Industry Update

The latest developments in therapeutic delivery

This month's industry update covers the period 16 October–15 November 2010. A common feature of this time-frame were the number of deals involving novel technologies for actively targeted therapeutics (Wilex and Heidelberg; Algeta and Lumiphore; Boehringer Ingelheim and MacroGenics; Access Pharmaceuticals and undisclosed partner) illustrating the level of sophistication and diversity in approach that is developing in this area. Rare diseases were also a focus with GlaxoSmithKline joining forces with Fondazione Telethon and Fondazione San Raffaele to develop gene therapy for rare genetic diseases and the CHDI Foundation agreeing to provide funding for a novel silencing ribonucleic acid device combination being co-developed by Alnylam and Medtronic for the treatment of Huntington's disease. As ever, the information is mainly taken from drug-delivery websites and press releases.

BUSINESS DEVELOPMENT

Acquisitions & mergers

Wilex & Heidelberg Pharma

On 3 November, Wilex AG (Munich, Germany) announced it had agreed to acquire Heidelberg Pharma AG (Ladenburg, Germany) by way of a noncash capital increase with Heidelberg shareholders receiving shares in the new merged company [1]. The acquisition valued Heidelberg at €19.2 million and will involve the issuing of 3,200,000 new Wilex shares, excluding shareholders' subscription rights. The acquisition, which is still subject to approval by Wilex shareholders, will allow Wilex to take advantage of Heidelberg's novel conjugate platform for therapeutic antibodies to enhance its own pipeline of cancer therapeutics and diagnostics and generate revenue through outlicensing of the technology.

If the purchase is approved, Heidelberg will become a fully owned subsidiary of Wilex.

Licensing & collaboration agreements

GlaxoSmithKline, Fondazione Telethon & Fondazione San Raffaele

GlaxoSmithKline (GSK) plc (London, UK) Fondazione Telethon (Rome, Italy) and Fondazione San Raffaele (Milan, Italy) released a press statement on 18 October that they have formed a strategic alliance to research and develop treatments for rare genetic disorders [2]. These treatments will involve gene therapy on stem cells taken from the patient's own bone marrow *ex vivo*. The alliance is based on research at the San Raffaele Telethon Institute for Gene Therapy (HSR-TIGET), a joint venture formed between Fondazione Telethon and Fondazione San Raffaele in 1995.

Under the terms of the agreement, GSK will gain an exclusive license to develop and commercialize an investigational gene therapy for adenosine deaminase (ADA)-deficient severe combined immunodeficiency (SCID). This is a rare, life-threatening condition resulting from a defect in a single gene that affects approximately 350 children worldwide. Phase I/II studies have already indicated that this treatment can restore long-term immune function and protect against severe infections in children with ADA deficiency. In addition, GSK will co-develop with Fondazione Telethon and Fondazione San Raffaele, six further applications of *ex vivo* stem cell therapy, using a new gene transfer technology developed by HSR-TIGET scientists. In turn, Fondazione Telethon, one of Italy's biggest biomedical charities, will receive an upfront payment of €10 million from GSK and further payments upon successful completion of agreed development milestones.

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Licensing & collaboration agreements

Particle Sciences & SoluBest

Particle Sciences Inc. (Bethlehem, PA, USA) stated on 19 October that it had entered into a licensing and technology development agreement with SoluBest Ltd (Ness Ziona, Israel) [3]. As a result, Particle Sciences will be the exclusive US contract research provider for SoluBest's Solumer™ technology and provide Solumer formulation services and clinical trial supplies to pharmaceutical and biotechnology companies. The Solumer technology consists of drug-polymer complexes based on pharmaceutically acceptable polymers that form colloidal dispersions on contact with aqueous medium and act to improve drug solubility and bioavailability.

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Licensing & collaboration agreements

Algeta & Lumiphore

On 21 October, Algeta ASA (Oslo, Norway) a company developing targeted α -emitter radiopharmaceuticals for the treatment of cancer, made public that it had signed a technology access agreement with Lumiphore, Inc. (Richmond, CA, USA) [4]. The agreement will give Algeta exclusive access to Lumiphore's novel, patented Lumi4® chelator technology, which will be evaluated for its ability to bind the α -emitter thorium-227 and link it to tumor-targeting molecules, such as antibodies. Lumiphore's isophthalamide technology is based on a new class of chelators that form a novel cage structure around lanthanide and actinide metals (thorium is an actinide). In turn, this cage can be coupled to a range of molecules. Use of this technology is expected to result in faster, more efficient and cost-effective chelation and conjugation processes, and increased conjugate stability.

As a result of the agreement, Algeta will obtain a 12-month option to exclusively license Lumiphore's Lumi4 chelator technology for use within the field of therapeutic radiopharmaceuticals. This license would also enable Algeta to utilize this technology in companion imaging radiopharmaceuticals for determining either the suitability of patients for treatment and/or the effectiveness of treatment. Algeta will pay Lumiphore a fee on signing the option agreement and will make further payments should it exercise the option and take up the license.

Licensing & collaboration agreements

Boehringer Ingelheim & MacroGenics

Boehringer Ingelheim (Ingelheim, Germany) and MacroGenics Inc. (Rockville, MD, USA) announced on 26 October [5] that they have formed a global alliance to discover, develop and commercialize antibody-based therapeutics based on MacroGenics' Dual-Affinity Re-Targeting (DART™) platform. The alliance will explore up to ten combinations of molecular targets.

The DART technology is based on bispecific antibodies that can simultaneously target two different antigens and can be produced in both bacterial and mammalian expression systems. The two variable regions of differing epitope specificity are linked by a proprietary linker, which the company claims confers the DART molecule with superior stability, optimal heavy and light chain pairing and predictable antigen recognition. The antibodies can

also be designed with an Fc domain, to enable their binding to Fc receptors and prolong their half-life [5,6].

Under the terms of the agreement, both companies will share responsibility for discovery and certain preclinical activities. Boehringer Ingelheim will have sole responsibility for all subsequent preclinical, clinical, regulatory, commercial and manufacturing activities. MacroGenics will receive approximately US\$60 million in the first 3 years of the collaboration, including an upfront payment, annual maintenance fees, R&D funding, and near-term research-based milestones. In addition, Boehringer Ingelheim expects to make a future equity investment in MacroGenics. MacroGenics may also be eligible to receive development, regulatory and commercial milestone payments that could reach up to US\$210 million for each of the ten DART programs if full commercial success of multiple DART products is achieved. In addition, MacroGenics may receive tiered royalties on net product sales.

Licensing & collaboration agreements

Immune Design & MedImmune

On 26 October, the Immune Design Corp. (Seattle, WA, USA) announced that it had signed a license and development agreement with MedImmune (Gaithersburg, MD, USA), the global biologics unit of AstraZeneca [7]. The agreement concerns the use and commercialization of Immune Design's proprietary glucopyranosyl lipid adjuvant (GLA), and grants MedImmune exclusive worldwide rights to research, develop, use and commercialize the GLA adjuvant in vaccines for specific indications. As a result, Immune Design will benefit from payment of an upfront fee and will be eligible for up to a further US\$212 million contingent on the achieving of agreed development, regulatory and commercial milestones. In addition, the company will receive royalty payments on sales of marketed products.

Glucopyranosyl lipid adjuvant is a synthetic Toll-like receptor (TLR-4) agonist. It is designed to activate human TLR-4 receptors, induce Th1 CD4 helper cells and, hence, elicit broad humoral immunity. GLA was also shown to be safe and well-tolerated in human subjects in a Phase I clinical study in combination with Sanofi-Pasteur's influenza vaccine, Fluzone® [8].

Licensing & collaboration agreements

Access Pharmaceuticals & undisclosed partner

On 27 October, Access Pharmaceuticals Inc. (Dallas, TX, USA) released a press statement that it has signed a prelicensing feasibility

agreement with a leading biopharmaceutical company to develop an oral formulation of a prostate cancer compound using its proprietary vitamin B12-based CobOral™ technology [9]. This technology takes advantage of the fact that diseased tissue takes up certain vitamins or vitamin analogs to a greater extent than normal tissue, and involves the attachment of Cobalamin™ (a vitamin B12 analog) and several molecules of the drug to a polymer, or encapsulating the drug in nanoparticles coated with Cobalamin™ [10].

The terms of the agreement remain undisclosed. However, Access indicated that any successful formulation developed will be jointly owned and subject to a subsequent full licensing agreement.

Licensing & collaboration agreements

SurModics & Edge Therapeutics

SurModics Inc. (Eden Prairie, MN, USA) and Edge Therapeutics Inc., (Newark, NJ, USA) announced on 3 November that the companies have entered into a licensing agreement for drug-delivery technology [11].

This follows an earlier press release on 21 July that made public a feasibility collaboration between the two companies to develop a novel biodegradable, sustained-release formulation of the calcium-channel blocker, nimodipine (NimoGel™) for local brain delivery for the treatment of delayed cerebral ischemia, a complication of ruptured brain aneurysms or traumatic brain injury [12].

Under the licensing agreement, Edge will lead and fund development and commercialization of the product with SurModics, providing Edge access to certain proprietary technologies for sustained release as well as technical and manufacturing expertise. As a result, SurModics will be eligible to receive licensing fees and milestone payments if the development program results in a commercialized product. In addition, SurModics will be entitled to royalties on product sales.

Licensing & collaboration agreements

Alnylam, Medtronic & CHDI Foundation

On 3 November, Alnylam Pharmaceuticals, Inc. (Cambridge, MA, USA), Medtronic Inc. (Minneapolis, MN, USA) and the CHDI Foundation, Inc. (NY, USA) issued a statement that they had formed a collaboration to progress the development of a novel drug-device combination for the treatment of Huntington's disease [13]. The drug-device

combination, ALN-HTT, comprises a silencing RNA therapeutic targeting huntingtin, the gene responsible for Huntington's disease, which will be delivered to the CNS via an implantable infusion system.

ALN-HTT is the result of an existing collaboration between Alnylam and Medtronic. The new agreement will result in CHDI (a not-for-profit organisation dedicated to accelerating the development of therapies for Huntington's disease) funding up to 50% of the work required to file an investigational new drug (IND) application. The agreement between Alnylam and Medtronic will remain as a 50:50 partnership in the USA, with Medtronic having the right to commercialize the drug-device combination. With respect to the US market, Alnylam will receive a proportional share of the profits from the new therapy if it invests in clinical development through to product launch. In Europe, the terms are slightly different with Medtronic being solely responsible for development and commercialization, and Alnylam having the right to receive milestones and royalties.

REGULATORY NEWS

Bydureon

October did not bring good news for Amylin Pharmaceuticals, Inc. (San Diego, CA, USA) Eli Lilly and Company (Indianapolis, IN, USA) and Alkermes, Inc. (Waltham, MA, USA) with respect to their extended-release formulation of exenatide, Bydureon™. On 19 October, the companies issued a press release that the US FDA had requested a thorough QT study to study the potential of higher than therapeutic exposures to exenatide to cause adverse effects on the heart (a prolonged QT interval increases the potential for cardiac arrhythmia) [14]. In the same complete response letter, the US FDA also requested data from the DURATION-5 study (a head-to-head trial of Bydureon and the currently marketed exenatide twice-daily injection, Byetta®, in patients with Type 2 diabetes [15]) to evaluate the efficacy, and the labeling of the safety and effectiveness, of the commercial formulation of Bydureon. This is the second time the companies have received a complete response letter from the FDA for this product. The first in March 2010 concerned manufacturing processes, risk mitigation and labeling. The latest letter is a major set-back for the commercialization of the product. The companies plan to submit their reply by the end of 2011.

BEMA® fentanyl (Breakyl®)

On 20 October, BioDelivery Sciences International, Inc. (Raleigh, NC, USA) and Meda AB (Solna, Sweden) announced that fentanyl formulated in BioDelivery's BioErodible MucoAdhesive (BEMA®) oral film technology had been approved in Europe under the decentralized procedure, with Germany acting as Reference Member State [16]. As a result, national marketing authorization approvals are anticipated over the next few months in other EU states. Meda owns the exclusive global rights to commercialize this product, except in Taiwan.

BEMA fentanyl is indicated for the management of breakthrough pain in opioid-tolerant, adult patients with cancer. The product is identical to that marketed as Onsolis® (fentanyl buccal soluble film, CII) in the USA and Canada [17]. It will be commercialized under the tradename Breakyl® (fentanyl buccal film) in Europe.

Under the terms of the licensing agreement with Meda, BioDelivery will receive a milestone payment of US\$2.5 million as a result of Breakyl's first national marketing authorization, and another US\$2.5 million when the product is commercialized (expected before the end of 2011). In addition, BioDelivery is entitled to a double-digit royalty on net sales [16].

EMA pilots multistakeholder consultations in early-stage drug development

The EMA (London, UK) issued a press statement on 25 October heralding the initiation of multistakeholder consultations in early-stage drug development [18]. The purpose of this pilot scheme is to improve clarity and alignment among the stakeholders regarding what constitutes a medicine's value and the evidence required to demonstrate that value most effectively. The pilot initiative involves clinicians, health technology assessors, patient representatives, healthcare funders, regulators and drug developers from France, Germany, Italy, Sweden, the Netherlands, the UK and the EMA.

The participating companies will be able to obtain early advice regarding a medicine under development for the treatment of either breast cancer or Type 2 diabetes, with consultations planned over the next 4 months. Issues of therapeutic value will involve all participants, while those of economic value will be dealt with by health technology assessors and healthcare funders. The recommendations made will be nonbinding but the findings of this pilot scheme could influence the design of later initiatives on early consultation.

The scheme is funded by AstraZeneca, GSK and Johnson & Johnson, and it is led by Tapestry Networks (Waltham, MA, USA) a professional services company, in accordance with its principles and guidelines for public-private networks.

CLINICAL TRIALS

Pharmaxis

On 26 October at the North American Cystic Fibrosis Conference (Baltimore, MD, USA), Pharmaxis Ltd (Frenchs Forest, Australia) announced results of pooled data from its two large-scale, 6 month, Phase III trials of Bronchitol (inhaled mannitol) in cystic fibrosis patients [19]. The mannitol, which is administered via a dry powder inhaler, is thought to improve pulmonary and mucus clearance by hydrating the lungs [20].

The two studies were of similar design and involved 643 patients from 11 countries. The results showed that over a 26-week period, patients treated with Bronchitol had an average 7.3% improvement in lung function (forced expiratory volume in 1 s [FEV1]) compared with baseline ($p < 0.001$) and a highly significant improvement compared with patients in the control group ($p < 0.001$). The studies showed that the adverse events experienced in the group taking Bronchitol (7% withdrawal rate) were similar to those in the control group (4% withdrawal rate) and there was no increase in the numbers of bacteria present in the lungs. The most commonly reported adverse event related to treatment was cough.

Bronchitol has received orphan drug designation and fast track status from the FDA and orphan drug designation from the EMA. A marketing application has been submitted and is currently under review by the EMA.

Oramed

On 15 November, Oramed Pharmaceuticals Inc. (Jerusalem, Israel) presented data from a multicenter, placebo-controlled, randomized, Phase IIb, double-blind trial of its oral insulin product, ORMD-0801 at the Annual Meeting of the Diabetes Technology Society, in Bethesda, MD, USA [21]. The study involved 29 patients with Type 2 diabetes who were administered either ORMD-0801 (21 patients) or placebo for a period of 6 weeks. The oral insulin product was shown to be safe and tolerable with only two mild cases of transient hypoglycemia reported. ORMD-0801 administration resulted in a statistically significant decrease in both insulin and C-reactive protein levels. ORMD-0801 is formulated with several pharmacopoeial or

GRAS excipients that protect the protein in the gastrointestinal tract and promote its transport across the intestinal wall.

INTELLECTUAL PROPERTY

MonoSol Rx

On 9 November, MonoSol Rx (Warren, NJ, USA) released a press statement that the US Patent and Trademark Office (USPTO) had granted a patent covering the company's film products and methods of preparation [22,101]. The patent, entitled: "Method of making self-supporting therapeutic active-containing film", concerns methods for forming films containing a uniform distribution of a pharmacologically active component that can be dried at temperatures higher than the degradation temperature of the active without loss of potency [101].

Raptor

Again on 9 November, the USPTO granted Raptor Pharmaceuticals Inc. (Novato, CA, USA) a patent with the title "Receptor

associated protein (RAP) conjugates" [102]. This patent is based on the discovery that megalin ligands, such as RAP, can be used as carriers for the delivery of actives via transcytosis across the blood-brain barrier and/or to deliver agents to lysosomes within and without the CNS. The patent describes conjugates based on a RAP polypeptide linked to either a therapeutic or a diagnostic/investigational agent. Raptor is using its RAP targeting platform to develop treatments for primary liver cancer and brain disease [23].

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.

No writing assistance was utilized in the production of this manuscript.

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