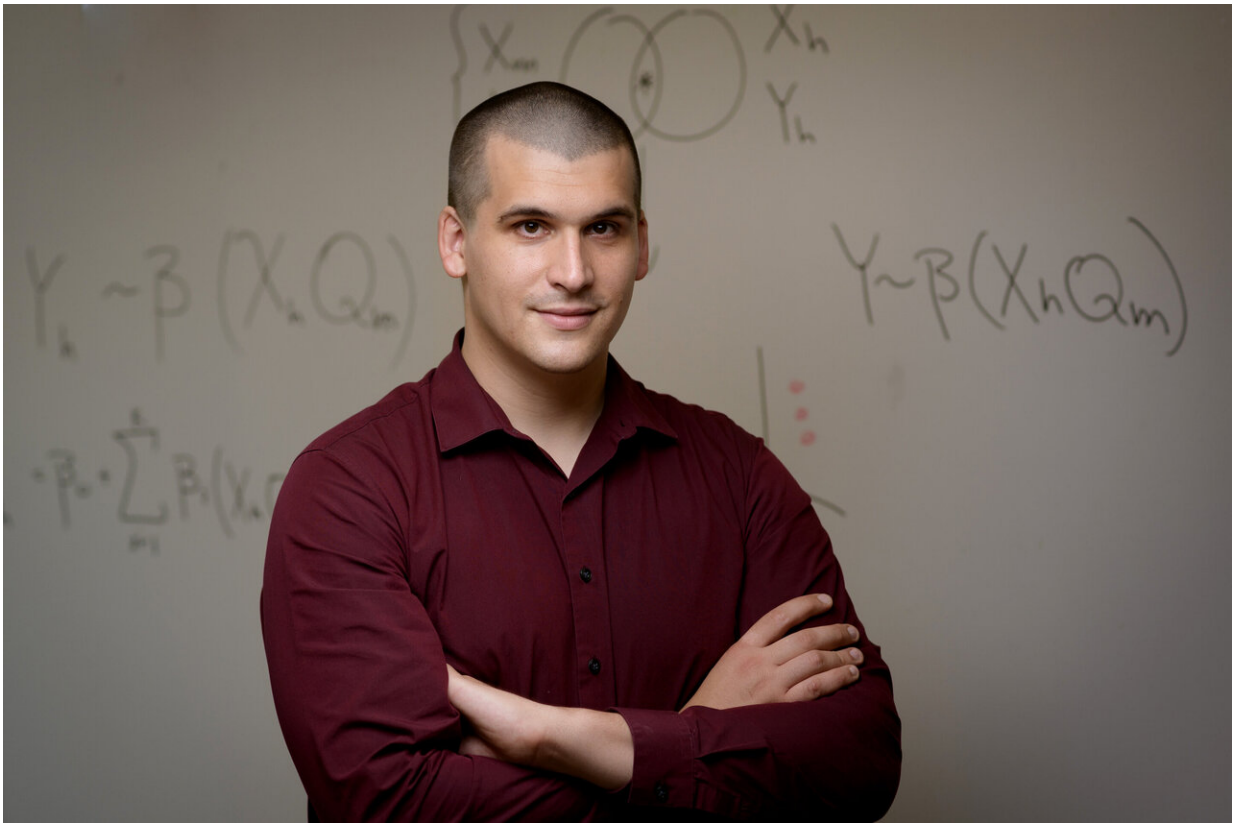


# Tool could improve success in translating drugs from animal studies to humans

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Doug Brubaker, a Purdue assistant professor of biomedical engineering, uses computational and experimental approaches to study host-microbiome interactions in cancers and inflammatory diseases. Credit: Purdue University /John Underwood

About 50% of people who take the drug infliximab for inflammatory

bowel diseases, such as Crohn's disease, end up becoming resistant or unresponsive to it.

Scientists might be able to catch problems like this one earlier in the drug development process, when drugs move from testing in animals to clinical trials, with a new computational model developed by researchers from Purdue University and Massachusetts Institute of Technology.

The researchers call the model "TransComp-R." In a study published in *Science Signaling*, they used the model to identify an overlooked [biological mechanism](#) possibly responsible for a patient's resistance to infliximab.

Such a [mechanism](#) is hard to catch in preclinical testing of new drugs because animal models of human diseases may have different biological processes driving disease or a response to therapy. This makes it difficult to translate observations from [animal experiments](#) to human biological contexts.

"This model could help better determine which drugs should move from [animal testing](#) to humans," said Doug Brubaker, a Purdue assistant professor of biomedical engineering, who led the development and testing of this model as a postdoctoral associate at MIT.

"If there is a reason why the drug would fail, such as a resistance mechanism that wasn't obvious from the animal studies, then this model would also potentially detect that and help guide how a clinical trial should be set up," he said.

TransComp-R consolidates thousands of measurements from an animal model to just a few data coordinates for comparing with humans. The dwindled-down data explain the most relevant sources of biological differences between the animal model and humans.

From there, scientists could train other sets of models to predict a human's response to therapy in terms of those data coordinates from an animal model.

For infliximab, data from a mouse model and human hadn't matched up because they were different types of biological measurements. The [mouse model](#) data came in the form of intestinal proteins, whereas data from patients were only available in the form of expressed genes, a discrepancy TransComp-R was able to address.

TransComp-R helped Brubaker's team to find links in the data pointing toward a resistance mechanism in humans.

The team collaborated with researchers from Vanderbilt University to test the predicted mechanism in intestinal biopsies from a Crohn's disease patient and then with experiments in human immune cells.

The researchers used single-cell sequencing of a sample from an infliximab-resistant Crohn's disease patient to identify the cell types expressing the genes related to the resistance mechanism predicted by TransComp-R.

They then treated immune cells with infliximab and an inhibitor of the receptor identified by the [model](#) to be part of the resistance mechanism. The experiment showed that inhibiting the receptor enhanced the anti-inflammatory effects of infliximab, enabling the drug to be more effective because it could better control inflammation.

With additional testing to figure out a way to more precisely measure the markers of this resistance mechanism, doctors could use information about the drug response to determine if a patient needs a different course of treatment.

Since this study, Brubaker has been working with his former research group at MIT to apply the mathematical framework behind TransComp-R to identify mouse models predictive of Alzheimer's disease biology and immune signatures of vaccine effectiveness in animal studies of COVID-19 vaccine candidates.

"The modeling framework itself can be repurposed to different kinds of animals, different [disease](#) areas and different questions," Brubaker said. "Figuring out when what we see in [animals](#) doesn't track with what's happening in humans could save a lot of time, cost and effort in the [drug](#) development process overall."

**More information:** An interspecies translation model implicates integrin signaling in infliximab-resistant inflammatory bowel disease, *Science Signaling* (2020). [DOI: 10.1126/scisignal.aay3258](https://doi.org/10.1126/scisignal.aay3258) , [stke.sciencemag.org/content/13/643/eaay3258](https://stke.sciencemag.org/content/13/643/eaay3258)

Provided by Purdue University

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