Board of Scientific Advisors

Meeting Minutes

July 12, 2004

Bethesda Hyatt Regency Hotel
Bethesda, Maryland

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Meeting Minutes

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The Board of Scientific Advisors (BSA), National Cancer Institute (NCI), convened for a 28th special session meeting on Monday. Dr. Frederick Appelbaum, Director, Clinical Research Division, Fred Hutchinson Cancer Research Center, presided as Chair.

The meeting was open to the public from 8:30 a.m. until 1:00 p.m. on 12 July for a speciial session for presentations and discussion on the NCI Alliance for Nanotechnology in Cancer RFA concepts.

Board Members present:
Dr. Frederick R. Appelbaum (Chair)
Dr. David B. Abrams (by telephone)
Dr. Hoda Anton-Culver (by telephone)
Dr. Esther G. Chang
Dr. Thomas Curran
Dr. Mary Beryl Daly
Dr. H. Shelton Earp III
Dr. William N. Hait
Dr. Hedvig Hricak
Dr. William G. Kaelin, Jr.
Ms. Paula Kim
Dr. Michael P. Link
Dr. Lynn M. Matrisian
Dr. W. Gillies McKenna (by telephone)
Dr. Enrico Mihich
Dr. John D. Minna

Board Members absent:
Dr. David S. Alberts
Dr. Neil J. Clendeninn
Dr. Raymond N. DuBois, Jr.
Dr. Patricia A. Ganz
Dr. Susan B. Horwitz
Dr. Eric Hunter
Dr. Kenneth W. Kinzler
Dr. Herbert Y. Kressel
Dr. Christine A. Miaskowski
Dr. Nancy E. Mueller
Dr. Mack Roach III
Dr. Ellen V. Sigal
Dr. Margaret R. Spitz
Dr. William C. Wood
Dr. Robert C. Young

NCAB Liaison:
TBN

Dr. Richard L. Schilsky

Others present: Members of NCI's Executive Committee (EC), NCI Staff, Members of the Extramural Community, and Press Representatives.

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I. CALL TO ORDER AND OPENING REMARKS - DR. FREDERICK APPELBAUM

Dr. Appelbaum called to order the 28th meeting, a special session of the BSA, and welcomed members of the Board, NIH and NCI staff, guests, and members of the public. He reminded Board members of the conflict-of-interest guidelines and future meeting dates. He noted that comments from the public regarding items discussed during the meeting may be submitted to Dr. Paulette Gray, BSA Executive Secretary, in writing within 10 days of the meeting.

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II. INTRODUCTIONS AND REMARKS - DR. ANNA BARKER

Dr. Anna Barker, Deputy Director for Advanced Technologies and Strategic Partnerships, NCI, informed members that four speakers would present their research, i.e., projects that capture mission-critical questions for nanotechnology and cancer and generate the translational research teams of the future. Dr. Barker stated that the NCI Cancer Nanotechnology Plan and the NCI Alliance for Nanotechnology in Cancer are groundbreaking initiatives that offer goals with deliverables, assessment tools, and paths for clinical trial development. Dr. Mauro Ferrari expressed his thanks for the opportunity to moderate a discussion of the various nanotechnologies that can integrate into cancer research

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III. NANOSYSTEMS BIOLOGY - DR. JAMES HEATH

Dr. James Heath, California Institute of Technology, noted that nanosystems biology is at the heart of the NCI's 2015 Challenge Goal. Dr. Heath discussed the Alliance for Nanosystems Biology, a cooperative venture between the University of California at Los Angeles (UCLA), California Institute of Technology, and the Institute for Systems Biology. The Alliance shares students, who travel back and forth between labs at the participating Institutes.

Dr. Heath noted that by focusing on genomic indicators of disease in the blood, disease can be stratified according to parameters such as progression and response to therapy. Nanotechnology offers the opportunity to transform a host of developmental tools into a single, useful guiding tool, suggesting that cancer patients will one day be empowered in a manner analogous to diabetic patients who take control of their disease by monitoring insulin levels.

He then discussed his work using Massively Parallel Signature Sequencing (MPSS) to identify 100 proteins that are modified in prostate, ovarian, and other cancers from a database of 79,000 proteins. Members were told that a method has been developed to remove high-molecular weight proteins that constitute the bulk of blood mass, allowing quantitation of these target proteins in serum. Dr. Heath stated that this research suggests a future diagnostic tool that measures 100-1000 proteins or genes in a fingerprick of blood. As such, the various metabolic processes that are activated as

cancer evolves can be targeted.

Dr. Heath described his work with integrated channels, valves and pumps for multiparameter diagnostics and molecular imaging probe synthesis. He noted that such nanowire “labs-on-a-chip” can be designed and built within a day. Two nanoliters of fluid are required for an analysis, and currently 500 measures can be made from a single prick of blood. One thousand sensors, which can be encoded with antibodies, can be constructed within the space of a single cell.

Members were told that the greatest challenge in transforming concept to reality is the ability to go from large- scale technologies (e.g., mass spectrometry, microarrays) to those on the nanoscale. Also, ways to bridge the molecular and manufacturing worlds, as well as various academic disciplines, must be sought. Initiatives are needed that allow students to travel and study between labs, as well as collaborative efforts with Cancer Centers.

In subsequent discussion, the following points were made:

- A member asked what the proposed initiative would enable that cannot be enabled without it. Dr. Heath proposed the counterexample of the National Science Foundation (NSF). Most of its nanotechnology funding has supported single-investigator grants, and progress has been trivial from a disease perspective. Cancer is overwhelmingly the best disease opportunity to vet this technology due to the tremendous database resources. In the absence of this program, there will be no avenue to support the throughput necessary to disseminate and develop the technologies.

- When asked to clarify the desired product, Dr. Heath responded that numerous centers currently profile tumors and serum for markers, and Centers can support the clinical trials to test and validate serum-based markers. Supposing that markers have been identified, why use a small device rather than a larger machine at an appropriate center? He noted that a biomarker is an intermediate goal, but an informative diagnostic test requires more information to measure how a tumor is responding. The proposed device will make 1000 measurements from a single fingerprick.

With the current prototype, the analysis will take 1 hour; in its final form, it will take 10 minutes.

- It was noted that a specific antibody is needed against each protein measured, thereby limiting the technologies. When asked how this technology interfaces with the wealth of current biomarker research taking place at SPOREs, Dr. Heath answered that public databases driven by SPORE research would be incorporated to take advantage of available research.

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IV. NANOTECHNOLOGY IN CANCER: TECHNOLOGY CONVERGENCE - DR. ARUN MAJUMDAR

Dr. Arun Majumdar, University of California, Berkeley, informed members that nanotechnology requires a multidisciplinary team representing fields from engineering to cancer pathology. Dr. Majumdar noted that there is growing evidence that screening multiple markers in a profile creates a “map” that is more sensitive and specific to a type of cancer. However, for screening of serum or other media, a cost-effective technology is necessary.

Dr. Majumdar focused his talk on research using nanoparticles, nanotubes and channels, and cantilevers in the development of nanofluidic biosensors. The challenge with these nanodevices is the navigation of the biological/non-biological interface, which is often the deciding factor in how to quantitate measured targets. Although currently possible to achieve single molecule resolution, the background is too high to use these nanoassays for clinical studies. However, the approach offers potential for multiple analyses, the generation of pattern maps, and cost-effective and high throughput assays that use extremely small volumes.

In subsequent discussion, the following points were made:

- When a member inquired how the proposed initiative would benefit his Dr. Majumdar’s research, since he has already established a background network, he noted that he could not have done this without NCI funding, and that NCI

nanotechnology funding proposed would make such projects more effective.

- A member having noted that the proposed research is limited by biological reagents (e.g., antibodies and proteins) asked how feasible is a multiplexed system for diagnosis? Dr. Majumdar noted that his team is currently applying the technology to serum banks and samples provided by the EDRN. Currently, multiplexing is possible using 100 antibodies per chip. He noted also that it is possible to move away from specific ligand-receptor interactions toward an independent signature if the isoelectric point is known. In this instance, nanotechnology offers an approach for 2D gel electrophoresis that is receptor-independent.

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V. NANOSHELLS: PLATFORM TECHNOLOGY FOR CANCER IMAGING AND THERAPY—DR. REBEKAH DREZEK

Dr. Rebekah Drezek, Rice University, noted that her research focuses on nanoshells interfaces bioengineering, medicine, and technology, with a predominant emphasis in early detection. Dr. Drezek stated that her research is funded by the National Science Foundation (NSF), NIH, the Department of Defense (DOD), the Whitaker Foundation, and Rice University. Members were told that nanoshells are 100 nm particles composed of a core surrounded by a gold shell of varying thickness. As the thickness changes, the shell's optical response (and its functionality) can be tuned.

Clinical applications of nanoshells include thermal ablation and photothermal cancer therapy. Nanoshells can be directed to a target by attaching an antibody or agonist. Heating the bound cells with a laser (which does not damage normal tissue) then results in selective ablation. The depth of heating is organ-dependent, but usually in the centimeter range for the organ and the millimeter range for the tumor. Preliminary experiments with direct injection of nanoshells into the tumor region have been successful in animal models, and experiments with systemic delivery are underway. Tumor growth upon irradiation with low power light can be

measured, and survival following therapy is excellent. The promising preliminary results for photothermal therapy suggest that this simple idea may have many diagnostic and therapeutic applications.

In discussion, the following points were made:

- When asked about the delivery of nanoshells to metastatic lesions, Dr. Drezek noted that in preliminary experiments, regions adjacent to the tumor did not contain significant accumulations of nanoshells. Experiments are planned with metastatic models. She also noted that photothermal and photodynamic therapies have not been compared on the same model system.

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VI. NANOPARTICLE BEACONS FOR MOLECULAR IMAGING AND TARGETED THERAPEUTICS—DR. SAM WICKLINE

Dr. Sam Wickline, Washington University School of Medicine, noted that he is associated with NCI through the Unconventional Innovations Program (UIP). Dr. Wickline noted that assembling interdisciplinary teams has been essential to translate and commercialize nanotechnology. He outlined his research strategy of molecular imaging, site-targeted therapeutics, and quantitative in situ evaluation of biomarker responses. Members were told that Nanotechnology is a key element in this approach, especially with regard to molecular imaging.

Dr. Wickline then described his work with nanoscale targeting agents, which are emulsions of liquid perfluorocarbon nanoparticles. He noted that hundreds of ligands (e.g., apatamers, small molecules, antibodies) can be added to these nanoparticles. The addition of gadolinium makes the particle visible using MRI, and drugs can also be added for targeted delivery. These nanoparticles, which can bind up to 100,000 gadolinium ions, are more sensitive than other MRI tools. Members were told that these nanoparticles have been used to study angiogenesis, both as imaging agents and as vehicles to deliver therapy. The serum half-

life of a particle when it does not bind is 10+ hours, and unbound particles are excreted hepatorenally. The toxicology profile of perfluorocarbons, which are exhaled through the lungs, is well known.

As an example of the potential of these particles, a hydrophilic drug (e.g., taxol) can be loaded into the outer lipid monolayer, and the particle can be placed near targeted cell membrane. By putting the nanoparticle within a few nanometers of the membrane, a stalk forms that facilitates the exchange of lipids and drug components. It is suspected, although not proven, that the nanoparticles roll on the surfaces of the cells. It has been shown also that cancer cells will uptake ligands that target receptor-mediated endocytosis. Currently, these nanoparticles are being synthesized using standards for good manufacturing practices (GMP).

In subsequent discussion, the following points were made:

- When asked what capabilities would be enabled by the proposed nanotechnology Center grants, Dr. Wickline responded that a team is necessary to make a contrast agent that works with an imaging tool. Thus, the Center grant must be large enough to engage these components. The expertise with imaging equipment that is required cannot be supported solely by R01 funding.

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VII. PANEL DISCUSSION

How does a graduate student involved in nanotechnology identify with a specific discipline?

This varies somewhat with every discipline, but students usually rotate through several labs and then choose a mentor. Training grants are not specific for nanotechnology; there is no training opportunity that would allow a student to identify nanotechnology as a specific discipline.

Where is the greatest need in training? Which areas will yield the best return for the Federal investment?

Funding of students and postdocs who wish to work with nanotechnologies is key; there is a gap in the cross-training for students. Also, funding for Centers that support non-R01 collaborations will yield results. Also, clinicians must become trained in the vocabulary of nanotechnology; nanotechnology must become integrated into the M.D. curricula, not added as a specific separate topic.

What about the commercial development of array-based techniques. Suppose 100 markers, with varying IP issues, have been isolated. Can these be simply used in an array?

Panelists noted that the semiconductor industry has implemented a broad licensing for hardware and technologies that the biotechnology industry could emulate. Also, NCI could play a role in facilitating such novel licensing.

Are the individual disciplines of nanotechnology developed suitably to address the complexity of cancer? Under the best circumstances, what can the proposed program accomplish in terms of proof-of-principle and the implementation of technologies?

Nanotechnology provides diagnostic tools for discovery, and these programs would help to distribute these and use them for multiple scenarios.

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VIII. PRESENTATION OF PROPOSED CONCEPT: THE NCI ALLIANCE FOR NANOTECHNOLOGY IN CANCER—DR. GREGORY DOWNING

Dr. Gregory Downing, Director, Office of Technology and Industrial Relations, informed members that the proposed Cancer Nanotechnology Concept now consists of three RFAs to address the objectives of the NCI Cancer Nanotechnology Plan (CNPlan) and the members concerns during the discussion at the June 2004 BSA meeting. The proposed three concepts are for 1) cooperative agreements (U54s) to create 3-5 Centers of Cancer Nanotechnology

Excellence (CCNEs) with the goal of integrating nanotechnology platforms into basic and applied cancer research to rapidly facilitate clinical applications; 2) investigator-initiated research projects RFA (R01) to create bioengineering research grants and bioengineering research partnerships, and 3) the creation of multi-disciplinary nanotechnology research teams and support for the career development of individual investigators who will become future team leaders (individual investigator awards are F33s and F32s.

Program Evaluation will occur in the six high-impact programmatic areas identified in the CNPlan: molecular imaging and early detection, in vivo imaging, reporters of efficacy, multifunctional therapeutics, prevention and control, and research enablers. Performance milestones have been established for each RFA at both the project and program level, and interfaces have been established with the NIH Roadmap Initiative.

Estimated costs for the 5-year project period is $144.3 M and a first year set-aside of approximately $16.2 M for 3-5 (U54), 15 (F32), 15 (F33), and 12 (R01).

In subsequent discussion, the following points were made:

- A member expressed excitement about the revised plan, noting that the NCI responded efficiently and thoughtfully to each of his queries. As such, it is entirely appropriate that the NCI assumes a leadership role in developing nanotechnology. The nanotechnology package as presented contains sufficient flexibility for future modification if necessary. Commenting that nanotechnology application to cancer should be viewed as a long-term process. It was also noted that the NCI must build a base of support from where the field can thrive. However, there are concerns with intellectual property and conflicts-of-interest that will accompany commercialization, as the sophistication of cancer biology lags behind that of technology. However, the Cancer Centers of Nanotechnology Excellence can provide a convenient interface.

- Another member noted that there is a slight disagreement between the revised proposal (which provides for senior and

postdoctoral fellows) and the original intent in terms of training (which included graduate students). Dr. Downing noted that the mid-career training component was identified by attendees at several NCI symposia. He also stated that National Research Service Award (NRSA) funding is separate from NCI budget funds. Thus, these awards do not impact the total NCI research budget unless increased slots are requested.

- When asked about the ultimate fate of the CCNEs, i.e. will they ultimately integrate into SPOREs? Also, for R01 awards granted through the BRG and BRP mechanisms, will Centers investigators benefit particularly or would the R01s be applicable to investigators outside the Centers? Staff responded that bridging these programs remains a key driver in the development of the initiative. Much interest has come from places not traditionally representative of centers, and it is expected that R01s will also come from external investigators as well. Regarding the "sunsetting" aspect, it is expected that the program will change over time. Modifications and refinements for the program would be vetted to the BSA. Limitations of cancer biology are the main issue when merging CCNEs with Cancer Centers. Regarding IP issues, the NCI has expertise in shared resources for genomics and proteomics, which has informed the shared resources component of this program.

  Dr. Downing also stated that NCI is working with NIST to develop a pathway for physical and biological characterization in conjunction with NCI's National Characterization Laboratory. The NCI is also developing shared resource fabrication facilities and is in discussion with the NSF on nanosystems programs. These are evolving, and the NIST memorandum of understanding (MOU) is expected in a matter of weeks.

  Dr. Downing noted that the NCI has been working with Dan Sullivan to address the overlap between contrast agents being developed under other cellular and molecular imaging centers and those that would be developed at the CCNEs. He stressed the multivalent aspects of this initiative, especially for drug delivery and targeting, that set it apart from other concurrent programs that support overlapping

technologies.

- A Board member expressed concern over the lack of any mention of the patient in the requirements for CCNEs and steering committees. Dr. Downing responded that patient advocacy groups would be included in these Centers and related steering committees.

- When queried the logistics of some investigators being within centers and others without, Dr. Downing responded by noting that there will be adequate review policies built in to ensure that the processes are smooth and that relevant parties are represented adequately. Standardization and prioritization processes will require steering committees.

Motion.A motion to approve the initiative as presented, with the requirement assuring input and involvement from patients and patient advocacy groups, was unanimously approved.

Dr. von Eschenbach thanked the Board for its careful scrutiny of the plan and noted that the BSA has forced the NCI to define, refine, and improve the initiative, ultimately improving its quality and scope

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IX. ADJOURNMENT

The 28th special session of the BSA was adjourned at 1:00 p.m. on Monday, 12 July 2004.

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