Combination Therapy for Leukemia and Solid Tumors
Mohammad Azam, PhD
Cancer Pathology Group
Division of Pathology and Laboratory Medicine
Background

• TKI resistance is a widespread phenomenon

• In particular, AML can be treated with TKIs, but cancer “stem cells” remain and cancer reoccurs.

LSC BCR/ABL

Imatinib (Gleevec), Nilotinib, Dasatinib

Innovation
C-Fos, Mkp1 and Zfp36 were found to be overexpressed in TKI resistant cells.
Genetic Depletion and Pharmacological Inhibition of Dusp1 and c-Fos in CML

Genetic Depletion

<table>
<thead>
<tr>
<th>Treatment</th>
<th>WT</th>
<th>Dusp1^-/-</th>
<th>Fos^-/-</th>
<th>Dusp1^-/-/Fos^-/-</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCR/ABL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCR/ABL + IM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pharmacological Inhibition

- DFC is a public domain c-Fos inhibitor
- BCI is a proprietary Dusp1 inhibitor (owned by University of Pittsburgh; unlicensed)
Pharmacological Inhibition of Dusp-1 and c-Fos in AML

NSGS mice transplanted with 0.25M cells; drugs injected after 2 weeks; BM analyzed 6 weeks after treatment

Mouse model of human AML resistant to chemotherapy and FLT 3 inhibition

Percent human CD45 in BM

In vivo leukemia

In vitro CFU assays

[DFC (0.2 uM), BCI (0.5 uM) and AC220 (1 nM)]
Pharmacological Inhibition of Dusp-1 and c-Fos in solid tumors

Lung Adenocarcinoma

Lung Sarcoma
Dusp1 as a critical node in myeloproliferative neoplasms

[A] WT- donor

[B] WBC (K/L) in PB

[C] Dusp1-/- donor

[D] WBC (K/L) in PB

Percent GFP and Cherry

Weeks

Cincinnati Children's
innovation
MARKET DATA

Cost of TKI treatment is very expensive despite being ineffective for many patients.
- The original drug in the tyrosine kinase inhibitors (TKI) drug class, imatinib (Gleevec, Novartis) launched in 2001 at a price of $30,000 per year and had a price hike in 2012 to $92,000 per year.
- There were three new drugs approved by the FDA in 2012 for CML — all BCr-Abl TKIs:
  - Ponatinib (Iclusig, Ariad) costs $138,000 per year
  - Omacetaxine (Synribo, Teva) costs $28,000 for induction and $14,000 for a maintenance course
  - Bosutinib (Bosulif, Pfizer) costs around $118,000 per year

TKI Resistance
- 15-30% of CML patients diagnosed in the chronic phase will meet some definition of resistance to imatinib.
  - Another study found an estimated 24% of patients showed primary or intrinsic resistance to imatinib.
- Internal tandem duplication (ITD) mutations in FLT3 are detected in approximately 20% of AML cases and are associated with poor prognosis.
- According an American Journal of Cancer Research publication, almost all NSCLC patients initially responding to gefitinib or erlotinib would inevitably progress to develop acquired resistance, mostly within 6-12 months.
  - Several underlying mechanisms have been discovered, but more efforts are needed since 30% of the acquired resistant cases remain unexplainable.
RESEARCH ACTIVITY

According to the American Cancer Society, many studies are being done to find more effective and safer treatments for AML, CML, and non-small cell lung cancer (NSCLC).

- Strategies/Research to Address TKI Resistance:
  - One potential strategy involves taking advantage of the requirement for BIM and enhancing TKI-induced apoptosis by adding a BCL-2 inhibitor.
  - For genomic alterations that co-occur with EGFR mutations, drug combinations could be pursued. For example, as IGF1R signaling can mediate disease persistence through the PI3K–AKT pathway, addition of a GF1R-specific antibody or a PI3K or AKT inhibitor to TKI treatment could be beneficial.
  - 2nd and 3rd Generation TKIs
  - Treatment options available for patients with imatinib-resistant CML include dasatinib, nilotinib, bosutinib, and ponatinib, as well as the non-TKI salvage agent omacetaxine mepesuccinate.
  - The National Comprehensive Cancer Network recommends a BCR-ABL kinase domain mutational analysis for all patients who have a suboptimal initial response to TKI therapy. Identification of the point mutation at the time of treatment failure is essential for determining the appropriate salvage therapy; second-line and third-line treatment options should be chosen based on the known effectiveness of a specific TKI for a specific point mutation.
  - According to research presented by Oliver Ottmann, MD, from Cardiff University in the United Kingdom, the small molecule ABL001 exhibits rapid anti-tumor activity in heavily pretreated patients with CML. Interim results of the first-in-human study provide “proof of principle of the effectiveness of allosteric inhibition of the BCR-ABL kinase in the treatment of CML.”
  - Clinical efforts have explored the therapeutic potential of inhibitors targeting kinases that are important in cell cycle progression and mitosis, such as aurora kinases, polo-like kinase 1 (PLK1), and cyclin dependent kinases (CDK).
  - Combination therapy: Inhibitors with improved single agent activity such as AC220 would have additional beneficial effect in combination with chemotherapy.
INTELLECTUAL PROPERTY

“Therapy for Leukemia”
• U.S. Continuation-in-Part Patent Application No. 14/048,806
• E.P.O. Patent Application No. 12774776.4
• Canadian Patent Application No. 2,832,860

“Therapy for Solid Tumors”
• PCT Application No. PCT/US2015/033269

“Therapeutic Targeting of Myeloproliferative Neoplasms by Dusp1 Inhibition”
• U.S. Provisional Patent Application No. 62/170,834

“Small Molecule Inhibitors of Dusp6 and Uses Thereof” (owned by University of Pittsburgh)
• U.S. Patent No. 9,127,016
• U.S. Patent Application No. 14/795,056
Future Work

- Test additional Dusp inhibitor analogs from University of Pittsburgh
- PK/PD in mice and possibly primates
- Test in additional AML mouse models to identify all relevant patient population
- Develop a formulation for the combination of Dusp and c-Fos inhibitors
- Crystallization and detailed understanding the target
- Test in additional indications