COMBATTING FUTURE BIOLOGICAL THREATS – HOST-DIRECTED INTERVENTIONS TO EMERGING THREATS FOR RAPID RESPONSE

Apolipoprotein-nanodisc As A Novel Tool For Solubilization And Delivery Of Medical Countermeasures.

Matthew Coleman Lawrence Livermore National Laboratory **Steven Hoang-Phou** Lawrence Livermore National Laboratory **Vjollca Konjufca** Southern Illinois University **Abisola Abisoye-Ogunniyan** Lawrence Livermore National Laboratory **Amy Rasley** Lawrence Livermore National Laboratory **Nicholas Fischer** Lawrence Livermore National Laboratory

We have developed biocompatible nanolipoprotein particles (NLPs) that can effectively solubilize insoluble biologicals and small drug molecules. NLPs can be an ideal “programmable” platform for medical countermeasure (MCM) solubilization, stabilization, and delivery, potentially allowing for the repurposing of existing MCMs against a wider range of biological threats. We demonstrate this capability using curcumin, a natural polyphenol derived from the spice turmeric (Curcuma longa) that has antioxidant, anti-inflammatory, antimicrobial, and anti-cancer properties. The most significant obstacle in realizing curcumin’s in vivo benefits is its minimal solubility in aqueous solutions. Formulating and solubilizing curcumin in NLPs can overcome this bottleneck, thus enhancing its bioavailability and efficacy. We have demonstrated that curcumin can be solubilized in lipids and subsequently formulated into NLPs during a self-assembly process. These nanoparticles are amenable to size-exclusion chromatography for purification and lyophilization for long-term storage. Nanoparticles loaded with curcumin maintain their disc shape and solubility after resuspension in water. Using this material, we have shown that the NLP-solubilized curcumin has superior bioavailability and is non-toxic compared to solvent-solubilized curcumin. Importantly, the curcumin-NLP formulation also maintains protective antioxidant properties when tested on cells in culture. Our formulations can also significantly ameliorate gut damage in C57BL/6 mice while maintaining microbiome diversity after ionizing radiation exposure. NLP formulations should broaden the uses of curcumin and other antioxidants. The use of curcumin as a potential antibacterial therapeutic has been previously proposed but many challenges need to be addressed. First, there are limited studies on the viability of nano-formulated curcumin for oral consumption; Second, the molecular mechanisms associated with gut bacterial responses in vitro and in vivo after antioxidant delivery are poorly understood. We propose future studies as the first step toward providing evidence-based randomized investigation of the therapeutic roles of NLP-based delivery systems for rapidly developing new therapeutic host regulated countermeasures against a broad class of emerging biothreats.

This work was performed under the auspices of the U.S. Department of Energy by Lawrence Livermore National Laboratory under Contract DE-AC52 -07NA27344. Support was also provided by TRISH-NASA, under contract NNX16AO69A.