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New compounds reduce debilitating inflammation

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Six Case Western Reserve scientists are part of an international team that has discovered two compounds that show promise in decreasing inflammation associated with diseases such as ulcerative colitis, arthritis and multiple sclerosis. The compounds, dubbed OD36 and OD38, specifically appear to curtail inflammation-triggering signals from RIPK2 (serine/threonine/tyrosine kinase 2). RIPK2 is an enzyme that activates high-energy molecules to prompt the immune system to respond with inflammation. The findings of this research appear in the *Journal of Biological Chemistry*.

"This is the first published indication that blocking RIPK2 might be efficacious in inflammatory disease," said senior author Derek Abbott, MD, PhD, associate professor of pathology, Case Western Reserve University School of Medicine. "Our data provides a strong rationale for further development and optimization of RIPK2-targeted pharmaceuticals and diagnostics."

In addition to Abbott and his medical school colleagues, the research team included representatives of Oncodesign, a therapeutic molecule biotechnology company in Dijon, France; Janssen Research & Development, a New Jersey-based pharmaceutical company; and Asclepia Outsourcing Solutions, a Belgium-based medicinal chemistry company.

The normal function of RIPK2 is to send warning signals to cells that bacterial infection has occurred, which in turn spurs the body to

mobilize white blood cells. The white blood cells identify and encircle pathogens, which cause blood to accumulate in the region. It is this blood build-up that leads to the red and swollen areas characteristic of inflammation. When this process goes awry, the inflammation increases dramatically and tissue destruction ensues. RIPK2 works in conjunction with NOD1 and NOD2 (nucleotide-binding oligomerization domain) proteins in controlling responses by the immune system that lead to this inflammation process.

In this research project, investigators applied state-of-the-art genetic sequencing to learn the unique set of genes driven specifically by NOD2 proteins. They ultimately zeroed in on three specific NOD2-driven inflammation genes (SLC26a, MARCKSL1, and RASGRP1) that guided investigators in finding the most effective compounds.

Oncodesign searched its library of 4,000 compounds that targeted kinases, and after exhaustive study, narrowed the selection down to 13. Then investigators tested the 13 compounds in mouse and human cells and found that two compounds, OD36 and OD38, were most effective in blocking RIPK2.

"Based on the design of OD36 and OD38, we have developed with Oncodesign fifth-generation compounds that are even more effective than the first-generation OD36 and OD38," Abbott said. "Our next step is to seek a larger pharmaceutical company that can move these compounds forward into Phase 1 clinical trials in humans."

Provided by Case Western Reserve University