New Funding Models for Biomedical Innovation

Andy Lo
MIT

Markus Brunnermeier
Princeton

4. February 2021
Innovation

- Non-rivalry of ideas (design/blueprints)
  - Water bottle, but idea of ral rehydration therapy (Paul Romer)
    (right proportion of salt in water to fight diarrhea)
- R&D externality > 0 underinvestment
Innovation

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**Interplay of**

- entrepreneur
- State
- VC funding
capitalists
Innovation and the **Government**

- **Basic Research**
  - Long horizon, high risk of investment

- Cost subsidy
- Demand pull/guarantee
- Patent protection: Grant temporary monopoly
  - Price discrimination
  - Withhold health from the poor (immoral)
- X-Prize    Michael Kremer

- Risk absorption ("de-risking")
  - Coinvest (also via taxes)
2 Innovation models

- Old model: Large cooperation
  R&D expenditures
  - Better risk sharing

- Start-up Model
  - R&D in small start-ups
  - Large firms
take over successful start-ups
use large distribution network
Welcome failure vs. bankruptcy stigma
Promoting risk taking via limited liability vs. ordoliberal “liability principle” or stigma
- Implies higher interest rate

Venture capitalism
- Optimal risk sharing + real options
- Expertise/advice
New Funding Models for Biomedical Innovation

Andrew W. Lo, MIT

Markus’ Academy, Bendheim Center for Finance

Princeton University

4 February 2021
“I went outside when it was snowing, and I was like, ‘Oh! I can see the snowflakes!’” Caroline said. “It was really cool to actually see something that I've never seen in my life before.”
PTC Therapeutics to Acquire Agilis Biotherapeutics

- Expands and diversifies current pipeline with four gene therapy programs -
- BLA submission in AADC deficiency expected in 2019 -
Biomedicine Is At An Inflection Point

The “omics” Revolution:

- Genomics
- Epigenomics
- Transcriptomics
- Proteomics
- Metabolomics
- Microbiomics

What About Economics??
Increasing Risk and Uncertainty

Why??
Investment Pop Quiz #1

Sharpe Ratio \( \equiv \frac{\mathbb{E}[R] - R_f}{\text{SD}[R]} \)

\begin{align*}
\text{SR} &= 0.43 \\
\text{SR} &= 2.98 \\
\text{SR} &= 0.54
\end{align*}
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

\[ E[R] = 11.9\% \]
\[ SD[R] = 423.5\% \]
\[ SR = 0.02 \]
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??  \[ \text{SR} = 0.34 \]
- 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 1.56% (BofAML AA 10-Yr as of 1/31/21)</th>
<th>Maximum Year-0 Proceeds at 1.64% (BofAML A 10-Yr as of 1/31/21)</th>
<th>Maximum Year-0 Proceeds at 2.16% (BofAML BBB 10-Yr as of 1/31/21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1 hit</td>
<td>99.95%</td>
<td>$12,289</td>
<td>$10,527</td>
<td>$10,444</td>
<td>$8,501</td>
</tr>
<tr>
<td>At least 2 hits</td>
<td>99.59%</td>
<td>$24,578</td>
<td>$21,054</td>
<td>$20,888</td>
<td>$17,003</td>
</tr>
<tr>
<td>At least 3 hits</td>
<td>98.18%</td>
<td>$36,867</td>
<td>$31,580</td>
<td>$31,333</td>
<td>$25,504</td>
</tr>
<tr>
<td>At least 4 hits</td>
<td>94.52%</td>
<td>$49,157</td>
<td>$42,107</td>
<td>$41,777</td>
<td>$34,005</td>
</tr>
<tr>
<td>At least 5 hits</td>
<td>87.44%</td>
<td>$61,446</td>
<td>$52,634</td>
<td>$52,221</td>
<td>$42,507</td>
</tr>
</tbody>
</table>
Financial Engineering Can Help

ICE Bank of America Single-A U.S. Corporate Index Effective Yield
Dec 31, 1996 to Jan 31, 2021
Diversification can lower the cost of capital.
Why Do Biotechs Have Such High Betas??

500-Day Rolling-Window Betas
25 Nov 1996 to 17 Sep 2020

\[ \mathbb{E}[R_i] = R_f + \beta_i (\mathbb{E}[R_m] - R_f) \]
FAQs (details, details...)

- Do we really need $30 billion?
- What’s the market failure; why hasn’t this been done already?
- Isn’t pharma already doing this? If not, isn’t government doing it?
- Is there enough capacity (projects, capital, and people)?
- Isn’t biomedicine too complex to manage as a large portfolio?
- Are there any other similar industries that use these techniques?
- How about drug pricing? Can we afford these therapies?
- What role can/should government play?
- Are there existing examples of megafunds?
Short Answer
Short Answer
Short Answer
Long Answer:


- **Alzheimers**: Lo, Ho, Cummings, Kosik (2014)

- **Vaccines and Anti-Infectives**: Vu, Chaudhuri, Kaplan, Mansoura, Lo (2019), Wong, Siah, Lo (2020)

- **Guarantees**: Fagnan, Stein, Fernandez, Lo (2013)

- **Rare diseases, NCATS**: Fagnan, Gromatzky, Stein, Lo (2014), Fagnan, Yang, McKew, Lo (2015), Kim and Lo (2016), Das, Huang, Lo (2019),

- **Dynamic leverage**: Montazerhodjat, Frishkopf, Lo (2015)

- **Drug mortgages**: Montazerhodjat, Weinstock, Lo (2016)


- **Estimating and forecasting clinical trial outcomes**: Wong, Siah, Lo (2019, 2020a,b), Siah, Wong, Lo (2019,2020)

https://bit.ly/3oDzxl1
How Much **Capital Do We Need?**

The Amount of Capital Needed Depends On:

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

Siah and Lo (2020)


Sourcecode:

[https://projectalpha.mit.edu](https://projectalpha.mit.edu)

Finance and Biomedical Experts Must Collaborate
Often due to mutation in a single gene, e.g., hemophilia, cystic fibrosis, ALS, Gaucher, paroxysmal nocturnal hemoglobinuria

- 30 million Americans suffer from over 7,000 rare diseases
- Smaller population, urgent need, higher prices, lower development costs, higher success rates (25%), faster approvals (3–7 years), 1983 Orphan Drug Act, etc.
- $400–$500 million of capital and 10–20 projects are sufficient

Lack of Correlation Is Critical!
### Table 1. Structure and function

Simulated performance comparing an all-equity structure (using no debt financing); an RBO structure using a senior and junior debt tranche paying 5% and 8% annual coupon rates, respectively; and a second RBO structure with a single guaranteed senior tranche. The senior tranche is paid before the junior (mezzanine) tranche, which is paid before the equity holder. In the event that the fund defaults or fails to meet its debt obligations, the guarantor will pay the difference. Each structure acquires only preclinical compounds, with a target goal of reaching phase 3 within a maximum horizon of 11 years. Dashes indicate cases in which the corresponding type of financing and/or guarantee is not used. IRR, internal rate of return; ROE, return on equity.

<table>
<thead>
<tr>
<th>Simulation results</th>
<th>All equity (similar equity)</th>
<th>Research-backed obligation (RBO)</th>
<th>RBO with guarantee (no mezzanine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equity tranche performance</td>
<td></td>
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<tr>
<td>Equity tranche performance</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Average IRR</td>
<td>26.7%</td>
<td>16%</td>
<td>N/A</td>
</tr>
<tr>
<td>Average MIRR (0% financing)</td>
<td>18.3%</td>
<td>21.6%</td>
<td>22.7%</td>
</tr>
<tr>
<td>Average annualized ROE</td>
<td>11.6%</td>
<td>14%</td>
<td>15.4%</td>
</tr>
<tr>
<td>Probability (equity wiped out)</td>
<td>1.3 bp</td>
<td>0.52%</td>
<td>0.34%</td>
</tr>
<tr>
<td>Probability (return on equity &lt;0)</td>
<td>8.0%</td>
<td>6.2%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Probability (return on equity &gt;10%)</td>
<td>61.9%</td>
<td>76.8%</td>
<td>78.6%</td>
</tr>
<tr>
<td>Probability (return on equity &gt;25%)</td>
<td>2.2%</td>
<td>10.4%</td>
<td>11.0%</td>
</tr>
<tr>
<td>Debt tranches performance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Senior tranche: default probability, expected loss (bp)</td>
<td>—</td>
<td>0.1, &lt;0.1</td>
<td>&lt;0.1, &lt;0.1</td>
</tr>
<tr>
<td>Junior tranche: default probability, expected loss (bp)</td>
<td>—</td>
<td>50, 15</td>
<td>—</td>
</tr>
<tr>
<td>Guarantee performance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability (cost of guarantee &gt;0)</td>
<td>—</td>
<td>—</td>
<td>0.3%</td>
</tr>
<tr>
<td>Expected cost, 2% discount ($)</td>
<td>—</td>
<td>65,000</td>
<td>—</td>
</tr>
<tr>
<td>No-arbitrage cost of guarantee ($)</td>
<td>—</td>
<td>110,000</td>
<td>—</td>
</tr>
</tbody>
</table>
New Business Models Are Emerging

ENDPOINTS NEWS

KKR backs monster $300M raise to build up a new-model biotech --

BridgeBio takes crown for biggest biotech IPO of 2019, as fellow unicorn Adaptive raises offering size and price

BridgeBio Pharma, Inc. (BBIO) NasdaqGS - NasdaqGS Real Time Price. Currency in USD

63.01 +5.58 (+9.72%) 63.00 -0.01 (-0.02%)

At close: 4:00PM EST After hours: 4:25PM EST

BridgeBio Pharma, founded in 2015, has a portfolio of companies focused on diseases that are driven by an individual genetic mutation. The company is focused on rare diseases and is developing treatments for a variety of conditions, including dermatology, neurology, endocrinology, renal disease, and oncology.

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New Business Models Are Emerging

<table>
<thead>
<tr>
<th>Pre-Clinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Commercial</th>
</tr>
</thead>
<tbody>
<tr>
<td>BBP-870 (Origin)</td>
<td>Synthetic cPMP for MOCD Type A</td>
<td></td>
<td></td>
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<tr>
<td>BBP-265 (Eidos)</td>
<td>TTR Stabilizer (AG10) for ATTR-CM</td>
<td></td>
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<tr>
<td>BBP-009 (PellePharm)</td>
<td>Topical HH Inhibitor (Patidegib) for Gorlin Syndrome</td>
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<tr>
<td>BBP-831 (QED)</td>
<td>FGFR 1-3 Inhibitor (Infgratinib) for FGFR+ Cancers</td>
<td></td>
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</tr>
</tbody>
</table>
New Business Models Are Emerging

Bain creates $1.1B fund for fresh round of life science bets

ARCH VENTURE PARTNERS ANNOUNCES $1.46 BILLION RAISED IN TWO NEW FUNDS TO INVEST IN TRANSFORMATIVE BIOTECHNOLOGY COMPANIES

Blackstone Announces $4.6 Billion Final Close of Life Sciences Fund

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Conclusion

I Want To Be Harvey Lodish!

With the right kind of financing and at the right scale, we can do well by doing good!

Finance Doesn’t Have To Be A Zero-Sum Game
Thank You!

https://alo.mit.edu
https://lfe.mit.edu
https://projectalpha.mit.edu

@AndrewWLo
Additional References

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