Bio: Dr. Mandana T. Manzari obtained a Bachelor of Science in Chemical and Biological Engineering at the Massachusetts Institute of Technology. She then spent one year at Eleven Biotherapeutics, where she developed protein-based therapeutics using yeast display. She then went on to conduct her Ph.D. research in Biomedical Engineering with Professor Ashutosh Chilkoti at Duke University, where she developed an interdisciplinary platform for overcoming delivery and resistance limitations of anti-cancer protein therapeutics. She is currently a postdoctoral fellow in Professor Daniel Heller's lab in the Molecular Pharmacology and Chemistry department at Memorial Sloan Kettering Cancer Center. With interests at the interface of engineering and medicine, her research goal is to bring precision delivery to precision medicine by integrating delivery technologies into the initial phases of drug development.

Title: Improving precision medicine: integrating protein engineering, drug delivery, and genomics for cancer therapy

Abstract:

Despite decades of research and significant progress in the field of cancer therapy, drug resistance, toxicity, and delivery barriers substantially limit treatment efficacy in the clinic. To address these issues, we have recently developed a novel cross-disciplinary platform that integrates the powers of protein engineering, drug delivery, and genetic screening. This platform is founded on the ideas that 1) proteins can be engineered toward exquisite specificity for their targets, 2) improved delivery of recombinant proteins can facilitate their potential for success in the clinic, and 3) functional genomic screens can be used to rationally nominate targeted drug combinations that overcome intrinsic resistance. We have implemented this platform to develop combinations of pro-apoptotic proteins (PROPs) with targeted small molecule drugs for colorectal cancer therapy. The issues of delivery and drug resistance were systematically addressed by 1) engineering a sustained-release formulation of a highly potent pro-apoptotic protein fusion and 2) conducting a CRISPR/Cas9 knockout screen to rationally nominate targeted sensitizer drugs that overcome intrinsic resistance to these proteins. Combination of the sustained-release PROP fusions with the sensitizer drugs dramatically inhibits tumor growth and improves survival in patient-derived xenografts (PDX) of PROP-resistant colorectal cancer in mice. By addressing both delivery and resistance issues with our multidisciplinary platform, we have demonstrated its value in overcoming key obstacles to clinical translation of non-antibody biologics. Our rational approach provides optimal protein-small molecule drug combinations that elicit a robust anticancer response, exhibit minimal toxicity, and combat drug resistance. More broadly, this strategy may provide a precision medicine approach to overcome similar challenges with other protein-based targeted cancer therapies.