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Berkeley, California

Keith Yamamoto

Keith Yamamoto: The Sandler Foundation and the Program in Breakthrough Biomedical Research at UCSF

The Marion and Herbert Sandler Oral History Project

Interviews conducted by
Martin Meeker
in 2018

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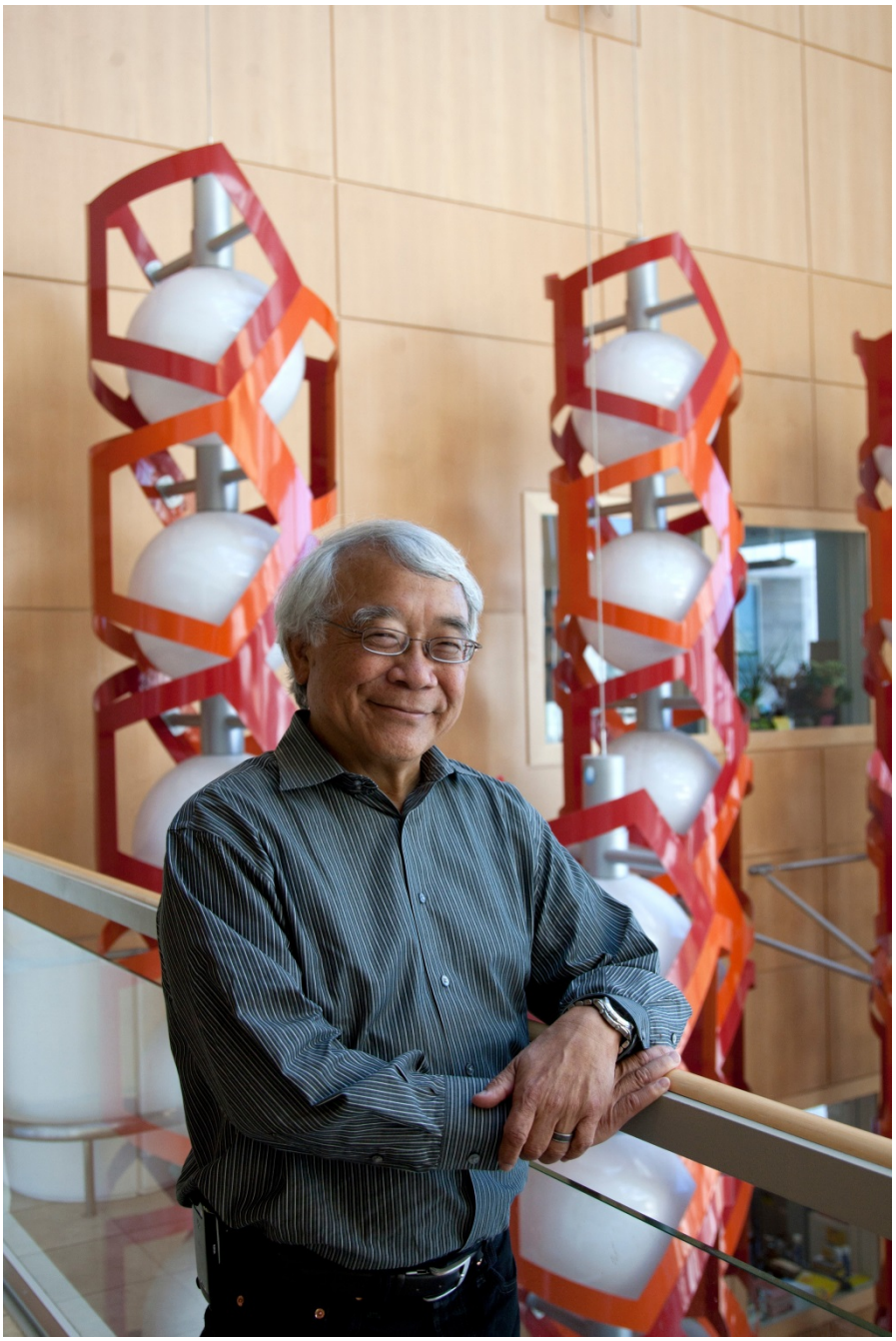

Keith Yamamoto

Photograph courtesy of Keith Yamamoto

Keith Yamamoto is Professor, Vice Chancellor for Science Policy and Strategy, and Director for Precision Medicine at UCSF, where he oversees strategic planning as well as research activities. After earning a PhD at Princeton, he came to UCSF in 1973. He served as chair of the Department of Cellular and Molecular Pharmacology from 1994 to 2003. Dr. Yamamoto is regarded as an international leader in studying the mechanisms of signaling and gene regulation by intracellular receptors. In this interview, Dr. Yamamoto discusses the following topics: meeting and getting to know Herb and Marion Sandler; the development and expansion of the Program in Breakthrough Biomedical Research (PBBR); and the achievements and future promise of PBBR. Note that the Oral History Center has interviewed Dr. Yamamoto twice before in oral histories in which he recounts the full sweep of his career in research and administration.

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Project History: the Marion and Herb Sandler Oral History Project

Herb Sandler and Marion Osher Sandler formed one of the most remarkable partnerships in the histories of American business and philanthropy—and, if their friends and associates would have a say in things, in the living memory of marriage writ large. This oral history project documents the lives of Herb and Marion Sandler through their shared pursuits in raising a family, serving as co-CEOs for the savings and loan Golden West Financial, and establishing a remarkably influential philanthropy in the Sandler Foundation. This project consists of eighteen unique oral history interviews, at the center of which is a 24-hour life history interview with Herb Sandler.

Marion Osher Sandler was born October 17, 1930, in Biddeford, Maine, to Samuel and Leah Osher. She was the youngest of five children; all of her siblings were brothers and all went on to distinguished careers in medicine and business. She attended Wellesley as an undergraduate where she was elected into Phi Beta Kappa. Her first postgraduate job was as an assistant buyer with Bloomingdale's in Manhattan, but she left in pursuit of more lofty goals. She took a job on Wall Street, in the process becoming only the second woman on Wall Street to hold a non-clerical position. She started with Dominick & Dominick in its executive training program and then moved to Oppenheimer and Company where she worked as a highly respected analyst. While building an impressive career on Wall Street, she earned her MBA at New York University.

Herb Sandler was born on November 16, 1931 in New York City. He was the second of two children and remained very close to his brother, Leonard, throughout his life. He grew up in subsidized housing in Manhattan's Lower East Side neighborhood of Two Bridges. Both his father and brother were attorneys (and both were judges too), so after graduating from City College, he went for his law degree at Columbia. He practiced law both in private practice and for the Waterfront Commission of New York Harbor where he worked on organized crime cases. While still living with his parents at Knickerbocker Village, he engaged in community development work with the local settlement house network, Two Bridges Neighborhood Council. At Two Bridges he was exposed to the work of Episcopal Bishop Bill Wendt, who inspired his burgeoning commitment to social justice.

Given their long and successful careers in business, philanthropy, and marriage, Herb and Marion's story of how they met has taken on somewhat mythic proportions. Many people interviewed for this project tell the story. Even if the facts don't all align in these stories, one central feature is shared by all: Marion was a force of nature, self-confident, smart, and, in Herb's words, "sweet, without pretentions." Herb, however, always thought of himself as unremarkable, just one of the guys. So when he first met Marion, he wasn't prepared for this special woman to be actually interested in dating him. The courtship happened reasonably quickly despite some personal issues that needed to be addressed (which Herb discusses in his interview) and introducing one another to their respective families (but, as Herb notes, not to seek approval!).

Within a few years of marriage, Marion was bumping up against the glass ceiling on Wall Street, recognizing that she would not be making partner status any time soon. While working as an analyst, however, she learned that great opportunity for profit existed in the savings and loan sector, which was filled with bloat and inefficiency as well as lack of financial sophistication and incompetence among the executives. They decided to find an investment opportunity in California and, with the help of Marion's brothers (especially Barney), purchased a tiny two-branch thrift in Oakland, California: Golden West Savings and Loan.

Golden West—which later operated under the retail brand of World Savings—grew by leaps and bounds, in part through acquisition of many regional thrifts and in part through astute research leading to organic expansion into new geographic areas. The remarkable history of Golden West is revealed in great detail in many of the interviews in this project, but most particularly in the interviews with Herb Sandler, Steve Daetz, Russ Kettell, and Mike Roster, all of whom worked at the institution. The savings and loan was marked by key attributes during the forty-three years in which it was run by the Sandlers. Perhaps most important among these is the fact that over that period of time the company was profitable all but two years. This is even more remarkable when considering just how volatile banking was in that era, for there were liquidity crises, deregulation schemes, skyrocketing interest rates, financial recessions, housing recessions, and the savings and loan crisis of the 1980s, in which the entire sector was nearly obliterated through risky or foolish decisions made by Congress, regulators, and managements. Through all of this, however, Golden West delivered consistent returns to their investors. Indeed, the average annual growth in earnings per share over 40 years was 19 percent, a figure that made Golden West second only to Warren Buffett's Berkshire Hathaway, and the second best record in American corporate history.

Golden West is also remembered for making loans to communities that had been subject to racially and economically restrictive redlining practices. Thus, the Sandlers played a role in opening up the dream of home ownership to more Americans. In the offices too, Herb and Marion made a point of opening positions to women, such as branch manager and loan officer, previously held only by men. And, by the mid-1990s, Golden West began appointing more women and people of color to its board of directors, which already was presided over by Marion Sandler, one of the longest-serving female CEOs of a major company in American history. The Sandlers sold Golden West to Wachovia in 2006. The interviews tell the story of the sale, but at least one major reason for the decision was the fact that the Sandlers were spending a greater percentage of their time in philanthropic work.

One of the first real forays by the Sandlers into philanthropic work came in the wake of the passing of Herb's brother Leonard in 1988. Herb recalls his brother with great respect and fondness and the historical record shows him to be a just and principled attorney and jurist. Leonard was dedicated to human rights, so after his passing, the Sandlers created a fellowship in his honor at Human Rights Watch. After this, the Sandlers giving grew rapidly in their areas of greatest interest: human rights, civil rights, and medical research. They stepped up to become major donors to Human Rights Watch and, after the arrival of Anthony Romero in 2001, to the American Civil Liberties Union.

The Sandlers' sponsorship of medical research demonstrates their unique, creative, entrepreneurial, and sometimes controversial approach to philanthropic work. With the American Asthma Foundation, which they founded, the goal was to disrupt existing research patterns and to interest scientists beyond the narrow confines of pulmonology to investigate the disease and to produce new basic research about it. Check out the interview with Bill Seaman for more on this initiative. The Program for Breakthrough Biomedical Research at the University of California, San Francisco likewise seeks out highly-qualified researchers who are willing to engage in high-risk research projects. The interview with program director Keith Yamamoto highlights the impacts and the future promise of the research supported by the Sandlers. The Sandler Fellows program at UCSF selects recent graduate school graduates of unusual promise and provides them with a great deal of independence to pursue their own research agenda, rather than serve as assistants in established labs. Joe DeRisi was one of the first Sandler Fellows and, in his interview, he describes the remarkable work he has accomplished while at UCSF as a fellow and, now, as faculty member who heads his own esteemed lab.

The list of projects, programs, and agencies either supported or started by the Sandlers runs too long to list here, but at least two are worth mentioning for these endeavors have produced impacts wide and far: the Center for American Progress and ProPublica. The Center for American Progress had its origins in Herb Sandler's recognition that there was a need for a liberal policy think tank that could compete in the marketplace of ideas with groups such as the conservative Heritage Foundation and the American Enterprise Institute. The Sandlers researched existing groups and met with many well-connected and highly capable individuals until they forged a partnership with John Podesta, who had served as chief of staff under President Bill Clinton. The Center for American Progress has since grown by leaps and bounds and is now recognized for being just what it set out to be.

The same is also true with ProPublica. The Sandlers had noticed the decline of traditional print journalism in the wake of the internet and lamented what this meant for the state of investigative journalism, which typically requires a meaningful investment of time and money. After spending much time doing due diligence—another Sandler hallmark—and meeting with key players, including Paul Steiger of the Wall Street Journal, they took the leap and established a not-for-profit investigative journalism outfit, which they named ProPublica. ProPublica not only has won several Pulitzer Prizes, it has played a critical role in supporting our democratic institutions by holding leaders accountable to the public. Moreover, the Sandler Foundation is now a minority sponsor of the work of ProPublica, meaning that others have recognized the value of this organization and stepped forward to ensure its continued success. Herb Sandler's interview as well as several other interviews describe many of the other initiatives created and/or supported by the foundation, including: the Center for Responsible Lending, Oceana, Center on Budget and Policy Priorities, Learning Policy Institute, and more.

A few interviewees shared the idea that when it comes to Herb and Marion Sandler there are actually three people involved: Marion Sandler, Herb Sandler, and "Herb and Marion." The later creation is a kind of mind-meld between the two which was capable of expressing opinions, making decisions, and forging a united front in the ambitious projects that they accomplished. I think this makes great sense because I find it difficult to fathom that two individuals alone could do what they did. Because Marion Sandler passed away in 2012, I was not able to interview her, but I am confident in my belief that a very large part of her survives in Herb's love of "Herb and Marion," which he summons when it is time to make important decisions. And let us not forget that in the midst of all of this work they raised two accomplished children, each of whom make important contributions to the foundation and beyond. Moreover, the Sandlers have developed many meaningful friendships (see the interviews with Tom Laqueur and Ronnie Caplane), some of which have spanned the decades.

The eighteen interviews of the Herb and Marion Sandler oral history project, then, are several projects in one. It is a personal, life history of a remarkable woman and her mate and life partner; it is a substantive history of banking and of the fate of the savings and loan institution in the United States; and it is an examination of the current world of high-stakes philanthropy in our country at a time when the desire to do good has never been more needed and the importance of doing that job skillfully never more necessary.

Martin Meeker, Charles B. Faulhaber Director, Oral History Center, UC Berkeley

List of Interviews of the Marion and Herbert Sandler Oral History Project

Interview 1: June 1, 2018

01-00:00:03

Meeker: Good day, today is the first of June, 2018. This is Martin Meeker interviewing Professor Keith Yamamoto for the Oral History Project of the Sandler Foundation. Thank you very much for inviting me here to your office at UCSF [University of California San Francisco] in San Francisco.

What we're going to do today is a little bit different than most oral histories that I conduct, in which we start with your place of birth, and walk you through education. Thankfully, we already have a substantive interview or two with you, that cover that, so what I'd actually like to do is jump in, and have you take me back to the mid-1990s, and kind of walk me through the landscape of what the funding options were like for people who had high-risk ideas, maybe unconventional ideas, ideas that the NIH [National Institutes of Health] wasn't going to be ready to throw a bunch of money at, because of their public trust and more conservative funding nature. What resources were available to researchers?

01-00:01:17

Yamamoto: Essentially, none. The federal funding enterprise is founded on peer review, which, as Churchill said about democracy, "is the worst system for allocating research dollars in the world except for all of the other systems." [laughter] Peer review is fantastic because it means that scientists themselves are making judgments about the merits, scientific merit, of grant applications that come in. The problem with it is that it's intrinsically conservative. If the people who are judging the applications are the people who created the current paradigm, then they're going to defend that paradigm, even if not consciously, but commonly consciously. And so somebody who comes in with a grant application that says, "Oh no, that's probably wrong. Here's another idea, another way to think about it, another approach," then those grants have a hard time.

So the result is that the federal system is very strong at being able to establish linear research that deepens our understanding of current paradigms, but not good at doing transformative research that changes the way that we think about something, or that establishes a new method, a new technological approach. Science is technology driven. It has been for a long time, but now it's getting really solely, almost solely driven by new technologies, occasional brilliant ideas, but usually new technologies that generate those new ways of thinking.

And the NIH was also very hesitant to fund ideas for a new technology. There was an addiction to this notion of hypothesis-driven research: come in with an idea, question that you want to test, and show us how you'll get the answer. So instead to come in and say, "I have an idea for a new way of measuring something," right, then that wasn't approved either. So, there were these two gaps in the ways that the federal system worked. As you implied, at the time, there was really nothing that would allow those ideas to move forward.

01-00:03:40
Meeker: Were you aware of this discovery fund that Chancellor Martin had been trying to find supporters of?

01-00:03:48
Yamamoto: I was, and we had been able to launch the discovery fund with one donation from Ann Getty, who put in some money, who was captivated by this idea to put together a local, UCSF fund that would support UCSF scientists that had bold ideas. But it was a very small amount of money, and had been not languishing, but been able to support just only a couple of people, for a short time. But Joe Martin, the chancellor at that time, was very enthusiastic about trying to grow this. But finding donors that understand the connection between fundamental discovery, curiosity-driven research where an investigator has an idea about how something might work, and an approach to try to get to the answer, was not something that—it's not easy. Such donors are not around, were much more commonly grateful patients who want to support a physician who has helped them or their family, totally understandable. But that's at the other end of the research endeavor.

So, finding those kinds of donors was very difficult, and I think the proof of that, unfortunately, is that the Sandler Program, now twenty years later, is still the only program that I know of that's a philanthropically supported program to drive this idea of "give us your boldest idea," then see what we can do with it.

01-00:05:36
Meeker: At what point did you become aware of Herb and Marion Sandler?

01-00:05:40
Yamamoto: It was after Joe met with them, and had an initial meeting, and so I'm not sure of the history of how that came about. I know that the Sandlers were looking for ways to have impact in biomedical research, and it was in that, and I know they had met with some groups at universities in Southern California. And Joe, when they met with Joe, he raised this discovery fund idea, and that captured them, and that then generated a meeting that I and Mike Bishop and Reg Kelly, and Holly Smith, I think, were involved in that, then began to talk with them about how they might have an impact on this kind of research.

We actually, in that meeting, in that initial meeting, talked to some about endowing a graduate program, and made the point that graduate students are not only the seed corn of the next generation, but they're the people that actually carry out the experiments and the really, really imaginative ones, the extraordinary ones are also generating ideas at the same pace. They're right there with the work and they see what's going on, and they have great ideas about how to try to move it forward.

The Sandlers chose not to do that. They didn't want to put money into endowment, first of all, and they wanted to see immediate impact. But they

said, “Come back and tell us about a program that would actually support research projects. Students will be involved in it—it’s not a problem—but instead of endowing the graduate program, what if we give you some money, and on a year-to-year basis, that would enable this bold kind of research to be done?” So that’s how it got started.

01-00:07:30
Meeker: What did you make of them personally when you first met them?

01-00:07:35
Yamamoto: That’s a good question. [laughter] So, I was, well, I was very impressed at their kind of penetrating questions that they asked, and it was clear from the outset that—and something that, of course, is characteristic of them—that their main drive was excellence and impact, that they were uncompromising in their drive for excellence, and they wanted that excellence not to be just excellence in its own right, but to actually make a difference. And so they were looking to put their money into something that would do that. I learned later that, in fact, this is the way they’ve operated throughout, this is the way they put their business together, and the way that they have chosen or launched other philanthropic concerns to support. So this is a part of the pattern in the way that they operated. It was in their DNA.

01-00:08:48
Meeker: Most other folks that I’ve interviewed, from John Podesta to Anthony Romero and beyond, talk about the Sandler interview, in particular, Marion’s role in the Sandler interview. Were you put to test in that way?

01-00:09:06
Yamamoto: Oh yeah. Marion was a tough customer, and she was a no-BS person. There was no kind of slipping something slippery past her. And with years of interaction with her, it was common that she would bring her knitting to these meetings, and she would sit there as Herb introduced an idea, or somebody responded to questions, and she’d be knitting away, and then suddenly, she would come out of the blue with some totally pointed, well-focused, right-on-the-mark question that she expected a similarly clear and direct answer. And if she didn’t get it, she just kept drilling. So she was tough but in a great way. So yeah, it could be intimidating, talking with them, but in a way that left you totally respectful of what it is that they were trying to do, and the rationale behind the way that they interrogated you.

01-00:10:14
Meeker: Did you know much about Golden West or World Savings at this point?

01-00:10:17
Yamamoto: Nothing. Well, maybe that that was their company, but I knew nothing about the company.

01-00:10:22
Meeker: Can you walk me through the process, going from these initial conversations to the establishment—I think it was originally called the Sandler Program in Basic Research—to what's now called the Program in Breakthrough Biomedical Research, otherwise known as [pronounces as "pibber"] PBBR? How did you get from those initial conversations to the establishment of an actual program?

01-00:10:43
Yamamoto: Ah, so, after that first meeting where we suggested that they might want to endow the graduate program, they left us with a charge, and said, "No, come back to us with something that would support research projects, and don't worry about the fact that—and we do care about students"—they cared greatly about young people and the next generation of scientists, and women and minority scientists, and so forth. They said, "Don't get us wrong, but come back to us with an idea about supporting research that trainees will be involved in, and let's see what we can do. It won't be endowment. We want to be able to control the money. We can do it a lot better than UCSF can. [laughter] But we would like to have you let us know what can be done that would change the scenario that you outlined in the beginning, that federal system is good at linear research, but not good at quantum leaps. What can be done in that realm?"

And so we sat down and outlined a plan, put together a budget of the kind of thing that we thought would have impact: a set of small, one-year grants, the idea of a UCSF fellows program that would bring PhDs directly out of their degrees into their own laboratory to start a research project. You know, biological sciences and biomedical sciences really have an extended training period, where after getting the PhD degree, there's a post-doctoral training period that now is going on five, six, seven years.

But we had a theory, based on some evidence from a couple of other institutions that had put together programs, that there exists a cohort of extraordinary PhDs that are ready to go, that have their own ideas, that have demonstrated success at being able to generate independent ideas they could make work. And so a fellows program was another idea, helping new faculty members who are hired get started, by giving them a seed grant to get their research launched while they're then running around to get NIH support. Programs of that sort. So then we put together a package for them, and proposed that, and they said, "Let's do it." So they started, that's how that original basic science program got started.

01-00:13:22
Meeker: So the program in basic science included what would now be the grants that are administered under PBBR as well as the Sandler Fellows?

01-00:13:33
Yamamoto: That's right.

01-00:13:34
Meeker: Okay. Oh that's interesting. And were they willing to fund it at the level that you thought appropriate?

01-00:13:42
Yamamoto: I don't remember what number we proposed to them, but what they suggested—so I think the original input from the Sandlers was a million and a half a year, and that was matched by the institution. The current number, three million a year, it's been that way for some time, and that is now matched by our institution. There are other little wiggles along the way, but that's basically how it is.

So, for a number of years now, it's been a six-million-dollar-a-year program. That number is about a third of a percent of our annual research funding income, and so you might think, gee, a third of a percent, [laughs] if it disappeared, there'd be no impact, and if it tripled, there would be no impact. And so the notable thing is that those dollars are considered in the research community here as the most valuable dollars that you can get. Why? Because of what we talked about at the beginning, because the fund is set up to invite and support bold research ideas that couldn't be funded any other way, and it's had a huge impact in that sense.

01-00:15:12
Meeker: Well that's interesting. I mean, bold research toward quantum leaps in knowledge and understanding, the other side of that, is that in more cases than not, you're probably going to end up with some sort of failure, or it's just not going to pan out in the way that you thought it was going to. And so you're going to have to have funders that have a stomach for failure, at the same time they've got great hopes for quantum leaps. How do you communicate that side of the equation to the funders, and how do you talk about that internally, as well?

01-00:15:49
Yamamoto: Mm-hmm. Yeah, an important element of what you're talking about is that academia does not sustain failure, that failure in academia—failure to get a grant, or to attract students into your laboratory, to publish high-profile papers, to be invited to chair meetings—these kind of conventional metrics of success don't align well with a program like this. And so, we discussed that with the Sandlers early, and again, they completely understood. I said that if every grant that we fund, by the year this program is successful, then we're not shooting high enough. The definition of bold and transformative research is that there's a good chance of failure. Obviously, they wouldn't be so happy if every grant failed, [laughs] so where do we hit, is there a happy medium that we can establish?

An important element of this is that evaluating a program that seeks to operate above the norm, using normative standards, drags the program down. And again, the Sandlers completely understood that, and so they were happy with

the idea that we would put together a faculty committee, internal to the institution, that was directed to seek out grants, grant applications that were above this norm. And in our call for proposals, every time it goes out—there are two calls per year—every time it goes out, the directive to the applicants is, "If you have a great idea for an NIH grant, the application, write in 'NIH grant application.' We don't want it. But if you have something that they would laugh out of the room, [laughs] at the NIH, then send it in." And it's two pages; we limited the length.

That does two things, by the way: it really makes the investigator focus on the idea, right? Bold ideas, you don't really know in detail, exactly, the methods that you're going to use to get there, and the buffer concentrations, and all the little details. And on two pages you shouldn't have time to present that anyway. And, it made it easier for the reviewers, just because there's less reading, but also because the focus is on the idea, to then make an assessment of, "Is this the right thing to be doing? Is this going to really make a difference?" And the process has worked well.

01-00:18:50
Meeker: Can you talk a little bit more about the process? Because it is a non-normative selection process, based on non-normative standards of excellence, I think it would be interesting to hear a little bit more about how that works out.

01-00:19:05
Yamamoto: So we've a faculty committee—I think right now, there's eleven people on it—and the grant applications come in, and the administrator, Linda Reilly, in that currently—she does a fantastic job—is then charged with compiling those applications for me. And I then assign each of the applications to three reviewers, out of this eleven-member committee, and those three are charged with reading every word, and making an assessment of the quality of the application. And then there's a grant review meeting, which the whole committee gets together, and we—oh, and sorry, and those three reviewers assign a score to the application: one's best and ten's worst.

And then the committee meets, and Linda has averaged the scores of the three reviewers, so those numbers are available, and we use that order as the order in which we actually review the grant applications. Simply having that preliminary score doesn't guarantee anything except, it puts you in an order of the reviews. So we get a little bit of a view of what the committee thought were the very best things first, to measure everything else against. Things do move around, but that's the basic paradigm.

The grants, each application is discussed. The primary reviewer, the reviewer number one, actually gives a little summary of what's in the application, and then a statement of what he or she thought of the application, why she gave it a score of three, and then the other two reviewers chime in. They add any comments that the first reviewer didn't make, or a different take that they

might have, and why they gave their score, and then we move on, and then come back at the end and decide which ones to fund or not.

There's a kind of delicate element here, because it's an internal mechanism. And so, people are reviewing their next door neighbors, or the people that they hired, or the people that hired them, and so to maintain trust in the process, I've eliminated myself from applying for these funds, and for the duration—so that's been now twenty years [laughter]—and for the duration of people's service on the committee. There's not a set term, so some people have been on for like a decade, and so they're not eligible to apply either. And so at least that element of the conflict of interest is moderated. We don't hide the membership of the committee, but we also don't advertise it. And I can think of only a couple of instances in twenty years where applicants have come back disgruntled with the review, and said, "Who's on the review committee? I want to know who's on the review committee."

So, people basically trust the process, and I think that it's been of a high-enough quality that the community has confidence in it.

01-00:22:34
Meeker: I wonder if you can walk me through the kind of conversations that must happen in terms of, is this breakthrough, is it not breakthrough enough, is it maybe a little too extreme? How did those conversations happen?

01-00:22:49
Yamamoto: So, it's a good question. So, the first test is whether this would be—so is it a good idea? And then if so, is it an NIH grant, something that would take a linear step, or is it something that has this opportunity for a quantum advance? And so if it's a reasonable idea, but only at the NIH level, then the grant is not considered further.

Then the fun starts. So now you've got a bunch of applications that are bold, and have a chance of doing something remarkable: Some are them are to develop new technologies, as we said, to really help to drive the field in that way. Others are a new way of thinking about a process, and an approach to doing that, to understanding it. And then the committee has to wrestle with whether the approach that's laid out is going to be fruitful. And again, the really bold ideas, you really don't know. It's taking something that's really untested, and the investigator saying, "I'm betting that this will work. I don't have preliminary data." NIH grants are constantly rejected because of lack of preliminary data. Review committees are conservative and they want to be able to spend their money wisely, and so they want to have confidence that the idea is going to work.

We don't do that. We don't have the benefit of that, and so it really requires the scientific judgment of the committee members. And as you're implying, there's not always agreement, and some lively conversations ensue about

whether, “This is a great idea, but I don’t think this approach is the right one,” and, “Oh no! This is exactly what should be done,” and we wrestle our way through that. It’s fun!

01-00:25:07
Meeker: Hmm. Interesting. Can you tell me a little bit about the administrative process that was established? Given that it’s a relatively small amount of money each year, you’re not probably building a big office around this, right?

01-00:25:22
Yamamoto: No. There’s an administrator, Linda Reilly, as I mentioned, who oversees this; an accounts person: Vicky Chan’s terrific. They both sit right outside this door. And that’s it. And I’ve chaired the committee for many years, and then I recruit members onto the review committee, and a lot of them, as I said, are really loyal, and are willing to sustain not being able to apply for the funds. We eliminated Howard Hughes professors from eligibility, not because they’re [laughs] not generating bold ideas—they’re obviously fantastic—but that other wonderful resource of the Hughes funding provides them a lot of support that is not available to the non-Hughes faculty. I say that because several of the members on the committee are Hughes professors.

01-00:26:29
Meeker: You referred, I think, a bit to the fact that there’re actually two awards that are given: one is a New Frontier Research award; another one is Technology, Methodology, and Cores. Can you talk about how these are different and how they came to be?

01-00:26:47
Yamamoto: Yeah. So that evolution came from, eventually, we had a family of I think five or six such award types, and our external advisory committee, who we haven’t discussed yet, but our external advisors, who now come biannually to visit for a day, at one point, along I guess maybe ten years ago, advised us to just consolidate the funds. The Sandler Foundation was, in my view, very wise in giving the review committee complete latitude of how they spent and how they allocated the dollars into these different funds. But nevertheless, the external advisors felt that it was getting unwieldy. There were many different review types, and one of the funding mechanisms, which was a startup award for new faculty, was beginning to sort of take over all the money, because UCSF was hiring lots of faculty, and we wanted to give support to those new faculty as they came in.

So, driven by that, we then collapsed to these two awards: New Frontiers, and, Technologies, Methodologies, and Cores. And the ways that they differ are that the New Frontiers awards are generally hypothesis driven—not always, but generally hypothesis driven. I guess you could argue, investigators would argue that certain types of observational grants or schemes to screen through all the genes in the genome for a certain kind of characteristic, it’s not really hypothesis driven; it’s just collecting information. Those kind of grants are

also not funded by the NIH, and so we're happy to see those as well. But New Frontiers awards were an idea; you have a shower that you say, "Geez, if we could figure this out, it would really make a big difference." And so now you can come in and sit down and write two pages and have a shot at it. And so that's the New Frontiers.

Technology, Methodologies, and Cores acknowledged that this is a technology-driven discipline, and the discovery or invention of new technologies and approaches can have a huge effect; it's not supported by the NIH. And the Cores part of the Technology, Methodologies, and Cores said that there are facilities or instrumentation that, if present at UCSF, would benefit the whole community. It's expensive stuff, and a cryo, yeah, cryo-electron microscope is millions of dollars investment to purchase the machine, a couple million dollars to rig up the room to receive it, and then very expensive maintenance contracts and things of that sort. But when that instrument's in place, then the community can do things that it couldn't otherwise do. So those are the elasticity of seed grants, and they're very, very enabling, and generate lots of exciting new approaches.

01-00:30:33
Meeker: At what level do the recipients receive funding for each of these grants?

01-00:30:39
Yamamoto: So the New Frontiers awards are generally in the $150,000 range. So it's for one year, and so the proposals have to convince the committee that something could really move in that period of time. Some of those ways that things can move is simply to craft an idea, and then design an experiment, to really see whether there's anything really behind it or not, in that much of a blue sky. And the committee can be very supportive of applications like that.

01-00:31:23
Meeker: What are they typically spending that hundred thousand dollars on? I'm sure their salaries are covered already. Is it mostly lab assistants, or—

01-00:31:32
Yamamoto: So, it can be to help support trainees—yeah, faculty salaries are not eligible for funding in the PBBR [Program for Breakthrough Biomedical Research] arena. But it can help support trainees, and buy supplies and equipment that's needed for the experiment. So the TMC [Technologies, Methodologies, and Cores] awards, in contrast, can be substantially larger, and so there's not an upper limit placed on the size of those, and the review process for those is a little more complicated.

I should have mentioned that a pre-proposal comes in that describes the idea for the new technology approach, and says how, if it would work, it would benefit the research in the community. For core, research core, in fact, there has to be a list of faculty that have already been contacted about this and said, "If we had this instrumentation here, would you want to use it for your

research, and how would it be used?" And, those go through this pre-proposal vetting, in which the committee says, "This sounds good; come back to us with a full description of what you're really thinking of," and then the committee makes a decision.

So it's a two-step process. Those applications, as I said, don't have an upper limit—for instance, equipment's expensive, things can take a long time to develop—and so some of those grants are several hundred thousand dollars.

01-00:33:20
Meeker: Over a longer period of time.

01-00:33:22
Yamamoto: Sometimes. Sometimes we're able to take a bit bite and fund a several hundred thousand dollar grant right away. But if it's a million dollars, it'll be over a period of time.

01-00:33:32
Meeker: Mm-hmm. You had mentioned an advisory committee. Tell me about that.

01-00:33:37
Yamamoto: So, the Sandlers wanted, from the beginning, to have an outside look at the process. I don't think [laughs] it's because they didn't trust us, but rather that it's a smart thing to do, that having wise people that can come in and provide an outside perspective of whether the program is doing what it's claiming to do, and if there are changes that could be installed to make it better, would be good.

So, from the beginning the Sandlers wanted an outside committee of three people. Herb likes Nobel Laureates, and so two of them, at least two, have always been Nobels. But the characteristic that they were looking for and have found, in the committees that we've had, is people who are of themselves bold thinkers, who recognize a bold idea when they see it. They're generalists in science who don't have to be working in that discipline, to know whether something would make a difference. And those are the people they were looking for. We've always had fantastic journal advisors, who again, are really dedicated to the excellence of the program.

01-00:35:04
Meeker: Do the external advisors play a role in the selection process, or they mostly step back and look at what the selectors have come up with?

01-00:35:12
Yamamoto: Yes. So, we report to the external advisors and to the Sandler Foundation, once a year, with an extensive written report, and that describes the projects that are ongoing; and the process that we use that you and I've just discussed, to select the applications; and something about the investigators that are actually getting the awards, and the progress that they're making. And then every other year, the external advisors who get the annual report, every other

year, they actually come to San Francisco for a day to visit and I organize a day of presentations for them, with a spectrum of investigators who have gotten awards that year, or maybe in prior years, to talk about their progress that they've made.

And the reviewers have lunch with a set of, commonly now, UCSF fellows, the young people—it's usually with a group of four or five of those people—and then come back in the afternoon, with sort of more presentations, and then a meeting with the Sandler Foundation board, and then with me. Although in recent years, the Sandler board has just said, "Oh, just have one meeting—it's okay, we're all going to say the same things—and give us advice." And then the reviewers, after this kind of oral presentation, each go home and each write a rather detailed letter, to the Sandlers, Sandler board, of what they heard, what they thought was especially significant, any changes that they would recommend, and then we then act on those things.

01-00:37:13
Meeker: What kind of recommendations have come your way? You had talked about breaking down from five to two, the categories. Any other significant recommendations?

01-00:37:24
Yamamoto: Yeah! This was really founded as a basic science program, and a few years ago, the committee, the external advisors said, "All good stuff, but there's a little more translational and clinical stuff than we're thinking of." They said, "That's interesting." It's interesting because the current research is easy to reach, and has more immediate applicability to health and medicine than ever before. When I started writing grants in the mid-seventies, we were required by the NIH to have a line in our abstract of how the work applied to health and medicine. And for the most part, we were just making stuff up, and everybody knew it. The reviewers knew it; the NIH knew it. And we're just imagining things, and it was okay.

And now, that's really changed. Now that we can see much more clearly what the connections are between a fundamental discovery or a little piece, little bit of understanding of how biological process works, and then doesn't work in disease, then it's pretty easy to imagine how that connection can be drawn. Where at UCSF, we have tremendous excellence on the clinical population research, and on the basic science side, and so one of those funds, those five funds that collapsed, was called Integrative Research, where the directive to the researchers was to join up a basic scientist with a clinician, or with a population scientist, and imagine a project that would apparently move forward along those fronts. That was one of the programs one iteration of the advisory committee said, "No, let's kill that and just make it simpler."

So we did, but a few years ago, the committee said, "You know, it's a little more translational and clinical stuff than we're looking for. Let's go back to

first principles of those crazy ideas in the shower, and focus a little more on that," and we did, and I think they're quite happy this time. We just met with them a month ago or so, and they're quite happy the last couple of times we've met that we've gotten back to a level that they feel is more appropriate, and has a bigger chance of having a big impact.

This finding that balance, now that that immediate applicability is imminent to everyone, can be tricky sometimes. But I think the advisors are wise in making that recommendation. I think that that really acknowledges that biology is still largely not understood, and that if we think that we're at a stage where we understand enough that we can just drive for application, then we're really in trouble. But there's still so much to be discovered about the fundamentals, and it's those discoveries of the fundamentals that really allow us to do things of real significance on the application side.

01-00:41:01
Meeker: Well, let's talk a little bit about the projects that you funded, then, in some examples. But first, we've already talked a bit about how the application selection process works. Can you tell me like roughly how many applicants you get each year, and how many grants you make? Is it a popular, competitive thing?

01-00:41:26
Yamamoto: Yeah, it's very competitive. But our funding rates are actually better than the NIH. I think there's a certain amount of pre-selection that goes on within the community. Let's see, in this last round, I think we had fifty or so applications, and we funded, I believe, fourteen NFRs, and asked four TMCs to advance. So it's quite competitive, but I think that the committee does a good job, and the community has confidence in it. So, it is competitive.

01-00:42:12
Meeker: I'm sure that you would feel maybe a little uncomfortable calling out some of the projects that were failures, but I'd like you to talk about some, to the extent that you're willing to, or that you can do maybe without providing too many detail, [laughs] but I'm curious about some of these high-risk ideas that came in that just didn't pan out.

01-00:42:37
Yamamoto: Yeah. I'll mention two that I think are notable because they illustrate what is almost always the case with these applications from these investigators who come in with a bold idea, and that is that those investigators are not only brilliant and thinking about what might be, but their eyes are always wide open. And so the illustrations I'll give you, of a couple of examples of failed projects, are, I think, highlighted by the fact that, in the course of those failed investigations, they made important discoveries, and that is almost always the case as well. So one of the selling points that we've had to the Sandlers—I will get to those examples, but one of the selling points we've had to the Sandlers, that we had to them throughout, is that the money is unlikely to be

wasted in the sense that we hand over a bunch of money and say, “Go, figure this out,” and, “Oh, it didn’t work. Thanks very much.” But almost always, there’s an observation along the way. Some of them are really important ones.

So one idea that came from an early iteration of the program, I think in 2000, came from two investigators who wanted to use this microarray technology to try to understand signaling pathways in yeast. And they made an exciting and bold proposal; they tried it; it didn’t work. And so they said, “Oh well, that failed, but in the course of doing that, we can use this method to evaluate, or classify the mutations that come out of this genetic stream.” They try that; that didn’t work. [laughs] So they had two failures.

In the course of doing the evaluations, they discovered a new class of chromosomal proteins that have a function that hadn’t even been imagined before, that, when this gene is mutated, allow the packaging machinery that packages the DNA—it’s got so-called chromatin—to spread. So that chromatin can be packaged into really tight packaging that doesn’t allow genes to be expressed, turned on, and then a looser packaging that says, “Okay, you can go ahead and be expressed.” And so you can see that in a developing organism, for example. Your liver cells may have this tight package chromatin over the brain genes, but not over the liver genes, and vice versa for the brain cells, right? So they discovered a kind of chromosomal protein that puts a stop to the migration of the closed chromatin, and that became a huge discovery that has affected many research programs around the world trying to understand how these chromatin domains get laid down and limited. So, it was a great thing that came out of it, even though they failed twice, [laughs] to try to get an idea that would move forward.

A second one, that I think also characterizes the PBBR grants, was a proposal for two investigators to move into a completely new field, to study malaria. And one was a molecular biologist and one was a chemist, and their idea was to then to ask, “Can we use these microarrays to be able to screen through compounds that could actually have an effect in treating malaria?” And so they set up all the biological systems to be able to grow these parasites, and then be able to test whether the microarrays that were scoring the X gene expression for the parasites would be useful for testing these drug candidates.

No, it wasn’t, and it turns out that that same laboratory discovered the reason why, and that is that the drugs that are affecting the malarial lifecycle don’t actually affect this gene expression part of the lifecycle. So there’s a relatively little effect there, but in the course of doing that, the chemist generated some drug candidates that have now actually gone forward into the clinic. So, good things happen when you put smart people together and have them focus on a problem, and the investigator—this is again, a grant, I think it was in 2001—that investigator’s still working on malaria.

So, I think that there's an understanding in the community that this is a way to be able to sustain failure, and that in doing it, if the idea is good and you keep your eyes open, you're likely to discover something significant.

01-00:48:38
Meeker: What about the successes?

01-00:48:40
Yamamoto: They've been great. [laughter]

01-00:48:44
Meeker: Do you have any that you think are particularly worth remembering?

01-00:48:47
Yamamoto: Well, I think that I could call out a couple. Charlie Craik, in 1998—that might have been the first year—proposed that he could find proteases that were particularly important in cancer. This is an idea that many in the community thought had come and gone. That is to say that the idea that proteases are involved in cancer makes logical sense, that if a tumor is going to metastasize and spread, it does it by actually invading tissues, and so, that can be driven by proteases that help to chew their way in through a blood vessel and in to another tissue. So that made sense, but drug companies had tested, tried to make drugs that would attack proteases, but it'd been no effect, and so that idea had sort of gone out the window.

Charlie was an expert in proteases, and felt that he could make a contribution in this area, and he had an idea for a way to discover proteases that were specifically involved in cancer, rather than looking in a much more generic sense. And so he wrote a proposal back in 1998 that is still bearing fruit. He discovered a new class of membrane-bound serine proteases that has effects in cancer; was able to classify that family of proteases by a very clever set of assays that would distinguish their specific targets where they liked to cut proteins. And so he could separate, classify them in that way and classify the proteases that acted in certain kinds of cancers.

He used that; he patented the idea, started a company—this moved products into the clinic—and continues to work in that area and make major contributions. But at the time, it was an idea that the NIH felt had come and gone, and it wasn't going to be fruitful anymore, and he wouldn't have been able to get NIH support for that, or in fact, maybe he tried and failed to do that.

Wendell Lim got two PBBR grants: one in 2001 and one in 2006. He's had others as well, but the ones I'm thinking of were ones that really launched his approach to so-called cell engineering, fantastic new areas of synthetic biology, many call it. I recruited Wendell when I was a department chairman, and his idea then—he'd been a post-doc at Yale and was a fantastic young scientist, and his idea even back then was to ask: Can we understand the

circuitry within cells that allow signals to be carried, and then had to have specific effects, by making our own synthetic circuits?

The true test of understanding something is whether you can make it yourself. So he's always wanted, throughout his career—he was hired in 1995, and in 2001, got a PBBR grant to ask if he could rewire a signaling circuit by making recombinant regulatory domains of proteins that would switch, that would receive one incoming signal that normally was driving a specific process, and take the signaling piece off of another piece and add it on to this one, and see if he could switch the sense of the signaling. And, it was a crazy idea when he posed it but it worked, and he was able to understand something about how these regulatory circuits evolve, how they could get pieced together, in very much an engineering sense, and then be able to generate his own pathways in that way.

So that work proceeded beautifully, lots of papers came out of it, and in 2006, we gave him another PBBR grant, and this was to ask a really vexing question, and that is that, by then, Wendell and people here, Kevan Shokat and others, who were studying protein kinases in cells, had begun to appreciate how large the protein kinase family is, that there's hundreds of these different kinases that are swimming around in the cells. So kinases all do one thing, and that is that they put a phosphate residue onto a protein. And so there were hundreds of these genes. Many of them would target to the same sites, and yet, they were doing different things. So it made it very hard to ask, "For this kinase that I'm interested in, what proteins in the cells are actually hit by that?" Kevan Shokat had worked out genius technology to figure that out, but the question that underlies that is, how does this cell sort it out?

Okay, we get it that there's specificity and this kinase affects that process, and that other kinase affects this process over here. But how does it happen? The kinases are just swimming around in the cell; the proteins are floating around in the cell. How does all that work, to have a signal transduction pathway, and yet there's all these options for many, many kinases that can be used? And then Wendell came in with an idea, simply asking: Are there multi-protein complexes that are governing these specific signaling pathways? And what he discovered was amazing, and that is that there are so-called scaffold protein. He called them scaffold proteins, that are little anchors that all these enzymes in a pathway latch on to, and so they're localized with each other, and they govern a pathway in that way. So the scaffolds are the specificity drivers for these pathways, and that was the second grant we've given him.

From that kind of basis and background, Wendell's been able to do an enormous number of really innovative and important things in cell engineering, as he calls it, and has been working on the so-called CAR T cells, these T cells that have hybrid antigen receptors that are able to target T cells to specific tumors and kill them. And so this is the kind of the hot area in amino oncology, and so he's making big contributions there as well.

01-00:56:41
Meeker: Well, it's interesting. Here you're talking about innovations in basic science that, it's not too long before the translational medicine starts to happen into the clinic.

01-00:56:52
Yamamoto: That's right.

01-00:56:52
Meeker: It was interesting when you were talking about that earlier, in terms of guidelines about what kind of research PBBR should be funding. It sounds to me like maybe you're beginning to think that the previously large gulf between basic science and clinical research is starting to shrink a little bit.

01-00:57:14
Yamamoto: It is, it is. I've been involved for years now in developing a notion called precision medicine. This came, a term and the concept, came out of a National Academy of Sciences report that I was involved in, and that a former UCSF chancellor, Susan Desmond-Hellmann, was able to persuade a chair the study committee and I served on it. And precision medicine says that we've reached a point in biomedical research where we really need to build a seamless continuum, from fundamental discovery out to clinical care, and advice about health to the populations. And so the precision medicine notion says, "If we could build a computational knowledge network that links together, uses super computer to link together all of this biological information, we could eventually know enough to be able to give you health advice, or diagnosis, or treatment, or therapy, or predication of what the likelihood and course of disease is going to be; give you advice that's relevant to you—not to a statistical group like you, but to you."

And so we're reaching for that here, and building a knowledge network at UCSF that has begun to pull that kind of information together. And it really recognizes what you just said, and that is, that gulf is now disappearing; it is being maintained artificially in some ways by the bureaucratic separation between departments and programs and things of that sort. The precision medicine report said, "We need to stop even classifying disease by organs and symptoms, and start classifying it by mechanisms, molecular mechanisms, because there are diseases that look different that are caused by the same mechanism, and there are mechanisms that cause different diseases that don't look like each other." So if we can understand the mechanisms, then we'll be at the right place to be able to try to understand how to treat and cure the diseases.

01-00:59:52
Meeker: Is the NIH interested in funding this work in precision medicine that you're talking about?

01-00:59:57
Yamamoto: So, we were able to persuade President Obama to make precision medicine one of his primary initiatives in 2015, and that then generated support in Congress and the NIH budget. And it shouldn't be the only player. This is a big initiative. It's going to require huge amounts of computation, first of all, so I've been doing a lot of work with the Department of Energy, which has the national laboratories which have all the biggest computers in the country, and also fantastic computer scientists, I might add, in collaboration to build this knowledge network.

But yeah, the NIH continues to support this. They've put the funds for precision medicine currently into building a million-person cohort of Americans, that mirror the demographics of the country, that will volunteer to put their data into a data pool, and I don't think the NIH have yet gotten to the point of asking, "How do we build a computer network to make this happen?" but we're trying to get ahead of that at UCSF by working with the national labs to move it forward. So there is funding. There was a bill passed last year, I guess 2016, called Twenty-first Century Cures Initiative, that actually assured funding. Right at the end of the Obama administration, they assured funding for the next decade for precision medicine, and so it will continue to move forward.

01-01:01:37
Meeker: That's fascinating, and every time I come to UCSF, I always leave feeling more optimistic about the world that we live in, so, that's what I'm going to latch onto today. But you had mentioned the review process, and the meeting with the Sandler Foundation Board of Directors. Can you tell me a little bit about what that's like, what they're interested in hearing? A lot of foundations these days are very interested in metrics, and measuring impact. Is that what you're getting from them, as well?

01-01:02:13
Yamamoto: That's interesting. I meet quarterly with the board, and the meetings have kind of a set format that the board seems to be happy with, and that is that—so the board, now that Marion has died, is really Herb and the two kids, Jim and Susan, wonderful people, and Steve Daetz. And so I sit across the table from them, and start the meetings by telling them a story, of some application we just funded that we thought was really cool. So tell them some cool science, or maybe it's a project that we funded a few years ago that has really born fruit, and start with that. And then just give them an update on how the program is going. Are we experiencing particular problems, or are we wrestling with this advice that we got from the advisors about how to implement it? And how many grants have we funded relative to the applications that came in?

So the kind of update of current status, and then finally a little projection idea of where we seem to be going. Are there things that are changing in the community, at UCSF in particular, hiring practices, people that we brought in that have specific needs that we think that the program should address? And

those conversations, not infrequently, turn to a question usually from Herb, that says, "What's limiting you? If there was more money, could you do more, or are you pretty much funding the applications that you think should be funded?" He sent me back to actually test that, and we did a projection. We looked at the first grants not being funded. Are those ones that we really wanted to fund, and they are, and so we knew that the fund can grow in that way.

And then for a few years, years back, we offered the possibility of renewal for a second year, and that changed the kinds of applications we got. People would send in ideas that really needed a two-year horizon to really be able to test them. And so we came back and reported to the Sandlers that yes, actually, more money could be used in two ways: one is that we're not funding some spectacular work, and the second is that having the option for a second year, at least for some of the applications, would be something that we think could change the impactful aspect of the applications. So, this is something that Herb is pushing us to be able to look for: how can we grow this fund, could we make it a ten million dollar fund, and so forth.

So those meetings are focused on those kinds of things. In parallel, they do want to have conventional metrics reporting, and they want to know, what has been our lie, if you will. And so, collecting that data from twenty years of investigation—so, a grant that we funded in 2003 may still be generating great outcomes in the laboratory, in our UCSF labs. And so, every year we go back to the investigators and say, "Can you give us an update? Published any papers relevant to that award you got way back then, that really came from that directly?" And so we've just collected some data like that, and relevant to 2017, which would be our twentieth year, at the end of 2017, and we only—so with about 72 to 75 percent, something in that range, reporting, so we're far short of knowing the full number, but with the eighty-five or so million total dollars that have been invested, the follow-on funding is now 1.34 billion, at 72 to 75 percent reporting, so it's substantially higher than that, of course.

And let's see. Over 450 NIH grants have been generated as a follow-on to those ideas that the NIH wouldn't fund. More than 2,700 papers, more than seventy patents have been generated. So the leveraging is fantastic, and it really says that it really works to support these crazy ideas, and makes a big difference in the ways that we're able to do research at UCSF.

01-01:07:52

Meeker: Then why haven't more funders stepped forward to add to this here or replicate it elsewhere, or have they?

01-01:08:00

Yamamoto: So, we work on that all the time. We get small donations, well under three million, but small donations every year. We're continuing to talk, we're actually talking with another donor that could a substantial donation now. But

the Sandlers are really unique, unfortunately. Around the country, in our community and around the country, there aren't donors like them that really say, "I get it," that "this kind of research makes a big difference, and can be leveraged in these demonstrable ways," and they're much more at the other end of the spectrum saying, "We want to enable the surgeon that helped my aunt Mary." As I said, totally understandable, but it doesn't have the kind of impact that a program like this does. Finding people that really do understand that, and have the kind of insatiable drive for excellence and impact that the Sandlers have demonstrated in everything that they do, is rare.

01-01:09:23
Meeker: Have other universities around the country replicated or attempted to, or shown an interest in?

01-01:09:30
Yamamoto: A lot have shown interest; in fact, it's just common that our external advisors try to get the Sandlers interested in supporting their institutions. [laughter]

01-01:09:43
Meeker: But of course. [laughter]

01-01:09:46
Yamamoto: But they basically haven't really been successful. University of Texas Southwestern Medical Center in Dallas has a donor who has built a fund to support new investigators. And so it's one component of the kinds of things that we do, and I think that's had a big impact, where that donor recognizes that getting these young people started is really key, which is great. So that's kind of a little piece of what we're talking about, but there really aren't other programs like it, unfortunately.

01-01:10:29
Meeker: I assume you've been to some of the lunches?

01-01:10:33
Yamamoto: Yeah, yeah.

01-01:10:34
Meeker: The roundtables? Can you tell me about what those are like?

01-01:10:36
Yamamoto: You mean, when the external advisors are here?

01-01:10:39
Meeker: Yeah, or just at the Sandlers' home.

01-01:10:42
Yamamoto: Oh! [laughs] They're great. So, the ones I'm really familiar with are when the advisors are here, there is a dinner that Herb, formerly Herb and Marion hosted, and they have a wonderful apartment in the city. They have a house in the East Bay. They have a wonderful apartment in the city that has a bridge-

to-bridge view, and sitting right in the middle is a table that seats twelve. And so Herb and Marion, and the three advisors and me, and Steve Daetz usually is really there, and kids are sometimes there, and then several other people who made presentations during the day that the external advisors met—often a mix of UCSF fellows, and grantees—gather around this table.

And again, there's a strict protocol, and that is that usually Herb—Marion would occasionally do this, but usually Herb—lays out the ground rules that says that "this is a common table, that means that we're all here together and so there are no side conversations." So, if we're going to talk, then everybody is there and involved. And then, one of them, usually Herb, then frames what the topic's going to be. And we either go around—it might be politics; it might be personal, your personal history: how you got involved in science, or, "Tell us about your family that generated the kind of person that you now are," or some topical area of science policy that might be broiling in Washington—and discuss these things.

And so people either just throw in randomly ideas or sometimes he just said, "Through *x* that we go around the table and tell us about how your family got here, and how you ended up at UCSF, and what drives you. What are the things you wanted to do before you were a scientist, or may want to do now that you are a scientist?" And so we drilled down on a specific topic. Always lively and interesting, they keep it that way, and the questions that Herb and Marion would ask would kind of keep people's focus, and make it interesting. So those discussions were really terrific.

01-01:13:35
Meeker: Tell me about the future for PBBR.

01-01:13:38
Yamamoto: I hope we can grow. I think that it was revealing to us when the Sandler board asked us to make a projection of what would happen, what would be the impact if it were bigger. So, I see it being maintained. Herb has told us many times that he would see as this program going on after he's gone, and the kids have been involved in wonderful ways, and so we're hopeful that that support is maintained. We've never, ever been threatened with withdrawal of the funding, and that says something, because I said, they're highly opinionated. They care enough to push, to make sure that they're getting what they're looking for. And so you might think that that would translate it into a certain fear that they were going to say, "Okay, that's it." Never have I felt that way. They won't let us be lackadaisical about our approach, but they don't do it by threatening to take the money away, and I think that, again, is their strategy in philanthropy, that they find something they think makes a difference, then they'll stick with it. They'll keep your feet to the fire, to make sure that the excellence is there, but they'll stick with you.

And so I see the program going on, continuing to have an impact. I'm hoping, and Herb is very much hoping, that other institutions do see the value in this, and that other programs like it grow up around the country because people see what the leveraging really is, and that we could begin to find donors that increasingly see that. So, I'm confident about the future life of the program.

01-01:15:31
Meeker: Great. Do you have any final thoughts that you'd like to add?

01-01:15:36
Yamamoto: Only that, just amplifying on this notion that the Sandlers are really remarkable people, that two of them came out of this kind of modest New York start, took a flyer on this little savings and loan in Oakland, and grew it into this spectacular business that was able to sustain economic downturns and scandals and everything else. And so it seems like a puzzle of how they managed to do that, until you get to know them, and when you did, and you saw the way that they set their standards, the care that they took in making their decisions, always with this demand for excellence and impact, then you can understand why the business flourished, and their decision to be able to use the success of their business generated in terms of income and funding money, to do things that made a difference in society.

I think that really sets them apart from many. They don't kind of hang out in the philanthropy community. They're not flying around with circles that are supporting the San Francisco Ballet and the symphony. These are things that are wonderful and I support them, but their tendencies are known to say that "those are great and that's fine, I'm glad there are people to support those things, but we want to do things that have more of a social impact." And so those standards that push for excellence, their decisions for how they've lived their lives that have come, washed over from their business endeavors, their personal standards to business endeavors, to the philanthropy, is quite distinctive, and they just deserve an enormous amount of credit and respect for that.

01-01:17:43
Meeker: Thank you very much.

[End of Interview]