Oncoology Drug Discovery in an Academic Setting: Pipeline or Pipedream?

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Drug Discovery Unit
Paterson Institute for Cancer Research

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• I do not consider myself to be an Academic
• I have only worked in Oncology for 8 years
MCRC Drug Discovery Unit Background

- Manchester Cancer Research Centre
- Paterson Institute for Cancer Research
- Specialist cancer research institute core funded by Cancer Research UK
- Co-located with Christie Hospital
- Focus on niche cancer targets with clear route to clinical evaluation
- Targets include cell metabolic pathways, DNA repair mechanisms and epigenetics
- Access to PICR investigators
- Access to the clinic and translational medicine
• Target Identification
• Hit Identification
Talk Structure

• Context
  – Drug discovery in Oncology setting
  – Target selection

• Screening
  – Subset screening
  – Fragment screening

• Collaborations
  – Pharma
  – Hit finding

• Bioinformatics
  – Collateral vulnerability
Challenges of Drug Discovery in Oncology

- **Initial cancer diagnosis & staging**
- **Only primary tumour detected**
  - Debulk
  - Operable
  - Surgery
    - Neo adjuvant
    - Adjuvant & wait
      - Watch & wait
      - “Cured”
  - Inoperable
    - Metastatic
      - 1st line
      - 2nd line
      - 3rd etc.
      - Palliative
      - Local or Metastasis
      - Relapse
    - Increasingly refractory
    - Early Drug Development

**New drugs are tested first on the most refractory/resistant population**
Target identification: Strategic Considerations

CRUK strategy:
- Novel/higher risk
- Leverage locality

Areas of biology:
- Addiction, RTx, stem cells, DDR, hypoxia, metabolism but not cell cycle, inv/met, angiogenesis, immunology

MCRC strategy:
- Lung, melanoma, haems, RTx, women.
- Local PIs

Competition:
- Avoid mainstream unless advantage
- Consider niches

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## Prioritising Targets: Clinical Line of Sight

<table>
<thead>
<tr>
<th>Will it work?</th>
<th>Clinical Hypothesis</th>
<th>How clear is the path to clinical testing?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical Hypothesis</td>
<td>How strong is the preclinical target concept?</td>
<td></td>
</tr>
<tr>
<td>Chemical Feasibility</td>
<td>Can we deliver the required drug attributes in a molecule?</td>
<td></td>
</tr>
<tr>
<td>Biological Feasibility</td>
<td>Can we measure the desired biological profile?</td>
<td></td>
</tr>
<tr>
<td>Competitive Position</td>
<td>Can we compete in this area (or not)?</td>
<td></td>
</tr>
</tbody>
</table>

### Emphasis on clinical alignment

- **Ratings:**
  - Normal risk profile for a drug discovery project
  - Significant risk to be addressed in project plan
  - Major risk to be addressed *before* starting project

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Automation of *in vitro* HTRF assays on the Labcyte access workstation platform

Emma E. Fairweather, Samantha J. R. Fritzl, Alexandra I. J. Stowell, Graeme J. Thomson, Ian D. Waddell and Donald J. Ogibie

Cancer Research UK Drug Discovery Unit, Paterson Institute for Cancer Research, University of Manchester, Wilmslow Road, Manchester, M20 4BX, UK
Subset Screening: Kinase Inhibitor Design

- Targeting a tyrosine kinase associated with a niche oncology setting
  - Aim to improve selectivity over related kinases implicated in clinical toxicity

**Structure-Guided Optimisation**
- Exploit X-ray structures and literature scaffolds
- Focused med chem optimisation

**Library Screening**
- Virtual screening
- Fragment library screen
- Kinase subset library

Early insight into SAR relating to affinity/selectivity
Identification of diverse scaffolds for optimisation
• Kinase library profiled against 2 kinases
  – 9000-cpd combinatorial library based on diverse kinase inhibitor scaffolds
  – Single-point % inhibition at both 30 & 100mM
  – Confirmation and expansion around selected hits by re-synthesis and IC50 determination

• Screening data typically presents challenges in analysis
  – Few actives among many inactives
  – Single-point data noisier than full IC50
  – Chemical integrity/interference

• Does combinatorial library offer advantages for understanding SAR?
  – i.e. 10’s of scaffolds represented by 100’s of compounds
• Explore activity profile for individual sub-libraries

Simple activity classification → As pie chart – full library → Pie charts per sub-library

Docking of cores E & H examples

R1 R2
Subset Screening: Decision Tree Analysis

Which descriptors are related to observed activity/inactivity?

- Two activity classes: **HIGH** (>50%) or **LOW** (<50%) inhibition for Kinase A

- Descriptors: 2D properties (MW, xLogP, H-bond counts, etc) plus core labels

Core H: low MW + low LogP → high affinity for Kinase A

But similar results found for Kinase B
• Core H compounds
  – Highlights that none were particularly selective to start with
  – Classical analysis did not predict active compounds
  – Simple software tool to better predict the features we want

Classical drug discovery
<table>
<thead>
<tr>
<th>Target Validation</th>
<th>Pre-Hit Identification</th>
<th>Hit Identification</th>
<th>Lead Optimisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
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<td>13</td>
<td></td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>15 (AZ)</td>
<td></td>
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</tr>
</tbody>
</table>

**DDU Portfolio**

**3**

**14**

**13**

**15 (AZ)**

**Partner**
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Fragment screening: As a Target Selection Tool

- Prioritisation of potential new targets
  - Biological – technical feasibility
  - Chemical – ligandability,

- Fragment screening as an approach to quantify ligandability
  - 3000-compound diverse fragment library
  - Various screening platforms – biochemical assay, biophysical (SPR, thermal melt)
  - Assess against existing targets – use to prioritise future targets

Heat-map of fragment library
hits from biochemical screening
Dark green >50% inhib @ 500uM, light green 25-50%.
Horizontal axis: specific compounds.
**Fragment screening data broadly in accord with structural features**

- **Protein kinase** – typical kinase binding site, known ligands in literature
- **Epigenetics target** – large polar binding site
- **DNA repair target** – open, solvent exposed site, phosphate-binding sub-site
- **Dehydrogenases** – small polar substrate site adjacent to large co-factor site

**Heat-map of fragment library hits from biochemical screening**

Dark green >50% inhib @ 500uM, light green 25-50%.
Horizontal axis: specific compounds.
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Progressing Projects: Partnership Models

- **Target Selection**
- **Hit Identification**
- **Lead Identification**
- **Lead Optimisation**
- **Preclinical Development**
- **Clinical Development**

**In vitro POP**

**In vivo POP**

**Clinical POP**

**DDU**

**Partner**

**DDU**

**Partner**

**DDU/Partner**

**DDU**

**Partner**

- DDU role is to “de-risk” target for a commercial partner
- Timing of handover will be when POP* data reduces risk to acceptable level for partner
- Earlier engagement of partners during HI
- First refusal at agreed milestone

* POP = Proof of Principle (i.e. compound produces desired biological effect in test system)
Press Release

CRT, University of Manchester and AstraZeneca work together to seek new cancer drugs

Friday 14 June 2013

Cancer Research Technology Press Release

Cancer Research Technology, the commercial arm of Cancer Research UK, the University of Manchester and AstraZeneca today announced two agreements to seek new cancer drugs.

In the first agreement, scientists at the Cancer Research UK Paterson Institute for Cancer Research at the University of Manchester will develop potential new drugs which target a key protein involved in DNA damage response. AstraZeneca will provide the preliminary compounds, the basic building blocks for the development of the drugs, as well as the shape and structure of the target to best determine which compounds can interact with it.

AstraZeneca has first rights to the molecules discovered through the agreement and can choose to continue further development after the agreement. In return, Cancer Research Technology will receive royalty payments when the project reaches certain milestones and has the option to develop the molecules further if AstraZeneca declines to do so.*

*This work demonstrates how industry and academia can work together and use their experience to develop projects that may otherwise have never progressed and deliver patient benefits sooner.

**AstraZeneca DDU Collaborations**

**Project 1**
- Joint target of interest
- DNA Repair
- AZ HTS
- AZ Crystal Structure
- AZ Hits

**MCRC DDU**
- Progress to agreed criteria
- AZ have first right of refusal

**Project 2**
- Joint target of interest
- Screening agreements
- DDU access AZ HTS and other screening facilities

**MCRC DDU**
- Progress to agreed criteria
- AZ have first right of refusal

*Poster 30*
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What is Collateral Vulnerability?

- The concept was presented originally in a paper in Nature - Muller at al 2012.

**Passenger deletions generate therapeutic vulnerabilities in cancer**

Inactivation of tumour-suppressor genes by homozygous deletion is a prototypic event in the cancer genome, yet such deletions often encompass neighbouring genes. We propose that homozygous deletions in each passenger genes can expose cancer-specific therapeutic vulnerabilities when the collaboratively deleted gene is a member of a functionally redundant family of genes carrying out an essential function. The glycolytic gene enolase 1 (ENO1) in the 1p36 locus is deleted in glioblastoma (GBM), which is tolerated by the expression of ENO2. Here we show that short-hairpin RNA-mediated silencing of ENO2 selectively inhibits growth, survival and the tumorigenic potential of ENO1-deleted GBM cells, and that the enolase inhibitor phosphosaccharide hydrazine is selectively toxic to ENO1-deleted GBM cells relative to ENO1-intact GBM cells or normal astrocytes. The principle of collateral vulnerability should be applicable to other passenger-deleted genes encoding functionally redundant essential activities and provide an effective treatment strategy for cancers containing such genomic events.

ENO2 proposed as a target for a subpopulation of glioblastoma in which ENO1 is deleted (1p36 locus).

Demonstrated experimentally that ENO2 inhibition by small molecules or RNA knockdown was selectively toxic to ENO1-null cells.
- We developed a bioinformatics pipeline to identify genes where the concept could be applied.

- **Simple workflow:**
  - Identify genes near to known deletion loci (e.g. PTEN locus).
  - Use the Cancer Genome Atlas dataset to calculate percentage of cases in which the nearby genes were deleted.
  - Select deleted genes having a small number of paralogs.
  - Select genes that have an essential function.
  - Select genes that are chemically tractable (i.e. are suitable for a small molecule drug hunting project)
Strategic Importance of Lung Cancer to MCRC
Chose lung adenocarcinoma as the first cancer type:
230 samples in TCGA with RNA-seq, copy number, and sequencing data.
One of the most common cancer types with high unmet need; even a treatment for 2-3% of cases would be of value.

957 genes identified in 20 deleted regions from Tumourscape.
535/957 genes > 2%
296/535 genes 1-4 paralogs
58/296 many:1 fly lethal
21/296 many:1 worm lethal
67/296 fly or worm lethal

10 ‘follow up’
21 ‘reserve’
37 ‘rejected’.
<table>
<thead>
<tr>
<th>Top 4 genes</th>
<th>Paralog siRNA</th>
<th>Paralog Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Jak2</td>
<td>- Yes</td>
<td>- Yes</td>
</tr>
<tr>
<td>- LTK</td>
<td>- Yes</td>
<td>- Yes</td>
</tr>
<tr>
<td>- PP2R2A</td>
<td>- Yes</td>
<td>- Yes</td>
</tr>
<tr>
<td>- Target X</td>
<td>- Yes</td>
<td>- ?</td>
</tr>
</tbody>
</table>

Work with a world leading lung cancer PI to validate the hypothesis with known targets and known inhibitors.
Drug Discovery Unit:

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AstraZeneca Discovery Science