeting of Young Onset Parkinson's. The work is expected to span 2 years with an equal contribution from both collaborators.

Synpromics CSO Dr Michael Roberts commented,

"Tightly controlling the therapeutic gene is an essential element in the development of any successful gene therapy and Synpromics' technology offers the best means to achieve that control. This collaboration will allow the company to develop a gene therapy approach for a largely unmet clinical need, where tight gene control is an absolute requirement. It also gives us the opportunity to work with UCL, one of the few world-leading institutions actively developing novel gene-based therapies."



EXOSOME DEVELOPERS CODIAK RAISE \$76.5 MILLION IN SERIES C ROUND

Codiak Biosciences, a biotech founded in 2015, has raised \$76.5 million in a round of Series C funding. This latest windfall will allow the company to take their lead candidate to clinical trialling.

Originally backed by \$31 million of venture funding, Codiak is developing exosomes as an alternative platform for the introduction of macromolecules and other nucleic acids into cells; allowing these to bypass immune responses and mechanisms.

Among others, previous investors Arch Venture Partners and

Flagship Ventures returned for this latest round. These were joined by new investors including the Qatar Investment Authority who has previously invested in FlipKart and Uber.

Codiak's leadership team is headed by Doug Williams, previously of Biogen. He commented,

"Investors are clearly seeing the versatility of exosomes as a therapeutic platform that has broad utility and the capacity to address currently undruggable targets, offering multiple paths to clinical and commercial success."



ONES TO WATCH

Codiak, which is developing a therapeutic platform using exosomes, successfully raised \$77 million to progress its lead candidate into the clinic. The company is backed by world-

class investors, including Flagship and Arch. For years the biotech community has discussed the possibility of leveraging exosomes for delivery of therapeutic payloads, but there have been setbacks in our understanding of how exosomes function in the body and also having access to a manufacturing platform that produces a consistent and quality product. Codiak has pushed through and is now on the cusp of generating clinical data that could validate exosomes as a therapeutic modality.

– Mark Curtis



TYPE 1 DIABETES BIOTECH SEMA RAISES \$114 MILLION IN SERIES B ROUND

Novartis backed biotech Sema has raised \$114 million in a Series B round of funding for the

development of a potentially curative treatment for Type 1 diabetes. It is expected that this latest round

will see the company through clinical proof of concept, as well as funding exploration into further regenerative options.

Sema's work centers around the creation of pancreatic beta cells from undifferentiated pluripotent stem cells. Successful administration of the cells to a patient would potentially initiate insulin production, but this requires efficacious delivery devices for the cells, as well as the bypassing of the immune system. Since starting work on the concept in 2014, the company is now approaching

preparedness for testing the cells and their delivery in human trials.

The round was co-led by Eight Roads Ventures and Cowen Healthcare Investments with contributions from JDRF T1D Fund, MPM Capital, F-Prime Capital Partners, ARCH Venture Partners and ORI Healthcare Fund among others. Notably the round also attracted backing from Novartis and Medtronic who own devices that would be competitors in the case of Sema's successful commercialization of their concept.



EXPERT PICK

CLOSE TO CLINICAL EVALUATION OF CT FOR DIABETES

Semma has raised another big tranche of money (\$114 million) to bring its PSC-derived beta cells into the clinical for treatment of Type 1 diabetes. Cell therapy treatment of diabetes is no small feat. First you have to produce functioning beta cells, and do so in a way that is commercially feasible, and then design a medical device to house the cells that isolates them from the host's immune system. Semma has risen to the challenge with a multi-faceted technology that includes PSC-derived beta cells, manufactured in a 3D setting, and then seeded into a medical device that can be transplanted to deliver therapeutic insulin. Developing this type of technology burns cash quickly. Fortunately for Semma this financing gives them plenty of funding to deploy for generating clinical data.
– Mark Curtis



EXONICS THERAPEUTICS SECURES \$40 MILLION OF SERIES A FINANCING

The venture capital firm The Column Group (TCG) has backed biotech company Exonics Therapeutics with \$40 million of Series A financing. The funds will facilitate the advancement of the company's focal Duchenne muscular dystrophy

program. Additionally TCG's managing partner and principal – David Goeddel and JJ Kang – will be joining the Exonics board of directors.

Exonics' work looks at leveraging and developing SingleCut CRISPR technology to correct the mutations

that underlie certain neuromuscular diseases. The company is presently generating data to support the advancement of a gene editing approach to treating Duchenne. Pre-clinical murine data has suggested that the therapy can identify and repair the exon mutations, which prevent dystrophin from being produced in Duchenne patients.

Exonics CEO John Ripple stated, "This funding from a leading healthcare venture capital firm further validates the potential for

Exonics' novel gene editing technology to help correct many of the mutations that cause Duchenne and other neuromuscular diseases. We look forward to working with TCG to translate our science into a meaningful treatment for the many Duchenne patients and their families. We're grateful to Cure Duchenne Ventures for its support in founding the company and providing the seed financing, which has enabled Exonics to establish a strong scientific and corporate foundation to build upon."



JULIAN ADAMS NAMED AS NEW GAMIDA CELL CEO

Israeli biotech Gamida Cell has announced the move of current chair Julian Adams to the post of CEO. Dr Adams will be moving to the company from his current position as Chief Scientific Officer at Clal Biotech.

The company is currently undergoing Phase 3 trialing of its lead candidate – an umbilical cord blood-based alternative for bone marrow transplant patients who are unable to identify a suitable donor. The therapy – NiCord – has

received both breakthrough and orphan drug designation statuses. The company hopes to expand its operations in the US, which it envisions as NiCord's first market. Julian Adams' role will be integral in leading this expansion whilst the company's former CEO Yael Margolin will focus on Israel-based efforts from his role as company president.

Julian Adams brings an extensive history of work in the biotech field to Gamida Cell, having held roles at Millennium Pharmaceuticals, Infinity Pharma,

Boehringer Ingelheim, LeukoSite and ProScript.

Yael Margolin commented, "Julian is one of the most respected leaders in the biotechnology industry and has successfully led the global development and registration of multiple clinical programs. This is a dynamic time at Gamida Cell and as we advance the pipeline including our lead candidate, NiCord, we are excited to have Julian join us and support our objectives of expanding Gamida Cell's global presence in the US market."

IAN CLARK APPOINTED TO AVROBIO'S BOARD OF DIRECTORS

AvroBio's Board of Directors will be joined by ex-Genentech CEO Ian Clark, effective immediately. Clark has extensive experience in the biopharmaceutical sector and currently sits on the board of Agios Pharmaceuticals, Corvus Pharmaceuticals, and Shire. He has extensive commercial operations experience having worked

for Novartis, Roche and Genentech across the UK, Canada and USA.

AvroBio CEO Geoff Mackay commented, "Ian brings decades of experience leading some of our industry's most innovative companies to AVROBIO. His breadth of knowledge and strategic insight will be invaluable to the Company

as we continue to focus on rapid expansion of our portfolio of gene therapies to treat rare diseases. We are thrilled to welcome him to the AVROBIO team and we look forward to his contributions."

Ian Clark holds a BSc in biological sciences and an honorary doctorate, both from Southampton University.