

Wharton Lecture Entrepreneurship

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Entrepreneur, Entrepreneurship

Originally:

Undertaking a task

Recent:

Starting and running a risky business

Successful entrepreneur:

Starting and running a risky business and
achieving multi-billion dollars in sales

List of Successful Entrepreneurs

	Year Born
• Thomas Edison	1847
• Henri Ford	1863
• Steve Jobs	1955
• Bill Gates	1955
• Mark Zuckerberg	1984
• Elon Musk	1971

On all the lists of successful entrepreneurs I looked at, I never found a pharmaceutical executive

Have you Heard of?

- Charles Pfizer, founded Pfizer in 1840
 - Today's sales \$52B; market cap \$196B
- George Merck, founded Merck in 1891
 - Today's sales \$40B; market cap \$208B
- Herbert Boyer, founded Genentech in 1976
 - Sold to Roche for \$100B with \$3.7B in sales
 - Today's Roche sales \$52B; market cap \$274B

Why? What is Different About Drug Development?

- It takes too long from invention to commercialization
- The inventor-scientist is rarely the pharmaceutical executive
- Two exceptions from the Philadelphia area
 - Hubert Schoemaker; Centocor, sold to J&J in 1999 for \$5.2B; died in 2006 after battling brain cancer for 10 years
 - Frank Baldino; Cephalon, died in 2010 of leukemia, sold to Teva in 2011 for \$6.8B

How Long Does it Take?

- Monoclonal antibodies were invented at the MRC in London by Cesar Milstein and George Koehler in 1975
- Humira was invented and patented by the MRC in 1996, licensed to Cambridge Research Institute and then sold to Abbott
- First approval for rheumatoid and psoriatic arthritis in 2005
- 2016 annual sales \$14B
- Patent ran out in December 2016
- It took over 40 years to get a monoclonal antibody blockbuster drug

Today's Start-Ups Move Faster than Last Century's



The ImmunoOncology Companies

Phenomenal new science field, where the body's own immune system is used to fight cancer

Juno, Kite, Venture U.Penn/Novartis
NantHealth

Pros and cons of CAR-T and NK

Car-T is very likely going to be replaced soon by bi-specific antibodies

Chimeric antigen receptors – T cells

Natural killer cells

Successful Unicorn

The biotech unicorns, whose market cap has increased, are the ones with an approved drug:

Car-T and gene therapy

Their technologies are solid and their clinical studies were successful.

To take yet another look at the time it takes to develop a new technology: Gene therapy was invented in 1972 and the first patient was treated in 1990. After being around for over 50 years, there finally is a drug on the market.

Jeff Marazzo, CEO of Spark, did not invent gene therapy. He is a very successful manager, not an ultimate entrepreneur.

Fate of Unicorns with Approved Drugs

Method	Company	Sold	Price
CAR-T	Juno	Celgene	\$9B
	Kite	Gilead	\$11B
	U.Penn/Novartis		
Gene Therapy	Spark	Roche	\$4.8B

Prices for therapy without doctor and hospital costs \$350,000 to \$500,000

Other Unicorns



Axovant was founded by Vivek Ramaswamy by buying a discarded 5HT6 antagonist from GSK for \$5million and going public for \$2.4B.

The phase 3 studies totally failed and Axovant switched to gene therapy.

Theranos is the brainchild of a young ambitious lady, Elizabeth Holmes. She wanted to be the Steve Jobs of biotech.

She had terrible advisors and did not listen. The two factors together killed the company and got her into a lot of trouble.

Why has one been able to raise more money for a different approach and the other may be going to jail?



Starting a Company: Personality

How about age?

Older entrepreneurs (>40) have a 5x higher chance of founding a successful company than younger ones

How about innovation?

Older scientist have more patents; median age of innovators is 47

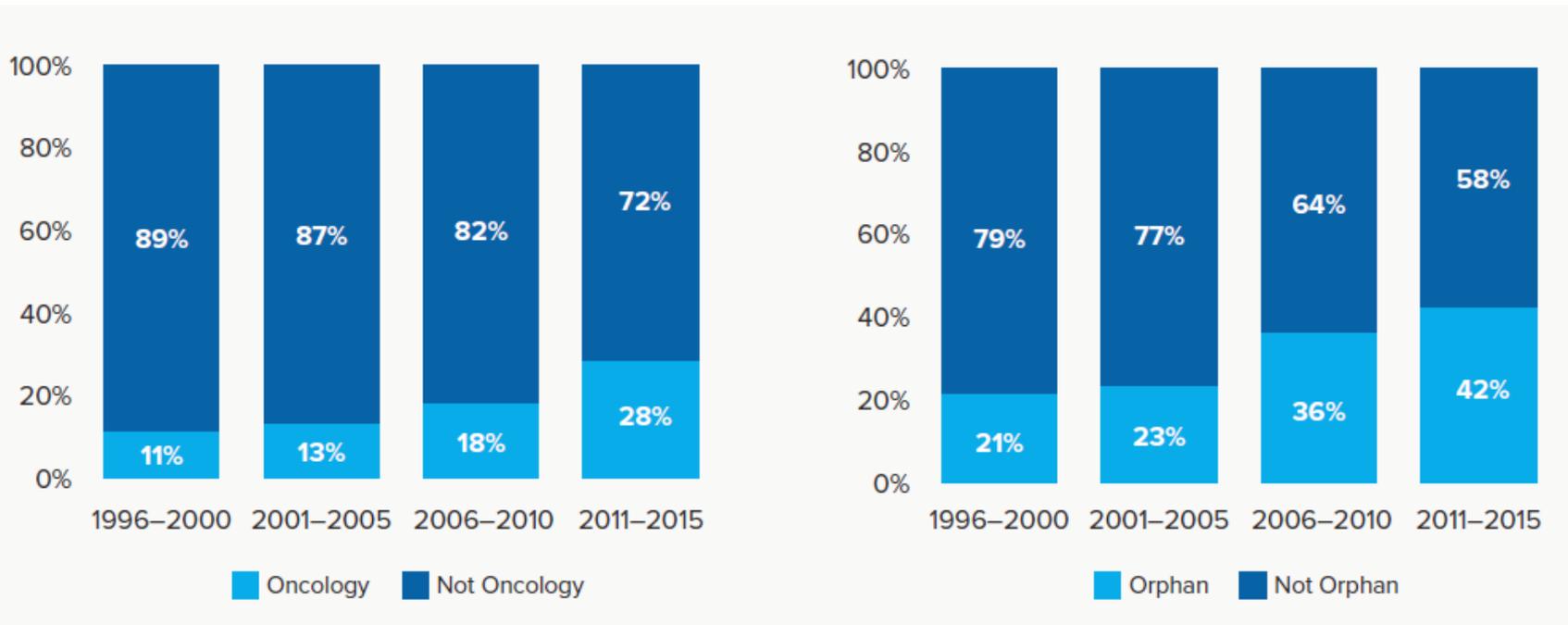
How about management capabilities?

The brightest people are usually not the best at running a company and managing employees. It takes more of a generalist with people skills. These skills are usually acquired with age

Starting a Company: Technology

- New Active Substances (NAS)
 - chemical, biologic, nucleic acid, cells
- Reformulation of existing drug
 - Usually of a generic
 - Better absorption, longer half-life, less side effects or just because to get a new patent/drug
- Approval of existing drug for new indication
 - Usually of generics

Over the years oncology and orphan indications have grown substantially



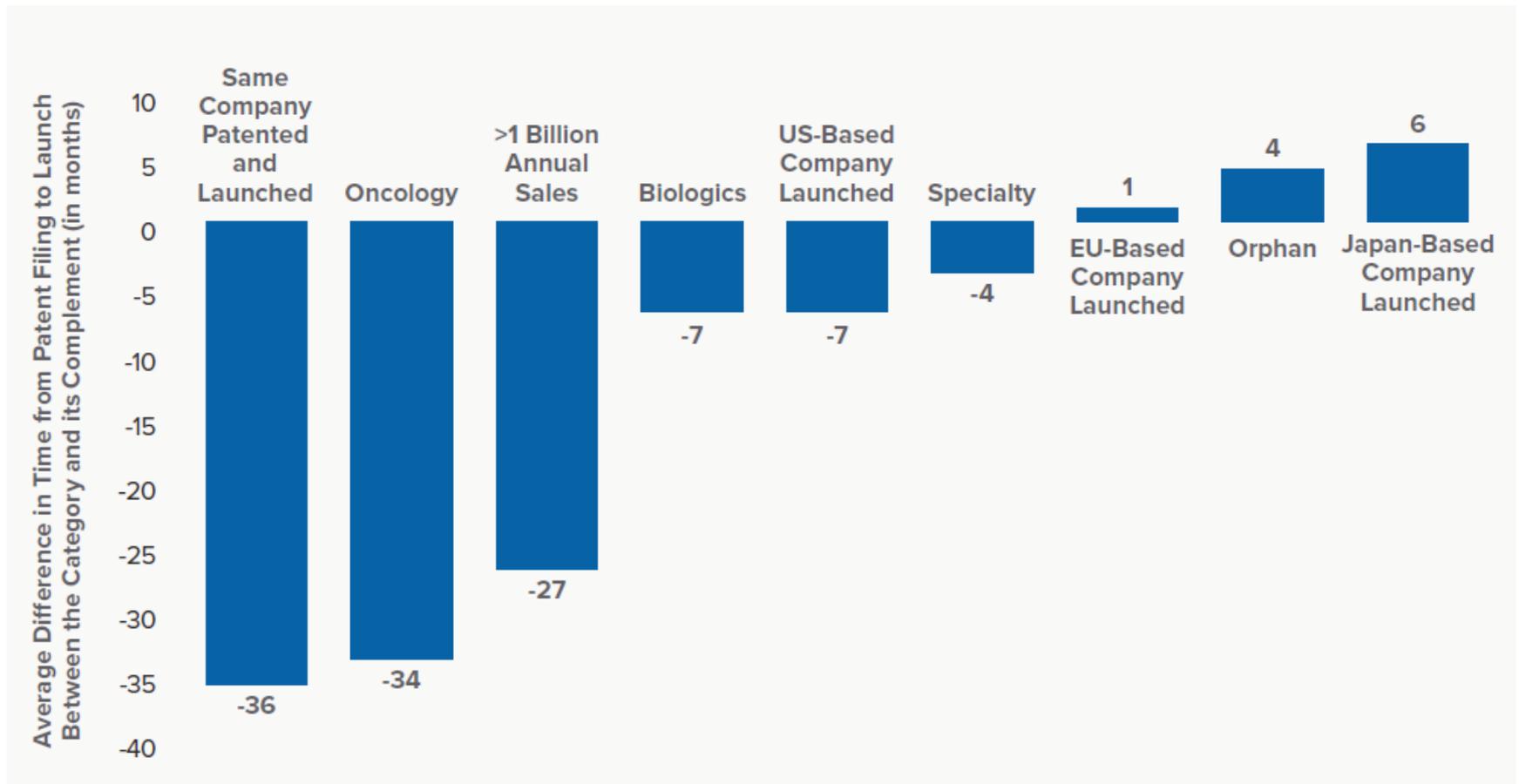
Starting a Company: Stage

- Research
 - Most common, because it can be your technology or interesting technologies are readily available from universities or research institutions
 - Preclinical
 - Also sometimes available from universities or research institutions
 - Phase I
 - Phase II
 - Phase III
- It costs money to license a later stage drug from a company.**
- If it is cheap, ask:
What is wrong with it?**

Starting a Company: Patents

- Without patents you will never be able to raise money
- Patents are the barrier to entry for everybody else. Patents make the effort worthwhile and allow for return on investment
- Patent life in the whole world is 20 year from filing. Depending on when you get FDA approval you have more or less time to recoup your investment

Average Time from Patent Filing to Launch



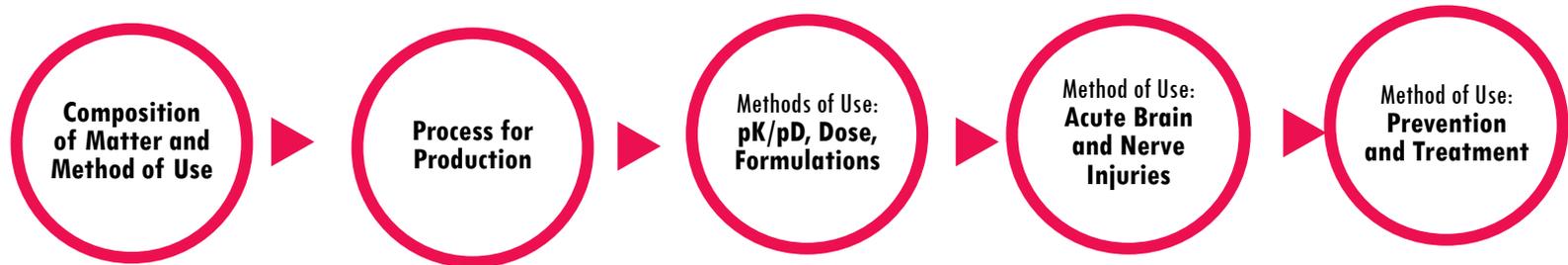
Posiphen Patents Are Getting Old

Humira's patent ran out in December 2016. AbbVie has filed an additional 78 patents to protect the life of the drug

- We have filed 3 new families and are in the process of filing additional patents to protect Posiphen
- How well does the strategy work? It depends on the:
 - Innovation described in the new patents
 - Savvy of the IP lawyer
 - Money invested

Corporate Patent Estate

Multi-layer strategy



Patent/Application	Subject Matter	Status US	Expiry US
PCT	ANVS401 and 405 - Method of use of MOA for prevention and treatment of diseases	Pending	2038
PCT	ANVS405 - Acute brain and nerve injuries	Pending	2036
PCT	ANVS401 - pK/pD, low doses, formulations Neurodegenerative Diseases	US 10,383,851 for PD Issued August 2019 AD allowed March 2020	2031
In-licensed patents	Composition of matter, manufacturing, method for treating AD and DS	Granted	2022-25

Starting a Company: Logistics

- Incorporate - C Corp, LLC
- Bring technology into company
 - License or option to license
 - If at all possible, obtain patent prosecution
- Raise capital
 - Friends and family, angels, economic development agencies (in PA Ben Franklin, BioAdvance)
 - Venture capital

Easier Ways

- Spark: Chop put in \$50 million to get it going
- VC founded companies with VC selected technology
 - Safe salary, safe cash
 - Shorter life span for CEO and technology, when things don't work out
 - Proteostasis was founded by VCs with \$120M to solve all protein interactions and to understand life. It changed CEO 4 or 5 times and changed technology to cystic fibrosis and still doesn't have a drug.

Other Ways

- Reverse merger into a shell, instant public presence with no analyst coverage
- IPO, only with excellent story (sizzle) and some analyst coverage



Actually maybe not:

Maybe you can be, who you are

I was told that my story was refreshing and that my company has the best technology seen so far

Financing History

***The Good, The Bad,
The Ugly
and The Good Again***

Case Study – Annovis Bio, Inc.

- Maria Macccecchini started her first company in 1992: Symphony Pharmaceutical, Inc. to protect nerve cells from dying after stroke. Symphony acquired 3 companies and changed its name to Annovis. Annovis was sold in 2001
- She then started her second company in 2009: Annovis to protect nerve cells from dying in degenerative diseases.
- I am still at it and I believe this time I got it

History of Annovis

2008: met inventor, Nigel Greig, from NIA/NIH skiing at a Neuroscience meeting
Posiphen inhibits the synthesis of APP, precursor to Abeta

2009: licensed technology and started company
raised \$2million from local State development agencies and angel investors
and \$1M from NIH and MJFF

2010: conducted human study mentioned in 5 MCI patients

2011 – 2014:

study was too small for pharma
not able to reproduce Nigel's data
Posiphen inhibits other proteins
mechanism not as described by Nigel
unable to raise additional money
board wants to replace me
fine with me, nothing is working anyway



2015: DOD awards \$1.5 million, NIA \$2.5 million, new investors and new Series A/A-1
of \$2.5 million, new Board to replace old Board

2015-19: a lot of data on mechanism, toxic cascade, efficacy in animal models

2020: IPO on NYSE

Doggedness

Every MBA would have closed the company

Most scientists would have closed the company

I didn't

- because the data we had in humans and in animals looked good. We didn't understand why Posiphen did what it did, but it did it
- Because I had made money by selling my previous company and was able to invest. I put \$2 million into Annovis to keep it alive

The jury is still out

But

- we have a great mechanism of action
- we have great animal data
- we were able to attract the most famous key opinion leaders to our SAB
- we are conducting the phase II study with Posiphen
- we are bolstering the patent portfolio
- **We can conduct TWO phase 2 studies - in AD and in PD**

Next Steps

2017: continue work on mechanism of action

expand patent portfolio

publish 5 or so papers

finish phase II study – STILL NOT DONE

2018: raise \$50 million to conduct phase III/pivotal study sell

and retire in 2021 – *NO WAY*

2019: IPO, several banks told us that we have the best

Alzheimer asset they have seen - *DONE*

2020-2021: Conduct two phase 2 studies, one in AD

and one in PD patients, use data of these two

phase 2 studies to achieve 2018 goal

IPO process

Perfect Accounting:

audit firm to review and restate everything for the previous 2-3 years of accounting

Perfect Legal:

legal and IP firm to fully review and guarantee all transactions

Perfect SEC Filing:

All of the above to write and review Form S-1, also known as the registration statement under the Securities Act of 1933. Form S-1 requires companies to provide information on planned use of capital proceeds, current business model and competition and prospectus of the planned security itself, offering price methodology and dilution

It is the most time and money consuming process I couldn't have possibly invented, if I really tried

JANUARY 29, 2020

NEW YORK STOCK EXCHANGE

NYSE OPENING BELL

ANVS
LISTED
NYSE AMERICAN

ANNOVIS

ANVS
LISTED
NYSE AMERICAN

