Rethinking cancer

Researchers seeking to understand cancer have mostly viewed it in terms of chemistry and genetics. **Paul Davies** argues that physicists should now bring their insights to bear – by considering living cells as material objects that can be controlled using physical forces

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Cancer touches almost everyone in some way. It is now nearly 40 years since US President Richard Nixon declared a scientific "war on cancer", but while many other major killers like heart disease and pneumonia have shown dramatic improvements and spectacular advances in treatment, the mortality and morbidity rates for most cancers have remained almost unchanged (figure 1). Billions of dollars have been spent on cancer research and a million research papers have been published, yet most cancer sufferers have not benefited greatly from that effort, although prevention campaigns – against smoking, asbestos and excessive sunbathing, for example – have proved effective. With the exception of a handful of cancer types, such as childhood leukaemia, progress on treatments has been limited to baby steps, with incremental improvements in drugs leading to marginal extensions of life expectancy. Lacking so far is any major breakthrough that would dramatically transform the human and economic impact of the disease. Cancer biology is a subject about which a vast amount is known but very little is understood. So could it be that researchers cannot see the wood for the trees?

In a spectacularly enlightened initiative, the US National Cancer Institute (NCI) – America's leading federally funded cancer-research agency – has appealed to the physics community for help, by creating 12 new centres aimed at encouraging physical scientists, mathematicians and engineers to tackle the problem of cancer. The five-year initiative, which currently has a budget of $35m per year, is largely the brainchild of the NCI's deputy director Anna Barker. The new Physical Science-Oncology Centers are located at major US research institutions – including Princeton University, the Massachusetts Institute of Technology, the University of California and Arizona State University – as well as established cancer centres such as Sloan Kettering in New York. All of the new centres involve oncologists and cancer biologists working closely alongside physical scientists or mathematicians.

Physicists bring unique conceptual insights that could augment more traditional approaches to cancer research. By looking at an old problem with fresh eyes, some radically new ideas might emerge

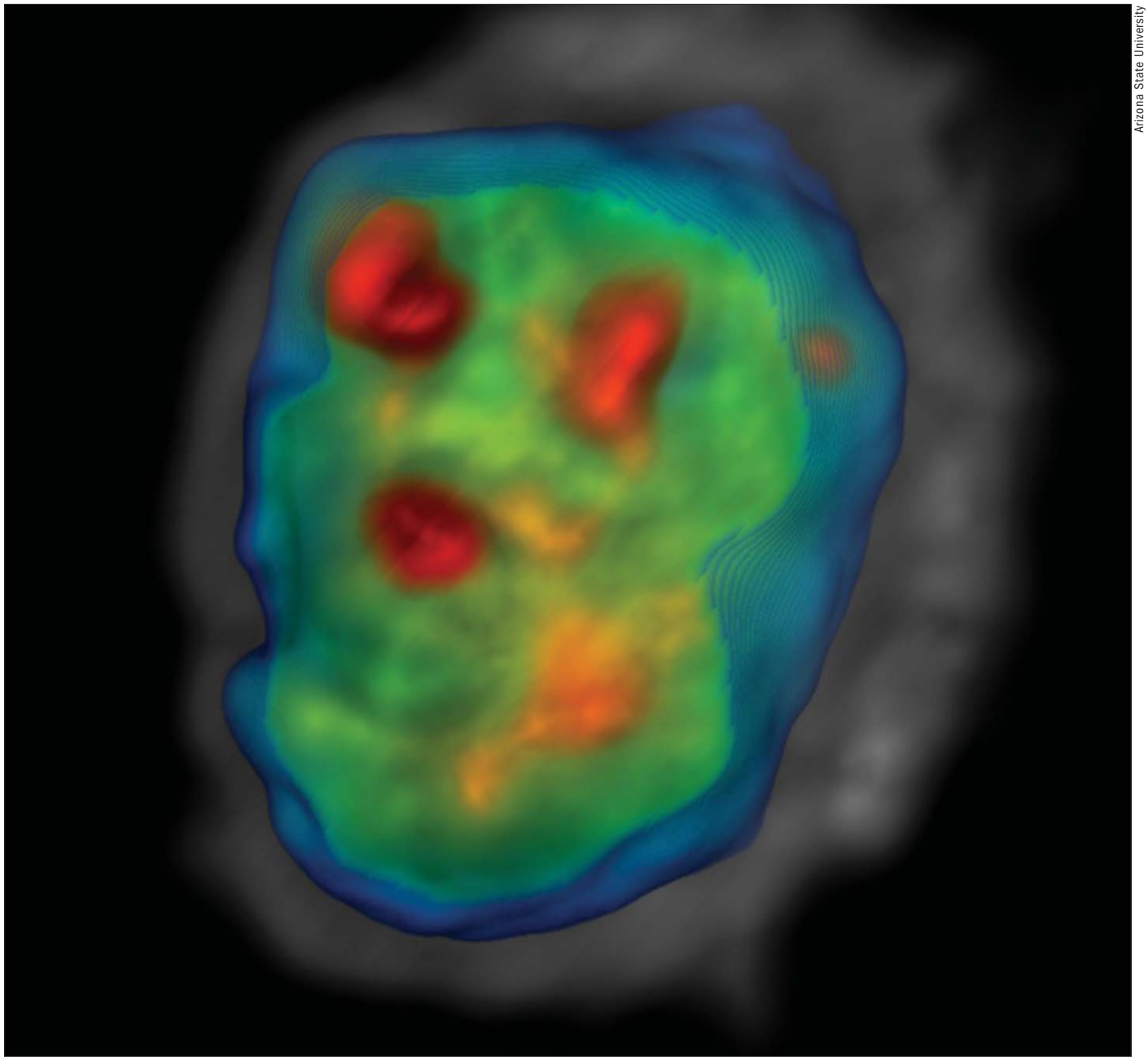
Physicists have long been at the forefront of cancer diagnosis and treatment, having pioneered the use of X-rays and radiation therapy. What is new about the NCI initiative is the conviction that physicists bring unique conceptual insights that could augment the more traditional approaches to cancer research. Thus it is not just the tools of physicists but their ideas that are now being sought. By looking at an old problem through fresh eyes it is hoped that some radically new ideas might emerge. Physicists have, of course, a good track record of successfully tackling subtle and complex problems – from particle physics to the theory of black holes. Part of this success stems from the physicist's ability to cut through a bewildering fog of details to identify key parameters and underlying principles that lead to a deep understanding of a system, as opposed to the mere ability to model it quantitatively. The question is whether this approach works for something as complicated and distinctive as a living cell or tissue.

Making sense of cells

So far there is no "theoretical biology" in the same sense as there is theoretical physics. Biologists do have a unifying principle – Darwinian evolution – but no fundamental mathematical laws with good predictive power. Nor is it clear that such laws even exist. After all, each living cell is a unique object possessing a baffling autonomy that makes the study of life both fascinating and frustrating for the physical scientist. Indeed, for a long time cells were regarded as some sort of "magic matter", animated by a mysterious vital force.

Cells eventually came to be seen as bags of complex chemicals made of ordinary atoms, albeit combined in extraordinary ways. But then, about 60 years ago, a new perspective emerged: the living cell was seen to function as an elaborate information-processing system, with a digital database in the form of DNA sequences that include the genes. Although these chemical and genetic models are crucial, there is also a third view, which regards cells as physical objects with mechanical, electrical and optical properties. Their innards contain Lilliputian pulleys, ropes, levers, conveyors, pumps, rotors and other paraphernalia familiar to the physicist and engineer that influence – and are influenced by – the overall macroscopic properties. The challenge is now to unify all three pictures – chemical, genetic and mechanistic.

To make a start on this grand quest, it is helpful to stop thinking of cancer as a disease to be cured. Some



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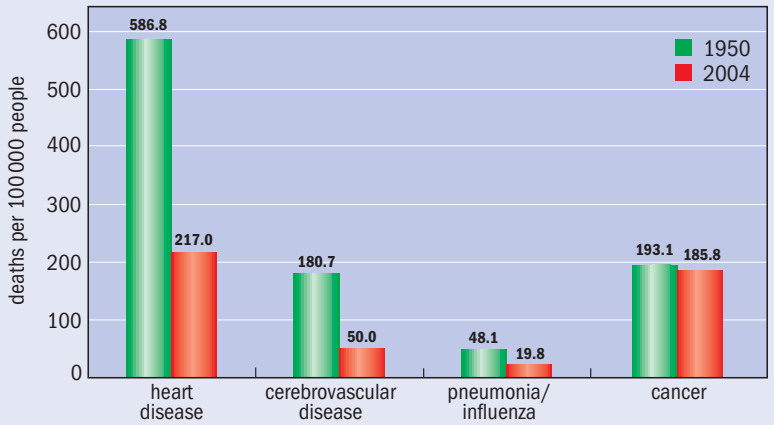
New perspectives
A 3D image of a cancer cell obtained using computerized tomography.

cancers are known to be triggered by infections, but cancer cells are not themselves "germs"; rather, they are part of one's own body, misbehaving in a manner that may produce undesirable consequences for the organism. We do not need a "cure"; rather, we need to better control and manage how cancer cells behave and, ideally, prevent cells turning malignant in the first place. It is a misconception to think that people either "have cancer" or not. Cancers usually go through a progression from mostly innocuous progenitor cells to full-blown malignancy, and at any given time most people (at least those of middle age and beyond) harbour cancer cells and even small tumours in their bodies that produce no ill effects. Cancer cells are not the invincible enemy of folklore, but recalcitrant variants of healthy cells that face their own struggle for survival against the body's immune system.

Cancer is pervasive among all organisms (not just mammals) in which adult cells proliferate. There is a simple – some may say simplistic – Darwinian explanation of cancer's insidiousness, which is based on the fact that all life on Earth was originally single-celled. Each cell had a basic imperative: replicate, replicate, replicate. However, the emergence of multicellular organisms about 550 million years ago required individual cells to co-operate by subordinating their own selfish genetic agenda to that of the organism as a whole. So when an embryo develops, identical stem cells progressively differentiate into specialized cells that differ from organ to organ – be it kidney, brain or lung.

All these cells contain the same genes, but not all of the genes are constantly active. The body has a number of chemical mechanisms to switch genes on and off, which allow cells in different organs to have different properties that can vary with time. The colon, for example, needs to rapidly replenish cells sloughed off by the passage of food, whereas the cells in other organs, such as in the brain, have a slow turnover and reproduce only

1 Still dangerous



The proportion of people dying from heart disease, cerebrovascular disease and pneumonia or influenza fell sharply in the half century between 1950 and 2004. However, the death rate from cancer has remained largely unchanged over the same period. The figures shown here relate to the US, although the story is similar in most other nations where reliable data exist. The data have been adjusted to reflect the US age profile in the year 2000. Sources: National Center for Health Statistics (NCHS) and Centers for Disease Control and Prevention (CDC) (2004 data); CDC/NCHS National Vital Statistics System (1950 data)

rarely. When and if a given type of cell reproduction occurs is critical, and is legislated by a complex regulatory network honed by natural selection. With advancing age, however, that command and control system develops flaws.

If a cell does stop responding properly to the regulatory signals, it may go on reproducing in an uncontrolled way, forming a tumour specific to the organ in which it arises. A key hallmark of cancer is that it can also grow in an organ where it does not belong; for example, a prostate-cancer cell may grow in a lymph node, or an ovarian-cancer cell in the liver. This spreading and invasion process is called "metastasis". Metastatic cells may lie dormant, like spores, for many years in foreign organs, evading the body's immune system while retaining their potency. Healthy cells, in contrast, soon die if they are transported beyond their rightful organ.

Although tumour cells struggle to obtain oxygen from the normal blood supply, in response they can switch their metabolism to a low-oxygen cycle, thereby creating acidic conditions as a by-product that can harm other cells. In some respects, the self-centred nature of cancer cells is a reversion to an ancient, pre-multicellular lifestyle. Nevertheless, cancer cells do co-operate to a certain extent. For example, tumours create their own new blood supply, a phenomenon called "angiogenesis", by co-opting the body's normal wound-healing functions. Cancer cells are therefore neither rogue "selfish cells", nor do they display the collective discipline of organisms with fully differentiated organs. They fall somewhere in between, perhaps resembling an early form of loosely organized cell colonies.

Let's get physical

Nowadays, most cancer researchers adopt a "follow-the-genes" approach, based on the notion that an accumulation of defective (mutated) or misbehaving genes are the primary cause of cancer. Humans have between 20 000 and 30 000 genes in total, but many are switched off depending on the type of cell or its stage of growth. A lot of attention has been given to finding specific "oncogenes", which, when they get switched on out of turn, initiate a cascade of physical and chemical changes that bestow malignancy. Other, "tumour-suppressor", genes, which control unlegislated cell proliferation, may also become defective or silenced, thus permitting runaway growth.

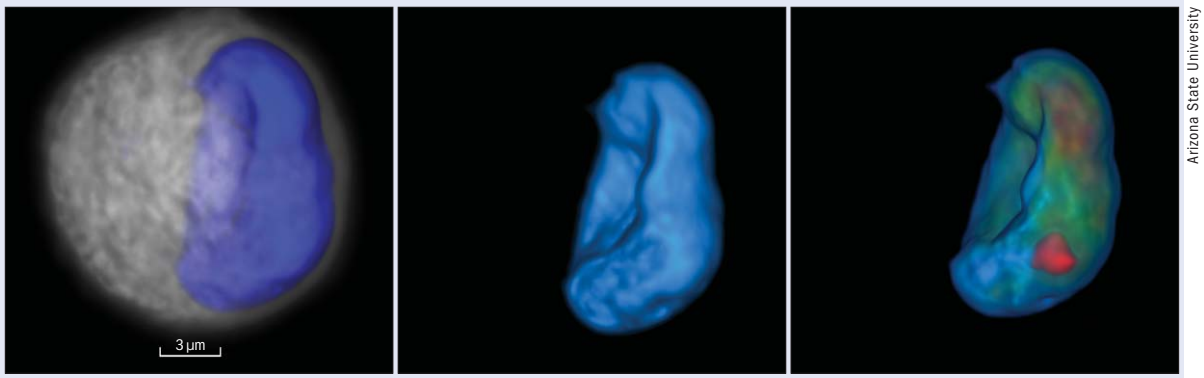
What is interesting for physicists is that whether a gene is switched on (or not) depends on a number of physical factors. For example, the nucleus of each human cell contains about 2 m of DNA, which has to be carefully packed and folded to fit inside the cell's nucleus. The DNA is enveloped in proteins to form a strand known as "chromatin", which winds round little cotton-reel-like objects made of a certain class of protein molecules called histones. This system is then further wrapped and folded. Gene switching, which involves attaching small specialized molecules such as the methyl group to strategic points on the DNA, can proceed properly only if the relevant section of chromatin is unpacked and exposed to the enzymes responsible for carrying out the attachment process.

The physical rearrangement of the chromatin is just one example of an additional level of cellular control, known as "epigenetics". The "epigenome" can be envisaged as a sort of "shadow" information network that controls much of the human genome but is very poorly understood. It works through a series of gene-switching events, whereby one gene switches on or off, triggering another switch and then another, eventually setting off a whole network or cascade of epigenetic changes. Importantly, epigenetic information is altered by the cell's environment, but it may nevertheless be heritable. And unlike genetic changes, epigenetic changes can be reversible.

As part of the new NCI-sponsored centre at Arizona State University (ASU), biophysicist Stuart Lindsay from ASU and Steve Henikoff, a geneticist at the Fred Hutchinson Cancer Research Center in Seattle, have developed a project to shed light on epigenetics. It involves studying the structure of chromatin, which behaves in many respects like an elastic string obeying basic Newtonian mechanics. The way in which chromatin moves and is packed is regulated by chemical "markers" that naturally attach themselves either to the DNA or to the histones forming the little cotton reels that spool up the DNA. The normal processes of cell operation require the chromatin to undergo dynamical changes, such as the packing and unpacking process, during which gene switching may occur. But the smooth functioning of this complicated reorganization may be compromised if a variant form of histone substitutes for the normal one. Henikoff and Lindsay hypothesize that the presence of a specific deviant histone is implicated in cancer by affecting the reorganization of the chromatin and the gene switching associated with it.

To investigate this hypothesis, the researchers plan to find out where these various chemical modifications are, how they affect the chromatin structure, and how these patterns may become modified as cancer progresses in malignancy. They will do this using an atomic force microscope (AFM) that Lindsay has adapted so that it can recognize specific molecules within the

2 Cancer markers



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These 3D images of a metastatic breast-cancer cell were produced using a new computerized tomography (CT) technique developed by researchers at Arizona State University led by Roger Johnson. The colours represent the density of chromatin (the protein-wrapped DNA found in a cell's nucleus) ranging from green (low) to red (high). The left-hand image depicts the cytoplasm (grey haze) and the surface of the cell's nucleus, the middle image shows just the nuclear membrane, while the right-hand image reveals the inside of the nucleus. The distorted, highly irregular shape of the nucleus and the coarse, clumpy distribution of chromatin may be biomarkers for an aggressive cancer. Simply put, cancer cells get bent out of shape and have distorted nuclei.

chromatin. The technique involves attaching a customized "recognition molecule" to the AFM tip so that it responds in a distinctive way when it comes into contact with a designated target molecule, such as the variant histone. By combining these chemical maps of the chromatin with nanometre-resolution images of the molecule, it should be possible to determine how chemical alterations correlate with structural changes in the chromatin as the cancer progresses. In this way, Lindsay and Henikoff hope to identify the relevant epigenetic markers that signal trouble.

Structural deformation

Alterations in chromatin packing are not the only physical manifestations of cancer. A cluster of tumour cells will also usually display gross structural changes that pathologists use for diagnosis: cells look visibly deformed and are often enlarged, with swollen and misshapen nuclei; and the chromosomes are distributed eccentrically. In an attempt to study these changes more accurately, researchers at ASU's Biodesign Institute have developed an optical computerized tomography (CT) scan for individual cells. Like its better-known brain-scan counterpart, the cell version can create 3D images of single cells held in a gel-like suspension (figure 2), which eliminates the physical distortion inherent in mounting cells on slides to produce 2D optical images.

Not only do cancer cells change shape and structure, they alter their metabolism too. To examine the link between the two, Deirdre Meldrum and Roger Johnson at ASU are using microfluidic techniques to measure the metabolic activities of cancer and healthy cells. Single cells are selected and implanted in a nutrient culture medium to keep them alive and comfortable, then sealed inside a microscopic "well" in which the rate of oxygen consumption by the cell can be monitored using micro-optical sensors. The sensors, which are deposited in the lid of the microwell, consist of polymer dots impregnated with platinum-based powders that emit light when excited by a laser pulse. The intensity of the emitted light is inversely proportional to the concentration of oxygen, which means that the sensor emits more and more light as the cell consumes oxygen. This increase in sensor-emission intensity over time can then be used to calculate how fast oxygen is consumed by the cell. The way now lies open for the use of 3D tomography to correlate morphological changes in cells with alterations in their chemical, physiological and genetic properties as a function of cancer progression.

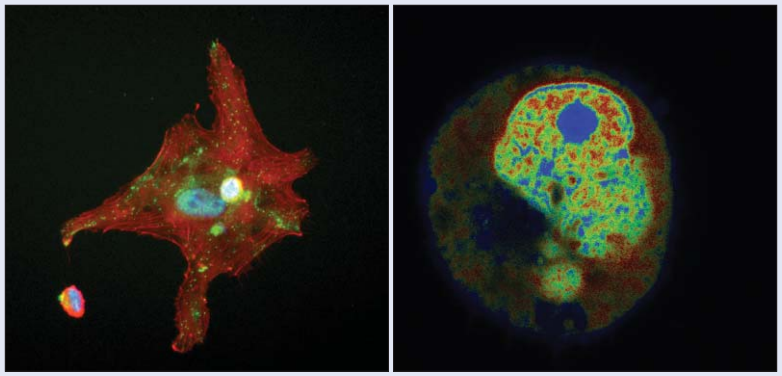
But how do the cells change physically as these structural alterations take place? We know that the architecture of a cell depends in part on a system of microtubules known as the cytoskeleton, which provides a mechanical frame that can grow and shift in response to physical and chemical signals. It has also been known for some time that cancer cells can modify their overall viscoelastic properties, generally becoming softer and more compliant. To get a better understanding of what causes these changes, ASU physicist Robert Ros has developed a technique in which a confocal microscope acts in concert with an AFM. The flexing of the cantilever to which the AFM tip is attached is used to measure the resistance of the cell's membrane to both pushing and pulling forces. By using the confocal microscope to monitor precisely where the cell's membrane is being prodded by the AFM tip, Ros's team can create a 3D elasticity map. Ros hopes to refine the technique to also explore elastic changes in the nuclei of cancer cells.

Surrounding impact

The elastic and morphological changes to cancer cells are ultimately a consequence of certain genetic and epigenetic alterations, but what is remarkable is that the opposite is also true. In other words, the physical forces acting on cells can directly affect when a gene is switched on, or, to use the jargon, "expressed". Cheryl Nickerson, who is at ASU's Biodesign Institute, has obtained dramatic evidence for this link by growing Salmonella bacteria onboard two separate space-shuttle missions in 2006 and 2008, finding unique changes in their virulence, morphology and gene expression in response to the microgravity environment. Evidently,

Physical forces acting on cells can directly affect when a gene is switched on

3 Dying cell



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The images show dying (left) and healthy (right) cancer cells obtained by staining with a fluorescent dye, which enables the internal structure of the cell to be probed. The fluorescence lifetime of the dye varies greatly with the different structures in the nucleus to which it binds.

cells can respond to tiny forces in their neighbourhood, such as pressure and sheer stresses, in a way that directly affects disease progression.

Indeed, the ability of a cell to sense its mechanical environment extends to the properties of surfaces. In other words, the way that cells grow and differentiate can depend on such things as the firmness and cohesiveness of nearby tissue, or the density of surrounding cells. Little rods known as integrins jut through the cell's membrane and act as tiny nanosensors that communicate mechanical information about the surroundings to the cell's innards and so trigger both structural and chemical changes right down to the chromatin. In effect, integrins are mechano-transducers. They can communicate in the other direction too – from inside the cell to outside. This establishes a feedback loop between a cell and its immediate environment, with each affecting the physical properties of the other.

The fact that the properties of cells are sensitive to external forces could have profound implications for cancer. It has been found, for example, that the efficacy of chemotherapy depends on the stiffness of the tissues in which the tumour is situated. When tumours start shedding cells into the bloodstream and lymphatic system, allowing the cancer to spread around the body, a secondary tumour may then develop in organs far removed from the original. The mere presence of cancer cells in the body is not in itself necessarily a danger; it is their ability to target, invade and cling to other tissues that leads to problems. This metastatic stage usually signals a serious downturn in a patient's prognosis, although it is often a mystery as to why the mere proliferation of tumours is a cause of death.

What is interesting is that the viscoelastic properties of the site of the secondary tumour play a crucial role in the tumour's progress. So if something could be done to control metastasis, either by reducing the amount by which cancer cells move or altering the physical properties of the site, the prospects for managing cancer would improve dramatically. To reach the target organs, metastatic cells – usually regarded as those shed from a tumour – face a hazardous journey, crossing various physical barriers by squeezing through small gaps and penetrating membranes. Just why these breakaway cancer cells embark on this course of action, or why they target particular remote sites, is unclear, but physics clearly plays a part.

It is important to note that the metastatic cells do not float about in isolation; rather, they reside within the extra-cellular matrix (ECM) of the host organ. The ECM is a complex mesh of proteins that fill voids between cells, and it participates in the development of both healthy and cancer cells through chemical and mechanical signalling. There is evidence that changes in the stiffness of the ECM affect the signalling and hence the progress of the cancer. In turn, it seems that the cancer cells can interact with the ECM to trigger the very physical changes that favour the tumour's development. Thus, in effect, metastatic cells create a "nest" suitable for the cancer to propagate successfully.

Towards a therapy

What everybody wants to know, of course, is how insights from physics might translate into effective therapies that can kill cancer cells (figure 3). Most existing cancer treatments involve trying to remove a tumour surgically or destroying it with radiation, coupled with chemotherapy in which a variety of drug regimes try to stymie cell division, block problematic gene pathways or retard angiogenesis. Although drug design is informed by an understanding of molecular and cell biology, it is still something of an art, dependent on long and costly clinical trials. Indeed, oncologists are often in the dark about why certain drugs actually work, or why normal dose–response relationships do not seem to apply. Cancer cells are notorious for mutating rapidly, often developing resistance to specific drugs or undergoing a resurgence years later with an acquired immunity somehow remembered. Chemotherapy can be effective at shrinking tumours and prolonging life somewhat, but it usually has unpleasant side effects and can even be counter-productive by leaving a handful of resistant cells alive with no competition to arrest their explosive spread. As a result, drugs are rarely the perfect solution.

Treatments that take into account the physics of cancer cells and tumours could, however, offer radically new approaches, especially when combined with nanotechnology. As far as the NCI initiative is concerned, it is mainly focused on pure research and is not seeking to develop new treatments, although one group at the Houston Physical Sciences-Oncology Center in Texas, led by Mauro Ferrari, is trying to get gold nanoparticles inside cancer cells to see if microwaves can literally cook the cells to death. The holy grail, for me at least, would be to discover a simple on–off switch for cancer that could be thrown by manipulating a well-understood parameter such as temperature or electrostatic potential. That dream may be naive, but a physics approach to cancer management could at least open up a new front in the war on cancer. For example, if a way could be found to "disrupt the nests" of metastatic cancer-cell clusters, such as by changing the physical properties of the ECM near the secondary tumours or by altering the surface adhesion – and perhaps even the dielectric properties – of the cancer cell's membrane, then the breakaway cell's prospects for taking up residence and proliferating would be less favourable.

4 Across disciplines

Jordan Yaron/Arizona State University

This cell computerized-tomography system is one of the physics-based techniques being used by researchers at Arizona State University to gain insights into cancer as part of a new five-year initiative funded by the US National Cancer Institute.

Calling for collaboration

These admittedly rather vague suggestions for managing cancer are clearly something of a long shot, but the 12 new Physical Science-Oncology Centers are just starting up (figure 4), and over the coming years they will work together to compare ideas and results from their experimental and theoretical investigations. The success of the initiative will depend on how well the scientists involved can form links between traditional disciplines.

A good model is provided by astrobiology, which studies the origin, evolution and distribution of life in the universe. Physicists, chemists, astronomers, earth scientists and biologists have been able to come together to tackle such problems as how life began; whether life could exist on Mars, Europa or Titan; and what range of extreme environments micro-organisms may tolerate. So far, there has been little dialogue between cancer biologists and astrobiologists, but this is set to change. Astrobiologists have a deep grasp of the nature of life and evolution, and could have much to contribute to the war on cancer. Nor is this a one-way street. I believe that cancer provides a window on the nature of life itself. Modifying something slightly to understand it is a well-established experimental procedure in science. In the case of cancer, nature is doing the experiment for us.

Some 60 years after physicists helped to initiate the molecular-biology revolution that has produced so many medical miracles, biophysics is a growing discipline worldwide. Yet in spite of the spectacular advances in understanding the cell's molecular machinery, something as widespread and pervasive as cancer remains a stubborn and growing medical problem. As the population ages, so the burden of cancer on society and on the economy is set to worsen. If physicists can bring a new perspective to bear on cancer, it could bring about major clinical progress and open up a new chapter in the science of living matter.

● cancer-insights.asu.edu