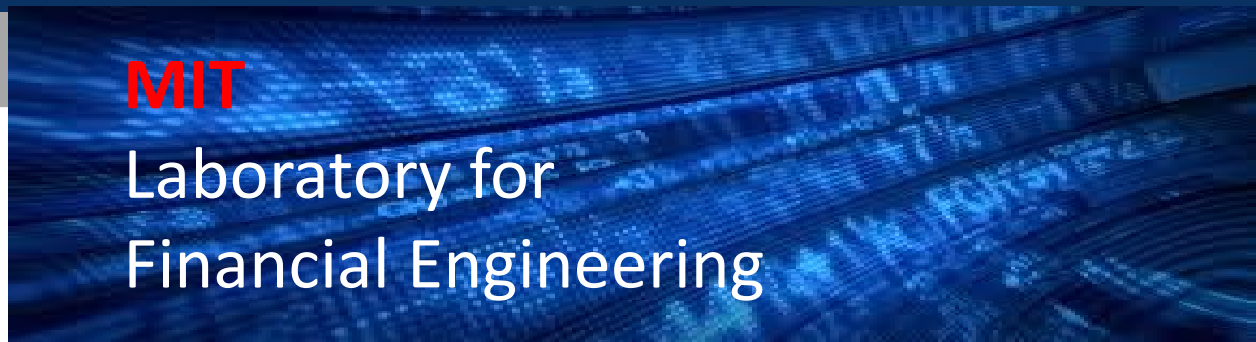
Can Financial Engineering Cure Cancer? New Business Models for Accelerating Biomedical Innovation

Andrew W. Lo, MIT

16 October 2022

Andy Abel Festschrift Symposium



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."

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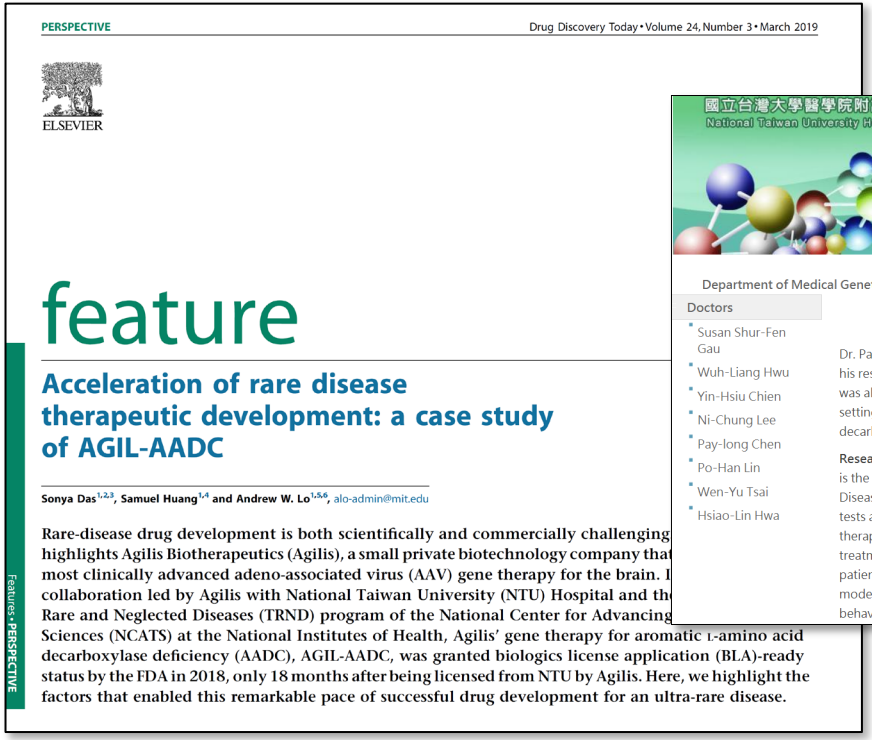
Biomedicine Is At An Inflection Point



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

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feature

Acceleration of rare disease therapeutic development: a case study of AGIL-AADC

Sonya Das[1,2,3], Samuel Huang[1,4] and Andrew W. Lo[1,5,6], alo-admin@mit.edu

Rare-disease drug development is both scientifically and commercially challenging highlights Agilis Biotherapeutics (Agilis), a small private biotechnology company that most clinically advanced adeno-associated virus (AAV) gene therapy for the brain. I collaboration led by Agilis with National Taiwan University (NTU) Hospital and th Rare and Neglected Diseases (TRND) program of the National Center for Advancing Sciences (NCATS) at the National Institutes of Health, Agilis' gene therapy for aromatic L-amino acid decarboxylase deficiency (AADC), AGIL-AADC, was granted biologics license application (BLA)-ready status by the FDA in 2018, only 18 months after being licensed from NTU by Agilis. Here, we highlight the factors that enabled this remarkable pace of successful drug development for an ultra-rare disease.

Features • PERSPECTIVE

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

Doctors

Department of Medical Genetics Home Doctors Service Division 中文版

Doctors
- Susan Shur-Fen Gau
- Wuh-Liang Hwu
- Yin-Hsiu Chien
- Ni-Chung Lee
- Pay-Iong Chen
- Po-Han Lin
- Wen-Yu Tsai
- Hsiao-Lin Hwa

Dr. Paul Wuh-Liang Hwu completed his medical and PhD degrees at National Taiwan University, and completed his residency at NTUH. He has done fellowship at the Department of Genetics at Johns Hopkins University, and was also a Visiting Scientist at the Department of Medical Genetics at the Mayo Clinic. Dr. Hwu leads his group setting up the Newborn Screening Program for Pompe Disease and the gene therapy for aromatic l-amino acid decarboxylase deficiency clinical trial which both are world-leading programs.

Research interests: Dr. Hwu is dedicated to innovative diagnosis and treatment for human genetic diseases. He is the former director of the Taiwan Newborn Screening Laboratory at NTUH, at that time he established Pompe Disease newborn screening. He is now still the director of the biochemical genetics laboratory and is developing tests and offering clinical laboratory service for lysosomal storage diseases. Dr. Hwu is now focusing on gene therapy for genetic diseases, specifically, for aromatic l-amino acid decarboxylase (AADC) deficiency. The treatment includes injection of adeno-associated virus into the human brain. The treatment results from 4 patients have been published in Science Translational Medicine. In order to develop this gene therapy, a mouse model of AADC deficiency has been created in the lab. These mice are being characterized by histochemical and behavior sciences. And studies of gene therapy for these mice are also ongoing.

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Biomedicine Is At An Inflection Point

Top 30 Drugs in 2000

	Product	Marketer(s)	Sales ($, mill)	Responsible for Discovery / Development: Biotech Co. or Product	
1	Prilosec	AstraZeneca	$6,260		
2	Zocor	Merck	$5,280		
3	Lipitor	Pfizer	$5,030		
4	Norvasc	Pfizer	$3,361		
5	Prevacid	TAP Pharma	$2,740		
6	**Procrit**	**J&J**	**$2,709**	**Amgen → J&J**	
7	Celebrex	Pharmacia	$2,614		
8	Prozac	Eli Lilly	$2,585		
9	Zyprexa	Eli Lilly	$2,366		
10	Paxil	GSK	$2,349		
11	Claritin	Schering-Plough	$2,194		
12	Vioxx	Merck	$2,160		
13	Zoloft	Pfizer	$2,140		
14	**Epogen**	**Amgen**	**$1,963**	**Amgen**	
15	Premarin	Wyeth	$1,870		
16	Augmentin IR	GSK	$1,847		
17	Vasotec	Merck	$1,790		
18	Pravachol	Bristol-Myers	$1,766		
19	Glucophage IR	Bristol-Myers	$1,718		
20	Cozaar	Merck	$1,715		
21	Tylenol	J&J	$1,680		
22	**Insulin**	**Novo Nordisk**	**$1,671**	**--**	
23	Cipro/Ciprobay	Bayer	$1,648		
24	Risperdal	J&J	$1,603		
25	Taxol	RTI → Bristol-Myers	$1,561		
26	Zithromax	Pliva → Pfizer	$1,382		
27	**Intron A**	**Schering-Plough**	**$1,360**	**--**	
28	Viagra	Pfizer	$1,344		
29	Neurontin	Pfizer	$1,334		
30	Flixotide/Flovent	GSK	$1,334		
	Total WW Sales		**$69,374**	**$7,702**	**4**
	Biologics			**11%**	**13%**

Top 30 Drugs in 2018

	Product	Marketer(s)	Sales ($, mill)	Responsible for Discovery / Development: University / Hospital	Biotech Co. or Product
1	**Humira**	**AbbVie**	**$20,476**	**Cambridge; Scripps**	**CaT → Knoll**
2	**Revlimid**	**Celgene**	**$9,816**	**Boston Children's**	**Celgene**
3	**Opdivo**	**Bristol Myers**	**$7,524**	**--**	**Medarex**
4	**Enbrel**	**Amgen (Immunex) / Pfizer**	**$8,538**	**MassGen**	**Immunex**
5	**Keytruda**	**Merck**	**$7,198**	**LifeArc**	
6	**Eylea**	**Regeneron / Bayer**	**$7,164**		**Regeneron**
7	**Herceptin**	**Roche (Genentech)**	**$7,140**	**UCLA**	**Genenetch**
8	**Avastin**	**Roche (Genentech)**	**$7,004**	**--**	**Genenetch**
9	**Rituxan**	**Roche (Genentech)**	**$7,547**	**--**	**Idec → Genenetch**
10	**Eliquis**	**Bristol Myers**	**6438**	**--**	**Bristol Myers**
11	**Xarelto**	**Bayer**	**$6,166**	**--**	**--**
12	**Remicade**	**J&J (Centocor) / Merck**	**$6,002**	**NYU**	**Centocor**
13	**Prevnar 13**	**Pfizer**	**$5,901**	**--**	**--**
14	**Stelara**	**J&J**	**$5,293**	**--**	**Centocor**
15	**Lyrica**	**Pfizer**	**$5,004**	**Northwestern**	**--**
16	**Genvoya**	**Gilead**	**$4,737**	**Leuven, Emory**	**Triangle, Gilead**
17	**Neulasta**	**Amgen**	**$4,596**	**MSK**	**Amgen**
18	**Imbruvica**	**Abbvie / J&J**	**$4,454**	**--**	**Pharmacyclics**
19	**Tecfidera**	**Biogen**	**$4,274**	**--**	**Fumapharm**
20	**Lantus**	**Sanofi**	**$4,211**	**--**	**--**
21	**Ibrance**	**Pfizer**	**$4,118**	**--**	**Onyx**
22	**Januvia**	**Merck**	**$3,984**	**Demuth, Tufts**	**Prosidion**
23	**Victoza**	**Novo Nordisk**	**$3,857**	**--**	**--**
24	**Lucentis**	**Roche / Novartis**	**$3,743**	**--**	**Genenetch**
25	**Botox**	**Allergan**	**$3,577**	**--**	**--**
26	**Soliris**	**Alexion**	**$3,563**	**Oklahoma Medical Research**	**Alexion**
27	**Triumeq**	**Pfizer / ViiV / GSK**	**$3,535**	**--**	**--**
28	**Zytiga**	**J&J**	**$3,498**	**Institute of Cancer Research**	**Cougar**
29	**Mavyret**	**Abbvie**	**$3,438**	**--**	**--**
30	**Gilenya**	**Novartis**	**$3,380**	**Kyoto University**	**Novartis**
	Total WW Sales		**$176,175**	**$87,932**	**$149,569**
	Biologics			49.9%	85%

Source: Royalty Pharma

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Biomedicine Is At An Inflection Point

The "omics" Revolution:

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

What about Economics?

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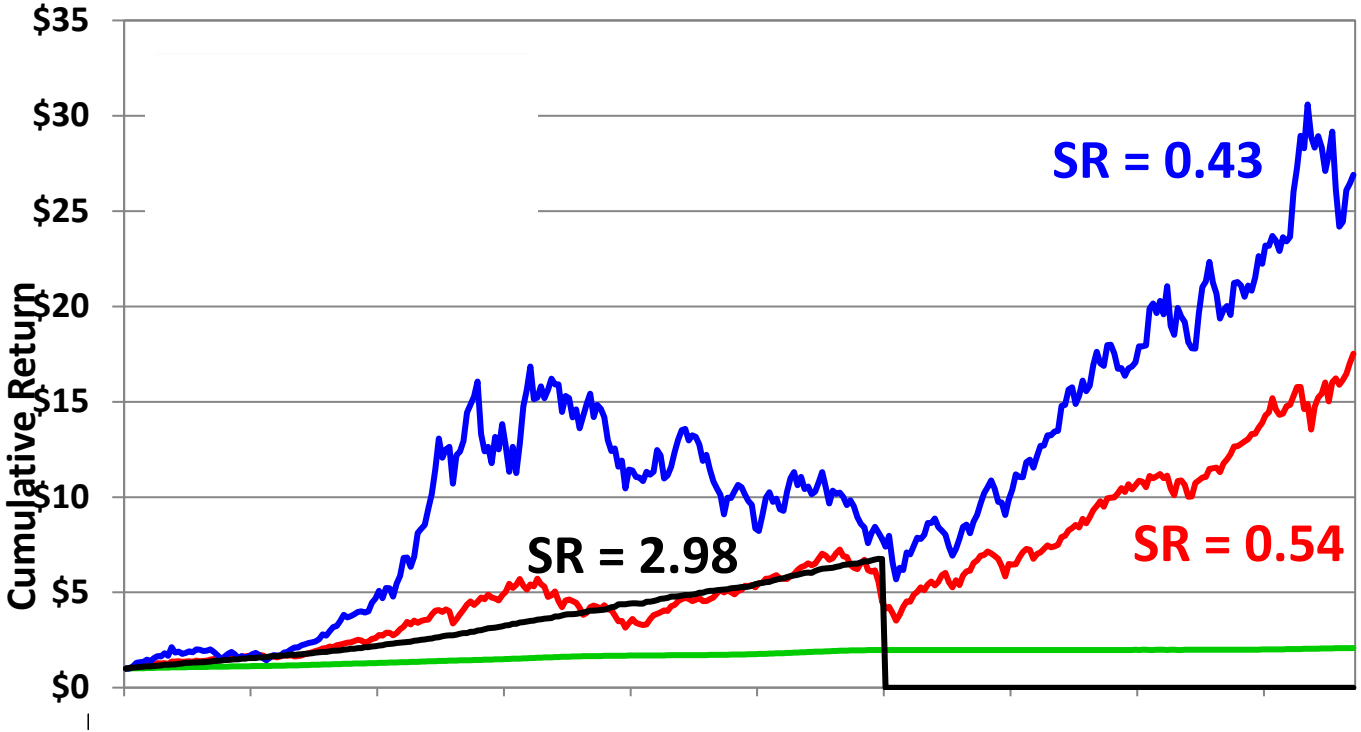
Increasing Risk and Uncertainty

Why??

Investment Pop Quiz #1

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



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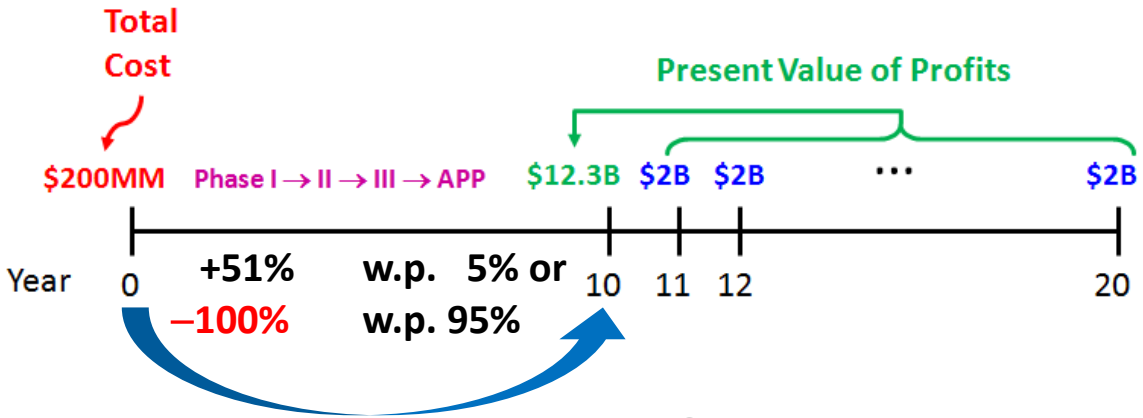
Investment Pop Quiz #2

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

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Financial Engineering Can Help

MIT LFE

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:

$$\mathrm{E}[R] = 11.9\%$$

$$\mathrm{SD}[R] = 423.5\%/\sqrt{150} = 34.6\%$$

- But can we raise $30B??

→ **SR = 0.34**

- It depends on the portfolio's risk/reward profile (correlations?)

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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 4.96% (BofAML AA 10-Yr as of 10/7/22)	Maximum Year-0 Proceeds at 5.38% (BofAML A 10-Yr as of 10/7/22)	Maximum Year-0 Proceeds at 6.02% (BofAML BBB 10-Yr as of 10/7/22)
At least 1 hit:	99.95%	$12,289	$7,573	$7,277	$4,221
At least 2 hits:	99.59%	$24,578	$15,147	$14,554	$8,442
At least 3 hits:	98.18%	$36,867	$22,720	$21,830	$12,663
At least 4 hits:	94.52%	$49,157	$30,293	$29,107	$16,884
At least 5 hits:	87.44%	$61,446	$37,866	$36,384	$21,105

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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?

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Short Answer

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Short Answer

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Short Answer

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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 (2022), 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), Xu et al. (2022)
- **Dynamic leverage**: Montazerhodjat, Frishkopf, Lo (2015), Lo and Siah (2021)
- **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), Siah et al. (2021)

And 15.482, 15.480, Outreach Activities

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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 (JSF 2021)

- Sourcecode available in R and Matlab

https://projectalpha.mit.edu

Finance and Biomedical Experts Must Collaborate

- Cultures are very different; value created in bridging this gap

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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 all rare diseases
- Smaller population, urgent need, higher prices, lower development costs, higher success rates (20%), faster time to approval (3–7 years), 1983 Orphan Drug Act, etc.
- $400–$500 million of capital and 10–20 projects are sufficient

Lack of Correlation Is Critical!

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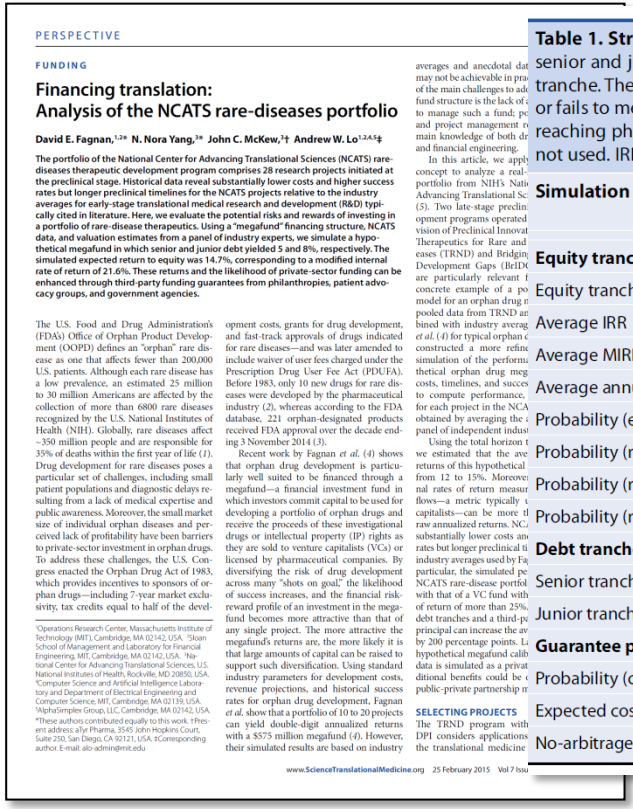
Fagnan, Yang, McKew, Lo (2015)



PERSPECTIVE

FUNDING

Financing translation: Analysis of the NCATS rare-diseases portfolio

David E. Fagnan,[1,2]* N. Nora Yang,[3]* John C. McKew,[3]† Andrew W. Lo[1,2,4,5]‡

The portfolio of the National Center for Advancing Translational Sciences (NCATS) rare-diseases therapeutic development program comprises 28 research projects initiated at the preclinical stage. Historical data reveal substantially lower costs and higher success rates but longer preclinical timelines for the NCATS projects relative to the industry averages for early-stage translational medical research and development (R&D) typically cited in literature. Here, we evaluate the potential risks and rewards of investing in a portfolio of rare-disease therapeutics. Using a "megafund" financing structure, NCATS data, and valuation estimates from a panel of industry experts, we simulate a hypothetical megafund in which senior and junior debt yielded 5 and 8%, respectively. The simulated expected return to equity was 14.7%, corresponding to a modified internal rate of return of 21.6%. These returns and the likelihood of private-sector funding can be enhanced through third-party funding guarantees from philanthropies, patient advocacy groups, and government agencies.

The U.S. Food and Drug Administration's (FDA's) Office of Orphan Product Development (OOPD) defines an "orphan" rare disease as one that affects fewer than 200,000 U.S. patients. Although each rare disease has a low prevalence, an estimated 25 million to 30 million Americans are affected by the collection of more than 6800 rare diseases recognized by the U.S. National Institutes of Health (NIH). Globally, rare diseases affect ~350 million people and are responsible for 35% of deaths within the first year of life (*1*). Drug development for rare diseases poses a particular set of challenges, including small patient populations and diagnostic delays resulting from a lack of medical expertise and public awareness. Moreover, the small market size of individual orphan diseases and perceived lack of profitability have been barriers to private-sector investment in orphan drugs. To address these challenges, the U.S. Congress enacted the Orphan Drug Act of 1983, which provides incentives to sponsors of orphan drugs—including 7-year market exclusivity, tax credits equal to half of the development costs, grants for drug development, and fast-track approvals of drugs indicated for rare diseases—and was later amended to include waiver of user fees charged under the Prescription Drug User Fee Act (PDUFA). Before 1983, only 10 new drugs for rare diseases were developed by the pharmaceutical industry (*2*), whereas according to the FDA database, 221 orphan-designated products received FDA approval over the decade ending 3 November 2014 (*3*).

Recent work by Fagnan *et al.* (*4*) shows that orphan drug development is particularly well suited to be financed through a megafund—a financial investment fund in which investors commit capital to be used for developing a portfolio of orphan drugs and receive the proceeds of these investigational drugs or intellectual property (IP) rights as they are sold to venture capitalists (VCs) or licensed by pharmaceutical companies. By diversifying the risk of drug development across many "shots on goal," the likelihood of success increases, and the financial risk-reward profile of an investment in the megafund becomes more attractive than that of any single project. The more attractive the megafund's returns are, the more likely it is that large amounts of capital can be raised to support such diversification. Using standard industry parameters for development costs, revenue projections, and historical success rates for orphan drug development, Fagnan *et al.* show that a portfolio of 10 to 20 projects can yield double-digit annualized returns with a $575 million megafund (*4*). However, their simulated results are based on industry averages and anecdotal da… may not be achievable in pra… of the main challenges to ad… fund structure is the lack of … to manage such a fund; pa… and project management r… main knowledge of both dr… and financial engineering.

In this article, we appl… concept to analyze a real-… portfolio from NIH's Natio… Advancing Translational Sc… (*5*). Two late-stage preclin… opment programs operated … vision of Preclinical Innovat… Therapeutics for Rare and … eases (TRND) and Bridging … Development Gaps (BrIDG… are particularly relevant … concrete example of a po… model for an orphan drug … pooled data from TRND an… bined with industry averag… *et al.* (*4*) for typical orphan d… constructed a more refin… simulation of the perform… thetical orphan drug meg… costs, timelines, and succes… to compute performance, … for each project in the NCA… obtained by averaging the … panel of independent indust…

Using the total horizon … we estimated that the ave… returns of this hypothetical … from 12 to 15%. Moreover, … nal rates of return measu… flows—a metric typically … capitalists—can be more t… raw annualized returns. NC… substantially lower costs an… rates but longer preclinical t… industry averages used by Fa… particular, the simulated pe… NCATS rare-disease portfol… with that of a VC fund with … of return of more than 25%, … debt tranches and a third-p… principal can increase the av… by 200 percentage points. L… hypothetical megafund calib… data is simulated as a privat… ditional benefits could be … public-private partnership …

SELECTING PROJECTS

The TRND program with … DPI considers applications … the translational medicine …

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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%	N/A	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

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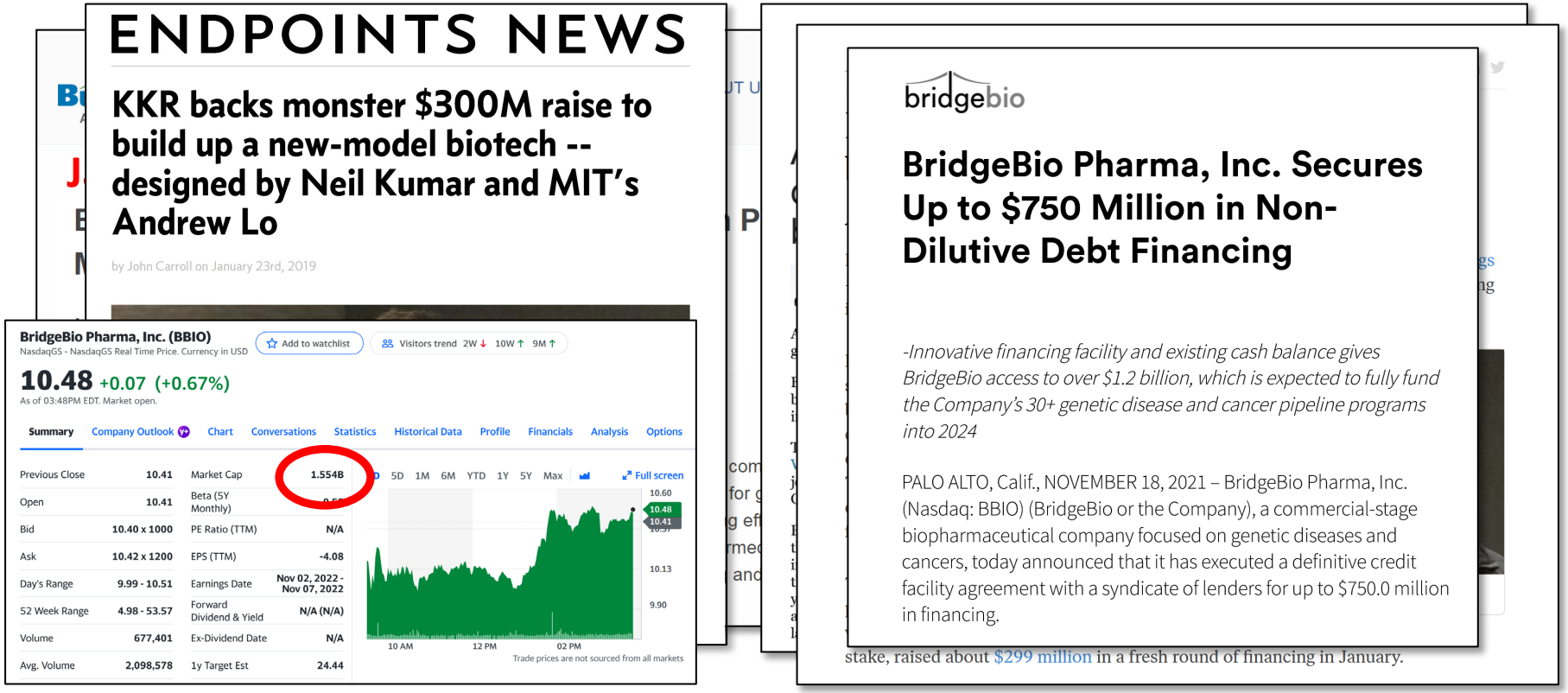
New Business Models Are Emerging



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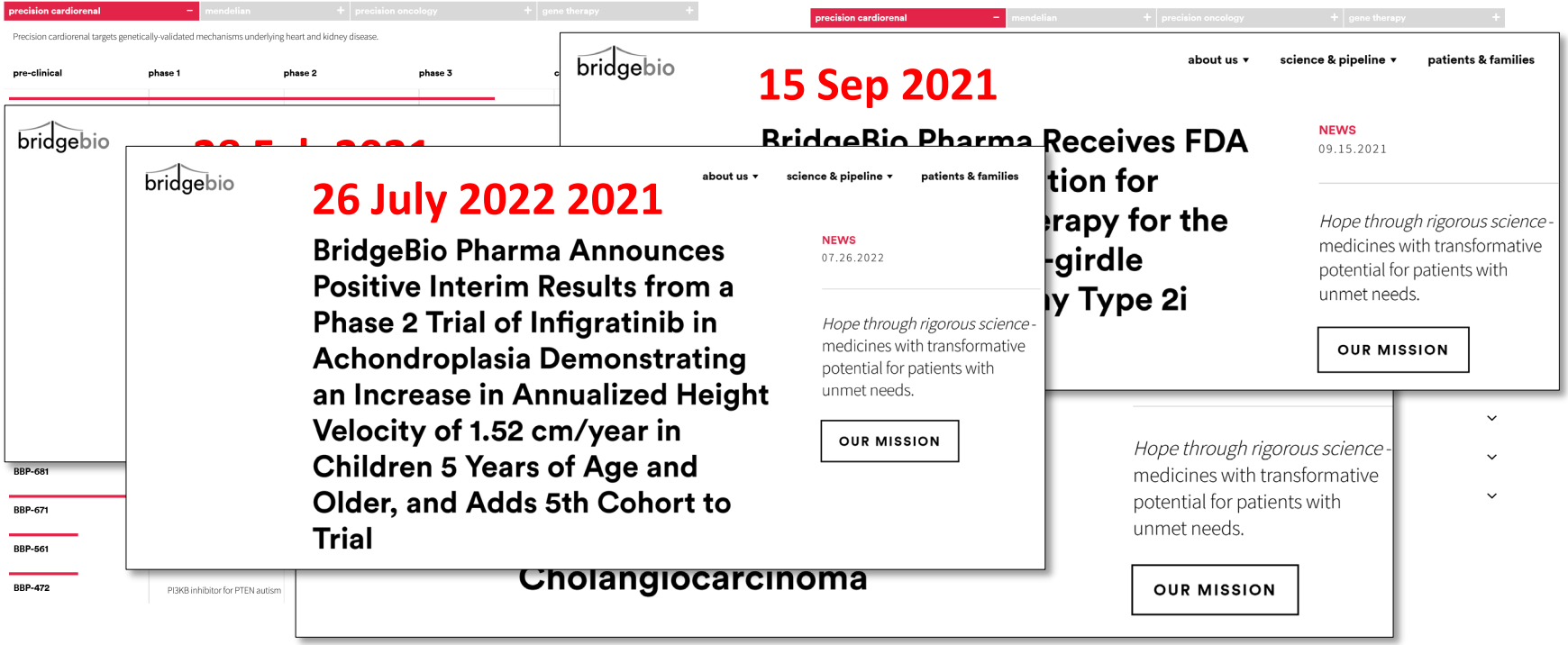
New Business Models Are Emerging



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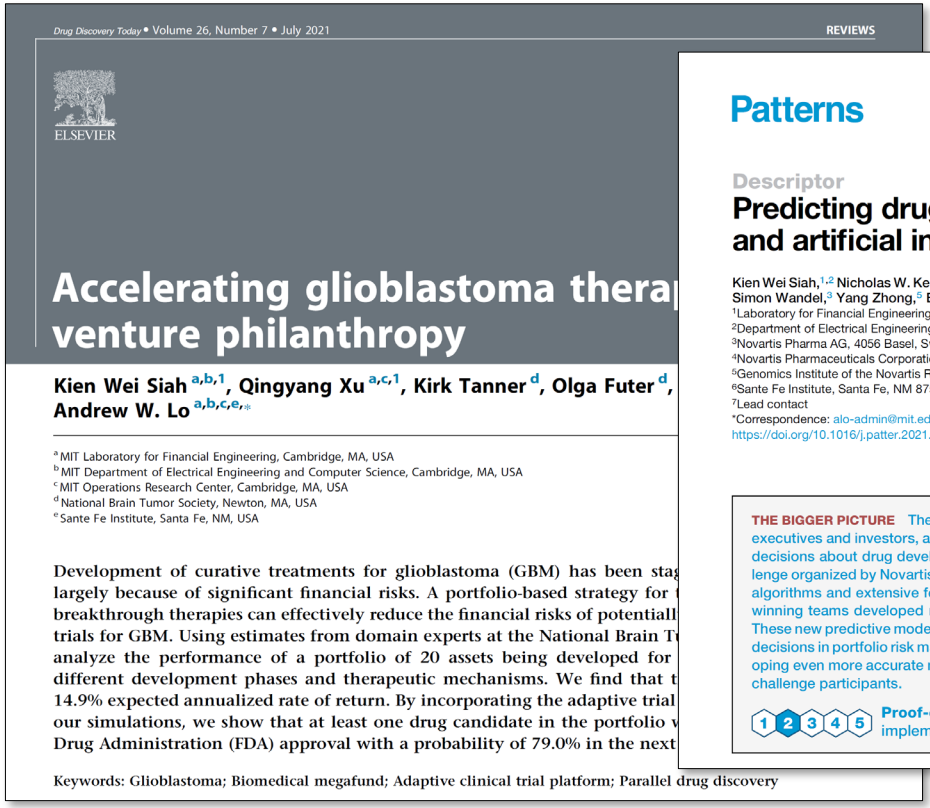
New Business Models Are Emerging



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Accelerating glioblastoma therap
venture philanthropy

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Development of curative treatments for glioblastoma (GBM) has been stag
largely because of significant financial risks. A portfolio-based strategy for t
breakthrough therapies can effectively reduce the financial risks of potentiall
trials for GBM. Using estimates from domain experts at the National Brain T
analyze the performance of a portfolio of 20 assets being developed for
different development phases and therapeutic mechanisms. We find that t
14.9% expected annualized rate of return. By incorporating the adaptive trial
our simulations, we show that at least one drug candidate in the portfolio w
Drug Administration (FDA) approval with a probability of 79.0% in the next

Keywords: Glioblastoma; Biomedical megafund; Adaptive clinical trial platform; Parallel drug discovery

Patterns

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Descriptor

Predicting drug approvals: The Novartis data science and artificial intelligence challenge

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THE BIGGER PICTURE The probability of success is a key parameter that clinical researchers, biopharma executives and investors, and portfolio managers focus on when making important scientific and business decisions about drug development. We describe an in-house data science and artificial intelligence challenge organized by Novartis in collaboration with MIT researchers. Using state-of-the-art machine-learning algorithms and extensive feature engineering augmented by domain expertise in drug development, two winning teams developed models that outperformed the baseline MIT model proposed in a prior study. These new predictive models can be used to augment human judgment to make more informed data-driven decisions in portfolio risk management and capital allocation. These results suggest the possibility of developing even more accurate models using more comprehensive and informative data, and a broader pool of challenge participants.

1 2 3 4 5 **Proof-of-Concept:** Data science output has been formulated, implemented, and tested for one domain/problem

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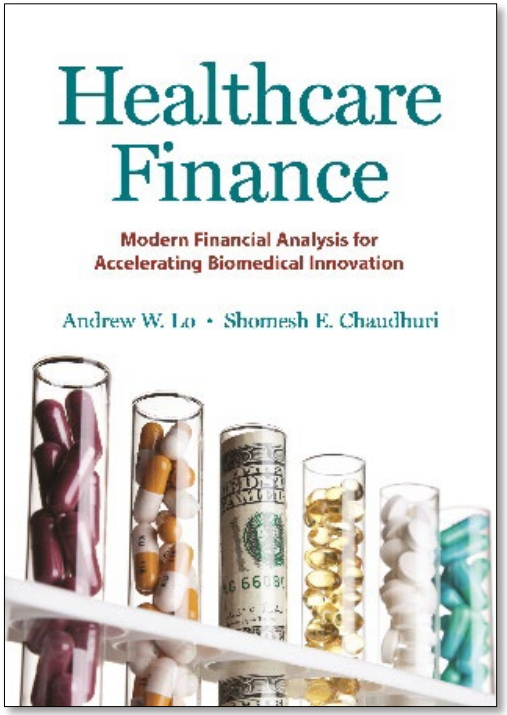
New Business Models Are Emerging



https://healthcare-finance.org

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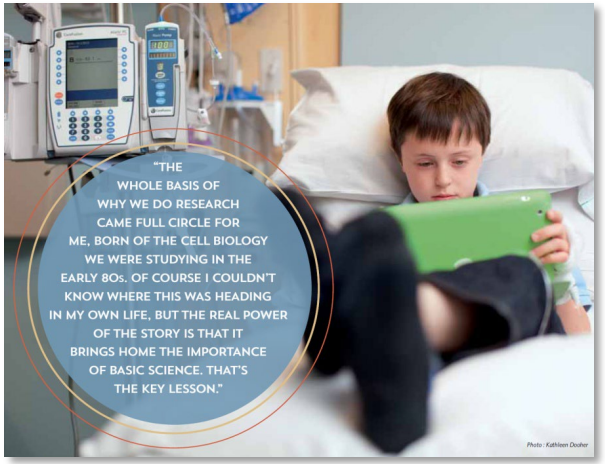
Conclusion

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

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Happy Birthday Andy!

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