

# Brain Metastasis: Opportunities in Basic and Translational Research

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## Introduction

Brain metastasis is a major public health problem. An alarming increase in the incidence of brain metastasis in patients with otherwise well controlled systemic cancer has drawn attention to this important, yet understudied, dimension of the cancer problem. Today's practicing oncologist encounters many patients with excellent quality of life who appear to have "beaten the odds," yet subsequently develop metastatic disease in the brain, resulting in progressive physical and cognitive impairment and culminating in death, often within a few months. Our ability to address this growing problem is hampered by meager advances in the treatment of brain metastasis, an elemental understanding of the pathophysiological forces underlying brain metastasis, inadequate model systems, reagents, and biospecimens, and a systematic failure to consider the impact of the blood brain barrier on drug distribution as a critical parameter in guiding cancer drug development.

The Biology of Brain Metastasis Workshop was organized by the Division of Cancer Biology (DCB) at the National Cancer Institute (NCI) to describe the clinical problem, identify the critical points of therapeutic failure, and summarize the current state of knowledge of the genetics and biology of brain metastasis. The overarching goal of the Workshop was to generate a set of research priorities that would stimulate integrated scientific and clinical investigation directed at understanding basic processes of brain metastasis and translating such insights to clinical care as rapidly as possible. The recognition that basic mechanisms of metastasis and tumor cell growth in the brain are inextricably linked to the clinical phenotype helped build a framework of issues and opportunities in this critical area of unmet need. The meeting summary is presented here in a way that integrates the clinical, translational and basic science vantage points for each of the key areas presented by a group of leading clinical investigators who care for patients with brain metastases as well as a group of basic and translational scientists spanning a diverse spectrum of cancer science disciplines of potential relevance to the brain metastasis problem.

## The Clinical Problem

### Presenters

Elizabeth Maher (UT Southwestern Medical Center, Dallas, TX), Howard Fine (NCI, Washington, DC), Eric Winer (Dana-Farber Cancer Institute, Boston, MA), Minesh Mehta (University of

Wisconsin School of Medicine and Public Health, Madison, WI), Eric Holland (Sloan-Kettering Institute for Cancer Research, New York, NY), Deepak Khuntia (University of Wisconsin School of Medicine and Public Health, Madison, WI), Carlos Arteaga (Vanderbilt University, Nashville, TN), and Bruce Chabner (Massachusetts General Hospital, Boston, MA) were presenters.

The incidence of brain metastasis is expected to exceed 200,000 cases per year in the United States by 2010, more than 10 times the incidence of primary brain tumors such as glioblastoma. Untreated, the median survival time is 2–3 months and with aggressive treatment is extended only marginally to 4–12 months (1). The staggering impact of the short survival times is reflected in the total numbers. Over the past 25 years, approximately 4,250,000 cancer patients have died with brain metastases. That this is only now being recognized as a major clinical problem reflects a shift in the relative contribution of brain metastases to the overall survival time of cancer patients. Historically, metastasis to the brain was a late complication of systemic cancer after the establishment of metastases in lung, bone, and/or liver and at a point in a patient's disease course when treatment was largely ineffective for these sites. Although treatment in the brain was directed at palliating symptoms and was often effective in delaying progression in the brain, the patient's overall poor prognosis was felt to be due to the burden of systemic disease. As a result, patients with brain metastases were excluded from clinical trials of new drugs for metastatic disease over many years, and there has been no systematic attempt to develop drugs specifically for brain metastases. It was hoped that better systemic treatment would reduce metastases in all organs, including brain. However, the problem has been compounded by the lack of attention to drug distribution in the brain, and, in fact, many of the first-line agents currently being used do not penetrate the blood brain barrier, or do so minimally. Most notable among these are the monoclonal antibodies that have been so effective in treating systemic metastases and the use of which has expanded into first-line therapy. The net effect has been to create the situation in which brain metastases develop in the absence of other sites of metastatic disease when patients are well and, even in some cases, felt to have been cured. The overall impact is reflected in the lack of effective therapies currently available for brain metastasis and an unchanging median survival time, thus shining a spotlight on this devastating complication.

### Current Treatment

**Surgery and radiation therapy.** Standard treatment for brain metastasis includes surgical resection in a limited number of clinical scenarios. First, biopsy or complete resection may be performed for diagnosis, although histologic confirmation is often not needed in the setting of metastatic disease. Second, large (>3 cm) or symptomatic masses are removed to palliate symptoms. Whole brain radiation, in which the whole brain is treated with

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a uniform dose of external beam radiation, is the mainstay of treatment. It is used to reverse acute neurological deficits and diminish intracranial relapse, and it has been shown to prolong survival by 2–7 months (2). High-dose, focused radiation (radiosurgery) has also been used extensively to treat brain metastases with a maximum target volume of 3–4 cm and up to three metastases at a time. Radiosurgery provides good local control while sparing normal brain. The capacity to spare normal brain is critical, as radiation-induced neurocognitive decline is of great concern, especially as patients live longer with well controlled systemic disease. However, data suggesting that the development of micrometastatic disease is associated with an incremental decline in neurocognitive function that predates the appearance of MRI-detectable metastases by at least 1–2 months (3) underscores the need for systemic preventive strategies as part of initial cancer therapy.

**Chemotherapy.** A central question in drug therapy for brain metastasis is whether cells metastasize after they have developed resistance to initial therapy or metastasize early but remain dormant or “protected” behind an impenetrable blood brain barrier. The clinical experience with *EGFR* mutant non-small cell lung cancer (NSCLC) provides invaluable data that begins to address this question. Sequencing analysis of a series of resected NSCLC brain metastases demonstrated that only tumors harboring an activating *EGFR* mutation were sensitive to the *EGFR* inhibitor gefitinib, recapitulating the experience in primary lung tumors (4). These cases demonstrated that the tumor cells growing in the brain microenvironment did not lose their dependence on the dominant oncogenic pathway driving proliferation, and that a drug capable of penetrating the blood brain barrier could be effective therapy. This was the first example of “right drug, right clinical setting” for the treatment of brain metastasis and is a major milestone.

Also informative has been the clinical experience with trastuzumab (Genentech), a monoclonal antibody directed against the extracellular domain of the HER-2/neu protein. In a phase II trial, 37 women with HER-2-positive breast cancer who developed brain metastases while on trastuzumab were treated with the *EGFR*/HER-2 dual kinase inhibitor lapatinib (GlaxoSmithKline), a drug with good central nervous system (CNS) penetration (5). All patients had received prior whole brain radiation. Several patients had a reduction in tumor volume, one with a good partial response, and 18% of patients had no disease progression over the course of 18 weeks. Even limited shrinkage of brain tumors suggested that (a) the cells that metastasized to the brain in some patients were not resistant to HER-2 inhibition as a result of prior exposure to trastuzumab and (b) the metastatic focus in the brain retained, at least to some extent, its oncogenic dependence on the HER-2 pathway. The lack of response in the other patients is also important in addressing basic mechanisms. Did metastasis in these patients develop late, after the development of some degree of trastuzumab resistance? Are there genetic modifications in the tumor cells such that they lose their dependence on the HER-2 pathway, perhaps as a response to radiation or to interaction with the brain microenvironment? These data also raise the issue of tumor cell dormancy in the brain and its contribution to response or lack of response.

The importance of the data generated in these clinical trials cannot be overstated. Examination of response and lack thereof will provide an experimental framework and stimulate new hypotheses with the potential to drive progress in this area. Obtain-

ing tumor tissue from patients in these trials for correlative studies was recognized by Workshop participants as a critical step in this process.

### Translating Clinical Observation into Basic Investigation

Brain metastasis is operationally defined as the growth of a tumor in the brain that had its origins in a cancer derived from an organ outside the CNS. While it is common to refer to brain metastasis as a single disease entity and develop global treatment strategies for this entity, it grossly oversimplifies a complex problem that has enormous patient and tumor heterogeneity. At the core is a fundamental question of what is the relative biological importance of the underlying cell of origin versus growth of the tumor cell in the microenvironment of the brain. Added to this is the complex dynamic of the brain as a relatively “privileged” site, with the blood brain barrier restricting the efficacy of many therapeutics. Incorporating issues of the uniqueness of the primary tumor as well as differences among the tumor subtypes in their susceptibility to chemotherapy and radiation provides a broader foundation for studying all aspects of the process by which a tumor cell metastasizes to the brain. Comparison among the tumor types will likely provide insights into basic mechanisms and identify opportunities for preventive therapy as well as targeted approaches to treatment in the brain. An example of this principle is reflected in the differences in metastatic potential among the primary tumors. NSCLC and breast cancer account for 65%–75% of the brain metastasis cases, reflecting the relative incidences of these two cancers in the general population among cancer subtypes that metastasize to the brain. Melanoma and renal cell cancer account for 5%–10% of cases, numbers disproportionate to their incidences, reflecting a high predilection for metastasis to the brain. From an absolute risk perspective, advanced melanoma has a several fold greater likelihood of metastasizing to the brain compared to other malignancies, and the uniqueness of this predilection may lie in trophic mechanisms that are poorly understood. The clear differences in metastatic potential raise the question as to whether some tumors are “hardwired” to metastasize to the brain. Does a molecular signature exist that either induces “homing” to the brain or provides the necessary genetic alterations for the cell to interact at a microenvironmental level to grow in the brain? If such a genetic program exists, is it common among the various primary tumors? Clearly, the answer would have a profound impact on strategies to develop interventional therapies as well as preventive strategies that could potentially either impede the metastatic potential of the primary tumor or eliminate intracranial microscopic disease before it becomes clinically manifest. Thus, although brain metastasis will continue to be referred to as a single disease entity for simplicity in nomenclature, the wealth of information that can be gained by cross-subtype comparison at the clinical and basic science levels is recognized. Recommendations for clinical, translational, and basic science research in brain metastasis (see below) will reflect the broader inclusion of the primary tumor subtypes.

### The Biology of Brain Metastasis

#### Presenters

Josh Fidler (MD Anderson Cancer Center, Houston, TX), Lynda Chin (Dana-Farber Cancer Institute, Boston, MA), Joan Massague (Sloan-Kettering Institute for Cancer Research, New York, NY),

Ronald DePinho (Dana-Farber Cancer Institute, Boston, MA), Robert Sackstein (Harvard Institute of Medicine, Boston, MA), Bruce Zetter (Children's Hospital, Boston, MA), Zena Werb (University of California, San Francisco, CA), Rakesh Jain (Massachusetts General Hospital, Boston, MA), Patricia Steeg (NCI, Washington, DC), Robert Kerbel (University of Toronto, Toronto, ON, Canada) Michael Clarke (Stanford University, Palo Alto, CA), Evan Snyder (University of California, San Diego, CA), and John Minna (UT Southwestern Medical Center, Dallas, TX) were presenters.

Although the major cause of cancer-related death is uncontrolled metastatic disease that resists conventional therapy, most investigation has been directed at primary tumors. Primary neoplasms are phenotypically heterogeneous, resulting from marked genomic instability and local tumor microenvironment selection pressure(s). From the primary tumor emerge tumor cells endowed with the capacity to disseminate by hematogenous and/or lymphatic routes to distant sites and establish metastasis through a series of sequential, interrelated stereotypic steps, which have been formalized as the seed (tumor cells from the primary tumor) and soil (the relevant organ microenvironment) hypothesis, first articulated by Paget in 1889 and reviewed by Dr. Fidler. The traditional view has been that the ability to metastasize is a late-stage event in tumor progression, although recent findings suggest that this view may require significant revision. It is quite possible that small numbers of cells enter the circulation in early stages of the disease and form occult brain metastases that become clinically apparent at advanced stages.

### Genetics and Genomics

One of the fundamental questions with implications across the translational spectrum is whether a primary tumor is endowed upfront with "brain metastasis-capable genetic events" or, alternatively, full brain metastatic competency is acquired stochastically during progression over time. Dr. DePinho described the role of telomere dysfunction in driving the large number of genomic alterations required to drive epithelial cells across the benign-to-malignant transition. His data and associated model, derived from both murine models and an analysis of staged human epithelial cancer, indicate that telomere dysfunction and deactivated DNA damage checkpoint responses (e.g., loss of *p53* in particular) are responsible for driving epithelial carcinogenesis in the aged and for shaping the cancer genome (6). Importantly, these events occur very early in the life history of evolving cancers, and, thus, even early-stage tumors appear to possess the vast majority of genomic alterations required for full malignant progression. Whether these myriad genomic alterations are sufficient for metastatic potential is not known. It is possible that additional genomic/genetic/epigenetic/transcriptional changes occur with progression of the primary tumor or after successful establishment of micrometastasis that reflects adaptations to the local microenvironment. Dissecting the relative importance of each component will be critical to understanding metastasis to the brain. The wealth of genomic data that have been generated for the common cancer subtypes has shown clear differences in genomic alterations while at the same time defining a subset of common genetic changes and signaling pathway alterations. However, little insight into the genetics of brain metastasis can be gleaned from examining the primary cancer subtypes in the absence of a comprehensive view of the brain metastasis genome in each of the subtypes and without knowledge of the normal genetic polymorphisms that might

influence cancer metastasis to the brain in each of the tumor subtypes. Thus, a comparison of the brain metastasis genome, epigenome, and transcriptome among the tumor subtypes will likely lead to important mechanistic insights. Clearly, the functional evaluation of genes identified from these comparisons will benefit from the generation of model systems in metastasis (see below) and was highlighted in the presentation by Dr. Chin. Through her work on melanoma, she demonstrated that a critical component of unraveling the enormous complexity of the human cancer genome is cross-species comparison with refined genetically engineered mouse models of human cancer (7).

Dr. Clarke discussed self-renewal and related data from chronic myelogenous leukemia in which it has been shown that the transformed cell can arise from two functionally different cells and that no single gene regulates self-renewal. Discussion centered on two important questions. When in the process does a cell develop that is endowed with the genetic program permissive for oncogenic transformation and brain metastasis? Is this program unique for brain growth, or is there a "generic metastasis program" that is necessary for growth in any organ, and that brain growth is determined by additional factors and/or genetic changes?

An important, but as yet unexplored, area is the role of stem-like neoplastic cells in determining the metastatic phenotype. The so-called "cancer stem cell" shares properties with normal stem cells, including rapid clonal expansion by self-renewal, resulting in exponential growth, as well as the production of terminally differentiated progeny, resulting in more indolent growth. Dr. Snyder reviewed basic principles of stem cell biology and noted that there is a paucity of information in several critical areas that make it difficult to determine whether brain metastasis fulfills the functional criteria for cancer stem cells. It is of interest, and possibly of therapeutic utility, that exogenous neural stem cells (NSCs), including those armed with oncogenic genes, will home to metastatic neoplasms in the brain (both following intracranial administration and intravascular injection) and deliver their "payload," reducing the tumor burden. The homing signals directing normal NSCs are only now being identified, but they might overlap with signals that direct the metastasis of "cancer stem cells."

### The Brain Microenvironment

The brain's microenvironment as a unique niche for metastatic tumor cell growth is largely unexplored. However, there have been significant strides made in understanding the growth of glioma cells in the brain, and several participants outlined changes in astrocytes, microglia, and immune cells that may be relevant. In addition, insights derived from the work on glioblastoma and medulloblastoma were felt to be of great relevance to understanding processes of metastatic tumor cell growth in the brain.

Tumor cell dormancy dominated the discussion of the brain microenvironment, as it is intimately linked to the debate over early versus late metastasis and represents a critical issue in the development of therapeutics. The concept of the brain as a "sanctuary site" for cells that have "escaped" treatment with drugs that did not penetrate an intact blood brain barrier invokes dormancy as a model for long latency. However, it is difficult to differentiate dormant tumor cells from brain micrometastases; operationally, these are defined as distinctly different entities. Dormant cells are defined as being in a state of cell cycle arrest, yet they retain the potential to reenter the cell cycle, whereas micrometastases are actively proliferating cells, although they are often undetectable by current imaging techniques. The Workshop

participants agreed that identifying dormant tumor cells in the clinically asymptomatic brain remains an important unmet need. Dr. Jain discussed imaging and reported that detecting dormant cells will likely not be amenable to conventional imaging techniques, but, speculatively, future technologies based on high-resolution spectroscopy may make this feasible. Biomarkers of dormant metastases may be detected in the circulation, especially if signals from the tumor are amplified by astrocytes or other cells in the brain. This will be of particular importance to clinicians who need to know whether a cell metastasized prior to treatment with an agent that could not penetrate an intact blood brain barrier.

Dr. Sackstein described the role of cell-specific membrane glycosylation in determining the microenvironmental lodgment and the metastatic potential of cancer stem cells. A greater understanding of cancer cell-specific carbohydrate modifications could yield novel targets for antibody-based therapy of cancer. Apart from the display of novel “glycotopes,” surface glycosylation critically alters the biology of membrane glycoproteins; thus, a more comprehensive understanding of the role(s) of cell glycosylation of membrane glycoproteins could yield critical insights into tumor growth, resistance to chemo/radiotherapy, and metastasis.

### Modeling Brain Metastasis

Enormous progress has been made over the past 10 years in modeling human cancer in the mouse. Using sophisticated genetic engineering, models are increasingly able to recapitulate the range of phenotypes seen in primary human cancers, providing a resource that is invaluable to translational research efforts. The development of the Mouse Models of Human Cancer Consortium (MMHCC) at the NCI has been central in this effort. To date, no models of spontaneous brain metastasis have been developed, although cell lines injected intravenously have, in a few instances, established tumor foci in brain as well as other organs. Spontaneous models will undoubtedly arise when there is a deeper understanding of the genetic switches driving brain metastasis. Equally valuable, it is clear that discoveries in the mouse have enlightened understanding of the human disease, and having a variety of models has been shown to accelerate the discovery process. For the field of brain metastasis, the complexity of the metastatic process will be unraveled in a far more efficient manner by cross-comparison among models of different cancer subtypes.

### Current Brain Metastasis Mouse Models

Organ specificity has been investigated by Dr. Massague's group by using an *in vivo* mouse model to identify MDA-MB-231-derived breast cancer lines with specific organotropism for bone and lung (8, 9). In rare cases, foci of tumors grew in brain, and after successive rounds of systemic injection, they were able to isolate an outgrowth of cells with increased propensity for brain metastasis compared to the parental population of breast cancer cells. Functional characterization of genes differentially expressed in the brain metastasis is under investigation with a focus on determining which gene or set of genes may be critical for establishing growth in the brain.

Dr. Kerbel has established advanced metastatic disease in mouse models of breast cancer and melanoma (10) for preclinical studies of therapeutics. His group had not detected brain metastases in the mice that developed advanced visceral metastases. However, effective treatment of mice with advanced visceral metastases resulted in a number of mice that developed brain metastases, reminiscent of the similar clinical phenotype in patients with well

controlled systemic HER-2-positive breast cancer. Cell lines were established from the tumor foci in the brain and, upon reinjection, retained the ability to establish metastases in the brain and the lung from a primary orthotopic transplant that was surgically resected. Cell lines established from the lung metastases, however, metastasized to the lung only, providing preliminary evidence for brain-tropic factors or brain-specific genetic alterations in the circulating tumor cell that is able to spontaneously metastasize to the brain from a primary tumor. Having brain metastases grow out in this setting is invaluable for studying several aspects of the biology as well as providing an important preclinical model for studying drug-resistance mechanisms.

Dr. Werb described an orthotopic model system of injecting human breast cancer cells into the fat pads of mice with a focus on determining when the cells acquire the ability to disseminate and then colonize an organ and grow (11). This model affords the advantage of being able to study the interaction between tumor and stroma, including the function of brain microglia and inflammatory cells recruited to the site of tumor cell growth.

Dr. Steeg described work with a brain metastatic variant of the MDA-MB-231 breast cancer cell line (231BR), transfected with *HER-2* to study brain metastases after intracardiac injection (12). She has shown that *HER-2* overexpression has no effect on tumor cell arrival in the brain or formation of micrometastases, but it stimulated the development of large brain metastases (comparable to an MRI-detectable lesion in a human brain) by 2.5- to 3-fold.

Dr. Minna described lung cancer mouse xenograft models that he is developing in which human lung cancer cell lines from patients with and without brain metastases are being used to generate preclinical models of brain metastases. Comparison of the primary tumors may yield insights into markers of brain metastatic potential.

## Research Priorities

### A. Genetics of Brain Metastasis

- Comprehensive molecular analysis of brain metastases. Priority should be given to (a) paired analysis of primary tumor and brain metastasis, (b) paired brain and other organ metastases, and (c) primary tumor samples annotated to have metastasized to brain.
- Comparison of molecular profiles among brain metastases from the cancer subtypes (e.g., breast cancer, NSCLC, melanoma, renal cell cancer).
- Identification of novel molecular targets for prevention and treatment of brain metastases.
- Brain metastasis gene discovery and validation via comparative oncogenomics and proteomic approaches.
- Functional evaluation of brain metastasis gene candidates in model systems.

### B. Biology of Brain Metastasis

- Delineate pathogenic mechanisms of metastasis to brain.
- Understand the commonalities between systemic disease and metastasis to the brain versus other organs.
- Understand heterogeneity among different brain metastatic lesions to differentiate between indolent and aggressive lesions.
- Investigate issues related to the “stem cell” features of metastasis cell.
- Identify mechanisms underlying tumor cell homing to the brain.

### C. Biology of the Blood Brain Barrier

- Identify the cellular constituents of the blood brain barrier and understand mechanisms of drug transport.
- Develop strategies for modification of the blood brain barrier to enhance drug delivery.
- Develop model systems, including imaging, for preclinical evaluation of drug transport and distribution in the brain.

### D. Role of the Brain Microenvironment in Brain Metastasis

- Understand the interaction between the tumor cell and brain stroma.
- Delineate the role of brain stromal cells, astrocytes, and extra-CNS cells in enabling growth of tumor cells in the brain.
- Understand the interaction of tumor, blood vessels, and the brain microenvironment in tumor angiogenesis.
- Identify treatment-induced changes in the brain microenvironment that modify tumor cell growth.
- Identify targets in the brain microenvironment for therapeutic development.

### E. Modeling Brain Metastasis in the Mouse

- Develop models for each of the tumor subtypes using both genetically engineered mice as well as human cell line xenograft models.
- Develop reporter lines for use in imaging studies.
- Develop preclinical models for biomarker validation and therapeutic testing.

### F. Pharmacology and New Therapies

- Identify and validate compounds that permeate an intact blood brain barrier.
- Modify existing effective, systemically acting compounds for penetration into the CNS.
- Understand mechanisms of resistance in early versus late brain metastasis.
- Develop and evaluate radio-sensitizing compounds for use with whole-brain radiation and/or radiosurgery.
- Develop methods for quantification of the uptake of compounds into the normal brain, micrometastases, MRI-detectable metastases, and peri-tumoral microenvironment of the brain.
- Develop imaging to quantify drug delivery and molecular targeting in addition to early identification of micrometastases.

### G. Translational Research Opportunities

- Perform comprehensive molecular profiling of activated signaling pathways in surgically resected, clinically annotated, brain metastases across tumor types and compare to the primary tumor.
- Develop biomarkers of brain metastasis risk, detection, and response to treatment.
- Develop clinical imaging systems for earlier detection of metastatic foci in the brain.
- Adapt existing clinical trial design to include patients with existing brain metastases and define novel biological and clinical endpoints.
- Understand differential responses among brain metastatic lesions to therapy.
- Develop clinical trials of novel therapies for the prevention of brain metastasis.

- Adapt mouse models for preclinical testing of novel therapeutics and the development of valid endpoints that can be used in clinical studies of brain metastasis.

## Resources Needed

### A. Brain Metastasis Working Group

The meeting participants strongly endorsed the development of a working group that included representative clinicians, neuropathologists, and translational and basic scientists who would meet regularly. The goal of the group would be to ensure that the multiple research agendas are moving forward on parallel tracks.

### B. Biospecimens

The participants felt that the infrastructure for biospecimen collection, banking, and distribution should be the highest priority for the NCI. Optimal analysis of the brain metastasis should include a comparison with the primary tumor, any other organ metastasis, normal cells, and cerebrospinal fluid (CSF) with detailed clinical information available for each clinical case and/or specimen. Fresh-frozen viable tissue and cells as well as formalin-fixed, paraffin-embedded (FFPE) samples are required in order to fully exploit the array of technologies that are available. The complexity of developing a central tissue repository or disease-specific repositories was recognized, but the meeting participants felt that it was worth the time, effort, and funding necessary to obtain the invaluable specimens. In addition, the infrastructure should include the development of tissue microarrays of primary and metastatic tumors from each of the cancer subtypes.

### C. Antibodies

For the validation of novel biomarkers, it is critical that sufficient resources be allocated to develop antibodies and make tissue microarrays widely available to the brain metastasis investigators.

### D. Bioinformatics

Mining the NCI-sponsored clinical trial databases: The large NCI-sponsored cooperative group trials are a potential source of highly valuable clinical information regarding the development of brain metastasis. In particular, the Workshop participants felt that a meta-analysis of the ten clinical data sets that are available from treatment of lung cancer patients should be used to determine the incidence of brain metastases in these patients and look for any clinical factors that may identify predisposing characteristics or other clinical events that may be correlated with the development of brain metastasis. These data should be made available to the brain metastasis community.

### E. Animal Models of Brain Metastasis

The Workshop participants encouraged investigators working in brain metastasis to develop communication and collaborations with investigators funded by the NCI Mouse Models for Human Cancer Consortium (MMHCC). The participants identified the need to develop immuno-competent models of brain metastasis.

## Overall Summary

As the number of patients who develop clinically significant brain metastasis continues to increase in the face of improving cancer therapeutics for systemic disease, there is an urgent need for the development of a comprehensive, multidisciplinary, fully integrated clinical, basic, and translational research effort to tackle this important problem. The Workshop participants concurred that research on the biology of brain metastasis is essentially

absent from the NCI portfolio due largely to a paucity of grant applications focusing on this subject. Whereas many investigators are making progress in understanding distant metastases such as lung, liver, and bone, research in the brain metastasis field is hampered by the lack of a critical mass of investigators focusing collectively on the problem. The lack of useful models, reagents, and annotated biospecimens exaggerates this problem and clearly has been further exacerbated by 25 years of drug development that ignored the blood brain barrier as a critical factor in drug distribution. The "Research Priorities" and "Resources Needed" sections (above) address many of these deficiencies. It will be imperative that cooperative groups be established among the basic and translational investigators so that drugs in early development are more easily evaluated and more rapidly brought into the clinical arena. To this end, it is clear that brain permeability needs to become a central focus in all phases of investigation. Finally, the clinical community and industry will need to be steadfastly committed to including patients with brain metastases in clinical trials of novel compounds using endpoints that will advance the understanding of brain metastasis growth and treatment response

without compromising the overall evaluation of a drug's therapeutic benefit. The cooperation among surgeons, medical oncologists, and pathologists in collecting and annotating tumor specimens and making them available to the brain metastasis research community is recognized as a critical component of progress in this field. The participants recognized the need to build a "community" that inspires a collaborative spirit that spans the multidisciplinary landscape in a way that will lead to rapid and decisive progress for this devastating complication of cancer.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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