



Provocative questions in cancer research

Harold Varmus and **Ed Harlow** explain how an innovative initiative is opening up neglected areas of oncology.

What is the best way for large research organizations to guide the expenditure of their funds? Governmental funding agencies, major philanthropic foundations and industrial firms bear a primary allegiance to those who pay for them — taxpayers, benefactors and shareholders, respectively. They are also dedicated to long-term goals — solving problems posed by disease, environmental change or national defence.

The issue is hotly debated. At one end of the spectrum, organizations place decisions about the direction of research on the shoulders of individual investigators who conceive new proposals and the peers who judge their value. At the other, they define the research programmes and direct them towards their goals from the top down.

As the director of the US National Cancer Institute (NCI) and a senior adviser to the director, we and others have developed a different way to manage a significant portion of the agency's research portfolio. Our Provocative Questions initiative asks investigators

to propose intriguing questions in cancer research that need attention but would usually find it difficult to get. The initiative does not replace the NCI's traditional reliance on the imaginations of individual investigators; nor does it intend to restate obvious goals. Instead, it aims to engage a diverse range of scientists in a challenging intellectual exercise to define then solve the major unsolved or neglected problems in oncology.

The initiative builds on a rich history of scientific discoveries that have stemmed from well conceived questions. Such questions recognize the role of natural phenomena, reflect technical feasibility and convey the importance of a satisfactory answer. They point to alternative directions in research, new uses of technologies, forgotten observations or under-studied but important problems. They bypass the obvious and emphasize the provocative. Properly constructed and phrased, they excite curiosity, stimulate ideas and inspire progress.

Similar strategies in disciplines ranging

from mathematics to global health serve as precedents. These efforts have tended to set goals (the United Nations' Millennium Development Goals¹) or post challenges (David Hilbert's Grand Challenges in Mathematics² or the Gates Foundation's Grand Challenges in Global Health³). For the NCI, however, we chose to pose questions because we believe that good questions lie behind much of the best work in science. How does something work? Where are the key points of control? How can we explain unexpected observations or apparently contradictory findings in mechanistic terms?

Over the past 18 months, we have developed the Provocative Questions initiative from a concept into a pragmatic strategy for supporting new grants. We have hosted community-wide activities to gather questions; evolved ways to refine and select the most powerful ones; and solicited proposals to answer them.

To develop a list of key questions related to cancer, the NCI conducted 16 day-long workshops on the National Institutes

of Health (NIH) campus in Bethesda, Maryland, and at several other locations throughout the United States. Around 30 investigators from different scientific disciplines and at varying stages of their careers posed and discussed questions and judged their importance. We then moulded the most appealing ones into a format that explains the importance of the question, the likelihood that it will be answered and the ramifications of doing so. The workshops have been revelatory in another, less expected way. Minimally structured, they were immensely enjoyable, offering hours of uninhibited and unconventional exchanges.

To extend this exercise beyond the small number of people who could attend the workshops, the NCI has created a website (provocativequestions.nci.nih.gov). There, anyone can learn about the motivations behind the initiative, and people have been able to propose additional questions and comment on those suggested at workshops or online. The site now lists more than 100 questions and has been visited by more than 35,000 scientists throughout the world, at a rate of roughly 1,800 hits per day.

To formalize the initiative, the NCI has issued a request for applications and provisionally set aside US\$15 million from the budget for fiscal year 2012 to support the best ideas for answering any of the questions chosen from a list of 24. Applications for funding will be judged by special NCI study sections, the members of which will be asked to assess the relative power of the proposed ideas, rather than the supporting preliminary data or the reputation of an applicant.

Four examples of under-studied areas chosen for funding are outlined below. Detailed descriptions can be found at the website.

FOUR EXAMPLES

Drug mechanisms: Although conventional chemotherapy is often regarded as a sub-optimal treatment strategy, with high toxicity and less than curative outcomes in common adult cancers, there are several well documented situations (such as germ-line or paediatric cancers) in which these therapies can provide complete cures⁴. For example, cisplatin cures most patients with advanced testicular cancer and has been the standard treatment for decades. Perhaps because it has been so successful, few studies of this drug response are being conducted. Yet knowing why this drug and others can produce such durable cures could illuminate the search for similar opportunities for cancers that are less successfully treated.

Cancer evolution: The emergence of tumours resistant to both traditional chemotherapies and newer targeted treatments involves selection of cancer-cell variants that have acquired properties that block

or sidestep the action of the drug⁵. As an evolutionary biologist pointed out during one workshop, little attention has been directed to the application of ideas about how Darwinian selection by massive cell killing might drive the emergence of drug-resistant tumour cells. Applying such a strong selective pressure may not be the best way to undermine the behaviour of cancer cells.

Obesity risk: Epidemiologists have established that obesity dramatically increases the risk of developing some cancers, and in some cases the risk rivals that for tobacco⁶⁻⁸. One of the Provocative Questions asks scientists to consider how obesity promotes tumour development. Uncovering the molecular mechanisms by which this happens could help to identify new approaches to cancer prevention or treatment. Such an effort would be a powerful example of how to link risk identification to the molecular steps that drive carcinogenesis.

Ageing and cancer: Cancers are commonly considered to be associated with ageing, presumably because of the accumulation of mutations affecting cancer genes. However, some cancers peak in childhood, adolescence, young adulthood or middle age. Moreover, the occurrence of cancers does not correlate well with the lifespan of an animal: mice, which have a two-year life expectancy, are much more prone to cancer than are turtles or marine mammals that live longer than human beings. What accounts for these discrepancies? Does our understanding of the process of ageing help to explain the patterns of carcinogenesis as a function of age?

MEASURING SUCCESS

Because the Provocative Questions initiative is an experiment, the NCI is using a combination of subjective and objective assessments to measure its success. The workshops were welcomed enthusiastically: almost all invitations to participate were accepted, and we received many testimonials afterwards. The response to the request for applications has also been strong — perhaps not surprising at a time when success rates for new grants are at an all-time low across the NIH. We have processed more than 750 applications, with every question receiving interest from multiple investigators. The response suggests that the initiative is meeting a pent-up demand for more imaginative funding opportunities.

Of course, the proof of principle — finding satisfying answers to a significant number of Provocative Questions or developing sustained research programmes to expand the pursuit of answers — will take years to accomplish. In the meantime, we plan to expand the list of questions through additional workshops and the website, to invite requests for applications annually for at least

another two years and to consider whether to expand the initiative in the more distant future.

We believe that the Provocative Questions model will help funding agencies in other fields. The approach helps to define the boundaries between the known and unknown; it takes advantage of new developments to refocus a discipline's attention on historically intractable problems; and it highlights perplexing issues that may be raised by new evidence about traditional topics.

An initiative of this type combats the pressures for 'safe havens', which are common in eras of budgetary stringency. Reductions in funding tend to prompt all parts of the research community to become more conservative. Grant writers look to the safest harbours for research ideas and often converge on similar subjects, narrowing research portfolios. In turn, reviewers respond conservatively; popular ideas are likely to score well, again narrowing the scope of approaches.

By pooling the imaginations of the research community to address understudied areas, an initiative such as ours provides a useful compromise between two traditional approaches of funding agencies: one that focuses on goals set by portfolio managers and another that is entirely unstructured.

The benefits will also be evident in fields that are progressing rapidly. In our research area of oncology, we are witnessing an explosion of knowledge about the genetic basis and underlying biology of many cancers, matched by the development of powerful technologies for expanding and applying that knowledge to the classification and management of disease⁹. Under these circumstances it is easy to become overconfident in the progress that is occurring. Provocative Questions are welcome antidotes, as well as productive guides to future research. ■

Harold Varmus is the director of the US National Cancer Institute and **Ed Harlow** is a senior adviser to the director.
e-mail: harold.varmus@nih.gov

1. Annan, K. *We the Peoples: The role of the United Nations in the 21st Century* (United Nations, 2000).
2. Hilbert, D. *Bull. Am. Math. Soc.* **8**, 437–479 (1902).
3. Varmus, H. et al. *Science* **302**, 398–399 (2003).
4. Guminski, A. D., Harnett, P. R. & deFazio, A. *Lancet Oncol.* **3**, 312–318 (2002).
5. McCormick, F. J. *Surg. Oncol.* **103**, 464–467 (2011).
6. Calle, E. E., Rodriguez, C., Walker-Thurmond, K. & Thun, M. J. *N. Engl. J. Med.* **348**, 1625–1638 (2003).
7. Adams, T. D. et al. *N. Engl. J. Med.* **357**, 753–761 (2007).
8. Renehan, A. G., Soerjomataram, I. & Leitzmann, M. F. *Eur. J. Cancer* **46**, 2581–2592 (2010).
9. National Research Council. *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease* (National Academies Press, 2011).