SHINING LIGHTS
Individually, proposals for the Linac Coherent Light Source (LCLS) and the Next Generation Light Source (NGLS) do not meet the specifications called for by a panel that advises the US Department of Energy.

Proposed project	Repetition rate	Upper energy limit
LCLS upgrade	1 kHz	25,000 eV
NGLS	1,000 kHz	720 eV
Panel recommendation	100 kHz	5,000 eV

Kilohertz (kHz); electronvolts (eV)

the machine's capability to produce higher-energy, 'hard' X-rays, which could image the arrangement of atoms and penetrate deep into heavier elements. But its intense pulses would come at a lower repetition rate, ruling out movies of dynamic processes.

Both approaches would be likely to attract users. Lou DiMauro, an atomic physicist at Ohio State University in Columbus, is keen to run 'pump-probe' experiments, in which an initial X-ray pulse is used to excite an atom, and the next pulse is used to probe the atom's state. The closely spaced pulses of the NGLS design would be ideal for that. But Phil Bucksbaum, an atomic physicist at Stanford University in California, who uses the SLAC light source, says that the NGLS would not be able to probe heavier elements because it operates at too low an energy compared with an upgraded LCLS.

The DOE advisory group found that the broadest science case could be met by a single facility that combines the strengths of both the NGLS and the LCLS (see 'Shining lights'). The committee's recommendations will help the energy department to respond to members of the US Congress who have asked for a more compelling case for a future free-electron laser. Building two, smaller, less-capable machines "is not the best science per dollar", says Barletta.

In response to the panel's recommendation, the Berkeley lab and SLAC have been scrambling to extend the reach of their proposals, and jockeying to be the front-runner to host a single site. Paul Alivisatos, director of the Berkeley lab, says that the NGLS design had an upper energy limit of 720 electronvolts (eV) to keep project costs below US$700 million. Increasing the budget to $1.2 billion would allow the electron-beam accelerator to be lengthened and would boost the upper energy limit to 3,000 eV, not far from the advisory panel's desired level of 5,000 eV. "It's a straightforward extension of our proposal," he says.

"You want to make a revolutionary machine that really stands out."

Uwe Bergmann, associate director of the LCLS, says that an upgrade to his machine could get it to a repetition rate of 10 kilohertz (kHz), but the current proposal boosts it to only 1 kHz. To get near the panel's recommendation of 100 kHz, he acknowledges that his facility would need to replace its accelerator with a superconducting one — a key feature of the Berkeley lab's proposal. But ultimately, he says, the idea of upgrading an existing machine may be more realistic in a cost-constrained environment than the advisory panel's ambitious vision. "A committee suggests something — but the committee doesn't foot the bill."

The tight fiscal climate has exacerbated competition between the two proposals, says accelerator physicist Michael Borland of Argonne National Laboratory in Illinois. "There is limited funding, and government agencies need to decide which machine to build first," he says. But he sees at least one way to combine the two projects: the electron source and superconducting linear accelerator from the NGLS proposal could be put in the existing LCLS tunnel to take advantage of its undulator magnets. "This seems to make more sense than starting from scratch with a higher-energy NGLS."

For users, a new plan cannot come too soon, says Thomas Russell, a polymer scientist at the University of Massachusetts Amherst. Russell wants to use a fast-repeating X-ray source to watch the crystallization of photoactive materials used in solar cells. The current LCLS is not fast enough to make the movies he wants, and moreover, as the premier free-electron laser in the United States, the LCLS turns away four scientists for every one that is granted time. He has visited all four of the US X-ray synchrotrons, but the diffuse nature of their light would make it impossible for him to understand his crystal structures. "You reach a certain limit and you just can't do the experiment you want to do," he says. "The light sources that exist just don't provide enough oomph." ■

BIOMEDICINE

NIH mulls rules for validating key results

US biomedical agency could enlist independent labs for verification.

BY MEREDITH WADMAN

In biomedical science, at least one thing is apparently reproducible: a steady stream of studies that show the irreproducibility of many important experiments.

In a 2011 internal survey, pharmaceutical firm Bayer HealthCare of Leverkusen, Germany, was unable to validate the relevant preclinical research for almost two-thirds of 67 in-house projects. Then, in 2012, scientists at Amgen, a drug company based in Thousand Oaks, California, reported their failure to replicate 89% of the findings from 53 landmark cancer papers. And in a study published in May, more than half of the respondents to a survey at the MD Anderson Cancer Center in Houston, Texas, reported failing at least once in attempts at reproducing published data (see 'Make believe').

The growing problem is threatening the reputation of the US National Institutes of Health (NIH) based in Bethesda, Maryland, which funds many of the studies in question. Senior NIH officials are now considering adding requirements to grant applications to make experimental validations routine for certain types of science, such as the foundational work that leads to costly clinical trials. As the NIH pursues such top-down changes, one company is taking a bottom-up approach, targeting scientists directly to see if they are willing to verify their experiments.

There is the looming

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SCIENCE EXCHANGE

MAKE BELIEVE

Reproducibility problems have led the National Institutes of Health to consider verification rules for some experiments.

SEPTEMBER 2011 Bayer HealthCare finds inconsistencies between in-house and published data in almost two-thirds of 67 projects.

MARCH 2012 Amgen publication shows that the findings from only 11% of 53 landmark papers can be replicated by company scientists.

JANUARY 2013 Elizabeth Iorns (pictured), chief executive of Science Exchange, asks more than 22,000 study authors if they want her company to arrange verification of their experiments; nearly 2,000 say yes.

MAY 2013 A survey at the MD Anderson Cancer Center finds that more than half of its respondents have tried and failed to reproduce published data.

JULY 2013 Science Exchange launches a verification programme for commercially sold antibodies.

question, however, of who will pay for it all. Independently validating the results of a major paper that has *in vitro* and animal experiments can cost US$25,000, says Elizabeth Iorns, chief executive of Science Exchange, a company in Palo Alto, California, that matches scientists with verification service providers.

Last year, the NIH convened two workshops that examined the issue of reproducibility, and last October, the agency's leaders and others published a call for higher standards in the reporting of animal studies in grant applications and journal publications. At a minimum, they wrote, studies should report on whether and how animals were randomized, whether investigators were blind to the treatment, how sample sizes were estimated and how data were handled.

The NIH is just beginning to take active measures, says Lawrence Tabak, the agency's principal deputy director. "There is certainly sufficient information now that the NIH feels it's appropriate to look at this at a central-agency level," he says. This summer, he and other senior NIH officials, including Story Landis, director at the neurology institute, and Harold Varmus, director at the cancer institute, are assessing input gathered from the directors of the agency's 27 institutes and centres. They will then confer with NIH director Francis Collins, who will decide what steps to take.

Proposals under consideration include modifying peer review to bring greater scrutiny to the work a grant application is based on — perhaps just for applications that are likely to lead to clinical trials. In a June meeting of Collins's advisory committee, Tabak imagined implementing such a scenario. "If the premise isn't validatable, then we're done; it doesn't matter how well you wrote the grant," he said. Agency officials are also considering a requirement that independent labs validate the results of important preclinical studies as a condition of receiving grant funding.

The very idea of a validation requirement makes some scientists queasy. "It's a disaster," says Peter Sorger, a systems biologist at Harvard Medical School in Boston, Massachusetts. He says that frontier science often relies on ideas, tools and protocols that do not exist in run-of-the-mill labs, let alone in companies that have been contracted to perform verification. "It is unbelievably difficult to reproduce cutting-edge science," he says.

But others say that independent validation is a must to counteract the pressure to publish positive results and the lack of incentives to publish negative ones. Iorns doubts that tougher reporting requirements will make any real impact, and thinks that it would be better to have regular validations of results, either through random audits or selecting the highest-profile papers.

Science Exchange would clearly benefit from a new flow of business should the NIH impose such a mandate on even some studies. The company's Reproducibility Initiative, launched last year, arranges for the independent replication of study results for authors who request the service — and the first batch of academic validations began in May. In January, Iorns asked more than 22,000 corresponding authors of original biomedical papers published in 2012 if they would allow the experiments in their reports to be independently verified, should funding be made available. Of those who responded, 1,892 scientists said yes and 416 declined.

Iorns says that there are plenty of important papers among those published by the 1,892 — they had a readership that was, on average, an order of magnitude higher than that of ▶

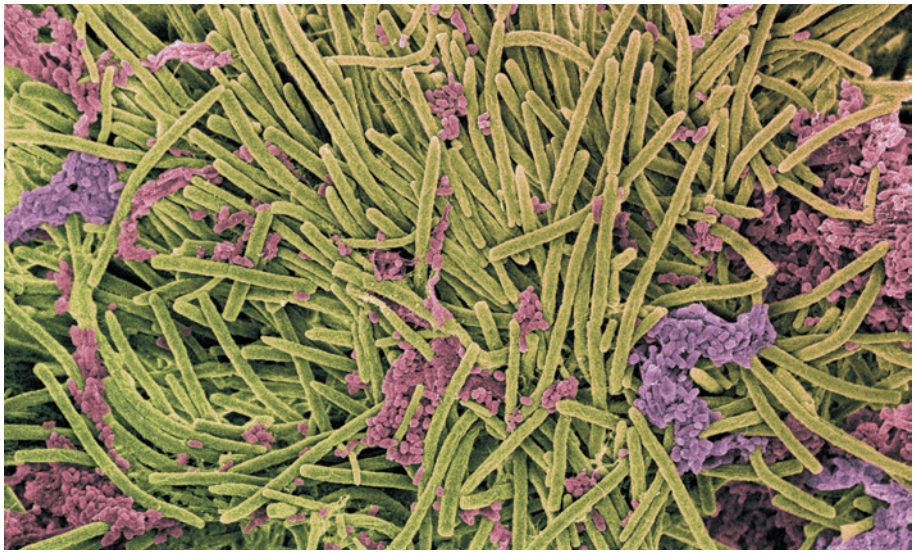
the papers whose authors declined, as measured by downloads to a free online reference manager, Mendeley. The Laura and John Arnold Foundation, based in Houston, Texas, says that it is actively considering funding Science Exchange to validate cancer-cell biology papers within Iorns' cohort.

Some at the NIH are coming round to the idea that validation is best contracted out. Shai Silberberg, who is responsible for reproducibility issues at the agency's neurology institute, has almost finished a pilot study in which several academic labs tried to reproduce findings from studies aiming to move drugs to a stage at which they are ready to be tested in humans. He points out that it has already taken two and a half years. "It's too slow," he says. He now favours speedier contract-research organizations.

Iorns, for her part, is not waiting for the NIH to take action. On 30 July, Science Exchange launched a programme with reagent supplier antibodies-online.com, based in Aachen, Germany, to independently validate research antibodies. These are used, for example, to probe gene function in biomedical experiments, but their effects are notoriously variable. "Having a third party validate every batch would be a fabulous thing," says Peter Park, a computational biologist at Harvard Medical School. He notes that the consortium behind ENCODE — a project aimed at identifying all the functional elements in the human genome — tested more than 200 antibodies targeting modifications to proteins called histones and found that more than 25% failed to target the advertised modification.

With antibodies, the companies that make them have an incentive to prove the quality of their products, and Iorns hopes that they will pay the thousands of dollars that such validation costs. Antibodies that pass muster will receive an 'independently validated' green tick in the antibodies-online.com catalogue.

But with budgets stretched thin — and with Congress well aware of the reproducibility issues — the NIH also has an incentive to make sure that its $29-billion budget is spent on verifiable science. "We are obligated to consider how we want to address this," says Tabak. ■



STEVE GSCHMEISSNER/SPL

The tongue is one of many sites to have its bacteria catalogued by the Human Microbiome Project.

MICROBIOLOGY

Microbiome research goes without a home

Scientists say core tools and expertise remain necessary.

BY BETH MOLE

Trillions of microorganisms call the human body home. But 'home' for many US scientists studying these microscopic squatters is about to change, as funding for human microbiome research scatters across 16 of the 27 centres of the US National Institutes of Health (NIH).

Last year, researchers completed the $US173-million Human Microbiome Project, which took five years and generated a slew of reference data, mostly genetic sequences of all the microbes that dwell on and inside humans. But the project's scientists fear that a lack of standards and expertise in data-gathering and analysis are hampering efforts to extract meaning from this information.

At a meeting last week in Bethesda, Maryland, they reiterated that identifying the microbes is just the first step. Researchers must also focus on how bacteria interact with each other and the human body to cause — or prevent — disease. Yet these calls for action are coming as the project faces significant downsizing: by the beginning of 2014, microbiome researchers will no longer be able to depend on centralized resources based at the NIH's National Human Genome Research Institute (NHGRI) in Bethesda.

"The microbiome has so much appeal," says Christian Jobin, an immunologist at the University of Florida in Gainesville, who studies the interplay between gut microbes, inflammation and cancer. "But we're lacking direction right now."

In 2012, the project culminated with a flurry of publications (D. A. Relman *Nature* **486,** 194–195; 2012). But, says Lita Proctor, the project's programme director, some efforts still seem too

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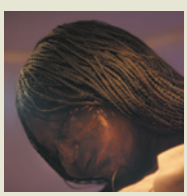

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