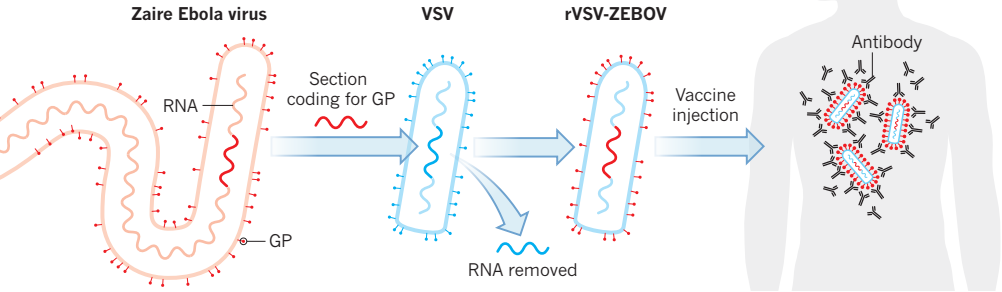
MASTERS OF DISGUISE

The rVSV-ZEBOV vaccine is made by genetically engineering a weakened form of vesicular stomatitis virus (VSV) so that it impersonates the Zaire species of Ebola virus, which caused the epidemic in West Africa.



1. Researchers snip out the RNA that codes for the virus's surface glycoprotein (GP), which allows the virus to latch onto human cells.

2. They then remove the stretch of RNA that codes for the VSV's surface protein and replace it with that for the Ebola GP.

3. The resulting vaccine tricks the human immune system into mounting a response against the Zaire Ebola virus.

Other vaccine trials, including the one that Hill is involved in, are testing for longer-term protection. But the fall in the number of Ebola cases — to 20–30 per week over the past few months — means that the trials may struggle to provide clear results.

Could the rVSV-ZEBOV vaccine help to end the epidemic in West Africa?

The vaccine will continue to be used in Guinea as part of the clinical trial. Many researchers hope that it will be used in Liberia and Sierra Leone too, to end the epidemic — although case numbers have plummeted, there is a continued risk of flare-ups as well as of spread to nearby countries (see page 27). However, some regulatory hurdles need to be cleared first. Deployment in those nations could occur as part of an expanded clinical-trial regime or through emergency authorization by regulators, says Gregory Hartl, a spokesperson for the WHO. The authorities there are now considering whether the available data are sufficient to license the vaccine for use outside a clinical-trial setting, a process that could take weeks to months, according to the WHO.

Is it unusual to do a trial during an outbreak?

Yes. Getting clinical trials approved by regulators usually takes years, as does conducting the gold standard of randomized controlled trials. That means that outbreaks tend to be over before trials can even begin. Clinical trials are also usually done in well-equipped research hospitals, and quality trials have generally been considered impossible to carry out in the often-atrocious field conditions of deadly outbreaks (see *Nature* **513,** 13–14; 2014). The urgency of tackling Ebola changed all that. In September, the WHO-supported collaboration pulled out all the stops to accelerate testing of treatments and vaccines that had shown promise in animals. It cut through the red tape and came up with trial designs that could quickly provide data at least good enough to inform efforts to control the outbreak. The rVSV-ZEBOV trial is one of several that came about as a result.

Can the fast-track approach be applied to other diseases?

Hill suggests that vaccines could quickly be developed for many other epidemic threats. He recommends that research on vaccines against such pathogens be accelerated so that clinical trials can be done now to test their safety; those that pass muster would be stockpiled, ready for efficacy tests as soon as an outbreak occurs. Pathogens considered priority health threats include Marburg virus, which is in the same family as Ebola, and the viruses that cause Middle East respiratory syndrome (MERS), Lassa fever and chikungunya.

Are lessons likely to be learned from rVSV-ZEBOV's success?

The hope is that it will provide a model for dealing with future outbreaks. "This is illustrating that it is feasible to develop vaccines much faster than we've been doing," says Hill. And there seems to be support for change at the highest level. Margaret Chan, director-general of the WHO, said on 31 July that the agency is developing a "blueprint" for accelerated development of measures to counteract potential epidemics. The plan aims to reduce the time from the recognition of an outbreak to availability of countermeasures to four months or less, and would include putting trial designs and regulatory approvals in place in advance of an outbreak. "No one wants to see clinicians, doctors, left empty-handed ever again," said Chan. ■

ONCOLOGY

Cancer–physics project accused of losing ambition

Trailblazers of physical oncology complain that US National Cancer Institute programme has lost sight of its mission.

BY GABRIEL POPKIN

An ambitious initiative that has deployed physics in the fight against cancer since 2009 has awarded a second round of grants. But some pioneers of the field, known as physical oncology, protest that the US National Cancer Institute (NCI) has lost sight of the programme's original vision.

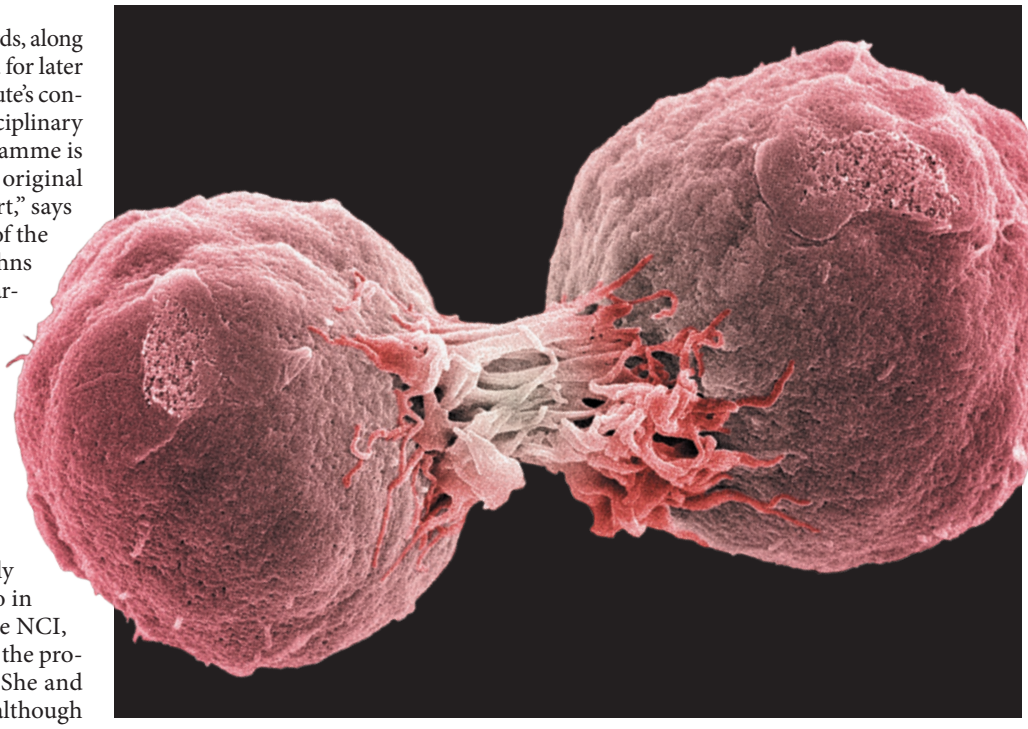
In June, the NCI announced that it would give each of four Physical Sciences-Oncology Centers (PS-OCs) around US$2 million a year for five years. But the funded projects are too unambitious to produce major paradigm shifts, argues Robert Austin, a physicist at Princeton University in New Jersey who helped the NCI to lay the groundwork for the programme, and whose centre was not funded in the second round.

The programme is "losing patience with those of us who want to understand the

fundamentals", says Austin.

NCI officials say that the latest awards, along with two rounds of funding planned for later this year or next year, show the institute's continuing commitment to the interdisciplinary approach. "The fact that this programme is renewed, while it's not in the same original form, is still an indication of support," says Larry Nagahara, a former director of the programme who left the NCI for Johns Hopkins University in Baltimore, Maryland, this month. Officials insist that there has been no move away from physics, although the programme also embraces related fields such as engineering and applied mathematics. "We're sort of agnostic on the spectrum of research that people are working on," says current programme head Sean Hanlon.

The PS-OC programme was largely the brainchild of Anna Barker, who in 2007–08, as a deputy director at the NCI, set up workshops that helped to lay the programme's intellectual foundation. She and other proponents pointed out that although billions of dollars of research investment into drugs and therapies have reduced mortality for some cancers, they have not produced a fundamental understanding of the disease. Programme leaders proposed to open a new front in the war on cancer by recruiting physicists to study cancer as a physical rather than strictly biological phenomenon.



STEVE GSCHMEISSNER/GETTY

Cell division and other cancer processes are being studied by physicists looking for fundamental insights.

A DIFFERENT PERSPECTIVE

In 2009, the NCI gave grants averaging $2.5 million a year for 5 years to 12 centres, each co-directed by a physical scientist and a cancer biologist. Some researchers attempted to re-envision cancer from the bottom up. For example, physicist Paul Davies of Arizona State University in Tempe, who along with Austin was involved in the initial programme workshops (see *Nature* **474,** 20–22; 2011), has proposed that a cell becomes cancerous when it reverts to a primitive evolutionary state. He is investigating whether ancient genes become activated during cancer development (P. C. W. Davies and C. H. Lineweaver *Phys. Biol.* **8,** 015001; 2011). Austin has explored the evolution of drug resistance by using microfluidic devices to expose tumour cells to chemical gradients (A. Wu *et al. Proc. Natl Acad. Sci. USA* **110,** 16103–16108; 2013), and has suggested that cancer might result from environmental stress rather than from genetic mutations.

Others have sought to develop or refine mathematical or biophysical tools for cancer research. At the Dana-Farber Cancer Institute in Boston, Massachusetts, for example, researchers have built computer simulations to predict which genetic and cellular changes are most likely to lead to certain cancers, and which treatment approaches are most likely to succeed. Other centres have used advanced microscopy and spectroscopy. Such projects are valuable, but do not seek the kind of fundamental understanding of cancer that is the hallmark of the physics approach, says Herbert Levine, a physicist at Rice University in Houston, Texas, who studies cancer but has not received PS-OC funding.

The awards announced in June went to existing centres at Northwestern University in Chicago, Illinois, and Dana-Farber, as well as to two new ones — at Columbia University in New York City and the University of Pennsylvania in Philadelphia. Neither Austin nor Davies had their proposals funded. Those decisions may reflect the tangible results produced by less paradigm-challenging projects, Levine says. He thinks that projects seeking fundamental breakthroughs, such as Austin's, need more time to achieve their visions. "The lofty goal of helping find a new set of directions in biology with the help of physicists, computer scientists, whatever — I don't think they quite got there."

"The lofty goal of helping find a new set of directions in biology — I don't think they quite got there."

Barker, who left the NCI in 2010 and is now at Arizona State, says that the PS-OCs have made progress in a number of areas, including understanding cancer evolution, predicting when a cell will become metastatic and developing biomarkers for cancer. But she agrees that five years was probably too short for the more ambitious efforts. "For these large consortia, it takes about the first three years to get them all working together, to get a common language in place, to get common core resources developed," she says. "In terms of judging the programme, I'd like to have seen it a couple years hence."

NCI programme managers say that the plan was always to reopen the funding competition after five years, rather than simply to extend existing sites. More researchers applied for the second round of funding, they say, and there was not enough money for everyone. But they point out that physical oncologists now have more funding options. "I think most people will find somewhere to have their work supported," says Hanlon, whether through future PS-OC awards, other NCI programmes or external sources.

Levine, for example, has funding from the state of Texas and has been involved in a partnership between the US National Science Foundation and private donors. The Francis Crick Institute, set to open this year in London, promises to bring more physicists into biomedical research (see *Nature* **509,** 544–545; 2014). Austin and Davies say they may look overseas or to private foundations to continue their work.

NCI programme managers say that the diversification of funding sources shows that the field is gaining support and recognition. They also point to the journal *Convergent Science Physical Oncology*, launched in June by IOP Publishing of Bristol, UK, and to standing sessions on physics and the evolution of cancer at the American Physical Society's annual March meeting and at meetings of the American Association for Cancer Research. "Those types of sessions didn't exist five years ago — now you can find them at several of these meetings," says Nagahara. "That's a sign of success." ■