Peter Keating and Alberto Cambrosio, "21st Century Oncology: A Tangled Web." *Lancet* 382 (December 14, 2013), e45-e46

21st-century oncology: a tangled web

Researchers and clinicians in the field of oncology have now entered the second decade of targeted therapy, widely held to be a revolutionary new form of cancer therapy research. The present era is regarded as the end of brute empiricism: as laboratory researchers slowly unravel the mechanisms of oncogenes and their protein products, and as small molecules and antibodies target specific cell-surface and intracellular receptors, therapeutic research is now seen as a direct application of laboratory knowledge in the clinic. The poster child for this revolution has been the astonishing success of imatinibtyrosine kinase (TK), in chronic myelogenous leukemia (CML). In this essay we revisit the imatinib story to show that, despite substantial progress in the understanding of cancer, therapeutic research more closely resembles a tangled web than a deductive chain leading from the laboratory to the clinic.

To begin with, much has been said about how the longstanding molecular knowledge of the cause of CML provided a rational background for the successful search for imatinib, developed by Novartis in collaboration with US oncologist Brian Druker. Indeed, the translocation that produces the BCR-ABL fusion gene had been described at the beginning of the 1960s and its ubiquity in cases of CML was well known by the mid-1970s. The protein product of the gene fusion and its ability to cause cancer *in vitro* was established by the late 1980s. An *in vivo* demonstration of the direct role of the protein in the production of CML followed shortly thereafter at the beginning of the 1990s, when Nobel prize-winner David Baltimore reproduced CML in an animal model of the disease by transfecting mice with a gene for the defective enzyme. And yet, this deep understanding of the molecular mechanisms of CML did not by itself provoke a search for a means to block the enzyme even though some researchers clearly saw the need.

Throughout the 1980s, multinational pharmaceutical companies maintained a comparatively low profile in the field of cancer therapeutics. The few companies in the field struggled to keep research programs afloat. At the start of the 1980s, Novartis' precursor, Ciba-Geigy, shut down its cancer research unit. By the mid-1980s, however, with the first wave of partnerships with biotechnology start-up companies, a number of programs, including one at Ciba-Geigy, searching for compounds to block TKs began to emerge. In 1988, researchers from Ciba-Geigy, led by John Lydon, traveled to Boston to meet researchers at the Dana-Farber Cancer Institute. There, they encountered Brian Druker, who worked on CML as a post-doctoral fellow in oncology. The Ciba-Geigy group had originally sought to learn a technique developed by Druker to measure TK activity in cells, but Druker convinced them that CML would be an interesting target for a TK blocker. Although they added CML as a target to their screening panel, their interest in the disease was secondary-- the primary target was another enzyme (protein kinase C or PK-C) implicated in heart disease. It was only after a compound for this target had been isolated and during the optimisation phase of the PK-C inhibitor in 1993 that they

noticed, unexpectedly, that the compound that would become imatinib blocked the BCR-ABL enzyme. Retrospectively rational, the observation was itself empirical.

In the meantime, however, Druker had lost contact with Ciba-Geigy but renewed his collaboration in 1993 when he accepted a position with the University of Oregon and renewed his collaboration with the Swiss multinational. Shortly after receiving a batch of compounds containing imatinib, Druker made the crucial observations that showed the compound to be effective against CML. Despite knowing that imatinib targeted a specific TK, the initial trial organized by Druker was more than a test of the drug. However much had been already learned, there were still significant unknowns. The crystal structures of protein kinases, for example, had been available since 1991 and had suggested that a compound blocking one kinase would block many others. In fact, the reason why imatinib worked did not become clear until after the trial in 2000 when the X-ray structure of imatinib binding with the kinase was published, showing that the TKs have very different structures depending on whether or not they are in an active or inactive mode. In the turned-off mode, they have remarkably different sites. Imatinib, it turned out, binds the inactive structure; hence its remarkable selectivity and the experimental nature of the trial.

Indeed, lacking exact knowledge of the mechanism of the drug's action, the initial Phase I trial was also a clinical experiment, and patient selection clearly expressed this orientation. Had this been a normal Phase I trial, the researchers would have chosen patients in the terminal phase of disease or, in other words, those who would most likely not have benefited from the treatment. Hoping to show some curative effect, however, the trial organizers selected 83 chronic-stage CML patients who had failed standard therapy but who were nonetheless healthy enough so that any positive effects would not be clouded over by end-stage complications. In the end, the trial produced unprecedented results: patients experienced remarkable recoveries, and imatinib was hailed, on the cover of *Time* magazine, as the long sought-after magic bullet for cancer.

Then something equally as unusual happened: imatinib encountered gastrointestinal stromal tumours (GIST). Imatinib emerged from this intersection as a truly targeted therapy. In the late 1990s researchers had shown that GIST tumour cells harbored an oncogene known as c-kit, which coded for yet another tyrosine kinase. As shown by *in vitro* tests in 1999, imatinib not only blocked this enzyme but also the growth of GIST cells. As imatinib moved into Phase II and Phase III CML trials, patients suffering from GIST and their organizations closely followed the quickly paced events. In March of 2000, an international team led by George Demetri at the Harvard Medical School tested the drug on a single patient. Obtaining a favorable result, they initiated a Phase II trial with 147 patients in July of the same year. Results published in 2002 demonstrated a sustained response in over half the patients.

The dates here are important because they show the uncommon speed with which the events transpired. A novel oncogene discovered in 1998 in an untreatable disease had found a treatment a mere 4 years later. The fact that a known substance could be taken off-the-shelf, so to speak, and used almost immediately in a clinically unrelated context

gave new meaning to the notion of "targeted". More than a few clinicians have since referred to the use of imatinib against GIST, rather than CML, as the true beginning of targeted therapy. And indeed, the GIST success story has sparked the frantic search for drugs targeting specific molecular pathways in other, more common types of cancer, which characterises today's oncology. Thus, while the story of imatinib in the case of CML qualifies as one of a drug looking for a disease, GIST was a case of a disease looking for (and finding) a drug in a direct way, based on the knowledge of the molecular anomalies characterising the disorder. Yet, imatinib is not quite the magic bullet that it first appeared to be: in spite of its unprecedented efficacy, some patients can cease to respond, and this has led clinicians to search for new compounds to overcome therapeutic resistance. Moreover, targeted therapies in other kinds of cancer, while promising, have so far not been able to obtain imatinib's path-breaking results.

What lessons about the nature and dynamics of clinical research in the targeted era can we learn from the imatinib story? First, we suggest that the vagaries of the empirical world continue to bedevil clinical cancer research. Lacking exact knowledge of the mechanism of the drug's action, the initial Phase I trial of imatinib against CML was also a clinical experiment. Even with the TK inhibitors in hand, at the time many leading researchers concluded that there was no compelling reason to think that blocking the BCR-ABL enzyme would work. The chromosomal translocation and its oncogene product could be viewed as simply the initiating events, and, once underway, cancer cells may no longer need the oncogene to continue proliferation. Cancer treatment would, as in the past, require a multi-drug cocktail to combat the downstream lesions. The astounding efficacy of imatinib against CML was thus an unexpected experimental result.

Imatinib acted as both a therapy and as a tool for understanding the mechanisms of the disease, since it was subsequently used to dissect the molecular pathways involved in both CML and GIST. Indeed, the study of resistance to targeted therapy set research on a new course. Before the targeted era, the study of resistance largely amounted to the search for a single mechanism to account for resistance across cancers and had to a great extent settled on the study of drug pumps that flush toxic substances out of cells. The study of the development of resistance to imatinib in CML uncovered a number of heretofore-unknown mutations in the BCR-ABL fusion gene and led to the development of new drugs targeting these mutant forms.

Therapeutic progress is now more than ever directly related to progress in knowledge of cancer pathogenesis and progression, a state of affairs that is captured by the term "translational research". In a sense, rather than therapy's failure, resistance to chemotherapy in the targeted era casts a shadow that outlines future research by pointing the way to new pathways and new mechanisms of cancer pathology. But, far from a neat downstream path from laboratory results to the clinic, translational research resembles a busy, tangled intersection characterised by multiple, reciprocal exchanges between a diverse community of biomedical actors. The mechanical or engineering-like application of preclinical knowledge has yet to chase out the empirical, as clinical research continues to generate important, unexpected questions and results. In this regard, we suggest that

clinical research on targeted therapies can in some respects be regarded as a clinical experiment rather than merely a test of therapy.