# Cancers 'change spots' to avoid immunotherapy

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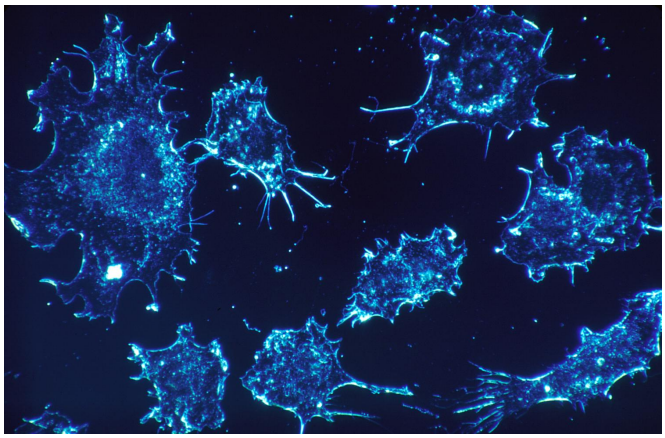

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Cancers can make themselves harder for new immunotherapies to see by 'changing their spots' - and switching off a key molecule on the surface of cells that is otherwise recognised by treatment.

Researchers found that they could test samples from patients with bowel cancer to identify which were most likely to respond to immunotherapy by assessing molecular changes within miniature tumours grown in the laboratory.

Using the mini tumours, the researchers identified existing drugs that could potentially be used in combination with immunotherapy to make it work for many more patients.

The team at The Institute of Cancer Research, London, and The Royal Marsden NHS Foundation Trust believe their findings could help increase the effectiveness of the antibody-based drug cibisatamab, and open up ways of assessing whether patients will respond to immunotherapy in the lab.

The study is published today (Monday) in the *Journal for Immunotherapy of Cancer* and was funded by Cancer Research UK and the NIHR Biomedical Research Centre at The Institute of Cancer research (ICR) and The Royal Marsden.

Immunotherapy is proving an exciting new way of treating cancer for a subset of patients, but there is no way currently of telling apart those who will benefit from those who will not, or of boosting the numbers of responders.

Cibisatamab is a promising new immunotherapy which acts as a matchmaker between cancer cells and the immune system.

One 'arm' attaches to a molecule called carcinoembryonic antigen (CEA) which is found on the surface of several types of cancer cell and is so common in bowel cancer that it is used to test for the disease. The other arm pulls over and activates a type of immune cell called a T cell, which can then attack the tumour.

But the team at the ICR and The Royal Marsden found that many mini bowel cancers grown in the laboratory were able to hide from treatment—they were able to 'change their spots' by switching from high to low levels of the CEA molecule.

Cibisatamab has shown promising results in early trials, but the researchers wanted to find out why some bowel cancers were resistant to treatment, and to identify ways of making it work for more patients.

They took biopsy samples from eight bowel cancer patients and used an innovative new technique, developed at the ICR, to grow mini replicas of their tumours in the lab.

The team found there were three groups of cells—those with high levels of CEA on the surface of most cancer cells in the tumour, those with low levels of CEA on most cells, and those with a mix.

Treatment with cibisatamab reduced growth by 96 per cent in tumours with high levels of CEA, but by only 20 per cent for low CEA, and 53 per cent in tumours with mixed levels of CEA.

Using specialised equipment, the researchers separated out individual cells with high or low CEA and let them settle for a month to grow back into tumours. They found that the CEA levels had changed in the regrown tumours—suggesting cells can quickly switch to a different state and could use this to hide from immunotherapy.

However, looking closely at the genes that were active in the mini tumours, they found that cells with low levels of CEA on their surface had increased activity in the WNT pathway of genes—which is targeted by several new drugs that are in development.

Treating the bowel cancer mini tumours with WNT pathway targeting drugs known as tankyrase inhibitors and porcupine inhibitors raised CEA levels—increasing their vulnerability to immunotherapy.

Study leader Dr. Marco Gerlinger, Team Leader in Translational Oncogenomics at The Institute of Cancer Research, London, and Consultant Oncologist at The Royal Marsden, said:

"Cancer is very good at hiding from the body's immune system. The latest successful immunotherapies work by acting as a matchmaker to bring the immune system together with cancer, so that it can see it and attack it.

"Our study has found that bowel cancers have a way of dodging even the newest of immunotherapies—changing their spots by altering the levels of a key molecule on the surface of cells, so that they become harder to recognise.

"We used a new technique for growing miniature replicas of tumours to develop a way of testing whether patients will respond to immunotherapy. And best of all, we were able to identify an existing inhibitor of the WNT pathway which could be used to reverse this process. We hope that this could in future help immunotherapies work in more patients, by making cancer cells more visible to immune cells."

Professor Paul Workman, Chief Executive of The Institute of Cancer Research, London, said:

"As we move away from one-size-fits-all therapy for cancer, it's so important that we are able to identify which patients are most likely to respond to a drug, and do everything we can to avoid resistance to treatment for as long as possible.

"This research reveals a way in which cancers are able to hide from a promising new type of immunotherapy. Although the work is still in its early stages, it could be used to develop a test for who is most likely to respond to the drug, and points to possible drug combinations that might prevent or delay resistance."

Dr. Andrew Beggs, a Cancer Research UK expert on bowel cancer, said:

"Mini lab-grown tumours have the potential to transform the way we test drugs before clinical trials. From a tiny biopsy, we can recreate the tumour in the lab to better reflect a patient's cancer than with traditional ways of growing cells.

"This study is an example of creating mini bowel cancer tumours, known as organoids, to guide future research of an experimental immunotherapy. And we can use organoids to learn more about how cancers might respond to drugs, testing many treatments simultaneously to find potential vulnerabilities we might target. Organoid models are increasingly being used in this way to help researchers study, develop and refine possible treatments to test in clinical trials."

Provided by Institute of Cancer Research