

Profile of an Early-Career Researcher

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Our theme for this month's issue involves exploring the emerging intersections between epigenetics and metabolism, and this month's Early Career Investigator's research encompasses both of these areas. Kabirul Islam, Ph.D. is currently an Assistant Professor at the University of Pittsburgh, Pittsburgh, Pennsylvania, USA. Kabirul started his independent career at Pitt in 2013 after completing his postdoctoral studies with Minkui Luo at Memorial Sloan Kettering. One of the Luo lab's first trainees, Kabirul developed "bump-hole" strategies for studying protein methyltransferase enzymes involved in epigenetic regulation of gene expression. Specifically, Islam showed that synthetic S-adenosylmethionine (SAM) analogues could be used by engineered ("bumped") methyltransferases to discover novel enzyme substrates using click chemistry followed by LC-MS/MS proteomics. Prior to the Luo lab, Kabirul did a short fellowship in Tarun Kapoor's group at Rockefeller University developing inhibitors of the cytoskeletal motor myosin V. Kabirul earned his PhD in chemistry at the Indian Institute of Science in 2008 under the tutelage of Goverdhan Mehta, where he worked on the total synthesis of natural products.

In his independent career at the University of Pittsburgh, Kabirul's group has extended his interest in novel applications of enzyme engineering and "bump-hole" strategies towards two distinct areas. First, they have developed functionalized analogues of 2-ketoglutarate that are biologically inert towards most lysine demethylases, but can specifically activate enzymes engineered to accommodate their increased steric bulk in the active site. In the future, this chemical control may be used in combination with cell permeable analogues to rapidly activate lysine demethylases in cells and permit the identification of direct enzyme substrates. Alternatively, these molecules can be readily converted to substrate analogues, which could allow engineered 2-ketoglutarate-dependent dioxygenases, but not other natural dioxygenases, to be turned off with exquisite temporal control. Notably, several lysine demethylases have been proposed to be targets of "oncometabolites" such as 2-HG. The development of bump-hole methods may highlight novel targets of these enzymes for whom disrupted demethylation plays a critical role in IDH-mediated tumorigenesis. In a second and related project, the Islam group has pioneered the use of photoactivatable amino acids to identify novel proteins that interact with epigenetic reader proteins. These approaches use unnatural amino acid mutagenesis to insert photocrosslinkers such as azidophenylalanines into active-sites that interact with specific epigenetic protein modifications, allowing the capture of normally transient interaction partners. This "interaction-based protein profiling" approach has the potential to identify novel protein-protein interactions of epigenetic reader proteins known to play important roles in cancer, such as BRD4, and thus may provide new insights into their mechanism as well as therapeutic targeting. Kabirul has coauthored 29 peer-reviewed publications and has been an invited to present his work in prestigious settings including Pacifichem, the 2016 FASEB Kabirul Acetylation Meeting, and the 2018 Bioorganic

Gordon Research Conference. We look forward to additional discoveries at the metabolism epigenetics interface from Kabirul!