Driver mutations and new cancer genes have been emerging at a steady rate over the last few years, and some of them make good targets for new drugs, such as BRAF and vemurafenib (Zelboraf; Genentech). However, a lot of the emerging cancer genes are recessive cancer genes (tumor suppressor genes), which aren’t easy to use as targets for novel cancer therapeutics because they are already inactivated.

But knowing the whole cancer landscape is what’s important. Because we’re beginning to see so many combinations of mutated cancer genes even in one type of cancer, we are seeing clearly now how heterogeneous a disease cancer really is. The implications of this heterogeneity are not completely clear, however. On the one hand, it may turn out that all these different combinations of mutated cancer genes feed into the same biologic pathways, making the number of biologic states in cancer cells much smaller and potentially making it easier to target them. On the other hand, these different combinations of mutated cancer genes may cause so much biologic diversity that we begin to understand why cancers have such heterogeneous responses to therapy.

If we had wanted to create cancer in a way that we could treat, this is not how we would’ve designed it.

**What are the major challenges that we now face in sequencing cancers?**

Around the world in the International Cancer Genome Consortium, which includes The Cancer Genome Atlas in the United States, we have to build up really large sample collections—ultimately tens of thousands of samples—that we can use in sequencing experiments.

Building on this, we have to deliver a “legacy product” that cancer researchers will mine for decades to come. For that, we need whole-genome sequencing of tens of thousands of human cancers. The genome is finite. We can explore everything, and that’s what we should do.

We should do it to high-enough coverage so that we find most of the mutations in each of these tens of thousands of cancer samples, and we should complement these data as much as possible with expression data and with epigenetic data, particularly methylation data. Of course, all sorts of levels of information could be added—from proteomics and so on. But practically speaking, in this first phase of large-scale cancer genomics, that’s what we can deliver and, in my opinion, it will transform our perception of the disease.

PhD students entering the field in future years will wonder how cancer researchers ever tried to understand and treat this disease when we had so little understanding of the diversity of the biologic abnormalities that drive it. “Know your enemy” is a robust maxim, and our burgeoning insights into the cancer genome are dramatically improving our understanding of the foe!
Q&A: Michael Stratton on What’s Next in Sequence

Cancer Discovery 2011;1:460.

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