The Lilly Open Innovation Drug Discovery Program: Present and Future

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11-14 September 2011
Churchill College, Cambridge, UK
I. Origin of the Concept
   • Chemical Diversity Strategy
   • Launch & Implementation of the PD² Initiative

II. PD² Metrics and Outcomes to Date
   • Institutions, Users & Compound Diversity
   • PD² Collaborations

III. Open Innovation Framework/Business Model
   • PD² plus TargetD² & Computational models
   • Lilly TB Drug Discovery Initiative

IV. What’s Happening & What’s Next
Presentation Overview

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IV. What’s Happening & What’s Next
Key Investments to Enable Strategies for Drug Discovery

“Distinct Target(s) Hypotheses”

Molecular
Fragment Based & Molecular Design
Molecules built for purpose

Biochemical
Target Directed Screening
Repurpose/modify existing molecules

Cellular
Phenotypic Drug Discovery
Uncover/optimise molecule signatures

In Vivo

• HT Crystallography
• SPR
• HDX
• F-NMR
• High conc. Assays
• Fragment diversity

• Gene family platforms
• Diversity/iterative screening
• Compound libraries
• Computational models/informatics
• Structural Biology
• Cellular and biochemical assays

• High Content Imaging
• Advanced informatics
• Alternative molecular diversity
• Advanced cellular assays
• Stem cells

• Pathway analysis
• Target(s) ID
Strategic Role of Lilly Compound Collection

Informatics Tools and Predictive Models

New Discovery Paradigms
- Phenotypic Drug Discovery
- Multi-Targeted Ligands

Diversity Gap Analysis

How to Enrich the Collection?
Unique Compound Growth in Lilly Compound Collection

Library Sciences Initiated

<table>
<thead>
<tr>
<th>Year</th>
<th>Collection</th>
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<tbody>
<tr>
<td>2001</td>
<td>310K</td>
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<tr>
<td>2002</td>
<td>359K</td>
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<td>2003</td>
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<td>2004</td>
<td>577K</td>
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<td>2005</td>
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<tr>
<td>2006</td>
<td>752K</td>
</tr>
<tr>
<td>2007</td>
<td>818K</td>
</tr>
<tr>
<td>2008</td>
<td>884K</td>
</tr>
<tr>
<td>2009</td>
<td>938K</td>
</tr>
</tbody>
</table>
Cassettes are dynamic knowledge-based ensembles of structures
811K Screening set of entire collection is also available
An Alternative Concept to Gathering Chemical Diversity

Are we done with the compound collection?
• No, the compound collection needs to be dynamic and responsive to our emerging areas of disease and target strategies

What challenges & barriers do we have to evolving our compound collection?
• Identification of new sources of compounds and maintenance of a large collection brings quality & financial challenges

Are there distinct sources of molecules available that we should consider (academia and small biotech)?
• We could engage external scientists to access their compounds and ideas in a collaborative framework to advance common interests

Opportunity for Open Innovation
We want to

- “expand” our discovery organization through access to external global scientific talent, assets and resources
- established unbiased partnerships with academics and small biotechs
- explore alternative models for interaction and value creation that leverage Lilly science

While ensuring that we

- do it via incremental costs on top of existing internal investments
- have a measurable return on investment
Implementation of the Lilly Open Innovation Drug Discovery Program

First: test the concept, then, expand on what works

**September 2009** – launched Phenotypic Drug Discovery Initiative (PD²)

- Institution-level affiliation (universal MTA covers entire institution)
- External submitters gained no-cost access to select phenotypic assay panel
- Full experimental data report returned to investigators
- *Lilly has first right of negotiated access or collaboration* for promising molecules (pay for performance)
- Otherwise investigator is free to publish

**August 2011** – added Target Drug Discovery Initiative (TargetD²) and neglected disease research module (TB)

- Leverage existing engaged community and business process
- Dynamic assay panel evolution: state-of-the-art, relevant
- Offer value to participants: data, models, feedback, scientific discussion
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IV. What’s Happening & What’s Next
PD² Global Network

252 Affiliations in 27 Countries:
• 174 Research Universities and Institutes
• 78 Small Biotechs

Legend:
- University
- Research Institute
- Small Biotech
- Lilly Site
Cumulative PD² Structure & Sample Metrics

**Compound Activity Evolution**

- Compounds Submitted (in silico)
- Compounds Accepted for Screening
- Samples Submitted
- Data Report Provided to Investigator

~60% of Compounds Accepted for Screening

**Exclusion:**
- Fail Med Chem Rules
- Insufficient Novelty
- Similar to Tested Compounds
- Similar to Controlled Substances
Structural Diversity of PD^2 relative to the Lilly Compound Collection

The PD^2 collection to date offers compounds with structural diversity relative to the Lilly Collection.
Structural Diversity of PD² relative to the PubChem Collection

Many molecules are similar to those in PubChem, but a large proportion are significantly (> 0.15) different.

PubChem is a database that provides information on the biological activities of small molecules. It is a component of NIH's Molecular RoadMap Library Initiative. It contains roughly 20 million unique structures.
Property Space Comparisons Among Alternative Diversity Sources

Projection of collections on the *first two principal components* of property space defined by:

- Molecular weight
- $\text{clogD}$ at pH7.4
- Aromatic density
- Fraction of SP₃ atoms
- Hydrogen bond donor and acceptor
Shape Diversity Comparisons

rod-like

ball-like

disk-like
PD² Screening Metrics

Primary Assay Module Hit Rates

70% PD² compounds specific for 1 module
22% PD² compounds active in 2 modules
~8% PD² compounds active in 3 modules

PD² significantly complements internal compound collection with access to diverse, biologically active molecules.

J. Biomol Screening, Volume 16, Issue 6 July 2011, pp. 588 - 602
PD² vs Lilly Project Actives Comparison

Normalized Relative Ratios for Selected Computational Properties (avg values)

*All bars represent statistically significant deltas excepting those marked with the symbol #
Based on screening results to date:

- 115 structures requested for disclosure
  - 97 structures shared with Lilly for evaluation
    - 91 structures evaluated
      - 13 “Yes” (6 scaffolds)

- 2 signed collaborations
- 1 in final negotiations
- 2 in early discussions
- 1 targeted for joint publication

Details available online:
# Summary of Selected Opportunities

<table>
<thead>
<tr>
<th>Institution</th>
<th>Compound Phenotype</th>
<th>Data Summary</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Notre Dame</td>
<td>Oncology: Anti-Angiogenesis</td>
<td>• Non-G2M phenotype</td>
<td>1 yr collaboration Signed Dec. 2010</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Non-kinase MOA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Amenable to SAR</td>
<td></td>
</tr>
<tr>
<td>University #2 (US)</td>
<td>Diabetes: Insulin Secretion</td>
<td>• Active in rat and human islets</td>
<td>2 yr collaboration Signed May 2011</td>
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<tr>
<td></td>
<td></td>
<td>• Unique scaffold</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Amenable to SAR</td>
<td></td>
</tr>
<tr>
<td>University #3 (Spain)</td>
<td>Oncology: Anti-Angiogenesis</td>
<td>• Non-G2M phenotype</td>
<td>Collaboration terms being finalized</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Non-kinase MOA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Amenable to SAR</td>
<td></td>
</tr>
<tr>
<td>University #4 (US)</td>
<td>Oncology: Cell Cycle</td>
<td>• Unique blockade of cell cycle in anaphase</td>
<td>Preparing joint publication</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Natural product</td>
<td></td>
</tr>
<tr>
<td>University #5 (US)</td>
<td>Oncology: Anti-Angiogenesis</td>
<td>• Potential novel Anti-Angiogenic MOA</td>
<td>Entering discussions</td>
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<tr>
<td>Small Biotech (Canada)</td>
<td>Oncology: Anti-Angiogenesis</td>
<td>• Equipotent VEGF/FGF-driven activity</td>
<td>Entering discussions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Non-kinase MOA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Novel Scaffold</td>
<td></td>
</tr>
</tbody>
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Open Innovation Drug Discovery Program and Website

To provide LRL with access to novel small-molecules that influence biological targets or pathways of therapeutic area interest

openinnovation.lilly.com/dd

Governed through a universal MTA and affiliation process

The Lilly TB Drug Discovery Initiative
Open Innovation Drug Discovery

Integrated Business Process

Institution Signs MTA* to establish Membership
Investigators Create Individual Web Accounts
Investigators Submit Compounds for Screening
Lilly Integrated Screening Panels Screens

Lilly Open Innovation Team Identifies Opportunities
Institution Decides Whether to Reveal Structures
Investigators Receive Biological Report

Lilly Evaluates Structure & Potential for Further Work
Institution Decides Whether to Enter Further Discussions
Optionl Data Publication
Possible Agreement Negotiations

External consultants employed to provide expert diligence on chemical structures and associated literature. Protects both User IP and Lilly scientists
What are we Looking For?

**Phenotypic Drug Discovery Initiative, PD²**
- compounds representing unique MOAs and differentiated profiles
- potential for SAR optimization and IP tool compounds for pathway/target(s) identification through profiling and chemoproteomic approaches
- compounds found to be active against known targets of interest
- compounds that may be hits for desired polypharmacology profiles

**Target Drug Discovery, TargetD²**
- compounds active against specific targets where we have failed with our internal lead generation approaches, or
- where it is desirable to have additional chemotypes (IP, tox risk, etc,) in emerging areas with no prior experience
- assay panel will be very dynamic and responsive to internal program needs

**Lilly TB Drug Discovery Initiative**
- compounds active in TB screens and made available to the not-for-profit initiative

Additional outcomes from relationships created with investigators, universities and small biotechs (new science, technologies, capabilities)
## Available Assay Panels

<table>
<thead>
<tr>
<th>Discovery Approach</th>
<th>Endocrine/Cardiovascular</th>
<th>Oncology</th>
<th>Neuroscience</th>
<th>Tuberculosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD²</td>
<td>• Insulin Secretion</td>
<td>• Anti-Angiogenesis</td>
<td></td>
<td>• TB Screening Module (IDRI)</td>
</tr>
<tr>
<td></td>
<td>• Wnt Pathway Activator</td>
<td>• K-ras/Wnt Synthetic Lethal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• GLP-1 Secretion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TD²</td>
<td>• GPR119 Receptor Agonist</td>
<td>• Hexokinase 2 (HK2) Inhibitor</td>
<td>• mGlu2R Allosteric Antagonist</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Apelin (APJ) Receptor Agonist</td>
<td></td>
<td>• CGRP Receptor Antagonist</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Sodium Phosphate Transporter 2b (NTP) Inhibitor</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*Details available online: [https://openinnovation.lilly.com/dd/science-of-open-innovation стратегические области интереса.html](https://openinnovation.lilly.com/dd/science-of-open-innovation стратегические области интереса.html)*
Target Drug Discovery (TargetD²)

Computational tools provided to aid compound design and selection
Protection of Chemical Structures

Chemical fingerprints required for:
• application of informatics filters
• diversity and properties analysis
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Additional Scientific Directions to Provide Value to Participants

Molecular Weight Distribution of OIDD Compounds

Additional source of novel fragment diversity

Fragment Based Drug Design
Target Directed Screening
Phenotypic Drug Discovery

HT Crystallography
SPR, HDX, F-NMR, High conc. assays

Fragment screening and evaluation can be done in structure-blinded fashion
Ongoing Activity

• **13 September 2011**: new OIDD website-based application available to all users worldwide

• **30 September 2011**: first-generation PD² Material Transfer Agreement terminated and replaced by integrated OIDD MTA

• **Late 2011/Early 2012**: first Structure-Property models available online

• **During 2012**: enablement of Structure-Activity models and other scientific tools

• **Commitment to timely delivery, crisp decision-making and continuous process improvement throughout entire cycle**
Our Commitment to Participants

attention to process performance and continuous improvements for timely report delivery

- Cpds progressing thru entire assay panel
- Cpds progressing to secondary assays
- Primary assay evaluation
- Advanced evaluation

Number of days

A - Total (Create to Report)
B - Transit & Processing
C - Research
Enhancing Small Molecule Innovation

“Providing high quality molecules to test clinical hypotheses in patients”
## Open Innovation Drug Discovery

### Design Challenges

#### Foundational
- Business model and universal MTA design
- Building trust
- IP ownership
- Biological data as up-front transactional currency
- Confidentiality of chemical structures
- Ability for academics to publish
- Compliance and consistency

#### Operational
- Website design and enablement within Lilly
- Managing multiple partnerships across the globe
- Compound logistics
- Timely data turnaround and communication
- Crisp internal decision-making
Flow Schemes for PD² Modules
Flow Schemes for TargetD² Modules
Flow Scheme & Assay Measures for TB Module

TB Research Module & Assay Measures
(for OIDD participants)

Primary Assays
Whole cell activity H37Rv cells SP (% Inhibition)

1 mL LA Cytolux CellTiter-Glo SP / CRC (% Inhibition / IC50)

Secondary Assay
MIC H37Rv cells CRC (IC50)

Whole cell activity H37Rv; SP (IDRI)

Cytotox CTG H37Rv; SP / CRC (Lilly)

Minimum inhibitory concentration (MIC) H37Rv; CRC (IDRI)

Confirmatory TB Assays
(for Lilly TBDDI collaborators)

- VERO cell toxicity (IC50)
- Cidal activity
- Kill kinetics
- Resistance frequency
- Activity against non-replicating cells
- Spectrum of activity
- Minimum bactericidal concentration
First in Class

Fig 3: Cumulative distribution of new drugs by discovery strategy

a) First-in-class drugs: lag is not strongly apparent in a comparison of the cumulative number of small-molecule new molecular entities (NMEs) that were discovered from the different approaches during the period analyzed

b) Follower drugs: ratio of small-molecule NMEs discovered through target-based screening to those discovered through phenotypic screening appears to increase in the second half of the time period
Our philosophy is to use all available approaches and tools at our disposal, and share those with our participants globally in order to help expedite Drug Discovery efforts.
Open Innovation Benefits

Interview with Intuit Susan Harmon

- **Speed:** Rapid development and deployment of solutions by partnering
- **Skills:** Complement the company’s skill sets with those of partners (including suppliers), especially around technology, but also concerning alternative business models, customer community
- **Focused R&D investment:** With each partner contributing its resources in the area that can be considered its core, the company can reduce spend on non-differentiating (context) functionality and can have more innovation initiatives ongoing in parallel
- **New strategies require extensive partnerships:** Innovative strategies often require solutions as part of their architecture that are not available inside the company. Partnerships can help the organization learn about a new domain at a lower cost than it would take an internal team to get up to speed
- **BIG disruptive ideas:** Organizations suffer from myopia and tend to fail to identify breakthrough concepts. Open innovation can bring the diversity necessary to identify these ideas
- **New markets:** New markets, such as emerging markets, often have particularities different from the home market and partnering can increase the chances of success