What can biofuel commercialization teach us about scale, failure, and success in biotechnology?

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Abstract

This paper examines the history of four biofuel firms (KiOR, Amyris, REG, and Novozymes) to draw lessons for the development and commercialization of cell-cultured meat. Findings include the strategic advantage of pursuing high-margin, low-volume products before low-margin, high-volume products, the pitfalls of overpromising with respect to timelines and product, the trap of technological inflexibility, and the way that many different firms pursuing parallel vertical integration strategies can spread fragility within an industry.

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> One constant among the elements of 1914—as of any era—was the disposition of everyone on all sides not to prepare for the harder alternative.
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> — Barbara Tuchman, *The Guns of August*

Introduction

The history of biofuels offers underexplored lessons about what companies should do when they encounter technical problems and cost overruns, particularly when scaling production. Near the end of the 20th century, work to produce fossil fuel equivalents like biodiesel using microorganisms and chemical reactions on renewable substrates like corn and cellulose intensified. Ethanol from corn had been manufactured in the US from the 1970s, but the 1990s through the 2010s saw waves of new biofuel production processes, eventually divided into second, third, and fourth generation biofuels. These generations promised to derive fuel from inedible matter like cellulose rather than edible matter like corn. They also promised higher efficiency, lower costs, improved sustainability, and ease of use. From the mid-2000s to about 2013, biofuels were increasingly seen as a solution to oil shortages and rising carbon emissions. Investment flooded in. By the mid-2010s, enthusiasm and investment had drained away in the face of repeated failures. Talk of fixing the world energy system was replaced by talk of a biofuel winter. The rise and fall of advanced biofuel firms remains one of the most-discussed failures of a sustainability technology. Cultured meat advocates and firms should consider what realistic rearguard action would look like in various bad-case scenarios in which affordable cultured meat takes one to four decades longer than any firm has predicted. Answers to these questions could help mitigate bad-case scenarios. To illustrate the potential impact with some high-level estimates, effective mitigation could mean the difference between, e.g., a 40-year delay in cultured meat adoption (in the event of large overreach, investor flight, and resulting cell-ag winter) and a 15-year delay in cultured meat adoption (in the event that scaling is harder than most firms thought, but a more careful and distributed strategy remains resilient against industry collapse). We estimate the difference between these two scenarios in years of farmed animal suffering to be in the high tens of trillions to low hundred trillions.

This paper examines the histories of four biofuel firms as proxies for wider trends within the industry. I present eight analogies and fourteen disanalogies or differences of unclear sign between the biofuels and animal-free food fields. I offer implications and findings for alternative protein projects on the basis of these comparisons.

Summary of key implications

A summary of implications and findings is at the end of the report.

Biofuel lessons in four companies

This section examines four biofuel companies: KiOR, Amyris, Renewable Energy Group, and Novozymes. Each of these firms offers a different set of lessons from which the cultured meat industry can learn. KiOR[1] is notable for its sharp rise in prominence, inability to realize its technological promise, and rapid decline. Amyris also ran into technical trouble, but managed to stay alive by pivoting to smaller-scale, higher-margin products like cosmetics. Renewable Energy Group (REG) uses a more conservative approach than KiOR or Amyris and remains the largest biodiesel producer in the United States in part because of this approach. Unlike KiOR, Amyris, or REG, Novozymes has not built an end-to-end business model in which a fuel is derived from feedstock and sold to consumers. Instead, Novozymes develops and sells enzymes used in fuel production (among other applications), often to biofuel firms. Novozymes' lack of interest in producing biofuels in a vertically-integrated way has, somewhat counterintuitively, contributed to the development of enzyme-based fuel production. The achievements and missteps of these firms suggest different paths and pitfalls for cultured meat projects.

KiOR

The technical failure of catalytic pyrolysis

In the second week of November 2014, the biofuel company KiOR filed for Chapter 11 bankruptcy protection in Delaware. From 2008 to 2011, KiOR had been widely regarded as one of the most promising firms working on next-generation biofuels.[2] KiOR proposed to use

[1] "The name doesn't mean anything; it was just one of many four-letter names Khosla Ventures had trademarked." Katie Fehrenbacher, "A Biofuel Dream Gone Bad," *Fortune*, December 4, 2015, http://fortune.com/kior-vinod-khosla-clean-tech/.

[2] A "bold, We-Are-Black-Swans, detailed descriptions of yields, costs, downstream partners, brand-name board members and timelines to commercial scale… had been the style of… KiOR." The company "was exciting, dramatic, and fast, and the headlines it produced between 2008 and 2011 were candy for a renewables-hungry

catalytic pyrolysis to transform biomass feedstock into hydrocarbons to be used as fuel. What would become KiOR's largest plant, in Columbus, Mississippi, used woodchips as feedstock. The aim, as with many second- and third-generation biofuel ventures, was to produce useful fuel not from edible feedstock like corn, but from the cellulose in waste products like woodchips and cornstalk. Using inedible waste as feedstock sidestepped concerns that crops and land that would have produced food would instead be used to produce fuel.[3] Second- and third-generation biofuel efforts also promised to reduce rather than increase total agricultural waste and to generate lower lifecycle carbon emissions when compared with conventional fossil fuels and first-generation biofuels from crops.

KiOR's failure, although not unusual in an industry where setbacks have been common, generally arrived as a surprise. How could a publicly-traded company with ample funding, government-backed loans, and a large public offering fail to achieve even a fraction of its yield and cost targets? An unusual amount of information about KiOR's decline has entered the public record. The state of Mississippi sued KiOR for fraud, the SEC charged KiOR for withholding information about biofuel yields, a group of KiOR investors sued KiOR executives for misleading them, the company's Chapter 11 filing made thousands of internal documents public, and several highly-placed people in the firm, including those involved with the company's technology, have since spoken to trade publications like *Biofuels Digest* about their time at KiOR. The lawsuits have rendered a large amount of documentation public and the interviews with former executives and scientists have led to long, detailed articles about KiOR's ascent and implosion.

KiOR's first-choice strategy for converting biomass into usable hydrocarbons ran into early trouble. By the spring of 2008, lab results revealed "excessive amounts of water, coke, gas and

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world." Jim Lane, "KiOR: The inside true story of a company gone wrong," part one, *Biofuels Digest*, May 17, 2016, http://www.biofuelsdigest.com/bdigest/2016/05/17/kior-the-inside-true-story-of-a-company-gone-wrong/.

[3] "Now that food crops can be converted into fuels, a new factor must be considered—the link between the price of food and the price of petroleum. As petroleum fuels get more expensive, biofuels become more profitable; therefore, biofuel producers can afford to pay more for their feedstock.

"According to [Lester] Brown, this new relationship puts hungry people in direct competition with empty gas tanks. 'Historically the food and energy economies have been largely separate, but now with the construction of so many fuel ethanol distilleries, they are merging,' he says. 'If the food value of grain is less than its fuel value, the market will move the grain into the energy economy. Thus, as the price of oil rises, the price of grain follows it upward.' David J. Tenenbaum, "Food vs. Fuel: Diversion of Crops Could Cause More Hunger," *Environmental Health Perspectives* 116 (2008): A254–A257.

char and a relatively small amount of bio-oil that had a low acidity."[4] Bio-oil was good, but high levels of water, coke, gas, and char were not. Their presence made it harder and less economical to upgrade the bio-oil into usable fuel. KiOR would have to find a way to reduce levels of undesirable material and to increase hydrocarbon output.

Moreover, the proprietary catalyst used in the early tests was expensive. For KiOR to achieve its cost targets, its catalyst would have to be relatively cheap (at least in the low four figures of US dollars per metric ton) and its process would have to use limited amounts of catalyst. KiOR ended up relying on ZSM-5 type catalysts, which are quite expensive (between six and eight thousand USD per metric ton).[5] Weak results with an expensive catalyst were worrying, but not a death knell. It had always been essential to KiOR's business plan that costs would come down and yields rise as production scaled.

A third and final problem arose as tests proceeded. KiOR researchers found that the yields from their pyrolysis were low, even with high-end catalysts. For KiOR to hit its cost and output targets, it would need to produce more than 60 gallons (~227 liters)[6] of liquid hydrocarbons per ton (~907 kg) of dry biomass put in. In its initial public offering, KiOR estimated its yield at 67 gallons per bone-dry ton (BDT), with a yield target as high as 90 gallons/BDT at commercial scale.

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[4] Lane, "Inside," part one, 8.

[5] ZSM-5 stands for Zeolite Socony Mobil–5, a porous aluminosilicate material used as a high-end industrial catalyst mostly in oil and gas applications. ZSM-5 remains expensive because it is somewhat complicated and energy-intensive to produce. (For more on the synthesis of zeolites, see e.g. this patent search: patents.google.com/?q=process&q=precursor&q=zsm&q=alumina+hydrate&q=alkali+metal.) The catalytic pyrolysis KiOR proposed to use for biomass was not radically different from the use of fluidized catalytic cracker units in modern petroleum refining. *Biofuels Digest* reporter Jim Lane writes that "fluidized catalytic cracker [FCC]... is a standard unit at more than 400 oil refineries worldwide; one-third of the world's crude oil is processed in a FCC reactor," and the "use of synthetic zeolites and their modified forms, as FCC and hydrocracking catalysts, has revolutionized the petroleum refining business. The use of zeolite-based FCC catalysts has made possible to achieve substantially higher conversion yields of gasoline and diesel fuel from each barrel of crude oil refined." KiOR hoped to achieve similar yield gains by using their own catalytic pyrolysis, though they hoped to avoid using a catalyst as expensive as ZSM-5. (They would be defeated in that hope. Paul O'Connor, a KiOR board member, reflected that "[i]t was the worst decision ever made, ZSM-5. We all knew that to make this process economic we needed a cheap catalyst. ZSM-5 is one of the most expensive around. Plus, you are dealing with a biomass with calcium and many other things in it, and with ZSM 5 you kill the catalyst. It's so strange they went in that direction.") See Lane, "Inside," part one, 3, and part two, 8.

[6] KiOR sticks to gallons as their unit of measurement and virtually all technical materials about yield numbers are in gallons per bone-dry ton. This convention is maintained here. In metric, KiOR needed to hit yields between 227 and 340 liters per ton of biomass, but they were usually closer to 80 liters per ton.

Most early tests found yields in the low 20 gallons/BDT range, and "never above 30 gallons per bone dry ton of biomass," reported KiOR's science director, Conrad Zhang, in late 2008.[7] KiOR tried repeatedly over the next four years to bring its yields into the 60-gallon/BDT range. The problem of low yields would precipitate several splits within the company over different technical approaches. On and off, internal splinter groups, convinced KiOR's main approach, biomass catalytic cracking (BCC),[8] would never produce yields as high as the company needed, worked in quasi-secret on different technological approaches.[9] They hoped to find some alternative process [10] that would improve yields in a way that KiOR's BCC approach had not.

These attempts failed. Yields never touched 60 gallons/BDT, costs never reached the promised $1.80 per gallon, and KiOR filed for chapter 11 bankruptcy in 2014.

This leads to an important strategic question: to what extent was this failure due to inherent technical challenges of biofuel production versus KiOR's own mistakes? In his letter of resignation, KiOR board member Paul O'Connor wrote: "The reason for [KiOR's difficulties], in my opinion, is not because of the failure of the technology itself, but because of several wrong choices made during the development and commercialization of the technology."[11] In truth, technological shortcomings combined with decisions about how to develop and scale the

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[7] Lane, "Inside," part one, 17.

[8] Essentially another way of saying catalytic pyrolysis—"cracking" refers more generally to a process of breaking down molecules, and here KiOR uses it to designate a variety of pyrolysis that uses catalysts.

[9] "Two KiOR scientific wings emerge… No one was more emphatic about the pilot plant results than scientist Robert Bartek, who sent an email 'More Math on BCC' on December 7th, stating:

'We are in a period of denial. We must forget that our original conceptions of BCC are not right and must do something radically different to save the Project.'

"By the end of 2008, it is clear from discussions with multiple KiOR sources that the KiOR scientific staff had divided into two groups. One group believed that the BCC Technology had been sufficiently tested, was not working, had no value to KiOR's business and should be immediately stopped.

"The other group, which was headed by O'Connor, focused on improving the BCC Technology, and on support of the three European Labs doing so. The controversy over the R&D Plan for 2009/2010 — to the extent that it exacerbated a growing rift between O'Connor and Ditsch — would have far-reaching consequences as 2009 unfolded." See Lane, "Inside," part two, 1. Emphasis in the original.

[10] Among other tweaks, the alternative approach relied on the expensive ZSM-5 catalyst. While it was able to bring yields from the 20 gallons/BDT range to the 40 gallons/BDT range, it was unable to raise yields into the target range of (at first) 67 gallons/BDT and (later) 80 to 90 gallons/BDT.

[11] Paul O'Connor, "LETTER OF RESIGNATION," Exhibit 17.1, Securities and Exchange Commission, August 31, 2014, https://www.sec.gov/Archives/edgar/data/1418862/000119312514421847/d824230dex171.htm.

technology led to failure. KiOR committed a variety of technical and strategic mistakes, particularly during the six crucial years from 2008 to 2013. These mistakes offer valuable lessons for contemporary firms attempting to move technologies from demonstration to commercialization. However, KiOR's catalytic pyrolysis process failed time and again to produce the results needed. The underlying fact is that positive technical results never appeared in time for KiOR to bring transport fuels to market.

Almost all firms working on cultured meat will experience setbacks similar to KiOR's at some point. How these firms respond to technical difficulties will determine not only their success but in many cases the success of the technology in question. KiOR was unable to bridge the "valley of death"[12] between demonstration and commercialization. Cultured meat firms will have to learn from the failure of biofuel companies like KiOR to avoid vanishing into the same gap.

Strategic fixedness and overcommitment

KiOR's researchers and management team were probably less open to alternative technological approaches than they otherwise would have been because they felt pressured to bring products to market quickly. They were also constrained and confused by an inflexible management team prone to infighting. KiOR's "strategy in rushing towards demonstrating the BCC technology at a multi-barrel-per-day scale," former Director of Technology Jacques De Deken wrote in 2008, "without corroborating experimental data, under the pretense of self-deception of 'creating value', is a recipe for technical failure. Indeed, I do not believe that we currently have the experimental results, catalyst(s) or science base to justify the rush and expense of a [BCC] unit or demonstration... at this time."[13] As early as 2008, KiOR was overcommitted to one approach, moving too hastily in part because of investor pressure, and unwilling or unable to explore alternative solutions.

By 2010, KiOR's troubles had deepened. Yields remained low and its biocrude remained acidic and highly oxygenated. In response, KiOR management began to shut out employees critical of the technological approaches favored within the firm. For example, KiOR, when constructing their demo plant in 2010, kept Robert Bartek, De Deken's successor in overseeing plant design and testing, out of the design loop. While the plant's development might have run more smoothly in the short term without Bartek identifying problems, the decision eventually led to delays and

[12] See Clyde Frank et al., "Surviving the 'valley of death': A comparative analysis," *The Journal of Technology Transfer* 21 (1996): 61-69.

[13] Quoted in Lane, "Inside," part one, 9. Punctuation *sic*.

cost overruns in the demo unit, including having to replace the unit's main reactor with a different design, an astonishing and costly error.[14] Bartek left KiOR soon after, further weakening the company's ability to self-correct.

Industry reporter Jim Lane describes these failures on KiOR's (and other biofuel firms') part as of a piece with the institutional errors made at NASA in the Space Shuttle era. "The NASA cautionary tale is instructive," he writes, because "there are correlations between KiOR and [the] *Columbia* [and *Challenger* disasters]… Specifically, reluctance to test to understand why systems were not performing in accordance with requirements, organizational barriers that prevented effective communication of critical information and stifled professional differences of opinion; lack of integrated management across program elements; and the evolution of an informal chain of command and decision-making processes that operated outside the organization's rules."[15]

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[14] "In January 2010, though, focus was on a potential 20% bio-oil yield improvement possible by employing CPERI's reactor design, compared to the yields obtained by the present design of the KCR Pilot plant (a[n] FCC type).

"The Pilot Plant was remodeled with the CPERI design, but to the surprise of the team, the Demonstration Unit design was not changed. According to those familiar with the timelines, the Demo Reactor was already fabricated and was soon to be delivered to KiOR for installation, based on the old, obsolete original KiOR Pilot Plant Reactor design.

"Eventually, the large Reactor of the Demo Unit, with a 10 ton per day capacity, would have to be dismantled and be replaced by the new Frustum Reactor licensed from CPERI. Resolution of the problem would lead to sensational additional costs and delays in the operation of the Demo Unit.

"How could this have happened? As it turns out, Robert Bartek, described by one team member as "the expert who had supervised the Pilot plant testing work at the KBR Pilot Plant after De Deken had left, who had managed the design and operation of KiOR' KCR Pilot Plant and who had worked closely with Prof. Vasalos and Dr. Lappas in transferring their Reactor design to KiOR," was left almost completely out of the loop.

"According to KiOR team members of the time, Bartek "was intentionally kept in the dark and out of the design work of the Demo Unit until almost to the end of the project."

"Why? Perhaps because Bartek was openly and clearly criticizing the BCC Technology and its Catalyst for being 'a failure and useless to KiOR'.

"'Suggestions and disagreements were considered to be politically incorrect, and rather blasphemies against the party-line prevailing in 2009, supporting and promoting exclusively the BCC Technology and its Catalyst,' remarked Dennis Stamires, when asked about the crisis. More than one KiOR team member contended that the decision to exclude Bartek from the Demo design process, among other consequences, convinced Bartek to resign." See Lane, "Inside, part two, 9. Punctuation *sic*.

[15] Lane is relying on the *Columbia* Accident Investigation Board's report, which, quoted more extensively, reads:

"The Board recognized early on that the accident was probably not an anomalous, random event, but rather likely rooted to some degree in NASA's history and the human space flight program's culture. Accordingly, the Board broadened its mandate at the outset to include an investigation of a wide range of historical and organizational issues, including political and budgetary considerations, compromises, and changing priorities over the life of the Space

One way of promoting institutional structures that can self-correct is to bring engineers into decision-making processes otherwise controlled by non-technical management and investors. For example, in January 2011, Dennis Stamires, a senior scientist at KiOR, wrote in an email that his team was "still looking for a suitable catalyst, hopefully without containing ZSM, or at least a small portion. You can see how frustrated I am , after two or three years and all the work we have done, millions of dollars spent , we are now stuck in a Hole with the ZSM." That same month, however, "in management circles, there wasn't a corresponding sense of gloom. In fact, there was a celebration going." KiOR had taken an important step toward securing a federal loan guarantee, and the management team, which was more concerned with financing than with engineering problems, remained less informed and concerned about technical questions than they should have been.[16] This continued gap between researchers and engineers' knowledge and the expectations of KiOR management hampered the company's ability to self-correct.

Shuttle Program. The Board's conviction regarding the importance of these factors strengthened as the investigation progressed, with the result that this report, in its findings, conclusions, and recommendations, places as much weight on these causal factors as on the more easily understood and corrected physical cause of the accident….

"The organizational causes of this accident are rooted in the Space Shuttle Program's history and culture, including the original compromises that were required to gain approval for the Shuttle, subsequent years of resource constraints, fluctuating priorities, schedule pressures, mischaracterization of the Shuttle as operational rather than developmental, and lack of an agreed national vision for human space flight. Cultural traits and organizational practices detrimental to safety were allowed to develop, including: reliance on past success as a substitute for sound engineering practices (such as testing to understand why systems were not performing in accordance with requirements); organizational barriers that prevented effective communication of critical safety information and stifled professional differences of opinion; lack of integrated management across program elements; and the evolution of an informal chain of command and decision-making processes that operated outside the organization's rules.

"This report discusses the attributes of an organization that could more safely and reliably operate the inherently risky Space Shuttle, but does not provide a detailed organizational prescription. Among those attributes are: a robust and in-dependent program technical authority that has complete control over specifications and requirements, and waivers to them; an independent safety assurance organization with line authority over all levels of safety oversight; and an organizational culture that reflects the best characteristics of a learning organization.…

"The pressure of maintaining the flight schedule created a management atmosphere that increasingly accepted less-than-specification performance of various components and systems, on the grounds that such deviations had not interfered with the success of previous flights."

See *Columbia* Accident Investigation Board, "*COLUMBIA* ACCIDENT INVESTIGATION BOARD REPORT EXECUTIVE SUMMARY," Vol. I, August 2003, https://www.nasa.gov/columbia/home/CAIB_Vol1.html.

[16] Lane, "Inside," part three, 1-2. Punctuation in Stamires's email *sic*. For context, SEC filings indicate that KiOR had 107 total employees by March 2011, 80 of whom were classified as "scientists or technical support personnel." SECURITIES AND EXCHANGE COMMISSION, Amendment No. 7 to Form S-1, KiOR, Inc., June 22, 2011, https://www.nasdaq.com/markets/ipos/filing.ashx?filingid=8006029#H80686A7SV1ZA_HTM_H80686101.

High levels of stress and fear can stem from technical setbacks, which can further paralyze a firm's ability to respond. By late 2011, the firm had grown to 160 employees, but KiOR's low yields seemed as intractable as management's inability to think clearly about them. At this time, "[a] KiOR insider... described... a 'fearful working atmosphere'.... For employees 'to survive and keep their jobs, and not being isolate [*sic*] or fired, they had to remain silent and accept the 'party-line' involving the fraudulent and deceiving information fed to the public and investors."[17] Of course, fraud and deceit were not necessary for KiOR to continue to work on the technical problem of low yields.

It could be suggested that if deceiving investors were to have lengthened KiOR's runway and this lengthened runway had contributed to solving the technical problems they faced, deception would have to be evaluated as a net positive for the technology's sake if nothing else. However, KiOR's attempts to hide its technical struggles stemmed from panic and paralysis rather than from long-term strategy. This same culture of fear fueled KiOR's inflexibility toward different technical approaches and their hesitance to perform engineering due diligence that would have given researchers the data they needed to discern which approaches and designs would work and which would not. KiOR's paralyzed response in the face of technical setbacks is evident in the firm's strategy of refusing to openly acknowledge adverse results, which damaged its ability to explore and fix the technical problems underlying these results.

Investor pressure affected KiOR in a number of ways. In particular, it tended to decrease the firm's likelihood of conducting engineering due diligence. For example, in the second half of 2008, KiOR was testing different materials and reactor designs for their pyrolytic process. Several researchers argued for conducting a variety of baseline tests to better isolate the effect changes in materials and design would have on later tests.[18] These tests, according to one employee, were not particularly difficult, but would take money and time.[19] However, Paul O'Connor (who would

[17] Ibid., part three, 11. SEC filings show 163 employees by the end of 2011.

[18] "A dispute erupted within the KiOR community in September 2008 over the testing program for the FCC Pilot Plant at the KBR facility in Houston. Issues included the biomass feed, which included the pretreated biomass feeds, catalysts and process conditions…. Some [KiOR staff] emphatically stated that before any new materials be tested under different process conditions, and with other process variables, a systematic calibration of the equipment and processing scheme should be first done to establish a reference base-line." Lane, "Inside," part one, 15.

[19] "'Especially since this FCC Pilot Plant had not be used before for pyrolyzing biomass in the presence of a catalyst,' as one KiOR staffer would recall later…. It was not a difficult test series to mount. Well known process parameters were available from many similar tests and equipment used before, and there was research papers published regarding optimum process conditions for maximizing bio-oil yields, using sand as a heat carrier, in the absence of a catalyst. Ensyn, for example, had been using sand for years as a heat carrier in a pyrolysis reaction…. The purpose? An equipment check and standardization test, including the duplication of published similar test results, would have

later criticize KiOR management for making decisions like these), CTO at the time, wrote a memo to all staff in September 2008 in which he "objected doing any calibration to establish a baseline," effectively killing the effort to do so.[20] Lane reports that O'Connor's "reasoning is not clear," but guesses that "costs and… timelines, based on KiOR's timelines to scale and available cash," played a role. These costs and timelines were, of course, driven by KiOR's venture capital funders. As KiOR's problems deepened, its main investor, Khosla Ventures, became more involved in the firm's decision-making.

KiOR's "modus operandi was 'Reckless rush to Commercial,'" recalled senior scientist Dennis Stamires.[21] According to Stamires, KiOR's haste to commercialize was spurred by venture capital investment. The firm had accepted large investments from biofuel enthusiast and venture capitalist Vinod Khosla, who took an active interest in the firm's decisions and development timelines. "Khosla and [Samir] Kaul made the important decisions," Stamires reported, "while Ditsch and Cannon simply executed the orders. And Ditsch, Hacskaylo, Artzer, and Cannon set the [day-to-day] policies, and communicated with the public and investors. The rest of the management team were kept in the dark." Andre Ditsch, Fred Cannon, John Hacskaylo, and Chris Artzer were all KiOR upper management, whereas Vinod Khosla and Samir Kaul worked at Khosla Ventures. The active involvement of investors in KiOR's management generated a further split in the company. It meant that when KiOR's technological development started to run into roadblocks, actors in the company strove to obscure its difficulties not only from the public, but also from other employees in the firm. The involvement of investors and the split between managers who carried out their orders and managers who were kept in dark "created confusion, poor morale, fear, discord, and mismanagement" at KiOR.[22]

In January 2012, Stamires began his efforts to save KiOR by retooling the firm's technological approach. He quit the management team and "notified the CEO, Fred Cannon, that [he] would devote… [his] time and available resources to developing a new, economically feasible technology

given information to confirm that the equipment was working as intended, and given a baseline of performance for this FCC pilot unit, compared to pyrolyzing biomass in different reactor designs, under same process conditions and with the same heat transferring medium. In short, setting a starting point where the impact of a new KiOR reactor design and a new catalyst could be measured." Ibid., 15-16

[20] Lane, "Inside," part one, 14-17.

[21] Ibid., part four, 2.

[22] Ibid.

capable of meeting KiOR's business objectives."[23] Stamires "requested the formation of a task force, called 'Project Team Oil Yield', operating separately from Hacskaylo' R&D group and reporting directly to CEO Fred Cannon, with the objective to introduce in the DEMO Unit and subsequently to the Columbus plant," a new technological solution for producing hydrocarbons from biomass. Lane writes, "At that time, Professor Vasalos had also agreed to participate. BioeCON founder and former KiOR board member Paul O'Connor was in support…. Stamires recalled that, at the time he explained to CEO Fred Cannon, 'it was very important to conduct a technology review and assessment in the presence of an Independent expert. It would make the findings and conclusions more credible. It could have convinced the board, and Khosla to act swiftly. It could have saved KiOR.'"[24] It is hard to know whether the matter was as straightforward as Stamires presents it, as people tend to overweight the effectiveness of their own recommendations.[25] However, Stamires's independent technology group represented a genuine effort to address the core of KiOR's problems—yields from current cracking technology were too low—and demonstrates one path available to firms who run into deep-rooted technological trouble when trying to scale from demonstration to commercialization. One way of responding to technical challenges is to rethink fundamental approaches, even if large amounts of time and capital have been sunk into the current path. Biofuel firms that failed largely neglected to rethink their technical approaches when their primary approach failed (or they ran out of time and money before they could rethink much of anything). Biofuel firms that succeeded almost always did so because they were able to alter their technical approach, often in tandem with finding a new market for higher-cost, lower-volume versions of their original product.

Over-competitiveness

Often, KiOR and its investors saw themselves as being chased by other biofuel firms. The accomplishments of rivals were used as a spur within the company. In March 2012, Paul O'Connor mentioned in a technology assessment letter to KiOR's board of directors that his "concerns [about product yields] are further amplified given the fierce, rapidly evolving and well-funded competitive technologies in this space. One example is the [joint venture] between

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[23] Stamires quoted in Lane, "Inside," part four, 2. *Sic*.

[24] Lane, "Inside," part four, 3.

[25] See Svenson, O. (1981). Are we all less risky and more skillful than our fellow drivers? *Acta psychologica*, 47(2), 143-148 and Camerer, C., & Lovallo, D. (1999). Overconfidence and excess entry: An experimental approach. *American economic review*, 89(1), 306-318.

Ensyn and UOP."[26] But none of these rivals were eventually successful in the way they thought they'd be. Firms perceived themselves as racing toward cheap, sustainable biofuels produced at scale. None of them crossed the finish line. In fact, no one did. The lure of being first to market impeded these firms' ability to slow down and rethink previous assumptions that could have led to an escape from a technological dead end. This could have saved individual firms and the viability of biofuels writ large. Repeated setbacks, especially when large amounts of time and money have been sunk into a project, can dissuade investors and researchers from pursuing a technology more broadly. For example, because of earlier failures like KiOR, "Capital for commercial-scale biorefineries is still exceedingly tough to find" as of 2017.[27] Avoiding the kind of collapses and disappointments that beset biofuels may help avoid a "cultured meat winter" (analogous to "AI winter") in which new investment is hard to come by. Technical problems could delay cultured meat for months or years, but industry collapse could delay it for decades.

Management and personnel

In April 2012, O'Connor wrote another letter to the board in which he summarized KiOR's two main stumbling blocks as a lack of "the people with experience, vision and leadership to move forward with necessary improvements of the technology (yield improvement and catalyst cost reduction) and operations (capacity, ramp-up and time on stream)."[28] Partly this complaint is a reflection of the fact that KiOR's chosen technology path wasn't working. There is little evidence that KiOR was working with weak scientists. The firm was hiring top PhDs in physics and engineering.[29] It's possible that KiOR's talent pool was slightly shallower than it would have

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[26] Paul O'Connor, "KiOR Technology Assessment - March 2012," SEC, appendix C1, https://www.sec.gov/Archives/edgar/data/1418862/000119312514421847/d824230dex171.htm. The joint venture O'Connor refers to is probably "Envergent Technologies," which describes itself as "a joint venture between Honeywell UOP and Ensyn [that] provides licensing, engineering services and equipment supply related to RTP [rapid thermal processing] biomass conversion equipment, with performance guarantees, to RFO [residual fuel oil] production projects worldwide. Under this joint venture, engineering of the RTP equipment is subcontracted to Honeywell UOP…. Ensyn's RTP technology is a non-catalytic analogue to Fluid Catalytic Cracking (FCC) technology." See Ensyn, Honeywell UOP, accessed September 2, 2018, http://www.ensyn.com/honeywell-uop.html.

[27] Jim Lane, "Earnings season: An advanced bioecononomy's health and wellness check-up,"*Biofuels Digest*, August 14, 2017, https://www.biofuelsdigest.com/bdigest/2017/08/14/earnings-season-an-advanced-bioecononomys-health-and-wellness-check-up/.

[28] Lane, "Inside," part four, 11.

[29] "As Paul O'Connor observed, "no one [in power] analyzed the pilot plant data. Andre [Ditsch] would say 'oh, go out and hire MIT PhDs.' But they are not the ones who are going to scale up a process. Fred let Andre go his way, and they hired too many people from Albemarle across the street. Catalysts are important; you need a few people. But you need a lot of process people, and that balance went wrong." See Lane, "Inside," part five,

otherwise been because of the decision to site the company in Houston.[30] "By locating in Houston," Jim Lane writes, "there was a very limited number of qualified technical personnel with the type of expertise needed by KiOR available to be hired, or willing to move to Houston to work for KiOR. Therefore, a lot [of] personnel was hired [*sic*] who had no experience in the area of KiOR's business or qualified for the job. Some were friends or ex-colleagues to Cannon and O'Connor."[31]

O'Connor's complaint gets at the fact that KiOR was unable to course-correct when their technology wasn't working. The problem is with "vision and leadership," not scientific acumen. The technical problems proved to be daunting, but the labor of a dozen more high-end PhDs is unlikely to have mattered. The second part of the complaint gets at the fact that KiOR should have been more attentive to the specifics of scaling up and the personnel needed for such a task. Engineers and operations experts likely should have been involved earlier in the ramp-up process.[32]

In addition to the factors already mentioned (and more outlined in later sections), "most agree that KiOR made poor hiring decisions as it staffed up. The result was a relative preponderance of lab researchers with PhDs and a dearth of people with technical, operational experience running energy facilities." *Fortune* reported that "The lack of people with real operational experience 'hurt KiOR a lot,'" quoting Paul O'Connor.[33]

Additionally, investor involvement gave KiOR the capital it needed to scale, but at serious strategic cost. "The venture capitalists and the executives took another step that would put pressure on the company: selling KiOR stock to the public. That would subject the company to the scrutiny and burdens of the markets and outside shareholders—before it had ever sold a

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http://www.biofuelsdigest.com/bdigest/2016/11/24/kior-the-story-of-a-company-gone-wrong-part-5-the-collapse/.

[30] "By locating in Houston, there was a very limited number of qualified technical personnel with the type of expertise needed by KiOR available to be hired, or willing to move to Houston to work for KiOR. Therefore, a lot [of] personnel was hired [*sic*] who had no experience in the area of KiOR's business or qualified for the job. Some were friends or ex-colleagues to Cannon and O'Connor." Lane, "Inside," part one, 7.

[31] Lane, "Inside," part one, 7. *Sic*.

[32] Adam Flynn has argued that a lack of engineer involvement in early stages is how firms arrive at unrealistic estimates of yields and eventual cost. See Flynn, "Industry Parallels: Algal Biofuels," New Harvest 2018 Conference, July 21, 2018, https://www.pscp.tv/futurefoodshow/1ZkKzNvMNqwKv.

[33] Katie Fehrenbacher, "A Biofuel Dream Gone Bad," *Fortune*, December 4, 2015, http://fortune.com/kior-vinod-khosla-clean-tech/.

single drop of fuel."[34] Even before the IPO in 2011, investor pressure affected the company from the very beginning, altering not just tactical decisions but the structure and mission of the firm:

> One of the most fateful decisions occurred even before the company was founded. O'Connor was considering licensing his technology to a big oil company. But Khosla—who can be almost as brusque and certain in his conclusions as he is intelligent—disagreed, according to O'Connor. He argued that there was no reason to solicit VC funding if O'Connor planned to sell the technology…. Khosla's ambition was much bigger. He wanted to make KiOR a producer—a biofuel version of Exxon. That would require massive capital expenditures and huge teams with extensive technical know-how. O'Connor agreed, and says he relinquished a research and development agreement he had struck with Petrobras and stopped pursuing technical discussions with Chevron.[35]

These decisions contributed to KiOR's financial difficulties and, eventually, to its end.

The end of KiOR

Meanwhile, the alternative technology group within KiOR (the so-called "Stealth team") was still chipping away at the problem of low yields. In October 2012, "Stamires delivered to Cannon a detailed Technical Report entitled: 'Proposal for Commercial Use of an Efficient, Cost-effective Integrated Process for the Conversion of Biomass to Liquid Fuels.'" This alternative report represented "a sign of KiOR's progress from a collaborative group of technologists to a group o[f] fearful employees working in silos."[36] KiOR was moving toward a model in which they could respond to technological setbacks, try new approaches, and work toward a saleable product.

It would prove to be too little, too late. KiOR continued its slow slide through 2013 until its bankruptcy filing in November 2014. The state of Mississippi's lawsuit against KiOR alleges five major failings on the company's behalf, as summarized by Lane:

> **1. KiOR's total process yields** were not high enough to render the Company profitable.

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[34] Ibid.

[35] Ibid.

[36] Ibid., part four, 14. *Sic.*

2. KiOR's catalyst costs, catalyst replacement rate and capacity creep all contributed to render the Company unprofitable.

3. KiOR did not make a high quality crude oil, but instead made a biocrude that was high in oxygen and acids which made the biocrude difficult to refine within the standard equipment of major oil companies.

4. KiOR had been informed by [Catchlight Energy] and other major oil companies that they were unable and unwilling to refine the Company's biocrude in quantities that the parties found acceptable.

5. Due to its inability to convince a major oil company to refine its biocrude, KiOR was forced to construct and operate its own refinery in Columbus. These additional costs had not been included in the Company's financial modeling and projections.[37]

In short, KiOR paid too much for catalysts for an inefficient process that produced poor-quality biocrude and (as a result) couldn't secure partnerships with established oil companies.

KiOR's most fundamental problem, however, had to do with its inability to rethink its technological approach. There is evidence that KiOR staff knew about problems with their existing catalytic cracking method from their first tests of it. When these problems deepened rather than resolved themselves with scale, KiOR resisted exploring new approaches (or even widely acknowledging the problem) from a combination of managerial inflexibility, path dependence, and concern about spooking investors, especially after the company's 2011 IPO. As early as 2008, Jacques De Deken wrote that, within KiOR, "genuine efforts to establish a dialog about relevant technical issues have been met with systematic attempts to downplay or dismiss virtually every issue as soon as it is brought up. Clearly, the creation of lasting value is not possible without also developing credible, sound and robust technology. KiOR's obvious lack of commitment to building a strong and much-needed R&D effort to make this possible is a further indication that KiOR is not really serious about developing successful technology."[38] De Deken is probably slightly cynical in his assessment of KiOR's motivations. It is more consistent with the evidence that KiOR was "really serious" about "developing successful technology," but was

[37] Lane, "Inside," part five, 9. Brackets *sic*.

[38] Quoted in "Lane," part one, 10.

unable to do so in part because the technical problems it faced were difficult and because the firm was insufficiently flexible in its approach.

One-pot reactor design

An illustrative example of KiOR's tendency to wed itself to one technological paradigm appears in one-pot design,[39] an approach popular in biofuels circa 2008. KiOR became attached to the idea even as its shortcomings surfaced:

> Members of the R&D team were beginning to see a fatal problem emerging with the one-pot design, in test results obtained at the ITQ Valencia Lab, as well as later on by the tests done at KBR's Pilot Plant in Houston and subsequently at KiOR's own KCR Pilot Plant…. The two distinct reactions taking place at the same time (i.e., the physical/Thermolysis and the chemical/decarboxylation/cracking), as it turns out, require individual customized process variables optimizations, and are different for each reaction. So, there's what one source familiar with KiOR's process described as "a gross compromise of the individual efficiencies of these two different processes, resulting in a very poor liquefaction and Bio-oil and Bio-oil yield, while a substantial amount of carbon and hydrogen are converted to carbon oxides and water."[40]

KiOR should have switched to a less-fashionable two-pot approach, but persisted with a one-pot design even in the face of discouraging test results. "[T]here was disappointment in the efficacy of a single reactor to conduct both reactions simultaneously. It's not surprising given the novelty of running biomass through a[n] FCC reactor, modified or otherwise. Complicated physical and chemical reactions are taking place simultaneously, with side and cross reactions." KiOR persisted even when "[a] new 'Two-pot' system, having individual reactors for thermolysis and for cracking, could have been pursued aggressively at this inflection point [2008-2009]. In fact, Brady, Cordle, Stamires and Loezos filed a patent application on such a KiOR technology, which was granted in 2012," but this was too late. "Prior to the IPO… steps" toward a two-pot system "were not taken in a systematic way." Even after the one-pot reactor had been proven ineffective, "the BCC one-pot reactor and the previous catalyst were not discarded... work proceeded exclusively on these systems 'for over one more year,' according to one staffer, 'while delaying

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[39] A reactor design in which the cooking part of the reaction (thermolysis) and the molecule-rearrangement part of the reaction (cracking) occur in the same, well, pot.

[40] Lane, "Inside," part one, 14.

KiOR for another year in starting to develop a new feasible Technology.'"[41] This delay burned through KiOR's runway of cash and time, both of which would have been needed to explore alternative reactor designs. KiOR repeated this error nearly every time they hit a serious technical problem: Management insisted on trying and re-trying a difficult path instead of seeking another way to higher yields, more economical production, increased output. This negatively affected the company, contributing to its eventual bankruptcy, and probably hindered the development of catalytic pyrolysis as a technology.

Amyris

Like KiOR, Amyris began by promising inexpensive, sustainable biofuels from a novel technological process. Like KiOR, Amyris would not produce inexpensive, sustainable biofuels at scale. Unlike KiOR, Amyris still exists (as of early 2019), sells products, and conducts research and development that contribute to biofuel production.

Genetically engineered yeast

Amyris first proposed to use genetically engineered yeast to convert the carbon in plant material into useful hydrocarbons. These hydrocarbons could be used to produce diesel or other transport fuels, as Amyris originally proposed, or they could be used in cosmetics, medicines, and other smaller-scale applications.

While attempting to use genetically engineered yeast to produce biofuel components at scale, Amyris realized that their production process was too expensive and inefficient to scale up into making large quantities of price-competitive biodiesel. Though their biofuels were largely regarded as a technical success, meeting and "exceed[ing] technical and pollution standards," they remained "commercially.... anything but successful."[42] After years of research and trying different technical and business approaches, Amyris has emerged as a functional (though not yet profitable)[43] firm selling a variety of products and ingredients based on hydrocarbons produced

[41] Lane, "Inside," part one, 14-16. *Sic.*

[42] "In purely technical terms, Amyris's farnesene fuels have been a success: Car manufacturers and aviation companies have tested their jet fuel and their synthetic diesel and found that it complied with and even exceeded technical and pollution standards. Commercially, the biofuels that Amyris has produced have been anything but successful." See Almuth Ernsting, "Not cheap and not plentiful: Hyped-up synthetic biology claims take another blow as malaria drug production plant shuts down," *SynBioWatch*, http://www.synbiowatch.org/2016/02/not-cheap-and-not-plentiful/?lores.

[43] Amyris's operating income in 2017 was negative 39.5 million USD, up from a loss of $95.9 million in 2016 and a loss of $148.5 million in 2015. Gross profit and revenue increased sharply from 2016 to 2017, from $10.5 million in

by yeast. The company's yeast-produced farnesene is used to make ingredients like liquid rubber, hemisqualane, and squalane prominent in plant-based cosmetics lines like Biossance. Amyris has also "developed yeast strains to produce sclareol, patchouli, bisabolol and one more undisclosed molecule, which based on the company's shipping manifests is manool. These are all high-value fragrances and cosmetic ingredients, which Amyris produces at low volumes, but sells at high margins."[44]

Amyris' roots extend to the early 2000s, when chemical engineer Neil Renninger began working with others, including well-known chemical engineer Jay Keasling, to start a company that would use yeast to produce scarce or hard-to-manufacture substances. Their efforts in 2005-2006 to engineer yeast to produce artemisinic acid, a naturally-occurring compound effective in the treatment of malaria, attracted the attention of the Bill and Melinda Gates Foundation. Artemisinic acid was hard to procure cheaply, because "[o]nly one plant in the world, Chinese sweet wormwood," produces the substance. This raises the price of antimalarial drugs, which costs lives. Making artemisinic acid "in vats with bioengineered yeast would make the drug cheaper" than harvesting it from wormwood. Some estimated that wider access to artemisinin (the drug derived from artemisinic acid) could save 655,000 lives per year. "The Bill and Melinda Gates Foundation," journalist Daniel Grushkin writes in an extensive *Fast Company* article on Amyris's rise and fall, "then already campaigning worldwide to eradicate malaria... granted $42.6 million to the Institute for OneWorld Health, which then partnered with [Jay] Keasling's students. Renninger still has the wire statement for the first $3.7 million. It had more zeros than he had ever seen on a check, and it was made out to a mostly nonexistent biotech company that he and his friends had called Amyris."[45]

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profit on revenue of $67.2 in 2016 to $80.7 million in profit on revenue of $143.4 in 2017. Research and development spending rose steadily, from $44.6 million (2015) to $51.4 million (2016) to $57 million in 2017. As do virtually all firms, Amyris maintains that their path to profitability is clear. Some analysts argue that the firm could turn a small profit as soon as 2019, although this is based on optimistic growth projections. See NASDAQ, Amyris, Inc. (AMRS) Income Statement, accessed September 6, 2018, https://www.nasdaq.com/symbol/amrs/financials?query=income-statement and Jennifer Prater, "When Will Amyris Inc (NASDAQ:AMRS) Become Profitable?" Yahoo! Finance, March 15, 2018, https://finance.yahoo.com/news/amyris-inc-nasdaq-amrs-become-131834831.html.

[44] "Amyris Is Growing Too Fast To Ignore," *Seeking Alpha*, June 5, 2018, https://seekingalpha.com/article/4179559-amyris-growing-fast-ignore.

[45] Daniel Grushkin, "The Rise And Fall Of The Company That Was Going To Have Us All Using Biofuels," *Fast Company*, August 8, 2012, https://www.fastcompany.com/3000040/rise-and-fall-company-was-going-have-us-all-using-biofuels. For more charting Amyris's trajectory, see Securities Class Action Clearinghouse at Stanford Law School, *David Browning v.*

Amyris's scientific accomplishment was significant: "In March 2006, after two years of work, Keasling, Renninger, and the team had engineered the right combination of gene parts. Nothing like it had ever been done. By way of comparison, Monsanto, which has a billion-dollar research budget, has only ever commercialized a corn strain with eight new genes; Amyris had engineered 13 into yeast."[46] Yeast-produced artemisinin was a scientific success[47] but produced no direct profits for Amyris. Keasling's lab at UC Berkeley had granted a free license to Amyris to use their artemisinin yeast technology on the condition that the company did not sell the drug at a profit in the countries that most needed it.

"Set your sights on diesel"

Around this time, Vinod Khosla (the main investor in KiOR) told Amyris: "Set your sights on diesel... It's the hardest thing you'd want to do, but it's the biggest market out there, and you'll build an incredible company."[48] For an ambitious biotech firm like Amyris, "[f]inding an alternative to petroleum had the same ring as battling malaria: The world would be better for it."[49] Khosla's advice to Amyris echoed his advice to KiOR to become "a biofuel version of Exxon."[50]

Amyris "debated making lubricants and high-value chemicals for perfumes. All of these, however, seemed to lack the nobility of battling malaria." Biofuels seemed benevolent and high-impact, so Amyris became more interested in them during 2006 and 2007. They aimed to engineer yeast to produce farnesene, a group of chemical compounds that can be "converted to a diesel-like fuel without any apparent downsides."[51] Amyris planned to build a plant in Brazil and use the country's cheap sugarcane as feedstock.

Amryis, Inc., consolidated class action complaint, October 25, 2013, http://securities.stanford.edu/filings-documents/1050/AMRS00_01/20131025_r01c_13CV02209.pdf.

[46] Grushkin, "Rise."

[47] Its public-health impacts are more uncertain. See Mark Peplow, "Synthetic biology's first malaria drug meets market resistance: Commercial use of genetically engineered yeast to make medicine has modest impact," *Nature* 530 (2016): 389–390, https://www.nature.com/news/synthetic-biology-s-first-malaria-drug-meets-market-resistance-1.19426.

[48] Quoted in Grushkin, "Rise."

[49] Grushkin, "Rise."

[50] Fehrenbacher, "Biofuel Dream."

[51] Grushkin, "Rise."

Early results were encouraging. Amyris "had begun to demonstrate that its farnesene, when developed into fuel, met or surpassed industry standards. General Electric and Embraer, the Brazilian airplane manufacturer, tested Amyris's jet fuel and found it no different from regular fuel. Mercedes took sample orders for diesel. They too said it was nearly identical."[52] The firm had raised $156 million from private investors, but scaling would require more capital. The board decided to take Amyris public and the company planned an initial public offering for late 2010.[53]

Even before it was held, the IPO made Amyris accountable to investors and markets in a way it had not been. When CEO John Melo announced in September 2010 that "his 'no compromise' fuel could be poured straight into tanks without having to retool engines [and] promised that by 2011, Amyris would produce 6 million to 9 million liters of farnesene, and another 40 million to 50 million liters by 2012," these statements "started a clock."[54] Amyris now had technical targets to which it was publicly accountable.

Neil Renninger describes "Melo's promise [as] the tragic misstep of Amyris's young and turbulent life." He argues that Amyris's "problems are not problems of technology but problems arising from the pitiless expectations of Wall Street. 'We were chasing that number,' Renninger says of the 50 million liters [Melo had promised by 2012]. Amyris would have to meet the quotas Melo had presented or lose credibility," which for a publicly-traded company could lead to a falling stock price, lawsuits, and SEC charges (as KiOR would soon be able to attest). Part of Melo's ambitious targets resulted from a failure to anticipate the difficulties of scaling a production process built on a new technology. "Coming from the petroleum industry," Grushkin writes, Melo viewed targets like 40 to 50 million liters "as laughably small." But "Amyris was not an oil company, and it still didn't have a full-scale plant. 'The regret is not realizing how hard it was to

[52] Ibid.

[53] "By then, Amyris's board had decided it was time for the company to go public. That way, it could raise the hundreds of millions of dollars it would need for manufacturing and distribution. The technical specs on the product now seemed excellent–a huge victory. And on paper, farnesene appeared as if it could compete, in price, with petroleum. Whether Amyris could produce the chemical cheaply at a real plant, however, was still unproven. What's more, no one had ever built a business like Amyris's before. Getting its plants to run efficiently, getting its yeast bug to produce optimally–it could take decades to catch up with an oil industry that had a lead of nearly a century. Also, despite the incredible biotech tools Amyris had developed, company directors knew going public meant they'd have to open the books to the market, which only cared about one question: When would Amyris turn a profit?" See Grushkin, "Rise."

[54] Ibid.

get the scale up,' says Melo now. He soon discovered it would take a lot longer for a fermentation and manufacturing system to work than his team had estimated."[55]

A class action suit filed against Amyris and Melo in 2013 by investor David Browning alleges that Amyris's misunderstanding of the difficulties that would come with scaling were both more pervasive and intentional than Melo and industry reporting lets on. Relying on an Amyris employee referred to in court documents as CW, the suit alleges that "estimates by Amyris scientists were that the Company's capability to produce commercial Biofene [Amyris's brand name for their farnesene] was roughly 'five fold lower' than what the Company was publically projecting…. the Company's management was aware that it would not be able to translate peak yields of Biofene, produced in lab settings, to stable and reliable production at factory scale." The suit notes that it

> is widely known in the industry, and was known to Defendants during the Class Period, that scaling biofuels is a massive engineering feat that requires fine-tuning to maximize performance. Unlike some industries where being first to market is advantageous, in renewable energy, there is often a first mover disadvantage because scaling the initial technology for commercialization is as difficult (or more so) than proofing the technique in the lab.

Moreover, "CW believes that Amyris management, including CEO John Melo either… ignored its scientists' realistic recommendations concerning projections of yield, or cherry picked the… best available data from tests at every step of the process, then accelerated that data based on knowingly unrealistic projections in technological advancement to create numbers for the projected yield that they disclosed to investors…. CW states that the only way Amyris' 2011 projections numbers of 6-9 million liters of Biofene production could be justified was to make assumptions beyond the 'state of the art' technology."[56] (The quoted document, a class action complaint, has an incentive to retell the Amyris story in as negligent terms as possible, just as Melo has the opposite incentive. The suit was dismissed in March 2014 by a California judge for lack of particularity, a legal term that means that its claims were not specific enough.) In any

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[55] Ibid.

[56] *Browning v. Amyris*, 10. The case was dismissed in 2014 with prejudice with respect to Browning and his co-plaintiff, Steven Tsao, but without prejudice with respect to the putative class of future plaintiffs. See Kurt Orzeck, "Amyris Dodges Suit Alleging Earnings Misstatements," Law360, March 25, 2014, https://www.law360.com/articles/521539/amyris-dodges-suit-alleging-earnings-misstatements.

event, Amyris's manufacturing process would take much longer to bring online and costs would prove far harder to bring down than Melo and Amyris had anticipated.

Scaling and timeline issues

In their 2010 IPO presentations, Amyris projected that their biobased farnesene would be cost-competitive with conventional petroleum as they scaled up. The path toward cost-competitiveness involved scaling up production by building a plant in Brazil fed by sugarcane.

Amyris at first rented a hangar in São Paulo and set up two fermenters, each two stories tall.[57] By June 2011, this facility was operational but "beset with problems." Occasionally, "the process worked as it had in the California labs. Other times, the enormous tanks frothed with the carcasses of exploded yeast cells."[58] Amyris faced recurring problems with both the changed environment (yeast cells are living organisms and remain sensitive to their living conditions) and the problems, new to most of the team, of scaling up production plants.

Meanwhile, public pressure mounted on Amyris. In the five months following Amyris's IPO, the stock price had increased from $285 per share in October 2010 to $500 per share in February 2011. After the IPO, Amyris "announced 20 collaborations with major chemical and commodity companies around the world. 'We led the IPOs, the first one out, and we were viewed as a leader in this industry,' Renninger recalls. 'I remember going to a conference in San Diego in January and having people come up and say, 'Hey, realize that we're all depending on you. If you guys don't succeed, we're not going to have the opportunity.'"[59] When the São Paulo hangar came online in July 2011, the stock had cooled to $399. As production problems mounted, Amyris stock underwent three major slides, in July and August 2011 (down to $280), November 2011 (to $151), and February 2012 (to $73). It would eventually bottom out around $2.50 in 2017.[60]

As with KiOR, yield issues contributed to Amyris's falling stock price and rising pressure on management. "Theoretically," Amyris's yeast "could convert 27% of the sugar it digested into

57 "A 100-million-liter-a-year plant in Sao Martinho was still years from completion. To meet Melo's goals, the company had to rent a hangar in rural Sao Paulo from an animal-feed producer called Biomin and installed two 200,000-liter stainless-steel fermenters, each the size of a two-story house." Grushkin, "Rise."

58 Ibid.

59 Ibid.

60 As of February 12, 2019, AMRS trades at $5.01 a share.

farnesene." Amyris, however, "was struggling to make a strain that yielded more than 20%."[61] Moreover, costs for what they did produce were too high:

> In 2011, the company entered into contracts to supply its sugar-cane derived diesel to the transit authorities for use in buses in Rio de Janeiro and São Paulo. At an exorbitant cost of $7.80 per litre, this required a significant public subsidy…. [But] even this was well below the cost of manufacture. Thus, the more farnesene-based diesel Amyris produced and sold, the greater the company's losses were…. Amyris's directors had been hoping from the outset that their company could sell farnesene at its real production cost of $20 – $50 per litre, or $3,180 to $7,949 per barrel, which would mean selling it for use in expensive, niche products.[62]

The plaintiffs in Browning v. Amyris rely on a chemical engineering paper, their CW informant, and a team of consultants to argue that four main technical problems beset Amyris: metabolic flux, metabolic burden, genetic instability, and contamination. Metabolic flux describes how rapidly molecules move through metabolic networks and can lead to "bottlenecks as a result of flux imbalances, which lead to the diversion of molecules away from the desired product. The accumulation of toxic intermediates can thus occur. This is particularly problematic when several different enzymes, which may be derived from different organisms, are introduced into one cellular host." Metabolic burden refers to how an "overproduction of non-essential proteins may trigger stress responses within the cell and slows its growth." Genetic instability describes a situation "where the metabolic burden 'shouldered' by a plasmid-bearing or transgenic producer cell places it at a disadvantage relative to a nontransgenic nonproducer cell, which leads to genetic instabilities in the engineered cells. Genetic instability can be mutation in either the transgene or the plasmid DNA vector, as well as losses of plasmid DNA vector. This may be present when an increase in cell growth is seen, while product titers decrease." The complaint identifies what "appears to be the introduction of extraneous microbes by contamination" as the final technical cause of Amyris's scaling trouble.[63] At one point, the Brazil plant had been so "poorly designed and constructed… that it needed to be retrofitted to reduce major problems with

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[61] Grushkin, "Rise."

[62] Almuth Ernsting, "Not cheap and not plentiful: Hyped-up synthetic biology claims take another blow as malaria drug production plant shuts down," SynBioWatch, accessed September 21, 2018, http://www.synbiowatch.org/2016/02/not-cheap-and-not-plentiful/?lores. References to Grushkin article omitted.

[63] See *Browning v. Amyris*, 21, citing in part Sujata K. Bhatia, "Biology as a Basis for Chemical Engineering," *American Institute of Chemical Engineers*, July 2013, http://www.aiche.org/sites/default/files/cep/20130740.pdf.

cross-contamination by foreign yeast and bacteria."[64] (Even in well-designed production facilities, contamination by foreign agents remains a concern for biotech firms of all types, as E. coli outbreaks on hydroponic farms have shown.)[65]

Amyris also probably tried to scale too fast. In an effort to meet its production targets, the company attempted to "create several other manufacturing facilities, including a second plant in Sao Paulo in conjunction with a small sugarcane mill called Paraiso Bioenergia." Amyris's attempt to get their main plant working while also bringing other plants online compounded rather than repaired their mistakes. "Given a chance to do it over again," Melo said in an interview with *Fast Company* in 2012, "I would focus on our Paraiso plant and getting that one up and not all the others." Jay Keasling agreed, telling the same reporter: "[m]aybe [Melo] could have been safer. Maybe he could have just done one facility at a time. I don't know a lot of the thinking that went into it, because that was kind of beyond my time. I'm not a business guy; I'm a science guy. So maybe hindsight is 20/20."

Consultants retained in the *Browning* suit suggest that Amyris's difficulties scaling up also

> appear... to be caused by a violation of the 10x (10 fold) rule. Consultants believe standard chemical engineering rules dictate that no process should be scaled at levels beyond 10x volume or weight. Consultants' review points to the Amyris stated levels of scale were as follows:
>
>> Research used 2 liter fermenters.
>>
>> The Emeryville Pilot plant used 300 liter, as well as the pilot plant in Campinas, Brazil.
>>
>> The Demonstration facility used 5,000 liter (Campinas, Brazil).
>>
>> Contract manufacturing showed in company literature that 60,000 to 200,000 liter vessels (reactors) were used and the "Capital Light" production presented a JV design at 600,000 liter.

[64] *Browning v. Amyris*, 18.

[65] See "BrightFarms recalls greens from Mariano's out of E. coli concerns," *Chicago Tribune*, October 23, 2017, https://www.chicagotribune.com/business/ct-biz-bright-farms-recall-20171023-story.html and Emma Cosgrove, "Indoor Farmers Are 'Way Too Complacent' About Food Safety," *AgFunderNews*, June 20, 2018, https://agfundernews.com/indoor-farmers-complacent-food-safety.html.

> Under standard chemical engineering models 10x (10 fold) scale, the lab would be 2 liter, the pilot would then be 20 liter, the demonstration units would be 200 liter while the full scale would be 2,000 liter…. based on what was known at the time, Amyris' projections were unreasonable.[66]

Melo's promises of producing six to nine million liters in 2011 and forty to fifty million liters by 2012 were made in 2010, when Amyris had its Campinas facilities online and therefore possessed a production capacity of about 5,000 liters. It was proposing something like a 1,500-fold increase from 2010 to 2011 and a 9,000-fold increase from 2010 to 2012. If Amyris had retained their 40-50 million liter target, but pushed the date out in accordance with standard 10x scaling models, their ramp would have looked something like: 50,000 liters in 2011, 500,000 in 2012, five million in 2013, and 50 million in 2014. This would itself have been hugely ambitious: order-of-magnitude increases every twelve months with no serious delays is the kind of thing common to IPO prospectuses but rare in reality.[67] Assuming more conservative twenty-four month steps, Amyris would have reached 50 million liters in late 2018.[68]

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[66] Ibid., 23, partially quoting consultants' report. For examples of scaling-up theory, see A M. Rozen and A. E. Kostanyan, "Scaling-up Effect in Chemical Engineering," *Theoretical Foundations of Chemical Engineering* 36, no. 4 (2002): 307-313 and Yu Che et al., "CFD prediction of scale-up effect on the hydrodynamic behaviors of a pilot-plant fluidized bed reactor and preliminary exploration of its application for non-pelletizing polyethylene process," *Powder Technology* 278 (2015): 94-110. For an industry example, see Pat Coval, "Use the 10x Rule to Guide Your Food Production Expansion," *Lee Industries*, April 30, 2018, leeind.com/blog/equipment-design/use-the-10x-rule-to-guide-your-food-production-expansion.

[67] Stephens et al. note that "Mesenchymal stem cell expansion is relatively well established at bench scale 'ready' for clinical scale (since the vast majority of tissue engineering to date focuses on cell therapies). Publications demonstrate expansion in bioreactors up to 5 litres, but with current commercially-available technologies there is potential for bioreactors up to 2000 litres (Schnitzler et al., 2016). To put into context the scale of cultured meat production, in the region of 8×10^{12} cells are required to acquire 1 kg of protein from muscle cells, which would need a 'traditional' stirred tank bioreactor in the order of 5000 litres. While this volume is commonplace in established bioprocessing it is as yet unproven in tissue engineering and mesenchymal stem cell expansion. Other bioreactor configurations are available that can, in theory, achieve higher cell densities, including fluidised bed bioreactors and hollow fibre membrane bioreactors, but are considerably less established for cell expansion at this point in time."

See Stephens et al., "Bringing cultured meat to market: Technical, socio-political, and regulatory challenges in cellular agriculture," *Trends Food Sci. Technol.* 78 (2018): 155–166.

[68] Building a biofuel refinery large enough to make tens of millions of gallons per year takes about three to four years. (See Annie Web, "What does it take to build an advanced biofuels plant?" BioFuelNet Canada, August 7, 2013, biofuelnet.ca/nce/2013/08/07/what-does-it-take-to-build-an-advanced-biofuels-plant/.) Smaller plants take less time. The literature lacks robust work on exactly how much time each size of plant can be expected to take, in part because a variety of factors influence construction times. Extrapolating from individual cases, I would roughly estimate a doubling in build time for every 10x increase in capacity. In the above example, therefore, twelve months is quite aggressive and twenty-four months, once each capacity jump has been averaged out, is more realistic. (For

Even if Amyris could have climbed these slower production ramps without running into intractable technical issues, it's not clear that investors would have been patient with such long timelines. Like chemical engineering, venture capital and startup communities talk about growing by orders of magnitude, but these ideas do not resemble the growth models in chemical engineering. Venture capital models emphasize speed, focus on individual factors like effort rather than physical constraints, and advise courses of action like

> every time you have to make a hard decision, ask yourself this question: 'Is this going to propel the company, person, or project by a factor of 10?'.... Once you've found your next big 10X thing, then double down. If you know that this is a game-changing 'massive action' that will drive significant results for your business, it requires 2,000 percent of your time, energy, and focus.[69]

Investor beliefs about what rapid growth is and how it is best achieved remain at odds with chemical engineering models of scaling.

Investors are sometimes willing to show patience, even with publicly-traded companies (while the story that Amazon has never turned an accounting profit is folklore, the firm took more than a decade to achieve consistent profits[70]), but this patience often results from a particular set of circumstances and interactions between companies and investors.[71] Choices within a company's control include management being forthright about the fact that profitability is a long-term question and that years of development and scaling may come first and at great cost. It is difficult but probably advisable to avoid promising an aggressive ramp-up that brings immense profitability in a short period of time. It remains the case that even the most talented companies

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instance, applying the 2x time per 10x capacity guideline for expanding production capacity from 5,000 to 50 million gallons yields an average step time of 1.875 years, or 22.5 months.)

[69] Sangram Vajre, "Why Every Entrepreneur Must Follow the 10X Rule," *Inc.*, August 5, 2016, https://www.inc.com/sangram-vajre/why-every-entrepreneur-must-follow-the-10x-rule.html, citing in part Grant Cardone, *The 10X Rule* (Hoboken, NJ: Wiley, 2011).

[70] See Benedict Evans, "Why Amazon Has No Profits (And Why It Works)," Andreessen Horowitz, September 5, 2014, https://a16z.com/2014/09/05/why-amazon-has-no-profits-and-why-it-works/. This graph, from Recode, is also striking.

[71] While longer-term investment strategies like value investing exist, startups working on new technology are unlikely to attract value investment, at least at early stages. Moreover, the influence of long-term investment philosophies like "patient capital" is often drowned out by short-term movements in stock prices driven by short-term concerns.

cannot outrun physical constraints and the technical problems that emerge within complex systems.[72]

Counterfactuals

It is impossible to know the counterfactual case of a slow-burning, careful KiOR or Amyris. Amyris's pivot to non-biofuel products on a modest scale (but still sufficient to sustain its research and development efforts) suggests that a slower, more careful approach that focuses on high margin applications while the technology is still expensive may one day lead to a technology that works at scale.[73] Amyris presents a potential example of how to carry a technology forward even when its main application has failed. "Amyris has trademarked the phrase No Compromise," Lane wrote in 2018, "but of course the entire company's mission is a compromise and in fact it is the source of Amyris' strength, it[s] ability to adapt to changing conditions and find new ways to pioneer when the expected pathways to success turned out poorly for them."[74]

The consultants retained in the *Browning* suit argue that Amyris's business model "at inception was appropriate had they had remained focused on small scale biological products for malaria and related biotechnologies for human and veterinary diseases, as Jay Keasling… did by licensing the Artemisinin-based anti-malarial technology." Amyris didn't, however, even though "based on the existing state of technology during the Class Period, they could not have reasonably projected [their publicly] stated projections for production in biofuels." Amyris's move away from riskier,

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[72] For an overview and examples of these sorts of problems, see John Ross and Adam P. Arkin, "Complex Systems: From chemistry to systems biology," *PNAS* 106 (2009): 6433-6434.

[73] Jim Lane writes in 2015 that it is "tempting to see the story of Amyris as one of unexpected redemption… as if Orpheus had gone down to the underworld and rescued biobased farnesane from certain oblivion.

"But it probably is more of a mundane case of Chicken Littles amongst industry observers — the plant was not ready for prime-time when first launched, a gigantic learning curve was embarked on in the harsh light of public company reporting, and what we are seeing is success delayed, rather than the deliverance of a soul from the underworld. Turns out that Chicken Little, in looking at the 10-Ks and declaring that the sky was falling in, was wrong yet again.

"Now, if the company spent a considerable amount of time in the penalty box, that it understood — this market in these times is always happy to whack a technology stock that mistimes the forward projection of its arrival at break-even. There is little doubt that the Amyrisians up in Emeryville would like to have arrived in 2012 where they are today, and that they have been chopped up in the public markets for running the trains late." See Jim Lane, "Amyris," *Biofuels Digest*, January 4, 2015, http://www.biofuelsdigest.com/bdigest/2015/01/04/amyris-biofuels-digests-2015-5-minute-guide/.

[74] Jim Lane, "Amyris In The Age Of Rapid Change," Alternative Energy Stocks, July 12, 2018, http://www.altenergystocks.com/archives/2018/07/amyris-in-the-age-of-rapid-change/.

capital intensive moonshots like biofuel production likely saved the company and kept money flowing into engineered yeast research that would have otherwise have gone elsewhere.[75] It represents one potential model for cultured meat firms if early targets, especially with respect to cost and volume, prove more difficult to reach than initially thought.

REG

Renewable Energy Group (REG) is, as of late 2018, the largest biodiesel producer by volume in the US. REG uses a transesterification-based process to turn feedstock like inedible corn oil, used cooking oil, and animal fats into biodiesel.[76] REG also sells byproducts from their biodiesel production process like naphtha and glycerin. The company operates 14 refineries and a feedstock processing facility.[77]

The firm's basic business model appears to be profitable even after subtracting subsidies and tax credits.[78] REG has bounced between profit and loss over the last five years, reporting an operating income of negative $89.8 million on revenue of $2.16 billion in 2017, down from an operating income of positive $64.5 million on revenue of $2.04 billion in 2016. In 2018, the firm reported an operating income of $322 million on revenue of $2.38 billion.[79]

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[75] Note that other biofuel firms have, like Amyris, successfully shifted their technical focus. Onetime biofuel company Heliae "switched to its current focus on nutraceutical ingredients and specialty products for agriculture and aquaculture in 2012. In… another story of a biofuels company [turning to] a high value market, Heliae is now feeding fish with algae ingredients and has several agricultural and nutraceutical products on the market. They still face challenges of course, like algal biomass production costs, but... who ever said change was easy? They found a way to survive… during a weakened biofuels market." See Helena Tavares Kennedy, "Top 10 Transformations — Pivotal Pivots for survival in the bioeconomy," *Biofuels Digest*, July 15, 2018, http://www.biofuelsdigest.com/bdigest/2018/07/15/top-10-transformations-pivotal-pivots-for-survival-in-the-bioeconomy/.

[76] Transesterification involves mixing feedstock oil with an alcohol and a catalyst, heating and agitating the mixture, and drawing off a glycerin byproduct from the biodiesel product. In industrial production, this is followed by purifying and testing the biodiesel.

[77] Renewable Energy Group, "About REG," https://regi.com/about-reg.

[78] "[T]he numbers in the second-quarter 2018 earnings report… seem to indicate that the business can be sustainably profitable without any help from federal subsidies for renewable fuels." Maxx Chatsko, "Here's Why Renewable Energy Group Rose 58.1% in August," *The Motley Fool*, September 4, 2018, https://www.fool.com/investing/2018/09/04/heres-why-renewable-energy-group-rose-581-in-augus.aspx.

[79] MarketWatch, "REGI Annual Income Statement," https://www.marketwatch.com/investing/stock/regi/financials.

REG's story does not resemble those of Amyris or KiOR. There are no high-profile lawsuits, glaring management errors, or jilted investor groups. The firm has its roots in an Iowa-based company, West Central Cooperative, which began experimenting with biodiesel production in 1997. REG was spun out of West Central as a biodiesel venture in 2003[80] and began to pursue a strategy marked by the transesterification of cooking oils and plant acquisition. Transesterification, a process common to biodiesel production first documented in 1853, benefits from technological advances, but does not depend on them to become viable the way genetically-engineered yeast or new types of pyrolysis do. REG's technology risk is therefore lower, although its eventual technological ceiling may be lower as well given that transesterification has been refined for 160 years and few step changes in efficiency remain to be found.

REG is known for being "allergic to hype."[81] Unlike other biofuel firms, which have acquired a reputation for promising production numbers and cost reductions that they then fail to meet, REG tends to make conservative projections that it often beats. REG tends, as industry observer Maxx Chatsko notes, to "set a low bar and leap over it."[82] The epigraph for the company's own promotional history lacks ornamentation or soaring promises: "methodically" is the only adverb.[83]

Should cultured meat firms pursue a low-hype strategy? The stories of Amyris and KiOR suggest that high levels of publicity attracted investment but also contributed to the firms' accelerated schedules and eventual setbacks.[84] REG, a more successful biofuel producer than Amyris or

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[80] "West Central forms Renewable Energy Group, LLC and partners with Todd & Sargent to build biodiesel production facilities for partner investors." Renewable Energy Group, *Enabling a Cleaner World: The History of Renewable Energy Group 1995–2015* (Ames, IA: Renewable Energy Group, 2017), ii.

[81] "Renewable Energy Group, which has the 'bad' habit of setting a low bar and leaping over it, has gone so far as to call [another firm's technology acquired by REG] 'the most efficient industrial biotechnology method for the synthesis of hydrocarbon chains (fatty acids)'. Not a bad review from a company that is allergic to hype." Maxx Chatsko, "The LS9 Update You've Long Been Waiting For," SynBioBeta, August 14, 2014, https://synbiobeta.com/news/ls9-update-youve-long-waiting/.

[82] Ibid.

[83] "Together our team has methodically built a company we can be proud of and that has done great things for our world, our communities and our families." See REG, *Enabling*, v-vi.

[84] For context, REG's $64 million net-proceeds IPO was smaller in absolute terms than Amyris (who raised about $85 million) or KiOR (~$150 million). As a fraction of current revenue, however, Amyris and KiOR raised much more money than did REG. Amyris and KiOR had little revenue at the time of their public offerings whereas REG reported revenue of $824 million in 2011. (Comparing public offerings like this is slightly too clean, of course, because each firm had different sources of private funding before their IPOs.) See REG, "Renewable Energy Group

KiOR, is sufficiently committed to maintaining a low profile that public discussion about it is remarkably low: it produces a lot of biodiesel, turns a profit most years, and doesn't make big promises.

It is impossible to know the outcomes of different counterfactual scenarios, of course. If REG had promoted itself and its technology more aggressively and attracted larger and more prominent investment than it otherwise did, would the firm be making more biodiesel at lower cost today? The evidence from biofuels indicates that slower-growing, conservative, low-hype firms are better able to withstand downturns and tend to survive longer, produce higher volumes of product, and contribute more to research and development over longer timelines than do rapid-growth, high-publicity firms.

A final example of a successful conservative firm is Novozymes.

Novozymes

The Danish firm Novozymes is older than most biofuel-related firms. It was spun out in 2000 from a series of predecessor businesses dating to the efforts of Harald and Thorvald Pedersen to produce insulin in the 1920s. Novozymes has from its inception specialized in enzyme research and development. Today, its website reports that it is responsible for two thirds of the world's investment in enzyme research.[85]

Enzymes are quite important in biofuels. For example, enzymes represent between 13% and 36% of the "cash costs" in cellulosic ethanol production.[86] Novozymes seeks to capture a large portion of enzymes' "cash cost" by selling them to biofuel firms. Instead of using a vertically-integrated business model, Novozymes positions itself midstream in the biofuels supply chain. It primarily develops and sells enzymes to other biofuels firms. Novozymes, therefore, is not organized around a lab-to-consumer model. The firm does not purport to develop novel production processes in its labs, scale them up, and produce biofuels or other lipids at commercial scale. The lab-to-consumer model remains prevalent among both biofuel companies

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Reports Fourth Quarter and Full Year 2012 Financial Results," March 4, 2013, http://investor.regi.com/news-releases/news-release-details/renewable-energy-group-reports-fourth-quarter-and-full-year-2012.

[85] About Novozymes, Novozymes, accessed August 16, 2018, https://www.novozymes.com/en/about-us.

[86] Johnson, E. (2016). *I*ntegrated enzyme production lowers the cost of cellulosic ethanol. *Biofuels, Bioproducts and Biorefining, 10(2), 164–174*. doi:10.1002/bbb.1634.

(particularly early, more ambitious biofuel companies) and cultured meat startups and widely covered in the press compared to other firm structures. Alternative ways of organizing a business, therefore, can be non-obvious, even though they remain common in established industries like oil and gas.[87]

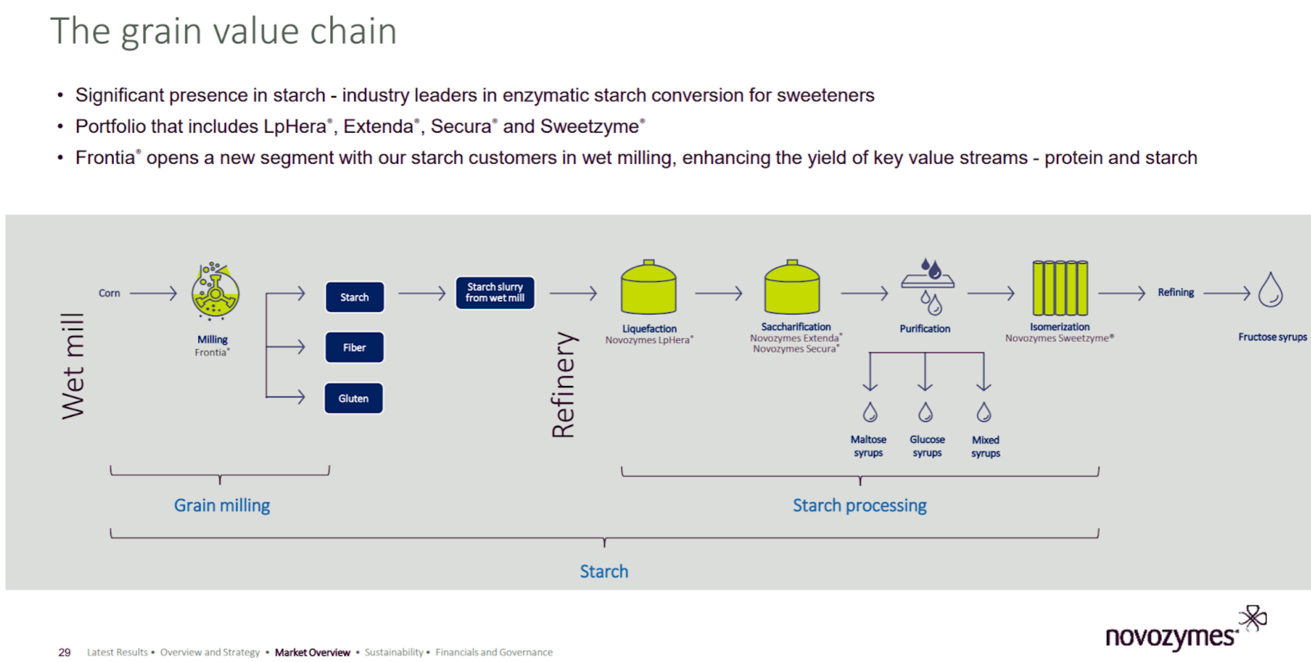

Fig. 1. Novozymes's role in grain milling and starch processing. Lime-colored illustrations represent places in the value chain where Novozymes enzymes can be used.[88]

The enzymes Novozymes develops and markets can be used, for example, to improve starch extraction from corn, to convert cellulosic material into sugars and alcohols (including ethanol), and as an additive in detergent to catalyze reactions that break down proteins, starches, and fats.

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[87] At least one startup, Cubiq Foods, works on cell-based fat. See Press Dispensary, "Healthy cell-based fats startup, CUBIQ FOODS secures EUR 12m investment by Moira Capital Partners," January 23, 2019, http://pdpr.uk/es94393/eu-cell-based-fats-startup-cubiq-foods-secures-eur-12m.html. Other firms, like New Age Meats, have considered selling their automation technology to other companies, and many companies may one day sell or license their eventual cultured meat production process to large food producers.

[88] Novozymes, 2018 Q1 Results Presentation, slide 29, https://s21.q4cdn.com/655485906/files/doc_financials/Quarterly/Q1_2018/2018_Q1_Novozymes_Roadshow-presentation_FINAL.pdf.

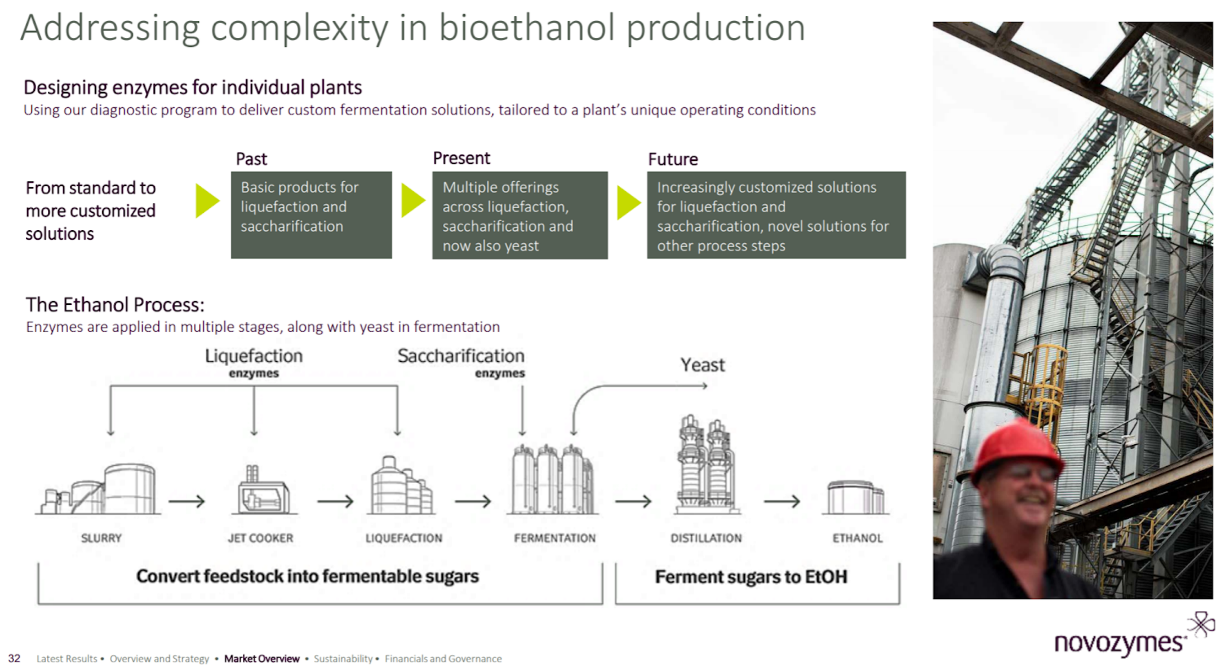

Fig. 2. Novozymes enzymes aimed at ethanol producers.[89]

By participating in the biofuels market as supplier of enzymes rather than as a vertically integrated producer, Novozymes was able to weather several rounds of bankruptcies and crashes in biofuels from the 2000s through the mid 2010s. The firm was able to contribute technologically during adverse conditions for biofuel firms. For example, in 2013, in the midst of a biofuels shakeup precipitated by technological failures to increase yields and reduce costs, Novozymes introduced a new enzyme mix that "boost[ed] yields to 2.9 gallons [of ethanol] per bushel" of corn (from 2.77) and "add[ed] 13% yield in corn oil extraction while dropping energy usage."[90] This had the effect of both continuing Novozymes's presence in and development of biofuel production and contributing to cost decreases for ethanol production rather than folding,

[89] Ibid., slide 32.

[90] Lane, "New Ethanol," https://www.biofuelsdigest.com/bdigest/2013/06/11/novozymes-new-ethanol-enzyme-tech-saves-up-to-5-corn-8-energy/ . Effects at scale: "By using Avantec, Olexa and Spirizyme Achieve, a standard 100 million gallon ethanol plant would save up to 1.8 million bushels (45,000 tons) of corn while maintaining the same ethanol output, and generating up to $5 million in additional profit. Despite the dip in corn usage, overall corn oil extraction would increase by 7% to 9000 tons for a standard plant, while DDGS production would dip to 282,000 tons based on lower corn inputs."

being acquired, or withdrawing from biofuels as did so many other firms in the 2000s and 2010s.[91]

Novozymes's history suggests that an established firm's presence in a supply chain may increase the resilience of the industry built around that supply chain. It also implies that occupying one well-defined position in a supply chain can render a firm more resistant to downturns. Finally, it suggests that a supply chain made up of different contributing companies can lead to more resilient, technologically-robust industries than when many firms try to create siloed end-to-end processes.

Likely analogies between biofuels and cultured meat

Expensive products were feasible, but higher volumes and lower costs were not.

Consider the difference between commercializing expensive high-end cultured meat products and commercializing mass-scale cultured meat products that are cheaper than slaughtered meat. Expensive products will happen in a relatively soon (as early as 2019) timeframe. Mass-market products lie much further along the experience curve: High-volume cultured meat will take far longer and require more engineering advances and cost reductions than early products.

Cultured meat production, at this early stage, is most similar to areas like biofuels or algae in the mid 2000s, which would go on to produce expensive products for a niche market while the chasm to more ambitious applications, e.g. replacing all oil or factory farm production, remained unbridged by existing industry or firm structures. (This gap between demonstration and commercialization is sometimes called the "valley of death."[92]) The initial goal remained possible but often required far more money and patience than was ever predicted. In practice, being mission-driven may not mean moving at breakneck speed, but instead moving somewhat cautiously, preferring slow burns and long-term projects where they might otherwise be inclined toward rapid expansion and aggressive gambles.

[91] See e.g. the well-documented struggles of Choren, Solazyme, Range Fuels, KiOR, LS9, Codexis, Dynamotive, et al. around this time.

[92] See Clyde Frank et al., "Surviving the 'valley of death': A comparative analysis," *The Journal of Technology Transfer* 21 (1996): 61-69.

Firms often pursued low-margin, high-volume products when it was more advantageous to pursue high-margin, low-volume products.

Biofuels firms often took wing on the promise of cheap, sustainable fuel for the world. James Collins, professor of biomedical engineering at Boston University, suggests in an interview with technology reporter Martin LaMonica that "while the science behind biofuel companies was promising, 'in most cases, they were university lab demonstrations that weren't ready for industrialization.'" Collins argues that "We're never going to have biofuels compete with $20-a-barrel oil—period… I'm hoping we have biofuels that compete with $100-a-barrel oil."[93] Researchers knew early on that hydrocarbons could be made via exotic methods like engineered yeast and cellulose pyrolysis, but it took biofuel firms more than a decade to discover that they could not be made as cheaply as oil could drilled, at least without significant technical advances. They could not be price-competitive with retail gasoline, but they could be price competitive with cosmetics and medicine.

The lesson for cultured meat is to start with products that are more expensive, especially those with high production costs. Adam Flynn, CEO of Forelight (which is working on a fungible protein replacement for blue dye no. 1), points out that insurance companies could effectively pay thousands of dollars per kilogram for a mature cultured collagen product if it is used to make replacement intervertebral discs, but collagen used for meat has to compete with steaks that are $19/kg.[94]

In the cellular agriculture industry (this includes companies developing cultured meat but also dairy, eggs, and other animal products made without animal farming), at least one company based in California, Geltor, is already commercializing recombinant animal proteins at high prices in a niche market. Geltor's core product, collagen made with genetically engineered yeast, was first sold for pharmaceutical applications in 2017. It was sold at a much higher price point than the collagen used in gelatin for food, but the pharmaceutical industry prizes high-quality, homogenous product, which is more easily produced with cellular agriculture.[95]

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[93] Martin LaMonica, "Why the Promise of Cheap Fuel from Super Bugs Fell Short," *MIT Technology Review*, February 5, 2014, https://www.technologyreview.com/s/524011/why-the-promise-of-cheap-fuel-from-super-bugs-fell-short.

[94] Flynn, "Parallels," 47:00 timestamp.

[95] Reese, Jacy. *The End of Animal Farming*. Boston: Beacon Press, 2018. 81-82.

Another company, Finless Foods, based in California, has argued that a focus on expensive fish products like bluefin tuna, which sells to restaurants for over $300 per kilogram at high-end auctions and for about $40 for farmed bluefin, sets a more attainable price target than a focus on inexpensive products like ground beef, which wholesales closer to $3.50/kg in the United States.[96]

The most prominent biofuel startups focused on vertical integration and consumer products rather than business-to-business sales.

The history of Novozymes, Amyris, REG, and others suggest that cultured meat firms should not neglect business-to-business sales.[97]

The cultured meat supply chain is still emerging. As it does, different places to contribute will develop. Right now the majority of cultured meat companies are focusing on a vertically-integrated brewery-to-supermarket model. However, many biofuels firms were able to contribute to biofuel development after their own attempt at the popular model of feedstock-to-gas-tanks had fallen short by specializing in business-to-business products and/or technical contributions like converting "first-generation ethanol and biodiesel plants into advanced biorefineries."[98] See, for example, REG's interest in plant design and acquisition and

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[96] "There were 1,729 tuna sold in Sunday's first auction for 2014, according to the city government, down from 2,419 last year. The 32,000 yen ($305) per kilogram paid for the top fish this year compares with 700,000 yen per kilogram last year…. Prices for bluefin tuna imported from other regions are much lower. A 189-kilogram (417-pound) farmed tuna imported from Spain sold for 662,000 yen (about $6,400) on Sunday, or 3,500 yen ($34) per kilogram, compared with a price of 4,800 yen ($46) a kilogram for the same type of fish sold at last year's first auction." AP in Tokyo, "Price of bluefin tuna falls at Tokyo auction," The Guardian, January 5, 2014, https://www.theguardian.com/world/2014/jan/05/bluefin-tuna-tokyo-auction. Beef numbers are for blended ground beef, 81% lean. "Wholesale Price Update," Beef, October 19, 2018, https://www.beefitswhatsfordinner.com/sales-data/wholesale-price-update. See also JUST's deal to extract cells from high-end Wagyu cows, whose meat retails for around $500 per kg. Chase Purdy, "The science that will make Wagyu beef affordable for everyone," *Quartz*, December 11, 2018, https://qz.com/1490425/the-science-that-will-make-wagyu-beef-affordable-for-everyone/.

[97] Adam Flynn also argues against neglecting business-to-business sales.."Venture capital pushes [startups] in the wrong direction. All they know is... a consumer-facing model. I think that's a huge mistake. I think the [cellular agriculture] companies we're talking about are very obviously [business-to-business]... If you could plug [a cellular agriculture application] into the largest Asian egg producers… that would really do a lot more for your business model as opposed to… slowly growing a company over 20 years, they would put more capital than that into it in two [years] if it really works." Ibid., 53:00.

[98] This has been Aemetis's stated strategy. See Aemetis, "About Aemetis, Inc.," http://www.aemetis.com.

Novozymes's development of Fermax, a compound that reduces foaming in cane ethanol production.[99]

As discussed earlier, KiOR had a chance to diversify but chose to go with radical vertical integration instead. "O'Connor was considering licensing his technology to a big oil company," but Khosla, KiOR's primary investor, opposed a B2B strategy. He "wanted to make KiOR a producer—a biofuel version of Exxon." Khosla's view won out. O'Connor "relinquished a research and development agreement he had struck with Petrobras" and ended "technical discussions with Chevron." This decision almost certainly left KiOR and the biofuels industry worse off than if KiOR had tried a different strategy.

Additionally, there may be advantages for a technology in general by having many firms positioned along the supply chain. In biofuels, firms can, out of pure self-interest, sell enzymes or license technologies to each other that make other firms' approaches work better. This is probably preferable to a model in which many firms try to bring a complete brewery-to-supermarket product to market: this latter system duplicates effort, promotes potentially deleterious levels of competition, and is unlikely to lead to modular breakthroughs that can be used in a variety of settings. In a parallel-effort model, a firm that has an excellent pretreatment system but a rather poor approach to processing could exist alongside a firm with excellent downstream processing but terrible pretreatment and both companies could go out of business. In a more distributed model, they could license or sell their breakthroughs to one another and both could move forward, or at least the best overall approach could.[100] This more distributed model offers more informational value about what's failing and succeeding. It also partitions disaster (as well as success, potentially). Consider how Novozymes sells enzymes to a variety of companies, many of which end up out of business because certain parts of their

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[99] See "Renewable Energy Group Achieves One Billion Gallon Milestone," REG, April 21, 2014, https://www.youtube.com/watch?v=peeHpIG0-WE and Meghan Sapp, "Novozymes launches Fermax to prevent foam development during cane ethanol production," *Biofuels Digest*, November 9, 2016, https://www.biofuelsdigest.com/bdigest/2016/11/09/novozymes-launches-fermax-to-prevent-foam-development-during-cane-ethanol-production/.

[100] See Isabel Lane, "Blue Sun, Vieselfuel utilize new lipase from Novozymes, *Biofuels Digest*, July 14, 2014, https://www.biofuelsdigest.com/bdigest/2014/07/14/blue-sun-vieselfuel-utilize-new-lipase-from-novozymes/ and "Novozymes enzymes confirm 6% production edge," *Biofuels Digest*, August 11, 2014, https://www.biofuelsdigest.com/bdigest/2014/08/11/novozymes-enzymes-confirm-6-production-edge/. Keep in mind one potential drawback of (especially for a mission-driven firm) being positioned low in a supply chain is that other firms may control your access to consumers: Jim Lane, "Novozymes: 'Oil companies are the only interface to consumers' for advanced biofuels," November 3, 2014, Jim Lane, https://www.biofuelsdigest.com/bdigest/2014/09/03/novozymes-oil-companies-are-the-only-interface-to-consumers-for-advanced-biofuels/.

production process remain difficult or immature technologically. This state of affairs both imparts information about what technological bottlenecks are in a supply chain and also allows Novozymes to continue to develop their own technology and sell enzymes to the next generation of firms attempting to solve the bottlenecks. The presence of midstream firms can help avoid an investment winter. "A lot of cultured meat companies," New Age Meats cofounder Brian Spears argues, "are… trying to be supermen, to do all the elements in-house, the cell lines, the cell culture, the scaffolding, and the bioreactors each of which is a multi-million dollar industry. But I think the industry will fail if it tries to do everything itself."[101] Vince Sewalt (Senior Director of Product at DuPont Industrial Biosciences), quoting an old adage, echoes this sentiment: "Don't do it alone... If you want to go fast, do it alone. If you want to last long, do it together."

Jim Lane argues that "diversification beats a pivot every time… The great ones in the bioeconomy, they diversify, but they rarely abandon the field." That is, rather than converting over their technical approach wholesale, companies ought to spread their effort and funding across multiple approaches and product types. "REG," Lane continues, "has become a lot more than just biodiesel, but they were serious about their first business and serious about getting good at managing the cycle, not hopping elsewhere at the first sign of trouble. POET-DSM and Novozymes have been much the same — enter markets with purpose, then expand, rather than abandoning ship."[102] In general, biofuel companies that successfully pivoted or diversified moved toward business-to-business sales and to higher-end, more niche products. In many cases (particularly for firms less established than REG and Novozymes), the revenue generated by newer, smaller-scale products make it possible for a firm to remain involved with its "first business." (Although many companies, like Amyris, come to essentially abandon this first business.)

A final pragmatic note in favor of diversification within an industry: selling goods to customer-facing producers is often a better business model than becoming one. "As we can see with Novozymes, its [*sic*] a smoother road for the supplier companies than the producers," Lane

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[101] Quoted in Elaine Watson, "New Age Meats: People are being fooled into thinking clean meat is just around the corner," *Food Navigator*, August 14, 2018, https://www.foodnavigator-usa.com/Article/2018/08/15/New-Age-Meats-People-are-being-fooled-into-thinking-clean-meat-is-just-around-the-corner. There are some potential exceptions to the lab-to-consumer model (e.g., firms aiming to produce fat cells and license this technology to other cultured meat companies), but these ventures remain early and outnumbered.

[102] Lane, "In for a Penny."

points out. "[A]s was discovered 160 years ago in the California Gold Rush by companies like Levi Strauss, you can mine the miners more reliably than the miners mine the gold."[103]

Expectations grew rapidly, increasing pressure and risk.

As documented above, a sharp rise in expectations outstripped (by several orders of magnitude) the production capacity of firms like KiOR and Amyris. Often, promises and forecasts by these firms about their ability to scale and brings costs down drove these expectations.

Flynn, who previously worked in algal biofuels, argues that "consumer enthusiasm, government grants… basically set [algal biofuels] up to fail… You look at it from a perspective of 'we have products that are worth thousands of dollars but we're going to... make $2 per kilo biofuel'—why didn't you make all those other products first?" The answer, Flynn argues, is poorly set priorities: "there was a whole lot of heat around the idea of carbon-negative fuel, so people went after" it instead of higher-margin products. Certain product choices (e.g. going for cheap fuel right out of the gate, when the technology was still immature) were like "setting the video game on the highest difficulty setting before you know the rules."[104]

Vinod Khosla argued for the opposite approach, which in at least two cases (Amyris and KiOR) seemed to have turned out to be the wrong advice: "'Set your sights on diesel,' Khosla told the Amyris team, according to [early Amyris employee Jack] Newman. 'It's the hardest thing you'd want to do, but it's the biggest market out there, and you'll build an incredible company.' Finding an alternative to petroleum had the same ring as battling malaria: The world would be better for it."[105]

Even if a case existed in, say, 2013-2014 for increasing media attention to draw in cultured meat investment, the pendulum has since swung toward high levels of investment and attention. Few, if any, firms have failed to raise sufficient initial funding because levels of attention to cultured meat projects remain quite high. The case against hype is much stronger in 2019 than it was in the early 2010s.

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103 https://www.biofuelsdigest.com/bdigest/2017/08/14/earnings-season-an-advanced-bioecononomys-health-and-wellness-check-up/

104 Adam Flynn, "Parallels," 6:05 timestamp.

105 Grushkin, "Rise."

Some firms drew on the same feedstock, correlating commodity risks.

Feedstock (e.g., corn, sugarcane, used cooking oil—the substances used to make biofuels) sharing exposes firms to a variety of risks. If the demand each firm has for feedstock now falls on the same supply, this exerts upward pressure on prices. Moreover, it means multiple firms (and their suppliers and consumers) are now at risk from supply disruptions in one feedstock. "Scale ruins relationships, when a feedstock is shared," write the editors of *Biofuels Digest*.[106] For feedstock, a "system of fungibility is the dinosaur in the system. It is what links all the markets together and causes them all so much economic pain when rising demand for one leads to rising price for the other."[107] For cultured meat, this represents a reason to be wary of multiple firms relying on the same input, e.g. a specific growth factor like fetal bovine serum.

Early promoters made claims on behalf of the technology that were unlikely to hold up.

As documented above, biofuel firms and supporters tended to make outsize claims on behalf of biofuels. It will surprise no one that this tendency is alive and well in cultured meat development. Cultured meat is predicted to improve nutrition, supplant factory farming, produce carbon-neutral food, transform global land, and so forth. Adam Flynn identifies the suggestion that cultured meat could be carbon-neutral or -negative[108] as an example of one such exaggeration. He points out that even though algal biofuels "were built on top of a photosynthetic process that [was] ultimately carbon negative," producers were unable to make algae, which is "photosynthetic and carbon negative" to begin with, into a carbon-negative final product. It seems unlikely, then, that cultured meat, which is not built on a carbon-negative process, will be carbon neutral. Its early iterations in particular seem likely to produce large amounts of carbon (though not relative to factory farming[109]). Flynn argues that it is difficult to

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[106] *Biofuels Digest*, "The Third Way: Advanced biofuels as a system of systems," September 27, 2011, https://www.biofuelsdigest.com/bdigest/2011/09/27/the-third-way-advanced-biofuels-as-a-systems-of-systems/.

[107] Ibid.

[108] "Carbon capture and sequestration: the contained nature of cell cultivation could allow producers to capture carbon dioxide as the cells 'exhale,' leading to carbon-negative meat." https://www.gfi.org/images/uploads/2018/10/CleanMeatEvironment.pdf.

[109] Claims that cultured meat, if efficiently produced, could reduce emissions from conventional animal farming by between 78% and 96% remain well-supported, in part because conventional farming is extremely carbon-intensive.

envision "a situation where you put... 100,000 tons of steak inside a warehouse environment and it's not producing a ton of CO_2." Carbon-neutral or -negative cultured meat is not impossible, but it is, for the moment, unlikely (at least without extensive offsetting).

A further example comes in the form of cost and scale estimates. Flynn argues that lack of engineers in early stages is how firms arrive at unrealistic estimates of yields and eventual cost: "ultimately the goal here seems to be a steak or a chicken breast.... [but] you're not trying to produce that. You're... trying to produce a machine that produces that. And in that the biology is one small part." The algal biofuels industry made too-optimistic estimates when "everything was led by biologists and… biological projections. And that's why you had these projections in the late '90s that said 100,000 liters of fuel per hectare per week. And in reality nobody [had] ever done better than... five thousand, ten thousand maybe. That's what happens when the engineers get involved late."

In Flynn's view, many cultured meat firms "massively underestimat[e] the fact that you're not building an animal, you're building a machine. Engineers should be involved in the conversation from day one, and when they're not, you're going to find out that your projections don't really line up and investors are going to be disappointed, next thing you know you've lost 100 billion dollars, and… you've made it harder" for firms that might attempt similar applications. A "Brazilian collagen company," for example, "is not going to be able to raise money, even though it might be a very good sustainable business model, because everybody's lost their shirt in the industry and it will be like 15 years before they'll come back around. And we see that in algal biofuels too… and we're going to see that bloodbath with some of [the cellular agriculture] companies."[110]

Biofuel startups often hired many researchers but few operations experts.

The history of biofuels turns out to swing upon operational (and engineering) questions more than it does upon pure biology and chemistry. Firms were more likely to fail because they could not coordinate the logistics of plant construction than because the behavior of chemical bonds during pyrolysis was not well understood. KiOR, for example, hired "a relative preponderance of

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See H.L. Tuomisto and M.J. Teixeira de Mattos, "Environmental Impacts of Cultured Meat Production," Environmental Science and Technology 45 (2011): 6117-6123.

[110] Flynn, "Parallels."

lab researchers with PhDs and a dearth of people with technical, operational experience running energy facilities," reports Fehrenbacher, who cites Paul O'Connor as saying that the "lack of people with real operational experience 'hurt KiOR a lot.'"[111] Later on, "The [KiOR] facility was bedeviled by production problems. The conveyor mechanism that delivered wood chips was often on the fritz. Cleaning systems routinely jammed with a tarlike substance. The company spent tens of millions of dollars more than it had expected, and its researcher-heavy staff couldn't untangle the problems."[112]

Shifts in commodity prices affected the viability of firms and their technologies.

Feedstock costs were a major determinant of the economic viability of biofuels. "Regardless of the production platform," Karatzos et al. wrote in 2014, "the major interconnected parameters that are influencing the rate of commercialization of drop-in biofuels are capital and operating expenditures, process yields and productivities, and feedstock sourcing."[113] Biofuel firm balance sheets often reflected insufficient tolerance for shifts in commodity prices. For example, crude oil dropped to $35 per barrel in 2015 from well over $100 in the five preceding years, sending several firms into a tailspin. Many biofuel companies had been planning to replace oil at $100 per barrel. The point at which their products would become price competitive had dropped by 60% in six months. Because cost reductions have a nonlinear relationship with scale,[114] hitting a $35/barrel price target was orders of magnitude more difficult than reaching a $100/barrel target. It took

[111] Fehrenbacher, "Biofuel Dream."

[112] Ibid.

[113] "2014 Drop in Biofuels Report Final PDF," accessed August 11, 2019, https://www.scribd.com/document/252126172/The-Potential-and-Challenges-of-Drop-in-Biofuels-A-Report-by-IEA-Bioenergy-Task-39.

[114] "The experience curve shows that the cost of doing a repetitive task decreases by a fixed percentage each time the total accumulated volume of production (in units) doubles.... For example, the total cost might drop from 100 when the total production was 10 units, to 85 (=100 X 0.85) when it increased to 20 units, and to 72.25 (= 85 x 0.85) when it reached 40 units." Arnoldo C. Hax and Nicolas S Majluf, "Competitive cost dynamics: the experience curve," Interfaces 12 (1982): 50–61. For an experience curve study of sugarcane ethanol, see J.D. van den Wall Bake et al., "Explaining the experience curve: Cost reductions of Brazilian ethanol from sugarcane," Biomass and Bioenergy 33 (2009): 644-658. (The authors find that for every doubling of cumulative production, ethanol from sugarcane has become 20% cheaper, mostly because of increased yields. They predict that by 2020, ethanol prices will have fallen from $340 per cubic meter to between $200 and $260/$m^3$.)

many firms' to-market roadmap from "difficult, but doable in 18 months if everything goes right" to "maybe someday."

Biofuel firms sometimes fell afoul of the "Natural Law of Alternative Commodity Markets," which predicts that "no one will use a commodity to make another commodity of lower value."[115] (Or, at least, not for long.) If bean oil is expensive and heating oil is cheap, for example, it is inadvisable to spend money and time to turn the first into the second. Cultured meat firms, at least in the current research stage, ignore the law of alternative commodity markets: it is common to use fetal bovine serum (anywhere from $200 to $1,200/liter) to make ground beef ($3.50/kg). (Note that fetal bovine serum is used as a research tool rather than a commercial ingredient, but the price difference gives some indication of the magnitude of the gap left to bridge.) It is important, therefore, to keep a close eye on commodity prices and to plan for scenarios in which input costs climb while prices for end products stagnate.

Many biofuel firms use a BOHO (bean oil-heating oil) spread index to track the price difference between bean oil and heating oil. A similar index of the spread between cultured meat inputs and outputs[116] is likely to shed light on the viability of cultured meat ventures and the economic competitiveness of a given technical path.

The obvious options for responding to unfavorable commodity price spreads are change which commodities you buy, which you sell, or both. Ensyn, a Canadian company specializing in forest biomass, has moved to producing biocrude rather than biofuels. Amyris, as noted, has moved from biofuels to business-to-business sales in cosmetics and medicine.

Likely disanalogies

Cultured meat is likely to be marketed directly to consumers.

Cultured meat probably faces more consumer rejection risks than do biofuels because consumer choice plays a larger role in food purchasing than fuel purchasing. Possible consumer backlash

[115] http://www.altenergystocks.com/archives/2018/07/amyris-in-the-age-of-rapid-change/

[116] (you could call it GMME, "gimmie," the growth media-meat price index)

around cultured meat is better understood by studying the adoption paths of more consumer-facing technologies like GMOs.[117]

Fossil fuel is more widely recognized as a major climate issue than animal agriculture.

Fossil fuel use remains more central to concerns about climate change and efforts to reduce greenhouse gas emissions than does animal agriculture. This means that cultured meat may receive comparatively less support and attention from climate-motivated actors than biofuels did or would. Overall levels of discussion about climate change and animal agriculture's role in it are higher now than they were when the biofuel firms covered in this report were forming (roughly the 1990s through the late 2000s), which could reduce this discrepancy somewhat.

Unclear relationship

A first mover disadvantage likely affected early entrants.

As the plaintiffs in *Browning v. Amyris* write, "It is widely known in the industry… that scaling biofuels is a massive engineering feat that requires fine-tuning to maximize performance. Unlike some industries where being first to market is advantageous, in renewable energy, there is often a first mover disadvantage because scaling the initial technology for commercialization is as difficult (or more so) than proofing the technique in the lab."[118] This concern might not cancel the usual effects that constitute a first mover advantage, but it can be difficult to fundraise and grow as a company that's known to have failed to scale.

Most often, biofuel firms that attempted to break new ground failed. Successful companies in biofuels remain disproportionately older, better-established firms that have adapted cutting-edge work to profitable ends.

[117] See J. Mohorčich, "What can the adoption of GM foods teach us about the adoption of other food technologies?" *Sentience Institute*, June 20, 2018, https://www.sentienceinstitute.org/gm-foods#perceptions-of-corporate-secrecy-and-arrogance.

[118] *Browning v. Amyris*, 9.

Government mandates requiring biofuel use furthered development of the technology, especially in the US.

Government mandates like the Renewable Fuel Standard (RFS) in the US were instrumental in furthering biofuels.[119] RFS and programs like it require standard fuels to be blended with renewable fuels like corn ethanol. These requirements establish a baseline of demand for biofuels, providing stability and incentivizing production. No analogous program exists in the US for cultured meat.

Programs in countries that wish to encourage cultured meat production (e.g., Singapore and others) may require some proportion of food be domestically-produced (or impose tariffs on imported meat), which could drive cultured meat development. The Agri-Food & Veterinary Authority of Singapore, for example, aims to supply 30% of the island's eggs via domestic production.[120]

Pressures generated by venture and public funding harmed the industry.

Funding is necessary for scaling any emerging technology. However, the dynamics generated by both private and public funding can have deleterious effects. Lane argues that when "venture capitalists and executives [decided to begin] selling KiOR stock to the public," this decision "would subject the company to the scrutiny and burdens of the markets and outside shareholders—before it had ever sold a single drop of fuel."[121] The pressures of venture funders had already pushed KiOR toward bolder gambles than it should have taken. The forces exerted by public funding contributed to the firms' collapse.

Flynn argues that "Venture capital pushes [startups] in the wrong direction. All they know is... a consumer-facing model" partly because of their experience with tech companies, so they ignore

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[119] See Meghan Sapp, "RFS key to Novozymes' cellulosic ethanol success," *Biofuels Digest*, October 8, 2014, https://www.biofuelsdigest.com/bdigest/2014/10/08/rfs-key-to-novozymes-cellulosic-ethanol-success/ and more generally https://www.biofuelsdigest.com/bdigest/?s=RFS.

[120] The Food We Eat, AVA, accessed November 6, 2017, http://www.ava.gov.sg/explore-by-sections/food/singapore-food-supply/the-food-we-eat and J. Mohorčich, "What can nuclear power teach us about the institutional adoption of cultured meat?" November 28, 2017, https://www.sentienceinstitute.org/nuclear-power-clean-meat.

[121] Fehrenbacher, "Biofuel Dream."

business-to-business applications in favor of products for supermarket shelves.[122] As an example of an alternative business-to-business strategy, Flynn suggests if, instead of products for supermarkets, "you could plug [a cellular agriculture application] into the largest Asian egg producers… that would really do a lot more for your business model. As opposed to… slowly growing a company over twenty years, they would put more capital than that into it in two [years] if it really works."[123]

Investor pressure tends to promote haste and to interfere with due diligence practices in particular. Recall that KiOR canceled important baseline tests in 2008 as a result of timelines and cash availability set by investors.

It is likely that investors and public expectations push firms away from longer-term strategies and toward aggressive moves aimed at gratifying investors, public opinion, and their own understandings of themselves and their mission. "It has become perhaps Silicon Valley's favorite cliché to rhapsodize about the virtues of 'failing fast,' and KiOR certainly accomplished that," technology reporter Katie Fehrenbacher writes. "But what is the practical lesson of that failure—that inventing new biofuels is even harder than it looks? Or that fast-moving venture capital investors are ill-suited to tackle such a technically demanding, time-consuming endeavor?"[124] The answer is obviously both, but the first seems to be widely understood and the second a much-disputed hypothesis.

Biofuel companies that wedded themselves to one technological approach were less able to respond when facing problems.

As noted above, KiOR's director of technology, Jacques de Deken, sent a 2008 internal memo summarizing the technical problems with KiOR's chosen approach, a form of biomass catalytic cracking, and advocated switching away from the technique. KiOR resisted a changed approach possibly because management worried about switching costs and that changing approaches would signal to investors and the public that KiOR had failed. "[G]enuine efforts to establish a dialog

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[122] Flynn, "Parallels," 52:30 timestamp.

[123] As a corollary, Flynn suggests skepticism of "anyone who courts the public as a way of getting traction" and funding. See Flynn, "Parallels," timestamp 52:45.

[124] Fehrenbacher, "Biofuel Dream."

about relevant technical issues," De Denken wrote in 2008, "have been met with systematic attempts to downplay or dismiss virtually every issue as soon as it is brought up."

Moreover, changing approaches does not mean death for a firm. A variety of firms, including Amyris, Virent, Aemetis, Codexis, Heliae, and Green Plains, underwent different waves of retoolings, product category switches, and technical transitions in order to survive.[125]

Breakthroughs were possible with difficult technologies that had failed many times.

Even if initial attempts to streamline a technology fail, later and more modest technological advances can render a production process viable. In 2013, Novozymes, in the aftermath of a biofuel downturn precipitated by technological failures to increase yields and reduce costs, managed to produce a new enzyme mix that "boost[ed] yields to 2.9 gallons per bushel [from 2.77]" and "add[ed] 13% yield in corn oil extraction while dropping energy usage."[126]

POET survived the biofuels culling of the 2010s in part by transitioning from first generation (e.g., ethanol from edible corn) to advanced biofuel production. As recently as late 2017, the firm reported a nontrivial advance in cellulosic biofuel production via a superior pretreatment process.[127]

Different technological approaches went in and out of fashion.

Lane, summarizing the biofuels industry, wrote in June 2018 that

> we've seen the product and feedstocks fads roll onto the shoreline with numbing regularity…. We had ethanol until there was biodiesel, and algae until there was jet fuel.

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[125] Kennedy, "Transformations."

[126] https://www.biofuelsdigest.com/bdigest/2013/06/11/novozymes-new-ethanol-enzyme-tech-saves-up-to-5-corn-8-energy/ . Effects at scale: "By using Avantec, Olexa and Spirizyme Achieve, a standard 100 million gallon ethanol plant would save up to 1.8 million bushels (45,000 tons) of corn while maintaining the same ethanol output, and generating up to $5 million in additional profit. Despite the dip in corn usage, overall corn oil extraction would increase by 7% to 9000 tons for a standard plant, while DDGS production would dip to 282,000 tons based on lower corn inputs."

[127] Helena Tavares Kennedy, "Breaking the Bottleneck," *Biofuels Digest*, March 28, 2019, http://www.biofuelsdigest.com/bdigest/2017/11/03/breaking-the-bottleneck-poet-dsm-achieves-cellulosic-biofuel-breakthrough/.

> Then, chemicals until there was Brazil, and drop-in fuels until there was methane. We had greenfields until there were bolt-ons, gene transformation until there was CRISPR. We had plastics until there was nylon, and fatty acids until there were polyketides. We had jatropha until there was miscanthus, soybeans until there was algae, and choice white grease until there was yellow grease. Corn was the answer until there was corn stover, wood was the answer until there was sawdust, and waste oil was the answer until there was MSW [municipal solid waste].[128]

It is possible that this glut of feedstocks and processes reflects a productive industry trying many new approaches and selecting from them its best option. One troubling aspect of Lane's list has to do with how these approaches catch on the way flus or jeans do: they're transmissible and fashionable. Industrial spaces no less than any other are social spaces in which new approaches can trend not because they are superior but because they seem interesting. Biofuels has probably not been helped by occasional stampedes (especially among younger companies) toward new ideas every 18-24 months. Cultured meat is too young to have developed the litany that Lane recites for biofuels. It is, however, as susceptible as any new technology to growing a menagerie of attractions.

Many biofuel companies lacked a robust contingency plan for responding to technical setbacks.

KiOR and other failed biofuel firms responded to technical setbacks by shutting out those who could help and increasing investment in a technical approach that was failing.

Amyris's retooling, described above, presents a potential example of how to survive technical failures. "[T]he entire company's mission is a compromise," Jim Lane writes, "and in fact it is the source of Amyris' strength, it ability [*sic*] to adapt to changing conditions and find new ways to pioneer when the expected pathways to success turned out poorly for them."[129]

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[128] Jim Lane, "Protein, Protein: The bioeconomy's latest technology fad is, actually, a pivot back to an ancient and enduring concern [*sic*]," *Biofuels Digest*, July 5, 2018, http://www.biofuelsdigest.com/bdigest/2018/07/05/protein-protein-the-bioeconomys-latest-technology-fad-is-actually-a-pivot-back-to-an-ancient-and-enduring-concern/.

[129] Jim Lane, "Amyris: Same As It Never Was," *Biofuels Digest*, July 11, 2018, http://www.biofuelsdigest.com/bdigest/2018/07/11/amyris-same-as-it-never-was/.

Above all, the histories of successful and failed biofuel firms suggest that the wisest course of action in the event of technical failure is to remain calm: do not falsify data, lie to the SEC, shut out independent experts, or intimidate colleagues. Even many well-meaning biofuel firms violated these putatively obvious rules when met with technical setbacks.[130]

Firms occasionally formed strategic alliances, often increasing resilience.

Alliances between firms, especially if they occupy different parts of the supply chain, can be useful by strengthening industry coordination and resilience. See, as one example among many, Novozymes and Monsanto's 2014 "BioAg Alliance."[131] cultured meat firms have made some nascent efforts in this direction.[132]

Older companies were overrepresented among surviving firms.

Older, more established companies like POET, REG, Novozymes, and (to a degree) Amyris were more likely to survive successive waves of retrenchment and downturn than younger startups were. The full implications of this fact for alternative protein is unclear, but it suggests that a maturing industry is a more resilient one in part because it will have produced a more diverse group of firms generally, including middle-aged firms that seem to be hardier in a range of conditions. There is also the possibility of bringing in firms outside the cultured meat industry,

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[130] See Lane, "Inside," all parts, the KiOR section of this report, and more generally all *Biofuels Digest* articles tagged "fraud": biofuelsdigest.com/bdigest/tag/fraud/.

[131] The alliance is intended to "bring... together Novozymes' commercial BioAg operations and capabilities within microbial discovery, development and production with Monsanto's microbial discovery, advanced biology, field testing and commercial capabilities. The result will be a comprehensive research, development and commercial collaboration for sustainable microbial products to help farmers globally meet the challenge of producing more with less – for the benefit of agriculture, consumers, the environment and society at large." See Jim Lane, "Novozymes, Monsanto complete closing for BioAg Alliance," *Biofuels Digest*, February 11, 2014, https://www.biofuelsdigest.com/bdigest/2014/02/11/novozymes-monsanto-completed-closing-on-bioag-alliance/.

[132] See Deena Shanker and Lydia Mulvany, "Lab-Meat Growers Wants Help From Industry They Seek to Disrupt," *Bloomberg*, November 26, 2018, https://www.bloomberg.com/news/articles/2018-11-26/lab-meat-growers-seek-help-from-industry-they-seek-to-disrupt and Elaine Watson, "Cultured meat cos agree to replace term 'cultured meat' with 'cell-based meat' and form trade association," *Food Navigator*, September 10, 2018, https://www.foodnavigator-usa.com/Article/2018/09/10/Cultured-meat-cos-agree-to-replace-term-clean-meat-with-cell-based-meat-and-form-trade-association.

such as meat producers or biotech companies, to add resilience, though there are concerns about the effect of mergers and acquisitions resulting from such entry.[133]

Older, larger companies came to control 100% of productive biofuel plants.

All four US biofuel plants that have been successfully commissioned and were producing fuel as of 2015 were built by large companies like DuPont and INEOS.[134] As with the previous point, the full implications are unclear, but it probably counts as evidence in favor of the involvement of larger firms and investors, though pitfalls remain.[135]

When faced with difficult economics in a major market like the US, firms looked elsewhere.

Novozymes, for example, has expressed interest in Pakistan and India, both of which have experienced growing demand for oil paired with biofuel blend requirements.[136] Expanding alternative protein to markets like Singapore is, as the Sentience Institute has argued previously,[137] a viable route to market given more promising economic and regulatory environments.

Because of failures resulting from previous periods of enthusiasm, biofuel investment became more difficult.

Biofuels appear to confirm the ‘technological winter’ thesis familiar from domains like artificial intelligence research. “Capital for commercial-scale biorefineries,” Lane reports as of August

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[133] J. Mohorčich, “What can the adoption of GM foods teach us about the adoption of other food technologies?” *Sentience Institute*, June 20, 2018, https://www.sentienceinstitute.org/gm-foods#perceptions-of-corporate-secrecy-and-arrogance.

[134] Fehrenbacher, “Biofuel Dream.”

[135] See Mohorčich, “GM foods.”

[136] E.g. “Industrial enzymes leader Novozymes to expand India operations,”*The Economic Times*, Nov. 16, 2016, https://economictimes.indiatimes.com/industry/indl-goods/svs/chem-/-fertilisers/industrial-enzymes-leader-novozymes-to-expand-india-operations/articleshow/55458704.cms and Tariq Ali et al., “AN OVERVIEW OF BIOFUELS SECTOR OF PAKISTAN: STATUS AND POLICIES,” *Int. Journal of Eco. Res.* (2012): 69-76.

[137] Mohorčich, “Nuclear.”

2017, "is still exceedingly tough to find" after multiple waves of disappointment in the 2000s and early 2010s.[138]

Summary of implications and findings

- Don't overhype. In general, firms like KiOR that attracted high levels of attention early did worse than firms like REG that avoided such attention.
- Overpromising and overhyping risks backlash, disappointment, and a technological "winter" (a period in which investment is scarce and technology does not advance in part because of the implosion of past promises made on its behalf). Investment and interest in most technologies ebb and flow, but the difference between a low ebb in an otherwise functional industry and a period of near senescence can be the difference between a technology's arriving later than experts had predicted and between its being postponed indefinitely.
- Stick to reality-based scaling models. Exceeding the 10-fold scaling guideline used in chemical engineering models is probably inadvisable regardless of what investors argue.
- Avoid aiming for low-cost, high-volume products first. Consider high-margin, low-volume products while scaling production and decreasing costs.
- Firms should avoiding wedding themselves to one technological paradigm. Maintain flexibility, even or especially when thinking about investor pressure.
- The histories of successful and failed biofuel firms suggest that the wisest course of action in the event of technical failure is to remain calm: do not falsify data, lie to the SEC, shut out independent experts, or intimidate colleagues. Even well-meaning biofuel firms violated these putatively obvious rules when met with technical setbacks.
- Venture and public funding may lead to pressures that can harm the long term viability of a technology. In particular, investment pressure tends to produce more aggressive timelines and reduce due diligence.

[138] Lane, "Earnings Season."

- In general, it is essential to develop a rigorous, thought-out-in-advance way of responding to technical failures. It's hard to overstate the stress technical setbacks exert on a firm. These failures immolated many biotech companies.

- Industrial diffusion and redundancy is probably too low in cultured meat. Moving from an industry model in which nearly all firms are racing to build parallel lab-to-consumer pipelines to a model in which different suppliers and producers sell to one another in a more distributed manner almost certainly adds resilience and might have technological development benefits. On the lab-to-consumer model, a stumbling block anywhere in a supply chain could take down company after company, cause a cascade of investor flight, and risk an alternative protein winter. In a diffuse model, a stumbling block might damage firms who exist at the same place in the supply chain as the problem, but will leave the broader industry intact—hurt, but able to change direction and work around problems.
    - As a corollary: don't discount business-to-business sales or overemphasize customer sales.

- Adam Flynn argues it is advantageous to be more ruthless about which ideas are strong and weak, especially early. The cellular agriculture industry, he says, "has always been very nurturing and very accepting, and I think that's very nice. I have never seen a technology like this come out of a nurturing and accepting [place]." Cellular agriculture is trying to advance at a rate comparable to "the Manhattan project, or nuclear reactors during the Cold War, when we went from the first state nuclear reaction to a nuclear submarine in under nine years. That's what you want to do, but every idea" is treated as good, which, Flynn argues, is incompatible with the rigor necessary for rapid, overwhelming success.[139] Funding and promoting subpar ideas spreads thin the available flow of focus and finances. (I do not think Flynn is unduly pessimistic here, but he may be, for our purposes, overly focused on the survival of single firms rather than a technology as a whole. Trying and funding many things has certain advantages for an industry, though it is bad for the firms that fail.)

[139] Flynn, "Parallels."

- If you're pursuing a technical problem, don't site your company in a place without a deep technical labor pool. And don't hire your friends if they don't have relevant technical expertise. Biofuel firms repeatedly violated these putatively obvious rules.[140]

- Vince Sewalt argues that firms should "think of regulatory safety as an investment. It can pay dividends in the same way" as an investment.[141]

- Prepare contingency plans for shifts in commodity prices. When oil dropped to $30/barrel in the mid-2010s, many biofuel companies struggled. They had been targeting $100/barrel oil and now it was a third of that price. Today, most biofuel firms keep an eye on BOHO and other commodity price ratios. Keep in mind the "Natural Law of Alternative Commodity Markets," which dictates that "no one will use a commodity to make another commodity of lower value."[142]

- Firms ought to start with high-margin products advantageous on a price per kilo basis. For example, Finless Foods' focus on expensive fish products like bluefin tuna, which sells to restaurants for over $300 per kilogram at high-end auctions and for about $40 for farmed bluefin, sets a more attainable price target than a focus on inexpensive products like ground beef, which wholesales closer to $3.50/kg in the United States.[143]

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[140] See the KiOR section and also Jim Lane, "No Shortcuts to the Top," *Biofuels Digest*, May 20, 2014, https://www.biofuelsdigest.com/bdigest/2014/05/20/no-shortcuts-to-the-top-a-digest-special-report-on-scale-up-in-industrial-biotechnology/.

[141] For example, Sewalt cites as a model for alternative protein how the Enzyme Technical Association worked to "develop... standard safety evaluation methodology for food enzymes produced with rDNA technology, expanded its scope to food enzymes, and… started to leverage the Safe Strain Lineage concept" as a way of ensuring safety and quality. Moreover, Sewalt suggests that firms should not "ignore NGOs that are critical of you or your product. They're an important part of the process for getting these things to work." Panel at New Harvest 2018 conference, Cambridge, MA, July 21, 2018.

[142] Jim Lane, "Amyris in the Age of Rapid Change," *Alternative Energy Stocks*, http://www.altenergystocks.com/archives/2018/07/amyris-in-the-age-of-rapid-change/.

[143] "There were 1,729 tuna sold in Sunday's first auction for 2014, according to the city government, down from 2,419 last year. The 32,000 yen ($305) per kilogram paid for the top fish this year compares with 700,000 yen per kilogram last year…. Prices for bluefin tuna imported from other regions are much lower. A 189-kilogram (417-pound) farmed tuna imported from Spain sold for 662,000 yen (about $6,400) on Sunday, or 3,500 yen ($34) per kilogram, compared with a price of 4,800 yen ($46) a kilogram for the same type of fish sold at last year's first auction." AP in Tokyo, "Price of bluefin tuna falls at Tokyo auction," *The Guardian*, January 5, 2014, https://www.theguardian.com/world/2014/jan/05/bluefin-tuna-tokyo-auction. Beef numbers are for blended ground beef, 81% lean. "Wholesale Price Update," *Beef*, October 19, 2018, https://www.beefitswhatsfordinner.com/sales-data/wholesale-price-update.

- Government mandates like the Renewable Fuel Standards in the US were instrumental in furthering biofuels.[144] Governments interested in food security could require some standard of domestically-produced food, etc., which could prop up demand for alternative protein at higher price points.
    - Detailing a policy proposal for government support for cultured meat analogous to the Renewable Fuel Standard could be an effective research project.
- If implementing a production process dependent upon biological processes, localization cannot be ignored: "Localize the strain before implementing at commercial scale. Testing on the local substrate [and ingredients] is a must… Best way: pilot scale operations in the country where you operate."[145]
- "Hire the Production Team as early as possible so they can be involved in equipment check-out and commissioning" when designing and constructing a plant. It is also advisable to "involve the manufacturing/process engineers in the design"[146] and to use a flexible layout for the plant "in case the downstream process changes."[147]
- Early sterility testing in production facilities "will save time" and decrease the risk of controversy over safety issues "in the long run."[148] *E. coli* outbreaks on vertical farms demonstrate that merely assuming that a cleaner-seeming process offers a higher level of safety than conventional farming is misguided.[149] Alternative protein should not be only slightly cleaner than factory farmed meat. It is advisable for it to be orders of magnitude cleaner than factory farming because the repercussions for a public recall will be orders of magnitude higher.[150]

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[144] Sapp, "RFS."

[145] Lane, "No Shortcuts."

[146] This echoes Flynn's point about having engineers involved early.

[147] Lane, "No Shortcuts."

[148] Ibid.

[149] Niyati Gupta at the 2018 New Harvest conference: "Initially [the] idea of growing in clean rooms made everyone think vertical farming would be much safer. However, humans still carry germs and there was an *E. coli* recall. People were too lax."

[150] See Michael Siegrist and Bernadette Sütterlin, "Importance of Perceived Naturalness for Acceptance of Food Additives and Cultured Meat," *Appetite* 113 (2017): 320-26, which found that "the same risk associated with meat consumption was much more acceptable for traditionally produced meat compared with in-vitro meat [and] that the

- Many simultaneous problems will arise while scaling production. When in triage, do not attempt to "solve everything at once." Instead, focus on "Quality, COGS [cost of goods sold] & LCA [life-cycle assessment], and productivity increase."[151]
- "Utility back-up systems are a must."[152]

perceived naturalness of the meat (i.e., traditional or cultured meat) had a full mediation effect on participants' evaluation of the acceptability of the risk of colon cancer associated with the meat consumption. Even if the new production method (i.e., cultured meat) was more environmentally friendly and less harmful to animals, the perceived lack of naturalness might reduce the acceptability of the risk associated with such a product."

[151] Lane, "No Shortcuts."

[152] Ibid.

Appendix: Excerpts from biofuel industry presentations on how to commercialize successfully

Here are the ten lessons derived from a series of presentations by biofuel executives on the problems of scale-up:

1. No skipping or skimping of steps – pilot, demo, commercial.

2. Collaboration and feedback is key.

3. Technology scale-up and market pull go hand in hand, for technical as well as commercial reasons.

4. Understand the real "disaster risk" factors like flawed utilities, compressed schedule, rushed commissioning or inadequate aseptic design.

5. Strain development and adequate local testing is key, for fermentation technology.

6. Pilot where you will operate.

7. Changing technology horses in midstream can be a nightmare. [This fact, combined with the idea that firms need to be flexible about technology paradigms, presents a real pitfall. A potential lesson is that firms should front-load their flexibility.]

8. Strong mathematical and economic modeling is a must; data must be comparable.

9. Avoid after-thought approach to safety, regulatory, utilities.[153]

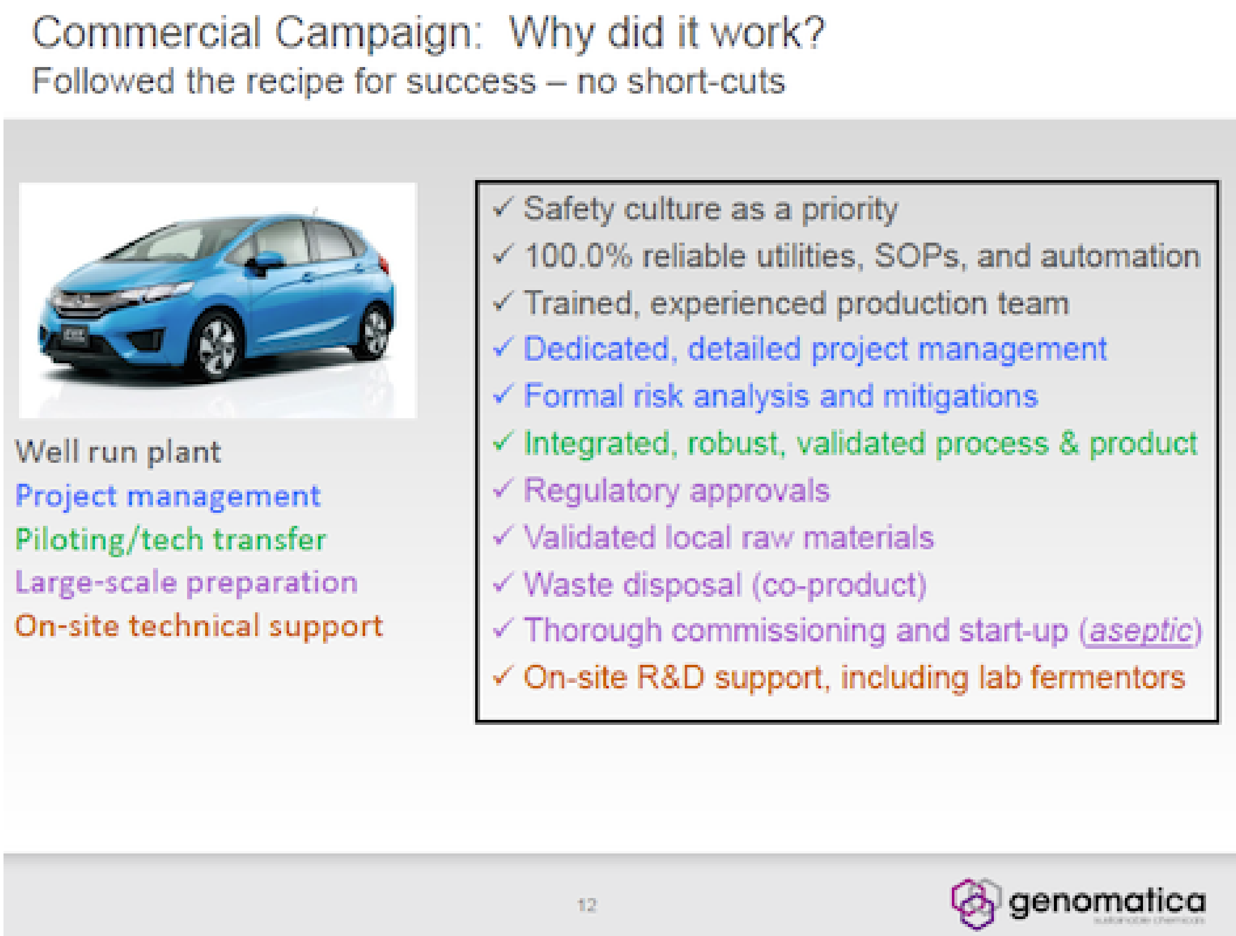
10. Get the most experienced team you can find.

Moreover, one of the slides notes that safety culture should be a priority, reliable SOPs, formal risk analysis and mitigation are all crucial.

Excerpt from slide deck:[154]

[153] Ibid.

[154] Ibid.



A further slide worth considering:

Scale-up Risk Factors – where it can go wrong

Learning the Hard Way

Minor (few months disruption)
- Automation and human errors
- Part-time project manager
- SOPs written during start-up

Serious (>6 mo, large losses)
- Project manager new to ferment'n
- Unreliable utilities, deficient PM
- Mothballed plant, deficient SOPs
- Silo mentality

Fatal (> 1 yr, plant closed)
- Flawed utilities, no maintenance
- Inadequate aseptic design
- Compressed schedule, rushed commissioning, unreliable utilities

Recipe for Failure
- Demand seriously lags production
- Product quality is not robust (cost pressure)
- Safety is an after-thought
- Process not robust and/or representative at small scale
- Regulatory is an after-thought
- Raw material surprises
- Heavy process waste loads
- Parallel plant design and process development
- Inexperienced, disconnected design team
- Poor construction project management
- Unreliable utilities
- Short-cuts in commissioning and start-up
- Inexperienced production team
- Contamination by foreign microbes
- No on-site R&D support

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