Medicinal chemistry experts in pharma are helping us to generate freely available novel probes, in order to facilitate target discovery.

Chas Bountra
Professor of Translational Medicine, Dept of Clinical Medicine
Associate Head of Medical Sciences
Chief Scientist, SGC
Drug discovery is a lottery

• Most pioneer targets (90%+) fail in Phase II
  - we are not good at target validation
  - target validation occurs in clinic

• Many academics and pharma groups work on same targets in competition
Nearly all novel targets fail at clinical POC

<table>
<thead>
<tr>
<th>Target ID/Discovery</th>
<th>HTS</th>
<th>Hit/Probe/Lead ID</th>
<th>LO</th>
<th>Clinical candidate ID</th>
<th>Tox./Pharmacy</th>
<th>Phase I</th>
<th>Phase IIa/IIb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50%</td>
<td>10%</td>
<td></td>
<td>30%</td>
<td>30%</td>
<td>30%</td>
<td>90+%</td>
</tr>
</tbody>
</table>

...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

...and outcomes are not shared
Most companies have patents for TRPV1
...in probably all therapeutic areas
We tend to work under the lamp post
Genomic responses in mouse models poorly mimic human inflammatory diseases

Junhee Seok\textsuperscript{a,1}, H. Shaw Warren\textsuperscript{b,1}, Alex G. Cuenca\textsuperscript{c,1}, Michael N. Mindrinos\textsuperscript{a}, Henry V. Baker\textsuperscript{c}, Weihong Xu\textsuperscript{a}, Daniel R. Richards\textsuperscript{d}, Grace P. McDonald-Smith\textsuperscript{e}, Hong Gao\textsuperscript{a}, Laura Hennessy\textsuperscript{f}, Celeste C. Finnerty\textsuperscript{g}, Cedlia M. López\textsuperscript{c}, Shari Honari\textsuperscript{f}, Ernest E. Moore\textsuperscript{h}, Joseph P. Minei\textsuperscript{i}, Joseph Cuschieri\textsuperscript{j}, Paul E. Bankey\textsuperscript{k}, Jeffrey L. Johnson\textsuperscript{h}, Jason Sperry\textsuperscript{l}, Avery B. Nathens\textsuperscript{m}, Timothy R. Billiar\textsuperscript{l}, Michael A. West\textsuperscript{m}, Marc G. Jeschke\textsuperscript{o}, Matthew B. Klein\textsuperscript{n}, Richard L. Gamelli\textsuperscript{o}, Nicole S. Gibran\textsuperscript{f}, Bernard H. Brownstein\textsuperscript{a}, Carol Miller-Graziano\textsuperscript{k}, Steve E. Calvano\textsuperscript{j}, Philip H. Mason\textsuperscript{o}, J. Perren Cobb\textsuperscript{s}, Laurence G. Rahme\textsuperscript{f}, Stephen F. Lowry\textsuperscript{r,2}, Ronald V. Maier\textsuperscript{r}, Lyle L. Moldawer\textsuperscript{c}, David N. Herndon\textsuperscript{g}, Ronald W. Davis\textsuperscript{a,3}, Wenzhong Xiao\textsuperscript{a,4}, Ronald G. Tompkins\textsuperscript{5,3}, and the Inflammation and Host Response to Injury, Large Scale Collaborative Research Program\textsuperscript{4}

\textsuperscript{a}Stanford Genomic Technology Center, Stanford University, Palo Alto, CA 94305; Departments of \textsuperscript{b}Pediatrics and Medicine, \textsuperscript{c}Anesthesiology and Critical Care Medicine, and \textsuperscript{d}Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114; \textsuperscript{e}Department of Surgery, University of Florida College of Medicine, Gainesville, FL 32610; \textsuperscript{f}Ingenuity Inc., Redwood City, CA 94063; \textsuperscript{g}Department of Surgery, Massachusetts General Hospital, Boston, MA 02114; \textsuperscript{h}Department of Surgery, Harborview Medical Center, Seattle, WA 98195; \textsuperscript{i}Shriners Hospitals for Children and Department of Surgery, University of Texas Medical Branch, Galveston, TX 77550-1220; \textsuperscript{j}Department of Surgery, University of Colorado Anschutz Medical Campus, Denver, CO 80045; \textsuperscript{k}Department of Surgery, Parkland Memorial Hospital, University of Texas, Southwestern Medical Center, Dallas, TX 75390; \textsuperscript{l}Department of Surgery, Harborview Medical Center, University of Washington School of Medicine, Seattle, WA 98195; \textsuperscript{m}Department of Surgery, University of Rochester School of Medicine, Rochester, NY 14642; \textsuperscript{n}Department of Surgery, University of Pittsburgh Medical Center Presbyterian University Hospital, University of Pittsburgh, PA 15213; \textsuperscript{o}Department of Surgery, St. Michael’s Hospital, University of Toronto, Toronto, ON, Canada M5B 1W8; \textsuperscript{p}Department of Surgery, San Francisco General Hospital, University of California, San Francisco, CA 94143; \textsuperscript{q}Division of Plastic and Reconstructive Surgery, Department of Surgery, University of Toronto, Toronto, ON, Canada M4N 3M5; \textsuperscript{r}Department of Surgery, Stritch School of Medicine, Loyola University, Chicago, IL 60153; \textsuperscript{s}Department of Anesthesiology, Washington University, School of Medicine, St. Louis, MO 63110; and \textsuperscript{t}Department of Surgery, University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, New Brunswick, NJ 08903

Contributed by Ronald W. Davis, January 7, 2013 (sent for review December 6, 2012)
No correlation in gene changes
Debates post clinical studies

• Wrong target
• More selective molecule/ more “dirty” molecule
• Wrong dose
• Insufficient exposure/ target engagement
• Poor CNS penetration
• Animal models are not predictive
• Wrong biomarker
• Placebo response
• Wrong patient group

.................
Consequences of current system

• Wasting public and private funds

• Wasting peoples careers

• Needlessly exposing patients to ineffective or harmful molecules: unethical
The answer is not:

shift the problem to China
The solution is:

• Increase our knowledge-base
• Bring together best people irrespective of organisation
• Pool resources and share risk
• Do it quickly: delay IP
• Identify the 1 in 10 target that shows efficacy in patients/ is developable: then let the competition can begin
SGC only works on new proteins and generates:

- New target validation tools
  - Proteins
  - Assays
  - Inhibitors
  - Antibodies
  - Structures

- New target disease associations
  (with academia-pharma network)

....everything freely available
SGC has become a hub for:

- pharma (>8)
- academia (>250)
- innovation

...pool resources, share risk, crowd-source early discovery
Our focus

Family/ target

• Epigenetics
• Kinases
• Metabolic enzymes
• Ubiquitylation proteins
• Growth factor signalling
• Ion channels
• Rare disease/ genetically validated targets

Therapeutic

• Cancer
• Inflammation
• Neuroscience
Now solved as many kinase structures as rest of academia

Academia, SGC, Industry, Other genomics
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 human ion channel in UK: TREK2/ KCNK10

- Dimeric 2 pore K channel
- 3.3Å resolution
- Deposited 30 June 2013
- Will probably be published 4Q13/ 1Q14
First inhibitor for BRD sub-family - JQ1
JQ1 reduces proliferation in two patient derived cell lines

KI67 positive = proliferating
JQ1 induces apoptosis

Annexin V, marker of early apoptosis
PI = propidium iodide, marker of late apoptosis
STA = Staurosporine
JQ1 reduces tumour size
JQ1 reduces sperm count and motility.
JQ1: Impact on science & drug discovery

- Published Dec 23 2010
  - cited >200 times
  - 172 papers by 12 May 2013
- Distributed to >300 labs/companies
  - profiling in several therapeutic areas
- Pharmas started proprietary efforts
- Harvard spin off: Tensha
  - $15 M seed funding
I-BET762 prevents and inhibits LPS induced endotoxic shock

Preventative = 1hr before LPS
Therapeutic = 1.5hrs after LPS
C57BL/6 mice
BDOIA518: a potent CBP/EP300 inhibitor

ITC: 21nM
BLI: 41nM
Alpha: 69nM

ITC: 38nM
...is highly selective
FRAP: 1μM

P53 reporter gene: 1.3μM

...is active in cellular assays
Novel inhibitor for demethylase JMJD3 - GSK-J1

Inhibition of enzyme activity (% of total activity inhibited)

Log [GSK-J1] (μM)

JMJD3
JMJD2A
JMJD2C
JMJD2D
JMJD2E
GSK-J1 produces dose related inhibition of TNF release from human macrophages

IC$_{50}$ = 9 µM

Inhibitor
- increases K27me3,
- decreases RNApolII
- no change in H3
GSK-J1 reduces bone resorptive activity in osteoclasts

RANKL = receptor activator of nuclear factor KB ligand
RANK = osteoclast cell surface receptor
GSK-J1 increases apoptosis in human breast cancer cells (MCF7)

Red dots: propidium iodide stained apoptotic cells
D3 inhibition, increases K27me3, decreases BCL2, increases apoptosis
Pipeline (May 13)

**Probe/ Tool Compound**

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

**Screening / Chemistry**

- **In vitro assay**
  - **BRD1**
  - **PCAF**
  - **FALZ**
  - **EP300**
  - **MLL**
  - **MMSET**
  - **SMYD2**
  - **SETDB1**
  - **BAZ1B**
  - **WDR9**
  - **EZH1**
  - **SUV42**
  - **NSD1**

- **HMT**
  - **L3MBTL1**
  - **LM3BP1**
  - **SPIN1**
  - **LSD1**
  - **UHRF1**

- **KDM**
  - **SUV39H2**
  - **SUVRH201**
  - **JMJD1**

- **Me Lys Binders**
  - **JMJD2**
  - **JMJD2B**

- **TUD**
  - **JMJD2C**

- **2OG Oxygenase**
  - **JMJD3**

**Potent & Selective**

- **BRD9**
  - **CECR2**
  - **SETD2**
  - **SETD2**

- **PRMT3**
  - **FBXL11**

**Potent**

- **BRD7**
  - **JARID1A**

**Weak**

- **JMJD2 2nd**

**None**

- **EP300**
  - **SETD8**
  - **BAZ2B/A 2nd**
  - **JMJD1C**
  - **JMJD3 3rd**
  - **CREBBP 2nd**
  - **BAZ2B/A 2nd**
  - **TIF1α 2nd**
  - **JARID1C**
  - **JMJD3 3rd**
  - **CREBBP 2nd**

**In vitro assay**

- **BRD9**
  - **CECR2**
  - **SETD2**
  - **SETD2**

- **PRMT3**
  - **FBXL11**

**Cell assay**

- **BRD9**
  - **CECR2**
  - **SETD2**
  - **SETD2**

- **PRMT3**
  - **FBXL11**

**Cell activity**

- **BET**
  - **B’sporine**
  - **G9a/GLP**
  - **G9a/GLP 2nd**
  - **EZH2**
  - **EZH2 2nd**
  - **DOT1L**

- **SETD7**
  - **JMJD3**
  - **L3MBTL3**

- **Pan 2-OG**
  - **PHD2**

- **JMJD2 2nd**

**Legend**

- **BRD**
- **HAT**
- **HMT**
- **KDM**
- **Me Lys Binders**
- **TUD**
- **WD Domain**
- **2OG Oxygenase**
EMA401 in PHN

- Randomised, double-blind, placebo controlled
- 6 countries
- 100mg b.i.d. for 28 days
- 183 patients
- Patients were not responding to single agent
- Allowed to continue taking one agent

Day
-14 -7 -1 1 8 15 22 28 (PK a.m. Day 29) 42

Screening & Baseline Pain Assessment
Treatment Phase
Follow-up
1° Endpoint
EMA401 reduces mean pain intensity at 4 weeks
EMAP401 reduces mean pain intensity

<table>
<thead>
<tr>
<th>Description</th>
<th>Per Protocol</th>
<th>Intent to Treat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EMA401</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>Baseline Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>[number of patients]</td>
<td>6.298 (1.057) [79]</td>
<td>6.353 (1.115) [79]</td>
</tr>
<tr>
<td>Week 4 Mean (SD)</td>
<td>3.817 (2.069) [79]</td>
<td>4.767 (1.951) [79]</td>
</tr>
<tr>
<td>[number of patients]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from Baseline (SD)</td>
<td>-2.481 (1.741)</td>
<td>-1.586 (1.700)</td>
</tr>
<tr>
<td></td>
<td>Difference of Adjusted LS Means (SE)</td>
<td>-0.8950 (0.2747)</td>
</tr>
<tr>
<td></td>
<td>95% CI for Difference of Adjusted LS Means</td>
<td>Not available</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>0.0014</td>
</tr>
</tbody>
</table>
MOA: Angiotensin AT2 blockade!!!

AT$_1$ antagonists for hypertension e.g. losartan

30-40% homology with AT1
Proposal: PPP to validate pioneer targets in patients

• Treat as a knowledge creation endeavour
• Access academics quickly and freely
• Targets selected by partners and academics
• Patient groups and regulators will be active participants
• Industry will subsequently create proprietary assets for clinically validated/ de-risked targets
Reagents and publications will facilitate collaboration, leveraged funds, and POCMs

Lead identification

Lead optimisation

Preclinical

Phase I

Phase II

POCM

in vitro probe

in vivo probe

Efficacy in cellular assays

Efficacy in in vivo "disease" models

ADME, toxicology

Human safety & tolerability

Efficacy in patients
Who will do....?

• Target selection
  - Academics
  - Industrial partners

• Lead identification
  - SGC
  - Public screening infrastructures
  - CROs

• Lead optimisation
  - CROs

• Preclinical
  - CROs

• Phase I
  - Academics

• Phase IIa
  - Academics
What happens after POCM?

- **Invalid mechanism**: Publish quickly
- **Developable molecule**: Auction IND
  - Develop molecule*
  - Proceeds to independent fund
  - Develop proprietary molecules
- **Valid mechanism**: Non developable molecule
- **Non developable molecule**: Develop proprietary molecules

*Based on existing market exclusivity laws
Patient groups helping to reduce costs and increase speed

- will facilitate recruitment
- will minimise payments
Unprecedented relations with regulators

• will help design new clinical studies
• will help validate new biomarkers
• will help pave path for new targets
• will host data
Benefits

Improved access to
• Best academics/clinicians
• Best scientists in industry
• Regulatory scientists
• Patients/patient databases
• NHS infrastructures
• Multiple public and private funds

Reduced
• Wastage of resource
• Wastage of careers
• Patient harm
Status

• Project initiated in cancer (KDM4B – rhabdomyosarcoma)

• Writing business plan for neuro-psychiatry
  - CIHR meeting in Ottawa, July 8 2013
  - willing to seed with $30M
  - 8 Pharma R&D/ CNS heads attended
  - will attract other public and philanthropic funds
  - have to agree disease/ targets

• Discussions ongoing re VEO IBD
  - Scott Snapper/ Fiona Powrie
  - Helmsley Trust
Summary

• Pioneer drug discovery is too high risk, too expensive, and takes too long. For some disease areas it is becoming impossible for any one organisation

• We have to pool public and private resources, access global academia, work with patient groups and regulators to de-risk pioneer targets

• Target validation occurs in patients, not cells or animal models. We have to get to Phase II as quickly as possible

• Target validation dependent on quality clinical molecules. We have to make use of med chem expertise in industry
Acknowledgements

• SGC : Aled Edwards, Stefan Knapp, Udo Oppermann

• SAGE Bionetworks: Stephen Friend, Thea Norman

• Harvard: Jay Bradner

• Imperial College: Praveen Anand

• Spinifex: Tom McCarthy, Bob Dworkin, Andrew Rice, Andrew Rice, Alan Naylor

• CIHR (Tony Phillips), Genome Canada, Ontario, Wellcome Trust

• GSK (Rab Prinjha), Novartis, Pfizer (Kevin Lee), Lilly, Abbvie, Takeda, Janssen, BI