Day 2 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!
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!

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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.

<table>
<thead>
<tr>
<th>Era</th>
<th>Biotechnological Events</th>
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<tbody>
<tr>
<td>7000 B.C.</td>
<td>Consumption of wild plants</td>
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<td>Yeast used in making bread, vinegar and beer/wine (6000 B.C.)</td>
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<td></td>
<td>Organized agriculture; crop rotation (3000 B.C.)</td>
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<td></td>
<td>Application of curd molds on wounds (500 B.C.)</td>
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<td></td>
<td>Transfer of features from parents to offspring (Socrates, 420 B.C.)</td>
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<td>Anton Van Leeuwenhoek observes live cells (1673)</td>
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<td>1700 A.D.</td>
<td>Edward Jenner’s smallpox vaccine (1796)</td>
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<td>Microbial fermentation by Louis Pasteur (1863)</td>
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<td>Mendel’s laws of inheritance (1865)</td>
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<td>Pasteur and Roux develop rabies vaccine (1885)</td>
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<td>Robert Koch’s postulates for pathogenicity (1890)</td>
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<td>Mutation theory by Hugo de Vries (1900)</td>
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<td>Sutton discovers Chromosomes (1902)</td>
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<td>Morgan establishes role of chromosomes in heredity (1907)</td>
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<td>Johannsen coins the word “gene” (1909)</td>
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<td>Griffith reports “transforming principle” as genetic material (1928)</td>
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<td>Flemming finds out Penicillin as an antibiotic (1928)</td>
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<td>Watson and Crick reports DNA double helix (1953)</td>
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<td></td>
<td>Beginning of recombinant DNA technology and genetic engineering (1970s)</td>
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Cumulative returns of the market

Panel A: Continuous Sample from 1930-2015, excluding Biotech

Panel B: Sample from 1930-1980 and 1980-2015, including Biotech

Credits to Andrew W. Lo, 15.482.
Figure 3: Projected Biggest Selling Drugs in 2021

- Humira (adalimumab) – (Autoimmune; Abbvie) - 20.0
- Keytruda (pembrolizumab) – (Cancer; Merck & Co) - 16.8
- Revlimid (lenalidomide) – (Cancer; Bristol Myers Squibb) - 12.7
- Eliquis (apixaban) – (Blood thinner; Bristol Myers Squibb/Pfizer) - 10.5
- Eylea (afibercept) – (Macular degeneration; Regeneron/Bayer) - 8.9
- Opdivo (nivolumab) – (Cancer; Bristol Myers Squibb) - 8.8
- Stelara (ustekinumab) – (Autoimmune; J&J) - 8.4
- Biktarvy (bictegravir, emtricitabine & tenofovir alafenamide) – (HIV; Gilead) - 8.4
- Imbruvica (ibrutinib) – (Cancer; Abbvie/J&J) - 7.6
- Xarelto (rivaroxaban) – (Blood thinner; Bayer/J&J) - 7.6

2021 Sales ($ Bn)

Note: excludes COVID-19 projects.

Source: EvaluatePharma, Evaluate Ltd.
• It is 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.
Refreshing Question 1!

• What is the J-Curve?
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.
Better Late than Never!

• For our ice breaker event, we will demonstrate how evaluating entities works in cases of many unknowns, a scenario that many would say is exemplified by the biotech industry.
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).
Decision and Reception

• Finding that Congress had intended patentable subject matter to "include anything under the sun that is made by man," Chief Justice Warren E. Burger concluded:
  
  • Judged in this light, respondent's micro-organism plainly qualifies as patentable subject matter. His claim is ... to a non-naturally occurring manufacture or composition of matter—a product of human ingenuity.

• This decision would have direct legal consequences in the US alone, but other countries tried to prevent similar conflicts by bringing up the discussions themselves.
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.
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.

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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.
How Did We End Up There?

• The Thalidomide disaster and the Kefauver-Harris Amendment of 1962 resulted in much safer regulatory processes for drug approval, but which also significantly increased the costs of R&D.

• Major pharmaceutical companies focused on medications for common ailments (such as hypertension and diabetes), whereas smaller companies and biotech ones were struggling to enter the market.

• The Orphan Drug Act of 1983 then provided enhanced patent protection and marketing rights, tax incentives, clinical research subsidies and professional advice.
WHAT IS THE ORPHAN DRUG ACT?

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.

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?

BUT APPROXIMATELY 95% of rare diseases are still without an FDA-approved treatment.

Please support the Orphan Drug Act!

Credits to the Jack McGovern Coats’ Disease Foundation. © 2021 by Arbri Kopliku

SPIKE IN ORPHAN DRUG NODS SEEN UNDER TRUMP

The number of prescription drugs approved to treat rare diseases during Trump’s first two years in office is 174.

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

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 these uses.

Data: FDA and J-M.K via Axios

Source: Axios

Average annual cost per patient of the **TOP 100 ORPHAN DRUGS** — excluding blockers with additional orphan uses **>$47,306**

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

Source: EvaluatePharma, 2018

The year the Orphan Drug Act was passed, establishing market exclusivity and financial incentives for drugs approved through the “ORPHAN PATHWAY” is 1983.
What Could Go Wrong?

• Government-endorsed market exclusivity indeed provides a great incentive ensuring companies that if their drug gets approved, it will surely be recommended first by doctors everywhere.

• However, it also implies that the companies behind successful drugs can single-handedly raise the prices of drugs thanks to this monopoly.

• This led to a Congressional hearing on the anticompetitive incentives of the Act, which provides a curious case study for the intersections of Biotechnology and Society.
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”.

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Fast Forward to the Present

• The case of Spark Therapeutics, whose gene therapy treatment for a particular Inherited Retinal Disease costs $850,000 for a one-time administration.

• The case of Gilead Sciences, whose oral tablets Truvada that prevent HIV cost $2,100 for a month.

• The case of Biogen Inc, whose monoclonal antibodies Aduhelm treating Alzheimer’s disease are expected to sell at $56,000 for a year.

➢ One of the above cases did not end up in a Congressional hearing, and by the very fact of me having to mention this, you can guess which one!
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.

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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.
EXTRAS: **Character Spotlight – Andrew Lo**

• Financial engineer, corporate advisor, entrepreneur, inventor, and Charles E. and Susan T. Harris Professor of Finance at the MIT Sloan School of Management.

• Director of MIT’s Laboratory for Financial Engineering, where his team comes up with innovative financial structures that can “turn the tables” of market incentives.

• Created multiple interdisciplinary courses to bridge the gap between life science experts and businesspeople, after his personal sour experience with cancer therapies.

• One of the Forbes World’s 100 Most Influential People (2012).

• Among his most famous projects, he collaborated with the NIH portfolio of rare disease projects and made it successful enough for hedge firms to get involved.
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