ONCOLOGY

Getting physical

Physics, maths and evolutionary biology are among the scientific disciplines providing cancer research with fresh perspective and therapeutic approaches.

BY JENNIE DUSHECK

Biology has always had its roots firmly planted in the physical world. From the earliest scientific experiments to the most recent biomedical inventions, natural philosophers and modern biologists have used all the available tools of science to study living organisms. Optics, classical mechanics and mathematics have all informed the study of life.

With the rise of biochemistry, however, the application of biology became narrower and more specific. The power and spectacular success of molecular biology — from elucidating gene function to exposing complex molecular cascades — invigorated this approach. Yet as biologists developed the tools to probe deeper into gene expression pathways, they began to neglect the big picture, a world of whole cells, tissues and organisms.

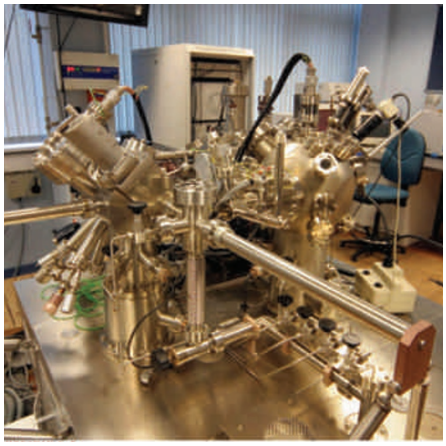
As biology begins to confront the limits of the molecular approach — which has yielded vast amounts of data but not always clear understanding — some scientists have returned to a more biomechanical view of life, and their research is starting to bear fruit. Nowhere has this change been more evident than in the field of cancer research. Cell biologist Cynthia Reinhart-King, whose lab at Cornell University studies the disruption of tissue architecture in cancer, says: "The kind of work I do in cell mechanics is often considered a new field, but if you actually look at it historically, there was a big population of scientists doing it in the 1930s, 1940s and 1950s." That older research laid a lot of important ground work, she says. "But now we have tools that allow us to probe much deeper."

The move towards a more physical approach to cancer research stems in part from a deep well of disappointment with the war on cancer. In the 1950s and 1960s, lung cancer rates among men skyrocketed, the result of a 40-fold increase in smoking between 1910 and 1965. Spurred by these sobering statistics, President Nixon signed the US National Cancer Act in 1971, which more than doubled the annual funding for the National Cancer Institute (NCI) in just two years and charged the institute with finding a cure for cancer.

But the miracle drug never materialized. Since the 1950s, age-adjusted cancer mortality rates have declined by only 11%. Prevention, screening and successes with a handful of cancers have saved millions of lives, but the prognosis for someone with metastatic cancer is as grim today as it was 50 years ago. The sense of failure is palpable. In 2008, *Newsweek* ran a story titled "We Fought Cancer…And Cancer Won." When cancer geneticist Harold Varmus became director of the NCI in 2010, he told an audience: "We have not succeeded in controlling cancer as a human disease."

TURNING TO PHYSICS

By the mid-2000s, Anna Barker, then deputy director of the NCI, noticed that many physicists, engineers and mathematicians were beginning to think about cancer, and she decided to harness their skills. "We had reached an inflection point where we knew enough about the biology to bring in other fields," Barker says. In 2009, the NCI issued grants to 12 interdisciplinary centres around the United States, where investigators from both the physical sciences and oncology collaborate to address questions in one of five areas: metastasis, microenvironment, information processing, energy use, and the evolution of cancer cells.



The scanning tunnelling microscope gives researchers a nanoscale view of cancer.

REX FEATURES

The United States is not alone in fostering such collaborations. Cross-disciplinary oncology research in Europe receives funding from the European Union, at a national level, and at the institutional level, reports Reinhart-King, who co-authored a study on cancer research in Europe[1]. In some ways, European multidisciplinary research in oncology has a longer history and deeper roots, with clinicians, basic researchers and engineers at many institutions working side by side in ways that would be unusual in the United States. But such endeavours were not explicitly funded until recently. Scientists from other fields bring an array of different kinds of knowledge and tools to cancer research. Some are specialists in microfluidics, nanoparticles, computer science or evolutionary biology, and many have started to reframe questions about cancer. "Most [molecular] biologists don't think in three dimensions," Barker says.

Biomedical engineer and cancer researcher Mauro Ferrari, president of the Methodist Hospital Research Institute in Houston, Texas, gives an example. Consider that two metastases from the same primary tumour are growing in the same organ yet respond differently to the same drug, he says. A biologist wonders how identical tumours could have different levels of drug resistance, or assumes that the two metastases are not identical. But the tumours are genetically identical — what differs is their three-dimensional position in the organ, he says.

"What's missed is the physics part of the story," Ferrari explains. The nanoparticles that deliver the drug can penetrate the organ and reach one tumour but not the other; the difference could be due to fluid dynamics, shear forces on the blood-vessel walls, the velocity of the drug particles, and the permeability of local tissues, among other things. "If you design particles with the right physics, it changes entirely where they go," Ferrari says (see 'Carrying drugs', page S58)[2]. "I can make particles of a certain type and they will concentrate in the lung, or I can make other particles that will go to the spleen."

"As a cancer community, we are barking up the wrong tree," he adds. We don't need more drugs, just better ways of deploying the ones we have.

Mathematics and complexity theory are also becoming indispensable tools. Information flows from cell to cell, from tissue to tissue, and from macroenvironment to microenvironment and back, forming intricate feedback loops that are best understood using mathematical approaches. Computational biologist Franziska Michor of the Dana-Farber Cancer Institute Physical Sciences–Oncology Center in Boston, Massachusetts, designs mathematical models to predict, and perhaps to help prevent, the evolution of cancer cells towards drug resistance or metastasis (see 'Forecasting cancer', page S66). Each cell, she explains, has a set of probabilities: of dividing, of dying, or

A HELPING HAND FROM PHYSICS

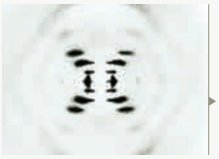
Biology and the physical sciences have a long history of relying on each other for major advancements. In the late 1970s, however, molecular biology began to lose touch with its physical and mathematical roots.

1600s
New microscopes made by Galileo, Antonie van Leeuwenhoek and others magnify up to x500, revealing bacteria, spermatozoa, and the banded pattern of muscle fibres.

1865
Gregor Mendel uses combinatory mathematics to explain inheritance in pea plants, laying the foundation for genetics.

1920s
Mathematicians Alfred Lotka and Vito Volterra develop simple equations for predator-prey interactions, and R. A. Fisher lays the foundations for modern statistics, population genetics and the evolutionary synthesis.

1937
Dorothy Hodgkin exploits the new field of X-ray crystallography to solve the structure of cholesterol, as well as that of penicillin (1945), vitamin B12 (1955) and insulin (1969).



1940s
Donald Griffin and Robert Galambos discover echolocation in bats.

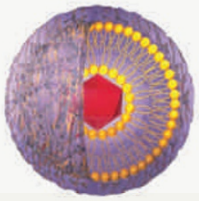
1953
Rosalind Frankind's X-ray crystallography measurements of DNA help James Watson and Francis Crick build a model of DNA.

1972
First recombinant DNA molecule.

1977
First genome sequenced.

1990
RNA interference.

1990
First gene therapy by W. French Anderson.

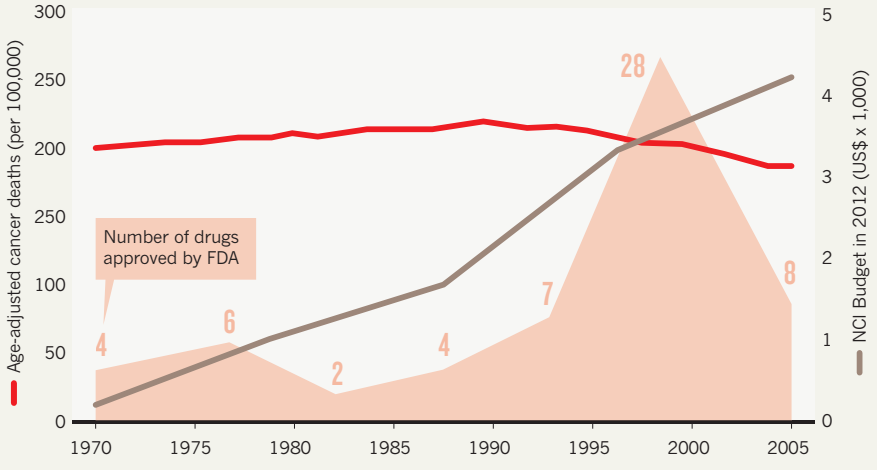


1995
First nanoparticle drug carrier approved: Doxil.

2002
Mathematical models of the evolution of cancer cells.

DIMINISHING RETURNS OF CANCER RESEARCH

Number of cancer deaths versus spending on cancer research versus drug approval



of developing resistance. From these, it is possible to calculate the probability that a cell line will evolve resistance in different situations, and to suggest drug dosing strategies accordingly[3]. "One way to make progress in cancer," Michor says, echoing Ferrari, "is just to use existing drugs in a smarter way." Powerful insights are coming from the realization that cancer cells (as well as normal cells) respond strongly to their physical microenvironment. "Tumour cells respond to mechanical forces," says Reinhart-King, "and those mechanical forces have been implicated in promoting cancer progression" (see 'The forces of cancer', page S56)[4].

DON'T STRESS

Physical stresses can provoke cells to turn on a set of stereotypical responses that lead to metastasis. These changes — including proliferation, increased motility and mutation — are the same strategies that bacteria use to escape danger, explains Thea Tlsty, a research oncologist at the University of California, San Francisco, and half of the duo that runs Princeton University's Physical Sciences–Oncology Center in New Jersey. "What we've been trying to do so far is kill the cancer cells," says Tlsty. "But when you try to kill them, you stress them. And that gives the cells access to the primitive, fundamental pathways and the generation of diversity — a heterogeneity that is the hallmark of cancer."[5]

Increasingly, researchers are wondering whether a soothing microenvironment for cancer cells might allow patients and their cancer cells to live in tenuous peace. There is considerable evidence that cancer already does this in a quarter or more of healthy adults[5]. "We are riddled with pre-malignancies and even little malignancies that don't yet manifest," says Tlsty. "They don't express symptoms and they are being held under control. So many people die *with* these things, not *of* them."

Cancer researchers now recognize that taming wild cancer cells — populations of cells that evolve, cooperate and roam freely through the body — demands a wider-angle view than molecular biology has been able to offer. Cross-disciplinary collaborations can approach cancer at greater spatial and temporal scales, using mathematical methods more typical of engineering, physics, ecology and evolutionary biology. The sense of failure so evident five years ago is giving way to the excitement of a productive intellectual partnership. ■

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2. Adrian, G. *et al. Biomaterials* **33,** 5504–5513 (2012).
3. Michor, F. *et al. Nature Rev. Cancer* **11,** 657–670 (2011).
4. Lambert, G. *et al. Nature Rev. Cancer* **11,** 375–382 (2011).
5. Zhang, Q. & Austin, R. H. *Annu. Rev. Condensed Matter Phys.* **3,** 363–382 (2012).