Scientists create first mathematical model that predicts immunotherapy success

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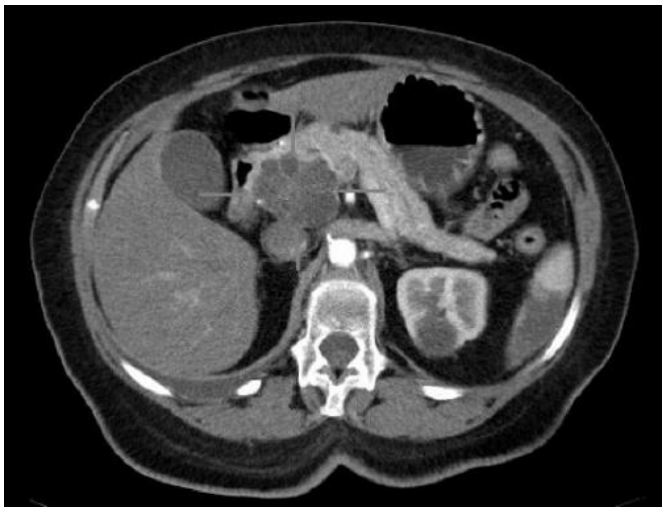

Axial CT image with i.v. contrast. Macrocystic adenocarcinoma of the pancreatic head. Credit: public domain

Researchers at the Icahn School of Medicine at Mount Sinai have created the first mathematical model that can predict how a cancer patient will benefit from certain immunotherapies, according to a study published in *Nature*.

Scientists have long sought a way to discover whether patients will respond to new checkpoint inhibitor immunotherapies and to better understand the characteristics that indicate a tumor can be successfully treated with them. The proposed mathematical model, which captures aspects of the tumor's evolution and the underlying interactions of the tumor with the immune system, is more accurate than previous genomic biomarkers in predicting how the tumor will respond to immunotherapy.

"We present an interdisciplinary approach to studying immunotherapy and immune surveillance of tumors," said Benjamin Greenbaum, PhD, the senior author, who is affiliated with the departments of Medicine, Hematology and Medical Oncology, Pathology, and Oncological Sciences at The Tisch Cancer Institute at the Icahn School of Medicine at Mount Sinai. "This approach will hopefully lead to better mechanistic predictive modeling of response and future design of therapies that further take advantage of how the immune system recognizes tumors."

This novel model also has the potential to help find new therapeutic targets within the immune system and to help design vaccines for patients who do not typically respond to immunotherapy.

To create this model, researchers used data from melanoma and lung cancer patients being treated with immune checkpoint inhibitors. The model tracked many properties within the immune response to the drugs, particularly neoantigens, which are specific to mutating and growing tumors.

Neoantigens have the potential to be prime immunotherapy targets, and the proposed framework will likely be useful in studies of acquired resistance to immunotherapy and may be crucial for understanding the circumstances in which immunotherapy causes autoimmune-like side effects.

The first author of the study is Marta Luksza, PhD, a computer scientist from the Simons Center for Systems Biology at the Institute for Advanced Study. Dr. Greenbaum and Dr. Luksza also played an integral role in a companion piece of research led by researchers Vinod P. Balachandran, MD, Taha Merghoub, PhD, and Steven D. Leach, MD, at Memorial Sloan Kettering Cancer Center (MSK) that was also published in Nature today. That study showed how a similar model can be used to understand immune response in patients with pancreatic cancer who survive longer than others. Both studies demonstrate that this is a likely path forward to understanding when the immune system

will lead to productive recognition of a tumor.

"This research represents a big step forward in understanding why some tumors are more aggressive than others and being able to predict rationally which neoantigens will be the most effective at stimulating an immune response," said Dr. Balachandran, a member of the David M. Rubenstein Center for Pancreatic Cancer Research at MSK, and corresponding author of the companion study in *Nature*.

More information: A neoantigen fitness model predicts tumour response to checkpoint blockade immunotherapy, *Nature* (2017). nature.com/articles/doi:10.1038/nature24473

Identification of unique neoantigen qualities in long-term survivors of pancreatic cancer, *Nature* (2017). nature.com/articles/doi:10.1038/nature24462

Provided by The Mount Sinai Hospital

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