JAPAN P

"Healthcare and Medical Technology" field

Achievement : Development of a new therapeutic drug targeting cancer-specific molecules

Dr. Janet D. Rowley

Born : April 5, 1925 (Age 86)

Blum-Riese Distinguished Service Professor of Medicine, Molecular Genetics & Cell Biology and Human Genetics, The University of Chicago

Dr. Brian J. Druker

Born : April 30, 1955 (Age 56)

Professor and Director of OHSU Knight Cancer Institute, Oregon Health & Science University

Dr. Nicholas B. Lydon

Born : February 27, 1957 (Age 54)

Founder and Director, Blueprint Medicines

Summary

Chronic myelogenous leukemia (CML) is a disease which is caused when a hematopoietic stem cell in the bone marrow turns cancerous. In 2001, with the introduction of the molecularly targeted drug imatinib, treatment results dramatically improved. The origin of imatinib began in 1973 when Dr. Janet Rowley discovered that chromosomes 9 and 22 were recombined in the white blood cells of patients with CML. Dr. Brian Druker and Dr. Nicholas Lydon succeeded in developing a drug which suppressed the activity of the BCR-ABL protein which occurs as a result of the chromosomal recombination. At present, molecularly targeted drugs are indispensable to the treatment of cancer and autoimmune diseases, and the results obtained from the studies of Dr. Rowley, Dr. Druker and Dr. Lydon underscored the importance of developing molecularly targeted drugs, providing a guiding post for future research.

Understanding the molecular mechanism that triggers chronic myelogenous leukemia

Decoding of the human genome in 2003 and rapid improvements in technologies for genetic analyses have led to high expectations for the medical applications of these technologies. In cancer research, many of the genetic abnormalities that cause cancer have been discovered and many drugs targeting these molecular abnormalities are being introduced.

The forerunner of molecularly targeted drugs is imatinib for CML. The research leading to the development of imatinib goes back to the 1960's and 70's when gene analysis technologies as we know them today, had not been introduced. The first breakthrough was the detection of an abnormal chromosome, the Philadelphia chromosome, in the white blood cells of patients with CML.

Around that time, Dr. Janet Rowley had received a doctorate from the University of Chicago School of Medicine and was leading a fruitful life as a doctor, medical researcher and a mother. In 1962, she studied in the U.K. for 1 year as a researcher dispatched from the NIH (U.S. National Institutes of Health) where she learned methods to distinguish healthy chromosomes from abnormal ones.

After returning home, Dr. Rowley continued her research in the Department of Hematology at her alma mater. One of the subjects she worked on was the Philadelphia chromosome. By using quinacrine fluorescence and Giemsa staining of chromosomes, the leading-edge research methods of the time, Dr. Rowley clarified the chromosomal mechanisms that created the Philadelphia chromosome. A human cell nucleus has 22 sets of autosomal chromosomes and 1 set of sex chromosomes, but in patients with CML, chromosomes 9 and 22 recombine (reciprocal translocation), causing the Philadelphia chromosome to be formed.

Dr. Rowley's research had an enormous impact on the understanding of the chromosome abnormalities that cause cancer. Dr. Rowley also made the connection between acute myelogenous leukemia and the reciprocal translocation of human chromosomes 8 and 21.

Aiming to develop side effect-free anticancer drugs that target specific genes

Dr. Rowley's studies, carried out in the 1970's, opened the way for the development of an effective therapy for CML. Discoveries from several international research groups led to the recognition that the reciprocal translocation between chromosomes 9 and 22 caused the *ABL* gene found on chromosome 9 to be combined with the *BCR* gene on chromosome 22. This abnormal fusion gene, *BCR-ABL*, produces a protein with elevated tyrosine kinase activity that causes CML.

Tyrosine kinases are essential enzymes that regulate various cellular functions, including cell differentiation, proliferation and immune reactions. Thus, in the early 1980's, many oncologists began to think that "tyrosine kinases which had gone out of control could cause cells to turn cancerous." Dr. Brian Druker who was beginning his career as an oncologist at the Dana-Farber Cancer Institute in Boston, U.S., was one of them.

Dr. Druker who focused his research on CML, embarked on finding a drug to inhibit the action of the BCR-ABL protein, and established a collaboration with Dr. Nicholas Lydon of Ciba-Geigy. At the time, most anticancer drugs killed the tumor, but also damaged normal cells. Both Dr. Druker and Dr. Lydon agreed that by inhibiting the action of the BCR-ABL protein, which only CML patients have, they could develop an effective drug with minimal side effects. It heralded a new drug development technique in which a drug specifically targets a causative molecular abnormality in cancer.

However, there were many issues. In the human body, there are more than 90 tyrosine kinases. If several tyrosine kinases were inhibited, there was a possibility that serious side effects would be seen. In 1986, Dr. Lydon working at the pharmaceutical company Ciba-Geigy (now Novartis Pharma) established a program to identify compounds that could inhibit the enzymatic activity of tyrosine kinases using a reagent provided by Dr. Druker from his research on tyrosine kinases. Dr. Lydon's group made good progress and in 1993, after Dr. Druker had established his own laboratory, they began a collaboration aimed at determining the clinical application of compounds discovered by Dr. Lydon and his research team. In 1996, Dr. Druker and Dr. Lydon published an article about a new compound, imatinib that killed cultured cells containing the *BCR-ABL* gene without affecting normal cells.

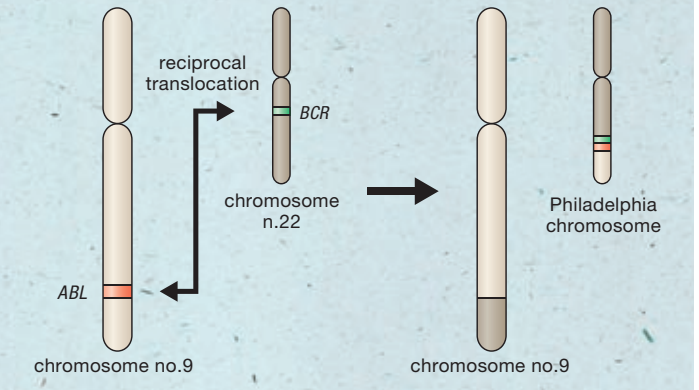
Progress in molecularly targeted drugs opens the way for the treatment of intractable diseases

The article published by Dr. Druker and Dr. Lydon immediately attracted the attention of oncologists. In 1998, Novartis Pharma began clinical trials with imatinib with Dr. Druker serving as the principal investigator. The trials verified that imatinib inhibits the action of the BCR-ABL protein and by doing so led to dramatic improvements in the survival of patients with CML. The remarkable effectiveness and safety of the drug for patients with CML led to regulatory approval of imatinib (trade name Glivec) in the US and Japan in May 2001 and November 2001, respectively.

The molecular mechanism of action of imatinib has also been made clear. Tyrosine kinases are activated when they receive an external stimulus. This leads to binding of ATP (adenosine 3 phosphate), which allows the activated tyrosine kinase to send a proliferation signal to the cell nucleus. In contrast, the BCR-ABL protein is constantly activated, binding ATP, causing the cells to proliferate in a deregulated way (resulting in cancer). By binding to the ATP binding site of the BCR-ABL protein, imatinib prevents ATP from being bound to and activating the BCR-ABL protein. As a result, a cell proliferation signal is not transmitted, enabling the proliferation of CML cells to be inhibited.

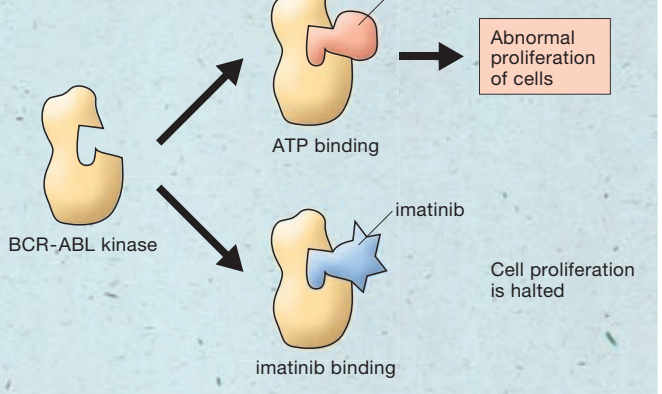
CML is a disease which occurs in 40,000 people worldwide per year. Historically, if the disease reached the blastic phase, there was no effective treatment. Owing to the introduction of imatinib, resulting from the studies of Dr. Rowley, Dr. Druker and Dr. Lydon, the blastic phase can largely be avoided and CML has been converted to a manageable condition. Their work has allowed molecularly targeted drugs including low-molecular weight compounds such as imatinib and antibodies to become the focus of drug development for intractable diseases such as cancer and autoimmune disorders.

Diagram 1 : Recombination of chromosomes discovered by Dr. Rowley



In many CML patients, a recombination of chromosome no. 9 and no. 22 can be seen. As a result, the *ABL* gene and the *BCR* gene are fused, forming BCR-ABL kinase.

Diagram 2 : Imatinib mechanism



BCR-ABL kinase binds itself to ATP without any signal transmission substance and causes unlimited proliferation. By attaching itself to the ATP binding site, imatinib inhibits this process.