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

MIT
Laboratory for
Financial Engineering

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
- 2008: First cancer genome (leukemia) sequenced by Wash U. Genome Institute, Nature 456 (2008):66-72.
- 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??

NIH funding, FY 1950–2019

in thousands of constant 2013 BRDPI adjusted dollars

MENU

$60,000,000
$50,000,000
$40,000,000
$30,000,000
$20,000,000
$10,000,000
$0

1950 1960 1970 1980 1990 2000 2010

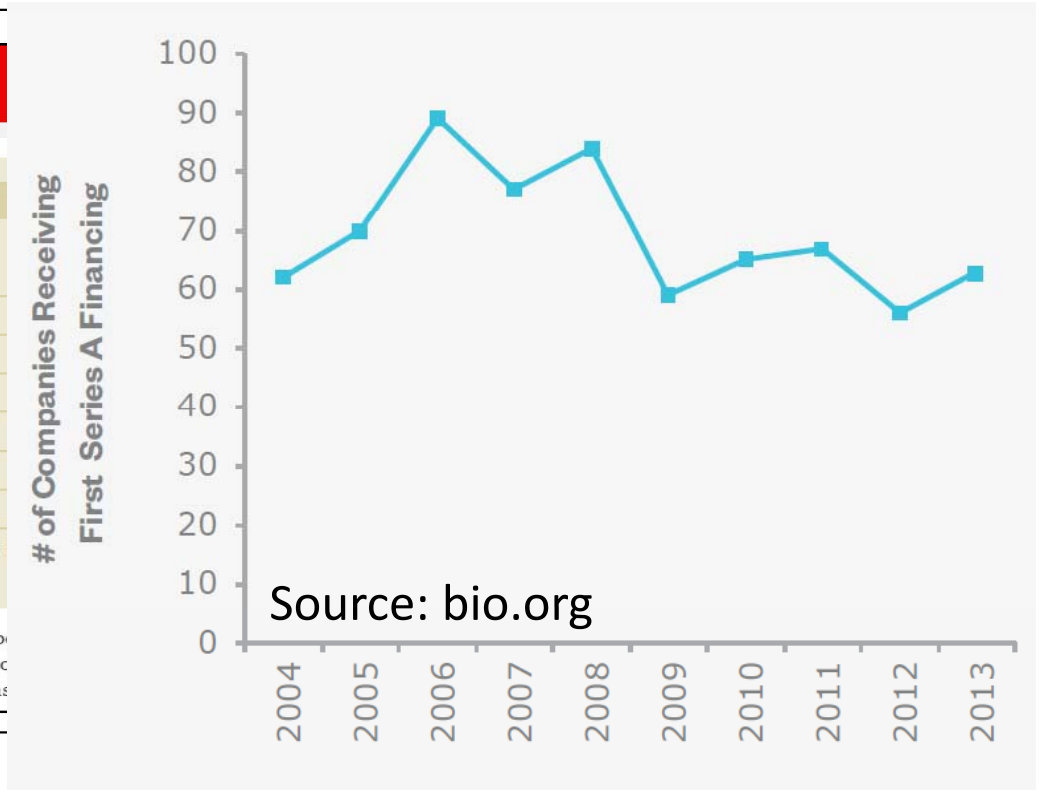
Table 2 Number of active VC firms

Region	2008	2009	2010
Canada	10	5	10
China	2	4	5
Europe	105	106	111
India	1	3	1
Israel	12	6	5
United States	201	163	143
Global total[a]	309	256	252

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

Source: NIH funding figures through FY 2014 are based on total budget authority. Projected NIH funding figu are based on data from the Congressional Budget Office.

Since p 500 Bic twice as



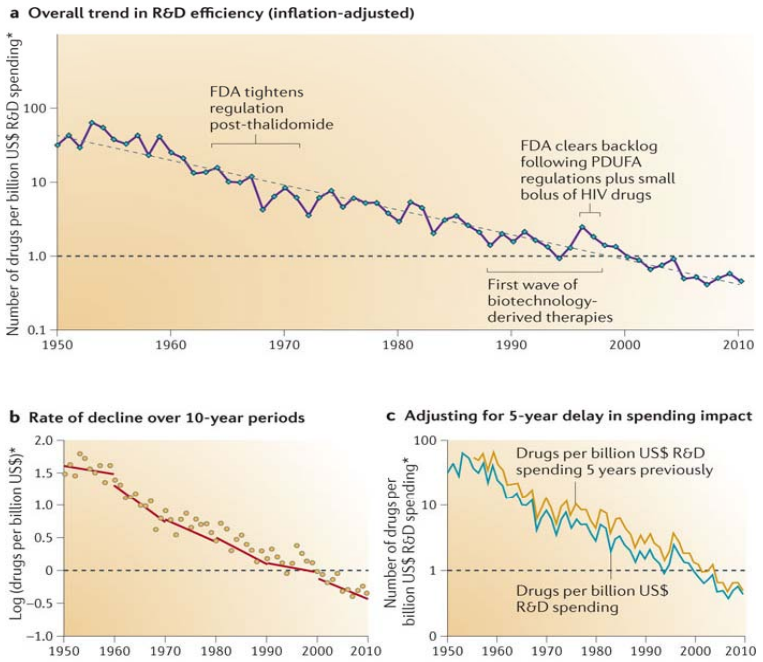
Why??

The Challenge of Drug Development

Example: Combination Therapies

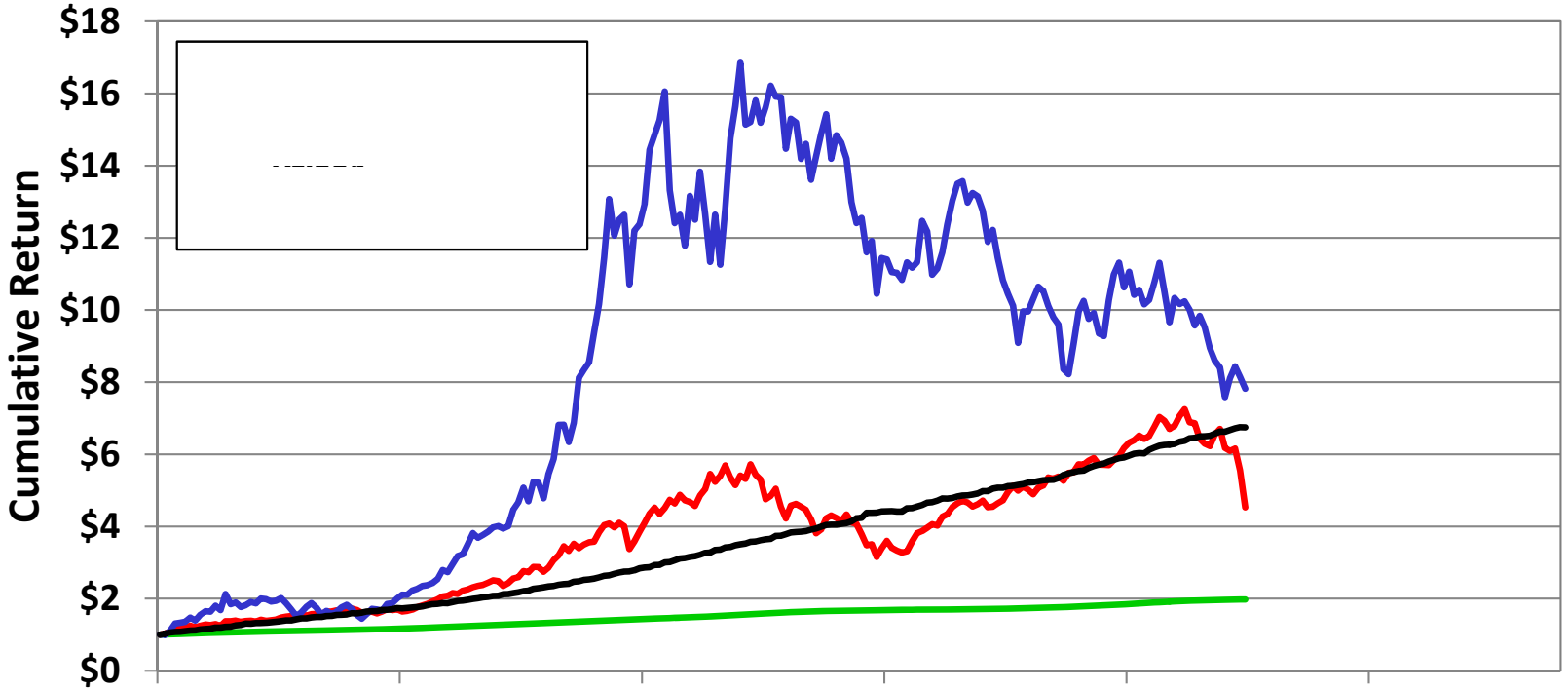
- 2,800 approved drugs
- 3,918,500 pairs
- 3,654,747,600 triples
- Dosage regimens?
- Biomarkers?
- Resistance?
- Side-effects, litigation?
- Pricing, FDA, etc. ?

Eroom's Law

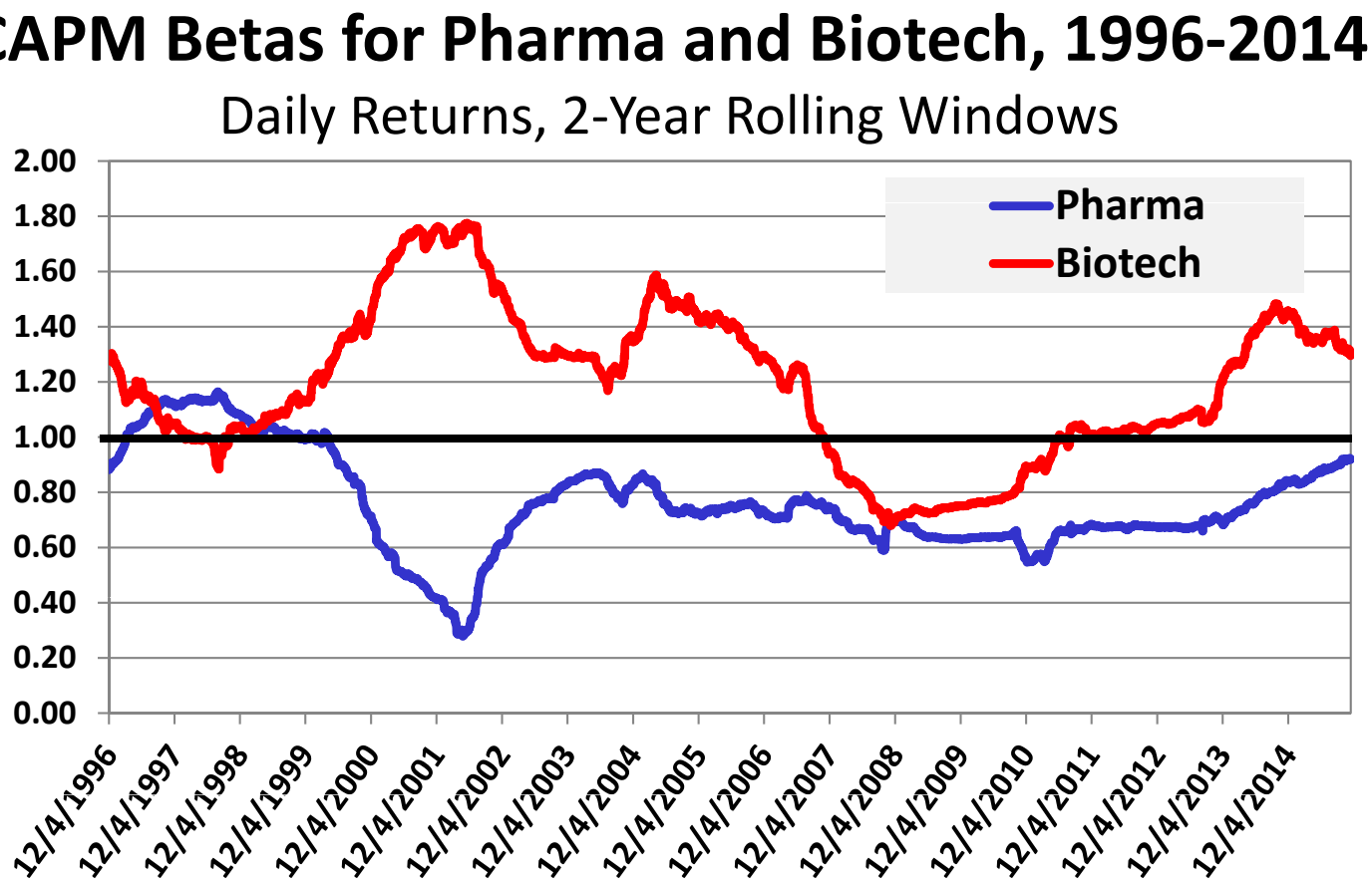


Source: Scannell et al. (NRDD 2012)

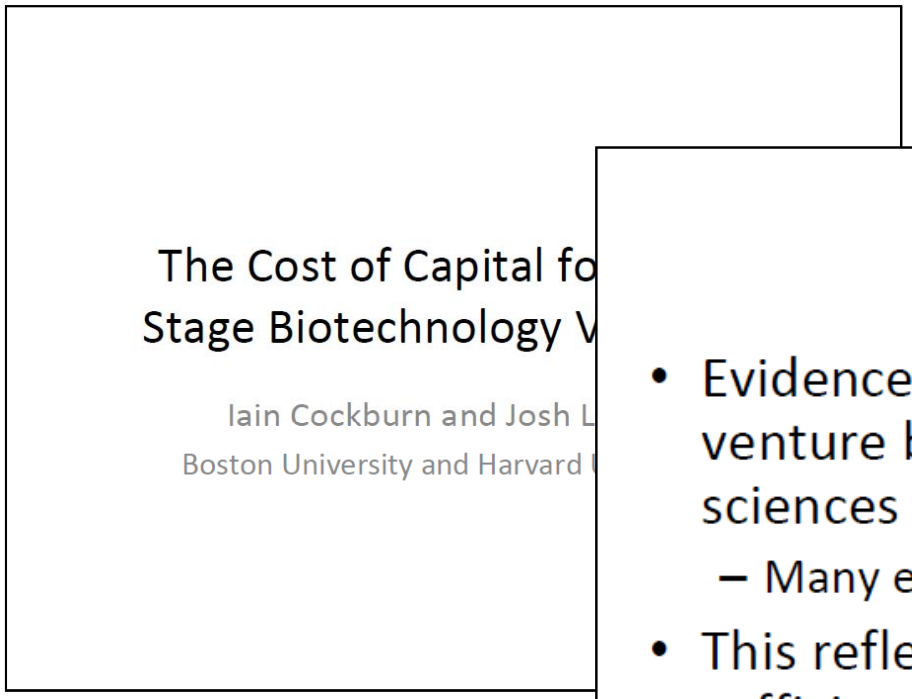
Risk and Reward



Risk and Reward



Risk and Reward


The Cost of Capital fo
Stage Biotechnology V

Iain Cockburn and Josh L

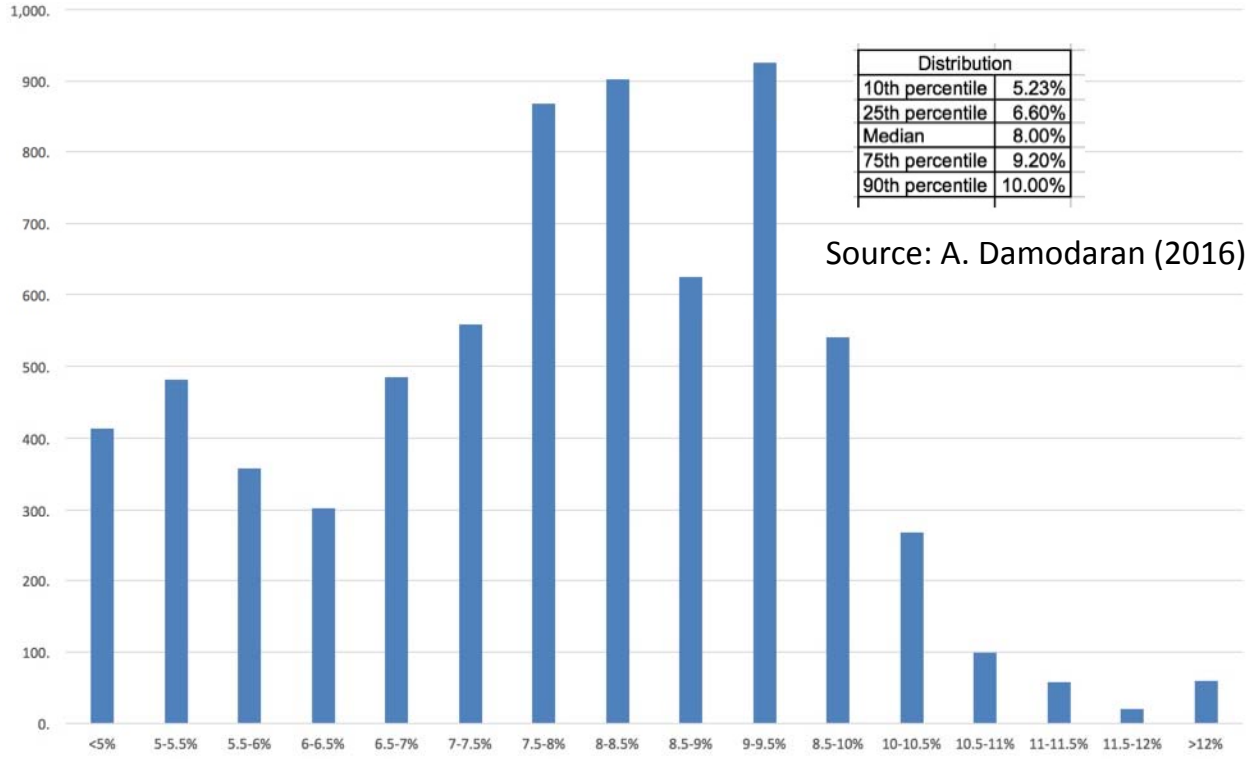
Boston University and Harvard

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



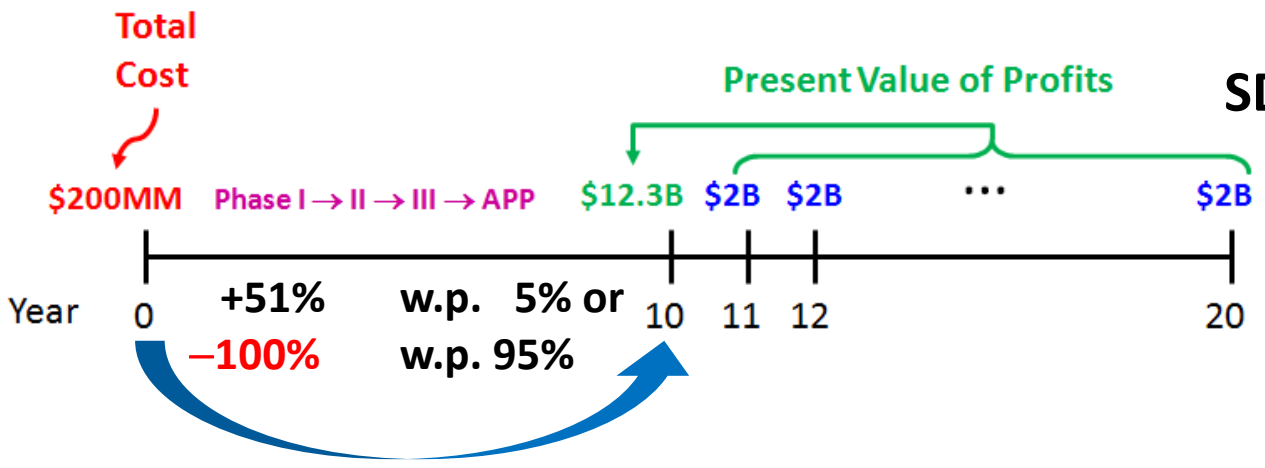
Distribution	
10th percentile	5.23%
25th percentile	6.60%
Median	8.00%
75th percentile	9.20%
90th percentile	10.00%

Source: A. Damodaran (2016)

Risk and Reward

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:

$$\begin{aligned} \mathrm{E}[R] &= 11.9\% \\ \mathrm{SD}[R] &= 423.5\%/\sqrt{150} = 34.6\% \end{aligned}$$

- But can we raise $30B??
- It depends on the portfolio's risk/reward profile (correlations?)

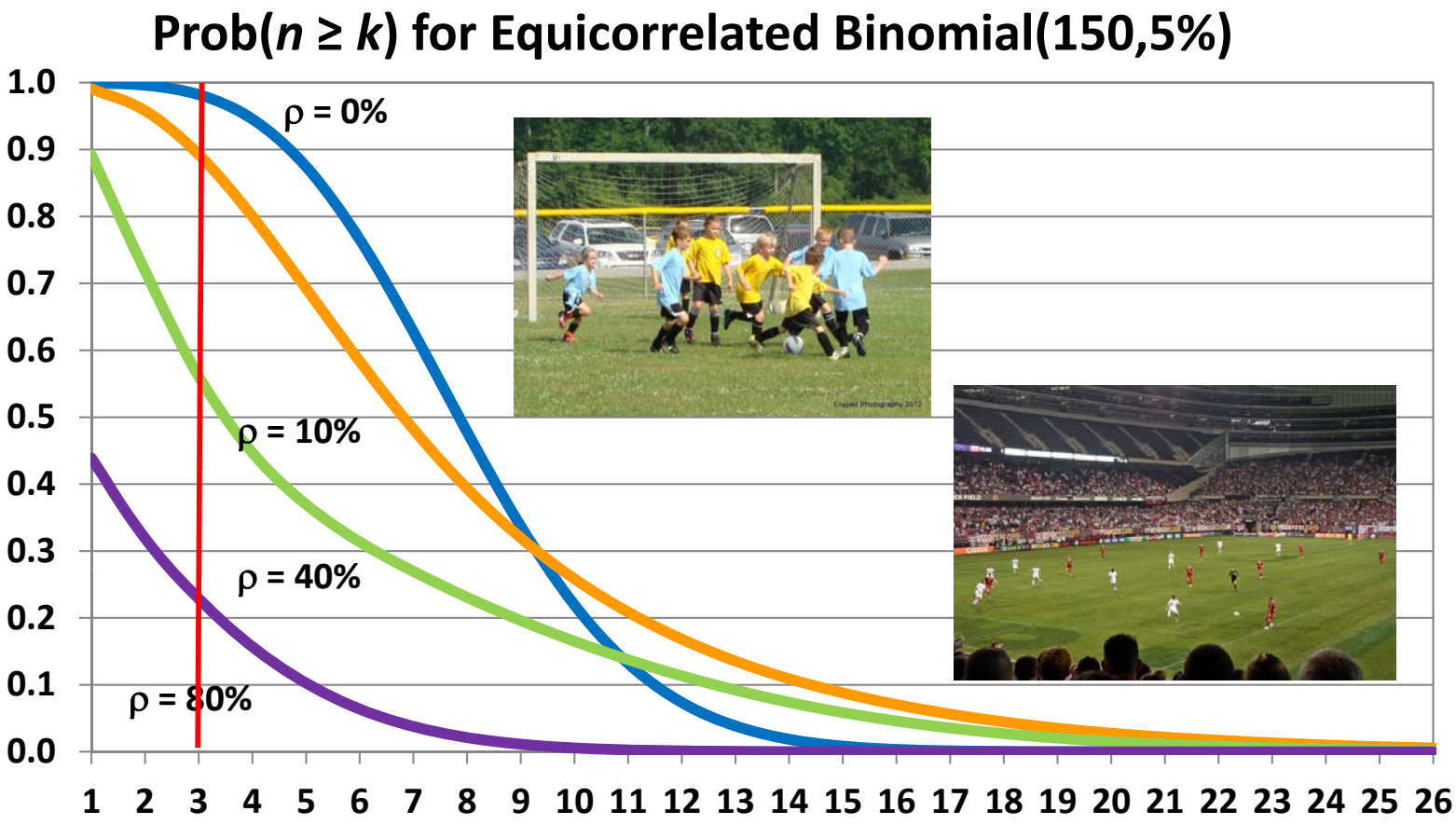
Financial Engineering Can Help

What If We Invest In 150 Programs Simultaneously?:

- With reduced risk, debt-financing is feasible!

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

Financial Engineering Can Help

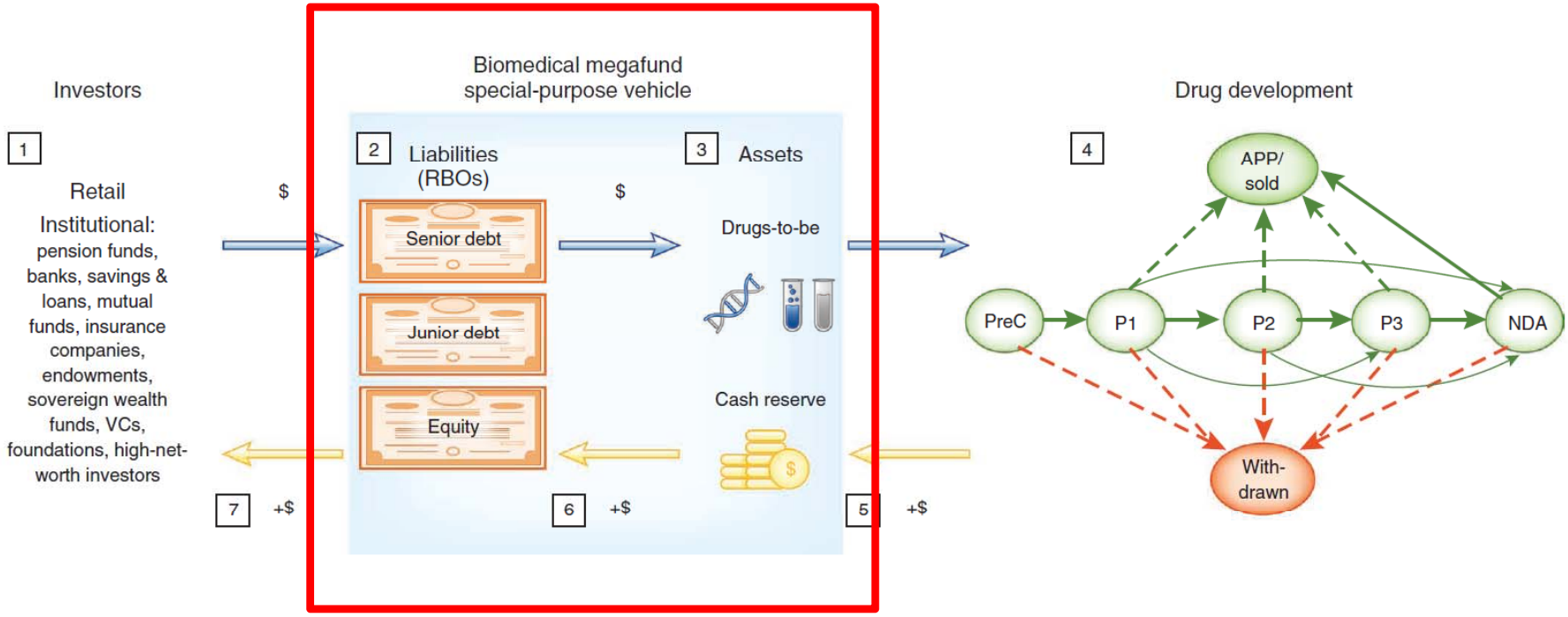


Research

Overview

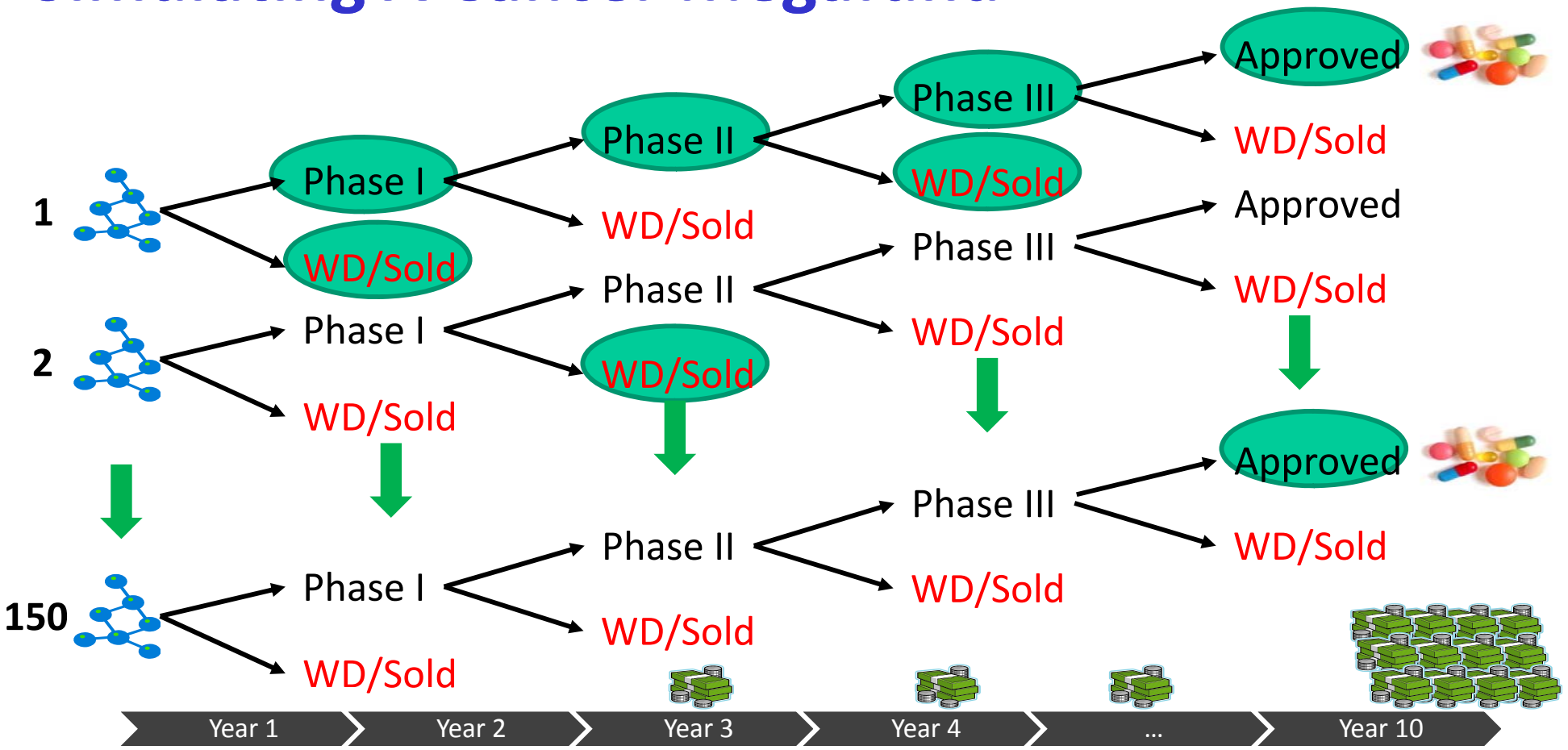
- Cancer: Fernandez, Stein, Lo (NBT, 2012)
- Guarantees: Fagnan, Stein, Fernandez, Lo (AER, 2013)
- Orphan drugs: Fagnan, Gromatzky, Stein, Lo (DDT, 2014)
- Alzheimers: Lo, Ho, Cummings, Kosik (STM, 2014)
- NCATS: Fagnan, Yang, McKew, Lo (STM, 2015)
- Dynamic leverage: Montazerhodjat, Frishkopf, Lo (DDT, 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

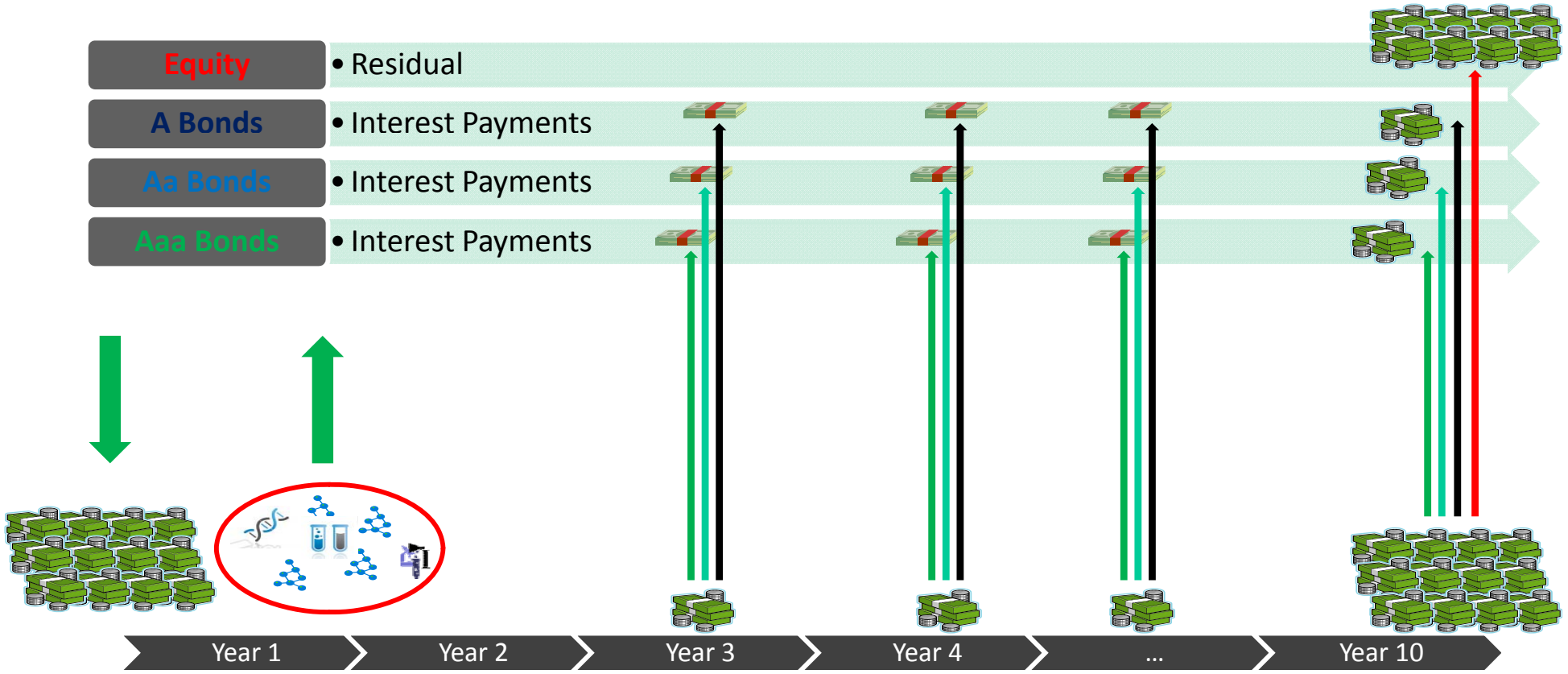


Simulating A Cancer Megafund

BFI



Simulating A Cancer Megafund



Fernandez, Stein, Lo (2012)

Simulate Historical Investment Performance

- Cost assumptions:
  - DiMasi, Hansen, Grabowski (2004), Adams & Brantner (2006), DiMasi & Grabowski (2007), Paul *et al*. (2010)
- 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 $\Rightarrow$ 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)

Fernandez, Stein, Lo (2012)

Stage	Total	in %
Approved:	38	5%
Discontinued (NDA)	2	0%
Discontinued (Phase I)	174	24%
Discontinued (Phase II)	171	23%
Discontinued (Phase III)	30	4%
Still in process as of end compilation period:		
In NDA	4	1%
In Phase I	17	2%
In Phase II	221	30%
In Phase III	76	10%
Total	733	100%

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

$$\mathcal{P} = \begin{array}{l} \\ \text{Preclinical}_t \\ \text{Phase I}_t \\ \text{Phase II}_t \\ \text{Phase III}_t \\ \text{NDA}_t \\ \text{Approved}_t \\ \text{Withdrawn}_t \end{array} \begin{pmatrix} \text{Preclinical}_{t+1} & \text{Phase I}_{t+1} & \text{Phase II}_{t+1} & \text{Phase III}_{t+1} & \text{NDA}_{t+1} & \text{Approved}_{t+1} & \text{Withdrawn}_{t+1} \\ 50.0 & 34.5 & 0.0 & 0.0 & 0.0 & 0.0 & 15.5 \\ 0.0 & 80.8 & 13.3 & 0.5 & 0.0 & 0.0 & 5.3 \\ 0.0 & 0.0 & 84.5 & 6.7 & 0.3 & 0.1 & 8.5 \\ 0.0 & 0.0 & 0.0 & 84.8 & 6.8 & 2.1 & 6.3 \\ 0.0 & 0.0 & 0.0 & 0.0 & 56.7 & 41.2 & 2.2 \\ 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 100.0 & 0.0 \\ 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 100.0 \end{pmatrix}$$

Source	Time Period	Number of Compounds	Preclinical to Phase I	Phase I to Phase II	Phase II to Phase III	Phase III to NDA	NDA to Approved
Megafund*	1990–2010	733	69.0%	72.4%	45.2%	58.6%	95.2%
Natanson*	1988–May 2010	164	—	72.6%	40.3%	66.7%	90.6%
Reichert et al.*	1990–2006	920	—	78.0%	43.0%	52.0%	89.0%
Walker et al.*	1995–2007	974	—	77.0%	44.0%	52.0%	—
Dimasi et al.	1993–2002	838	—	76.8%	59.4%	57.1%	—
Paul et al.	15 years	—	69.0%	54.0%	34.0%	70.0%	91.0%

*These probabilities are calculated only for cancer related compounds.

Table 5: Comparison of cancer compound transition probability by development phase.

Fernandez, Stein, Lo (2012)

Table 4 Performance summary statistics of the biomedical megafund simulations

	Simulation A		Simulation B	
Variable or summary statistic	All equity	Research-backed obligations	All equity	Research-backed obligations
Number of compounds				
Preclinical	50	100	—	—
Phase 1	50	100	—	—
Phase 2	—	—	40	100
Phase 3	—	—	—	—
Research impact				
Number of compounds to reach phase 2	52.8	101.7	—	—
Number of compounds sold in phase 3 and NDA	0.9	2.3	6.0	21.3
Number of compounds sold once APP	0.6	1.0	5.1	7.6
Liabilities				
Capital ($ millions)	2,500	5,000	6,000	15,000
Senior tranche ($ millions)	—	1,250	—	6,000
Junior tranche ($ millions)	—	1,250	—	3,000
Equity tranche ($ millions)	2,500	2,500	6,000	6,000
Equity tranche performance				
Average annualized return on equity	7.2%	8.9%	7.2%	11.4%
Prob. (return on equity < 0)	17%	20%	17%	10%
Prob. (return on equity > 5%)	61%	68%	63%	79%
Prob. (return on equity > 15%)	15%	35%	14%	40%
Debt tranches performance				
Senior tranche: default prob., expected loss (bp)	—	1, <1	—	6, <1
Junior tranche: default prob., expected loss (bp)	—	87, 27	—	60, 30

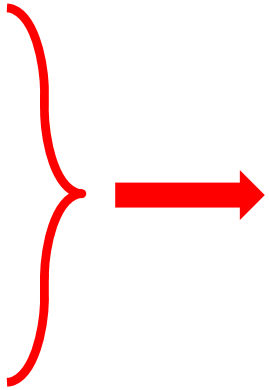
bp, units of basis points or 0.01%; prob., probability.

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

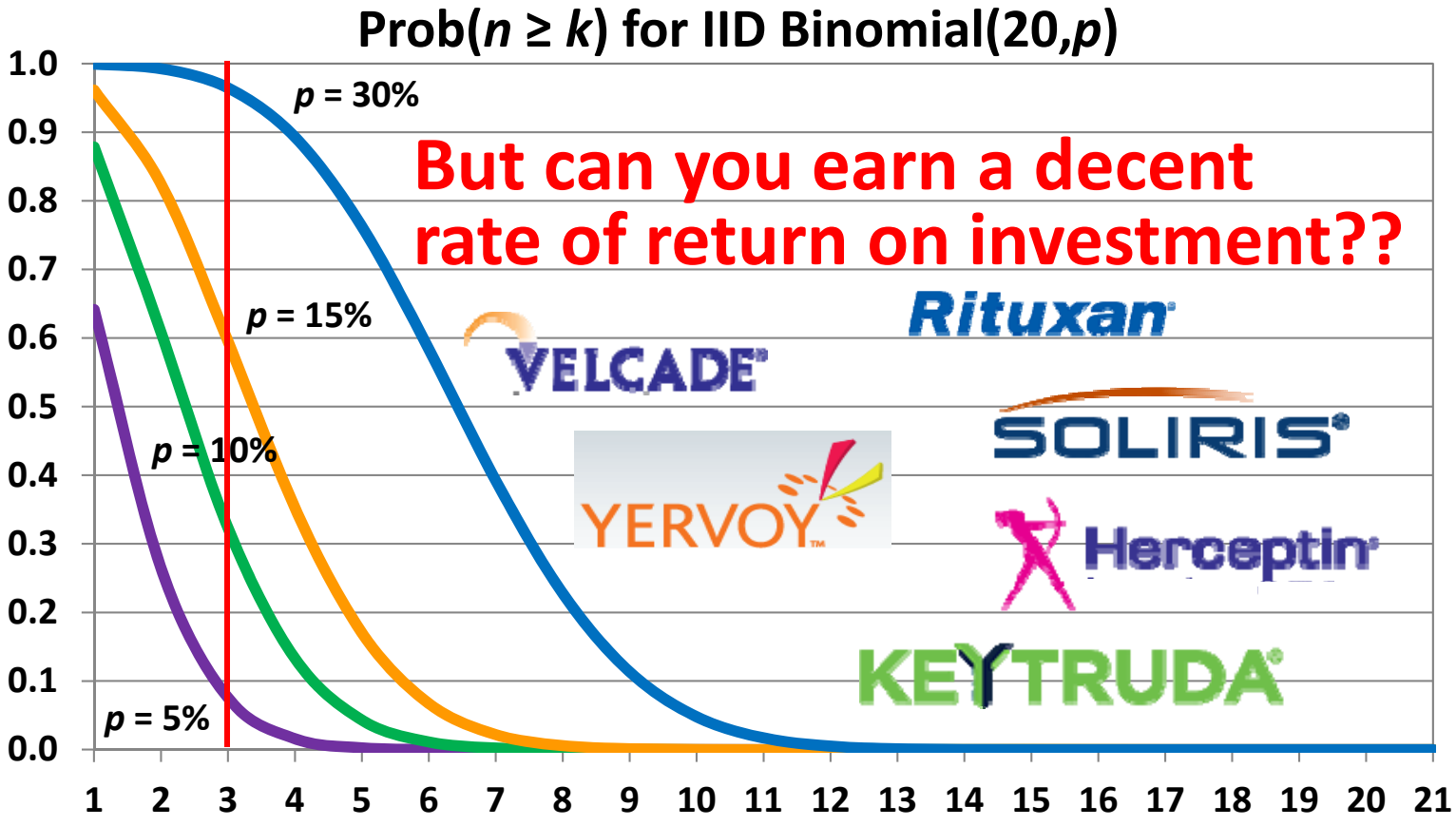
Finance and Biomedical Experts Must Collaborate

- 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



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

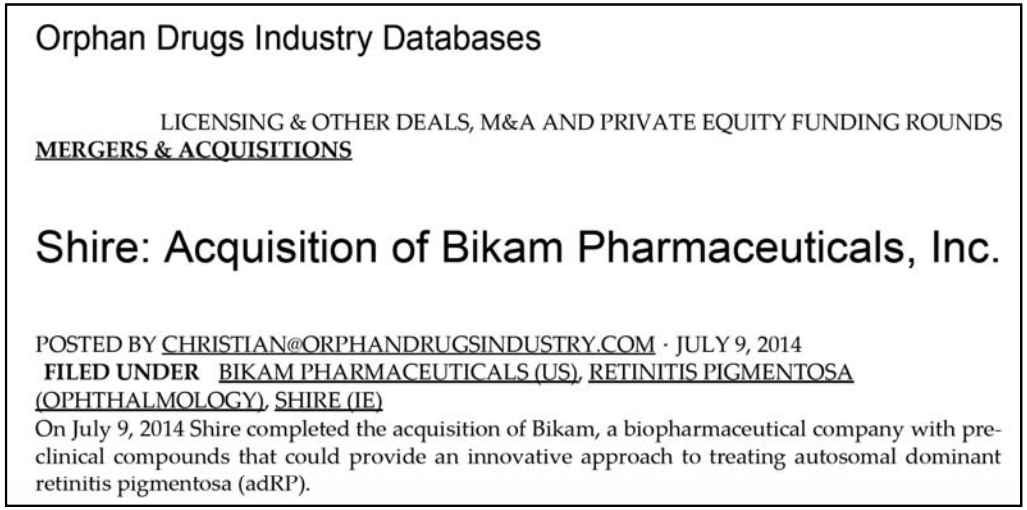
NIH National Institutes of Health
Turning Discovery Into Health

Embargoed for Release: Wednesday, July 9, 2014 9 a.m. EDT

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

LICENSING & OTHER DEALS, M&A AND PRIVATE EQUITY FUNDING ROUNDS
MERGERS & ACQUISITIONS

Shire: Acquisition of Bikam Pharmaceuticals, Inc.

POSTED BY CHRISTIAN@ORPHANDRUGSINDUSTRY.COM · JULY 9, 2014
FILED UNDER BIKAM PHARMACEUTICALS (US), RETINITIS PIGMENTOSA (OPHTHALMOLOGY), SHIRE (IE)
On July 9, 2014 Shire completed the acquisition of Bikam, a biopharmaceutical company with pre-clinical compounds that could provide an innovative approach to treating autosomal dominant retinitis pigmentosa (adRP).

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 $\leq$ 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
- 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?

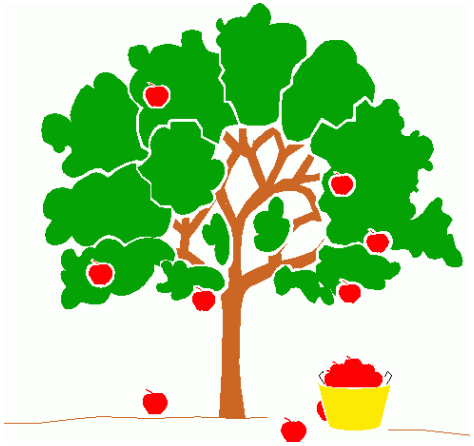
How Many New AD Drugs Were Approved In 2012?

⋮

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

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

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?

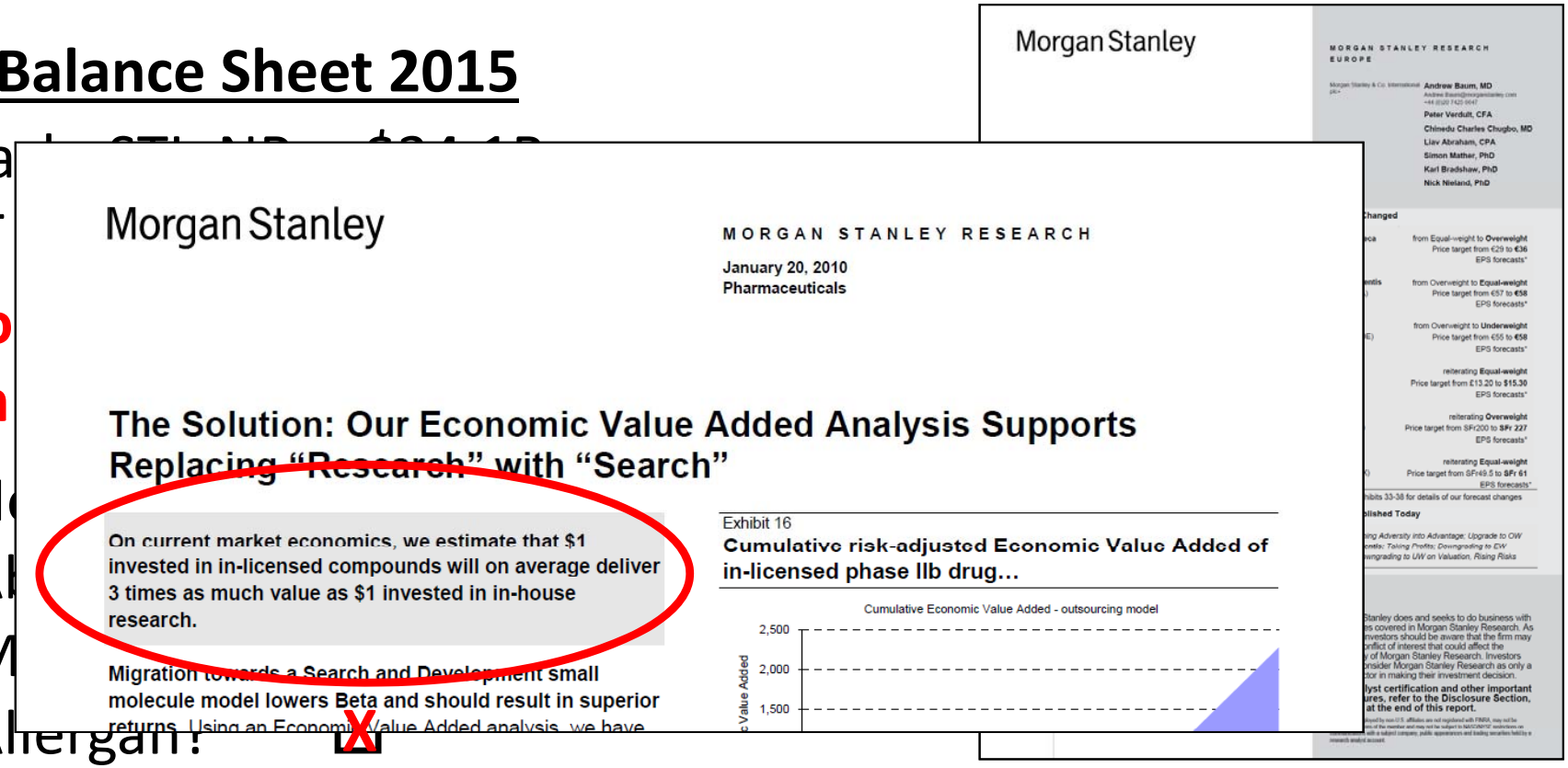
BFI

Pfizer Balance Sheet 2015

- ✓ Ca
- ✓ LT

Why do
cash on

- H
- Al
- M
- Allergan? [X]



Isn't Pharma Already Doing This?

Pharma Job Cuts, 2008–2013

Company	Job Cuts

FiercePharma

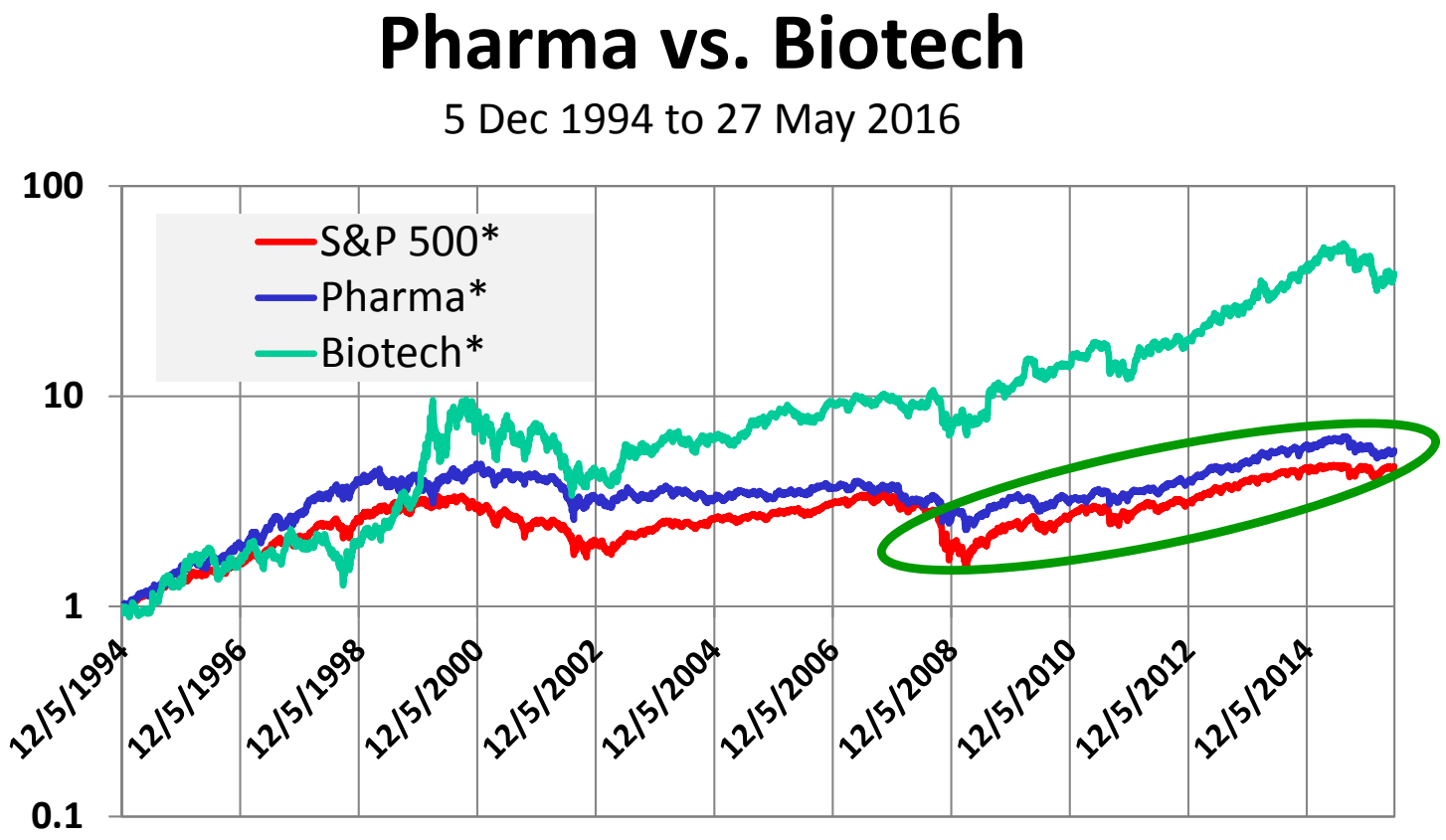
Published on FiercePharma (http://www.fiercepharma.com)

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?

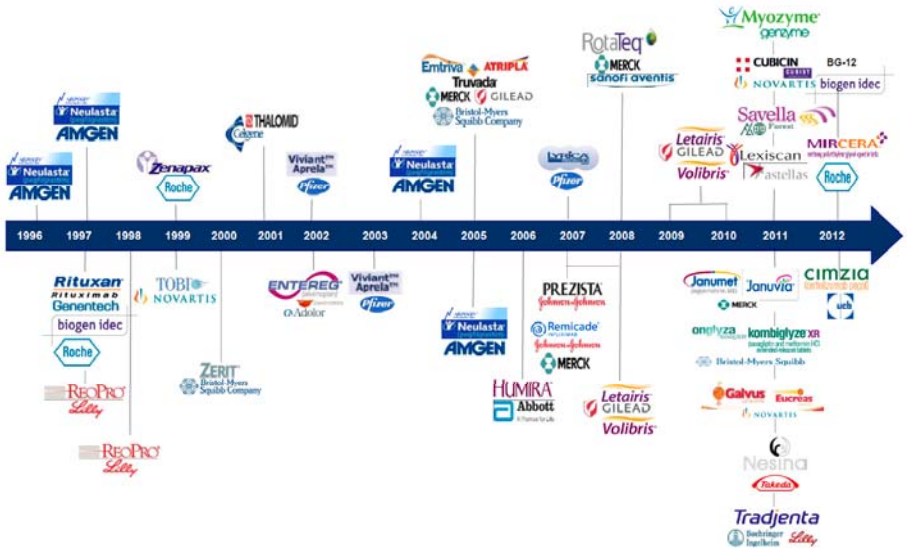


FAQs:
Are There Any Existing Examples of Megafunds?

Existing Business Models That Are Close

Drug Royalty Investment Companies Already Exist

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

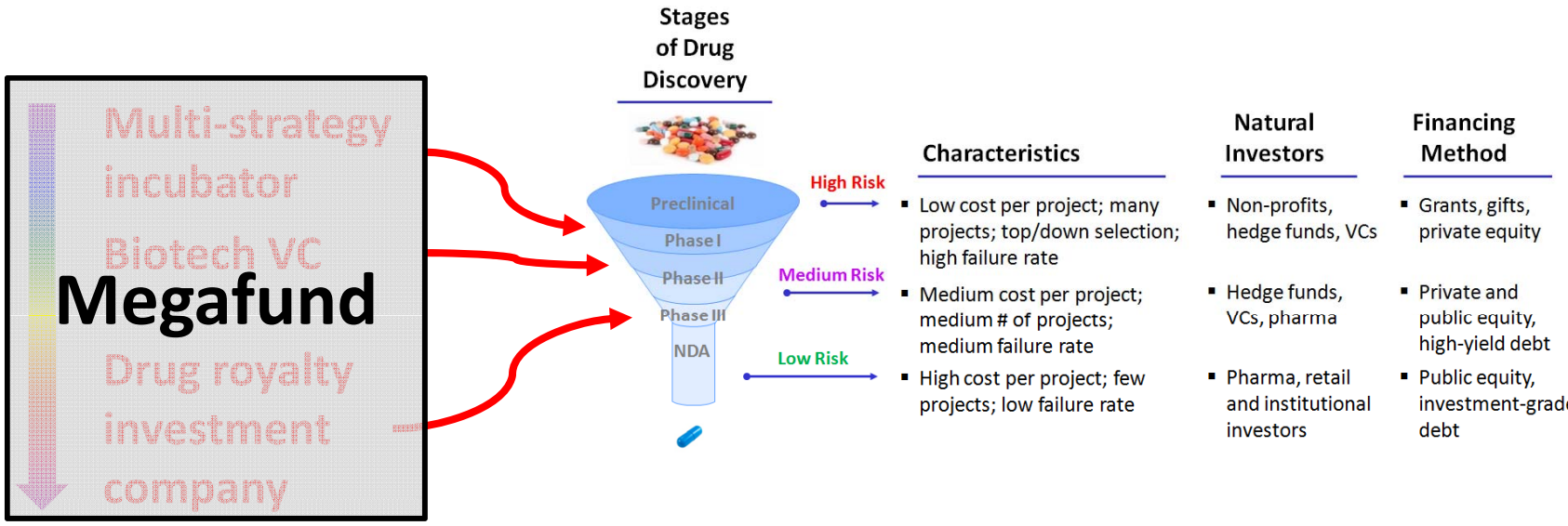


	Product	Company	Sales ($ in millions) 2010	2016
1	Humira	Abbott	$6,742	$9,696
2	Avastin	Roche	6,214	8,731
3	Rituxan	Roche, biogen idec	6,113	7,684
4	Crestor	AstraZeneca	6,106	7,518
5	Enbrel	AMGEN, Pfizer	7,257	7,190
6	Seretide/Advair	GSK	8,067	6,953
7	Januvia	MERCK	3,503	6,800
8	Herceptin	Roche	5,221	6,466
9	Remicade	Johnson&Johnson, MERCK	6,520	6,107
10	Prevnar	Pfizer	2,416	5,805
11	Lantus	sanofi aventis	4,658	5,585
12	Revlimid	Celgene	2,469	5,550
13	Incivek	Vertex, Johnson&Johnson	...	4,226
14	Lyrica	Pfizer	3,077	3,998
15	Xarelto	Bayer, Johnson&Johnson	100	3,991
16	Atripla	GILEAD, Bristol-Myers Squibb Company	2,927	3,687
17	NovoRapid	Novo Nordisk	2,120	3,672
18	Neulasta	AMGEN	3,558	3,442
19	Xgeva/Prolia	AMGEN, GSK	41	3,361
20	Truvada	GILEAD	2,746	3,345

- 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
  - Corporate bonds: $8.2T ($1.5T
  - Mortgage-related: $8.7T ($1.7
  - Asset-backed securities: $1.3T
  - Money-market funds: $2.8T
- Norwegian sovereign wealth
- CalPERS: $304B
- Target return of 126 public funds (2012): ~~8%~~ 7.5%

6/15/2014 MIT Borrows for the Long Run With a $750-Million 'Century Bond' - Administration - The Chronicle of Higher Education

THE CHRONICLE OF HIGHER EDUCATION
Administration

May 12, 2011

MIT Borrows for the Long Run With a $750-Million 'Century Bond'

By Goldie Blumenstyk

The Massachusetts Institute of Technology this week borrowed $750-million by issuing taxable bonds that it plans to repay not over 30 years, the usual term for capital borrowing by universities, but over 100 years.

In 2015, Total U.S. VC AUM Was?

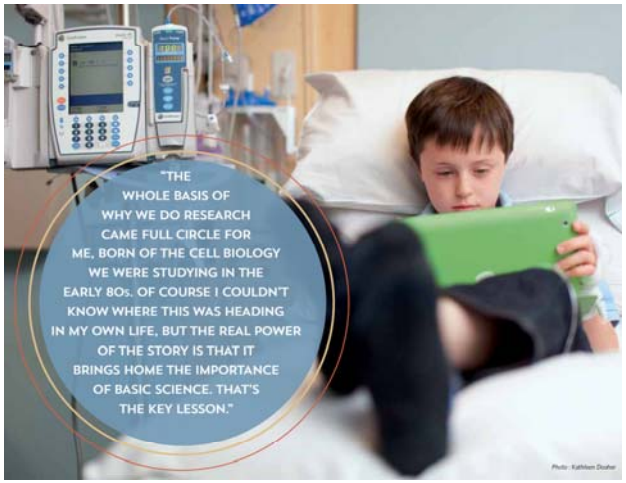
Is This Realistic?

With Some Imagination, Megafunds Are Viable!

- Imagine creating a $30B "Cure Cancer" megafund
- Imagine creating an advisory board of experts:
  - David Baltimore, Francis Collins, Susan Desmond-Hellmann, Lee Hood, Eric Lander, Bob Langer, Frank McCormick, Richard Scheller
  - 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**)

Thank You!

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