Small molecule PAICS inhibitors for metastatic breast cancer

MRC Technology

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The challenge: breast cancer

• Breast cancer is the most commonly occurring cancer in women – 1.5 million women worldwide are diagnosed each year
• Despite progress in early screening programmes and the development of targeted therapies, ~0.5 million women die of breast cancer a year
• Triple negative breast cancer is a particularly aggressive subtype (~15% of breast cancers) and is prone to relapse and metastases
• There are still no effective therapies for metastasis, and most current cancer therapies target primary disease

• A novel therapeutic that targets both primary tumour growth and metastases would be of significant benefit in breast cancers, as well as other cancer types
PAICS is a novel cancer metabolic target

- PAICS is a bifunctional enzyme involved in the *de novo* purine biosynthesis pathway.

- Rapidly dividing cancer cells are more dependent on *de novo* purine biosynthesis than normal cells, which grow more slowly.

- **Potential therapeutic window** for targeting PAICS.

- Targeting cancer metabolism is an area of interest for both biotech and pharma companies.

Inhibitors of PAICS
SAICAR synthetase domain

Synthetase domain

Carboxylase domain

(phosphoribosylaminomimidazole carboxylase, phosphoribosylaminomimidazole succinocarboxamide synthetase)
Target validation for PAICS

- **PAICS mRNA is upregulated in various tumour types:** breast, colon, lung, melanoma, prostate

- Knockdown of PAICS in breast cancer cells **inhibits proliferation and migration in vitro**

- shRNA knockdown of PAICS **inhibits primary tumour growth and metastases in vivo** mouse models of breast cancer, lung cancer and melanoma
Development of small molecule PAICS inhibitors

- MRCT developed a biophysical assay and carried out fragment screening of PAICS
- Follow up medicinal chemistry was carried out on hits to obtain highly potent, bioactive PAICS inhibitors
- Compounds show good potency and good PK properties in vivo
- Key compounds are tolerated very well in mice (14 day study)
- Filing composition of matter IP around these inhibitors in progress

<table>
<thead>
<tr>
<th>Compound</th>
<th>Biochemical IC50 (nM)</th>
<th>Cell IC50 (nM)</th>
<th>Average LogD</th>
<th>Kin Sol (M)</th>
<th>Mouse t1/2 (po)</th>
<th>Mouse Clint (mL/min/kg)</th>
<th>Mouse Bioavailability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound 1</td>
<td>11.5</td>
<td>180</td>
<td>1.3</td>
<td>218</td>
<td>3.2</td>
<td>35.0</td>
<td>97*</td>
</tr>
<tr>
<td>Compound 2</td>
<td>3.4</td>
<td>75</td>
<td>1.6</td>
<td>224</td>
<td>3.1</td>
<td>15.0</td>
<td>73</td>
</tr>
</tbody>
</table>

Mean plasma exposure (ng/mL) v time for po dosing (10mg/kg) in mice
Red: compound 1
Blue: compound 2
Biological effects of PAICS inhibitors

- PAICS inhibitors have a potent cytostatic effect
- Inhibit 2D and anchorage-independent 3D breast cancer cell growth and cellular migration
- Inhibitors have been profiled in panel of >200 cell lines, 12 tumour types
- PAICS inhibitors have potential beyond breast cancer
- PAICS inhibitors outperform existing folate anti-metabolite methotrexate in breast cancer cells, sparing normal human mammary epithelial cells

![Graphs showing growth inhibition of MDA-MB-231 TNBC cell line and Normal human mammary epithelial cells]
Cellular target engagement studies

- Metabolomic studies confirmed a dose-dependent decrease in AICAR/SAICAR and accumulation of the precursor AIR consistent with cellular IC$_{50}$ values
In vivo efficacy studies currently underway

- Murine xenograft model of breast cancer metastasis being tested
  
- Assessment of orthotopic growth
  - tumour volume
  - weight
  - bioluminescent imaging (BLI) quantification
  
- Assessment of spontaneous metastasis
  - real time BLI
  - Q-PCR
  - Histology
  - ex-vivo imaging

Ex vivo confirmation of metastases
Summary

PAICS is an emerging, exciting therapeutic target for cancer growth and metastasis

- Targeting PAICS may have potential in a number of different cancer indications
- We have generated novel, potent inhibitors of PAICS that it will be possible to gain an IP position for
- Inhibitors have on-target activity and demonstrate phenotypic effects
- Inhibitors are tolerated in vivo and have suitable PK to enable in vivo proof of concept studies
- Key in vivo xenograft experiment currently underway and data will be available at the end of May

- We are interested in finding commercial partners for further collaborations or licencing to explore the potential of these novel inhibitors further