Ravindra Gupta, a microbiologist at the University of Cambridge, UK, who led the team that treated Castillejo, says that the latest study "cements the fact that CCR5 is the most tractable target for achieving a cure right now".

The Düsseldorf patient had extremely low levels of HIV, thanks to ART, when he was diagnosed with acute myeloid leukaemia. In 2013, a team led by virologist Björn-Erik Jensen at Düsseldorf University Hospital in Germany destroyed the patient's cancerous bone marrow cells and replaced them with stem cells from a donor with the CCR5Δ32/Δ32 mutation.

Over the next five years, Jensen's team took tissue and blood samples from the patient. In the years after the transplant, the scientists continued to find immune cells that specifically reacted to HIV, which suggested that a reservoir remained somewhere in the man's body. It's not clear, Jensen says, whether these immune cells had targeted active virus particles or a "graveyard" of viral remnants. The researchers also found HIV DNA and RNA in the patient's body, but these never seemed to replicate.

A 'very rocky road'

In an effort to understand more about how the transplant worked, the team ran further tests, which included transplanting the patient's immune cells into mice engineered to have human-like immune systems. The virus failed to replicate in the mice, suggesting that it was nonfunctional. The final test was for the patient to stop taking ART. "It shows it's not impossible – it's just very difficult – to remove HIV from the body," Jensen says.

The Düsseldorf patient said in a statement that the bone marrow transplant had been a "very rocky road", and added that he planned to devote some of his life to supporting research fundraising.

Timothy Henrich, an infectious-disease researcher at the University of California, San Francisco, says the study is very thorough. That several people have been successfully treated with a combination of ART and HIV-resistant donor cells makes the chances of achieving an HIV cure in these individuals very high.

Gupta agrees, although he adds that in some cases the virus mutates inside a person and finds other ways to enter their cells. It's also not clear, he says, whether the chemotherapy that the people received for their cancer before their bone marrow transplants might have helped to eliminate HIV by preventing infected cells from dividing.

But it's unlikely that bone marrow replacement will be rolled out to people who don't have leukaemia, because of the high risk associated with the procedure, particularly the chance that an individual will reject a donor's marrow. Several teams are testing the potential to use stem cells taken from a person's own body and then genetically modified to have the CCR5Δ32/Δ32 mutation[2,3], which would eliminate the need for donor cells.

Jensen says that his team has performed transplants for several other people affected by both HIV and cancer, using stem cells from donors with a CCR5Δ32/Δ32 mutation, but that it is too early to say whether those individuals are virus-free.

1. Jensen, B.-E. O. *et al. Nature Med.* https://doi.org/10.1038/s41591-023-02213-x (2023).
2. Holt, N. *et al. Nature Biotechnol.* **28**, 839–847 (2010).
3. Xu, L. *et al. N. Engl. J. Med.* **381**, 1240–1247 (2019).

BIG DINO, LITTLE DINO: HOW *T. REX*'S RELATIVES CHANGED THEIR SIZE

'Impressive' fossil analysis reveals why some dinosaurs were massive but their cousins were tiny.

By Dyani Lewis

A sweeping analysis of shin bones has given researchers a glimpse into how some dinosaurs evolved into mega-beasts such as *Tyrannosaurus*, and others into smaller, bird-like creatures. The work reveals that dinosaurs used more than one evolutionary trick to become larger – or smaller – over time (M. D. D'Emic *et al. Science* **379**, 811–814; 2023).

Prevailing wisdom held that large-bodied animals are bigger than their smaller-bodied relatives because they grow faster during their most rapid period of growth. That trend holds true for modern animals including birds and mammals – elephants and ostriches grow faster than chihuahuas and sparrows, for example.

It's not the case for all animals. Crocodiles and alligators, for instance, become large because they grow for a long time. But palaeontologists had assumed that for theropod dinosaurs – a group that includes the iconic *T. rex* and which spawned modern birds – large species got big through rapid growth spurts. "It's kind of become the established idea in dinosaurs," says palaeontologist Michael D'Emic at Adelphi University in Garden City, New York.

But that's not what D'Emic found when he sawed into the bones of *Majungasaurus*, a 7-metre-long *T. rex* relative that lived 66 million years ago on what is now Madagascar. The speed of growth in dinosaurs is recorded in rings laid down each year in their bones. Instead of seeing wide rings corresponding to a rapid adolescent growth spurt, D'Emic

MARCO ANSALONI/SPL

Theropod dinosaurs such as *Tarbosaurus bataar* grew large or small in a range of ways.

found lots of narrow growth rings, suggesting that *Majungasaurus* had become large over a prolonged period.

"I was very surprised," he says. The next dinosaur he examined, a similar-sized beast called *Ceratosaurus*, was the opposite – a big dinosaur that grew fast during its growth spurt, says D'Emic.

Bone growth rings

Over a decade, D'Emic and his colleagues amassed bone growth-ring measurements from 42 theropod species to see which strategies led to large and small bodies. They found that 31% of theropod species were larger than their ancestors because of faster growth and 28% because of prolonged growth. Meanwhile, 21% became smaller than their ancestors by shortening their growth spurts, and 19% by slowing growth.

The study covered theropod species that lived between 230 million years ago and the end of the Cretaceous period 66 million years ago, when a mass-extinction event wiped out the non-avian dinosaurs. It's "a huge evolutionary timescale" to include in an analysis, says Vera Weisbecker, an evolutionary biologist at Flinders University in Adelaide, Australia. "That is really impressive," she says. "It's just fascinating that there are so many developmental ways to become big or small."

Palaeontologist Kevin Padian at the University of California, Berkeley, says the analysis is the kind of work that needs to be done, animal group by animal group, to understand how body size evolves.

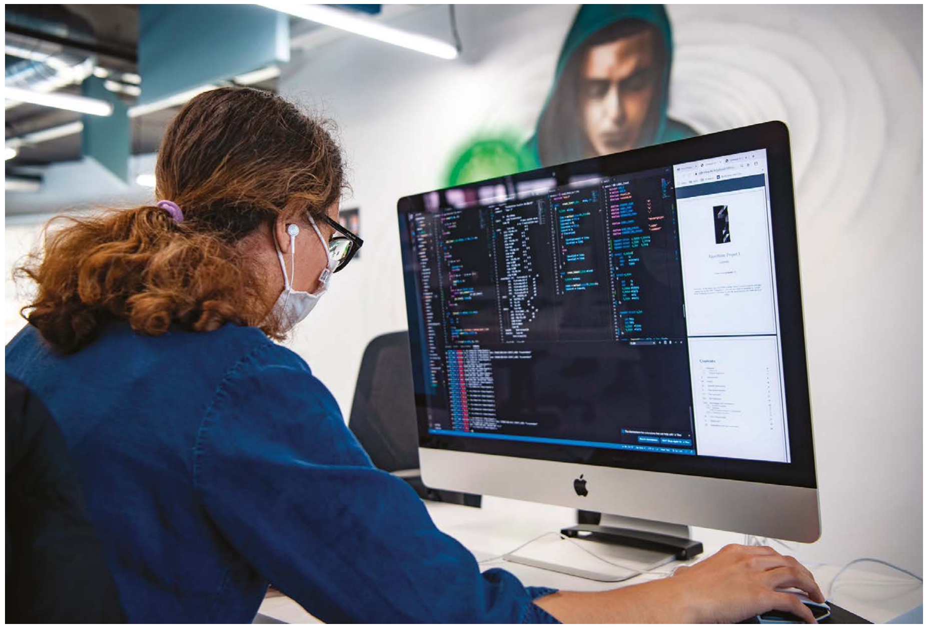
Drivers of change

But Meike Köhler, an evolutionary palaeobiologist at the Catalan Institution for Research and Advanced Studies in Barcelona, Spain, says the findings are not surprising because previous work has shown a range of growth strategies across animal species. Köhler would like to see an analysis that considers what ecological circumstances influenced how animals changed in size over time.

Weisbecker says that the growth strategy used might be related to evolutionary pressures. "If you looked at all the ones with explosive early growth, you might be able to test if they happen to be the ones that are more likely to be predated on, for example," she says.

For each species, the growth strategy that led to its individual body size probably related to its unique environment, says Padian. "It's not a one-size-fits-all, which is a good thing for us to learn," he says. "We might have thought that, but they've documented it."

D'Emic says he and his team are conducting similar analyses on other groups, including mammals – a group that contains many more species to sample – to see whether the diversity is found in other branches of the evolutionary tree.



FADEL SENNA/AFP/GETTY

AI tools have allowed researchers to solve complex mathematical problems.

HOW WILL AI CHANGE MATHEMATICS?

AI tools already help formulate new theories and solve problems. But they're set to shake up maths even more.

By Davide Castelvecchi

As interest in chatbots spreads like wildfire, mathematicians are beginning to explore how artificial intelligence (AI) could help them to do their work. Whether it's assisting with verifying human-written work or suggesting new ways to solve difficult problems, automation is changing the field in ways that go beyond mere calculation, researchers say.

"We're looking at a very specific question: will machines change math?" says Andrew Granville, a number theorist at the University of Montreal in Canada. A February workshop at the University of California, Los Angeles (UCLA), explored this question, aiming to build bridges between mathematicians and computer scientists. "Most mathematicians are completely unaware of these opportunities," says one of the event's organizers, Marijn Heule, a computer scientist at Carnegie Mellon University in Pittsburgh, Pennsylvania.

Akshay Venkatesh, a 2018 winner of the prestigious Fields Medal who is at the Institute for Advanced Study in Princeton, New Jersey, kick-started a conversation on how computers will change maths at a symposium in his honour last October. Two other recipients of the medal, Timothy Gowers at the Collège de France in Paris and Terence Tao at UCLA, have also taken leading roles in the debate.

"The fact that we have people like Fields medallists and other very famous big-shot mathematicians interested in the area now is an indication that it's 'hot' in a way that it didn't used to be," says Kevin Buzzard, a mathematician at Imperial College London.

AI approaches

Part of the discussion concerns what kind of automation tools will be most useful. AI comes in two major flavours. In 'symbolic' AI, programmers embed rules of logic or calculation into their code. "It's what people would call 'good old-fashioned AI'," says Leonardo de Moura, a computer scientist at Microsoft Research in Redmond, Washington.

The other approach, which has become extremely successful in the past decade or so, is based on artificial neural networks. In this type of AI, the computer starts more or less from a clean slate and learns patterns by digesting large amounts of data. This is called machine learning, and it is the basis of 'large language models' (including chatbots such as ChatGPT; see page 20), as well as the systems that can beat human players at complex games