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Industry Update

The month of May 2014 brought the news that AstraZeneca had rejected Pfizer's last and final offer to take over the company, while Valeant's attempts to acquire Allergan continued (both topics are covered in detail in last month's edition of *Therapeutic Delivery*). Companies that did agree to work together in May, at least in the form of licensing and collaboration agreements, included Avalanche and Regeneron (gene therapy via an adeno-associated virus-based delivery system), AADi and Celgene (in-licensing of sirolimus or rapamycin, formulated as albumin-bound nanoparticles), AntiOp and Reckitt Benckiser (nasal naloxone), Bristol-Myers Squibb and CytomX (Probody™ antibodies against immuno-oncology targets) and PolyTherics and Alpha Cancer Technologies (novel drug conjugates of alpha-fetoprotein). May also brought good news for Veloxis in the form of a positive opinion from the Committee for Medicinal Products for Human Use for its MeltDose® formulation of tacrolimus, and for RXi Pharmaceuticals which received a Notice of Allowance from the United States Patent and Trademark Office on a key patent for its self-delivering RNAi technology.

Mergers & acquisitions

Opko & Inspiro

On 22 May 2014 OPKO Health, Inc. (FL, USA) made public that it had completed its acquisition of Inspiro Medical Ltd [1] (Misgav, Israel) that it first announced on 17 April 2014 [2]. The Israeli company has developed a dry powder inhaler called Inspiromatic™. It employs an internal microcontroller and flow sensor coupled with micropump technology to disperse the drug particles at the correct velocity and enable the delivery of drugs at flow rates as low as 6 L/min [3]. The inhaler is fitted with a green or red flashing light to inform the patient if inhalation has been successful and a beeper to indicate that the dose has been delivered. The construction also includes a built-in logger that stores inhalation data allowing later downloading and review by doctors. OPKO plans to use the inhaler to administer its heparin-derived oligosaccharide candidate for the treatment of asthma and chronic obstructive pulmonary disease.

Licensing & collaborations

Regeneron & Avalanche

Regeneron Pharmaceuticals, Inc. (NY, USA) and Avalanche Biotechnologies, Inc. (CA, USA) announced on 5 May 2014 that they will collaborate to discover, develop and commercialize gene therapy vectors and proprietary molecules using Avalanche's adeno-associated virus-based drug discovery and development platform, Ocular BioFactory™ [4]. This platform consists of a novel vector screening and optimization system based on directed evolution, and which can be easily scaled using Avalanche's own baculovirus production system. With this delivery system clinically relevant expression of the therapeutic protein is achieved in 6–8 weeks and there is evidence that such levels are maintained for at least one year in humans. thus, potentially eliminating the need for frequent injections in conditions such as wet age-related macular degeneration [5]. The deal involves up to eight different targets and Regeneron will have exclusive global rights to the products it progresses

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to clinical development. However, Avalanche has the right to choose two of the targets and share in the costs and profits generated by products targeting them. The agreement will result in Avalanche receiving cash upfront and further remuneration of up to \$640 million on attaining certain development and regulatory milestones. In addition, Avalanche will be eligible for royalties on global net sales of products that result from the collaboration.

The agreement also gives Regeneron a time-limited right of first negotiation for certain rights to AVA-101, Avalanche's gene therapy product targeting vascular endothelial growth factor (VEGF). This is being currently tested in a Phase IIa clinical trial for the treatment of wet age-related macular degeneration.

AADi & Celgene

On 20 May 2014 AADi, LLC (CA, USA) issued a press release stating that it had in-licensed ABI-009 from the Celgene Corporation (NJ, USA) [6]. This is the mTOR inhibitor, sirolimus or rapamycin, formulated as albumin-bound nanoparticles (same technology as Abraxane®). The company, which is led by the inventor of Abraxane, Dr Neil Desai, plans to develop ABI-009 for oncology and cardiovascular indications. To this end it has started to enroll patients in a multicenter Phase I/II clinical trial of the product for the treatment of nonmuscle invasive bladder cancer. It also proposes to initiate studies of ABI-009 in peripheral artery disease and pulmonary arterial hypertension.

AntiOp & Reckitt Benckiser

Also in May 2014 AntiOp, Inc (KY, USA) announced that it had agreed with Reckitt Benckiser Pharmaceuticals Inc. (VA, USA) to collaborate in order to accelerate the production and global marketing of the firm's intranasal naloxone product for the rescue treatment of opioid overdose [7]. Recent statistics indicate that incorrect use or abuse of prescription opioid medicines result in around 16,500 deaths per year in the United States alone, while it is estimated that annually 800,000 emergency call-outs in the United States are the result of over-dosage or suspected over-dosage with opioids. At present the only approved naloxone formulations are for injection, although atomizers have been used by emergency workers to deliver the drug nasally. AntiOp's single-dose, disposable naloxone nasal spray combines a commercially marketed nasal spray device with a stable, concentrated naloxone solution. The product entered its final clinical trial in June this year [8].

Bristol-Myers Squibb & CytomX

Close to the end of the month Bristol-Myers Squibb (BMS; NY, USA) and CytomX Therapeutics,

Inc. (CA, USA) made public that they had signed a global research collaboration and license agreement to discover, develop and commercialize medications against immuno-oncology targets using CytomX's proprietary Probody™ Platform [9]. The platform enables the development of monoclonal antibodies that are selectively activated by proteases within the tumor microenvironment [10]. These tumor-specific proteases cleave a linker between the antibody and a masking peptide to enable its binding and, hence, activity within tumor tissue. However, within normal tissue antibody binding to healthy cells is hindered by the presence of the peptide and, hence, unwanted side-effects are minimized. Preclinical data generated to date have shown that the technology has the potential to increase the therapeutic index of well-known antibodies such as cetuximab.

In all the deal covers up to four oncology targets including the clinically validated inhibitory checkpoint inhibitor, CTLA-4. In addition, the agreement confers BMS certain rights to substitute up to two of the targets. In return for its work CytomX will receive \$50 million upfront plus research funding. CytomX is also entitled to additional preclinical payments and up to \$298 million in future development, regulatory and sales milestone payments for each collaboration target, as well as tiered mid-single-digit rising to low-double-digit royalty payments on net sales of each product resulting from the collaboration.

The BMS deal is the third that CytomX has signed in the last year. Both Pfizer and ImmunoGen have collaborations with the company for the development of Probody drug conjugates.

PolyTherics & Alpha Cancer Technologies

On 28 May 2014 PolyTherics Limited (London, UK) made public that it had signed an agreement to collaborate with Alpha Cancer Technologies Inc. (Toronto, Canada) to develop novel drug conjugates based on Alpha's recombinant alpha-fetoprotein technology (AFP) [11]. The fetoprotein delivery technology is based on AFP, a shuttle protein that binds to AFP receptors. These receptors are a characteristic of many cancer types (e.g., ovarian, lung, colon, gastric, liver, pancreatic cancers, leukemia, breast) but are rarely found on healthy tissue. The protein therefore may provide a method of specifically targeting diseased cells. ACT's lead product (ACT-901) combines AFP with paclitaxel and is in preclinical development for the treatment of ovarian tumors.

PolyTherics will exploit its proprietary ThioBridge™ technology to produce the conjugates. The ThioBridge™ technology enables site-specific conjugation of cytotoxic drugs to disulfide bonds in proteins

and antibodies with the aim of forming more stable and homogenous conjugates. No financial details of the deal were disclosed.

Product approvals

Envarsus®

Veloxis Pharmaceuticals A/S (Hørsholm, Denmark) announced in May 2014 that its once daily formulation of tacrolimus, Envarsus®, had received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) [12,13]. The product is indicated to prevent organ rejection in both kidney and liver transplant patients and is available as 0.75, 1 and 4 mg prolonged release tablets. The product is based on Veloxis Melt-Dose® technology which has been employed to improve the bioavailability, decrease dosing frequency and reduce the peak-to-trough variability of tacrolimus compared with existing immediate release formulations [14].

Envarsus may be administered to new patients immediately after transplantation or to patients already stabilized on tacrolimus. It can also be used for the treatment of organ rejection resistant to other immunosuppressant treatments. Approval was based on the results of two Phase III studies, one in stable kidney transplant patients and one in newly transplanted kidney transplant patients, together with data from a number of Phase II and I trials. The Phase III studies proved that Envarsus was not clinically inferior to the originator product, Prograf®, which is administered twice daily, while data from the earlier clinical phase studies enabled broadening of the product indication to liver transplant patients.

The company has also submitted a NDA to the US FDA and expects to obtain a response from the authority in October 2014. The product will be marketed in Europe by Chiesi Farmaceutici S.p.A (Parma, Italy).

Natesto™

On 28 May 2014 the FDA approved Natesto™ nasal gel from the Trimel Pharmaceuticals Corporation (Mississauga, Canada) [15,16]. The gel contains the male hormone, testosterone. It is indicated for replacement therapy in males over 18 years for conditions associated with a deficiency or absence of the hormone such as congenital or acquired primary hypogonadism and hypogonadotropic hypogonadism. The bioadhesive gel is administered via a specially designed metered dose pump three-times daily and results in controlled release of the drug. Each actuation of the pump delivers 5.5 mg testosterone so that the gel can be administered once in each nostril to achieve the 11 mg dose required. Approval was based on the results of a multi-center, open-label, 90-day Phase III study involving 306 men

with hypogonadism in which 90% of the men treated with Natesto three-times daily (total daily dose of 33 mg testosterone) had normal testosterone levels at the end of the study. This is the first nasal testosterone product approved in the United States. It will compete in a crowded market that already contains a variety of other formulations, for example, gels applied to the skin, subcutaneous depots, transdermal patches, intramuscular injections, oral tablets plus a buccal patch. Natesto can be rapidly self-administered with minimal risk of nonpatients being accidentally exposed to the hormone and this may give it an advantage in the market place.

Clinical trials

Asterias Biotherapeutics

On 22 May 2014 Asterias Biotherapeutics (CA, USA) presented data from a Phase I study of its stem cell product, AST-OPC1, in subjects with spinal cord injury at the American Society for Gene and Cell Therapy (ASGCT) Annual Meeting in Washington, DC, USA [17]. The trial was the first in man of a cell therapy derived from human embryonic stem cells (hESCs) and involved five patients with neurologically complete thoracic spinal cord injury. AST-OPC1 contains predominately oligodendrocyte progenitor cells (OPCs) but also neural progenitors and infrequently other cell types [18]. AST-OPC1 is thought to promote healing through manufacture of neurotrophic factors, stimulation of vascularization and induction of remyelination of denuded axons.

In the trial the patients received a dose of two million AST-OPC1 cells at the site of injury 7–14 days postinjury. They were then maintained in a state of low immunosuppression for 60 days and followed up for 2–3 years. No serious adverse effects that could be attributed to the treatment were observed immediately after dosing, during the immunosuppression phase or during the 2–3-year follow-up period. In addition, during follow-up there was some evidence of a decrease in spinal cord cavitation and spinal cord tissue deterioration echoing the findings of animal studies of AST-OPC1. In these preclinical studies AST-OPC1 administration led to remyelination of axons, improved hindlimb and forelimb locomotor function, reduced injury-related cavitation and significant preservation of myelinated axons traversing the injury site. Follow-up on the five patients from this trial will continue for a total of 15 years.

Covidien

On the same day Covidien (Dublin, Ireland) announced positive 24-month results from its ILLUMENATE trial at the EuroPCR Scientific Congress in Paris, held on 20–23 May 2014 [19]. The multicenter, single-arm

ILLUMENATE study tested the company's Stellarex™ angioplasty balloon coated with paclitaxol using EnduraCoat™ Technology in the treatment of peripheral arterial disease. The first-in-man study showed that the balloon is safe and effective over the 2-year period. The balloon employs the company's EnduraCoat™ technology, to prevent drug loss during transit and enable its controlled release at the treatment site. The trial involved 50 patients with superficial femoral and/or popliteal lesions. The arteries of these patients were first dilated with an uncoated balloon before the insertion of the Stellarex balloon. The findings of the trial showed that at 24 months primary patency (defined as the treated artery remaining open without further treatment being required or renewed blockage detected by ultrasound scanning) was 82.3%. In addition, in 87.9% of patients there was no clinically-driven target lesion revascularization. Covidien is currently carrying out large clinical trials on the Stellarex balloon.

Patents

BioLight

BioLight Israeli Life Sciences Investments Ltd (Tel Aviv, Israel), a biomedical innovation investment firm, released a press statement on 14 May 2014 that the US Patent and Trademark Office (USPTO) had issued patent number 8722739 [20,21]. This patent will help protect the proprietary formulation of latanoprost in its controlled release Eye-D® subconjunctival insert for the treatment of glaucoma. BioLight, through a subsidiary, has an option to a global exclusive license to any use of the insert technology which is owned by Novaer LLC. The patent concerns the chemical structure of the active ingredient as the latanoprost free acid arginine salt and its release from the insert plus its use in patients with glaucoma and ocular hypertension. The patent should provide protection until April 2030. The global market for glaucoma treatment is thought to be \$4 billion annually.

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RXi Pharmaceuticals

RXi Pharmaceuticals Corporation (MA, USA) made public that it had received Notice of Allowance from the USPTO on its core patent application, titled 'Reduced Size Self-Delivering RNAi Compounds' [22,23]. This patent covers the composition and methods of use of its novel, self-delivering RNAi platform (sd-rxRNA®). The sd-rxRNA technology produces lipophilically-enriched RNA.antisenseRNA antisense hybrids [24]. Each molecule consists of a single-stranded phosphorothioate region, a short duplex region and various nuclease-stabilizing and lipophilic chemical modifications. The technology aims to produce compounds that combine the good tissue distribution and cell uptake properties of anti-sense molecules with the intracellular potency of silencing RNA. It results in compounds that have high potency, target specificity, serum stability, reduced immune response activation and efficient cellular uptake and that do not require to be incorporated into a specialist vehicle in order to be delivered. This differentiates these compounds from other RNAi products in development. The first of RXi compounds, RXI-109, which designed to inhibit production of connective tissue growth factor (CTGF), is currently being tested in Phase II for its ability to reduce dermal scarring (fibrosis).

Once issued, the patent will not expire until 2029.

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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