An industry update: what is the latest news in the therapeutic delivery field?

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The present industry update covers the period 1–31 December 2017. Information was sourced primarily from scientific literature and various news websites, company press releases, regulatory and patent agencies. The most representative (not all) examples of research are herein described and they are mainly focused on metabolic diseases, cancer, blood pressure diseases, eyes diseases and, in some cases, in rare diseases. In this paper, there was a clear positive approval tendency for several companies where they offered novel therapeutic delivery candidates. Some patents related to the therapeutic field were also published during this month. Finally, the US FDA announced the availability of a draft guidance for industry for products containing nanomaterials (investigational, pre-market and post-market submissions).

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Research & development

Nanoparticles against antibiotic resistance in mucoviscidosis

Mucoviscidosis is a lung disease where the self-regulatory function of the lung is disturbed because the mucus in the lung is colonized by bacteria and then several chronic infections follow. In these patients, the lung is so significantly damaged that they often die or need to have a lung transplant. In general, the permanent treatment with antibiotics cannot completely avoid the colonization by bacteria but it can keep it in check for a longer period of time. In this case, bacteria produce some biofilms underneath the layer of mucus. Dagmar Fischer from the University of Jena (Thuringia, Germany) and Mathias Pletz developed Tobramycin PEG-coated nanoparticles in a polyester polymer [1]. Those researchers showed that the nanoparticle coating improves the impact of the antibiotic against the biofilms by a factor of 1000. Additionally, this research group established and evaluated a new model for tracking the polymeric particles in fluorescently stained biological material [2]. As well, in Pletz's research group, a new test system was developed in order to mimick the chronically infected lungs.

Nanoparticles for malaria diagnosis

Each year, the WHO has reported an estimated 429,000 malaria deaths. Tropical and subtropical regions are mostly affected by this disease and, in particular, the African continent [3]. The Institute of Tropical Medicine at the University of Tübingen, the Fraunhofer Institute for Molecular Biology and Applied Ecology, and the Fraunhofer Institute for Silicate Research became partners for the development of a new highly sensitive and reliable rapid diagnostic test to detect malaria. It is called 'NanoFRET'. In this test, the detection of the pathogen will be based on time-resolved fluorescence resonance energy transfer (TR-FRET) in combination with the antibodies and nanoparticles. This research project is planned to be completed by 2019 and, if successful, it will be adapted to other infectious diseases.

newlands
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Gene therapy for hemophilia

Hemophilia A results from mutations in the gene encoding coagulation factor VIII. The patients with severe hemophilia A are susceptible to spontaneous or provoked bleeding in joints and soft tissue, elevated risks of intracranial hemorrhage and, in some cases, early death. When bleeding occurs, many patients receive the exogenous factor VIII. However, the relatively short half-life of factor VIII implies the need of frequent infusions. Alternatively, vector-mediated gene therapy has been successful in the long-term correction of underlying deficiencies in several genetic diseases. Clinical researchers at Barts Health NHS Trust and Queen Mary University of London had found that patients with hemophilia A showed interesting results with codon-optimized adeno-associated virus serotype 5 (AAV5), which is a vector encoding a B-domain-deleted human factor VIII (AAV5-hFVIII-SQ) [4]. Thus, nine participants were sequentially enrolled into three dose cohorts at five sites in the UK from September 2015 through to April 2016 and they received a single dose of AAV5-hFVIII-SQ into a peripheral vein, which was infused over 1 h. Over a period of 1 year in six of seven participants who received a high dose, the infusion of AAV5-hFVIII-SQ was associated with the normalization of factor VIII activity level, with a profound reduction in factor VIII use and a stabilization of hemostasis in all seven participants. No safety events were noted in this study and, consequently, no safety conclusions can be drawn.

Novel combinatorial therapy for melanoma

Cutaneous melanoma is the most deadly form of skin cancer and, unlike the majority of other cancers, the incidence rates of melanoma are still on the rise [5]. Previous research has demonstrated that a drug used for rheumatoid arthritis, leflunomide, also holds a potential therapeutic value for melanoma, particularly if it is used in combination with vemurafenib (the mutant BRAF inhibitor) [6]. In fact, recent experiments had revealed that leflunomide reduces the cell proliferation and causes cells to arrest in G1 of the cell cycle [7]. A synergistic effect in the tested cell lines was demonstrated with the combination of selumetinib. When tested *in vivo* compared with each drug alone, this combination also led to an enhanced decrease in tumor size, which demonstrates its potential for melanoma as a novel combinatorial therapy.

Endometrial cancer targeted nanoparticles

Uterine serous carcinoma is one of the most aggressive types of endometrial cancer. This type of cancer is characterized by mutations in the tumor suppressor p53. A combination of paclitaxel with antiangiogenic molecular inhibitor BIBF 1120 was loaded into nanoparticles creating a selective, targeted and lethal cancer treatment [8]. This combination specifically promoted changes in cells with the loss-of-function p53 mutation and led to a marked inhibition of tumor progression and extended survival. One of the most interesting results is that both drugs were already approved and so, the use of this technology is believed to be available soon. This new treatment could improve the survival rates for the approximately 6000 women in the USA that are diagnosed with type II endometrial cancer every year and, in addition, it represents an important step in the development of targeted cancer therapies.

Advances in multiple sclerosis

According to recent data, multiple sclerosis affects about 2.5 million people worldwide. Multiple sclerosis is a disabling autoimmune neurological condition where the immune system attacks the brain and spinal cord, leading to the loss of myelin [9]. Nowadays, there is much interest in potential therapeutics that promote remyelination like the leukemia inhibitory factor (LIF) [10]. LIF plays a key regulatory role in self-tolerant immunity and it was identified as a promyelination factor. This protein acts on stem and precursor cells being able to activate these cells and repair tissue damage. However, its metabolic characteristics and short half-time required the use of nanoparticles. Poly(lactic-co-glycolic acid)-based nanoparticles of approximately 120 nm diameter were designed with LIF. The nanoparticle surface was modulated against NG-2 chondroitin sulfate proteoglycan, expressed on oligodendrocyte precursor cells. *In vivo* studies showed that NG2-targeted LIF-NP increased the myelin repair, both at the level of increased number of myelinated axons, and increased the thickness of myelin per axon. Moreover, this study also showed that a single NP dose delivering picomolar quantities of LIF was sufficient to increase remyelination. This technology called LIFNanoRX is currently at the preclinical stage and the clinical trials may begin in 2020.

Also, in this disease, another recent research showed that the antidepressant drug, clomipramine, may also alleviate symptoms of multiple sclerosis, specifically in its progressive form, in other words, when it occurs without relapses or remissions. Researchers found that clomipramine additionally inhibits B-lymphocyte activity [11]. Clomipramine

ameliorates clinical signs in mice of chronic and acute phases with experimental autoimmune encephalomyelitis. Histologically, clomipramine preserves axonal integrity, and reduces microglial activation and inflammation.

Novel prophylactic drug against nonspecific influenza virus infections

It is estimated that during epidemics influenza virus infections cause 250,000–500,000 influenza-related deaths and 3–5 million severe illnesses worldwide [12]. The antiviral protective effects of heat-killed LAB strain *Lactobacillus casei* DK128 (DK128) on influenza viruses was investigated by Sang-Moo Kang (Georgia State University, GA, USA). By lowering viral loads and lessening weight loss, the intranasal treatment of mice with DK128 led to the protection against different subtypes of influenza viruses. The protection via heat-killed DK128 was correlated with reduced levels of proinflammatory cytokines and innate immune cells, early induction of virus specific antibodies, and an increase in alveolar macrophage cells in the airways and lungs. In this study that were protected against primary viral infection (as a result of pretreatment with heat-killed DK128), mice were shown to develop subsequent heterosubtypic immunity against infection with secondary virus. As inferred from studies that used knockout mouse models, B cells and partially CD4 T cells (but not CD8 T cells) were required for the protection against influenza virus via heat-killed DK128 pretreatment.

Niclosamide in Parkinson's disease (PD)

Parkinson's disease (PD) is a long-term degenerative disorder of the central nervous system. According to the recent data, worldwide an estimated 7–10 million people have PD. The prevalence of the disease ranges from 41 people per 100,000 in the fourth decade of life to greater than 1900 people per 100,000, among those who are 80 years and older. PINK1 mutations are causal for autosomal recessive early onset PD, and previous studies have suggested that the activation of PINK1 could be a potentially useful therapeutic strategy. Researchers at Cardiff University (Cardiff, Wales) in collaboration with the University of Dundee (Dundee, Scotland) identified an anthelmintic drug: niclosamide and its analogues. Niclosamide and its analogues were capable of activating PINK1 in cells via reversible impairment of the mitochondrial membrane potential [13]. They showed that the PINK1 pathway was active and it was detectable in primary neurons, which suggested that niclosamide and its analogs could hold promise as a future therapeutic strategy for Parkinson's and its related disorders.

Crizanlizumab in painful vaso-occlusions

Vaso-occlusive crises occur episodically when sickle-shaped red blood cells block the blood flow through the blood vessels. The blockade of P-selectin can maintain blood flow and in small blood vessels prevent the painful vaso-occlusion. Crizanlizumab (SEG101) is an investigational humanized anti-P-selectin monoclonal antibody that binds platelets in the blood vessels and P-selectin on the surface of endothelial cells, causing a blockade of the P-selectin. SUSTAIN was a randomized, double-blind, placebo-controlled, Phase II 52-week study where 67 patients received Crizanlizumab and 65 patients received the placebo [14]. Compared with placebo in most of the subpopulations investigated, the treatment with Crizanlizumab significantly delayed the time to first on-treatment in sickle cell pain crises. In those individuals taking hydroxyurea who had still experienced two to ten sickle cell pain crises, Crizanlizumab was also effective, which indicates that compared with hydroxyurea alone, P-selectin inhibition provides an additional beneficial treatment effect.

New approvals

AstraZeneca

AstraZeneca announced that the US FDA has accepted the use of Tagrisso (Osimertinib) in the first-line treatment of patients with metastatic non-small-cell lung cancer whose tumors have EGFR mutations, specifically exon 19 deletions or exon 21 (L858R) substitution mutations [15]. Osimertinib is a third-generation irreversible EGFR tyrosine kinase inhibitor (EGFR-TKIs) with clinical activity against central nervous system metastases. The acceptance was based on data from FLAURA, which was a double-blinded randomized Phase III trial with 556 patients across 29 countries. When compared with current first-line EGFR-TKIs (Erlotinib or Gefitinib), this trial showed that the progression-free survival in previously untreated patients with locally advanced or metastatic EGFRm non-small-cell lung cancer was significantly improved by Tagrisso.

Mylan

On 1 December, Ogivri (Trastuzumab-dkst), a Mylan's biosimilar version of Trastuzumab, was approved by US FDA [16]. This drug can be used in patients with HER2-positive breast and metastatic stomach cancers. Ogivri is highly similar to US.-licensed Herceptin (Roche) and there are no clinically meaningful differences between the products. Ogivri has been approved as a biosimilar and not as an interchangeable product. The submission of Ogivri included results from the Phase III, Heritage study, which demonstrated that the proposed biosimilar product, formerly known as MYL-1401O, is highly similar to Herceptin. Mylan reached an agreement with Roche concerning patents covering Herceptin. This new approval contributes to the growth of the number of biosimilar approvals.

Novo Nordisk, Inc.

The number of people with diabetes has increased from 108 million in 1980 to 422 million in 2014, according to the recent data from WHO. In addition, diabetes was the direct cause of 1.6 million deaths in 2015 and the high blood glucose was the cause of another 2.2 million deaths in 2012. Over time, diabetes increases the risk of serious health complications, including heart disease, blindness and nerve and kidney damage. The improvement of the glycemia control can reduce the risk of some of those complications. On 5 December, US FDA approved Ozempic® and it will be available as a solution for injection. The active substance of Ozempic is Semaglutide, a glucagon-like peptide 1 (GLP-1) receptor agonist. Like GLP-1, Semaglutide leads to an increase of the glucose-dependent insulin secretion and a reduction in glucagon release [17]. The benefits with Ozempic® are related to its beneficial effect on body weight.

Sunovion

WHO reports a prevalence of 251 million cases of chronic obstructive pulmonary disease in 2016. It is estimated that 3.17 million deaths were caused by the disease in 2015 (that is, 5% of all deaths globally in that year). This disease is characterized by airflow limitation and persistent respiratory symptoms that are due to lung and/or airway abnormalities, which are usually caused by significant exposure to toxic gases or particles. On 5 December, it was approved the first nebulized long-acting muscarinic antagonist, Lonhala Magnair® (Glycopyrrolate), for the treatment of chronic obstructive pulmonary disease in the USA, including chronic bronchitis and emphysema [18]. Sunovion expects Lonhala Magnair® to be available in US pharmacies in early 2018. This technology is a virtually silent, portable and a closed system nebulizer that is designed to deliver the drug in 2–3 min.

Ferrer Internacional S.A.

On 11 of December, US FDA approved XEPI™ from Ferrer International S.A. (a cream with Ozenoxacin at 1%) for impetigo treatment in patients 2 months of age and older [19]. In conjunction with scabies, the under-recognized impetigo disease comprises a major childhood dermatological condition, with, if untreated, potential lifelong consequences. In the USA, this skin disease is estimated to account for approximately 10% of skin problems observed in pediatric clinics. Xepi™ belongs to a new generation of non-fluorinated quinolones and it has the potential to offer a safe and effective option for impetigo. This approval was based on a clinical development program that included the results of two Phase III multicenter randomized, double-blind, controlled trials with 877 subjects where Xepi™ showed an excellent antibacterial activity against *S. aureus* and *S. pyogenes*.

Sanofi-Aventis US

On 11 December, Admelog® (Insulin Lispro injection) was approved by US FDA for glycemia control in pediatric and adult patients [20]. Admelog® is the first short-acting insulin approved as a 'follow-on' product submitted through the agency's 505(b)(2) pathway. It can be administered subcutaneously (either by injection or via insulin pump) or even intravenously (by infusion). Admelog® dosage depends on the administration route, the patient's metabolic needs, blood glucose monitoring results and glycemic control goal.

GlaxoSmithKline

The chronic rare disease known as Eosinophilic Granulomatosis with Polyangiitis is caused by inflammation in the walls of blood vessels that are small-to-medium sized. Generally, the global incidence is reported to be in the range of 1–4 per million, with an estimated prevalence of approximately 14–45 per million. The disease can be life threatening for some patients and 48 years is the mean age of diagnosis. The first targeted treatment

for rare eosinophil-driven disease, Nucala[®], was approved on 12 December [21]. The approval for Eosinophilic Granulomatosis with Polyangiitis is based on the results from the pivotal, 52-week, Phase III, named as MIRRA study [22]. Nucala (Mepolizumab, an IL-5 antagonist monoclonal antibody [IgG1-κ]) is produced by recombinant DNA technology in Chinese hamster ovary cells. In 2015, this drug was approved to treat a specific group of asthma, in patients aged 12 years and older.

Pfizer, Inc.

US FDA approved on 13 December a chimeric human-murine monoclonal antibody named as IXIFI[™] (Infliximab-qbtx, PF-06438179, a new biosimilar of Pfizer similar to Remicade[®] (Infliximab)) [23]. This drug is a TNF (Tumor Necrosis Factor) blocker that is indicated for Crohn's disease mainly because in adult patients with moderately to severely active Crohn's disease, with an inadequate response to conventional therapy, it led to a reduction of signs and symptoms and induction and maintenance of clinical remission. In adult patients with fistulizing Crohn's disease, it also led to a reduction in the number of draining enterocutaneous and rectovaginal fistulas and maintained fistula closure. It is also indicated for ulcerative colitis and pediatric Crohn's disease. It is indicated in cases of elimination of corticosteroid use in adult patients with moderately to severely active ulcerative colitis. Infliximab is also indicated to rheumatoid arthritis. It is indicated to inhibit the progression of structural damage, reduce signs and symptoms, and to improve physical function in patients with moderately to severely active rheumatoid arthritis, when used in combination with Methotrexate. Ankylosing spondylitis, psoriatic arthritis and plaque psoriasis are additional indications. IXIFI[™] is administered by intravenous infusion over a period of not less than 2 h.

Aerie Pharmaceuticals, Inc.

Glaucoma is a leading cause of irreversible blindness that affects more than 60 million people worldwide. Currently, the only therapeutic option demonstrated to slow damage to the optic nerve and preserve vision is the reduction of intraocular pressure. Rho-associated protein kinase inhibitors represent a new class of trabecular outflow drugs currently in clinical development. Rho-associated protein kinase is a serine/threonine kinase that serves as an important downstream effector of Rho GTPase which drives actomyosin contraction, promotes extracellular matrix production, and increases cell stiffness. Rhopressa[®] was approved on 19 December (Netarsudil, a Rho kinase inhibitor) [24]. This medicine is an ophthalmic solution being indicated for the reduction of elevated intraocular pressure in cases of open-angle glaucoma or ocular hypertension.

Spark Therapeutics, Inc.

The isomerohydrolase RPE65 is expressed in retinal pigment epithelium and it is critical for the regeneration of the visual pigment that is necessary for both cone and rod-mediated vision. Leber's congenital amaurosis and other forms of autosomal recessive retinitis pigmentosa that are associated with early onset blindness are caused by mutations in human RPE65. In the case of biallelic RPE65 mutation-associated retinal dystrophy, this mutation affects approximately 1000–2000 patients in the USA. Therefore, US FDA approved on 19 December a new gene therapy named Luxturna (Voretigene neparvovec-rzyl) [25]. Luxturna was approved for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy, which leads to vision loss and may in certain patients also cause complete blindness, and also received Orphan Drug designation. With Luxturna, a normal copy of the RPE65 gene is directly delivering to retinal cells [26]. In a clinical development program, the safety and efficacy of Luxturna were established. In this program, all participants (41 patients in total) had confirmed biallelic RPE65 mutations. Regarding their ability to complete the obstacle course at low light levels, the group of patients that received Luxturna showed a significant improvement compared with the control group.

AEterna Zentaris

AEterna Zentaris announced on 21 December that the US FDA has granted the marketing approval for Macrilen[™] (Macimorelin), an orally available ghrelin agonist, to be used in the treatment of patients with adult growth hormone deficiency [27,28]. Macrilen stimulates the secretion of growth hormone from the pituitary gland into the circulatory system. AEterna Zentaris intends to make Macrilen commercially available in the USA during the first quarter of 2018. This medicine will be available as granules in a pouch.

La Jolla Pharmaceutical Company

Giapreza® (Angiotensin II) was approved on 21 December by US FDA [29]. This medicine is an intravenous infusion to increase the blood pressure in adults with septic or other distributive shock with aim to treat the low blood pressure. Compared to those treated with placebo, a greater number of patients responded to treatment with Giapreza in a clinical trial of 321 patients with a critically low blood pressure and shock.

Roche

For Alecensa® (Alectinib), a marketing authorization has been granted by the EMA as a monotherapy for the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive, advanced non-small-cell lung cancer (NSCLC) [30]. This fact was announced by Roche on 21 December. ALK-positive NSCLC is a lung cancer commonly affecting those who have a light or nonsmoking history. Generally, every year approximately 75,000 people are diagnosed with ALK-positive NSCLC. The Phase III ALEX study showed that, compared with Crizotinib, Alecensa® significantly reduced the risk of death or the risk of the disease worsening by 53% [31]. Additionally, when compared with Crizotinib, it also reduced the risk of tumors growing in or spreading to the CNS or brain by 84%. As compared with Crizotinib, Alecensa® showed a higher efficacy and lower toxicity in primary treatment of ALK-positive NSCLC.

Examples of patents

Recently, four US patents have been granted to Vedanta Biosciences, which cover pharmaceutical compositions of therapeutics targeting inflammatory bowel disease and other immune-mediated and infectious conditions [32]. More specifically, those patents cover compositions including Clostridium bacterial strains and methods of use for therapeutic products, including consortia of bacterial strains and spore-forming fractions based on beneficial bacteria. These four patents (US 9,801,933; US 9,808,519; US 9,827,276 and US 9,833,483) are available in US Patent and Trademark Office's site.

Additionally, Lincoln Pharmaceuticals has been awarded a patent with Number 258915 by the Indian government for anti-malarial drug in India [33]. Arteether injection will be available in the market in 3 and 2 mL ampules form.

On 5 December, a US Patent 9,833,428 by Leo Laboratories Ltd (Dublin, Ireland) described ingenol angelate as a potent anticancer agent that can be stabilized by dissolving it in an aprotic solvent in the presence of an acidic buffer [34]. While leaving healthy cells unaffected, it has been found to be highly toxic for skin cancer cells via cell death by primary necrosis and rapid mitochondrial disruption.

During this month, another US Patent (9,845,352) was submitted by Axon Neuroscience (published date 19 December) and it was related to a protein-based therapy and diagnosis of τ -mediated pathology in Alzheimer's disease [35].

Other news

On the 12 December, US FDA announced in their Docket Number FDA–2017–D–0759 the availability of a draft guidance for industry entitled “Drug Products, Including Biological Products, that Contain Nanomaterials.” [36] This draft guidance will include recommendations for applicants and sponsors for the products which contain nanomaterials under investigational, pre- and post-market stages.

Ignitya, which is a biotechnology company focused on precision medicine in oncology with the aim to test, identify and treat patients who have cancers that harbor specific rare mutations, was fully acquired by Roche. Entrectinib (Ignitya's lead molecule) is an orally bioavailable CNS-active tyrosine kinase inhibitor developed for tumors harboring fusions of NTRK or ROS1 [37]. Dual NDA submissions will be supported by an ongoing pivotal Phase II clinical trial, if the trial is successful. Entrectinib targets tumors with one of two genetically defined gene rearrangements: fusions of NTRK across a broad range of solid tumors, and fusions of ROS1 in NSCLC.

Finally, Boehringer Ingelheim marks a great progress in immuno-oncology with research partnerships in 2017 that complement their research strategy [38]. A comprehensive oncology pipeline is included in this strategy, of which encompasses over ten clinical stage assets in development for various tumor and cancer types. University of California (CA, USA), Siamab Therapeutics (MA, USA), AbeXXa Biologics (TX, USA and MA, USA) are some collaborators of Boehringer Ingelheim's strategy relating to immunology and oncology.

Financial & competing interest 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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