

Inner Workings: Tyrosine kinases, their discovery and impact

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While working in his laboratory at the Salk Institute in 1979, Tony Hunter took a shortcut. Hunter decided not to make up fresh buffer for his electrophoresis run. That decision would alter his career, significantly influence the field of cancer biology, and ultimately lead to new cancer treatments.

Hunter was studying Rous sarcoma virus, the first known cancer-causing virus, reported in 1911 by Peyton Rous, who showed it caused cancer in chickens. Rous's discovery, which earned him the Nobel Prize in 1966, would eventually spur the search for other cancer-causing viruses, provide cancer researchers a way to study cancer at a molecular level, and lead to the discovery of the first oncogenes (1).

Hunter wanted to understand the enzyme responsible for triggering tumor growth by the virus, which had already been identified

as a protein kinase: an enzyme that adds a phosphate to another protein (2). The buffer's pH had fallen slightly as it sat on the bench, which caused two amino acids—phosphothreonine and phosphotyrosine—to separate from each other on the electrophoresis plate, when normally they would have run together. This separation revealed that the target for the cancer-causing protein kinase was tyrosine.

It was the first report of a tyrosine kinase (3), a class of proteins that would prove to be crucial in cell signaling. Hunter and his colleague, Bartholomew Sefton, had expected to find a serine or threonine kinase, which had been identified previously. Instead, it was tyrosine. "It was a big deal because it wasn't what everyone expected," says cancer biologist Owen Witte of the University of California, Los Angeles.

At the same time, Witte and his colleagues reported that the cancer-causing Abelson virus, which acts in mice, worked via another protein that added a phosphorous to tyrosine. But, this occurred through self-phosphorylation (4).

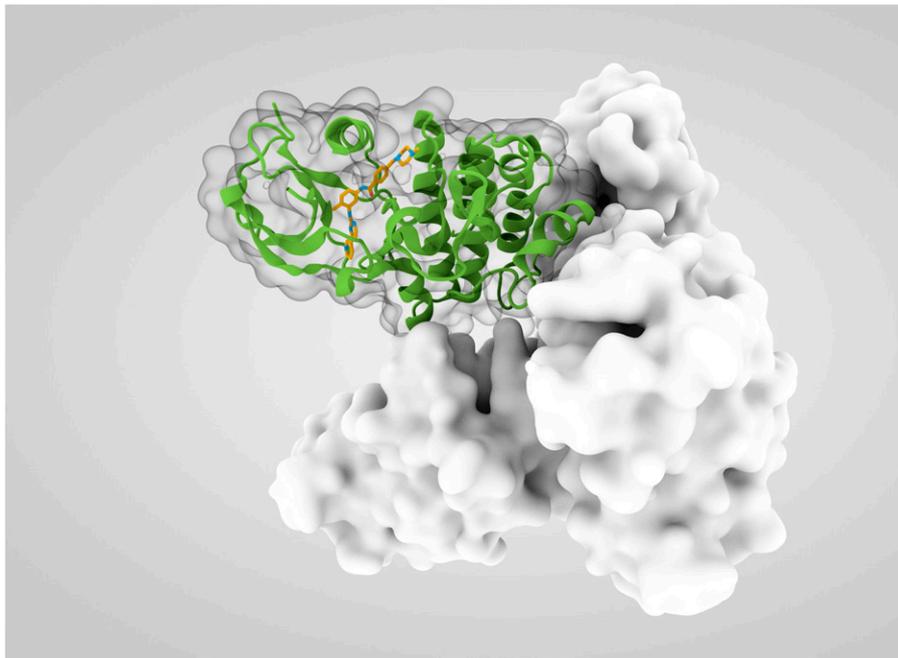
Tyrosine kinases act as a signal relay that control many cellular pathways, including cell growth. When the kinases become mutated in cancer, cell division spirals out of control. This understanding ultimately led to the development of a whole new class of cancer drugs known as tyrosine kinase inhibitors.

"People immediately realized that many kinases may be tyrosine kinases," says Stanley Lipkowitz of the National Cancer Institute. Researchers began looking for other tyrosine kinases, and they found them everywhere: in other types of cancer and in central cell-signaling pathways unrelated to cancer. A flurry of papers came out within just a few months of the first report.

"It went from an interesting curiosity of a mouse virus and a chicken virus, to 'every mammalian cell has this activity,'" Witte says. As researchers continued to look for tyrosine kinases in subsequent years, they found that not only mammalian cells, but nearly all eukaryotes, aside from yeast, use tyrosine kinases as part of their cellular signaling machinery, he says.

Knowing that tyrosine kinases could be oncogenes suggested they were possible cancer treatment targets. But studies of the human genome revealed 500 protein kinases, and many researchers initially feared it would be impossible to inhibit the activity of an oncogenic tyrosine kinase without inhibiting all of them, says Brian Druker, an oncologist and the director of the Knight Cancer Institute at Oregon Health & Science University. "There wasn't a huge amount of enthusiasm, and companies weren't jumping in to develop kinase inhibitors," Druker says.

Nevertheless, work by Druker and the pharmaceutical company Ciba-Geigy, now Novartis, ultimately led to the Food and Drug Administration approval of imatinib, popularly known as Gleevec, in 2001. The first tyrosine kinase inhibitor, Gleevec effectively treats chronic myelogenous leukemia and several other cancers driven by activated tyrosine kinases. Before Gleevec, roughly half



The discovery of tyrosine kinases paved the way for the cancer drug Gleevec. Here a human Abl tyrosine kinase domain is depicted in complex with Gleevec. Image courtesy of Shutterstock/bitsite.

of chronic myelogenous leukemia patients lived five years, Druker notes. Now 90% do.

“It really stops that kind of leukemia in its tracks,” says Witte. “In the early phase of the disease, it’s as close to a cure as you’re going to imagine.”

Gleevec was the first, but now more than 20 approved cancer drugs are tyrosine kinase inhibitors, Hunter says. Even more are in clinical trials, not only for cancer, but for autoimmune disorders and other illnesses.

“We’re going to learn so much more about the role of kinases in various diseases over the next 10 to 20 years, and this will lead to the development of specific inhibitors to treat those diseases,” says

Druker. Cancers also can become resistant to tyrosine kinase inhibitors over time. “We need to stay a step ahead of [cancer],” he adds. “We need multiple generations of inhibitors.”

1 Weiss RA, Vogt PK (2011) 100 years of Rous sarcoma virus. *J Exp Med* 208(12):2351–2355.

2 Collett MS, Erikson RL (1978) Protein kinase activity associated with the avian sarcoma virus src gene product. *Proc Natl Acad Sci USA* 75(4):2021–2024.

3 Hunter T, Sefton BM (1980) Transforming gene product of Rous sarcoma virus phosphorylates tyrosine. *Proc Natl Acad Sci USA* 77(3):1311–1315.

4 Witte ON, Dasgupta A, Baltimore D (1980) Abelson murine leukaemia virus protein is phosphorylated in vitro to form phosphotyrosine. *Nature* 283(5750):826–831.