Can Financial Engineering Help Cure Cancer?

Andrew W. Lo, MIT
(based on joint work with Jayna Cummings, David Fagnan, John Frishkopf, Jose-Maria Fernandez, Carole Ho, Austin Gromatzky, Ken Kosik, John McKew, Vahid Montazerhodjat, Roger Stein, Richard Thakor, David Weinstock, Nora Yang)

September 30, 2016
Paradox

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)
- 2014: Keytruda approved, PD-1 immunotherapy
So Why Is Funding Declining??

Table 2: Number of active VC firms

<table>
<thead>
<tr>
<th>Region</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>10</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>China</td>
<td>2</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Europe</td>
<td>105</td>
<td>106</td>
<td>111</td>
</tr>
<tr>
<td>India</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Israel</td>
<td>12</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>United States</td>
<td>201</td>
<td>163</td>
<td>143</td>
</tr>
<tr>
<td>Global total</td>
<td>309</td>
<td>256</td>
<td>252</td>
</tr>
</tbody>
</table>

*The global total is not a sum of all regions, as an investor that total. Source: Dow Jones VentureSource.*

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Slide 3
The Challenge of Drug Development

Example: Combination Therapies

- 2,800 approved drugs
- 3,918,500 pairs
- 3,654,747,600 triples
- Dosage regimens?
- Biomarkers?
- Resistance?
- Side-effects, litigation?
- Pricing, FDA, etc. ?

Eroom’s Law

Source: Scannell et al. (NRDD 2012)
Risk and Reward

Cumulative Return

BFI

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Risk and Reward

CAPM Betas for Pharma and Biotech, 1996-2014

Daily Returns, 2-Year Rolling Windows

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Risk and Reward

The Cost of Capital for Venture Backed Early Stage Biotechnology Ventures

Iain Cockburn and Josh Lu
Boston University and Harvard University

Executive Summary

- Evidence shows that the Cost of Capital for venture backed early stage companies in life sciences is high:
  - Many estimates suggest 20% or higher
- This reflects investors’ expectation of a return sufficient to compensate them for taking on extraordinary risk
Risk and Reward

Cost of Capital for U.S. Companies, Jan 2016

Source: A. Damodaran (2016)
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

\[
E[R] = 11.9\% \\
SD[R] = 423.5\%
\]
Financial Engineering Can Help

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:

  \[ E[R] = 11.9\% \]
  \[ SD[R] = 423.5\% / \sqrt{150} = 34.6\% \]

- But can we raise $30B??
- It depends on the portfolio’s risk/reward profile (correlations?)
Financial Engineering Can Help

What If We Invest In 150 Programs Simultaneously?:

- With reduced risk, debt-financing is feasible!

<table>
<thead>
<tr>
<th>Event</th>
<th>Probability</th>
<th>Minimum Year-10 NPV</th>
<th>Maximum Year-0 Proceeds at 2.17% (BofAML AA 10-Yr as of 9/26/16)</th>
<th>Maximum Year-0 Proceeds at 2.50% (BofAML A 10-Yr as of 9/26/16)</th>
<th>Maximum Year-0 Proceeds at 4.30% (BofAML Baa 10-Yr as of 9/26/16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1 hit:</td>
<td>99.95%</td>
<td>$12,289</td>
<td>$9,915</td>
<td>$9,600</td>
<td>$6,508</td>
</tr>
<tr>
<td>At least 2 hits:</td>
<td>99.59%</td>
<td>$24,578</td>
<td>$19,830</td>
<td>$19,201</td>
<td>$13,016</td>
</tr>
<tr>
<td>At least 3 hits:</td>
<td><strong>98.18%</strong></td>
<td><strong>$36,867</strong></td>
<td><strong>$29,745</strong></td>
<td><strong>$28,801</strong></td>
<td><strong>$19,524</strong></td>
</tr>
<tr>
<td>At least 4 hits:</td>
<td>94.52%</td>
<td>$49,157</td>
<td>$39,660</td>
<td>$38,401</td>
<td>$26,032</td>
</tr>
<tr>
<td>At least 5 hits:</td>
<td>87.44%</td>
<td>$61,446</td>
<td>$49,574</td>
<td>$48,001</td>
<td>$32,540</td>
</tr>
</tbody>
</table>

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Financial Engineering Can Help

Prob\( (n \geq k) \) for Equicorrelated Binomial(150, 5\%)

\[ \rho = 0\% \]
\[ \rho = 10\% \]
\[ \rho = 40\% \]
\[ \rho = 80\% \]

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Research
Overview

- Cancer: Fernandez, Stein, Lo (NBT, 2012)
- Guarantees: Fagnan, Stein, Fernandez, Lo (AER, 2013)
- Orphan drugs: Fagnan, Gromatzky, Stein, Lo (DDT, 2014)
- Alzheimers: Lo, Ho, Cummings, Kosik (STM, 2014)
- NCATS: Fagnan, Yang, McKew, Lo (STM, 2015)
- Dynamic leverage: Montazerhodjat, Frishkopf, Lo (DDT, 2015)
- Drug mortgages: Montazerhodjat, Weinstock, Lo (STM, 2016)
- Work-in-progress: FDA approval process, historical success rates, risk/reward of biopharma, case studies (SPARK, I-SPY, Solid)
Megafund Structure

1. Investors
   - Retail: pension funds, banks, savings & loans, mutual funds, insurance companies, endowments, sovereign wealth funds, VCs, foundations, high-net-worth investors

2. Biomedical megafund special-purpose vehicle
   - Liabilities (RBOs)
     - Senior debt
     - Junior debt
     - Equity

3. Assets
   - Drugs-to-be
   - Cash reserve

4. Drug development
   - PreC
   - P1
   - P2
   - P3
   - NDA
   - APP/sold
   - Withdrawn
Simulating A Cancer Megafund

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

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

150
   - Phase I
   - WD/Sold

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

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Slide 16
Simulating A Cancer Megafund

- **Equity** • Residual
- **A Bonds** • Interest Payments
- **Aa Bonds** • Interest Payments
- **Aaa Bonds** • Interest Payments

Year 1, Year 2, Year 3, Year 4, …, Year 10

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Fernandez, Stein, Lo (2012)

Simulate Historical Investment Performance

- **Cost assumptions:**

- **Historical data for revenues (valuations) and transitions:**
  - DEVELOPMENT optimizer (Deloitte Recap, LLC), Center for the Study of Drug Development (Tufts); January 1990 to January 2011: +2,000 ⇒ 733 compounds
  - Bloomberg

- **Seven-state Markov chain (PreC, Phases I–III, NDA, APP, WD)**
  - Simulation A (PreC to Phase II), Simulation B (Phase III to APP)
  - run 500,000 simulations for each

- **Financial structure of the megafund:**
  - Senior tranche (5% coupon), junior tranche (8% coupon), equity tranche
  - 7.5-year tenor
  - 0.5% annual management fee,
  - $5B for Simulation A (2:1 leverage), $15B for Simulation B (2.5:1 leverage)
Table 2: Composition of the final database of 733 oncology compounds in various clinical phases (percentages do not sum to 100% due to rounding).
### Fernandez, Stein, Lo (2012)

**Simulate Historical Investment Performance**

<table>
<thead>
<tr>
<th>Source</th>
<th>Time Period</th>
<th>Number of Compounds</th>
<th>Preclinical to Phase I</th>
<th>Phase I to Phase II</th>
<th>Phase II to Phase III</th>
<th>Phase III to NDA</th>
<th>NDA to Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Megafund*</td>
<td>1990–2010</td>
<td>733</td>
<td>69.0%</td>
<td>72.4%</td>
<td>45.2%</td>
<td>58.6%</td>
<td>95.2%</td>
</tr>
<tr>
<td>Natanson*</td>
<td>1988–May 2010</td>
<td>164</td>
<td>—</td>
<td>72.6%</td>
<td>40.3%</td>
<td>66.7%</td>
<td>90.6%</td>
</tr>
<tr>
<td>Reisdorph et al.*</td>
<td>1990–2006</td>
<td>929</td>
<td>—</td>
<td>78.0%</td>
<td>43.0%</td>
<td>52.0%</td>
<td>89.0%</td>
</tr>
<tr>
<td>Walker et al.*</td>
<td>1995–2007</td>
<td>974</td>
<td>—</td>
<td>77.0%</td>
<td>44.0%</td>
<td>52.0%</td>
<td>—</td>
</tr>
<tr>
<td>Dimasi et al.</td>
<td>1993–2002</td>
<td>838</td>
<td>—</td>
<td>76.8%</td>
<td>59.4%</td>
<td>57.1%</td>
<td>—</td>
</tr>
<tr>
<td>Paul et al.</td>
<td>15 years</td>
<td>—</td>
<td>69.0%</td>
<td>54.0%</td>
<td>34.0%</td>
<td>70.0%</td>
<td>91.0%</td>
</tr>
</tbody>
</table>

*These probabilities are calculated only for cancer related compounds.

Table 5: Comparison of cancer compound transition probability by development phase.
Table 4. Performance summary statistics of the biomedical megafund simulations

<table>
<thead>
<tr>
<th>Variable or summary statistic</th>
<th>Simulation A</th>
<th></th>
<th>Simulation B</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All equity</td>
<td>Research-backed obligations</td>
<td>All equity</td>
<td>Research-backed obligations</td>
</tr>
<tr>
<td>Number of compounds</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preclinical</td>
<td>50</td>
<td>100</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Phase 1</td>
<td>50</td>
<td>100</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Phase 2</td>
<td>—</td>
<td>—</td>
<td>40</td>
<td>100</td>
</tr>
<tr>
<td>Phase 3</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Research impact</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of compounds to reach phase 2</td>
<td>52.8</td>
<td>101.7</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Number of compounds sold in phase 3 and NDA</td>
<td>0.9</td>
<td>2.3</td>
<td>6.0</td>
<td>21.3</td>
</tr>
<tr>
<td>Number of compounds sold once APP</td>
<td>0.6</td>
<td>1.0</td>
<td>5.1</td>
<td>7.6</td>
</tr>
<tr>
<td>Liabilities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capital ($ millions)</td>
<td>2,500</td>
<td>5,000</td>
<td>6,000</td>
<td>15,000</td>
</tr>
<tr>
<td>Senior tranche ($ millions)</td>
<td>—</td>
<td>1,250</td>
<td>—</td>
<td>6,000</td>
</tr>
<tr>
<td>Junior tranche ($ millions)</td>
<td>—</td>
<td>1,250</td>
<td>—</td>
<td>3,000</td>
</tr>
<tr>
<td>Equity tranche ($ millions)</td>
<td>2,500</td>
<td>2,500</td>
<td>6,000</td>
<td>6,000</td>
</tr>
<tr>
<td>Equity tranche performance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average annualized return on equity</td>
<td>7.2%</td>
<td>8.9%</td>
<td>7.2%</td>
<td>11.4%</td>
</tr>
<tr>
<td>Prob. (return on equity &lt; 0)</td>
<td>17%</td>
<td>20%</td>
<td>17%</td>
<td>50%</td>
</tr>
<tr>
<td>Prob. (return on equity &gt; 5%)</td>
<td>61%</td>
<td>68%</td>
<td>63%</td>
<td>79%</td>
</tr>
<tr>
<td>Prob. (return on equity &gt; 15%)</td>
<td>15%</td>
<td>35%</td>
<td>14%</td>
<td>40%</td>
</tr>
<tr>
<td>Debt tranche performance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Senior tranche: default prob., expected loss (bp)</td>
<td>—</td>
<td>1, &lt;1</td>
<td>—</td>
<td>6, &lt;1</td>
</tr>
<tr>
<td>Junior tranche: default prob., expected loss (bp)</td>
<td>—</td>
<td>87, 27</td>
<td>—</td>
<td>60, 30</td>
</tr>
</tbody>
</table>

bp, units of basis points or 0.01%; prob., probability.

Source: Fernandez, Stein, Lo (2012)
Do We Really Need $30 Billion?

The Amount of Capital Needed Depends On:

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

Fernandez, Stein, Lo, (NBT 2012)

- Sourcecode available in R and Matlab

Finance and Biomedical Experts Must Collaborate

- Cultures are very different
- Value created in being able to bridge this gap
Orphan Diseases

- Often due to mutation in a single gene
- e.g. Huntington’s, cystic fibrosis, Gaucher, paroxysmal nocturnal hemoglobinuria
- 25 million Americans suffer from all rare diseases
- Smaller population, urgent need, higher prices, lower development costs, higher success rates (20%), faster time to approval (3–7 years)
- $400–$500 million of capital and 10–20 projects sufficient
Orphan Diseases

$$\text{Prob}(n \geq k) \text{ for IID Binomial}(20, p)$$

But can you earn a decent rate of return on investment??

$p = 30\%$

$p = 15\%$

$p = 10\%$

$p = 5\%$
Orphan Diseases

Simulation Using Data From Live Portfolio

- National Center for Advancing Translational Sciences (NCATS); part of NIH established in 2012
- Therapeutics for Rare and Neglected Diseases (TRND) and Bridging Interventional Development Gaps (BrIDGs), 28 projects in various stages of development
- Used actual expenses borne by NCATS and researchers, convened valuation panel of experts to estimate market value
- Fagnan, Yang, McKew, Lo (2015): modified IRR of 21.6%
Orphan Diseases

Simulation Using Data From Live Portfolio

First drug candidate from NIH program acquired by biopharmaceutical company

Potential treatment targets sickle cell disease

A drug candidate developed by researchers at the NIH’s National Center for Advancing Translational Sciences (NCATS) and its collaborators to treat sickle cell disease has been acquired by Baxter International’s BioScience business. The drug candidate, Aes-103, is the first specifically developed to target the underlying molecular mechanism of sickle cell disease. Baxter now will advance the clinical development activities required for regulatory approval and commercialization.

Orphan Drugs Industry Databases

Shire: Acquisition of Bikam Pharmaceuticals, Inc.

Stock market reaction = $238.3 million for Baxter
$423.1 million for Shire
And Now The Bad News...

For Alzheimer’s, $30 Billion May Not Be Enough!

- Lo, Ho, Cummings, Kosik (STM, 2014)
- 13-year development time, not 10; $500M to $600M in out-of-pocket costs; probability of success ≤ 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
- We have to “invest” in basic science of AD biology
- The private sector will not do this
And Now The Bad News...

How Many New Cancer Drugs Were Approved In 2015-2016?
How Many New AD Drugs Were Approved In 2015-2016?
How Many New AD Drugs Were Approved In 2014?
How Many New AD Drugs Were Approved In 2013?
How Many New AD Drugs Were Approved In 2012?

How Many New AD Drugs Were Approved In 2004?
How Many New AD Drugs Were Approved In 2003?
“Investing” in Basic Science

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 Private Reward

Sharpe Ratio = \frac{\text{Excess Expected Return}}{\text{Risk}}
FAQs

- Aren’t pharma and biotech VCs already doing this?
- What’s the market failure; why hasn’t this been done already?
- Is there enough capacity (projects as well as capital)?
- Is this realistic? Can you manage large biomedical portfolios?
- How about drug pricing?
- What role can/should government play?
- Are there existing examples of megafunds?
- Are you trying to launch a megafund?
FAQs:
Isn’t Pharma Already Doing This?
Isn’t Pharma Already Doing This?

Pfizer Balance Sheet 2015
✓ Cash+STI+NR: $34.1B
✓ LT Debt: $32.8B

Why do pharma keep so much cash on its balance sheet?

- Hospira
- AbbVie
- Mylan
- Allergan

The Solution: Our Economic Value Added Analysis Supports Replacing “Research” with “Search”

On current market economics, we estimate that $1 invested in in-licensed compounds will on average deliver 3 times as much value as $1 invested in in-house research.

Migration towards a Search and Development small molecule model lowers Beta and should result in superior outcomes. Using an Economic Value Added analysis, we have...
Isn’t Pharma Already Doing This?

Pharma Job Cuts, 2008–2013

<table>
<thead>
<tr>
<th>Company</th>
<th>Job Cuts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott</td>
<td>5,900</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>25,733</td>
</tr>
<tr>
<td>Bristol-Myers Squibb</td>
<td>5,285</td>
</tr>
<tr>
<td>Eli Lilly</td>
<td>6,525</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>8,687</td>
</tr>
<tr>
<td>Johnson &amp; Johnson</td>
<td>9,200</td>
</tr>
<tr>
<td>Merck &amp; Co.</td>
<td>46,140</td>
</tr>
<tr>
<td>Novartis</td>
<td>53,900</td>
</tr>
<tr>
<td>Pfizer</td>
<td>16,517</td>
</tr>
<tr>
<td>Roche</td>
<td>6,750</td>
</tr>
<tr>
<td>Sanofi</td>
<td>7,684</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>143,536</strong></td>
</tr>
</tbody>
</table>

Published on FiercePharma (http://www.fiercepharma.com)

**Biogen axes 800-plus jobs to keep Tecfidera sales engine running**

October 21, 2015 | By Emily Wasserman

Source: Bloomberg
Isn’t Pharma Already Doing This?

Pharma vs. Biotech

5 Dec 1994 to 27 May 2016

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FAQs:
Are There Any Existing Examples of Megafunds?
Existing Business Models That Are Close

Drug Royalty Investment Companies Already Exist

- Royalty Pharma, $15B in assets, 21 full-time employees

- But it currently only invests in late-stage drugs (Phase II)
Existing Business Models That Are Close

- A new business model is required
  - Not a pharma company; not a biotech VC; not a mutual fund
FAQs: Is This Realistic?
Is There Enough Capital?

In 2015:

- U.S. bond market: $39.9T ($6.4T issued)
  - Corporate bonds: $8.2T ($1.5T issued)
  - Mortgage-related: $8.7T ($1.7T issued)
  - Asset-backed securities: $1.3T
  - Money-market funds: $2.8T
- Norwegian sovereign wealth fund: $873B
- CalPERS: $304B
- Target return of 126 public funds (2012): 8% 7.5%

In 2015, Total U.S. VC AUM Was?
Is This Realistic?

With Some Imagination, Megafunds Are Viable!

- Imagine creating a $30B “Cure Cancer” megafund
- Imagine creating an advisory board of experts:
  - Warren Buffett, Bill Gates, Jacob Goldfield, Pablo Legorreta, Mark Levin, Bob Merton, Elon Musk, Bill Sharpe, Jim Simons
- Imagine sovereign wealth funds, foundations, endowments, insurance companies investing as well
- Imagine government tax incentives, credit enhancement, etc. (think Fannie Mae, Freddie Mac!)
Is This Realistic?

With Some Imagination, Megafunds Are Viable!

- Imagine households investing $3,000 of their 401(k)
Conclusion

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
Conclusion

- **Research**: Identify major funding obstacles to translational medicine, and develop better financial models (we need more *data and analytics!*)

- **Education**: case studies and executive teaching for life sciences professionals

- **Outreach**: bring biomedical stakeholders together to explore new business and financing models (e.g., 10/14 meeting, 10/26-28 CanceRx 2016 [http://CanceRX.mit.edu](http://CanceRX.mit.edu))
Thank You!
Additional Readings

Additional Readings

Additional Readings