AI/ML AND VIRTUAL HUMAN PLATFORMS FOR THREAT AGENT HAZARD ASSESSMENT AND MEDICAL COUNTERMEASURE DISCOVERY AND DRUG DEVELOPMENT

Demonstrating Biological Protection Using Nanoparticle Technologies To Improve Neutrapharmecueticals Bioavailability For Cbrn:

Matthew Coleman Physical and Life Sciences Directorate, Lawrence Livermore National Laboratory, Livermore, CA, USA **Angela Evans** Physical and Life Sciences Directorate, Lawrence Livermore National Laboratory, Livermore, CA, USA **Christopher Porada** Wake Forest Institute for Regenerative Medicine, Wake Forest University School of Medicine , Winston-Salem, NC, USA **Graça Almeida-Porada** Wake Forest Institute for Regenerative Medicine, Wake Forest University School of Medicine , Winston-Salem, NC, USA **Takamitsu Kato** Department of Environmental & Radiological Health Sciences, Colorado State University, Fort Collins, CO, USA **Paul Wilson** Biological Sciences Division, Earth & Biological Sciences Directorate, Pacific Northwest National Laboratory. Richland, WA, USA

Over the last few decades there has been a ramped-up effort to identify novel biological, chemical and radiation protectors and mitigators to treat people after exposure. We have constructed a multi-faceted nanoparticle for drug loading and delivery that may enhance the application novel neutrapharmecueticals. Our nanoparticles are based on high density apolipoprotein A involved in cholesterol transport in the human body. The protein naturally forms 20 nm disc that compartmentalizes as well as solubilizes lipids, insoluble proteins, small molecules and drugs. They are highly biocompatible and represents a new recombinant technology approach for enhancing biological availability of molecules of interest. The nanoparticles are highly effective at drug solubilization and biocompatibility which may increase the efficacy of therapeutics failing to make it through the current therapuetic pipelines. To demonstrate this capability we focused on first showing curcumin, a natural polyphenol derived from the spice turmeric (Curcuma longa), which contains antioxidant, anti-inflammatory, and anti-cancer properties. However curcumin is inherently non-bioavailable due to poor water solubility and metabolic uptake. First, we successfully incorporated curcumin into “biomimetic” nanolipoprotein particles (cNLPs) consisting of a phospholipid bilayer surrounded by apolipoprotein A1 and amphipathic polymer scaffolding moieties. Our cNLP formulation improved the water solubility of curcumin over 30-fold and produced nanoparticles with ~350 µg/ml total loading capacity for downstream in vitro and in vivo applications. We found that cNLPs were well-tolerated in AG05965/MRC-5 human primary lung fibroblasts compared to cultures treated with curcumin solubilized in DMSO (curDMSO). Pre-treatment with cNLPs of quiescent G0/G1-phase MRC-5 cultures improved cell survival following 137Cs gamma ray irradiations. Using both qRT-PCR and RNASeq-based transcriptomic analyses, we show that cNLP treatments result in altered gene expression profiles that differed depending on the timing of administration (pre- or post-IR) and compared to IR-alone groups, activated key antioxidant response genes within the Nrf2 pathway, and modulated select Tp53 transcripts independent of IR exposures more effectively than curcumin dissolved in DMSO. These studies are useful for establishing “nanodiscs” as a method for improving the bioavailability of other insoluble antioxidants for administration as radioprotective or radiomitigative agents against ionizing radiation (IR) exposures. We also demonstrate that our process pipeline is amenable to solubilizing other neutrapharmecueticals of interest that may play a role in maintaining warfighter health as well as provide novel protective countermeasures to chemical and biological exposures.

This work was supported by the NASA Translational Research Institute for Space Health (TRISH) through Cooperative Agreement NNX16AO69A. This work was also funded by LLNL Directed Research Program Award 19-SI-003. Work was also performed under the auspices of the U.S. Department of Energy by Lawrence Livermore National Laboratory under contract DE-AC52-07NA27344.

This work was supported by the NASA Translational Research Institute for Space Health (TRISH) through Cooperative Agreement NNX16AO69A. This work was also funded by LLNL Directed Research Program Award 19-SI-003. Work was also performed under the auspices of the U.S. Department of Energy by Lawrence Livermore National Laboratory under contract DE-AC52-07NA27344.