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Kinetic Target-Guided Synthesis: A Ms-Based Fragment Evolution Platform

Roman Manetsch[1,2]*, Prakash Parvatkar[1], Katya P Nacheva[3], Sameer S Kulkarni[3], Niranjan K Namelikonda[3], David L Flanigan[3] and **Andrii Monastyrskyi[3]**
[1]Department of Chemistry and Chemical Biology, Northeastern University, USA
[2]Department of Pharmaceutical Sciences, Northeastern University, USA
[3]Department of Chemistry, University of South Florida, USA

The Manetsch laboratory focuses on the development and implementation of LC/MS-based lead discovery and optimization platforms. Herein, the development of kinetic Target-Guided Synthesis (TGS) and its implementation for the identification of small molecules modulating protein-protein interactions will be presented. In kinetic Target-Guided Synthesis (TGS), the biological target is actively engaged in the irreversible assembly of its own inhibitory bidentate ligand from a pool of smaller reactive fragments. The screening method can be as simple as determining whether or not the inhibitory product has been formed in a given test mixture. To date, kinetic TGS has exclusively been applied to enzymatic targets and these TGS applications have been successful because of a unique combination of (a) the slow nature of the chemical reaction combining the two fragments into a single molecule and (b) the use of reactive fragments showing moderate to high affinity towards binding pockets of the enzyme. Compared to kinetic TGS screening of enzymes, however, the discovery of inhibitory compounds against "undruggable" targets is more challenging and thus requires major modifications over the existing kinetic TGS approaches. The Manetsch laboratory demonstrated that the sulfo-click reaction, an amidation reaction between thio acids and sulfonyl azides, is suitable for a kinetic TGS approach targeting the proteins of the Bcl-2 family. Furthermore, the use of a triple quadrupole mass analyzer improved the data quality and increased the throughput by approximately 200-fold rendering the platform industrial robustness.

Biography:

Dr. Roman Manetsch received his PhD in Chemistry in 2002 from the University of Basel under the guidance of Wolf-Dietrich Woggon. He joined the group of K. Barry Sharpless at the Scripps Research Institute working on click chemistry. In 2005, he moved to the University of South Florida and established a research group focusing on medicinal chemistry. In 2014, Dr. Manetsch assumed a position of an Associate Professor at Northeastern University. His current research focuses on lead discovery and optimization using synthetic chemistry in close conjunction with mass spectrometry.