Counterpoint: Data first

Large, unbiased genomic surveys are taking cancer therapeutics in directions that could never have been predicted by traditional molecular biology, says **Todd Golub**.

Despite decades of research, cancer-related death and suffering remains a massive public-health problem, with half a million deaths each year in the United States alone. Yet cancer researchers feel a growing optimism. This stems from a spate of observations that drugs targeted at the molecular 'drivers' of cancer can have dramatic benefits for patients with particular genetic mutations. These discoveries are being fuelled by genomics-based screening technologies, which are providing a powerful new source of leads about cancer development.

This large-scale, data-harvesting approach to biological research has significant advantages over conventional, experimental methods. Take the case of imatinib (Glivec), perhaps the most famous genome-inspired drug, which is now the standard treatment for chronic myeloid leukaemia (CML). CML was previously curable only with bone-marrow transplantation, a toxic, highly invasive treatment. Imatinib, taken as a simple pill with few side effects, has almost doubled five-year survival rates to 90%.

The story begins in the 1960s, when microscopic examination of chromosomes of CML patients revealed a recurring genetic abnormality, shown to be a merging of part of chromosome 9 with part of chromosome 22. This causes the *BCR* gene on chromosome 22 to fuse with the *ABL* gene on chromosome 9, resulting in the permanent activation of the ABL kinase enzyme.

This breakthrough was followed by decades of conventional hypothesis-driven cancer biology, which led to a more complete understanding of the consequences of ABL kinase activation and, in the 1990s, the design of imatinib to inhibit the enzyme. Yet the key discovery, the *BCR/ABL* fusion, came from genetic epidemiology — from the belief that the best way to find the drivers of cancer was to compare the genomes of tumour cells to normal cells. Today, cancer genomics benefits from advanced, high-resolution tools that, as they improve, will enable the sequencing of an entire human genome in a matter of days for thousands rather than millions of dollars, but the power of genome analysis has been known for some 50 years.

Pattern recognition

Recently, there has been a flurry of similarly encouraging stories. In many cases, these began with large-scale efforts to uncover the genes that are frequently mutated in tumours and moved rapidly to testing drugs that target the mutated proteins — often without extensive understanding of the underlying biology. Several of these have led to effective treatments, including drugs that target gastrointestinal tumours, lung cancers and melanomas. Drug resistance is common and there is much to be worked out. But cancer research is finally on a path towards effective treatments.

It is no coincidence that these clinical successes come during a period of explosive technological development in DNA sequencing, paving the way for thousands of tumour genomes over the next few years. This genetic roadmap will be a guide to discovering cancer drugs at, I hope, an unprecedented pace.

It will also send cancer researchers in unanticipated directions. Recently, for example, mutations in the isocitrate dehydrogenase metabolic enzyme, not previously thought to be important in cancer, were discovered in the brain tumour glioblastoma. Within a year, researchers in labs around the world had used DNA sequencing to establish the frequency of these mutations across other tumour types, along with their functional consequence, opening the way for the development of new therapies.

Despite this promise, it is reasonable to wonder whether the onslaught of cancer genome data will clarify or complicate our understanding of cancer biology. Comparing the genomes of any two tumours reveals significant genetic complexity, yet comparing hundreds of genomes will reveal biologically important patterns. Such efforts are already showing that although a huge variety of genetic abnormalities can cause tumours, mutant proteins make their effects felt through a much smaller number of biological mechanisms. Without comprehensive cancer genome data sets it will be difficult to distinguish signal from noise. Although hypothesis-driven, experimental research should remain central to the field, unbiased surveys of cancer genomes afford an unprecedented opportunity to generate new ideas.

There are some big challenges ahead. For example, the recently developed targeted cancer therapies focus primarily on a small slice of the root causes: the kinases. Genetic aberrations in cancer are not limited to kinases, but include classes of proteins such as transcription factors that are traditionally considered 'undruggable' as researchers have been unable to find ways of targeting them. The battle to decipher the molecular basis of cancer will surely be won over the decade ahead, but without the chemical tools to correct the cellular processes triggered by genetic abnormalities, it will be a hollow victory. To make the most of genomic approaches to cancer, the research community must be as innovative and systematic about finding these chemical tools as it has been about uncovering the genetics. ■

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