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11am-12pm
PWEB 150

ABSTRACT:

Drug delivery strategies to access inflamed peripheral nerves

The acute inflammatory demyelinating polyneuropathy (AIDP) subtype of Guillain-Barré syndrome (GBS) is a debilitating autoimmune peripheral neuropathy. Current treatments, focused on nonspecific immune modulation, are often ineffective. Systemic or local delivery of several candidate therapeutics can attenuate the severity of experimental autoimmune neuritis (EAN), an established rat model of AIDP; however, advancing these approaches clinically has been limited by non-translatable dosing and administration routes. While the blood-nerve barrier (BNB) normally restricts access of circulating molecules to the endoneurium, during the acute inflammation associated with some peripheral neuropathies, including AIDP, the BNB exhibits increased permeability and enables immune cell infiltration. These pathological changes contribute to disease, but they may also offer a unique opportunity to access the otherwise restricted peripheral nerve microenvironment for therapeutic delivery. Drug-loaded polymeric nanoparticles (NPs) represent a promising strategy to leverage BNB pathology and deliver therapeutics to affected tissue while avoiding off-target toxicity. We previously showed increased BNB permeability to small molecules at EAN onset and passive accumulation of NPs (138 nm) in nerves during intermediate to peak disease stages. Our current work focuses on the development of active targeting strategies to maximize NP delivery, and one such strategy consists of rat macrophage plasma membrane vesicle coated NPs (mNPs). We isolated plasma membrane vesicles from rat alveolar macrophages using nitrogen cavitation and differential centrifugation and demonstrate retention of key adhesion proteins using western immunoblot. mNPs exhibit specificity for inflamed over quiescent primary BNB endothelial cells in vitro. Further, mNPs accumulate more readily in nerves of EAN rats compared with healthy rats, and labeled mNPs accumulate in inflamed nerves to a greater degree than free dye alone. Our results suggest that BNB permeability enables delivery of NPs to affected nerves during EAN and that macrophage membrane coating imparts further specificity to the inflamed BNB.

BIOGRAPHY:

Dr. Langert is an Assistant Professor in the Department of Pharmacology and Neuroscience at Loyola University Chicago's Stritch School of Medicine who is establishing her laboratory at the intersection of neuroscience, pharmacology, and bioengineering. She completed her undergraduate degree with majors in Neurobiology and Psychology at the University of Wisconsin- Madison and went on to obtain a Ph.D. in Neuroscience at Loyola in 2012. Her thesis focused on the effects of statins on the endothelial cells that form the blood nerve barrier. She received postdoctoral training in Biomedical Engineering at the Illinois Institute of Technology in the lab of Dr. Eric Brey. She has maintained consistent support for her research from the Department of Veterans Affairs since 2014, including pre- and postdoctoral fellowships, a five-year Career Development Award that facilitated her transition to a tenure track faculty position at Loyola, and starting this fall a four-year VA Merit award. Her lab studies targeted drug delivery to the peripheral nervous system in rat and mouse models of neuropathy that feature inflammation.

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For questions, please contact Dr. Sina Shahbazmohamadi sina@uconn.edu or Sarah Dunnack sarah.dunnack@uconn.edu