Lemonex Inc.
www.lemonexbio.com

Small but mighty: transforming immuno-oncology and RNA medicine with the power of nanobiotechnology

Lemonex is opening a new era of safe and highly effective immunotherapy and RNA therapy with a pipeline of candidates based on DegradaBALL, its proprietary porous nanoparticle drug-delivery platform

The creative spark to invent new technologies can come from many sources. For Lemonex, Inc., based in Seoul, South Korea, the inspiration came from a natural phenomenon: the porous lava rock found on the volcanic island of Jeju, 130km off the coast of the Korean Peninsula.

Lemonex is dedicated to developing innovative technology from the laboratory bench to the patient's bedside, and creating highly effective therapies that allow for the highest quality of life. Taking a lead from nature, Lemonex has created a next-generation and potentially best-in-class porous nanoparticle (NP) drug-delivery platform called DegradaBALL that increases the efficacy and safety of a wide range of therapeutic modalities, from small interfering RNAs (siRNAs) and mRNAs to cytokines and antibodies. Building on this platform, Lemonex has established a pipeline of candidates that combine DegradaBALL technology with these modalities and which have demonstrated great promise in preclinical studies (Fig. 1).

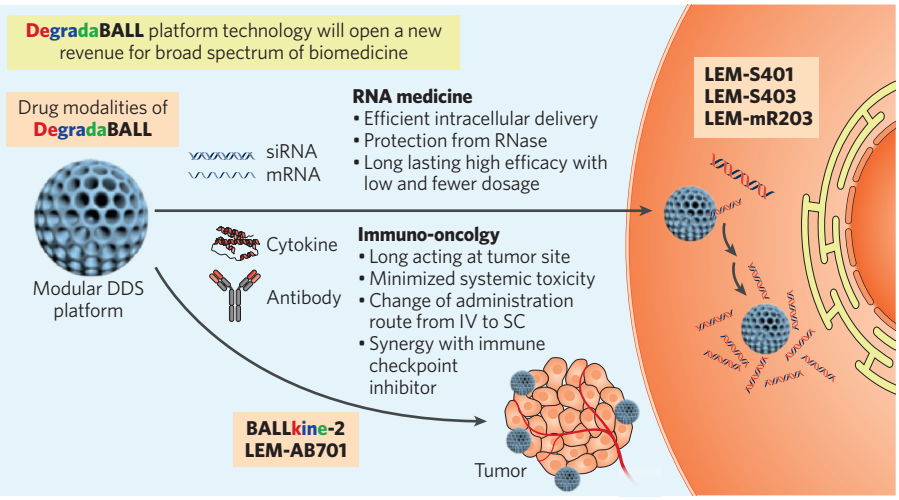

Fig. 1 | Drug modalities delivered by DegradaBALL. DegradaBALLs are able to carry these four different drug modalities: siRNA, mRNA, cytokines and antibodies. IV, intravenous; SC, subcutaneous.

The power of small

Getting therapeutics to the right tissues and cells in sufficient quantities to achieve a therapeutic effect while avoiding toxicity is an ever-present challenge for drug developers. One solution is to package therapeutic agents inside, or attach them to, NPs.

NPs enable site-specific and target-oriented delivery of medicines, and their small size means that they can easily penetrate tissue at the administration site and are readily taken up by cells through endocytosis. Yet current NP formats are far from optimal as drug-delivery vehicles.

To enable their clinical utility, Lemonex has created an NP drug-delivery platform based around porous inorganic silica nanoparticles called DegradaBALL, whose distinguishing feature lies in the way it carries a payload. Rather than attaching a given therapeutic agent to the particle surface or encapsulating it in a hollow sphere, DegradaBALLs are porous, like volcanic lava rock, and carry their payload in these pores, where it is protected from degradation and enables sustained release to dramatically improve drug half-life.

Lemonex's DegradaBALLs can be precisely manufactured, with complete control over their physical and chemical characteristics. The overall diameter and pore size of DegradaBALLs can be precisely engineered and their surface chemistry can be easily manipulated to facilitate carrying different kinds of therapeutic payloads. The manufacturing process also ensures that all DegradaBALLs in a given batch are of a uniform particle size and pore size, and therefore carry the same amount of therapeutic cargo, unlike other NP systems such as liposomes.

DegradaBALLs offer a number of advantages over existing NP delivery systems. Many such platforms have poor toxicity profiles because of the materials used to make them. DegradaBALLs, however, are biodegradable and, once inside cells, are hydrolysed to release their therapeutic cargo, with no toxic by-products. No adverse effects of DegradaBALLs were observed in safety pharmacology studies performed in mice and monkeys. DegradaBALLs did not induce any severe or irreversible changes in standard toxicity and antigenicity studies, and no immunogenicity was observed.

DegradaBALLs are compatible with a wide range of administration routes, including subcutaneous (SC), intra-tumoral (IT), peri-tumoral (PT), intramuscular (IM), intradermal (ID), intravenous (IV) and trans-arterial (TA) via microcatheter. And due to the way DegradaBALLs shield their cargo within their pores, the active pharmaceutical ingredient (API) does not necessarily need the physical or chemical modifications that other delivery systems require, which can lead to severe systemic toxicity and attenuate drug efficacy by interacting with physiological substances in vivo.

As it takes time for DegradaBALLs to dissolve completely in vivo, the API loaded inside the pores is released gradually over time—in contrast to other NP platforms like liposomes that burst once they enter the cell and release all of their contents in one go. The increased half-life and sustained release of therapeutic payload by DegradaBALLs means that they do not require frequent administration as with other NP modalities, which reduces the burden of treatment and increases patient compliance.

DegradaBALLs are also easier to store, as they are manufactured in a solid powder form and are stable at room temperature. Other NP powders aggregate and precipitate upon addition of water, and require very harsh condition for re-dispersion such as sonication and/or vortexing for many hours. Unlike other NPs, DegradaBALLs are very convenient to work with: add water, mix and shake, and they are ready for use.

The large-scale, consistent manufacturing of existing NP drug-delivery systems, in which particle size and physico-chemical properties are well controlled, is extremely difficult to establish. Lemonex, however, has developed a standardized DegradaBALL manufacturing process and built a GMP manufacturing facility, a crucial resource for

developing DegradaBALLs as a first-in-class drug-delivery vehicle. Lemonex's production steps are defined to deliver target functionality and quality of DegradaBALL in an efficient and reproducible way, and can produce ~20,000 vials of DegradaBALLs per batch. With a reliable source of DegradaBALLs, and the ability to precisely engineer their characteristics under a GMP setting, Lemonex is well placed to develop a diverse drug-development pipeline with many collaborators simultaneously, while tailoring DegradaBALLs to the specific needs of each candidate product.

Growing pipeline: LEM-S401, an siRNA therapy

The advantages of using DegradaBALLs have been demonstrated by the four candidates in Lemonex's pipeline, each of which combines DegradaBALL technology with a different drug modality: siRNA, mRNA, cytokine, and antibody.

The most advanced candidate, LEM-S401, is a DegradaBALL-siRNA being developed to treat skin fibrosis, and which has completed GLP-toxicity studies, with a phase 1 clinical trial to begin in the first quarter of 2021. Skin fibrosis, such as hypertrophic scar, cicatrix, and keloid, frequently occurs in wound or surgical resection, and current anti-fibrosis treatments are not as effective as needed. The global market of scar is estimated at about US$25 billion, and growing.

A common cause of fibrosis across diverse organs is uncontrolled overexpression of connective tissue growth factor (CTGF). LEM-S401, which can be administered ID, SC, and IM, delivers siCTGF to localised regions of tissue to inhibit CTGF expression and minimise systemic adverse events. Compared with other approaches, DegradaBALLs enhance the therapeutic efficiency of siRNA, while the siCTGF cargo—requiring no chemical modification and stored safely in DegradaBALL pores—is protected from RNase-mediated degradation in vivo, resulting in longer exposure time even with administration of lower doses (Fig. 2).

LEM-S401 dramatically down-regulates the expression of *CTGF* and downstream genes such as collagen types I and III, which are over-expressed in fibrotic tissues in vitro and in vivo. In preclinical efficacy studies, LEM-S401 effectively inhibited the formation of hypertrophic scars in wound-associated dermal fibrosis mouse models, during wound healing and recovery. LEM-S401 causes no severe or irreversible changes in standard toxicity studies, and achieves higher efficacy at much lower doses—50–1,000-fold—than comparable therapies. LEM-S401 is also a starting point for other therapies: it can easily be modified for other indications by simply changing siRNA sequences.

BALLkine-2, a cancer immunotherapy

Lemonex has also developed BALLkine-2, a DegradaBALL loaded with recombinant human interleukin-2 (rIL-2, aldesleukin), as a locally injectable cancer immunotherapy for solid tumors. High-dose, IV rIL-2 has been clinically explored as a highly potent cytokine for cancer immunotherapy, but its clinical utility has been limited by severe systemic toxicities, including vascular leak syndrome (VLS), pulmonary oedema, and hypotension, as well its short half-life in circulation and its ability to predominantly expand regulatory T (T_{reg}) cells.

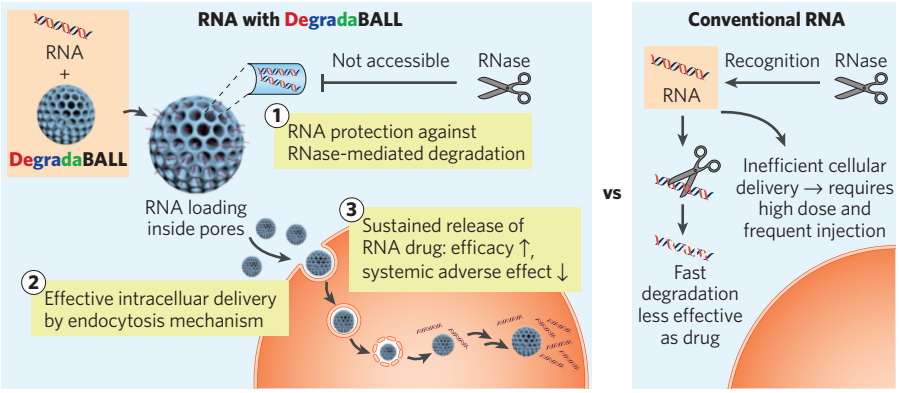

Fig. 2 | Delivery of RNA with the DegradaBALL platform. The platform enables effective intracellular delivery of RNA such as siRNA and mRNA.

Yet it would be clinically attractive to combine rIL-2 with immune checkpoint inhibitors to achieve potent antitumor responses. BALLkine-2 enables this, by locally targeting tissue with slow-release rIL-2, resulting in minimized systemic adverse effects by lowering the serum rIL-2 concentration.

SC or PT injection of BALLkine-2 forms a kind of drug depot at the injection site, which releases BALLkine-2 over time to provide direct and sustained effects in the tumor microenvironment (TME). BALLkine-2 is also efficiently taken up by dendritic cells in the TME and then distributed to secondary lymphoid organs, where it elicits a systemic antitumor immune response.

BALLkine-2 has been proven to have excellent local and systemic anti-cancer effects. In pharmacokinetic (PK) studies, cynomolgus monkeys receiving SC injection of BALLkine-2 showed much-reduced systemic exposure of rIL-2 compared with IV or SC injection of rIL-2. At the same time, in the B16F10 melanoma model BALLkine-2 led to higher intratumoral concentration of rIL-2 than IV or SC injection of rIL-2. SC-injection of BALLkine-2 also dramatically reduced pulmonary oedema and VLS in the B16F10 melanoma model, and was more effective in recruiting tumor-infiltrating lymphocytes such as $CD8^+$ T cells and activated natural killer cells.

One of the unwanted side effects of rIL-2 in anti-cancer immunotherapy is the expansion of T_{reg} populations, which suppress immune responses and maintain tolerance to antigens. BALLkine-2, even though loaded with unmodified rIL-2, does not induce expansion of T_{reg} populations, and T_{reg} levels remain significantly lower than seen with IV rIL-2.

BALLkine-2 can safely be combined with immune checkpoint inhibitors in immuno-oncology. Even better, locally injectable BALLkine-2 potentiates and synergises anti-programmed cell death protein 1-antibody (aPD-1 Ab) therapy. In a melanoma mouse model, relative tumor volume growth curves of individual mice showed that BALLkine-2 treatment with aPD-1 Ab achieved more suppression and consistent control of tumor growth than aPD-1 Ab alone, and a much higher response rate (8 of 8 mice). BALLkine-2 combined with aPD-1 Ab combination also improved overall survival rate compared with aPD-1 Ab combined with rIL-2. BALLkine-2 has shown similarly impressive therapeutic efficacy in metastatic melanoma mouse models and renal cell carcinoma models.

With highly encouraging preclinical results from tumor models and PK data obtained from non-human primates, Lemonex is planning to proceed with clinical trials of BALLkine-2. The versatility of DegradaBALL means it can easily deliver other cytokines, and Lemonex is interested in collaborating with pharmaceutical companies to develop new cytokine therapies using DegradaBALL.

LEM-AB701, a DegradaBALL-antibody, is currently in preclinical research, which shows surprisingly effective therapeutic outcome with lower and fewer doses in solid tumor models. Finally, LEM-mR203, a DegradaBALL-mRNA product, will also begin GLP-toxicology studies.

Opportunities

Lemonex welcomes discussions with potential partners who want to advance biologic therapies and contribute to a better future for patients. The opportunities of the DegradaBALL technology in enabling highly effective biotherapies are limitless.

Lemonex is interested in collaborative opportunities to further develop highly potent drug candidates that require an effective drug delivery system, perhaps to enable effective intracellular delivery of RNA drugs or to prolong the half-life of peptide/protein drugs. Lemonex also invites discussions about collaborative opportunities for non-exclusive out-licensing of the DegradaBALL platform, as well as strategic partnerships that would grant worldwide use of the technology for a licensed therapeutic.

The DegradaBALL platform also offers a powerful technology for transforming existing biologics into biobetters that can be administered at lower doses without sacrificing efficacy. Combining biologics with DegradaBALL technology provides a way of changing the administration route from conventional systemic IV infusion to convenient local SC injection. Lemonex is interested in establishing external partnerships to breathe new life into ageing products by creating a new formulation of existing drugs with new or extended applications.

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