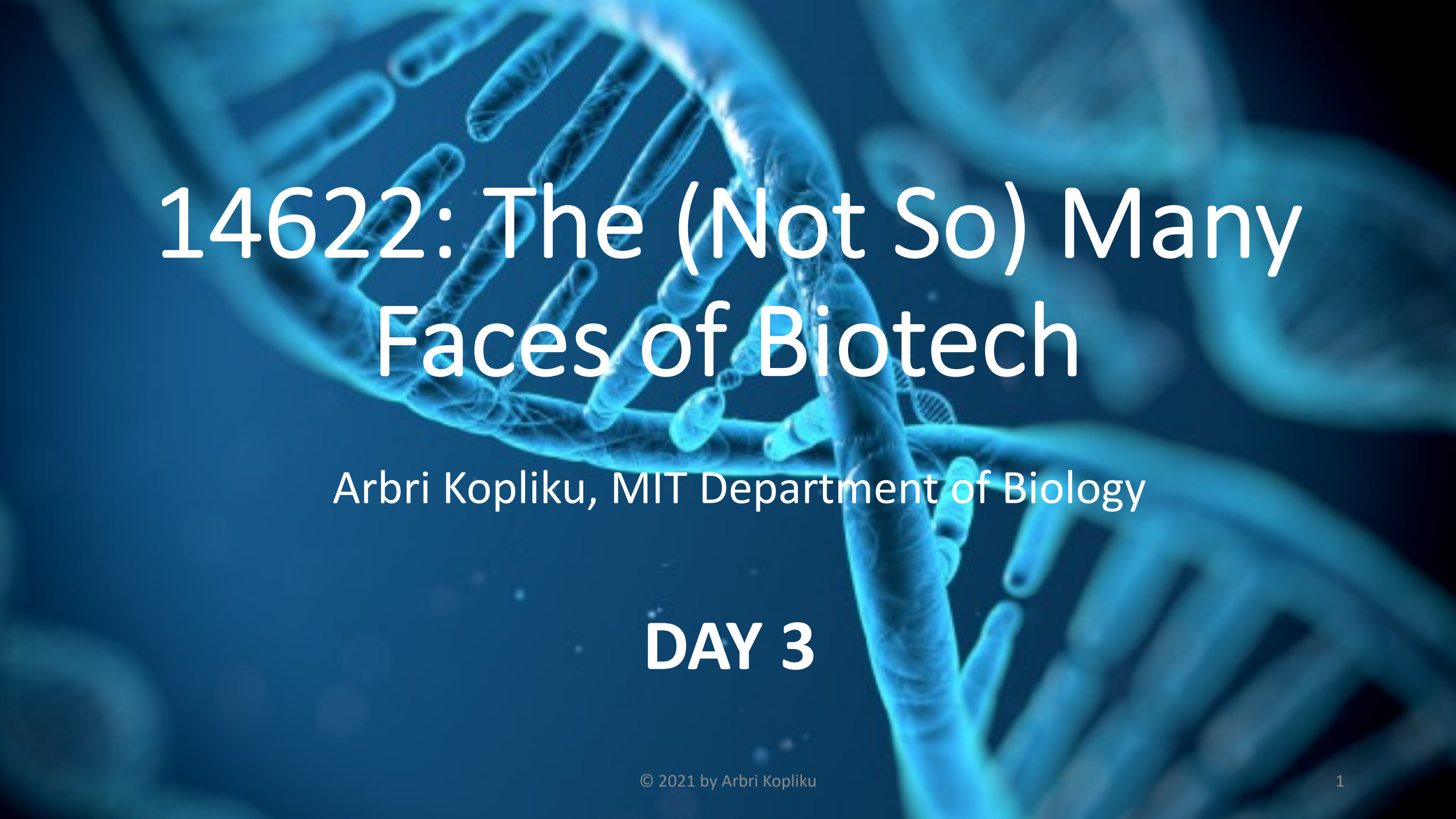


14622: The (Not So) Many Faces of Biotech

Arbri Kopliku, MIT Department of Biology

DAY 3

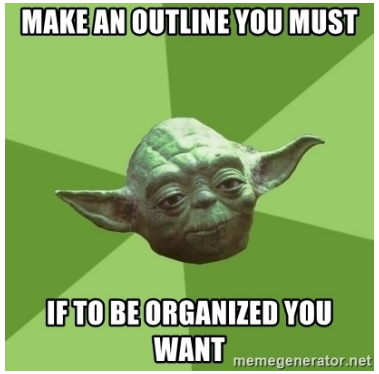
Day 3 Outline

- *Previously on… The Not So Many Faces of Biotech X2*
- Time to look at another logical inconsistency and see if we can fix it.
- A rather drastic but quite important detour into pharmaland.
- Our very own Clash Royale, ladies and gents.
- A reliable market as the third theme of the biotech-innovation romance.
- Applying our wisdom to the Breakthrough Drug Designation.
- Some more wisdom applications to the very present day!
- Our last Character Spotlight!

Day 1 Recap (a.k.a. Outline)

- Introductions and structure of the series
- Very quick ice-breaker
- Definitions, definitions… with a crash course on medications!
- Pharma against biotech or just biopharma?
- How to tackle a Herculean problem *like a pro* -> Innovation
- *This sounds elementary, dear Watson, but it isn't.*
- Niche creation as the first theme of the biotech-innovation romance.
- Magic bullets and their legacy
- Some extra ideas to inspire our next sessions, including Character Spotlight!

Day 2 Recap (a.k.a. Outline)



- *Previously on… The Not So Many Faces of Biotech*
- Some much-needed refreshing questions popping up around here!
- A rather extreme ice-breaker…
- Converting an idea to an asset
- Our first court case of interest… Boston Legal anyone?
- The Orphan Drug Act of 1983
- Price gouging vs. Doing justice to the server
- Flexibility of ownership as the second theme of the biotech-innovation romance.
- Character Spotlight of the week!

What counts as Biotechnology?

- “Biotechnology is a broad area of biology, involving the use of living systems and organisms to develop or make products. Depending on the tools and applications, it often overlaps with related scientific fields.”
- Not the most specific of definitions, as it doesn’t give us a consistent window of time or applications!

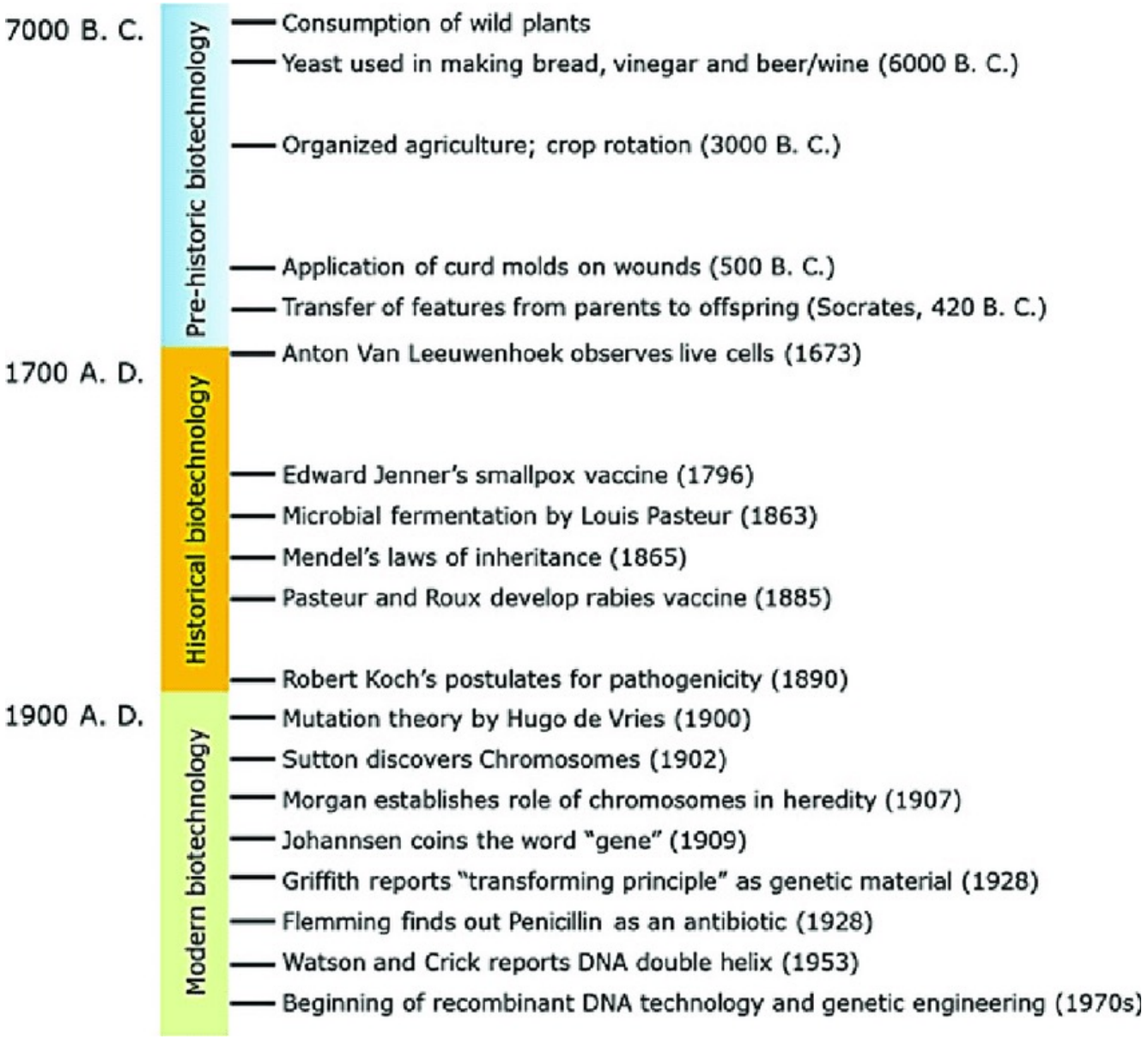
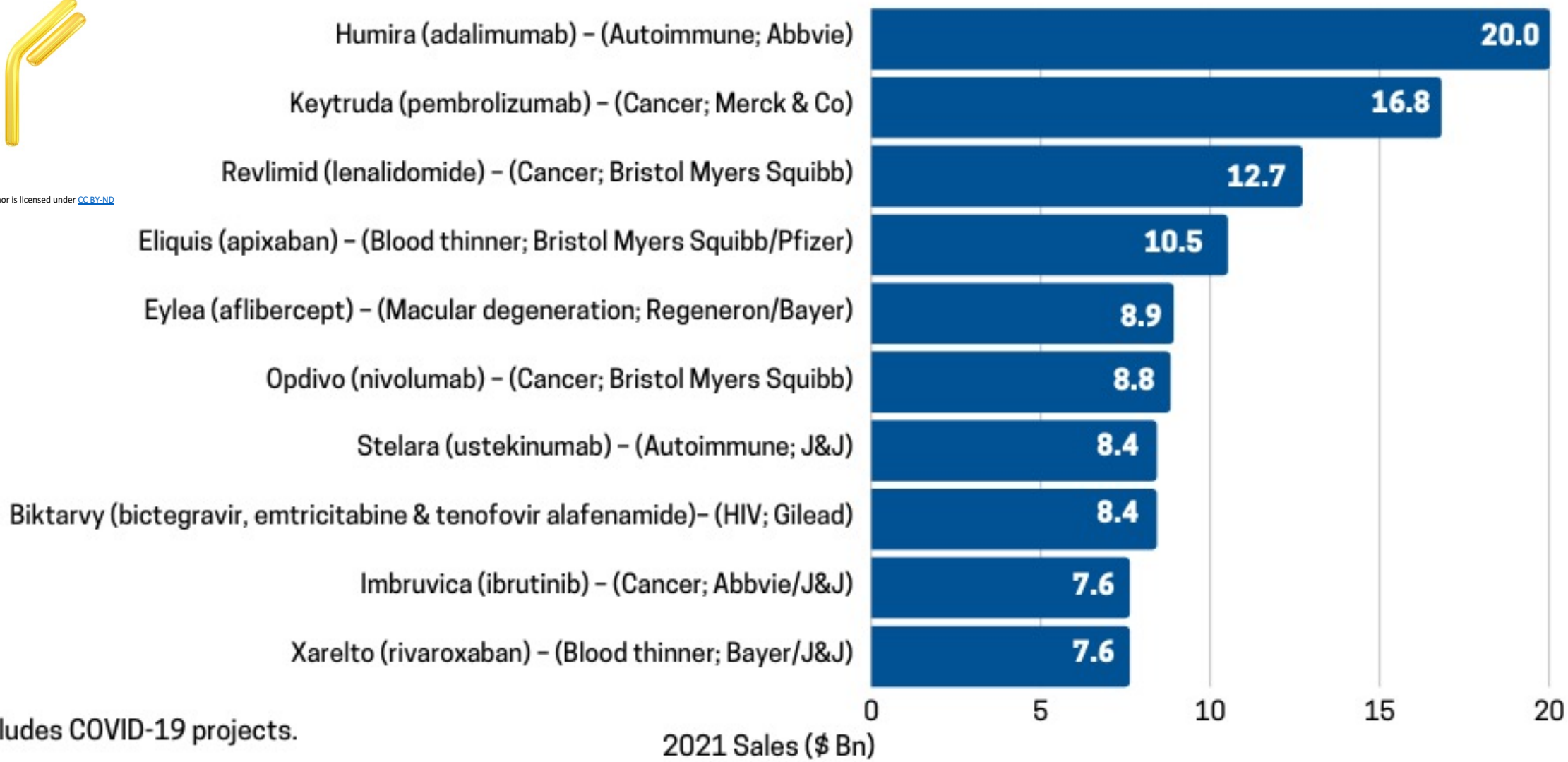


Fig. 1: Concise timeline of biotechnology in its entirety, broken down into 3 categories. Verma, Gaurav & Ravichandran, Srividhya. (2020). Evolution of Biotechnology as a Million Dollar Market: The Management and Commerce of a Biotech Start-up. 10.1007/978-3-030-36130-3_9.

Figure 3: Projected Biggest Selling Drugs in 2021



Note: excludes COVID-19 projects.

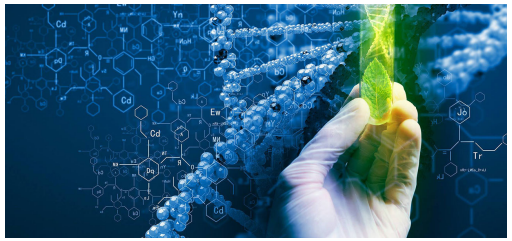
Source: EvaluatePharma, Evaluate Ltd.

Back to the Defining Board

- It as an acceptable, though surely not exhaustive, approach to defining modern biotechnology as the intersection between university-exclusive practices (where all the basic science originated from) and mechanical/chemical engineering formats of generating commodities.
- As such, biotechnology formed its own labor market distinct from the above two fields, and also to a great extent separate from pharmaceutics.

Theme of the Day: Niche Creation

- This is what we were building up to, and denotes one of the three key themes in the relationship of biotech to innovation.
- We are using this very relationship to define modern biotechnology as a whole, and niche creation gives us the right context to begin with.
- Comparing the biotech and tech revolutions gives us more insight on what makes biotech so unique and at the same time so rewarding to characterize, as we will soon see.

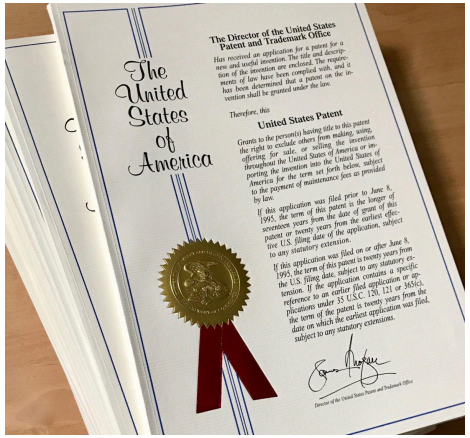


But How Can All of This Make Sense?

- Intuitively, it doesn't seem right that the esoteric concept of innovation coupled with some *very* statistically risky investments sufficed to shake an incredibly robust pharma industry.
- On the other end however, we can say for sure that pockets of innovative opportunity were quickly snatched by small biotech companies, making them key market players in the process.

Let's Answer a Question with Another!

- What is the most direct way of materializing an idea? In other words, how can you raise money for your projects by saying that your idea is reliable enough?
- ANSWER: Exclusivity, and it goes hand in hand with its enforcement through patenting.
- We will start by the textbook example of patenting in biotech history, without which, one can argue, we would never witness the sheer scale of genetic engineering as we do today.



The Diamond vs. Chakrabarty Case

- It marked the symbolic moment of witnessing the lucrative prospects of biotech innovation as well as all the bioethical concerns that came with recognizing a living creature as patentable.
- In 1972, a genetic engineer working for General Electric called Ananda Chakrabarty created a genetically modified bacterium that could break down crude oil.
- The original patent request by GE was rejected by a patent examiner because at the time, living things could not be patented as inventions (and they technically lacked a human inventor).

Consequences in Europe

- A small transatlantic detour is necessary to understand the possibilities that were forgone by the ruling in favor of Chakrabarty.
- Twelve years later, the full European Parliament would take up the issue, and would invoke the *ordre public* clause to ascertain the importance of moral considerations before issuing patents.

TO PATENT OR NOT TO PATENT: THE EUROPEAN UNION'S NEW BIOTECH DIRECTIVE

Credits to Lydia Nenow.

Consequences in the US

- The question of “What really is the best public interest” in the American context was determined by a purely legal answer: making sure that a potentially groundbreaking new industry, biotech, has enough room to thrive by intellectual property protections would very likely lead to economic growth.
- This ruling established that ideas can now quickly become assets that can be bought and sold, and Genentech was among the supporters of the plaintiff.
- The converting mechanism from an applied science discovery to potential IPO interest was finally uncovered.

Genentech

The Orphan Drug Act of 1983

- An en masse utilization of proprietary knowledge intended, as anticipated by the Supreme Court ruling, to provide some breathing room to the new biotech industry.
- Despite the drug development techniques being in rapid growth and refinement, orphan diseases were too risky and not rich enough in incentives for private companies to take them up.
- The Orphan Drug Act, through its market dominating benefits, aimed to change that.

WHAT IS THE ORPHAN DRUG ACT?

NORD RARE INSIGHTS

1983

The Orphan Drug Act (ODA) of 1983 is a federal law that incentivizes biopharmaceutical companies to develop drugs and biologics, known as "orphan drugs," for individuals with **rare diseases.**

A RARE DISEASE IS ANY CONDITION AFFECTING FEWER THAN 200,000 AMERICANS

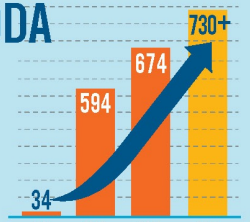
HOW DOES THE ORPHAN DRUG ACT WORK?

There are **4** **INCENTIVES** in the law that encourage biopharmaceutical companies to develop orphan drugs.

- **7 YEARS OF EXCLUSIVITY** that prevent competitors from selling the same product
- **25% TAX CREDIT** for qualified clinical testing expenses incurred in clinical trials
- **~$18 MILLION** in FDA research grant funding
- **~$2.5 MILLION** FDA user fees waived

HAS THE ODA WORKED?

YES!



(# of approved orphan indications)

BUT APPROXIMATELY

95% of rare diseases are still without any FDA-approved treatment.

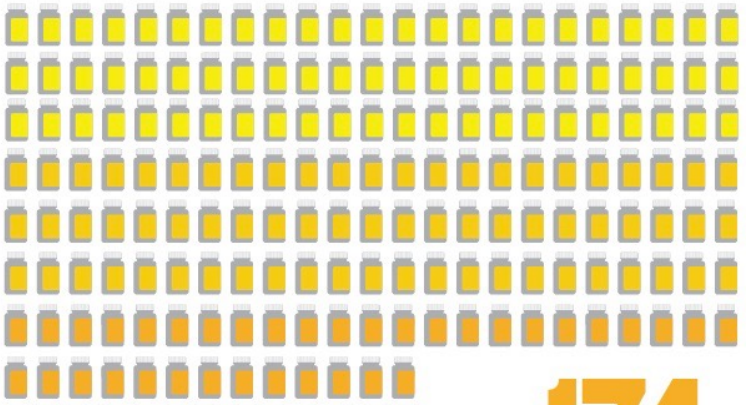
PLEASE SUPPORT THE ORPHAN DRUG ACT!

Source: FDA Orphan Drug Database; Drugs@FDA Database, FDA websites, IQVIA Institute, Sep 2018 for Human Data Science.
Note: The graphic was created using a curated list of indications and approvals based on the FDA Orphan Drug Database. Includes drug approvals through Aug 2018. NORD is a 501(c)(3) charity organization. For more information, visit: rarediseases.org. NRD-1159

NORD National Organization for Rare Disorders

SPIKE IN ORPHAN DRUG NODS SEEN UNDER TRUMP

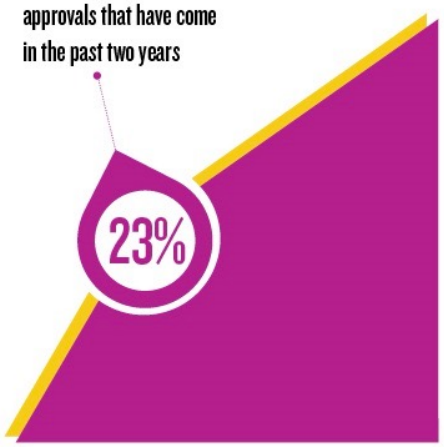
Source: Axios



The number of prescription drugs approved to treat rare diseases during Trump's first two years in office

174

Percent of all orphan approvals that have come in the past two years



Newly developed orphan drugs approved in 2018 > > > **58%** of the **59** novel drugs approved last year

FDA's Center for Drug Evaluation and Research (CDER), 2018

Existing blockbuster drugs have also added orphan approvals, and their accompanying financial incentives. Per Axios, six of the eight best-selling biologic drugs in 2017 have orphan approvals, and three — Humira, Rituxan, and Avastin — still have extra exclusivity for some of those uses.

Data: FDA and I-MAK via Axios

Best-selling biologic drugs, 2017

	# Orphan approvals	Latest orphan exclusivity	On market since
Humira	7	Oct. 2025	2002
Rituxan	7	June 2025	1997
Enbrel	1	May 2006	1998
Herceptin	1	Oct. 2017	1998
Remicade	3	Sept. 2018	1998
Avastin	11	June 2025	2004
Lantus	0	-	2000
Eylea	0	-	2018

Average annual cost per patient of the **TOP 100 ORPHAN DRUGS** — excluding blockbusters with additional orphan uses > **$147,308**

Average cost for the **TOP 100 NON-ORPHAN DRUGS** > **$30,708**

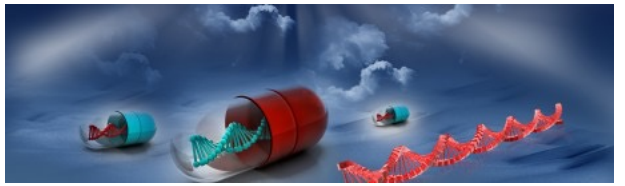
Source: Evaluate Pharma, 2018

The year the Orphan Drug Act was passed, establishing market exclusivity and financial incentives for drugs approved through the **"ORPHAN" PATHWAY**

1983

Credits to the Jack McGovern Coats' Disease Foundation.

The Case Against Biopharma



- It is worth noting that in these hearings, the defendant was a unified entity enclosing both pharmaceuticals and biotechnology companies as a single “biopharma”.
- The real purpose behind the orphan drug designation, mainly increasing patient accessibility, came to light once the Cystic Fibrosis Foundation expressed their support for the existing prices.
- The Congress’ argument revolved around how the high list prices are not justified by the low R&D costs of certain medications, which are now known as “sunk costs”.

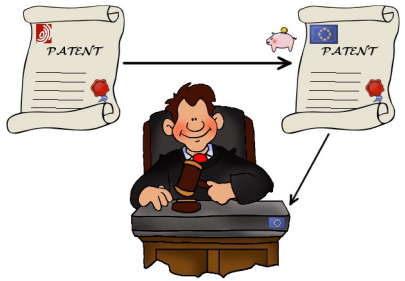
CYSTIC FIBROSIS FOUNDATION
ADDING TOMORROWS

Mr. Termeer's wise words

- Henri A. Termeer was a Dutch MBA who has the legacy of being the longest-serving CEO in the biotechnology industry.
- He was a self-proclaimed "advocate for the Massachusetts biotech industry", a role which he very clearly played in the 1985 hearings against the Orphan Drug Act.
- Mr. Termeer's argument was simple, yet it summed up the nature of biotech startups then and now: receiving the orphan drug designation was a milestone which added value to biotech companies, even when they didn't have a product ready to leave the pipeline.
- He also stressed that, without the high retail prices, there is no reason for biotech companies to not be one-hit-wonders and just exit the market.

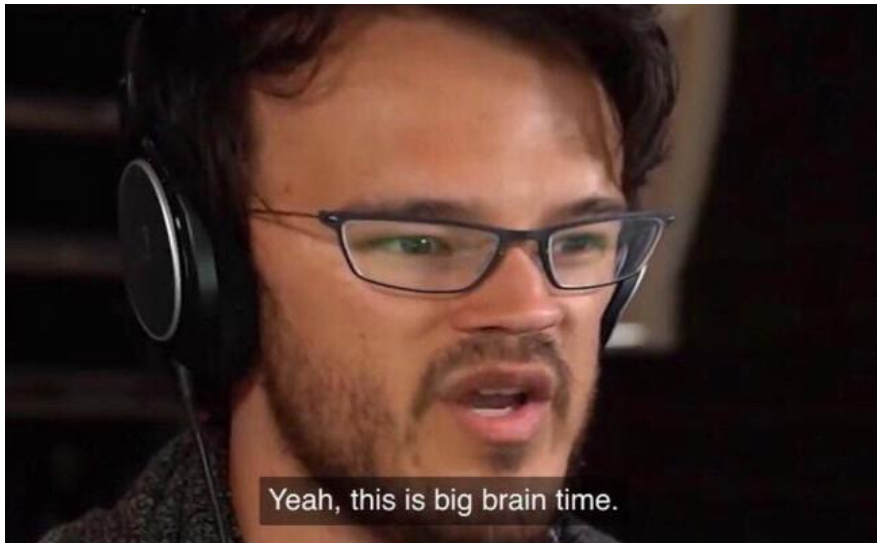
Theme of the Day: Flexibility of Ownership

- A way of protecting innovation and allowing ideas to have market value.
- This way, more scientist-entrepreneurs are incentivized to come up with new ideas, since there is a system in place guaranteeing that, if the idea is successful in the market, its costs will be justified.
- With great power comes great responsibility: exclusivity brings with it the ability of companies to unilaterally nudge prices, which although not always damages the customers, it certainly has the capacity to!
- The example of Orphan drugs showed us why patents matter as a form of proprietary knowledge, and how they translate to benefitting patients.



Refreshing Question 1!

- What was the name given to the “scientific wonder” aspect of early biotechnology endeavors?



Another Logical Bottleneck…

- Just like last lecture, where we ran into difficulties applying the “niche creation” theme to the long run of the biotech story and thus needed patenting, applying the “flexibility of ownership” also seems to provide a challenge which we will look at.
- More specifically, if we assume to have a very well-protected idea that has been appropriately patented, how do we really know that it is in fact well protected?

Peculiar but Important Detour

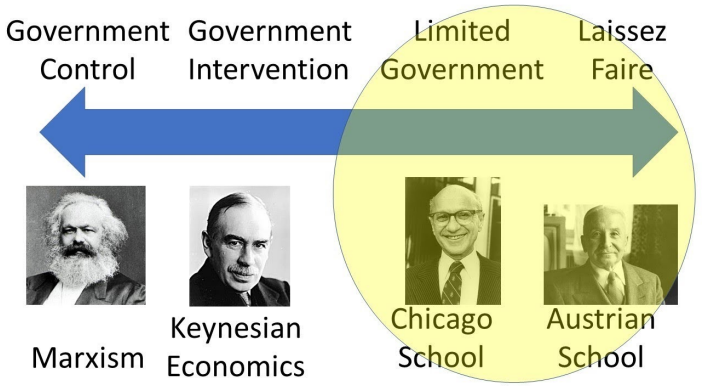
- The Center for the Study of Drug Development (hereon CSDD), was founded in 1979 by Dr. Louis Lasagna, and its purpose was in a way to promote neoliberalism in pharmaceutical science.
- To track back, neoliberalism “is contemporarily used to refer to market-oriented reform policies such as eliminating price controls, deregulating capital markets, lowering trade barriers and reducing, especially through privatization and austerity, state influence in the economy.”

The Fight Against Populism… a.k.a. the FDA

- The CSDD offered spaces, often in the shape of seemingly peer-reviewed journals, for pharmaceutical companies to share their research results via an advertisement-like language, and without risking further scrutiny by the FDA.
- In collaboration with the American Enterprise Institute, the CSDD in essence formed an echo chamber of pharmaceutical interests, with a main focus on fighting populism in medicine.
- One could surely argue that the many court cases we saw last time could be an example of such populism, since companies were being forced to comply with market ethics.

The Clash Royale

- Very much influenced by the Chicago School of Economics, pharmaceutical neoliberalism and particularly the CSDD stressed the risks of allowing Congress to pass redundant regulations, and they announced this agenda through multiple conferences and papers.
- It is worth noting however, that a discrepancy has arisen between what we saw as guaranteeing a stable market through exclusivity in patenting, and leaving enough room for innovation by not over-interfering in the free market.

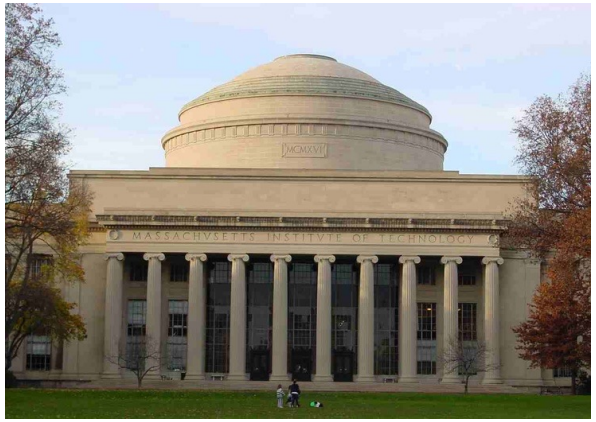


Back to the Orphan Drug Act

- The ideological clash that we just went over in fact explains some of the arguments against any amendments to the Orphan Drug Act of 1983: a non-reliable market that changes its financial incentives midway through a contract (here a patent) does not promote innovation. Instead, it goes against the very concept of patenting as a guarantee of market presence.

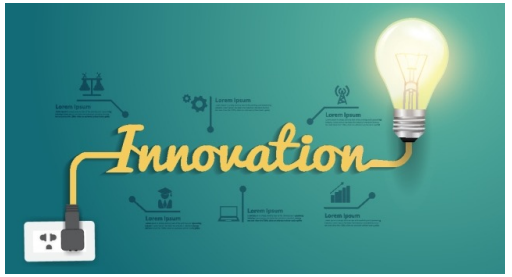
Question for the Esteemed Audience

- Should the healthcare (both drugs and services) market be an ideally free market? In other words, should it be governed more like the market for laptops or the education one?



Theme of the Day: A Reliable Market

- Thanks in part to the pressure by the CSDD and their affiliates, the role of the US government remained largely catalytic in rare drug manufacturing (as opposed to the EU), thus keeping the status quo of patenting intact.
- This exposes our third and final theme of the innovation-oriented characterization of biotechnology, the importance of a reliable market.
- It is in fact quite effective to consider how the importance of reliable markets is as much a factor in determining the approaches adopted by biotech-pharma companies as pursuing proprietary knowledge.



Time to Apply Some of This Wisdom

- The “breakthrough drug” designation was conceived on Congress in 2012, as a way to expedite the testing and approval of novel medications treating very serious or fatal conditions, based mostly on preliminary evidence and post-approval follow-up.
- Initially concepted for treatments that “knock your socks off”, this designation is reminiscent of the early characterizations of biotechnology (think magic bullets), and yet between 2014 and 2016 24% of all FDA-approved drugs had this designation.

The Breakthrough Drug Designation

- The parallels reach further back in our lecture series: from the words of Mr. Termeer, biotech companies rely on prospects much more than big pharma have to. Here, designation requests can be made when there is little data present to support the hypothesis, similar to attracting investments without having any drugs in the market.
- For companies that have developed their composition around very particular treatments (our niche creation theme), the designation would narrow down the competition even further, much thanks to the very constricted definition of “existing therapies”.

Brief Case Study: Vertex Pharmaceuticals

- Despite its name, Vector Pharmaceuticals offers many more of the traits typical of biotechnology companies.
- Their flagship drug, Ivacaftor, was among the 26 breakthrough-designation approved drugs mentioned earlier, and was later coupled in treatment with Lumacaftor, also from Vertex. It treats CF.
- Without patent protection, focusing on the objectively small target group of Cystic Fibrosis patients would be far too risky to have any prospective profits. Furthermore, focusing on the same drug for the 26 years of development that Ivacaftor needed would be impossible in an unpredictable market.

VERTEX®

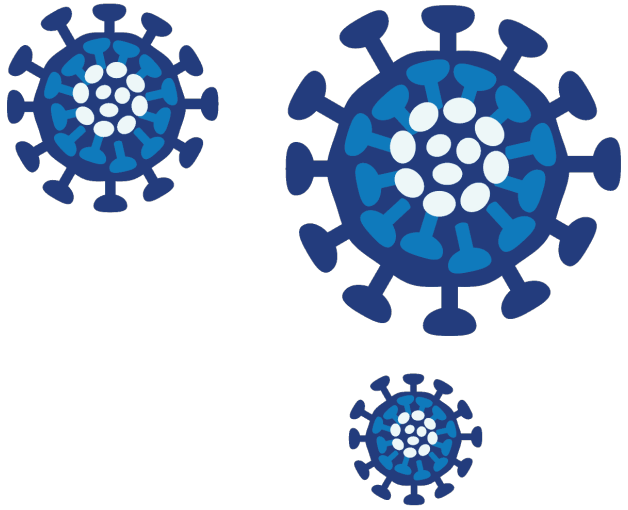
A More Contemporary Scenario: Now.

- Until-recently quite small biotech companies, like Moderna and Biontech, have now become household names throughout the world: publicity, as we saw with magic bullets, can truly feed cash into biotech projects.
- Moderna's and Pfizer-Biontech's respective vaccines are the first examples of mRNA technology applications in humans, illustrating a prime example of successful biotech-pharmaceutical innovation.

BIONTECH

Quick Thought Experiment

- Take as the hypothetical premises that vaccine development and distribution is completely government-funded and operated. Would the timeline as well as the very scientific approach employed in this scenario resemble at all what we are observing in real life?



Meanwhile an Ocean Away:

- Another interesting partnership in COVID-19 vaccine development was the University of Oxford-AstraZeneca one, but little has been said about the role of Vaccitech, a small Oxford biotech spinoff, in this deal.
- In fact Vaccitech owned the full proprietary rights to the ChAdOx platform, which was used to manufacture the vaccine, but was forced to give up its rights on this particular COVID-19 application for the Astrazeneca deal to be completed.
- AstraZeneca's “non-profit pledge” only added to the business complications of this partnership, resulting in a rather uncomfortable situation for Vaccitech.

vaccitech

AstraZeneca

A Rather Sticky Situation

- As many biotech startups aim to, Vaccitech found its niche with the ChAdOx platform, the applications of which could extend to vaccines for many infectious diseases.
- This waving of rights could be considered a preview of a potential scenario here in the US, had the standard of proprietary rights protection not been so rigorously maintained.
- With all this unreliability surrounding Vaccitech's situation, their prospective IPO offering in September does not have the best of prospects.

EXTRAS: Character Spotlight – Susan Hockfield

- Neuroscientist, cancer researcher, corporate advisor and trustee.
- Served as MIT's 16th President, and was the first female or life scientist to do so.
- Former Provost, Professor of Neurobiology and Dean of the Graduate School of Arts and Sciences at Yale.
- Director of General Electric, Qualcomm and Pfizer.
- Overseer of the Boston Symphony Orchestra.
- Trustee of the Carnegie Corporation of New York.
- Pioneered the use of monoclonal antibodies in brain research and discovered a gene heavily involved with brain cancer.
- She was at some point hired to work at the Cold Spring Harbor Laboratory, with the special request of John Watson.

Day 3 Outline

- *Previously on… The Not So Many Faces of Biotech X2*
- Time to look at another logical inconsistency and see if we can fix it.
- A rather drastic but quite important detour into pharmaland.
- Our very own Clash Royale, ladies and gents.
- A reliable market as the third theme of the biotech-innovation romance.
- Applying our wisdom to the Breakthrough Drug Designation.
- Some more wisdom applications to the very present day!
- Our last Character Spotlight!