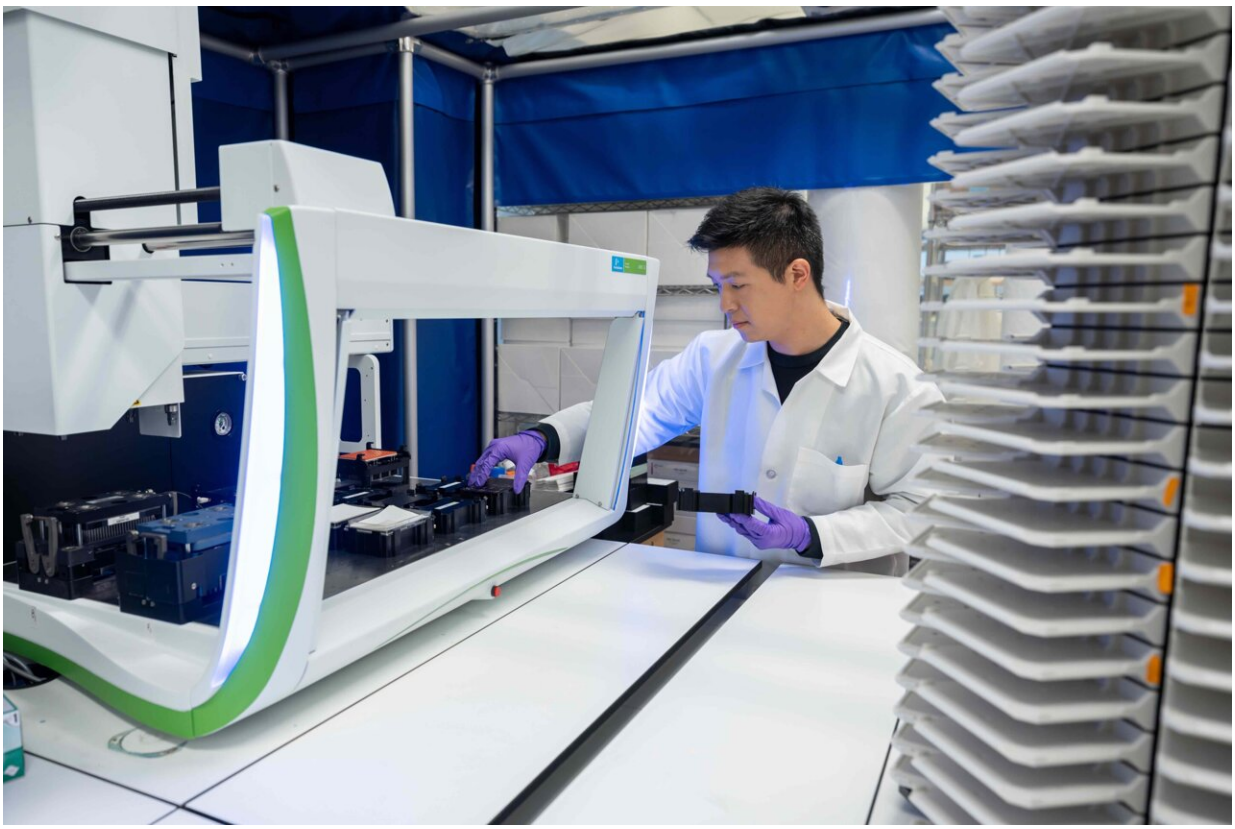
Researchers boost vaccines and immunotherapies with machine learning to drive more effective treatments

November 18 2023, by Emily Ayshford



In a potential first for the field of vaccine design, researchers at UChicago Pritzker School of Molecular Engineering used machine learning to guide the discovery of new immune pathway-enhancing molecules, finding one particular small molecule that could outperform the best immunomodulators on the market. Credit: Jason Smith for University of Chicago

Small molecules called immunomodulators can help create more effective vaccines and stronger immunotherapies to treat cancer.

But finding the molecules that instigate the right immune response is difficult —the number of drug-like small molecules has been estimated to be 10^{60}, much higher than the number of stars in the visible universe.

In a potential first for the field of vaccine design, machine learning guided the discovery of new immune pathway-enhancing molecules and found one particular small molecule that could outperform the best immunomodulators on the market. The results are published in the journal *Chemical Science.*

"We used artificial intelligence methods to guide a search of a huge chemical space," said Prof. Aaron Esser-Kahn, co-author of the paper who led the experiments. "In doing so, we found molecules with record-level performance that no human would have suggested we try. We're excited to share the blueprint for this process."

"Machine learning is used heavily in drug design, but it doesn't appear to have been previously used in this manner for immunomodulator discovery," said Prof. Andrew Ferguson, who led the machine learning. "It's a nice example of transferring tools from one field to another."

Machine learning to screen molecules

Immunomodulators work by changing the signaling activity of innate immune pathways within the body. In particular, the NF-κB pathway plays a role in inflammation and immune activation, while the IRF pathway is essential in antiviral response.

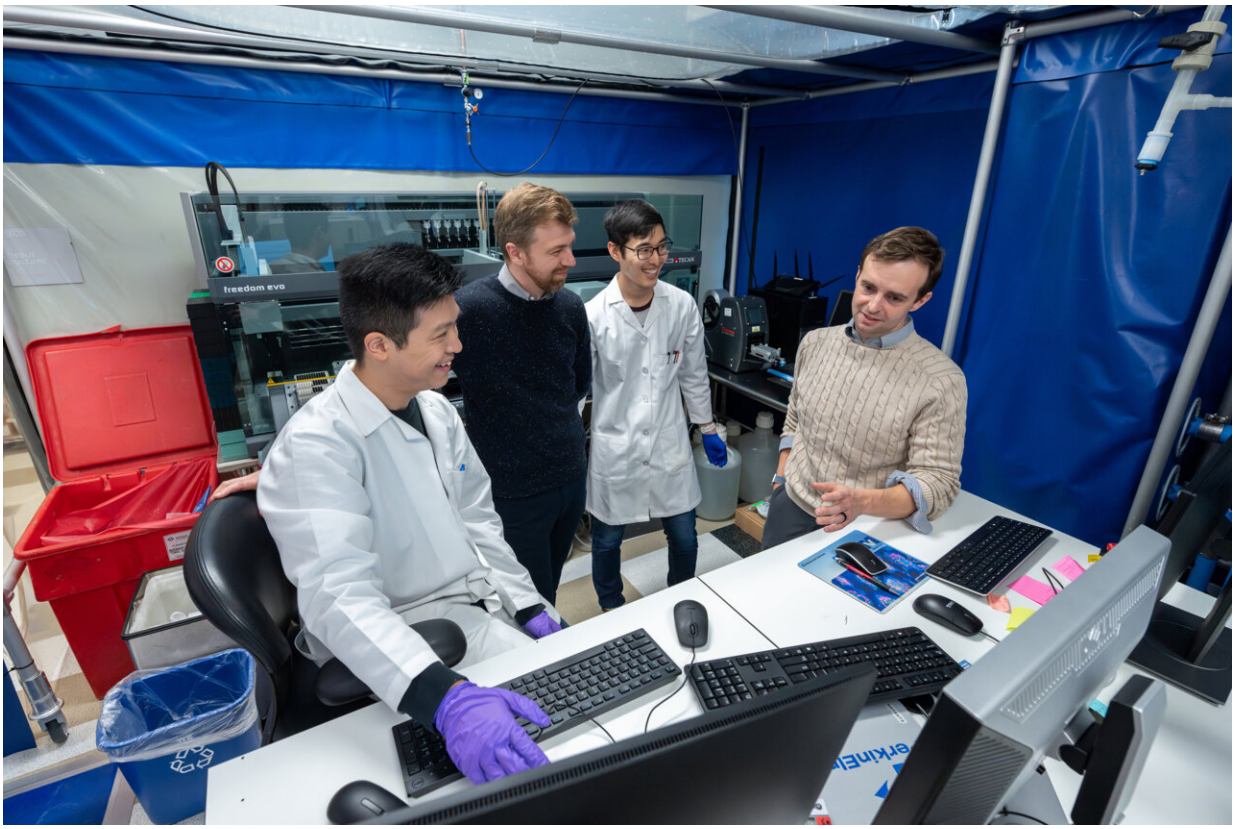
Earlier this year, the PME team conducted a high-throughput screen that looked at 40,000 combinations of molecules to see if any affected these

pathways. They then tested the top candidates, finding that when those molecules were added to adjuvants—ingredients that help boost the immune response in vaccines—the molecules increased antibody response and reduced inflammation.

To find more candidates, the team used these results combined with a library of nearly 140,000 commercially available small molecules to guide an iterative computational and experimental process.

Graduate student Yifeng (Oliver) Tang used a machine learning technique called active learning, which blends both exploration and exploitation to efficiently navigate the experimental screening through molecular space. This approach learns from the data previously collected and finds potential high-performing molecules to be tested experimentally while also pointing out areas that have been under-explored and may contain some valuable candidates.

The process was iterative; the model pointed out potential good candidates or areas in which it needed more information, and the team conducted a high-throughput analysis of those molecules and then fed the data back into the active learning algorithm.



(From left): Graduate student Yifeng (Oliver) Tang, Assoc. Prof. Andrew Ferguson, graduate student Jeremiah Kim, and Prof. Aaron Esser-Kahn review the results of the high-throughput experimental screening. Credit: Jason Smith for University of Chicago

Molecules that outperform the rest

After four cycles —and ultimately sampling only about 2% of the library—the team found high-performing small molecules that had never been found before. These top-performing candidates improved NF-κB activity 110%, elevated IRF activity by 83%, and suppressed NF-κB activity by 128%.

One molecule induced a three-fold enhancement of IFN-β production

when delivered with what's called a STING (stimulator of interferon genes) agonist. STING agonists promote stronger immune responses within tumors and are a promising treatment for cancer.

"The challenge with STING has been that you can't get enough immune activity in the tumor, or you have off-target activity," Esser-Kahn said. "The molecule we found outperformed the best published molecules by 20 percent."

They also found several "generalists"—immunomodulators capable of modifying pathways when co-delivered with agonists, chemicals that activate cellular receptors to produce a biological response. These small molecules could ultimately be used in vaccines more broadly.

"These generalists could be good across all vaccines and therefore could be easier to bring to market," Ferguson said. "That's quite exciting, that one molecule could play a multifaceted role."

To better understand the molecules found by machine learning, the team also identified common chemical features of the molecules that promoted desirable behaviors. "That allows us to focus on molecules that have these characteristics, or rationally engineer new molecules with these chemical groups," Ferguson said.

The team expects to continue this process to search for more molecules and hope others in the field will share datasets to make the search even more fruitful. They hope to screen molecules for more specific immune activity, like activating certain T-cells, or find a combination of molecules that gives them better control of the immune response.

"Ultimately, we want to find molecules that can treat disease," Esser-Kahn said.

A team from the Pritzker School of Molecular Engineering (PME) at The University of Chicago tackled the problem by using machine learning to guide high-throughput experimental screening of this vast search space.

More information: Yifeng Tang et al, Data-driven discovery of innate immunomodulators via machine learning-guided high throughput screening, *Chemical Science* (2023). DOI: 10.1039/D3SC03613H

Provided by University of Chicago

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