The Lilly Open Innovation Drug Discovery Program: Present and Future

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Lilly
Answers That Matter.

Presentation Overview

I. Origin of the Concept

- Chemical Diversity Strategy
- Launch & Implementation of the PD^2 Initiative

II. PD^2 Metrics and Outcomes to Date

- Institutions, Users & Compound Diversity
- PD^2 Collaborations

III. Open Innovation Framework/Business Model

- PD^2 plus TargetD^2 & Computational models
- Lilly TB Drug Discovery Initiative

IV. What's Happening & What's Next

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Key Investments to Enable Strategies for Drug Discovery

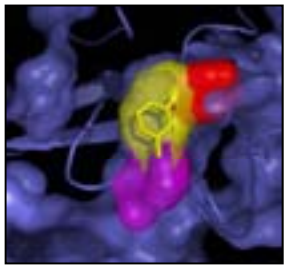
"Distinct Target(s) Hypotheses" ⟷ **"Biological Systems Hypotheses"**

Molecular

Fragment Based & Molecular Design

Molecules built for purpose

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

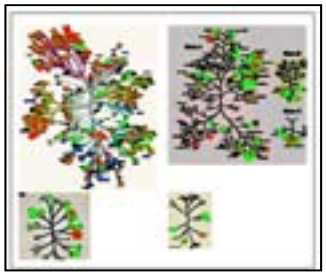


Biochemical

Target Directed Screening

Repurpose/modify existing molecules

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

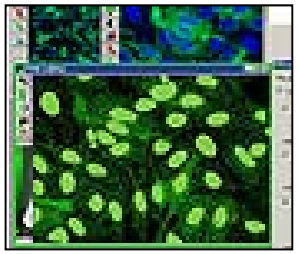


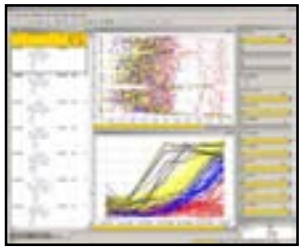
Cellular / *In Vivo*

Phenotypic Drug Discovery

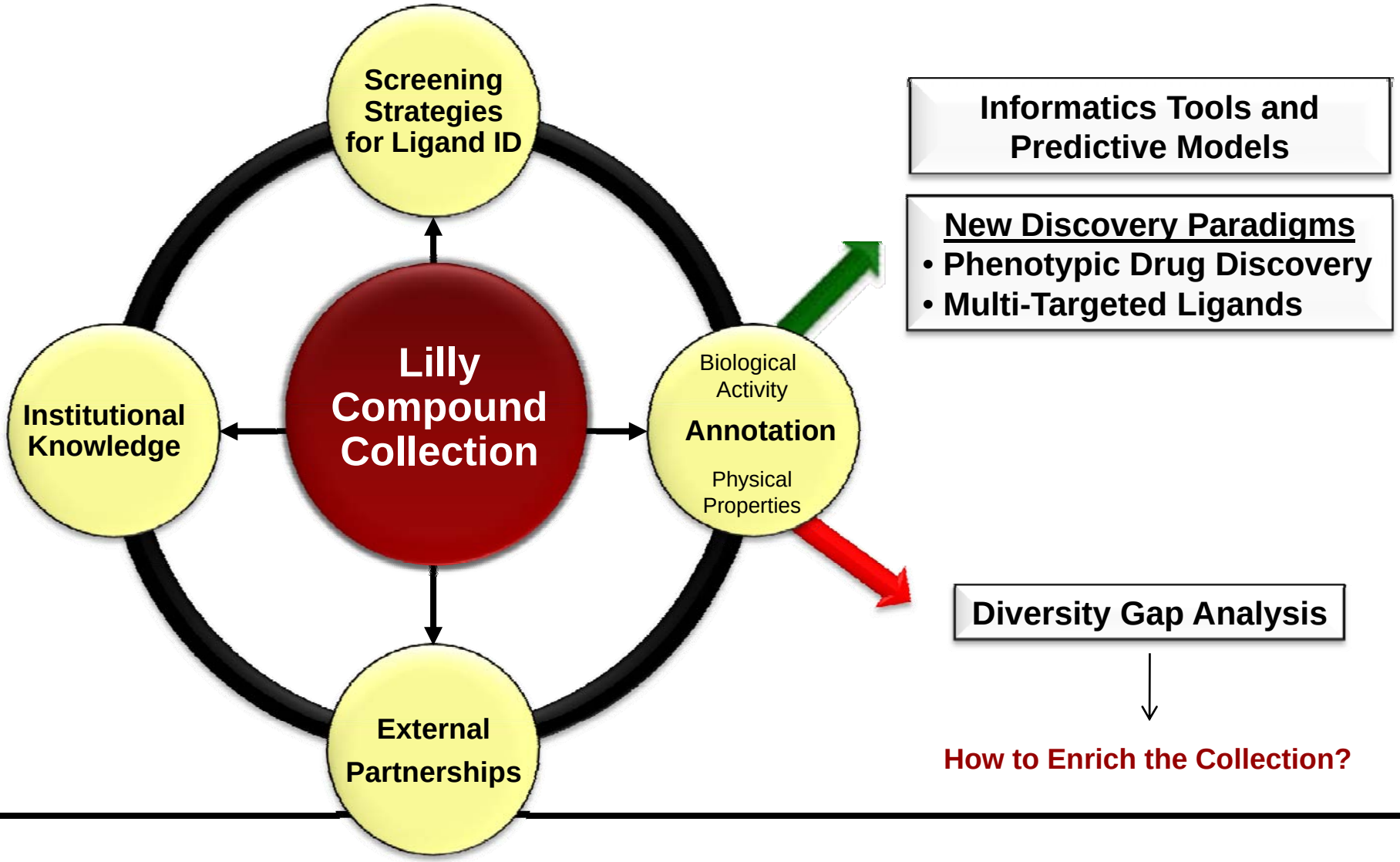
Uncover/optimize molecule signatures

- High Content Imaging
- Advanced informatics
- **Alternative molecular diversity**
- Advanced cellular assays
- Stem cells
- Pathway analysis
- Target(s) ID

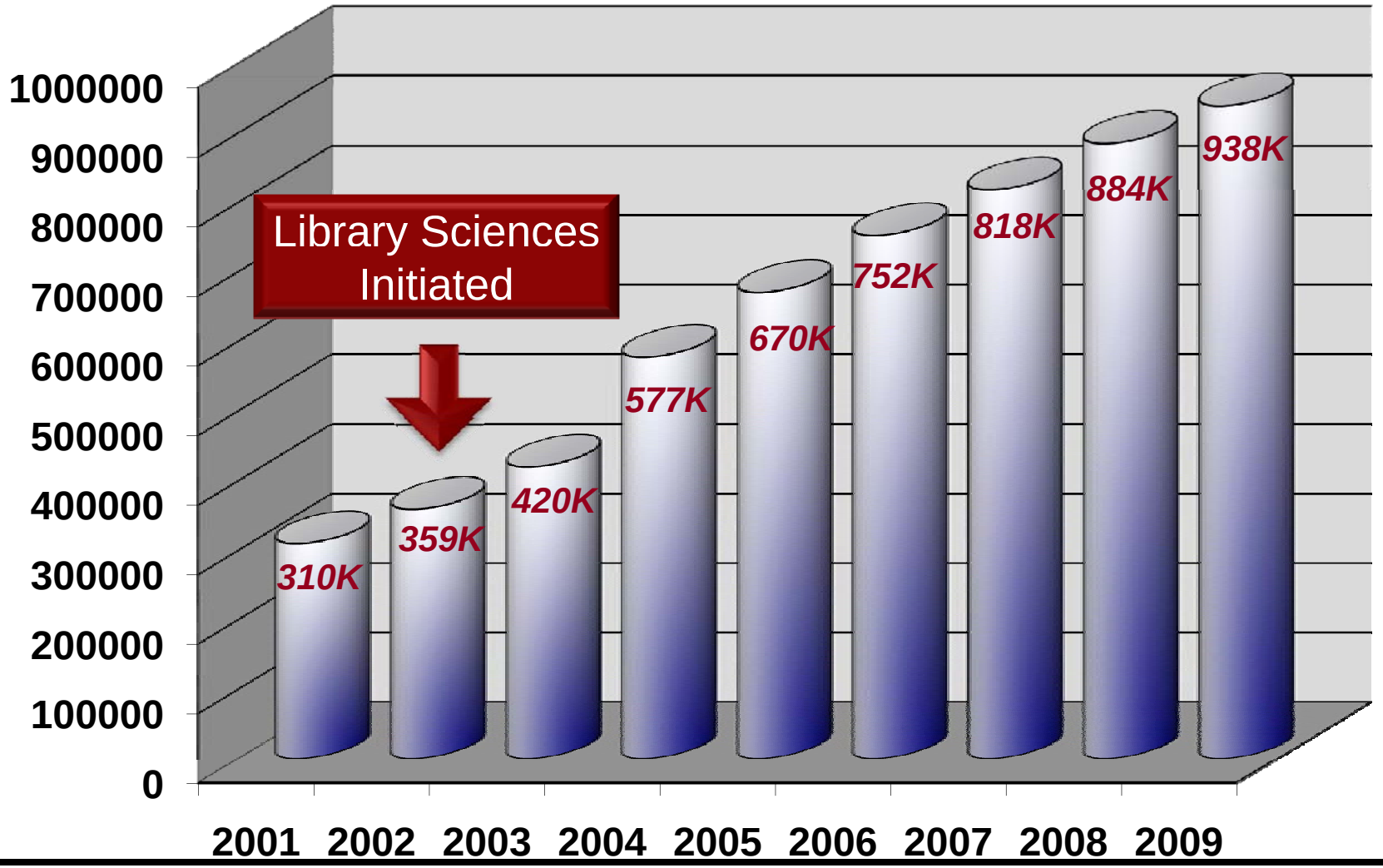




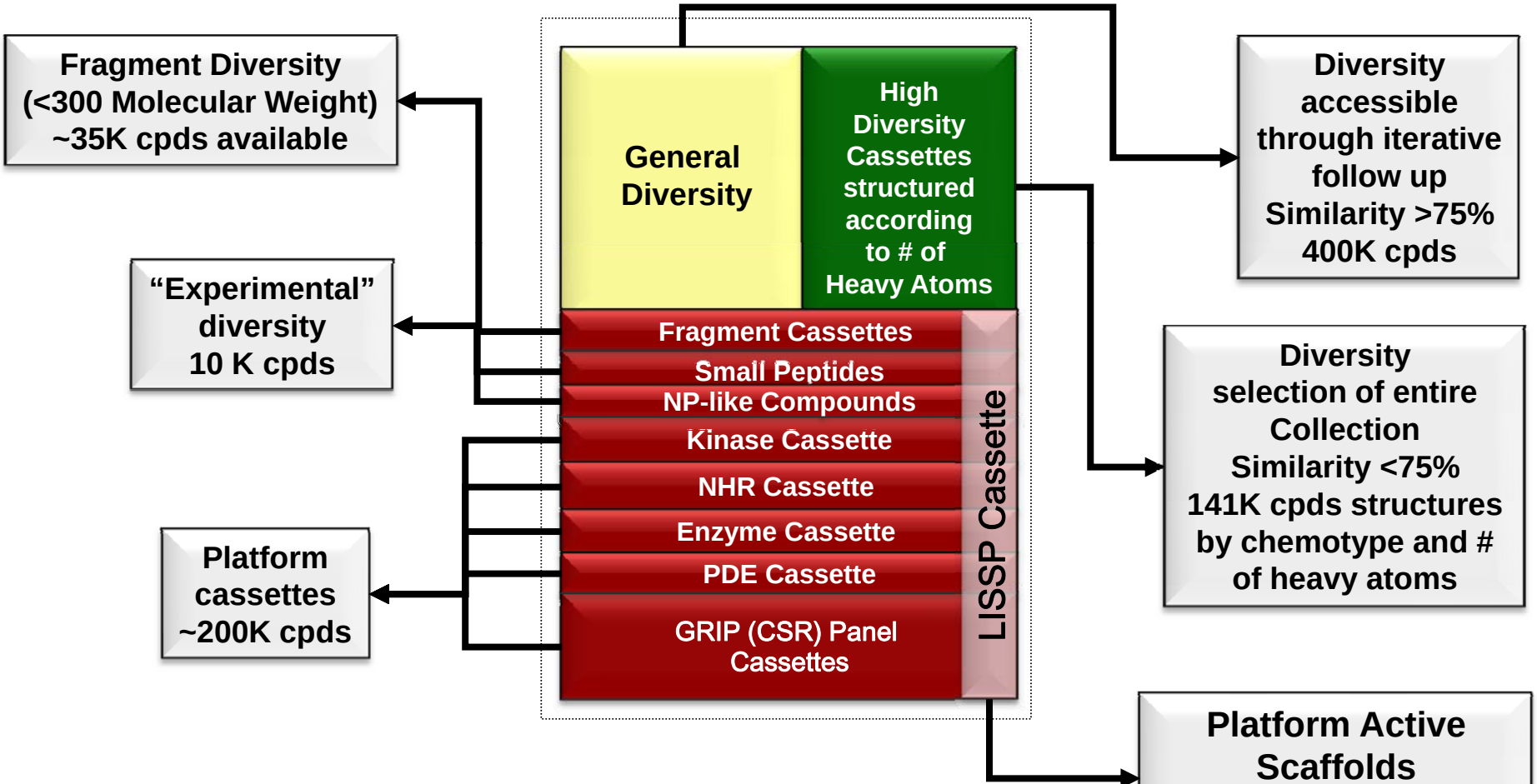
Strategic Role of Lilly Compound Collection



Unique Compound Growth in Lilly Compound Collection



Structure of Lilly Compound Collection 2010



- *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

The Lilly Open Innovation Concept

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 (PD^2)

- 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 ($TargetD^2$) 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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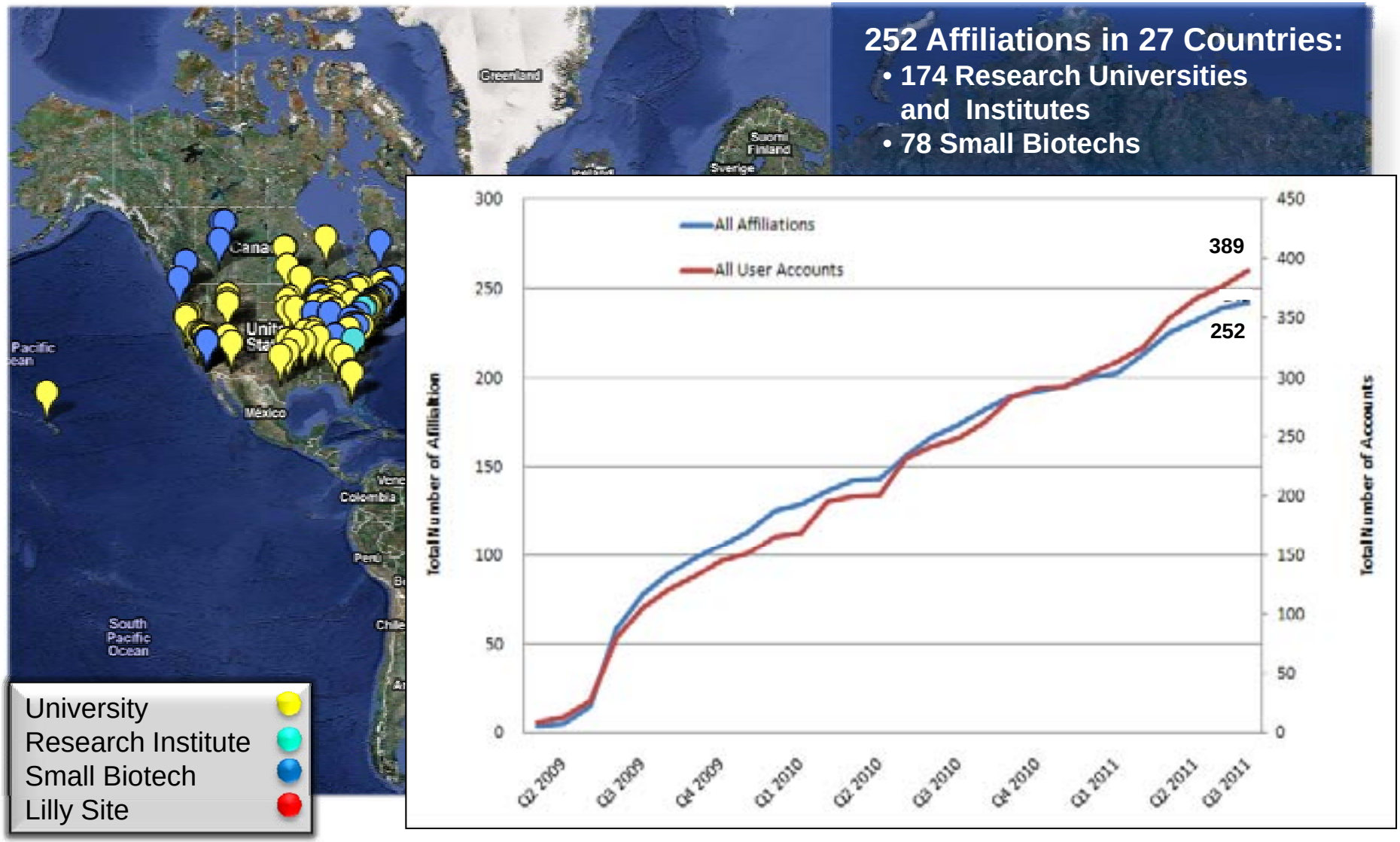
PD² Global Network

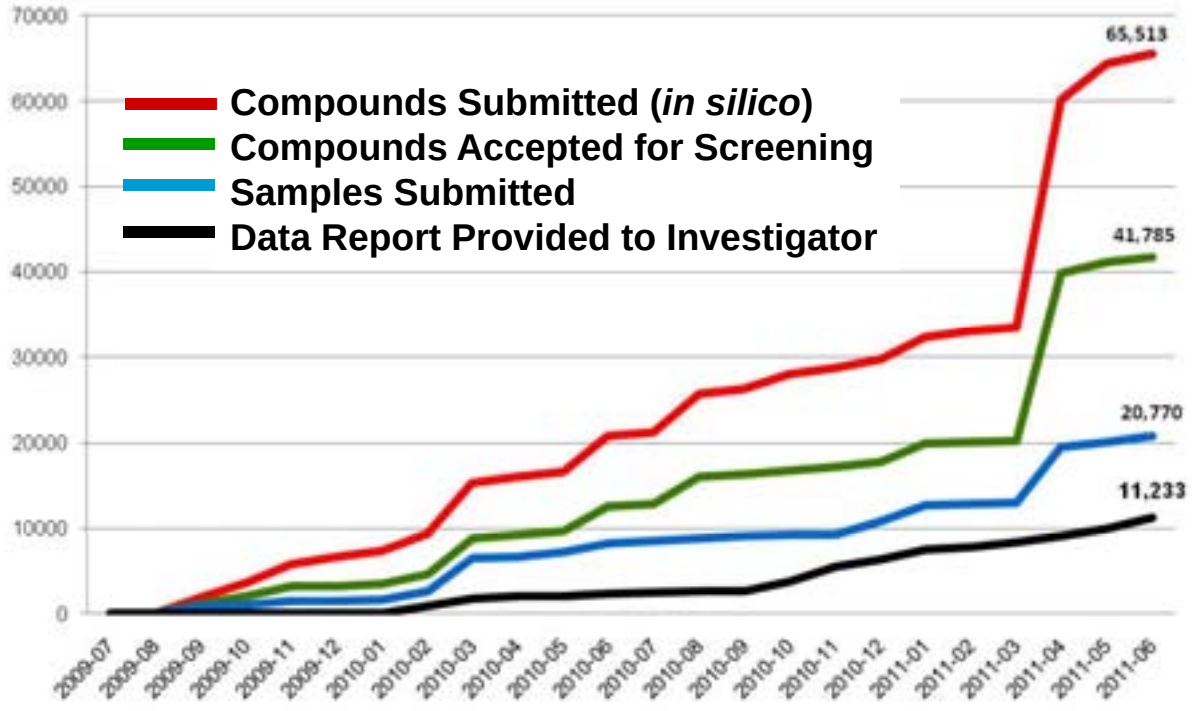


252 Affiliations in 27 Countries:

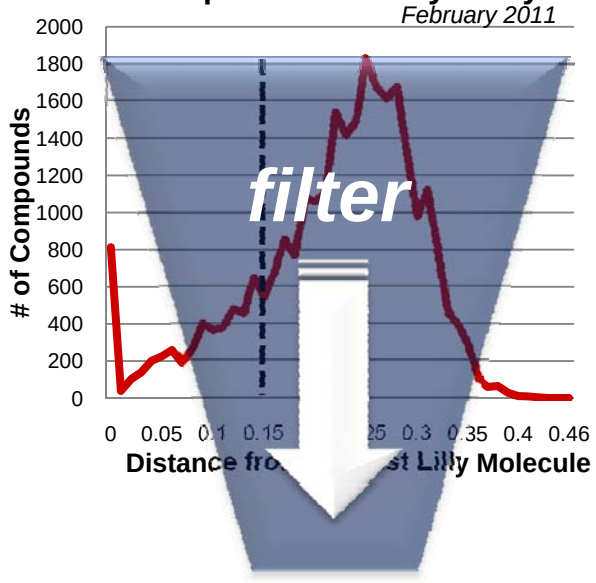
- **174 Research Universities and Institutes**
- **78 Small Biotechs**

Cumulative PD² Structure & Sample Metrics

Compound Activity Evolution



PD² Compound Diversity Analysis

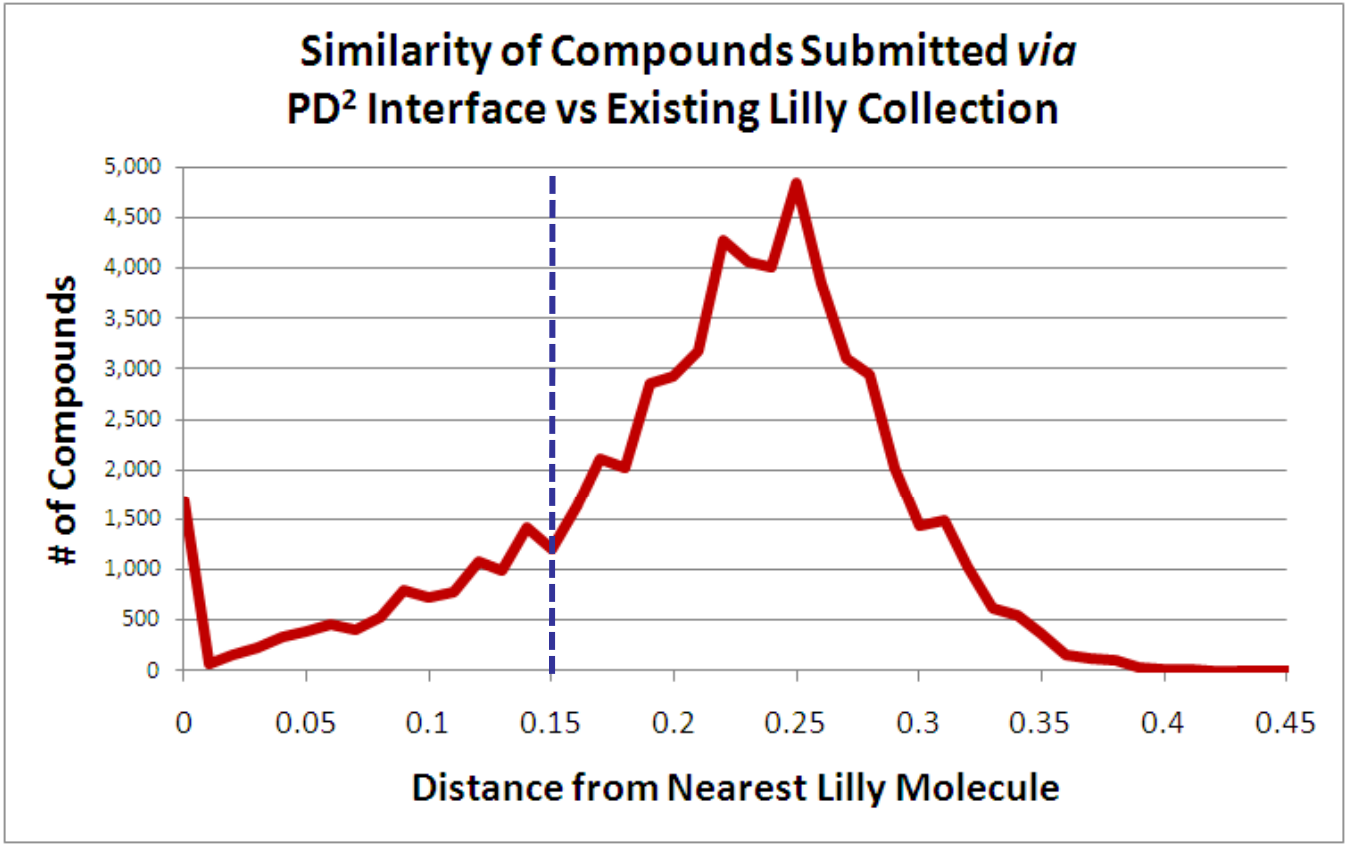


~60% of Compounds Accepted for Screening

Exclusion:

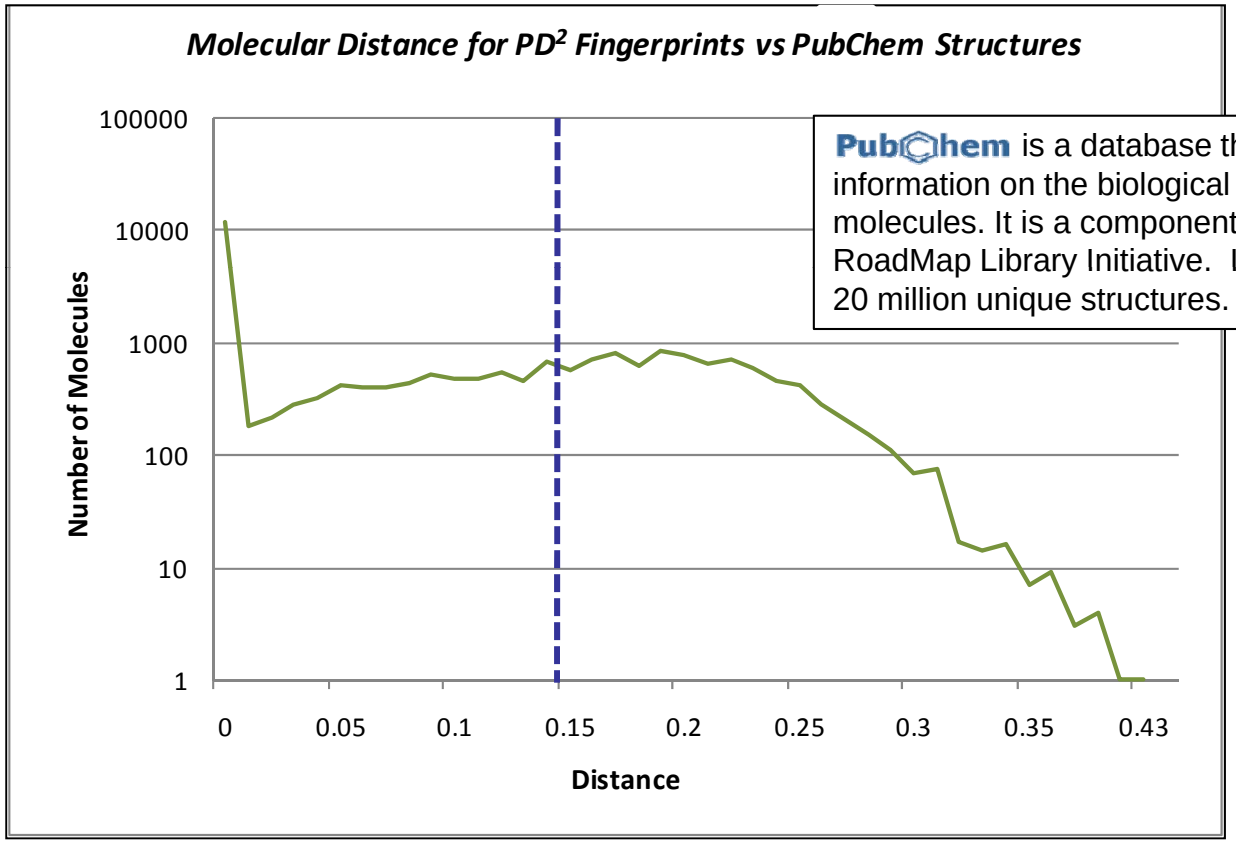
- Fail Med Chem Rules
- Insufficient Novelty
- Similar to Tested Compounds
- Similar to Controlled Substances

Structural Diversity of PD^2 relative to the Lilly Compound Collection



PD^2 collection to date offers compounds with structural diversity relative to the Lilly Collection

Structural Diversity of PD² relative to the PubChem Collection



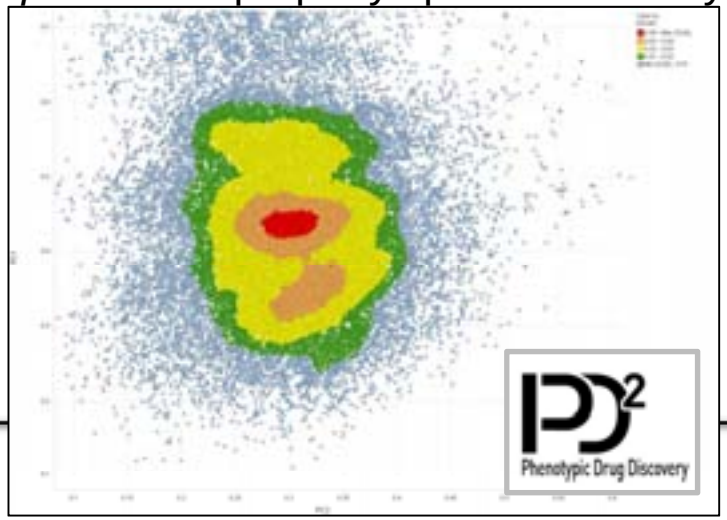
PubChem is a database that provides information on the biological activities of small molecules. It is a component of NIH's Molecular RoadMap Library Initiative. It contains roughly 20 million unique structures.

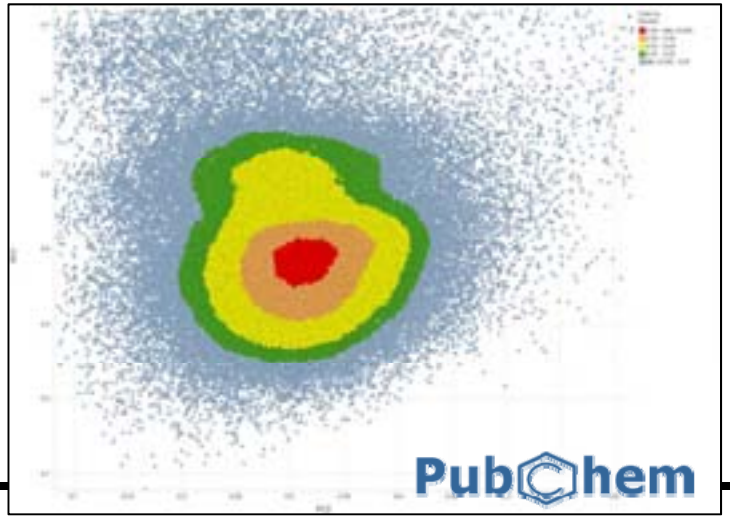
Many molecules are similar to those in PubChem, but a large proportion are significantly (> 0.15) different.

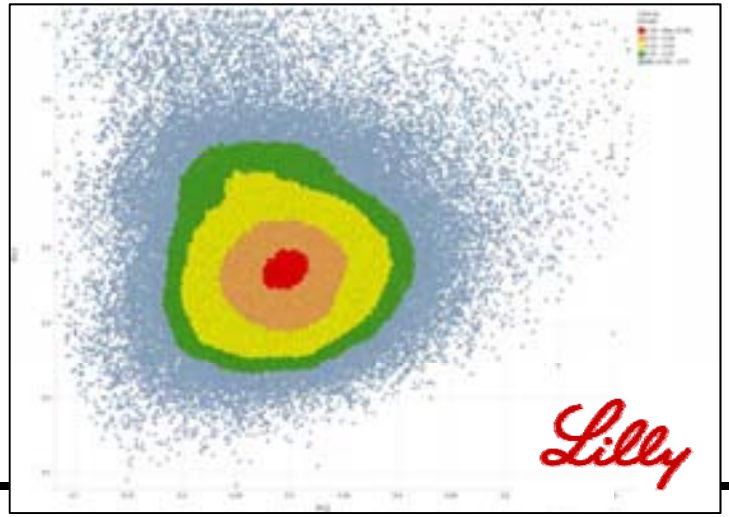
Property Space Comparisons Among Alternative Diversity Sources

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

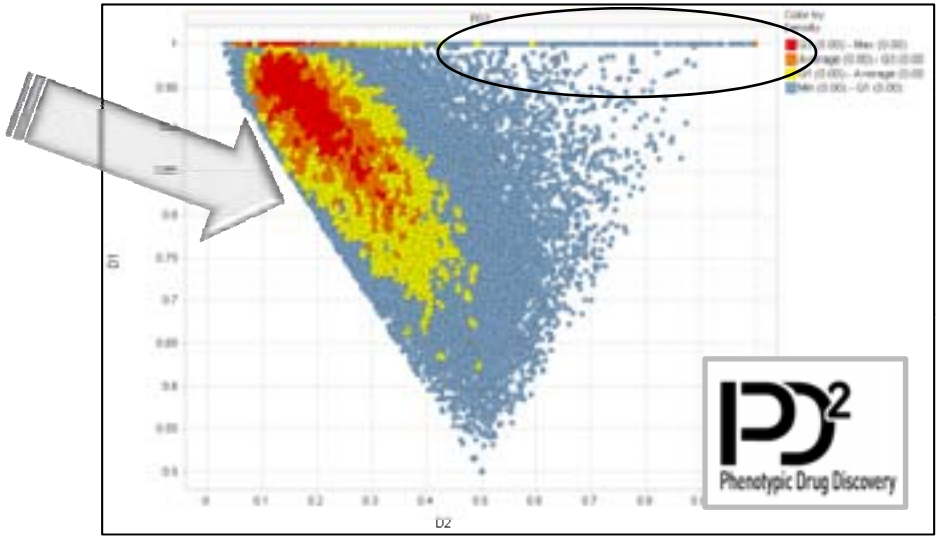
- Molecular weight
- clogD at pH7.4
- Aromatic density
- Fraction of SP_3 atoms
- Hydrogen bond donor and acceptor

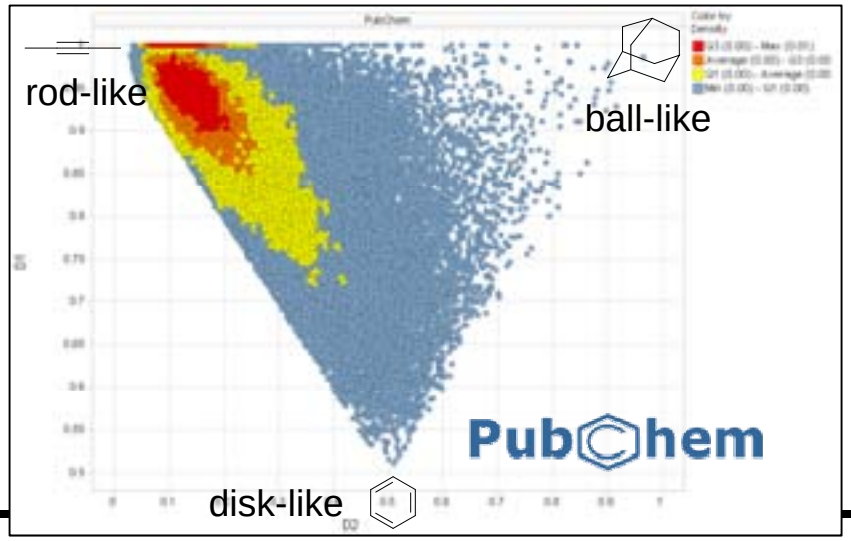


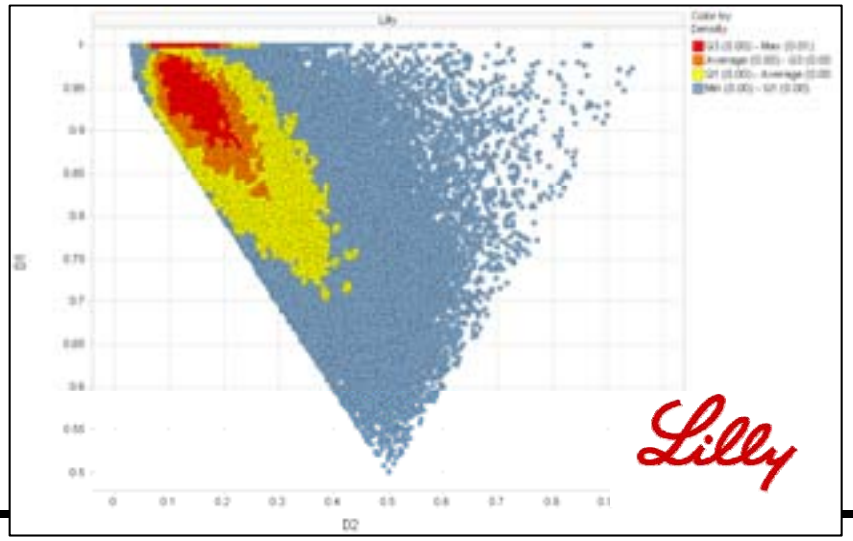




Shape Diversity Comparisons



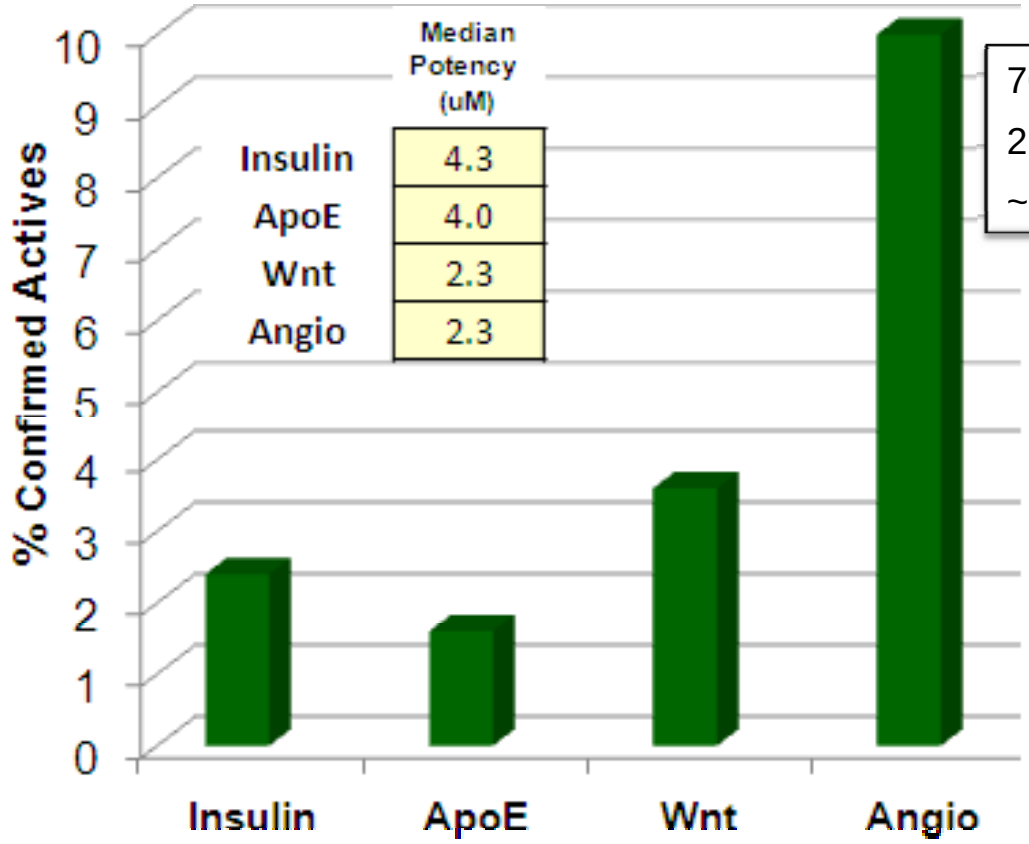




PD² Screening Metrics

Primary Assay Module Hit Rates

First 5,000 compounds



70% PD² compounds specific for 1 module

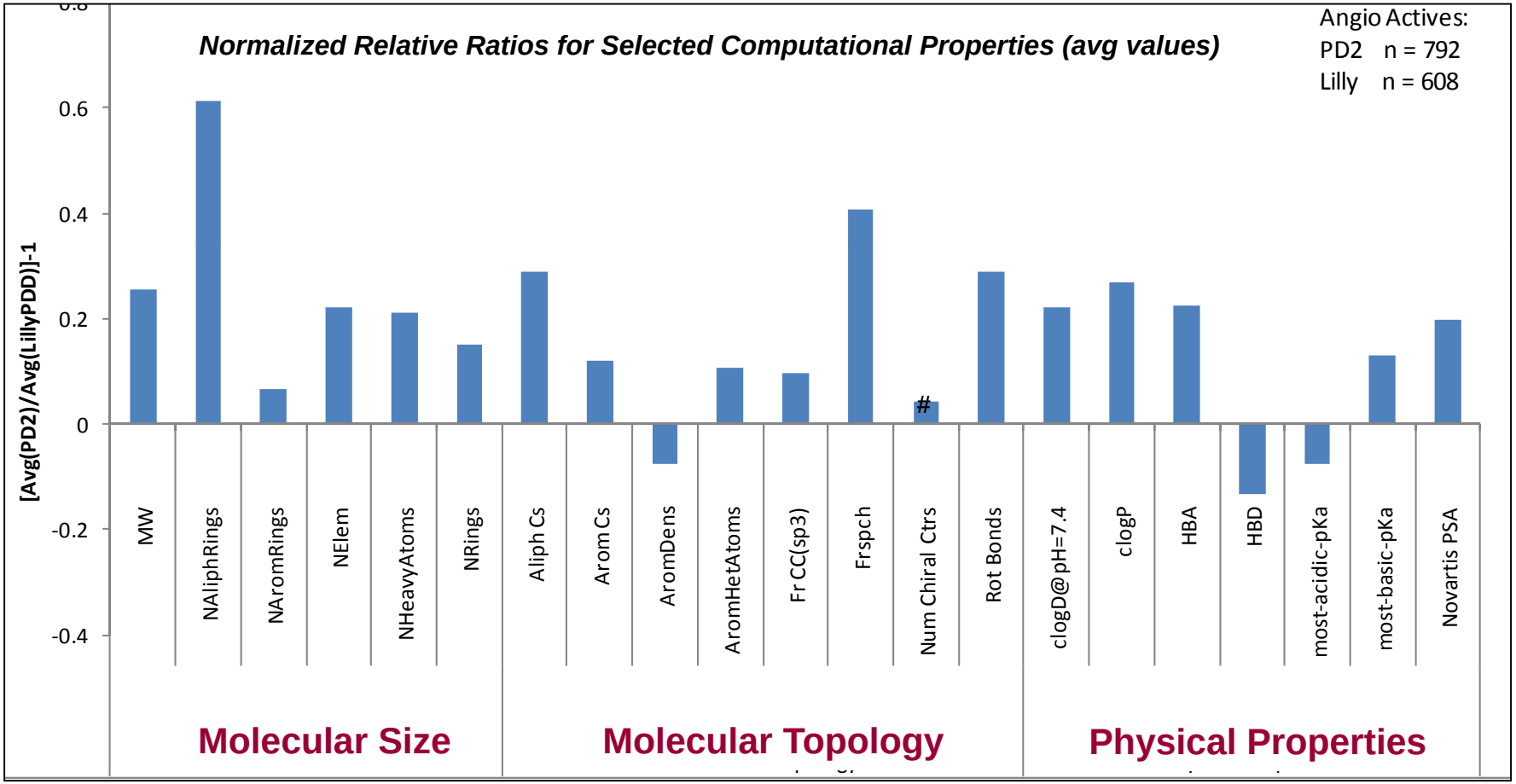
22% PD² compounds active in 2 modules

~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



*All bars represent statistically significant deltas excepting those marked with the symbol #

PD^2 Opportunity Evaluation Process

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:

https://openinnovation.lilly.com/dd/partnering-in-drug-discovery/structure-review-process.html

Summary of Selected Opportunities

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

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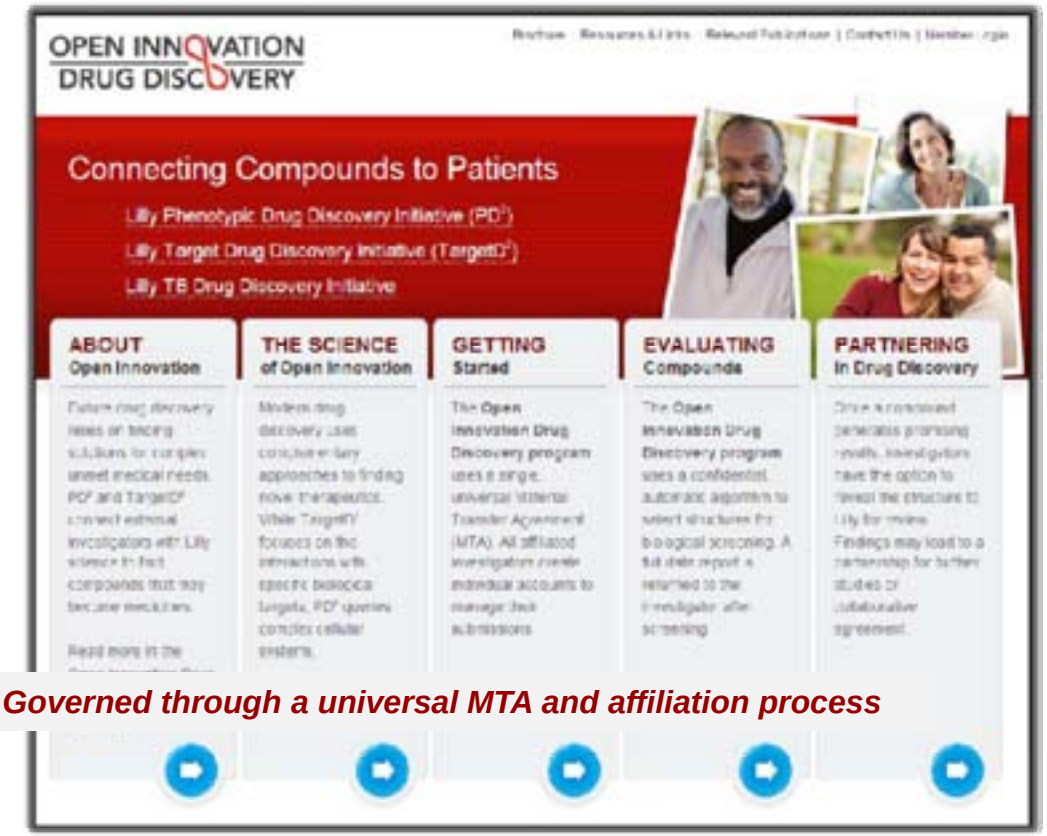
Open Innovation Drug Discovery Program and Website

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



Governed through a universal MTA and affiliation process

openinnovation.lilly.com/dd

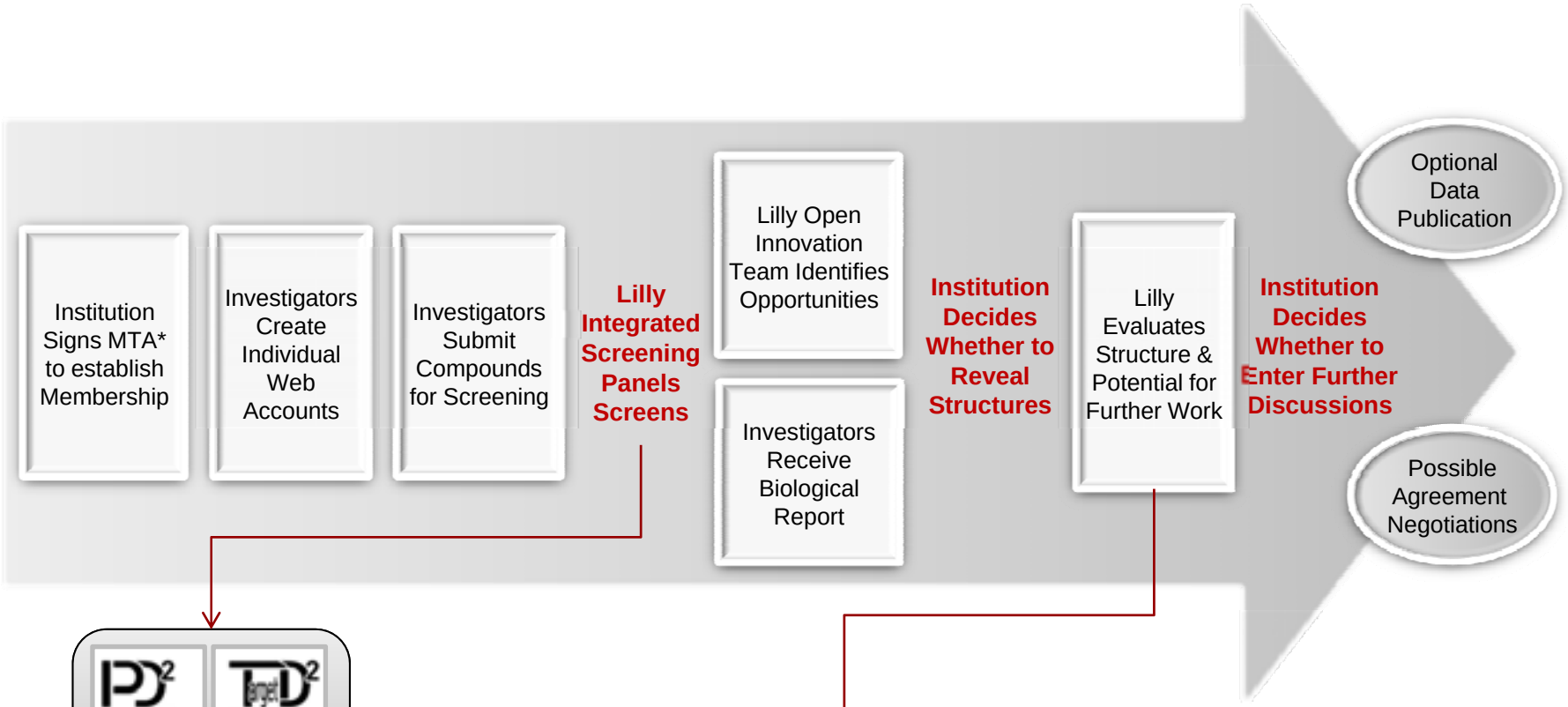
PD² Phenotypic Drug Discovery

TargetD² Target Drug Discovery

The Lilly TB Drug Discovery Initiative

Open Innovation Drug Discovery

Integrated Business Process



What are we Looking For?

Phenotypic Drug Discovery Initiative, PD^2

- 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, $TargetD^2$

- 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)

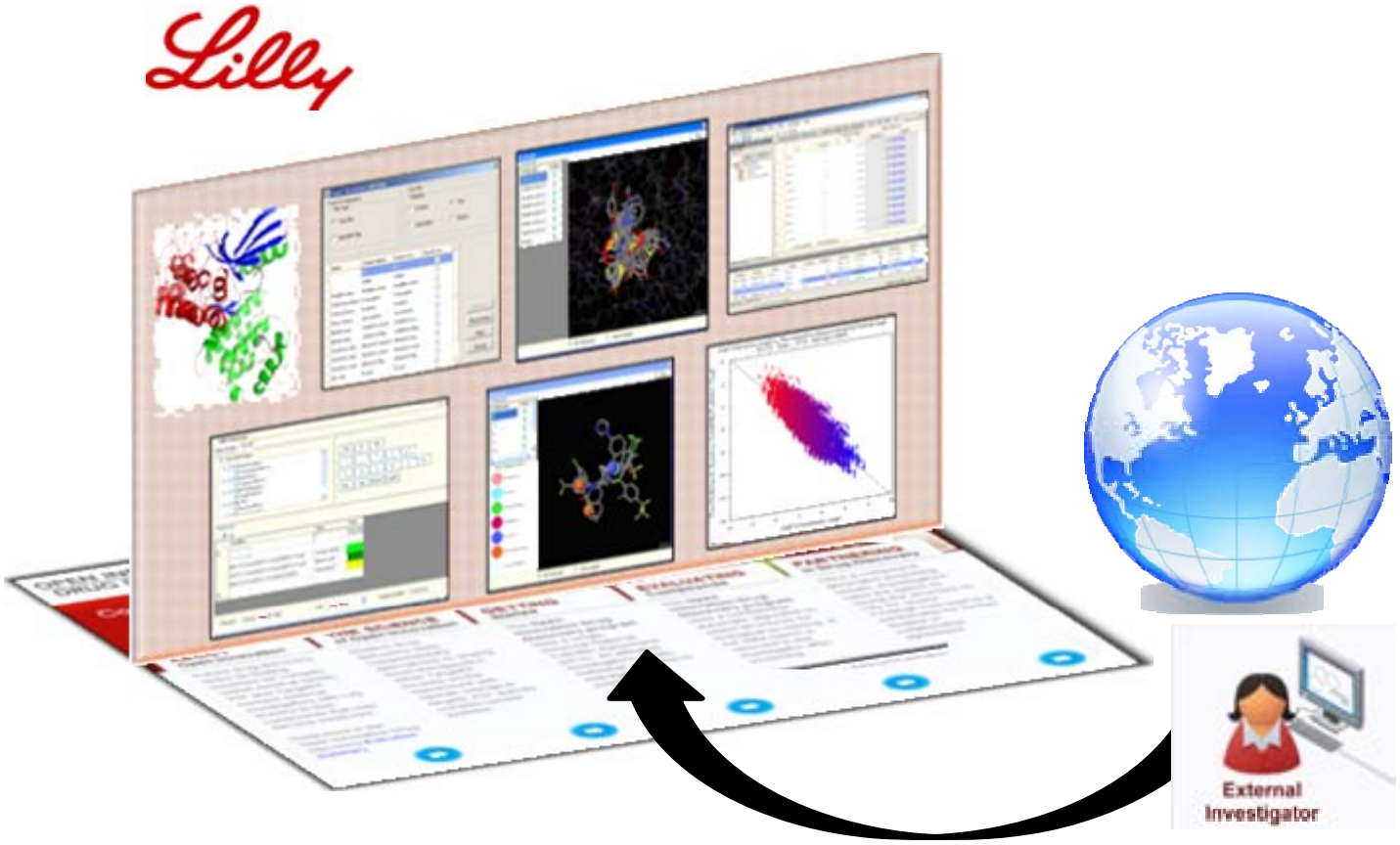
Open Innovation Drug Discovery Available Assay Panels

Discovery Approach	Endocrine/ Cardiovascular	Oncology	Neuroscience	Tuberculosis
PD² Phenotypic Drug Discovery	• Insulin Secretion • Wnt Pathway Activator • GLP-1 Secretion	• Anti-Angiogenesis • K-ras/Wnt Synthetic Lethal		• TB Screening Module (IDRI)
TargetD² Target Drug Discovery	• GPR119 Receptor Agonist • Apelin (APJ) Receptor Agonist • Sodium Phosphate Transporter 2b (NTP) Inhibitor	• Hexokinase 2 (HK2) Inhibitor	• mGlu2R Allosteric Antagonist • CGRP Receptor Antagonist	

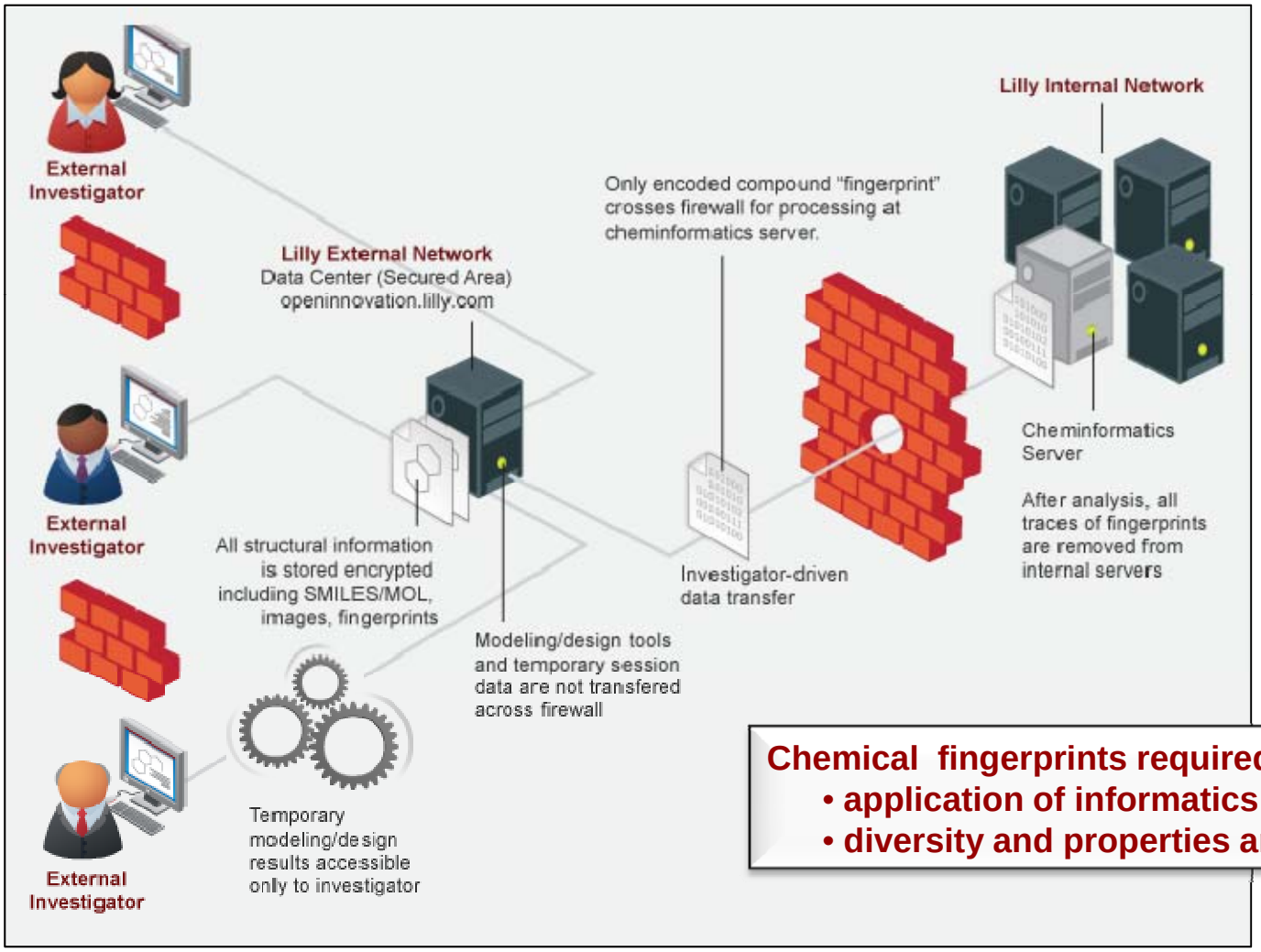
Details available online:
https://openinnovation.lilly.com/dd/science-of-open-innovation/strategic-areas-of-interest.html

Target Drug Discovery (TargetD^2)

Computational tools provided to aid compound design and selection



Protection of Chemical Structures



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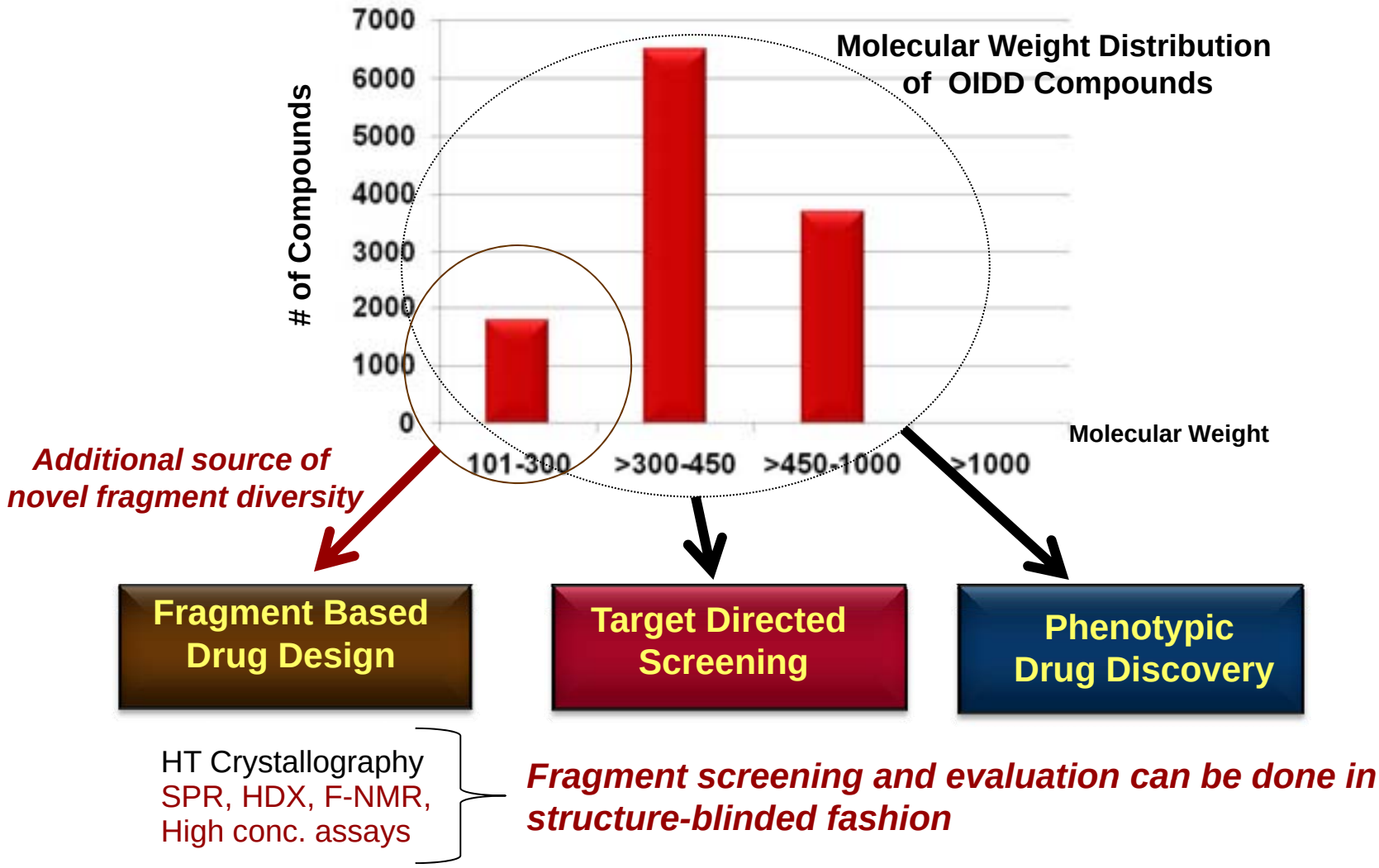
Additional Scientific Directions to Provide Value to Participants

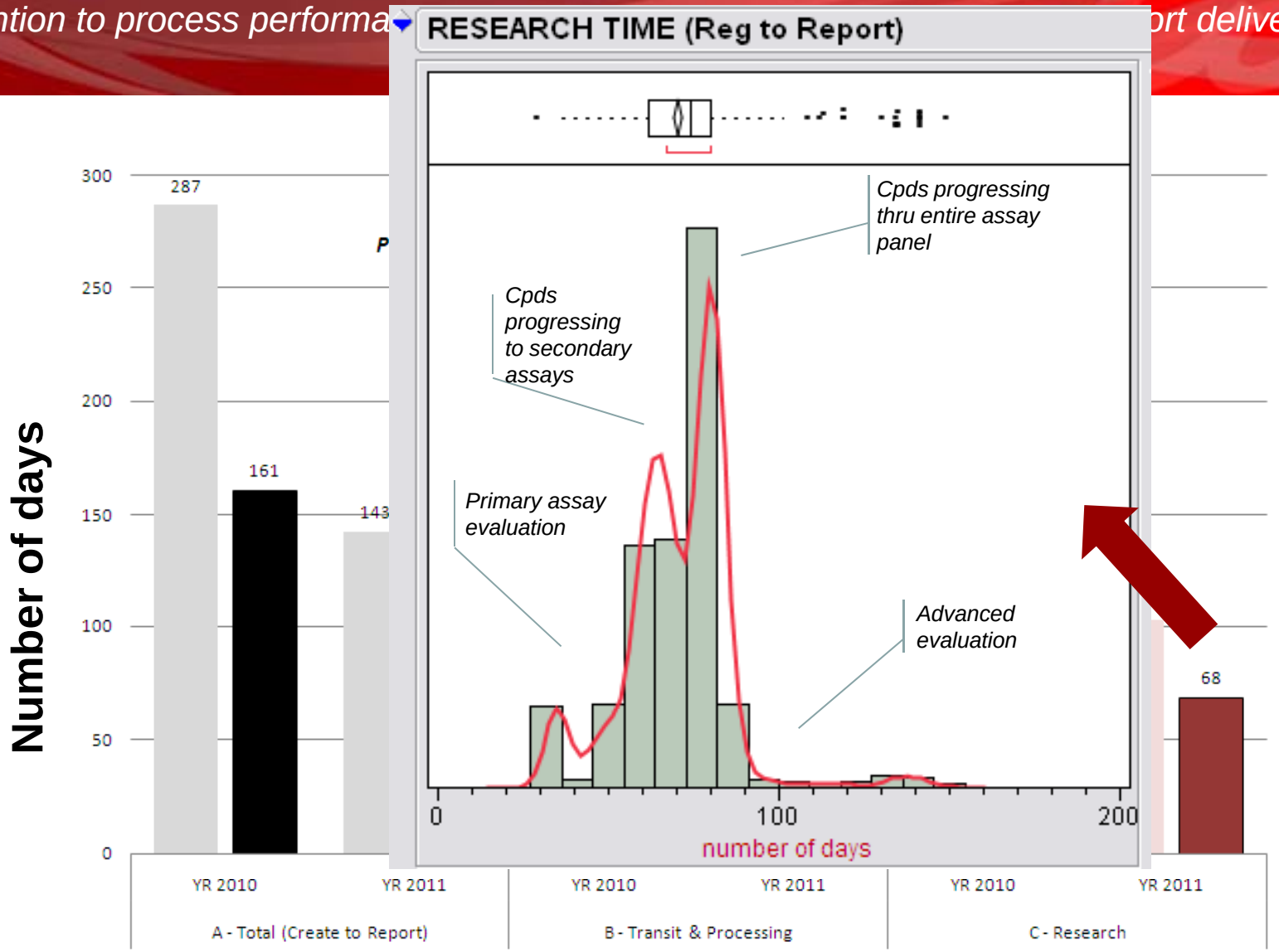


Ongoing Activity

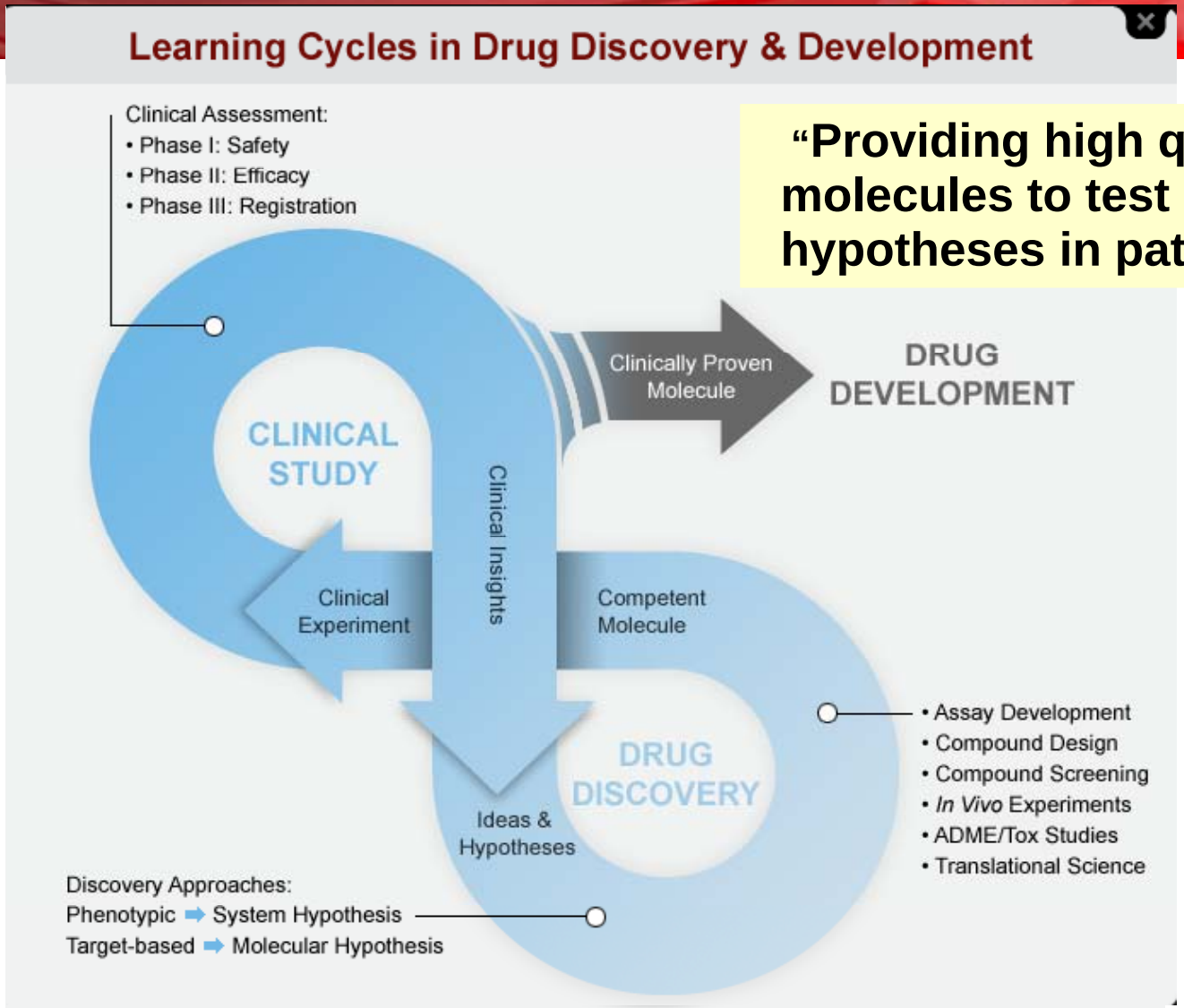
- 13 September 2011: new OIDD website-based application available to all users worldwide
- 30 September 2011: first-generation PD^2 Material Transfer Agreement terminated and replaced by integrated OIDD MTA
- Late 2011/Early 2012: first Structure-Property models available online
- During 2012: enablement 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 performa *ort delivery*



Enhancing Small Molecule Innovation



"Providing high quality molecules to test clinical hypotheses in patients"

Open Innovation Drug Discovery Design Challenges

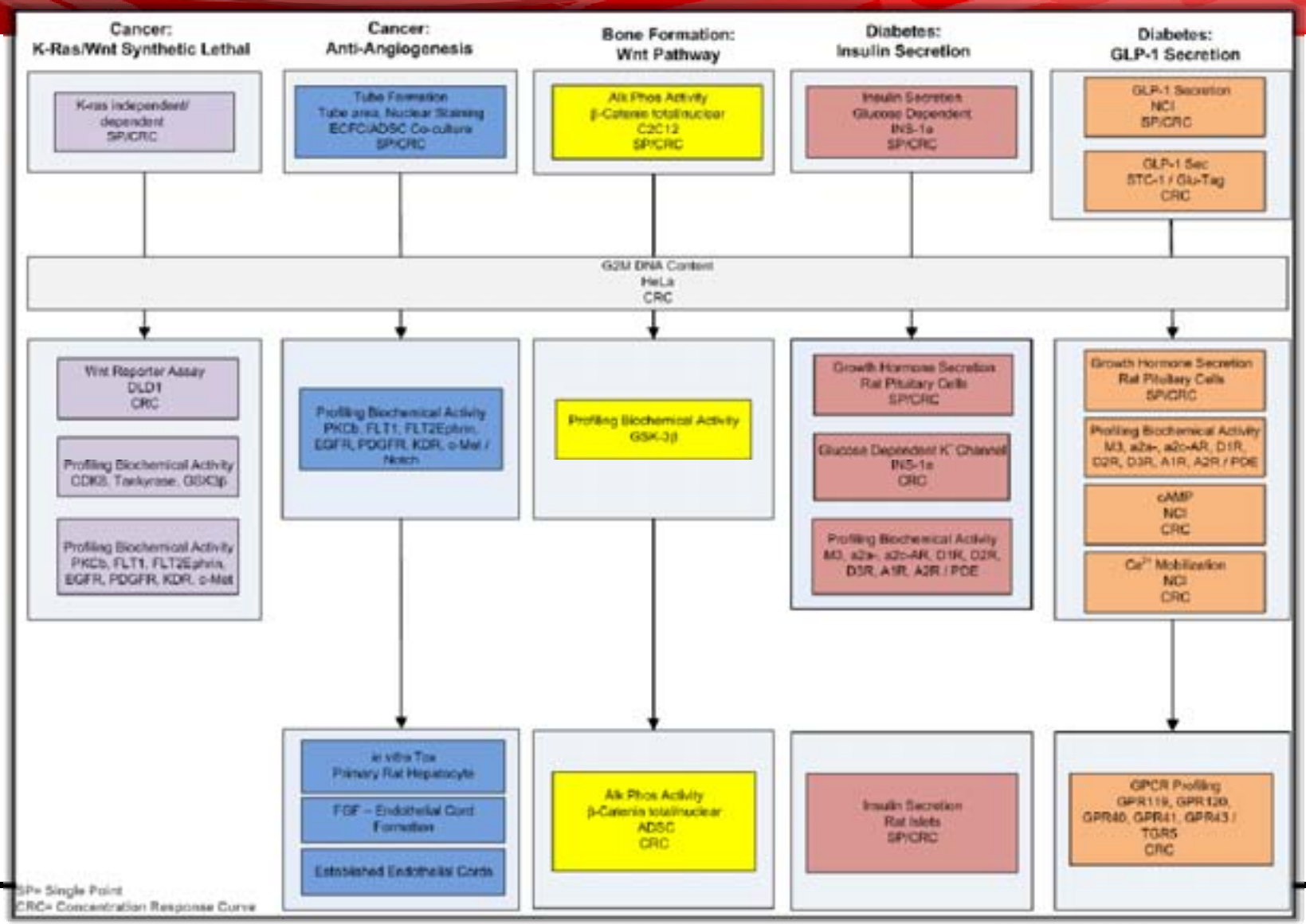
Foundational

- 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

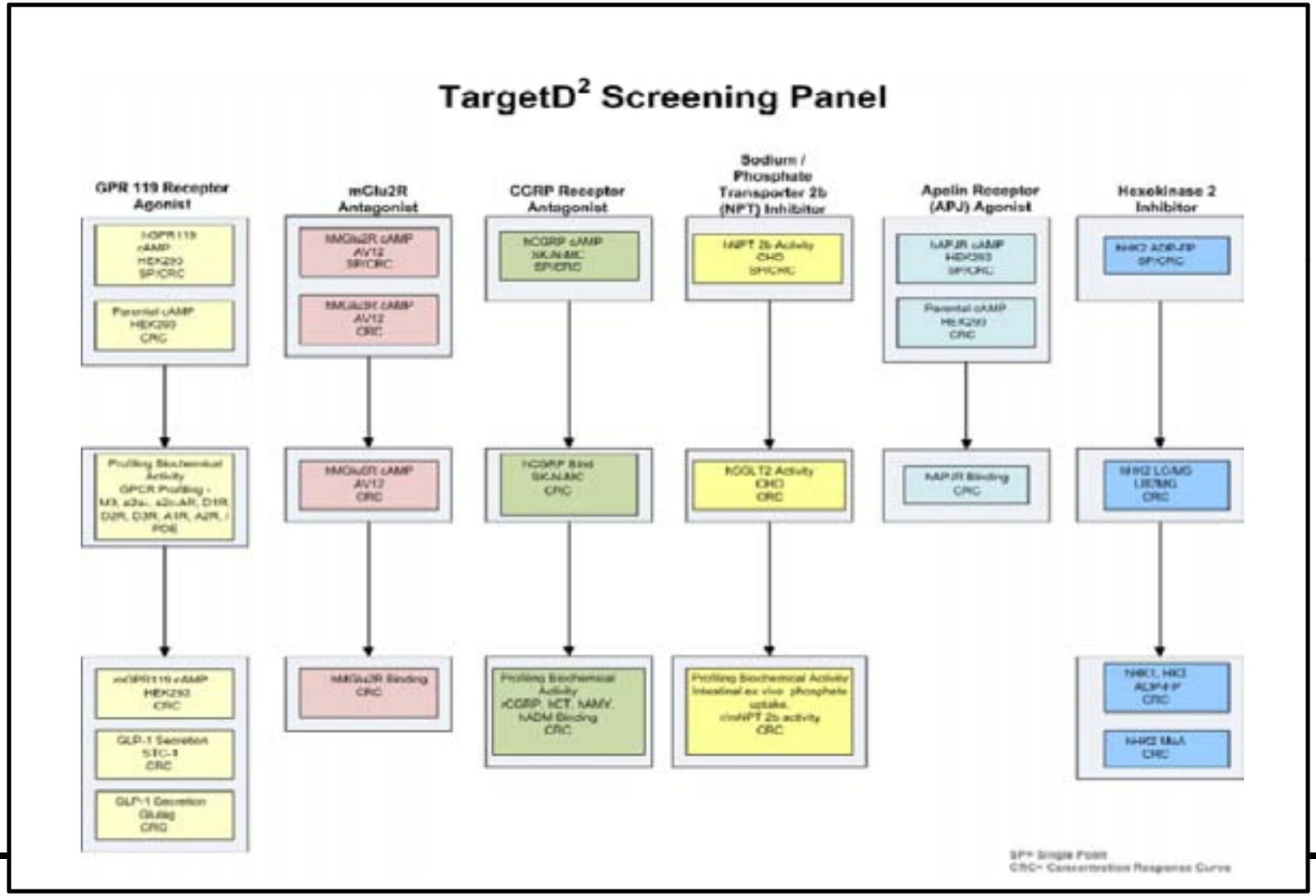
Operational

- Website design and enablement within Lilly
- Managing multiple partnerships across the globe
- Compound logistics
- Timely data turnaround and communication
- Crisp internal decision-making

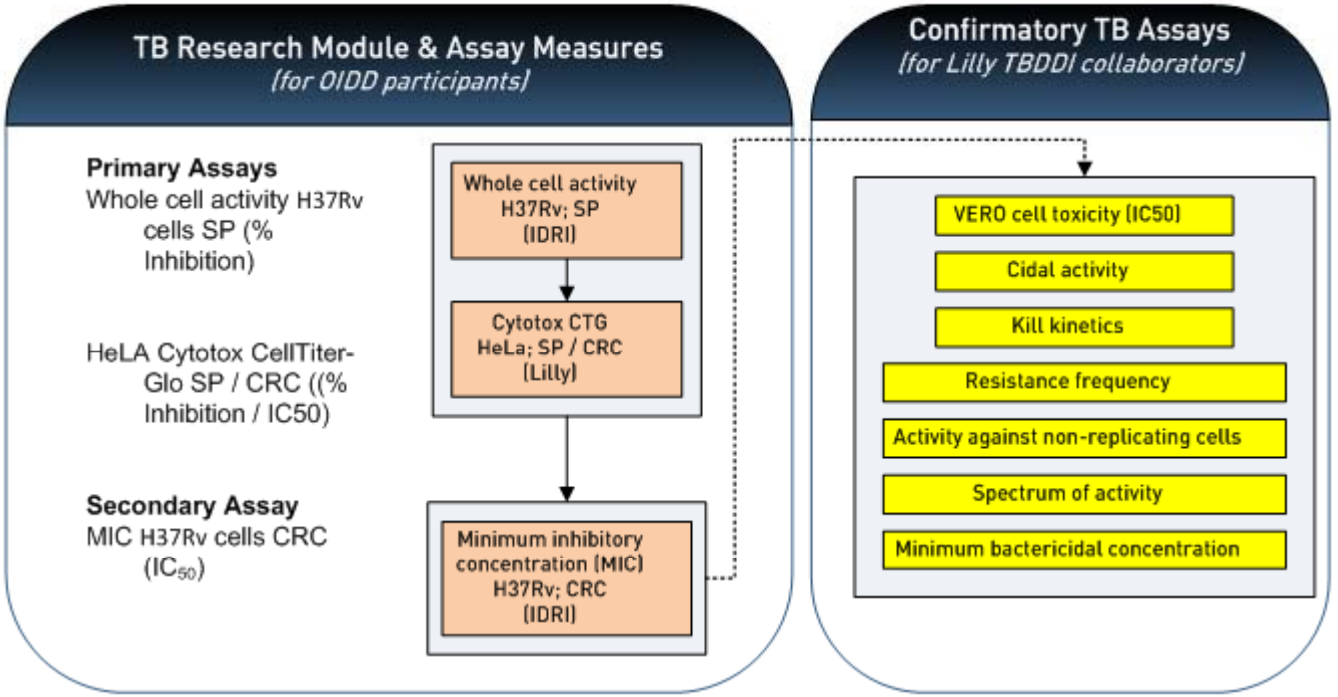
Flow Schemes for PD² Modules



Flow Schemes for TargetD^2 Modules



Flow Scheme & Assay Measures for TB Module



How were new medicines discovered?

David C. Swinney & Jason Anthony, ***Nature Reviews Drug Discovery*** *10, 507-519 (July 2011)*

First in Class

Follow-on Drugs

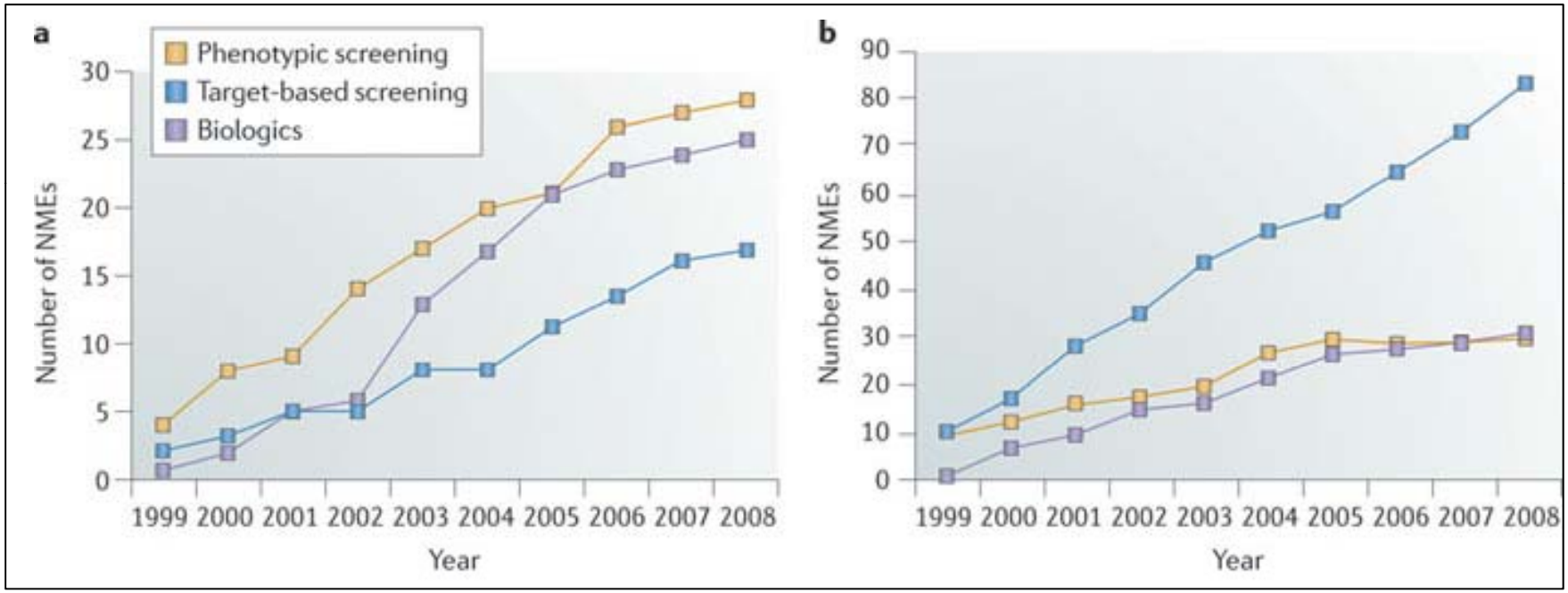


Fig 3: Cumulative distribution of new drugs by discovery strategy

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

Debating Value & Quality of Published Target Validation Studies

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*