Alex Liu
December 15, 2017
History of Therapeutics
Professor Servos

Biotech, Genentech, and Syntex

Introduction

On October 14, 1980, the air crackled with anticipation on the stock market, before igniting into what the LA Times described as "a frenzy the likes of which hasn't been seen on Wall Street since the go-go days of the 1960s."[1] The ringing of the opening bell barely ended before the stock skyrocketed from $35 to $80, peaking at $89 in twenty minutes, before closing at $71.[2] The WSJ described it as "one of the most spectacular market debuts in recent history."[3]

The stock ticker was GENE, the company was Genentech, and the IPO sparked dreams of a multi-billion dollar industry, biotechnology. Biotech was meant to revolutionize medicine but the IPO demonstrated its potential to generate mind-boggling wealth – Swanson, a co-founder of Genentech, was described as "not a big man unless standing on his wallet."[4]

It is thus no surprise that much attention has focused not only on Genentech and the Biotech industry's scientific achievements but its business innovations. Hughes describes "Genentech exemplified a novel corporate form and milieu for business in biology, notably different from anything the pharmaceutical industry offered."[5] Bugos states "As much as it was a hotbed of science, Genentech was a hotbed of financial innovation."[6]

---

[1] Hughes, 158
[2] Hughes, 158
[3] Hughes, 158
[4] Hughes, 35
[5] Hughes, 165
[6] Bugos

Pisano, a Harvard Business School professor, notes that "Perhaps most critical, Genentech pioneered an entirely new business model for entrants into the pharmaceutical industry."[7]

Always mentioned in passing as the last Fully Integrated Pharmaceutical Company, or FIPCO, before Genentech is Syntex Corporation. Yet the venture capitalists[8] behind Genentech, the co-founders[9], and other key executives[10] at Genentech all cite Syntex as a key guide in their path towards becoming a FIPCO. The LA Times even ran an article with the title "Syntex Serves as Model for Young Firms: Now Major Player in Drug Field, It Also Has Some Headaches," quoting the President of Cetus Corp. a biotech company founded earlier than Genentech, that Syntex was the model to follow.[11]

Syntex as a corporation has not received the same level of analysis as Genentech, despite having also achieved Wall Street notoriety. Syntex's share price rose from a low of $11 in 1962 to a high of $190 in 1964,[12] and one its earliest scientists, Djerassi, bought 1200 acres of land in the Santa Cruz mountains and assembled a leading art collection, nicknaming it SMIP, an acronym for Syntex Made It Possible.[13]

This paper attempts to correct this disparity by first focusing on the origins of Genentech and key aspects of its business strategy that are claimed as novel inventions. The second part parallels the first, but this time focusing on Syntex Corporation. In the conclusion, a resulting comparison shows how many of Genentech's supposedly original methods had already been achieved decades ago.

---

[7] Pisano, 85
[8] Perkins, 24
[9] Swanson, 79
[10] Kiley, 57
[11] Day, "Syntex Serves as Model for Young Firms: Now Major Player in Drug Field, It Also Has Some Headaches"
[12] "Syntex Corporation."
[13] Wood, "Father of the Pill"

Analyzing the historical dynamics of business practices in biotech is important as it provides an unique perspective on the challenges faced in creating and capturing value in science and balancing basic versus commercial science. It is especially necessary in the biotech industry as Pisano notes, "…vast scientific success has yet to translate into financial success or improved drug R&D productivity."[14]

Finally, I have enormous gratitude for Sally Smith Hughes and her colleagues at Berkeley for the treasure trove of oral history from key figures in the history of biotechnology and for making it available online. Pisano's book *Science Business* provided an invaluable overview and history of business practices in biotech. There is a significant paucity of literature on Syntex's business practices. Kornberg in *The Golden Helix* provides a personal look at the characters involved in Syntex, whereas Gereffi in *The Pharmaceutical Industry and Dependency in the Third World* provides an excellent overview of Syntex's business and historical context. Finally, Djerassi's autobiography *The Pill, Pygmy Chimps, and Degas' Horse* provided an irreplaceable inner look at Syntex's research and operations.

Genentech

On a Friday in January 1976, twenty-eight year old Bob Swanson, a recently unemployed venture capitalist, was hoofing to UCSF to meet a professor that, after a few minutes of badgering on the phone, capitulated and offered 10 minutes of his time.[15] The professor was Herbert Boyer, who in 1973 along with Stanley Cohen, completed a series of experiments that Stanford's Nobel laureate Joshua Lederberg claimed "may completely change the pharmaceutical industry's approach to making biological elements such as insulin and

[14] Pisano, 6
[15] Hughes, 34-35

antibiotics."[16] The technology was recombinant DNA, whereby scientists could simply and efficiently select genes from any organism and accurately reproduce the genetic material through bacteria in unheard of quantities. The 10 minute meeting between Swanson and Boyer led to a 3 hour conversation at a nearby bar, at least as many beers, and the founding of Genentech.[17]

Swanson was driven by both desperation and an outsider's faith in rDNA. He had graduated from MIT with a BS in Chemistry and MS in Management and then worked for four years at Citibank's venture investment group, before working at Kleiner Perkins for a year. At Kleiner Perkins he was assigned to oversee, and hopefully rescue, their investment in Cetus Corporation, which was founded in 1971 to commercialize technology to automate microorganism selection. Cetus then had a star-studded scientific advisory board, including Stanley Cohen, one of the co-inventors of rDNA, and Swanson caught the rDNA bug from a glowing description of its potential from Nobel Laureate Donald Glaser.[18] Yet Cetus believed that commercialization of the technology was far off, and rebuffed Swanson's proposal that he work for Cetus to lead a rDNA program.[19] Investors were criticizing Cetus for a lack of productivity and their "wide ranging, apparently indiscriminate eclecticism"[20] in research, calling it a "playground for academic scientists."[21] Kleiner Perkins too soon soured on their investment, with Perkins calling Cetus a "high-class fraud,"[22] and when they exited Cetus, Eugene Kleiner also let Swanson go.

As fate would have it, Swanson soon found himself knocking on the door of Kleiner Perkins again, this time armed with a business plan and the dream of leveraging rDNA

---

[16] Hughes, 20
[17] Hughes, 35-36
[18] Hughes, 31 -32
[19] Swanson, 13
[20] Vettel, 202
[21] Glaser, 105
[22] Perkins, 3

technology to build a FIPCO, or Full Integrated Pharmaceutical Company. After some convincing from Boyer, Perkins decided to put in $100,000 dollars for 25% of the equity, and on April 7, 1976, Genentech was incorporated.[23]

For the next two years, Genentech was essentially a Swanson, a secretary, and a desk in Kleiner Perkins. Boyer acted as a consultant, assisting Swanson in crafting the research direction, finding the best scientists and labs, and shaping Genentech's culture. As a proof-of-concept of rDNA technology, Genentech tried to produce human somatostatin. Licensing with the City of Hope, University of California, and Caltech, in 1977 they achieved what was later described by Philip Handler, president of the National Academy of Sciences, as a "scientific triumph of the first order."[24] Ronald Cape, one of the founder of Cetus, later described the revolution that was launched in basic science which dumbfounded some of the best in academia:

> "Herb Boyer was speaking to a great international congress of microbiology in Munich. And they had just announced the somatostatin success. Somebody gets up after he's given his talk and asks the question, "Dr. Boyer, do you realize that not only for somatostatin, but the principles that you've just enunciated, could be used for a whole host of other proteins, like insulin and stuff?" And Herb said, deadpan, "The thought has never entered my mind." [laughter] I thought that was one of the great comebacks."[25]

The production of somatostatin was not just an academic achievement, but a business achievement as well. Genentech had started for 2 years and only spent $515,000.[26] Ron Cape as Cetus noted the economy of Genentech's model, stating: "One of the mistakes [Cetus] made was not to realize the enormous leverage you get from using a university laboratory… It is enormously cost effective. You're using labs and other goodies that are already there…"[27] Moreover, the decision to demonstrate "proof-of-concept" before further funding was a new

---

[23] Hughes, 41
[24] Hughes, 49
[25] Cape, 19
[26] Hughes, 63
[27] Cape, 32

model[28] and, as Perkins notes, helped "remove much of the risk from the entire venture... For next to nothing we had removed a world class question about risk."[29]

The next step for the fledgling company was their true business target, human insulin, a hormone with a large, established market that was being underserved by Eli Lilly. Eli Lilly dominated global insulin production, yet, as Irving Johnson, Eli Lilly's VP of research, noted, "Even if we could collect all of the pancreases from all the pigs in China, you couldn't produce enough insulin to treat all of the people diabetics in the world."[30] Genentech entered the race to produce human insulin against Rutter-Goodman at UCSF and Wally Gilbert at Harvard, both of which were the labs the hottest in molecular biology and stuffed to the gills with swaggering young researchers. After a false scare – a rumor spread that Gilbert had produced a precursor to insulin, which later turned out to be rat insulin – Genentech's group of young, unknown scientists created human insulin on August 21st, 1978.[31]

Genentech's underdog victory was even more notable because young, unproven scientists lead the charge on these projects, a differentiated business structure. Kornberg notes how "Unlike other biotech ventures, with a seasoned scientist or a distinguished board of scientific advisors for guidance, Genentech relied on its 'Young Turks,' unheralded but talented, industrious, and highly motivated to succeed."[32] Genentech's directly employed three-man team in insulin synthesis was led by David Goeddel, later referred to as the "kamikaze scientist"[33] for his indomitable work ethic. When Goeddel joined Genentech in 1978, he had barely spent a year at Stanford Research Institute after graduating from the University of Colorado in 1977. At the

[28] Powell, 91
[29] Perkins, 6
[30] Johnson, 19
[31] Hughes, 91
[32] Kornberg, 200
[33] Kornberg, 199

time of Genentech's insulin success, Goeddel was 27, and Genentech's third scientist, David Yansura, formerly Goeddel's University of Colorado lab partner, was 27 as well.[34] Critically, while Herb Boyer did provide crucial scientific guidance, he continued to keep his full-time position at UCSF. Goeddel remarked that "I don't think Herb came as often as Bob wanted him there… He said, "This is your project; you're going to get credit." He wasn't putting his name on the papers. I think his approach of letting the young scientists do the work really paid off well."[35]

Genentech scientific success with insulin precipitated a reckoning of the tensions between academia's tradition of open publication and industry's needs to monetize intellectual property. The first tremors surfaced in the production of somatostatin. Tom Kiley, then Genentech's legal counsel and later Vice President, had to give the first in a series of explanations of the need to patent quickly and broadly. Before he filed four patents in the wake of the discovery, Kiley had to resolve disputes over claims of inventorship, as he later remarks, "…learned from that [somatostatin dispute] never to assume that all authors on a paper are of necessity inventors on a patent. [There is] much more politics involved in authorship determination."[36] However, the issue came a head after Genentech's landmark success of creating human insulin. Swanson was hesitant to allow the scientists to publish, but Boyer, steeped in academic tradition, persuaded him to not only allow, but encourage, Genentech scientists to publish.

Hughes argues that this was a new model for pharmaceutical companies, stating:

> "Genentech was not unique in granting its employees publication privileges. Such rights were more or less common in high-tech companies in Silicon Valley and some research-based firms elsewhere… Yet in the pharmaceutical industry, intellectual

[34] Hughes, 89
[35] Goeddel, 21
[36] Kiley, 37

> property concerns and trade secrecy tended to dominate drug research, with company scientists by and large reticent to reveal research details to outsiders."[37]

In traditional pharmaceutical companies, researchers were often career employees, as even having their name on a critical patent was often insufficient to generate attention out of the corporate R&D lab.[38] However, Genentech's policy, allowed it to recruit the best scientists and learn from interactions with their academic peers. Perkins argues that beyond putting Genentech together, Swanson's second greatest contribution was to craft an "academic-like environment, but even better than an academic environment" and how "Over the years, Genentech scientists have published as many papers as some of the leading research institutions in the field… the scientific excellence of Genentech is directly attributable to Bob Swanson."[39] This is proven in the scientific record. Genentech published more highly-cited bioscience papers than any other institution except MIT between 1980 and 2001.[40]

Genentech, however, couldn't run off of scientific adulation. Fulfilling Swanson's dream of becoming a FIPCO required financing the enormous costs of R&D and marketing – it's estimated that a new entrant needed to fund $300 million (in 1970 dollars) of R&D costs over ten to twelve years to bring a drug to market.[41] Once the insulin victory was announced, Eli Lilly ended months of negotiations and sent their Executive VP and a patent attorney on a corporate jet straight for Genentech. Four days later, Genentech had a landmark agreement, where Eli Lilly received exclusive worldwide marketing rights to insulin and Genentech received $500,000 dollars upfront and 6 percent royalties.[42] Genentech was now a force to be reckoned with.

---

[37] Hughes, 101
[38] Powell, 33
[39] Perkins, 7
[40] Levinson
[41] Pisano, 85
[42] Hughes, 94

The agreement is also considered a milestone in the formation of the biotech industry. Hughes describes the contract as a "new organizational arrangement in the pharmaceutical industry—the big company–small company alliance… template that Genentech and Lilly promulgated in molecular biology would become a prominent organizational form in a coming biotechnology industry."[43] This claim has been oft-repeated in the literature of the biotech industry. Pisano states that "When pharmaceutical companies did fund R&D at external sources, these almost always took the form of sponsored research agreements with universities or specialized technical consulting. The Genentech-Lilly agreement represents the first time that a pharmaceutical company essentially conducted a proprietary R&D program through collaboration with an external for-profit enterprise."[44]

The agreement is also noted in literature as including milestone payments, whereby Eli Lilly would pay Genentech when they reached certain benchmarks.[45] This was reasonable for Eli Lilly to demand, as critical technical risks still remained in making insulin commercially viable. Genentech's first batch was only enough to give a partial dose to a small mouse.[46] Suddenly, Genentech needed to manufacture kilograms, 50 times their current yield.[47]. The company's fate hung in the balance. As Kleid notes:

> "Then another nice [meant facetiously] thing in the agreement was there were dates. If we didn't make these benchmarks by a certain date written in the agreement, then Eli Lilly could take where we were at that stage, go off with the bacteria, and not owe us a dime."[48]

The milestone-led development partnership established by Genentech and Eli Lilly shaped similar future contracts, but its benefits are arguable. Although this partnership allows small

---

[43] Hughes, 97
[44] Pisano, 86
[45] Powell, 94
[46] Yansura, 27
[47] Kleid, 56
[48] Kleid, 56

companies access to capital without diluting equity, the average R&D alliance in biotechnology lasts less than four years, which is one-third of the expected product development cycle, indicating that many development projects fail.[49] Moreover, Swanson and Boyer had excluded the scientists from negotiations with Eli Lilly, and set highly optimistic benchmarks for drug production. Kleid, Yansura, and other scientists were highly frustrated, with Kleid exclaiming that "The only one that could possibly help us out was God. Nobody had ever made a protein in a bacterium with that kind of yield…Yet Bob says, 'What are you talking about, 'impossible'? I don't like hearing that word.'"[50] Swanson contends that this model involved scientists directly in the business, noting how: "Well, who was responsible for delivering those results? The scientists. And it was wonderful because they understood that we were trying to break even as a company so we wouldn't have to continually raise money and dilute the stock, and that they were responsible…And at some point when we were public, I remember scientists staying up until eleven o'clock at night on March 31 to ship ten grams of material to Japan so it would make it into the first quarter, because there was a million dollars riding on that."[51]

Genentech pursued the same big-company-small-company partnership with a string of research deals. Two major deals include deals with Kabi to produce human growth hormone and Roche to produce interferon. By 1987 licenses for Roche's alpha interferon, marketed under trade name Referon, and Lilly's insulin were bringing in licensing revenues of $5 million apiece.[52]

They followed on research deals with global licensing deals for HGH, t-PA, and gamma interferon, a business practice that Genentech claims as its own innovation and a model later

---

[49] Pisano, 155
[50] Kleid, 61
[51] Sanson, 59
[52] Chandler, 267

companies like Amgen and Genzyme followed.[53] James Gower, then Genentech's head of Marketing and Swanson states "We did it first because we were there first. Growth hormone was approved, when was it? Four years before Amgen's first product was approved, and it worked."[54] Swanson and Gower centered the strategy around the mantra "Sell the product three times,"[5556] referring to how they licensed their products to other companies in Japan and Europe while keeping the US market to themselves.[57] As Swanson argued, "Eighty-five percent of the total world pharmaceutical market is Japan, U. S., and Europe. It's divided a third, a third, a third--a little less in Japan, a little more in Europe, but roughly that way… We're not going to be able to market in Japan for a while… Europe would be easier, but let's try and keep the U.S. rights. So we then used these different financing vehicles to try and cover our expenses while we were building the company--while we were pushing these products to the market."[58] Kiley argues that their licensing strategy was "…certainly new in the extent to which it was practiced by Genentech and was permitted only because suddenly we had a very powerful toolkit that could do many things."[59]

The toolkit was their platform technology of rDNA, which created enough products that they could conduct a strategy they used to call "selling our children – to gain enough substance to promote the other children through the approval process..."[60] Kiley also notes, however, that this licensing strategy was inspired from another source, stating "I remember Bob Swanson saying often that his positive role model was Syntex, because Syntex, the last company to pull

---

[53] Gower, 35
[54] Gower, 35
[55] Gower, 34
[56] Swanson, 96
[57] Swanson, 96
[58] Swanson, 97
[59] Kiley, 57
[60] Kiley, 57

itself into existence in the pharmaceutical industry prior to Genentech, had managed to hip off some of its technology to others, while keeping enough to grow on and to become a real company."[61]

Genentech later sold a 60% stake to Roche in 1990 for $2.1 billion, and the remaining 40% in 2009 for $47 billion.[62] In between it would experience a record setting IPO, undergo failed projects, endure constant litigation, and face fierce competition. However, the company can lay claim to have jumpstarted the modern biotech industry and brought to market multiple life-saving treatments. Genentech's story and model have inspired legions of follower companies, but another story deserves to be told on the company that inspired Genentech's founders and guided its business strategy, the story of Syntex. To do that, we need to go back 40-odd years and deep into the forests of southeastern Mexico and examine a special Mexican yam.

Syntex Corporation

Sex hormones are now so common that the Pill is a common reference to birth control pills. However, hormones as a term were only coined in 1905.[63] The sex hormones were isolated in pure form between 1929 and 1935, and corticosteroids, which are commonly used to treat inflammation, between 1935 and 1938. By the 1930s, three European drug companies, Schering A.G. of Germany, Ciba of Switzerland, and Organon of Holland built a cartel around process patents and cross-licensing agreements which gave them a tight grip on the production and sale of all synthetic sex hormones.[64]

---

[61] Kiley, 57
[62] Cage and Cutler "TIMELINE: Roche strikes deal with Genentech"
[63] Vaughan, 8
[64] Gereffi, 81

The initial market for sex hormones was needed for simple "replacement therapy," as the hormones would be used to either to supplement a lack of naturally occurring hormones or as a substitute for naturally occurring hormones. However, supply at first was extremely limited, as "The sex hormones progesterone, testosterone, and estrone had at first been isolated from tons of sow ovaries, bull tests, and horse urine, respectively."[65] Later methods included the successful isolation of hormones from male and female urine starting in 1929[66], and the synthetic production of hormones through the intermediate product of animal cholesterol, which was developed between 1934 and 1940.[67]

However, with hormones being marketed as cure-alls for a variety of sexual ills, supply could not keep up with demand, and American firms were itching to break the European monopoly. Parke-Davis heavily sponsored research by Russell Marker, a chemist at Pennsylvania State University. Between 1935 and 1943 he published 147 scientific papers on sterols, a subgroup of steroids, and took out seventy-five patents for Parke-Davis.[68] The search for cheap and abundant steroids drove him to focus on sapogenins, a sterol, and particularly on a rare sapogenin called diosgenin, isolated by Japanese chemists in 1936. Marker elucidated the chemical structure of sapogenins in 1939 and successfully converted diosgenin into progesterone, the pregnancy hormone, in 1940.[69]

The search for a cheap source diosgenin led Marker to Mexico, where he was able to find a good yield from a black, lumpy vine that grew wild in southeastern Mexico called *cabeza de negro.* Marker failed to convince American pharmaceutical companies to set up shop in Mexico, so instead he resigned from Penn State and set up his own Mexican laboratory. He then showed

---

[65] Gereffi, 80
[66] Laveaga, 746
[67] Geferri 80
[68] Maisel, 258
[69] Gereffi, 82

up at the doorsteps of a Mexican company named Laboratorios Hormano S.A., which marketed hormones, with two kilograms of progesterone that he manufactured himself. It was worth roughly $160,000 at the market price. The two founders of the company, the Hungarian Emeric Somlo and German Dr. Federico Lehmann, recognized the value of Marker's discovery and founded a new company to industrialize the production of progesterone. Syntex was thus incorporated in January of 1944.[70]

Syntex managed to produce 40 kg of steroid hormones in its first year, but Marker alleged in his memoir that he was swindled out of his 40% equity in the corporation, and left the company. It was the arrival of Rosenkraz, in 1945 and Djerassi in 1949, both brilliant young chemists, that restored Syntex's research capability.[71] Rosenkraz escaped Nazi terror in Hungary and Djerassi, raised in Vienna, escaped the Holocaust by emigrating to the US through Bulgaria.[72] Rosenkraz was able to product progesterone through a different process than Marker's in 1945 and, later leading Syntex's scientific operations, was able to synthesize from diosgenin all four major types of steroid hormones: progestogens, androgens, estrogens, and corticosteroids.[73] Syntex was soon a major world supplier of sex hormones, driving the price of progesterone down from 80 dollars a gram in 1943 down to 0.48 dollars per gram in 1952.[74] This broke down the European cartel, and by the 1950s, 80 to 90 percent of all steroid production came from Mexico.[75]

Syntex's first major research victory was the race to produce another method of synthesizing cortisone, which was then believed to be a wonder drug for treating inflammatory

---

[70] Lehmann et al., 198
[71] Kornberg, 65-66
[72] Kornberg, 66
[73] Gereffi, 84
[74] Gereffi, 88
[75] Gereffi, 89 - 90

diseases, particularly arthritis. Djerassi recalls how "Philip Hench, one of Reichstein's fellow Nobel Prize winners from the Mayo Clinic, had shown movies in 1949 of helpless arthritics receiving cortisone and then, in days, getting up to dance."[76] However, Merck had the only known method of producing cortisone from ox bile, which took 36 steps, and resulted in a cost of $200 per gram.[77]

Syntex faced a formidable array of challenges. It was based in Mexico City, but in the world of science, it might as well have been on another continent – Djerassi describes how phone calls with Cambridge, MA "resembled radiotelephone communications in the Himalayas."[78] Its competitors included Robert Burns Woodward of Harvard, considered the leading American synethetic chemist of the 20th century.[79] However, this group of unknowns' silver bullet was diosgenin. Djerassi noted how "Diosgenin from Mexican yams was so abundant, its cost so low, and the ease of degradation of the side chain to a useful steroid hormone intermediate so great, that we gambled and put most of our intellectual and physical resources on that portion of the problem."[80] After switching to a two-shift operation which enabled the lab to run from 8am to midnight,[81] their method of synthesis from diosgenin proved successful. After mailing their "Communication" to the Journal of Americans Chemical Society, all they could do was wait. They scraped their way to victory by the skin of their teeth, as the Journal received their notification in June 22, and Woodward's on July 9 1951.[82] *Harper's Magazine* later breathlessly commemorated this shocking victory:

> "As perhaps no other recent development, it [cortisone] .. also underscores a point often overlooked in a big-money age. Big minds rather than big research budgets lead to big

[76] Djerassi, 34
[77] Djerassi, 34
[78] Djerassi, 40
[79] Djerassi, 41
[80] Djerassi, 40
[81] Djerassi, 44
[82] Djerassi, 44

discoveries … Last but not least, it should be noted that the leader in the race was a chemical manufacturer in presumably backward Mexico."[83]

Their remarkable scientific victory was even more impressive considering the young, motley crew that synthesized cortisone. Given that Mexico didn't even have a PhD program in Chemistry[84] and its status as a scientific backwater, there were no superstar academics to assemble a star-studded advisory board. Rosenkraz, 35 in 1951, had previously only worked at a "primitive pharmaceutical laboratory" in Cuba.[85] Djerassi, convinced by Rosenkraz to join was only 28 in 1951. However, Rosenkraz was given utmost discretion in assembling a scientific team, investing in facilities, and determining research policy.[86] Thus, even though Djerassi's friends thought him mad for going to Mexico to establish a scientific reputation, he went for the opportunity to compete in the race for cortisone and the guarantee that all discoveries would be published.[87] As Djerassi describes, "…instead of having patent attorneys run the show in terms of deciding whether and when to publish, Syntex operated in the reverse manner: here Rosenkranz and I called the shots – extraordinary for a pharmaceutical company."[88] This is not to say Syntex did not patent its products – for example, Djerassi took extra care to note that "On 31 August 1953, well over a year after my first public report on norethindrone, Frank D. Colton filed a patent for the synthesis of a closely related compound…"[89] Through a research-first business policy and the empowerment of young scientists, Syntex achieved global recognition. In 1959, Louis Fieser, a Harvard chemist, reported that Syntex had published more than any

[83] Djerassi, 45
[84] Mandaro, "Scientist George Rosenkranz; Innovate: His determination helped millions ease their pain, plan their families"
[85] Kornberg, 66
[86] Rosenkraz, 10
[87] Djerassi, 27
[88] Djerassi, 27
[89] Djerassi, 58

academic or industrial laboratory in the steroid field[90] and called Syntex the "University of Steroids."[91]

However, Syntex's pioneering scientific successes did not immediately translate into business success. Syntex had dominated the bulk hormone market by enlisting the support of the Mexican government and limiting foreign entry through export tariffs and permits to gather the barbasco root.[92] However, after 1955, the Mexican state buckled against US antitrust pressures.[93] It was only after a conflict between the owners, who wanted Syntex to remain a bulk producer of intermediate products, and the researchers, who wanted Syntex to enter the finished goods market, that Syntex saw a transition in its business model.

In 1956, Syntex was sold to Ogden Corporation .[94] The owner of Ogden was Charles Allen, a New York financier, who went against his lawyers advice to purchase Syntex as he was impressed by the science and believed Syntex could be the first to develop an oral contraceptive.[95] Critically, he placed Rosenkraz and another brilliant scientist, Zaffaroni, into management. They were able to persuade Djerassi to come back as Director of Research from his academic job at the Wayne State University in Detroit.[96] In 1961, Syntex established its first research unit outside Mexico, the Institute of Molecular Biology at Palo Alto, near Stanford University. Syntex was now fully committed on becoming a FIPCO.

First, Syntex had to solve the problem of funding R&D. In September, 1959, Syntex and Eli Lilly signed a research agreement. Uniquely, this agreement had none of the benchmarks that

[90] Djerassi, 28
[91] Kornberg, 66
[92] Gereffi, 90
[93] Gereffi, 110
[94] Gereffi, 109
[95] Kornberg, 69
[96] Kornberg, 69

were included in the Genentech – Lilly agreement, which by then had become industry standard when negotiating relationships with smaller partners.[97] As Djerassi, states in his autobiography:

> "Our greatest coup, and indirectly the most meaningful accolade extended to us, was when Eli Lilly, then one of the two biggest American pharmaceutical companies, committed itself to fund for a five-year period 50 percent of our research, with the choice of research topics and ownership of patents remaining with Syntex, provided Lilly would get co-marketing rights for any inventions."[98]

Eli Lilly essentially wrote Syntex a blank check, committing to "clinical investigations of promising new compounds,"[99] and the collaboration produced a cornucopia of products. A safe option for Lilly was financing clinical investigations into the norethindrone, a critical ingredient of the first birth control pills. However Lilly also helped:

> "…create a second progestational agent (chlormadinone, which Lilly eventually marketed as an estrogen-free contraceptive), the powerful anabolic oxymetholone, the best-selling topical corticosteroid Synalar, a systemic corticosteroid related to prednisone, and finally dromastonolone propionate, a steroidal breast cancer palliative, which Lilly brought to the US market in the early 1960s."[100]

Impressively, Eli Lilly knew that it wasn't the only claimant to Syntex's record research productivity and sales of noretherindrone. In 1956, Syntex reached an agreement with Parke-Davis where they received an exclusive license to market norethindrone in the US.[101] Later, they signed a license with Schering AG that gave a license for the rest of the world. In an innovative measure, Syntex received not a royalty, but a fixed percentage of total earnings, not royalties based on a percentage of sales.[102] While this cut into Syntex's earnings, this licensing strategy helped Syntex gain access to many other large pharmaceutical firms. Parke Davis later got cold feet and refused to market norethindrone as an oral contraceptive, due to fears of a Catholic

---

[97] Johnson, 39
[98] Djerassi, 96-97
[99] "Two Join in Drug Research", NYT
[100] Djerassi, 87
[101] Chandler, 265
[102] Chandler, 265

boycott of their products.[103] Syntex, with Zaffaroni leading negotiations, was able to sign a deal with the Ortho Division of Johnson & Johnson. While Searle, a competitor, released a contraceptive pill in 1960 formulated with norethynodrel, by 1962 J&J released Syntex's product as Ortho-Novum. Parke-Davis woke to its senses in 1964 and licensed a derivative of norethindrone, norethindrone acetate, from Syntex and started marketing it as an oral contraceptive.[104] By that time Syntex had developed its own sales force and was marketing its own contraceptive pill, under the trade name Norinyl.[105]

Syntex also went on a worldwide licensing spree to market their products broadly. Rosenkraz states, in rather similar language to Djerassi, how:

> "Our biggest coup was to create a worldwide distribution of our new compounds practically overnight and without a cent of investment. This novel approach consisted of selecting as a partner one of the top five drug firms in a European country. We proposed to provide them with the active ingredients, not for a fixed price and royalty, but for 30% of the net sales price. We would have no say in the pricing. The label would bear the Syntex name jointly with theirs. They would have right of first refusal for our future products. But again, we retained our right for marketing under our own label. This arrangement was unheard of in those days, but our research productivity proved to be convincing. Eventually among others, Syntex-ICI, Syntex- Recordati, and Syntex-Astra products were launched."[106]

In contrast to Genentech, Rosenkraz, a scientist, led the charge on these business decisons, This is corroborated by New York Times reports. For example on December 7, 1960, Rozenkraz announced a deal with Les Laboratories Cassene of Paris, an affiliate of the Roussel Corporation, which will distribute Syntex pharmaceuticals to France, Algeria, Tunisia, Morocoo, Vietnam, and other French territories.[107] On July 25, 1961, Rosenkraz announced further deals with Recordati Laboratorio Farmacologico, S. p. A. Milan, which would distribute in Italy, Ethiopia,

---

[103] Djerassi, 62-63
[104] Djerassi, 63
[105] Gereffi, 111
[106] Rosenkraz
[107] "Syntex in Foreign Deal: Will Sell Hormone Products in French Market Areas."

Eritrea, Somaliland, and Libya, and a deal with Instituto Farmacologico Latino S. A. Madrid. which would distribute in Spain and Spanish territories in Africa.[108] Syntex wasn't just selling their drugs three times, but to multiple European submarkets.

Syntex's multitude of research and licensing deals was enabled by a "platform technology" of their own, diosgenin. The Mexican yam was cheap and plentiful, making diosgenin as an intermediate product economically accessible, but the true benefit lied in its chemical structure. As Gereffi notes, "The real superiority of diosgenin lies in its extraordinary versatility as a steroid starting material. When cholesterol is broken down chemically, only two of its intermediate compounds can be transformed into commercial products. Diosgenin, however, produces an intermediate compound known as 16-dehydropregnenolone (16-D), from which chemists can move to almost all other pharmaceutically interesting steroids in any desired ratio."[109] Thus Syntex not only captured value through patents, but also through its prodigious research into diosgenin, was able to obtain invaluable knowhow in steroid synthesis and development. Consequently, while Syntex heavily licensed one of its best products, norethindrone, in 1961 it started selling Andral, a corticoid used for those chronically underweight, and Synalar, a related corticoid as a skin anti-irritant.[110] The development of Synalar can be directly attributed to Rosenkraz and Djerassi's experiments in creating many hydro-cortisone-like compounds.[111]

---

[108] "Syntex Expands Distribution"
[109] Gereffi, 89
[110] Chandler, 265
[111] Kornberg, 69, notes how: "The Rosenkraz-Djerassi team of bright and energetic chemists synthesized a variety of hydrocortisone-like compounds… But the labor and time needed to make each of these compounds limited their number and range. Alex used adrenal extracts to perform the difficult introduction of the signature unit of steroids, the hydroxyl group in position 11-B. Now a very much larger number of synthetic compounds could be assayed; those with a fluorine atom replacing hydrogen in position 6 were found to be especially active against inflammation – a breakthrough in therapy that became a marketing success as Synalar."

Syntex achieved blockbuster success with norethindrone and anti-inflammatory steroids (which included Synalar) and rode their sales to become a FIPCO. In 1965, anti-inflammatory steroids accounted for 48% of the companies total sales, and oral contraceptives only accounted for less than 40% of sales, showing how both Syntex was able to achieve marketing success with its own drug and its near complete shift from being a bulk hormone producer.[112] Thus, by the mid-1960s, Syntex was able to free itself from research and license deals with other pharmaceutical companies.[113] Syntex now had the size to finance its own R&D, a worldwide marketing network, and diversification into multiple product lines.

Syntex went on to not only launch another two blockbuster drugs, Aarane and Naprosyn, but also face Senate hearings on the harm of birth control pills, undergo a FDA investigation into Naprosyn, acquire a dental equipment manufacturer, face a Congressional investigation into Syntex manufactured baby-powder, and diversify into various other products.[114] However, by 1994, its drug development pipeline didn't produce a blockbuster in time for the expiration of Naprosyn, its blockbuster arthritis treatment, and Syntex was sold to Roche in 1994[115]

Conclusion

Historians resort to periodization in order to facilitate the study of history and provide a framework of understanding. However, finding the beginning or end of any period is rather arbitrary and in many cases has changed over time. Genentech's science was revolutionary and shifted medicine into a new paradigm. Although many have ascribed Genentech as the first

[112] Gereffi, 112
[113] Gereffi, 112
[114] "Syntex Corporation." International Directory of Company Histories.
[115] Freudenheim, Milt. "Roche Set To Acquire Syntex."

business prototype in the biotech industry, it is much more difficult to attribute the same novelty to Genentech's business practices. As noted in *Logics of Organization Theory*:

> "A major source of this difficulty [demarcating an unambiguous start or origin of an activity, industry, or population] occurs, we think, because we lack the analytical framework to identify and describe the early steps in industry or form emergence…As a next step, ethnographic and other qualitative research might prove extremely useful in simply identifying and describing interesting relevant cases."[116]

This case study of Syntex in relation to Genentech hopes to be this next step and demonstrate how many of Genentech's lauded business practice innovations were in fact either directly inspired from or done before by Syntex.

A critical aspect is the policy of encouraging scientists to publish, thereby emulating the university in the corporation but cutting out the grant chasing and struggle for tenure. Genentech was praised in its era for being the first to publish basic science breakthroughs, specifically in rDNA, that astounded both the corporate and academic worlds. However, Syntex had done the same 30 something years before with its groundbreaking synthesis of all four sex steroids from diosgenin.

As a corollary to Genentech's dominant focus on state-of-the-art, near basic science, it empowered fresh and unknown graduates and unleashed their energy and hunger for recognition into the all-or-nothing atmosphere of a financially precarious startup. This was notably different from Cetus, which was founded earlier, and other biotech firms, like Genex and Amgen, which relied on an all-star scientific board to drive the scientific direction. Yet Syntex, by the mere fact of its location in Mexico in the 1940s and 50s, meant that it had to hire young, relatively unknown scientists by promising them full discretion on research budgets, the freedom to tackle cutting-edge science, and academic recognition.

---

[116] Hannan, Polos & Carroll, 58.

In its dreams of becoming a FIPCO, Genentech financed R&D costs for its breakthrough human insulin hormone through a research partnership with Eli Lilly. This practice has been hailed as a crucial innovation in the establishment of biotech as a discrete industry from traditional pharmaceuticals. However, Syntex faced the same R&D problems, and developed a similar solution by signing an astonishingly liberal research deal in 1959 with, coincidentally, Eli Lilly.

Finally, Genentech executives claim that their cutting-edge platform technology enabled a novel licensing strategy. First was the ability license multiple products while retaining enough products to sell themselves. Second was their ability to break up the global market and license separately to multiple regions. Syntex's unique advantage wasn't initially a technology, but a Mexican yam that yielded plentiful quantities of the chemical rock-star diosgenin. However, it was able to leverage its initial edge into a platform of sex hormone and corticosteroid products. This enabled as well extensive licensing of its products in development, and global deals with multiple pharmaceutical companies.

Genentech remains a remarkable achievement and its story a testament to human resourcefulness, drive, and naiveté. However, by turning the spotlight onto the similarly phenomenal story of Syntex, a new perspective on the emergence of biotech as a discrete industry emerges. Importantly, Syntex shows how innovation is not necessarily bounded into geographic clusters, and points to how future entrepreneurs can achieve scientific and business triumphs from unlikely origins.

Bibliography

Bugos, Glenn E. 2002. Introduction to "Kleiner Perkins, Venture Capital, and the Chairmanship of Genentech, 1976-1995," an oral history conducted in 2001 by Glenn E. Bugos for the Regional Oral History Office, The Bancroft Library, University of California, Berkeley, 2002.

Cage, Sam, and Cutler, David. "TIMELINE: Roche strikes deal with Genentech." Reuters. March 12, 2009. Accessed December 15, 2017. https://www.reuters.com/article/us-roche-genentech-timeline-sb/timeline-roche-strikes-deal-with-genentech-idUSTRE52B2BF20090312.

Djerassi, Carl. The pill, pygmy chimps, and Degas horse: the autobiography of Carl Djerassi. New York: Basic Books, 1992.

Freudenheim, Milt. "Roche Set To Acquire Syntex." The New York Times. May 02, 1994. Accessed December 15, 2017. http://www.nytimes.com/1994/05/03/business/company-news-roche-set-to-acquire-syntex.html.

Gereffi, Gary. The pharmaceutical industry and dependency in the third world. Princeton University Press, 2017.

Gower, James M., “Business Development and Marketing Strategy at Genentech, 1982-1992,” an oral history conducted in 2004 by Sally Smith Hughes, Regional Oral History Office, The Bancroft Library, University of California, Berkeley, 2006.

Hannan, Michael T., László Pólos, and Glenn R. Carroll. Logics of organization theory: Audiences, codes, and ecologies. Princeton University Press, 2007.

Hughes, Sally Smith. Genentech: the beginnings of biotech. University of Chicago Press, 2011.

Johnson, Irving S., “Eli Lilly & the Rise of Biotechnology,” conducted by Sally Smith Hughes, 2004, Regional Oral History Office, The Bancroft Library, University of California, Berkeley, 2006.

Kleid, Dennis G., Ph.D., "Scientist and Patent Agent at Genentech," an oral history conducted in 2001 and 2002 by Sally Smith Hughes for the Regional Oral History Office, The Bancroft Library, University of California, Berkeley, 2002.

Kornberg, Arthur. The golden helix: Inside biotech ventures. University Science Books, 2002.

Lehmann, Pedro A.; Bolivar G., Antonio; and Quintero R., Rodolfo. 1973. “Russell Marker: Pioneer of the Mexican steroid Industry.” Journal of Chemical Education 50, no. 3 (March): 195-199

Levinson, Arthur D. 2001. Introduction to “Robert A. Swanson: Co-founder, CEO, and Chairman of Genentech, Inc., 1976-1996.” An oral history conducted in 1996 and 1997 by Sally Smith Hughes, Regional Oral History Office, The Bancroft Library, University of California, Berkeley, 2006.

Maisel, Albert Q. (1965). The Hormone Quest. New York: Random House.

Mandaro, Laura (8 August 2005). "Scientist George Rosenkranz; Innovate: His determination helped millions ease their pain, plan their families". Investor's Business Daily.

Perkins, Thomas J., "Kleiner Perkins, Venture Capital, and the Chairmanship of Genentech, 1976-1995," an oral history conducted in 2001 by Glenn E. Bugos for the Regional Oral History Office, The Bancroft Library, University of California, Berkeley, 2002.

Pisano, Gary P. Science business: The promise, the reality, and the future of biotech. Harvard Business Press, 2006.

Rosenkraz, George. "The Early Days of Syntex." Chemical Heritage 23, no. 2 (2005): 8-12. June 30, 2005. Accessed December 10, 2017. https://issuu.com/chemheritage/docs/syntex_rosenkranz-zaffaroni.

"Syntex Corporation." International Directory of Company Histories. Accessed December 15, 2017. http://www.encyclopedia.com/books/politics-and-business-magazines/syntex-corporation.

"Syntex in Foreign Deal: Will Sell Hormone Products in French Market Areas." New York Times, December 7, 1960, p. 69. ProQuest Historical Newspapers [ProQuest]

“Two Join in Drug Research.” New York Times, 16 Sept. 1959, p. 63. ProQuest Historical Newspapers

Vaughan, P. (1970). The Pill on trial. New York: Coward–McCann.

Wood, Gaby. "The Father of the Pill." The Guardian. April 14, 2007. Accessed December 15, 2017. https://www.theguardian.com/lifeandstyle/2007/apr/15/healthandwellbeing.features1.

Yansura, Daniel G., "Senior Scientist at Genentech," an oral history conducted in 2001 and 2002 by Sally Smith Hughes for the Regional Oral History Office, The Bancroft Library, University of California, Berkeley, 2002.