Shedding New Light on the Fundamental Nature of Cancer


Jonathan Widom


Jonathan Licht

Within every one of the estimated 50 trillion to 100 trillion cells of the human body are 6 meters (6.6 yards) of DNA. These cells are not 6 meters long, as we all know; one cell, for example, might be 6 microns long (one millionth of 6 meters). The underlying mechanical and biological mechanisms of both normal healthy cells and potentially cancerous cells that make it possible for the human body to stuff that much DNA into such a tiny space are subjects for the basic research now being done at Northwestern's Physical Sciences and Oncology Center (PS-OC).

"What's missing from the current understanding of the cancer problem isn't just specific bits of medically relevant information, but absolutely fundamental concepts about how cells work and evolve and how the molecules that underlie those processes work," says Jonathan Widom, biochemistry, molecular biology and cell biology (BMBCB), and principal investigator of the PS-OC. "These are processes where the physical sciences can shed a lot of light."

Last fall the National Cancer Institute (NCI) awarded cooperative agreements to 12 leading institutions to build a collaborative network of physical science-oncology centers. The NCI funded these centers to develop new fields of study based on the application of physical science approaches to major questions and barriers in cancer research. Northwestern's PS-OC was established last October, with Widom as principal investigator, and Jonathan Licht, chief, medicine: division of hematology-oncology, serving as senior scientific investigator.

Northwestern's PS-OC comprises five research projects, two core facilities, pilot projects, additional projects across the NCI network, education, training, and outreach programs. The Chemistry of Life Processes Institute and the Robert H. Lurie Comprehensive Cancer Center of Northwestern University jointly administer the PS-OC. Sheila Judge, operations and outreach director for CLP Institute serves as the program manager. The PS-OC team includes members from Children's Memorial Hospital, California Institute of Technology (Caltech), the University of Chicago, and the Weizmann Institute of Israel. Northwestern faculty from BMBCB, biomedical engineering, chemistry, materials science, applied mathematics, chemical and biological engineering, physics and astronomy on the Evanston campus and from medicine in the Feinberg School of Medicine are members of the center.

"Tumor biologists and oncologists typically seek to identify genetic and molecular changes that distinguish normal cells and tumor cells and to develop therapeutic agents that can

Photos on this page: Widom: by Rick Gaber; Licht: by Deidre Weber

exploit these differences," says Benette Phillips, co-director of education and outreach at PS-OC and scientific program director of the Robert H. Lurie Comprehensive Cancer Center. "NCI is hoping that physical scientists and engineers will ask different kinds of questions, investigate different parameters such as energetics, entropy, and mechanical forces, and employ a more quantitative and theoretical approach to trying to understand cancer."

How will this research lead to better treatments for cancer? "There are now certain cancers that can be treated very effectively," says Widom. "Yet an enormous diversity of diseases that are completely distinct at the molecular level looked the same to pathologists and got called this type of cancer or that. Because there are so many diseases, will all of them be cured in our lifetime? Probably not. But the efforts of these 12 centers are surely going to lead to discoveries that will motivate whole new kinds of therapies."

Five Central Projects

The overarching theme of Northwestern's PS-OC is the coding, decoding, transfer, and translation of information in cancer. Its five central projects all explore newly discovered types of information encoded in the human genome as well as in proteins.

Project one, Information Encoded in the Sequence-Dependent Mechanics of DNA, is headed by Robert B. Phillips, of Caltech. He has developed techniques to measure the flexibility of DNA and is studying how the ability of DNA to bend and loop affects how sequence information is used by the cell. Widom, who has demonstrated that the flexibility of a region of DNA is in turn influenced by the sequence, is collaborating with Phillips in this project.

Widom heads project two, DNA Sequence-Encoded Nucleosome Positioning and Gene Regulation, which seeks to understand and predict where nucleosomes are located along DNA strands. Nucleosomes are spool-like subunits of chromosomes in which DNA is wrapped around a complex of proteins called histones. The location of the spools has a large influence on which genes are expressed, or activated. "One way of thinking about what distinguishes a cancer cell is that it represents a particular genetic state," says Widom. "That state is a set of genes that are expressed in certain amounts. What we are seeking is a quantitative, predictive understanding of that."

John Marko, BMBCB and physics and astronomy, heads project three, DNA Information and Organization at

Sheila Judge

Benette Phillips

John Marko

Photos on this page: Phillips: courtesy of Benette Phillips; Judge and Marko: by Rick Gaber.

Vadim Backman

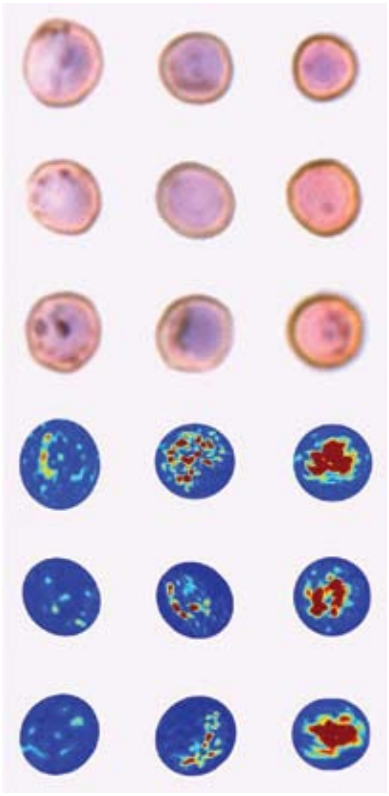
William Kath

Andreas Matouschek

Photos on this page: Backman: by Sam Levitan; Kath by Jasper Chen; Matouschek: by Rick Gaber.

Supranucleosomal Scales: Chromatin Folding and Higher Order Structure, Heterochromatin, and Domain-Wide Repression. Marko's laboratory conducts micromechanical studies of chromosomal structure and protein-DNA interactions in the chromosome. In this project, PS-OC researchers are exploring the higher levels of chromosome architecture in both normal cells and in certain malignant-cell lines. They are seeking to understand the basic nature of this chromosomal architecture and how it influences a phenomenon in which the expression of multiple genes in a long stretch of DNA is completely suppressed.

Vadim Backman, biomedical engineering, is a key team member on project three. He has developed novel, minimally invasive methodologies for detecting tumors. The cellular changes that these techniques report are due to alterations in the statistics of nanoscale cell architecture. The light-scattering technique used is detecting changes in the chromosomal architecture in these seemingly normal cells. One of the main objectives of the project is to elucidate the genomic consequences of this reorganization of the nanoscale nuclear structure.



Colon cancer cell lines genetically modified to reflect different stages of malignancy (Columns 1- 3) look similar under conventional microscopy (Rows 1-3). When observing these cells under the light-scattering technique developed by Backman's group (Rows 4-6), a clear difference in the nanoscale molecular density of the cells can be observed (Subramanian et al., *PNAS*, 105(51), 20124-20129, 2008).

The leader of project four, Dynamic Nucleosome Signatures in Epigenetic Memory and Cancer Development, is William Kath, engineering sciences and applied mathematics. Changes in gene expression that occur without changes in DNA sequence and which are potentially reversible are termed "epigenetic changes." Kath and his colleagues are using sophisticated mathematical analyses and computational modeling to analyze the stability of these changes in both normal cells and cancer cells. »

Project five, Encoding and Interpreting Information at the Protein Level, is headed by Andreas Matouschek, BMBCB. This project also investigates sequence information, but in this case, the focus is on the sequence of the amino acids in proteins. Once made in a cell, proteins persist for varying amounts of time before being degraded. How much of a particular protein is in a cell at a given time depends both on how fast it is made, by stringing the amino acids together, and how fast it is degraded. Matouschek will be examining cancer cells for partial degradation products that play a role in maintaining the cell's malignant characteristics.

Cancer researchers and clinicians from the Robert Lurie Cancer Center are involved in all projects, in part to make sure that the model systems being analyzed are meaningful in cancer biology. "Jon Licht, a clinician who also runs a big cancer biology research group, and others from the cancer center are involved and help keep a clear cancer focus on all five projects," says Widom. "They even are involved in project one, which had only an indirect—although essential—cancer link to begin with."

Core Facilities

Two research cores directly support PS-OC investigators. The bioinformatics core, headed by Ji-Ping Wang, statistics, provides a platform for interaction between computational scientists and biologists or cancer researchers and creates training opportunities for postdoctoral fellows and graduate students. Peter Kopp, medicine: endocrinology, directs the deep-sequencing core, which provides the instrumentation and support to conduct high-throughput DNA sequencing.

Center investigators also have access to an extensive network of other core facilities housed on both Northwestern campuses.

Outreach and Education

Critical features of the PS-OC include extensive interactions among the 12 centers of the NCI network, mandated pilot projects, data sharing, and educational and training programs designed to produce a new generation of scientists who understand both the physical sciences and cancer biology. "For example, we will be holding summer workshops to introduce basic principles of tumor biology to trainees in the physical sciences and principles in the physical sciences to tumor biologists," says Phillips. "The center also is sponsoring summer research experiences for undergraduates and medical students that will provide cross-disciplinary training and education."

Ji-Ping Wang

Peter Kopp

To further inform the Northwestern community and the general public about its activities, the PS-OC will sponsor seminars, an annual open house, and an annual symposium.

Encouraging extensive dialogue among physical scientists and engineers and tumor biologists, the PS-OC holds quarterly all-day "science jams" where the five projects are discussed. An annual investigators' meeting and regular conference calls among leaders of the 12 network centers are also planned.

One of the mandates of the NCI grant is that Northwestern collaborate with the other physical science-oncology centers throughout the country. "NCI is really driving us toward team science," says Sheila Judge, program manager and co-director of education and outreach at PS-OC. "They want to see synergy between the centers."

"We've had less than a year and are on track by all the milestones," says Widom. "NCI is supporting this with large amounts of money and wants real discoveries in return. And we want that too. Everybody is really motivated. It's a huge challenge and a huge opportunity."

For more information, visit the PS-OC web site at www.psoc.northwestern.edu. — *by Joan Naper*

Photos on this page courtesy of Chemistry of Life Processes Institute.