An industry update: what's new in the field of therapeutic delivery?

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Industry update August 2017

This issue's update gives a snapshot of the news from the field of therapeutic delivery in August 2017. The news this month featured important developments in the field of stem cell based therapy. The biggest story was the US FDA's approval of Novartis' Kymriah[®] (tisagenlecleucel) for refractory or relapsed B-cell precursor acute lymphoblastic leukemia in children and young adults. On the business front, both CSL Behring and Gilead acquired stem cell based assets through their takeover of Calimmune and Kite Pharma respectively, with Gilead forking out nearly \$12 billion for Kite due to its lead candidate, axicabtagene ciloleucel, being in the fast lane for the FDA and EMA approval. The news is, as usual, sourced from press releases and company websites.

Mergers & acquisitions

BMS to buy IFM for \$2.3 billion

The month started with Bristol Myers Squibb (BMS) (NY, USA) announcing that it had signed a deal to purchase IFM Therapeutics, Inc. (IFM) (MA, USA) [1]. The 2-year-old Boston Company's research is focused on developing therapies that target the patient's innate immunity to treat cancers, autoimmunity and inflammatory diseases [2]. It has both STING (stimulator of interferon genes) and NLRP3 agonists in its preclinical portfolio aimed at activating the immune system to attack tumor cells in noninflamed tissues.

The takeover will result in IFM initially receiving \$300 million with the possibility to gain up to \$1.01 billion for both the first STING and NLRP3 agonists developed, if certain milestones are successfully achieved. IFM is also eligible for additional milestone payments relating to further products arising from these two research programs. The acquisition of IFM's preclinical programs expands and adds to BMS' existing immunotherapeutic portfolio.

The acquisition will result in a new entity, IFM Therapeutics LLC, based in IFM's existing facilities, which will carry out work on its other research programs including an NLRP3 antagonist program against inflammatory diseases and fibrosis. BMS may also gain rights to this program at closing including first right of refusal in return for an additional payment and investment in the future.

CSL Behring to purchase Calimmune & its stem cell gene therapy assets

On 28 August CSL Behring Ltd. (Melbourne, Australia) made public its plan to expand its research base to gene and stem cell therapies by acquiring Calimmune, Inc. (CA, USA) for \$91 million [3]. The transaction, which is expected to close within 2 weeks, also foresees payment of up to \$325 million over the next 8 years dependent on the achievement of performance based milestones.

The privately owned Calimmune is developing *ex vivo* gene therapies for hematologic diseases such as sickle cell disease and β -thalassemia using its proprietary technologies, Select+TM and CytegrityTM [4]. These therapies involve harvesting hematopoietic CD34⁺ stem cells and CD4⁺ T-cells from an individual's own blood, treating these cells with the therapeutic vector, expanding, freezing and testing the selected cells prior to release and administration of the modified cells to the same patient. The patient undergoes a low dose conditioning regimen in an outpatient setting prior to cell administration to improve the chance of engraftment of the cells.

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Select+ is a technology, which facilitates the selection of genetically modified cells *in vivo* by modifying the cells to provide 6-thioguanine resistance. This technology improves the efficiency of transfected cell engraftment and removes the need for harsh conditioning regimens and high dose chemotherapy to ensure successful gene therapy. Cytegrity is a technology that enables the scalable GMP production of the lentiviral vectors used to deliver the gene therapy to 250 litres and beyond.

Through the acquisition, CSL Behring gains these technologies and Calimmune's CAL-H (a hematopoietic stem cell gene therapy under preclinical investigation for sickle cell disease and β -thalassemia), which slots into its own portfolio of treatments for hematological conditions. The deal is also in accordance with CSL Behring's strategy to bring therapies for rare and serious diseases to market, while Calimmune's technologies and pipeline both complements the Australian company's existing expertise in protein-based drugs [5] and extends it into the field of gene and stem cell based pharmaceuticals.

Gilead buys Kite Pharma for \$11.9 billion

CSL Behring was not the only company announcing the purchase of cell therapy assets on 28 August 2017. On the same day Gilead Sciences, Inc. (CA, USA) and Kite Pharma, Inc. (CA, USA) made public that they had signed an agreement that will see Gilead purchase Kite for \$180.00 per share in cash [6]. Kite is developing chimeric antigen receptor (CAR) and T cell receptor engineered cell therapies for cancer [7]. The transaction, which values Kite at approximately \$11.9 billion, reflects the fact that the firm's lead candidate, axicabtagene ciloleucel (axi-cel), is undergoing Priority Review by the FDA and Expedited Review in the EU by the EMA for the treatment of refractory aggressive non-Hodgkin lymphoma. It is expected that it will be approved in November 2017 by the FDA and in 2018 in Europe, based on the impressive response rate after one infusion in patients for which all other treatments had failed (39% complete response after a median of 8.7 months follow-up). Kite is currently testing axi-cel in a number of clinical trials to extend the patient population for which it is indicated and also has a pipeline of other clinical candidates under investigation for the treatment of blood cancers and solid tumors. In order to complete the clinical trials quickly and prepare for commercial launch, it has established manufacturing facilities and infrastructure in the USA to manufacture cell therapies within 14 days on a commercial basis. This ability goes a significant way to mitigating one of the key issues with cell-based therapies: a long lead time.

With this acquisition, Gilead hopes to repeat the financial and clinical success of Sovaldi[®] (their treatment for Hepatitis C), which they acquired as part of their purchase of Pharmasset in 2011 for \$11 billion but which went on to have sales of \$12 billion in its first year.

Funding

Celularity, Inc. to harness potential of placental stem cells for new therapies

Celularity, Inc. (NJ, USA), a newly formed biotechnology company, announced on 21 August that it had completed Series A financing [8] through contributions from Sorrento Therapeutics, Inc. (CA, USA) [9], United Therapeutics Corporation (MD, USA) [10] and Human Longevity, Inc. (CA, USA) [11] plus other investors. Celularity plans to exploit its postpartum placental stem cell and tissue platform to discover new treatments for cancer and also chronic and degenerative conditions such as Crohn's disease, diabetic peripheral neuropathy and wound care.

The company was set-up by Robert Hariri, who previously was a CEO at Celgene Cellular Therapeutics and is an expert in human placenta-derived cellular therapeutics and biomaterials. The company's assets include several clinical candidates and a preclinical pipeline in the field of immuno-oncology and regenerative medicine, its own allogeneic immunotherapy platform, over 200 patents and patent applications and two commercial stage products: Biovance[®] and Interfyl[®] (extracellular matrices used in wound care and orthopedics).

Licensing & collaborations

Mundipharma & CellAct collaborate to develop CAP7.1, a prodrug of etoposide

In early August Mundipharma International Ltd. (Cambridge, UK) and CellAct Pharma GmbH (Dortmund, Germany) signed a deal that will pave the way for the global development and commercialization of CAP7.1, a prodrug of the anticancer, etoposide [12]. Cap7.1 is converted to its active form by enzymes in the gut whose activity is higher in cancer cells compared with normal cells. The prodrug approach therefore has the potential to reduce the risk of side effects as the drug is mainly released within the target cells and allows higher levels of active to be dosed. The drug, which was originally invented by Charité – Universitätsmedizin (Berlin, Germany), is being developed for biliary tract tumors, a group of cancers with no second-line treatment options, and has an orphan

drug designation. This biliary tract cancer is increasing and is thought to result in approximately 140,000 deaths globally per year. CAP7.1 showed significant improvements in 1 year survival rates in Phase II studies compared with current treatments but requires to be reformulated for Phase III to allow scale-up. The clinical development will be carried out by one of Mundipharma's partner companies, Mundipharma EDO GmbH (Basel, Switzerland), which specializes in oncology drugs.

Mundipharma obtained the world-wide development, commercialization and manufacturing rights to CAP7.1 for \$250 million (upfront payments and milestones) plus undisclosed sales-related milestones and tiered royalties on sales.

Evotec spinout Topas in multi-year deal with Lilly

In August, Topas Therapeutics GmbH (Hamburg, Germany), a company specializing in developing therapies to induce or restore immune tolerance, made public that it will collaborate with Eli Lilly and Company (IN, USA) to discover drug candidates capable of inducing antigen-specific tolerance in a multi-year research agreement [13]. The research collaboration, which will initially focus on external antigens associated with promoting inflammation and/or autoimmune disease, will exploit Topas' proprietary technology for immune tolerance induction [14]. This technology has applications in the treatment of autoimmune disease, allergy and in the development of anti-drug antibodies. It involves conjugating disease relevant peptide antigens to polymer-coated superparamagnetic iron oxide nanoparticles. These nanoparticles are phagocytosed by liver sinusoidal endothelial cells in a similar manner to blood-borne antigens. These cells then present them to T cells under tolerogenic conditions. Liver sinusoidal endothelial cells are capable of promoting tolerogenic conditions due to their ability to activate latent TGF- β (an important anti-inflammatory mediator) on their surface and through induction of anti-inflammatory regulatory T cells (T_{regs}), which play a key role in antigens being recognized as self by the immune system. The company currently has two candidates that are planned to enter clinical testing in 2018, one for multiple sclerosis and the other for an orphan disease.

The agreement makes Topas responsible for carrying out the preclinical proof-of-principle studies required to identify potential drug candidates with the support of Eli Lilly. The US firm has an option to license in and further develop all candidates generated as part of the collaboration. For access to its technology and its work, Topas will receive R&D funding and be financially rewarded for the success of compounds in-licensed by Lilly. However, further financial details have not been disclosed.

Astra Zeneca signs up with Ethris for mRNA in respiratory disease

On 23 August it was announced that Astra Zeneca (London, UK) and its global biologics division, Medimmune (MD, USA) have entered into a 5-year strategic research collaboration to investigate the potential of Ethris GmbH's (Munich, Germany) proprietary SNIM[®] RNA technology to develop novel stabilized nonimmunogenic modified RNA medicines for the treatment of respiratory conditions such as asthma, chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis [15]. The Ethris SNIM RNA technology overcomes the two challenges of mRNA delivery namely, immune system activation and stability *in vivo* [16]. The German company also possesses proprietary delivery systems for delivery of mRNA into the cell.

In the course of the collaboration Ethris will receive an initial €25 million plus research funding. The agreement also foresees Ethris receiving future research and development milestones, including sales-related royalties upon commercialization with AstraZeneca and MedImmune having the opportunity to obtain an exclusive global license for each target within the collaboration.

Caprion Biosciences & the FNIH Biomarkers Consortium partnership aims to improve monitoring in early Alzheimer's disease

On 23 August it was announced that the contract research laboratory Caprion Biosciences, Inc. (Montreal, Canada), which provides specialist large-scale proteomics and immune monitoring services to the pharmaceutical and biotech industries [17], will collaborate on a new study with the Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium to improve disease progression monitoring in early Alzheimer's disease [18]. The project [19] sets out to monitor progression by measuring alterations in concentrations of proteins in cerebral spinal fluid over time in healthy subjects and patients with mild cognitive impairment and Alzheimer's disease. It is hoped that this research will identify suitable biomarkers for Alzheimer's which are more applicable to early diagnosis and drug development for this condition than those currently known (A β , τ Tau, pTau).

The collaboration will build on earlier work in which 142 potential biomarkers were monitored in both patients and healthy controls [20]. The new study, as with the previous one, will exploit Caprion's targeted multiple reaction monitoring mass spectrometry-based platform to quantify large numbers of proteins in less than 0.1 ml of cerebral spinal fluid. It will concentrate on the absolute quantification of five potential biomarkers identified from the initial study in samples taken over 3 years or more from over 200 subjects participating in the Alzheimer's Disease Neuroimaging Initiative (ADNI). The changes in these biomarkers with time, together with imaging and clinical data generated from the ADNI, will be correlated to assess the proteins' suitability as biomarkers for disease progression.

In the course of this study over 140 additional protein markers will be measured. A number of these proteins are thought to be associated with Alzheimer's or other brain diseases.

Daiichi Sankyo licenses selective RET inhibitor for solid tumors to Boston Pharmaceuticals

On 28 August the Daiichi Sankyo Company Ltd. (Tokyo, Japan) and Boston Pharmaceuticals, Inc. (MA, USA) made public that they have signed a global licensing agreement for Daiichi Sankyo's ret proto-oncogene RET kinase inhibitor, DS-5010 [21]. This molecule is in preclinical development and has the potential in the treatment of non-small-cell lung, colorectal and thyroid oncology where RET rearrangements and activating mutations are common.

The deal provides Boston with global R&D, manufacturing and commercialization rights to this potent and highly selective kinase inhibitor. Under the terms of the agreement Daiichi Sankyo will work together with Boston to complete the preclinical studies necessary for an Investigational New Drug Application and enable clinical development of the compound to commence. After this, Boston will have sole responsibility for all development and manufacturing activities associated with DS-5010 and its future commercialization. Although the financial terms of the agreement were not disclosed, it is understood that they include an upfront payment and potential for clinical, regulatory and sales milestone payments in addition to global royalties on global sales.

DS-5010 is the fifth compound to be licensed in by Boston, a relatively new company (founded in late 2015) whose business model is to access molecules at a late preclinical/early clinical stage and take them through clinical proof of concept (Phase II) [22]. After this the intention is to either partner with other companies for later stages of development and commercialization or develop its own late-stage pipeline.

Milestone news

Seattle Genetics exercises its option on tisotumab vedotin for solid tumors

It was good news for Genmab A/S (Copenhagen, Denmark) at the end of August when its long-term partner, Seattle Genetics, Inc. (WA, USA), agreed to exercise its option to codevelop and commercialize tisotumab vedotin, an antibody–drug conjugate for the treatment of solid tumors [23].

The conjugate was the subject of a commercial license and collaboration agreement signed in October 2011, which allowed Seattle to exercise its option following completion of Phase I development. The compound, which has been designed using a combination of Genmab's UltiMAB[®] transgenic mouse technology [24] and Seattle Genetics' clinically validated expertise in antibody–drug conjugates [25], is currently being evaluated in Phase I/II clinical studies. The antibody portion of the conjugate targets tissue factor which is involved in signaling and angiogenesis and has the two desirable properties of high expression on the surface of a number of cancers and rapid internalization. It is bound through a cleavable linker to monomethyl auristatin E, a potent cytotoxic drug.

Tisotumab vedotin has potential in the treatment of different types of solid tumor but the selected lead indication is recurrent cervical cancer, as preliminary data from the Phase I/II trials released earlier this year indicated that tisotumab vedotin (GEN701) had both antitumor activity and a satisfactory safety profile in patients with this cancer. Genmab and Seattle will share 50:50 of all future costs and profits in connection with the codevelopment and commercialization of tisotumab vedotin. Under the terms of the agreement, Seattle is responsible for commercializing the product in USA, Canada and Mexico with these activities being carried out by Genmab in all other countries, although there is provision for co-promotion.

Product approvals

Kymriah: the first gene therapy product ever approved in the USA

The month of August ended with the FDA taking the historic step and approving the first ever gene therapy in the USA [26]. Kymriah (tisagenlecleucel) from Novartis is an adoptive T-cell immunotherapy for the treatment

of pediatric and young adults up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse. Its approval represents a major step forward towards the personalization of medicine.

There are estimated to be 3100 new cases of acute lymphoblastic leukemia in children and young adults annually in the USA, with B cells being most commonly affected. Of these around 15–20% will not respond to current treatment or relapse. Treatment with tisagenlecleucel starts with the patient's T cells being collected and a gene is inserted encoding a CAR against the tumor-specific antigen, CD19 at the manufacturing site. Following modification, expansion, testing and release they are readministered to the patient.

Tisagenlecleucel was shown to be highly effective in one multicenter clinical trial of 63 patients with the total remission rate being 83%, 3 months following administration of the genetically modified cells. However, treatment with tisagenlecleucel, like other adoptive T-cell immunotherapies, is associated with severe, sometimes life-threatening side effects. These include high fever and flu-like symptoms due to cytokine release syndrome (CRS). This syndrome is in response to the activation and proliferation of CAR-T cells. Other significant side effects include serious infections, the risk of which may be present over a longer period of time as normal B cells, which also bear the CD19 antigen, will also be killed, hypotension, kidney injury, hypoxia and neurological adverse events.

In order to ameliorate the risk of death from CRS, the FDA also approved Actemra® (tocilizumab) [27], an interleukin-6 (IL-6) receptor antagonist from Genentech (CA, USA) normally used to treat arthritis, in CAR-T-cell-induced severe or life-threatening CRS in patients of 2 years and above. One or two doses of this antibody had been previously given to patients in trials who were experiencing CRS as a result of administration of CAR-T cells. Its use was demonstrated to cause CRS to resolve within 14 days in 69% of patients and, as part of the risk evaluation and mitigation strategy (REMS), Kymriah can only be administered if tocilizumab can be administered immediately once CRS symptoms appear.

Clinical trials

Trials to start on KAF156, a novel treatment for multidrug-resistant malaria

Novartis (Basel, Switzerland) and the Medicines for Malaria Venture (MMV) (Geneva, Switzerland), a product development partnership [28], announced on 21 August 2017 that they had initiated a Phase IIb combination trial to investigate the potential of a novel imidazolopiperazine antimalarial, KAF156, to treat drug-resistant malaria [29]. The trial will start with adult malaria sufferers in Mali but will expand later to include centers in nine different countries in Africa and Asia, with teenage and pediatric patients also being enrolled. It will assess the efficacy of KAF156 in combination with a new formulation of the already approved antimalarial, lumefantrine, in multiple dosing combinations and dosing schedules of the two drugs. The study will also evaluate the feasibility of treatment using a single dose in the three different age groups.

KAF156 was shown in an earlier Phase IIa study to eradicate malaria infection rapidly and block its transmission. In this trial the compound was demonstrated to be potent at a number of stages in the parasite's lifecycle and clear infections caused by both *Plasmodium falciparum* and *Plasmodium vivax*. It is hoped that as a result of this complex trial, an effective treatment for malaria including drug-resistant forms of the disease will come one step closer.

KAF156 was discovered through the Wellcome Trust, MMV and Singapore Economic Development Board supported research in conjunction with the Novartis Institute for Tropical Diseases, the Genomics Institute of the Novartis Research Foundation, and the Swiss Tropical and Public Health Institute. Its development by Novartis is supported by the MMV both scientifically and financially in collaboration with the Bill & Melinda Gates Foundation.

Mirogabalin shows positive results in diabetic peripheral neuropathic pain

On 31 August 2017 the Daiichi Sankyo Company, Limited (Tokyo, Japan) released positive top-line results from its Phase III REDUCER study which evaluated mirogabalin in patients with diabetic peripheral neuropathic pain at various centers across Asia [30]. Mirogabalin binds to the $\alpha 2\delta-1$ (alpha-2 delta-1) subunit of calcium channels in neurons thought to be involved in pain transmission and processing. In all, 700 patients took part in the four-arm study which investigated the effect of 15 mg mirogabalin once daily, 10 mg twice daily, 15 mg twice daily and placebo on diabetic peripheral neuropathic pain. The 14-week double-blind, randomized, placebo-controlled trial was followed by a 52-week open-label extension.

The top-line results showed that oral administration of mirogabalin (10 or 15 mg twice daily) achieved the study's primary end point of a statistically significant reduction in pain compared with placebo based on the change in the weekly average daily pain score from baseline to week 14. The initial data also indicate that no significant safety issues with mirogabalin arose during the course of the study.

These results bring hope to the approximate 11–26% of diabetic patients who experience peripheral neuropathic pain, to date a poorly treated and unreported condition. Mirogabalin is also being developed for the treatment of postherpetic neuralgia and pain associated with fibromyalgia.

Patents

MilliporeSigma obtains 'Notice of Intention to Grant' from European Patent Office for CRISPR technology patent

At the beginning of the month, MilliporeSigma (MA, USA), a subsidiary of Merck KGaA, received a 'Notice of Intention to Grant' from the European Patent Office for a patent application dealing with the use of its clustered regularly interspaced short palindromic repeats (CRISPR) technology to integrate an external DNA sequence into eukaryotic chromosomes [31,32]. The patent, which will afford broad protection for the company's technology, follows the granting of a similar patent in Australia earlier in the year.

The CRISPR genomic integration technology enables the replacement of a mutation with a beneficial or functional sequence and has applications in the production of disease models, in basic research through insertion of transgenes and in the treatment of disease with gene therapy. The granting of this patent will have interesting repercussions. CRISPR technology is currently the subject of a patent dispute in USA between Emmanuelle Charpentier of the Max-Planck Institute, Berlin, Jennifer Doudna of the University of California (CA, USA) and the University of Vienna (Vienna, Austria) on one side and the Broad Institute of MIT (MA, USA) and Harvard (MA, USA) on the other. The dispute centers on whether the patents granted to Feng Zhang (of the Broad Institute), on the application of the technique to eukaryotic cells interfere with the original Charpentier and Doudna patent application, which was filed earlier. Charpentier and Doudna lost the first round of interference proceedings but the University of California is appealing. In Europe the pair were granted a broad patent including applications to human cells. However, the granting of the MilliporeSigma patent will complicate the patent landscape further [33,34].

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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