Reconstructing Cancer's Universe at the Dawn of the 21st Century

SANDRA ORŠULIĆ

Associate Professor & Director
Women's Cancer Biology
Women's Cancer Program
Cedars-Sinai Medical Center
Los Angeles, CA, USA
E-mail: sorsulic@partners.org

The early 21st century was a time of renewed enthusiasm for finding a cure for cancer. There was good reason to be optimistic. High-throughput technologies were being developed at an amazing speed. For the first time in history, cancer researchers organized large international consortia and collaboration networks. It was clear that in several years, it would be possible to profile hundreds if not thousands of cancer tumor samples to determine which genes are mutated, amplified, deleted, methylated, or aberrantly transcribed in each individual cancer. It was predicted that within a decade, we would know the entire universe of every major cancer. The development of high-throughput molecular technologies was not only a transformative event for science but also for medicine. It was presumed that the molecular makeup of a tumor correlates with clinical outcome and thus can be used to predict prognosis and plan treatment approaches. Understanding the vulnerabilities of a tumor should enable physicians to not only predict which patients are likely to respond to conventional therapies but also pinpoint new therapeutic targets in resistant patients. Many physicians believed that the use of rational combinations of targeted therapies based on an understanding of the genetic alterations that drive a patient's tumor would be more effective and less toxic. They embraced the idea that "molecular oncology" would become routine in cancer care.

A decade later, we realized how naive we were. We have catalogued the genome, transcriptome, epigenome, proteome and metabolome of several common cancers, and additional information is compiled every day as new technologies emerge. Unprecedented amounts of publically available molecular data are mined by researchers around the world. The hope was that profiling a large number of cancers would reveal molecular alterations that are common to many cancers. Recurrent alterations were not only likely to be important for cancer progression but would also enable the targeting of a larger population of cancer patients with the same drug. It was at this point that revelations about the true behavior of cancer abounded.

The first surprise came with cancer gene sequence and copy number analyses. We learned that each cancer contains tens, sometimes hundreds, of genetic abnormalities, many of which form redundant signaling networks. It became clear that only combination therapies would be successful in blocking the multi-pronged pathways that drive cancer progression. Also disappointing was the discovery that very few genetic alterations were common to more than a handful of cancers. The hope for a universal cure for cancer was shattered and focus was turned to "individualized" therapy.

The exploration of patient-tailored, or individualized, therapy led to the second surprise: the discovery of extreme intratumoral heterogeneity in each patient. Most tumors consisted of multiple clones, each with different combinations of genetic alterations. It was found that molecularly targeted therapy that is effective in killing cells in one clone may not be effective in another clone. This may be the reason for frequent tumor recurrence due to chemotherapy resistance. Therapy that was initially successful in eliminating most of the tumor bulk may contribute to the evolution and expansion of tumor clones that are driven by different molecular alterations. Currently, our understanding of tumor plasticity is limited. The molecular profile data are only a snapshot in tumor evolution. By the time we interpret the data and decide upon the most rational therapeutic approach, the tumor may have a completely different profile.

The third surprise involved the efforts to map all coding RNAs, non-coding RNAs, epigenetic signatures, and post-translational modifications in each individual cancer. It was anticipated that these data would somehow make sense once they fell into place, similar to solving a 3-dimensional puzzle. However, instead of bringing clarity to the puzzle, each "ome" added a new layer of complexity. Genomic, epigenomic, proteomic, and metabolomic data formed separate galaxies of information with very little overlap. Future explorations of tumor microenvironment and microbiome are likely to document even more differences between individual cancers as well as changes within clones of the same cancer. How are we going to integrate these galaxies of data to reconstruct the comprehensive multi-dimensional universe of cancer? While the unexpectedly heterogeneous and complex nature of cancer currently stands as an obstacle to finding a cure, it is conceivable that new developments in systems biology will have the power to predict interacting pathways and identify the most vulnerable nodes that could serve as targets of intervention and platforms for making therapeutic decisions.

Indeed, there is good reason to believe that a better understanding of cancer will save lives. It has already saved the lives of many patients with chronic myelogenous leukemia (CML). Diagnosis with CML was a death sentence until 2001, when a new drug called Gleevec entered the clinic and changed the 5-year survival rate to 95%. This drug targets a specific chromosomal defect that is found in more than 90% of patients with CML. Gleevec provides a proof-of-principle that rationally designed therapies work. It is probably not a coincidence that researchers have been studying this cancer for a very long time.

The story of rational therapy design for CML began in 1960 with the discovery that cells from CML patients had a specific chromosomal rearrangement, now known as the Philadelphia chromosome. CML is a „simple" cancer dominated by a single rearrangement resulting in the fusion protein BCR-Abl, which is the sole driver of the disease. Yet, it took us 40 years to combat this cancer. It required improvements in microscopy and a better understanding of chromosomes to identify the fusion protein; a revolution in molecular biology for the functional understanding of fusion proteins and their oncogenic potential; the development of structural biology and high-throughput chemical library screens; and coordination of infrastructure between the basic researcher, clinic, industry and government. Each of these technical advancements took about a decade. Will it take 40 years to develop rational therapies for cancers that we have just started to understand at a molecular level? One thing that we have learned from experience with Gleevec is that knowledge eventually leads to life-saving therapies. The sooner we start, the closer we are to success.