National Cancer Institute

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Provocative Questions Initiative

An update

Ed Harlow

BSA Meeting

November 5, 2012

Provocative Questions Initiative

- Goals are (1) to identify compelling research questions in new or understudied areas and (2) to fund great new science in these areas
- An EXPERIMENT: The BSA has given approval to run a 3 year trial of the RFA.
- We now have two years of question gathering experience: Web-based access for everyone and workshops for direct contact with community
- NCI has run two PQ RFAs: First completed in early summer, second issued with submission deadline in early Dec: 24 PQs/RFA; $22M in new awards for 2011 RFA, $30M committed for 2012 RFA; For both R01s and R21s
- Initiative operationally sits between Investigator-initiated research and traditional RFA

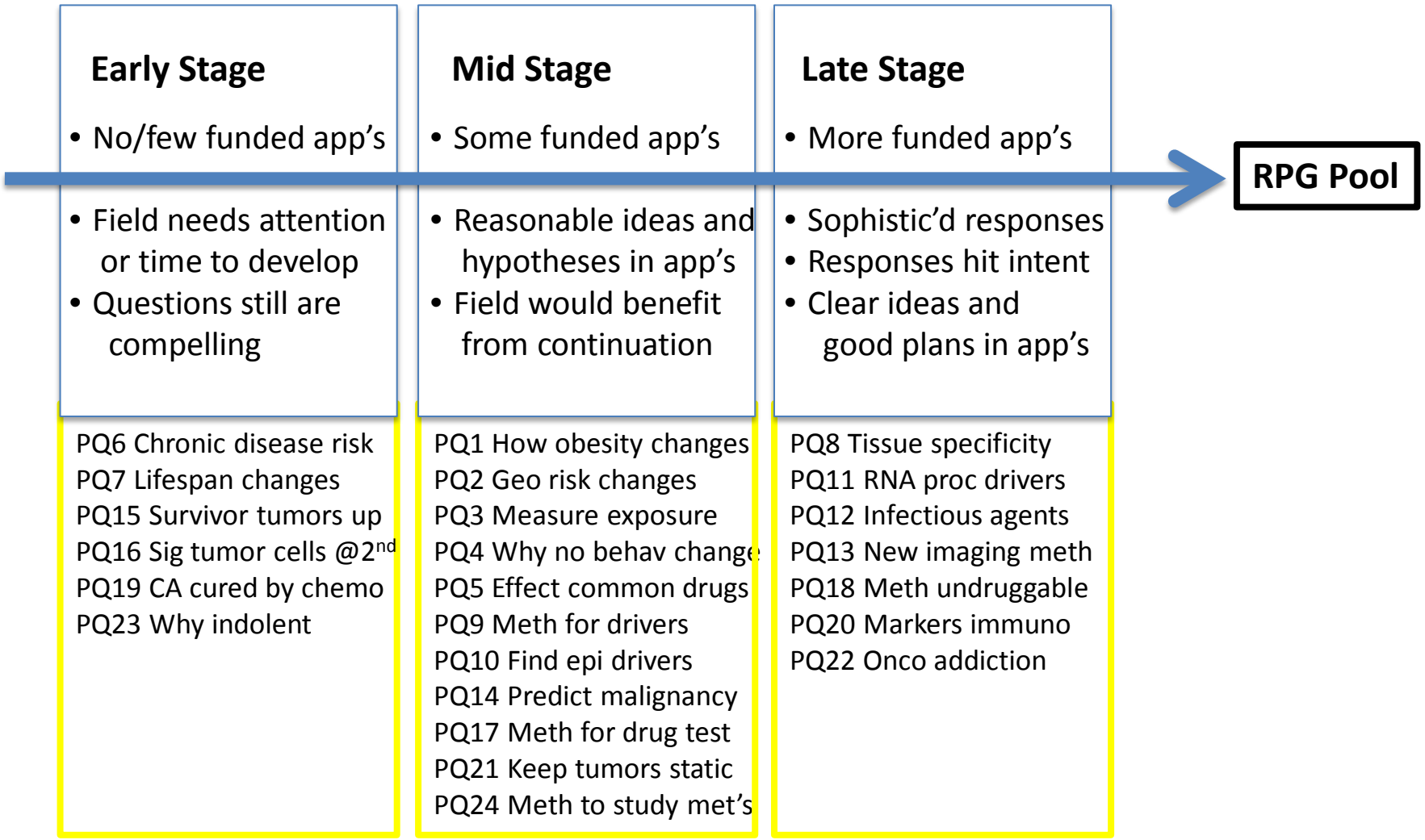
Provocative Questions Initiative: Useful Characteristics

- Power of formulating each project as a research question: *Questions highlight most important nuance of an area*
- Asking the community to nominate questions for consideration: *Community ownership, not NCI*
- Demanding that the questions be on understudied or underappreciated subjects: *New tentacles into hard problems*
- Using a series of community-based workshops to nominate questions: *Community talks, argues*
- Assembling questions from a wide spectrum of our research interests: *No, or few, research areas are ignored*
- Potential counter to conservative thinking and reviewing in tight financial times: *Spreads the focus of research thinking and reviewing*

2011 Provocative Question RFA:
Fun Facts (and some interpretation)

- 738 reviewed applications
- Number of submitted app's per PQ varied from 82 to 7.
- 57 app's were funded, or 7.7% of total submitted.
- The most successful PQs had success rate of ~20%
- Four PQs had no funded applications. PQ15 (Why survivors have higher rate of 2nd tumors), PQ16 (What is significance of tumor cells at 2nd site), PQ19 (Why chemo works sometimes), PQ23 (Why indolent tumors change). PQ15, PQ16, and PQ19 had the 3 fewest submissions of all PQs.
- Maximum number of funded app's/PQ is 6 (PQ1, obesity; PQ18, new methods for undruggable). 5 app's funded for 2 PQs (PQ5, commonly used drugs; PQ12, new infectious agents)
- By my interpretation, 46 of 57 funded applications (81%) were directed to the intent of the PQ.

2011 Provocative Question RFA:
Characterization of Question Success



Work Flow for New PQs for 2012 RFA

- Continued to run workshops in community and at NCI; Continued to collect questions on website

- (All questions from On-line) + (All questions from workshops) = 556, became *The Question Book*

- Editorial Board

  R Ballard-Barbash, S Chanock, E Greenspan, M Hare, P Hartge, T Hecht, K Howcroft, J Lee, C Mackall, L Minasian, T Misteli, S Mitchell, B Spalholz, P Wagner, and J Zwiebel

- 14 New Proposed PQs

2012 PQ RFA

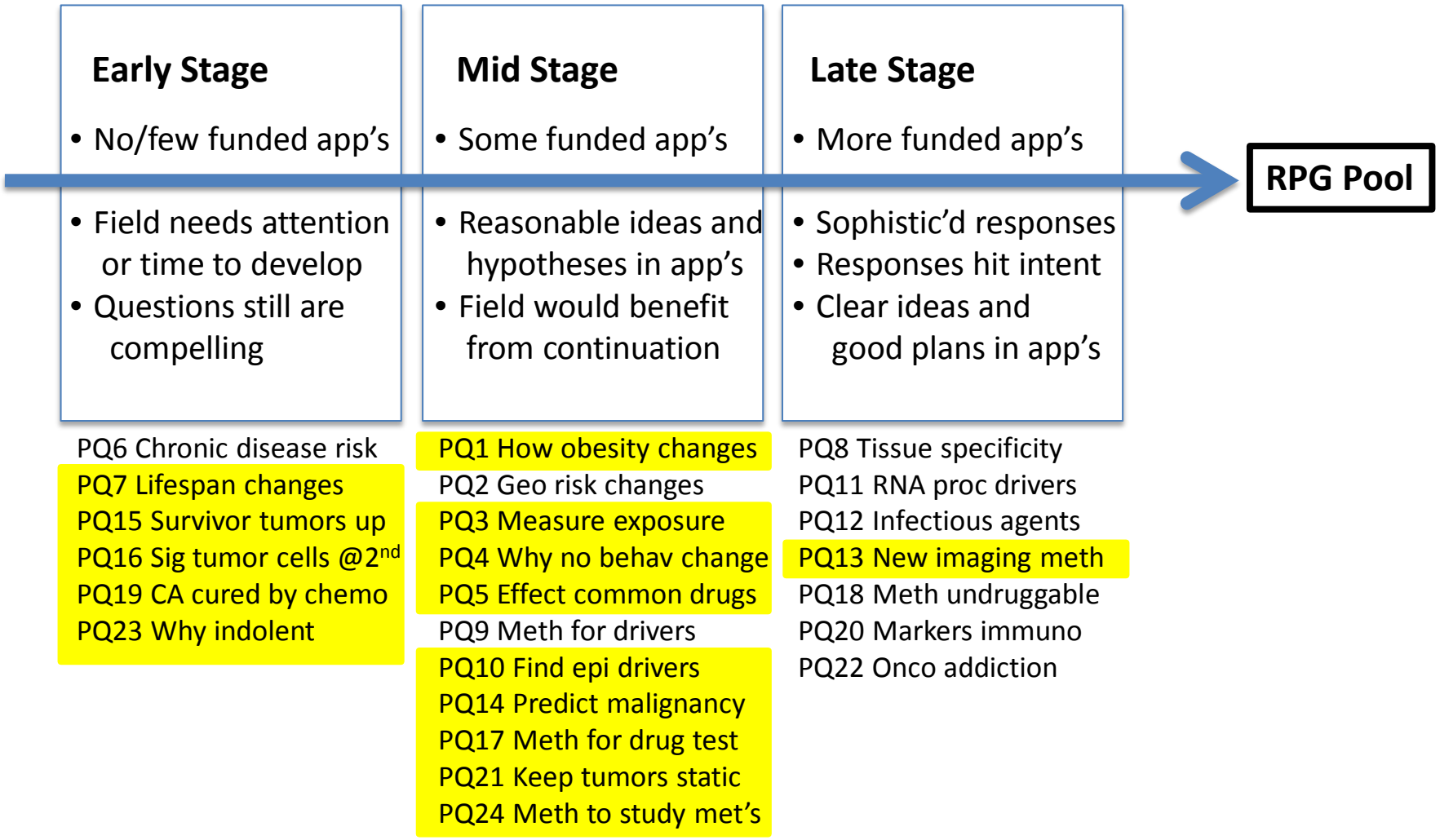
24 PQs for 2011 RFA

14 Potential PQs
From 2012 Collection

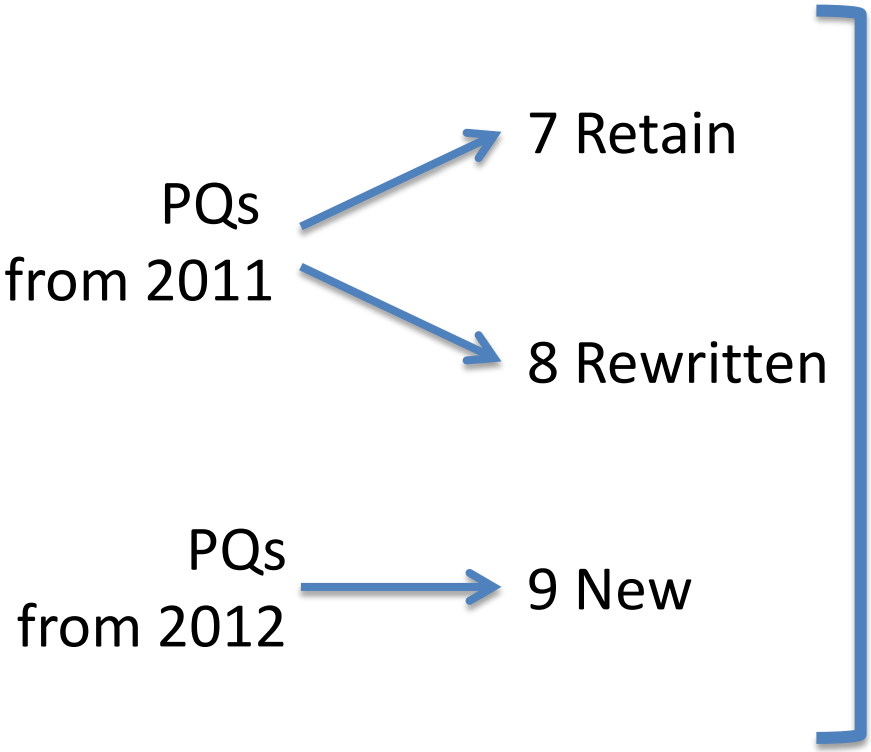
- Ed Board & PQ Program Recommendations
- SPL Decision

24 PQs
2012 RFA

2011 Provocative Question RFA:
15 Subject Areas Saved for 2012 RFA



2012 PQ RFA(s)



RFA 1:
Prevention & Risk
4 PQs 2011
2 PQs 2012

RFA 2:
Mech of Tumor Dev & Recurrence
4 PQs 2011
2 PQs 2012

RFA3:
Detect, Diag, & Prognosis
4 PQs 2011
2 PQs 2012

RFA 4:
Therapy & Outcomes
3 PQs 2011
3 PQs 2012

2012 PQ RFAs

RFA 1: Prevention & Risk

PQ1. (Retain) How does obesity contribute to cancer risk?
PQ3. (Re-written) As modern measurement technologies improve, are there better ways to objectively ascertain exposure to cancer risk?
PQ4. (Re-written) How do cognitive processes such as memory and executive function interact with emotional or habitual processes to influence lifestyle behaviors and decisions, and can we use this knowledge to design strategies to change behaviors that increase cancer risk?
PQ5. (Re-written) What is the molecular mechanism by which a drug (such as aspirin or metformin) that is chronically used for other indications protects against cancer incidence and mortality?
PQ25. (New) How does the level, type, or duration of physical activity influence cancer risk and prognosis?
PQ26. (New) How does susceptibility of exposure to risk factors change during development?

RFA 2: Mech of Tumor Dev & Recur

PQ7. (Re-written) What mechanisms of aging, beyond the accumulation of mutations, promote or protect against cancer development?
PQ10. (Retain) As we improve methods to identify epigenetic changes that occur during tumor development, can we develop approaches to discriminate between “driver” and “passenger” epigenetic events?
PQ15. (Retain) Why do second, independent cancers occur at higher rates in patients who have survived a primary cancer than in a cancer-naïve population?
PQ24. (Retain) Given the difficulty of studying metastasis, can we develop new approaches, such as engineered tissue grafts, to investigate the biology of tumor spread?
PQ27. (New) What molecular and cellular events determine whether the immune response to the earliest stages of malignant transformation leads to immune elimination or tumor promotion?
PQ28. (New) How does the order in which mutations or epigenetic changes occur alter cancer phenotypes or affect the efficacy of targeted therapies?

2012 PQ RFAs

RFA3: Detect, Diag, & Prognosis

PQ13. (Retain) Can tumors be detected when they are two to three orders of magnitude smaller than those currently detected with in vivo imaging modalities?

PQ14. (Retain) Are there definable properties of pre-malignant or other non-invasive lesions that predict the likelihood of progression to metastatic disease?

PQ16. (Re-written) How do we determine the significance of finding cells from a primary tumor at another site and what methods can be developed to make this diagnosis clinically useful?

PQ23. (Retain) Can we determine why some tumors evolve to aggressive malignancy after years of indolence?

PQ29. (New) What molecular events establish tumor dormancy after treatment and what leads to recurrence?

PQ30. (New) How can the physical properties of tumors, such as a cell's electrical, optical or mechanical properties, be used to provide earlier or more reliable cancer detection, diagnosis, prognosis, or monitoring of drug response or tumor recurrence?

RFA 4: Therapy & Outcomes

PQ17. (Re-written) Since current methods to predict the efficacy or toxicity of new drug candidates in humans are often inaccurate, can we develop new methods to test potential therapeutic agents that yield better predictions of response?

PQ19. (Re-written) What molecular properties make some cancers curable with conventional chemotherapy?

PQ21. (Re-written) How does the selective pressure imposed by the use of different types and doses of targeted therapies modify the evolution of drug resistance?

PQ31. (New) What properties of cells in a pre-malignant or pre-invasive field—sometimes described as the result of a cancer field effect—can be used to design treatments for a tumor that has emerged from this field or to block the appearance of future tumors?

PQ32. (New) What mechanisms initiate cachexia in cancer patients, and can we target them to extend lifespan and quality of life for cancer patients?

PQ33. (New) What underlying causal events—e.g., genetic, epigenetic, biologic, behavioral, or environmental—allow certain individuals to survive beyond the expected limits of otherwise highly lethal cancers?

2012 PQ RFAs

- PQ1. (Retain) How does obesity contribute to cancer risk?

- PQ19. (Re-written) What molecular properties make some cancers curable with conventional chemotherapy?

- PQ33. (New) What underlying causal events—e.g., genetic, epigenetic, biologic, behavioral, or environmental—allow certain individuals to survive beyond the expected limits of otherwise highly lethal cancers?

Issues for Consideration

- Increase attention to PQ process and RFA
- Increase critical thinking on question subjects
- Get Divisions more deeply involved
- How hard to push for new PQs?
- PAs or PARs as questions cycle off?
- “Questions” website?

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Provocative Questions
THANKS

Maureen Johnson

Samantha Finstad, Elizabeth Hsu

R Ballard-Barbash, S Chanock, E Greenspan, M Hare, P Hartge, T Hecht, K Howcroft, J Lee, C Mackall, L Minasian, T Misteli, S Mitchell, B Spalholz, P Wagner, and J Zwiebel

Jerry Lee, Emily Greenspan, + Program Staff

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