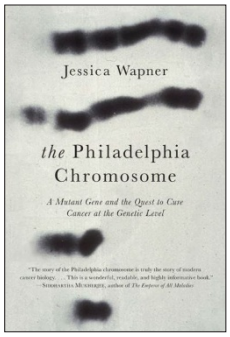
Getting personal with cancer



The Philadelphia Chromosome: A Mutant Gene and the Quest to Cure Cancer at the Genetic Level

Jessica Wapner

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Reviewed by Neil P Shah

The successful treatment of chronic myeloid leukemia (CML) with small-molecule tyrosine kinase inhibitors (TKIs) is a triumph of modern medical science. TKIs have transformed what was a fatal condition to one that can usually be chronically managed. Although the extent to which TKIs are improving the survival of patients with CML cannot be definitively known given their recent availability, it is projected that the majority of patients with CML today will not die from their disease. In *The Philadelphia Chromosome*, Jessica Wapner admirably attempts to condense the salient scientific and clinical studies that occurred over a 50-year period into 271 pages through extensive research and interviews with many of the people involved in the research that culminated in the first clinical trial of the TKI imatinib (Gleevec; formerly known as STI-571) in patients with CML.

Wapner endeavors to explain a complex story, rife with technical intricacies, to a lay audience, and she largely succeeds. She painstakingly traces the combination of careful observation, scientific curiosity, perseverance and, to a certain extent, luck, that ultimately led to the successful translation of a compelling preclinical idea to an exciting new era in cancer treatment. She takes us from the original identification of the Philadelphia chromosome in nearly all patients with CML in 1960 to an understanding of the genes involved in the disease. She explains the molecular impact of the chromosome rearrangement on the enzymatic activity of the CML-specific tyrosine kinase BCR-ABL and preclinical models that confirmed that BCR-ABL is sufficient to cause a CML-like state. She astutely recognizes that scientific discovery frequently results from the convergence of parallel threads, and, in the case of the Philadelphia chromosome, she poetically likens the culmination of this process to a "scientific masterpiece" painted over 25 years by many scientists without any awareness of what others were painting or what the final product may be.

The pioneering efforts of Brian Druker of Oregon Health Sciences University and Nick Lydon, who was employed at Ciba-Geigy Pharmaceuticals, to develop and test a selective BCR-ABL inhibitor preclinically and ultimately in patients with CML are described in detail. A substantial portion of the book is devoted to explaining the many obstacles they faced and ultimately circumvented. She details the lack of enthusiasm, primarily driven by financial concerns, of several people within Novartis Pharmaceuticals, the conglomerate that arose when Ciba-Geigy was absorbed as part of a merger, for the development of imatinib; she contrasts this with the tireless efforts of Druker and others, including some individuals at Novartis, to give the TKI a chance to demonstrate its safety and efficacy. The preclinical toxicity studies that raised false concerns and triggered lengthy but ultimately reassuring toxicity studies, as well as problems with procuring an adequate supply of STI-571, led to frustrating delays in launching clinical trials. In light of this fact, many patients with CML must have missed out on TKI therapy and lost their battle with the disease as a consequence.

The crucial role of the physician-scientist in driving translation from bench to bedside and back is clear in *The Philadelphia Chromosome*. But the book describes a medical and scientific world that contrasts with that of today. The lay public seems considerably less engaged today in understanding and supporting cancer research than in decades past. Lifetime government research grants, such as that given to Peter Nowell, the astute physician who first noted the Philadelphia chromosome abnormality in the leukemia cells of patients with CML, are now nonexistent. A very high proportion of grant applications for cancer research are not funded. It is increasingly difficult for academicians to collaborate effectively with the pharmaceutical industry. Shrinking resources for conducting laboratory research, coupled with the ever-increasing documentation required for clinical trial research, threaten the feasibility of a physician-scientist career like never before.

From my perspective as a physician-scientist who has been immersed in the Philadelphia chromosome story for much of the past quarter-century, I found the book to be quite illuminating. The book does contain a few glaring scientific inaccuracies, such as the author's statement that drug-resistant mutations in BCR-ABL change the structure of cells, result in a cellular component becoming totally foreign and provide an explanation for why some patients never respond to imatinib, and on occasion delves unnecessarily into the personal matters of some of the profiled individuals. Nevertheless, I would enthusiastically recommend it to the lay public, people living with cancer and cancer researchers.

The Philadelphia Chromosome traces a momentous period in history, from the time when cancer was suspected to be largely the result of infectious agents, through Richard Nixon's signing of the National Cancer Act of 1971, to today, when tumor genomes can be sequenced in days at low cost. Although technologic advances have accelerated the pace of medical progress, cancer's enormous complexity at the molecular level, and the ease with which cancer cells can adapt and render even rationally designed therapeutics ineffective, are all too clear now. The book therefore evokes some wistfulness as it alludes to the naive hope that many of us used to have: that our understanding of CML might be widely applicable to other cancers. Nonetheless, the story of the Philadelphia chromosome—the scientific creativity and dedication it celebrates and the medical scientific triumph it represents—is one that deserves to be cherished for eternity.

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COMPETING FINANCIAL INTERESTS
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