

# 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 majority of the news around gene therapy this month has related to financing and the question of whether the IPO window is still open in the USA? Wave and Voyager got their IPOs away, with Wave achieving the share price they wanted, whilst Voyager had to cut back a bit. Unfortunately GenSight Biologics from Paris, has pulled its IPO in New York. Getting an IPO away at the moment looks difficult but only time will tell and it will be interesting to see what happens in the New Year.



**GENE THERAPY**  
**Alan Boyd**  
CEO, Boyds, UK



**CELL THERAPY**  
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**CELL THERAPY:** Japan has shown an insatiable thirst for all things regenerative medicine. This was compounded by recent revisions, in November 2014, to the Pharmaceutical Affairs Law that introduced a conditional approval pathway for regenerative medicine products that allows for their development and marketing in only a few years. While the Japanese pharmaceutical market is one of the largest in the world, the country has lagged its peers in the commercialization of regenerative medicine products by a significant margin. Two notable regenerative medicine acquisitions were posted this year by Japanese companies; the first was Fujifilm's acquisition of Cellular Dynamics International, a company founded in 2004 by stem cell biologist James Thomson

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that carved itself a niche in the manufacture of research-grade cells. The second, which came to light this past month, is Astellas' plans to acquire Ocata Therapeutics (formerly Advanced Cell Technology), a company focused on regenerative ophthalmology, for \$379 million.



### OCATA THERAPEUTICS TO BE ACQUIRED BY ASTELLAS PHARMA

Ocata Therapeutics, Inc. a biotechnology company primarily focused on the development of cell therapies addressing unmet medical needs in ophthalmology has entered into a definitive agreement with Astellas Pharma Inc.

With the boards of directors of both Astellas and Ocata having approved the agreement, the acquisition of Ocata highlights Astellas's desire to establish a presence in the ophthalmology market and a leading position in cell therapy.

"We highly value Ocata's R&D capabilities, including its world-leading researchers in cell therapy," commented Yoshihiko Hatanaka, President and CEO of Astellas. "We're confident that we will turn innovative science into value for patients through the creation of new value by combining both companies' capabilities under 'One Astellas,' where Ocata will be taking a key role in Astellas' R&D in ophthalmology and cell therapy."

Paul Wotton, PhD, President and CEO, Ocata said,

"I am impressed by the vision and commitment of Astellas and believe that with their global resources behind our regenerative platform, patients suffering from debilitating diseases like AMD and SMD will soon benefit from having access to regenerative medicine."

The offer price represents a premium of 79% to Ocata's closing share price of US\$4.75 on November 6, 2015. The all-cash transaction is valued at approximately US\$379 million including the purchase of all common shares, options, warrants and other securities. - *M Jayawardena*



### IMMUNOCELLULAR THERAPEUTICS ANNOUNCES AGREEMENT WITH UNIVERSITY OF TEXAS MD ANDERSON TO ADVANCE STEM-TO-T-CELL PROGRAM

ImmunoCellular Therapeutics Ltd, has entered into a research agreement with Dr Cassian Yee at the University of Texas MD Anderson Cancer Center. Dr Yee is a leading expert in identifying and isolating cytotoxic T cells and his primary focus will be on

identifying T cells that strongly bind and kill tumor cells expressing an undisclosed target antigen. The T cell receptors (TCRs) will be sequenced and their corresponding DNA will be placed into stem cells to create preclinical therapeutic candidates for

further evaluation. This should allow for a clinical program that will utilize hematopoietic stem cells isolated from the patient and engineered in the lab before being returned to the patient with the goal of creating a population of antigen-specific killer T cells that target and kill the tumor. ImmunoCellular's Stem-to-T-cell platform technology has the potential to overcome the issue of short-lived T cell responses seen with the present forms of T cell and CAR T-cell therapies.

"The work on which Dr Yee and ImmunoCellular are collaborating is both exciting in what it represents for immuno-oncology, and potentially ground breaking, as it has not previously been accomplished on a large scale," said Steven Swanson, PhD, ImmunoCellular Senior Vice President, Research. - *M Jayawardena*



## PROGENITOR CAR CELLS

Engineering HSCs to express CARs is a novel paradigm emerging in cell-based immunotherapy that will help increase persistence of T cells in settings where duration of T cell response has been a limiting factor. ImmunoCellular Therapeutics' collaboration with the MD Anderson Cancer Research Center positions the company to bring this approach into the clinic. While ImmunoCellular will take an

autologous approach to the development of its Stem-to-T-Cell program, this approach can also be developed in an allogeneic setting. Seattle-based Nohla Therapeutics, which was recently formed to commercialize IP relating to cord blood from the Fred Hutchinson Cancer Research Center, cites progenitor cell CARs in its pipeline, but will use non-HLA-matched (universal) cord blood stem cells.



## PFIZER SNAPS UP CELLECTIS' UCART19 US RIGHTS

Hot on the heels of last week's news that their universal CAR T-cell (UCART19) therapy had been successfully used to treat a critically ill 1-year old leukemia patient at Great Ormond Street, UK, Cellectis announced today that it has granted Pfizer the US marketing rights to the treatment.

In a slight twist, the rights are actually transferred from French drug company Servier who had originally been given an option to pick up the rights to UCART19 in 2014. There was the expectation that Servier would choose to exercise its option once UCART19 had completed a phase 1 trial but it's little surprise that following the promising news

of their first patient's positive clinical response, Servier have already pulled the trigger.

That deal saw Servier pay Cellectis \$38.2 million upfront, with a commitment of up to \$300 million in milestone payments for the global rights to UCART19. With Pfizer now securing US rights, for an undisclosed amount, the two pharma companies will share the costs of moving the therapy through clinical trials.

The move by Pfizer is further indication of their drive and desire to catch up with some of their Big Pharma competitors who were much quicker off the mark in establishing a strong base in the burgeoning cancer immunotherapy field.



## INTERIM TRIAL DATA FROM STEMCELLS, INC. SHOWS MOTOR IMPROVEMENT IN PATIENTS WITH CERVICAL SPINAL CORD INJURY

One of the industry leaders in the research and development of cell-based therapeutics for the treatment of CNS disorders StemCells, Inc. have released the results for the first cohort from its ongoing Phase II Pathway™ Study in cervical spinal cord injury. The company's proprietary human neural stem cells

(HuCNS-SC cells) were transplanted into patients with traumatic injury in the cervical region of the spinal cord. Motor function assessments were carried out including dexterity tests which demonstrated improvements in both motor strength and function. The data indicate that four out of six patients from the first cohort demonstrated an improvement in motor function as measured by both a gain in strength and function.

Patients that were eligible for the study had complete loss of motor control below the level of injury. The first cohort of the Pathway Study was designed to determine the safety, preliminary signs of efficacy of cell administration into the cervical cord and to have the appropriate dose level for the second 40-patient cohort. This second cohort will be a randomized, controlled and single-blinded arm of the trial. - *M Jayawardena*

"These are the results we have been waiting to see in our spinal cord injury program. For the first time, we have seen improvements in strength and motor function. While preliminary, these results should come as really exciting news for spinal cord injury patients and their families, until now, they have had little hope for a therapy that might improve the quality of their lives."

- **Martin McGlynn**, CEO, StemCells Inc.



## KITE PHARMA INITIATES PHASE II CLINICAL STUDY OF KTE-C19 IN PATIENTS WITH RELAPSED OR REFRACTORY MANTLE CELL LYMPHOMA

Kite Pharma, Inc. has initiated a phase 2 clinical study of KTE-C19 (ZUMA-2) for the treatment of relapsed or refractory Mantle Cell Lymphoma (r/r MCL). Kite, which focuses on developing engineered autologous T cell therapy (eACT™)

products, intend to use the investigational therapy to genetically modify a patient's T cells to express a chimeric antigen receptor designed to target the CD19 antigen, a protein expressed on the cell surface of B-cell lymphomas and leukemias.

Additionally, Kite initiated a phase 2 study of KTE-C19 (ZUMA-1) in patients with refractory, aggressive non-Hodgkin's lymphoma (NHL).

"In addition to ZUMA-1 in refractory, aggressive NHL and ZUMA-2 in r/r MCL, we expect to initiate two additional pivotal KTE-C19 studies in acute lymphoblastic leukemia by the end of this year."

said Arie Belldegrun, MD, FACS, Chairman, President and Chief Executive Officer

As with Kite's Phase 2 trial with ZUMA-1 in patients with NHL, the trial for ZUMA-2 will proceed as a single arm, open-label, multi-centre study, that will be used to determine the efficacy and safety of KTE-C19 in patients with MCL. The study plans to enrol 70 subjects. - *M Jayawardena*



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## KITE RAPIDLY PROGRESSING TO COMMERCIALIZATION

With the launch of two ZUMA registration studies for KTE-C19 in November (and a third in December), Kite is on track for commercialization of its first CAR product in 2017 for NHL, mantle cell lymphoma, and ALL. As the worlds of Juno and Kite merge in leukemia and lymphoma, their ability to differentiate will likely be on the stage of cost and manufacturing. Kite is making moves to address the latter, announcing a collaboration with GE Global Research that will focus on innovation and automation in T cell manufacturing systems. At the recent CAR T Summit in Boston it was clear that CARs are only one piece of the puzzle. Combinatorial approaches with biologics, drugs, and oncolytic viruses will be needed, not only to enhance efficacy, but for cell-based immunotherapy companies to remain competitive. Kite has put in place a number of partnerships, with the likes of GE, Amgen, and bluebird bio, in order to remain a firm leader, along with Juno



## ADAPTIMMUNE INITIATES PHASE I/II TRIAL OF ITS T-CELL THERAPY LUNG CANCER

Adaptimmune Therapeutics, a leader in the use of engineered T-cell therapies to treat cancer, have initiated a phase I/II study of their affinity enhanced T-cell therapy targeting the NY-ESO-1 cancer antigen in patients with Stage IIIb or Stage IV non-small cell lung cancer (NSCLC). The development of the affinity enhanced T-cell therapy is conducted under a collaborative agreement with GlaxoSmithKline.

Patients carrying a specific allele (HLA-A\*0201, HLA-A\*0205, and/or HLA-A\*0206), whose

tumor expresses the NY-ESO-1 tumor antigen, and who meet study entry criteria will be eligible to receive a single dose of autologous genetically modified T-cells expressing affinity optimized T-cell receptors specific for NY-ESO-1.

The primary objective of this study will be to evaluate the safety and tolerability of Adaptimmune's affinity enhanced T-cell therapy targeting NY-ESO in patients carrying the HLA-A\*0201, HLA-A\*0205 and/or HLA-A\*0206 alleles with NY-ESO-1-positive advanced NSCLC. Secondary objectives include

evaluation of efficacy in these patients, measurement of persistence of genetically modified cells in the body, and evaluations of the

phenotype and functionality of genetically modified cells isolated from peripheral blood or tumor post infusion. - *M Jayawardena*

“This new study marks an important step toward further elucidating the tolerability profile and anti-cancer activity of our promising therapeutic candidate in another cancer, and towards potentially reaching our goal of offering cancer patients an efficacious alternative therapy to current treatments.”

- **Dr. Rafael Amado**, CMO, Adaptimmune



### NEW DATA ADDS UNCERTAINTY TO BLUEBIRD'S GENE THERAPY

Although Bluebird Bios share prices have soared over the course of the year, thanks to the promise that their gene therapy may represent a cure for a rare blood disease, a new set of clinical data suggests that not all patients respond to the treatment in the same way. This new information could somewhat diminish the potential of Bluebird's lead treatment.

Bluebird's therapy is used as a treatment for beta-thalassemia major which results from a defective beta-globin gene, stopping patients from producing hemoglobin, often resulting in severe anemia. The treatment, LentiGlobin BB305, was given to nine patients as a

one-time infusion to alleviate the need to depend on frequent blood transfusions. Of the nine patients, six remain free of the need for transfusions after between 6 and 18 months. The remaining three, which carry a more severe mutation of the gene did not respond as well, with two having received a single transfusion and one still entirely dependent on new blood.

The latest data set have dampened initial excitement surrounding Bluebird's gene therapy as demonstrated by a drop their shares, down by more than 20%.

Bluebird plans to enrol two more beta-thalassemia studies for BB305 with 15 patients each, following subjects for 2 years with a primary endpoint of transfusion independence. The results will inform the company's chosen regulatory paths in the US and Europe. - *M Jayawardena*

“...a new set of clinical data suggests that not all patients respond to the treatment in the same way.”



## UNIQURE DROPS PLANS TO SEEK FDA APPROVAL FOR GLYBERA

UniQure have abandoned their ambition to win FDA approval for their gene therapy, Glybera. The decision to no longer seek approval to market their \$1.2 million-per-course gene therapy in the USA came after the FDA made the request to see data from two clinical trials of the lipoprotein lipase deficiency (LPLD) therapy.

As the product has uncertain commercial prospects, with LPLD affecting 1 in a million people, uniQure won't be bringing Glybera to market in the USA. Having already gone through clinical trials and regulatory approval in Europe, the move will not harm the commercial prospects of uniQure as Glybera was the first commercially available gene therapy in history.

"We do need to face the reality that the disease that Glybera treats...is extremely rare,"

said UniQure CEO Jörn Aldag. Aldag stressed that patient identification and reimbursement are major barriers for the uptake of Glybera but should however, "not be extrapolated to other gene therapies", as this could shed a bad light on the whole sector.

As uniQure's stock has fallen by more than 40% since the publication of data from a Phase I/II trial in patients with Sanfilippo B syndrome, they now have an opportunity to rectify the situation where they will present data from a Phase I/II trial of their hemophilia B gene therapy at a JPMorgan conference.  
- *M Jayawardena*

The story from Bluebird in relation to the results that they are obtaining from their  $\beta$ -thalassemia major programme with LentiGlobin BB305 continues to emerge. In this latest release they have presented data from nine patients in total. Of these patients, six remain transfusion free whilst three of the patients have not responded well and have needed additional blood transfusions. The financial markets responded to this news with a fall in Bluebird's share price. In going into the detail about these poorly responding patients, the company have stated that they have a more severe gene mutation. Is this result surprising? Probably not, as it is unlikely that a 'one-size-fits all' solution will occur giving the variability of mutations seen in this population. I look at it from a clinical pharmacology perspective in that if you consider small molecules and their use as therapeutics, not all patients with a particular disease will all respond to a particular treatment and this is well established in clinical practice. Given the differences in specific gene mutations that we are now attempting to treat with gene therapy, the same probably applies and we are now just beginning to discover this. The important thing is that some patients are responding – the trick will be to identify those who do respond and those who do not.



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### CELLULAR BIOMEDICINE OPENS FACILITY IN CHINA FOR CART-T CELL PROCESSING

A new facility has been opened in China by Cellular Biomedicine, a biotech company that is working on chimeric antigen receptor T cells (CAR-T) as a treatment for cancer.

The company is currently developing stem cell products to treat joint and autoimmune disorders, and has in-licensed CAR-T immuno-oncology technology from the Chinese PLA General Hospital of Beijing. With operations in both China and California, Cellular Biomedicine announced the opening of a 1,400 square meter facility located in the PKUCare Industrial Park in Beijing. 800 square meters of this new facility will be equipped with four production lines capable of producing product for clinical work and commercial production.

Once opened, Cellular Biomedicine will have three GMP facilities

in China with nine independent production lines. Combined, this will give the company enough capacity to process more than 200,000 individual cell sources.

This announcement came as a number of other companies prepare to submit applications for their own CAR-T treatments to the FDA. Companies, Kite Pharma and Juno Therapeutics, which have relied on contract manufacturers are currently working on facilities in the USA that will allow them to handle clinical supply and eventually commercial production. The major challenge for drug manufacturers is making the process cost-effective, as this is what led Dendreon to file for bankruptcy resulting in their facility being purchased by Swiss drug maker, Novartis. - *M Jayawardena*



### NEW ENTERPRISE ASSOCIATES PITCHES \$35M FOR NIGHTSTARX

NightstaRx is currently seeking to add to its pipeline of projects by recruiting New Enterprise Associates to pitch in on a \$35 million funding round. The gene therapy company have had some early clinical success with their lead product, AAV.REP1.

The University of Oxford spinout seeded by the Wellcome Trust's Syncona subsidiary, is currently working on a potential one-time treatment for choroideremia, a rare inherited form of progressive

blindness that originates from a genetic defect. NightstaRx's gene therapy, AAV.REP1 made headlines when it was found to improve the vision of six patients with the disease in a Phase I study. The success of this allowed them to raise \$25 million in Series A funds.

With cash in hand, NightstaRx is licensing five more retinal programs from Oxford's tech transfer department whilst working on a Phase II trial for AAV.REP1. With plans to invest in the necessary infrastructure



to get several projects into clinical development, the hope is to build NighstaRx into a commercial-scale gene therapy company.

“Gene therapy has huge potential as a treatment for many patients who are suffering from retinitis pigmentosa and other genetic forms of blindness,” MacLaren said in a statement. “We have established an internationally renowned team around the choroideremia program and I am delighted that this additional funding will allow us to develop our other retinal gene therapy projects into real treatments for patients.” Robert McClaren, Academic Founder.

- M Jayawardena



Good news for NightstarRx this month in that NEA have joined in the latest round of funding with the Wellcome Trust, which will allow them to bring into the company more retinal programmes from Oxford and Robert MacLaren’s lab to fill their pipeline. The company have also announced that they have recruited more ophthalmology expertise into their Management Team. From all this activity, it is clear that the investors are planning great things for NightstarRx in growing it into a much larger organisation in Europe, like Spark Therapeutics has become in the USA.



## WAVE AND VOYAGER RAISE \$172M

With Wall Street opinion currently fluctuating when it comes to the biotech sector, time may be running out before the IPO window closes. Demonstrating that the 2015 biotech boom is still not through, Voyager Therapeutics and Wave Life Sciences have raised a combined total of \$172 million this month.

Voyager raised \$70 million by moving 5 million shares at \$14 each which was below its expected price range; whilst Wave raised \$102 million from around 6.4 million shares at \$16, right around its expected mid point.

The funds will provide support for Voyager’s Sanofi-partnered gene therapy for Parkinson’s disease, currently in Phase I, as well as early-stage programs for Friedreich’s ataxia, ALS, Huntington’s disease and spinal muscular atrophy.

Wave is currently developing a pipeline of nucleic acid therapies as targeted treatments for Huntington’s disease, Duchenne muscular dystrophy and inflammatory bowel disease. With all of Wave’s assets in preclinical study, the company is expected to file for new drug applications over the next 2 years.

- M Jayawardena



## GENSIGHT SCRAPS IPO PLANS

GenSight Biologics have delayed their plans to go public, marking a further downsizing in their ambitions. The company had

set out to raise \$100 million with their first filing over the summer, to fund the development of their gene therapy for rare vision-destroying

diseases. Having gradually scaled back their planned offering already this year, the company looked to be settling for a price point around

\$13–15 for each of the 4.7 million shares. It will be interesting to see what their next move will be in 2016. - *M Jayawardena*



### VERTEX SETS SIGHTS ON GENE THERAPY RNA DEALS

Vertex is looking to quash talks of a takeover by Big Biotech by focusing on expanding their pipeline into gene and RNA therapies using cash flow from their recently approved cystic fibrosis drug Orkambi.

Vertex CEO Jeff Leiden noted that biotechs developing gene therapies and RNA drugs are on his radar. Local gene therapy players: Bluebird bio, Dimension Therapeutics and Voyager Therapeutics meet their criteria, as well as RNA

specialists Alnylam Pharmaceuticals and Dicerna Pharmaceuticals.

Leiden believes that Vertex is better off through 'wheeling and dealing' their way to the status of a sustainable standalone business and not by courting a takeover bid. "There's complete alignment in the employees, the management and the board that we can create more value for patients and we can create more value for shareholders by being independent," Leiden said. - *M Jayawardena*



### AID FROM EIGER BIOPHARMA MAY HELP PUSH CELLADON BACK ONTO WALL STREET

Eiger BioPharmaceuticals have made a deal to merge with Celladon, the ailing gene therapy biotech. This deal will potentially allow Celladon to make its way back onto Wall Street and enable them to continue working on treatments for rare diseases.

The deal will allow for Eiger's shareholders to take control of Celladon. Celladon showed early promise but saw a sharp decline in their share value following the failure of their lead gene therapy product, Mydicar, to reach primary or secondary endpoints in a late-stage clinical trial. Following this disappointment, the company had no choice but to lay off most of their workforce, wind down their R&D and accept the resignation of CEO Krisztina Zsebo.

Eiger have put an initial \$6 million into the company to support their plan, with an additional \$33.5 million when the merger closes. This is expected to occur at some point in the first half of 2016.

If signed off, the combined companies will conduct business under Eiger's name and will move forward with over \$60 million in cash.

The failure of Mydicar, Celladon's gene therapy for heart failure, led to the company's downfall in April this year.

If the merger does go through, all of Celladon's directors and officers will resign and it is expected that current Eiger CEO David Cory, will lead the combined companies. - *M Jayawardena*



## RETROSENSE RAISES \$6M IN FUNDING FOR VIRAL VECTOR GENE THERAPY CANDIDATE FOR RESTORING EYESIGHT

A \$6 million Series B funding round had been raised by RetroSense Therapeutics to fund a Phase I/II study of their gene therapy for vision restoration. After having raised \$7 million from a Series A round of funding earlier this year will bring their total haul to \$13 million.

Recruitment for the trial is currently underway for the genetic eye condition, retinitis pigmentosa. As there is no other drug on the market for this eye condition, RetroSense's gene therapy candidate received the FDA's Orphan Drug Designation in 2014.

Degenerative diseases like retinitis pigmentosa and dry age-related macular degeneration result in the death of photoreceptive cells in the retina. RetroSense's candidate is designed to insert a gene into the eye that will create new photoreceptors

in retinal cells, restoring vision. The gene will be delivered in the form of a viral vector, delivered into the eye as a one-time injection.

New investors of the funding round include: Venture Capital companies RBA Capital, ExSight Capital, and strategic backer Santen Pharmaceutical of Japan. Existing investors include BlueWater Angels.

*"The follow-on participation from Series A investors, combined with new institutional investors in the Series B financing, demonstrates the great enthusiasm for RetroSense Therapeutics' promise in ocular gene therapy,"*

said RetroSense CEO Sean Ainsworth. - *M Jayawardena*



## ROBERT AZELBY APPOINTED AS CHIEF COMMERCIAL OFFICER JUNO THERAPEUTICS

Juno Therapeutics has appointed Robert Azelby as Executive Vice President, Chief Commercial Officer. Prior to joining Juno, Mr Azelby was at Amgen, where he was Vice President and General Manager of Amgen's Oncology Business Unit.

"Bob is a tremendous leader who will build a world-class commercial

team at Juno," said Hans Bishop, Juno's Chief Executive Officer and President. "His experience in growing an impressive oncology business, including planning commercial strategy and overseeing multiple launches, will play a critical role in Juno's next phase of growth."- *M Jayawardena*



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