Long History of Productive Academic & Government Collaborations with the Pharmaceutical Industry

• Industry-Academia relationships flourished between WWI & WWII.

• Increasing independent research capability by industry required academic expertise
  • Basic research began to replace “botanicals” a source of new medicines
  • Lilly and U of Toronto (1922) collaboration to produce insulin
  • Lilly & Indianapolis City Hospital (1926) open Research Clinic to study pellagra and other disorders
  • Lilly & U of Rochester (1931) collaboration to Rx pernicious anemia

• Nat’l Res. Council Survey (1940)
  • 50 companies supporting 370 projects at 70 universities

D. Blumenthal, NEJM, 2003, 349:2452-8
Historical Perspective

(continued)

Later decline in collaborations post WWII
• Greater independence of industry
• Increasing federal support of academic research through mid ~1970’s

Fully integrated pharmaceutical firms owned & controlled most of the drug development process.
• Attempted to mimic AT&T’s Bell laboratories, IBM’s Watson Research Center and Xerox’s Palo Alto Research Center which produced Nobel Prize winning research.

Bayh-Dole Act 1980
• Foster translation of scientific discovery to commercial products.
• Collaboration seen by Congress as a means to advance product development
• Allowed universities to patent & license IP derived from federally funded research
• $MM flowed to universities with shift from chemistry & engineering to life sciences
• Late 1990’s: 90% of firms, 25-50% of faculty
• Most universities had equity in their sponsoring companies


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Widely Acknowledged Conflicts in Industry-University Collaborations

• “Industry-sponsored clinical research: a double edged sword”, (J. Montaner Lancet 2001)

• “Collaborating with Industry-Choices for the Academic Medical Center,” (H. Moses et al NEJM 2002)

• “Regulating Academic-Industrial Research Relationships”, (T. Stossel, NEJM 2005)

• “Uneasy Alliance: Clinical Investigation and the Pharmaceutical Industry”, (T. Bodenheimer, NEJM 2000)

“In simple terms industry has a primary responsibility to generate profits for shareholders while academics are preoccupied with issues pertaining to scientific inquiry and career advancement.” (J. Montaner Lancet 2001)

There needs to be a clear separation between research and marketing activities.

The financial arrangements need to be transparent and well justified.
Distinct Cultures and Resources

**Academia**
- Resource limited
- Institutional support limited
- Diverse talent pool
- Project is premier
- Any interesting outcome is valued
- Continuous focus of activity (decades)
- Several missions

**Industry**
- Limited Intellectual & legal freedom to operate.
- Strong Institutional support
- Narrowly talent pool
- Portfolio is premier
- Only specific outcomes valued
- Areas of interest changes with business climate
- Single mission
Balance of Drug Discovery and Development
Collaboration must address concerns & likely benefits

<table>
<thead>
<tr>
<th>areas for concerns</th>
<th>expected benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integrity of the university's teaching and research mission</td>
<td>Expedites the public’s access to new and important medicines</td>
</tr>
<tr>
<td>Willingness to disseminate new discoveries</td>
<td>Returns public value from government investment in research</td>
</tr>
<tr>
<td>Exchange of scientific reagents, tools and technologies</td>
<td>Fosters business development</td>
</tr>
<tr>
<td>Patient protection</td>
<td>Increases support for educational institutions</td>
</tr>
<tr>
<td>Conflict of interests at several levels</td>
<td>Enhances the performance of both institutions</td>
</tr>
<tr>
<td>Ownership</td>
<td></td>
</tr>
</tbody>
</table>
Where does the industry need help in advancing innovative medicines?

1. Target identification and validation
2. Understanding patient heterogeneity
3. Biomarker development
4. Identifying unique subsets of patients responsive to a new drug with a novel mechanism of action
5. Providing tools to help physicians manage complex information and derive therapeutic decisions
1. Target Identification and Validation

Older drugs were based on chance pharmacology

- The observation of clinical activity of a compound leads to clinical development. The mechanism of action is later uncovered.

- Physiologic observations
  - Alkylating agents
  - Natural Products (ACE inhibitors, Digitoxin)
  - Aspirin

Newer drugs are derived from basic academic research

The genetics of rare diseases with extreme phenotypes gives insight into biochemical pathway that lead to new drug targets.

- CETP (cholesterol metabolism)
- PCSK9 (cholesterol metabolism)
- CTLA4 (autoimmunity)*
- NAV1.7 (pain) †
- SOST (bone mineralization)
- Retinoblastoma (cancer)
- Amyloid Precursor Protein/Aβ peptide (Alzheimer’s Disease)
- Myostatin (muscle growth)

*P Lindsey, BMS, † D. McHale, Pfizer
2. Understanding Patient Heterogeneity

- “The suppression of participant heterogeneity in rigorous clinical trials helps to explain why the published clinical literature is overwhelmingly explanatory rather than pragmatic; that is, focused on what works rather than on informing real-world decisions among alternative clinical interventions”


We need to use patients’ clinical and molecular information to make better treatment decisions
About half of all patients fail to respond to medicines they are prescribed.

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Efficacy Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s</td>
<td>30</td>
</tr>
<tr>
<td>Analgesics (Cox-2)</td>
<td>80</td>
</tr>
<tr>
<td>Asthma</td>
<td>60</td>
</tr>
<tr>
<td>Cardiac Arrhythmias</td>
<td>60</td>
</tr>
<tr>
<td>Depression (SSRI)</td>
<td>62</td>
</tr>
<tr>
<td>Diabetes</td>
<td>57</td>
</tr>
<tr>
<td>HCV</td>
<td>47</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Efficacy Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incontinence</td>
<td>40</td>
</tr>
<tr>
<td>Migraine (acute)</td>
<td>52</td>
</tr>
<tr>
<td>Migraine (prophylaxis)</td>
<td>50</td>
</tr>
<tr>
<td>Oncology</td>
<td>25</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>48</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>50</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>60</td>
</tr>
</tbody>
</table>

Using markers to target patients results in smaller possible market, but peak sales are increased

Example: Peak sales increase for marker with 25% frequency

<table>
<thead>
<tr>
<th>Measure</th>
<th>Base</th>
<th>With marker (3 scenarios)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Market size (patients)</td>
<td>200k</td>
<td>50k</td>
</tr>
<tr>
<td>Response rate</td>
<td>25%</td>
<td>50%</td>
</tr>
<tr>
<td>Peak share</td>
<td>20%</td>
<td>80%</td>
</tr>
<tr>
<td>Patients prescribed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responders</td>
<td>40k</td>
<td>40k</td>
</tr>
<tr>
<td>Non-responders</td>
<td>30k</td>
<td>20k</td>
</tr>
<tr>
<td>Total cycles*</td>
<td>120k</td>
<td>160k</td>
</tr>
<tr>
<td>Price per cycle</td>
<td>$1k</td>
<td>$1k</td>
</tr>
<tr>
<td>Peak sales</td>
<td>$120m</td>
<td>$160m</td>
</tr>
</tbody>
</table>

*6 per Responder, 2 per Non-responder

+33%  +66%  +122%

Extent of benefits depends on frequency of and response rate with marker.
3. Biomarker Development

• Biomarkers serve a variety of needs
  • Target engagement – does the drug inhibit the target in humans?
  • Pharmacodynamic effect – does the drug modulate the pathway of interest?
  • Efficacy – can the short term biochemical effects be related to overall clinical benefit?

• Most biomarker have very little “proprietary value”.
  • The value of the biomarker goes up when widely used, understood and accepted.
## The Biomarkers Consortium: Projects Supported by Lilly (through 2009)

<table>
<thead>
<tr>
<th>Project Name/ Committee</th>
<th>Description</th>
<th>Total Project Value &amp; Duration</th>
<th>Eli Lilly Investment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin Project (Metabolic Disorders SC)</td>
<td>Determine whether adiponectin has utility as a predictive biomarker of glycemic control</td>
<td>$0 (in-kind data sharing project) (18 months) Completed April 2009</td>
<td>1 of 4 companies to provide data and in-kind legal/scientific support</td>
</tr>
<tr>
<td>Sarcopenia Consensus Summit (Metabolic Disorders SC)</td>
<td>Generate a consensus definition of sarcopenia to provide guidelines for diagnosis/better regulatory decisions</td>
<td>$463,000 over 24 months 2010-2011</td>
<td>$100,000 (1-time payment; project to conclude in 2011)</td>
</tr>
<tr>
<td>Alzheimer’s Disease Targeted CSF Proteomics Project (Neuroscience SC)</td>
<td>Qualify a multiplexed panel of known AD CSF-based biomarkers; examine Beta-Site APP Cleaving Enzyme levels in CSF; and qualify a mass spectroscopy panel</td>
<td>$586,100 over 12 months 2Q 2010-1Q 2011</td>
<td>$100,000 (1-time payment; project to launch in 2Q 2010)</td>
</tr>
<tr>
<td>PET Radioligand Project (Neuroscience SC)</td>
<td>Develop improved, more sensitive radioligands with higher binding to the peripheral benzodiazepine receptor</td>
<td>$560,500 over 24 months 2009-2010</td>
<td>$93,417 (payable over 2 years in 2009 and 2010)</td>
</tr>
<tr>
<td>Placebo Data Analysis in AD and MCI Cognitive Impairment Clinical Trials (Neuroscience SC)</td>
<td>Combine placebo data from large industry trials and analyze them to provide better measures of cognition and disease progression</td>
<td>$556,620 over 36 months 2010-2012</td>
<td>$95,000 (1-time payment)</td>
</tr>
<tr>
<td>I-SPY TRIAL 2 (Cancer SC)</td>
<td>A personalized medicine trial that promises to accelerate the pace of identifying effective novel agents for breast cancer; patients will be classified according to biomarker profiles and randomized to control therapy</td>
<td>$26,000,000 over 60 months 2010-2014</td>
<td>$200,000 (to date)</td>
</tr>
<tr>
<td><strong>TOTAL (Consortium Programs)</strong></td>
<td></td>
<td><strong>$588,417</strong></td>
<td></td>
</tr>
</tbody>
</table>
# FNIH Partnerships with Lilly

<table>
<thead>
<tr>
<th>Project</th>
<th>Description</th>
<th>Federal Investment</th>
<th>Private Investment</th>
<th>Total Investment</th>
<th>Lilly Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroscience Fellowship Program (2004-06)</td>
<td>Allows a young physician researcher apply clinical experience and cellular/molecular research techniques to the field of neurophysiology. NIH partner: NIMH</td>
<td>$0</td>
<td>$200,000</td>
<td>$200,000</td>
<td>$200,000</td>
</tr>
<tr>
<td>Overcoming Barriers to Early Phase Clinical Trials (2002-2008)</td>
<td>Investigate barriers that prevent patients, especially minority and elderly populations, from participating in early-phase clinical trials of innovative cancer therapies. NIH partner: NCI</td>
<td>$2,450,000</td>
<td>$2,550,000</td>
<td>$5,000,000</td>
<td>$600,000</td>
</tr>
<tr>
<td>Fogarty International Center 40th Anniversary (2008)</td>
<td>Scientific meetings on global health, other events. NIH partner: Fogarty</td>
<td>Not quantified</td>
<td>$200,000</td>
<td>$200,000</td>
<td>$50,000</td>
</tr>
<tr>
<td>Promise of Public Private Partnerships: Forging New Alliances in Global Health (2008)</td>
<td>Meeting to explore implementation science and training needs and forge new collaborations to improve global health. NIH Partner: Fogarty</td>
<td>$0</td>
<td>$21,000</td>
<td>$21,000</td>
<td>$5,000</td>
</tr>
<tr>
<td>The Science of Eliminating Health Disparities Summit (2008)</td>
<td>Summit to establish research agenda. NIH partner: NCMHD</td>
<td>Not quantified</td>
<td>$1,375,000</td>
<td>$1,375,000</td>
<td>$25,000</td>
</tr>
<tr>
<td>Psychiatric Genome-Wide Association Consortium (2007-2009)</td>
<td>Analyze GWAS data for ADHD, autism, bipolar disorder, major depression disorder, and schizophrenia, to move the entire field of mental health genetic research forward. NIH partner: NIMH</td>
<td>$0</td>
<td>$125,000</td>
<td>$125,000</td>
<td>$125,000</td>
</tr>
<tr>
<td>Alzheimer's Disease Neuroimaging Initiative (2003-10)</td>
<td>Collects clinical and biomarker data as a public resource to identify promising biomarkers of disease progression for use in AD clinical trials. NIH partner: NIA</td>
<td>$40,000,000</td>
<td>$20,000,000</td>
<td>$60,000,000</td>
<td>$2,500,000</td>
</tr>
<tr>
<td>Mutational Analysis of the Melanoma Genome (2010-11)</td>
<td>Sequence whole genome of 5 tumor samples and 5 normal samples, analysis, gene sequencing, deep sequencing of mutated genes. NIH partner: NHGRI</td>
<td>Not quantified</td>
<td>$250,000</td>
<td>$250,000</td>
<td>$225,000</td>
</tr>
<tr>
<td>Best Pharmaceuticals for Children Fund (2001-present)</td>
<td>Clinical trials of drugs approved for adults that are used to treat children. Supports studies of baclofen and hydroxyurea. NIH partner: NICHD</td>
<td>Not quantified</td>
<td>$5,000,000</td>
<td>$5,000,000</td>
<td>$500,000</td>
</tr>
<tr>
<td>Measures for Clinical Trials of the Treatment of Cognitive Impairment (2006-present)</td>
<td>Identify a widely accepted model for assessing efficacy of cognition enhancing drugs for schizophrenia and translate and adapt an assessment battery for use in international trials of new drug treatments. NIH partner: NIMH</td>
<td>Not quantified</td>
<td>$2,233,000</td>
<td>$2,233,000</td>
<td>$203,197</td>
</tr>
<tr>
<td>ADNI Cerebral Spinal Fluid (CSF) Extension (2007-present)</td>
<td>Extends collection of cerebral spinal fluid (CSF) in ADNI subjects for a second year. NIH partner: NIA</td>
<td>$0</td>
<td>$913,954</td>
<td>$913,954</td>
<td>$100,000</td>
</tr>
<tr>
<td>Drug Induced Liver Injury Network pledged (2010-2015)</td>
<td>Increase understanding of DILI and effective screening, diagnostic, and treatment options. NIH partner: NIDDK</td>
<td>$16,250,000</td>
<td>$1,000,000</td>
<td>$17,250,000</td>
<td>$500,000</td>
</tr>
<tr>
<td>Observational Medical Outcomes Partnership (2007-present)</td>
<td>Improve the monitoring of drugs for safety by researching methods that are feasible and useful to analyze existing healthcare databases to identify and evaluate safety and benefit issues of drugs already on the market. Federal partner: FDA</td>
<td>$0</td>
<td>$20,000,000</td>
<td>$20,000,000</td>
<td>$1,500,000</td>
</tr>
<tr>
<td>Biomarkers Consortium Membership (2007-present)</td>
<td>Core infrastructure to facilitate development of biomarkers projects. Federal partners: NIH, FDA, CMS (projects listed on next page)</td>
<td>Not quantified</td>
<td></td>
<td></td>
<td>$350,000</td>
</tr>
</tbody>
</table>

**TOTAL, general programs** $6,883,197
4. Identifying unique subsets of patients responsive to a new drug with a novel mechanism of action


“Our data demonstrate that a subset of NSCLC patients may express a transforming fusion kinase that is a promising candidate for a therapeutic target as well as for a diagnostic molecular marker in NSCLC.”

PF-02341066, a C-met inhibitor

Phase I all comers study → Phase III randomized open label trial in marker positive subjects
Information Overload

Stephen Friend 2009

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5. Tools to help physicians manage complex information and derive therapeutic decisions.

- **Significant limitations of current guidelines**
  - Guidelines not patient-specific enough to be useful and rarely allow for individualization of care.
  - Most guidelines have a one-size-fits-all mentality and do not build flexibility or contextualization into the recommendations. (Shaneyfelt & Centor JAMA, 2009)

- **There are limits on our capacity for processing information.**
  The magic number is 7 ± 2. (Miller, Psych. Review, 1956;63(2):81-97)

- **Clinicians may already be discarding important information simply due to cognitive limits.**

- **Many new medicines will require the co-launch of a decision-making tool**
Tests to Select Therapies

• Safety
  ⇒ CYP2D6 genotypes’ effect on metabolic rate for drugs
  ⇒ HLA allele B*1502 as a marker for carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis
  ⇒ HLA B5701 genotype for risk of hypersensitivity in patients taking abacavir and flucloxacillin
  ⇒ KRAS mutation for inefficacy of cetuximab, panitumumab

• Effectiveness
  ⇒ HER2 positive breast cancer patient selection for trastuzumab
  ⇒ Oncotype Dx screen for ER+, node negative patients considering treatment options

• Dosing
  ⇒ VKORC1 and CYP2C9 genotype to predict warfarin dose.

c.f. Gene Pennello, DIA Statistics Forum, April 2010
Ranges are derived from multiple published clinical studies. Other clinical factors (e.g., age, race, body weight, sex, concomitant medications, and comorbidities) are generally accounted for along with genotype in the ranges expressed in the Table. VKORC1 −1639 G → A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose. Patients with CYP2C9 *1/*3, *2/*2, *2/*3 and *3/*3 may require more prolonged time (>2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen.

<table>
<thead>
<tr>
<th>VKORC1</th>
<th>CYP2C9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>*1/*1</td>
</tr>
<tr>
<td>GG</td>
<td>5-7 mg</td>
</tr>
<tr>
<td>AG</td>
<td>5-7 mg</td>
</tr>
<tr>
<td>AA</td>
<td>3-4 mg</td>
</tr>
</tbody>
</table>

Table 5: Range of Expected Therapeutic Warfarin Doses Based on CYP2C9 and VKORC1 Genotypes†
Warfarin Dosing

Is this patient new to WarfarinDosing.org?
- New patient
- Existing patient

Warfarin doses taken so far*: 0

*Required

http://www.warfarindosing.org/Source/DoseResults.aspx
### Warfarin Dosing

Required Patient Information

- **Age:** 50
- **Sex:** Male
- **Ethnicity:** Non-Hispanic
- **Race:** African American or Black
- **Weight:** 180 lbs or 81.8 kgs
- **Height:** 5 feet and 10 inches or (177.8 cms)
- **Smokes:** Yes
- **Liver Disease:** No
- **Indication:** Atrial fibrillation
- **Baseline INR:** 1.0
- **Target INR:** 2.5
- **Amiodarone/Cordarone® Dose:** 0 mg/day
- **Statin/HMG CoA Reductase Inhibitor:** Atorvastatin/Lipitor®/Caduet®
- **Any azole (eg. Fluconazole):** No
- **Sulfamethoxazole/Septa/Bactrim/Cotrim/Sulfatrim:** No

**Genetic Information**

- **VKORC1-1639/3673:** AA (warfarin sensitive)
- **CYP4F2 V433M:** CC (wildtype)
- **GGCX rs11676382:** CC (wildtype)
- **CYP2C9*2:** CC (wildtype)
- **CYP2C9*3:** CC (homozygous mutant)
- **CYP2C9*5:** CC (wildtype)
- **CYP2C9*6:** AA (wildtype)

[http://www.warfarindosing.org/Source/DoseResults.aspx](http://www.warfarindosing.org/Source/DoseResults.aspx)

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Clopidogrel Mechanistic Model

PK $\Rightarrow$ PD $\Rightarrow$ Clinical Outcomes

Data used for this model includes:

- in vitro liver microsomal data
- in vitro competitive inhibition data
- Published data about Ki
- Healthy volunteer PK data
- Diseased patient PK data
- Healthy volunteer PD data
- Healthy volunteer PD data with other drugs
- Diseased patient PD data
- Published data on platelets
- ACS patients’ genotype, PD and clinical outcomes

- 31 ordinary differential equations for PK
- 30 ordinary differential equations for PD
- 25 input variables
- 11 baseline patient characteristics
- 6 genetic parameters (including 2C19, 2C9, & ABCB1)
- 8 concomitant medications
- PK/PD to clinical outcomes still being constructed
Summary of Areas of Collaboration

• **Pre-clinical Research**
  – Target Identification and Validation
  – Understanding which patient subgroups would benefit from targeted therapies with specific mechanisms of action.

• **Clinical Research**
  – Biomarker Research
    • Pharmacogenomics
    • Disease specific markers of benefit
  – Comparative Effectiveness Research
    • Who needs what medicine and why?
  – Pharmacoeconomic Research
    • What is valued? What benefit at what cost?
  – Advance Regulatory Science
    • What constitutes the appropriate data?
  – Implementing Personalized Medicine in a Regulated Environment
    • Designing robust decision-making tools for Physicians and Healthcare providers
Key Aspects of Successful Collaborations

• Clear expectations of the objectives, timelines, resources and overall mission
• Frequent interactions
• Interdependence of knowledge and resources.
• Consistent with both the corporate goals and the academic mission.
• Absolute transparency in all aspects of collaboration
Answers That Matter.