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Meeting Report: NCI Think Tanks in Cancer Biology

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Abstract

Over the past year and a half, the Division of Cancer Biology of NCI has been assessing the state of cancer biology, with the goal of developing a research agenda for the near future that would accelerate progress in cancer research. Our goal was to identify emerging concepts and promising opportunities for investigation across nine scientific areas with unusual promise for rapid progress. A series of meetings called Think Tanks was convened, each involving a panel of 15-25 experts. In all, over 160 leaders in cancer research and related fields discussed the current state of science in their disciplines, projected its trajectory and recommended what NCI could or should do to facilitate progress. In addition to emphasizing the importance of continued support for investigator-initiated research, the Think Tanks permitted identification of a number of overarching themes. Critical among them was the need to support the development of integrative cancer biology and to encourage studies of the tumor microenvironment by establishing an infrastructure for interactive research. There was also consensus about the importance of comparative studies of normal and tumor states, and development of mechanisms for supporting collaborative, interdisciplinary research and training. (Cancer Res 2005; 65(20): 9117-20)

Introduction

It has been recognized for some time that cancer is largely a disease of genes, in which cumulative mutations in a spectrum of proto-oncogenes and tumor suppressor genes lead to the initiation and progression of cancer. However, it is also very clear that mutations in these genes alone do not determine the disease. The roles of these other factors are just beginning to be understood. To identify emerging areas that are extending our understanding of the cancer process, the Division of Cancer Biology of NCI sponsored a series of Think Tanks that focused attention on events downstream of cancer genetics, in the continuum of initiation/progression/metastasis. Although a significant amount of cancer biology research in these areas already is supported by NCI through investigator-initiated grants, proactive initiatives are occasionally needed to facilitate research progress. Such initiatives may support creation of resources that are not easily developed on grants, or allow researchers to work together in ways that are not possible through grants to individual investigators. The goal of the Think Tank series was to summarize the state of knowledge in each of nine areas across the cancer continuum and to determine whether there are near-term ways in which the NCI could accelerate progress. The topics covered by the Think Tanks were:

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tumor immunology, tumor microenvironment, tumor stem cells, cell decisions in response to DNA damage, cancer etiology, epigenetic mechanisms, inflammation, cancer susceptibility and integrative cancer biology. Although each Think Tank provided unique insights and recommendations on the specific needs of that research area, a few common themes emerged that go well beyond cancer biology and challenge the ways NCI, and NIH overall, support fundamental research. In this article, we summarize the discussions and recommendations of the Think Tanks, highlighting the common themes. The complete reports, which represent the opinions of the participants, with special input from the Chair or Co-Chairs, are available at http://cancer.gov/think-tanks-cancerbiology.

Overarching Themes in the Recommendations

Each Think Tank resulted in a series of important, specific recommendations that are detailed in the full report and will be addressed individually by NCI. In addition, there were recommendations that appeared more than once. All nine Think Tanks strongly recommended continued support for investigator-initiated grants, and especially the R01. Investigator-initiated research has spawned many exciting discoveries worthy of further development in each of the Think Tank areas, and will continue to benefit all cancer research. This summary will concentrate on three overarching scientific and one support-mechanism themes that emerged independently in multiple Think Tanks.

Integrative cancer biology. The first scientific theme common to all of the Think Tanks was the need to support the emergence of integrative cancer biology as a field. To address the complexity of the many interactive and interdependent processes in normal and cancer cell biology, the classical reductionist studies must be complemented by an integrative systems approach. Advanced bioinformatics tools need to be developed and applied to the analysis of a comprehensive "parts list" derived from highthroughput measurements of critical parameters, to construct predictive computational models of the cancer process. Although to date integrative biology has focused mostly on the analysis of signal transduction pathways and other regulatory circuits within a single cell, it is equally applicable to complex processes involving multiple cells and extracellular molecules. For example, a complete characterization of the tumor microenvironment depends on combining high-throughput analytical methods with bioinformatics to generate predictive models of the interactions that drive the microenvironment. This need was stressed by the Tumor Microenvironment Think Tank, but is equally true of all of the other areas explored in the Think Tank process.

The Think Tanks provided strong evidence that this need is an important direction for the Institute to pursue and that its influence will be felt throughout cancer research. Thus, in September 2004, NCI funded a series of Integrative Cancer Biology Programs (http://icbp.nci.nih.gov/), the first organized foray into systems biology in the context of cancer.

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The tumor microenvironment. The second overarching scientific theme was the need to understand the tumor microenvironment, its composition and interactions with the tumor. Growth and migration of normal epithelial cells are subject to many levels of regulation by neighboring cells, extracellular matrix, and local levels of soluble signaling molecules. Cancer cells lose critical aspects of these controls, but they lose them gradually and rarely lose them all. Thus, one way of looking at cancer initiation and progression is as an iterative and progressive renegotiation of constraints carried out between a developing clone of epithelial cancer cells and its stromal microenvironment. This perspective suggests two principal lessons. First, attempts to understand tumor behavior or to treat cancers must take into account far more than the intrinsic properties of the malignant cells to be successful. And second, attempts to model tumor behavior must go beyond using tumor cell lines cultured on plastic surfaces, to three-dimensional culture systems and in vivo studies. The Tumor Microenvironment Think Tank provided a detailed blueprint for integrated studies; many of the other Think Tanks emphasized specific aspects of the microenvironment that are often overlooked in overviews of the subject.

While the Think Tank participants emphasized the importance of expanding support for investigator-initiated research of the tumor microenvironment, they also recommended the formation of a network or alliance to encourage cooperative, interdisciplinary studies. Such a network would bring investigators experienced in this area together with scientists with complementary expertise. It would leverage existing individual grant support by providing incremental funding for cooperative projects and for the creation of freely accessible, common resources that would benefit the entire research community. As envisioned by the Think Tank participants, a network would address many current barriers to progress, which are described in detail in the report, but its key goals would be to:

- 1. Characterize all of the cellular and non-cellular components of the normal and wounded tissue, tumor and tumor stem cell microenvironments. Characterization would involve probing the genomics and proteomics of stromal and tumor cells; data derived from these studies would be stored in public databases. Antibodies and other reagents useful for visualizing, quantitating and comparing different microenvironments would be developed cooperatively; these resources and relevant methodologies would be made generally available. Static characterization would rapidly be extended to studies of dynamic interactions, using real-time imaging methods.
- 2. Delineate the role of the microenvironment in tumor progression and metastasis, and in response to radiation and/or chemotherapy, including characterization of the metastatic tumor microenvironment.
- 3. Determine the role of inflammatory processes both in shaping the tumor microenvironment in the earliest phases of tumor initiation and during progression and in facilitating or inhibiting the development of effective antitumor immune responses.
- 4. Develop and sponsor interdisciplinary training programs.
- 5. Translate the basic knowledge obtained to improve diagnosis and early detection of cancer, and to discover and validate therapeutic targets derived from the tumor microenvironment.

The challenge of comparing the normal and the tumor state. The last overarching scientific theme was not an area of research so much as an approach. Impressive recent advances in understanding cancer biology - many of which were highlighted in the Think Tanks - have opened up an enormous array of promising areas of research. While it is tempting to pursue these opportunities by focusing exclusively on the cancer state, the participants in six of the Think Tanks explicitly recommended against this course of action, emphasizing the critical importance of understanding cancer in the context of normal biology. For example, as a tumor develops, the normal constraints imposed by the microenvironment on cell growth and mobility are gradually loosened. We need to know much more about these normal constraints individually, and about how they are coordinated at a systems level, before the tumor microenvironment can be fully characterized. Normal cellular responses to DNA damage are similarly complex and also must be better described before they can be manipulated for therapeutic benefit in cancer. In tumor immunology, the major advances in understanding that have occurred in the last ten years have come from conceptual advances in immunology as a whole. The critical questions that remain are the same for basic immunology, autoimmunity, chronic infectious diseases and cancer, although the perspectives on the questions differ slightly among these fields. Inflammation in cancer has a marked stimulatory effect on cancer growth not because of its intensity, but because it fails to resolve the way acute, physiological inflammation does. It shares this characteristic with autoimmunity and certain chronic infections. The stem-cell programs of several tissues appear to be involved in cancer progression, but so little is known about the regulatory program within the normal tissue stem cell and the cell-cell interactions of the stem-cell niche that it is difficult to characterize cancer stem cells or to determine the path by which they became transformed. Epigenetics is similarly a young field, in which a great deal of basic knowledge must be accumulated before its role in cancer can be clarified.

The challenge is to identify those elements of these fields that the NCI should attack with its own resources and those where it should work in coordination with other NIH Institutes and other funding agencies. Leveraging of resources is difficult, but necessary. The NIH Roadmap can serve to address some of the cross-cutting scientific issues identified by these workshops, but there remains a great need and an enormous opportunity for a focused effort. It can be anticipated that such research will inevitably yield results that can be broadly applied. While the NIH has some coordinated activities related to human embryonic stem cells, tissue-specific stem cells (with the exception perhaps of hematopoietic stem cells) have received scant attention. Similarly, there is no NIH-wide largescale project on epigenetics on the horizon, despite its documented importance in many human diseases. The Think Tank recommendations make it clear that catalyzing broadly-sponsored largerscale studies of some critical cross-cutting biological issues must be a high priority to provide the necessary context for progress against cancer.

Other common scientific themes. Two other commonly raised issues, though less pervasive than the three described above, deserve mention. Inflammation was recognized as important enough to deserve its own Think Tank, but it was surprising how prominent a role it occupied in other Think Tanks. This suggests that it needs an even more prominent role than had been envisioned in initiatives to study the tumor microenvironment, where inflammation is a nearly constant finding. A related common theme was the role of microbial flora as a cofactor in tumor development. While biological carcinogenesis, with an

emphasis on cancer caused by viruses, has always been supported within NCI, examination of a cofactor role for microbes that are not directly transforming has lagged behind. This is one of several areas that bridge cancer biology and etiology.

Mechanisms to foster collaborative, interdisciplinary research and training. The final overarching theme dealt with the mechanisms through which NCI supports research. NIH grants, built around the R01 traditional research grant, have been the engine of creativity that has brought us to the current exciting point in cancer research. The Think Tank participants uniformly acknowledged the past and continuing importance of R01 grants. During the Think Tanks, however, they focused on needs that are difficult or impossible to meet through this mechanism. These were generally large-scale efforts, especially those that required input from scientists in diverse disciplines. The Tumor Microenvironment Network, described above, is an example of the recommendations, but similar networks were suggested in immunotherapy, stem-cell research, epigenetics, etiology and susceptibility. The Think Tank panelists and the great majority of the scientific community want to see support for investigator-initiated research remain strong, but it is clear that a new balance must be struck that permits both smaller scale individual and larger scale collaborative/interactive approaches to cancer biology to flourish where they are most productive.

In some cases, less formal (and smaller scale) resources for collaboration were recommended. Many of the recommendations involved more coordination rather than direct research support. These recommendations were made because there are very few investigator-initiated NIH funding mechanisms that can support any of these varied activities. Critical problems in cancer research and other areas of biomedicine increasingly require a variety of expertise and/or the sharing of data or reagents in a manner that is not facilitated or sometimes even possible when support comes exclusively from grants to individual principal investigators. Constraints on collaborative and interdisciplinary research also exist at research institutions. Rigid departmental structures, intellectual property policies and concerns about indirect costs can make some types of research more difficult. With sufficient resources, these recommendations could all be addressed through NCI-directed mechanisms such as contracts, supplements and workshops. What may be needed, however, is a highly flexible, permanent program open to investigator-initiated applications to support modest-scale, collaborative, interdisciplinary research efforts.

Each recommendation for an interdisciplinary research program was accompanied by a recommendation for a program that would train students, postdoctoral fellows and established investigators to take optimum advantage of the opportunities such a program would create. Three types of suggestions about interdisciplinary training were made during the Think Tanks. One was to incorporate training into large-scale interdisciplinary initiatives. This was done in the Integrative Cancer Biology Programs. The second was to place some leverage back in the hands of graduate students by inaugurating individual pre-doctoral fellowships in which the range of subdisciplines and the mentor(s) could be determined by the graduate fellow and not the institution. The third was to reserve a portion of NCI postdoctoral training grants for explicitly interdisciplinary programs. While institutions are moving to respond to the need to change training paradigms, the Think Tank process made it clear that NCI must work to facilitate and accelerate such change.

Other common support issues. Support for technology development, in general, appears to remain a challenge despite

the addition of many new programs in recent years. Think Tank participants consistently reported limitations in funds for reagent preparation (e.g., monoclonal antibodies), model development (both genetically engineered animals and complex, three-dimensional tissue cultures), and state-of-the-art imaging. Funding for critical resources needs to be factored into plans in many areas, but it was also surprising that in some instances Think Tanks recommended that NCI make available resources, including reagents, databases, animals and facilities, that are already available. This indicates that more effort needs to be put into ensuring that all members of the cancer research community are aware of the resources NCI currently provides. If there are problems of quality or access with existing resources, these need to be evaluated as well.

Specific Recommendations of the Individual Think Tanks

In addition to the overarching themes of the Think Tanks, each one provided recommendations specific to its area. The principal recommendations of the individual Think Tanks were as follows:

- **1. Tumor Immunology,** The discussions emphasized the need for continued support of investigator-initiated research in basic and tumor immunology to ensure rapid progress in resolving critical issues in every aspect of immunology. Specific recommendations addressed the needs of translational research, including development of a mechanism to support collaborative, multi-disciplinary consortia focused on immunotherapy, steps to increase the availability of high-priority biologics for clinical testing, and resolution of regulatory barriers in clinical trials.
- **2. The Tumor Microenvironment.** The participants unanimously recommended the creation of an Interdisciplinary Tumor Microenvironment Network that includes pathologists, cancer biologists, cell biologists, oncologists, engineers, physicists, bioinformatics experts and industry representatives. Such a Network was envisioned to facilitate the study of normal and malignant tissue microenvironments by funding centralized resources and collaborative research in critical areas. It would serve as a focal point for the growing tumor microenvironment research community, which should be supported through a variety of funding opportunities.
- **3. Tumor Stem Cells and Self-Renewal Genes.** The panelists recommended consideration of a Research Consortium to facilitate transdisciplinary approaches and to provide specialized reagents that will advance research on tumor stem cells, their origins, and the genetic and epigenetic pathways important in maintaining the tumor stem cell state. They also recommended continued support for basic research relevant to this area, which led to the recent issuance of a Program Announcement on Stem Cells and Cancer (PA-05-086).
- **4. Cell Decisions in Response to DNA Damage: Survival vs. Apoptosis,** This Think Tank brought together experts in DNA damage and cell cycle, who usually do not meet, to consider how studies of the complex interplay between DNA damage sensing and repair pathways, the pathways controlling the cell cycle, and cell death mechanisms might lead to improvements in the response to radiation and/or chemotherapy of cancer. The participants recommended increased support of basic research that integrates studies of cell cycle checkpoints, DNA repair pathways and apoptosis with the DNA damage response and that investigates molecular targets for enhancing programmed

cell death in response to DNA damage. In addition they recommended a follow-up workshop be convened to identify specific reagents/resources and develop strategies to dissect the temporal order of mammalian DNA-damage response networks in real time-in cell culture, in tumor tissues and in vivo.

- **5. Cancer Etiology: Role of Exogenous and Endogenous Chemicals.** The participants discussed approaches to enhancing the connections between chemical carcinogenesis and areas such as inflammation, biological carcinogenesis, cancer susceptibility, and systems biology. They recommended that the research focus expand from DNA adducts and mutation analysis to a broader spectrum of damage resulting from exposure to carcinogens throughout the process of tumorigenesis, from initiation through metastasis. To support this effort, they identified specific needs within the areas of biomarkers, animal models, technology development, and recruitment and training of the next generation of researchers. They emphasized the importance in these activities of forming good working relationships between biologists and chemists.
- **6. Epigenetic Mechanisms in Cancer.** As the basic epigenetic mechanisms are being established, increasing emphasis needs to be placed on understanding epigenetics in the context of disease mechanisms. The participants endorsed the concept of a Human Epigenome Project, which would develop a baseline of epigenetic information across the genome and improve analytical methods and bioinformatics tools. They suggested that a Working Group be established to outline and plan such a Human Epigenome Project. To this end, a workshop and planning meeting were recommended.
- 7. Inflammation and Cancer. The complexity of inflammation is reflected in its opposing positive and negative influences on cancer, including those due to infectious agents. The Think Tank emphasized the need to bring together experts from different disciplines to address the role of inflammation in cancer and to develop more effective strategies for cancer prevention and treatment. To this end, they recommended sponsorship of a series of transdisciplinary workshops and/or interactive fora on inflammation and cancer, and creation of mechanisms to stimulate multi-agency, multi-institutional, and transdisciplinary collaborations to more rigorously define the interactions that occur between tumor cells and their inflammatory microenvironment.
- **5. Cancer Susceptibility and Resistance.** The Think Tank identified the primary research goals as: a) understanding the complex interactions of genetic and environment influences in the prediction of risks of cancer for individuals and populations; and b) developing approaches to enhance prevention, early diagnosis, targeted treatment, and better prognosis prediction. The recommendations of the Think Tank were to focus on improving methods of cancer-related phenotyping, examining all cancer-related biological processes that are likely to be sources of individual variation, and creating new computational, mathematical, and statistical models and analytical tools that take into consideration the complexity of variation in suscep-

tibility and resistance to cancers. This approach needs to be applied using large human populations, and hypothesis testing and candidate gene validation in rodent models.

9. Integrative Cancer Biology. Based on the recommendation to facilitate the emergence of this important field, an RFA was issued for Integrative Cancer Biology Programs, to support the development of predictive computational models of cancer-related processes, coupled with experimental testing in biological systems. The Programs also include training and outreach components. This was the first major initiative to emerge from the Think Tank process, and awards were made at the end of Fiscal Year 2004.

Concluding Remarks

The Think Tanks provided a substantial blueprint for NCI actions in support of cancer biology. Their recommendations included a major initiative in integrative cancer biology, which has been funded, and will serve as the basis for a series of major initiatives related to the tumor microenvironment. Smaller initiatives of several types, responsive to specific recommendations from individual Think Tanks, have appeared or are under development. Current and planned initiatives have to take into account the fact that the NIH grants system, which continues to be an efficient engine of discovery for individual investigators, provides limited opportunities for those who want or need to work in larger groups, particularly those that are interdisciplinary in nature.

As much as the Think Tanks focused on needs in cancer biology. they provided powerful illustrations of the interdependence of different areas of cancer research. Tumor immunology, as the report demonstrates, can no longer be discussed without considering immunotherapy. As modern, clinical immunotherapy has had increasing impact, it has provided more valuable feedback to guide research in basic immunology. In turn, the path to translational development for basic discoveries has become clearer (although, as the report also illustrates, this path is littered with obstacles). Productive research in cancer susceptibility requires a familiarity with human population studies and mechanistic cancer biology, in particular the use of genetically engineered animal models of cancer. In turn, susceptibility information directly informs prevention research. Inflammation is equally cross-cutting, uniting cancer biology, treatment and prevention. Many other examples could be cited. Cancer biology has always had strong ties to many other disciplines, inside and outside the cancer research community. The Think Tanks show that these ties contribute to the continued intellectual vitality of the field.

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