Profile of an Early-Career Researcher

Jonathan Ostrem, PhD

“Mutant Ras protein”. It is a chilling phrase – one that strikes fear into doctors and patients alike, as they understand that, with very few effective treatment options available, the battle may be even tougher than they thought. The same phrase produces a similar reaction in the drug discovery scientist who understands just how difficult it has been to discover and develop new drugs that reign in the rampant excessive Ras-based cellular signaling that underlies nearly 30% of all human cancers.

This issue’s Early Career Profile highlights Dr. Jonathan Ostrem, whose thesis work at the University of California, San Francisco comprises one of the more dramatic recent advancements toward the goal of discovering a targeted Ras therapy. This work has earned Dr. Ostrem several accolades, including being named to the Forbes 30 under 30 in Science and Healthcare in 2014. After obtaining a Bachelor of Science in 2007 from the University of California, San Diego, where he was presented with the Joseph E. Mayer Award for outstanding research in chemistry (among several other awards and decorations), Dr. Ostrem completed his Ph.D. in late 2013 at UCSF and subsequently his Doctor of Medicine in 2016. He is currently a Clinical Fellow in residence at Brigham and Women’s Hospital in Boston, Massachusetts.

Dr. Ostrem’s graduate work, performed in the lab of Professor Kevan Shokat, introduced to the world a new direction toward the discovery of true, targeted Ras inhibitors. In the novel approach discovered by Ostrem and colleagues, an electrophilic small molecule is presented to the cysteine inherent to a common Ras mutant, G12C.

The small molecules inhibitors, which can contain disulfide, vinyl sulfonamide, or acrylamide electrophiles, were originally discovered using the tethering screening platform first utilized by Professor Jim Wells. The new inhibitors that the team discovered were found, by X-ray co-crystallography, to bind to a pocket on the Ras protein underneath the Switch II region. Utilizing an iterative structure-guided design process, the team improved on the initial hits to obtain compounds that more effectively react with the mutant protein.

The Switch I and II regions of Ras are conformationally labile and form the basis for the protein-protein interactions that drive both the regulation of Ras and its downstream effector signaling. Importantly, binding to this new pocket disrupts both switches and causes Ras to preferentially bind GDP, resulting in an inactive protein incapable of initiating downstream oncogenic signals. Indeed, the new compounds were shown to impair Ras signaling and induce apoptosis in G12C-containing cancer cell lines.

While this work has clearly opened new doors to the inhibition of Ras, significant concern over the use of an electrophilic molecule will remain in the minds of most chemical biologists, chemists, and drug discovery scientists. However, Ostrem and colleagues demonstrated that these inhibitors do not react with several other proteins and do not affect cell lines lacking the key G12C mutation. It is this confirmation of selectivity, perhaps, that has given confidence to other researchers in the field that these may be a true breakthrough toward the elusive goal of Ras inhibition.

Follow-up efforts from the Shokat lab and from a small pharmaceutical company that has spun off from the work have demonstrated that electrophilic molecules that utilize this pocket and novel mechanism of action sample intracellular Ras in its GDP-bound state and thus sequester it in the inactive form. Further, electrophiles targeting the nucleophilic cysteine in mutant Ras can be made to be exquisitely selective, and have demonstrated in vivo activity. Further, recently reported efforts following up on Ostrem's original work are aimed at the extension of this approach to additional oncogenic Ras mutants.

The work of Dr. Ostrem described above has had a profound effect on the Ras community, and has formed part of the so-called "Ras renaissance". It has served to reinvigorate pharma and academic efforts toward the discovery of true, targeted Ras inhibitors.

Going forward, Dr. Ostrem will start fellowship training in oncology in 2018 and intends to continue a career in the field of chemical biology, with a focus toward small molecule development for cancer therapy as well as the development of chemical tools to study cancer signaling. He also expresses an interest in the application of chemical biology to immunotherapy - particularly in the design of even more sophisticated cell-based therapies. This researcher has already made waves in the community and we look forward to additional, exciting developments in the future.