SGC:
catalysing the discovery of new medicines through open access research

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Situation 1

• R&D becoming unaffordable
• Many new medicines becoming unaffordable
• Need for new medicines is increasing
• Massive duplication in biomedical research
• Most targets/ assets fail in Phase II
Situation 2

• Poor understanding of human disease: inadequate biomarkers, poorly predictive pre-clinical assays

• Pharma has many strengths: HTS, LO, Tox, ADME, Pharma dev, IIb/ III clinical studies

• Academia has better access to clinicians, patients, patient materials and patient databases, but lacks good tools
Nearly all novel targets fail at clinical POC

...we can generate “safe” molecules, but they are not developable in chosen patient group

this is killing our industry
This failure is repeated, many times

<table>
<thead>
<tr>
<th>HTS</th>
<th>Hit/Probe</th>
<th>Clinical candidate</th>
<th>Toxicology/Pharmacy</th>
<th>Phase I</th>
<th>Phase IIa/b</th>
</tr>
</thead>
<tbody>
<tr>
<td>30%</td>
<td>30%</td>
<td>90+%</td>
<td>10%</td>
<td>30%</td>
<td>30%</td>
</tr>
</tbody>
</table>

...and outcomes are not shared
### All Phase III trials in AD have failed

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target/Mechanism</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>HMG CoA reductase</td>
<td>Negative</td>
</tr>
<tr>
<td>Dimebon</td>
<td>Mitochondrial function</td>
<td>Negative</td>
</tr>
<tr>
<td>LY450139</td>
<td>Gamma secretase</td>
<td>Negative</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Inflammation</td>
<td>Negative</td>
</tr>
<tr>
<td>Phenserine</td>
<td>Cholinesterase/Amyloid</td>
<td>Negative</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>PPAR gamma agonist</td>
<td>Negative</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>HMG CoA reductase</td>
<td>Negative</td>
</tr>
<tr>
<td>Tarenflurbil</td>
<td>Gamma secretase</td>
<td>Negative</td>
</tr>
<tr>
<td>Xaliproden</td>
<td>Serotonin antagonist</td>
<td>Negative</td>
</tr>
<tr>
<td>Bapineuzumab</td>
<td>amyloid beta (passive immunization)</td>
<td>Negative</td>
</tr>
<tr>
<td>Solanezumab</td>
<td>amyloid beta (passive immunization)</td>
<td>Negative*</td>
</tr>
<tr>
<td>IVIG</td>
<td>amyloid beta (passive immunization)</td>
<td>Negative</td>
</tr>
</tbody>
</table>

* Benefit in mild: will be tested in A4 and DIAN trials (amyloid positive, pre-symptomatic and mild AD)
We tend to work under the lamp post.
The solution is:

- Increase our knowledge-base
- Bring together best people irrespective of organisation
- Pool resources
- Do it quickly (delay IP)
- Identify the 1 in 10 target that shows efficacy in patients, then compete
SGC works on new human proteins

- Generate new target validation tools
  - Proteins
  - Assays
  - Inhibitors
  - Antibodies
  - Structures

- Everything made freely available
SGC has become a hub for:

• innovation

• pharma (9)

• academia (>250)

...pool resources, share risk, crowd-source early discovery
Now solved as many kinase structures as rest of academia
Rapid dissemination reduces wastage

- **May 12**: Deposited structure of human membrane protein ZMPSTE24 ("premature ageing")
- **Summer 12**: enabled another lab to solve yeast structure
- **Nov 12**: paper submitted
- **April 13**: both papers published together in Science
First inhibitor for BRD sub-family - JQ1
JQ1 reduces proliferation in NUT midline carcinoma

KI67 positive = proliferating
JQ1 reduces tumour size
JQ1 cancer publications

- NUT midline carcinoma
- AML/ CML
- Multiple myeloma
- Burkitts lymphoma
- B cell ALL
- B cell non Hodgkins lymphoma
- Erythroleukaemia
- Lung adenocarcinoma
- Merkel cell polyomavirus

- Papillomavirus
- Epstein Barr virus
- Glioblastoma
- Neuroblastoma
- B cell lymphoma
- Prostate
- Primary effusion lymphoma
- Metastatic melanoma
JQ1 reduces sperm count and motility

Cell August 17, 2012
JQ1 reverses cardiac hypertrophy

JQ1: 1.5-28 days post TAC
HW: heart weight
BW: body weight

Anand (2013), Cell, 154, 569
I-BET762 prevents and inhibits LPS induced endotoxic shock

Preventative = 1hr before LPS
Therapeutic = 1.5hrs after LPS
C57BL/6 mice
JQ1: Impact on science & drug discovery

- Distributed to >400 labs/companies
- Published Dec 2010. By May 2013
  - cited >200 times
  - further 172 papers
- Started proprietary efforts
  - now 6 molecules in clinic
- Collaborator created spin off
  - Tensha: $15 M seed funding
Pipeline (Nov 13)

**Probe/ Tool**
- Potent & Selective
- Potent
- Weak
- None

**Screening / Chemistry**

**In vitro assay**
- PRMT3
- BRPF1B
- PCAF
- FALZ
- PB1/SMARCA
- EP300
- MLL
- MMSET
- NSD3
- SETD8

**Cell assay**
- BRD9
- FBXLI11
- CECR2
- BAZ2B/A
- CREBBP
- TIF1α
- JARID1A

**Cell activity**
- BET
- BET 2nd
- CREBBP
- CREBBP 2nd
- SMARCA4
- BAZ2B/A
- Bromosporine
- BRD7
- JARID1A

**Probe/ Tool**
- Potent & Selective
- Potent
- Weak
- None

**In vitro assay**
- BRD
- HAT
- (H)MT
- KDM
- TUD
- WD Domain
- 2OG Oxygenase
- Pharma partner

**Cell assay**
- Pan 2-OG
- DOT1L
- SETD7
- EZH2
- EZH2 2nd

**Cell activity**
- Pan 2-OG
- DOT1L
- SETD7
- EZH2
- EZH2 2nd
Proposal: PPP to validate pioneer targets in patients

- Generate open clinical probes
- Evaluate in patients
- Identify 1/10 target that has potential to be a medicine
- Industry will then create proprietary assets
- Benefit for industry and patients
Reagents and publications will facilitate collaboration, leveraged funds, and POCMs.

**Lead identification**

- **Lead optimisation**
  - Efficacy in cellular assays
  - Efficacy in *in vivo* “disease” models

**Preclinical**

- ADME, toxicology

**Phase I**

- Human safety & tolerability

**Phase II**

- Efficacy in patients
Patient groups will:

• facilitate recruitment

• minimise payments
Regulators will:

- help design new clinical studies
- help validate new biomarkers
- help pave path for new targets
Status

- Project initiated in cancer
  - with CRUK

- Takeda will fund new target for AD
  - (5 Feb 2014)

- Writing business plan for neuro-psychiatry
  - CIHR will seed with up to $30M
Creating a new ecosystem for medicines discovery (in Oxford)

- **Biotechs** freely giving access to proprietary platforms
- **Patient groups** want to advance our outputs
- **CROs** want to commercialise our outputs
- Building **BioEscalator** to catalyse the creation of new biotechs
- Enabled creation of a new **Target Discovery Institute**
- Have facilitated funds for a **Big Data Institute**
- Have aggregated activity in **rare diseases**
- Are planning a new **Brain Institute**, a **Chemistry for Medicine Centre** and human disease assay platforms for improved target discovery
Summary

• Open reagents and rapid publications enable
  – Partnering with multiple companies
  – Fast collaborations with academics
  – Easier access to patient materials and patient databases
  – Reduces duplication and wastage
  – Catalyses science and drug discovery
  – Allows pooling of resources and sharing of risk
Acknowledgements


- Toronto: Aled Edwards

- Harvard: Jay Bradner

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- DiscoverX: Sanj Kumar

- Spinifex: Tom McCarthy, Bob Dworkin, Andrew Rice

- CIHR, Genome Canada, Ontario, Wellcome Trust

- GSK, Novartis, Pfizer, Lilly, Abbvie, Takeda, Janssen, BI, Bayer
What happens after POCM?

POCM

90%

Valid mechanism

30%

Non developable molecule

70%

Developable molecule

Auction IND

Develop molecule*

Proceeds to independent fund

Develop proprietary molecules

Develop proprietary molecules

*Based on existing market exclusivity laws
Crowd sourcing early discovery and target validation in patients

New targets

Open, quality tools

Crowd source science

Human disease cells

Open clinical candidates

Epigenetics
Inflammation
Genetics

Drugs for patients

Proprietary Phase IIb/III

Proprietary assets

Open Phase Ila studies