

► for TB Drug Development (TB Alliance), a public-private partnership in New York City that sponsored the study on the latest combination therapy.

Spigelman's group wants to speed the development of such treatments. "After a new drug reaches the market, the traditional route is to work from the standard of care and substitute one drug for another. But if you do it in an incremental way, that will give you incrementally better results," Spigelman says. "Our goal is to shorten the path to getting a new, cohesive regimen out there in one fell swoop."

The new combination therapy consists of PA-824, a novel drug in the TB pipeline; moxifloxacin, an antibiotic for treating pneumonia and sinus infections; and pyrazinamide, a TB drug developed in 1952. During a two-week trial, the combination eliminated more than 99% of *M. tuberculosis* in patients' sputum. It promises to be far less taxing for patients than the current regimen for drug-resistant TB, which entails injections and two years of swallowing as many as 20 tablets a day with side effects that can include vomiting, seizures, painful nerve damage and permanent hearing loss. The results, described at the AIDS meeting, were subsequently published on 23 July (A. H. Diacon *et al. Lancet* <http://doi.org/h34>; 2012).

If full clinical trials confirm its promise, the therapy could prove a boon for HIV-infected people. TB, which is common in its latent form in many parts of the developing world, often becomes active in those who are HIV-positive because of their weakened immune systems.

"When I worked in West Africa," says John Farley, deputy director of the antimicrobial product division at the FDA, "there were times when our HIV patients would die of drug-resistant TB before we could even get them their antiretroviral therapy." Unlike some existing

RENEWED ATTACK ON TB

After a long gap, several drugs and a combination therapy for tuberculosis are moving through the pipeline.

Drug	Developer	Clinical phase	Class
Delamanid	Otsuka Pharmaceutical	III (filed for approval for drug-resistant TB)	Nitroimidazole
Bedaquiline	Janssen Pharmaceuticals	II (filed for approval for drug-resistant TB)	Diarylquinoline
SQ109	Sequella	II	Diamine
PA-824	TB Alliance	II	Nitroimidazole
Sutezolid	Pfizer	II	Oxazolidinone
AZD5847	AstraZeneca	II	Oxazolidinone
Combination: PA-824, moxifloxacin, pyrazinamide	TB Alliance	II	Nitroimidazole, fluoroquinolone, nicotinic acid derivative

Source: 2012 Pipeline Report (iBase/TAG, 2012).

therapies, the new combination does not seem to interact adversely with drugs for HIV.

The therapy was discovered during a broader search for untested permutations of emerging and existing drugs that the TB Alliance began in 2007 with funds from the Bill & Melinda Gates Foundation, the US Agency for International Development, Irish Aid and UK Aid. Its developers hope that the FDA's new guidelines for combination therapies — reserved for emergencies in which patients are dying for lack of treatments — will allow speedy approval. In the past, the FDA requested data to ensure the safety of each independent component of a combination therapy before approving it, says Farley. "But now we think there are other ways to answer that question, through studies in animal models and innovative human trial designs."

The FDA rule change is new enough that most drug developers are still focusing on individual compounds, but that quest has made progress too (see 'Renewed attack on TB'). One drug, delamanid from Otsuka

Pharmaceutical based in Tokyo, is under review at the European Medicines Agency. And on 2 July, Janssen Pharmaceuticals, headquartered in Raritan, New Jersey, applied for FDA approval of its TB drug, bedaquiline.

Sequella, a biotechnology firm in Rockville, Maryland, is testing combinations of its drug SQ109 and bedaquiline in mice in anticipation of Janssen's drug getting approval. But Sequella's executive vice-president for corporate development, Alan Klein, says that the company is filing an independent application for its new drug because the FDA's process for combination therapies is simply too new. "It can be risky for both parties because if you don't show good results in combination studies, it might impact your ability to get approval alone," he says.

Like many of the 21,000 attendees at the AIDS meeting, the TB Alliance wants donors to get the message that years of research will soon pay off in lives saved — as long as the money flows. "If we can get the resources to follow this study up," Spigelman vows, "we'll get this combination out." ■

FUNDING

Cuts loom for US science

As budget bills line up, agencies anticipate post-election panic.

BY IVAN SEMENIUK AND HELEN THOMPSON

In an ordinary year, a flat budget for the US National Institutes of Health (NIH) would be considered dire news. This year, it is far from the worst possible outcome. Hanging over the effective decrease in support proposed by the House of Representatives last week is the 'sequester', a pre-programmed budget cut that research advocates say would starve US science-funding agencies.

A sharply divided Congress is showing few signs that it can defuse the situation before the

self-imposed fiscal time bomb explodes, in less than six months' time. And even if Congress does manage to introduce last-minute legislation, as many observers expect, the sequester will have cast a shadow over the contentious process of funding science in a time of fiscal constraints — and in an election year.

The sweeping cut, scheduled to take effect on 2 January, is a by-product of last year's Budget Control Act, which requires law-makers to find ways to reduce the federal deficit (see *Nature* **476**, 133-134; 2011). When a congressional committee failed in its remit to do just that last

November, the clock began ticking towards an automatic cut that will claw the required amount from across the federal government, including all military and non-military spending that is not required by law. The precise amount to be cut depends on several variables, including tax revenue, but an estimate by the Congressional Budget Office puts it at 7.8% in 2013 for the non-military component.

"Nobody wants to see the sequester, because it's a terrible budgetary tool," says Mike Lubell, director of public affairs for the American Physical Society in Washington DC. "You don't

just take a meat axe and chop off one finger from every pair of hands.”

Although no one doubts that the sequester would have a major impact on US science funding (see ‘Winners to losers’), no agencies have announced what they will do if it happens. This is mainly because of ambiguity in how the sequester is supposed to be applied: the cuts are described as across-the-board, but how much latitude agencies will have to manage reductions at the programme level remains unclear.

Grants to extramural investigators are likely to be hit particularly hard, because they can generally be scaled down more quickly than internal costs such as salaries or long-term programme commitments. “You can’t cut everything right away,” says Jennifer Zeitzer, director of legislative relations for the Federation of American Societies for Experimental Biology in Bethesda, Maryland.

SEEKING CLARITY

On 18 July, the Republican-led House passed ‘transparency’ legislation that would force President Barack Obama’s administration to specify how the cut would be applied. If the Senate were to pass a parallel bill, the administration would be forced to provide the details within 30 days.

“Hopefully, with the transparency bill we’ll get some answers on how to allocate those cuts,” says Matt Hourihan, director of the research and development budget and policy programme at the American Association for the Advancement of Science in Washington DC.

Research advocates are particularly concerned that the sequester might be adjusted to prevent cuts to defence. If that happened, non-military programmes would be forced to bear more than twice the currently mooted cut. Such an extreme measure would threaten entire facilities and sideline thousands of research grants. “A lot of programmes wouldn’t survive. They’d be vaporized,” says Lubell.

WINNERS TO LOSERS

If a 2013 budget sequester enacts a predicted across-the-board cut of 8%, then most of the US science agencies expecting to see modest gains next year will instead experience deep cuts.



With the sequester lurking in the background, the latest move in the annual budget chess match came on 17 July, when the House subcommittee that oversees the budgets for the NIH and the Centers for Disease Control and Prevention in Atlanta, Georgia, released its version of a spending bill for fiscal year 2013 (see ‘State of play’). For the NIH, which has a US\$30-billion annual budget and is the biggest non-military research funder in the United States, the House bill offers little comfort. Overall, the legislation keeps the agency’s funding at the same level as in 2012 — a net decrease once inflation is taken into account. This matches Obama’s 2013 budget request to Congress in February (see *Nature* **482**, 283–285; 2012), but contrasts with the Senate version of the spending bill, which boosts the agency’s funding by about \$100 million.

With a trillion-dollar federal deficit at the forefront of legislators’ minds, a clamp on spending is not as surprising as the unusually hands-on way in which the NIH portion of the House bill is written. The bill specifically requires NIH director Francis Collins to spend 90% of the agency’s budget on extramural

activities, 10% on intramural activities and at least 55% on basic science, and instructs the agency to maintain at least 16,670 training research awards (a category intended for doctoral students and postdoctoral fellows). That is roughly how many awards the agency currently makes, but fixing the number in the bill reduces the NIH’s flexibility. The bill also prohibits the NIH from funding research that compares the relative effects of treatments on patients, part of a broader move by the House to thwart Obama’s health-care reforms. Finally, the bill restricts travel by Collins and his staff until the NIH implements a pilot study on the medical-insurance coverage of patients in clinical trials that was requested by Congress last year.

Spending bills introduced in the House and Senate from April offer a brighter year for some other agencies: the rises proposed for the US National Science Foundation and the US National Institute of Standards and Technology at least approach those called for in the president’s request (see ‘State of play’). But the Department of Energy’s Office of Science faces a stiff cut in the House bill as do the Food and Drug Administration and the Environmental Protection Agency, owing to political differences between House Republicans and the Obama administration. The reverse is true for the NASA science budget, with the House aiming to resist an administration cut that would jeopardize a sample-return mission to Mars.

In theory, the 2013 budget must be enacted by 30 September, the end of the 2012 fiscal year. That would require the House and Senate to agree on a bill and Obama to sign it. In practice, however, Congress is not expected to settle the budget until after the general election on 6 November. But the outcome will be just the tip of the fiscal iceberg if Congress cannot avert the sequester.

“Conventional wisdom at this point is that the sequester won’t happen,” says David Moore, senior director of government relations at the American Association of Medical Colleges in Washington DC. “But when you press legislators on what’s going to happen to avert this, there’s no consensus.” ■

STATE OF PLAY

A comparison of available 2013 US budget figures for selected science agencies (in US\$ millions). Some House and Senate numbers are yet to be voted on.

Agency	2012 enacted	2013 request	2013 House	2013 Senate
National Institutes of Health*	30,623	30,623	30,623	30,731
Centers for Disease Control and Prevention†	6,883	6,660	6,068	7,234
Food and Drug Administration	2,506	2,517	2,481	2,530
National Science Foundation	7,032	7,372	7,333	7,273
NASA (science)	5,074	4,911	5,095	5,021
Department of Energy Office of Science	4,874	4,992	4,801	4,909
National Institute of Standards and Technology	761	860	830	826
Environmental Protection Agency	8,450	8,344	7,055	Not tabled
National Oceanic and Atmospheric Administration	4,894	5,054	4,962	3,419‡
US Geological Survey	1,068	1,102	967	Not tabled

Sources: Office of Management and Budget; House and Senate appropriation committees; Centers for Disease Control and Prevention. *Includes only Department of Health and Human Services allocation. †Includes prevention and public-health fund. ‡Includes moving of satellite budget to NASA.