Anatomy of a Breakthrough in Targeted Cancer Treatments

Brian Druker, MD

Knight Cancer Institute
at Oregon Health & Science University

Breakthroughs Take Time

The 20th Century

Leading causes of mortality

1900

1) Pneumonia
2) Tuberculosis
3) Enteritis
4) Heart Disease
5) Stroke
6) Liver Disease

The 20th Century

Leading causes of mortality

	1900	2000
1)	Pneumonia	Heart Disease
2)	Tuberculosis	Cancer
3)	Enteritis	Stroke
4)	Heart Disease	COPD
5)	Stroke	Accidents
6)	Liver Disease	Pneumonia/Influenza

Factors Leading to Eradication and Treatability of Infections

- Improved sanitation and refrigeration — Prevention
- Antibiotics — Specific treatments
- Vaccination — Immune modulation

Historical Perspective on Chronic Myeloid Leukemia (CML)

1845	1985	2001
First description of CML	BCR-ABL	Specific therapy for CML

Clinical Description of CML

LEUCOCYTHEMIA,

OR

WHITE CELL BLOOD,

IN RELATION TO THE

PHYSIOLOGY AND PATHOLOGY OF THE LYMPHATIC GLANDULAR SYSTEM.

BY JOHN HUGHES BENNETT, M.D., F.R.S.E.,

PROFESSOR OF INSTITUTES OF MEDICINE AND OF CLINICAL MEDICINE IN THE UNIVERSITY, AND PRESIDENT OF THE PHYSIOLOGICAL SOCIETY, EDINBURGH.
MEMBER OF THE AMERICAN PHILOSOPHICAL SOCIETY; OF THE IMPERIAL SOCIETY OF PHYSICIANS OF VIENNA; OF THE MEDICAL ASSOCIATION OF PRUSSIA; OF THE ANATOMICAL AND BIOLOGICAL SOCIETIES OF PARIS; OF THE MEDICAL SOCIETIES OF SWEDEN, COPENHAGEN, ETC. ETC.

WITH TWO COLOURED LITHOGRAPHS, AND NUMEROUS WOODCUTS.

EDINBURGH: SUTHERLAND AND KNOX.
LONDON: SIMPKIN, MARSHALL, & CO.

MDCCCLII.

Weißes Blut.

Außer sehr wenig rothen Blutkörperchen bestand der ungleich größere Theil aus denselben farblosen oder weißen Körpern, die auch im normalen Blut vorkommen, nämlich kleinen, nicht ganz regelmäßigen Protëinmolecülen, größeren, körnigen, fetthaltigen, kernlosen Körperchen und granulirten Zellen mit einem rundlichen, hufeisenförmigen oder kleeblattartigen oder mit mehreren napfförmigen, distincten Kernen. Die größeren dieser Zellen hatten ein leicht gelbliches Aussehen. Das Verhältniß zwischen den farbigen und farblosen Blutkörperchen stellte sich hier ungefähr umgekehrt, wie im normalen Blut, indem die farblosen die Regel, die farbigen eine Art von Ausnahme zu bilden schienen. Wenn ich daher von weißem Blute spreche, so meine ich in der That ein Blut, in welchem die Proportion zwischen den rothen und farblosen (in Masse weißen) Blutkörperchen eine umgekehrte ist, ohne daß eine Beimischung fremdartiger chemischer oder morphologischer Elemente zu bemerken wäre.

ich würde mich glücklich schätzen, der Wissenschaft dadurch zu einer neuen und, wie es mir scheint, nicht unwichtigen Thatsache verholfen zu haben. —

Dr. Virchow.

Chronic Myeloid Leukemia (CML)

- 15 - 20 % of all leukemias
- 1 - 2 cases per 100,000 per year

Average age of onset - 50 to 60 yrs of age

Median survival – 3 to 5 years

Breakthroughs Require Knowledge

Molecular Pathogenesis of CML

A Minute Chromosome in Human Chronic Granulocytic Leukemia

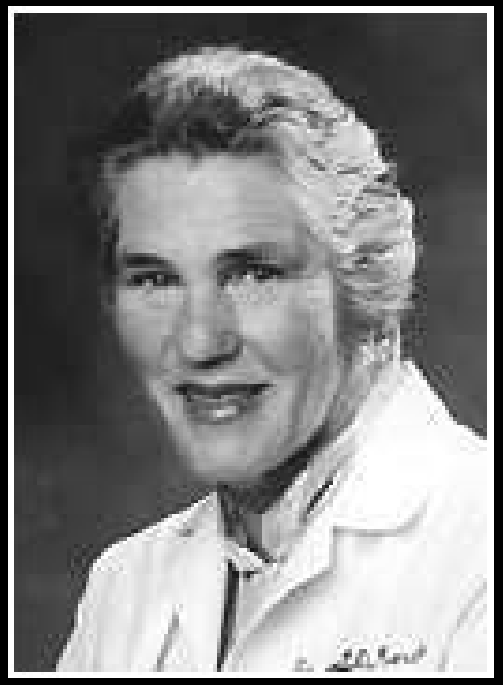
In seven cases thus far investigated (five males, two females), a minute chromosome has been observed replacing one of the four smallest autosomes in the chromosome complement of cells of chronic granulocytic leukemia cultured from peripheral blood. No abnormality was observed in the cells of four cases of *acute* granulocytic leukemia in adults or of six cases of acute leukemia in children. There have been several recent reports of chromosome abnormalities in a number of cases of human leukemia [including two of the seven cases reported here: Nowell and Hungerford, *J. Natl. Cancer Inst.* **25**, 85 (1960)], but no series has appeared in which there was a consistent change typical of a particular type of leukemia.

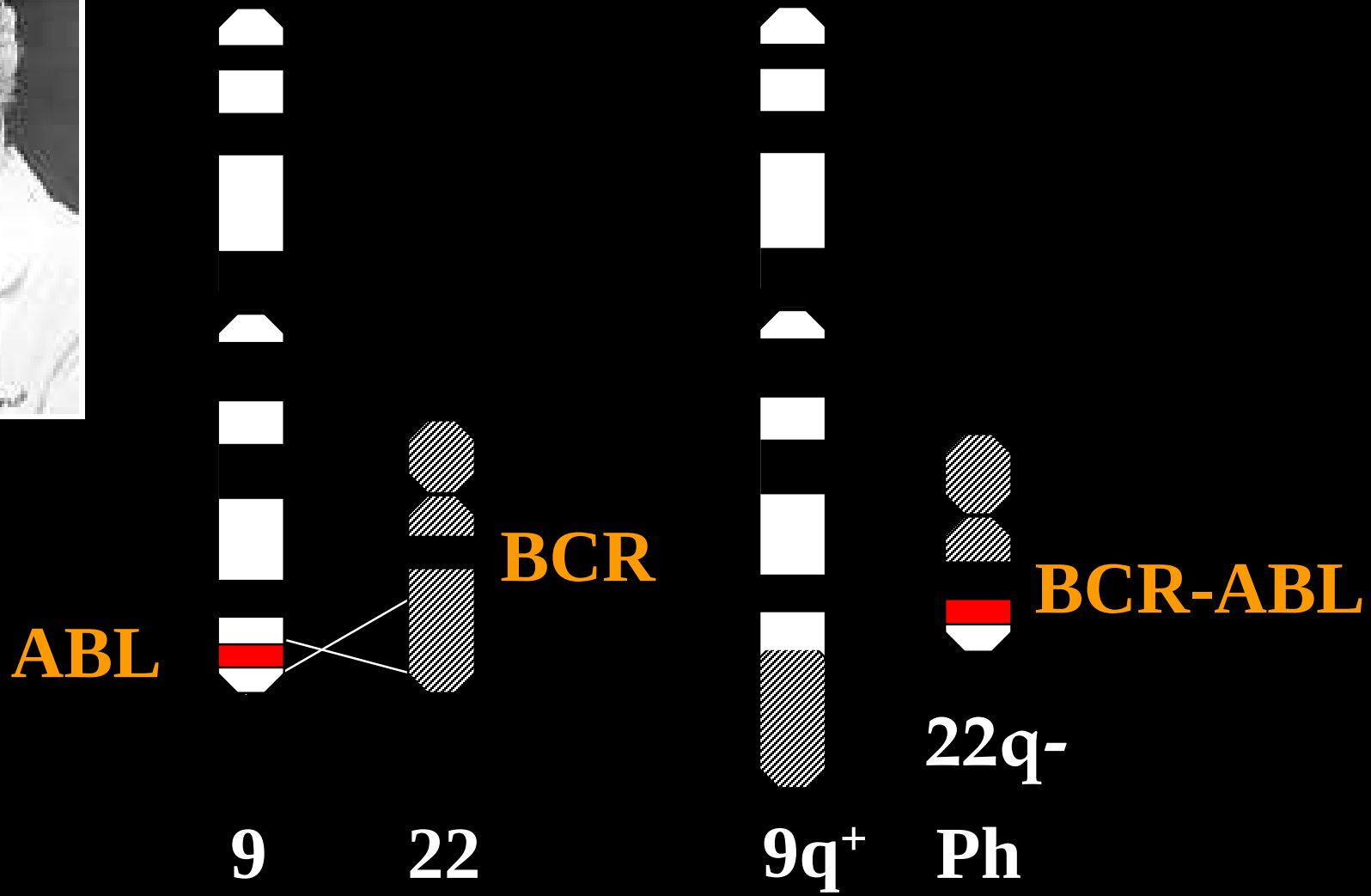
Cells of the five new cases were obtained from peripheral blood (and bone marrow in one instance), grown in culture for 24–72 hours, and processed for cytological examination by a recently developed air-drying technique (Moorhead, *et al., Exptl. Cell Research*, in press). The patients varied from asymptomatic untreated cases to extensively treated cases of several years duration in terminal myeloblastic crisis. All seven individuals showed a similar minute chromosome, and none showed any other frequent or regular chromosome change. In most of the cases, cells with normal chromosomes were also observed. Thus, the minute is not a part of the normal chromosome constitution of such individuals.

The findings suggest a causal relationship between the chromosome abnormality observed and chronic granulocytic leukemia.

PETER C. NOWELL
School of Medicine,
University of Pennsylvania
DAVID A. HUNGERFORD
Institute for Cancer Research

Nowell & Hungerford, 1960 Science 132.1497

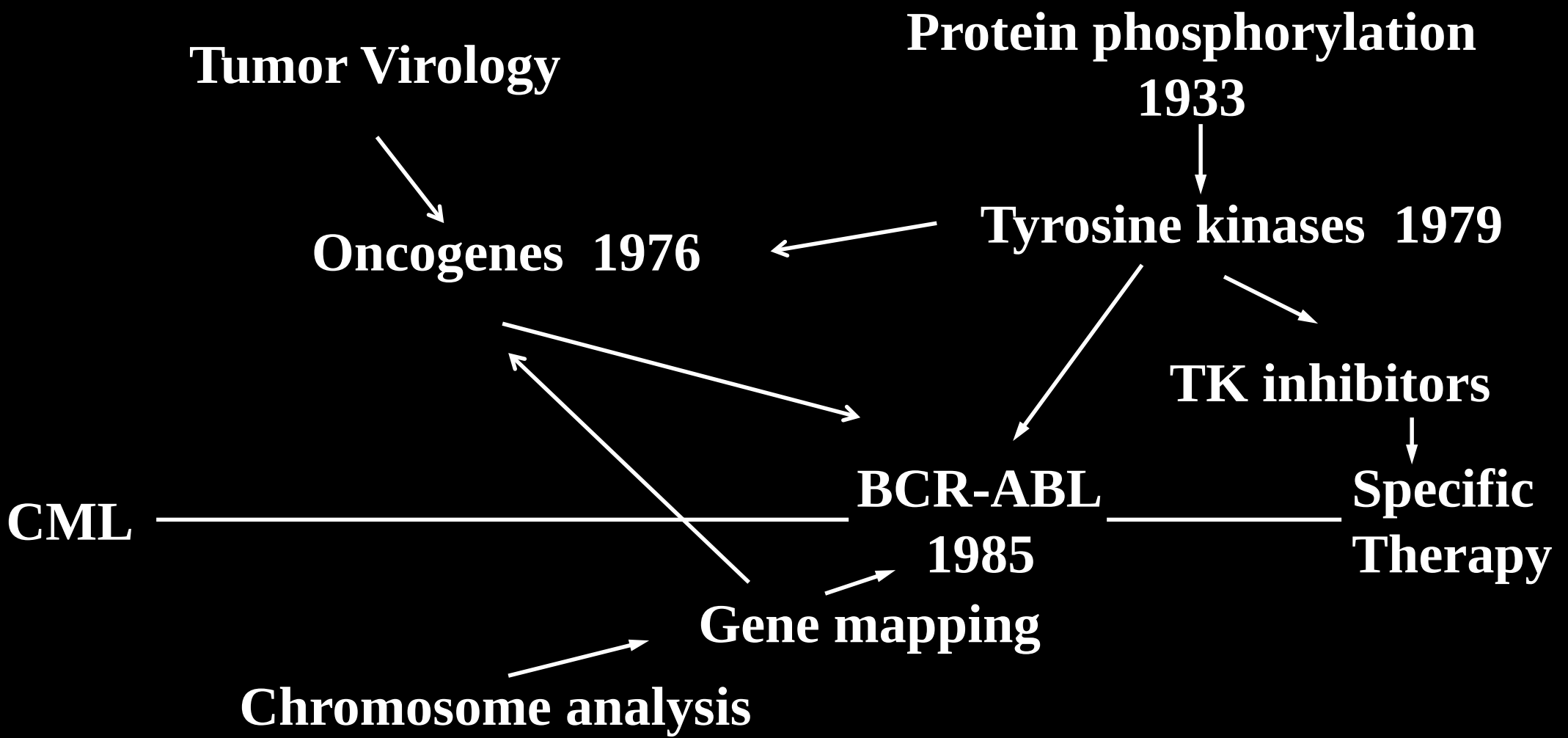



ABL
BCR
BCR-ABL
22q-
9
22
9q+
Ph

Breakthroughs Often Occur When Different Fields of Investigation Converge

And the Right Technology is Applied to the Right Problem at the Right Time

Historical Perspective on CML



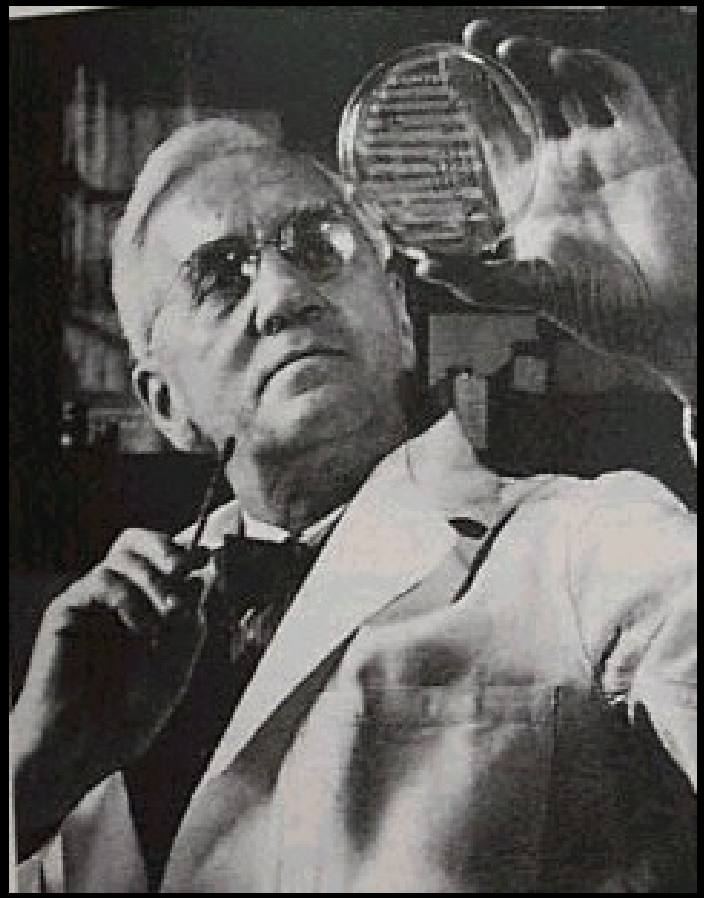
Breakthroughs Requiring Seeing Things Differently

Even if the Answer is Right in Front of You

Velcro

George de Mestral

Penicillin

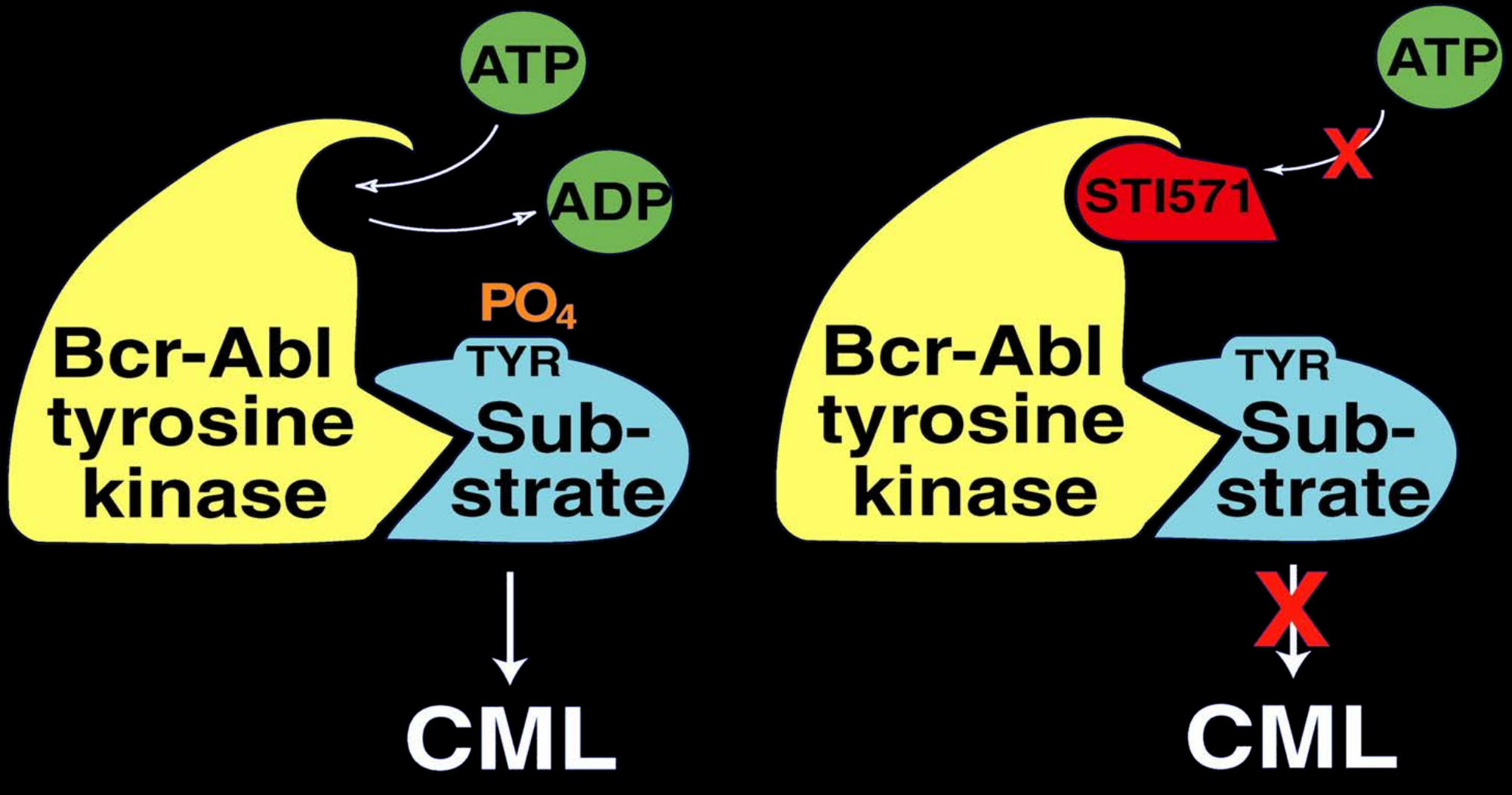


Alexander Fleming

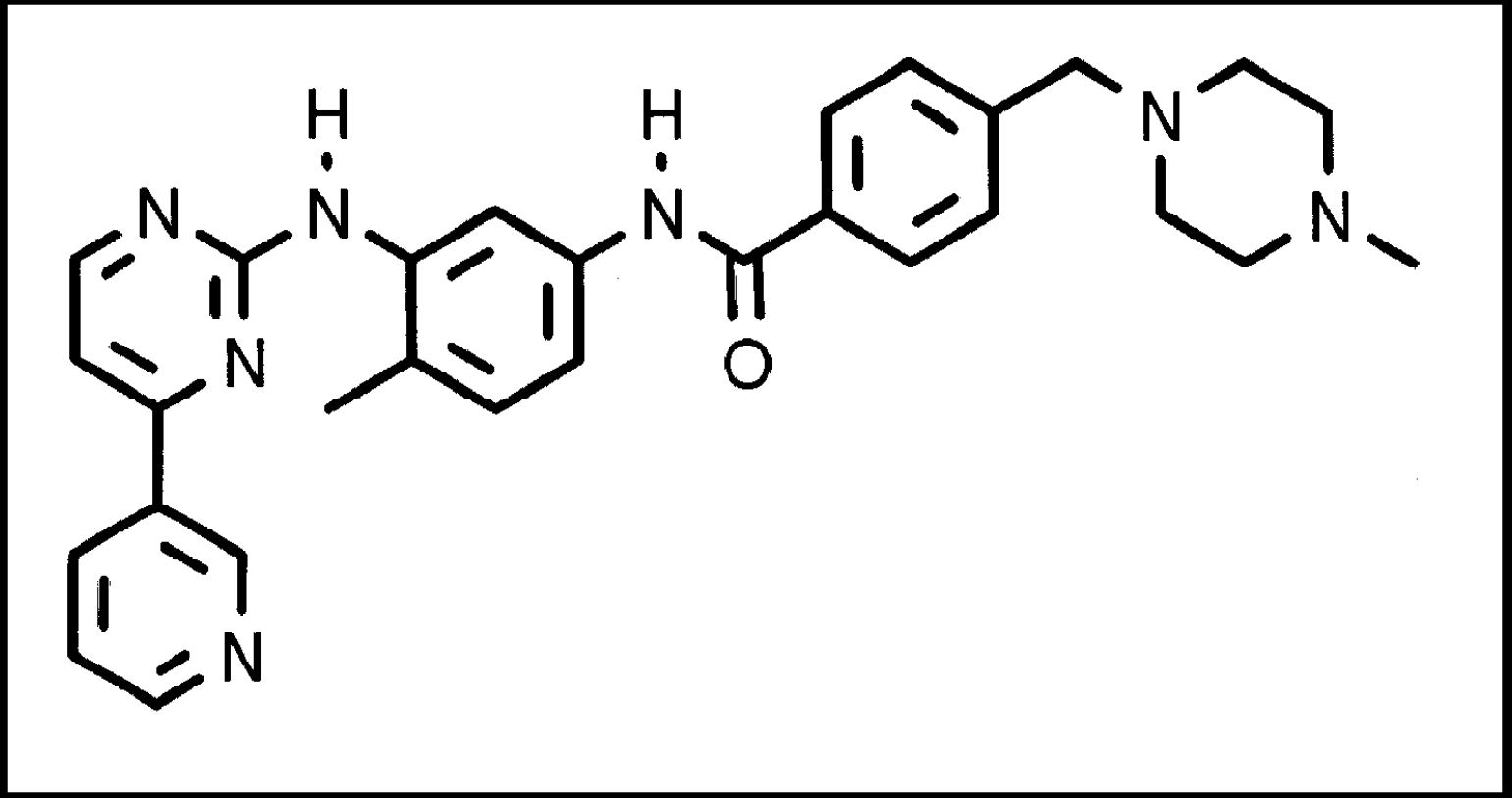
BCR-ABL As a Therapeutic Target for CML

- Product of the Philadelphia chromosome
- Present in all patients with CML
- Causative molecular abnormality of CML
- BCR-ABL is a constitutively activated intracellular tyrosine kinase
  - Tyrosine kinase activity of BCR-ABL is required for function

BCR-ABL As a Therapeutic Target for CML



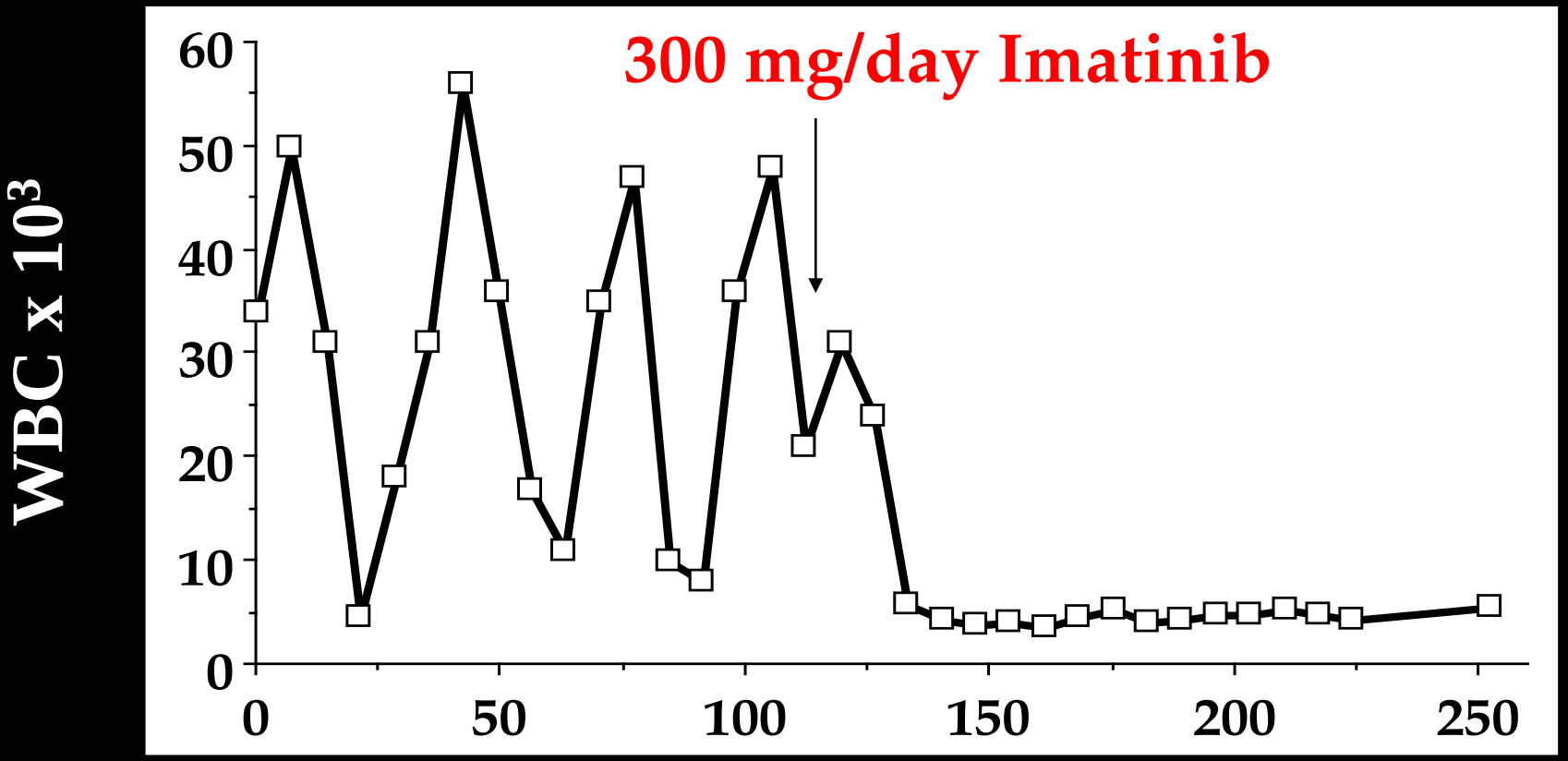
STI571 (CGP 57148B)
Imatinib mesylate
Gleevec™, Glivec®



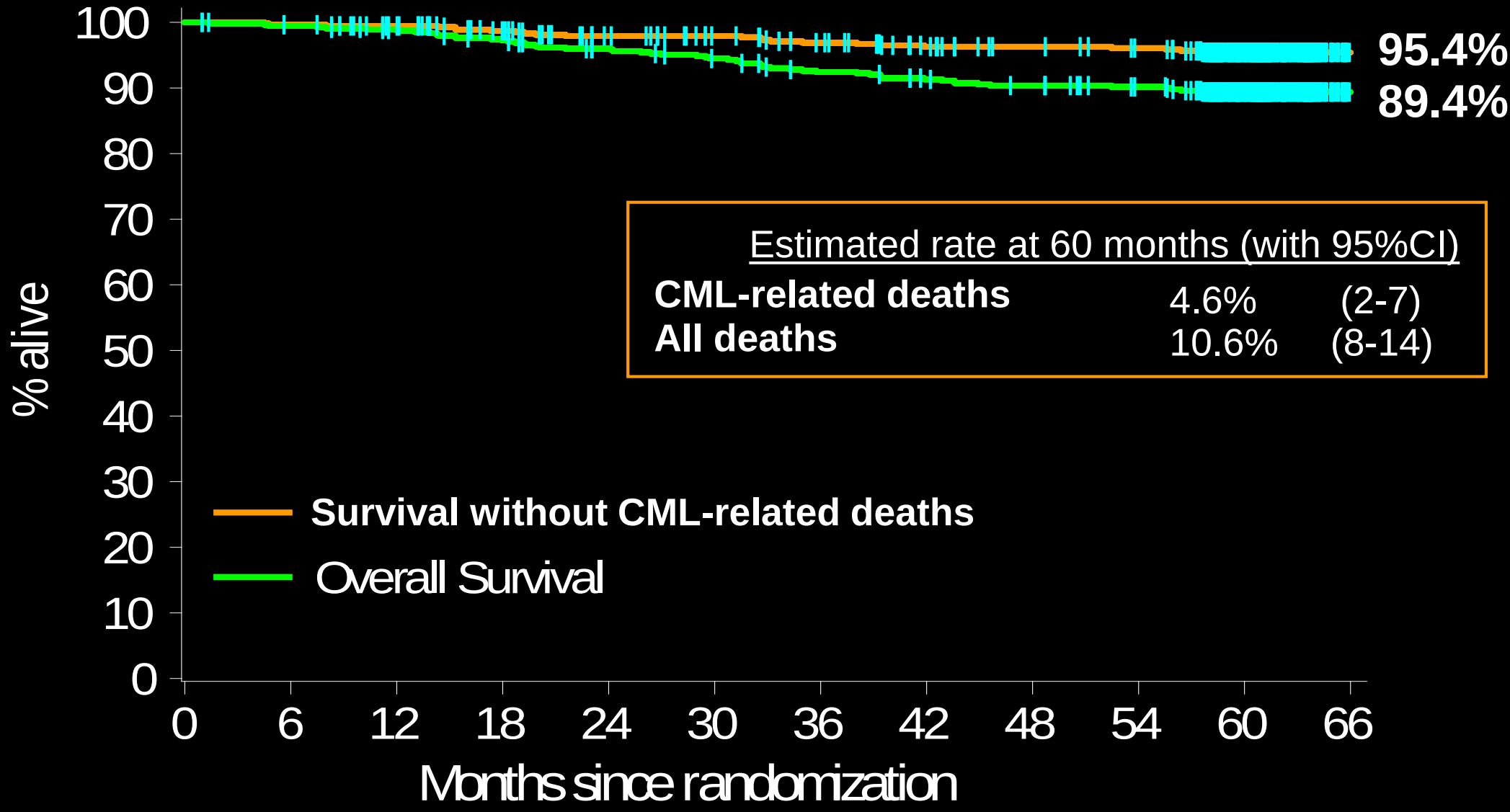
Reasons Not to Develop Gleevec

- You can’t make a drug against this target
- The drug will never work
- It will be toxic
- The drug will never make enough money to justify its development

Pt 0101


300 mg/day Imatinib
WBC x 10³
60
50
40
30
20
10
0
0
50
100
150
200
250
Days

Overall Survival on Imatinib

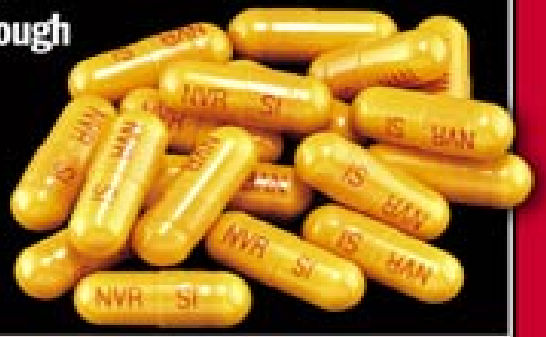


MAY 28, 2001

TIME

THERE IS NEW AMMUNITION IN THE WAR AGAINST CANCER. THESE ARE THE BULLETS.

Revolutionary new pills like GLEEVEC combat cancer by targeting only the diseased cells. Is this the breakthrough we've been waiting for?

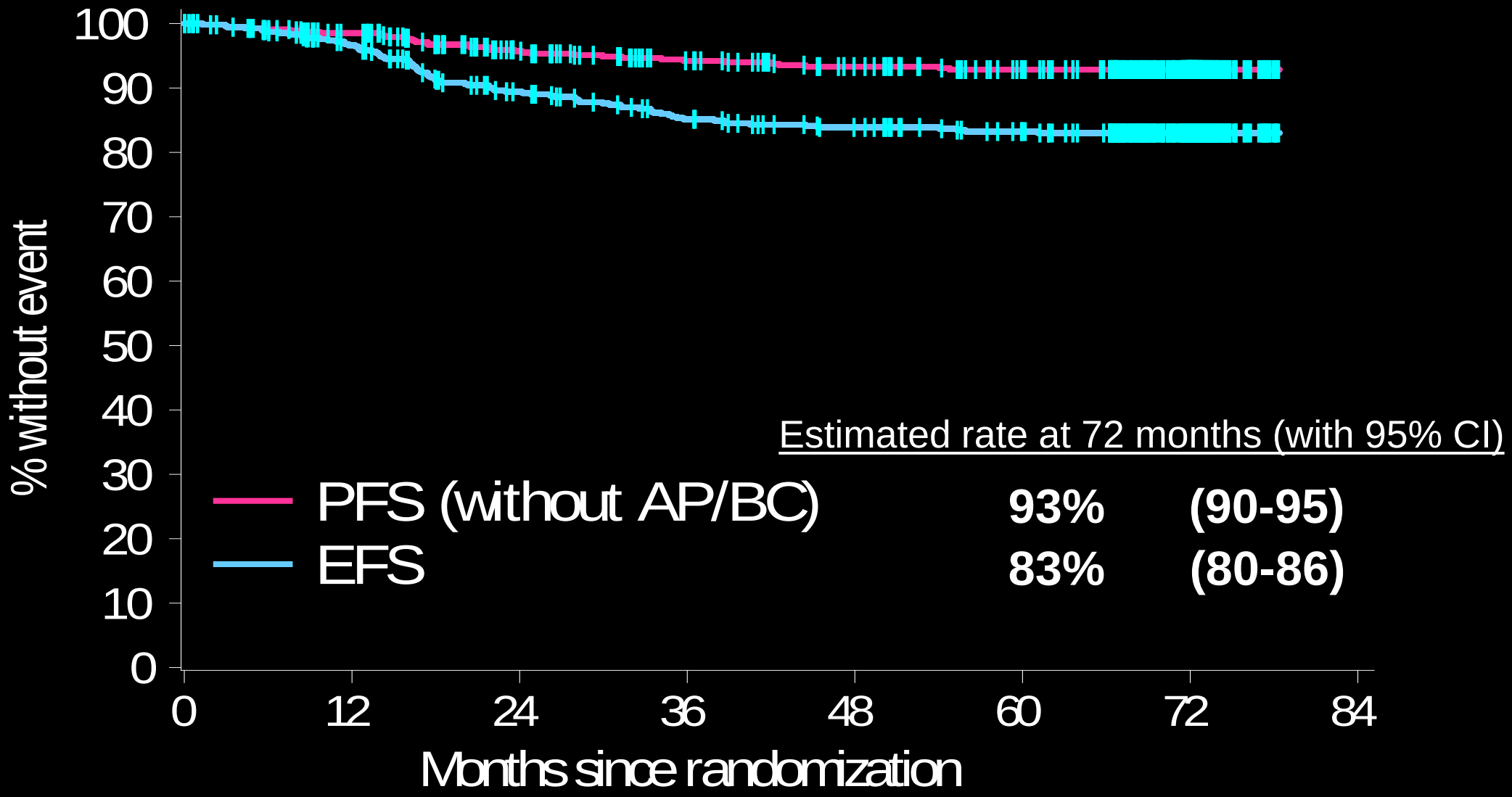


Survival According to Molecular Response

At 18 mos	Major Molecular Response or Better	No Major Molecular Response	P Value
Patients, n	164	89	
Deaths, n (%)	12 (7.3)	13 (14.6)	
Not due to CML	12 (7.3)	4 (4.5)	
Due to CML	0	9 (10.1)	
Estimated 10-year overall survival, %	93.0	85.6	.0367
Estimated 10-year freedom from CML-related death, %	100	90.5	< .0001

Hochhaus et al, NEJM 376:917, 2017

Relapses and Disease Progression



AP/BC, accelerated phase/blast crisis; EFS, event-free survival; PFS, progression-free survival

Hochhaus A. *et al*, Blood. 2007; 110, 11. Abstract 25. ASH 2007 Oral Presentation

CML Summary

- Imatinib is current standard therapy
  - Significant prolongs disease duration
- Relapses mostly due to kinase domain mutations
  - Novel ABL inhibitors have significant activity and are being used in newly diagnosed patients
- CML has been converted to a manageable condition

Where Else Has Gleevec Worked?

- Gastrointestinal stromal tumor
- Melanoma
- Hypereosinophilic syndrome
- Dermatofibrosarcoma protuberans (DFSP)

Lessons Learned From Clinical Trials With Gleevec

IT'S THE TARGET!

Good Target + Good Drug

=

Good Results

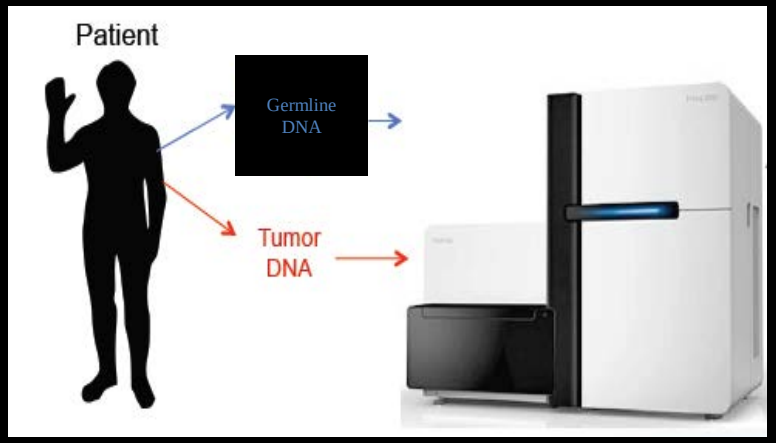
Translating the Success of Gleevec to Other Malignancies

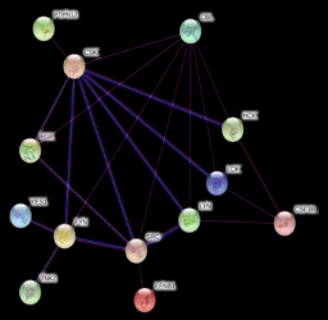
- Identify the appropriate therapeutic targets
  - Early molecular changes
- Treat early in the course of the disease
  - Develop reliable techniques for early detection
- Match the right patient with the right drug

Where Are We Now?

- Cancers are treated by site of origin (breast, colon, lung, prostate)
- Treatments are largely empiric and toxic
- Response rates are relatively low and which patients will respond cannot be predicted

The Future of Cancer Treatment

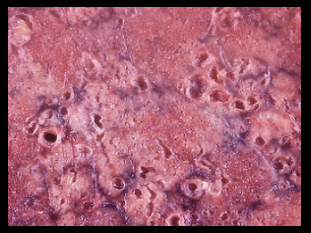




Patient Sample → OMIC Analysis → Treatment Options

The Future of Cancer Treatment

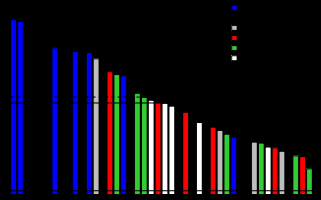
Patient sample



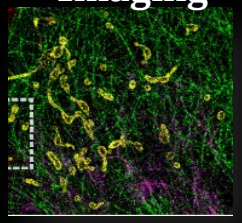
Preclinical data

Mutation

Subtype

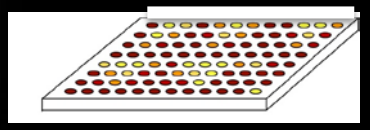


Imaging



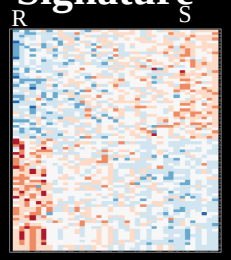
Functional Screens

In Vitro

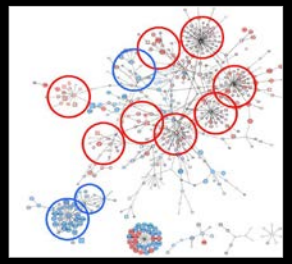


In Vivo

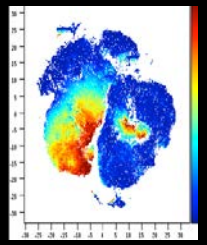
Transcriptional Signature



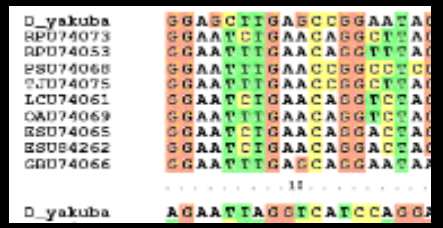
Pathway Activity



Immunopheno-typing



Computational biology



Data from all sources are integrated with clinical data to inform patient care

The 21st Century

Broad-based approach to cancer

- Specific therapies directed at critical targets
- Immune modulation
- Prevention and early diagnosis


LIGHT
NIGHT