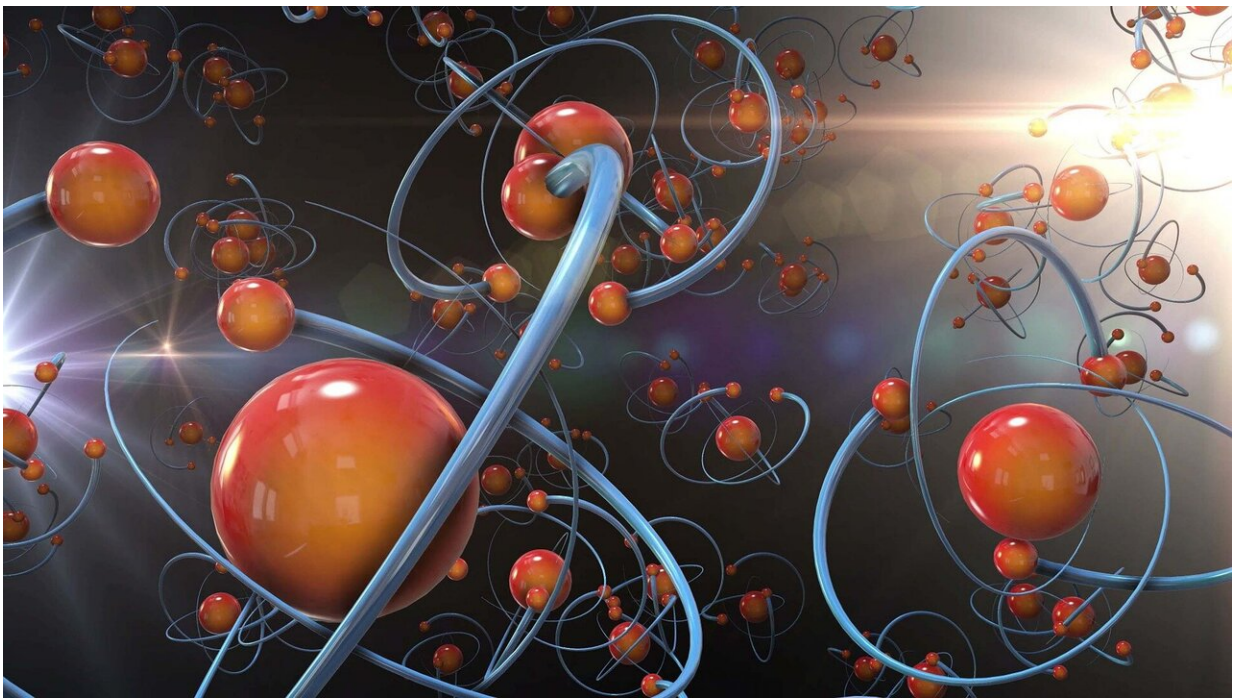


Researchers develop a small molecule that could make immunotherapy available to all cancer patients

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Researchers at Tel Aviv University and the University of Lisbon have jointly identified and synthesized a small molecule that could be a more accessible and effective alternative to an antibody that is successfully used to treat a range of cancers. Behind the groundbreaking development

is an international team of researchers led by Prof. Ronit Sachi-Fainaro, Head of the Center for Cancer Biology Research and Head of the Laboratory for Cancer Research and Nanomedicine at the Sackler Faculty of Medicine, Tel Aviv University, and Prof. Helena Florindo and Prof. Rita Guedes from the Research Institute for Medicines at the Faculty of Pharmacy, University of Lisbon. The results of the study were published in the *Journal for ImmunoTherapy of Cancer*.

"In 2018, the Nobel Prize in Medicine was awarded to James Allison and Tasuku Honjo for their contribution to the study of immunotherapy, the treatment of cancer through activation of the immune system," says Prof. Satchi-Fainaro, a 2020 Kadar Family Award recipient. "Honjo discovered that [immune cells](#) called T cells express the protein PD-1 that disables the T-cells' own activity when it binds to the protein PD-L1 expressed in cancer cells. In fact, the interaction between PD-1 and PD-L1 allows cancer cells to paralyze the T cells, preventing them from attacking the cancer cells. Honjo developed antibodies that neutralize either PD-1 or PD-L1, thereby releasing the T cells to fight cancer effectively."

The antibodies against PD-1/PD-L1 proteins are already approved for [clinical use](#) and are considered the great promise in the fight against cancer. This immunotherapy can significantly improve patient outcomes, without the [severe side effects](#) that accompany treatments such as chemotherapy. But the antibodies are expensive to produce, and hence not available to all patients. Moreover, the treatment does not affect all parts of the solid tumors because the antibodies are too large to penetrate and reach less accessible and less exposed areas of the tumor. Now, researchers at Tel Aviv University and the University of Lisbon have used bioinformatic and data analysis tools to find a smaller, smarter alternative to these antibodies.

"Post-doctoral researcher Dr. Rita Acúrcio started with thousands of

molecular structures, and by using computer-aided drug design (CADD) models and databases, we narrowed down the list of candidates until we reached the best structure," says Prof. Satchi-Fainaro.

"In the second stage, we confirmed that the small molecule controls tumor growth as effectively as the antibodies—it inhibits PD-L1 in animals engineered to have human T cells. In other words, we have developed a molecule that can inhibit PD-1/PD-L1 binding and remind the immune system that it needs to attack the cancer. Moreover, the new molecule has some major advantages over the antibody treatment.

"First of all, the cost: since the antibody is a biological rather than a synthetic molecule, it requires a complex infrastructure and considerable funds to produce, costing about \$200,000 per year per patient. In contrast, we have already synthesized the small molecule with simple equipment, in a short time and at a fraction of the cost. Another advantage of the small molecule is that patients will probably be able to take it at home, orally, without the need for IV administration in the hospital."

In addition to accessibility considerations, the experiments show that the small molecule improves the activation of immune cells inside the solid tumor mass.

"The surface area of a solid tumor is heterogeneous," explains Prof. Satchi-Fainaro. "If there are fewer blood vessels in a particular area of the tumor, the antibody will not be able to get inside. The small molecule, on the other hand, diffuses, and is therefore not entirely dependent on the tumor's blood vessels or on its hyperpermeability. I believe that in the future, the small molecule will be commercially available and will make immunotherapy affordable for [cancer](#) patients."

More information: Rita C. Acúrcio et al, Therapeutic targeting of

PD-1/PD-L1 blockade by novel small-molecule inhibitors recruits cytotoxic T cells into solid tumor microenvironment, *Journal for ImmunoTherapy of Cancer* (2022). [DOI: 10.1136/jitc-2022-004695](https://doi.org/10.1136/jitc-2022-004695)

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