Overview of the AACR Clinical and Translational Cancer Research Think Tank Meeting

Kenneth C. Anderson¹ and Raymond N. DuBois²

On January 17–18, 2010, the American Association for Cancer Research (AACR) hosted a Think Tank meeting in San Francisco that brought together a group of clinical and translational research thought leaders to identify the most promising scientific priorities and opportunities for the future of this field. This meeting was held over 2 days and included specific presentations on key areas such as animal models; the impact of genomics on personalized cancer therapy; innovative clinical trial design; imaging strategies, controversies, and opportunities; and biomarkers and companion diagnostics. Breakout sessions focused on research, information sharing, standardization, validation, regulatory issues, and education. The overall goal of this gathering was to provide a forum for thoughtful input and discussion about the strategies needed to help catalyze progress in the field of clinical and translational cancer research.

A number of key issues were discussed over this 2-day period, and several opportunities and barriers were identified. The group reached a general consensus regarding the following needs: (i) establishment of a national database to provide access to clinical trials data, biomarker data, and educational information for researchers, providers, decision makers, and the public; (ii) additional support for team science in the academic, private, and governmental sectors; (iii) mechanisms for sharing data and approaches more effectively; (iv) education of the research, advocacy, and decision-maker communities about the current and future challenges of clinical and translational cancer research; (v) involvement and engagement of survivors and advocates in supporting team science and clinical/translational research in general; (vi) biomarker-driven clinical practice for both cancer prevention and treatment; and (vii) outreach and involvement of the pathology community, especially in the area of biomarker development to help establish better standards and adopt new science.

An ongoing challenge in the field is to develop the most effective strategies for using biomarkers and companion diagnostics to effectively direct the care of cancer patients who are undergoing treatment with targeted therapies. The group also viewed the lack of appropriate funding as the primary challenge in translational research, followed by clinical trial design and the cost-effectiveness of cancer prevention.

Dr. Susan Desmond-Hellmann gave the keynote address at a meeting entitled "Accelerating Innovation: Oncology Translational Research." She reviewed the progress in the field and remarked on certain guiding principles that will be critical for the future. She stated that rituximab, trastuzumab, and imatinib mesylate are 3 drugs that have changed cancer medicine because they each address a major unmet need, are based on biomarker-driven patient selection, can extend survival, and are well tolerated by patients. She noted that the barriers that currently make cancer research so slow, expensive, inefficient, and uncertain must be addressed if additional similar products are to be developed. Going forward, she noted that the most important metric for success should be predictability; specifically, cancer researchers have not gone far enough to decrease uncertainty, and this is a technical challenge that needs to be overcome.

Currently, the ultimate failure rate for the development of new cancer drugs is exceedingly high. Enormous resources are expended to get a drug candidate from the point of basic discovery to the preclinical testing stage and finally to the patient. Primarily, the current paradigm for drug development does not effectively rule out poor drug candidates early on in their development. Over the next decade, cancer researchers must strive to better understand the biologic drivers of cancer and explore novel approaches to bench-to-bedside research. To build the next generation of nimble, flexible investigators, today’s leaders must value, espouse, and teach new methods and models for research that stress the importance of translational research.

The Think Tank meeting included some very productive breakout sessions in which recommendations were made to improve the effectiveness of clinical/translational research overall. Each group was charged with defining top priorities, summarizing the state of the science, identifying obstacles and challenges, and recommending new directions and opportunities for progress.

Five breakout groups discussed the following areas:

- Cancer biology and drug development
- Biomarkers and clinical trials
- Targeted therapies
- New technologies and imaging
- Prevention

Authors’ Affiliations: ¹Division of Hematologic Neoplasia, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts; ²Departments of Cancer Biology and Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas

Corresponding Author: Kenneth C. Anderson, Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115. Phone: 617-632-2144; Fax: 617-632-2140; E-mail: kenneth.anderson@dfci.harvard.edu

doi: 10.1158/1078-0432.CCR-11-3228

©2012 American Association for Cancer Research.
The following is a synthesis of the breakout groups’ reports, in which common themes are identified and recommendations are summarized according to the potential action area.

Cancer Biology and Drug Development

**Top priorities**

- Increase efforts to identify and develop stratification markers (host-genetic in addition to diseased-tissue markers).
- Obtain genetic, tissue, and clinical databases from trials with wide access to the scientific community.
- Improve interactions between basic and clinical scientists.
- Enhance the use of imaging for predictive medicine.
- Enhance understanding of tumor heterogeneity by increasing access to tissues pre- and post-treatment.
- Improve animal models and other biology-driven models.

The cancer biology and drug-development breakout group focused on many challenges facing investigators. The group expressed concerns regarding the lack of predictable animal models, a lack of understanding of the magnitude of tumor heterogeneity, and whether a specific subset of cells, such as tumor-initiating cells, should be the appropriate target for therapy. The group noted the need to better integrate basic and clinical scientists, and to strengthen academic–industry partnerships. One overriding theme was the need for data to be available to and interpretable by scientists. This will require the availability of national databases that include tools for analysis, well-defined data elements, and strict quality standards. If the scientific community identifies this as a significant need, nonprofit organizations (such as SU2C) could be approached for support. A similar effort could be made in the area of patient access to clinical trials and clinical information. The AACR could fill several roles, including policy, advocacy, and education. For example, the AACR could coordinate a national and international network for data infrastructure or develop a clinical trials website that would provide information to patients in a different and more comprehensive way than is currently available.

Biomarkers and Clinical Trials

**Top priorities**

- Identify active markers for clinical management of patients.
- Standardize all steps in the process of marker testing from the acquisition of specimens to analysis and publication of data.
- Help develop coordinated guidelines regarding levels of evidence for biomarker development [i.e., the potential for adoption by the U.S. Food and Drug Administration (FDA)].
- Encourage post-approval research to validate the clinical action taken.

The biomarker and clinical trials breakout group identified major areas for improvement as the foundation for progress. Currently, biosamples are acquired, stored, and annotated in a nonstandardized and not necessarily optimized fashion. Standards, guidelines, and blueprints are needed, especially for biospecimen collection. Although this has been clear for some time, the effort to achieve standardization faces significant hurdles stemming from the lack of data to support an evidence-based standard operating procedure, the lack of an arbiter to enforce standardization, and the existence of numerous local standards that have been in place for some time. To really enforce new standards, we must change professional behavior by establishing some combination of requisite procedures and training for accreditation, paying providers to follow protocols (through the Centers for Medicare and Medicaid Services), and educating providers about the use and importance of quality sample collection. New methods of collecting biosamples, such as circulating tumor cells and plasma DNA, should be developed and standardized. In addition, we need to develop systems to provide ready access to and release of biosamples needed to validate biomarker testing. Regulatory pathways to incentivize personalized biomarkers are now being established and should be refined to optimize integration into clinical trials. As drugs and therapies become more targeted, we will need to develop new statistical methods to identify effects and adverse events in small populations. In addition, adaptive trial designs that include a discovery phase and a validation phase will reduce the study time and allow researchers to focus on the most promising outcomes.

Targeted Therapies

**Top priorities**

- Accurate target identification and measurement
- Acceleration of early leads that are more likely to succeed
- Definition of nonresponders
- Combination therapy
- Cost recovery

The breakout group for targeted therapies focused on the need to identify susceptible populations to maximize the
efficacy of targeted therapy. There is a need to identify, at a minimum, populations of patients who will not respond to treatment, and thereby enrich clinical trials with patients whose disease is more likely to be susceptible to the new therapy. This will also reduce the costs of clinical trials and health care and avoid unnecessary side effects. The group foresaw a need for better databases to input test data and link them to outcome data.

Two additional areas were highlighted that need further incentives for study in the development of targeted therapies. Combination therapies are difficult to develop, particularly if only marginal results are obtained in the initial stages of single-agent trials. Companies often lose interest before the biology of the new agent has been fully explored. A second area is the need to evaluate how a particular molecular target evolves over time, that is, whether new mutations or adaptations occur that can alter the response to targeted therapy. This requires a detailed analysis of the pathways that surround or bypass individual protein targets.

New Technologies and Imaging

Top priorities

- Preselection of target populations
- Monitoring of dose and dose scheduling (pharmacodynamics and pharmacokinetics)
- Validation of treatment efficacy and time course of efficacy
- Individual patient management
- Imaging to guide biopsy sites for genomics/proteomics

The imaging breakout group discussed the importance of linking imaging targets to susceptibility genes, therapeutic targets, and outcome measures. They noted the need to identify new imaging targets, such as those located in the tumor microenvironment. A new approach would be to include the radiation-oncologist community in imaging activities. New probes to image specific components of tumor metabolism are being developed, and imaging is becoming increasingly important for direct radiation therapy and monitoring of tumor response.

The group noted some important obstacles to the application of imaging agents in clinical trials and the clinic, including cost, the complexity of validation, and the regulatory pathway to FDA approval. A number of currently available imaging techniques are not being used in clinical trials because of cost and patient burden. In fact, the group noted that the per-patient cost of positron emission tomography could be twice as much as the entire per-patient cost of a clinical trial. The group expressed the hope that the AACR could lead in advocating a mitigation of imaging costs for clinical trials. In addition, the AACR could get involved early in the development of imaging technologies to convene stakeholders in order to focus efforts on tools that address the relevant health care questions and are scalable, patient focused, and reasonably priced.

Prevention

Top priorities

- Better (personalized) risk assessment to improve risk/benefit decisions
  - Integration of molecular markers (germline, somatic, expression, and imaging)
  - More precise exposure measurements
- Personalized predictive markers
  - Efficacy
  - Toxicity
  - Progression markers
  - For disease subtypes
- Personalized prevention
  - High-risk monoclonal gammopathy of undetermined significance (MGUS) example as paradigm
- Applying/Translating what we know works globally
  - Vaccines for human papilloma virus and hepatitis B
  - Smoking prevention and cessation

The prevention breakout group discussed the need for early recognition and treatment of disease. Thanks to early diagnoses, it is becoming possible to identify patients who do not require dramatic treatment. However, true prevention through risk assessment is still in its infancy. It is unclear where intervention is appropriate. Predictive markers are embryonic. To date, there has been limited engagement on the part of industry. Opportunities for progress lie in the integration of prevention, secondary prevention, early detection, and treatment. The group raised the idea of a patient-oriented website that would allow individuals to enlist in a registry and perhaps submit simple biologic samples. The resulting database could be used for tracking, education, and information dissemination.

The group suggested that the AACR should establish multidisciplinary teams to integrate approaches to prevention. The organization could take a leadership role in using cancer vaccines to eradicate cancers that are caused by viruses. In examining cancer, the AACR must see it as a global health problem, and could support immunologic approaches to decrease the cancer burden worldwide.

High-Priority Issues

It is clear from the discussions highlighted above that much work remains to be done. Several general themes emerged, including the need for a national database to provide access to clinical trial data and biomarker data; the need to support team science more broadly; the need to share data, methods, and standards for biomarker development; and the need to engage advocates and survivors in supporting clinical/translational research. The following is an overall assessment of the
highest-priority issues raised and discussed during the Think Tank meeting.

Research

- Increase efforts to identify and develop biomarkers in both healthy and diseased tissue to aid drug development.
- Increase the use of imaging for predictive medicine, diagnosis, preselection of target populations, dose and dose scheduling, validation of efficacy, and better patient management.
- Link imaging to outcome measures in clinical trials.
- Use susceptibility genes to guide image screening (e.g., mammography).
- Use imaging techniques to guide biopsies, and better integrate such techniques with genetic, genomic, and proteomic technologies.
- Create better animal models that can lead to in silico model building for better prediction of efficacy, dosing, and toxicity.
- Identify accurate biomarkers for active management of disease.
- Improve target identification and measurement of therapy effects.
- Accelerate early leads by monitoring research more closely and allowing more funding flexibility.
- Define nonresponders to targeted therapies to ensure better-focused trials.
- Establish multidisciplinary teams to integrate the use of molecular markers and develop more precise exposure measurements to improve individual risk assessments for prevention.
- Develop and refine predictive markers of disease and methods for prevention tailored to individual patients (or stratified populations).

Information sharing

- Create genetic, tissue, and clinical databases from trials and give the scientific community access to the data.
- Increase access to pre- and post-treatment tissues to promote a better understanding of tumor heterogeneity.
- Bridge diagnostic and therapeutic development between academia and industry, perhaps with the AACR acting as a safe harbor.

Standardization and validation

- Establish national and international networks for the coordination of research data.
- Validate predictive biomarkers to reduce trial sizes.
- Validate biomarkers for prognosis and natural history.
- Standardize biomarker testing and assessment, including collection, analysis, and publication.
- Encourage post-approval research to validate clinical actions.

Regulation

- Create a blueprint for biomarker validation and statistical trial design to accelerate drug approval.
- Assist the FDA in drafting guidelines regarding the levels of evidence required for biomarker development.
- Assist in establishing guidelines for the development and assessment of combination therapies.

Education

- Use conferences, workshops, and educational sessions to support team-based research on animal model development, better use of imaging technologies, and information sharing.
- Engage advocates to stress the importance of clinical and translational research in general, and team science in particular.
- Educate policymakers about the need to coordinate research and regulatory agencies, and to reimburse for collection of biologic samples and imaging.
- Educate patients and physicians to get a buy-in on the value of biomarker-driven trials.
- Highlight examples of biomarker success stories that have accelerated the clinical application of a drug.
- Impress upon researchers and physicians the importance of paired samples (host, immunologic, and microenvironment biomarkers) and imaging trials to improve recruitment.
- Work with other professional societies to gain acceptance of imaging measures in clinical trials.
- Apply known methods [both therapy-based (e.g., vaccines) and behavior-based (e.g., smoking prevention and cessation)] globally.

Conclusions

The presentations and breakout sessions of the Think Tank meeting focused on current barriers to cancer research and led to a thoughtful discussion about the best approaches to take moving forward. Because some time has passed since the original meeting was held, we have elected to provide timely updates on these key areas from individuals who participated in that meeting, as well as other experts in the field. We have compiled five thoughtful mini-reviews on key issues under the following titles: (i) “Impact of Genomics on Personalized Cancer Medicine,” by Arteaga and Baselga; (ii) “Making Personalized Cancer Medicine a Reality: Challenges and Opportunities in the Development of Biomarkers and Companion Diagnostics,” by Parkinson, Johnson, and Sledge; (iii) “Genetically Modified Mouse Models for Biomarker Discovery and Preclinical Drug Testing,” by Kucherlapati; (iv) “Imaging: Strategies, Controversies, and
Opportunities," by Blasberg and Piwnica-Worms; and (v) "Reports from the 2010 Clinical and Translational Cancer Research Think Tank Meeting: Design Strategies for Personalized Therapy Trials," by Berry, Herbst, and Rubin.

We have only been able to touch on a few important areas we believe are critical for the future development of clinical and translational cancer research. We hope that you enjoy this CCR Focus section, and, more importantly, that it stimulates much-needed progress in the field.

Received December 14, 2011; accepted December 14, 2011; published online February 1, 2012.
Overview of the AACR Clinical and Translational Cancer Research
Think Tank Meeting

Kenneth C. Anderson and Raymond N. DuBois

*Clin Cancer Res* 2012;18:607-611.

**Updated version**
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/18/3/607

**E-mail alerts**
Sign up to receive free email-alerts related to this article or journal.

**Reprints and Subscriptions**
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

**Permissions**
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.