West Virginia University

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DEPARTMENT OF CHEMISTRY

Re-imagining Nature's Scaffold:
Designing Synthetic Proteins to Study Biomolecular Recognition

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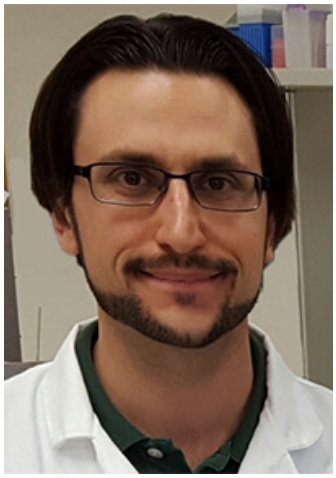

Recent evidence has shown that many protein-protein interactions (PPIs) found in nature occur between shallow, hydrophobic surfaces that are difficult or impossible to target using small molecules. Successful targeting of these seemingly "undruggable" interactions requires molecules that are able to mimic the size and structure of protein interaction domains. Importantly, the ability to target such large-scale PPIs would not only expand the repertoire of biomolecular interactions deemed "druggable," but would also allow the study of subtle intermolecular interactions involved in such binding events. We recently developed a series of synthetic proteins based on scyllatoxin (ScTx) designed to mimic the helical BH3 interaction domain of the pro-apoptotic BCL2 protein Bax. ScTx is a 31-amino acid protein that folds into an a/b structural motif stabilized by three disulfide linkages. Using diverse synthetic approaches, we designed a series of ScTx-Bax mimetics that surveyed all possible combinations of native disulfides and evaluated their ability to target anti-apoptotic BCL2 proteins *in vitro*. Here, it was shown that the number and position of disulfides had significant implications on the folding and activity of ScTx-Bax proteins. Specifically, well-folded ScTx-Bax variants containing two or three native disulfides were unable to target Bcl-2, while unstructured constructs with zero or one disulfide bound with nanomolar affinity. Furthermore, we demonstrated that binding could be precluded when a single native disulfide is placed near the N-terminus of the ScTx-Bax BH3 domain. These results suggest that favorable BH3:BCL2 interactions occur through an induced-fit binding mechanism and that stabilizing bonds within the helical Bax BH3 domain significantly influence Bcl-2 targeting. Notably, this study underscores the importance of structural dynamics in facilitating BH3:BCL2 interactions and validates ScTx-based ligands as novel tools to study biomolecular recognition.

Date: Wed, Feb. 13, 2019
Time: 4:30-5:30 pm
Location: 208 Clark Hall

Students, meet the speaker over coffee and cookies in the Bennett Conference room at 3:30 pm