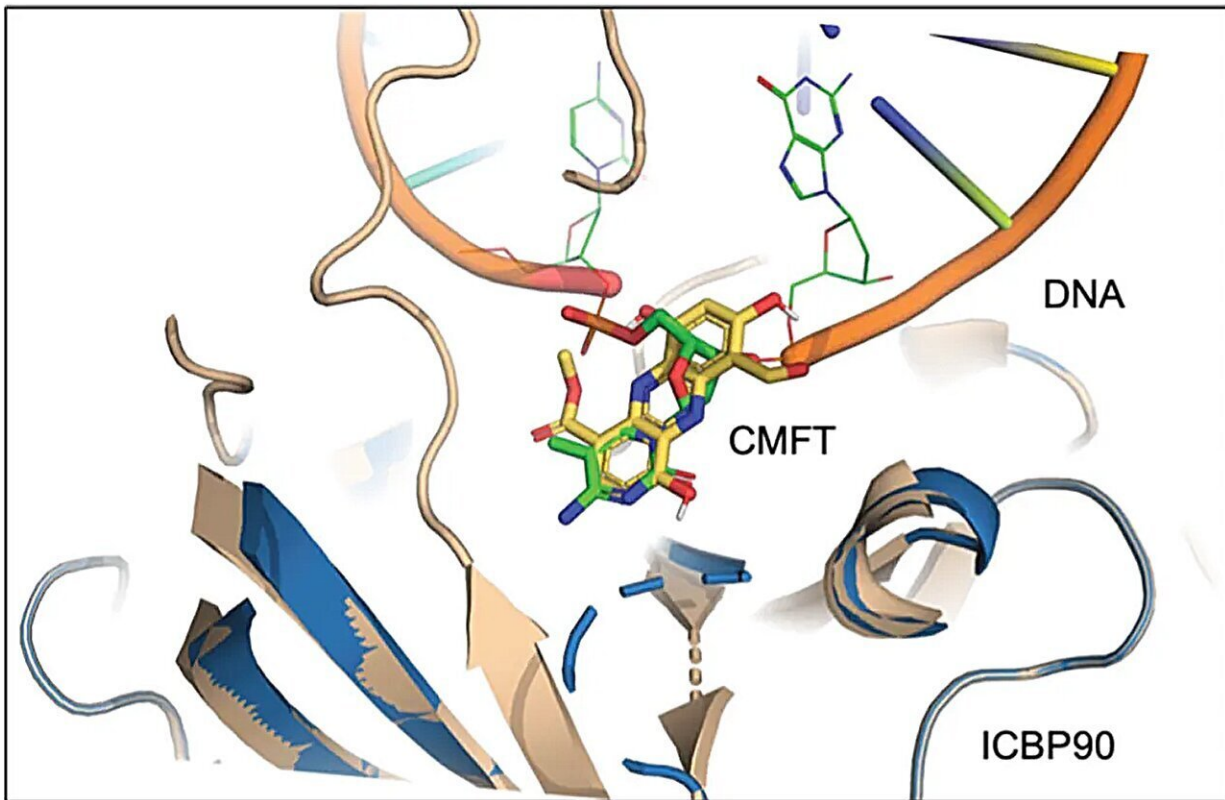


# Researchers pave way to target an autoimmune disease-associated gene variant

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Superimposed structures of the SRA domain bound to DNA double helix (orange) from the 3CLZ.pdb, modeled CMFT bound SRA (yellow) and methylated cytosine (green). Credit: *Journal of Biological Chemistry* (2024). DOI: 10.1016/j.jbc.2024.107443

In a new study, Yale researchers identified a molecule that binds to a

disease-associated macrophage migration inhibitory factor (MIF) gene variant. The discovery, they say, could lead to the development of a new generation of precision medicine-based therapies that address diverse autoimmune and inflammatory conditions.

The [findings](#) were published in the *Journal of Biological Chemistry*.

Many autoimmune and inflammatory diseases develop because of susceptibilities encoded by genetic variants in our DNA. MIF gene variants are common in people and confer risk for multiple autoimmune, infectious, and oncologic diseases, explains corresponding author Richard Bucala, MD, Ph.D., Waldemar Von Zedtwitz Professor of Medicine (Rheumatology) and professor of pathology and of epidemiology at Yale School of Medicine (YSM). MIF, an inflammatory mediator, plays a significant role in the body's immune response.

"These natural gene variants produce different levels of the MIF protein that influence the risk of developing a particular disease or of having an especially severe form of it," Bucala said.

Researchers in the Bucala lab developed a highly sensitive, high-throughput assay to identify molecules that could bind to the variant DNA sequence in the MIF gene and prevent its interaction with the transcription factor, or protein that controls the transcription of genetic information. The assay was used to screen tens of thousands of [molecules](#) to identify ones that might reduce MIF production in the high MIF gene-variant cells.

From a library of almost 30,000 compounds available at the Yale Center for Molecular Discovery, the researchers found that the druglike molecule 1-carbomethoxy-5-formyl-4,6,8-trihydroxyphenazin (CMFT) selectively binds to a disease-associated MIF gene [variant](#) and inhibits the transcription factor ICBP90, which activates the MIF gene.

"The ability to inhibit MIF in a way that is selective for a disease-associated [gene variant](#) is the most precise means to interfere with MIF's disease-causing action and would likely be far less toxic than less selective treatments," Bucala said.

Co-author Elias Lolis, Ph.D., professor of pharmacology at YSM, considers the study a major advancement toward a therapeutic strategy in cases where greater protein expression is associated with disease pathology.

"It shows what is essential for the growing field of precision medicine using pharmacogenomics, or how our genes affect our response to medications," he said.

The DNA-based assay and prototype molecule demonstrate the feasibility of advancing the development of precision-based MIF inhibitors for many autoimmune and [inflammatory diseases](#), Bucala added.

"It provides a way to pharmacologically re-set one's genetic susceptibility toward a healthy state," he said.

**More information:** Jia Li et al, A small-molecule allele-selective transcriptional inhibitor of the MIF immune susceptibility locus, *Journal of Biological Chemistry* (2024). [DOI: 10.1016/j.jbc.2024.107443](https://doi.org/10.1016/j.jbc.2024.107443)

Provided by Yale University

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