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Novel drug-discovery technology based on intact protein masspectrometry

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Summary: We developed a novel fragment-based drug discovery platform, which we call irreversible tethering. In this method a mixture of cysteine reactive drug-like fragments is incubated with the protein of interest that contains druggable cysteines, followed by gel-filtration column to eliminate the excess of small molecules. Subsequent intact protein masspectrometry identifies covalently modified proteins, providing simultaneous readout on what drug-like fragments reacted with the protein of interest. The developed screening protocol allows us to screen 100 compounds in one day, without the use of any robotic equipment and only facility service is required. Importantly, the discovered technology platform is applicable to any proteins that contain both highly reactive catalytic cysteines and less reactive non-catalytic cysteines.

We subsequently used this platform to discover covalent inhibitors of Nedd4-1 ligase, which ubiquitinates and degrades tumor suppressor PTEN. Genetic deletion, inactivating mutation, or aberrant polyubiquitination and degradation of tumor suppressor PTEN contributes to the origins and progression of human cancers. To this end, pharmacological inhibitors of ubiquitin ligases that polyubiquitinate and degrade PTEN hold substantial promise as anticancer therapeutics. To further optimize discovered inhibitors we obtained a crystal structure of Nedd4-1-inhibitor complex, which revealed previously unknown druggable site present in this enzyme. We conducted SAR studies showing that identified small molecules can be converted into more potent leads.

Biography

Alexander V Statsyuk graduated from the Moscow State University, Russia in 1998, with the BS degree in chemistry. Subsequently, Alexander moved to the USA in January of 2001 to pursue his PhD studies at the University of Chicago under the direction of Prof. Sergey A. Kozmin, where he worked on the total synthesis and target identification of the cytotoxic natural product bistramide A, followed by postdoctoral work with Prof. Kevan Shokat (UCSF). Since 2010, Alexander V. Statsyuk has been an Assistant Professor in the Department of Chemistry at Northwestern University, where he directs his independent research program aimed at studying the ubiquitin-proteasome system. Alexander is a recipient of 2012 Pew Scholar Award.

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