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Researchers from the University of Lisbon and Tel Aviv University discovered a small molecule that stimulates the immune system to fight cancer

Researchers from the University of Lisbon and the University of Tel Aviv have discovered and synthesized a small molecule that may be a more affordable and effective alternative to antibodies used to treat various types of cancer. This work was developed by an international team led by Profs. Helena Florindo and Rita Guedes from the Research Institute for Medicines (iMed.ULisboa) of the Faculty of Pharmacy at the University of Lisbon, and by Prof. Ronit Satchi-Fainaro of Tel Aviv University School of Medicine, whose promising results 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 a discovery that led to a new class of cancer drugs based on releasing the “brakes” of the immune system, thus taking advantage of the activation of the patients’ immune system to destroy cancer. “Their discovery is based on the release of the body's natural defenses against cancer. This was a revolutionary discovery since, until then, the major aim was to directly target and destroy cancer cells, while this new therapy was based on a totally new principle targeting the negative immune checkpoints. On the one hand, Allison found that the CTLA-4 protein blocked the action of T lymphocytes, and developed a monoclonal antibody capable of inhibiting it, which was approved in 2011 by the FDA. On the other hand, Honjo discovered PD-1, another protein expressed on the surface of T cells, whose inhibition by monoclonal antibodies proved to be an effective strategy against cancer”, says Prof. Helena Florindo.

Antibodies against PD-1/PD-L1 proteins are also already approved for clinical use and have significantly improved the antitumor response of patients with different types of cancer, such as cutaneous melanoma, without the serious side effects associated to treatments such as chemotherapy. However, antibodies, as other therapies, also induce adverse effects, and the cost of treating a patient is around $200,000, which limits their wide availability to +patients. In addition, the size of monoclonal antibodies limits their penetration into less accessible and less exposed areas of solid tumors.

Now, this international team used computational and bioinformatic resources to find small molecules with the same ability to inhibit to PD-L1. “We defined specific criteria to discover molecules that would induce an antitumor effect by inhibiting the interaction between cancer cells and T lymphocytes by targeting the PD-1/PD-L1 interaction but would also have the ability cross plasma membranes. We would thus expect a stronger effect on the activation of these T

lymphocytes, in addition to being a cheaper alternative to monoclonal antibodies. It should be noted that an antibody is a biological molecule, not a synthetic one, and therefore has a complex structure" says Prof. Rita Guedes, the specialist in computational chemistry among this group of researchers.

"Post-doctoral researcher Dr. Rita Acúrcio developed this computational study which led to a list of promising candidates, which were further evaluated in tissues of patients with melanoma and breast cancer, both primary and metastatic, thanks to our close collaboration with Prof. Luís Costa and Sandra Casimiro, and Dr. Joaquim Brito, from Centro Hospitalar Universitário Lisboa Norte, as well as Dr. Marta Pojo and Vitor Farricha from the Portuguese Institute of Oncology in Lisbon. We were very happy to see a control of tumor growth, similar to the one obtained for the antibody used in the clinic, in addition to an increase in the number of active immune cells within the solid mass of this tumor. The next steps are also to evaluate its effectiveness when administered orally, since this would be a very important alternative for patients", says Prof. Helena Florindo.

This team continues to explore other candidates to regulate the immune response of cancer patients, so that in the future they may constitute therapeutic options for these patients, including those whose clinical condition does not allow their treatment with monoclonal antibodies.

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