

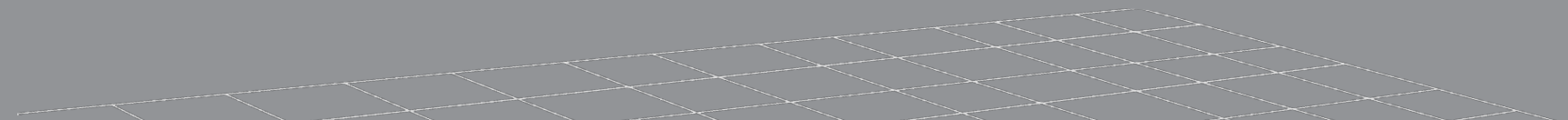


New Funding Models for Biomedical Innovation

Andy Lo
MIT

Markus Brunnermeier
Princeton

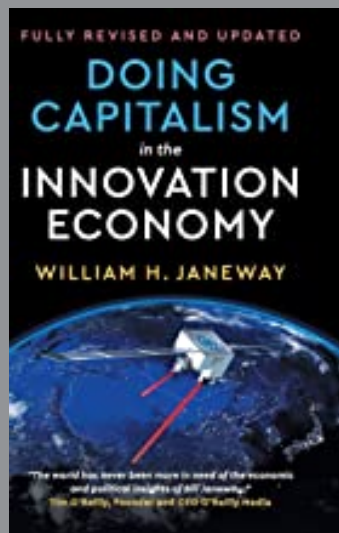
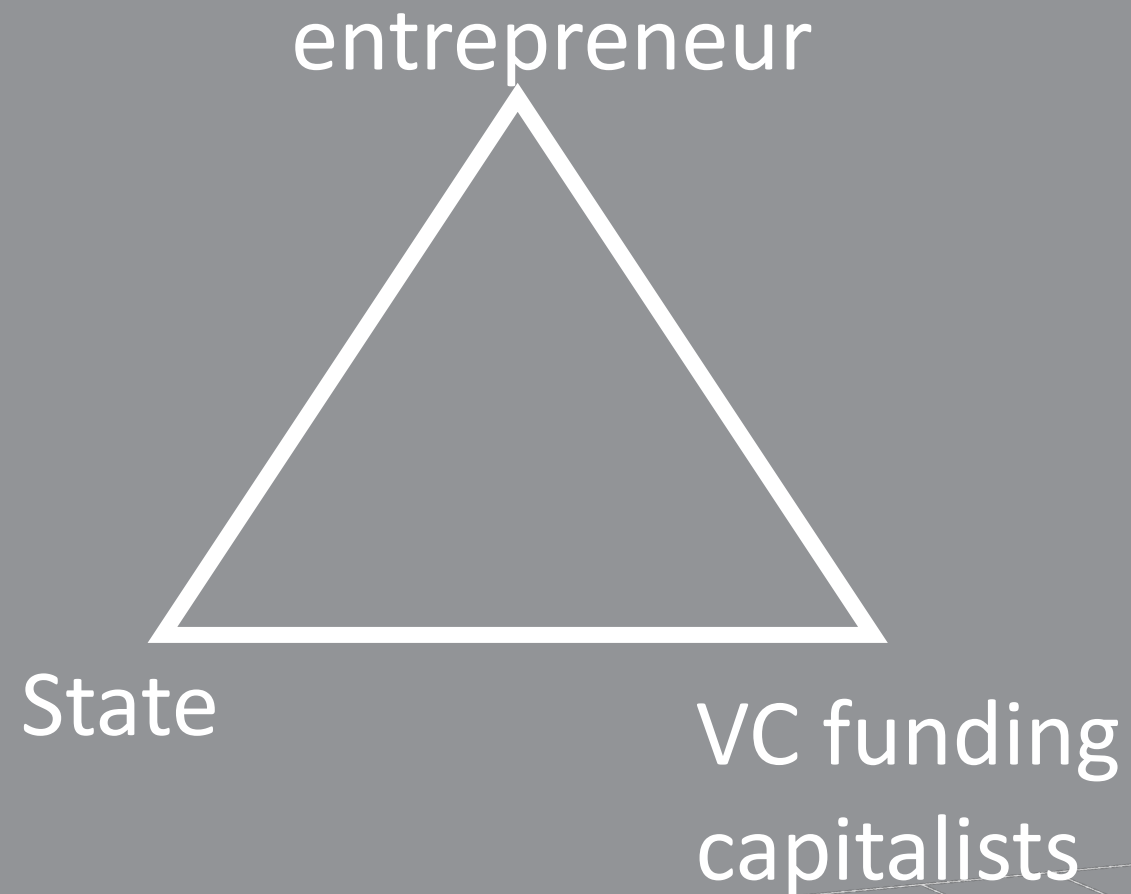
4. February 2021



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

- Non-rivalry of ideas (design/blueprints)
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■ Interplay of



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

MITLaboratory for
Financial Engineering

Biomedicine Is At An Inflection Point



“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.”

Biomedicine Is At An Inflection Point

PERSPECTIVE Drug Discovery Today • Volume 24, Number 3 • March 2019

國立台灣大學醫學院附設醫院
National Taiwan University Hospital

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Send a Release

PTC Therapeutics to Acquire Agilis Biotherapeutics

- Expands and diversifies current pipeline with four gene therapy programs -
- BLA submission in AADC deficiency expected in 2019 -

NEWS PROVIDED BY
PTC Therapeutics, Inc. →
Jul 19, 2018, 16:10 ET

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submission in 2018.

Biomedicine Is At An Inflection Point



The “omics” Revolution:

- Gen**omics**
- Epigen**omics**
- Transcript**omics**
- Prote**omics**
- Metabol**omics**
- Microbi**omics**

What About Econ**omics**??

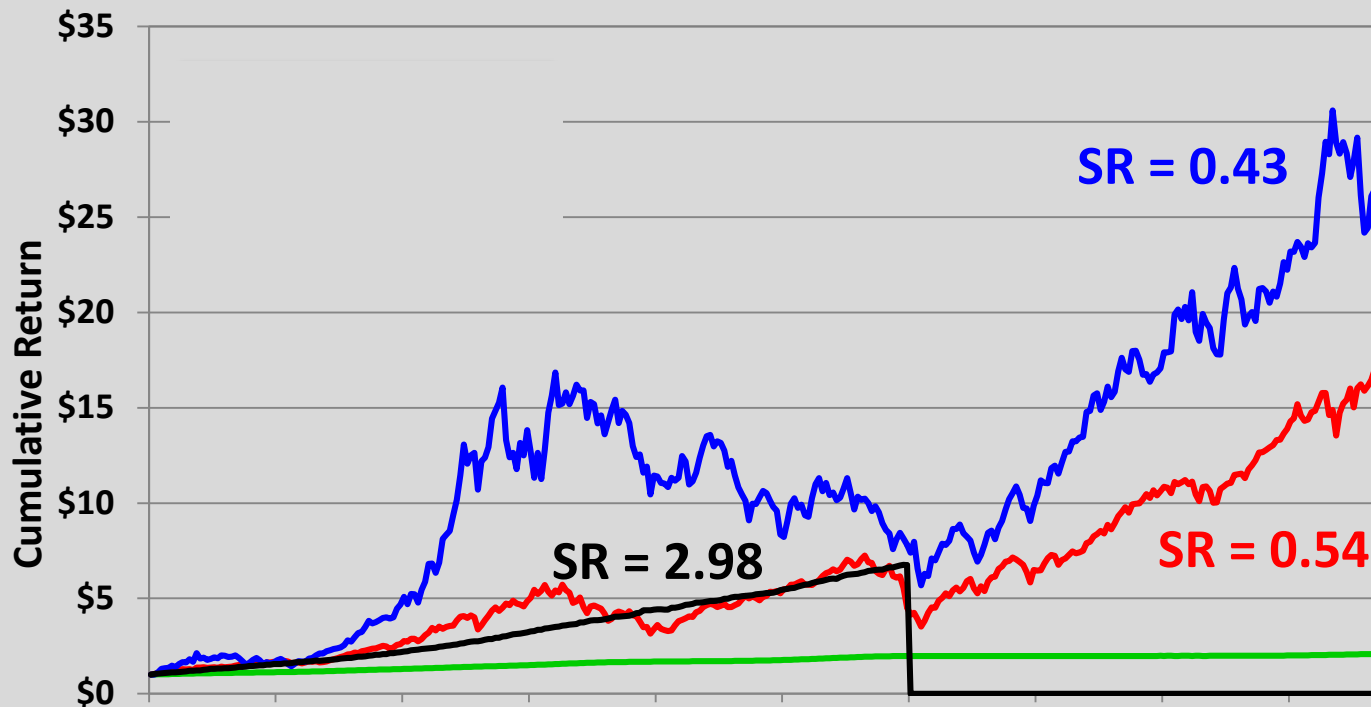
Increasing Risk and Uncertainty

Why??



Investment Pop Quiz #1

$$\text{Sharpe Ratio} \equiv \frac{E[R] - R_f}{SD[R]}$$



Investment Pop Quiz #2

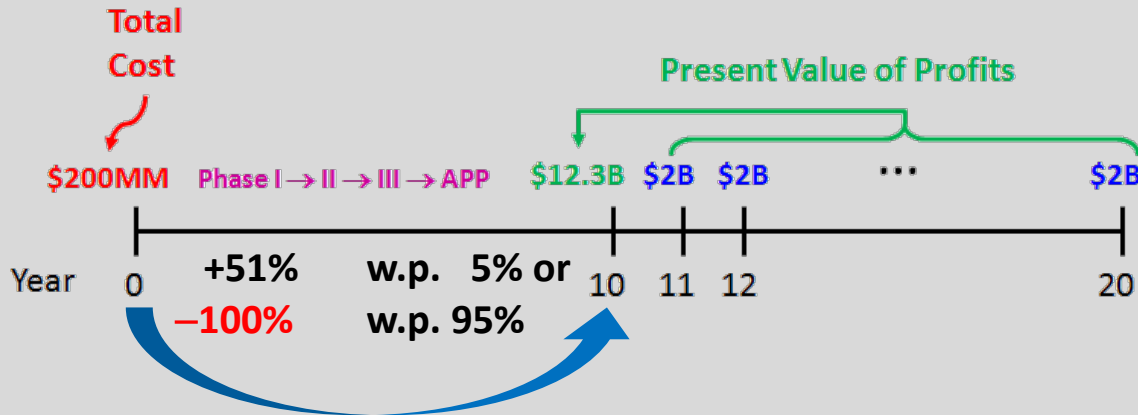
Consider The Following Investment Opportunity:

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

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

$$SD[R] = 423.5\%$$

$$SR = 0.02$$



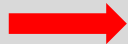
Financial Engineering Can Help

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??  **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!

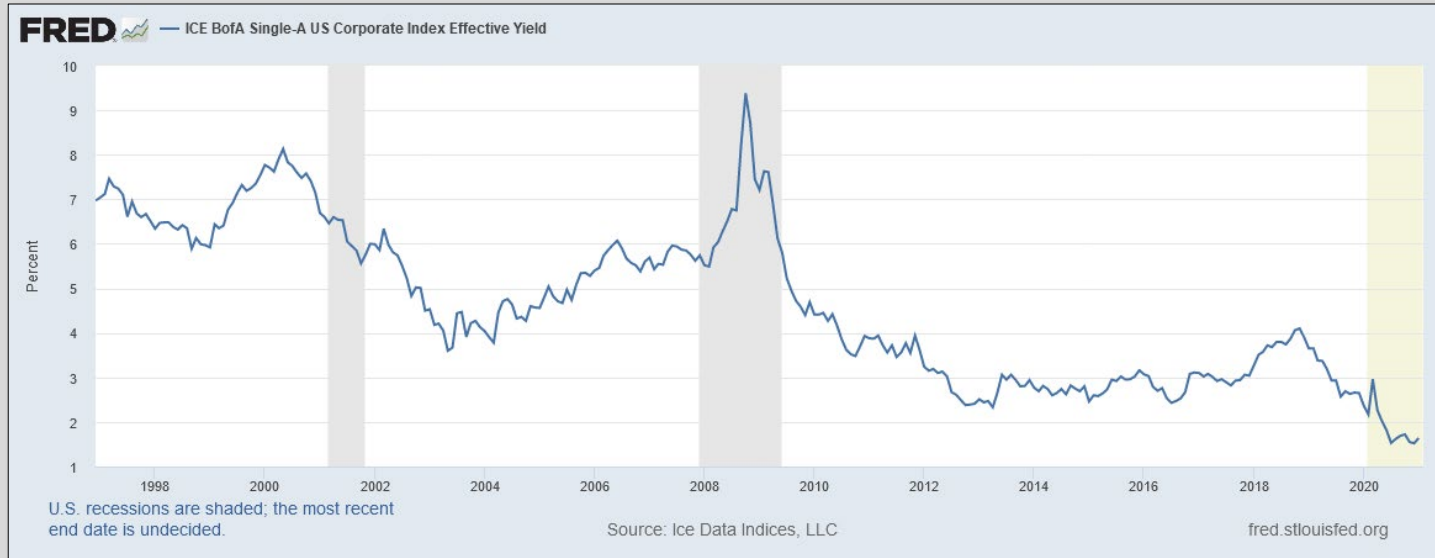


Event	Probability	Minimum Year-10 NPV	Maximum Year-0 Proceeds at 1.56% (BofAML AA 10-Yr as of 1/31/21)	Maximum Year-0 Proceeds at 1.64% (BofAML A 10-Yr as of 1/31/21)	Maximum Year-0 Proceeds at 2.16% (BofAML BBB 10-Yr as of 1/31/21)
At least 1 hit:	99.95%	\$12,289	\$10,527	\$10,444	\$8,501
At least 2 hits:	99.59%	\$24,578	\$21,054	\$20,888	\$17,003
At least 3 hits:	98.18%	\$36,867	\$31,580	\$31,333	\$25,504
At least 4 hits:	94.52%	\$49,157	\$42,107	\$41,777	\$34,005
At least 5 hits:	87.44%	\$61,446	\$52,634	\$52,221	\$42,507

Financial Engineering Can Help

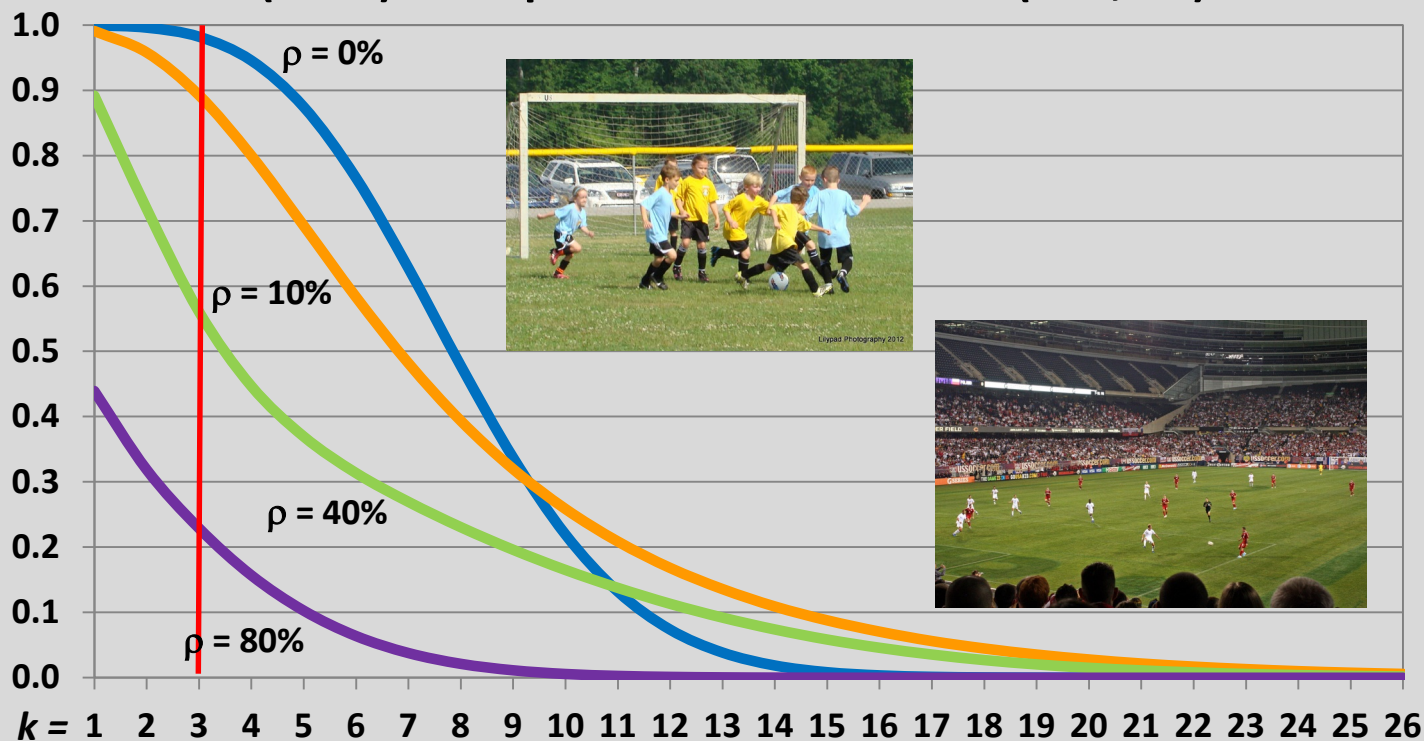
ICE Bank of America Single-A U.S. Corporate Index Effective Yield

Dec 31, 1996 to Jan 31, 2021



Financial Engineering Can Help

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

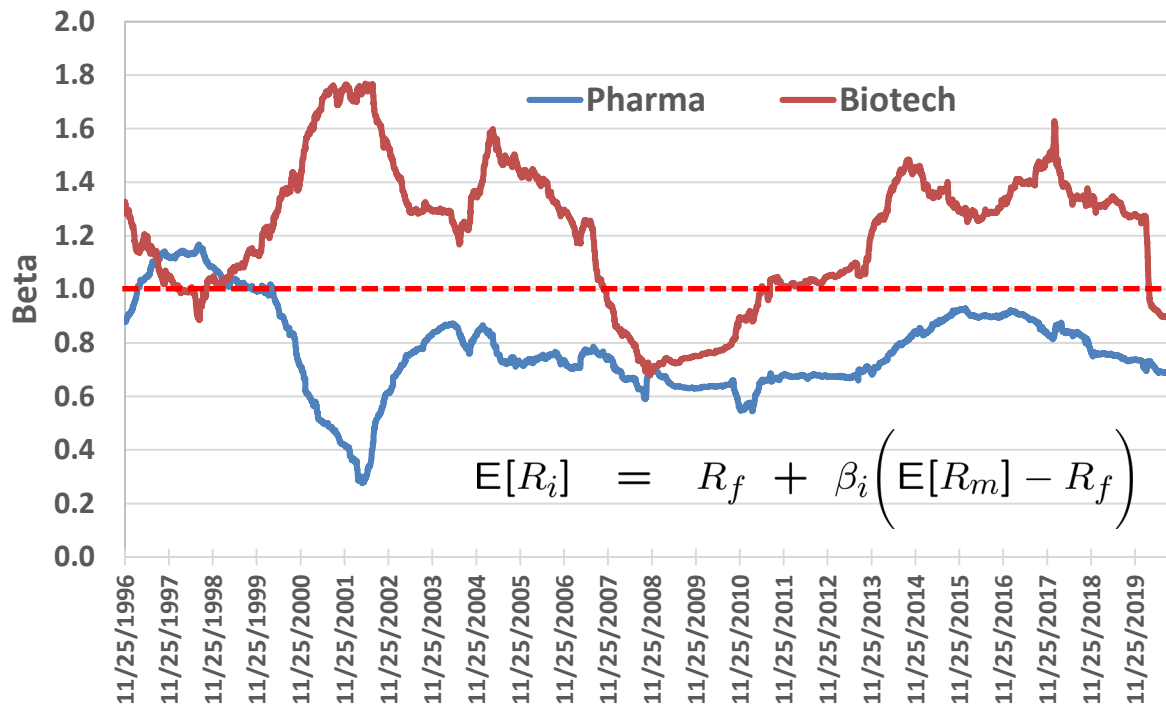


**Diversification
can lower the
cost of capital**

Investment Pop Quiz #3

500-Day Rolling-Window Betas

25 Nov 1996 to 17 Sep 2020



$$E[R_i] = R_f + \beta_i \left(E[R_m] - R_f \right)$$

Why Do
Biotechs Have
Such High
Betas??

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:

- **Cancer:** Fernandez, Stein, Lo (2012), Das and Lo (2017), Das, Rousseau, Adamson, Lo (2018), Chaudhuri, Cheng, Pepke, Rinaudo, Roman, Spencer, Lo (2019), Alexander et al. (2019), Wong, Siah, Lo (2019)
- **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)
- **Clinical trial design:** Montazerhodjat, Chaudhuri, Sargent, Lo (2017), Chaudhuri, Sheldon, Irony, Ho (2018), Isakov, Lo, Montazerhodjat (2019), Chaudhuri and Lo (2020), Xu, Chaudhuri, Xiao, Lo (2020)
- **Estimating and forecasting clinical trial outcomes:** Wong, Siah, Lo (2019, 2020a,b), Siah, Wong, Lo (2019,2020)

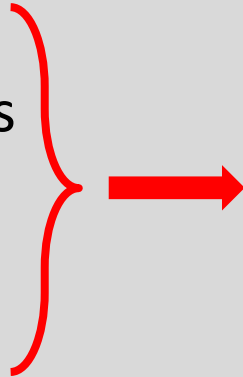
<https://bit.ly/3oDzxI1>



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)

<https://bit.ly/33Fpqdh>

Sourcecode:

<https://projectalpha.mit.edu>

Finance and Biomedical Experts Must Collaborate

Orphan Diseases

- 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!

Fagnan, Yang, McKew, Lo (2015)

PERSPECTIVE

FUNDING

Financing Analysis

David E. Fagnan

The portfolio of diseases that are the preclinical stage but longer averages for early cited in literature a portfolio of rare data, and valuation of the expected rate of return of enhanced through equity groups, and

The U.S. Food and Drug Administration (FDA) Office of Research and Innovation (ORI) is the case as one that U.S. patients. Although a low prevalence to 30 million. An collection of more recognized by the Health (NIH). G ~350 million people 35% of deaths with Drug development particular set of patient population suffering from a lack of public awareness, size of individual sized lack of private-sector. To address these issues enacted the which provides it plan drugs—including activity, tax credits

*Operations Research Technology (MIT), Car School of Management Engineering, MIT, Car National Center for Advancing Medical Research and Innovation (NCMIR) *Computer Science and Engineering Department Computer Science, MIT *These authors contributed equally to this work. Correspondence: a.fagnan@mit.edu, a.fagnan@car.mcgill.ca, a.fagnan@ncmir.nih.gov

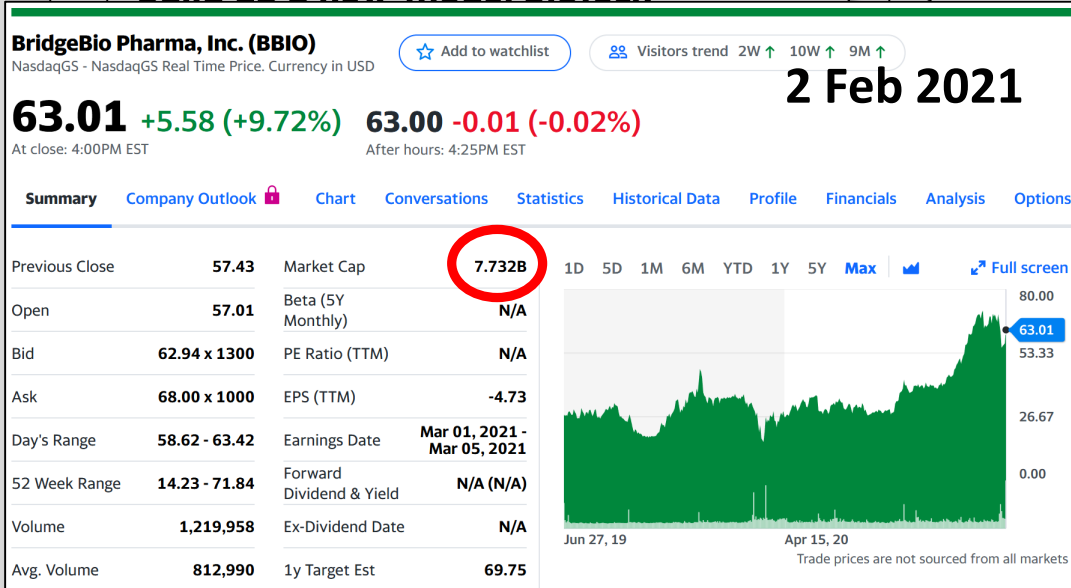
Table 1. Structure and function. Simulated performance comparing an all-equity structure (using no debt financing); an RBO structure using a senior and junior debt tranche paying 5 and 8% annual coupon rates, respectively; and a second RBO structure with a single guaranteed senior tranche. The senior 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.

Simulation results	All equity (similar equity)	Research-backed obligation (RBO)	RBO with guarantee (no mezzanine)
Equity tranche performance			
Equity tranche performance	3.25	5.14	5.32
Average IRR	26.7%	14.7%	N/A
Average MIRR (0% financing)	18.3%	21.6%	22.7%
Average annualized ROE	11.6%	14.7%	15.4%
Probability (equity wiped out)	1.3 bp	0.52%	0.34%
Probability (return on equity <0)	8.0%	6.2%	5.1%
Probability (return on equity >10%)	61.9%	76.8%	78.6%
Probability (return on equity >25%)	2.2%	10.4%	11.0%
Debt tranches performance			
Senior tranche: default probability, expected loss (bp)	—	0.1, <0.1	<0.1, <0.1
Junior tranche: default probability, expected loss (bp)	—	50, 15	—
Guarantee performance			
Probability (cost of guarantee >0)	—	—	0.3%
Expected cost, 2% discount (\$)	—	—	65,000
No-arbitrage cost of guarantee (\$)	—	—	110,000

New Business Models Are Emerging

ENDPOINTS NEWS

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



June 27, 2019 06:55 AM EDT Updated July 3, 07:14 AM | Natalie Grover | IPOs

in

BridgeBio takes crown for biggest tech IPO of 2019, as fellow unicorn

...tive raises offering size and price

Pharma and Adaptive Biotechnologies have not just [upsized IPO offerings](#) of unicorns have also raised their offering prices above the range, hauling in a total of \$648.5 million.

BridgeBio Pharma, founded in 2015, has a portfolio of companies focused on diseases that are driven by mutations in a single gene — encompassing dermatology, neurology, endocrinology, renal disease, and oncology — and cancers with clear genetic drivers. The company mill birthed a plethora of firms such as Eisai, QED Therapeutics and PellePharm, which are its subsidiaries.

BridgeBio, California-based company now has 16 subsidiaries, of which 4 are in or approaching late-stage development. The company, in which KKR owns a 10% stake, raised about [\\$299 million](#) in a fresh round of financing in January.



Neil Kumar Endpoints

New Business Models Are Emerging

mendelian

pre-clinical	phase 1	phase 2	phase 3	commercial
BBP-265/AG10 (Eidos)	TTR Stabilizer (AG10) for ATTR-CM			
Fosdenopterin (Origin)	Synthetic cPMP for MOCD Type A			

targeted oncology

pre-clinical	phase 1	phase 2	phase 3	commercial
BBP-831 (QED)	FGFR 1-3 Inhibitor (Infigratinib) for FGFR+ Cancers			
BBP-398 (Navire)	SHP2 Inhibitor for RTK Cancers			

pre-clinical

phase 1

phase 2

phase 3

commercial

**BBP-870
(Origin)**

Synthetic cPMP for MOCD Type A

BBP-265 (Eidos)

TTR Stabilizer (AG10) for ATTR-CM

**BBP-009
(PellePharm)**

Topical HH Inhibitor (Patidegib) for Gorlin Syndrome

BBP-831 (QED)

FGFR 1-3 Inhibitor (Infigratinib) for FGFR+ Cancers

BBP-761 (Fortify)

Succinate Phosphoging for UHON

New Business Models Are Emerging

Biotech

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

by N

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

Blackstone

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Blackstone Announces \$4.6 Billion Final Close of Life Sciences
Fund

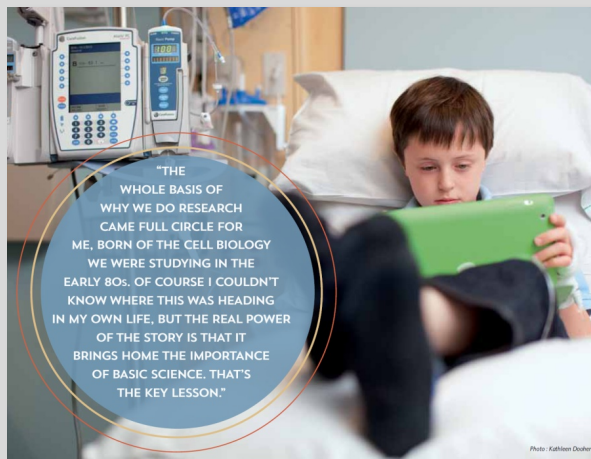
09 July 2020

-Largest Life Sciences Private Fund Raised to Date

BioBonds in
2021??

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

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