**Development of Exosome-based therapeutics: from the bench to the clinic**

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**Introduction.** Exosomes are promising drug delivery vehicles due to their stability, low immunogenicity, and tissue-targeting properties.

**Aims**. For effective delivery, therapeutic molecules should be encapsulated freely in the lumen rather than embedded in the exosomal membrane.

**Methods**. To achieve this, our team developed EXPLOR® (EXosome engineering for Protein Loading via Optically Reversible protein interaction), an optogenetic platform that enables the loading of high-molecular-weight proteins and nucleic acids into exosomes. Using this technology, we have developed engineered exosomes with improved pharmacokinetic properties.

**Results.** Among our exosome-based therapeutics pipelines, anti-inflammatory exosomes (ILB-202) loaded with super-repressor IκB (Exo-srIκB) have been thoroughly studied for their in vitro anti-inflammatory activities and in vivo efficacy in various preclinical disease models such as sepsis, ischemia/reperfusion-induced kidney injury and inflammation-associated preterm birth. In a single-center, randomized, double-blind, placebo-controlled phase 1 trial, a single ascending intravenous dose of ILB-202 was administered to 18 healthy volunteers, and the safety, tolerability, and preliminary pharmacodynamic effects were assessed. ILB-202 was well tolerated at all dose levels with no serious or dose-limiting toxicities. Single-cell RNA sequencing revealed subtle, time-dependent modulation of NF-κB-associated pathways.

**Discussion.** These findings support the safety and immunomodulatory activity of ILB-202 and pave the way for future trials in diseases characterized by dysregulated NF-κB activation.

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