UNIVERSITY OF RHODE ISLAND
Department of Chemistry
SEMINAR

3:00 P.M., Monday, September 15, 2025
Room 105 – Beaupre Center

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Broad Institute of Harvard and MIT
Harvard Medical School
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Protein editing using proximity-inducing molecules

HOST

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The information flow in biological systems involves protein editing, including the addition or removal of post-translational modifications (PTMs) by "writer" or "eraser" enzymes. Most used protein editors (e.g., PROTACs) are chimeric small molecules formed by the fusion of binders of a protein of interest (POI) and writer/eraser; these chimeras induce proximity between the POI and the enzyme to add/remove a PTM (Fig. 1A). However, as these chimeric molecules must recruit catalytically active writer/eraser, they employ non-inhibitory binders that are scarce, often of poor quality, challenging to discover, and some enzymes may not even contain non-inhibitory pockets. Such binders exist for only 4 of 600 ubiquitin ligases and are nearly non-existent for other writers/erasers. A design of chimeric molecules that employs existing enzyme inhibitors will be scalable and generalizable, enabling diverse laboratories to rapidly develop protein editors without engaging in ligand discovery campaigns that can be resource- and time-intensive.

Platform development: I will describe a scalable platform for protein editing using GRoup-transfer chimeras for Inducing Proximity (GRIPs), which consist of an inhibitor of a writer or eraser enzyme connected to the POI binder via a group-transfer handle (Fig. 1B). The inhibitor end of GRIP enables the transfer of the POI binder onto a Cys/Lys residue of the enzyme via a *transferase*-type reactivity. Competition with the (co)substrate or protein dynamics releases the inhibitor, enabling the enzyme to modify POI. We developed 42 group-transfer handles with tunable reactivity to Cys/Lys side chains. We developed GRIPs for > 50 inhibitor/enzyme pairs, comprising kinases, phosphatases, glycosyl transferases, glycosidases, and methyltransferases. To the best of our knowledge, we have not seen such scalability for any chimera platform.

Platform applications: GRIPs recruited endogenous phosphatase SHP2 to STAT3, thereby removing the latter's phosphorylation and switching off the JAK-STAT pathway. An AKT GRIP-induced Liprin phosphorylation that triggered the latter's phase separation, which is critical for neuronal exocytosis, with dose and temporal control. Finally, using GRIPs that dimerize and induce endogenous EGFR phosphorylation, we switched on the EGFR pathway. These GRIPs mimicked EGF in promoting the growth of cells used for the biomanufacturing of biologics, offering a proteolytically stable and low-cost alternative to EGF. These GRIPs also induced the death of cells with oncogenic, but not wild-type KRAS, potentially by perturbing the cancer cells' Goldilocks level of oncogenic signaling.

Overall, GRIPs enable programmable, scalable, and selective modulation of protein function across diverse biological systems, with applications in basic research, biomedicine, and biotechnology.

Fig. 1 (A, B). Classical chimeric small molecules **(A)** and GRIPs **(B)**.