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Rational and combinatorial engineering of protease inhibitors for cancer imaging and therapy

Niv Papo[1], Itay Cohen[1], Olumide Kayode[2], Alexandra Hockla[2], Banumathi Sankaran[3], Derek Radisky[2] and Evette Radisky[2]
[1]Ben-Gurion University of the Negev, Israel
[2]Mayo Clinic Comprehensive Cancer Center, USA
[3]Berkeley Center for Structural Biology, USA

Mesotrypsin, an enzyme that contributes to progression and metastasis of many cancers, constitutes a compelling therapeutic target. However, with its unique capability for cleavage and inactivation of proteinaceous inhibitors, mesotrypsin presents a formidable challenge to the development of biologic inhibitors. Our study identifies a promising mesotrypsin inhibitor – a triple mutant of the human amyloid precursor protein Kunitz protease inhibitor domain (APPI) with superior affinity, specificity and proteolytic stability as a starting point for the development of anticancer protein therapeutics. We demonstrate that the mutant acts as a functional inhibitor of mesotrypsin-dependent prostate cancer cellular invasiveness. Additionally, the crystal structure of the mutant/mesotrypsin complex provides new insights into the structural and mechanistic basis for the mutant's improved binding and proteolytic resistance. Finally, the study establishes proof-of-principle for a novel library screening approach that is widely applicable for simultaneously evolving proteolytic stability and a desired functionality for diverse protein scaffolds.

Biography

Niv Papo joined the BGU faculty in 2011 and his research focuses on the development of new nono-and multi-specific proteins and protein-small molecule conjugates that promises to aid in both the diagnosis and treatment of cancer. His areas of expertise include protein engineering, angiogenesis, metastasis, cancer biology, targeted cancer therapy, in vivo imaging, directed evolution, ligand-receptor interactions, molecular recognition, protein sequence-structure-function relationships, and synthetic biology. More generally, his research team is developing methods that allow us to design nono-and multi-functional proteins with optimized and targeted pharmaceutical properties, such as the protein's distribution in the body and how long it remains, resulting in enhanced alternatives to antibodies that will benefit both cancer therapy and diagnostics.

papo@bgu.ac.il

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