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First International Workshop on Provocative Questions (PQ) in Cancer Research, October–November 2014, New Delhi, Bengaluru, and Thiruvananthapuram, India

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Summary

In 2011, the National Cancer Institute (NCI, USA) introduced the Provocative Questions (PQ) Initiative, a new approach allowing active researchers to define major unsolved or neglected problems in oncology unaddressed by existing funding. Last year, the U.S. NCI teamed up with the Indian Department of Biotechnology (DBT) to pilot the PQ approach in three cities in India. Workshop outcomes included the generation of fundable “PQs” (perplexing questions understudied by the international scientific community), as well as the identification of several non-PQ projects and research-related issues of importance to DBT and other Indian funding groups. The workshops clearly indicated the need to expand beyond crafting “PQs” when considering the best areas for research funding in international settings. Nonetheless, the first set of PQ workshops provided a forum to discuss key issues regarding cancer research in India, including the paucity of cancer research funding, and the lack of relevant human resource training and technology sharing

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Conflict of interests
None.

platforms. Continued open debate between researchers, funders and policymakers will be essential to effectively strengthen the cancer research portfolio in India.

Keywords

Funding; India; Cancer Research; Provocative Questions; National Cancer Institute; Department of Biotechnology

Introduction

How best to allocate funds across a research portfolio is a key question for medical research funders. Within this context, funders often develop initiatives to stimulate research in specific understudied areas. In 2011, the National Cancer Institute (NCI, USA) proposed the Provocative Questions (PQ) Initiative, an innovative approach to define major unsolved or neglected problems in oncology that were unaddressed by existing funding, but still deserving of special attention. A key feature of the PQ Initiative is that questions are proposed not by the NCI or its leadership, but rather by active scientists within the continuum of cancer research, including prevention, risk, cancer biology, detection, diagnosis, prognosis, therapy, outcome, and clinical effectiveness¹. Given that the PQ Initiative was conceived in the context of NCI's already large, established program for funding across the cancer research continuum, its purpose was not to replace existing research funding, but rather to highlight areas of need and to stimulate inquiry in areas that receive less focus.

The concept of holding an International PQ workshop was first conceived in January 2014 during discussions held between Dr. Harold Varmus (Former Director, NCI) and Dr. K. Vijay Raghavan (Secretary, Department of Biotechnology, Government of India). Here, we summarize key outcomes from the first international PQ Workshops.

NCI Provocative Questions (PQ) Initiative in the United States

In the United States, most Provocative Questions have been generated through a set of moderated one-day workshops comprising a small group of leading scientists invited from the cancer research community. While some workshops have been open to participants with a wide range of research expertise, others have covered specific areas, such as aging and senescence, clinical practice, combination therapies, and small cohorts in epidemiology. Participants submit their most interesting question for discussion and consideration in advance, and the proposed questions are used to generate an agenda for the day's discussion. At the meeting, participants propose, refine, and prioritize research questions that address particularly compelling and understudied problems in cancer research. Augmenting the workshop process is a public website open to all researchers for submission of questions and comments (<https://provocativequestions.nci.nih.gov>).

Once a year, NCI staff review all PQs generated from the workshops and the website. The final set of questions is selected by expert judgment following an analysis of existing published literature and the funded portfolio of several major government funding bodies

including the National Institutes of Health (NIH), the National Science Foundation, the Department of Energy, and the Defense Technical Information Center. The final PQs are funded through requests for applications (RFAs) issued using two mechanisms: the Research Project Grant (R01) and the Exploratory/Development Research Grant (R21). A recent analysis of PQ applicants in the United States indicates that US PQ grants have attracted substantially more new investigators and applicants with medical degrees than the general NCI applicant pool². Since the program's inception in 2011, four separate RFA's have been issued, under which 47 unique Provocative Questions have been opened for grant applications. In the years 2011 through 2013, 1,822 applications were reviewed, 188 new grants approved, and \$74 million awarded in first year funding.

International NCI Provocative Questions (PQ) Initiative

In January 2014, Dr. Harold Varmus (NCI) visited India to define opportunities for collaboration in cancer research and prevention with leading Indian institutions. During discussions with Dr. K. Vijay Raghavan, Secretary of the Department of Biotechnology (a major funder of cancer research in India), the idea emerged of co-hosting an International PQ Workshop in India. Given differences in the cancer research portfolios, grant funding mechanisms, and funds available for research in the two countries, it was immediately evident that the workshop format would have to be modified to suit Indian needs, and that the process would continue to evolve after the first set of workshops. An organizing committee was comprised consisting of key individuals from NCI and DBT, and led by Dr. Edward Harlow, special advisor to the NCI Director.

To clarify the goals for the workshops, the organizing committee considered the following questions:

- Should the scope of topics be basic or applied, and should questions be restricted to those relevant to India, or should any questions relevant to cancer be considered?
- What were the expectations for PQ meetings in India, and what would the Indian partner agency (DBT) do with PQs identified through the process?
- Would DBT set aside funds and use RFAs to fund research in response to the questions developed (similar to the NCI), or would the questions be used in other ways?
- Would the PQ meetings be held with Indian scientists only or would US and other international scientists also be invited?
- Should a wide range of experts be invited to the workshop, or were there particular topics that DBT wished to focus on for specific workshops?
- Do we invite questions that seek to better understand the cancer research needs in the Indian context even though they may not be 'provocative' in nature?

The committee decided that the main goal of the meeting would be to generate scientific discussion followed by the identification of a number of key fundable questions. All questions relevant to cancer would be considered, whether basic or applied, and whether particularly relevant to India or not. The final set of questions from the workshop would be

funneled into both the usual NCI PQ process for generation of RFAs open to all investigators internationally, and would also be considered separately for funding in India. Given that various funding bodies exist in India, including the DBT, the Department of Science and Technology (DST), the Indian Council of Medical Research (ICMR), and the Department of Atomic Energy (DAE), and that these institutions fund different aspects of research in cancer, the specifics of funding in India would be decided after the questions were generated. The committee felt that the inclusion of both international and Indian scientists would be an important feature of the workshop. Three independent workshops would be held in different Indian cities, and each of these would be hosted by a leading research institution in that city: the National Institute of Immunology (NII) in New Delhi; the National Center for Biological Sciences (NCBS, Tata Institute of Fundamental Research) and the Stem Cell Institute *in Stem* in Bengaluru; and the Rajiv Gandhi Center for Biotechnology (RGCB) in Thiruvananthapuram. Although the organizing committee considered specialized workshops focused on particular research disciplines in different cities, it was decided that researchers across the spectrum would be invited to each. Each workshop would be limited to a maximum of 25 participants (15 from India and 10 from other countries across the globe) to allow small group discussion and deeper consideration of each question. The workshop swere jointly funded by the NCI and DBT.

During the development of the pilot PQ workshops in India, the organizing committee made a series of modifications to the usual U.S. format, summarized below.

1. Website—In order to facilitate participation from a wide range of Indian scientists and experts, the organizing committee felt strongly that the website should play a larger role in the Indian PQ Initiative than it has in the U.S. As a result, a special section for posting Indian PQs was added to the NCI PQ website. The link to the website was disseminated widely to Indian cancer investigators through the DBT, and researchers were invited to post questions on the website. Two months prior to the workshops, experts from NCI and India reviewed website-generated PQ's, and a small number of researchers who posed interesting provocative questions were invited to participate in person at the workshops.

2. Observers—Given the keen interest in participating in the workshops, and the limited number of available spots, each PQ workshop allowed a small number of observers who did not participate in the main discussions, but were invited to submit one question in writing at the time of the workshop. In addition, after presentation and discussion of each question, a brief amount of time was set aside for observer comments.

3. Visiting Scientist Interactions—As leading international scientists were invited to each workshop, the organizing committee used this opportunity to stimulate broader engagement with the Indian scientific community outside of the workshop. Several of the visiting scientists were each city, and all visiting scientists were invited to small and large group interactions with trainees (ranging from high-school to graduate students) and young scientists. In New Delhi, visiting scientists were further invited to comment and provide input on the planning of the proposed Indian National Cancer Institute at a special session organized by the All India Institute of Medical Sciences (AIIMS), which will host the new Indian NCI.

Three separate PQ workshops were held: in New Delhi (27th October), Bengaluru (1st November), and Thiruvananthapuram (4th November), India, in the fall of 2014. Each workshop comprised international and national leaders in cancer research, with expertise ranging across several disciplines of cancer research. There was widespread enthusiasm at the opportunity to engage in scientific discussion with national and international colleagues, and strong personal interactions were observed between Indian and international scientists. Visits to outside institutions provided further opportunities for one-on-one discussions and scientific collaboration.

Useful questions were presented at each of the PQ workshops. After the workshops, it was recognized that the questions generally fell into one of the three following categories:

1. perplexing questions that are understudied by the scientific community (“PQ’s”)
2. questions that may be perplexing and understudied in the Indian or other low to middle income settings, but are well studied in high income countries; or
3. research infrastructure needs that would be important to address in order to conduct high-quality research.

Following the workshop, meeting notes were shared with all participants for edits and comments, and the final list of proposed questions was shared among participants from all three workshops. A master list of 76 potential questions (30 from Delhi; 23 from Bengaluru and 23 from Thiruvananthapuram) was generated after initial edits, removal of duplicate questions, and assembly of common ideas. This master list provided the starting material for independent work by both DBT and NCI. At NCI, the master list of potential PQ’s was shared with the PQ Executive Committee, and processed along with other US workshop questions for consideration for the next PQ RFA. Given that many of the questions generated may be of interest to India but not to the U.S., either because these questions have been asked and answered in the U.S. setting, or because some of the issues identified are of high interest (e.g. research infrastructure questions) but not question-oriented as such, the list of 76 questions was considered independently in India.

NCI-DBT PQ Workshop Outcomes

Potential PQ’s, as per NCI criteria (perplexing questions that are understudied by the international scientific community), were generated at each of the three workshops. One of the twelve final selected PQs for 2015 originated in India (“How does mitochondrial heterogeneity influence tumorigenesis or progression?”) and elements of most of the others were discussed at the three Indian workshops. The NCI is currently inviting applications for these twelve questions: (http://provocativequestions.nci.nih.gov/rfa/mainquestions_listview).

In addition to the formal “PQs” workshop discussants identified several projects and research-related issues that were of interest to DBT and other Indian funding groups. For example, a participant at one session mentioned that there is currently a paucity of creation and distribution of cell lines, patient-derived tumor xenographs (PDXs), and other research materials for tumors that occur primarily in India. Such materials would obviously be of interest to US scientists as well, once they are produced. While

questions of who might prepare these and organize their distribution remained, the project was recognized as an issue of national importance.

The workshop resulted in the initiation of several personal interactions between Indian and U.S./other international scientists. Numerous collaborations and project ideas were discussed in breaks and after the sessions. The quantity and quality of these interactions was deeper than is typically observed at US workshops.

More generally, workshop participants and scientists at Indian research institutions commented on the need for deeper and more frequent interactions between Indian and U.S. researchers. Specifically mentioned were the need for more intellectual exchange, international collaborations, joint identification of important problems to solve, and specialized training.

Participants found the format of a small group interaction focused on scientific dialogue between international and national scientists from different institutions very stimulating, and several Indian scientists commented on the need for similar discussions with more frequency, perhaps not necessarily just around “PQs,” but also about scientific questions more generally.

Although the list of international invitees included a broad spectrum of potential travelers to India, the final list of individuals who agreed to participate was heavily skewed to groups with strong connections to India. This included persons of Indian origin who were motivated to give back to their homeland and/or had personal reasons to visit; researchers with grant connections to India; researchers committed to global health issues, or individuals searching for opportunities for new research activities. The number of individuals who joined solely for an exchange of ideas (more typical of a US PQ group) was quite limited. This concept may be useful for the organization of future international PQ efforts.

One issue that became clear during the workshop discussions and the post-workshop debrief was that the unique nature of Provocative Questions to explore understudied ideas might occasionally be inappropriate for a developing research community. In the US, which has a long and deep history of biomedical research, there is a natural value to looking for understudied or unexplored questions. In international settings where the research portfolio is more recent and therefore not necessarily as large, PQs in some research areas could be a distraction. In these settings, research funders will likely need to expand beyond crafting PQs when considering the best areas of research funding.

Nonetheless, the PQ workshops provided a forum to discuss key issues that have been generally set aside by most funding agencies. For instance, research resources around the oncology sector have remained elusive despite a growing recognition of the need for increased cancer research funding in the last decade. Similarly recognized was the imperative need for relevant human resources training and technology sharing platforms for effective cancer research. Following the PQ workshops, these aspects have been forwarded to Indian policy makers for action. Continued open debate between researchers, funders and policymakers will be essential in order to effectively strengthen the cancer research portfolio in the country.

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