Trust and Support in the Future of American Science and Biomedical Information with Fred Ramsdell

Kit Pogliano: Welcome to everyone in the audience. I'm so pleased you could all join us here today for this very important conversation about innovation and the future of American research. I'm Kit Pogliano. I'm the Dean of Biological Sciences at UC San Diego, and I'm really happy to say I've been at UCSD for 30 years and have seen this campus through a lot of changes. It's a beautiful place, and it's so great to welcome Fred back to the campus. Thank you so much, Fred, for joining us.

Fred Ramsdell: My pleasure.

Kit Pogliano: Thank you for agreeing to speak on this really important topic. As all of you know in the audience know, Fred is an esteemed scientist, Nobel laureate, and a leader in the biotechnology industry whose contributions to science have led to revolutionary new therapeutics. He's a UCSD alumnus, as Vice Chancellor P Khosla let us know. At this moment in time, the future of American research is really, on the one hand, the promise of research and the pace of discovery is accelerating, but on the other hand, there's lots of uncertainties and we do need to rebuild trust in science and we need to all understand how we can do a better job at that as scientists and community members. Fred, thank you for joining us.

Fred Ramsdell: My pleasure. It's great to be back. Thanks everyone for coming.

Kit Pogliano: Yeah, I'm really pleased. Before we get started, I thought it would be really fun for the audience to learn more about your journey into science and how you ended up here today, about your career and interests. I know you grew up in the Bay Area, and I was wondering if you could tell us a little bit about what sparked your early interest in science.

Fred Ramsdell: Yeah. I'll talk a little bit this on Saturday as well.

Kit Pogliano: Yeah, okay, you can.

Fred Ramsdell: I don't even remember what day today is, to be honest, but I will talk a little bit more on Saturday. I was essentially an only child, so my siblings were much older than I was, and it was a day when there were no cellphones. As long as I was home by dinner, I was good. My parents usually didn't know where I was, which worked out perfectly for me. I was a very curious kid, so I was out doing stuff all the time. I was always a really curious kid, and I always liked science. I went to community college in Northern California, Foothill Community College. Well, shout out to Foothill, in part because I wasn't quite sure what I wanted to do with my life and also in part because we didn't have enough money for me to go to four-year college and I wasn't smart enough to get a scholarship.

Spent two years doing that, which was great. Again, I highly recommend that for a lot of people. But when I got to UCSD, I think it was the third quarter of my junior year, but it might have been earlier than that. I took this course from the aforementioned **** Dutton, who is and was a really famous immunologist. Now, I did not know that at the time he was the guy who taught immunology. I got completely hooked at that point because it was very clear to me that the immune system is involved in basically every biological system we have, and I used to joke that the immune system was responsible for every disease except Huntington's

disease. That's actually far more true than it is false. If it's not responsible for it, it's at least involved in so many diseases that we see all the time, even things like ALS, which is not really an immunological disease, but a lot of the pathology is caused by the immune system.

Not that we knew that at the time. But the other thing that was really great about UCSD and **** and just the environment was I remember taking the file and getting a question wrong, and I didn't think I got it wrong. I thought I was right. I went into office hours in ****'s office and I said, I think I'm right. ****'s like, well, no. I said, well, wait, what about this and what about this? I had gone down a lot of rabbit holes, and in immunology, there were and still are a lot of caveats and a lot of exceptions to what are the rules. The question was designed for me to answer with the rule, but I went off script. After about three hours of arguing with ****, who, by the way, I'm sure will not remember me at all, he finally said, well, does it change your grade?

I said, well, of course, it changes my grade. Why would I be here? Yes, it changed my grade. But just to get me out of his office, I think he agreed with me. But I love the dialogue. I love the ability to have this conversation with someone who knew orders of magnitude more than I did at the time, but didn't treat me that way and was willing to have this conversation. I learned enormously not so much immunology at that moment, but I learned a lot about the scientific process and what it was to be a scientist. I mean, really, it was just a class I took, which seems crazy, but it was one class I took and it just flipped my whole perspective. I had been planning on going to medical school, and I just thought science is way more fun than medicine.

Sorry to MPs in the audience. I stand by my statement, but I'm sorry. I. But it was just so much more fun and I just really wanted to do it. That really got me going. There was this curiosity. But then when I got here, I realized there's a place for that and there's a way to utilize that and develop it, and that was just an amazing experience.

Kit Pogliano: Yeah, thank you. That's beautiful. After you got your PhD at UCLA and did your postdoc at the National Institutes of Health, you decided to pursue a career in biotechnology as opposed to the more traditional role, especially for Nobel laureates, of going to academia. What led you in that direction?

Fred Ramsdell: Well, I can first say that I certainly didn't, and almost no one I know thinks about winning a Nobel prize.

Kit Pogliano: Yes, I do.

Fred Ramsdell: I think those who do should stop.

Kit Pogliano: We need to have another conversation after this.

Fred Ramsdell: There's too many other variables, so I never thought about winning a Nobel Prize just to be clear, and that's been true for a long time. I was quite surprised when I didn't get the call. What was your question? Why did I go to biotech? Sorry. I went to biotech because I loved the idea of a collaborative scientific environment. At the NIH, I worked for a woman. I was her first postdoc and she's just gotten a lab, a woman named B J Fowlkes. B J was the most enthusiastic scientist I may have ever known. She was all about science. Now, she was a single mom, raising a I don't think he was a teenager yet, probably pre-teen boy. That must have been easy. Yet, she just instilled this enthusiasm, just infectious enthusiasm.

But it was always the two of us doing stuff, and then we bring in other people and it was a bunch of us doing stuff. I love the team science. I looked at academic positions as well. But I

love the idea of going to a place where I could work with biochemists who were way better biochemists than I was ever going to be and molecular biologists who were way better molecular biologists than I was ever going to be. I wasn't particularly good at either one of those. I could do cell biology. I could work with mice. I could do those things. I was pretty good at that. But if you wanted to make a difference and you wanted to really move things forward, and this is, again, before the genome was sequenced, so there was a lot to discover still, there still is, but those were very easy, tangible things like, I don't know what this gene does, I don't know if there is a gene here.

Those are very tangible things, and it was much better to do it in a team environment, and so I chose the team environment. I have a good friend who describes the academic environment as a flea market that you come in, you get your table, and you sell your wares, and your wares are data and interpretation. If you're good at it, you might get a second table assuming you can get someone to fund the second table, meaning another R01 grant or something else. If you're really good at it, you end up getting 10 tables. You can do that, and it is a great way to do unfettered research. As long as you can convince your peers that what you're doing is good and worthwhile and worth their money, essentially, because they're looking at a bunch of other choices, and if your stuff stands out, great.

I think it's a fantastic model, but it's not a team-driven model. Whereas in the biotech industry in general, and it was certainly true when I was coming up through it, we were all trying to solve a problem, whatever that problem might have been. You put a bunch of really smart people on the same problem and you give them the tools they need. It was just a very efficient, effective way to make progress. For me, that resonated much better than the academic route.

Kit Pogliano: Wonderful. I was wondering if you could tell us a little bit of a scientific story about how your work started, the impact of the scurfy mice that came out of the Manhattan Project and how that shaped your-

Fred Ramsdell: Yeah. Again, in the Seattle area, I ended up going to a small biotech company. It was a startup. One of the founders and one of the CEO had worked for the Department of Energy for a while. He was a molecular biologist out of USC of all places. But he worked for the Department of Energy for a while, and he knew of this group in Oak Ridge, Tennessee, Oak Ridge National Labs. Oak Ridge was built during the Manhattan Project as a secret city. People in Knoxville, which is the nearest city, didn't know what was going on. The whole point was you can't talk about it, and it was built in order to enrich fissile material for atomic bombs. That was its purpose in life. It was part of the Manhattan Project, started in the early to mid '40s.

In what I still think is a surprising amount of foresight for our federal government, they decided they should understand what radiation does to mammals, and so they brought in these two just superb mouse geneticists from Maine and had them set up a facility there. They had thousands of mice, and the idea was to basically expose mice to varying levels of radiation and figure out how bad is that. A little side anecdote. But before they actually had ways of controlling the amount of radiation they gave, they actually loaded up their Volvo with mice, they drove to White Sands, New Mexico, they placed cages of mice at varying distances from where the bomb went off. They went in bunker, got out, collected all the mice, drove back to Oak Ridge National Labs, and watched what happened.

Kit Pogliano: Wow.

Fred Ramsdell: A little crude, but it works. If you think about any of the things that measure or dictate how much radioactive exposure is okay for a person, they all came from those types of experiments. Not that particular experiment, but those experiments overall. The

CEO of this company knew about this facility and knew that there were a lot of animals in this facility that had genetically induced defects. One mouse in this facility was this mouse called scurfy. Half the males of any litter would die at about three weeks, and they died from what is essentially rampant autoimmune disease. They had diabetes, they had psoriasis, they had Crohn's disease, they had myocarditis. They had every autoimmune disease in one mouse, and the mouse couldn't survive it.

It was genetic. By the way, that mouse was never exposed to radiation. It was a spontaneous mutation in the colony, so it's good to be lucky sometimes. Not for the mouse, but for us. They knew it was genetic. They knew it was on the X chromosome because it was only boys and it was only half the boys, and we knew it was one gene. But in 1949, 1950s, there was no way to figure out what that was. There's just no way to clone and identify that gene. The technology wasn't good enough. But by 1995, we could sequence a lot of DNA, we could breed, and we could follow this. The Human Genome Project had started, and the Human Genome Project also had a huge mouse genome component to it in parallel. We got the mice to our facility in the Seattle area.

We didn't have a mouse room, so we confiscated a janitorial closet and put the mice in a janitorial closet. The only reason we used that was because it has sink, and anyone who works with mice knows they poop a lot. You need to be able to wash the cages, so we confiscated the janitorial closet. Three years later, we were able to breed enough mice and get the genetic region down. This is a really long story, sorry. Anyway, get the genetic region down small enough that we could sequence it. We got it to a point where we knew that there were 20 genes, 20 possibilities within the genome of this mouse, this whole mouse, that one of those had to be it. We had to assume that there was a mutation in the gene, which was a little bit of a guess, but it was a reasonable guess.

We lined them all up and we had to go through them one at a time and just look for mutations and changes in the gene in the defective mouse. We found it. It was the last gene on the list so by the time we'd gone through 19 other genes, I was getting pretty depressed. But we found it so that was great. But the key thing for us was we knew, based on what happened in this mouse, that this was going to be a really important gene in how the immune system worked, because normally for most people in this room, your immune system does not attack you. Ten percent of people have some form of autoimmune disease, but most people don't so why is that? We had some hints as to why that was. There's other filtering processes, but we knew that in this mouse that was messed up.

If we knew what was messed up, maybe we could use that and turn it around to understand, is that true in people? Does this lead us to ways we can actually treat people, et cetera? It turns out the biology in the mouse perfectly mirrors what you see in the human. There's about 200 families in the world that have a mutation in the same gene, and without a bone marrow transplant or other heroic means, they will also die very early in life. Now we can find them, we can identify them, and we can treat them, and hopefully we'll have much better treatments going forward. But it's really the focus on trying to find what I would describe as nodes of biology, that this is going to be important because it's going to control something fundamental and that's what we knew.

We were able we had enough time and enough funding and enough talent to be able to go through and figure that out. That was really, to me, the perfect example of what biotech and what this intersection of what public space can do, and I didn't mention this. The people in Oak Rich kept this strain of mice alive for 40 some odd years, a mouse lives, too. They had bred this mice for 40 some odd years without the ability to actually really understand it. But they knew it was important. Your tax dollars, well, you're probably all too young, our parents tax dollars paid for that. Our grandparents tax dollars paid for that to keep that alive and there's other ones in there as well that are also useful.

But you never know where it's going to come from and that's the key thing. That intersection of really smart people who have the resources and the capability to pursue that and then us having the technology to be able to capitalize on it was a beautiful Venn diagram.

Kit Pogliano: And the ability to see that that mouse was special.

Fred Ramsdell: Absolutely.

Kit Pogliano: To you recognize it.

Fred Ramsdell: Absolutely.

Kit Pogliano: Fabulous. In 2017-

Fred Ramsdell: Is there time for any more questions? It seems like a really long answer.

Kit Pogliano: Look, I've got many people.

Fred Ramsdell: Okay. Sorry.

Kit Pogliano: Just kidding. You won the Crawford Prize in 2017 and it's a very prestigious international award for everyone in the audience who may not be aware of it. Is that why you believed you wouldn't be considered for a Nobel Prize, despite the [inaudible]?

Fred Ramsdell: When we did this 25 years ago, we figured this out in 1998. Part of it, Roli Khattri is a colleague and friend of mine sitting over here. Roli is the person who figured all that out, actually. I show her a notebook and I'll show her data from 1998 when we figured this out. Well, she figured it out, and I get the credit for it but we knew back then that this was really important. Once it got published and once the scientific community appreciated this, and it dovetailed with some work from a Japanese scientist named Shimon Sakaguchi who also shared the award. He had done some fundamental, really critical work in Japan, and what we did dovetailed in with what he did, and it was a perfect story.

We knew it was really important, but we couldn't figure out how to make a drug out of it so 20 years has gone by, and we finally figured that out. But was it important? Sure. Did colleagues and friends come up and say you've been nominated for the Nobel Prize in early 2010? People would say that to me, but 500 people a year get nominated for the Nobel Prize in physiology or medicine. To be nominated is nice, but it doesn't really mean a whole lot and when I got to Crawford, it's voted on by the same institution, which is the Karolinska Institution in Sweden, that votes on the Nobel Prize. My assumption was, we like your work, but not quite enough. Here's this really good prize and it was wonderful.

We had a great time. It was a lot of fun. You go in May, by the way, Stockholm's much nicer in May but it was great. We had a really good time, and it's beautiful. You meet the family, and it was a wonderful thing. I never thought about the Nobel Prize after 2017.

Kit Pogliano: Awesome. Thank you. Could you tell the audience how you learned you won the Nobel Prize? I know this has been around a lot, but I think it would be really fun for them from you here too.

Fred Ramsdell: I have the distinction of being the most difficult person to find to tell them they won a Nobel Prize. There's this very wonderful gentleman, Thomas, who calls everybody about somewhere 2-4 in the morning West Coast time because they want to tell the winners before they have a press release, seems reasonable. They were trying to call everybody, and they couldn't find me because my wife, Laura, and I and our two dogs were

in the Absaroka Mountains just east of Yellowstone National Park at 8,000 feet under 6" of fresh snow off the grid camping. We weren't even in a campground. We were in the middle of nowhere. No service. As all my friends will tell you, my phone is always on silent or airplane mode anyway so I still wouldn't have gotten the call, even if we'd been in service so we had no idea.

We woke up and I did manage to tow our little teardrop trailer out, and we went through Yellowstone. I think I saw the biggest bull elk I've ever seen in my life in Yellowstone. When we drove through one of the towns leading into Yellowstone, my wife's phone loaded up, I don't know, she communicates with people. I pulled over to let the dogs go run around and do their business. She yells out in the truck, and I look up like, what? She comes out, she says, You won the Nobel Prize. I said, No, I didn't. She reminds me, there was probably an expletive there someplace, but we're live streaming, so I want to do that. I'm like, No, I did not. She's like, I have hundreds of text messages from our friends that said, you won the Nobel Prize.

Now, my friends might try to prank me, but they are not that coordinated so there's no way 200 of them got together at 6:00 in the morning to send me a text message. Then we still had no service at that point. We still had an hour's drive when I think we said nine words to each other for the whole hour she's reading things, and I'm thinking, Okay. What now? We got into Livingston, Montana. I started making phone calls. I called Sweden. Well, I called Thomas in Sweden. He'd gone to bed because it's 1:00 in the morning in Sweden so I left him a message. Then I called Mary Bronco, my co laureate and good friend in Seattle, and we talked, and I started calling other friends and colleagues and started responding to text messages and emails of which there were far too many for me to respond to.

We finally decided we needed to get some dinner, and we're in Livingston, Montana, population 5,000-ish. We went to the Irish pub, because it was a Monday night, sat around the bar watching Monday night football and having fish and chips and beer in this packed pub. I'm looking around thinking, no one in this room has any idea what just happened to me. This is crazy. It was really funny. I will tell you, though. Apparent, the next morning, the woman who had checked us in pulls in to go to work, and we're out walking our dogs. Dogs feature a lot in most of my life, and we're out walking the dogs and she comes up and she says did you really win the Nobel Prize? I said, I did. She says, I've never known someone who won the Nobel Prize.

Fortunately, in my head and not out my mouth, I'm thinking, you live in Livingston, Montana. The odds of you meeting a Nobel Prize winner is really small. I said, Well, you have now? She just looked at me, and this is when I knew my life was going to be different. She looked at me and said, Can I hug you? That was my response. Exactly.

Kit Pogliano: So sweet.

Fred Ramsdell: Sure. This is weird. That's when I knew life was really going to be.

Kit Pogliano: Wow. That's amazing. Thank you for sharing that. As a new Nobel laureate, you have said that you would like to use your new platform to communicate with the next generation of scholars and leaders, as well as to address issues related to the public perception of science. I'm really grateful you're joining us here to speak to our graduates at the commencement this Saturday and tonight to talk about the public perception of science. To start this part, I thought I would give you a little local context of what's been happening at UC San Diego with the federal research funding. The current climate is really challenging, as Vice Chancellor Pete Asa alluded to in her introduction. We are seeing the current funding environment is really affecting us.

Fewer dollars are flowing to campus, which means fewer grants are getting funded. There's even uncertainty amazingly about whether if you have a five year grant, if you'll get year two or year three of that grant funding, which has never been the case in the history of federal research funding, that's having a huge impact on our ability to train the next generation of scholars. Here, this is affecting especially PhD students in fields such as biology, where they're primarily supported. By federal research. Our PhD cohort in biology is typical of such fields at UC San Diego, where it's gone from 50 students to 40, to 30, and now for this coming year, just 15 new PhD students will be joining us.

That's going to have a really huge impact. It's also decreasing the pace of research, which is really hard for me to bear as a biology dean. Fred, can you tell us why this is so important to you, this topic?

Fred Ramsdell: Sure. Let me start out by saying, I'm actually hopeful in the long term, but there's obviously and certainly going to be short term pain. When I left my post op, the pay line at NIH was 4%, 4.5. It's three now. It's been bad before. Some of the other problems are new. I totally agree. It's gone up and down, and it will continue to go up and down based on all sorts of factors. Is it challenged? Sure. Has it been challenged before? Sure. I do think there's some differences now, and I personally believe we will get through those, but not without some pain. I think that's absolutely correct. Actually, I think some of the ways we get through them, and I hope this is true in California, I know at least there was a probability of having a ballot measure coming up this fall, which will provide another source of funding, which will at least provide some stability.

I'm sure it won't replace everything the federal government does, but it'll be a backstop for something, so I think that would be great but it is true that it's incredibly difficult to predict where these advances will come from. Hugh Auchincloss, who I think he's an outgoing congressman from Massachusetts, gave a speech on the congressional floor one day and basically said research of this nature is designed to be at some level inefficient. Because we are not smart enough to figure out where the innovation is going to come from. We need to try a lot of things that don't work. Anyone who does research knows stuff goes wrong all the time. I have an entire speech where I talk about how I've been wrong.

If you're right all the time in research, you're probably working on something that's incredibly boring. You have to push the limits, and I think that's the only way to get innovation. I also think that we have to be much better about communicating the progress. I still have people come to me and say, Well, you can't cure cancer. I look and I'm like, bullshit. Sorry, it's light stream. Apologies. BS. Sorry. We can. Now, not all cancers and not in everybody, but when I was in grad school in the '80s, every person who came in with malignant melanoma was dead in 12 months. Now, 35% of those people die of a heart attack much later in life or being hit by a bus or some other reason that's not related to malignant melanoma.

We have made progress, and that's true for non small cell and other types of cancers as well. We have made progress. There are drugs that are incredibly good at treating a fraction of people with autoimmune diseases. We're talking 10, 20, maybe 30% of the population. Pick any disease, well, not any of these, many of the diseases, they can be treated and very successfully treated. Not everybody, and we need to figure out how to do that better. There's still a lot of room for growth. But there has been progress. We have turned the fundamental discoveries every one of which was made at the basic level with federal taxpayer dollars, every single one. Without that, you wouldn't have made any of that progress.

Has it been enough? I don't know how you define enough. But without that, we would be in much worse shape. To begin to relinquish that to me is problematic, I think you can make that same argument if you want to make it a nationalistic argument. I won't speak for chemists and physicists, but in the biomedical world, the United States, with due respect to

my European colleagues, has led the charge for generations in innovation and risk taking because that's what we do really well. I would hate to cede that to anybody else if you want to take a nationalistic view. If you want to take an economic view, you can document the economic value of biomedical research and drug development, etc, in the United States.

It's an incredibly powerful driver of our economy. Is it perfect? Do drug companies make too much money? It's not perfect. I get it. There are ways we should work on that, but it doesn't mean you abandoned everything that got us to where we are.

Kit Pogliano: Thank you. I recently had the opportunity to travel to China with BioCom and the investment that was going on in the life sciences in particular in the biotechnology industry was truly stunning. It is really hard for me as the biology dean, to see the pace of research here slowing down at the very time when our tools are really exploding and we can now discover new potential drug targets more quickly and translate that to therapeutics because you can quickly, just with a pause, end up years behind other nations. I'm not saying it shouldn't be a global enterprise. Clearly, it should, but do you have suggestions for how we can frame this or additional thoughts on how we can frame this so we don't lose the opportunity of the present moment.

Fred Ramsdell: I'm not sure if they're good ideas or not. My feeling is that we've lost a lot of trust with a lot of the population, I've recently read that that's not true. There was I just read a study, although there are only 1,000 people in the study, so the n is not big. But I'm terrible at statistics, so maybe it's perfectly valid. But scientists and research were the top in terms of what's the word I'm looking for? Respect or, we'll call it respect for a second, followed by, I think it was people in the military and firefighters. It was all north of 70%. Politicians were single digits which is, I don't think, terribly surprising and yet we mostly reel the same politicians, which is an interesting social study, I think.

But I still believe that there is a gap in people's understanding and appreciation. We are very good at talking to ourselves, to scientists, to people who believe the same thing we believe. We're not so good, and I don't think we even try very hard to talk to people on their terms and talk more importantly with people, who don't have the same philosophy. I spend a good chunk of my time in Montana. Not a bastion of biomedical research. There's actually a couple of really good places, but by and large, we're not talking Boston, San Francisco, Seattle, San Diego. I gave the longest interview I've given to anybody to a person from the Flathead Beacon, which is circulation of, I don't know, 10,000.

I'm not even sure. But it's in Montana. They said, well, why? I said, because these people here don't interact with people like me very often, I could not have had my career. Sorry to sound, guys. I could not have had my career if I'd lived in Montana full time. It's just not feasible. But it doesn't mean I don't share some of the values of people in Montana. I certainly have different values than other people in Montana, but that's true anywhere. I think having that conversation and actively listening and understanding what is important and what reticence is, etc, is really important because I still believe, and maybe I'm a naive old guy here, but it's almost certainly true, that if the populace really wants this to happen, it will happen.

If they really want people to support biomedical research, their elected officials will do so because you can get rid of them. We can all get rid of them. I know that's not the only factor for anybody, but I do believe that you can put pressure on people if they're in your camp and if you're on the same page. Getting on the same page, I think is the challenge. I was joking with somebody earlier today. One of the comments I made to the woman in Flathead Beacon was, I said, tell us something that people wouldn't appreciate. I said, I can tell you that winning the Nobel Prize in October completely messed up my deer hunting season last year. She looked, and I said, I don't normally say that the NPR or somebody else because it

may not resonate, but in Montana, that resonates.

It's absolutely true. It did mess up my deer running season. I think having a conversation with people where you have some of the common values is really important. Now, how do you do that on a bigger scale? I don't know, but I think we all need to try.

Kit Pogliano: I agree. Thank you. It's fabulous. Just this week, we learned of new proposed rules from the federal government that would fundamentally change how grants are administered, the role of peer review and would further cause additional chaos. Do you have any thoughts on those changes or what we might be able to do to help steer the government away from more chaos?

Fred Ramsdell: I haven't read the legislation specifically, obviously due to time. I worked at the NIH for four years. Core government, if there was an effective Department of Government Efficiency, that would be awesome. I can tell you that the NIH is not an efficient organization. But the version we had didn't help. In fact, it almost certainly made it worse. We'll come back to the CBP thing or OMB thing in a second, but I'm not opposed to the idea of making things more efficient and more effective. But the idea of having a political bent to that is certainly problematic. I think if the idea is, let me be generous for a second, that the idea is to better use taxpayer dollars, sure. How you define that and how you go about that matters enormous.

I think you can agree on the principle, but not the execution. To me, there's got to be a way to say, we understand that no one wants their tax dollars wasted. I don't want my tax dollars wasted. But some of them will be, and I'm okay with that because I haven't paid taxes in a long time. It's fine. But I think we need to find a way to communicate that some of the principle maybe is okay, but doing it in a political way in a political manner is not. Let's do it in a way that actually makes the end product, the science, the research feels better. That's not the way we're headed right now, and I don't know how to get to that, but to me, that should be the goal, not just a political objective.

Kit Pogliano: Thank you. That's great to hear. This rule would introduce more chaos, and it is a rule that I would encourage you-all to read up on and maybe add to the public comments period, because this could, in my opinion, make it science less efficient by causing researchers if a grant can be canceled really quickly, that means that you'll have to stop a research project that was planned for multiple years. It has a terrible impact on employees, the staff and the trainees on these funding projects. We need to work really together to fix this. Trust and confidence in science from some measures, I know you had one metric that was really strong. You have a more recent survey. Then there are other metrics that trust in science is really not where it should be, and it's been shaken.

There's been some really prominent stories of foundational research on which very expensive drug trials and drug development programs were based that ended up being false. How can we implement changes that are needed and really revert and restore faith in foundational research?

Fred Ramsdell: I don't have a great answer to that. I think we have to be clear that a lot of the fundamental basic science, I want to say won't work because that's not true. What happens is you learn. You can do stuff, you have a hypothesis of theory, you work on it, and it turns out, well, that's not right, but now I've learned something that I'm going to apply somewhere else. But to a casual observer, well, that failed. Why would we give you more money? That's not the way science works. I think we need to be much better at being able to describe that process and understand how that happened. I described earlier, we tested 19 things before we found the right one. We failed 19 times, but then we got the right one.

The right one is really important and has changed the way we think about the immune system and how we study it. I think that that premise needs to be communicated so that people can be on board that that's the way this works. That's the way it's always worked, and it's actually helped us enormously. We've made incredible progress using that model. Sure, can we try to be more efficient about it? Yes, but not at the cost of innovation and not at the cost of being able to take risks. Because if you can't take risks, we'll make no progress. How do we have that dialogue in that conversation? It's difficult to answer that. I've talked in front of a Congressional subcommittee about this, and will that help?

I don't know. I have as much skepticism as I think most people will. But I think as long as we keep doing that, at some point, the mass will hopefully win out. But it's a difficult challenge right now. It really is.

Kit Pogliano: Well, thank you for your commitment and engagement in this. I was wondering before we turn to questions from the audience, if there was a question I didn't ask you or something you'd like to leave for the audience, something or say to the next generation of scholars here?

Fred Ramsdell: The only thing and I'll touch on this on Saturday, but the thing I would say, since there's not a lot of students in here, but the thing I will say is, it is incredibly difficult to predict where fundamental discoveries are going to come from. Everyone who has a research program thinks that their research program is going to change the world. Sometimes that's true, sometimes it's not. Sometimes it's a big change, sometimes it's a small change. But it's important to have, I guess I would use the hockey analogy, a lot of shots on goal because it is really hard to know how successful things are going to be. The more smart people we have taking innovative, risky at times, approaches to solving problems, the better off we're going to be.

Kit Pogliano: Fabulous. Thank you. That's really helpful. Audience, this is now your time to ask questions, and there will be a mic ready to pass around, and please do not be shy. This is UC San Diego, we're not shy here.

Fred Ramsdell: Wait, ladies first.

Speaker 1: Thank you. I also went to community college also for financial reasons, and I'm curious if you see any future where there might be research opportunities for students made available at the community college level.

Fred Ramsdell: Ooh, interesting idea. I don't see why not. In the college itself, the infrastructure to put in place a significant lab is really huge. But I don't see an impediment where community colleges couldn't align themselves with biotech companies, Pharma companies, chemistry companies, etc. We would take interns and things, maybe there are such programs. I don't know about them. You could have formal alliances where people could come in and do a project, and I think that's incredibly feasible and doable, and I had not thought of it, so that's great. Thank you.

Kit Pogliano: Very nice.

Speaker 2: Hey, fellow alum, question for you. In the year that you received your Nobel Prize, had you been on the committee, who would you have given the prize to?

Fred Ramsdell: Well, the committee's got 40 some people, so my vote would have been one out of 40 some. After I won the Crawford, I do get to nominate. I've been nominating for a while. There are two people who I believe deserve a Nobel. There's a lot of people, one of which is in the room someplace here that you could argue should get a Nobel Prize. Steve

Hedrick, who's Professor Emeritus. One of the most impactful discoveries of my scientific life was something called the T cell receptor, which is how lymphocytes, how all our white blood cells recognize pathogens and everything else. We didn't know that until 1980, I'm going to say five. I can't remember what year it was. It could be three. Steve will correct me later at dinner.

But there are a lot of people involved in that. Only three people can ever win a Nobel Prize. That's a challenge. But there's another fundamental discovery, which is the ability of lymphocytes to have distinct functions. You can think of them. We call them TH1s and TH2s, and there's a whole bunch of them. But there's classes of lymphocytes that drive allergy versus other diseases and other responses, viral responses, other things. There's a couple of people named Tim Mossman and Bob Kaufman who discovered that at a biotech company, I might point out in the Bay Area in the early '80s, and they really showed for the first time that these distinctions exist, which has really changed, again, the fundamental way we think about immunology.

I still to this day believe that that's worthy of a Nobel Prize.

Kit Pogliano: That's great. Thank you.

Speaker 3: You're now in the process with Sonoma of translating some of the research that you've done. In 2021, you raised a lot of money. What did you do? What was the process, the experience of convincing these investors to believe in that pretty basic research at the time? Just thinking about the progress and getting to a product, what are the hurdles that you've had to overcome to this point?

Fred Ramsdell: How much time do I have to answer that question? I'll give you a short version of this. Full disclosure, yes, I helped start a company in 2019 with a colleague and friend of mine, actually, three colleagues and friends of mine called Sonoma Bio. The goal of the company is to take the information we got that ended up winning the Nobel Prize several years later and create a new therapy based on cell therapy. The idea is we take cells out of patients who have autoimmune disease. We re engineer in the lab the regulatory cells. That is, these cells that we know are responsible for keeping most of us safe, but don't work as well as they could in these autoimmune patients. We re engineer them in the lab, we grow up a boatload of them, we put them back.

Now, we do that, and I'm actually an advisor for the company. I'm not with the company any longer. There's about four or five other companies doing the same thing, and there's a bunch of academic groups doing it. Everyone has a slight twist on how they do it. The idea really is to not treat disease, but if this works, you'll restore someone's normal I will say homeostatic immune function so that you'll convert these cells so that they respond to that disease, but you won't disturb the rest of the immune system like most drugs do. Everything else should still stay intact. Now, warrant clinical trials. I don't know if that's going to work yet. No one knows if that's going to work yet. But your point was, how do we convince people to give us a bunch of money to do that?

The reason we're able to do that is my oncology fellows and colleagues and friends have proven that you can take cells out of a cancer patient, engineer them in the lab, grow up a boatload, give them back, and cure those patients. That is a viable drug. It has to be significant. It has to be a big deal. But it is. You can cure people doing it. The oncology people basically pay for the path for the autoimmunity people. It's a little easier on oncology because patients were probably going to die. They don't have a lot of options. A lot of those patients didn't have a lot of options they do now. Autoimmune patients, not a lot of people die from rheumatoid arthritis or psoriasis or some of these other things.

The safety bar is higher. But I think we're getting through the safety bar pretty readily. We understand that. The oncology people gave investors enough confidence that this is a viable therapeutic drug. Now we just need to prove that we're right so that they can say that they're right.

Kit Pogliano: Great. Thank you. A question.

Speaker 4: Hello. I'd like to ask about the point you made about, I guess, the approach to risk in the general public generally being, I guess much more risk averse than what would happen in academia. My question is, did you see that when you went from the transition to academia into industry, and what was your approach to making what would normally be an acceptable risk into one that's, sorry, making a risk that's probably more acceptable for academia, but less palatable in industry, and then just communicating it to those people.

Fred Ramsdell: It's a great point. I didn't go into this, but when we did all the work that got the prize, we were funded by Bill Gates and Paul Allen. Bill Gates and Paul Allen are the richest people on the planet. They were not in this business to make money. They were in it to make a difference. Their motivation is different from every other venture capitalist I've ever met and worked with. They all want to make a difference, but they also all want to make money. That's part of the deal. Which is the way the system works. It's not a judgment thing, but it's different. Right now, in particular, in Biotech and in Pharma, which reports its earnings every quarter, risk tolerance is pretty low. It's extraordinarily low right now.

I think that's a big problem. I think that there's a huge gap because there's a ton of capability in the private sector which is focused on very narrow questions, very short term questions. Academia doesn't do that, although, given the current funding situations, there's nervousness around this, and I get it. That's why a lot of grants are five years. Because it takes that long to figure something out. Stopping them at two is going to be devastating and is incredibly shortsighted and shooting yourself in the foot and lots of analogies you could use. How do you get that risk tolerance back in the private sector? I'm not so sure. I think that, to me, is a huge challenge. I don't know what the answer to that is.

I know that a lot of people are trying to figure out how to do that, and maybe there's a role for foundations as opposed to venture capitalists and doing some of that. I think being able to bring that risk tolerance back in a part of the economy that can make real progress is a tremendous opportunity, but it's really a big challenge today.

Speaker 5: We heavily concentrate US biomedical funding in a small number of elite institutions like UCSD and institutions in the Bay Area and Boston. Based on the best data we have, publications, patents, startups, or clinical outcomes, do we actually know whether this concentration maximizes total national innovation or might a more geographically distributed funding model produce more breakthroughs per dollar?

Fred Ramsdell: I don't think we know. I would be shocked if we knew. I'm not even sure how we would know, to be perfectly honest, whether it works or not. I'm not sure how you'd measure that. I will say the one benefit of doing that is by having talent in a particular area, there's a lot of cross fertilization. Whether that's in engineering to biomedical research or chemistry or physics or, instrumentation, etc, having that co-located at some level is some level synergistic. I think there are some advantages to doing that. I'm sure you see that on this campus. There is and actually, some of the appended institutions around here. I think there's an advantage to doing that, but can I actually prove it's better than a distributed model?

No. I am 100% sure we are leaving really good ideas and good people behind because they live somewhere in rural Oklahoma or wherever. There's plenty of smart people all over the

country that are not willing to come to one of these places. I'm sure we're leaving things on the table we shouldn't. But would a model that enabled someone in a non centralized area be efficient and effective? I don't know how to answer that. I really don't.

Kit Pogliano: Great.

Fred Ramsdell: There was something over here somewhere.

Kit Pogliano: One more question here.

Speaker 6: How do you approach conversations with a person or people that have major misconceptions about how science works?

Fred Ramsdell: I ask why a lot. Tell me what got you to that point, and sometimes it won't work. Let me tell you right there. Sometimes it's not going to work. But my strategy is to say, why do you think that way? How did you get to that point? Let's talk about that. I try to initially, at least, listen, not interrupt and say, you're wrong. No one likes being told they're wrong, including me, and I'm wrong a lot. I still don't like hearing it. To listen and try to understand and then have a dialogue, it's challenging, and sometimes it does not work. I've had to walk away from conversations. If I stay here, it's going to get ugly, so I'm going to leave. But a lot of times, people get a perception and part of it's right, but not all of it's right.

Or it's different from me. I'm not even say right or wrong, but it's different from me. They might value something that I don't value the same way. That's a value difference. Fine. I'm not going to suggest that my values are better than your values. That's silly. But it's really listening and dialogue and asking them how and why and where does this come from and help me understand why you think the way you do without sounding patronizing. That doesn't help either.

Kit Pogliano: That's beautiful. Can we do one more? Yeah, one more.

Fred Ramsdell: I'll try to make it shorter.

Speaker 7: Thank you. Yes. I'll try to make it short, too. The question I have is that right at the moment, one of the most horrible things that are happening to us is that people from all around the world are no longer flocking to America because this is the place to come. That is going to put as big a crimp in our science as any of these other things we've been talking about. I'd like to in a very tiny way, a little bit of that system. I think once we lose that, we lose so much that we're going to really, regret further down the line. How can we get around that?

Fred Ramsdell: Well, that comes back, I think, to what Kit was saying earlier, which is until we change the mindset, and some of that, unfortunately, is politics, but until we change the mindset that we're going to support this, you're absolutely right. In fact, it's even worse. Not only people not coming, people are leaving. That is going to be a tragedy if we can't find a way to stop that. But it's not going to stop unless we recommit to supporting fundamental research. Again, whether it's writing your congressperson, all of those things are good. I'm not sure what the most effective thing is going to be, but I think we have to do that because you're absolutely right. It will affect progress. It will affect innovation.

It will affect the economy. It will affect national security. However you want to phrase it, it's going to affect all of those things in a negative way. That is a big concern, you're spot on.

Kit Pogliano: Well, thank you. That was a great way to wrap it up. Please join me and thank you, Fred.