levels and mitochondrial function in cultured mouse liver cells. The authors therefore developed chemical inhibitors of ACMSD, and tested whether these inhibitors could improve outcomes in mouse models of two ageing-related diseases: diet-induced fatty liver disease and acute kidney injury.

Earlier work had already described a beneficial effect of augmenting NAD^+ in each of these settings[9,10]. Katsyuba and colleagues' data confirmed the potential for therapeutic NAD^+ augmentation — treatment with their inhibitors protected against disease in these models. The results also suggest that increases in the *de novo* NAD^+ synthesis pathway alone are sufficiently robust to ameliorate liver and kidney diseases associated with low NAD^+ levels. However, proving this will require a demonstration that the benefit of ACMSD inhibition derives from the increase in NAD^+, rather than from another mechanism such as depletion of the molecule picolinic acid, which is produced by ACMSD-mediated degradation of ACMS. If proved, this finding would be consistent with a study[11] that identified a different enzyme in the Trp pathway, quinolinate phosphoribosyltransferase, as a determinant of susceptibility to acute kidney injury.

Several basic questions merit further consideration. For instance, what evolutionary pressures could have led to the conservation of multiple biosynthetic routes to NAD^+? And why is the *de novo* pathway most active in organs involved in detoxification of the body in mammals? One attractive possibility is that the liver and kidney are more exposed than other organs to toxic stressors that stimulate NAD^+ consumption. The fact that these organs export Nam to the rest of the body[8] might explain some aspects of inter-organ metabolic relationships in health and disease — for example, why people with chronic liver disease often develop impaired brain and heart function.

The ACMSD inhibitors developed by Katsyuba *et al.* are indicative of the interest in harnessing NAD^+ augmentation in the clinic. It has been nearly 20 years since NAD^+ was first proposed to be a determinant of lifespan[12]. But because ageing is so complex, a clinically testable definition has been lacking. Trials to examine the relationship between NAD^+ augmentation and human lifespan would take too long to be financially feasible. If, instead, a definition of ageing incorporated waning resistance to acute stressors such as infections, trauma or surgery, then clinical testing of NAD^+ modulators could become more viable. Another study has recently applied this logic, reporting a trial of orally administered Nam among people undergoing cardiac bypass surgery — an invasive procedure often performed on older individuals and associated with post-operative kidney injury[11]. The beneficial effect of NAD^+ augmentation on acute kidney injury observed in that work, although preliminary, illuminates a translational track for NAD^+ manipulation.

However, oral consumption of NAD^+ precursors might not be an efficient way to increase NAD^+ levels[8], so there is a need to consider more-targeted pharmacological approaches. The ACMSD inhibitors developed by Katsyuba and colleagues are therefore a valuable proof of concept. Given the enrichment of enzymes of the *de novo* pathway in the kidney and liver, this particular strategy also raises the intriguing possibility of tissue-specific NAD^+ manipulation.

The list of conditions potentially amenable to NAD^+ augmentation is varied and growing, from glaucoma[13] to neurodegenerative conditions[14] and metabolic syndrome[15]. A confluence of work using distinct approaches — human genetics[3], radiochemistry[8], comparative phylogeny[1] and clinical studies[11] — now indicates that the Trp pathway is both a major gatekeeper of NAD^+ levels and a target for medical exploration. ■

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MEDICAL RESEARCH

HIV rebound prevented in monkeys

Antiviral drugs prevent HIV from replicating, but the virus can hide in the cells of infected individuals in a non-replicating, latent form. A two-pronged approach to target this latent virus shows promise in monkeys. SEE ARTICLE P.360

SHARON R. LEWIN

Advances in the management of HIV over the past three decades have been spectacular, thanks to the development of antiretroviral drugs that prevent the virus from replicating. These drugs have very few side effects, prolong life and block sexual transmission. However, the virus is never eliminated — instead, it hides in immune cells called $CD4^+$ T cells in a non-replicating, latent form. If treatment is stopped, the virus rapidly re-emerges from this latent reservoir[1]. Given the cost of antiretroviral drugs, the need for ongoing engagement in care and the persisting stigma for people living with HIV, there is intense focus on finding a way to target the latent virus so that treatment can be safely stopped without viral re-emergence. On page 360, Borducchi *et al.*[2] report remarkable findings that may have achieved just that in a monkey model of HIV.

Disappointingly, no intervention has so far managed to eliminate the latent HIV reservoir in people[3]. Borducchi and colleagues set out to investigate whether a combination of two treatments could do so in monkeys. The first treatment, GS-9620 (vesatolimod), is an oral drug that activates the Toll-like receptor 7 (TLR7) protein. TLR7, in turn, activates immune cells — not only $CD4^+$ T cells, but also $CD8^+$ T cells and natural killer (NK) cells, both of which can h unt out and destroy virus-infected cells[4]. Activation of latent HIV contained in $CD4^+$ T cells is thought to render them more susceptible to destruction by other immune cells[5]. The second treatment, PGT121, is an antibody, one end of which recognizes and binds to key HIV proteins on the surface of infected cells, with the opposite end triggering other immune cells to destroy the target cell[6].

Borducchi and colleagues infected 44 monkeys with a hybrid of HIV and the simian immunodeficiency virus. Seven days later, they began to treat the animals with a potent combination of antiretrovirals, similar to that used in humans. HIV rapidly disappeared from the blood of all monkeys, as expected. After 96 weeks, the authors split the monkeys into 4 randomized groups of 11 — one group received no intervention, a second was given GS-9620, a third was injected with PGT121, and a fourth received both GS-9620 and PGT121. The monkeys received these treatments until week 114, then continued to

50 Years Ago

For some years after 1970, West Germany may be expected to have the largest fully steerable radio telescope in the world. A 100 metre (333 feet) instrument is now under construction in the sparsely populated Eifel mountains 40 km south-west of Bonn, and is due to be commissioned in April 1970 … Work on site clearance and access began about a year ago and if the erection phase goes as smoothly, the Effelsberg telescope will take over leadership as the most powerful precision instrument at short centimetre wavelengths from Jodrell Bank Mark I.

From *Nature* 16 November 1968

100 Years Ago

The turmoil which has shaken the civilised world to its foundations since August, 1914, ceased with the signing of the armistice with Germany on Monday, November 11 … Let us hope that the immoral militarism which led to the war, and sacrificed all principles of faith-keeping, justice, and humanity to attain its purpose, has been vanquished for ever … The war has shown that spiritual qualities count for much more than mere numbers. Our system of education was inefficient, but it produced a nation of young heroes … Though war is not an exact science … tactics are constantly affected by the progress of science, and disaster may ensue if its effect is not correctly appreciated … [T]here will be no end to the rich gifts which science will pour into the lap of the human race. Then, if men are worthy of the fruits showered upon them, there will be an end of the night of weeping, and the advent of the morn of song which is our highest heritage. Let us do what we can to hasten the coming of this time, when men shall stretch out their hands to one another and encircle the world.

From *Nature* 14 November 1918

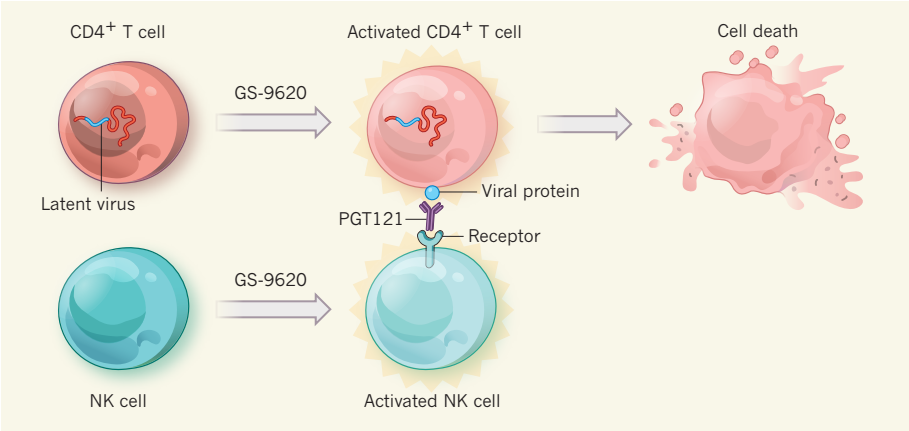

Figure 1 | 'Shock and kill' for latent HIV. Antiretroviral drugs prevent HIV from replicating. However, the virus hides in immune cells called CD4$^+$ T cells in a latent, non-replicating form that can re-emerge once antiretroviral treatment is stopped. Borducchi *et al.*[2] report a two-pronged approach that targets the latent virus during antiretroviral treatment, thus preventing viral rebound. The authors gave monkeys who were infected with a hybrid of HIV and simian immunodeficiency virus and receiving antiretroviral drugs a combination of two treatments — a drug called GS-9620 and an antibody called PGT121. The authors propose that the treatment acts through a mechanism dubbed shock and kill. Under this model, GS-9620 'shocks' CD4$^+$ T cells, such that viral proteins become visible on the cell surface. The drug also activates immune cells called natural killer (NK) cells. PGT121 then binds to the viral proteins on the activated infected CD4$^+$ T cells. NK cells, in turn, bind to PGT121, and so target infected T cells for destruction.

receive antiretroviral therapy until week 130. The investigators then stopped antiretrovirals and waited to see whether the virus rebounded.

The researchers detected the virus in the blood of all 11 animals that received no intervention, within a median of 21 days after stopping antiretroviral treatment. Viral rebound was also seen in 10 and 9 animals in the groups given only GS-9620 and PGT121, respectively. In stark contrast, only 6 of the 11 monkeys treated with both GS-9620 and PGT121 showed signs of the virus rebounding by week 28 after antiretroviral treatment had ceased. The other 5 monkeys in this group remained completely clear of any detectable virus, even using sensitive assays.

Why was the approach so effective? Borducchi *et al.* found that CD4$^+$ T cells and NK cells were activated in all monkeys that received GS-9620. But activating these cells clearly is not sufficient to destroy infected cells, because treatment with GS-9620 alone did not prevent viral rebound, consistent with a previous report[4]. GS-9620 has also been shown to activate latent virus, 'shocking' it out of its hiding place in monkeys to enable targeting by the immune system[4]. The authors did not find evidence for this in the current study, but that might be because they began treating their monkeys soon after infection. This meant that the animals had only a small reservoir of virus, which would be difficult to detect.

Although potent neutralizing antibodies such as PGT121 are being widely tested as a way to prevent HIV infection, it has been unclear whether these antibodies actually kill infected cells in the presence of antiretrovirals. There is an added layer of complexity if the virus is latent — can the antibody even recognize these cells? The authors propose that GS-9620 treatment activated the CD4$^+$ T cells harbouring latent virus, rousing the virus and so allowing the antibody to target the infected cell, perhaps with assistance from activated NK cells that are directed to the cell by the antibody (Fig. 1). This type of approach is referred to as 'shock and kill'.

Borducchi and colleagues' findings are exciting, and offer hope of a cure for HIV, but there are a few reasons for tempered enthusiasm. First, because the authors began treating the monkeys with antiretrovirals extremely soon after infection, the pool of latently infected cells was small and potentially easier to clear than if the virus had had longer to replicate. Most people living with HIV are diagnosed months to years after infection. In the current study, the monkeys that did not rebound were those with the lowest pretreatment viral loads, supporting the idea that a lower burden of virus before treatment might make the reservoir easier to eliminate. Indeed, this has been shown recently in another monkey model[7].

Second, the hybrid virus used here is potentially easier for the monkey immune system to control than are other monkey viruses[8]. Also, for people infected with HIV, control of virus is extremely rare, even if antiviral treatment is started within days of infection[1]. Third, the monkeys were followed for only about six months after antiretroviral treatment was stopped. In people with HIV who stop antiretroviral treatment, rebound of the virus can be delayed for as long as two years[9,10], so longer follow-up of these monkeys is needed. Finally, and most importantly, we don't yet know whether interventions in monkey models of HIV reflect what will happen in humans.

The biggest test will now be to see whether administration of GS-9620 and PGT121 (or a

related antibody) can produce similar results in people. These clinical trials are being planned, and the results are eagerly awaited. In the meantime, antiretrovirals remain the best and only option for the long-term treatment of HIV infection. ■

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EARTH SCIENCE

Water takes a deep dive into the Mariana Trench

A tectonic plate descending into the Mariana Trench carries sea water deep into Earth's interior. It seems that much more water enters Earth at this location than was thought — with implications for the global water budget. SEE LETTER P.389

DONNA J. SHILLINGTON

The subduction zones at which the tectonic plates beneath the sea thrust into the deep Earth act as gigantic conveyer belts, carrying water, fluids and volatile compounds into our planet. Water in Earth's interior is released back into the oceans and atmosphere by volcanoes. These inputs and outputs constitute a global deep-Earth water cycle, but quantifying the total water input from oceanic plates has proved difficult. On page 389, Cai *et al.*[1] report that the Pacific plate, which subducts in the Mariana Trench, contains much more water than was previously supposed — a finding that has major ramifications for Earth's water budgets.

Water is as crucial to the workings of Earth's interior as it is to Earth's surface processes: among other things, it triggers magma generation beneath volcanoes, lubricates deep fault zones, and fundamentally alters the strength and behaviour of Earth's mantle. Sea water seeps into the oceanic lithosphere through fractures and pores, and reacts with minerals in the crust and mantle to form hydrous minerals (such as serpentine) that store water in their crystal structures.

Water infiltration occurs at a couple of key stages of an oceanic plate's life cycle. The first is at mid-ocean ridges, when water circulates through hot, newly formed oceanic plates[2]. But at fast-spreading ridges (which are the primary 'diet' of the subduction zones that ring the Pacific Ocean), circulation and hydration are mainly restricted to the plate's upper crust. The accumulation of sediments subsequently seals off most of the oceanic plate from the ocean, but seamounts (underwater mountains) and fracture zones provide pathways for further water input and output, so that circulation continues away from the mid-ocean ridge[3]. The final infiltration occurs at the 'outer rise' of a subduction zone, where the oceanic plate bends before entering the trench. Here, extensional faults form in response to bending, and are thought to enable pervasive, deeply penetrating hydration of the crust and upper mantle[4–6].

The evidence for water entering subduction zones is clear, but several knowledge gaps have hindered attempts to quantify the total volume of water going down these hatches, even at individual subduction zones. One unknown is the depth to which water penetrates the oceanic plate. Most constraints on estimates come from controlled-source seismic data, which are produced by measuring seismic waves generated by artificial sources using dense arrays of recording instruments. These data provide excellent constraints on hydration of the crust and shallow mantle, but, with one notable exception[7], do not constrain the full depth of hydration. It is clearly not possible to tally the total volume of subducted water without knowing the full hydration depth.

Another important challenge is to untangle all the factors that alter the speed at which seismic waves travel through different parts of the plate; measurements of such seismic waves are one of the primary means of estimating the amount of water in the subducting oceanic plate. Most estimates assume that any reduction in wave speed results from the replacement of olivine (the main mineral found in the mantle) by serpentine. However, in the crust and shallow mantle, water-filled cracks can also contribute to velocity reductions[8]. To complicate things further, seismic-wave speeds in the upper oceanic mantle are anisotropic — they depend on the direction of propagation. This is because olivine crystals align in the direction in which the sea floor spreads when new oceanic plates are created at mid-ocean ridges. Further anisotropy can result from fractures formed at the outer rise.

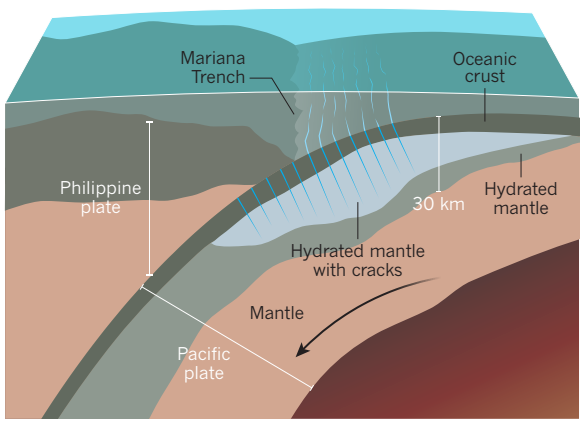

Figure 1 | Hydration of the Pacific tectonic plate at the Mariana subduction zone. At the Mariana Trench in the Pacific Ocean, the Pacific plate slips (subducts) beneath the adjacent Philippine plate, transporting sea water into the deep Earth. The water seeps through cracks and pores in the plate, and reacts with minerals in the crust and mantle to form hydrated regions consisting of minerals that store water in their crystal structures. Cai *et al.*[1] have used seismic measurements to show that water penetrates to depths of about 30 kilometres below the ocean floor. (Approximated from Fig. 2d of ref. 1.)

Cai *et al.* tackle all of these issues by presenting constraints on the hydration of the approximately 150-million-year-old Pacific plate as it subducts at the Mariana Trench. The authors analysed seismic waves from distant earthquakes, recorded by an array of seismometers on the sea floor. This allowed them to model seismic-wave speeds to much greater depths (albeit at lower resolution) than is possible using controlled-source seismic data.

The researchers find that, impressively, the full hydration depth of the lithosphere extends to approximately 30 kilometres below the sea floor (Fig. 1). They were also able to examine velocity reductions in deep regions at which the pressure would be sufficiently high to close all cracks, thus allowing them to eliminate the possible contribution of such cracks to velocities in these regions. Finally, because the authors recorded waves travelling in all directions across their array, they were able