National Cancer Institute
National Institutes of Health
U.S. Department of Health and Human Services

4th Annual NCI Center for Strategic Scientific Initiatives (CSSI) Science Day
Building 35A, Porter Neuroscience Center
Room 620/630
Wednesday, June 8, 2016

AGENDA

8:30 a.m. – 9:10 a.m. **Welcome remarks and introductions**

8:30 a.m. – 8:50 a.m. **Overview of the NCI Center for Strategic Scientific Initiatives**
Jerry S.H. Lee, Ph.D.
Office of the Director
Center for Strategic Scientific Initiatives
National Cancer Institute, NIH

8:50 a.m. – 8:55 a.m. **Goals and Intent of Science Day**
Sean Hanlon, Ph.D.
Office of the Director
Center for Strategic Scientific Initiatives
National Cancer Institute, NIH

8:55 a.m. – 9:10 a.m. **Highlights of CSSI Pilot Projects and Resources**
Michelle Berny-Lang, Ph.D.
Office of the Director
Center for Strategic Scientific Initiatives
National Cancer Institute, NIH

9:10 a.m. – 2:00 p.m. **Scientific landscape of the next 5 to 10 years**
Goals: Hear and discuss emerging opportunities across the cancer research landscape.

9:10 a.m. – 9:45 a.m. **Session 1: Rigor and Reproducibility**
Moderator: Michelle Berny-Lang, Ph.D.
Office of the Director
Center for Strategic Scientific Initiatives
National Cancer Institute, NIH

9:10 a.m. – 9:45 a.m. ***Data Access, Analyses, and Reproducibility in Cancer Research***
Keith Baggerly, Ph.D.
MD Anderson Cancer Center

9:45 a.m. – 10:15 a.m. **Break and Group Meet & Greet**

10:15 a.m. – 11:25 a.m. **Session 2: Advancing Tools and Technologies**
Moderator: Chris Kinsinger, Ph.D.
Office of Cancer Clinical Proteomics Research
Center for Strategic Scientific Initiatives
National Cancer Institute, NIH

10:15 a.m. - 10:50 a.m. ***Genetic and Epigenetic Engineering in Cancer Research***
David Segal, Ph.D.
University of California Davis
and
Peggy Farnham, Ph.D.
University of Southern California

10:50 a.m. – 11:25 a.m. ***CancerBase, Intersection of Computational Models and Clinical Care***
Peter Kuhn, Ph.D.
University of Southern California

11:25 a.m. – 12:50 p.m. **Lunch**

12:50 p.m. – 2:00 p.m. **Session 3: Advancing Clinical Care**
Moderator: Chris Hartshorn, Ph.D.
Office of Cancer Nanotechnology Research
Center for Strategic Scientific Initiatives
National Cancer Institute, NIH

12:50 p.m. – 1:25 p.m. ***Molecular Imaging: From Chemistry to Clinic***
Martin Pomper, M.D., Ph.D.
Johns Hopkins University

1:25 p.m. – 2:00 p.m. ***Tumor Evolution and Therapeutic Resistance***
Larry Norton, M.D.
Memorial Sloan Kettering Cancer Center

2:00 p.m. – 3:30 p.m. **Breakout Group Discussions**
Goals: Identify and discuss broad, emerging areas of cancer research that require further exploration.

3:30 p.m. – 4:00 p.m. **Break**

4:00 p.m. – 5:00 p.m. **Breakout Group Reporting**

5:00 p.m. – 5:15 p.m. **Wrap-Up**
Moderator: Jerry S.H. Lee, Ph.D.
Office of the Director
Center for Strategic Scientific Initiatives
National Cancer Institute, NIH

5:15 p.m. **Adjournment, Day 1**

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AGENDA

8:30 a.m. – 8:50 a.m.	**Summary/Observations of Day 1** Jerry S.H. Lee, Ph.D. Office of the Director Center for Strategic Scientific Initiatives National Cancer Institute, NIH
8:50 a.m. – 9:00 a.m.	**Charge for Day 2** Sean Hanlon, Ph.D. Office of the Director Center for Strategic Scientific Initiatives National Cancer Institute, NIH
9:00 a.m. – 9:30 a.m.	**Day 2 Topic Overviews** Topic Discussion Leaders
9:30 a.m. – 11:00 a.m.	**Breakout Group Discussions** **Goals:** Refine specific actionable topics and identify and begin work on concrete next steps (e.g., write a review, hold a workshop, develop a new resource, launch a pilot project).
11:00 a.m. – 11:30 a.m.	**Break**
11:30 a.m. – 12:30 p.m.	**Breakout Group Reporting**
12:30 p.m. – 12:45 p.m.	**Feedback, Final Discussion, and Wrap-up** Moderator: Jerry S.H. Lee, Ph.D. Office of the Director Center for Strategic Scientific Initiatives National Cancer Institute, NIH
12:45 p.m.	**Adjournment, Day 2**

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SPEAKER BIOSKETCHES

Keith Baggerly, Ph.D.
The University of Texas MD Anderson Cancer Center

Dr. Baggerly is the Ransom Horne, Jr., Professor of Cancer Research in the Department of Bioinformatics and Computational Biology at The University of Texas MD Anderson Cancer Center, where he has worked since 2000. He has worked extensively with data from a wide variety of high-throughput assays. Dr. Baggerly is best known for his work on "forensic bioinformatics," in which reexamination of raw data shows the need for careful experimental design, preprocessing, and documentation—the careful application of basic statistics and sanity checks. His work prompted an Institute of Medicine review of the evidence that should be required before omics-based assays are used to guide patient therapy. Dr. Baggerly has been profiled in the Journal of the National Cancer Institute and is a Fellow of the American Statistical Association. Today, like the rest of us, he is struggling with the issues associated with distilling useful information from the wide variety of public data sources.

Peggy Farnham, Ph.D.
University of Southern California

Dr. Farnham is the William M. Keck Professor of Biochemistry and the Chair of the Biochemistry and Molecular Biology Department at the Keck School of Medicine at the University of Southern California in Los Angeles. She received her bachelor's degree from Rice University and her Ph.D. degree from Yale University and performed her postdoctoral training at Stanford University. Dr. Farnham previously held professorships at the McArdle Laboratory for Cancer Research at the University of Wisconsin-Madison and at the University of California, Davis, where she was the Associate Director of the University of California, Davis Genome Center. She is an international leader in the study of chromatin regulation and its control of transcription factor binding and function. Dr. Farnham is a member of an international consortia of genomic scientists working on the ENCODE (Encyclopedia of DNA elements) Project, a past member of an NIH Roadmap Reference Epigenome Mapping Center, and a member of PyschENCODE. Based on her contributions to biomedical research, she was elected as a fellow of AAAS in 2010, and in 2012 she received the American Society for Biochemistry and Microbiology's Herbert Sober Award, which recognizes outstanding biochemical and molecular biological research with particular emphasis on the development of methods and techniques. Current projects in Dr. Farnham's lab are focused on the transcriptomic and epigenomic changes that occur during neoplastic transformation, using genome-wide technologies such as ChIP-seq, RNA-seq, and whole-genome bisulfite-seq. She is also characterizing cancer-associated enhancers using genomic nucleases and targeted epigenetic regulators.

Peter Kuhn, Ph.D.
University of Southern California

Dr. Kuhn is a scientist with a career-long commitment in personalized medicine and individualized cancer patient care, focusing on the redesign of cancer care. His research is shedding new light on how cancer spreads through the body and evolves over time. This new science will lead to a personalized care strategy that is biologically informed and clinically actionable. Leveraging the laboratory's spatiotemporal disease-mapping innovation, the Convergent Science Initiative in Cancer is advancing daily the forefront of both improving health care effectiveness for cancer patients by providing drug guidance and increasing our understanding of cancer as a disease in each individual patient. Dr. Kuhn is a physicist who trained initially at Julius Maximilian University in Würzburg, Germany, before receiving his master's degree in physics in 1993 and his Ph.D. degree in 1995 at the University of Albany in New York. He then moved to Stanford University, where he later joined the faculties of medicine and accelerator physics. From 2002 to 2014 Dr. Kuhn established a translational science program at The Scripps Research in La Jolla, CA. He has published more than 180 peer scientific articles and has filed 16 patents as a result of his research. Dr. Kuhn joined the University of Southern California in 2014.

Larry Norton, M.D.
Memorial Sloan Kettering Cancer Center

Dr. Norton is Sarofim Chair in Clinical Oncology; Medical Director, Lauder Breast Center, Memorial Sloan Kettering Cancer Center, and Professor of Medicine, Weill-Cornell Medical College. Among other leadership roles, he has served on the NCI's National Cancer Advisory Board and as President of the American Society of Clinical Oncology and has served as Scientific Director of the Breast Cancer Research Foundation. Dr. Norton's research is broad, but he is best known for mathematical modeling in therapeutic development. Among the many honors he has received are the American Society of Clinical Oncology's Karnofsky and Bonadonna Awards, the McGuire Lectureship at the San Antonio Breast Cancer Symposium, MSKCC's Whitmore Award for Clinical Excellence, the Physicians and Surgeons Alumni Association's Gold Medal for Outstanding Achievement in Medical Research, and the Thomson Reuters Highly Cited Researcher Certificate.

Martin Pomper, M.D., Ph.D.
Johns Hopkins University

Dr. Pomper is the William R. Brody Professor of Radiology and Director of the Division of Nuclear Medicine and Molecular Imaging at Johns Hopkins Medical School. He received undergraduate, graduate (organic chemistry), and medical degrees from the University of Illinois at Urbana-Champaign. Dr. Pomper completed his postgraduate medical training at Johns Hopkins, including internship on the Osler Medical Service, residencies in diagnostic radiology and nuclear medicine, and a fellowship in neuroradiology. He is board certified in diagnostic radiology and nuclear medicine and has been on the radiology faculty at Johns Hopkins University since 1995, along with several other joint appointments. Dr. Pomper's interests include the development of new radiopharmaceuticals, optical probes and techniques for molecular imaging and therapy of cancer, and central nervous system disease and other disorders.

David Segal, Ph.D.
University of California, Davis

Dr. Segal is a Professor of Biochemistry and Molecular Medicine in the School of Medicine at the University of California, Davis. He holds joint appointments in the University of California, Davis Genome Center, the MIND Institute, and the Department of Pharmacology. Dr. Segal received his Ph.D. degree from the University of Utah in 1996 and performed postdoctoral training with Carlos Barbas at The Scripps Research Institute, where he helped develop one of the most widely used methods for engineering zinc finger DNA-binding proteins. He joined the University of Arizona in 2002 and University of California, Davis in 2005. Dr. Segal's research continues to focus on the development of zinc fingers, TALEs, CRISPR/Cas9, and NgAgo as targetable nucleases, transcription factors, and epigenetic reprogrammers for gene therapy and genomic research. He currently has more than 70 publications in this field.

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ABSTRACTS

Session 1: Rigor and Reproducibility

Data Access, Analyses, and Reproducibility in Cancer Research

Keith Baggerly, Ph.D.
The University of Texas MD Anderson Cancer Center

Modern high-throughput biological assays let us ask detailed questions about how diseases operate and promise to let us personalize therapy. Careful data processing is essential, because our intuition about what the answers "should" look like is very poor when we have to juggle thousands of things at once. When details of such processing are absent, we must apply "forensic bioinformatics," aka reverse engineering, to infer what the methods must have been. We present several case studies where simple errors identified through such efforts may have clinical implications. As we generate new types of exciting data, it is worth adopting the mindset that "someone else should be able to check this easily."

Session 2: Advancing Tools and Technologies

Predictive Test to Enable Clinical Decision-Making: From Concept to Patient Care

Peter Kuhn, Ph.D.
University of Southern California

Predictive biomarkers that are applicable to an entire patient population are a requirement and an imminent need in cancer care. Cancer evolves over time under both natural and treatment pressures. Drug development efforts are providing a substantially increased number of options for therapeutic intervention in all areas of chemotherapy, targeted therapy, and immunoncology, which adds additional urgency to develop patient-specific stratification approaches. A comprehensive approach to disease characterization will require integration of multi-modality data from primary and metastatic tissue as well as the fluid phase. These multi-modality concepts have to be developed with a regulatory pathway in mind. Work previously supported by the CSSI's PSOC, IMAT and other exploratory programs, as well as the NCI's SBIR program, in addition to private investments, have now led to the first CLIA-certified novel CTC test that has peer-reviewed data demonstrating its predictive power in patients with metastatic castrate resistant prostate cancer.

Molecular Imaging: From Chemistry to Clinic

Martin Pomper, M.D., Ph.D.
Johns Hopkins University

Although most clinical diagnostic imaging studies employ anatomic techniques such as computerized tomography and magnetic resonance imaging, much of radiology research currently focuses on adapting these conventional methods to physiologic imaging as well as on introducing new techniques and probes for studying processes at the cellular and molecular levels in vivo (i.e., molecular imaging). Molecular imaging promises to provide new methods for the detection of minimal disease and support for precision therapy. This summary will focus on experimental and near-term translational molecular imaging agents and methods using prostate cancer as an example.

Genetic and Epigenetic Engineering in Cancer Research

David Segal, Ph.D.
University of California, Davis

Peggy Farnham, Ph.D.
University of Southern California

Abstract: Cancer is caused by alterations in genetic (DNA sequence) as well as epigenetic (reversible chemical modifications of the DNA or proteins that package the DNA) information. Tumor heterogeneity and drug resistance have been shown to involve epigenetic changes, and many cancer-causing genetic variants fall within enhancer elements, the function of which is regulated by epigenetics. Thus, a better understanding of cancer epigenetics is important for cancer research and therapy. However, our understanding of the functional consequences of epigenetic modifications is still far from complete, and our ability to engineer specific modifications in a targeted manner is in its infancy. Drugs affecting epigenetic information are in clinical use for cancer but cause broad changes in gene expression due to lack of specificity. Tools that can edit information at specific loci are needed. Advances in gene editing technology allow us to envision a toolbox of easy-to-use, highly specific, and targetable modifying factors that can manipulate the epigenome in a predictable manner. Limited success has been achieved in attaching epigenetic enzymes to programmable DNA-binding domain such as zinc fingers (ZF) or TALEs. However, the ease of use and high binding specificity present CRISPR/Cas9 as a far more useful system to modify the epigenome. A well-characterized toolbox of CRISPR-based epigenetic modifiers of histone and DNA marks could form a foundation from which numerous applications in tumorigenesis, drug resistance, and new targeted therapeutics could be developed.

Putting it All Together

(Accepted for publication in npj Breast Cancer, 2016)

Larry Norton, MD

Contemporary intellectual life struggles to deal with heaps upon heaps of data. These accumulate not only from the existence of massive machinery for the generation of information but also by the ease with which such is disseminated and made accessible by electronic means. The microcosm of oncology—basic as well as clinical science—is no exception to this macro-phenomenon. There is so much "out there" that no one human mind, or even one collection of minds in any one disciple, can comprehend the extent and fluidity of the field.

Imagine a painting that captures the essence of human experience. Now cut that painting into puzzle pieces and scatter them in different rooms of a multi-tiered museum. All the answers to our burning questions are there, but without the assembly of most of the pieces they are of no value to anyone, even the diligent puzzle solvers occupying only one room or even one whole floor. When a few pieces are put together into a tiny part of the whole, the construction of a recognizable object like a flower or a human face for example, this might be cause for celebration—the equivalent of publication in the word of science—but that is far from grasping the real meaning of the entire painting.

In oncology, do we need more pieces of the puzzle? Surely, the more pieces we discover the greater is the likelihood that the whole picture can be assembled without missing parts. And the finding of pieces is in fact one of the dominant activities of current cancer research, from clinical markers down to pathways descriptions, protein interactions, chromosomal aberrations, changes in RNAs of several types, DNA alterations and even electrochemical abnormalities. The heaps grow wider and deeper. But to capture the fundamental nature of the full picture, how do we put it all together?

A critical step in that direction, time may tell, might have been the proposal by Hanahan and Weinberg of a group of bins, which they called *hallmarks,* within which puzzle pieces may be collected.(1, 2) These oft-quoted overviews focused on *functions* rather than *structural elements*: hyperproliferation, immortality, evading growth and survival suppressors including host immunity, angiogenesis, invasion, metastasis, genome instability, stimulation by inflammation and altered energy metabolism. The implication of their analysis, supported well experimentally, is that any one function may be rooted in more than one molecular change, or even no specific change but rather the dysfunctional interaction of singular elements that are themselves normal in isolation. (As when two fine people still create a poor marriage.) This, of course, could seem at first to present serious conceptual problems for practitioners of precision medicine who search for actionable mutations and drugs to attack them. Yet, this line of thinking does not obviate the need for precise medicines once appropriate targets—which may be functions rather than mutations—are identified.

But what remains is the question of how to arrange the bins to facilitate the assembly of a comprehensive vision of neoplasia. How many times do we see a diagram depicting a

highly erudite and scrupulous dissection of an aspect of cancer biology end with the abstraction "proliferation, invasion, metastasis" or even "dedifferentiation," as if that is all one needs to know to connect laboratory-derived detail with complex clinical disease? Restated, what we need is a definition of cancer that is broadly encompassing and quantifiable; a framework within which our expanding pile of puzzle pieces may fit and begin to make usable sense. We need a model of cancer that is as intellectually satisfying as the elements of which it is composed.

While it would be preposterous for me to propose a specific solution in this editorial, I would like to offer an example of a form of conceptual model that might eventually prove helpful. In 2006 my colleague Joan Massague and I proposed a previously unappreciated aspect of malignancy: the ability of cancer cells to self-seed—that is, leave and return to a mass—and cross-seed from one mass to another.(3) Subsequent laboratory data confirmed the existence of this phenomenon.(4) Clinical data has also been supportive.(5, 6) Moreover, the concept has theoretical and practical clinical implications.(7, 8, 9)

However, here I focus not on the biology *per se* but rather on the equation in the 2006 paper, an equation motivated by the idea of self-seeding. The equation says that a tumor's growth rate is equal to a number proportion to the number of cells on the mass's surface minus a number proportional to the number of cells not in contact with the surface. This equation generates a growth curve effectively indistinguishable from that produced by the equation created in 1825 by Benjamin Gompertz; Gompertz' equation has been shown to fit tumor growth with remarkable accuracy.(10, 11) Hence, the new equation is more than hypothetical in that it replicates real observations but does so, unlike Gompertz' equation, using components—numbers of cells, the tumor's surface area—that are tangible, even obvious, and quantifiable.

Why surface area? The surface area is not only the location to which self-seeds or cross-seeds may relocate via blood vessels but also the point of contact of cancer cells with other parts of their micro-environment. The equation suggests that the natural state of the cancer cells is progression toward death, the second part of the equation, but that they could be salvaged by contact with their microenvironment. The perfect oncogene, then, would be one that would be lethal if left to its own devices but, paradoxically, provides a survival and growth advantage if exposed to some micro-environmental factor. Moreover, the mass could be replenished at its surface by seeds that bring with them endothelial and hematologic cells and their influences, as shown in the laboratory.(4) What specific factors the seeds or their companions or organ-specific host cells produce to rescue otherwise doomed cancer cells remains to be elucidated, although hints abound.(12, 13, 14) Chemotherapy, hormonal therapy and immunotherapy could disrupt processes at the surface area. Such drug therapies could also hasten the inevitable death of cancer cells in parts of the tumor that are not in contact with the microenvironment.

The equation therefore connects constituent parts—the predispositions of the mutant cancer cells, the anatomy of the surface area, the yin-yang influences of the microenvironment—that are addressable biologically and measureable operationally, rendering it testable, modifiable, even disposable as evidence accumulates. I cite this

equation, therefore, not to claim its universal validity but merely to illustrate one sort of approach to comprehensiveness. The approach is mathematical. My assertion is that from gene to signaling molecule to function, some overarching conceptual framework focused on biology, not structure, will be needed to assure progress in defeating cancer. Puzzle pieces do not self-assemble. Mathematics has proven quite effective in this regard in the chemical and physical sciences, and there is no reason to presuppose that it would not prove similarly productive in the oncologic sciences too.

This editorial, then, is a challenge to our community to use logical argument, experimental observation, clinical insight and quantitative thinking to formulate an inclusive, expansive but rigorous model of cancer. We have many puzzle pieces and are gathering more at an accelerating rate. We have many bins of function within which to organize them. Now let us put it all together.

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