The sciences converge to fight cancer

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The Physical Sciences–Oncology Centers in the US bring together scientists from all backgrounds to tackle some of the most important questions in cancer research.

There's a common notion that we have reached the end of the century of the physical sciences, and the twenty-first will be the century of the biological sciences. Instead, we believe that we are entering a time for the convergence and unity of all sciences. The merging of engineering, physics, mathematics, technology and medicine will be one of history's most fruitful unions.

The field of cancer research has expanded exponentially in the past few decades with numerous significant discoveries in molecular biology: defining the key molecular signals involved in intracellular pathways and extracellular communication with the microenvironment, for example. Additionally, the past decade has seen an explosion of data and increasing integration of different technologies such as genome sequencing and proteomic and metabolomic analysis to attain a more complete understanding of cancer. Nonetheless, the overall cancer mortality rate around the world has not decreased significantly. To help address the problems of cancer research in a transformative way, the National Cancer Institute in the US launched the Physical Sciences–Oncology Centers (PS–OC, http://opso.cancer.gov) initiative in 2009. The PS–OC programme is a virtual network of 12 research centres, each combining many academic institutions and led by a physical scientist and a cancer biologist or oncologist. The investigators in these centres conduct a variety of integrated research projects aimed at addressing important questions in cancer biology or clinical oncology. These can be broadly organized into four main topics: (1) the physical laws and principles of cancer; (2) evolution and evolutionary theory of cancer; (3) information coding, decoding, transfer and translation in cancer; and (4) de-convoluting cancer's complexity. To push the boundaries of research, the PS–OC programme also fosters new and 'out-of-the-box' thinking through pilot projects used to test and explore high-risk, high-reward ideas that, if successful, can be developed into bigger projects. Additionally, the programme encourages and explores new ideas from the broader community of physical scientists and cancer researchers through outreach projects, cross-disciplinary training and public forums.

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The PS–OC at the University of Southern California convened teams from seven academic research institutions to develop several data sources so that modellers in the group can build a 'virtual tumour'. These data sources are diverse. For example, single-cell sequencing sheds light on the 'pokability' of an individual cancer cell. When we say 'pokability', we mean exactly that: the ability to physically poke a cell with a tiny little instrument and thus obtain a potential coarse-grained view of many individual aspects of the cell, including the underlying biology of that cell and its environment. Based on this information, the plan is to model a cancer and its interactions with the host and develop new and hopefully better strategies to control it. The key to doing this is to build a multiscale model that includes the cancer cell, the tumour, the organ and the body. We can then start to play with the virtual tumour and see what happens. What if I mutated this gene? What if I changed the system here? The programme is on-going, but simple elements of the multiscale model are emerging.

The PS–OC at the Dana–Farber Cancer Institute is also multi-institutional, involving eight academic institutions and a multitude of investigators with expertise as diverse as evolutionary biology, surgery, computer science and animal modelling. The goal of this PS–OC is to advance our understanding of the physical principles that govern cancer initiation, progression, response to treatment and the emergence of resistance. The aim is to incorporate the theories of evolution with experimental approaches to better define, understand and control cancer at all levels. From an evolutionary standpoint, tumours can be viewed as collections of cells that accumulate genetic and epigenetic changes, which are then subjected to the selection pressures within a tissue. These normally heritable variations can lead to adaptations of the cells such as induction of angiogenesis, evolution of resistance or evasion of the immune system. As the evolutionary dynamics of a tumour can best be described and studied using mathematical constructs, the goal of the PS–OC is to develop mathematical and computational models of evolutionary processes arising within tumours. These mathematical models are then validated with experimental approaches and finally implemented in the clinic.

Progress is coming from all parts of the PS–OC network. In the past three years, the programme has developed new tools to examine all dimensionalities of cancer, new concepts, and new models and theories to answer some of the most challenging questions in cancer research. Investigators at the Dana–Farber PS–OC, for instance, developed a new hypothesis to explain the mechanisms

underlying the molecular evolution of tumour genome modifications. Although the identity of many of these alterations have been known for decades, it is not understood how they emerge or why they are located where they are. To shed some light on this question, the researchers performed genome-wide analyses of DNA breakpoints associated with so-called somatic copy-number alterations using several databases of different cancer types[1]. This enabled them to identify several structures and processes that could be driving factors of the generation of somatic copy-number alterations that lead to a cancerous phenotype. These findings were then further expanded by researchers at both the Dana–Farber PS–OC and the Massachusetts Institute of Technology PS–OC, who observed that the higher-order organization of genomic material, as well as the replication timing of genomic regions, determine the length distribution of somatic copy-number alterations[2–3]. These alterations lead to higher-order genome structure modifications that are now being exploited for cancer diagnosis. For example, scientists from the Northwestern University PS–OC have developed partial-wave spectroscopy, a microscopic technology that can sense the spatial distribution of macromolecular density[4]. This technology is capable of separating normal from cancerous tissues based on changes in higher-order genome organization and is currently being validated in several cancer types. These advances can make a big difference in the lives of patients if cancerous cells can be distinguished from normal cells much earlier, before large tumours develop and before they metastasize.

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Traditionally, metastasis is thought to be a late event in cancer progression. However, as demonstrated by investigators from the Johns Hopkins University PS–OC, the initiation of breast cancer metastasis in the lung takes place early on in the disease and may be initiated by changes in the mechanics of the metastatic niche[5]. Other scientists have shown that breast cancer cells are able to colonize the lung only after the arrival of bone marrow-derived cells into the metastatic sites[6] that occurs after the crosslinking of the collagen. With this knowledge, the Hopkins research team demonstrated in mice how to block the development of metastases. These findings have important therapeutic implications in that certain aspects of the mechanism of metastasis formation may be targeted for therapy.

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Another important avenue of research has been preventing the emergence of drug resistance in cancers. For many years, scientists have developed drugs that target rapidly proliferating tumour cells. However, after an initial response, the tumour usually comes back much more aggressively and is then resistant to treatment. Researchers at the Princeton University PS–OC have been studying bacterial evolution of antibiotic resistance[7]; their findings have the potential to provide insights into the evolution of chemotherapy resistance seen in cancer. Meanwhile, investigators at the Dana–Farber PS–OC have developed a physical-sciences-based approach to identify better treatment strategies for targeted drugs in non-small-cell lung cancer. These strategies are predicted to delay the emergence of resistance against these drugs[8], and are now being implemented as clinical trials in the US and Asia. This work was later extended to a collaborative study led by investigators from several PS–OCs that demonstrated how such mathematical modelling can be applied to combination-treatment strategies, forming the basis for new clinical trials[9]. Such results are an example of the strong collaborative environment of the PS–OC network aimed at supporting high-risk projects at the intersection of the physical sciences and oncology.

The PS–OCs are also researching other systems that can benefit cancer research: the development of the mouse intestinal crypt, for example. Researchers at the Massachusetts Institute of Technology PS–OC used mathematical modelling to explore the design principles that determine how the infant mouse intestine, starting from a single stem cell, develops into a mature crypt. Through the combination of this model and biological experiments, the investigators showed that stem cells use a strategy called bang-bang, which consists of rapid symmetric stem cell divisions to first establish the stem cell pool, followed by a sharp switch to asymmetric stem cell divisions[10]. This approach may be useful for uncovering similar design principles in other systems, including tumours.

As is the case in almost every research institution, physical scientists and biologists have always existed in separate schools and buildings. They think about issues in different ways and use different terms to describe the same phenomena. One of the hurdles that the PS–OC programme had to overcome was the communication barrier between these two types of researchers, as clear communication is the basis for starting collaborations, sharing knowledge, making break-through discoveries and moving the field forward. The technologies to create a coarse-grain view of cancer and the expertise to build predictive models and devise new interventions will yield perspectives that can make a difference in the cancer domain. We are obliged to think differently and act accordingly to make progress against cancer. This goal will require a convergence of several domains working together, and the PS–OC programme is a powerful start to such progress. ❐

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