Physics Today

Physicists offer a different approach to cancer research

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Citation: Physics Today **67**(11), 22 (2014); doi: 10.1063/PT.3.2578
View online: http://dx.doi.org/10.1063/PT.3.2578
View Table of Contents: http://scitation.aip.org/content/aip/magazine/physicstoday/67/11?ver=pdfcov
Published by the AIP Publishing

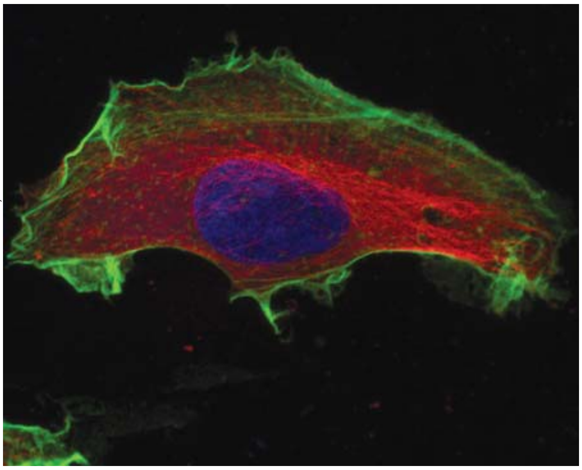
Physicists offer a different approach to cancer research

Quantitative methods and modeling complement the work of biologists and oncologists. But US money for innovative centers supporting that research has run out.

Peter Kuhn believes that his and colleagues' research might significantly prolong the lives of thousands of lung cancer patients each year. Researchers with Kuhn's physics oncology team at the Scripps Research Institute in La Jolla, California, and at the University of Southern California (USC) discovered through mathematical modeling of clinical data that lung cancer will sometimes metastasize to adrenal glands relatively early in the progression of the disease. The model also helped determine that the adrenal gland cancers are "spreaders," very likely to metastasize, says Kuhn, a physicist. Together with anecdotal clinical evidence, the research suggests that surgical removal of adrenal-gland metastases will arrest the spread of the disease for a small subset of about 8000 lung cancer patients a year.

Any two of the four disciplines—mathematics, physics, medicine, and biology—involved in the collaboration might have come together in a traditional research framework, he says. But it was a mechanism known as a physical sciences–oncology center (PS–OC) that brought all of them to the project, and all were needed to put the pieces of the puzzle together in a meaningful way.

Kuhn's team is one of a dozen PS–OCs that were created as a forward-looking initiative by the National Cancer Institute (NCI) in 2009. Their express purpose was to team physical scientists with biologists and oncologists to seek a new understanding of cancer development that could lead to improved treatments and diagnostics (see PHYSICS TODAY, May 2010, page 27). Located at universities and other institutions around the US, the PS–OCs were supported by the NCI for five years; that funding ran out on 1 September. The NCI has requested proposals for new centers, and some applications were submitted by the initial June deadline, says



ANJIL GIRI, JOHNS HOPKINS PS–OC

Researchers at the Johns Hopkins University Physical Sciences–Oncology Center are working to identify proteins that control the process of metastasis. In this image, a human fibrosarcoma cell has been stained for microtubule cytoskeleton (red), actin cytoskeleton (green), and nucleus (blue).

Larry Nagahara, director of the PS–OC initiative at the NCI. Applications will be reviewed by a panel comprising physical scientists, cancer biologists, oncologists, and engineers. Proposals deemed to have merit will be sent directly to the National Cancer Advisory Board for funding approval.

However, NCI director Harold Varmus says he expects the new round of centers will be only half the number of original PS—OCs. Since no funds have been set aside for the new centers this time, proposals will have to compete with other NCI centers for funding. The NCI's inflation-adjusted appropriations have been declining for years, and success rates on grant applications are at a dismal 17%. Four of the original PS–OCs, including Kuhn's, had been created with one-time funding from the American Recovery and Reinvestment Act and then rolled into appropriated funding after two years.

Whereas a PS–OC will typically have two or three research projects, individual investigators unaffiliated with a center can apply for a new type of NCI grant known as a physical sciences–oncology project. Awardees of the new grants are free to collaborate or interact with centers and centers can interact with other centers, Nagahara says. As with PS–OCs, no funding is set aside for project grants.

The lapse in NCI support leaves investigators at the existing centers scrambling for other sources of sponsorship. Any new funding won't begin to flow until April 2015 at the soonest. Kuhn has been recruited to USC to lead a new initiative in convergent sciences and has teamed up with USC's own PS–OC to shape the future research program in physics oncology. That work will receive support from USC and other sources, he says. Though Kuhn is hoping to win a new PS–OC grant, he says he is determined to bring his research concepts to fruition with or without an award.

Ideas lab

As the PS–OC program is downsized, NSF, the NCI, and two nonprofit cancer groups kicked off a program in September to lure physicists—theorists in particular—into cancer research. The $11.5 million effort will gather 15–30 prominent physicists and life scientists for an "ideas lab," a five-day brainstorming workshop, scheduled for early next year, that is expected to generate proposals for theoretical biophysical cancer research. Most of the proposals are likely to be reviewed favorably and funded, says Krastan Blagoev, director of NSF's Physics of Living Systems program.

Apart from its well-known contributions to imaging and radiation therapy, physics adds to cancer research a method of thinking that differs from that of biologists and oncologists, say physicists working in the field. Researchers "need a conceptual framework in which we can answer the fundamental questions about cancer, like why does it exist and what are its deep evolutionary roots," says Paul Davies, a cosmologist who is the lead investigator at Arizona State University's PS–OC. "Cancer research is far too much money chasing far too few ideas. We need to think our way to a solution, not spend our way to a solution."

Both experimental and theoretical physics are useful in understanding and modeling metastasis, says Davies. The process requires cancer cells to transition from static to slippery and motile, squeeze through the tissue around the tumor, and secrete membrane-dissolving chemicals to get into the bloodstream. Getting out of the blood and colonizing a remote organ to form a new tumor is another complex process. (See the article by Chwee Teck Lim and Dave Hoon, PHYSICS TODAY, February 2014, page 26.)

One project at the Arizona State center used atomic force microscopy to measure the degree to which cancer cells soften as the disease progresses. To determine the Young's modulus of cancerous cells, researchers prodded them with the tip of the atomic force microscope. "That change in Young's modulus is critical to the whole metastatic process, the squeezing through gaps," Davies says.

"What has become abundantly clear over the last few years is that the physical microenvironment, not just the chemical microenvironment, can play a critical role in cell behavior. Just pressure forces, or even shear stresses, can affect gene expression," Davies notes.

A deeper understanding

Robert Austin, principal investigator at the PS–OC at Princeton University, explores the evolution of drug resistance: why and how cancer cells develop resistance to chemotherapy. "Some very deep theories about evolution dynamics . . . have developed over the years, which involve things like the influence of small populations and gradients and how mutations are transmitted," he says. "We try to use those ideas of evolution dynamics to understand why it is that we continue to fail using chemotherapy and why a cure may actually be an impossible concept."

A better understanding of the evolution of resistance could lead to improved dosing regimens. Some theoretical models have been developed and are starting to be tested using data from observations, says Nagahara. "[The models] themselves aren't dictating how we give clinical treatment, but at least the thought process is starting to enter the cancer research communities." One indicator of the growth of physics in cancer research has been the recent addition of a dedicated session on the topic at the annual March meeting of the American Physical Society, Nagahara notes.

Austin, who uses game theory to try to predict how a particular cancer community in a body is going to change over time, says that physicists bring a deeper view of evolution compared with biologists. "There is a very beautiful set of equations that you can use that involve chaos and determinism," he says. "It's one thing to say natural selection; it's another to try to compute the rate at which these things are happening, and that's usually quite a bit beyond a normal biologist's background or area of expertise."

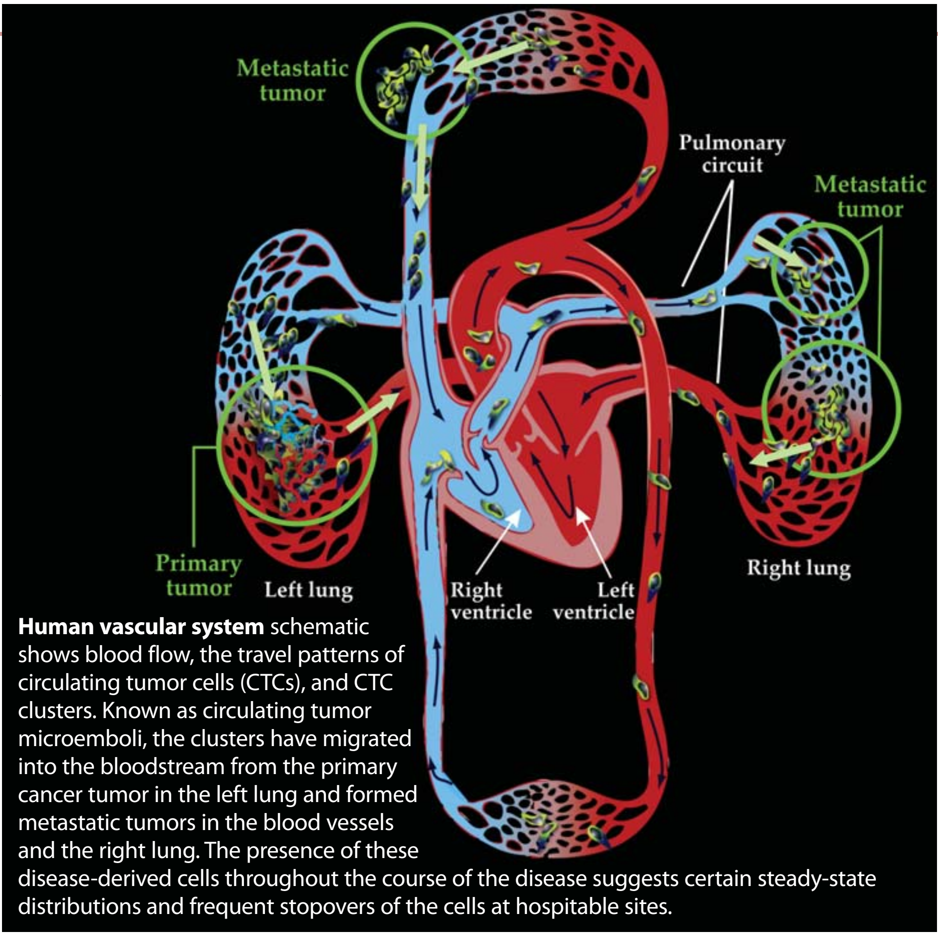
Blagoev says that improved imaging techniques have produced a wealth of cancer data that will enable theorists to better discriminate between different models and theories. "Theoretical physicists are trained to look at data and think of models that can explain the data and what the data tell based on models that are previously explored," he says.

"Just as mathematical models indicated in the '90s that a cocktail of treatments would be effective to treat HIV, theoretical-physics approaches can be effective in searching for basic principles in human cancer in a quantitative way that helps us better understand this disease," Blagoev says. Physicists also have contributed to the understanding of how bacteria grow and of how they die during drug treatment, he adds.

Physicists in cancer research aren't confined to the NCI centers, of course. But work outside the centers tends to be more applied. Indrin Chetty, with the Henry Ford Health System, works on improving image-guided radiation therapy; he's determining the optimum angles for beam delivery to maximize the dose to tumors and minimize exposure to healthy tissues. Those calculations are confounded by the movement and deformation of the targeted organs, he says. Chetty also has been using Raman spectroscopy for assessing the effectiveness of radiation therapy. Several studies have shown that the technique can determine with greater than 99% accuracy whether a cell is cancerous or healthy.

Daniel Low, a physicist at UCLA, works on optimizing radiation therapy using robotics and on mapping and modeling human breathing. Although the immediate application of the breathing research will be in radiation therapy and imaging, Low expects it will have other applications. "Our hypothesis is that diseases like COPD [chronic obstructive pulmonary disease] or severe asthma might benefit from being able to characterize a specific patient's breathing internal motion characteristics," he says. (For more on radiation in the treatment of cancer, see the September 2002 special issue of PHYSICS TODAY.)

Physicists contribute to research on applying gene therapy to increase the effectiveness of radiation therapy, says Chetty. They're also working in the field of imaging genomics; the combination of diagnostic imaging and genomic data looks promising for determining whether a tumor is susceptible to certain drugs. "Fundamentally, you are dealing with radiation interactions in matter, which is a physics problem," he notes. "Who's more expert on the physics of radiation and its interaction with matter than a theoretical physicist?"



Human vascular system schematic shows blood flow, the travel patterns of circulating tumor cells (CTCs), and CTC clusters. Known as circulating tumor microemboli, the clusters have migrated into the bloodstream from the primary cancer tumor in the left lung and formed metastatic tumors in the blood vessels and the right lung. The presence of these disease-derived cells throughout the course of the disease suggests certain steady-state distributions and frequent stopovers of the cells at hospitable sites.

An unruly mix?

Bringing physicists together with oncologists and cancer biologists presents both challenges and opportunities. A key difference is the language that is spoken: "Mathematics keeps the logic straight. Without mathematics [scientists] are not very good at understanding complicated relations," says Blagoev. "Biologists traditionally are not trained in this way." Physicists and mathematicians differ more subtly, in that physicists are trained to work with data from the natural world.

Just as physicists will never provide patient care or design a clinical trial, the treating oncologists will never develop a fundamental mathematical model, notes Scripps's Kuhn. "As a team we are developing meaningful theoretical models that are intellectually coauthored by the oncologists, the biologists, and the mathematicians," he says. "That requires us to work together a long time, and that's what the PS–OC allowed us to do."

Physicists may be alarmed at the softness of the data in cancer research, Austin warns. He points to several studies that suggest the vast majority of the published preclinical cancer biology literature is not reproducible. In two such published reviews, Amgen and Bayer HealthCare separately reported that they could reproduce only a small fraction of highly cited preclinical research findings—in Amgen's case, the biotech giant could confirm the results of just 6% of the 53 projects that were reviewed.

"Most physics papers are probably right, and if you think a paper is wrong then you have somebody go and try to reproduce it," says Austin. "That is not the way they work in oncology. It's not a good career move to try to prove some other papers are wrong. You're working with a much dirtier data set than in physics, and you have to get your mind around that." **David Kramer**

Bridging academia and industry the Fraunhofer way

Winning contracts and sending products to market are the measures of success in the German organization's not-for-profit research model.

"We file at least two patents per day—one in the morning, one in the afternoon," says Georg Rosenfeld, director of research at the Fraunhofer Gesellschaft (Fraunhofer Society), Europe's largest organization for applied research. "Most are generated within our own research activities. But everything we do is geared toward the needs of industry."

The Fraunhofer Gesellschaft was founded in 1949 in postwar Germany. Today in that country it boasts 67 institutes in all major branches of engineering, a budget of €2.1 billion ($2.6 billion), and some 23 000 employees. Sites outside Germany are smaller and are called centers; there are seven in the US—with a total of about 180 researchers—and eight scattered across Europe and elsewhere. Fraunhofer representatives in Asia, the Middle East, and South America look for industrial opportunities and research partners. In total, the society has around 10 000 joint projects with industry each year. It's no surprise that Fraunhofer is a household name in Germany. And President Obama points to it as a model for his $1 billion initiative to create a network of institutes for manufacturing innovation.

At a 30 September celebration of Fraunhofer's 20 years in the US, Andre Sharon, who heads the Boston University–based Fraunhofer Center for Manufacturing Innovation (CMI), said the key to the society's success is