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Nanomedicine for acute lung injury

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Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) represent a heterogenous group of lung disease in critically ill patients. Despite the increased understanding of the molecular pathogenesis of ARDS, the mortality remains unacceptably high, ranging from 34% to 64%. Hence, ARDS represents an unmet medical need with an urgency to develop effective pharmacotherapies. Several promising targets that have been identified as potential therapies for ARDS have been limited because of difficulty with delivery. In recent years nanomedicine has become an attractive concept for the targeted delivery of therapeutic and diagnostic compounds to injured or inflamed organs. Nanoscale drug delivery systems have the ability to improve the pharmacokinetics and increase the biodistribution of therapeutic agents to target organs, thereby resulting in improved efficacy and reduced drug toxicity. We have developed novel long-acting biocompatible and biodegradable phospholipid micelles (size, approximately 15 nm) to inhibit triggering receptor expressed on myeloid cells 1 (TREM-1) a key effector that contributes to the pathogenesis of lung injury. Realizing short half-life of peptide drugs (minutes) hampers their clinical use, we invented micellar TREM-1 blocking peptide and glucagon-like peptide-1(7-36) amide (GLP-1) where each peptide drug is stabilized in its active form (alpha-helix) and its bioactivity is prolonged for hours in vivo. These long-acting micellar nanomedicines provide significant advancement in the treatment of experimental ALI which has the potential to be extended to treat patients with this devastating disease.

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Targeted drug and gene delivery by pulsed laser-induced photomechanical waves

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We have demonstrated highly site-selective gene transfer and transvascular drug delivery in rodents by using pulsed laser-induced pressure waves, which are called photomechanical waves (PMWs). A PMW is generated by irradiating a light-absorbing material with a nanosecond laser pulse. For gene transfer, PMWs were applied to tissue injected with plasmid DNA or siRNA, enabling efficient targeted gene transfer to various tissues in vivo. Gene therapy experiments were performed by using this method. Adhesion of grafted skin was accelerated by delivering hepatocyte growth factor plasmid DNA to the graft and recovery of motor function was enhanced by delivering siRNAs targeting the intermediate filament proteins to spinal cord injury in rats. We also found that PMWs could selectively enhance the permeability of blood vessels. An Evans blue (EB) solution was injected into the rat tail vein and a PMW(s) was applied to the skin, muscle and brain. We observed laser fluence-dependent extravasation of EB in the tissues that had been exposed to a PMW(s). Uptake of leaked EB into cells in the extravascular space was also observed in the targeted tissues, indicating the capability for site-specific transvascular drug delivery by using a PMW(s). The results for the brain indicated opening of the blood–brain barrier. Since EB molecules are strongly bound with serum albumin in blood, this method can be applied to macromolecules. The method is currently being applied to gliomas in rats to enhance the delivery efficiency of an antitumor drug.

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