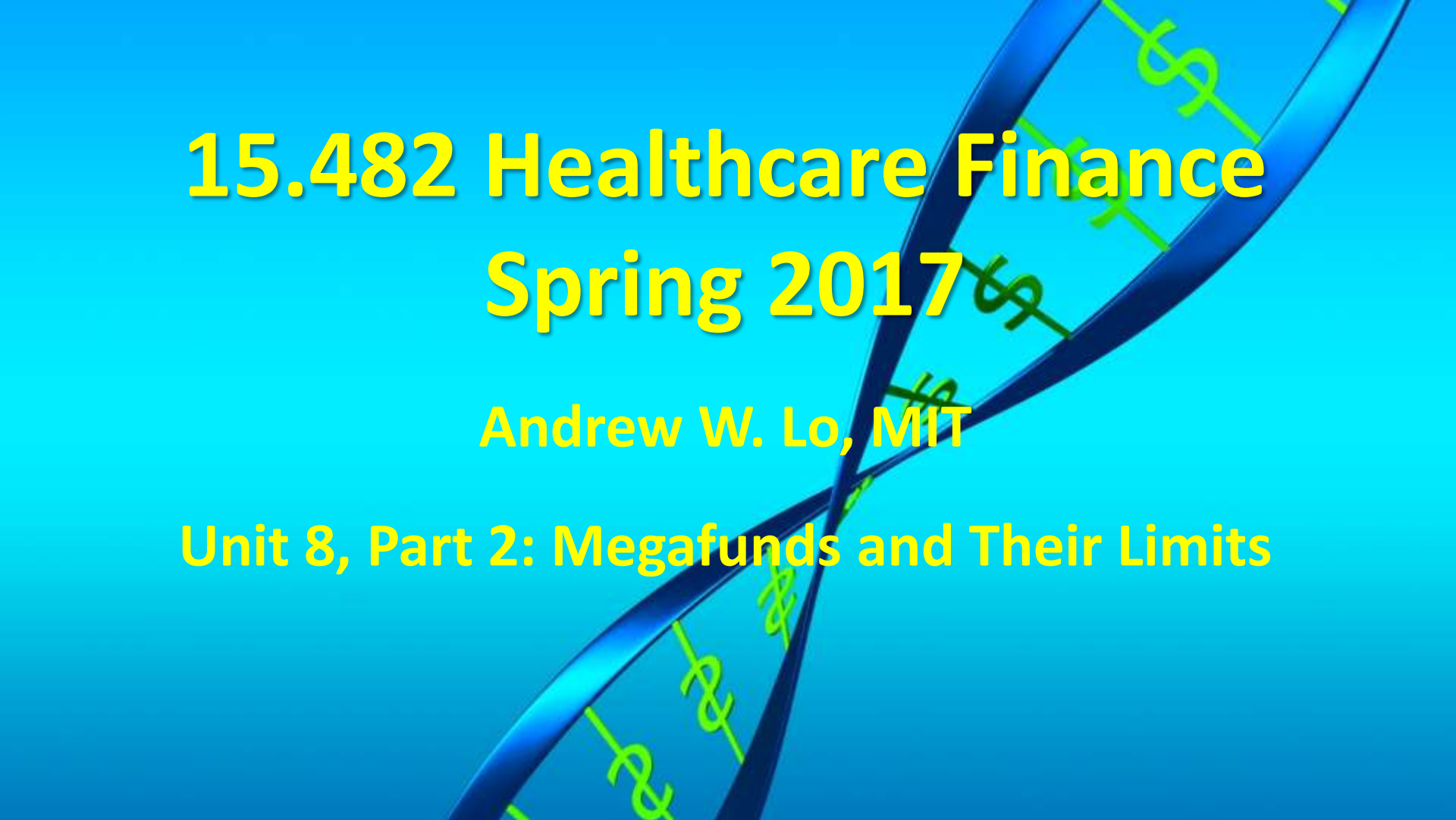
15.482 Healthcare Finance
Spring 2017

Andrew W. Lo, MIT

Unit 8, Part 2: Megafunds and Their Limits

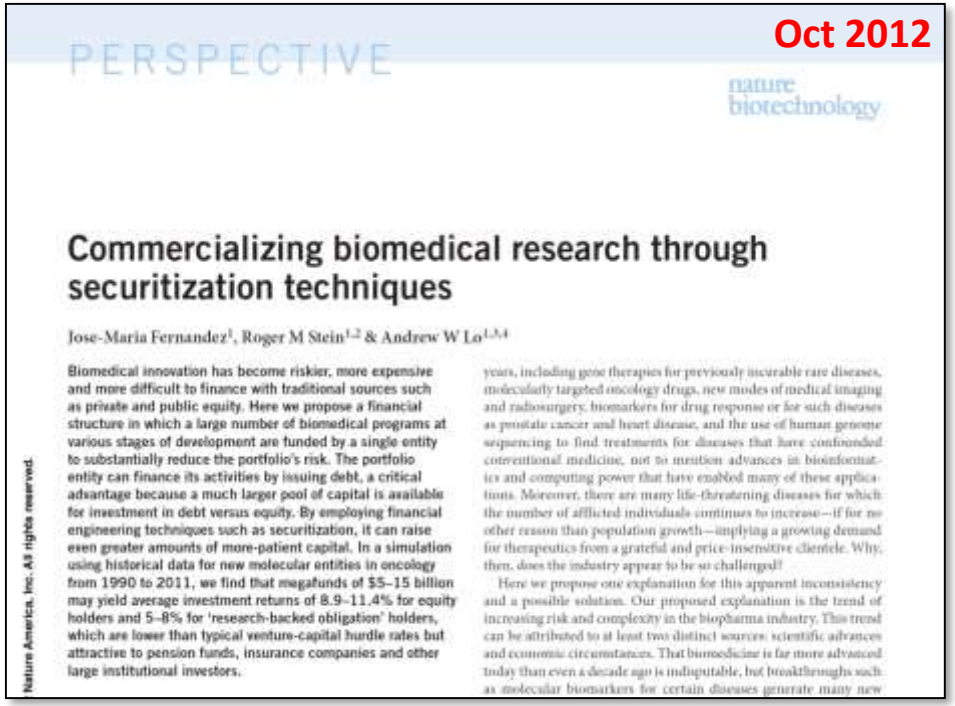


Unit Outline

- The Financial Crisis and Securitization
- Megafunds
- Sizing Megafunds and Modeling Correlation
- When Megafunds Fail

Megafunds

Megafunds



PERSPECTIVE

Oct 2012

nature biotechnology

Commercializing biomedical research through securitization techniques

Jose-Maria Fernandez[1], Roger M Stein[1,2] & Andrew W Lo[1,3,4]

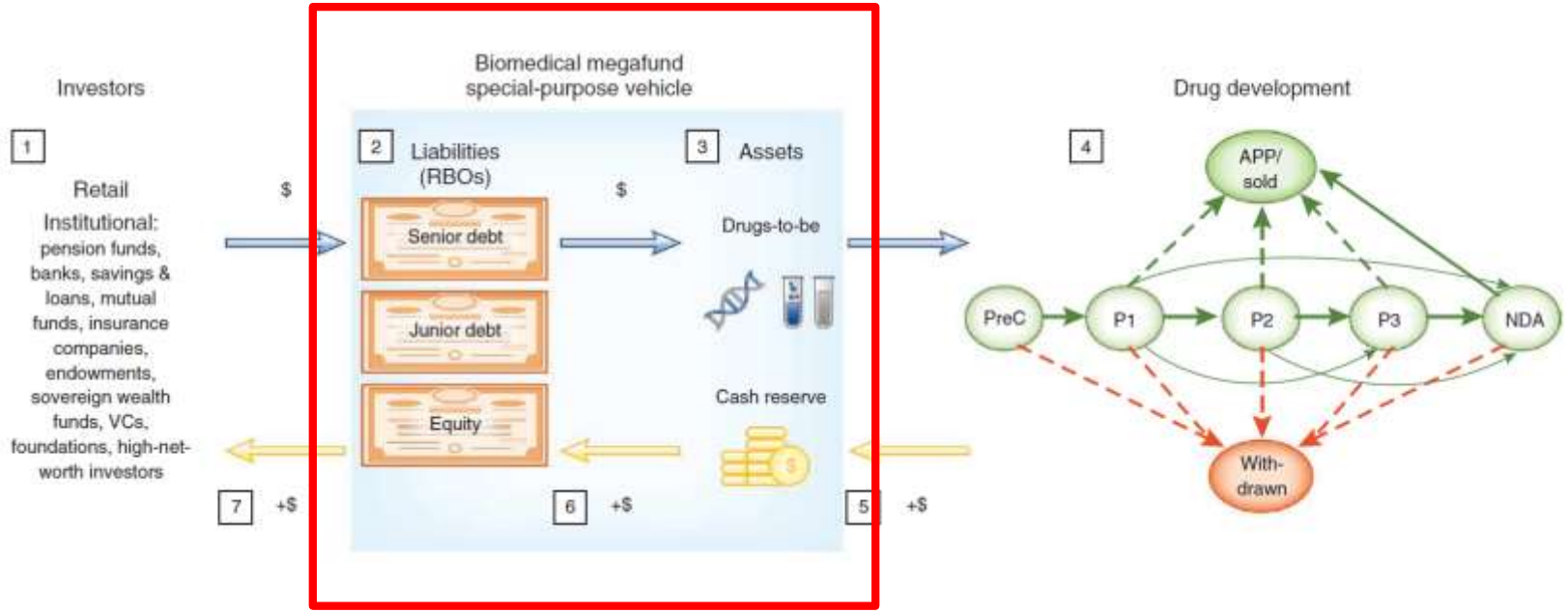
Biomedical innovation has become riskier, more expensive and more difficult to finance with traditional sources such as private and public equity. Here we propose a financial structure in which a large number of biomedical programs at various stages of development are funded by a single entity to substantially reduce the portfolio's risk. The portfolio entity can finance its activities by issuing debt, a critical advantage because a much larger pool of capital is available for investment in debt versus equity. By employing financial engineering techniques such as securitization, it can raise even greater amounts of more-patient capital. In a simulation using historical data for new molecular entities in oncology from 1990 to 2011, we find that megafunds of $5–15 billion may yield average investment returns of 8.9–11.4% for equity holders and 5–8% for 'research-backed obligation' holders, which are lower than typical venture-capital hurdle rates but attractive to pension funds, insurance companies and other large institutional investors.

years, including gene therapies for previously incurable rare diseases, molecularly targeted oncology drugs, new modes of medical imaging and radiosurgery, biomarkers for drug response or for such diseases as prostate cancer and heart disease, and the use of human genome sequencing to find treatments for diseases that have confounded conventional medicine, not to mention advances in bioinformatics and computing power that have enabled many of these applications. Moreover, there are many life-threatening diseases for which the number of afflicted individuals continues to increase—if for no other reason than population growth—implying a growing demand for therapeutics from a grateful and price-insensitive clientele. Why, then, does the industry appear to be so challenged?

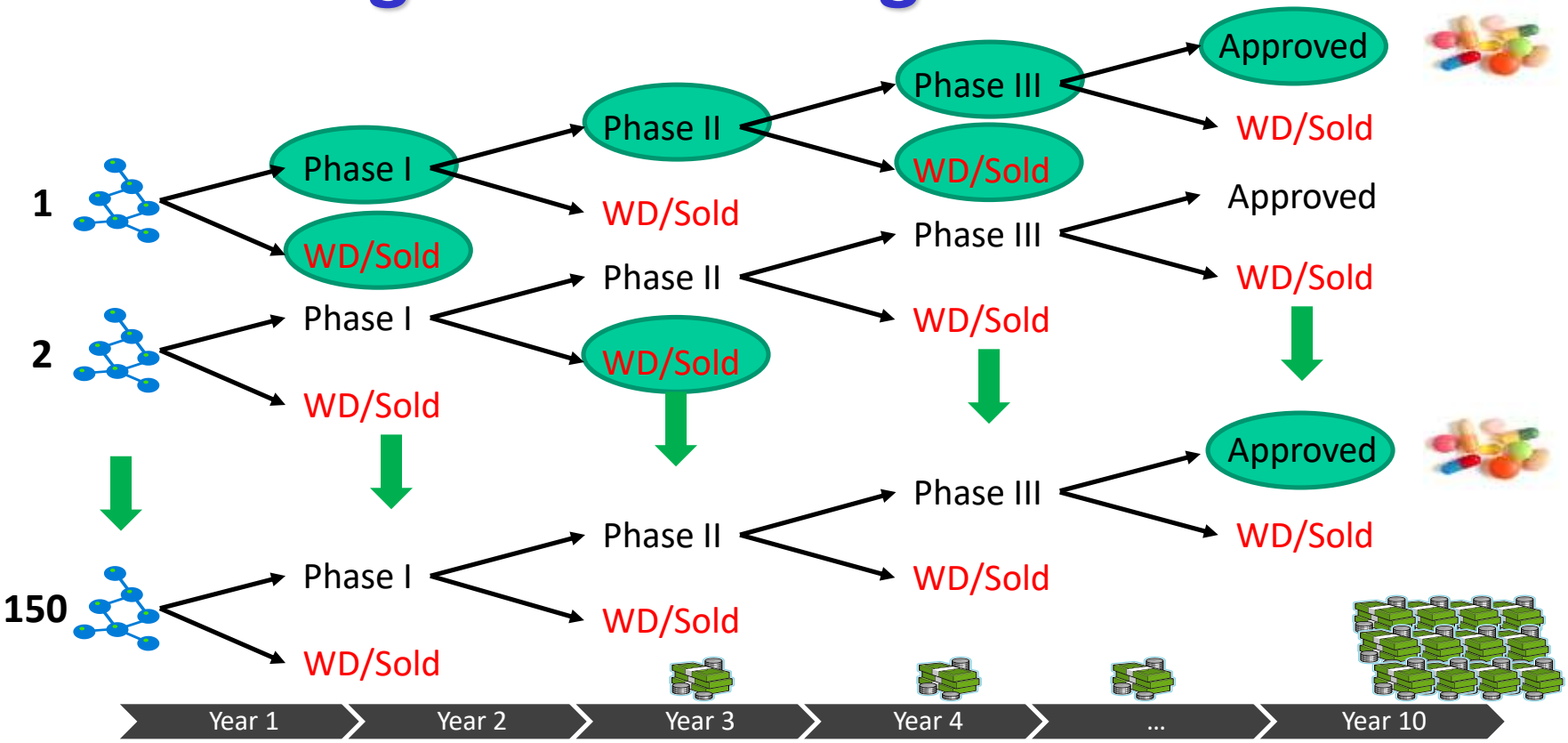
Here we propose one explanation for this apparent inconsistency and a possible solution. Our proposed explanation is the trend of increasing risk and complexity in the biopharma industry. This trend can be attributed to at least two distinct sources: scientific advances and economic circumstances. That biomedicine is far more advanced today than even a decade ago is indisputable, but breakthroughs such as molecular biomarkers for certain diseases generate many new

- Can we use these same techniques to fund cancer drug development?
- **Should** we use these same techniques…?

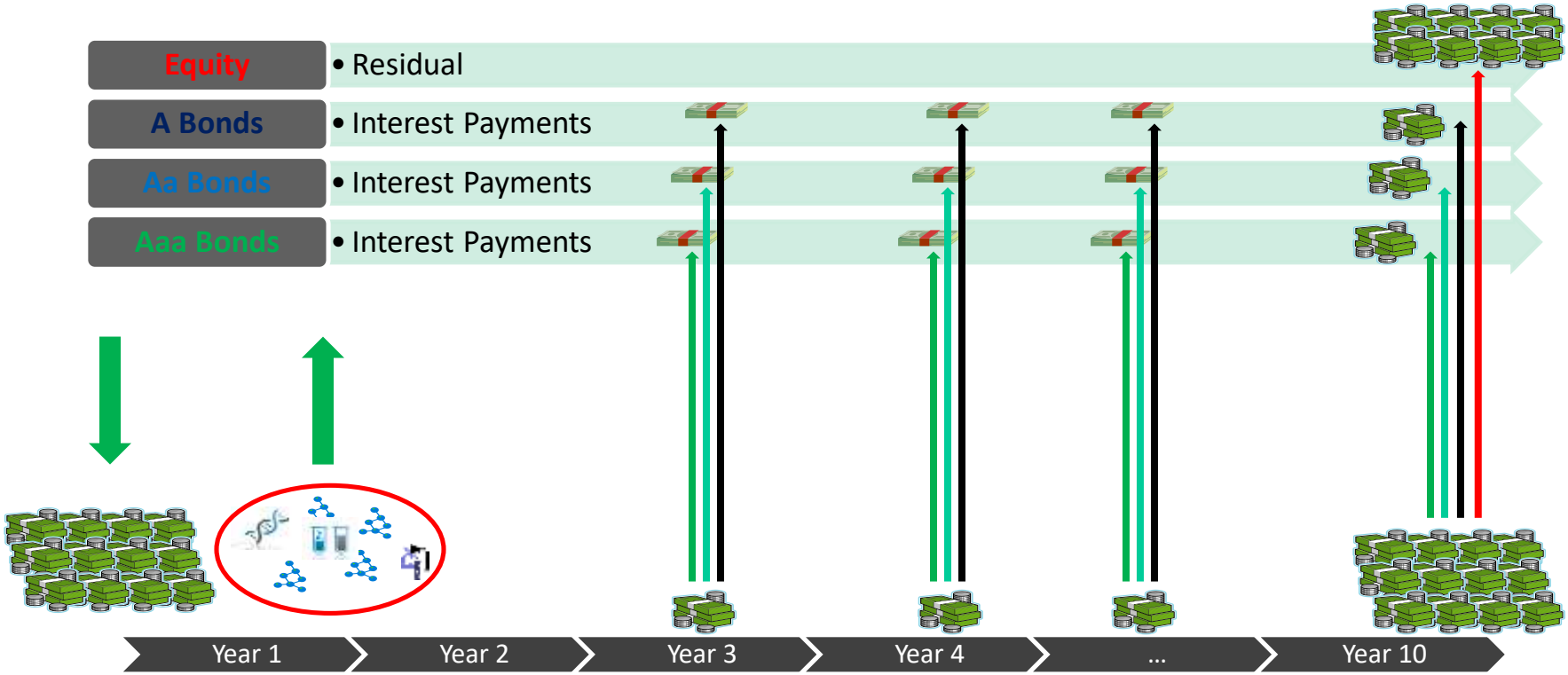
Megafund Structure



Simulating A Cancer Megafund



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

Variable or summary statistic	Simulation A		Simulation B	
	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%	[illegible]	17%	[illegible]
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.

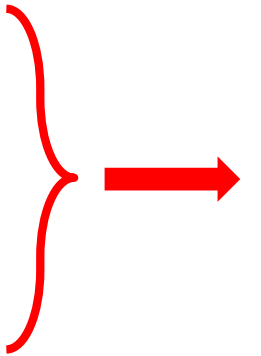
Source: Fernandez, Stein, Lo (2012)

Sizing Megafunds and Modeling Correlation

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



Fernandez, Stein, Lo, (NBT 2012)

- Sourcecode available in R and Matlab

Finance and Biomedical Experts Must Collaborate

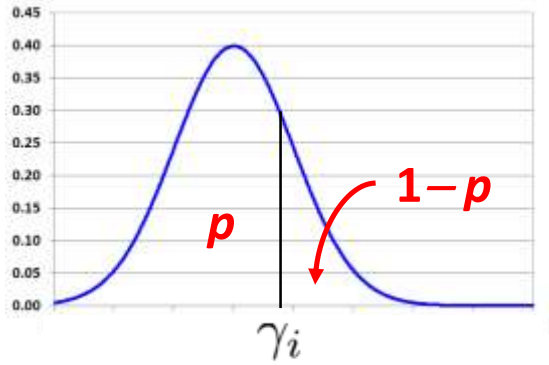
- Cultures are very different
- Value created in being able to bridge this gap

Modeling Correlations Is Key

Denote Success/Failure of Project *i* By $I_i = \{0,1\}$

- Payoff is $(I_1 + I_2 + \cdots + I_n) \times$ rNPV
- What is $\Pr(I_1 + I_2 + \cdots + I_n = k)$? For IID:

$$\Pr\left(\sum_{i=1}^{n} I_i = k\right) = \sum_{j=0}^{k} \binom{n}{j} p^j (1-p)^{n-j}$$



- How does correlation effect these probabilities?

$$I_i = \begin{cases} 1 & \text{if } X_i > \gamma_i \\ 0 & \text{if } X_i \le \gamma_i \end{cases}, \quad X_i \sim \mathcal{N}(\mu_i, \sigma_i^2) \qquad \begin{bmatrix} X_1 \\ X_2 \\ \vdots \\ X_n \end{bmatrix} \sim \mathcal{N}(\mu, \Sigma)$$

What is this?

Modeling Correlations Is Key

$$\Sigma = \begin{bmatrix} \sigma_1^2 & \sigma_{12} & \cdots & \sigma_{1n} \\ \sigma_{21} & \sigma_2^2 & \cdots & \sigma_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ \sigma_{n1} & \sigma_{n2} & \cdots & \sigma_n^2 \end{bmatrix}$$

$$= \begin{bmatrix} \sigma_1 & 0 & \cdots & 0 \\ 0 & \sigma_2 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \sigma_n \end{bmatrix} \begin{bmatrix} 1 & \rho_{12} & \cdots & \rho_{1n} \\ \rho_{21} & 1 & \cdots & \rho_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ \rho_{n1} & \rho_{n2} & \cdots & 1 \end{bmatrix} \begin{bmatrix} \sigma_1 & 0 & \cdots & 0 \\ 0 & \sigma_2 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \sigma_n \end{bmatrix}$$

- If project A fails, does that change your mind about project B's prospects?

Orphan Diseases

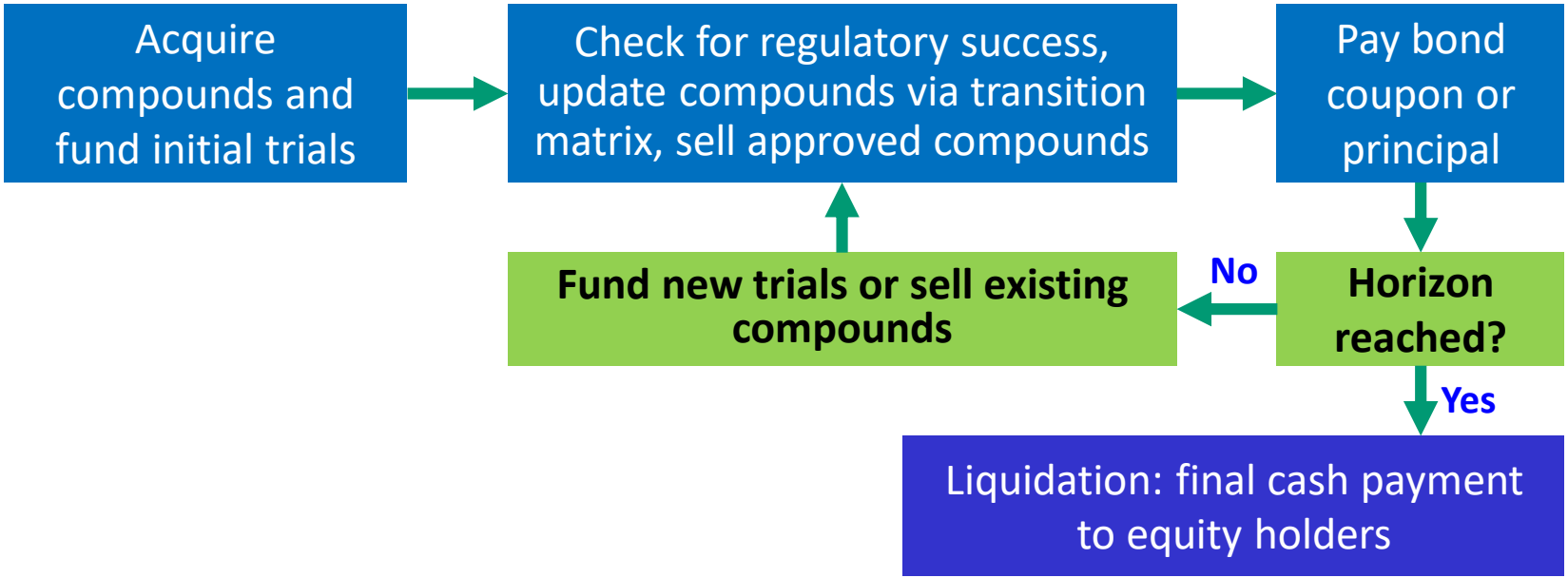
- Often due to mutation in a single gene, e.g, Huntington's, cystic fibrosis, Gaucher, paroxysmal nocturnal hemoglobinuria
- 25 million Americans suffer from all rare diseases
- Smaller population, urgent need, higher prices, lower development costs, higher success rates (20%), faster time to approval (3–7 years)
- $400–$500 million of capital and 10–20 projects sufficient
- **Lack of correlation is critical!** (see Fagnan, Stein, Gromatzky, Fernandez, Lo, 2014, DDT)

Fagnan, Yang, McKew, Lo (2015)

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)*



*This is a simplified flowchart intended to highlight the overall structure of the simulation—please see the MATLAB code for the details.

Fagnan, Yang, McKew, Lo (2015)

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%	[illegible]	N/A
Average MIRR (0% financing)	18.3%	21.6%	22.7%
Average annualized ROE	11.6%	[illegible]	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

Fagnan, Yang, McKew, Lo (2015)

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 a
biopharmaceutical company

Potential treatment targets sickle cell disease

A drug candidate developed by researchers at the NIH's National Center for
(NCATS) and its collaborators to treat sickle cell disease has been acquired
business. The drug candidate, Aes-103, is the first specifically developed to
mechanism of sickle cell disease. Baxter now will advance the clinical devel
regulatory approval and commercialization.

Orphan Drugs Industry Databases

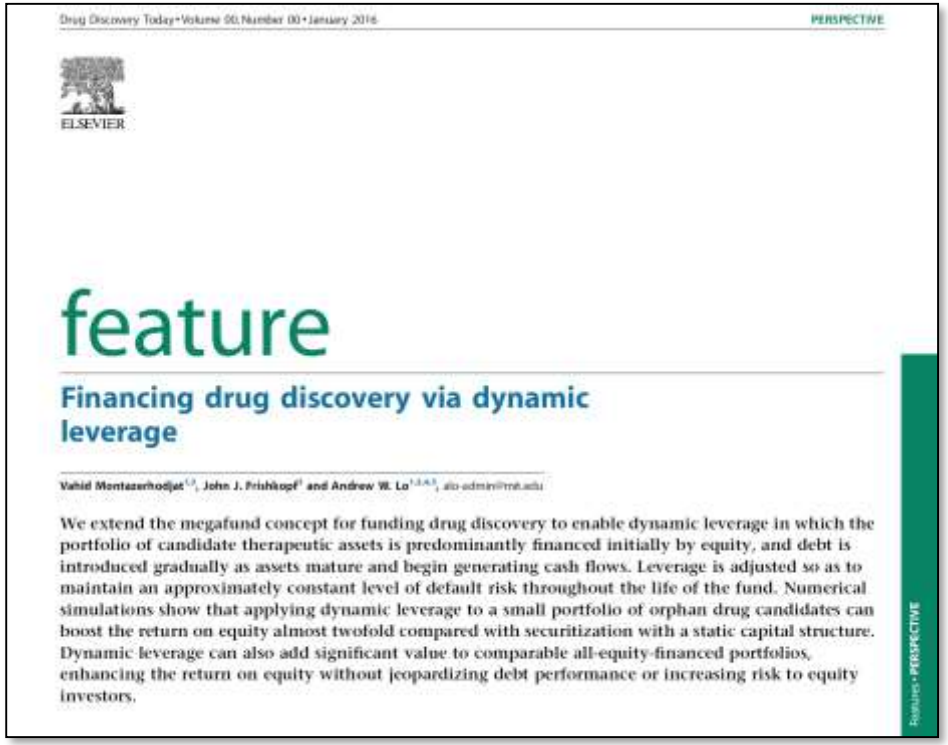
LICENSING & OTHER DEALS, M&A AND PRIVATE EQUITY FUNDING ROUNDS
MERGERS & ACQUISITIONS

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

What About Early Stage Assets?



Drug Discovery Today • Volume 00, Number 00 • January 2016 PERSPECTIVE

ELSEVIER

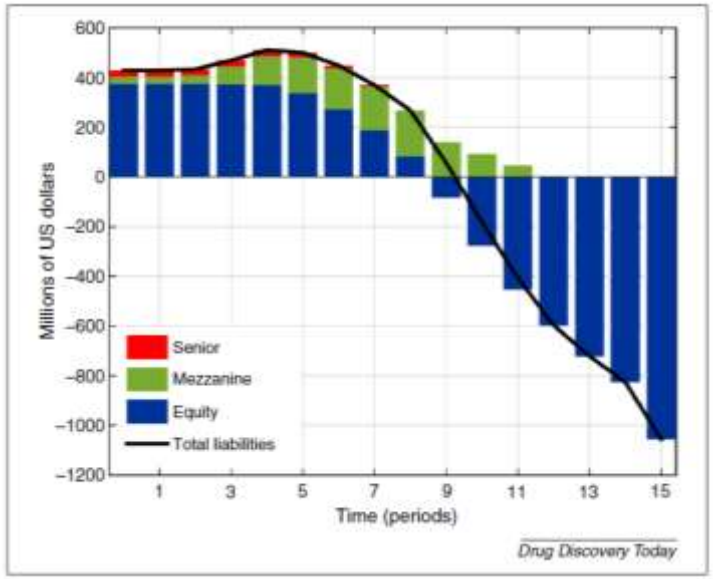
feature

Financing drug discovery via dynamic leverage

Vahid Montazerhodjat[1,2], John J. Prishkop[3] and Andrew W. Lo[1,2,4,5], alo-admin@mit.edu

We extend the megafund concept for funding drug discovery to enable dynamic leverage in which the portfolio of candidate therapeutic assets is predominantly financed initially by equity, and debt is introduced gradually as assets mature and begin generating cash flows. Leverage is adjusted so as to maintain an approximately constant level of default risk throughout the life of the fund. Numerical simulations show that applying dynamic leverage to a small portfolio of orphan drug candidates can boost the return on equity almost twofold compared with securitization with a static capital structure. Dynamic leverage can also add significant value to comparable all-equity-financed portfolios, enhancing the return on equity without jeopardizing debt performance or increasing risk to equity investors.

Features • PERSPECTIVE



- Start off with mostly equity and increase leverage over time as cash flows increase

When Megafunds Fail

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…

Cummings *et al. Alzheimer's Research & Therapy* 2014, 6:37
http://alzres.com/content/6/4/37

2014

alzheimer's research

RESEARCH

Alzheimer's disease drug-development pipe
few candidates, frequent failures

Jeffrey L Cummings[1*], Travis Morstorf[2] and Kate Zhong[1]

Table 1 Overview of Alzheimer's disease clinical trials from clinicaltrials.gov

Year registered	Phase 1	Phase 2	Phase 3	Total
2002	0	2	3	5
2003	0	5	7	12
2004	1	9	4	14
2005	4	19	9	32
2006	5	14	6	25
2007	16	22	8	46
2008	25	27	9	61
2009	28	30	14	72
2010	16	24	11	51
2011	15	26	4	45
2012	14	28	8	50
Total	124	206	83	413

"The failure rate since 2002 (excluding agents currently in Phase 3) is 99.6%"

And Now The Bad News…

We Need Parallel Drug Discovery Efforts

- If a single project takes 13 years and has a 1% chance of success, how long is the average waiting time E[*T**] before the first success in a sequence of trials?

$$\mathrm{E}[T^*] \quad = \quad 13 \times \frac{1}{p} \quad = \quad 1{,}300 \text{ Years}$$

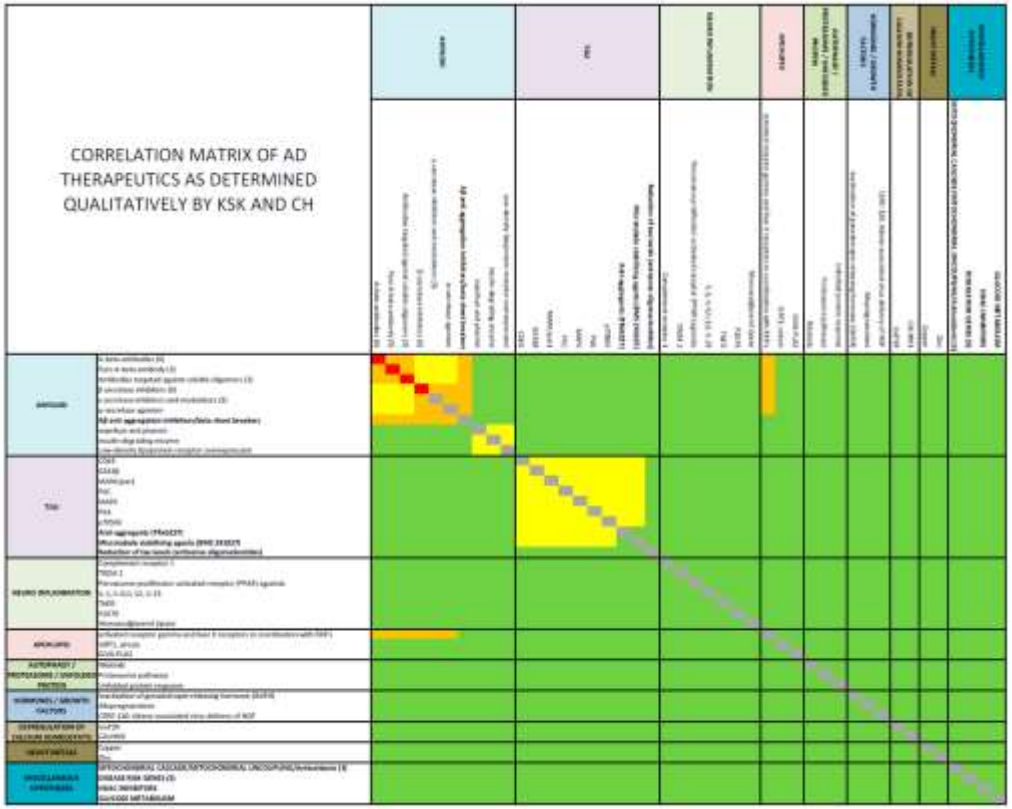
- Apart from diversification benefits, there are costs to waiting for success (in 2017, Medicare + Medicaid costs = **$175 billion**)

Lo, Ho, Cummings, Kosik (2014)

Projects	Degree of validation
AMYLOID	
Aβ Passive Immunotherapy	
A-beta antibodies (6)	high
Pyro A-beta antibodies (3)	high
Antibodies targeted against soluble oligomers (3)	high
Aβ Synthesis	
β secretase inhibitors (6)	medium
γ secretase inhibitors and modulators (3)	low
α-secretase agonism	low
Aβ anti aggregation inhibitors/beta sheet breakers	low
Aβ clearance	
neprilsyn and plasmin	low
insulin-degrading enzyme	low
Low-density lipoprotein receptor overexpression	low
TAU PATHWAY	
Phosphorlyation inhibitors	
CDK5	low
GSK3β	low
MARK/par1	low
PKC	low
MAPK	low
PKA	low
p70S6K	low
Anti-aggregants (TRx0237)	low
Microtubule stabilizing agents (BMS 241027)	low
Reduction of tau levels (Tau antibodies and antisense oligonucleotides)	low
APOE4 / LIPID METABOLISM	
activated receptor gamma and liver X receptors in coordination with RXR's	low
SIRT1, sirtuin	low
GIVA-PLA2	low

Projects	Degree of validation
NEUROINFLAMMATION	
Complement receptor 1	low
TREM 2	low
Peroxisome proliferator-activated receptor (PPAR) agonists	low
IL-1, IL-6,IL-12, IL-23	low
TNFR	low
P2X7R	low
Monoacylglycerol Lipase	low
AUTOPHAGY/PROTEASOME/UNFOLDED PROTEIN RESPONSE	
Nilotinib	low
Proteasome pathways	low
Unfolded protein response	low
HORMONES/GROWTH FACTORS	
Inactivation of gonadotropin-releasing hormone (GnRH)	low
Allopregnanolone	low
CERE-110: Adeno-associated virus delivery of NGF	low
DYSREGULATION OF CALCIUM HOMEOSTASIS	
InsP3R	low
CALHM1	low
HEAVY METALS	
Copper	low
Zinc	low
MITOCHONDRIAL CASCADE/MITOCHONDRIAL UNCOUPLING/Antioxidants (3)	low
DISEASE RISK GENES (3)	low
HDAC INHIBITORS	low
GLUCOSE METABOLISM	low

Lo, Ho, Cummings, Kosik (2014)



= 90% correlation

= 50% correlation

= 25% correlation

= 10% correlation

- Must ensure **positive definiteness**!
- Qi, H. and Sun, D., 2006, "A Quadratically Convergent Newton Method for Computing the Nearest Correlation Matrix," ***SIAM J. Matrix Anal. Appl.*** 28, 360–385

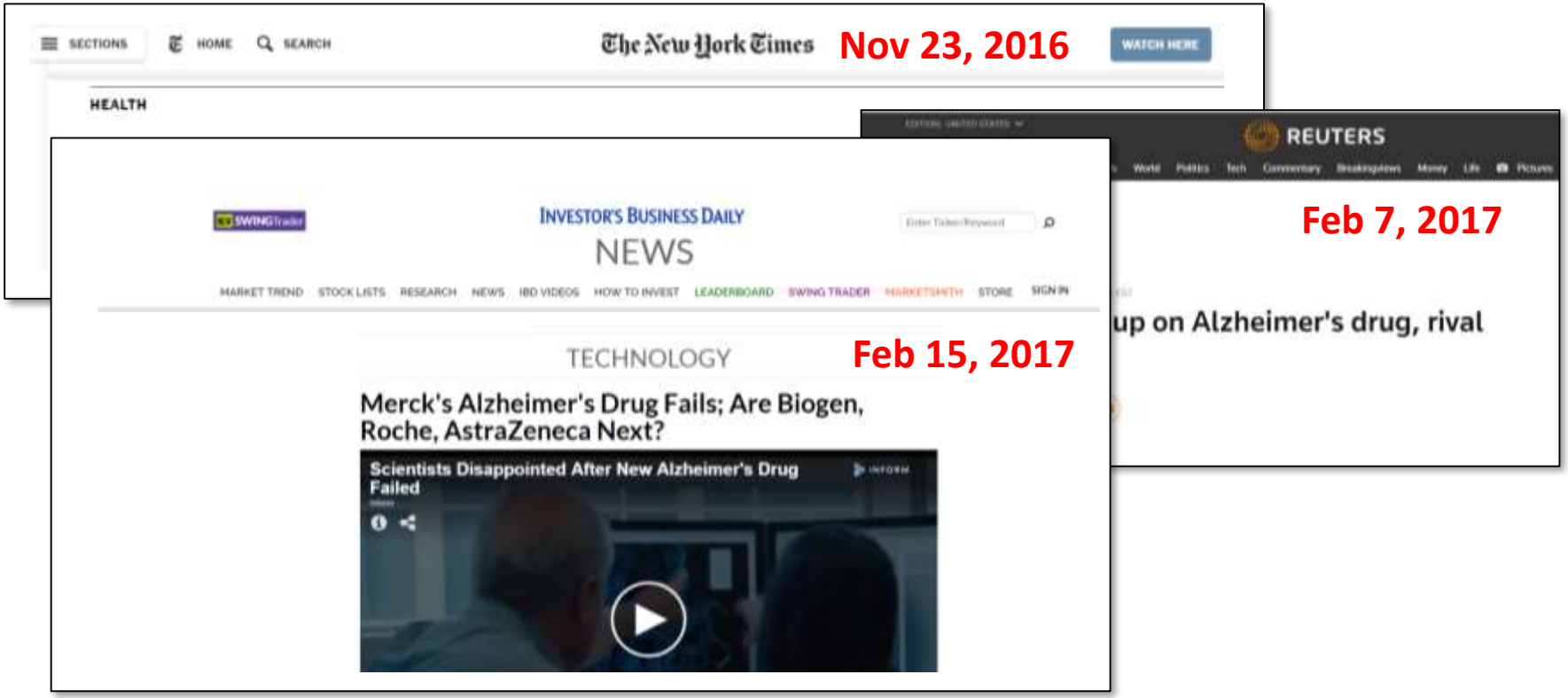
Lo, Ho, Cummings, Kosik (2014)

Simulated Return of AD Megafund

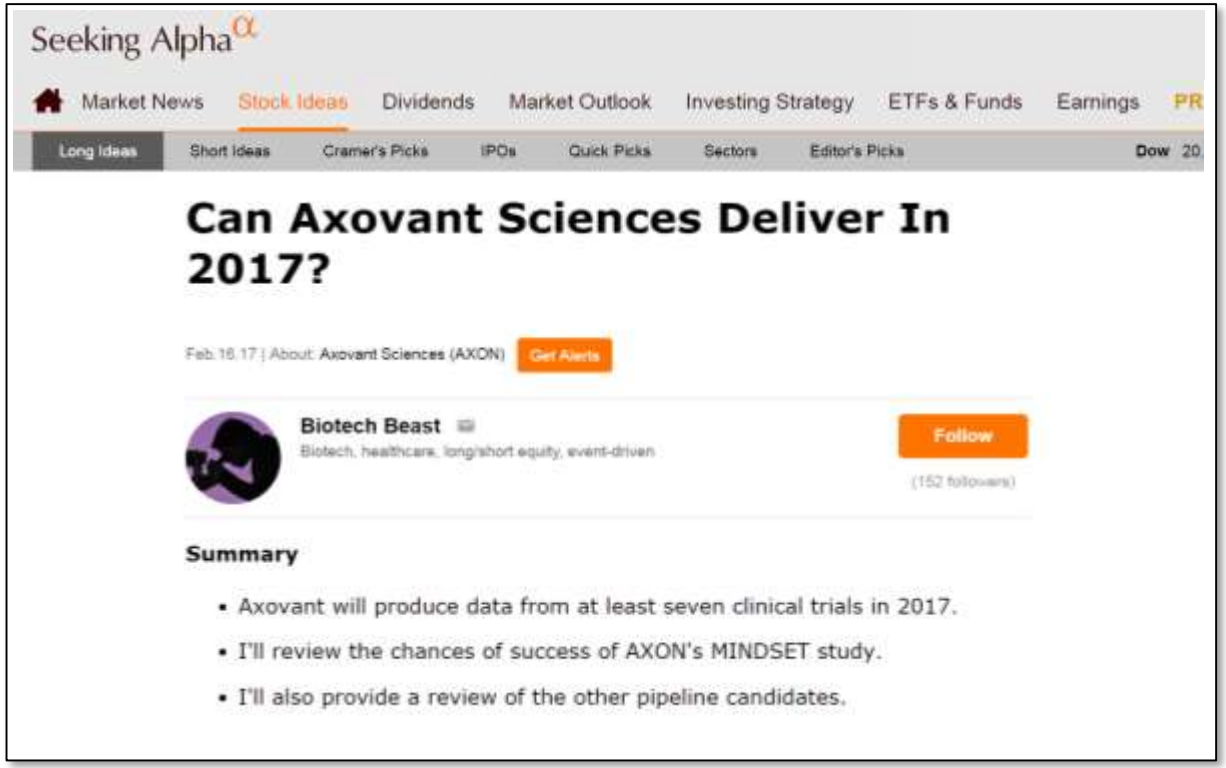
Parameters			Private-Sector Returns		M&M Returns Over Various Horizon (Years) Using AA Model											
					10	20	30	10	20	30	10	20	30	10	20	30
p (%)	ρ (%)	p_1 (%)	E[R]	SD[R]	E[R]: Delayed-Onset (T2) (%)			SD[R]: Delayed-Onset (T2) (%)			E[R]: Slowed-Prog. (T3) (%)			SD[R]: Slowed-Prog. (T3) (%)		
Expectation and Standard Deviation of Annualized Return																
5	0	96	-4.2	19.4	10.2	22.3	28.3	21.8	24.1	25.3	7.7	17.3	22.4	21.3	23.2	24.2
5	40	69	-32.5	46.0	-21.5	-13.0	-8.6	53.2	59.0	61.9	-23.3	-16.5	-12.9	52.0	56.6	59.0
5	80	40	-61.3	47.2	-54.0	-48.9	-46.4	56.1	62.3	65.4	-55.0	-51.0	-48.9	54.9	59.7	62.3
10	0	100	5.0	5.0	14.4	26.9	33.2	3.9	4.4	4.6	11.8	21.7	27.0	3.8	4.2	4.4
10	40	91	-7.2	29.4	4.5	15.9	21.7	32.3	35.9	37.7	2.2	11.2	16.0	31.6	34.4	35.9
10	80	46	-54.5	49.0	-46.8	-41.0	-38.0	57.1	63.4	66.5	-48.0	-43.4	-40.9	55.8	60.8	63.4
15	0	100	8.6	2.8	14.5	27.0	33.3	0.6	0.7	0.7	11.9	21.8	27.1	0.6	0.7	0.7
15	40	98	3.2	15.8	12.3	24.6	30.8	15.8	17.5	18.4	9.8	19.5	24.7	15.5	16.8	17.5
15	80	62	[illegible]		[illegible]			55.6	61.7	64.7	-30.6	-24.5	-21.2	54.4	59.2	61.7
KSK-CH		87	-14.3	33.4	-0.4	10.5	16.0	38.5	42.7	44.8	-2.6	6.0	10.6	37.6	41.0	42.8

Source: Lo, Ho, Cummings, Kosik (2014)

Recent Failures vs. New Approaches



Recent Failures vs. New Approaches



Recent Failures vs. New Approaches

LETTER

Nature (published online 12 Oct 2014)

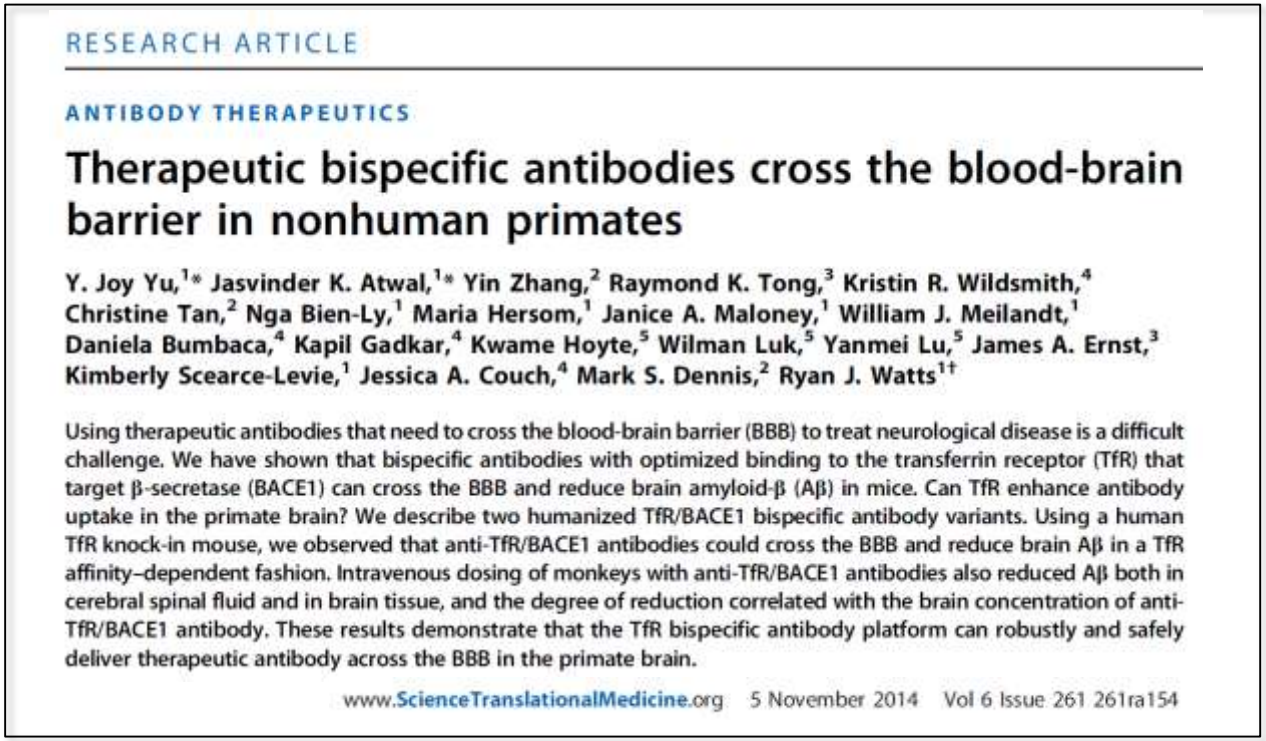
doi:10.1038/nature13800

A three-dimensional human neural cell culture model of Alzheimer's disease

Se Hoon Choi[1]*, Young Hye Kim[1,2]*, Matthias Hebisch[1,3], Christopher Sliwinski[1], Seungkyu Lee[4], Carla D'Avanzo[1], Hechao Chen[1], Basavaraj Hooli[1], Caroline Asselin[1], Julien Muffat[5], Justin B. Klee[1], Can Zhang[1], Brian J. Wainger[4], Michael Peitz[3], Dora M. Kovacs[1], Clifford J. Woolf[4], Steven L. Wagner[6], Rudolph E. Tanzi[1] & Doo Yeon Kim[1]

We have successfully recapitulated amyloid-β and tau pathology in a single 3D human neural cell culture system. Our unique strategy for recapitulating Alzheimer's disease pathology in a 3D neural cell culture model should also serve to facilitate the development of more precise human neural cell models of other neurodegenerative disorders.

Recent Failures vs. New Approaches



RESEARCH ARTICLE

ANTIBODY THERAPEUTICS

Therapeutic bispecific antibodies cross the blood-brain barrier in nonhuman primates

Y. Joy Yu,[1]* Jasvinder K. Atwal,[1]* Yin Zhang,[2] Raymond K. Tong,[3] Kristin R. Wildsmith,[4] Christine Tan,[2] Nga Bien-Ly,[1] Maria Hersom,[1] Janice A. Maloney,[1] William J. Meilandt,[1] Daniela Bumbaca,[4] Kapil Gadkar,[4] Kwame Hoyte,[5] Wilman Luk,[5] Yanmei Lu,[5] James A. Ernst,[3] Kimberly Scearce-Levie,[1] Jessica A. Couch,[4] Mark S. Dennis,[2] Ryan J. Watts[1†]

Using therapeutic antibodies that need to cross the blood-brain barrier (BBB) to treat neurological disease is a difficult challenge. We have shown that bispecific antibodies with optimized binding to the transferrin receptor (TfR) that target β-secretase (BACE1) can cross the BBB and reduce brain amyloid-β (Aβ) in mice. Can TfR enhance antibody uptake in the primate brain? We describe two humanized TfR/BACE1 bispecific antibody variants. Using a human TfR knock-in mouse, we observed that anti-TfR/BACE1 antibodies could cross the BBB and reduce brain Aβ in a TfR affinity–dependent fashion. Intravenous dosing of monkeys with anti-TfR/BACE1 antibodies also reduced Aβ both in cerebral spinal fluid and in brain tissue, and the degree of reduction correlated with the brain concentration of anti-TfR/BACE1 antibody. These results demonstrate that the TfR bispecific antibody platform can robustly and safely deliver therapeutic antibody across the BBB in the primate brain.

www.ScienceTranslationalMedicine.org 5 November 2014 Vol 6 Issue 261 261ra154

Recent Failures vs. New Approaches

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by **Tamara Bhandari** • January 25, 2017

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October 14, 2016

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