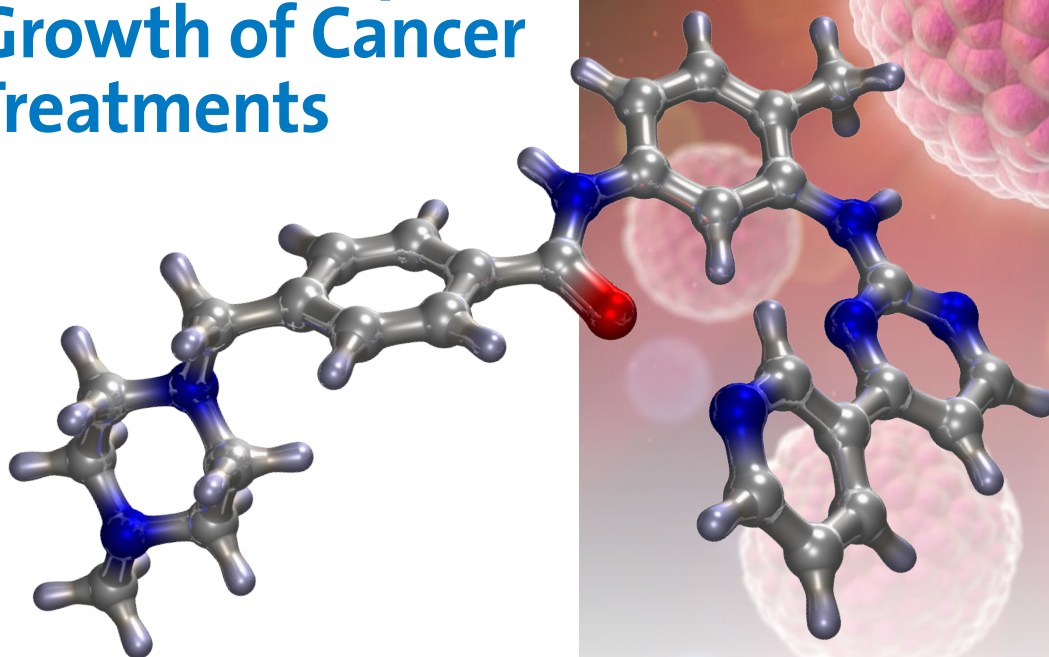


# CAS Chemistry Research Report

*Delivering the latest trends in global chemistry research*

## Human Genome Discoveries Spur Growth of Cancer Treatments



## Strength of the Human Genome Project and Targeted Drugs

In 2000, President Clinton announced that the draft sequence of the human genome was completed. This discovery held promise for personalized medicine to improve patient care and outcomes.<sup>1</sup> Those hopes were followed by a decade of discovery on many fronts. In particular, research about treatments for specific types of cancers grew exponentially.

This report examines the impact of the human genome on one major advance in the global effort to fight cancer. Researchers from Chemical Abstracts Service (CAS), a division of the American Chemical Society, studied recent publication trends in Chronic Myelogenous Leukemia (CML). They found that the patent success of Gleevec®, a first-generation drug targeting CML, has stimulated research and patent growth for second-generation drugs Tasigna® and Sprycel®.

Although the United States leads the world in journal article publications related to Gleevec, the patent

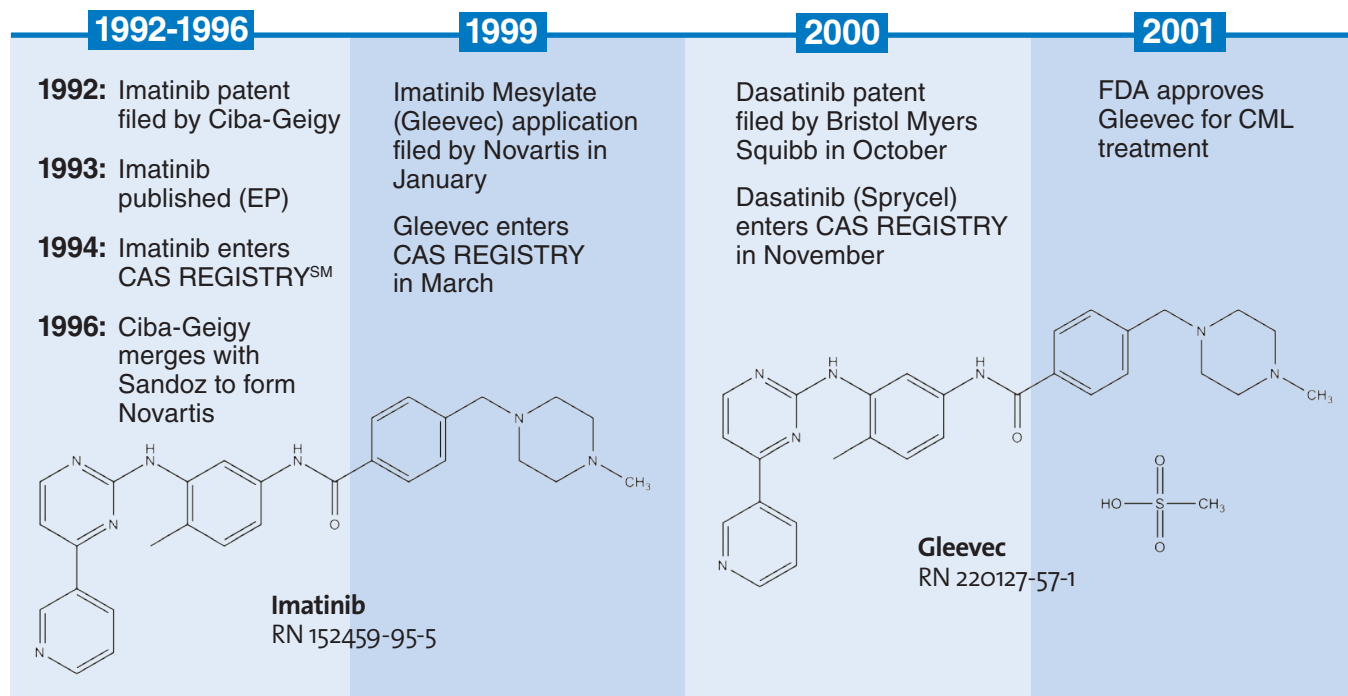
success of Gleevec and its successors (see **Table 1**) has been worldwide. The potential of Gleevec was realized through joint efforts between Novartis and Oregon Health and Science University Knight Cancer Institute researchers, led by director Brian Druker, M.D.

## Background on Personalized Medicine and Targeted Therapies

The hope for personalized medicine and genetic research was that a doctor could use a patient's genetic makeup to treat and prevent disease,<sup>1</sup> in much the same way a tailor alters clothing to fit a person's unique body type. Thus far, personalized medicine has fallen well short of that goal, achieving this level of care for only a small subset of individuals.

By contrast, targeted drug therapies have had a broad and powerful impact on cancer treatments with examples such as imatinib, gefitinib, and erlotinib.

## How Understanding Yields Discovery: the Power of the Human Genome is Realized



**Table 1. Gleevec and CML Therapy Successors**

Imatinib was originally designed to inhibit a different protein kinase than the defective ABL-kinase in CML. Novartis was persuaded to market the drug in a mesylate salt form following Dr. Druker's discovery that imatinib was able to cure CML. Gleevec's success propelled research into a second generation of drugs that also target the genetic abnormality causing CML.

The most famous targeted cancer drug of such stature is Gleevec, a first-line treatment for CML.

The bodies of patients with Chronic Myelogenous Leukemia produce too many granulocytes. Normally, granulocytes develop into blood cells that fight infection and disease. In CML patients, a genetic abnormality produces an active protein (BCR-ABL kinase) that causes overproduction of granulocytes, preventing their proper development. The cells become leukemic, leading to infection, anemia, and bleeding, all characteristics of CML.

## Gleevec changed the perception of CML therapy and personalized medicine.

As a simple, small pill with reduced side effects, Gleevec changed the perception of CML therapy and personalized medicine. Prior to Gleevec, the only cure for CML was a highly invasive bone marrow transplant. Today, Gleevec continues to be the leading treatment for patients with CML. As resistance to and intolerance

of Gleevec increases, however, a second generation of drugs targeting the abnormal protein has emerged.

“Gleevec taught us that molecular targeting works and enabled us to make significant progress in treating cancer. Leukemia patients are now living longer and the development of second- and third-generation drugs are building upon that success.”

*Brian Druker, M.D., Co-inventor on Gleevec patents and leader for Gleevec clinical trials*

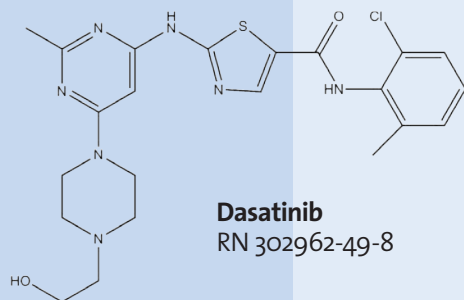
For this Chemistry Research Report, CAS analysts examined over 50 years of scientific research in global cancer treatments as represented in the CAS databases, the world’s most authoritative and comprehensive collection of chemistry and science-related information.

Analysts noted the accelerated growth in CML-related publications over the past 20 years. They also identified a shift in patent and journal article publications as the Gleevec patent term closes and second- and third-generations of targeted drugs begin to prevail.

### 2002-2005

Gleevec patents granted

AU: 02/28/02  
EPO: 10/01/03  
USPTO: 05/17/05



**Dasatinib**  
RN 302962-49-8

### 2004

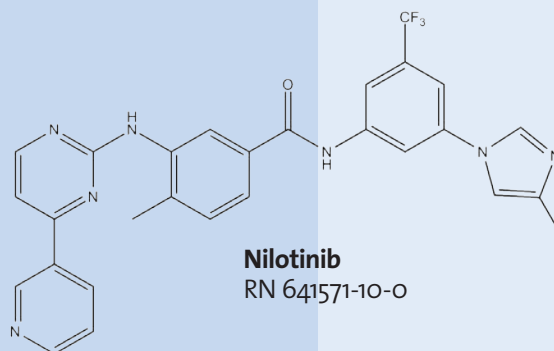
Nilotinib application filed by Novartis in January

Nilotinib (Tasigna) enters CAS REGISTRY in January

### 2005-2006

Sprycel patent granted

AU: 01/06/05  
USPTO: 12/26/06



**Nilotinib**  
RN 641571-10-0

### 2008

Nilotinib patent granted

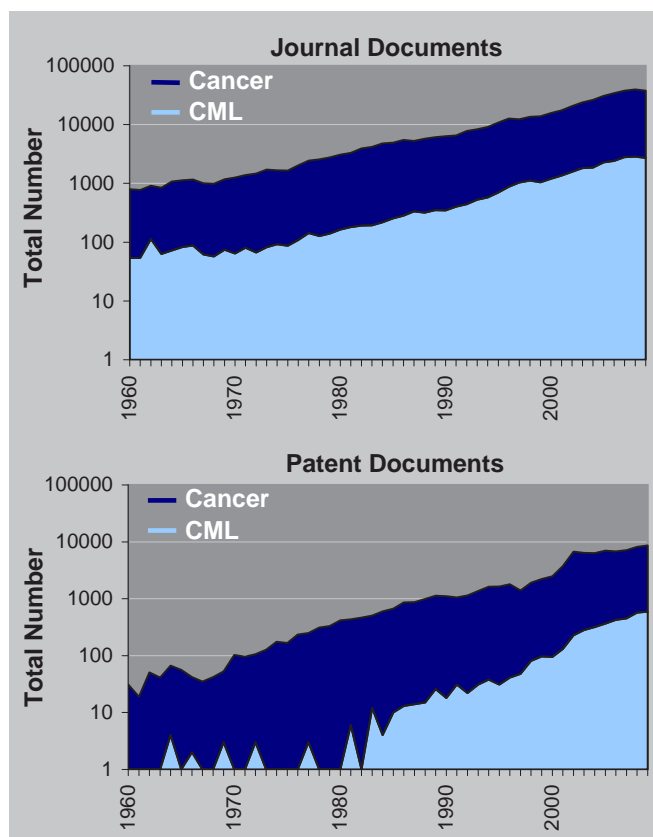
EPO: 11/09/08

## CML Patents Increase 700%

From 1960 to 2009, patent publications grew at a rate almost triple that of journal publications. Patent publications related to CML treatment increased eight-fold from the 1990s to the 2000s, surging 700 percent in the past decade alone. Cancer-related patent publications grew 318 percent during this same time (Figure 1). Cancer and CML-related journal article publications grew 200 percent during the past decade.

### Patent document growth represents the expansion of commercial interests in CML therapy

Patent document growth represents the expansion of commercial interests in CML therapy. The patent strength of Gleevec foretells the timely emergence of small drug therapies and the development of second generation drugs to target CML directly. Rational drug design and methodical chemical modifications make second-generation drugs Sprycel and Tasigna hundreds-fold more potent against CML.<sup>2,3</sup> Novartis designed Tasigna to bind ABL-kinase more strongly than imatinib increasing protein inhibition. Sprycel, designed by Bristol Myers Squibb, inhibits the active state of multiple kinases including ABL-kinase by reducing the number of drug and target interactions.



**Figure 1. Cancer Research Soars Over 50 Years**

Journal publications double each decade since 1960, while CML-related patent publications grow twice the rate of cancer-related patents.

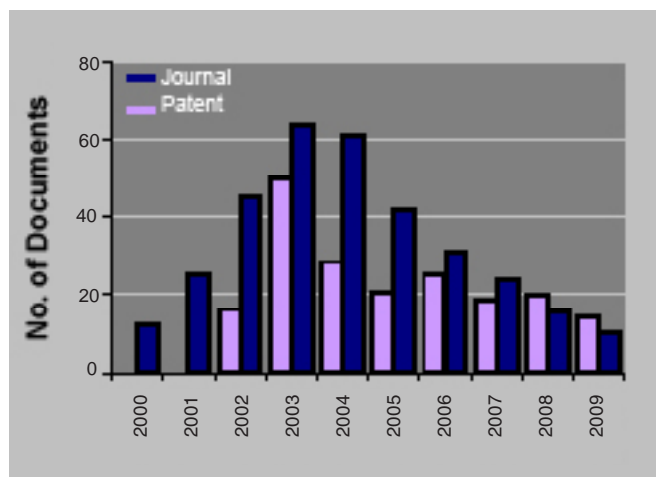
## Three Generations of Targeted Drugs Developed in CML Treatment

Non-proprietary Name	Proprietary Name	Manufacturer	Development Stage
Imatinib mesylate	Gleevec®	Novartis	First generation
Nilotinib	Tasigna®	Novartis	Second generation
Dasatinib	Sprycel®	Bristol Myers Squibb	Second generation
Bosutinib		Wyeth	Third generation
Busulfan	Myleran®	Glaxo Wellcome	Prior to Gleevec
Hydroxyurea	Hydrea®, Droxia®	Bristol Myers Squibb	Prior to Gleevec
Cytarabine	Cytosar-U®	Pharmacia & Upjohn	Prior to Gleevec

**Table 2. Targeted Drug Therapies Improve CML**

CAS researchers examined these small drug therapies and past therapies for publication trends in CML.

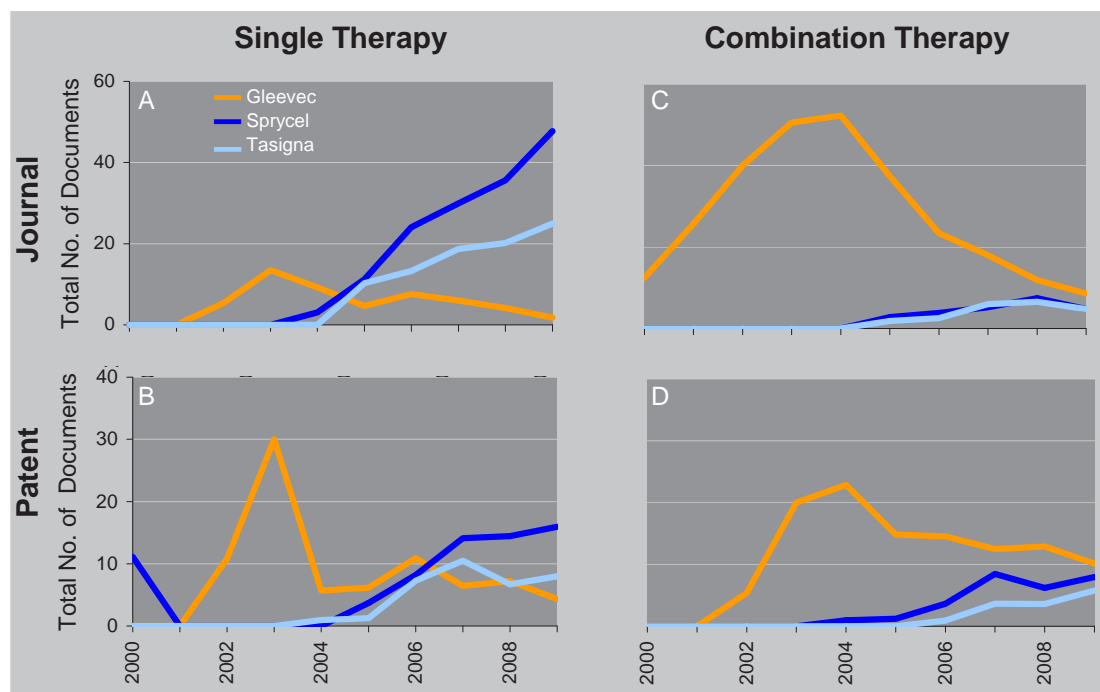
## Publications for Gleevec Single and Combination Therapy Decline as Second Generation Research Rises



**Figure 2. Decline in Gleevec Patent and Journal Publications**

Until 2008, journal publications for Gleevec-related CML therapy exceeded corresponding patent publications. Starting in 2008, CML therapy patents likely contributed to a reversal of this trend according to scientists at CAS. The steady decline in Gleevec-related CML research during this period is also likely due to the impending end of Novartis' patent protection for the drug.

## Research on New Generation Drugs Surpass Gleevec Single Therapy but Not Combination Therapy



**Figure 3. Combination Therapy Leader Falls in Single Therapy**

Gleevec continues to lead journal and patent publications in combination therapy, whereas Sprycel and Tasigna overtook Gleevec in single therapy publications

*Single therapy—  
a single drug  
used to treat  
CML*

*Combination  
therapy—  
multiple drugs  
used together  
to treat CML*

Sprycel- and Tasigna-related journal and patent publications exceeded Gleevec publications for single therapy (Figure 3A, 3B; Table 3). Gleevec has more journal and patent publications than other targeted drugs for combination therapy (Figure 3C, 3D; Table 3).

Gleevec demonstrates proof of concept for drug targeting. With unsurpassed sustainability in both journal and patent publications for combination therapy, Gleevec is a model for the patent strength of novel first-generation drugs.

## Research and Commercial Interests Increase for Sprycel and Tasigna while Gleevec Declines

	Journal Publications	Patent Publications
Single Therapy	% Increase 2005-2009	% Increase 2005-2009
Gleevec®	-62	-30
Sprycel®	326	330
Tasigna	142	546
Combination Therapy	% Increase 2005-2009	% Increase 2005-2009
Gleevec®	-77	-30
Sprycel®	70	119
Tasigna	154	538

Table 3. Journal and Patent Publication Increases for Single and Combination Drug Therapy between 2005 and 2009.

### Gleevec Absent from Three out of Top Five Patent Offices in 2009

Among patent authorities, the World Intellectual Property Organization (WIPO) has the most patent publications for Gleevec-related single drug therapy for CML at 20 percent (Figure 4). WIPO has more than double the amount of Gleevec single therapy patent publications than any authority in 2007 and again in 2009.

Within the last decade, five patent authorities represent nearly two-thirds of all Gleevec-related patent publications for single therapy. Of these five, only the United States Patent and Trademark Office (USPTO) and WIPO had patent publications in 2009.

The worldwide distribution of patent publications indicates a global need to protect and commercialize intellectual property. Worldwide patent activity also stimulates global interest in research related to that intellectual property. Gleevec and its influence on subsequent generations of targeted drugs provide a singular example of this research patent phenomenon.

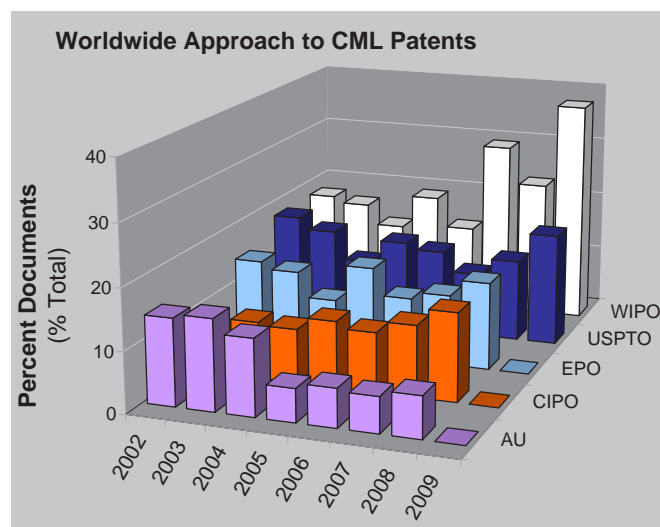


Figure 4. WIPO First in Patent Publications

Only two of the top five patent authorities (WIPO and USPTO) published Gleevec-related patents in 2009.

Patent authorities: World Intellectual Property Organization (WIPO), United States Patent and Trademark Office (USPTO), European Patent Office (EPO), Canadian Intellectual Property Office (CIPO), IP Australia (AU).

## U.S. Tops Gleevec Journal Publications

From 1999 to 2009, the United States (U.S.) authored 38 percent of journal article documents for Gleevec in CML single therapy. First author journal publications from the U.S. tripled the number from Japan, and more than quadrupled the totals from Italy, Germany, and the United Kingdom (U.K.). The U.S. has maintained this leadership role with 30 percent of journal publications in 2009. That same year, Italy moved to second with 13 percent more publications than Japan. Journal article publications from China grew beyond both the U.K. and Germany in 2009.

These trends in journal publications persist in patent publications for the same period. Again, Europe and the U.S. are well represented, while Japan and China play a greater role in publishing journal literature. These results hint at the dynamic interplay between commercial and research interests. Countries that lead commercially also tend to publish novel research.

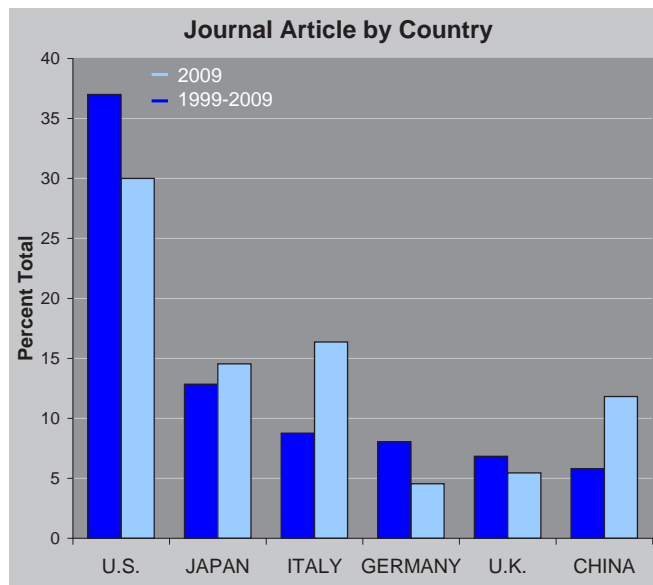
## Conclusion

Gleevec shifted the paradigm of cancer drugs that target genetic abnormalities. By radically improving patient outcomes and increasing the CML 10-year survival rate by 350 percent, Gleevec is singularly responsible for “transforming CML from a death sentence to a manageable disease for most patients,” according to a 2010 Reuters report.<sup>4</sup> Thanks to Gleevec, 90 percent of CML patients will be living 10 years after their diagnosis.

### ...“transforming CML from a death sentence to a manageable disease for most patients”

Second-generation drugs Sprycel and Tasigna provide hope for even greater success against CML. A recent study by Novartis found that twice as many patients treated with Tasigna responded significantly after 12 months when compared with Gleevec.<sup>2</sup> Sprycel had similar results.<sup>3</sup> Bosutinib-related journal documents increased 900 percent for CML single therapy since 2003 and is a third-generation CML targeted drug manufactured by Wyeth.

Ten years after the draft announcement of the human genome, the nearly 90,000 additional CML patients and thousands with other diseases for which Gleevec use is approved, are the chief beneficiaries of Gleevec’s success.



**Figure 5. U.S. Research Leadership Maintained**

U.S. has more first author journal publications than any other country. By 2009, Italy has closed some of the gap with more publications than Japan.

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