WILLIAM BONVILLIAN: I'm just going to do Venter very quickly since we went through this so thoroughly previously. But just a few wonderful snapshots, these are The *Nature* and the *Science* covers. So Venter did *Science* and Collins and the NIH Genome Project did *Nature.* Both published on the same day. It's kind of the truce that got arranged between the two sides. And there they are competing with each other.

And then there's Collins on his Harley and Venter on one of his wild racing yachts. And Venter is only interested in sailing if it's dangerous is best I can figure. So and then there's this classic picture Venter in the business suit and wearing the lab coat. You know this is all about the contradictions in the model he's trying to pursue, that fundamental Solara contradiction. So these are just a few.

AUDIENCE: Who's the dude on the motorcycle?

WILLIAM BONVILLIAN: That's Francis Collins who's currently head of NIH, who's also a blues singer too, by the way. So both these folks are a little out there. They're both terrific talents. They're remarkable talents. We've talked at length about Venter.

I think that for the purposes here, what I want to say is that, I put Venter in here as an example of someone who ran into all the contradictions in the life science innovation model, right? The fact that it was very hard for NIH to look outside of biology. It was all biologists all the time. Venter of course, was trained as a biologist but began moving into this computer territory, based upon some advances that Leroy Hood made before him and building on Hood's work and doing a lot of innovations like the genome shotgun approach that we talked about two weeks ago.

He ran into all of the other series of these institutional problems at NIH as an innovation organization. That it became very hard for him to stand up a completely different pathway to technology advance and science advance. That the system was locked into a different route, and they were very unaccepting. In fact, ostracized him as he moved in a different kind of

direction.

So he ultimately leaves. And then we run into this change agent kind of idea. He becomes a competitor and forces change in the institution which he left as it tries to keep pace with him so as not to be embarrassed. Hence the NIH Genome Initiative. And you know it's just an illustration and a very personal kind of way, which is why I put it in here, of some of the larger institutional challenges that we've been talking about before. So let me leave the Venter model here and go into the chapter, chapter seven in our textbook.

So it's not simply NIH, but it's the health care delivery system itself that has these legacy sector features. And as we talked about earlier on in class, the US is pretty good at standing up new technologies in open fields. It runs into real trouble trying to stand up technologies in these kind of established sectors.

So in the life science territory, we did pretty well by creating this completely new biotech model which was a we were able to get a lot of advance out of. But when it comes back to fixing the whole health care delivery system, that's proven far more problematic. And you know that's been a major thorny political issue for three administrations in a row now. And they've each had rocky results trying to pursue that question of how we're going to organize health care delivery systems.

So there's lots of legacy sector characteristics in health care delivery, perverse prices and price structures, established infrastructure and institutional structures like NIH, very powerful vested interests. We can see some of those in NIH. But we can certainly see them in other parts of the health care delivery system.

They're sustained by public habits. Right? So it's very hard to tell Medicare patients that their full cost repayment system with no patient stake doesn't make a lot of economic sense. They're not going to be enthusiastic about the alternatives. So these are structured and sustained by public habits. Steph?

AUDIENCE: Can you define no patient stake?

WILLIAM BONVILLIAN: You know Medicare is a full cost reimbursement system. And it was organized for medicine as we knew it 30 or 40 years ago, right? It was a professional delivery system. And you would pay for the cost of the service, whatever that was. You would not pay for results, because the results in the medical system are too uncertain.

It was very hard to figure out how to estimate a pay for results kind of outcomes oriented repayment system for these medical systems. So as a result, it became a fee for service, full payment system for the medical profession. And that created a huge incentive to run up costs for which the federal government would provide you full reimbursement, regardless of what the outcomes were. So trying to shift those economic signals has proven very problematic. You know, Obamacare attempted to change some of those, not without controversy within the medical professions.

It's averse to change and innovation. The established knowledge base tends to get locked in for the professions that are participants here. There's a real problem with collective action. In other words, it's scattered amongst thousands of institutions and getting them to act collectively in a different kind of organizational model is not simple. And there are serious governmental and institutional problems here.

So I won't go through the whole litany. But you begin to get a sense of how you can take the legacy sector analytical framework and apply it to a big economic sector that service based like health care. It's not just technology based like say energy, it's service based. But that analytical framework will work to a surprising extent for both kinds of sectors.

And let me go into-- let me go out and get this one on the table as well, the PCAST, propelling innovation and drug discovery. It's a very important critique of the system that came out in 2012. PCAST is the President's Council of Advisors on Science and Technology. They advise the president on science and tech policy. We had a very strong PCAST under Eric Lander during the Obama administration a lot did a lot of breakthrough reports.

I think frankly, this is one of the most significant. They really took a hard look at the health care innovation system and identified a lot of trouble, a lot of which we've been talking about today. But this really spelled a fair amount of it out.

So the NIH budget doubled between '98 and 2003. It hasn't kept up with the inflation costs since then. But in parallel, we've had rising costs of clinical trials, which have now actually reached, according this report $1.8 billion per drug. There's a new patent cliff that's looming for pharmaceutical companies. So you may have noticed that farmers are busy merging and divesting themselves of their R&D operations.

It looks like a problematic trend. So why is this? It's largely because of this upcoming patent

cliff. Drugs with annual sales of $200 billion dollars will go off patent between 2010 and I think it's 2015 actually. So this has already been happening. And this has forced a restructuring and amongst the historic pharmaceuticals.

Replacement revenues are not readily available. So hence this whole set of merger activities. And they've been, the pharmaceuticals have been curtailing their R&D as a result. Venture capital at the time this was written was in general decline for all sectors, including biopharma. Now frankly that's in significant part recovered now. That's now better than it was. This tends to be a cyclical kind of pattern for biotechs in the health care area.

But at this particularly time, first time these C deals for biotechs were down really quite significantly. And so that's always an issue that we're going to have to confront. In other words, biotechs only work if the venture capital system is willing to be quite supportive. So ups and downs in the venture capital sector can have a pretty strong effect as to whether we get drugs emerging into the marketplace that we need.

Despite R&D growth in past decades, drug output was flat and productivity was declining. And this report invented a concept called Eroom's law, which is the opposite of Moore's law. The cost of drug development doubles every nine years. And the results decline. So it's the opposite of Moore's law Martin?

AUDIENCE: I was going to ask, so VCs function on a seven year time cycle for an exit? So are biotech VCs on a 20 year cycle?

WILLIAM BONVILLIAN: No. No. But what they will do is they will go with different levels of funding, you know, A round, B round, C round, which they'll tie-- they'll benchmark often to the clinical trial process. So they'll be able to manage their risk in moving from one stage to another. And again, no other sector has thought of this. They haven't figured out an alternative model.

The failure rate for new drugs in clinical trials is increasing. So as of 2003, that was 91% fail. Imagine trying to construct a profit model around a 91% failure rate. It's not simple. Can still be done, because the rewards can be so big through the blockbuster model. And the guarantee of monopoly rents to the patents that you get for it.

AUDIENCE: [INAUDIBLE] Are things getting more stringent or are the diseases getting harder?

WILLIAM I think it's-- you know, what am I to say? And I don't think there are easy answers here on this,

BONVILLIAN: Max. I think that we've done the low hanging fruit. And the problem is getting much more complicated. Chris, you're nodding your head. Does that seem like a good answer to you?

AUDIENCE: Yeah, I think definitely. Because like the next frontier seems to be like personalized medicine, which is a huge kind of new moving problem. Because a lot of the difficulties of kind of commercializing that and kind of making that viable. Although there's a lot of hype around it, which is great.

WILLIAM BONVILLIAN: Right.

AUDIENCE: Don't get too much data. It could be that maybe they're not doing as many?

AUDIENCE: Yeah, well maybe now we're doing like way more. Or like, it's very easy. You know they say the worst lies are statistics.

WILLIAM BONVILLIAN: Yes, that's true. And all of these could be lies.

AUDIENCE: Well, it's just one way of looking at the problem, right? It's a way of showcasing it. But I would want to see the whole data to see why, the context behind it.

WILLIAM BONVILLIAN: Yeah. I mean generally speaking, this report was well received. In other words, the experts in the community thought that this PCAST report was on to something, that they had identified some pretty critical problems. So time to market for drugs has also been growing. So eight years to market was 50 years ago is 14 years to market now.

And the longer it takes, the more you eat up your monopoly rent period, which means you've got to make higher profits sooner, which means the short term charges for the drugs get higher. And you're driven and more and more towards a blockbuster recovery model. So this is problematic.

And you know it particularly affects small companies and biotechs that can't really manage that long term risk period. And there's a gap between research and product development as well. And the whole advances in science are requiring different kind of models here. So now there's much more focus on-- we'll talk about convergence in a little bit. But much more focus on multidisciplinary teams rather than solo individual investigator ROI type results.

You tend to have to cross over a series of fields now to get your medical advance out and that's more problematic. So ideas they propose, NCATS they cited, the translational medicine entity at NIH, that frankly has had trouble getting enough funding to really scale up to do what it needs to do, a DARPA type model, FDA exploring something called predictive toxicology, and predictive toxicity with a lab on a chip kind of approach. In other words, there's new technologies that could be breakthroughs here in trying to solve concept problems.

So let me-- let's get through these I think we can just touch very briefly on Craig Venter and then kind of dig into the legacy sector reading, into the PCAST report. Just a quick question on Venter. Yeah, you got him, Good.

AUDIENCE: I think Venter's discovery is one of the closest to [INAUDIBLE] ethical problems. And just now we had a discussion about how we want to speed up of all the research on antibiotics. So I want to ask, how do we balance this raising concern, by raising concerns of the public all this about related research and the need. There's a need for better drugs and better discoveries, in the sense that there is, like there is no mention the role of media in his discovery.

Is that without the media pushing his results, pushing his discoveries, his team and his work wouldn't be approved by this parent organization. And the kind of discussion raised in public kind of gave him enough support to continue this [INAUDIBLE] process. So I would say what are the other ways to kind of balance this raising concerns and this need for better drugs?

WILLIAM BONVILLIAN: It's a very interesting point, Luyao. The fact that Venter was able to mobilize media support, get them to understand the potential importance of these projects, and what the possibilities were, in effect help drive support for this whole genome initiative, whether it was Venter's or whether it was NIH's, it was a very powerful input. And we saw him and Collins on the cover of *Time Magazine.* That was just one example of the kind of media attention on this great scientific race.

AUDIENCE: [INAUDIBLE] everyone was saying, everyone has their genetic information, everyone was concerned. And how can this-- I mean, the future will probably be more concerns. Is there any possible way to address this balance?

AUDIENCE: So you're saying like change the structure so that somebody who has a good idea doesn't have to like completely go and fight the current structure for it?

AUDIENCE: I want to say like how do we inform the public of this, the potential benefits that it brings, but

also ensures that things are under--

AUDIENCE: Are actually worth-- yes I mean, I think a lot about like the cold fusion scandal. Where like they said they had it to the public so that they would get attention for it. But like the science wasn't super like sure. And so like there is a huge danger, especially in the scientific community, where you need to make sure something actually works and it's been tested by your peers before you go public, especially if it's a dramatic discovery, which I think the genomics project was.

And so that is a very hard position to be in. At the same time, though, I think he leveraged a good amount of that. I think it's more about being a little more slightly or Machiavellian in understanding the structure and like who can kill you in terms of like credibility or other stuff. So he did a good job of actually making sure the science was good, kind of having some stakeholders just approve his stuff.

But going to the media and saying, yo, this is why they're going to mess up and is why we're doing pretty well. And we're kind of a David versus Goliath. Check it out. It's pretty interesting.

WILLIAM BONVILLIAN: We don't usually talk about the role of media in innovation and science policy. But you are right to point us in this direction. Because this was a highly public competition. I mean as I say here, it creates-- that competition could be viewed as just duplicative, right? Why are private and public resources in effect duplicating each other in this race?

But on the other hand, it was incredibly creative and it spurred both sides to greatly accelerate and focus on the problems. So I think the duplicative research thesis really doesn't work here. But the other dimension you add here is, you know, how can innovators use public attention in helping to drive towards their goal. And we watched in the Boyer and Swanson case, how Swanson was able to mobilize media coverage and hold major press conferences when he had major announcements to make, he and Boyer had major announcements to make on their team.

So it's a dimension that I don't think anybody's really spent a lot of time looking at in an organized kind of way. But it's a very interesting one. How does public support affect your ability to drive an innovation project?

AUDIENCE: [INAUDIBLE] it seems to me that oftentimes, the general American public only gets really interested in the scientific topic when something's going really, really badly, like epidemic, is

where people are like hm, biology and medicine are important. Or like you know, my favorite example of the Apollo 13 disaster was when suddenly everyone cared about space, but only because people were about to die and it was exciting.

So maybe some sort of response to the science communication problem would be getting information out there about the value of preventing the ratings grabbing disasters, I guess.

AUDIENCE: It doesn't look as cool, though.

AUDIENCE: [INAUDIBLE] of science fiction. That's kind of the role of science fiction. There's like a utility principle that I-- her name is-- can't remember her last name I took a course on bioethics last semester. It was a part of something called the [INAUDIBLE] seminars for public writing at Wellesley. And this woman who was, I guess, was coming in to speak with us about the role of media in establishing bioethics, and specifically about genetic engineering.

And one of the points that she made to a question that I had asked was precisely that science fiction plays an enormous role in helping the public become comfortable with scientific advances far before the time that those scientific advances are even technically feasible. And so, maybe as the scientific community, or rather the scientific community should do a better job of involving themselves in the narrative storytelling process about what science is and has the potential to be in order to sort of set the stage for those scientific advancements when time comes.

And there is I think a huge market, thinking about Martin's sort of business proclivity in children's books about science fiction, and the ways in which we, as maybe someday parents, right, could be right in reading these stories to our children at night, having them think about the future and that aspect of science communication and especially science communication to the younger generations which will inherit the kinds of innovations that we create today, are immensely important.

But there's not a lot of storytellers who are equipped with the technical knowledge in order to communicate that adequately in a way that's palatable to children and it's also palatable to their parents and to the broader American market. So I think it's really important to think about this sort of storytelling dimensions of science communication, not just in the sense of, what's in the news, or what's going to be in the newspapers, but how we are orienting ourselves to make this an issue we care about socially.

AUDIENCE: Yeah, I like the idea of preparing the stage so that people are receptive to advancements when they happen, and not just the scientist makes a discovery and then suddenly is trying to drum up support for something that they have to explain, A, why it's important first of all, and then, B, why what they've discovered is the relevant. You make good points.

AUDIENCE: Do you remember who came up with the rockets, the original rocket that came from like Germany?

AUDIENCE: Von Braun.

AUDIENCE: Von Brian. Yeah, so that's a pretty good example. Because von Braun was having a lot of difficulty getting funding for the rockets originally. So what he did is he wrote a letter to Disney, because he was a foreigner. He was German, so like no one wanted him to actually do it. And they were kind of stifling him and they put him in a research facility where he wasn't really doing anything.

So he wrote Disney. Disney does a whole thing on space [INAUDIBLE]. But I think it's an important aspect in terms of really, who are you stakeholders as a scientist. You don't have-- unless you're like a billionaire, and even if you are a billionaire, you don't have the power to manipulate-- you're not like the president.

So you have to be able to figure out how you're going to persuade people and how you're going to use those different stakeholders in a very interesting-- well, in a very sort of pseudo Machiavellian but smart way, right? And how do you play the politics well?

WILLIAM BONVILLIAN: So maybe there's an amendment to the legacy sector book that we've been using as our textbook, which is part of the role of change agents is to use the media and to do storytelling. Because this was a great story. This was an amazing story, which people in the United States and the world followed for a significant period of time, this great rivalry.

And you know, Venter is almost made for media as a wonderful maverick, you know, fascinating character. And Collins is as well. So there was a powerful story to be told here and a great competition and a great race that made it a very powerful kind of media story for an extended period of time.

So Louis, I had not anticipated this tangent of the course. But thanks for pulling us into it. So let me go on to the next couple of readings. So our textbook, who's got that? Chloe, all yours.

AUDIENCE: So to set the stage for maybe the first question here. I went to a talk recently by a robotics entrepreneur, which seems unrelated. But I think he gave an interesting lesson as it relates, could relate to health care. He was talking about the problem he was dealing with, which was using robotics as an organizational tool in warehouses.

And it wasn't interesting to me at first. But he made the problem pretty interesting after a while. But the way that he framed dealing with his problems was that he practice having the mindset of evaluating the problem at zero and infinity, as he said. Which basically translated to removing all constraints that were pre-existing on the system and then seeing you know if he had infinite space or infinite money or infinite labor, what he could accomplish or what his engineering solutions would be.

And it was a really good way to sort of brainstorm an optimal solution to his problem. So I think it would be interesting to take the same approach to the inherent problems in health care delivery as a legacy sector. If we could-- like, you made the point that when you are recapping this chapter that our system is currently designed to suit medicine as it existed I guess 30 or 40 years ago, but not as it is moving into this exciting brave new world today.

So if we could wipe the slate clean and not have any of the residual costs, like everyone started out healthily today. No one had any illness and we didn't have any residual costs or anything, like perfect ideal world, and we had to redesign our health care system from the ground up, and --I know this is a massive question. But I'm just interested in what you guys think that might look like. Like what would our innovation in that area look like we had no constraints.

AUDIENCE: I mean obviously, you'd have a bunch of pharmaceutical companies would be producing infinite drugs, because they have tons of money. But from there, I think you'd have a significant bottleneck in terms of the FDA. So you'd have to expand that significantly.

AUDIENCE: I don't necessarily mean like they have the infinite resources. It's just like if we were starting to [INAUDIBLE].

AUDIENCE: Create a completely perfect system for this time and the next 50 years, how would we do it?

AUDIENCE: Yeah.

AUDIENCE: I mean, you want me to give you an answer of how to structure or how to figure out what the process is?

AUDIENCE: Just I guess, elements of what it might look like.

AUDIENCE: Well, I think a lot of it falls in what Chris was talking about and what Bill was talking about, the personalized medicine component. That's kind of how they're touting it. It's the fundamental reorganization of health care delivery. And one of the ways in which they're-- I guess, my understanding is that the sector is purporting to make that happen is through additive manufacturing. So the 3D printing [INAUDIBLE].

AUDIENCE: I was just going to say that.

WILLIAM BONVILLIAN: Well, 3D printing is going to be useful in a lot of health areas. So there's a new manufacturing institute that's organized around regenerative medicine and tissue engineering, for example, using 3D printing as one of the technologies they're looking at and combining that with synthetic biology. That's a very interesting and potentially very promising territory.

As we'll get into in the next reading, that's not biology, right? That's a whole series of new engineering strands that are starting to enter , and IT strands, that are starting to enter this territory. And how does a system that's not organized around that, change to accommodate those strands?

AUDIENCE: Well I think the container section of sort of the pharmaceutical industry and engineering, one of the most interesting articles that I read recently, was about the ways in which they're printing the pills in order to be better adapted to the person's absorption of the medicine. So they sort of-- they're starting to develop ways to gauge what a pill needs to look like for an individual to ingest it and also for the medicine to be delivered into their body.

And They can't do that in mass manufacturing. They can only do that in personalized medicine through additives. So I thought that was pretty cool. So that would be an answer to your question, right? That exists and does not require an idealized world. It would just require the sort of commercialization process and then the scaling up of what exists potentially, if it's not to be thwarted by the legacy sector.

WILLIAM BONVILLIAN: So the traditional production system for you know medicines is a batch processing system. You build a huge batch and you refine it so it has the perfect composition spread evenly throughout. And then you produce that. But that's frankly, not a modern manufacturing technology. So a continuous manufacturing process is much more flexible, potentially much

more modular and adaptive to different components in that system, i.e. Different elements and a different molecular structures and different components within a particular drug or a pill.

And 3D printing is a very interesting adaptive approach. So DARPA has been funding desktop pharmaceutical manufacturing with exactly that in mind. That we're going to have to move to personalized medicine. The military is going to have to have it for its own huge health care system, which is funded to the tune of about $50 billion a year, a major medical system.

AUDIENCE: [INAUDIBLE] That's 10 arc reactors. I'll take it.

WILLIAM BONVILLIAN: Well it's a very large medical system. And they're having to deal with changes and reforms in their own system, so they're moving on developing a whole new set of production technologies. And on that one, they've been working within an MIT team that's really quite interesting.

But that again, NIH doesn't do this. That's not in NIH's territory. It happened that the military was interested in this. This new DARPA biological technologies office happens to be intrigued with those set of possibilities. But that's kind of outside the box of the existing system.

AUDIENCE: So, plug and play manufacturing, plug and play personalized medicine?

WILLIAM BONVILLIAN: Good phrasing, Chloe.

AUDIENCE: Thank you.

AUDIENCE: I don't know. I think we're going to have to focus on the new sexy technologies, focus more on the structure. Because I think like, say I have to use the technology that we have now, I would think about how I'd restructure the organization. What are the problems and are they caused by incentives? So I think this health care crisis isn't a problem of technology or even people or even doctors.

I think it's an issue of incentives. So when I say I'm going to pay whatever you do, I'm like, oh well, let's stack it on, add more toppings. And like, I end up having a huge bill. And then also, as a generation, where now we have a huge kind of-- I don't-- we have a lot more elders than young people. And so we have to pay for these baby boomers. So it ignores that context.

So we also might want to focus on probably like most of our costs are going to go to elders,

not young people, because young people are fine. We have a huge portion of elders, so what are their diseases? How do they work? What are the main causes of those diseases? And how do I create my organization around that?

Or maybe I just want to create a whole new medical system, focus on this segment because I know that they're going to be huge, you know, costs. And I can get you know, laws of economics by having such a large segment that's, like that whole system is personalized for them. And they have different needs than somebody who is young. Who can just take an Uber or something.

Yeah. For them, you probably have to have somebody go directly to them, check how they're doing, check constant levels. So it's very different. And I think that could cut costs down. Or you could send somebody out to them.

WILLIAM BONVILLIAN: Or use an IT system or use robotics. Those are all part of the menu that we're starting to think about Chloe, a closing thought about this reading on legacy sectors?

AUDIENCE: Yeah. I think for me, it was really eye opening to see the part of the reading where you just listed the five or six specific characteristics of how health care delivery draws parallels to legacy sectors. And I think those are probably the areas where any sort of reformers or innovators would really hone in on and focus on lifting those restrictions to limber up the system a lot.

WILLIAM BONVILLIAN: OK. Let's go to the PCAST report.

AUDIENCE: Regarding this research, the drug development. We were just talking about how do we incentivize firms to take on more responsibility in developing some drugs that target minority groups or that don't have such a big market. And I want to introduce this model that Singapore has in incentivizing their small and medium sized firms to invest in R&D and trainings.

What they do is, you can get a tax return or you can get a set amount of funds as long as you are investing in your employees or in any forms of training that can improve your productivity and improves your research in any form. And I think Singapore was able to do that because they are really small scale. And they also count on their small and medium sized businesses to thrive as the economy.

But I want to know if this kind of model can be a good reference to develop the health care

research sector in the US. If you have any--

WILLIAM BONVILLIAN: So the model Singapore is using then is to give an incentive to companies that are making significant investments in the training of their employees and their research teams to kind of significantly upgrade their skill sets.

AUDIENCE: And they have give a lot of flexibility. As long as you can justify this amount of spending, or able to improve your productivity, they get this funding.

WILLIAM BONVILLIAN: That's what you have to show. You have to show some kind of increased performance coming out of that.

AUDIENCE: So what are your thoughts about this kind of approach that could kind of encourage a drug developments?

WILLIAM BONVILLIAN: So that's interesting. So that's like a roamer technology talent approach into a discussion we've been having on institutional innovation organization. So it's again, you bring us an interesting piece of the puzzle. I like it.

So let's go back to basics. Is there a talent need in this sector? Is there a talent shortage? Is there a talent enthusiasm issue here that we ought to be addressing as well?

AUDIENCE: From what I've seen in my very limited biotech experience, it seems like there isn't really much of a shortage. It seems like there's a lot of enthusiasm around the field. And like, as has been a continuing theme this class, our good old American spirit and our entrepreneurial drive toward packing up and moving out West or in this case west is genetic engineering and all that good stuff. So I don't know if the drive is really the problem.

AUDIENCE: I just think about-- I like to think about analogies. And often in urban planning, you know, people compare Scandinavian countries to the rest of the world. And say, well, why can't we be like them? And there's various factors that we don't take into consideration, the homogeneity of the population, their productive capacity, the resources they have accessible to them, the scale at which they're operating, maybe their colonial history and the ways in which they were able to sort of take advantage of some opportunities that we might not be able to as a country, et cetera.

And so in this instance, I'd like to sort of invoke that and cross apply that argument to sort of Luyao's point about Singapore, and then to really utilize that to challenge what Max just said.

Because I feel like we are situated in a very unique and incredible location for this kind of conversation. But where I'm from in Texas, the kinds of university systems and research system that exist there, these kinds of conversations probably don't happen to that extent. And the enthusiasm for commercialization is probably not to the same level.

And so I think I would come back to what Max is saying specifically, by saying that perhaps we need to then bring something, in a way, usual socialist ways, to say that perhaps it is the kinds of talent that is missing or rather, people from marginalized groups may have a decidedly public good approach to research. And so they might not want to commercialize in the same ways that people who are being trained in institutions like MIT and Stanford are.

And it is perhaps that it is precisely those people who the government should be funding, not major research universities that exist within a commercialization framework. Because those individuals are less likely to want to take the bigger piece of the pie and may potentially want to benefit and serve their communities much more, which could prove to be much more disruptive ultimately.

WILLIAM BONVILLIAN: Who wants to take on Steph's economic model?

[LAUGHING]

Plenty of volunteers.

AUDIENCE: One, you directly challenged me and you--

AUDIENCE: Please, please, please, please.

AUDIENCE: Well, I mean, it's nice and idealistic. I love thinking that, OK, everyone is just going to work for free.

AUDIENCE: Oh I don't think they're going to work for free, Max. That's not the insinuation. The insinuation is that the profit sharing is going to-- the. Profit sharing model is going to be much different I mean, I'm not going to [INAUDIBLE].

AUDIENCE: OK, so I understood it as they don't care about making big fish blockbuster drugs or we'll make like the drugs that are like [INAUDIBLE].

AUDIENCE: They can make the big fish blockbuster drugs. They just don't want to profit to that extent,

which ends up being good for everyone.

AUDIENCE: OK. So them not profiting [INAUDIBLE].

AUDIENCE: But the thing is, you could take the other side. The company's profiting means they can put that research-- put that money toward new drugs, as opposed to just develop one drug and then you basically break even. Then you're just like, what do I do now?

AUDIENCE: I think the focus on drugs maybe also kind of limited. Like I guess we still want more drugs, that's fine. But I think they have drugs that are targeted towards like, maybe if-- I guess we talked about like a disease portfolio that they look at and it's very narrow. And so there's two things here. So I wonder if such proposals might help expand that disease portfolio.

So you have people who care about more diseases and are able to do more research in sort of different areas. And then two, I wonder if those who actually subscribe to this sort of, let's say big pharma look kind of like we're in this age, FDA, drug an incremental advance type system, do they actually care to the extent that someone's trying to get at. Like are they actually interested in kind of solving this incremental advance problem or do they have a vested interest in what they're doing because they care about these sort of bigger fish, like kind of cure all drugs? But they don't have the funding opportunities and kind of the means to kind of get [INAUDIBLE].

AUDIENCE: The way institutions are specifically cited by the conversions reading, I think kind of really proved sort of where I'm coming from. They cited a Harvard, University of Texas at Austin, Carnegie Mellon, George Tech, U Chicago, and Tufts, obviously you know without saying, MIT, because most of the people on that commission had some relationship time or were researchers that graduated from MIT, were professors that MIT, were prominent political stakeholders at MIT.

So you know it occurs to me that there if, it is that we you know really revere people like Craig Venter, and, if it is that the convergence reading, which we will be talking about soon enough, is putting a lot of weight on the potential of community colleges and of local institutions to train the workforce in the life sciences, why is it that we don't give them the same access to funding opportunities that we're giving you know, the sort of blockbuster research universities?

AUDIENCE: I think the big thing is like, so it seems like a lot-- this is like a easy mental model for most people. What they do is they think about everything linearly. So the thing is like MIT, Harvard,

and luxury institutions just have a huge conglomeration of people. So they're exponentially much better at solving certain problems. And they have the credibility to go and get funding from outside sources, whether it be government, whether it be VC, so it is this huge you know, very unproportional nature of the institutes and the way the system works.

But there are some good things to that. What I worry more is like how do you create a new system to make all these smaller drugs and working on them more viable. So I think that's an interesting place for a startup, if you can figure out 3D printing of drugs or if you can figure out what is your kind of your competitive advantage in this problem. And what is the current structure for the company that focus on the big pharma. And how do you optimize for that.

So what are so it's pretty much like *Art of War.* It's like, OK, they already have their strategy. They have to focus on doing business with us. And there's also called the intervention dilemma, which is like they have to make $5 billion in revenue off of this drug. I don't need to make $5 million in revenue. I'm a smaller fish. I could, with like $5 million, right?

So like how do I create my systems so that I can make these kind of drugs and make a big company based on focusing on those smaller drugs that are important to society. That would be like the enterprise version. You can probably come up with some parallel using government funding and government support.

And maybe it might be that FDA approval, being more lax, or depending on the drug, I would have to figure out which ones are the best ones to go after in the beginning. But I don't think, except making the argument that, oh how do we, you know, I don't want to say democratize, but why can't everybody like be in the pool?

Especially when it's like those there are people that are Olympic swimmers and like institutes that-- I mean there are probably good high school swimmers, but like it just won't you won't get as much a run through of the same--

AUDIENCE: I guess it just concerns me that we pay so much lip service to the great groups model. And the great group model itself says that the drive for profit is not the greatest motivator to innovation. And if we are to consider that as true or to take that at face value in the ways in which the authors have presented their argument in the previous weeks, I don't know that the commercialization model for the life sciences is necessarily conducive to innovations in the ways in which we would hope that they would exist.

WILLIAM BONVILLIAN: So, Steph, you're driving us towards obviously some truly big picture issues. Look, we have taken a pretty radical capitalist model to solving this problem of innovation in life science, right? It's pretty amazing that we have focused on a high risk, high reward system that's completely dependent upon you know, monopoly rents and major returns as the way in which we're going to do innovation in the life science territory. It's absolutely fascinating.

How did we stumble into this? That wasn't what-- remember when we talked about Boyer and the conflicts he had with other UCSF faculty? When he went off to invent the biotech model with Swanson, he got a lot of flack for this. That was a radical departure. He was leaving a university based research system.

But let's think back to the reasons why he was doing that. Because he wanted his technologies to scale up and be available and that was the option that he saw for being able to do that, so he teams up with Swanson. I don't think we're going to resolve these questions today. But it is a radical capitalist model. And as we've discussed at length today, there are gaps in that model, right?

There's only some things that that model is going to be able to address given the structural limits that are coming into it, particularly the long term approval process that the FDA has to provide. So you know, drug companies hate the FDA because they have to spend seven years and $1.8 billion getting through their hurdles. But they also love FDA because it certifies their products and guarantees a market for them.

So it's this odd love hate relationship. In some ways that's symptomatic of what we've got over this whole system. And it is a system under stress at this point. Luyao why don't you give us a closing point on this and then we'll go right into what I think the next part of the story is on convergence. Because I think it fits nicely with this.

AUDIENCE: I realize we do focus on a lot of how to incentivize innovation in drug development. But I do think that you know we still have this scarcity problem with rising demand and limited supply. Why don't we also divert a little bit of focus on developing a healthy population. Can any form of drug development and kind of research that advance this process, so that we can reduce the unnecessary demand for certain type of health care. So that we can free up a bit of our funding and resources so that we can focus on the rest of the research programs.

WILLIAM BONVILLIAN: And look, your point earlier, which we debated about, is there a talent problem here? Romer's prospector theory would tell us, you're going to get a lot more innovation if you put more well-

trained prospectors on the problem, right? So I don't want us to kind of leave that point. I think there's an interesting underlying point you made in that area as well. All right, let's go on to the convergence study.

The report is called "The Third Revolution - The Convergence Of Life, Physical and Engineering Sciences." And it came out of MIT in 2011. You know my office, the MIT Washington office, helped work on this. The project was led by Phil Sharpe and Bob Langer, somebody from engineering, somebody from biology, obviously two of MIT's all time greats.

And the report tries to tell a story that the picture in the next advance wave, we're lacking a picture of the next wave of advance. The great thing the genomes piece gave us and we talked about Venter and the competition with Collins and the NIH, it gave us a story, it gave us a picture of what we're going to get for this massive investment in NIH. It enabled the public to see a story and be told a story and understand what the results were going to yield, right?

We don't have a story for the life sciences that's out there now that has nearly the kind of power as that genomic story. We haven't figured out how to tell the next story. And that's part of the reason why we've got funding stagnation for NIH and the life sciences in general. So the doubling was led by the genomics revolution. NIH needs a new picture.

So what are these different revolutions? So what this report argued was that really the kind of first revolution in recent time was the molecular biology revolution. And that was really the merger of physics and biology. So Max Delbruck comes out of the amazing pre-war German physics community.

He works with Niels Bohr in Copenhagen as part of that amazing community that were living in Bohr's house, being trained by him. Bohr produces this amazing talent team and this is the second generation. This is you know Bohr and Einstein are an earlier generation and Marie Curie and so forth. This is the next generation out. How are they going to find their project? What's their project going to be?

And Bohr kind of urges Delbruck, why don't you look at biology. We're coming along up with a lot of physics here. Is there a way of applying that to biology? And Delbruck does this and has to come to the United States. He has to flee Germany on the eve of the war. And in turn, Salvadore Luria, he is working with Enrico Fermi at the University of Rome. He's a medical doctor. He's trained in medicine.

And he is fascinated with physics. So he goes to work for Fermi, working on particle physics issues. So these are two people that actually lead this whole molecular biology revolution, in part because they're doing this crossover thing that we've talked about before. They're taking physics and moving it into this new biology territory with a whole new raft of ideas that help mature and create all kinds of new thinking in biology. And it really leads to molecular biology, right?

You know, the second revolution is really genome sequencing. We've talked a lot about that already. But essentially, that's another one of these crossovers, right? That's taking advances in computing and certain other kind of physical science areas and then bringing them into biology and creating a whole new set of applications in the biology field that are in turn transformative. So that's a second crossover.

The third revolution-- here, by the way, are some of the earlier revolution leaders. So that's Salvadore Luria, one of MIT'S greats, Nobel Prize winner. That's Luria and Delbruck teamed up together on the back porch of I think some Long Island beach resort. Luria works in Cold Spring Harbor. But that's you know, that's an amazing talent team. And they really do create the intellectual underpinnings for molecular biology.

That's Leroy Hood, inventor who you're familiar with. That's Eric Lander. They're leaders in the second revolution, the great genomic revolution, another crossover approach. And then we've got this whole new community. I've featured the MIT parts of it. But this revolution is happening at many other schools. But this is just the community that we're used to.

So Phil Sharp on the left and Bob Langer, who are the leaders on this particular report. Tyler Jacks who leads the Koch Institute here. Paul Hammond, who is chairman of the biochemistry department, no.

AUDIENCE: Chem E.

WILLIAM BONVILLIAN: Chemical engineering department. But is doing an enormous amount of research in the life science side. Susan Hockfield is president at Sangeeta Bhatia, who's doing amazing work on cancer. You know, it's an incredible community of talent, again from a whole series of different kind of fields. It's another crossover. It's engineering and physical sciences and computational sciences entering into the life science space with a whole new set of disciplinary perspectives, a whole new set of systems perspectives, a whole new way of thinking about how to organize research. And so this is the MIT community. You could duplicate this at other schools as well.

But it's a set of engineering tools are going to come here, but also a whole concept of engineering design comes here. So, life science systems tends to look at that complexity. They tend to look at complex systems and attempt to understand the elements in complex systems. That's the kind of way, the frame that biologists work from. Engineering works in a very different kind of way. It attempts to organize in a very hierarchical fashion and set priorities. Engineering design is a very different way of looking at the world.

So these two fundamental different perspectives now have the opportunity of coming together here, for what becomes actually a very different kind of research model. So there will be new knowledge bases here that come about as a result of this. Just as genomics gave us a whole new knowledge base, just as molecular biology gave us a whole new knowledge base, the convergence of these different fields is going to create a new knowledge base.

But convergence is somewhat different. Because it's also, particularly through the engineering side, it could lead us to a whole new set of therapeutic advances. So new technologies shift over from engineering in areas like imaging sensors, nanotechnology, simulation modeling, probability, these are all kind of engineering led sides of things that can now walk into the biology space. So this report at MIT kind of laid a lot of the groundwork.

And frankly Susan Hockfield saw the promise of what these folks were writing about and created you know just, up the road from us created the Koch Institute, so that we were walking the walk at the same time we were talking the talk here. So that Koch Institute was under way before this report was even finished, because it was just so clear that this was an incredibly promising set of new research opportunities that were going to create a lot of real breakthrough spaces in the life sciences.

So there's a whole series of strands that we had already seen, that you could call convergence-like strands, so synthetic biology and nano biology and systems biology, bioinformatics, computational biology, tissue engineering, these were all kind of strands at MIT and in life sciences generally. And the idea of convergence was, ah, these things are doing similar things. We can understand this in a larger kind of way and take more creative advantage of it.

So will convergence play a role in the medical costs problems that we've been talking about? We talked about the lack of incentives for cost controls in the system. So far, we've been thinking about health care as a, like rearranging the kind of financial plumbing, right?

Could we create different kinds of cost structures and cost incentives and so forth. There is another potential answer here, and it's back to the prospector theory in a way that you were suggesting. Maybe there are innovation answers here too, right? In other words, if you get a whole series of innovation based advances, that can tackle a lot of these problems.

So for example, you know, NIH working away in supporting life science research really enabled huge progress against heart disease, which you know, is breathtaking and really moved heart disease down a notch from a nightmare killer to much more manageable health problem. And that's occurred in the last 25 years. If you do that in a number of areas, you can really start to affect the whole kind of cost structure. And particularly, could you have healthier aging?

So one part of the dilemma for the current demographics challenge that's going to be upon you, is keeping my generation in the workforce longer with returns that are going into society. Can you make me and my generation work longer, generating returns that get distributed to all? That would solve a lot of problems.

That helps us, rather than walking off a cliff, it helps it manage much more of a curve. So if we could do that, that would be powerful. And may be that some of these convergence space technologies can really be significant enablers in ways that we kind of never saw before. So that's an innovation-based policy approach to a profound kind of societal challenge.

So there's a whole series of policy steps that the report argues need to be taken. We need to get across NIH stovepipes. NIH, which is all biology all the time on most days, needs to be encouraged to be able to look at and fund other fields. It's hard for NIH to do it because it's composed of biologists. If it analyzes proposals that involve complex engineering, how does it do the analysis?

How does it have multidisciplinary peer review systems? Is it able to encourage RO1s that have multiple PIs, not sole single PIs, that represent a series of different fields and disciplines. It's how do we do education and convergence? So we still have stove piped disciplinary fields, and they're producing a lot of talent. But how do they get educated in these other fields so they can take advantage of it?

Do we need a new kind of approach in life science education? And what are the of common language features going to be? Steph.

AUDIENCE: I feel like the report was really missing an element about the jobs in the convergence field, because there's not really many job opportunities for people who are trained in multidisciplinary understandings. And I feel like there would be an enormous insecurity or uncertainty for those people who are interested in pursuing the really innovative fields if they don't understand what the actual next step is after a university education.

WILLIAM BONVILLIAN: Right. There's no question about it. This is a dilemma. And look, this has been a dilemma for a while for bioengineering departments. I think we're getting out of that phase. I think those are starting to really kind of take off, in part because this model is taking off.

But we don't have clear pathways. So I mean the model is going to continue to be that you're going to be a biologist. But can you get access to a series of other fields? Maybe you're an engineer but you get significant access to a series of medical related fields as well. Can we adjust our training system and modify it so that-- there was a talented staffer in my office who said look, we we're going to need a new language here in life science innovation.

We're going to need kind of our convergence Creole, a mix of different languages from different fields so that people are going to be able to speak across these disciplinary lines and understand things across these disciplinary lines. That could be that could be pretty important. You know that's the heart of this report. MIT team subsequently went on in a much broader based report that went across many institutions.

And this past year, did a report looking at what could we get from convergence? In other words, what other promising convergence areas and what might be obtained from them in an attempt to get a much more strategic approach to convergence? Not just say convergence is neat, which is kind of what this report did. But really get a strategy together. I'm partly guilty. But actually get a strategy together around what territories in convergence might be particularly promising. So I urge you to take a look at that more recent report. That was much more widely shared across institutions. Luyao, some questions for us.

AUDIENCE: I think one of the most relevant discussions of the [INAUDIBLE] would be what are the possible features that we could expect in university level that will be probably encouraging this kind of confidence to take place? Yes.

AUDIENCE: I mean, we have the whole liberal arts college. It's essentially the liberal arts for science and engineering model.

AUDIENCE: But why is it currently not-- like since they're proposing this convergence of researchers, so why is it not happening with all this students with multidisciplinary backgrounds, why are they not currently working together across disciplines?

AUDIENCE: I would say, in no particular reference to our institution at Wellesley. I work a lot with multidisciplinary stakeholders for the incubator program that I am facilitating currently. And a big concern that faculty members have is that they, one, by the administration are not facilitated to do collaborations. And two, that a lot of people feel like having an entrepreneurship or a sort of innovation for the purpose of commercialization model goes against the spirit of a liberal arts education.

So I feel like in that sense, you know, research universities are very much well-designed to sort of adopt more of a liberal arts model than I think liberal arts colleges are designed to adopt more of a stem model. But you know, perhaps somewhere in there is a model that can arise about multidisciplinary coordination. But it would require facilitation by the administration to the extent to which I think MIT does a really great job of facilitating that at the institutional level.

AUDIENCE: The rise of kind of these collaborative projects, particularly culminating in your senior year, I think capstone projects are a great opportunity to start encouraging these collaborative efforts. I think Course Two does this pretty well with their 2.009 Mechancial Engineering kind of product design course. But the piece that I would take from that is at the beginning of the semester, they have you list all of your skills.

And they separate you out based on kind of backgrounds and then form teams that are like inherently collaborative, so you don't have sort of lumpiness and all the students that are interested, or have particular backgrounds in product design, they're not all on the same team. They kind of spread it out. And then I think if it be an interesting exercise to have MIT do sort of a school engineering capstone project. And sort of elect into a course where you have people that are interested in tissue engineering, but they come from the biology department, the chemical engineering department, and bioengineering department, and they work together to kind of formalize this.

AUDIENCE: In my impression, there's kind of two models. Either we train more multidisciplinary students like, for me, like my major is philosophy, politics, and economics. But I'm not actually in [INAUDIBLE]. So then the other option is to have like a lot of very focused students and bring

them together to work as a team. Which model do you think will be more effective in addressing health care change?

AUDIENCE: I think great groups model.

[INAUDIBLE]

AUDIENCE: You definitely like want people that like, what's the difference between--

AUDIENCE: It's the deep generalist. That's what they were calling them.

AUDIENCE: No. Well, you need one person who can gets it for every single one of the issues. But then you need somebody who-- you need somebody who is obsessed--

[INTERPOSING VOICES]

AUDIENCE: Yo, I read every single book. I read two, three books outside this course. You know, I know this and this and this. And the person is just like, like, knows so much that like, it's just like you hit them with like, any word and they're inspired. So like, you want-- but you definitely need somebody who knows it and understands how to lead really. Well. Because really great engineers tend to not be able to communicate greatly.

So you have to be able to figure out and ask what questions to ask that they won't tell you or figure out what they're not telling you, especially when hitting deadlines. And then another big part with groups, with these kind of groups, is to figure out where each person stands. So it's like, oh, I don't think you're doing a great job.

Or I know you have this deadline. You might may not make it. I know you're stressed. Don't be stressed. I'll check in at the 70% mark. How are you doing and then we'll figure it out from there. But I don't know, I think is more interesting to the research and the media lab kind of does that. But I don't know if it's been done for very, very hard research. What I would consider super, like solving like a very hard problem.

WILLIAM BONVILLIAN: It's all these problems are now at hand, as we start to seriously pursue this convergence model, exactly how we're going to cope with this. Susan Hockfield used to talk about it. And other people have talked about it too, T-shaped people. In other words, people with a deep disciplinary die, but capable of operating across fields as well. And that may well be a pretty key feature here.

And then combining that community so it's able to communicate with each other. But you draw on a series of different fields. So what the organizational model is going to be is really critical here. Because again as we've talked about two classes ago, innovation, you know, happens with people. It's not these institutional organizational models. And how do you optimize the opportunities for people to be creative?

So that's upon this model, right? Koch Institute is spending a lot of time thinking about this. But actually Koch Institute is only one part of the convergence going on at MIT. Something like 130 engineers are now working a significant amount of their time at I'm MIT on the life science side. And that's not unique. That's going on at a lot of institutions now.

And NIH is a problem here. Because it hasn't caught up to be able to manage that kind of transition and embrace these different fields. So that's the big funder. And how do we bring that institution along?

AUDIENCE: I think my big concern though, is like having all academics, like, yeah, we're getting T people but, let's define T like somebody who is like a grad student or undergrad at MIT. Like I don't know if the best answer is to have a great group of Ts. You know, I want some As. I want some Bs. I want some accents. I want some question marks.

Because like, I would use all sorts, like the background, right? Because it is the difference between, oh, I can make a really good like bistro sandwich versus I need to make 100, 1,000, 100,000. And I need to have the financials for all of the stuff, which is like McDonald's, right? So ideally, I would want somebody who's already been in the field, like somebody who has faculty experience.

Because I might start to build out a certain way. But they have just a big scene phenomena, right? Like a great example is, originally GE, when they were putting out the electrical lens, there was this guy named Steinmetz. He was this hunchback immigrant that couldn't even speak English when he got to the country, and didn't really have a great-- do you have Steinmetz on there?

WILLIAM BONVILLIAN: I don't.

AUDIENCE: It would be cool if you did. But, yeah, but he was just like this very, very kind of somebody who would never even be at MIT. Or like the Wright brothers, right? That it was just they had the

practice experience that, oh, I think I can do this and trying it out. Also like just because of, as in academics, there's always a flaw in any organization.

And you have to figure out, especially in business, you look at, oh, how can I expose their flaw and they're never going to be able to go here because of the way. This is their blind spot. And so like, you can definitely, like what happened at the Wright brothers, where it's like, I can't work on this problem because there's no perfect theory and it's too much of a risk.

And I'm already 50 years old. And I'm not trying to risk my reputation and make my friends make fun of me because that's too uncomfortable. And I've already kind of like gone my way. And there might be somebody that's like, you know, it's pretty crazy but I'm just going to try it and see what happens. And I think in that paper, there is a quote, where it's like, what's the point of research if you already know what's going to happen?

But the way the system is, sometimes it incentivizes you to just do like, oh, I know this is never going to-- I don't know if it's going to be perfect. But I know it's pretty much going to work out. And I think that's a very-- OK, as like somebody who likes capitalism, I think that's a huge opportunity. Because like, you don't just make your company look at all the blind spots.

But I think that's going to be one of the reasons why these models don't succeed. And it will be big failure too. If they fail, right? Because of you like you said. You spent all this money. You got all these smart people. And there can be a huge failure there.

WILLIAM BONVILLIAN: So let's close. I attempted to put the convergence reading last because it's basically a positive. In other words, there are huge innovation opportunities that are at hand that we're starting to move on. So despite all the problems in the innovation system in this sector and all of its organizational gaps, something really interesting is starting to happen.

So let me close with a comment from Elias Zerhouni, who is the Director of NIH before Francis Collins. He writes, "As science grows more complex, it is also converging on a set of unifying principles that link apparently disparate diseases through common biological pathways and therapeutic approaches. Today NIH research needs to reflect this new reality." So I think that's our innovation organization task here, I think summarized nicely in a couple of sentences from Zerhouni.

A closing thought, Luyao?

AUDIENCE: Well, I do think this reading sends a very positive message that we will need to search for a

holistic organization that kind of get our resources and tackle these problems. Still, I also feel like we are not addressing the problem of kind of, instead of tackling all these diseases, why don't we prepare, like kind of advocate this population to be more healthy, to encourage them to have a healthier lifestyle.

WILLIAM BONVILLIAN: Preventative medicine rather than just repair jobs. Right, right. An important thought.

AUDIENCE: And I do think--

WILLIAM BONVILLIAN: And there aren't incentives in this system particularly to do that either, which is problematic.