Anatomy of a Breakthrough in Targeted Cancer Treatments
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

<table>
<thead>
<tr>
<th>1900</th>
<th>2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Pneumonia</td>
<td>Heart Disease</td>
</tr>
<tr>
<td>2) Tuberculosis</td>
<td>Cancer</td>
</tr>
<tr>
<td>3) Enteritis</td>
<td>Stroke</td>
</tr>
<tr>
<td>4) Heart Disease</td>
<td>COPD</td>
</tr>
<tr>
<td>5) Stroke</td>
<td>Accidents</td>
</tr>
<tr>
<td>6) Liver Disease</td>
<td>Pneumonia/Influenza</td>
</tr>
</tbody>
</table>
Factors Leading to Eradication and Treatability of Infections

- Improved sanitation and refrigeration
- Antibiotics
- Vaccination

Prevention
Specific treatments
Immune modulation
Historical Perspective on Chronic Myeloid Leukemia (CML)

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1845</td>
<td>First description of CML</td>
</tr>
<tr>
<td>1985</td>
<td>BCR-ABL</td>
</tr>
<tr>
<td>2001</td>
<td>Specific therapy for CML</td>
</tr>
</tbody>
</table>
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, PORTUGAL,

ETC. ETC.

WITH TWO COLOURED LITHOGRAPHS, AND NUMEROUS WOODCUTS.

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

MDCCLII.

Weisses Blut.


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

Dr. Birchow.
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
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

- Tumor Virology
  - Oncogenes 1976
- Protein phosphorylation 1933
- Tyrosine kinases 1979
  - TK inhibitors
  - Specific Therapy
- BCR-ABL 1985
- Gene mapping
- Chromosome analysis
Breakthroughs Requiring Seeing Things Differently

Even if the Answer is Right in Front of You
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

![Diagram showing the inhibition of Bcr-Abl tyrosine kinase by STI571](image)
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

Days

WBC x 10^3
Overall Survival on Imatinib

- Estimated rate at 60 months (with 95% CI):
  - CML-related deaths: 4.6% (2-7)
  - All deaths: 10.6% (8-14)

- Survival without CML-related deaths:
  - 95.4%

- Overall Survival:
  - 89.4%
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

<table>
<thead>
<tr>
<th></th>
<th>Major Molecular Response or Better</th>
<th>No Major Molecular Response</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>164</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>Deaths, n (%)</td>
<td>12 (7.3)</td>
<td>13 (14.6)</td>
<td></td>
</tr>
<tr>
<td>Not due to CML</td>
<td>12 (7.3)</td>
<td>4 (4.5)</td>
<td></td>
</tr>
<tr>
<td>Due to CML</td>
<td>0</td>
<td>9 (10.1)</td>
<td></td>
</tr>
<tr>
<td>Estimated 10-year overall survival, %</td>
<td>93.0</td>
<td>85.6</td>
<td>.0367</td>
</tr>
<tr>
<td>Estimated 10-year freedom from CML-related death, %</td>
<td>100</td>
<td>90.5</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

Hochhaus et al, NEJM 376:917, 2017
Relapses and Disease Progression

Estimated rate at 72 months (with 95% CI)

- PFS (without AP/BC): 93% (90-95)
- EFS: 83% (80-86)

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

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

Patient

Germline DNA

Tumor DNA

[Diagram showing patient sample process]

[Flowchart illustrating OMIC analysis and treatment options]
The Future of Cancer Treatment

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