Using next-gen CRISPR tool, scientists create unprecedented molecular map of human immune response

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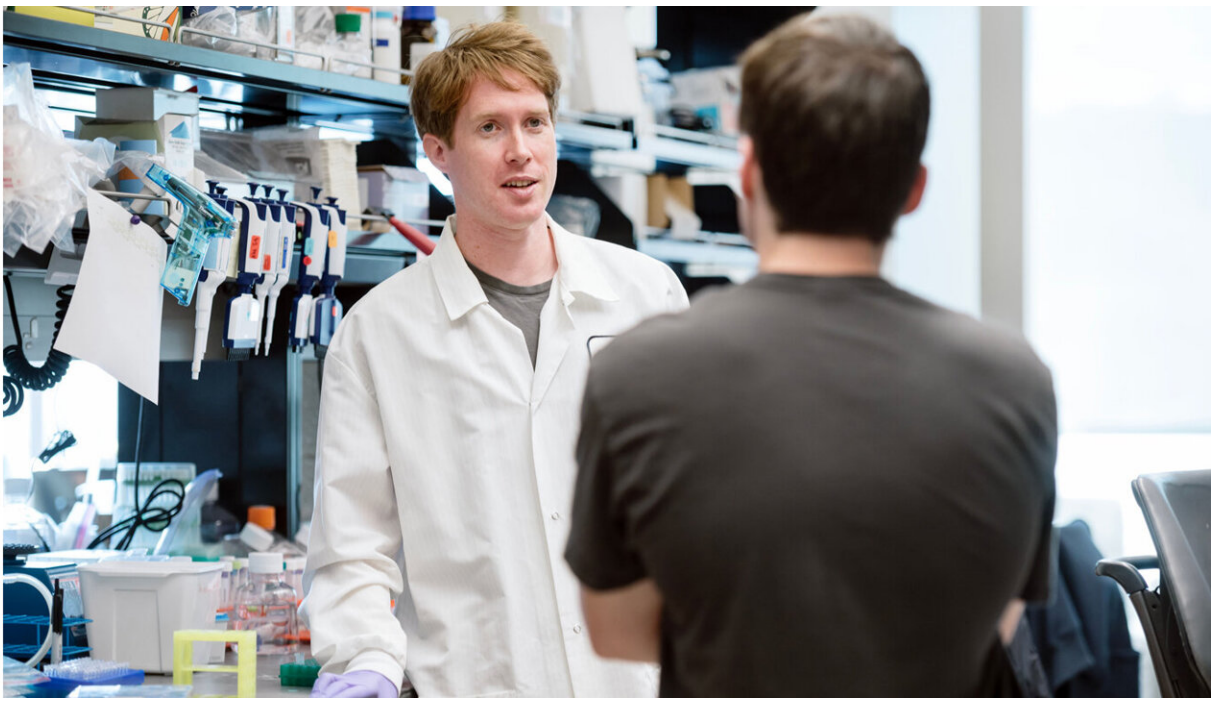

Carl Ward, PhD, a postdoctoral researcher in the Marson Lab at Gladstone Institutes, was co-first author of the landmark study in Nature, along with fellow co-first author Ralf Schmidt, MD, a medical fellow at the Medical University of Vienna who is a former postdoctoral researcher at Gladstone. Here, Ward speaks with Zev Armour-Garb, a student intern in the Marson Lab. Credit: Gladstone Institutes, 2023

In a study of historic scale, scientists at Gladstone Institutes have created an intricate map of how the immune system functions, examining the detailed molecular structures governing human T cells using the next-generation CRISPR tool known as base editing.

Their paper, "Base editing mutagenesis maps functional alleles to tune human T cell activity," published in *Nature*, uncovers detailed information that could help overcome the limitations of today's immunotherapies and identify new drug targets for a wide range of diseases, including autoimmune diseases and cancer.

Led by Gladstone Senior Investigator Alex Marson, MD, Ph.D., the team dove deep into the DNA of T cells, pinpointing specific nucleotides—the basic units of genetic information in DNA—that influence how immune cells respond to stimuli. In all, they scrutinized more than 100,000 sites across nearly 400 genes found in functioning human T cells.

Nucleotides serve as the basic code for constructing proteins in cells, so by identifying these specific units of DNA the scientists now have clarity into exact locations within proteins that tune immune responses critical for health. The results serve as a bullseye, marking sites that can be targeted with future immune-modulating drugs.

"We've created astoundingly precise and informative maps of DNA sequences and protein sites that tune actual human immune responses," says Marson, who is also director of the Gladstone-UCSF Institute of Genomic Immunology and the Parker Institute for Cancer Immunotherapy at Gladstone Institutes.

"Our mapped sites provide insights into mutations found in patients with immune disorders. The enormous genetic dataset also works as a sort of cheat sheet, explaining biochemical code that will help us program

future immunotherapies for cancer, autoimmunity, infections, and beyond."

T cells play a central role in immune response and regulation, making them of keen interest to scientists looking to solve complex diseases such as cancer or immune disorders. For the past decade, the Marson lab and others have established the gene-editing technology CRISPR to study how primary immune cells work.

For this study, the team went a step further, leveraging a newer CRISPR-based technology known as base editing to make more targeted changes to hundreds to thousands of DNA sites across individual genes—painting a much more nuanced picture at high resolution.

Because the study was conducted using primary T cells sourced from human blood donors, results hold great clinical relevance, noted Ralf Schmidt, MD, co-first author of the paper. Schmidt, a medical fellow at the Medical University of Vienna, is a former postdoctoral researcher at Gladstone Institutes.

"This study is zooming into the genetic basis of immune cell functions," Schmidt says. "We can now interrogate T cells at nucleotide resolution, generating blueprints for drug development, diagnostics, and further scientific endeavors."

With immense pools of data generated from the more than 100,000 sites on T cells, computational genomics became a critical piece of the study. Carl Ward, Ph.D., a Gladstone postdoctoral researcher and co-first author, led the team's efforts in this area, keying in on important measures of cell function to create what he hopes can serve as an indispensable resource for immunologists and drug developers alike.

"We can now assign functions to specific mutations that had been a

mystery," Ward says. "Our detailed functional maps also can be combined with existing datasets and AI tools to amplify our discoveries and predict new avenues of investigation."

Ward notes that the new *Nature* study is just the beginning of a new chapter of immune cell discoveries: "Our tools for solving disease are going to get better and better," he says. "We're nearing a point where we can use these maps to design therapies that can tune up the T cell function for cancer treatments or tune it down to treat autoimmune disease."

More information: Alex Marson et al, Base editing mutagenesis maps functional alleles to tune human T cell activity, *Nature* (2023). doi.org/10.1038/s41586-023-06835-6

Provided by Gladstone Institutes

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