CANCER THERAPEUTICS: A NOVEL APPROACH

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Outline

- Introduction
- Hit, HBRI1: identification & characterization
- Leads, HBRI2 & HBRI3: identification & characterization
- Next steps
### 2012 Estimated US Cancer Incidence & Mortality

#### 2012 Estimated US Cancer Deaths

<table>
<thead>
<tr>
<th>Disease</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>301,820</td>
<td>275,370</td>
</tr>
<tr>
<td>Prostate</td>
<td>9%</td>
<td>14%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>6%</td>
<td>7%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>All other sites</td>
<td>25%</td>
<td>24%</td>
</tr>
</tbody>
</table>

#### Causes of Death

- Lung & bronchus: 26%
- Breast: 14%
- Colon & rectum: 9%
- Pancreas: 7%
- Ovary: 6%
- Leukemia: 4%
- Non-Hodgkin lymphoma: 3%
- Uterine corpus: 3%
- Liver & intrahepatic bile duct: 2%
- Brain/other nervous system: 2%
- All other sites: 24%
Current Treatment Approaches, Issues

• **Standard Triple Threat**
  - Surgery
  - Chemotherapy (fluorouracil)
  - Radiation Therapy
  - Adverse effects on normal tissues

• **Targeted Therapies** - mAbs & Tyrosine Kinase Inhibitors
  - Avastin® - VEGF-Receptor mAb
  - Sutent® - VEGF-Rs & PDGF-Rs Tyr Kinase inhibitor
  - Costly, Production Limitations, Off-target Effects
HBRI Created First-in-Kind Non-Toxic Anti-Cancer Agents

- Breast Cancer
- Prostate Cancer
- Colon Cancer
- Pancreatic Cancer
- Other Cancers
Pathway Dysregulation in Cancer

- Increased proliferation
- Increased metastasis
- Resistance to apoptosis
Compound Screen: A Pathway-Selective Inhibitor
Compound Screen: A Pathway-Selective Inhibitor

- Screened 76,000 compounds via a pathway-selective assay
- Identified 181 primary “hits”
- Confirmed 101 “hits”
- 14 pathway-selective “hits”
- 1 potent & reproducible “hit” developed
HBRI1 Inhibits Pathway-Specific Transcriptional Activity

IC$_{50}$ 22nM

*HEK-293, normalized to DMSO
**HBRI1 Decreases Prostate Cancer Cell Proliferation & Cytotoxicity**

**LNCap Proliferation**

- IC$_{50}$ 60 nM

**LNCap Cytotoxicity**

- No effect at 5000 nM after 24 hrs
- Monitoring GAPDH release

**Primary Mouse Fibroblasts**

- No change in proliferation or viability with 1 week of HBRI1 treatment
Medicinal Chemistry Development of HBRI1:

- Weakly potent
- Lipophilic
- Poorly soluble

**Hit**

**Validated Hit**

**Structure-Activity Relationships**

**Structure-Property Relationships**

**Analog Synthesis**

**Several Cycles**

**Data Analysis**

**Biological Screen**

**Lead**

- Highly potent
- Drug-like properties
HBRI1 SAR Yields Potent Inhibitors, HBRI2 & HBRI3

- HBRI3 is 5-fold more potent than HBRI1
- HBRI3 is 10-fold more water soluble than HBRI1
HBRI1-3 Stimulate Prostate Cancer Cell Apoptosis & Regulate Target GeneExpression

**Apoptosis**

- HBRI1 induces apoptosis:
  - HEK-293
    Caspase-Glo (dose dependent increase)
  - HCT-116 (Colon Cancer)
    PARP cleavage observed (1μM, 16h)

![Gene Expression Graphs](attachment:image.png)
HBRI2 & HBRI3 Stimulate Prostate Cancer Cell (PC-3) Apoptosis

**HBRI2**

- EC₅₀ 117nM

**HBRI3**

- EC₅₀ 32nM

- Apoptosis monitored by Caspase Activation.
HBRI2 & HBRI3 Stimulate Colon Cancer Cell (HCT-116) Apoptosis

HBRI2
EC$_{50}$ 143nM

HBRI3
EC$_{50}$ 15nM
HBRI2 & HBRI3 Inhibit Breast Cancer Cell (MDA-MB-231) Proliferation

**HBRI2**
- **IC$_{50}$**: 250 nM

**HBRI3**
- **IC$_{50}$**: 24 nM
HBRI2 & HBRI3 Inhibit Pancreatic Cancer Cell (Mia-PaCa) Proliferation

- HBRI2: IC\textsubscript{50} 100nM
- HBRI3: IC\textsubscript{50} 55nM

- Similar decreases in proliferation of prostate & colon cancers were observed.
HBRI2 & HBRI3: Initial Pharmacokinetic Studies

Chemical & Metabolic Stability

<table>
<thead>
<tr>
<th></th>
<th>Chemical Stability (h)</th>
<th>Metabolic Stability (t_{1/2}, min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Human</td>
</tr>
<tr>
<td>HBRI 1</td>
<td>120</td>
<td>NA^{1}</td>
</tr>
<tr>
<td>HBRI 2</td>
<td>NA^{1}</td>
<td>NC^{2}</td>
</tr>
<tr>
<td>HBRI 3</td>
<td>NC^{2}</td>
<td>77</td>
</tr>
</tbody>
</table>

1NA = Not Tested
2NC = No Change

Rat in vivo studies: no acute toxicity of HBRI3
- Single dose at 200 mg/kg
- 7-days of daily dosing at 30 mg/kg: no effect on weight gain compared to vehicle-treated animals
Prostate Cancer Xenograft Study in Mice

- HBRI3 reduced PC3 tumor volume by 80%
Prostate Cancer Xenograft Study in Mice

Excised PC3 Tumors

- **Vehicle**
- **HBRI1** (original hit)
- **HBRI3** (the lead)

- **HBRI3** decreased PC3 tumor size in 80% of animals
Colon Cancer Xenograft Study in Mice

HCT116 xenograft nu/nu mice

- Vehicle
- HBRI3

Graph showing tumor volume in mm$^3$ over days.
Summary

• HBRI3 is a novel anti-cancer agent widely useful against a number of cancers

• In the presence of other anti-cancer drugs, HBRI3 may be useful as a synergist to increase the potency and decrease the toxicity or off-target action of anti-cancer drugs.

• HBRI3 appears to work on cycling cells such as cancer cells and does not appear to affect normal cells, hence the non-toxicity.

• HBRI3 may be useful for hypoxic tumors (solid tumors)
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