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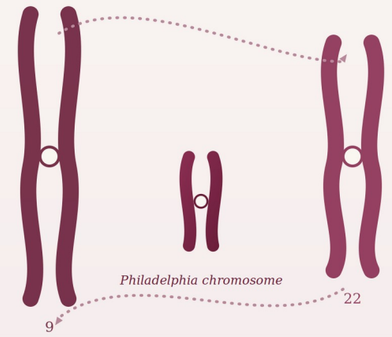

The History & Evolution of CML

A 20th Anniversary Keepsake

“Hope inspires our plans.”

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The History & Evolution of CML

From a 19th-century medical mystery to a targeted, life-saving therapy

Chronic myeloid leukemia (CML) has one of the most remarkable origin stories in modern medicine — a century and a half of careful observation, chance discovery, and international collaboration that turned a once-fatal disease into a manageable chronic condition. Here is that story, milestone by milestone.

The First Clues (1840s)

1845

Independent discovery in Scotland and Germany [1,2]

Edinburgh pathologist John Hughes Bennett and Berlin physician Rudolf Virchow independently published case reports, within weeks of each other, describing patients with enormously enlarged spleens and an overwhelming excess of white blood cells. Bennett believed it was an infection; Virchow suspected something new. Virchow went on to coin the term “leukämie” (“white blood”) — the origin of the word leukemia — and later proposed that the disease arose in blood-forming organs like the spleen and marrow, not from infection.

References

1. Deininger MW. Chronic Myeloid Leukemia: An Historical Perspective. Hematology Am Soc Hematol Educ Program. 2008;2008(1):418.
2. Geary CG. Chronic Myeloid Leukemia: A Historical Perspective. Semin Hematol. 2011.
3. The History of Chronic Myeloid Leukemia (CML): From Arsenic to Tyrosine Kinase Inhibitors (TKI). ScienceDirect review, 2025.
4. Bridges JM, Hayes DM, Nelson MG. Busulphan in the Treatment of Chronic Granulocytic Leukaemia. Br J Cancer. 1961;15:495–498.
5. Nowell PC, Hungerford DA. A minute chromosome in human chronic granulocytic leukemia. Science. 1960;132:1497.
6. Nowell PC. Discovery of the Philadelphia chromosome: a personal perspective. J Clin Invest. 2007;117(8):2033–2035.
7. Rowley JD. A new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. Nature. 1973;243:290–293.
8. Heisterkamp N, Stephenson JR, Groffen J, et al. Localization of the c-abl oncogene adjacent to a translocation break point in chronic myelocytic leukaemia. Nature. 1983;306:239–242.
9. Groffen J, Stephenson JR, Heisterkamp N, et al. Philadelphia chromosomal breakpoints are clustered within a limited region, bcr, on chromosome 22. Cell. 1984;36(1):93–99.
10. Mitelman F (Ed). Catalog of Chromosome Aberrations in Cancer. Cytogenet Cell Genet. 1983 (first edition).
11. Wang J, Zheng J, Lee EE, et al. A cloud-based resource for genome coordinate-based exploration and large-scale analysis of chromosome aberrations and gene fusions in cancer. (Describes the Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer.)
12. Sadowski I, Stone JC, Pawson T. A noncatalytic domain conserved among cytoplasmic protein-tyrosine kinases modifies the kinase function and transforming activity of Fujinami sarcoma virus P130gag-fps. Mol Cell Biol. 1986;6(12):4396–4408.
13. International CML Foundation. Past Meetings: Annapolis (1987), Cape Cod (1990), Martha's Vineyard (1992). cml-foundation.org.
14. International CML Foundation. Tribute to Professor John Goldman. cml-foundation.org.
15. Deininger M, Buchdunger E, Druker BJ. The development of imatinib as a therapeutic agent for chronic myeloid leukemia. Blood. 2005;105(7):2640–2653.
16. Lasker Foundation. Molecularly targeted treatments for chronic myeloid leukemia (2009 Lasker-DeBakey Award). laskerfoundation.org.
17. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med. 2001;344:1031–1037.
18. Monmaney T. A Triumph in the War Against Cancer. Smithsonian Magazine. May 2011. (Journalistic account, not a peer-reviewed source — included for the patient-advocacy narrative.)
19. The CML Society of Canada. Who We Are; The Story of Gleevec. cmlsociety.org. (Organizational source, not peer-reviewed — included for the patient-advocacy narrative.)
20. Chandra HS, Heisterkamp NC, Hungerford A, Morrissette JJD, Nowell PC, Rowley JD, Testa JR. Philadelphia Chromosome Symposium: commemoration of the 50th anniversary of the discovery of the Ph chromosome. Cancer Genet. 2011;204(4):171–179.
21. Mahon FX, Réa D, Guilhot J, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years (STIM trial). Lancet Oncol. 2010;11(11):1029–1035.
22. Mahon FX, Delbrel X, Cony-Makhoul P, et al. Follow-up of complete cytogenetic remission in patients with chronic myeloid leukemia after cessation of interferon alfa. J Clin Oncol. 2002;20(1):214–220.
23. Rousselot P, Huguet F, Rea D, et al. Imatinib mesylate discontinuation in patients with chronic myelogenous leukemia in complete molecular remission for more than 2 years. Blood. 2007;109(1):58–60.
24. Graham SM, Jorgensen HG, Allan E, et al. Primitive, quiescent, Philadelphia-positive stem cells from patients with chronic myeloid leukemia are insensitive to STI571 in vitro. Blood. 2002;99(1):319–325.
25. Etienne G, Guilhot J, Rea D, et al. Long-Term Follow-Up of the French Stop Imatinib (STIM1) Study in Patients With Chronic Myeloid Leukemia. J Clin Oncol. 2017;35(3):298–305.
26. Mahon FX, Dulucq S, Rea D, et al. Extended long-term follow-up and the survival of Stop Imatinib study. Blood Neoplasia. 2026;3(1):100177.
27. In memory of Tessa Holyoake and her work on chronic myeloid leukemia stem cells. PMC6745982 (peer-reviewed tribute and scientific summary).
28. Rastogi MV, Stork L, Druker B, Blasdel C, Nguyen T, Boston BA. Imatinib mesylate causes growth deceleration in pediatric patients with chronic myelogenous leukemia. Pediatr Blood Cancer. 2012;59(5):840–845. (Peer-reviewed; documents Carolyn Blasdel's clinical research role alongside Dr. Druker's team.)
29. Carolyn Blasdel, RN, FNP-BC, OCN — clinician biography. cmleukemia.com. (Organizational/biographical source, not peer-reviewed — used only for career narrative details.)
30. Simoneau CA. Treating chronic myeloid leukemia: improving management through understanding of the patient experience. Clin J Oncol Nurs. 2013;17(1):E13–E20. doi:10.1188/13.CJON.E13-E20. PMID: 23372106.

This brochure is for general historical and educational purposes. All scientific and clinical claims (refs. 1–17, 20–28, 30) are drawn from peer-reviewed journal articles or primary institutional/database records. References 18–19 and 29, covering patient-advocacy and biographical narrative, are journalistic or organizational sources rather than peer-reviewed literature, and are identified as such.

Treatment Without Understanding (1865–1959)

The 115 years between the first descriptions of CML and the discovery of its genetic cause were not empty ones. Physicians had no idea what caused the disease, but they steadily found ways to manage its symptoms — laying groundwork, and raising the survival bar, for the molecular era to come.

1865

Arsenic — the first documented therapy [2,3]

Twenty years after Bennett and Virchow's first descriptions, physician Heinrich Lissauer reported the first documented use of arsenic to treat CML. It could lower white blood cell counts, but there is little evidence it extended survival.

1902–03

Splenic radiotherapy [3,4]

The introduction of X-ray therapy to shrink the enlarged spleen became the mainstay of CML treatment for the next 50 years — more predictable than arsenic, though it did not stop the disease's eventual progression.

1953–59

Busulfan and the first modest survival gains [3,4]

The alkylating agent busulfan, introduced by Galton in 1953 and shown effective for blood-count control by 1959, became the first therapy to offer a modest, measurable prolongation of survival — though, like everything before it, it could not eliminate the underlying disease.

The Genetic Breakthrough (1960s–70s)

1960

The Philadelphia chromosome [5,6]

More than a century later, University of Pennsylvania pathologist Peter Nowell and graduate student David Hungerford, working at Fox Chase Cancer Center in Philadelphia, noticed an unusually small chromosome in the leukemia cells of CML patients. The discovery was serendipitous: preparing his slides, Nowell rinsed the cells with plain tap water instead of the proper laboratory solution — an accident he assumed had ruined the sample. Instead, the water caused the cells to swell and their chromosomes to spread apart, making them countable for the first time. As Nowell later put it, “it seemed a shame to throw this away.” Published as a 300-word paper in Science, it was the first time a specific chromosomal abnormality had ever been linked to a specific cancer — proof that cancer could have a genetic basis. It was named the Philadelphia chromosome, after the city of its discovery.

1973

Janet Rowley identifies the translocation [7]

University of Chicago geneticist Janet Rowley used newly developed chromosome-banding techniques to show that the Philadelphia chromosome was not simply missing material, as originally thought — it was the product of a translocation, a swap of material between chromosomes 9 and 22. Her discovery, published in Nature, proved that this genetic rearrangement was a cause of the leukemia, not a byproduct of it, and opened the door to understanding cancer as a disease of misplaced genes.

A Story That Continues

The scientists in this story — pathologists, geneticists, biochemists, and clinicians spread across Scotland, Germany, Philadelphia, Chicago, Toronto, London, Basel, Bordeaux, Glasgow, and Oregon — never worked in isolation. Each built on the last. Nowell and Hungerford’s accident gave the field its first genetic clue; Rowley, Heisterkamp, and Groffen turned that clue into a molecular target; Druker, Lydon, and a global network of advocates turned that target into a pill. But Holyoake’s discovery that a quiescent stem cell reservoir survives even the best therapy, and Mahon’s two-decade pursuit of the question of whether treatment could ever safely stop, are what closed the loop — turning “can we treat CML” into “can a patient's story end with the disease in the past, not just in remission.” That is the evidence base the CMLSC TFR Care Pathway stands on today.

“Hope inspires our plans. Evidence and advocacy make our plans work.™”

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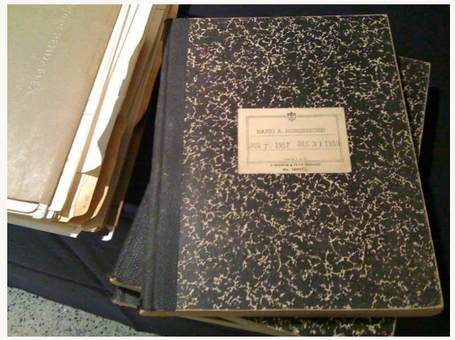
A Personal Thread Through This History

CMLSC co-founder and president Cheryl-Anne Simoneau attended the 2010 Philadelphia Chromosome Symposium and met several of the researchers featured in this timeline. Their photographs — and a glimpse of the original laboratory materials from the discovery itself — follow.

With Dr. Peter C. Nowell, co-discoverer of the Philadelphia chromosome (1960), at the 50th Anniversary Symposium, Philadelphia, September 2010.

With Dr. Janet D. Rowley, who in 1973 discovered that the Philadelphia chromosome arises from a translocation between chromosomes 9 and 22.

With Alice Hungerford, holding the actual microscope her husband David Hungerford used in the 1959 discovery of the Philadelphia chromosome.



David A. Hungerford's original laboratory notebook, June 1957–December 1959 — spanning the period of the discovery itself.

An original hand-annotated chromosome tracing from the Hungerford archive, showing how researchers mapped chromosome banding patterns by hand before digital imaging.

With Dr. Brian Druker (left), who led imatinib's development, and Dr. François-Xavier Mahon (right), who led the STIM trial proving CML patients could safely stop treatment [21] — the beginning and end of active CML therapy, in one photo.

Decoding the Mechanism (1980s)

1984

The BCR-ABL fusion gene is mapped [8,9]

Building on Rowley's work, researchers John Groffen and Nora Heisterkamp mapped the precise breakpoints of the 9;22 translocation, showing that a gene on chromosome 22 (later named BCR) had fused with the ABL gene from chromosome 9. This BCR-ABL fusion gene produces an abnormal protein that drives uncontrolled cell growth — giving researchers, for the first time, a precise molecular target to aim a drug at.

1983-

Felix Mitelman catalogues the genetic map of cancer [10,11]

In Lund, Sweden, cytogeneticist Felix Mitelman began systematically compiling every published chromosome aberration ever reported in cancer, first published in 1983 as the "Catalog of Chromosome Aberrations in Cancer." That effort grew into the Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer — today cataloguing more than 80,000 cytogenetic cases and over 34,000 unique gene fusions, including the BCR-ABL fusion that defines CML. It remains the field's encyclopedic reference for how chromosome changes map to specific cancers, still maintained and continuously updated today.

1980s

Understanding tyrosine kinase signalling [12]

In Toronto, at the Samuel Lunenfeld Research Institute, molecular biologist Tony Pawson helped unravel how oncogenic tyrosine kinases — the class of enzyme that BCR-ABL turned out to be — send abnormal growth signals inside a cell. His discovery of the "SH2 domain," the mechanism by which these kinases dock onto and activate other signalling proteins, became foundational to understanding how a single mutated enzyme like BCR-ABL could take over a cell's machinery — and, crucially, why blocking that enzyme's activity might stop the disease in its tracks.

A Global Research Community Forms (1987–1992)

1987–92

John Goldman and the birth of an international CML community [13,14]

As the molecular picture of CML came into focus through the 1980s, London hematologist John Goldman helped convene the first international meetings dedicated entirely to CML biology — starting in Annapolis, Maryland in 1987 (just 35 attendees), followed by Cape Cod in 1990, and Martha's Vineyard in 1992. These meetings pooled together, for the first time, everything the world's CML researchers knew about the disease's biology. Goldman's efforts to bring the field together evolved into what is now the International CML Foundation (iCMLf), and his sustained leadership — along with his own research on stem cell transplantation and early confirmation of imatinib's preclinical activity in 1997 — helped set the stage for the therapeutic breakthrough to come.

Patient Voices: Community Artwork

No account of CML's history is complete without the clinicians who translated laboratory breakthroughs into everyday, livable care — and the patients whose lives that care was built around.

Carolyn Blasdel, RN, FNP-BC, OCN, began caring for CML patients at Oregon Health & Science University at the start of the Phase I imatinib trial, working directly alongside Dr. Brian Druker. Her practice became a model for the field: side-effect management, patient education, and quality of life became as central to CML care as the molecular response numbers themselves. She co-authored peer-reviewed research alongside Dr. Druker's team, and generously allowed her work to be referenced in Cheryl-Anne Simoneau's 2013 publication on treating CML in the Clinical Journal of Oncology Nursing. When CMLSC invited her to speak to patients in Montreal, the community she addressed created the piece below together in response — a tangible record of what her work meant to the people living it.

Artwork created collaboratively by CMLSC patients with Carolyn Blasdel during her visit to Montreal.

A Half-Century Later (2010)

2010

Philadelphia Chromosome Day [6,20]

Fittingly, in the same year STIM1 was published, Philadelphia mayor Michael Nutter declared September 28, 2010 “Philadelphia Chromosome Day,” and Fox Chase Cancer Center hosted the “Philadelphia Chromosome Symposium: Past, Present and Future” at the Chemical Heritage Foundation, organized by Fox Chase scientist Joseph Testa. Honoured guests included Peter Nowell, Janet Rowley, and Alice Hungerford (widow of David Hungerford, who had died in 1993), alongside Nora Heisterkamp and other researchers whose work built the story of CML. Nowell himself shared the story of the discovery’s origin from the podium — recounting how, 50 years earlier, he had rinsed his slides with ordinary tap water instead of laboratory solution and initially assumed he had ruined the sample, only to find the accident had spread the chromosomes apart and made the Philadelphia chromosome visible for the first time. It stands as one of the few times this entire cast of discovery came together in one room, and its proceedings were formally published in the journal Cancer Genetics.

From Bench to Bedside (1990s)

1993

Druker and Lydon join forces [15,16]

Oncologist Brian Druker, newly arrived at Oregon Health & Science University, had spent years searching for a drug that could block BCR-ABL. He called his contact at the pharmaceutical company Ciba-Geigy (later Novartis), biochemist Nicholas Lydon, who was independently leading a search for tyrosine kinase inhibitors. Lydon sent Druker a set of experimental compounds — one of them, then known as CGP 57148 (later STI-571), killed CML cells in the lab with striking selectivity while leaving healthy cells unharmed.

1998

The first clinical trial [16,17]

After Druker persuaded a reluctant Novartis — CML was considered too rare a disease to justify the investment — the first human trial of STI-571 began in June 1998 with a small group of patients. The results were extraordinary: the vast majority of patients achieved complete remission, with minimal side effects, in a disease that had previously carried a life expectancy of only a few years.

1999

Patient advocacy tips the scales: Suzan McNamara [18,19]

Even remarkable trial results weren’t enough on their own — Novartis still had to be convinced to scale up manufacturing of a drug for a rare disease. Montreal patient Suzan McNamara, struggling on interferon therapy, called Dr. Druker directly; he told her the company might move faster if it heard from patients themselves. McNamara and a friend organized an online petition that drew thousands of CML patients demanding wider access to STI-571. Novartis expanded production, and McNamara entered the trial in January 2000, achieving complete remission. She went on to complete her PhD in experimental medicine and later co-founded the CML Society of Canada, where she serves as scientific advisor — living proof that patient advocacy helped carry Gleevec across the finish line.

2001

FDA approval of Gleevec [16,17]

Imatinib mesylate — brand name Gleevec (Glivec outside North America) — received FDA approval in May 2001, just two and a half years after the trial began, one of the fastest approvals in the agency’s history. It became the first molecularly targeted small-molecule cancer drug ever approved, transforming CML from a fatal diagnosis into a manageable chronic condition and appearing on the cover of Time magazine the same month as a symbol of a new era in cancer treatment.

The Root of Relapse: Quiescent Stem Cells (1999–2002)

Gleevec's approval looked like the end of the story. It wasn't — and understanding why is what eventually made a project like the TFR Care Pathway thinkable at all.

1999-02

Tessa Holyoake discovers why CML persists [24,27]

At the Terry Fox Laboratory in Vancouver, Scottish physician-scientist Tessa Holyoake identified that CML is driven by a small population of leukemic stem cells that can sit in a dormant, non-dividing ("quiescent") state. Returning to the University of Glasgow, she published landmark evidence in 2002 showing these quiescent stem cells are essentially insensitive to imatinib — because the drug only kills actively dividing cells. This explained, for the first time, why residual disease can persist even in patients with an excellent response to TKI therapy, and why relapse remains possible after stopping treatment. Holyoake, who went on to lead the Paul O'Gorman Leukaemia Research Centre in Glasgow, remained the field's leading voice on CML stem cell biology until her death in 2017. Her work continues today through the researchers she trained and the questions she raised — chief among them, how the immune system might be recruited to finish the job TKIs alone cannot.

The Road to Treatment-Free Remission

Even as Holyoake's lab explained why CML is hard to eradicate, French hematologist François-Xavier Mahon was independently asking the opposite question in the clinic: could some patients stop treatment anyway? His work, spanning more than two decades, built the evidence base that makes the TFR Care Pathway possible.

2002

The first hint: stopping interferon [22]

Before imatinib, Mahon and colleagues in Bordeaux followed 15 patients who had stopped interferon-alfa after achieving a complete cytogenetic response. After a median follow-up of 3 years, 7 of the 15 (47%) had not relapsed — an early, tantalizing signal that durable remission off treatment was possible for some patients, not just a theoretical curiosity.

2004-07

The imatinib pilot study — and an interferon clue [23]

Mahon's group extended the question to the new drug. Between March 2004 and July 2005, they enrolled patients with undetectable BCR-ABL for over 2 years and stopped their imatinib. The published results, in Blood in 2007, covered 12 patients: 6 relapsed early, while 6 remained in molecular remission. The striking pattern was that the 6 who stayed in remission had all previously been treated with interferon for at least 6 months — leading Mahon to suspect interferon might prime the immune system to help control residual disease after TKI withdrawal, a hypothesis that would drive much of his subsequent research.

At the same time, the question was no longer only academic. As more patients spent years on lifelong TKI therapy, complaints about chronic fatigue, muscle and joint pain, GI side effects, and the everyday burden of a daily pill — combined with its cost — grew louder within the patient community. That pressure, echoed in clinics across France and beyond, helped turn a small pilot observation into a formal, funded clinical trial.

2010

The STIM1 trial formalizes the answer [21]

Mahon led the prospective, multicentre Stop Imatinib (STIM1) trial across 19 French institutions — 100 patients who had sustained undetectable BCR-ABL for at least 2 years stopped imatinib under strict monthly PCR monitoring. At 12 months, 41% remained in treatment-free molecular remission; those who relapsed responded well to restarting imatinib. Published in Lancet Oncology, STIM1 was the first trial to formally establish that stopping TKI therapy was feasible and safe for a defined subset of patients — the founding evidence base for treatment-free remission as a clinical goal.

2017-

The evidence matures [25,26]

Long-term follow-up of STIM1, published in the Journal of Clinical Oncology in 2017, confirmed that remission durability held up over years, not just months. A further extended follow-up, published in 2026 with a median of nearly 13 years of monitoring, found molecular recurrence-free survival of 35–37% a decade or more after stopping — with no patient progressing to advanced-phase disease. What began as Mahon's small pilot observation has grown into a durable, decades-long evidence base, now the scientific foundation beneath programs like the CMLSC TFR Care Pathway.