NEWS IN FOCUS

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Immunotherapy offers hope to some people with hard-to-treat cancers — but it can backfire.

IMMUNOTHERAPY

Cancer drugs may speed tumours in some people

Scientists want to understand how immunotherapy may sometimes make cancer worse.

BY HEIDI LEDFORD

Powerful drugs that unleash the immune system hold the promise of wiping out cancer for some people with advanced disease. But two recent studies[1,2] suggest that these therapies, called PD-1 inhibitors, might backfire in some patients — speeding cancer's spread. Now scientists want to find out why.

The latest studies are too small to justify a change in how physicians treat patients. But the research has prompted calls for bigger clinical trials to explore how immunotherapy drugs that are intended to rein in tumours could instead spur them on.

"With these small numbers, you're always stuck being a little unsure," says Elad Sharon, a cancer researcher at the US National Cancer Institute in Bethesda, Maryland. What's needed, he says, is larger studies that make tumour images available for analysis by outside scientists. He would also like to see cancer researchers reach beyond their specialty. "What we should be doing probably is more cross-pollinating with other branches of medicine that look at the immune system," he says.

Over the past five years, immunotherapies have revolutionized the treatment of some stubborn cancers. Some of these therapies come with severe side effects, but the unwanted effects of PD-1 inhibitors are relatively mild.

This has led some physicians to give PD-1 inhibitors to people with cancer who have ▶

tried all other treatments — even if the immunotherapy has not been shown definitively to work for their disease, says Razelle Kurzrock, a cancer researcher and physician at the University of California in San Diego. "Even if there's a small chance of a response, the response itself can be so good," she says. "We've developed the attitude: let's go ahead and try it."

But one day Kurzrock compared notes with a colleague and found that each of them had a patient whose tumours had grown unusually fast during treatment with PD-1 inhibitors. Her colleague came back a few days later and noted that the patients shared the same rare genetic alteration: extra copies of the cancer-driving genes *MDM2* or *MDM4*.

Kurzrock began collecting anecdotes about people whose tumours had advanced rapidly after immunotherapy treatment. Even after collecting examples from several sources, she felt nervous about releasing her results. "We thought, 'Who's going to publish this? They're not going to believe us,'" she says.

Charles Ferté, an oncologist at the Gustave Roussy Institute in Villejuif, France, had stumbled on the same problem. He recalls a meeting in which several physicians reported bizarre responses to PD-1 treatment. "Some friends and colleagues were saying, 'I treated lung patients with that drug and the tumour completely exploded in two weeks,'" he says.

Ferté and his colleagues decided to launch a systematic study of tumour growth in their patients. Last November, they published their results: of 131 people who received anti-PD-1 therapies, 9% developed "hyperprogressive" disease, with accelerated tumour growth[1]. The phenomenon seemed to be more common in people over the age of 65.

GENETIC LINKS

On 28 March, Kurzrock and her colleagues published data on 155 people treated with PD-1 inhibitors and other immunotherapies[2]. Six of the people had extra copies of *MDM2* or *MDM4*, and 10 had mutations in a gene called *EGFR*, which is associated with cancer. The team did not see any correlation between age and rapidly worsening disease, but they did notice that tumours grew faster in four of those with the extra *MDM2* or *MDM4* genes, and in two of the people with *EGFR* mutations.

Both teams are still trying to understand how immunotherapy might backfire in cancer patients. Kurzrock speculates that the drugs could be unleashing proteins called growth factors that stimulate certain tumours. Sharon wonders whether clues could be gleaned from research on the PD-1 protein's effects on infectious diseases. Early studies found that blocking the protein could stimulate immune responses against some viruses, but it suppressed responses to the mycobacterium that causes tuberculosis.

For now, Sharon says there is still not enough evidence to say for sure that the rapid tumour growth can be pinned on immunotherapy. The measures that Ferté's team used to study tumour growth have not yet been widely tested for use in clinical studies, he notes. "What if this happens with other drugs as well, and we just weren't looking for it?" he says.

Ferté agrees that the evidence against immunotherapy is not strong enough to warrant dramatic changes in how patients are treated. "I would still prescribe it for older patients," he says. "But we will pay special attention." ■

1. Champiat, S. *et al. Clin. Cancer Res.* http://dx.doi.org/10.1158/1078-0432.CCR-16-1741 (2016).
2. Kato, S. *et al. Clin. Cancer Res.* http://dx.doi.org/10.1158/1078-0432.CCR-16-3133 (2017).

ECONOMICS

NIH grants yield windfall

More than 30% of biomedical studies funded by the US National Institutes of Health are later cited in commercial patents.

BY ELIE DOLGIN

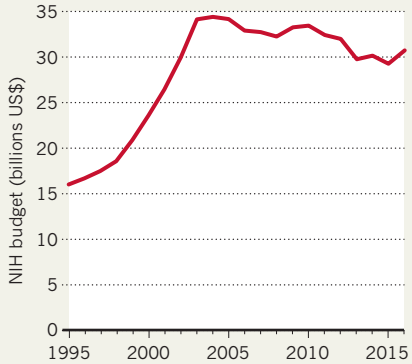
US President Donald Trump wants to gut government funding for biomedical research, but an analysis suggests that projects backed by the country's National Institutes of Health (NIH) have much broader economic benefits than suspected.

Between 1980 and 2007, 8.4% of NIH grants led directly to a patent, researchers report today in *Science*[1]. But more than three times that number — 30.8% — produced a scientific article that was later cited in a commercial patent for a drug, device or other medical technology. That indirect benefit was more pronounced for patents related to drugs sold in the United States, with less than 1% of NIH grants leading directly to patents but 5% spawning papers that were mentioned in a patent related to a drug that reached the market.

Politicians tend to focus on how often academic researchers obtain patents or create companies based on their work, says Marty Grueber, research director for the consulting firm TEConomy Partners in Cleveland, Ohio. But the analysis shows that research supported by the NIH has a surprisingly big indirect impact on patent activity — a proxy for overall economic benefit.

SCIENCE SPENDING

The US National Institutes of Health (NIH) is the world's largest biomedical research agency — but President Donald Trump wants to cut its budget by US$5.8 billion in 2018.



SOURCE: AAAS

"Whether we focus on scientific or technological advancement, these findings underscore the value of investing in a diverse portfolio," said Mike Lauer, the NIH's deputy director for extramural research, in a statement.

The *Science* analysis comes at a pivotal moment for the agency. Trump has proposed cutting the NIH's roughly US$32-billion budget by 18%, or $5.8 billion, in 2018 (see 'Science spending'). And the president is rumoured to be pushing for a $1.2-billion cut from the agency's 2017 budget. Although it's not clear whether Congress will accept Trump's plans, the proposals have made researchers nervous.

Lawmakers who want to shrink the budget of science-funding agencies often single out studies that they view as wasteful. In January, for example, Republican Senator Jeff Flake of Arizona lampooned the NIH's decision to spend $817,000 on a study about the evolution of proteins found in primate saliva — one of 50 projects that the senator highlighted in a report called 'Wastebook: PORKémon Go'.

But it's exactly this kind of basic research that can yield unexpected commercial