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Model can predict success of treatments that manipulate the gut microbiota

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A new mathematical model can predict the effectiveness of microbiome therapies that manipulate the immune system through live bacteria and could help doctors choose the most appropriate treatment for people with inflammatory or allergic diseases, a study in *eLife* reveals.

Until now, it was experimentally intractable to identify the optimal combination of bacteria that would generate the desired anti-inflammatory treatment response. But researchers have now developed a model that predicted the most effective treatment in mice.

Introduction of therapeutically potent bacteria into patients with infections or metabolic diseases is an emerging approach with great promise. But there are two challenges standing in the way of its success. First, the bacteria must be able to set up home alongside the already resident microbes. Second, in the context of autoimmune diseases, they must stimulate a range of immune responses that dampen down unwanted inflammation. This study focused on stimulating one such group of immune cells called regulatory T-cells, or Tregs.

Single bacterial strains are less effective than groups of different strains. But testing the huge number of potential bacterial combinations experimentally simply isn't feasible.

"In previous work, our collaborators and paper co-authors identified 17 different strains of bacteria that can generate the required immune response, but determining the best combinations from these strains

would need more than 130,000 independent experiments," explains senior author Professor Vanni Bucci, Assistant Professor at the University of Massachusetts at Dartmouth, USA. "The goal of this study was to develop a mathematical model to rapidly and systematically select groups of bacteria that would optimally produce the desired immune response."

The team built a model using published and newly generated data showing which bacterial strains were most efficient at colonizing the gut and at stimulating Treg cells in germ-free mice, both individually and together. They then combined this model with another that predicts the growth and expansion of bacterial colonies in mice over time.

This allowed them to determine both the growth of each bacterial strain in the mice, and the extent of each strain's contribution to the increase in Treg immune cells. Based on this, they developed a way of scoring how well groups of bacteria colonize together and stimulate an immune response. They then tested every possible bacterial combination generating a ranked list of bacterial combinations.

To measure the model's accuracy, they tested five different four-strain combinations of bacteria in germ-free mice. They found that the bacterial combinations with the highest scores predicted by the model not only stimulated immune cells more potently, but also colonized more stably the gut - proving the value of including both measures in the model.

"Treatment of immune or inflammatory diseases is not necessarily achieved by targeting a single biological function but will require simultaneous manipulation of multiple processes within the host-immune system," said lead author Dr Richard Stein, Research Associate at the Dana-Farber Cancer Institute, USA. "To our knowledge, this is the first model that allows for the simultaneous prediction of the dynamics of

both the microbiota and the immune response. It can be considered a stepping stone to the development and rational design of microbiome therapies."

More information: Richard R Stein et al, Computer-guided design of optimal microbial consortia for immune system modulation, *eLife* (2018). DOI: 10.7554/eLife.30916

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