Science Policy Reports

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Physical Sciences and Engineering Advances in Life Sciences and Oncology

A WTEC Global Assessment

APHELION NIH NSF Springer

Science Policy Reports

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Acknowledgments

We at WTEC wish to thank all the panelists for their valuable insights and their dedicated work in conducting this international assessment of physical sciences and engineering advances in life sciences and oncology (APHELION) research and development and to thank all the site visit hosts for so generously sharing their time, expertise, and facilities with us. For their sponsorship of this important study, our sincere thanks go to the National Cancer Institute at the National Institutes of Health (NIH), the National Science Foundation, and the National Institute of Biomedical Imaging and Bioengineering at the NIH.

WTEC, Lancaster, PA, USA R.D. Shelton

WTEC Mission

WTEC provides assessments of international research and development in selected technologies under awards from the National Science Foundation (NSF), the Office of Naval Research, and other agencies. Formerly part of Loyola University Maryland, WTEC is now a separate nonprofit research institute. Sponsors interested in international technology assessments and related studies can provide support for the program through NSF or directly through separate grants or GSA task orders to WTEC.

WTEC's mission is to inform US scientists, engineers, and policy makers of global trends in science and technology. WTEC assessments cover basic research, advanced development, and applications. Panels of typically six technical experts conduct WTEC assessments. Panelists are leading authorities in their field, technically active, and knowledgeable about US and foreign research programs. As part of the assessment process, panels visit and carry out extensive discussions with foreign scientists and engineers in their labs.

The WTEC staff helps select topics, recruits expert panelists, arranges study visits to foreign laboratories, organizes workshop presentations, and, finally, edits and publishes the final reports. Dr. R.D. Shelton is the WTEC point of contact: 717 299–7130, shelton@wtec.org.

Foreword

This study covers some of the applications of physical sciences and engineering to oncology and to biology generally. It provides an international perspective of the subject, through extensive visits to some of the leading labs abroad by a team of American peer reviewers. The results provide a unique snapshot of the status and trends in this field and help identify opportunities for further progress.

The main purpose of this foreword is to acknowledge the contributions of those who helped make the study a success. Most of all, we are deeply indebted to our foreign hosts who generously shared their research results with us and provided many constructive discussions. How many? Well, we visited 63 sites in Europe, Asia, and Israel and met with more than 200 host scientists. This does not count many others who presented at several workshops organized in Asia. The details are in Appendices B, C, and D. That is a lot of hospitality and a lot of travel by our indefatigable panelists.

The panel was ably led by Paul Janmey, who cheerfully managed to get everyone to provide their findings on time, despite their having a few other things to do. We much appreciate his hard work and that of the other panelists: Dan Fletcher, Sharon Gerecht, Ross Levine, Parag Mallick, Owen McCarty, Lance Munn, and Cynthia Reinhart-King. Our NCI sponsors were also closely engaged in the study, including attending many of the site visits abroad. Tito Fojo and Denis Wirtz provided sage advice when it was most needed. We continue to be impressed by the quality and insight of these scientists and the high regard with which they are held by members of the worldwide oncology community. It is their expertise that makes this report credible. Short bios are in Appendix A.

It takes resources to conduct a study like this. The study was planned by Jerry S.H. Lee, Larry Nagahara, and Nastaran Kuhn at the National Cancer Institute, which provided most of the funding. Program officers at the National Science Foundation (Kesh Narayanan, Mike Roco, Semahat Demir, Kaiming Ye, and Clark Cooper) and at the National Institute for Biomedical Imaging and Biotechnology (Chris Kelley) also contributed to the study.

Prof. Janmey has prepared an executive summary that reflects consensus conclusions by the whole panel. In his Introduction chapter, he provides the background and scope of the study. In particular, he details the process used, including sites visited abroad, and provides an overview of the chapters to follow, which use an analytical organization of the topics covered geographically in the site reports.

Two earlier versions of this report have been posted at:

- http://www.wtec.org/aphelion/AphelionEuropeanReport09.23.12.pdf
- http://www.wtec.org/aphelion/AphelionFinalReport-web.pdf

WTEC, Lancaster, PA, USA R.D. Shelton
February 11, 2015

Executive Summary

The mission of publically funded investments in health-related scientific work, including the billions of dollars invested in cancer research, is to determine the origins of diseases and thereby develop diagnostic methods and countermeasures to prevent, reverse, or control their devastating consequences. Cancer research in the United States and throughout the world has been dominated by programs in cell biology, genetics, biochemistry, and animal models of cancer, which have led to important scientific advances and improvements in the diagnosis and treatment of many cancers. However, in contrast to the enormous advances in the prevention, treatment, and cure of infectious disease, cardiovascular disease, and other major causes of death throughout the world, the diagnosis of cancer is as devastating a reality today as it was decades ago. The more we learn about cancer biology, the more it has become apparent that the relationship between a specific gene mutation and disease is often staggeringly complex, the interaction of cancer cells with their local environment is an essential but largely obscure aspect of the disease, and traditional methods of cancer biology research might not be sufficient to produce the results required for effective clinical improvements. In particular, concepts and methods of physical science in cancer biology research have until very recently been largely focused on engagement of physicists and engineers in design of instrumentation for diagnosis and therapy, rather than directly on issues related to how malignant cells arise, develop, and spread to produce clinical symptoms.

To address these issues, the National Cancer Institute (NCI) held a series of three Physical Sciences in Oncology Workshops and Think Tanks between February and October 2008 (http://physics.cancer.gov/workshops/). The aim of these meetings was to explore the opportunities to advance cancer research by integrating physicists and physical science approaches with the more traditional research effort in cancer biology. The ideas and discussions at these meetings helped guide an initiative within the NCI to establish an Office of Physical Sciences Oncology (OPSO). OPSO facilitates the development and implementation of physical science-based initiatives supporting cancer research for NCI and integrates such efforts in other divisions of the National Institutes of Health (NIH) and throughout the research community.

The focus of this effort is to go beyond involving physicists and engineers in the development of new instrumentation or methods and to engage the methods and concepts of physics to foster discoveries and new fields of study related to cancer research. Broadly speaking, the goal is to study cancer as a physical process. The National Science Foundation (NSF) has traditionally been involved in funding research in engineering and the physical sciences. Such efforts can have an important impact in biomedical research while maintaining a fundamentally basic research perspective. Recently, NSF and NCI have collaborated on a funding opportunity titled Physical and Engineering Sciences in Oncology (PESO) Awards that dovetails with the efforts of OPSO. The main mission of OPSO is to fund physical sciences-oncology research in various centers throughout the United States. As a result, 12 leading institutions were selected in 2009 to build a collaborative network of Physical Science-Oncology Centers (PS-OCs) (http://physics.cancer.gov/centers/).

PS-OCs are now reaching the fruition of their initial assignments. To compare the missions of this and other initiatives with related research efforts abroad, NCI, in cosponsorship with NSF, commissioned the World Technology Evaluation Center Inc. (WTEC) to undertake an international Assessment of Physical Sciences and Engineering Advances in Life Sciences and Oncology (APHELION).

On 18 January 2012, the sponsors/chair meeting of the WTEC APHELION study was held at NSF headquarters. The main goals of the sponsors' meeting were to provide an overview of the plans for the study, to solicit interest and participation of other US Government agencies, and to coordinate the study design with WTEC.

On 1 February 2012, the kickoff meeting of the WTEC APHELION study was held at NIH's Bethesda, MD, campus where the scientific panel and advisors met with the sponsors.

The initial phase of APHELION determined the status and trends of applying physical sciences and engineering principles to oncology research and development in leading laboratories and organizations in Europe via an on-site peer review process. The study group visited laboratories in France, Italy, Israel, Germany, the Netherlands, Spain, Sweden, and Switzerland, typically meeting with representatives of multiple institutions at each stop. Assessments of the activities in the physics/biomedicine interface at European sites are provided in Appendix B. This project was completed in 2012, and details of this stage of the study are available at http://www.wtec.org/aphelion.

On 12 June 2012, panel members presented a workshop at the Cloisters building lecture room on the NIH campus to report the findings of the study group's visit to European laboratories and to discuss these findings with the sponsors and the public. Details and documents presented at this workshop are available at www.tvworldwide.com/events/nih/120612/.

The second phase of APHELION was initiated in June 2013 with visits to laboratories in Asia working at the interface of physics and biomedical sciences. These visits involved sites in Singapore, China, Taiwan, Hong Kong, and Japan. A third phase of the project included visits from a subset of the committee to laboratories in England and Scotland in October 2013. Reports on the activities at sites visited in Asia and the United Kingdom are in Appendices C and D, respectively. Site visit

reports were also prepared for two sites in Brazil, and they are found in Appendix E. A final workshop to summarize findings in Asia and the United Kingdom and to discuss the findings with reference to research efforts in Europe took place at Fishers Lane Conference Center, Rockville, MD, on 21 November 2013. Details and documents presented at this workshop are available at www.tvworldwide.com/events/nih/131121/.

Scientific panel members:

- Daniel A. Fletcher, Ph.D., D.Phil. Professor of Bioengineering and Biophysics at the University of California, Berkeley
- Sharon Gerecht, Ph.D., Associate Professor of Chemical and Biomolecular Engineering at Johns Hopkins University
- Paul Janmey, Ph.D. (study chair) Professor of Physiology, Physics, and Bioengineering at the Institute of Medicine and Engineering at the University of Pennsylvania
- Ross Levine, M.D., Laurence Joseph Dineen Chair in Leukemia Research, Human Oncology and Pathogenesis Program, Memorial Sloan-Kettering Cancer Center
- Parag Mallick, Ph.D., Assistant Professor of Radiology, Bio-X Program, at the Canary Center for Cancer Early Detection, Stanford University
- Owen McCarty, Ph.D., Associate Professor of Biomedical Engineering at the Oregon Health and Science University
- Lance L. Munn, Ph.D., Associate Professor of Radiation Oncology at the Massachusetts General Hospital/Harvard Medical School
- Cynthia A. Reinhart-King, Ph.D., Associate Professor of Biomedical Engineering at Cornell University

Expert advisors to the study panel:

- Antonio Tito Fojo, M.D., Ph.D., Head, Experimental Therapeutics Section Medical Oncology Branch and Affiliates at the National Institutes of Health
- Denis Wirtz, Ph.D., Theophilus H. Smoot Professor, Department of Chemical and Biomolecular Engineering at Johns Hopkins University

Short biographies of the panel members and advisors are provided in Appendix A. The goals of the APHELION study are:

1. Compare the US research and development activities related to the interface between physics and oncology, or more generally between physical science and biomedicine, with similar work being done in Europe and Asia.
2. Identify the gaps and barriers for research groups and clinicians in the United States by working with leading European and Asian institutions.
3. Identify major innovations that are emerging abroad.
4. Identify opportunities for cooperation and collaboration with research groups and industry in Europe and Asia.
5. Guide US research investments at the physics/oncology interface.

The initial meeting of the working group and sponsors allowed for extensive discussion of the more important topics. We identified areas of research and technology development with the greatest potential to advance understanding and treatment of cancer and other diseases. As a result of this exchange, six topic areas were identified. Each study group member took responsibility for one topic, analyzed information collected during the site visits, and integrated their findings with the current state of understanding.

The following topics form the basis for each of the chapters in this book:

1. Information and complexity: New methods for dealing with the enormous data sets generated by modern imaging methods and integrating methods developed by the physics community to understand complex, nonlinear systems and emergent properties that cannot be predicted by traditional biological models.
2. Microenvironment: The influence of chemical composition, spatial patterning, nutrient supply, oxygen stress, and other features of the tissue and extracellular environment on the growth and homeostasis of normal tissues and tumors.
3. Cell and tissue mechanics: How the forces generated by cells and the viscoelasticity of the cell and extracellular matrix affect cell growth, survival, differentiation, and movement.
4. Transport: How the movement of cancer cells, nutrients, growth factors, drugs, and fluids affects cell survival and tissue mechanics. How the removal of metabolic waste products and cell debris is controlled and how they are altered in the tumor environment.
5. Dynamics: How the rates and patterns of cell shape change, migration, and division can be measured, understood, and integrated with biochemical and genetic information.
6. Devices and new diagnostic principles: New technologies based on physical principles, especially those in which the physical properties of tissues are exploited for cancer diagnosis or treatment.

Outcomes and Summary of Findings

The purpose of our visits was focused on learning about new scientific advances and plans for future studies. We also examined each institution's facilities, traditions, advantages, and challenges related to performing interdisciplinary or multidisciplinary work. There was a clear perception among the investigators at every site that the interface of physical and biomedical sciences is a growth area with potential for both scientific discovery and medical applications. In the context of cancer research, there is also a clearly evident trend to engage physicists in roles beyond those of traditional "medical physics" focused on radiation physics or diagnostic instrumentation. New research programs throughout the world increasingly engage scientists to consider cancer as a physical process that, despite its complexity and

heterogeneity, nonetheless has limits imposed by physical laws that can be addressed by thermodynamics, information theory, mechanics, hydrodynamics, and other fields in which physicists and engineers can act as partners with biologists.

It is impossible to generate a comprehensive analysis of the relative strengths of research efforts throughout Europe and Asia from the limited sites that were visited and the personnel constraints of this project, but several consensus views emerged from the study group. It is also evident that, especially in multidisciplinary projects, national boundaries are blurred and nearly all large groups include partners from other countries and very often collaborators in North America or other important research centers in India, Australasia, South America, and other sites to which visits could not be arranged.

At several sites, new research programs were explicitly motivated by the initiatives taken by OPSO and, in some cases, have involved researchers in the United States as advisors. More frequently, the initiatives started by the NCI have guided funding and scientific policy agencies in other countries to facilitate related efforts tailored to the expertise and traditions of existing research institutions. In other cases, for example, at the Institut Curie in France, integrated physics/biology programs have a long tradition and have become part of the established curriculum and research programs. At institutions in Heidelberg and Munich, Germany, there was even a sense that a critical mass of researchers at this interface might already have been reached. In most institutions we visited, interdisciplinary studies at the physics/biomedicine interface were highly attractive to graduate students and young faculty and were often increasingly supported by granting agencies. The funding mechanisms that support these efforts vary widely, ranging from support of individual researchers or groups by focused interdisciplinary grants (common in many countries) to massive investments in infrastructure, instrumentation, and new hiring in rapidly developing academic systems in Singapore and China Many of our hosts told us that interdisciplinarity cannot be optimized without a firm basic grounding in a specific physical or biological science in the education of students and young researchers.

Throughout Europe and Asia there is evidence that the vision of NCI and NSF to engage physics more deeply in cancer research coincided with initiatives based on similar beliefs that engagement of not only physicists but the concepts and methods of physics research could benefit cancer research. One example of this type of initiative is the document, “Progress in the Domain of Physics Applications in Life Science with an Invention for Substantial Reduction of Premature Cancer Deaths: The Need for a Paradigm Change in Oncology Research” (www.crosettofoundation.org/uploads/371.pdf) which received nearly 1,000 signatures from 29 to 31 January 2010. The document argues for the need to engage new ways of thinking in cancer research, including using physical science to combat cancer. This study surveyed the World Health Organization data to conclude that “despite annual cancer costs of $741 billion/year ($750/citizen), the 38 most industrialized nations had only a 5% reduction in cancer deaths over the past 50 year (heart disease was reduced by 64%).”

Such considerations have led to many new conferences and funding initiatives. For example, in 2012, the Cancer ITMOs and Health Technologies ITMOs of the French National Alliance for Life and Health Sciences, in partnership with the French National Cancer Institute, initiated a call for research projects in physics, mathematics, or engineering sciences related to cancer (https://www.eva2.inserm.fr/EVA/jsp/AppelsOffres/CANCER/index_F.jsp). New laboratories of excellence have also been funded in France, including CELTISPHYBIO, initiated in 2012 at the Institut Curie, to establish a center for physics in cell biology. In Sweden, the Science for Life Laboratory (http://www.scilifelab.se/), which integrates research across multiple intuitions to enable collaborations between technical universities, medicals schools, and basic science research, is one of the largest scientific investments in Swedish history. New funding programs for interdisciplinary projects at the physical science/biomedicine interface funded by the German Science Foundation and the Max-Planck-Society are almost too numerous to list. Overall, despite the many funding constraints for science throughout the world, this area of research appears to be robust and in some cases even growing. An expanded list of recent conferences focused on the interface of physics and biomedical research is provided in Appendix F.

Investments in new research efforts that combine physical and biological science are especially strong in Asia, in particular in Singapore and parts of China. A significant part of the research programs established by Singapore's Agency for Science, Technology and Research in 2002 have helped foster collaboration between biological and physical scientists and have helped provide momentum for more recent large programs such as the Center for Biomedical Imaging and the Mechanobiology Institute at the National University of Singapore, where collaboration of physical and biological scientists is integral to the future of these new facilities. State-of-the-art imaging by both light and electron microscopies, adapted to problems in cancer biology and other fields of biomedicine, appears to be especially active in Asia, with world-class imaging facilities also developed in Japan, Hong Kong, and elsewhere. An integrated approach involving a wide range of expertise in experimental as well as theoretical work to study specific problems in biology has long been developed in Japan with groundbreaking results; some examples are detailed in Appendix C. Taiwan also has active and highly productive collaborations among scientists at the biology/physics interface, with research groups in physics making important advances in improved methods for diagnostics, imaging, and design of new materials for biomedical research. In Asia as well as Europe, the integration of researchers with clinicians, as well as access of clinical specimens and data for laboratory research, depends on traditions of training clinical investigators or the existence of M.D./Ph.D. training programs, which vary widely from one country to another.

In summary, the vision of the NCI to bring fresh ideas and expertise from physicists and engineers to the study of cancer biology is now actively pursued in major research and clinical centers throughout the world. Some new or growing programs

have been directly influenced by the initiatives of the PS-OC, whereas in other centers such work has a long and independent history that provides opportunities for collaboration and new perspectives. The potential of physics and engineering approaches to contribute to cancer biology is in many places no longer a novel idea, but an established practice that is increasingly becoming a mainstream interest of young researchers. The following chapters in this volume provide some examples of the scientific directions where this field is now heading.

Paul Janmey

Preface

The National Cancer Institute (NCI) Office of Physical Sciences Oncology (OPSO) has initiated a large-scale interdisciplinary research effort at the interface of the physical sciences and oncology through 12 centers located throughout the United States. The NCI Physical Sciences-Oncology Center (PS-OC) program brings together experts from physics/engineering and cancer biology/oncology to enable cross-disciplinary research that merges these fields and defines a new physics of cancer. Physicists strive to explain nature by precise mathematical equations, which could bring a new perspective to cancer research.

From a molecular perspective, cancer is not a specific disease. Cancer arises as a result of a succession of randomly occurring mutations. Tumors are inherently molecularly diverse. This complexity might give the wrong impression that cancer is not accessible to physics, which strives to describe nature by precise quantitative laws. Nevertheless, statistical physics has proven to be able to find the laws behind the stochastic processes underlying thermodynamics, and nonlinear dynamics has even uncovered the principles that govern chaotic behavior in nature. Molecular background and pathogenesis of solid tumors may vary, but the pattern of tumor progression—uncontrolled proliferation, invasive growth, and metastasis—is the same. Defining and unifying physical laws that are rooted in soft matter physics are required to understand these three functions. The concept of functional modules developed in biological physics will greatly facilitate understanding the laws that govern tumor progression. In tumor cells, the modules that are responsible for division, tumor growth, and metastasis may not have identical molecular architecture, but the same physics is essential for their functions. All cells in a tissue can be motile and are viscous on long time scales, behaving very much like liquid droplets. Consequentially, tissue boundaries are comparable to fluid boundaries. Tissues can be described as a new form of fluid matter, which is a significant topic in the novel research area of active soft matter.

The most common chemotherapy agents act by killing cells that divide rapidly. Newer anticancer drugs act directly against cancer-specific proteins or inhibit tumor angiogenesis. In all these cases the goal is to reduce the tumor. Yet, the primary tumor can often be removed by surgery and radiation. It is the residual tumor cells

and their ability to transgress boundaries that have to be hindered. Inducing changes in physical and material properties of tumor cells that disrupt the functional modules required for metastasis will provide a broad treatment option.

The physics of cancer is substantially more than providing new techniques for oncology. Soft matter physics as a basis for the physics of cancer has been strong in Europe. Institutions such as the Institute Curie in Paris have traditionally demonstrated that a solid connection between physics and medicine is feasible. As well, the German strength in cell biophysics has provided a good foundation. The NCI PS-OC program, which is unfortunately not yet paralleled in Europe, will jumpstart the physics of cancer throughout the United States and will serve to guide similar initiatives worldwide.

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