**Ann K:**  So you consent to be interviewed.

**Interviewee:**  Yes.

**Ann K:**  You consent to be audio recorded.

**Interviewee:**  That's right.

**Ann K:**  And you consent to have a completely deidentified transcript included in the public repository.

**Interviewee:**  After my review, yes.

**Ann K:**  After your review. Okay, great.

**Ken T:**  And at that point you can elect to decline to have it included as well.

**Interviewee:**  Sure, yeah.

**Ann K:**  Do you want to say you consent to being recorded?

**Ken T:**  I consent to being recorded as well.

**Ann K:**  I consent to be recorded, because I guess in California everybody has to say. We are recording.

**Ken T:**  Start out with some background information on your involvement in gene therapy and clinical trial-related research and your involvement.

**Interviewee:**  Right. So the gene therapy, gene editing work has been the most recent, and it follows from participating on multi-center clinical trials from the early 1990s. So the gene therapy work specifically is in disorders where I have expertise, [redacted] disorders like [redacted] disease and [redacted], and it's part of a broader strategy to make these therapies available to more patients where curative therapies are currently rather restrictive, so I've had a lot of experience with these disorders, caring for them by supportive care means and then bone marrow transplantation, which is the current gold standard, and now into novel therapies like gene therapy and genome editing of a person's own stem cells.

**Ken T:**  What percentage of your work is focused on genome editing, other genome therapies and gene therapies and then non-gene manipulations?

**Interviewee:**  Yeah, about a third of my time is in the new, about a third in the old, and about a third in administrative and other medical-related clinical activities.

**Ken T:**  To what extent have you been in contact with regulators about commercial application or clinical work?

**Interviewee:**  Yeah, so I've presented some of our work to the RAC, the Recombinant DNA Committee, for feedback, mostly having to do with informed consent-- that was past the time when they were actually reviewing the science carefully-- and to FDA CBER committees, groups evaluating gene therapy and also pre-IND meeting about our own genome editing, so I've had interactions at a couple different levels.

**Ken T:**  Are you saying that you also had interactions with CBER about other...

**Interviewee:**  Yes, yeah, for the gene addition gene therapy work I've presented and answered questions about a novel approach to FDA CBER.

**Ken T:**  How did that interaction emerge?

**Interviewee:**  Yeah, it was really an update about a clinical trial that the FDA requested, and the sponsor of the research asked me to attend the meeting with them as an expert.

**Ken T:**  So you were an invited expert. You were not directly involved with that clinical trial.

**Interviewee:**  I wasn't running the...

**Ken T:**  Can you say who...

**Interviewee:**  Yeah, it was [redacted].

**Ken T:**  And the FDA people you met with? Can you say what levels, just generally where they were from?

**Interviewee:**  I don't remember. Pharmacology.

**Ken T:**  So from divisions of CBER.

**Interviewee:**  Yeah.

**Ken T:**  Within your IND and pre-IND meetings you don't have any gene editing in the clinic yet. Is that correct?

**Interviewee:**  That's right, nothing in the clinic.

**Ken T:**  What's the current status of what you...

**Interviewee:**  So the gene editing project has had a pre-IND meeting, and we recently procured funding to complete the pre-clinical IND-enabling studies, and so the next step would be filing the IND when the pre-clinical work is completed.

**Ken T:**  I don't want to take up too much of your time.

**Interviewee:**  Okay. Then I'm also-- you know I'm [redacted] for CBER in the cell and gene therapy?

**Ken T:**  No. We're not aware of that.

**Interviewee:**  Yeah, so they asked me to be [redacted], but they've never pulled the panel together yet even though I was asked and certified like a year ago, but that's probably imminent in the fall.

**Ken T:**  What is that panel?

**Interviewee:**  I guess we provide guidance to that branch of CBER about whatever they're interested in getting expert opinion about. I suspect it'll be focused on endpoints, but I'm not really sure.

**Ken T:**  So that's the cell and gene therapy branch.

**Interviewee:**  Yeah.

**Ann K:**  What was the certification process like?

**Interviewee:**  Oh, for the federal government it's mostly a review of your potential conflicts of interest. Yeah, and it's significant. I mean, how anyone in the Trump administration came through that is a-- because it seems like it's a different standard for us. It's pretty stringent, yeah.

**Ken T:**  Do you know how you were nominated?

**Interviewee:**  I think just because I'm active in this area of research.

**Ken T:**  Do you have a sense of the expertise of other panelists?

**Interviewee:**  No. Yeah, I don't yet because we haven't met.

**Ken T:**  And you haven't met, so you don't know what the process would be.

**Interviewee:**  Yeah, exactly. I'm interested to find out. Yeah, could be self-serving, huh? <laughter>

**Ken T:**  It'd be quite interesting for the purposes of our research.

**Interviewee:**  Yeah, yeah.

**Ken T:**  Do you have a sense if this is a common or extraordinary...

**Interviewee:**  I think it's pretty common.

**Ken T:**  ...panel or to have a panel like this?

**Interviewee:**  Yeah, they get advisory panels really.

**Ken T:**  Are these different from the advisory panels reviewing a product for a license?

**Interviewee:**  Yeah. Oh yeah. It's broader, a more general application.

**Ken T:**  Does it have a charge in terms of focusing on genome therapy, genome editing?

**Interviewee:**  I think it will, but until we meet I don't really know.

**Ken T:**  Switching to CRISPR technologies, how do you view those? You have a broad historical perspective on innovative technologies treating diseases that have severe unmet medical need. How do you view CRISPR as a technology and then gene editing more generally for addressing these unmet medical needs?

**Interviewee:**  Well, I mean, it's an opportunity, and it has all of the properties one would associate with a transformative therapy if it could be executed at a large scale at a cost that's reasonable and if it's safe, so those are high hurdles, but it seems to satisfy at least in principle all those requirements.

**Ken T:**  You said it meets the criteria for a transformative therapy. What are those criteria?

**Interviewee:**  Well, it has to be a cure, and it has to be a reliable cure, and we know from our transplantation experience where you replace a person's diseased blood-producing cells with those from a healthy compatible donor that once you exceed a threshold quantity of those healthy donor cells in the blood circulation that that's a cure. Now, there are toxicities related to the treatment that you have to deal with, but as far as the underlying sickle-related complications, those can be eliminated. So now in lieu of finding a healthy compatible donor we can make those changes in a person's own stem cells, and so we would predict that, again, if you reached a threshold level of circulating blood cells that have a wild-type healthy genotype that that should be a cure. It follows from past experience, so it's just now a question of can we accomplish those things at levels that's sufficient. So it may happen gradually. You may reach a level that's enough for making things better but not a cure, and as you modify the techniques and improve them then eventually you should be able to get where you want to be.

**Ken T:**  Do you think if you're dealing with other diseases where there's not a preexisting cure or a standard that lets you know-- when we're thinking of a number of neurological diseases we don't know exactly what needs to be done. Does that then create a higher burden for development in using this technology?

**Interviewee:**  Yeah, well, yes, because you have to deliver the reagents to a progenitor population, so doing that in the brain or the spinal cord is challenging, because you can't extract them with the pack [ph?], and the blood system is pretty accessible. Something like hemophilia, where we know the proteins that you need to make for clotting blood in the bloodstream are made in the liver, then you can design delivery systems that target liver cells or cells that line the blood vessels. So by the origin of the diseases that will I think assign the complexity of delivering the treatment, and I'm just fortunate in the blood system to have access to the stem cells. If I were a neurologist it would be really daunting, I would think.

**Ken T:**  What about for setting standards for evaluations of efficacy? Because you say you have a standard that exists. We've created a certain percentage of...

**Interviewee:**  Right, yeah, I think the bone marrow transplant experience will be important guidance.

**Ken T:**  In other diseases what type of challenge does that present?

**Interviewee:**  Yeah, well, I think it depends on whether or not there's a curative therapy yet, but if there is then, yeah, that becomes the...

**Ken T:**  I was asking of diseases where there isn't a curative therapy.

**Interviewee:**  Yeah, well, then-- right. But usually you can define cure. If you're blind and can see again I'm going to think the endpoints at a clinical level should be pretty easy to define, I would think.

**Ken T:**  And then does the mechanism to achieve those endpoints become more of a challenge?

**Interviewee:**  Yes. Yeah, and also because some of the toxicities are new or perhaps even unknown, so some of that is going to be iterative I suspect, so it's a little frightening, because we can't predict every toxicity by the pre-clinical work, because there are limitations in the assays, so unfortunately a lot of this comes from taking it to humans and seeing how it goes, so that's why the clinical trial design is terribly important to ensure safety of the human subjects, because you want to stop right away if you find something that's really terrible.

**Ken T:**  Could you describe your experience with the FDA in this pre-IND process you're undergoing?

**Interviewee:**  Yeah, it's pretty interesting. So they've seen a number of gene therapies, so this is when you use a lentiviral vector or some other method of delivering the replacement gene into the stem cell, so they have a lot of experience with that approach, and they've gotten good at virology, but this isn't virology, but it's similar in that you're manipulating a stem cell. So they're pretty good about certain aspects, but they full admit that they're still learning about gene editing, and so it's more of a collaborative process. That's how I would describe. I don't view it as adversarial at all. That's been my experience, which is interesting, because you sort of view the FDA as the holder of the stop sign because something's unsafe, right? But because they're learning we tend to go back and forth about what the best IND-enabling tests might be.

**Ken T:**  What's your sense of the scientific foundation and technical expertise of the regulators with whom you're working when dealing with that?

**Interviewee:**  Yeah. It's a good question. Well, they don't have the same level of expertise that we have in the field for obvious reasons, so I suspect they're applying their regulatory tenets to the new therapy without necessarily knowing all the vagaries of how you change a gene in the stem cell and what could go wrong, so that's really been the approach. I can't say that we've had people who are on a review panel that are expert in nucleases or even sickle cell disease, but they do have a lot of expertise in manufacturing and controls and ways to ensure reproducibility and just some basic regulatory processes that you apply to any therapy, so that's kind of been my experience.

**Ann K:**  Would you say that they're pretty upfront about when they don't know something? My assumption is that they know they're on a learning curve and know that one of the ways to learn is to interact with people in the field and figure out what they should be attending to. How does that process go? Do they say "We don't know what we should be testing for. We don't know what endpoints"? Are they very upfront about saying "Tell us how we should be regulating you"?

**Interviewee:**  Yeah, they'll say, yeah, "Well, what endpoints do you propose to use?" So we explain the endpoints and the rationale for them, and they could say "Yes, that's acceptable" or "No, it isn't. You need to give us more, an additional list," so it isn't really like "You're missing this thing." We just need something like it, and they ask a lot of questions, and you can learn a lot from a question about what they know or don't know, but, again, mostly the questions and the design is around how do we define efficacy and how do we define safety and how do we define reproducibility and how close is this safety testing system to what you're going to do in a human being, so it's those principles that...

**Ann K:**  Is that moving from an animal...

**Interviewee:**  It is, or if you lack an animal model, like we do, because you can't really-- for example, if you optimize your conditions to change a mouse stem cell that might or might not work in a human stem cell, so you could do it in a mouse, but it's not what you're going to do in a human, so you got to do it in human cells, so it's a completely different-- so then you got to put the human cells in a mouse we call xenografting, but that's not exactly a mouse model of sickle cell disease. It's just what human cells do in that particular environment that allows them to grow long enough so you can see what a stem cell makes over time. So it's a lot of back-and-forth about-- they'll ask "Well, why didn't you use-- there are mouse models of sickle cell disease," and we have to explain to them "Well, this is why that wouldn't really be helpful to us," and then they listen to your answer and they go "Hmm. That makes sense. Okay, that's acceptable." So it's really back and forth, asking questions, and they assess whether or not what we propose meets the standard, and if it doesn't then we have to do it a different way. And most of it's our proposing responses to their questions, then they're saying "No, you got to do it this way." Only a few things that they say "No, you got to do it this way."

**Ken T:**  Do you find when they're insistent on doing it in a way that you feel is not valid that it still has to be done?

**Interviewee:**  Oh yeah. <laughs> I mean, you could not do it and then argue in your IND that "See, I didn't need this."

**Ken T:**  Do you find that you can't...

**Interviewee:**  Yeah, it's strategy.

**Ken T:**  ...generally talk them out of it?

**Interviewee:**  Unless you have a very good reason, yeah, it's easier just to do it.

**Ken T:**  Say I was in that regulatory position and said "I need you to do this because this is how I've always seen it done." I don't really understand, and then you come back and give me all the good reasons, but I don't understand the...

**Interviewee:**  Yeah, I'll give you an example. So for gene editing I'm sure you've learned that one of the untoward things that could happen is you can modify a gene that you didn't intend to modify, and it could be a cancer-causing gene that you somehow activate inadvertently. So the way you do a toxicology study to see if that could ever happen in a real lot of human cells that you've manufactured exactly like you're going to do in the clinical trial-- you have to to the best of your ability see if anything like that happened. So this is a blood system, and blood cancers are called leukemia, and so we would argue that really all you got to look for is did you form a leukemia or something like a pre-leukemia in the blood cells that you've modified, but the FDA standard is "Well, you look at every organ in the mouse that you've injected those cells," so you got to dice and slice kidneys, pancreas, intestines even though we know based on our studies that that's extraordinarily unlikely to happen, that you should probably just look at the bone marrow or the blood cells, but that's what they said, so that's what we're doing. It's the standard. That's an example.

**Ann K:**  So you know once you slice and dice you're just not going to find any of the cells that they say you have to look for.

**Interviewee:**  Yeah, well, or you might find a tumor, but it's probably from a mouse cell, so that doesn't have any bearing on...

**Ken T:**  Do you see ways that the people you're working with are keeping up with the technology?

**Interviewee:**  Yeah, I think they are. In the last year, for example, they convened a two-day workshop in collaboration with the American Society of Hematology that's also a partner in developing these new techniques to better define endpoints in [redacted] for any of a number of therapies, not just cell therapies, so they reach out, and they can get expert advice, and a couple publications are going to come out of it.

**Ken T:**  You said they've developed substantial knowledge in gene therapy. What about for genome editing?

**Interviewee:**  Well, yeah, it's happening, but it's going to take some time.

**Ken T:**  How long have you been in dialog with your gene editing therapy...

**Interviewee:**  Oh, not very long. Four years.

**Ken T:**  Some might say that's long.

**Interviewee:**  <laughs> For a new therapy in humans? No.

**Ken T:**  No, I meant with the FDA.

**Interviewee:**  Oh yeah. So, yeah, we've had two meetings, what used to be called a pre-pre-IND and then a pre-IND where we've had dialog and guidance, and those were probably, oh, three years apart.

**Ann K:**  Do you see people from the FDA attending the conferences? If you're going to present at a conference are there FDA folks at those same conferences?

**Interviewee:**  Yeah.

**Ann K:**  Are they presenting work, or are they just there listening?

**Interviewee:**  Sometimes they will present a talk. They're invited to present a talk. I've invited FDA folks to give a talk at meetings that we've put together, yeah.

**Ann K:**  So specifically just on the regulatory process or...?

**Interviewee:**  Oh. Sometimes, yeah, but also what are they doing about these unlicensed, unregulated stem cell clinics, for example. How are you enforcing the rules that the rest of us abide by? So you sometimes ask them, or "You got any changes in the process?" If there's new guidance or draft guidance about how gene therapy or cell therapy will be evaluated you might ask them to be available to give a talk and then be available for questions.

**Ken T:**  Is there a particular level at the agency of people who show up to make those presentations?

**Interviewee:**  They tend to be, yeah, high-level or experienced.

**Ken T:**  Do you see people on the line or scientists at conferences?

**Interviewee:**  Yeah, I honestly don't know the answer, yeah. I think occasionally, but I don't know them as well as like, for example, the folks that manage our grants at the NIH. The project officers are often at the meetings, so they're just more visible because you have more contact with them.

**Ken T:**  So they may or may not be there. Do you think it would be useful for them to be attending scientific conferences?

**Interviewee:**  Yeah, I would think so. For sure.

**Ken T:**  In what way would they benefit as opposed to, for example, sitting in their offices reading journal articles?

**Interviewee:**  Well, it's just a more efficient way to gain knowledge. That's why we all go to meetings. And it's more current than what you read, so you get a better sense of trends. You also become more familiar with leaders in the field I would think when you're listening to them.

**Ken T:**  So it sounds like there's a networking, a currency and then you get more information more quickly than digesting articles. Over the history that you've been working with the FDA, are there ways in which you think the process could be made more efficient as you're bringing new technologies or new therapies online?

**Interviewee:**  Yeah, I don't know. I'm always careful about this, because safety is important, and I know everyone wants things to go faster, but there's a risk there, and in a vulnerable population like this one I worry about going too fast to be honest, so, yes, I mean, but some of the advances follow advances in science, so if you can replace, for example, a toxicology in a mouse that takes six months or longer to complete by doing it by some flow cytometric technique in a couple of weeks that means you can go faster, but I don't know if there's something specific to the FDA that would make that go faster. I think also these new designations, the regenerative medicine designation, the...

**Ken T:**  Breakthrough.

**Interviewee:**  ...breakthrough designation-- I think those have been really good, so the really exciting new therapies can get quicker, more focused attention.

**Ken T:**  Turning to the example you used of moving from a mouse model to, say, flow cytometry, say within the scientific community you were to become convinced this is equal or superior from a knowledge basis and obviously superior from a cost and time basis. How do you think the FDA would come to understand that that's really the case? This is validating the new test.

**Interviewee:**  Well, it's the same old potency, purity, sterility benchmarks that get applied. So right now we do all these steps, the ones where we take the cells out of the body, do the gene editing and then freeze the cells. That's all done in a GMP open manner, and it's expensive and rigorous and time-consuming, so maybe the next advance will be "Well, we'll just do it in a closed system where the cells never leave the sterile tubing. We do all the processing as they're coming out of the body of the donor, and then from there we gather aliquots that we need to test those things, and then we just freeze them right away." So that would be enormously time-saving and money-saving, so you just have to show along those steps that you're accomplishing the same thing that you did when you did them in an open room where everyone's gowned-up with sterile gear, etcetera, etcetera. So I think as things improve you just apply the old criteria to the new process.

**Ken T:**  I hear you saying that you would provide validating evidence.

**Interviewee:**  Yeah, present it to the agency.

**Ken T:**  Do you feel they would find that...

**Interviewee:**  I think so. Yeah.

**Ann K:**  Have you ever seen them slow something down where you didn't think they were doing so on valid grounds?

**Interviewee:**  Yeah, I mean, you hear about these things. Personally I haven't, no, but, yeah, you hear about kind of nightmares where things languish, and time is really-- can be very damaging to new products. Yeah.

**Ann K:**  How about the other, when they've slowed something down where you thought it was really good that they did? Are there those stories too?

**Interviewee:** Yeah.

**Ann K:** And have you had that experience where you’ve seen that happen? Or is it just sort of people in the field know about this well.

**Interviewee:** Well, yes. Or they've removed-- they've not approved a drug for adults, let's say, because it didn't show the efficacy that they had anticipated in adults with a type of cancer. But in children with the same type of cancer, maybe the results are different or would be different but it basically blocks the development of that drug in a different population because then the sponsor isn't going to pursue it if it's not-- if the market isn't right. So that's really frustrating because there are populations that might benefit from a thing, but because it doesn't apply to a larger population of sponsor may just stop this development.

**Ann K:** That’s interesting.

**Interviewee:** Yeah. That's happened, repeatedly,

**Q:** You’re saying because it doesn't apply from a regulatory, the sponsor believes it does apply from the…

**Interviewee:** The sponsor might agree completely like this didn't work in this population. But, you know, there are other populations that might benefit from it right but development sort of halts if it doesn't work in the target group. I don't really blame that on the FDA so much, more the whole industry.

**Q:** Are their skills that you think FDA regulators could-- or first off, do you think that there's skills or knowledge that they need to develop to move genome editing, in particular, along through the regulatory pathway in an expeditious way? For example, you said that there's a knowledge base about gene therapies, AV [ph?] and other viral vector therapies. Presumably, 20 years ago they didn't have that knowledge. And now you say, oh they seem to have this knowledge, so are there examples you could give us of the type of knowledge that they have about conventional gene therapies that they seem to have acquired over time? And are there knowledge bases for genome editing, CRISPR or others, that they lack which would be helpful so that let's say ten years from now in retrospect they’ll say, “Well, they didn't have that in 2019, but now they're moving things along in 2029 because they’ve acquired this knowledge”.

**Interviewee:** Yeah. Right. So let's see. In gene therapy, they learned a lot about the multiplicity of infection, the vector copy numbers that are achieved in the target cell population, all of which had something to do with safety and efficacy. And so they got pretty good at asking those questions. What was your MOI? What was the vector copy number? How many integration sites did you see? Do you have a plan for tracking integration site populations over time? Et cetera et cetera. So they're now developing that same expertise for gene editing, like how many alpha targets did you-- how did you document them? What techniques do you use for unbiased searches for all targets? So they're developing that language so that becomes part of the reports that you compile, how you did all those things and what kind of cells, what cells are you using? Are you just using a cell line? Or do you have something that's close to-- in the cell lines you use is it close to blood stem cell? Or is it more like a T-cell? And can you do that same technique primary human cells that aren't cell lines, that aren't immortalized? And if you did, what did you find? So they're beginning to you know-- but they also-- this is what's interesting that the interaction. If you explain to them that yes, we can do that technique of an unbiased search for an off target in a cell line, but we haven't been able to do it in a primary cell line. Yeah. And they say, okay, we'll do it in the closest thing to a blood stem cell that you can and include that in your report and then we'll evaluate it. So I think that's where it's going. And as we get better at looking for those things having to do with safety in the primary cell lines, then you know, I'm sure the agency will adopt those as their standards.

**Ann K:** And sometimes it sounds like they’re just sort of following what the…

**Interviewee:** What technology can support. Yeah.

**Ann K:** Can I just ask a sort of basic question? I probably should know this about CRISPR. I mean how soon after people discovered CRISPR-Cas9 was off target effects-- like as soon as-- was that an obvious thing as soon as CRISPR-Cas9 was developed that if you did this, if you used this medically that off-target effects were an issue?

**Interviewee:** Yeah, because, I mean, you're replacing the native guide RNA or with one that's been modified.

**Ann K:** So that's part of the conversation just from the get-go.

**Interviewee:** Yeah.

**Ann K:** Okay. So it sounds like FDA knew that that's what they had to be worried about just because if they were at the first meetings talking about this, that's what…

**Interviewee:** Yeah. But also because, you know, CRISPR-Cas9 is the current you know, what we think might be the optimal gene editing but it began with these things called zinc finger nucleases and then talons. And there are zinc finger nuclease trials are already ongoing. They've already learned from that experience, oh these are the questions we need to ask about CRISPR. And then, you know, there'll be do things. So as you get better with targeting-- by targeting I mean bringing the gene editing apparatus reagents directly into the cell that you want to modify. So you can imagine that you could put an arrow on the Cas9 itself with a bull's-eye on it. But any time you modify the Cas9 you modify how it works both good and bad. So all that stuff has to be repeated as you optimize the delivery system I would think.

**Q:** Our project focused very much on capacity and the capacity of the agency. So in hearing you talk there are two ways of thinking about-- I think of two ways of thinking about the capacity. One is something that's inherent to the agency itself. And the other that they acquire through this process that you're describing where you actually present-- they ask you a question, you present the data. They don't, in the sense, have the primary knowledge to do that work or to-- you’re very much guiding the conversation, I guess.

**Interviewee:** Yes, that's right.

**Q:** And could you give us a sense of balance and adequacy that a portion of the capacity that they’ve built up through their prior work either in gene therapy, but in this in the broader range, like I say, toxicology, pharmacokinetics and so forth versus what they actually have to rely on for you to provide them with knowledge?

**Interviewee:** Yeah. I worry about that. I think it's challenging for them to maintain a well-trained workforce because I think there are a lot of pressures to move into more lucrative areas with the same skills. So I don't know how-- we all face the same issue. It's, you know, in lifestyle and all that business, you know, I suspect they work very hard and they have lots and lots to do. And so it could be lifestyle issues too having to-- moving into a different field of CRO work or something like that. So, yeah, I don't know what the answer is to that. That’s a challenge, I would think?

**Q:** And do you see that are there situations where having drawn on their prior knowledge base and gene therapy that they overlook how a new technology is potentially both different and superior? I think, for example, I think we shared some of the comments that we wrote on the draft guidances. And that pointing out that the looking at gene editing or genome editing as a distinct subset of conventional gene therapy but it’s novel and therefore less known and therefore more risky overlooks real criteria and differences; for example, in the ex vivo editing that you're doing as opposed to in vivo editing. Is there-- have you had a sense of while you're in a sense being bound by the past as opposed to drawing on knowledge that's useful from the past? Not you, but the FDA.

**Interviewee:** Well, that's true of any new therapy. There's this initial burst of brilliance and excitement and then reality sets in as you gain more experience with it. So that's just the-- I think that's just the natural history of…

**Q:** I'm thinking then in terms of the regulators’, questions they ask you, requirements they impose and saying, “We always we always do it this way and but this is a different technology.” It's not…

**Interviewee:** Yeah. I mean there's definitely some of that and some of it is just driven by they have to show they've done due diligence. I mean they’re at risk, too What if something's overlooked and then somebody grows a unicorn the first time you try it. You know? They’re at risk, too, so they have to show they’ve done what they need to do to the best of their abilities to ensure safety, potency, purity and all of that. So I guess my experience has been a little bit different. I haven't done this for decades and decades interacting with the FDA, anyway. But I have found them to be pretty flexible actually in this learning phase of the new therapy. I think we've benefited from that. I think once they have more experience with it, they'll be probably a lot more rigid about what it is they will expect of you.

**Ann K:** Do you have any sense of what this is like for researchers who are trying to do the same kind of thing in Europe or with European regulators? And sort of just thinking about whether or not the FDA has a reputation of being…

**Interviewee:** Yeah. I don't have as much experience. They are quite different. When the FDA comes and does an audit of a study they seem really focused on documentation. And I think the European people are more focused on process and how you ensure like the identity of the product through its journey to the patient. The FDA seems to be more focused on what did you actually put in the database and does it match on what we have on paper? You know? Did you do what you said you did? If not, then we can't really trust your data and maybe that's a problem. But that's just based on pretty limited experience so far.

**Q:** You've sort of worked in the same disease area but using different not may be profoundly different but different technologies of cell therapy…

**Interviewee:** Or conventional. Yeah.

**Q:** …,yeah, and so forth. And one a therapy that had decades prior development to one way…

**Interviewee:** That’s right.

**Q:** When you're dealing with the regulators, do you find that because they have parts that’s not on a disease basis but technology basis, is that correct?

**Interviewee:** Yeah. Right.

**Q:** And do you find that there's a time-- that there's knowledge sharing so that they must have a lot of expertise on bone marrow transplants in the agency and including how that works for addressing the thelsian [ph?] news and the sickle cell disease. Do you find that that's important for the regulators you're dealing with in the gene therapy/gene editing area to have that knowledge? Or the disease specific knowledge is not important?

**Interviewee:** So I ran into this when-- umbilical cord blood is the blood that’s left over after birth of baby. It has stem cells that you can use perfectly well in a bone marrow transplant like setting. And so there are groups businesses that collect cord blood in \_\_\_\_\_\_\_\_ centers and freeze it and store it for use. So there was a period of time, a decade ago, where the FDA first started licensing granting BLAs to cord blood collection facilities, manufacturing facilities. So the way they approached it was, okay, we have to approve cord blood licensing as it pertains to these diseases. So we're only going to approve cord blood for diseases where we think there's proof. So their standard for a rare disorder, some of these are really rare disorders, that we know people die of at a really early age, their benchmark was you do a phase three randomized controlled clinical trial and show that bone marrow transplant is superior to the best available therapy. And they couldn't find very many examples of that in cord blood transplantation let alone bone marrow transplantation and that's because we know that you'll die of the condition. So it wouldn't be ethical to withhold a curative therapy just to show that the other thing that they're going to die of doesn't work. Okay? So we actually as a-- this was another one of these workshops where we were advisors and simply had to explain to them, you know, [redacted] it's the standard to do a bone marrow transplant when you begin to show signs of the disease. You know? Just give them the support of care forever until they die. And so that's kind of, you know-- that's why it's really important to have bioassays and clear endpoints defined for them that they can use other than survival in a randomized controlled clinical trial.

**Ann K:** And did they yield on that?

**Interviewee:** Yes. Not only did they yield gave BLAs broadly applicable to all these diseases because of advice we gave, I think.

**Ann K:** And that the we-- and that was you said there was an advisory panel. Did they convene that or was this an industry or a…

**Interviewee:** Yes. They convened it. At the request, though, I think primarily of patients. Patients had an incredible role. And there was a period of time for public comment where they brought in all these families that said, “Cord blood saved my life. Please approve it. Otherwise, I wouldn't be here today.” You know this real heart string kind of-- so, I mean, so they definitely went ahead.

**Q:** Did you have a couple minutes? Because I did want to ask you some questions about the patient community here because this is-- you are operating in an area where there’s a very robust patient and knowledgeable patient and involved patient advocacy community. Do you have any observations on how that-- you just gave us one in a sense and how that translates into the FDA. And that, I gather, the information transmission there was through notice and comment and some other public proceedings. Are there ways in which you see the patient advocacy community complementing the development of capacity when the FDA, for example, getting resources their way funding their way? Or having the FDA internally after they've been pressured, you gave an example, they adjusted their view. But we're thinking, again, looking at the capacity levels, are there ways in which you think the interactions or the activities of interactions where the activities of the patient develop elements of the capacity or shifting resources within the FDA?

**Interviewee:** Yeah. Well, I think patient advocacy in partnership with professional societies and political pressure have together catalyzed acceleration of therapies. And that's been shown in HIV, hemophilia, cystic fibrosis and now, finally, I think, sickle cell disease. But it's just taking a long time for obvious reasons for sickle cell disease. So I think it's a multiprong of which probably patient advocacy and political activism plays the most important role.

**Q:** And what do you think happens within the FDA? Or What observations have you seen happen within the FDA in response or in cooperation with those patient advocacy efforts?

**Interviewee:** Well, then then there's policy changes and shifts in emphasis that follow guidance, leadership guidance, I would think. But it's-- yeah, I think it shifts policy. Created an office of rare disease, the NIH, that worked with the FDA to accelerate new therapies for rare diseases. Give pharmaceutical companies certain advantages so that they're rewarded for developing drugs for rare diseases. You know? I think it happens at a couple different policy levels to realize the change. But at the center, I think, is advocacy and political activism that represents those affected by the disorders.

**Q:** And you see shifts within the resources at the FDA or more people at conferences when these were happening?

**Interviewee:** More FDA people classes?

**Q:** Yes.

**Interviewee:** Again, I don't really-- I can't say that I have tracked carefully that aspect of it. But I have seen-- well, the proof is that you see a lot more new therapies being developed, a lot more clinical trials being organized and carried out.

**Q:** Well, I think within the FDA are they then-- they'll seem like there have been more resources at the FDA.

**Interviewee:** Well, it must be because they've like quadrupled the number of studies they’ve got to review. So, yeah, I would think there are or they shifted existing resources. And I don't really know how they're managing the portfolio. And it is a larger portfolio for sure.

**Q:** And do you see any-- within the gene editing area with the facility that CRISPR provides that they'll be able to keep up with a larger portfolio if there are a lot of trials coming in, or pre-INDs coming in?

**Interviewee:** I think so. I don't think there are that many. It’s not that easy to do. I don't think it'd be more than half a dozen.

**Q:** So you don’t see…

**Interviewee:** I don't see them being overwhelmed. Well, but you mean for CRISPR across the spectrum in view of disease. Oh, yeah, it could be overwhelming, for sure. So, yeah, that's a good point. I mean, how are they going to prioritize which ones to give attention to?

**Q:** So when you said you don't see-- you only see six of it you’re saying that was within the blood disease area that you were talking about. If you look…

**Interviewee:** Yeah, you're right. It could be much, much larger.

**Q:** …across the board at all diseases it could be larger.

**Interviewee:** I've never really thought about it. It’s kind of a public policy strategy issue and how many of these things can the marketplace support, too? I don't know. I’d like to believe it could support lots of different things but I don't know.

**Q:** Are there other…

**Ann K:** Well, I wonder it is there anything that you thought we would ask you about that we haven't asked?

**Interviewee:** No. I guess I've from the type of questions you asked me you're worried about the FDA not being accommodating for this kind of therapy. And so I guess my experience has been a little different so far. Maybe is it because we're the

[redacted] to go through, one of the first ones to go through. But now I will be more interested to see how it evolves over the next five years.

**Ann K:** I think we're certainly interested just sort of what it's like for somebody who's kind of on the research and clinical trial side. Is the interaction with the FDA sort of a frustrating burdensome thing? Or does it feel like it's what you would expect, it's sort of what's necessary. So I think we're kind of trying to get…

**Interviewee:** You know**,** you're absolutely right. I have just completely lowered my expectations based on you hear because this IND just compiling it, it’s a massive undertaking. And, you know, without adequate funding I mean, this is [redacted] million grant award for only [redacted] months. If you don't have access to that kind of funding you cannot develop these therapies and these are highly competitive. So there's a chokehold on funding for sure. And I just have been fortunate to be at the right time in the right place. But five years from now when there's a panoply of competing similar-- a lot of those aren't going to get through. There just isn’t enough money.

**Q:** There's not enough money for them to develop. And it sounded like you were saying that they're developing a lot of data in response to questions from the FDA.

**Interviewee:** Yeah.

**Q:** So that I mean the FDA-- it may or may not be the case that the FDA has the capacity to review them.

**Interviewee:** Exactly. It might be more there's no funding to get the work done. Yeah.

**Q:** Which is to provide the FDA with the data as opposed to originating the FDA doing the research itself and originating it. Do you think you were asked any questions or made to undertake any studies that you said, “Wow, we didn't think about that but that's really good that you asked that question and then we did this study.” As opposed to, “We've already thought about that. Here's the information.”

**Interviewee:** Yeah. I haven’t had many of the former…

**Q:** Experiences where the FDA…

**Interviewee:** I think our team is pretty good. I mean we do have one professor on our team who has been through it like half a dozen times. There just aren't that many surprises when you have experience, I guess.

**Q:** Is it possible to get-- well, our final question was there other people who we should talk to and I'm wondering one of your-- whoever the…

**Interviewee:** Yeah. This is a gene therapy guy [redacted] at [redacted]. He's had the most experience because he's brought several vectors through approval and then clinical trial. But, yeah, there are other people in the gene therapy world that have quite a bit of experience.

**Q:** Are there names you could suggest or people we could…

**Interviewee:** Yeah. There’s a guy named [redacted], in [redacted].

**Q:** We have that in there, right? Okay.

**Interviewee:** He’s a good one. He's done a lot of work gene therapy and now gene editing. [redacted] but he's younger so he's not had as much experience but he's going through it now at [redacted] in the same field.

**Q**: Yeah. What about [redacted]?

**Interviewee:** Those are the names that come up that I know of.

**Q:** And actually just for the record, it might be helpful, could you give like, you know, just like one minute on here's the basic technology on ex vivo stem cell modification of this particular gene of the therapy that you're doing.

**Interviewee:** Oh sure. Yeah. Well, from start to finish in a clinical trial it involves identifying candidates who might be interested in the therapy, meeting with them. There's the informed consent process. And then once we have informed consent, we have to confirm that they're eligible, they’re in well enough medical condition to safely get through the fairly rigorous treatment. And then we collect the stem cells, which is usually accomplished in one to two to three separate procedures separated by a month or more in time, where we extract the stem cells from the circulation. Those are then shipped to a manufacturing facility where they're modified either by gene editing or gene addition, electro viral transduction electroporation with the CRISPR-Cas9 reagents. And then that drug product that we call it, or final cell product is then tested for specific release criteria to prove potency and sterility. So there's a series of tests that take about a month to complete to satisfy all those benchmarks. Then assuming that occurs you bring the patient back to the hospital. They're administered a chemotherapy drug. It completely wipes out there both bone marrow and immune systems for a short period of time and then the final cell product is thawed at the bedside and infused like a transfusion. So they stay in the hospital for four to six weeks recovering from the high dose chemotherapy until the modified cells recovery populate their immune system and blood system. And then there's a series of follow-up visits and testing to assess how well it's working.

**Q:** And the genome modification is it knocked out or is it-- you use a HDR or…

**Interviewee:** This is an HDR to replace the [redacted] allele with the regular wild type sequence.

**Q:** Right. I just wanted to get that <inaudible 00:28:50>.

**Interviewee:** Sorry.

**Q:** No, no, no problem. I just wanted just so we’re-- you know, it's really in different…

**Interviewee:** Yeah. The gene therapy is you just willy-nilly add a healthy copy of the gene wherever it happens to land in the genome. And, typically, you'll see thousands of different integration sites, which is a little worrisome in a stem cell population that you will be using for the rest of your life to make blood cells and that at any division could be prone to have a leukemogenic alteration. And if any of these integrations promotes that sort of thing no matter how rare because there's billions and billions of these cells that repop-- that have to be recycled that the chance of that happening is probably not insignificant, even though, it's not been seen so far. And the advantage of the CRISPR, of course, is that you're theoretically making a single modification exactly where you need to. And that there are thousands of thousands of different off-target integration events occurring. So that’s why we’re enthusiastic about it.

<group laughter>

**Ann K:** It’s like a step up.

**Interviewee:** It does.

**Q**: Well, thank you very much.

**Ann K:** Thank you so much.

**Q:** Oh, yeah. My pleasure.

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