Frontiers in Cancer Therapy

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Objectives

The Past: Alkylating agents

The Present: Tyrosine Kinase Inhibitors

The Future: Gene Expression, Metabolic cancers, CAR T-cells
The Hallmarks of Cancer
(adapted from Hanahan and Weinberg, Cell 2000; 100: 57-70)

- Sustained Angiogenesis
- Evading Apoptosis
- Limitless Replicative Potential
- Self-sufficiency in Growth Signals
- Insensitivity to Anti-Growth Signals
- Tumor Invasion and Metastasis
Cancer cells grow faster than normal cells

How can this difference be exploited?
Nitrogen mustard

British Army blinded by the Mustard gas
These guys noticed that soldiers dying of mustard gas poisoning had profound lymphoid hypoplasia and myelosuppression.
In 1942 Goodman and Gilman convinced a surgical colleague to treat a patient with non-Hodgkins lymphoma with nitrogen mustard. The patient went into remission for a few weeks. This initial discovery was the first alkylating agent. A type of cancer chemotherapy that continues to be widely used today.
Alkylating Agents

- Oldest effective chemotherapy drugs.
- Discovered accidentally after sulfur gas exposure in WWI.
- Currently used to treat many cancers (still used for lymphoma).
Alkylators: Mechanism

- Covalent bonding to proteins, RNA, DNA.
- DNA binding most critical to cytotoxicity, by limiting cell replication and leading to strand breaks.
- Selectivity derives from diminished repair capacity.
What are the advantages and disadvantages of this approach?
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- Effective for a broad array of cancers.
- Lots of side effects.
Change Gene Expression

Escape the Immune System

Independent of Growth Signals

Reprogrammed Energy Metabolism

Adapted from: Low and Tergaonkar TiBS September
Can we exploit any of these differences to treat patients with cancer?
Three Stories

- Chronic Myeloid Leukemia (CML)
- Gastrointestinal Stromal Tumor (GIST)
- CAR T-cells
Chronic Myeloid Leukemia (CML)

15% of adult leukemia

1) **Chronic Phase** (excess white blood cells that differentiate and function normally)
2) **Accelerated Phase**
3) **Blast Crisis** (acute leukemia)
In 1960 Peter Nowell and David Hungerford described a small acrocentric chromosome in CML cells.
In 1973 Janet Rowley figured out that the Philadelphia Chromosome was the product of a reciprocal translocation between chromosome 9 and chromosome 22.

In the 70’s and 80’s work on transforming retroviruses identified v-ABL (a murine leukemia virus). It was realized that the human homolog of v-ABL (c-ABL) was normally on the long arm of chromosome 9 but on chromosome 22 in CML cells.
Tyrosine Kinase

- An enzyme that can transfer a phosphate group from ATP to a protein.
- Acts as an “on-off” switch for enzyme activity.
- Can be activated by binding of a ligand to a receptor.
- Typically includes a catalytic domain and a regulatory domain.
A library of chemical compounds was screened to identify drugs that could block BCR-Abl kinase activity.

STI-571, Imatinib
Phase 2 clinical trials of imatinib for CML. The results of the phase 2 studies are shown in chronic phase patients who previously received interferon therapy, and accelerated phase and blast crisis patients.

Brian J. Druker Blood 2008;112:4808-4817
Figure 1. Survival with chronic myeloid leukemia over time (1993-2013): the German CML-Study Group experience. Courtesy of Prof H Kantarjian; adapted, with permission, from Harrison’s Principles of Internal Medicine, 2014.
**BOX 1. | Targets of tyrosine-kinase inhibitors.**

Selected tyrosine-kinase inhibitors, and the proteins they inhibit in vitro, are summarized below. The list of targets is not comprehensive and these drugs might also inhibit additional proteins that are not listed here. The majority of these drugs, which are either approved or in clinical testing, are multikinase inhibitors with activity against one or more of the downstream kinase partners of various fusion genes, in addition to other kinases depicted below. Notably, the in vitro inhibitory effects of these compounds have not always translated into clinical benefit in case reports and/or in clinical trials.

| Protein | Alectinib | Apatinib | Brigantinib | Cabozantinib | Ceritinib | Crizotinib | Dabrafenib | Dasinib | Dasatinib | Erlotinib | Gefitinib | Geftinib | Ipatinib | Lariquidib | Largactilinib | Lorlatinib | Nilotinib | Pazopanib | Ponatinib | Regorafenib | Sorafenib | Sunitinib | Vandetanib | Vemurafenib |
|---------|-----------|-----------|-------------|--------------|-----------|-----------|------------|--------|----------|-----------|-----------|----------|----------|-----------|-------------|-------------|-----------|----------|-----------|-----------|------------|-----------|----------|-----------|----------|
| ABL     |           |           | X           | X            | X         | X         |            |        |          |           |           |          |          |           |             |             |           |          |           |           |            |           |          |           |           |
| ALK     | X         | X         | X           | X            |           |           |            |        |          |           |           |          |          |           |             |             |           |          |           |           |            |           |          |           |           |
| AXL     |           |           | X           |              |           |           |            |        |          |           |           |          |          |           |             |             |           |          |           |           |            |           |          |           |           |
| BRAF    |           |           | X           |              |           |           |            |        |          |           |           |          |          |           |             |             |           |          |           |           |            |           |          |           |           |
| EGFR    | X         |           | X           | X            | X         |           |            |        |          |           |           |          |          |           |             |             |           |          |           |           |            |           |          |           |           |
| FGFR    |           |           |             |              |           |           |            |        |          |           |           |          |          |           |             |             |           |          |           |           |            |           |          |           |           |
| FLT3    |           |           |             |              |           |           |            |        |          |           |           |          |          |           |             |             |           |          |           |           |            |           |          |           |           |
| HER2    |           |           |             |              |           |           |            |        |          |           |           |          |          |           |             |             |           |          |           |           |            |           |          |           |           |
| KIT     | X         | X         | X           |              |           |           |            |        |          |           |           |          |          |           |             |             |           |          |           |           |            |           |          |           |           |
| MET     |           |           | X           |              |           |           |            |        |          |           |           |          |          |           |             |             |           |          |           |           |            |           |          |           |           |
| PDGFR   | X         |           | X           |              |           |           |            |        |          |           |           |          |          |           |             |             |           |          |           |           |            |           |          |           |           |
| RET     | X         | X         | X           |              |           |           |            |        |          |           |           |          |          |           |             |             |           |          |           |           |            |           |          |           |           |
| ROS     |           |           | X           | X            |              |           |            |        |          |           |           |          |          |           |             |             |           |          |           |           |            |           |          |           |           |
| SRC     |           |           |             |              |           |           |            |        |          |           |           |          |          |           |             |             |           |          |           |           |            |           |          |           |           |
| TIE2    |           |           | X           |              |           |           |            |        |          |           |           |          |          |           |             |             |           |          |           |           |            |           |          |           |           |
| TRK     | X         |           | X           |              |           |           |            |        |          |           |           |          |          |           |             |             |           |          |           |           |            |           |          |           |           |
| VEGFR   | X         | X         |             |              |           |           |            |        |          |           |           |          |          |           |             |             |           |          |           |           |            |           |          |           |           |
What are the advantages and disadvantages of this approach?
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- More specific
- Can be overcome by small changes in the target tyrosine kinase
- Overlap between different kinases
Gastrointestinal Stromal Tumor

- Tumor that typically arises in the stomach or intestines.
  Patients present with early satiety, anemia, abdominal pain.
- About 1% of all intestinal neoplasms.
- Treated by surgical resection.
- About 50% recur within 5 years following complete resection.
In 1998 Hirota and colleagues identified activating mutations of the tyrosine kinase c-kit in GIST samples. This was about the time CML patients were first being treated with Imatinib,

Why doesn’t Imatinib work in kids with GIST?

- Approximately 85% of GIST tumors in pediatric patients and 15% in adult patients do not have mutations in *KIT* or *PDGFRA* (wt-GIST).
- These tumors do not respond to Imatinib
- Approximately 88% of patients with wt-GIST are SDH deficient.

*Boikos, Helman, et al. (2016) JAMA Oncology*
What happens to our classification of different types of cancers as we learn more about the molecular biology of the diseases?
Increased Krebs Cycle metabolites inhibit TET DNA hydroxylases
How do we treat a Krebs Cycle Defect?
Using the Immune System to Treat Cancer

- Chimeric Antigen Receptor T-cells
Redirecting Specificity for Adoptive Cell Therapies

- Free of MHC restriction
- signals for full activation are self-contained

Adapted from Lee et al, Clin Can Res, 2012
Figure 1 Chimeric antigen receptor (CAR) structures

Figure 2 Different approaches to improving chimeric antigen receptor (CAR)-T-cell therapies

T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial

Daniel W Lee, James N Kochenderfer, Maryalice Stetler-Stevenson, Yongzhi K Cui, Cindy Delbrook, Steven A Feldman, Terry J Fry, Rimas Orentas, Marianna Sabatino, Niral Shah, Seth M Steinberg, Dave Stroncek, Nick Tschemria, Constance Yuan, Hua Zhang, Ling Zhang, Steven A Rosenberg, Alan S Wayne, Crystal L Mackall

- 60-80% CR Rate in multiple trials (NCI, Penn, MSKCC, Seattle)
- The majority of the early phase trials included children

Lancet, 2014
What are the advantages and drawbacks of this approach?
Every patient at the NIH Clinical Center is evaluated for a clinical trial