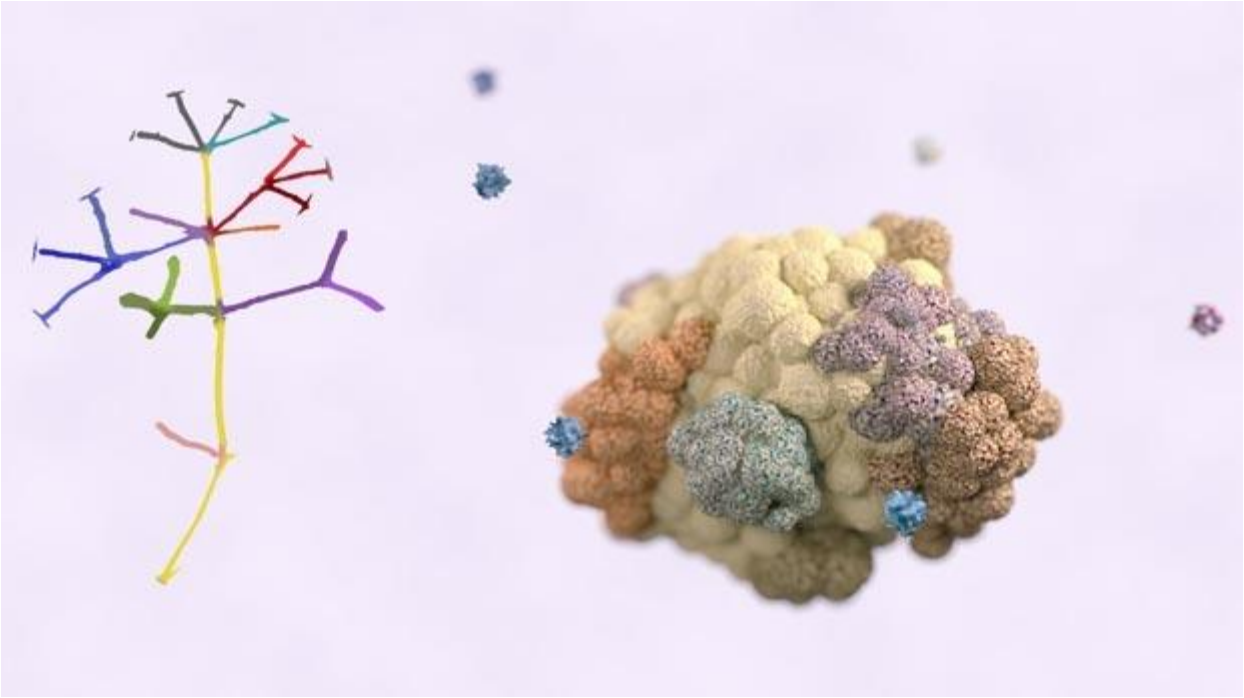
New immunotherapy discovery could give treatments the precision they need



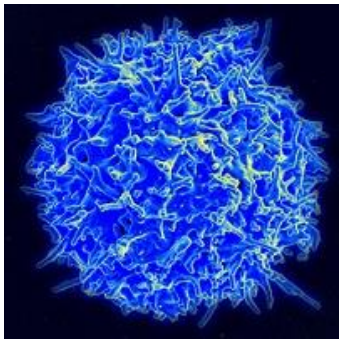
Over the past few years, immunotherapies – treatments which harness the power of the immune system to fight cancer – have been making headlines around the world.

These powerful new weapons are exciting because once the immune system has 'locked-on' to a cancer cell it's persistent and ruthless in taking it out. For patients in whom they work, immunotherapies can produce long-lasting effects. Some have even suggested they can cure certain cancers.

But the biggest challenges for immunotherapy have been identifying which molecules on the cancer cells are the best targets, as well as how to get past cancer's defences.

For now, the immunotherapy treatments available to patients are powerful-but-blunt weapons, which in some cases can result in a number of potentially serious side effects. What's urgently needed are treatments that can guide immune cells to specifically attack a tumour, while leaving healthy cells alone.

And today, Cancer Research UK scientists have published a new study in the journal Science that may have uncovered the intelligence needed to precisely guide these new weapons. But before we go into detail about what they found, and its implications for future research, let's recap how different immunotherapies work.



Helping the immune system spot cancer

Over the years, researchers have tried many different approaches to turn the immune system against cancer, such as cutting the brakes on immune cells, flagging cancer cells for destruction, or genetically engineering a patient's immune cells to directly target cancer cells.

But most of these depend on the immune system being able to recognize cancer cells as the true threat that they are. So how does this happen?

As we've written about before, almost all cells in our bodies display samples of the proteins they produce on their surface.

These small samples, called antigens, act as 'flags' for the immune system.

When a cell becomes damaged or infected, it changes the proteins it makes, displaying these as new antigens on its surface. Specialised immune cells, called T-cells, can then spot these antigens, releasing signals that destroy the damaged cell if the antigens aren't looking the way they should.

The DNA faults inside cells that lead to cancer can also change how proteins 'look' to the immune system. So, theoretically, once the immune system recognises a cancer specific antigen, it should destroy all cancer cells that carry that flag. But this doesn't always happen. And researchers have been working hard to find out exactly why.

Is recognition enough?

"Essentially there are two competing ideas", says Dr Sergio Quezada, from University College London, and one of the world's leading experts in how the immune system interacts with cancer.

"If immune cells waste precious resources chasing after antigens that aren't present on the surface of all the cancer cells then they risk missing parts of the tumour entirely"

One possibility is that the immune system simply needs to recognise cancer cells. Once it begins breaking open and killing tumour cells a domino effect takes place, allowing the immune system to recognise more and more 'funny looking' molecules.

"The other possibility is that the initial antigen that excites the immune system does matter. If immune cells waste precious resources chasing after antigens that aren't present on the surface of all the cancer cells then they risk missing parts of the tumour entirely."

Developing better immunotherapies is reliant on figuring out which of these ideas is true. But to answer this question would require an enormous amount of data from patients' tumours.

Fortunately, another Cancer Research UK- funded team, working on a different challenge, have developed a set of tools that might help provide that answer.

An evolving solution

The Francis Crick Institute's Professor Charlie Swanton is one of the world's leading experts in the genetics behind how tumours grow and change, and the gene faults (mutations) that fuel this.

"One of the reasons why some cancers – lung cancer and melanoma in particular – are so hard to treat is because they evolve so rapidly they quickly outpace the drugs we use to stop them," he says.

“These cancers have been exposed to many DNA damaging substances – such as cigarette smoke or UV light – and this damage gives rise to many different faults in their DNA.”

But as the data has poured in, Swanton’s team had begun to wonder whether this overwhelming complexity, which can make cancers so resistant to certain treatments, may be the very thing that reveals it to the immune system.

Swanton’s team has already shown that some early DNA faults at the ‘trunk’ of a tumour’s evolutionary ‘tree’ can persist late in its development. But if these early origins of a cancer’s development are also being presented as antigens on the surface of tumour cells, they could provide an ideal target for the immune system to attack.

So Swanton and Quezada’s team’s joined forces to find out if this is the case.

“We had suspected that the diversity of mutations we see in tumour evolution would be reflected by the antigens present on the cancer cells – but until now we had no proof”

Dr Nicholas McGranahan works in Swanton’s team, mapping how tumours evolve and change using complex software. Turning this computational firepower to analysing cancer’s immune signature was a new idea: “We have been using this type of analysis to predict what sorts of mutations are present across the tumour, so we wondered whether we could also use it to look for antigens shared on all tumour cells,” McGranahan explains.

“We had suspected that the diversity of mutations we see in tumour evolution would be reflected by the antigens present on the cancer cells – but until now we had no proof.”

To test this, they turned to a treasure trove of data called The Cancer Genome Atlas (TCGA), which records genetic data on thousands of patients who’ve been treated for cancer, alongside how they fared after treatment.

Using these data from over 200 patients with one of two different types of lung cancer (adenocarcinoma and squamous cell carcinoma) they predicted how many antigens a tumour contained, and the proportion that were common throughout the tumour.

Strikingly, in the lung adenocarcinoma patients, they saw that when the tumour cells contained many antigens that were shared across the tumour, the patients generally fared better.

But in people with squamous cell carcinoma the team didn’t find the same association. Instead, the squamous cell carcinoma cells tended not to display antigens on their surface – providing them with a potential way of escaping the immune system.

But to understand why there might be an association at all, the researchers took a closer look at tumour samples from two patients with lung cancer that had a similar smoking history.

After first running their antigen prediction analysis on the two tumour samples, the team then produced hundreds of these predicted antigens in the lab to ‘fish out’ any immune cells in the tumour samples that recognised and latched on to them.

Just three antigens were up to the job. One in the first sample and two in the second and, crucially, each of these antigens had originally been predicted to be present on every cancer cell in the tumour sample – as the animation below explains.

So if these immune cells were capable of recognising every cell in the tumour, why didn't they kill it?

Breaking down cancer's defences

Clearly, these tumours contained immune cells capable of recognising the cancer cells as dangerous, but somehow the cancer was keeping them at bay.

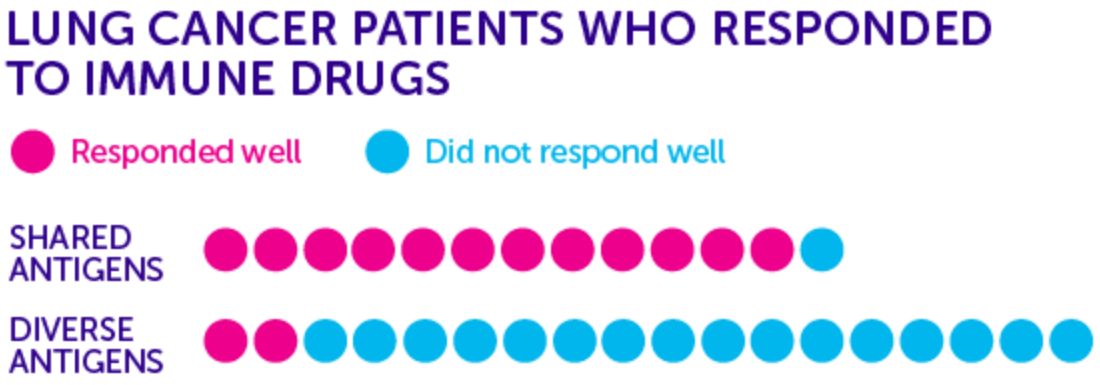
Tumours use tricks to escape destruction by immune cells, including releasing signals that suppress immune cells. To see if these signals might be holding the immune system back from recognising the shared antigens, the team reanalysed the adenocarcinoma samples from the TCGA. Crucially, they found that tumours containing lots of antigens that were shared across the tumour also produced high levels of an immune-dampening molecule called PD-L1.

This suggests that while these cancer cells should be highly vulnerable to immune attack – because they are covered in shared antigens – they have to find a way of holding the immune system at bay to survive.

To test this idea further, the team then looked at data from patients in a US study, who'd received a checkpoint immunotherapy drug called pembrolizumab (Keytruda), which blocks the immune cells from receiving the PD-L1 'stop signal'.

After running their antigen prediction programme, the team then grouped the tumours into those that had many antigens on all cancer cells and those that carried lots of different tumour antigens on their surface.

Of 13 patient tumours that had many shared antigens, 12 had responded well to the immunotherapy treatment. This compared with just two out of 18 patients responding well when the team found lots of different antigens across the tumour.



The picture was getting clearer. Tumours with many shared antigens attracted immune cells, which the cancer cells then had to suppress to stay alive. But if drugs were given that break through the cancer's

defences, patients whose cancers had antigens that were found across the tumour appeared to benefit the most.

So what next?

The immediate implications of this work are for researchers developing new immunotherapies. It shows that there are 'good' and 'bad' targets for immunotherapy treatments. And it strongly suggests the antigen the immune system recognises really does matter.

This is important, because many experimental treatments assume that simply showing any antigen to the immune system will be enough to wake it up. But if the target isn't present on all the cancer cells, then the treatment risks leaving some cells behind, where they can regroup and the tumour can come back.

The next step is to work out how doctors could use the team's prediction programmes to make better decisions over which treatments to offer patients.

"Although it's early days, it offers hope that we might just be able to turn the tide against advanced cancer – something we desperately want for our patients"

In some cases, cancers may be hiding the 'flags' that immune cells recognise, so other treatments may need to be explored.

But if scientists can harness the immune cells that do recognise these targets it could lead to new treatments.

For Swanton, the study reveals a welcome weakness behind cancer's sometimes baffling complexity.

"Since the true genetic complexity of a growing tumour began to be revealed a few years ago, we've all been scratching our heads trying to work out a way round it," he says.

But he now believes we are beginning to find ways to "develop truly effective treatments for advanced disease that exploit the underlying order in the chaos".

"It's incredibly exciting," he adds, "and although it's early days, it offers hope that we might just be able to turn the tide against advanced cancer – something we desperately want for our patients."

Swanton, Quezada and their teams are now working to turn this idea into something that could be applied to many more cancers, finding unique targets on all cancer cells and not the healthy cells.

Immunotherapy is an incredibly exciting weapon against cancer – as recent headlines make clear.

Thanks to the combined ingenuity of two of our teams of cancer researchers, we may have found the tools necessary to give immunotherapy the precision guidance that patients so desperately need.