PRESS RELEASE

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The Wistar Institute, The University of Leeds, and the Perelman School of Medicine Discover New 'Molecular Glues' as a Possible Therapeutic Approach for Autoimmune Conditions

The Collaborative Discovery Could Help Mitigate Inflammation in Autoimmune Diseases

PHILADELPHIA — (April 10, 2025) —The Wistar Institute's Joseph Salvino, Ph.D., — in collaboration with Elton Zeqiraj, Ph.D., of The University of Leeds and Roger Greenberg, M.D., Ph.D., of The Perelman School of Medicine at the University of Pennsylvania — has discovered a type of "molecular glue" that can be used to inhibit certain pathological protein interactions. Their findings were published in the paper, "Molecular glues that inhibit deubiquitylase activity and inflammatory signaling" from *Nature Structural & Molecular Biology.*

"Molecular glues are an exciting new area of research that allows us to fight disease by working with the body's systems rather than against them." said Dr. Salvino, Wistar professor. "By gluing together an inactive form of the BRISC complex with our system, we're able to reduce the continuous inflammatory signaling due to dysregulated BRISC complex activity in autoimmune diseases."

Deubiquitylases, or DUBs, are enzymes that regulate protein stability; A DUB removes the "ubiquitin mark" on a protein, normally targeting it for degradation, thereby stabilizing the protein resulting in aberrant signaling. Certain diseases, such as lupus, are due to aberrant inflammatory signaling. Approaches targeting this dysregulated DUB activity are expected to balance protein homeostasis and lead to pathogenic outcomes. Scientists are interested in methods that could therapeutically intervene to reduce DUB dysregulation and its pathogenic effects; however, until now, targeting DUB dysregulation has been challenging with small-molecule approaches due to lack of specificity and side effects.

Salvino and his colleagues took a different approach to overcoming the challenge with a new technology termed Molecular Glue. Unlike inhibitory small molecules, which block the active

processing site of an enzyme, molecular glues facilitate the formation of protein complexes. In this paper, the research team applied the molecular glue approach, for the first time, to form an inactive complex against pathological inflammatory signaling due to aberrant DUB activity.

A DUB in humans called BRISC complex regulates inflammatory signaling. When BRISC becomes dysregulated, excessive inflammation can flare up, and research suggests that BRISC dysregulation contributes to the persistent inflammation in autoimmune conditions like lupus.

After an initial high-throughput screen, Salvino and his co-authors identified compounds that functioned as molecular glues that selectively stabilize BRISC in a biologically inactive complex, which they confirmed with high-resolution cryo-electron microscopy and mass spectrometry. The BRISC molecular glues, or BLUEs, bind to BRISC in a way that causes it to form an inactive complex. The BLUE-induced inactive BRISC complex can no longer stabilize inflammatory signaling, caused by aberrant BRISC activity. The deactivated complex allows the ubiquitinated inflammatory signaling protein to be degraded under normal protein homeostasis conditions.

In preclinical testing, the researchers confirmed that the BLUEs were successful in reducing interferon signaling (a potent inflammatory response). This finding was particularly notable for reducing interferon signaling in blood samples from patients with scleroderma, an autoimmune disease in which interferon responses are abnormally elevated.

“One of the difficulties in drug development is that some ideal targets don’t have a clearly defined druggable site. This makes it incredibly difficult to design drugs against, because there’s nowhere for a drug molecule to attach itself to stop rogue activity. So, we need to find another way,” said Dr. Elton Zeqiraj, lead author, explaining his rationale for molecular glue design.

As Penn’s Dr. Roger Greenberg said, “Our approach allows us to fight inflammation by working with molecules rather than against them. By gluing BRISC shut, we’ve demonstrated a possible effective therapy for autoimmune conditions; I’m looking forward to seeing how our BLUE design can be used to develop possible treatments.”

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