New Models for Financing Biopharmaceutical R&D

Andrew W. Lo, MIT

(based on joint work with Jayna Cummings, David Fagnan, Jose-Maria Fernandez, Carole Ho, Austin Gromatzky, Ken Kosik, Roger Stein)

Pfizer Cambridge Collaborative Innovation Event
Breakthroughs In Biomedicine:

- 2001: Gleevec, first of a new class of drugs based on molecular biology (tyrosine kinase inhibitor)
- 2004: Avastin, angiogenesis inhibitor (VEGF)
- 2006: Sutent, approved for RCC and GIST simultaneously
- 2012: Dr. Lukas Wartman, Wash U. “cured” of acute lymphoblastic leukemia via RNA analysis and Sutent
- 2012: David Aponte “cured” of same type of leukemia using immunotherapy (T-cells targeting CD19)
**New York Times June 4, 2014**

*In a First, Test of DNA Finds Root of Illness*

By CARL ZIMMER | JUNE 4, 2014

Joshua Osborn outside his home in Cottage Grove, Wis., with his father, Clark Osborn. Joshua suffered from swelling in the brain, but tests, a spinal tap and a biopsy were inconclusive. John Merlidi.

Joshua Osborn, 14, lay in a coma at American Family Children’s Hospital in Madison, Wis. For weeks his brain had been swelling with fluid, and a battery of tests had failed to reveal the cause.

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**The NEW ENGLAND JOURNAL of MEDICINE**

**BRIEF REPORT**

**Actionable Diagnosis of Neuroleptospirosis by Next-Generation Sequencing**

Michael R. Wilson, M.D., Samia N. Naccache, Ph.D., Erik Samayo, B.S., C.L.S., Mark Biagton, M.D., Hiba Bashir, M.D., Guixia Yu, B.S., Shahrir M. Salam, M.D., Ph.D., Sneh Somasekar, B.S., Scot Federman, B.A., Steve Miller, M.D., Ph.D., Robert Sokolic, M.D., Elizabeth Garabedian, R.N., M.S.L.S., Fabio Candotti, M.D., Rebecca H. Buckley, M.D., Kurt D. Reed, M.D., Teresa L. Meyer, R.N., M.S., Christine M. Seroogy, M.D., Renee Galloway, M.P.H., Sheryl L. Henderson, M.D., Ph.D., James E. Gern, M.D., Joseph L. DeRisi, Ph.D., and Charles Y. Chiu, M.D., Ph.D.

**SUMMARY**

A 14-year-old boy with severe combined immunodeficiency presented three times to a medical facility over a period of 4 months with fever and headache that progressed to hydrocephalus and status epilepticus necessitating a medically induced coma. Diagnostic workup including brain biopsy was unrevealing. Unbiased next-generation sequencing of the cerebrospinal fluid identified 475 of 3,063,784 sequence reads (0.016%) corresponding to leptospira infection. Clinical assays for leptospirosis were negative. Targeted antimicrobial agents were administered, and the patient was discharged home 32 days later with a status close to his premorbid condition. Polymerase-chain-reaction (PCR) and serologic testing at the Centers for Disease Control and Prevention (CDC) subsequently confirmed evidence of Leptospira антитoxin infection.
Weak Performance In Biopharma Investments

- January 2002 to January 2012, NYSE/ARCA Pharma Index return: −1.2%
- 2001 to 2010 VentureXpert average biotech IRR: −1.0%

Public and Private Funding Is Declining
Why??

**NIH funding, FY 1950–2010**
in thousands of constant 2013 dollars

<table>
<thead>
<tr>
<th>Year</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950</td>
<td>60,000,000</td>
</tr>
</tbody>
</table>

---

**Source:** Huggett, NBT May 2013

### Table 2: No. of active VC firms

<table>
<thead>
<tr>
<th>Region</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
</tr>
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<tbody>
<tr>
<td>Canada</td>
<td>10</td>
<td>5</td>
<td>9</td>
<td>14</td>
<td>9</td>
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<tr>
<td>China</td>
<td>2</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Europe</td>
<td>105</td>
<td>100</td>
<td>106</td>
<td>71</td>
<td>68</td>
</tr>
<tr>
<td>India</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Israel</td>
<td>12</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>United States</td>
<td>201</td>
<td>163</td>
<td>140</td>
<td>136</td>
<td>136</td>
</tr>
<tr>
<td><strong>Global total</strong></td>
<td><strong>309</strong></td>
<td><strong>254</strong></td>
<td><strong>248</strong></td>
<td><strong>213</strong></td>
<td><strong>196</strong></td>
</tr>
</tbody>
</table>

*Note: the global total is not a sum of all regions, as an investor that invested in many regions counts only once in the global total. Source: Dow Jones VentureSource*

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**Why?? Increasing Risk and Uncertainty**

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“Everywhere I look in the pharmaceutical industry today, I see increasing complexity and uncertainty. Whether I am considering health care reform, the emergence of the generic drug market, therapeutic substitution, or even currency fluctuations, I see both volatility and risk.

As finance professionals, therefore, we must not only manage the risks that lie at the core of our business, such as the inherent risks in drug research, but also hedge or otherwise manage the risks we don’t want to retain, like the currency risks associated with doing business in 40 of the countries in which we operate. In addition, we must plan for and attempt to deal with the changes that health care reform will bring to the market.

To date, the risks and rewards in pharmaceutical research have mostly balanced out. In general, the returns the industry has realized on R&D have more or less equaled our cost of capital. As I look to the future, however, I see the marketplace dynamics changing, and that jeopardizes the delicate balance we have achieved.”
The Drug Development Process

Current Challenges In Biopharma

- As we get smarter, business risk increases
- The “Patent Cliff”, payer pushback, FDA, litigation, productivity, financial crisis, etc.
- VC/PE and public equity are not ideal

⇒ Funding is declining despite/because of better science

Financial Engineering May Offer A Solution

- Portfolio theory: multiple “shots on goal”
- Securitization: long-term debt, tranches, guarantees,...
Lessons from the Financial Crisis?

U.S. Real Home Price Index, 1890–2012

How Did This Happen??

Source: Robert J. Shiller

Population in Millions

Real Home Price Index

Home Prices

Population

Source: Robert J. Shiller
Lessons from the Financial Crisis?

U.S. Mortgage-Related Debt Issuance ($Billions)

What could possibly go wrong?

Source: SIFMA

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How Could This Have Happened?

Who Benefited From This Trend?:

- Commercial banks
- Credit rating agencies (S&P, Moody’s, Fitch)
- Economists
- Government sponsored enterprises
- Homeowners
- Insurance companies (multiline, monoline)
- Investment banks and other issuers of MBSs, CDOs, and CDSs
- Investors (hedge funds, pension funds, mutual funds, others)
- Mortgage lenders, brokers, servicers, trustees
- Politicians
- Regulators (CFTC, Fed, FDIC, FHFA, OCC, OTS, SEC, etc.)

“A Rising Tide Lifts All Boats”
Innovation Requires Financial Infrastructure!
- Private investment
- Accounting, legal, regulatory structures
- Systemic stability
- Well-functioning capital markets
- Proper design of securities

⇒ Incentives Are Needed To Motivate Action

Fear Works Faster; Greed Is More Sustainable
- Greed and altruism not always incompatible
U.S. Real Home Price Index, 1890–2012

Source: Robert J. Shiller
Consider the following investment opportunity:

- $200MM investment, 10-year horizon
- Probability of positive payoff is 5%
- If successful, annual profits of $2B for 10-year patent
Consider the following investment opportunity:

- $200MM investment, 10-year horizon
- Probability of positive payoff is 5%
- If successful, annual profits of $2B for 10-year patent

\[
p = 5\%
\]

\[
1 - p = 95\%
\]

\[
\hspace{1cm} +51.0\%
\]

\[
\hspace{1cm} -100.0\%
\]

\[
E[R] = 11.9\%
\]

\[
SD[R] = 423.5\%
\]
What If We Invest In 150 Programs Simultaneously?:

- Requires $30B of capital
- Assume programs are IID (can be relaxed)
- Diversification changes the economics of the business:

\[
E[R] = 11.9\%
\]

\[
SD[R] = \frac{423.5\%}{\sqrt{150}} = 34.6\%
\]

- But can we raise $30B??
What If We Invest In 150 Programs Simultaneously?

- Given the reduction in risk, debt-financing is possible!

![Graph showing the effective yield of BofA Merrill Lynch US Corporate AA from 2000 to 2014. The shaded areas indicate US recessions. The graph shows a steady decrease in yield with a notable dip in 2008 and a slight increase in 2010, ending at 2.43% as of 6/5/14.]
What If We Invest In 150 Programs Simultaneously?:

- Given the reduction in risk, debt-financing is possible!

- $19.3B of high-quality debt can be issued

- With securitization (CDOs), third-party guarantees (CDS), and other tools, debt capacity is even larger

<table>
<thead>
<tr>
<th>Event</th>
<th>Probability</th>
<th>Minimum Year-10 NPV</th>
<th>Maximum Year-0 Proceeds at 2.43% (BofAML AA Index as of 6/5/14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1 hit:</td>
<td>99.95%</td>
<td>$12,289</td>
<td>$9,666</td>
</tr>
<tr>
<td>At least 2 hits:</td>
<td><strong>99.59%</strong></td>
<td>$24,578</td>
<td>$19,332</td>
</tr>
<tr>
<td>At least 3 hits:</td>
<td>98.18%</td>
<td>$36,867</td>
<td>$28,998</td>
</tr>
<tr>
<td>At least 4 hits:</td>
<td>94.52%</td>
<td>$49,157</td>
<td>$38,664</td>
</tr>
<tr>
<td>At least 5 hits:</td>
<td>87.44%</td>
<td>$61,446</td>
<td>$48,330</td>
</tr>
</tbody>
</table>
The Finance of the Future

1. Phase I
   - WD/Sold
2. Phase I
   - WD/Sold
150. Phase I
   - WD/Sold

Year 1 → Year 2 → Year 3 → Year 4 → ... → Year 10

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The Finance of the Future

- Equity
  - Residual

- A Bonds
  - Interest Payments

- Aa Bonds
  - Interest Payments

- Aaa Bonds
  - Interest Payments

Year 1

Year 2

Year 3

Year 4

... Year 10
Simulating A Cancer Megafund

- Fernandez, Stein, Lo (Nature Biotech, Oct 2012)
  - Tufts Medical School CSDD + Deloitte/RECAP cancer compounds database from 1990–2011
  - 2,000+ compounds ⇒ 733 after cleaning data
  - Cost and revenue assumptions from historical data and literature (e.g., Bloomberg, DiMasi et al. 2003, etc.)
  - Estimate transition probability matrix and valuations

- Fagnan, Fernandez, Lo, Stein (AER, May 2013)
  - Pricing and impact of third-party guarantees on debt capacity and investment performance
## Simulation Results: Matlab and R Software Available

<table>
<thead>
<tr>
<th>Variable or Summary Statistic</th>
<th>Simulation A</th>
<th>Simulation B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All-Equity</td>
<td>RBOs</td>
</tr>
<tr>
<td>Number of Compounds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preclinical</td>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td>Phase I</td>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td>Phase II</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Phase III</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Research Impact</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of compounds to reach Phase II</td>
<td>63.4</td>
<td>103.1</td>
</tr>
<tr>
<td>Number of compounds sold in Phase III and NDA</td>
<td>1.1</td>
<td>2.2</td>
</tr>
<tr>
<td>Number of compounds sold once APP</td>
<td>0.8</td>
<td>1.1</td>
</tr>
<tr>
<td>Liabilities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capital ($ million)</td>
<td>3,000</td>
<td>5,000</td>
</tr>
<tr>
<td>Senior Tranche ($ million)</td>
<td>—</td>
<td>1,250</td>
</tr>
<tr>
<td>Junior Tranche ($ million)</td>
<td>—</td>
<td>750</td>
</tr>
<tr>
<td>Equity Tranche ($ million)</td>
<td>3,000</td>
<td>3,000</td>
</tr>
<tr>
<td>Equity Tranche Performance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average annualized return on equity</td>
<td>7.9%</td>
<td>9.1%</td>
</tr>
<tr>
<td>Prob (return on equity &lt; 0)</td>
<td>15%</td>
<td>19%</td>
</tr>
<tr>
<td>Prob (return on equity &gt; 5%)</td>
<td>65%</td>
<td>69%</td>
</tr>
<tr>
<td>Prob (return on equity &gt; 15%)</td>
<td>18%</td>
<td>34%</td>
</tr>
<tr>
<td>Debt Tranches Performance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Senior Tranche: default prob., expected loss (bp)</td>
<td>—</td>
<td>1, &lt; 1</td>
</tr>
<tr>
<td>Junior Tranche: default prob., expected loss (bp)</td>
<td>—</td>
<td>35, 10</td>
</tr>
</tbody>
</table>
Is This Realistic?

In 2012:

- U.S. bond market: $38.1T
- Mutual funds: $13.1T
- Money-market funds: $2.7T
- Norwegian sovereign wealth fund: $683B
- CalPERS: $237B (as of June 30, 2012)

Target return of 126 public funds (2012): 8%

In 2012, the Size of the Entire VC Industry Was:

$199B

MARKETS | June 4, 2013, 9:06 p.m. ET

One of Wall Street's Riskiest Bets Returns

By KATY BURNE

Investors are once again clamoring for a risky investment blamed for helping unleash the financial crisis: the synthetic CDO.

In a sign of how hard Wall Street is trying to satisfy voracious demand for higher returns amid rock-bottom interest rates, J.P. Morgan Chase & Co. and Morgan Stanley bankers in London are moving to assemble so-called synthetic collateralized debt obligations.
With Some Imagination, Megafunds Are Viable!

- Imagine creating a $30B “Cure For Cancer” megafund
- Imagine creating an advisory board of experts:
  - George Demetri, Eric Lander, Bob Langer, Mark Levin, Frank McCormick, Larry Norton, Phil Sharp;
- Imagine 10MM households investing $3,000 each
- Imagine corporate pension funds, foundations, endowments, insurance companies investing as well
- Imagine government tax incentives, credit enhancement, etc. (think Fannie Mae, Freddie Mac!)
It Depends...

- Fagnan, Gromatzky, Fernandez, Stein, and Lo (DDT, 2014)
- **Orphan Diseases**: smaller population, urgent need, higher prices, lower development costs, higher success rates (20%), faster time to approval (3–7 years)

<table>
<thead>
<tr>
<th>Phase</th>
<th>Clinical Trial Cost ($MM)</th>
<th>Clinical Trial Success Rate</th>
<th>Clinical Trial Duration (years)</th>
<th>Valuation ($MM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical</td>
<td>5</td>
<td>69%</td>
<td>1.00</td>
<td>7.1</td>
</tr>
<tr>
<td>Phase 1</td>
<td>5</td>
<td>84%</td>
<td>1.66</td>
<td>27.6</td>
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<tr>
<td>Phase 2</td>
<td>8</td>
<td>53%</td>
<td>2.09</td>
<td>75.6</td>
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<tr>
<td>Phase 3</td>
<td>43</td>
<td>74%</td>
<td>2.15</td>
<td>321.5</td>
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<tr>
<td>NDA</td>
<td>—</td>
<td>96%</td>
<td>0.80</td>
<td>701.9</td>
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<tr>
<td>APP</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>817.6</td>
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</table>
### Orphan Drug Fund Simulation

- $575 million fund yields attractive returns!

<table>
<thead>
<tr>
<th></th>
<th>All Equity (Same Equity)</th>
<th>RBO</th>
<th>All Equity (Same Capital)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Compounds</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preclinical</td>
<td>3</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Phase 1</td>
<td>3</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td><strong>Research Impact</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number sold in Phase 2</td>
<td>0.7</td>
<td>2.3</td>
<td>1.7</td>
</tr>
<tr>
<td>Number sold in Phase 3</td>
<td>1.8</td>
<td>4.6</td>
<td>5.0</td>
</tr>
<tr>
<td><strong>Liabilities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capital ($ millions)</td>
<td>230</td>
<td>575</td>
<td>575</td>
</tr>
<tr>
<td>Senior tranche ($ millions)</td>
<td>—</td>
<td>115</td>
<td>—</td>
</tr>
<tr>
<td>Junior tranche ($millions)</td>
<td>—</td>
<td>230</td>
<td>—</td>
</tr>
<tr>
<td>Equity tranche ($millions)</td>
<td>230</td>
<td>230</td>
<td>575</td>
</tr>
<tr>
<td><strong>Equity tranche performance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average annualized ROE</td>
<td>19.6%</td>
<td>33.8%</td>
<td>23.2%</td>
</tr>
<tr>
<td>Prob. (equity wiped out)</td>
<td>2bp</td>
<td>81bp</td>
<td>&lt;0.1 bp</td>
</tr>
<tr>
<td>Prob. (return on equity &lt; 0)</td>
<td>10.4%</td>
<td>2.5%</td>
<td>14bp</td>
</tr>
<tr>
<td>Prob. (return on equity &gt; 10%)</td>
<td>79.1%</td>
<td>95.4%</td>
<td>93.7%</td>
</tr>
<tr>
<td>Prob. (return on equity &gt; 25%)</td>
<td>40.5%</td>
<td>82.9%</td>
<td>45.7%</td>
</tr>
<tr>
<td><strong>Debt tranches performance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Senior tranche: default prob., expected loss (bp)</td>
<td>—</td>
<td>1.2, &lt;0.1</td>
<td>—</td>
</tr>
<tr>
<td>Junior tranche: default prob., expected loss (bp)</td>
<td>—</td>
<td>80, 27</td>
<td>—</td>
</tr>
</tbody>
</table>
The Amount of Capital Needed Depends On:

- Cost per shot
- Probability of success
- Duration of trials
- Correlation of shots
- Profits per success

Finance and Biomedicine Must Cooperate:

- Can we stratify patient populations so as to “orphanize” all disease? Orphan drug programs have $\rho \approx 0\%$
- Precision medicine has huge risk reduction benefits!
Prob$(n \geq k)$ for Equicorrelated Binomial(150,5%)
Prob\( (n \geq k) \) for IID Binomial(20, p)

- \( p = 20\% \)
- \( p = 15\% \)
- \( p = 10\% \)
- \( p = 5\% \)
For Alzheimer’s, $30 Billion Is Not Enough!

- Lo, Ho, Cummings, and Kosik (2014)
- 13-year development time, not 10
- $500 million in out-of-pocket costs
- Probability of success $\leq 5$
- But not enough “shots on goal” (beta amyloid, tau)
  - Correlated shots provide less risk reduction
- Basic science is not as developed as in oncology
- Number of new cancer drugs in 2013?:
- Number of new Alzheimer’s drugs in last decade?:

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National Cancer Act of 1971 + Human Genome Project

Orphan Drug Act of 1983 + Human Genome Project

National Alzheimer’s Project Act of 2011 + BRAIN Initiative
“Investing” in Basic Science

Government Funding Is Essential When:

- There is no **quantifiable** economic return
- The horizon is **too long**
- The costs are **too large**
- The probability of success is **too low** (or completely unknown)
- The **social impact** is large

The Market Failure Is **High Risk and Low Reward**

**Sharpe Ratio** = \(rac{\text{Reward}}{\text{Risk}}\)
There Are Many Challenges Ahead

- **Size**: managing large portfolios of complex R&D projects may require new management and governance structures (e.g., Manhattan Project)
- **Centralization**: must preserve the benefits of diversity as scale increases
- **Capacity**: is the talent pool large enough to match the scale of this venture?
- **Complexity**: can investors understand the risks and rewards of RBOs?
- **Excesses**: if successful, the potential for abuse will also increase
- **Ethics**: how to balance profit motive vs. social objectives for cures?
Next Steps

- Expose each stakeholder group to the tools, challenges, and opportunities of other stakeholder groups in the biomedical ecosystem
  - Clinicians, researchers, biopharma professionals, VCs, insurance companies, regulators, investors, financial engineers, patients, and students

- Identify major obstacles to private-sector funding of translational medical R&D

- Propose some potential solutions to these obstacles (see http://cancerx.mit.edu)
Don’t Declare War On Disease...

Put A Price Tag On Its Head Instead!

With Sufficient Scale, We Can Do Well By Doing Good

- Finance doesn’t have to be a zero-sum game
Thank You!