Medical Xpress

Fighting cancer across the disciplines

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Biophysicist Jan Liphardt is the director of the Bay Area Physical Sciences-Oncology Center and an associate professor of physics at UC Berkeley.

Still a mystery in the 21st Century, cancer has been known and documented since ancient times. The oldest known written description of cancer dates back to an Egyptian manuscript from 1,600 B.C.E. The Greeks used the term “oncos” — Greek for “hard swelling” — to describe cancer, a term that is used to this day for the field of medicine dealing cancer: oncology.

Two millennia and billions of breast cancer self-exams later, we still use our sense of touch — in addition to modern-day diagnostic tools — to detect those dreaded lumps. Most of us do not stop to wonder why that is, but researchers today increasingly do. How is tissue hardness related to cancer? What is the relationship between what we feel and what is really going on at the cellular level in terms of biological and physical processes?

Questions such as these, on the cutting edge of modern cancer research, lie at the interface of many disciplines. The answers are increasingly being sought not only by biologists but also by large, multidisciplinary teams that also include physicists, chemists, mathematicians, engineers, and computer scientists.

This approach to research is supported by the National Cancer Institute, which has recently started a network of 12 Physical Science-Oncology Centers nationwide, including one at UC Berkeley, funded at $15.7 million.

The Berkeley center brings together scientists and clinicians from institutions from across the Bay Area, including UC Berkeley, UC San Francisco, Lawrence Berkeley National Lab, the Helen Diller Family Comprehensive Cancer Center, and the California Institute of Quantitative Biosciences.

The effort here is being led by Jan Liphardt, an associate professor of physics at UC Berkeley. Its goal, he explains, is not to immediately race to develop new drugs or diagnostic tools, but to step back and try to approach cancer in novel ways.

“Biology is beginning to explicitly consider how physics and mechanics influence what cells and tissue do,” says Liphardt. The Berkeley center, started in 2009, focuses on the mechanobiology of tumor growth. Cells can sense and generate mechanical forces, which can influence what other cells do. Recent scientific discoveries point to a role of tissue mechanics in a variety of diseases, including cancer.

This NCI initiative, Liphardt says, reflects cancer incidence and outcome statistics that have not improved nearly as much as hoped. In spite of the tens of billions of dollars spent in the "war on cancer" over the last half century, cures remain elusive.

"If you look at how well we're doing in terms of actually changing outcomes, the field today is quite good at dealing with a relatively small number of cancers, but we're still doing much too poorly with most cancers," Liphardt says. "It's possible that some features of cancer are hard to address if you only study the problem from a cell biological or biochemical vantage point."

The mortality rate for cancer, Liphardt points out, has not gone down much over the last quarter of a century, especially once a cancer has metastasized. The likely reasons for this are many. To begin, "cancer" is a catch-all term for as many as a thousand related but yet distinct diseases — and that's just at the primary sites. Add to this cancer that metastasizes and the situation quickly becomes very complicated.

"Now you're actually dealing with a variety of malignancies in one patient. That means that a drug cocktail may well succeed in treating the cancer in one of the affected tissues but not all," Liphardt says.

Complicating matters further is the instability of the cancer genome. Cancer cells change their genomic composition and architecture in a way not unlike bacteria that become resistant to antibiotic treatment. "So as you keep treating the patient you're actually selecting for the cancers that are resistant."

This is where the new approach comes in. By focusing on mechanical forces that affect cell behavior, scientists in a sense try to get to the root of what makes these cells tick.

A sea change in the way we think of cancer was led by Mina Bissell of Lawrence Berkeley National Lab, who was one of the first to show that cells are constantly interacting with their microenvironment and changing their behavior according to it. Until then, the standard “cell-centric” view of cancer was that of “one cell gone bad” — the notion that when gene mutations within a cell reach a critical number they cause it to start dividing inappropriately and turning into a tumor.

“It turns out that cells are continuously interrogating the mechanical characteristics of their environment and they’re using that information to make decisions about what they should do,” he says.

A recent series of discoveries in stem cell biology, for instance, show that stem cells differentiate into different cell types depending on the surface on which they’re placed. A stem cell put on a squishy surface is more likely to differentiate into a neuron, whereas one put on a hard surface is more likely to differentiate into a bone cell.

Scientists at the PS-OC are trying to find out how cells sense their microenvironment and then how they use that information to make decisions. A key advance step in this line of research came out of Valerie Weaver’s laboratory at UC San Francisco. “Valerie’s group has shown in mice that drugs which prevent tissues from hardening also reduce the rate at which certain tumors grow.” This is one of the first discoveries of a direct connection between enzymatic tissue hardening and tumor progression.

While a big step forward for basic research, the discovery is not yet clinically relevant, and may not become so for a long time. One of the problems is that the same agents that inhibit tumor growth also impact other processes in the body that we cannot do without.

“The remodeling and crosslinking of the extracellular matrix is important for wound healing and the mechanical stability of tendons, among many other things," Liphardt explains. "One cannot simply put someone on a drug which broadly blocks collagen crosslinking, since this will result in significant side effects."

Moreover, the road from mouse experiments to treating humans is long. Even in the best of circumstances, Liphardt says, the time lag between a basic discovery and putting a drug on the market can be as long as 15 to 20 years. Nevertheless, he says, Weaver's work serves as direct proof that tumor progression can be slowed by modifying the mechanical characteristics of the extracellular matrix.

Beyond that, this experiment is a perfect example of the kind of breakthroughs that can be attained when basic scientists join forces with clinicians.

"Our center is an example of what question-driven research increasingly looks like," Liphardt says, pointing to other large multidisciplinary efforts, such as the Helios solar energy initiative. These projects are driven by specific scientific problems, not a particular field of study. Traditional research efforts and universities that are organized strictly according to traditional fields are increasingly obsolete, Liphardt says.

"As Richard Feynman said, 'Nature doesn't care what you call it!' It's either an interesting and important question or it's not, and it really doesn't matter if we label it as physics or biology or chemistry. There's increasing evidence that the way you solve these big problems — whether it's climate or energy or disease — is by bringing together the right kind of teams with the right talent in a sort of smart-mob-like structure, rather than worrying what to call it or which department it should be in.'"

As an experimental biophysicist and member of both the Physics and the

Molecular and Cell Biology departments, Liphardt is well positioned to lead the new center and look at the broad picture in cancer research. "The actual systems we work on in my lab are very biological. With our collaborators across campus and within the center, we look at fish and mice and people," he says. "But I have more of a physicist's approach to figuring things out."

In spite of the daunting obstacles faced by cancer researchers, the time scales that stretch over decades, and the elusive nature of cancer itself, Liphardt maintains an unwavering optimism about the eventual victory of science over this disease.

"It's a finite problem, after all," he says. "There's no magic here. Certain cancers such as testicular cancer can already be largely cured, so we know it can be done. It may be very hard and it may take a long time, but we know it's solvable. It's just a matter of finding those solutions."

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