TED LEWIS III

Cancer biology still needs physicists

Considering game theory and the role of physical forces could lead to better treatments for cancer, says **Robert Austin**.

Cancer is close to surpassing heart disease as the leading cause of death in the United States. The World Health Organization estimates that worldwide, new cases will rise by 70% in the next two decades. In concert, treatment costs are skyrocketing and could reach US$156 billion by 2020 in the United States alone, according to the US National Cancer Institute (NCI). A modest decline in US cancer mortality rates has been attributed to prevention, such as lower smoking rates, rather than better treatment. Yet, more than 150,000 papers on cancer have been published each year since 2013.

This month, application deadlines closed for several programmes in the US$1.8-billion Cancer Moonshot authorized by the US Congress in 2016. The extra funds to study cancer are badly needed, but we do not have a sufficient fundamental understanding of the disease for these investments to make a near-term difference in treatment.

Comparison of the cancer initiative to former US president John F. Kennedy's lunar challenge is misleading. When, in 1961, Kennedy declared the goal of landing on the Moon, we understood gravity well enough to be reasonably confident that if we built rockets powerful enough, we could do it. We could predict distant planetary orbits with startling precision. Getting an astronaut to a nearby satellite was an engineering feat. No new basic principles needed to be discovered.

This is not true for cancer. The deepest puzzle we must solve is how groups of cells behave, which networking theories developed in the physical sciences are well equipped to address. Cancer can move from a localized tumour to remote locations — a process called metastasis. Once that happens, individuals with cancer have a poor prognosis. Metastasis drives the costs of treatment skyward, but these therapies are, tragically, largely futile. Without a better way to explain and treat metastases, new clinical methods will do little to improve the situation.

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To be sure, there has been progress. A growing appreciation of how the immune system keeps cancer in check has brought a new class of therapies. Patient-specific chemotherapy and more-precise radiotherapy have also led to advances. But cancer needs more big ideas — and those of scientists from other disciplines should be taken more seriously.

In 2008, I attended a series of workshops organized by the NCI in Bethesda, Maryland, to bring together physicists, engineers, mathematicians and computer scientists to look for new ways of tackling the disease. These led to the creation in 2009 of a dozen designated physical-sciences oncology centres; I led the Princeton Physical Sciences–Oncology Center, based in New Jersey, from 2009 to 2015.

Over that time, large cancer-genome sequencing projects revealed millions of cancer-related mutations. The numbers found in individual tumours and types of cancer range widely. Exactly what causes this variation is unclear. In any case, genetically targeted treatments generally buy affected individuals, at most, a few more months of life.

Since the centres launched, there has been greater recognition of the potential contributions of physical forces to cancer-cell responses, such as the number and location of metastases, or how cells stick together. Networking and game theories — mathematical analyses of social and economic interactions that represent how humans do or don't cooperate to minimize costs and maximize gains — have also been adapted to model how cells behave during cancer growth and invasion. Particularly promising, in my view, are theories of the evolution of multicellularity, when cells had to develop mechanisms for living in communities — possibly at the cost of their own selfish, local goals of reproduction. I argue that these approaches have not yet had time to show their potential.

The cancer community has been unenthusiastic about the contributions of physical oncologists. When, several years ago, we proposed a special section on the physics of cancer for a high-profile journal, oncology referees were dismissive. One admitted: "I am not a big fan of the topic." Another reviewer rejected the proposal because genetics "is the Rosetta Stone with respect to treatment". Wrote another: "I did not recognize any of the proposed authors."

Too often, biologists see physicists as human calculators. The big ideas, they think, belong to them, with physicists filling in the details by performing quantitative analyses. To counter this attitude, the Francis Crick Institute in London, for instance, is actively searching for physicists with transformative ideas. We need to do more than hire 'quants' to crunch 'big data'.

To develop new conceptual approaches to cancer, scientists of all stripes must reach out. I have sometimes antagonized biologists by saying that their advice stifles creativity. But I am now working, along with medical physicist Robert Jeraj of the University of Wisconsin–Madison, to form groups within the American Physical Society that focus on oncology. These scientists have strong collaborations with biomedical researchers, but have historically been restricted to advancing imaging technologies — important, but far removed from bringing in ideas about the origins and progression of disease. I also serve on the editorial board of two journals designed as outlets for this sort of work. *Convergent Science Physical Oncology* was launched in 2015, by the Institute of Physics in Bristol, UK, and *Cancer Convergence* (published by Springer Nature, which also publishes *Nature*) will publish its first articles in the next few months.

We need to expand our questions — or risk remaining Earth-bound. ■

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