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

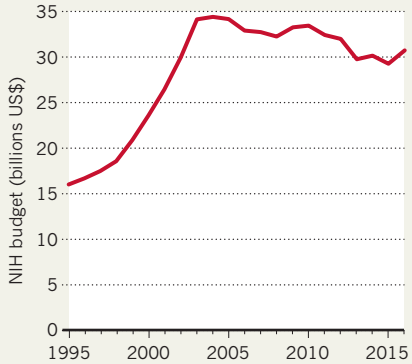
US President Donald Trump wants to gut government funding for biomedical research, but an analysis suggests that projects backed by the country's National Institutes of Health (NIH) have much broader economic benefits than suspected.

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

windfalls, says study co-author Danielle Li, an economist at Harvard Business School in Boston, Massachusetts. "Just because a grant doesn't seem to scream, 'I'm going to be extremely commercially relevant' or 'I'm going to cure cancer' doesn't mean it might not cure cancer," she says.

The study by Li and her colleagues, which examined more than 365,000 grants issued between 1980 and 2007, also considered whether funding for basic or applied research triggered more patents. The scientists tried every definition of 'basic research' they could think of, but in each of their analyses, basic and applied research were equally likely to be cited in patents.

"Their findings here demonstrate that there is commercial value to funding basic science," says Ross DeVol, chief research officer at the Milken Institute, an economics think tank in Santa Monica, California. "That may be the most important piece of this."

PAPER TRAIL

Li's study builds on a 2015 report in which Grueber showed that every $100 million the NIH hands out in grants leads to about six new patents[2]. Those estimates, however, omitted the knock-on effects of scientific papers — which are the main output of the academic system.

When Li and her colleagues included the impact of papers later cited by patents, they found that the average number of patents generated by a $100-million boost in NIH funding went up to 23. The researchers then used a series of rough calculations to extrapolate the commercial impact of those patents. As they report in a companion paper currently under review at an economics journal[3], each $1 in NIH funding generates an estimated $1.40 in drug sales — a figure that doesn't include the economic benefit accrued through the development of devices, surgical techniques, public-health improvements or other non-pharmaceutical applications of NIH-supported research.

From an economic standpoint, "we're under-investing" in biomedical research, says Pierre Azoulay, an economist at the Massachusetts Institute of Technology in Cambridge, and Li's co-author on both studies. "The idea that we're going to get to a better place by cutting [the NIH budget] is ridiculous." ■

1. Li, D., Azoulay, P. & Sampat, B. N. *Science* http://dx.doi.org/10.1126/science.aal0010 (2017).
2. Grueber, M. & Tripp, S. *Patents as Proxies Revisited: NIH Innovation 2000 to 2013* (Battelle Technology Partnership Practice, 2015).
3. Azoulay, P., Graff Zivin, J. S., Li, D. & Sampat, B. N. NBER Working Paper 20889 http://dx.doi.org/10.3386/w20889 (2017).

PAUL NICKLEN/NGC

The skull of 'Naia', a young girl whose bones were found in a cave on Mexico's Yucatán Peninsula.

PALAEOANTHROPOLOGY

Ancient bones show girl's tough life

Mexican teenager was malnourished but roamed widely.

BY TRACI WATSON

For more than 12,000 years, the adolescent girl's bones lay deep in a Mexican cave. Now, analysis of her skeleton is revealing details of her harsh existence in the early Americas — which probably included pregnancy and childbirth before an early death.

The bones show that the girl, whom researchers nicknamed Naia, is likely to have travelled long distances on foot, but didn't carry much on her journeys. The skeleton also reveals that Naia experienced severe and repeated nutritional stress that scarred her bones and teeth, according to results presented on 30 March at a meeting of the Society for American Archaeology in Vancouver, Canada.

"She's telling us a story," says James Chatters, an archaeologist with Applied Paleoscience in Bothell, Washington, and principal investigator of the research on Naia, a project of Mexico's National Institute of Anthropology and History in Mexico City. "It was a very hard life."

Naia has already helped to illuminate the origins of the first Americans. In 2014, Chatters and his colleagues reported that her DNA confirms the idea that a single group of Asian emigrants gave rise to both the earliest American settlers and modern Native Americans (J. C. Chatters *et al. Science* **344,** 750–754; 2014).

For that work, divers examined Naia in the water-filled cavern in the Yucatán Peninsula where she was discovered in 2007. But intruders subsequently tampered with her remains. To prevent further meddling, the bones were gently carried out of the cave in 2014 and 2016 — which also gave scientists easier access to the specimens. ▶