Moving discoveries from knowledge-based predictions and laboratory benches to patients’ bedsides

KNIME UGM MEETING – February 2015
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# How Much Does Pharmaceutical Innovation Cost? A Look At 100 Companies

No factor defines success and failure for a drug company more than this: Companies that invent more, better drugs at a lower cost do better than those that hemorrhage cash but never get.

## Research Spending Per New Drug

<table>
<thead>
<tr>
<th>Company</th>
<th>Ticker</th>
<th>Number of drugs approved</th>
<th>R&amp;D Spending Per Drug ($Mil)</th>
<th>Total R&amp;D Spending 1997-2011 ($Mil)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AstraZeneca</td>
<td>AZN</td>
<td>5</td>
<td>11,790.93</td>
<td>58,955</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>GSK</td>
<td>10</td>
<td>8,170.81</td>
<td>81,708</td>
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<tr>
<td>Sanofi</td>
<td>SNY</td>
<td>8</td>
<td>7,909.26</td>
<td>63,274</td>
</tr>
<tr>
<td>Roche Holding AG</td>
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<td>11</td>
<td>7,803.77</td>
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<tr>
<td>Pfizer Inc.</td>
<td>PFE</td>
<td>14</td>
<td>7,727.03</td>
<td>108,178</td>
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<td>Johnson &amp; Johnson</td>
<td>JNJ</td>
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<td>5,885.65</td>
<td>88,285</td>
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<tr>
<td>Eli Lilly &amp; Co.</td>
<td>LLY</td>
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<td>4,577.04</td>
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<td>Abbott Laboratories</td>
<td>ABT</td>
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<tr>
<td>Merck &amp; Co Inc</td>
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<td>67,360</td>
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<tr>
<td>Bristol-Myers Squibb Co.</td>
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<td>Novartis AG</td>
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<td>Amgen Inc.</td>
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<td>9</td>
<td>3,692.14</td>
<td>33,239</td>
</tr>
</tbody>
</table>

Sources: InnoThink Center For Research In Biomedical Innovation; Thomson Reuters Fundamentals via FactSet Research Systems
SERIOUS DRUG ADVERSE EVENTS

THE LANCET

Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study

David J Graham, David Campen, Rita Hui, Michele Spence, Craig Cheetham, Gerald Levy, Stanford Shoor, Wayne A Ray

Summary
Background Controversy has surrounded the question about whether high-dose rofecoxib increases or naproxen decreases the risk of serious coronary heart disease. We sought to establish if risk was enhanced with rofecoxib at either high or standard doses compared with remote non-steroidal anti-inflammatory drug (NSAID) use or celecoxib use, because celecoxib was the most common alternative to rofecoxib.

Methods We used data from Kaiser Permanente in California to assemble a cohort of all patients age 18–84 years treated with a NSAID between Jan 1, 1999, and Dec 31, 2001, within which we did a nested case-control study. Cases of serious coronary heart disease (acute myocardial infarction and sudden cardiac death) were risk-set matched with four controls for age, sex, and health plan region. Current exposure to cyclo-oxygenase 2 selective and non-selective NSAIDs was compared with remote exposure to any NSAID, and rofecoxib was compared with celecoxib.

Findings During 2302029 person-years of follow-up, 8143 cases of serious coronary heart disease occurred, of which 2210 (27.1%) were fatal. Multivariate adjusted odds ratios versus celecoxib were: for rofecoxib (all doses), 1.59 (95% CI 1.10–2.27, p=0.015); for rofecoxib 25 mg/day or less, 1.47 (0.99–2.17, p=0.054); and for rofecoxib greater than 25 mg/day, 1.58 (1.27–1.91, p=0.001). For naproxen versus remote NSAID use the adjusted odds ratio was 1.14 (1.01–1.30, p=0.05).

Interpretation Rofecoxib use increases the risk of serious coronary heart disease compared with celecoxib use. Naproxen use does not protect against serious coronary heart disease.

Introduction Cyclo-oxygenase 2 (COX2) selective non-steroidal anti-inflammatory drugs (NSAIDs) are prescribed for the treatment of arthritis and other musculoskeletal complaints because of the reduced occurrence of gastrointestinal toxic effects compared with non-selective NSAIDs. Questions about cardiovascular risk with these other NSAIDs, but high-dose rofecoxib was not assessed separately. Studies investigating the effect of naproxen on cardiovascular risk have yielded conflicting results. In three cohort studies, no reduction in risk was reported with naproxen use, whereas a cardioprotective effect was noted in three other studies. We sought to address these important questions about the cardio-
The world's first integrated predictive platform for drug discovery and safety evaluation
Prous Institute Symmetry® integrates computational tools and methods aiming to replicate all the processes through which new drugs are discovered, developed and approved.

- It enables the generation of new research hypotheses and predicts with accuracy the pharmacological and toxicological profile of a molecule.
- Aims to “de-risk” and prioritize projects and speed up drug discovery and development, reducing time, costs and attrition rates.
- Provide Safer & better Drugs to Patients.

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**Experimental validation**

**In silico research**

![Diagram showing stages of drug discovery and development](chart.png)

<= Higher Quality Lead Candidates

- Pre-Discovery Starting Points
- Focused Molecular Library Generation
- Activity Profiling
- Safety / ADME Profiling
- In Vivo
- Tox
- ADME
- Cell
- In Vitro
SYMmetry leverages KNIME Server

Web GUI (Spring + Dojo)

Input Data (SDF or SMILES)

Workflows

- Setting-Up Prediction Jobs & Building Models
- Reports
- Manage DB
- Prediction Results & Models

DB Models & Results

Web Reporting

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- Uncover potential toxicity and safety issues early in discovery
- Evaluate preclinical toxicology and human adverse effects endpoints of critical importance to regulatory authorities
- Determination of potential safety issues linked to targets associated with toxicities and human adverse effects
- Drug-drug interaction assessment
- Benchmark in silico safety profiles against other compounds
SYMMETRY APPLICATIONS: DRUG EFFICACY

- Virtual high throughput screening of compound libraries to elucidate potential mechanisms of action
- Emerging target assessment and pathway profiling
- Phenotypic studies
- Drug repositioning/ new indications discovery for drugs already on the market or under development
SYMMETRY APPLICATIONS
GLOBAL MECHANISM OF ACTION MODEL

• Screen chemical libraries against 700 mechanisms of action in a single predictive model
• Based on a proprietary multi-label learning algorithm.
• Manually-curated training set of > 1 million compounds.
• Predicts functional activity, going beyond a binding interaction.
• Extensive external validations have shown the model outperforms benchmark similarity-based approaches.
• Regularly updated with new data and algorithmic enhancements.
• Server architecture for multiple users/sites simultaneous access.
• Intuitive and user-friendly.
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