VERBATIM PROCEEDINGS

CONNECTICUT STEM CELL RESEARCH ADVISORY COMMITTEE

SPECIAL MEETING

JUNE 10, 2013

8:28 A.M.

SHERATON HARTFORD SOUTH
100 CAPITAL BOULEVARD
ROCKY HILL, CT 06067

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. . .Verbatim proceedings of the Connecticut Stem Cell Research Advisory Committee, Special Meeting, held at the Sheraton Hartford South, 100 Capital Boulevard, Rocky Hill, Connecticut, on June 10, 2013 at 8:28 a.m. . . .

MS. MARIANNE HORN: Good morning, and welcome to today's meeting of the Connecticut Stem Cell Research Advisory Committee. I'm Marianne Horn, Department of Public Health, and to my right is Dr. Mullen, who is the Chair of the Advisory Committee and will be Chairing today.

So, today, the panel is going to be making funding decisions on applications for up to 9.8 million dollars in grants and aid from the State Stem Cell Research Fund.

Please be aware that funding decisions are contingent upon the receipt of funds from the State Bond Commission.

I have a few housekeeping items and ground rules for the remainder of the meeting. As you saw on your way in, the washrooms are off to your left of the

door. Just feel free to get up during the meeting and take a break if you need it.

Regarding discussion and voting, please remember that only Committee members, who are eligible to vote on a grant, may participate in the discussion of a grant.

If you are not eligible to vote on a grant, due to a conflict of interest, please do not participate in the discussion.

This is a public meeting, and Committee members should restrict their comments during the reviews to the review criteria established by the Committee and to the materials submitted in the application.

Please do not engage in any discussion with any members of the public here today about any application pending before the Committee.

While no specific time frames have been set for the discussions this year, the agenda has been drafted to complete the core and group awards discussions before the 10:00 a.m. break, the established awards by the 12:00 noon lunch break, the seed awards by the afternoon break at 2:15, and final discussion and decisions on all of the awards will take place between 2:25 and the end of the meeting.

Keep in mind that there are 53 proposals to be reviewed today. CI has two timers that they will have to keep the reviews on track, so Cheryl has two timers and will just give a signal. Are they two-minute and four-minute?

MS. CHERYL ALLEVO: According to the notes that I have from Joe, core would be two minutes to intro, three minutes to discuss. For group, three minutes, the intro, seven minutes to discuss. For disease, it would be four and 10, established, two and 4.5, and, seed, 1.5 and two to keep everyone on track as much as possible.

MS. HORN: Okay, so, she's going to be giving you a high sign. That's really just guidance, as we looked at the limited amount of time we had, and those are ballpark figures, so you'll know when you're running out of time.

The checklist in front of you contains the criteria the Committee has established for its review today. It also contains specific details from this year's RFP of the award categories.

The first categories for consideration are those of the core facility awards and the two types of group project awards, group project awards and disease-directed collaboration group project awards.

Applications in the group and core awards categories, regardless of their peer review score, and the disease-directed collaboration group project award applications with the best five peer review scores will be described by a team of Committee members assigned to each to review the grant.

The description will be followed by a Committee discussion, after which the Committee will be asked if there are any objections to placing the grant application in a particular category, and, again, yes, no, or maybe, as determined by group consensus by Committee members, who are eligible to vote on the grant.

If you have an objection, are eligible to vote on the grant and wish to see an application placed in a category, other than that of the consensus of the eligible group, please make your objections known immediately.

That objection automatically places the application under the maybe category, so that this grant may be considered during the second phase of the project.

After all the core and both types of group project awards have been considered, the maybe and yes grants from these categories will, again, be discussed, and the no grants are eliminated, so we’re trying to

fine-tune each one of those categories as much as we can within the allocated time.

The remaining categories will be considered similarly, as follows. Seed grant award, proposals with a peer review score below 30, and established investigator proposals with a peer review score of 30 or below.

Full funding considerations will be held until the end of the consideration of all grant categories. Roll call votes will be conducted only for final decisions regarding grant funding. That comes in the afternoon, when we do the final voting on all of the grants.

As in past years, the Committee will establish a reserve list, in case a funded grant fails. There may be a need for this Committee to adjourn to Executive Session to consider a grant proposal with proprietary information contained in the proposal that's pertinent to our decision-making. During that time, the audience will be asked to leave the room.

We have two 10-minute breaks and a 30-minute lunch, so we're on a pretty tight schedule. We'll keep everybody rolling today.

Lunch will be provided to all Committee

members and designated support staff in a separate room at approximately 12:00 noon, so we appreciate your adherence to these time frames.

One note with regard to microphones. There are microphones around the table. Apparently, they pick up sound very well, but make sure that the court reporter is picking up who is speaking.

Again, thank you for your commitment to the Connecticut Stem Cell program and for all your hard work today and during the past year that enables this program to thrive. We really, really appreciate the commitment and the time that you take, particularly today, to review all of these grants and then sit here and help us allocate the money.

To the audience, thank you for being here today. As you've heard, there's a great deal of work to be completed by our Committee members. We thank you in advance for not addressing questions or comments about grants under consideration to Committee members on break, during lunch, or after the meeting.

There is a period of public comment that will take place at the end of the meeting, after all grant funding decisions have been made. We ask that you refrain from commenting until that time.

And I would ask everybody to please silence all electronic devices and whether there are any questions before we begin.

Let's go around and do introductions, because I realize we've got some new faces and people, who only get together once a year, so we could start with you, Sandra.

MS. SANDRA ENGLE: Hi. I'm Sandy Engle. I work at Pfizer.

DR. RON HART: Ron Hart from Rutgers University.

DR. ANN KIESSLING: I'm Ann Kiessling. I direct the Bedford Research Foundation.

DR. DAVID GOLDHAMER: David Goldhamer from the University of Connecticut.

DR. DIANE KRAUSE: Diane Krause from Yale.

DR. TREENA ARINZEH: Treena Arinzeh from New Jersey Institute of Technology.

DR. JAMES HUGHES: Jim Hughes of Trinity College.

MS. CLAIRE LEONARDI: Claire Leonardi from Connecticut Innovations.

CHAIRPERSON JEWEL MULLEN: Jewel Mullen, Connecticut Department of Public Health.

DR. PAUL PESCATELLO: Paul Pescatello, CURE.

DR. GERALD FISHBONE: Gerry Fishbone, nothing. (Laughter)

DR. MYRON GENEL: I'm Mike Genel, Yale School of Medicine.

DR. MILT WALLACK: Milt Wallack.

DR. RICHARD DEES: Richard Dees, University of Rochester.

MS. ALLEVO: Cheryl Allevo, Connecticut Innovations.

MS. TERRI CLARK: Terri Clark, Connecticut Academy.

MR. RICHARD STRAUSS: Rick Strauss, Connecticut Academy.

MS. HORN: Okay, could you pick up all of the names?

COURT REPORTER: Yes.

MS. HORN: Okay, very good. Okay, then, I think, at this point, we'll turn it over to CI, and CASE is assisting with the technology here today.

MR. STRAUSS: Okay, so, you're on to the group?

MS. HORN: We can do core, if you want.

MR. STRAUSS: I mean, I'm sorry, core. Sorry. Good start. So the first proposal is Yale, 01 core, and we have Paul and Milt.

MS. ALLEVO: So two minutes to present, three minutes to discuss.

DR. WALLACK: So I found the Yale core application to be well-organized. It seems as though it's a very, very well-run core, essential for the support of the stem cell program at Yale, as well as for the programs at UConn and at Wesleyan.

The core provides technical assistance, training and teaching services. I think it's of interest to note that, last year, the core was involved in the leveraging of State funds, which was approximately five to six million dollars, to attract an additional 41 million dollars, that's in the application on page 61, and the core was also -- has been over the years responsible for the publishing of over 600 articles that you can find on page 57.

All-in-all, I found the application, as I said, put together very, very well, and I strongly recommend funding of this core.

DR. PESCATELLO: I would agree with those comments, and I thought, too, the application, in terms

of description and collaboration with other research institutions, other researchers, those were exactly what we're looking for. The connection to future funding and outside (coughing) so I strongly support it, as well.

MS. HORN: Do we have a motion?

DR. WALLACK: Move to support the funding of this core.

MS. HORN: Second?

DR. GENEL: Second. I'll second.

MS. HORN: Further discussion?

DR. KIESSLING: I have a question. Are these on? We talked about cores numerous times, and I thought last year we decided that we were going to fund new areas of cores, not their underlying support, so what new area will this core be used for? Is there anything new?

DR. WALLACK: Ann, I know that we've discussed that. You and I have both discussed that in the past. I'm not sure that we absolutely decided that it would have to be new areas.

I do recall that at a meeting I think two years ago, we discussed that this takeoff of the idea of supporting the cores, the essential services that we provide in allowing all of the other aspects of the stem

cell program to go forward.

DR. KIESSLING: So this is just support for the same essential services? They're not adding any new technology?

DR. WALLACK: The Yale core that we just discussed, that seems to be accurate.

MS. ENGLE: Can I ask one more question, as well? Part of the discussion over the past has been leading the cores to self-sufficiency, so they were funded at a high level in previous years. This is the lower level.

In my take on the grant, I didn't see anything that suggested that they had a plan forward for further reducing --

DR. WALLACK: Sandra, can you -- I didn't hear the end of the question.

MS. ENGLE: So I didn't see in their proposal a plan for, you know, how they're going to deal for becoming more self-sufficient. Was that a requirement of the grant? Would we have liked to have seen that in there?

DR. WALLACK: So, as an extension of the answer to Ann's question, at that discussion approximately two years ago, I think that you're accurate

in what you asked, and that is that we ask both institutions to look into how they could otherwise fund their cores, and I think that Paul touched on it to some extent, and there seems to be some addition of philanthropic funding. That's the direction, I think, that some of us would like to eventually see it going into, but, certainly, they're not in a position as of yet to fund it entirely.

MS. ENGLE: Well I understand that, but in part of the directive, it was they must explain how they're going to increase it, and did you see that in the grant?

DR. WALLACK: I don't recall seeing it. Did we see any specific reference to how in the future they're going to otherwise, other than through the State funding, support their full program?

DR. PESCATELLO: There was a discussion about additional philanthropic support for the core, so I think you're correct, that that was part of our discussion. My take on it the cores are critical to the stem cell research in Connecticut. They do need support from all sorts of sources, so I would advocate including our support.

I don't think there's fundamentally a

unique new thing they're going to do with this funding, other than continue the good work that they're doing.

CHAIRPERSON MULLEN: Good morning, everybody. I was timing how long it would be before I said anything, other than all of the ground rules and welcome and introduction that Marianne already very graciously delivered.

A couple of days ago, when I told people we were back for my third time as Commissioner and at the stem cell review, nice to see you again, I said one of my greatest contributions as a non-basic science researcher is to really help everybody here around the walls.

I feel like we are living within the parameters that we established for ourselves, and, so, I appreciate your question about sustainability, because part of what I need to do is try to be a thread of memory around the kinds of conversations that we've had in the past, and I already feel as if we're sort of veering away from what we established last year, as saying we really want to see a plan and not derail ourselves with our first review, by saying, yeah, but, you know, our heart is in this, because we spent a lot of time on this and talking about this last year.

And for everybody, who sits around the

wall, since I also am the beneficiary of a number of phone calls after the review, when people have heard things that make them sort of take something personal in what's supposed to be a very objective process, you know, you need to have certainty that we're not rewriting the rules as we go along.

So we might want to just establish for ourselves now whether or not we're going to live within what we thought this program ought to do, and part of the reason I want to say that now is because I've spent a lot of time also talking with Claire Leonardi about our own visions for the future of the program.

And part of what we need to do is continue to move it from being sort of a nice local effort to that's a little bit mom and poppy, when you start moving away from the rules and the parameters into the rigorous process that we want to make sure everybody can have confidence in.

So I'll sit back and ask you whether or not you want to re-ask the question and get an answer that sounds more consistent with what we have on the checklist.

DR. PESCATELLO: I am looking at the summary, and there is a section, and there was obviously

more in the program. There's a section plan to obtain future funding, three components, federal grants, philanthropic support and cost to cover your services.

A FEMALE VOICE: What page is that, Paul?

DR. PESCATELLO: That's page 85. I think that's the right page. So, among other things, it talks about Haifan Lin's work for philanthropic support came to fruition in 2011 we get from the, correct me if I'm pronouncing it wrong, the Shing(phonetic) Foundation, so, I mean, I think they have, I think, more than other applications, addressed that issue, so there is a significant component. I didn't want to downplay that, but I think there's an importance to it, also.

DR. KIESSLING: I have another question. So what percentage of the total core operating budget is this $500,000?

DR. PESCATELLO: Oh, you want the budget from the grant.

DR. KIESSLING: Oh, I see.

A MALE VOICE: Yeah, but that's not the question. The question is how much of this --

DR. KIESSLING: What percentage of the core operating funds is this? And this is for one year, right?

DR. WALLACK: So you want me to pull up the proposal?

DR. PESCATELLO: The answer to your question --

DR. KIESSLING: Well, because a plan to obtain future funding is a very general paragraph, and it's too small, and it doesn't say what percentage they're trying to do.

I think the spirit of this was, you know, we've given these cores a lot of money. I probably am the most negative about cores of anybody on this group, because I've really seen them misused in the past, not that these cores are being misused, but I think we have to be really careful about providing money to a core instead of an investigator.

I mean we've got a lot of really good science. We're going to have a very small resource, so, I mean, I think the taxpayers of Connecticut need to understand that they have some really good science that's not going to get funded today, so I think you need to be careful, because it's half a million dollars, and if this is good use of it, that's great.

I didn't go through this budget, but we talked about cost recovery and how these cores need to be

sufficient from other funds that the investigators are bringing to this core. I just wanted to raise that.

MS. LEONARDI: I just want to jump in. I think that unless -- I mean what I'm hearing is they're doing the same things with the same amount of money, and, yet, we're saying we're going to raise dollars.

Unless you reduce the funding, I mean the money is going to go someplace else if it's philanthropic, so you could just reduce it by 100,000 each, and then you have another seed grant.

DR. KIESSLING: That's a discussion for later.

MS. LEONARDI: I know. I know. And the other thing is you do support the core through the other grants, because they pay into the core, as well.

DR. KIESSLING: Right.

MS. LEONARDI: The money is coming into the core in two ways.

DR. KIESSLING: If we didn't fund this, what would happen to this core? That's going to be kind an effect on what percentage of the core activity. If this core costs five million dollars a year to run, there's just 10 percent of the budget.

If it costs two million dollars a year to

run, this is 25 percent of the budget.

CHAIRPERSON MULLEN: And is that our responsibility to worry about that? I mean, technically, is that?

DR. WALLACK: Yes and no, right?

CHAIRPERSON MULLEN: Right, but it's not just yes.

DR. PESCATELLO: My sense is that I don't know the answer to your question, but -- I don't know. Are we allowed to ask representatives from Yale?

CHAIRPERSON MULLEN: No.

DR. WALLACK: So when we had the discussion about what, Ann, you're bringing up, I know I, for one, was the one, who, the person, who most directly challenged the two presenters, one from Yale and one from UConn, about the fact that they had to address, I think as, Jewel, you've indicated and Claire, sustainability.

We urge that they do more in the area of philanthropic fundraising. I think that there will be nothing wrong in advising them again of this discussion as part of their grant reward, hopefully, award, I should say. But, by the same token, I think, at this point, our charge was to examine the management of the core, the leadership of the core, the organization of the core, and

the services of the core, and I believe that's what the peer reviewers did, that's what we did, and, based upon that, not about a discussion of philosophical redirection, we're coming up with the recommendation of funding this core, and I, frankly, am one, who is strongly recommending that funding.

That's not to say we shouldn't have a discussion going forward about the things that we're addressing about sustainability, future sustainability, and to let them know, also, that this is a discussion that we will be having amongst ourselves.

DR. GOLDHAMER: Just one comment. I didn't read this year's grant. I know, in last year's grant, there was a listing of those activities of the core that were funded by other sources of revenue, so I'm wondering if that is also in this.

Even if there's not a hard number that we can get, as per Ann's question, it may be in the narrative that sense for what is funded by other sources of revenue.

I'd also like to say that I'm also in agreement with Milt, that I'm strongly in favor of funding the core. Now I'll say that, of all the grants I read, all or almost all require these services, these

established services of the core, and without those established services, then these other grants, a number of them, probably most, would not be successful, so I would also second Milt's sentiment of funding the core.

MS. HORN: Okay. I think we're going to call the question, and the motion on the floor is to fund the core, so we're going to take a group consensus of people, who are eligible to vote on that, so all in favor?

VOICES: Aye.

MS. HORN: Opposed?

DR. KIESSLING: Aye.

MS. HORN: Okay. I guess the other option would be to put it into the maybe, so we do have one opposed, but the consensus is to put it in the funding category. Okay, so, we are going to put that into the yes.

MR. STRAUSS: The next is UCHC 01 core. Again, Paul?

DR. PESCATELLO: So, yes, I'd like to support this core proposal that is slightly not as great a score as the previous Yale -- I think it is important, among other things, is the collaboration between UConn and Wesleyan. They do lay out three specific aims, three

new aims that they would use this funding for.

One of the most important, I think, is the event granting the acronym is TAENT, Transcription Activation Effective Nucleus Technology, so I think they have laid out a plan that sets this apart, this funding, from previous years.

DR. WALLACK: Yeah, so, my observation is similar to Paul's, and this is a collaborative effort between UConn and Wesleyan. The core provides essential services for the Stem Cell programs at UConn, at Wesleyan and, also, at Yale.

What's interesting is that we had some comments last year at this table about some of the things that we thought the core should be doing that might not have been doing in the way we had hoped for to do, and it seems to me, in reading the document, that, in the last year, it has adopted the recommendation of last year's grant review process.

It seems as though the organization of leadership has been enhanced, especially with Marc Lalande coming on board and taking more of a direct role in the management of the core.

This core continues to, as I've indicated, provide essential services, technology, training and

outreach. It has, as Paul alluded to, expanded these services to connect more with genomics, genetics and the engineering of human iPS cells, so that I think that its management has been enhanced, it's leadership has, and its services have been expanded, and those services, I believe, are essential for the Stem Cell program in the state to go forward.

Again, I strongly recommend and move the funding of this core.

MS. HORN: Do we have a second?

DR. PESCATELLO: Second.

MS. HORN: Any discussion?

DR. HART: Same question as last one. Did they -- future funding?

DR. WALLACK: My recollection, Ron, in reading the grant, that there was less reference for future funding in this application than there was in the Yale application.

DR. PESCATELLO: This seemed to be more -- I would echo what Milt said about addressing prior criticisms and critiques of the core than we presented to them. That was more the focus of this application, but they did not specifically address that, if I'm correct.

DR. HART: So this proposal was higher on

dealing with the point of bringing up new technologies. Yale was better on dealing with future funding.

DR. PESCATELLO: A little. Yeah. And I would just say, excuse me, the peer review, the weaknesses were so few, that that also was -- I think, again, that's (indiscernible) value of the core, but it would be harder to not fund them, given the (multiple conversations).

DR. GENEL: Genel. What I presume, though, that the same discussion that was held on the first core also is applicable to the second core?

DR. PESCATELLO: Yes.

DR. KIESSLING: Well it's a new core, evidentially. They want to put in a new -- they're trying to put in some new technology. They're not asking for any equipment. If you look at their budget, there's no equipment there, so they don't need new equipment. They just need people and supplies.

DR. GENEL: But in terms of future planning, is that the sense?

DR. WALLACK: Yeah, the narrative indicates that there's a desire to expand services and more towards the genetics, genomics, as I said, and the tissue.

DR. PESCATELLO: These are vibrant cores thinking about the future, not resting on their laurels.

DR. WALLACK: But, again, to Ron's point, as I indicated with Ann and as an individual, who has been personally involved in that kind of discussion of sustainability, I don't know if there would be any problem, certainly none from my perspective, if they be reminded that there might be a limit going forward.

We can't say that, because we haven't come up with a voted philosophy yet.

DR. HART: The issue always was and continues to be that we can't guarantee that there will be another pot of money next year.

DR. WALLACK: Right.

DR. HART: And that will happen every single year. Eventually, it's going to come true. And, so, if there is a plan in place to sustain what's been built here, it would be a great benefit to this entire project.

DR. WALLACK: Right.

DR. HART: I mean realize that from an organizational point of view, one way of running this entire Commission is to just give five million dollars to institute cores and let them award seed projects and so

forth within their own. That's a way of operating, if one chooses to go that direction.

We're trying to taper down something that was built to the point where it continues to be active long after we're gone.

DR. WALLACK: And, Ron, to your point, and for the members of the Committee, who haven't been here as long as some of us have been, I think you make a good point, and that is that the cores, and Ann always reminds us of this, also, years back was funded at a much, much higher level, and we understood that, because we understood that that was the only way that the program can get up and running --

DR. HART: It's the reduction of the core budgets that allows us to propose things like disease projects and so forth.

DR. PESCATELLO: And these are large institutions. I'm not worried that, because of our funding (indiscernible). I think we're also very mindful this is a 10-year program, and if it continues on, that's, in some sense to me, that's the juncture, where there's a very conscious decision about whether they want to make these kind of large grants.

I would be surprised if large institutions

like these were not mindful of that.

DR. HART: But they should tell us that.

MS. HORN: Okay, we're going to call the question on this one, as well. Do we have a motion on the floor to fund this grant? Do we have a consensus of those, who are eligible to vote?

DR. KIESSLING: I vote no.

MS. HORN: All in favor?

VOICES: Aye.

MS. HORN: The consensus is to fund.

DR. DEES: When you read the rules before, Marianne, you said, if somebody objected, it would automatically put it in the maybe category.

MS. HORN: Yes, I did. Thank you. So we're going to go back and look at these again, so that we can have a further discussion about any adjustments, or any other way we'd like to handle this. Okay, so, they're in the maybe.

Okay, so, we're moving onto the group. There's two categories of group grants. We're going to take the group project, non-disease-directed first. There was just one in this category.

(Multiple conversations)

DR. GOLDHAMER: I'll start. This is the

grant is Stem Cell derived gabaergic neurons for epilepsy therapy. This is a group grant from Wesleyan, three investigators with Dr. Naegele, and PI and co-PIs are Grabel and Gloster Aaron.

The goal of this, the long-term goal of this project is to develop human stem cell-based cures for the treatment of temporal lobe epilepsy.

There is a class of neurons in this form of epilepsy that it generates. These are called gabaergic neurons, and they provide inhibitory signals to the brain, and when those neurons degenerate, there's an excitatory wave of neuronal activity that results in seizures.

There's also other components to this condition, so there's other types of disabilities. Memory and cognition are also effected, and gabaergic neurons have been implicated in other types of conditions, such as autism and schizophrenia and Alzheimer's disease.

So they propose to develop stem cell therapies for TLE, temporal lobe epilepsy. There are three components, and each investigator has one project, so Dr. Grabel proposes to make this type of neuron in culture, this gabaergic neuron.

Dr. Naegele is going to do functional tests for this neuron. They're going to implant this into the brains of mice, and they are going to do functional studies to look to see if the neurons connect with other neurons and whether there's a phenotypic improvement in reducing episodes of epilepsy.

And, then, Gloster Aaron is a neurophysiologist, and he's going to do electrophysiological recordings to really, in fine detail, look at kind of the excitatory and inhibitory signals from these neurons. There's another test for integration of these stem cell-derived neurons.

So it was a very strong grant. I will say that it is a follow-up to two established investigator grants, one to Dr. Naegele that ended in May, and one to Dr. Grabel that ended, I believe, two years ago, so this is a longstanding collaboration between these three investigators.

With the prior stem cell funding they have been productive. It's hard to know exactly, but it looks like they published four to six papers on this subject, and I think it was the state stem cell funding that really made this collaborative effort between these investigators possible in the first place, so there's a

natural evolution and increase in sophistication -- I'll be done in one minute. In sophistication in what they're proposing, so the first study is, primarily, is mouse embryonic stem cells.

They've also used fetal four brain neurons to look at integration in this epilepsy model. This grant focuses almost entirely on human embryonic stem cells and on trying to develop ways, which they have preliminary data, for generating the specific type of neuron and culture.

So the reviewers were very positive. They liked this multi-pronged approach, where the three investigators bring in really distinct and complimentary expertise, so it was very, very positive.

There were a few criticisms, and I'll just list one of them, and one is that the investigators didn't pay attention to the possibility of the injected stem cells actually providing some kind of trophic effect for the endogenous brain, that there might be some remodeling going around with endogenous cells and not just from the implant, itself, but, by and large, both reviewers were very positive and pointed to their productivity and so forth.

My opinion is that this is exactly the

type of project that's intended by the group grant mechanism, that they've been productive with prior funding. Also, this is listed as a group grant. It easily could have been listed as a disease-directed grant, and, so, although there's priority for disease grants, that category, I think this easily falls into that scope of research.

And, so, I was very supportive and enthusiastic about this grant, and I recommend it for funding.

DR. ARINZEH: Not too much else to comment on, other than I think it's a good group, as well. The reviewers did point out I guess a minor thing, about the work here not being, the cell culture work not being GMP(phonetic) or lacking this GMP-directed approaches, and I guess, for these group projects and even the disease-directed group projects, eventually, I guess, after the four years of funding, we need to show that you'll be able to go into clinical, you know, clinical trials.

And, so, it's not clear to me that this grant would be ready after four years to move in that direction, so that would be my only thing there, and since the reviewers pointed it out, so I think that's a

part of the reason for the lower score on this, but, in general, I'm in support of the project.

MS. HORN: Do we have a motion?

DR. GOLDHAMER: The motion is to fund.

MS. HORN: Second?

DR. ARINZEH: Second.

MS. HORN: Okay. Discussion?

DR. HART: Can investigators apply for NIH funding at this point?

DR. GOLDHAMER: That's a good question. It's hard to tell whether they have applied for NIH funding for this project. They have not received NIH funding for this particular project. Dr. Grabel, in particular, has had prior NIH funding, so that's a very good question. You would hope that over time that they would be actively applying for NIH funding and hopefully being successful.

We can provide that you can't determine whether there were unsuccessful attempts at NIH funding for this project.

DR. HART: My other quick question is that there is now a lot of work being done in gabaergic differentiation. What's the different about what they're doing?

DR. GOLDHAMER: It's not my field, and I can't comment. I will say that they provided very much preliminary data that shows that they have now adopted some of the methods that have been published towards gabaergic neuronal differentiation using human ES cells. They have a reporter chain with NKX 2.whatever as a readout for having obtained this gabaergic phenotype, and they've shown in preliminary studies -- they show in preliminary studies that these neurons, when injected, do something.

I don't remember the details, but it looks like positive results, but I can't, Ron, answer your question about how the protocols differ.

DR. ARINZEH: And, you know, again, it's a good group. They're doing functional types of assays, electrophysiology, which I'm not really sure others have done, but, again, it's outside of my area.

DR. HART: Over the last year, I believe there's been several groups that have gotten -- certainly, this is a leading group.

DR. DEES: Can you comment about whether this work was innovative, and that's how peer reviewers?

DR. GOLDHAMER: I could look that up. I don't specifically remember what they said about

innovation. I think one of the strongest comments from the reviewers was that this team really has expertise in all the areas required, and that the expertise is complimentary, and, you know, there's not many groups with expertise in these three kind of distinct areas, including Dr. Aaron's work on electrophysiological aspects and readouts.

This is becoming more common, but to take that approach, along with the other types of approaches they're taking, is still I would consider, if not totally innovative, certainly the way to go.

DR. KIESSLING: I don't have it in front of me now, but I read the reviewer's comments on this particular application, and it seemed to me like they were much more enthusiastic than the 2.5 score reflects.

This morning, I listened to the podcast that was posted when they had their initial review thing, and a couple of the peer reviewers were really stressing please use all one to nine scoring, and, so, my impression from the sum of the scores versus the comments from the reviewers is that some of them were trying harder to use the one to nine scoring than others.

And I thought this review of this particular group was quite enthusiastic. I know there

was one or two technical negatives, and I just wondered if you guys thought the same thing.

DR. GOLDHAMER: I completely agree, that one group's 2.5 is not another group's 2.5, and I thought the reviews read very strongly, and 2.5 is what we have.

I will say, though, that both reviewers gave this grant a 2.5. It wasn't a situation, where one gave 1.75 and one gave a 4, which has happened.

This, there was consistency between the two reviewers, and they were both very favorable.

MS. HORN: Okay. Call the question. All in favor of funding this grant, say aye.

VOICES: Aye.

MS. HORN: Anybody opposed? Okay, we are going to give this a one. We're going to move onto the disease-directed.

MR. STRAUSS: The first project is grant 01, and the reviewer or committee members talking on this are Treena and Sandy.

DR. ARINZEH: I can start.

MS. ENGLE: Okay, you can start.

DR. ARINZEH: So this is a three-year disease-directed project, and, yes, it is addressing chronic obstructive lung disease, COPD, and, so, this is

a devastating condition that effects 600 million people, and is rapidly emerging the third leading cause of death throughout the world.

So they're identifying mechanisms, actually, to stimulate really new -- let me just make sure. New lung tissue in a controlled manner, and they are actually looking at six specific aims in this study.

Let me just make sure. Sorry. Just one minute here. So they will be looking at stem cells.

(Off the record)

DR. ARINZEH: So they will be looking at -- they have six specific aims. They are looking to clone upper distal airway stem cells, okay, in normal and disease patients, and then they will compare these stem cells for their ability to differentiate, and they'll be looking at a number of different markers.

They will also be looking at the efficacy of these stem cells and, actually, tissue engineering approaches with creating these, and then they will also be looking at various things in a mouse model to see whether these things can reverse this disease.

And, so, they have a number of methods, in order to do this, and they'll also be using some imaging, also, imaging modalities to examine this.

So with the team of investigators, again, that's the PIs at Jackson, and they'll be collaborating with UConn, and they also have collaborations with the smaller companies, one of which is this Johnson and Johnson division, so it's a very good group, with a lot of expertise here, and brings about a lot of expertise.

The reviewers gave very good scores here. They're pretty consistent here, 2.5 and 2.2. They had very little, actually, that first reviewer had very little, if any, weaknesses, so I'm not really sure why it was a 2.5. I didn't really see anything there, so it was a high degree of enthusiasm for the work.

The second reviewer had very mild weaknesses. Other than that, they thought the aims were maybe too extensive and may not be able to get done in the three years. Six aims does seem to be a large amount of aims, but, very, very enthusiastic for the work.

So I don't think I have any more comments here, so I'm in support of this project.

MS. ENGLE: Okay, so, I guess I had a slightly different take on this particular grant. I, too, am very concerned about the scope of this grant, six specific aims, and they only asked for funding for a couple of post-docs. It seems unrealistic.

Additionally, they're one clinical component, which is getting patients from a clinical trial. There was no clear discussion of what clinical trial and when the actual information would read out, so they'd be able to collect the patients prospectively, but there was no clear understanding of when the clinical trial would actual readout, so there was really no understanding in my mind in this grant whether they could accomplish the whole thing in the amount of time that they have, so I felt there were a lot of details that were missing to this.

In addition, there were just some odd things, like they requested funding for a technician to make and grow iPS cells, but the whole grant is about using human adult stem cells, so why would they need a technician to do this? That, to me, just speaks to sort of some sloppy details in the grant.

I felt that there were some concerns and inconsistencies about this. When I read it, it very much felt like multiple different grants shoved together, in order to make the sort of two million-dollar consortium disease-directed grant, so, overall, I was not as impressed with the quality of it, and I can certainly understand where the reviewers came in with their

understanding of the grant.

DR. ARINZEH: I guess my comment, I'm much more favorable, because it does involve this Johnson and Johnson group, a pharmaceutical company, which they will actually be doing the clinical trials, or providing those patients the cells from those patients.

MS. ENGLE: Yeah, but that's minimal collaboration. They're essentially saying, yeah, we're going to run the clinical trial anyways, and if you want to turn some samples into iPS cells, yeah, that would be nice, but there's no clear of where is that going to get us in the end.

DR. ARINZEH: That's their contribution. That's where the cells would be coming from. I guess, so, your understanding of the grant being weak in that area, but that's where they are getting the cells from, so I don't know, so I guess I'm a little enthusiastic, just because I feel like there is a -- there's a company connection here, and I think that's important, again, for these groups to kind of move forward into getting it more than just doing research, but, actually, getting this stuff closer to clinical, you know, clinical application.

I think it's important to have those types of connections in these grants, so I was a little more

enthusiastic.

DR. GENEL: I think all of those characteristics I think are also present in the other disease-oriented grants, by the way, so I think those characteristics of collaboration and so forth are not unique to this disease-oriented grant, so that alone would not provide, be sufficient for me to support it.

It's two million dollars. We've already allocated three and a half million dollars probably, so I think we've got to keep that in mind.

DR. KIESSLING: I was personally so excited to see so many disease-oriented grants. I looked at most of them. I looked at all of them. This principal investigator is very junior. She has maybe five public papers that she has written, and she is on the next application. She is a big part of the Tordy(phonetic) application, so I was very non-enthusiastic about this particular grant getting two million dollars.

I don't think the investigator knows how to manage two million dollars. I think, maybe, in the two years she will. She has a nice background, has a good background, but it's very, very junior and is a big part of the next application, which is being run by a

very senior, very productive individual, so I don't want to play these off of each other, but I think it's important for us to understand this is the two groups that have probably done what you said. They put together some applications.

DR. KRAUSE: I'd like to put this in some perspective scientifically. So this group, Weshan(phonetic) and others in the group, McKeon was the senior author, have really shown that they can make adult stem cells from primary tissue, and, so, they don't need iPS.

I didn't see that part of the grant. I think that's a little bit weird, but what's unique about them is that they can take primary human cells and make cells that grow in vitro, and then show that they function.

Now they're very early on in showing that they can function. A little bit further along in the lung than in the colon, which is later grant. I read all the group grants here.

What they did in the lung is they showed that the lung has more capacity to repair than we previously thought, and that's just the mouse model, where they damage it and watch it repair, and that's with

flu, influenza damage.

The jump to COPD is a big one, and the reviewers catch that. They say, come on, COPD has got to be a problem, but the microenvironment, as well, so the mouse models are very premature, but they need to be done. I

I thought it was a great grant. I've read them all. If I had to pick one, including Jen's, Jen Naegele's, I probably would say I like this one best, but I completely understand the weaknesses.

They don't have a mouse model yet. They don't know that COPD is the best target for these, but they really have a unique model at Jacks between McKeon and Sheon(phonetic), where they can make these cells and then see how they behave.

I also want to clarify the Johnson and Johnson collaboration. There's no money going to Johnson and Johnson, and this is not anything going to a clinical trial.

Johnson and Johnson is doing a clinical trial, and, through their connections, they're willing to provide material, and they can say this group didn't respond to our drug. This group did respond to our drug.

Do you see anything different when you

look at the epithelial cells? Well they might, but they might not, because there are going to be a lot of inter-individual differences, in addition to inter-group differences, but that's the goal, and, if they found it, that would be pretty cool, because then they could have something that's predictive of response to the Johnson and Johnson drug. I just wanted to clarify that.

MS. HORN: I think we're going to need to move it along here. Is there a motion to fund this grant? All in favor?

VOICES: Aye.

MS. HORN: Opposed?

A FEMALE VOICE: Aye.

MS. HORN: Okay, we'll put it in the maybe column.

MR. STRAUSS: The next proposal is UCHC 01 Tordy, and Sandy and Ron.

MS. ENGLE: Okay, so, this grant is optimization of nanotubes for thermal therapy, using oncogene-derived lung cancer stem cells.

The grant proposes to make nanotubes, which are small little components that have the interesting property that they seem to heat faster than the surrounding tissue, induced by near infrared light to

generate localized heat, and that can kill cancer cells faster than it can kill normal cells, is essentially their argument.

And their argument in the proposal is that these could particularly target cancer stem cells, and the argument is that cancer stem cells are resistant to conventional heat, but not to the nanotube-generated thermotherapy.

And, then, there's concern about treating these, so the team uses flavones(phonetic) to coat the nanotubes to increase their solubility and decrease their immunogenicity, because, when you put anything foreign into the body, the first thing the body wants to do is attack it, so they have to look for ways to introduce this into the body, where the body just won't immediately try to attack them and not pay attention to the cancer.

They have three specific aims, which they've proposed to attack over a four-year period with their two million dollars.

They want to optimize the nanotubes for thermotherapy by comparing the nanotubes with multi-wall and single-wall flavone on oncogene-derived tumors in adult stem cells from different lung regions, and then conjugate moieties, such as antibodies, to help actually

target the nanotubes to it, because, right now, if you just put the nanotubes in the body, they kind of go everywhere, so you're not really targeting the tumor.

So if they put antibodies that you would find or antibodies you find on the tumor, the idea is that those nanotubes would go directly to the tumor, and, so, you'd localize the therapy, so that, when you do the infrared sheet, it would really attack the cancer.

They want to define the mechanism of the thermotherapy resistance. Right now, they know it seems to do it. They have an effect, but they don't know why, so they'd like to investigate that more.

And, then, they'd like to optimize the nanotube therapy on patient xenografts, and what patient xenografts are is that you take tumors from people, who have them from surgical resection, and you actually implant them in mice that have their immune system deactivated, so the tumors will grow.

This gives you an actual in-animal model, as opposed to cells in a dish, because things can happen in a dish, where you don't have the whole biology around them and the whole body around them, that can't happen in the body, so you need to actually prove that what happened in the dish would still happen in the body. So

that's what they'd like to do with the money.

There were some concerns from the reviewers, generally. The reviews were reasonably good. There were concerns, and I have the same concern, is that the whole first specific aim of the grant focuses on using cancer cell lines, and these are cell lines that generally have been taken out from people a long, long time ago. They're really, really genetically-abnormal, and it's been shown that they tend not to represent what actually goes on when you see tumors.

They try to correct that, by using the patient xenografts later on in aim three, but you could ask why waste all the time with aim one, when you could just go directly to aim three, which is really going to be much more predictive of what you're going to actually see in the clinic.

So, overall, that's it. As we just mentioned, one of the key investigators on this grant was on the previous grant. I, personally, don't understand. She's also a component of a third and a fourth grant and some seed grants.

There is no way one person can really fully devote themselves to all of the projects this particular investigator is on. I think that needs to be

considered.

It uses, as I pointed out, adult airway lung cells, the stem cells that she made. The nanotubes will interestingly be delivered locally to the flanks of the mice, so the xenograft model is really about injecting those tumors on the flanks of the mice, which isn't quite the same thing as what would happen in the lung, right?

So your tumor on the skin is going to be much closer to the surface and easier to attack than one that's directly in. And given this is light-based and shining on it, technically, that's a bit of a challenge.

Overall, though, I thought that the fact that they were planning to look at 30 xenografts, so a good number of animals, and this had a clear, direct path, potentially, to the clinic, on a disease, which can kill you, which was important, so, overall, I thought it was a reasonably okay grant.

CHAIRPERSON MULLEN: Reasonably okay.

MS. ENGLE: Reasonably okay. It was not a thumbs down.

DR. HART: That was very complete, thorough and accurate. In my mind, I'll just summarize what I thought reading it. It's more like a standard NIH

R01 project. It didn't seem as developed to get to what we had in mind for a disease-oriented project.

I mean I was very positive about the project, but, in this category, I felt it didn't rise to the level that we had in mind for the category, so judging it only against our desired goals of what we were looking for in a diseased-oriented project, I felt it was short.

And I felt that the shortcomings were accurately identified by the reviewers and listed very nicely, so that the information is right there in the review.

Furthermore, the last point is reviewer two gave this grant a score of two, yet the review was clearly not a score of two. It was much worse than that.

So if we're looking at the score values, I don't think they're very accurate, based on the review context. I would read the review as close to a three to four range. In any case, I thought it was a very positive project, but just not quite what we had in mind for disease-oriented.

DR. GENEL: The second reviewer also recommended that the budget be cut in half.

DR. HART: Yes. Which would increase my

enthusiasm a great deal, considering how many other projects would have to be cut to fund one of these.

MS. HORN: I apologize for the noise next door. They were directly instructed to put us in our own room, so we would not encounter any of that. Do we have a motion?

DR. HART: The problem with this entire category in my mind is that, with the budgets requested and the amount of funds available, I almost feel like we should look at them all first, and then come back and prioritize them.

I think it's unfair to go one-by-one and just say plus, minus.

MS. ENGLE: Well we have to go one-by-one, just because you had to discuss each one, but I agree, that we're going to have to look.

DR. HART: I move for maybe.

MS. ENGLE: I was going to say I would support a maybe.

MS. HORN: We could put in maybe, and then go back.

DR. HART: That's exactly what I meant.

DR. PESCATELLO: The initial should all be maybe, unless some might be clearly no.

MS. HORN: I think the rest of the group, who have not necessarily reviewed --

DR. HART: Okay, so, I move for maybe.

MS. HORN: Okay, so, we have a move for maybe. Do we have any further discussion?

DR. GENEL: Ron, I thought you said no. (Laughter)

DR. HART: I'm not going to make a decision until I hear all the grants.

CHAIRPERSON MULLEN: So that means there is somebody in here, who, at this point, would say yes? Because if there's no one, who would say yes, that also makes a difference.

DR. HART: Yeah, but I still think it's too early to, all by itself, say no to this one grant. I think we should look at them all first.

CHAIRPERSON MULLEN: So that means you're saying at least -- okay.

MS. ENGLE: I agree with him, because I would say yes to this before I would say yes to the previous one, so that's why I said I'm in a maybe, because I don't know on the other one.

DR. HART: The next one may change our mind.

MS. ENGLE: Right.

MS. HORN: Okay. We have a motion and seconded for maybe. All in favor?

VOICES: Aye.

MR. STRAUSS: Okay. The next grant is ISP 01 with Treena and Ann.

DR. ARINZEH: It's a three-year group project that is -- so this group has recently discovered that a human embryonic stem cell-derived MSC, so the mesenchymal stem cells, can treat this mass model of autoimmune encephalomyelitis, and, so, this is a good model for or it's linked to multiple sclerosis.

And, so, they are -- they showed some very good preliminary data to demonstrate that these particular derived MSCs work better than I think it's the bone marrow-derived MSCs that are currently being investigated.

So they have three specific aims, and, so, they'll look at the peripheral anti-inflammatory actions of the ES, the embryonic stem cell-derived MSCs. They will optimize these MSCs to repair this disease, and they will do various in vivo models for that, and they will also prepare clinical-grade MSCs for clinical trials.

So it's proposed by a team of

investigators, again, at UConn, and I believe this investigator is also connected with a new startup company, as well, so they discussed that, how it can get to translation faster.

The reviewers gave consistent scores, 2.5, I think, each, and they do cite, however, that there is a lot of work. In terms of innovation, there is a lot of work just using MSCs in this area for multiple sclerosis, but the innovation does lie in the derivation of these embryonic stem cells into the MSCs, and, so, it appears to be promising, and, so, they're enthusiastic about that.

So no other comments there, other than that, you know, it appears, again, to be a good group of investigators, and the innovation here is this embryonic stem cell-derived MSC.

DR. KIESSLING: I was really excited when I saw this, because this was exactly what we had in mind for a group grant. They've got same basic science that they've spun off a little company, and the little company is going to be a new company in Connecticut.

It's going to make GMP-quality embryonic stem cell-derived MSCs for their clinical studies. It's like perfect.

The problem I had with it is that, when I looked into, and all the scientists' and the reviewers' comments were they didn't seem to get as good a result as bone marrow-derived MSCs as other investigators, which seems a little funny, but they feel that they can use their embryonic stem cells to amplify those. They certainly do -- they certainly can grow them to higher levels and a greater quantity than you can the bone marrow-derived, so that's a big advantage.

The problem I had with this application, and I'm a big fan of these investigators, is that the principal investigators have gotten a lot of Connecticut money since 2007, and the publications from Connecticut's money I think are pretty low. I'm a little concerned about that.

He was a principal investigator on a grant from '07 to 2011, and I don't find any publications for this in that application, so I think we need to talk about another two million dollars going to this group, in light of the publication efforts, which I -- there's three or four publications, but I didn't find any, and maybe somebody else knows more about this.

I actually even did a PubMed search to see that they have publications that they hadn't listed in

this application, and I think that publications for amount of money that has been spent on this group is kind of a problem here. I'm concerned about it.

Other than that, this is, you know, in many ways, exactly what we had in mind for this kind of a grant category, so if I recommended funding for this, I would like to see this go forward, because they're going to develop a new little company, and I think that's great, but I don't think I can recommend two million dollars to this group.

A MALE VOICE: What was the last?

DR. KIESSLING: I don't think I can recommend two million dollars for this group right now.

DR. ARINZEH: So they do have --

MS. HORN: Do we have a motion?

DR. ARINZEH: I'm sorry. Can I comment?

MS. HORN: Sure.

DR. ARINZEH: I don't know if these are associated with those other grants, but they do have patents listed, so that can tie up publications for a little bit.

DR. KIESSLING: Maybe, and maybe that's it, but there was a big project that was funded from 2007 to 2011 on this for bumps and things, and I only see one

publication that won't be related to that project.

DR. ARINZEH: So their patents are for method for generating primate trofoblast and feeder-independent extended culture of embryonic stem cells.

DR. KIESSLING: Right. The principal investigator can obviously run a really good human embryonic stem cell core, and I think he can make cells do things in vitro that other people don't do as well. I think that's clear.

I'm just concerned about the publication (interruption in recording).

DR. PESCATELLO: The plan was to set up a for-profit company. (Multiple conversations)

DR. KIESSLING: Right.

DR. ARINZEH: No. There actually is a company. It's already there.

MS. HORN: Okay. Do we have a motion?

DR. KIESSLING: Yeah, but it has implements there just for this project.

MS. HORN: Then we can have further discussion? Do we have a motion?

DR. KIESSLING: My motion for this, actually, would be to fund it at about a much lower budget.

MS. HORN: I think we're just, at this point, just making a -- putting it into a category of yes, no, maybe.

DR. KIESSLING: Then it's got to be maybe.

MS. HORN: Okay. Dr. Arinzeh?

DR. ARINZEH: Okay. Should I make a motion?

MS. HORN: Would you second it?

DR. ARINZEH: I'm going to second it.

CHAIRPERSON MULLEN: -- process breakdown too much, because we're doing really well, and I think we'll get the rest of the discussion out more if we do that, because, otherwise, people are going to lose what's valuable in the sidebar conversations, because you have a lot of valuable stuff. I wish I could put a microphone over there to hear it. I want to hear what you have to say.

MS. HORN: Okay, so, we have a motion to put in the maybe column that has been seconded. Further discussion?

DR. GENEL: I just have one question. Does this include model for MS?

DR. KRAUSE: That's a really good question, and the answer is it's not MS. It's an

experimental model, however, bone marrow-derived MSCs have already been able to show some functionality in patients with MS, so the question of why the bone marrow MSC don't work as well as the human ES or iPS-derived MSC is really key here.

If it's true, if that's highly reproducible, the ES-derived MSCs somehow are better than bone marrow-derived MSC, which I'm not sure they are, but that's kind of the contention of the grant, then it's really important to figure out why they're better, because the bone marrow MSC are already in clinical trials for multiple sclerosis.

DR. HART: And realize that, if that is true, it may be possible to engineer bone marrow-derived MSCs to be improved products.

DR. KRAUSE: Exactly, but I think that that's really where this grant is. I don't think we're disease-directed. Let's go. Let's make MSC and put them in patients, but that's actually what we asked for.

We want you guys to go to the clinic in four years, so give us a grant that goes. He's not ready to go to clinic. He's got to figure out whether bone marrow ones are better than human ES ones and really do the comparison, and that's an established investigator

grant.

DR. KIESSLING: But bone marrow-derived MSCs can't be expanded to the level that the --

DR. KRAUSE: They do great with bone marrow-derived MSCs. That's why there are whole companies that have made bone marrow MSCs, expanded them, have stocks, and they're in clinical trials, so, yes, they can be expanded. The companies that make them know how to expand them.

MS. HORN: Any further discussion?

DR. KRAUSE: And, in both cases, it's third party, meaning it's not an autologous cell that is going into the patient. And the idea here is MSCs are immunosuppressive, and lots and lots of logic trying to figure out why MSCs are immunosuppressive, because, down the line, they might even just put in whatever it is they're making.

We're not ready to have, you know, GMP made human ES-derived MSC and put them into patients.

DR. HART: The bottom line is that neither one of them may be the best way to go. You don't know yet.

DR. KRAUSE: That's, I think, an important grant, because if it really is better to have human ESC-

derived ones, that's key.

MS. ENGLE: This may be going to the sort of later discussion, but the argument here is we asked them to put together grants that had a clear path to the clinic.

DR. KRAUSE: I know that.

MS. ENGLE: I will say, in my opinion, this is one of the few grants that actually does have a clear path. We know. It's precedented. MSCs help in MS. We know that you can put in buckets of MSCs into people, and it doesn't cause a safety problem.

We know that the cells, themselves, die. It's clearly something they're secreting, so it's fine. There's a path to the clinic, and then let the marketplace decide whether they live or die, but it has a clear path to the clinic in the time frame that we gave them more or less with the amount of money that we gave them, because two million dollars isn't a whole lot to get anything to the clinic.

DR. KRAUSE: Oh, yeah. I think two million dollars in clinic -- (multiple conversations).

MS. ENGLE: That said and done, this is one of the closest that hit most of the marks that you set.

MS. HORN: Any further discussion? All in favor of moving this to the maybe category?

VOICES: Aye.

MS. HORN: Anybody opposed? Okay, moved to the maybe.

MR. STRAUSS: Okay. Next is Jack 02, and it's Ron and Diane, and, just for you to make a note, the peer review final score on this was 30, and the pink shading indicates that the study section review changed the score during their deliberations.

DR. HART: Okay. It's an excellent proposal from an organized group of experienced investigators to attack a very important problem, and it's very, very similar, almost parallel to the prior work we talked about here with epithelial cells.

In fact, most of the preliminary data is from the airway epithelial cell project, which has now developed techniques to culture location-specific adult stem cells from intestinal mucosa.

They propose to carefully characterize these cells and a differentiated potential before moving onto cultures made from subjects with ulcerative colitis.

In a fairly daring innovation, they'll then transplant these into intestines of mouse model

developed at Jacks to develop fully-functional in vivo mouse model for drug screening and hypoxic testing.

The reviewers were enthusiastic, but they point out that key elements of the preliminary results are lacking. I'll leave that to the reviews. In my opinion, the project doesn't really rise to the scope of a disease-oriented project vision, because it's largely developmental and only barely leads to a clinically-testable therapy concept.

Ideally, this project could lead to more pre-clinical -- to a more pre-clinical trajectory, with only a small amount more work, and maybe it's already been done by now. I don't know.

But, at this point, it's an excellent group project of established investigators that are still developing. Its expected models have a higher impact on disease.

It's the same problem we have with the airway project. It's a great project. It's a great idea. All these same people seem to be involved. I think that, based on the reviews I heard of the airway one, it sounded like there was a little bit more enthusiasm to this one, the reviewers had for this one, and it seems like they really ought to be completed.

I'm not sure it matches what we had in mind for disease-oriented project.

DR. KRAUSE: So this is identical in theory to the one that we mentioned for the adult epithelial stem cells, which is that they're going to take colonic tissue and make epithelial cell lines, and then the idea here is that, in patients with ulcerative colitis, use them to help repair the damage.

There's also the theory, I think the data are weak, saying that ulcerative colitis is a disease not only of the immune system, but, also -- well we already know it's a disease of the immune system and the microbiota, what microorganisms you have growing, but they argue that it's also a disease of the epithelial cells.

The argument there is that, amongst family members and identical twins, 10 percent concordance rate. That 10 percent is higher than outside of, you know, being an identical twin, so there's something genetic, but that genetic component does not need to be epithelial.

Now I don't think they've proven that the epithelial cells are key here. Secondly, the mouse model for engraftment of these cells doesn't exist yet. It's a

lovely idea, but it doesn't exist yet, and that's really what the reviewers were saying, is it's too soon.

In fact, one of the reviewers were saying let's just cut the funding and go figure out if your mouse model is going to work, because that's going to be key.

The third aspect is you're talking about a mouse model of ulcerative colitis with immunodeficient mice, so it's a little bit -- the trick here is not to show ulcerative colitis, but to test the barrier function of the cells that are going in, because you need them to function well as a barrier, and maybe patient samples don't function as well as a barrier, and that's kind of what they're testing.

Patients with ulcerative colitis, their cells don't function well, and, then, they also have the collaboration with J & J. It's identical. Get patient samples from patients, who responded to the J & J drug and those that didn't, and see if you can identify the difference. Again, inter-individual differences might be bigger than in group differences.

MS. HORN: Do we have a motion?

DR. HART: So based on the less-developed plan, the good idea, but, in fact, they don't have a

mouse model yet, my complaints about the disease-oriented issue and the reviewers' comments, I'd recommend no.

MS. ENGLE: I second the no.

MS. HORN: Okay, any discussion?

DR. KRAUSE: Yeah. I just want to add one thing, and that's that, in response to Dr. Kiessling's comment, Dr. Sheon, as you said, is quite junior. These grants are similar, and there are similar people working on them.

I think that there really is a team effort going on here, and that these are parallel grants, one is lung, one is colon, but to say no to this one and then say Sheon is too junior is kind of -- I think they kind of divided who is PI on each one.

That's all I'm going to say on that, because I don't know for sure. It's just a comment.

DR. DEES: But it sounds like, if you had to pick one of these two grants on the science alone --

DR. KRAUSE: I would pick the other one if I had to pick one, but McKeon is more senior.

DR. KIESSLING: But isn't Tordy --

DR. KRAUSE: No. She's part of the Tordy grant, too. Sharon makes the cell lines, as with McKeon, so they're part of the Tordy grant, in that they make the

adult epithelial lines.

DR. KIESSLING: Right.

DR. KRAUSE: Well you were saying it was spreading her too thin.

MS. ENGLE: You're looking at three diverse projects, and three diverse projects is still three diverse projects for a junior investigator, for a new investigator.

DR. KIESSLING: With all the same people.

MS. ENGLE: Right. It's a team.

MS. HORN: The motion is to --

DR. DEES: And of those three projects, that's the bottom line here.

DR. HART: Not with this mechanism, not at this time. I think it's a great idea. I really hope they succeed.

MS. HORN: Further discussion?

DR. GENEL: Just an observation. It seems like one of the problems we have is there's a lot of great ideas here, but they're prematurely being proposed for larger funding, when they might have been very, very highly rated if they were established investigator grants.

DR. HART: I agree.

DR. GENEL: Or even seed grants.

DR. HART: I agree.

MS. HORN: Okay, any further discussion? All in favor of the motion to place this grant in the no category, signify by saying aye.

VOICES: Aye.

MS. HORN: Anybody opposed? The grant goes in the no.

MR. STRAUSS: Okay. The final grant in this category is UCHC 02 with Diane and Ann.

A FEMALE VOICE: It's not the final grant.

MR. STRAUSS: The final grant to be discussed in the category.

DR. KIESSLING: Okay. This is an interesting application on osteogenesis imperfecta that comes from a very senior investigator. This investigator may be older than I am, and he is a real pioneer in this field and has done some wonderful work in the past.

My take on this is that the final score -- oh, okay. So this final score is actually probably much higher, and the lead reviewer gave it a four, and I think it's because, again, it's too premature for -- maybe I should describe the project a little bit better.

They want to get iPS cells from patients

with osteogenesis imperfecta, and then they plan to correct the mutation, which they know a lot about the mutation that leads to this disease. They want to correct that mutation in iPS cells, and then they plan to develop a method that can correct the disease in a mouse model after they have corrected the genetic defect in the iPS cells.

Now they basically know how to do most of this, but this is very far from being ready to translate into the clinic, and the track record for this senior investigator in the recent past has not been that great.

The two collaborators on this are former post-docs, and they are all in the same group, and my enthusiasm for this project is high for the science, but not as a disease-directed project at this time.

DR. KRAUSE: Okay, so, osteogenesis imperfecta is a disease of the connective tissue, and, specifically, collagen one is mutated, so they have very brittle bones. These kids just break their bones all the time. It's a terrible disease.

The idea here is human ES or iPS-derived MSCs that are corrected to make the appropriate collagen, you can have autologous marrow stromal cells, well MSCs, mesenchymal stem cells that you could inject into the

patients, remake the bone, and everybody would be happy.

I think it's really important to know where the clinical trials are on this already, so Ed Horowitz at CHOP in Philadelphia has done whole bone marrow transplants, which would include MSCs, and has done just MSC transplants in patients with osteogenesis imperfecta.

The great thing is he sees improvement transiently, so these kids they're not growing, they're not growing, they get their MSC, they grow and stop growing. They get a few more MSC, they grow, they stop growing, and then they don't respond so well.

So I think that it's premature to talk about iPS-derived MSCs, when we're still working on getting MSCs to work in these kids, but that's just my own opinion.

The concern of the reviewers was that he has not yet made iPS from OI patients, nor has he shown the mutation, so that's really why it's a little too soon, but it's a wonderful idea, and I think that it's something that could be a great disease-directed, got to the FDA kind of thing, but it's too soon.

MS. HORN: Do we have a motion?

DR. KRAUSE: It's a no at this point.

DR. KIESSLING: Yeah. I move that we don't fund this application.

MS. HORN: Further discussion? Okay, all in favor of moving this grant to the no category, please signify by saying aye.

VOICES: Aye.

MS. HORN: Any --

DR. KRAUSE: It's really good, good stuff that they're doing.

MS. HORN: Okay. So we have eliminated two grants from this category. We have three maybes to revisit at this point.

DR. GENEL: May I just pose a question? How are the three that we left maybe different from the two that we rejected?

MS. ENGLE: The two that were rejected are so preliminary, as to have really no rational chance for getting to the clinic anytime soon. There are too many basic questions left unanswered, whereas the other ones have many unanswered questions, but more opportunity to get there.

DR. GENEL: Okay.

MS. HORN: Okay. We have one in the group category, strictly group, that was maybe. Oh, that was a

yes. I'm sorry. Okay. Okay, so, in the disease-directed, we have three to revisit.

The object here would be to look at whether they should really be moved to the yes, or the no, or they should stay in the maybe for further discussion.

DR. HART: Just on the topic of the one that was supported in that group project, I mean we can always come back and discuss budgets later. I just wanted to remind everyone that.

MS. HORN: Thank you.

DR. KIESSLING: Do we have to make this decision now, or can we move on to another category?

MS. HORN: I think I'd like to take one more stab at getting a little more differentiation between the three maybes. We don't have a lot of time, but if we could do that now, before everybody forgets what they're all about?

DR. KRAUSE: So can I just summarize where we are with these? Actually, I didn't read the Naegele grant, but the Sheon grant it's for the COPD, it's a great idea, they can make these cell lines.

It's premature to know whether this would actually work in COPD. That's a bit of a stretch, but

they have beautiful, beautiful data on these stem cells, and they have data in a mouse model of influenza that mice can repair their distal airways better than we thought they could.

The Tordy grant has a lot of strengths, but the biggest weakness is that it's using just cancer cell lines, and we're not really sure that this heated nanofiber is actually going to be adequate enough to get rid of enough cancer. I mean, really, a 50 percent decrease in cancer you still have cancer.

And then the third grant, the Xu(phonetic) grant, is beautiful, and it really is talking about human ES MSC versus bone marrow MSC, and then if human ES-derived MSC are actually better, let's just make them a clinical GMP. Once we figure out how, we're going to send it to a company, and they'll make them with good manufacturing practices, and we'll be ready to do a clinical trial.

That's just kind of summarizing where we are with the three. They're all a little too soon. Some are more mature than others.

MS. HORN: I was just going to suggest we start at the top and revisit each.

DR. DEES: I'm not sure -- to talk about

these, because it seems like we're going to fund one, maybe two of these grants at the most, and, so, it seems like would you have cut the budget in comparison to each other.

A FEMALE VOICE: Say that again? I'm sorry.

DR. DEES: I said we're going to fund one, maybe two of these grants, and, so, we really need to talk about going against each other.

COURT REPORTER: One moment, please.

DR. DEES: Marianne was suggesting we talk about them one-by-one. I said, no, we need to talk about them all together.

MS. HORN: I just would remind you that there is a UConn grant in here, so people, who are conflicted with UConn, when we get into that kind of discussion, it gets a little tricky. Essentially, they're all UConn grants, but two are not labeled UConn. I understand that there are some UConn investigators in that.

Sometimes somebody is recused for one and not the other two, and, so, the discussion is complicated. Carry on.

DR. WALLACK: Having listened to the

discussion, I'm not sure if we, on the disease-directed grants we've been talking about, that I'm convinced that we're going to fund any of them.

Certainly, the first two I heard a lot of negatives, and I have to go through all the notes that I've taken down, but there was basically nothing here that at least I heard and took note of that would indicate in my mind that I would be anxious to fund.

The third grant it sounds as though maybe that one, especially because of how it came together with the companies and so forth, might be something that we would want to fund, but, on that one, from what I've noted, not at two million dollars.

Ann, I don't know if you were the one, who made that comment. I'm not sure. I don't think you offered another alternative about how much you thought it should be funded for, so, in my mind, I haven't seen anything at all that would indicate that the first two should go anywhere, but no, and the third one I think I heard, well, maybe we can do yes there, but in a much lower amount.

DR. HART: When you list all the reviews, I think what I heard anyway was that they were all good ideas, they all had, all five of them had good plans,

good concepts, good directions, but so many of them looked too preliminary.

One way to attack this is to say, well, you know, they need more development to get there. Take the allotment of one of these projects and split it either two or three ways, and let them go one or two years and come back to us. It's the Solomonic solution.

DR. WALLACK: So, Ron, I think we could do that, without allocating money, however.

DR. HART: Yes.

DR. WALLACK: Because this is a lot of money.

DR. HART: It is.

DR. WALLACK: And what I would be more comfortable in doing is taking your point, make the recommendations to the principal investigators, that we would welcome them to come back with a redesigned plan, maybe as an individual investigator, established investigator, or maybe a group.

DR. HART: And do what today?

DR. WALLACK: Redefine their expectations and how they're going to manage it, because I also heard that the management of the first grant we a question about.

DR. HART: But I mean doing what for funding today?

DR. WALLACK: Not funding it today.

DR. HART: I just want to make that clear.

DR. WALLACK: Right, not funding it today.

DR. FISHBONE: I have some concern if we don't fund any of the disease-directed grants for the program. We're saying we want to fund the disease-directed grants, we had six applications, and we say we're not going to give anybody any money, that might be a death knell for the program.

I like Ron's idea of saying to the first three that we'll give you some money to reorganize, you know, what you want to do, or what you can do. In other words, supporting them, in order that -- because you're saying they're good grants, but just a little premature of this category.

To me, it makes sense to fund them at some level, you know, a significantly-reduced level, until you refigure what you're going to do with that money.

DR. GENEL: I'm not sure I agree with that. We have a lot of very, very good proposals, with very high review scores. We already cut them off, probably higher than I would have liked for discussion

purposes.

I think we'd better just revisit this at the end of the day, when we've looked at the established and the cores and the seeds.

DR. HART: I think we have a tentative plan at this stage. This is such an important category. I don't think we should walk away and come back to it blank. I think we should have a tentative plan in place that we can revisit later.

DR. KIESSLING: Okay. I think the strongest grant for this particular group is the Xu grant. I think it meets the criteria the best. My concern is the amount of money going to it, but I think it meets what we wanted to do in spirit, and it's a beautifully-written application.

I'm not as enthusiastic about the first grant as Diane is, because I'm concerned about it. I'm concerned about the leadership, because I don't think this individual coming in needs two million dollars or even a million dollars.

If it had a different PI, I think I would be much more enthusiastic about it, because the preliminary data --

DR. PESCATELLO: I would just say I think

we should leave this category and go onto the established and see where we go there. If we use up all the money there, then we've answered our question, because I haven't heard any -- this is a lot of money for each one, and I've always thought that this is kind of, this is so aspirational to try to go right to the -- everybody wants that, but there's a lot of preliminary research that has to be done, and I hardly ever see that ability to jumpstart it, and we're trying to enforce it here and it's not working.

DR. HART: We're trying to leverage this with relatively small amounts of money for what we're asking for. We should realize that, that in any reasonable setting, there would be a lot more money, and the problem is to try to get it to fruition.

I think that for what we've asked these researchers to do and for what we've received, it's actually quite a success. I think our expectations were rather high, and, so, to look for an interim solution is a great way to keep the idea going, keep pushing the researchers toward medical application, which is really what we had in mind all along, and they've done this. We should reward that behavior, and I don't think we should leave this alone.

I think we should do this at the expense of established investigator awards.

MS. HORN: Okay, so, I'm hearing that we've got three in the maybe, leave them in the maybe, we'll come back and revisit the discussion when we've made other -- let me see what else is on the table.

So we're going to take a break. I'm sorry. Diane?

DR. KRAUSE: I was just going to say that there really is a strange dichotomy here, because this is a huge amount of money, because it's a large fraction of 10 million, and it's no money at all to actually take something to a clinical trial.

We're talking 25 million, 30 million, 50 million, and we don't have that, so here we are, in this little room, and we say we're the SCRAC, let's tell them to put in, you know, disease-directed grants, and they're going to go to the FDA, so they try. Every one of these grants is excellent and has wonderful preliminary data.

Okay, so, that's number one point. Number two point, if none of them were funded, people would still apply, because we all need funding, and if we have a good idea, we'll apply.

So it doesn't mean like, oh, no, last

year, they didn't fund any of them. I can't apply for that this year. If I actually have an idea that's more mature than these, I'll know, well, that one might compete, so I don't think you're going to get no applicants in the future, because you didn't fund any.

And, then, third, it sounds to me like none of these is ready for funding. Xu seems to have the most enthusiasm in the group, and perhaps it really should be funded at the level of an established investigator award, because really what they need to do is the bone marrow versus human ES studies before they go to the getting clinical grade cells.

DR. GENEL: So you're picking up on Ann, and you're actually saying 750,000. That's what I was asking you.

DR. KIESSLING: Yeah, something like that. Half to three-quarters would be good, because they're the closest to getting this framework in place.

CHAIRPERSON MULLEN: So is this the discussion we're supposed to be having at this point of the day?

I think the consensus of the group is we're not finished with this category, and there's a lot more to look at, and, in the same way that we wanted to

vote all of these before making a decision about one of these group disease-directed grants, we, you know, probably need to look at the rest of world and otherwise think about how we're going to allocate resources.

In a way, I hear where you're coming from, Ron, because it's almost as if, if we move on, then these fall off the map all together, so how about this?

You have my commitment, that I'll bring it back again, but for consideration, not necessarily for funding, but at least to get people to circle back, because, otherwise, we're going to continue to go down a path of discussion that's premature, I think.

MS. HORN: Okay, so, we're going to take a break here for about 10 minutes, and then we'll come back.

(Off the record)

MS. HORN: So we're going to start with the established, and, Rick, can you tell me how many we have in this category?

MR. STRAUSS: Seventeen to review.

MS. HORN: Seventeen to review. We are on schedule, but these are shorter grants, and, hopefully, we can pick up the pace here a little bit, so the first grant.

MR. STRAUSS: Okay. UCHC 06. That's Richard and Treena.

DR. DEES: So this proposal seeks to understand some DNA repair mechanisms and reduce core problems, embryonic stem cells by determining how the generic variations and the hereditary cancer, which is Lynch Syndrome, which it puts people at a higher risk for colorectal, endometrial and ovarian cancers, so looking at the (indiscernible) variations in this heredity cancer leads to problems in this particular mechanism, DNA repair mechanism.

This is a project that's kind of nicely linked clearly to a disease, but its real focus is on understanding how the mismatched repair genes function and how variations can disrupt the mechanisms. It's a basic science, but it clearly links to disease and is a nice balance in some ways.

The peer reviewers are really quite enthusiastic. The study investigates the study of disease, using novel techniques, but the mechanisms studied is so basic that results will have indications for other kinds of diseases, as well.

The only reservations they had was about whether the researchers have used patients derived by

(indiscernible). But they doubt that that would actually make that much difference in the end, so I'd recommend that we fund this, and that has a peer review score of 15, so I'm highly enthusiastic all around.

DR. ARINZEH: Yeah. It's just another comment, just that the investigator here is, I think, is -- yeah. So he's an associate professor at UConn, and he has great expertise here in this area in molecular genetics, and he also has received a recent R01 in this area, but for cancer cells, so it does compliment, you know, the work that he's currently doing and being funded for at the NIH, except now he's applying it to the stem cells, so I'm in strong support of funding this.

MS. HORN: Do we have a motion?

A MALE VOICE: I'll move to fund.

MS. HORN: And second?

A FEMALE VOICE: Second.

MS. HORN: Okay. Further discussion? All in favor of moving this grant to the fund column, signify by saying aye.

VOICES: Aye.

MS. HORN: Anybody opposed? Move to yes.

MR. STRAUSS: Okay. The next grant, Yale 06, Richard and Gerry.

DR. DEES: So this grant is a grant to increase our understanding of one of the basic factors using creative induced pluripotent stem cells. It seeks to understand how the exact chemical and physical mechanisms in the holding and unfolding of DNA using acp4 is able to create and maintain pluripotency and determine what other factors work with it to regulate the process.

This study is really a basic science of stem cells, so it's less connected to human disease, but it's looking at some really basic kinds of steps in pluripotency.

The peer reviewers here also vote inside the funding and importance of this work, its potential to improve ability to reprogram cells, in general, so it has broad applicability. The experiment that is well-design and well-controlled and some minor weaknesses in how to reprogram (indiscernible) they were both very enthusiastic. The peer review is 20, so I would recommend to fund.

DR. FISHBONE: I would agree. It seems like a very good basic grant and an important subject. The investigator has a very good history, a Ph.D. at Harvard, post-doc at Institute of Cancer Research, post-doc at Yale, and is now a member of the Yale Stem Cell

Center.

He's had no previous grants from SCRAC. He has an NIH grant until 2015, but I don't think there was any overlap, and it looks like a very good grant.

MS. HORN: A motion?

DR. DEES: Move to fund.

DR. FISHBONE: I'll second.

MS. HORN: Further discussion? All in favor of moving this to the yes category, please signify by saying aye.

VOICES: Aye.

MS. HORN: Opposed? The grant moves to the yes category.

MR. STRAUSS: Okay. The next Yale 10, with Sandy and Gerry.

MS. ENGLE: This grant is on the causes of vascular proliferative disease, and they use two patient genetic models to look at that. They propose making iPS cells from these disorders.

They actually are remaking them. They've already generated the IHS cells, and now they'll make them using a better method, and then they did a preliminary screen, and they identified one drug that seemed to help in the disorder and prevent proliferation,

and they propose doing an additional drug screen of commercially-available entities to find more molecules that may help in this disorder.

And, then, one of their specific aims is also looking at the mechanism of action of how these compounds actually improve the disorder, or how application of elastin improves the disorder.

The only thing I have to note is that the investigator is well-funded and also has concurrent funding from the State of Connecticut, running until 2016, but, otherwise, it's a very well-written grant. The reviewers were very enthusiastic about it. Do you have anything else to add?

DR. FISHBONE: Not really. It looks like it's a very good investigator, and there's just a question of I don't know if there's any overlap with funding. He's funded until 2015, and he has another proposal submitted to SCRAC at the same time. I think he has two requests.

This is also about (indiscernible) and the Williams, whichever it is, syndrome. I think this is a good proposal (indiscernible) problem that needs evaluation. I'm just not sure about where the other grant is. Do you know where the second grant is?

MS. ENGLE: No, I'm sorry. I don't have that written down.

DR. KIESSLING: It looks like it's got a score of four.

DR. FISHBONE: (indiscernible) so this one (indiscernible)

MS. HORN: Do we have a motion?

DR. FISHBONE: From me.

MS. HORN: Okay. The motion is to move to the funded category. Do we have a second?

MS. ENGLE: I second it.

MS. HORN: Okay. Further discussion?

DR. KIESSLING: I have a question. Is this really a stem cell grant? They're using iPS cells, but --

MS. ENGLE: I was going to say, so, there will be several grants that would be disqualified if that were the criteria, if they were just using stem cell-derived, or patient-derived stem cells as a model of a disease in a dish.

As you read through them, there are many grants that are predicated on that, so, in a sense, this grant is no different than those, so I would say that, yes, it is a stem cell grant. It's allowing you to make

a tissue type that you would not have access to otherwise, and then to use that to understand potential drug interactions.

DR. DEES: Do you know that this PI has two current established investigator grants running right now. I'm not sure to what extent that should be a consideration.

DR. KIESSLING: It should be a consideration.

DR. DEES: So that makes me less enthusiastic, even though the science is really good. Maybe spread the money around a bit.

DR. KIESSLING: I kind of reflect that, because I really think our job is to give the state taxpayers the biggest bang for their money, so I think that needs to be part of our consideration, how much money there is in each lab, not to say this reflects poorly on this investigator, but I think it's our job to make sure.

DR. WALLACK: I would note, also, on the other hand, I would note that the lead investigator has brought in two co-investigators that I believe are new to the stem cell process, at least our process, so I think this is positive.

How much time is Yang going to be putting into this grant, himself?

DR. FISHBONE: Two months per year.

DR. WALLACK: Two months a year.

DR. FISHBONE: And post-docs are doing 18.

DR. WALLACK: Well what about Kinch(phonetic) and Toledis(phonetic)?

DR. FISHBONE: Toledis, .6 months per year, and, Kinch, .3 months.

DR. WALLACK: .3.

DR. KIESSLING: .3 three months a year?

DR. FISHBONE: .3. I don't know how that works out.

DR. KIESSLING: What's that, two weeks?

DR. HART: And, again, if you're going to compare in that direction, then this costs on the order of, what, three and a half seed grants to fund this one? So if you want to talk about how many people you're bringing in the field, just realize that.

DR. WALLACK: Ron, I understand. That's why I asked the question.

DR. HART: Yeah.

MS. HORN: Any further --

DR. WALLACK: I was a little disappointed

in the answer.

DR. HART: No easy answers here.

MS. HORN: Any further discussion? The motion is to move it into the funded category. All in favor, signify by saying aye.

VOICES: Aye.

MS. HORN: So we've got a couple of ayes. Opposed?

DR. FISHBONE: I oppose.

MS. HORN: You oppose, okay. We'll move it into the maybe category.

MR. STRAUSS: Do you want to make a motion to move it into the maybe category?

DR. FISHBONE: I'll move that we move into the maybe.

MS. HORN: We don't need to make any motions.

MR. STRAUSS: The next grant, Yale 12, David and James.

DR. GOLDHAMER: This is a grant by Dr. Anthony Sow(phonetic). It scored a 20. The initial scores were three and a one, and through reconciliation it moved to a 2.0.

The grant is improving the fidelity of

human iPS cells with epigenetic and chemical genetic approaches, so Dr. Sow is an assistant professor since 2010, and, as far as I can tell, does not have prior Connecticut stem cell money as a PI.

So just a bit of background. Genomic stability is critical for ES cells and iPS cells for therapeutic applications, and there is some recent studies that indicate that there is a component of genetic instability or genomic instability in human iPSCs, and this is manifest as copy number variation in critical sensitive areas for genome, where genes are either lost or increased, and these changes in copy number can be short-stretched, relatively short stretches of DNA for 10 kilobases up to one mega base.

And the PI has evidence, based on mouse work, that there's a histone variant, called h2ax, that is involved in maintaining genomic integrity-directed genetic means, and the data looks very nice, and they've done quite a bit of work on mouse cells, and the goal of this project is to define epigenetic mechanisms for maintaining genomic integrity in reprogramming of human, towards human iPSCs.

There are three aims, but, basically, the idea is to evaluate the importance of this histone

variant, h2ax, in maintaining genomic stability, so the typical kinds of things one would do, you knock down expression of h2ax, and you see how that effects those hot spots where copy number variation is typically seen, and you look for an association between h2ax deposition of a genome and those hot spots and that kind of thing.

They also, in collaboration with (indiscernible) I think at the (indiscernible), he doesn't ask (indiscernible) they've identified a chemical compound, called part one, that protects the genome in human iPSCs, and they want to look at the relationship between this small molecule and its effects on h2ax deposition.

So onto the reviews. The reviews, there was one reviewer, who gave it a score of one and thought it was conceptually novel, outstanding, everything fine, very few criticisms, but reviewer one gave it a score of three and did note one, in their opinion, one major weakness, and that is, and I'm quoting, "that there appears to be zero preliminary data in the human system."

And, also, they commented, for people here working on human iPS cells, I'd like your opinion, also, there is some published controversy underlying the premise about on which the work is based, that being

whether or not iPSCs actually incur a significant amount of genomic instability during their derivation.

Okay, so, that seems to be rather fundamental, and I'm not sure where the field stands on that.

My summary of this grant is that they did an excellent job of presenting the significance and background. There was very little experimental detail, though, and anticipated results largely were restricted to what had already been observed in mouse cells.

The experiments are essentially a repeat of what's already been done in mouse, which, nevertheless, is important to study, but I would have been a little bit more enthusiastic if there was at least a bit of human data on hand, so I think the lack of any preliminary data in human cells is an issue, although I was overall enthusiastic about the proposal, but that was tempered a little bit, because of the reviewers' comments and the lack of innovation, because this work has already been done in the mouse.

The PI will devote 25 percent effort, so a relatively large effort for this grant on this four-year grant. The budget is appropriate, although I'll note now, which will come up later, if this does move into the

funding category, on the budget page, the investigator asked for $12,000 a year in travel. In the justification section, it was $2,000 a year, so there's a $40,000 differential between what was asked for in the budget and what's the in narrative on the justification, so just keep that in mind if those goes further, so I assume the $12,000 was a mistake.

So I was overall enthusiastic about this, but tempered by a few criticisms, and I was wanting to put this application in the maybe category.

DR. HUGHES: I would just add that, in the context of the other grants, I think that this one is far more distal from clinical applicability, although to address as a basic question clinical practice going forward, and I was taken aback by the reviewer's comments about the theoretical premises of the project and thought that that raised sufficient questions. I recommend that this go into the hold and review category.

DR. GOLDHAMER: Can someone in the room comment about what is known about genomic instability in human iPSC derivation, whether there's any kind of consensus that it's not as much of a problem as in mouse iPSC derivation, or is that still too early to know?

DR. HART: There's actually some fairly

definitive work by one of our grantees, Dr. Vaccarino at Yale, showing that most of the variation is due to variation in the cells of derivation. Skin cells, for example, cell-to-cell, are highly variable or relatively variable.

And, so, it seems as though the initial worry about genomic instability has been largely reduced, based on understanding that most of it comes from the source cells.

MS. ENGLE: That is my understanding, as well. So when I read this grant, I was a little bit taken aback that they were still so concerned, because the rest of the field has moved on.

DR. GOLDHAMER: So that's important information. I will say that they are collaborating with Onger Smengi(phonetic) in Toronto, who is supplying iPS cell lines, and they've done an initial preliminary characterization and apparently had found it's hard to evaluate, but some copy member variability in these iPSCs, so it does exist.

Whether it's relevant to our problem to devote this amount of money to this at this time, that's what I'm uncertain of.

MS. HORN: So do we have a motion to put

it into the maybe category?

DR. WALLACK: Before we do a motion, please, so this investigator is also on another grant that is very, very similar, and that's SCB Yale 13.

There's a lot of similarity, as far as I can tell, in the two grants, and this investigator actually takes over the management of the grant that just referred to in years three and four, so I'm, frankly, confused about why we're looking at two grants that are basically the same grants.

MS. HORN: I would like to have a motion that this be placed into the maybe category.

DR. GOLDHAMER: So I'll make that motion.

MS. HORN: Discussion?

DR. WALLACK: I made the point that I wanted to make.

DR. GOLDHAMER: I guess, Milt, you and I are on the Ivanova grant, so we'll discuss that in a little bit.

I think the research is quite different. They really focus on two entirely different proteins and probably mechanisms, as well, of genomic instability.

I also notice on the budget of Ivanova that Jow(phonetic) was listed in years three and four,

but I didn't see any evidence elsewhere in the application of a conscious, of a shift in management.

I thought that was maybe a clerical mistake, but we'll get to that.

DR. WALLACK: Okay.

MS. HORN: Any further discussion on this grant? Hearing none, if you agree with leaving it in the maybe category, please signify by saying aye.

VOICES: Aye.

MS. HORN: Any objection? Maybe.

MS. ENGLE: I was just going to say, can you say I think it should be just taken off the table now?

MS. HORN: I'm sorry. If it's in the maybe, it's in the maybe.

MR. STRAUSS: Okay. Yale 12, David and James. Is that the one we just did? Sorry. Yes. Do you want to do it again? UCHC 05, we have Ron and Mike.

DR. HART: I guess I can go first. So this group has been working on T cell differentiation from stem cells, and they have combined both the ability to produce T cells -- sorry. I looked over, and I thought you were --

DR. GENEL: No, no, no. Go ahead.

DR. HART: I'm sorry.

DR. GENEL: Go ahead. I'm just responding to the nudge I got. (Laugher)

DR. HART: So they both figured out how to make cells that resemble very closely accurate real T cells from stem cells, and they have worked on T cell receptor engineering techniques to try to put specific T cell receptors into these novel T cells.

So the reviews are quite positive. There's a little bit more complaints, a little more negatives listed in the reviews than the scores would indicate. When I read the text of the reviews, I was expecting about three, and they ended up between a 2 and a 2.2 area.

It's a novel approach to creating therapies for melanoma, and there's been recent movement in immune therapies for melanoma. Merck just had some success with a biological that seemed to show some effect in early clinical trials, so it's a good direction.

Built on prior expertise with T cell differentiation and T cell receptor engineering, the PI had prior seed grant award on a similar topic, and it seems to be developing appropriately.

All other funding seems to be ended or

ending very soon. I'm a little concerned about the ability to translate this to clinical practice, but it certainly seems worthwhile to continue testing it this phase of the work.

The team seems balanced, and some of the key personnel have published together previously, a successful interaction, so I was very positive.

I'm a little concerned about where we are on the list already with the established grants, so I don't think it's a good idea to propose an absolute yes at the moment. I knew I was going to get that response.

Otherwise, it was very positive. We're going to be not funding a great deal of excellent science. There's no question about it. This is one of my concerns about this. In a vacuum, I would have been very supportive.

DR. GENEL: Actually, this grant has several virtues. One is that it is a continuation of a work that was begun with the seed grant, which was the intent of the seed grants, was to establish.

The second is I think the reviews, the second reviewer said the protocol is of high risk, but it's well recent and could result in exciting results with a large impact, etcetera.

The third is the budget is only $600,000, as requested, so I think all of these virtues I would probably put it on the yes list, but one thing that confused me, Ron, maybe you can tell me, is what is this large effort led by Baltimore? Is that the Nobel Prize winner, or is that the city?

DR. HART: I was unaware of exactly what the reviewer was talking about, too. Is there anyone else in the room that's aware of a T cell project that would relate to this, who can speak?

MS. HORN: This is an 05. This is a Yale.

DR. HART: We can't ask Diane, unfortunately, who is the expert.

DR. KRAUSE: Wait. No, wait. You're talking about the T cells?

DR. HART: Yeah.

DR. KRAUSE: No, I don't have a conflict on this one.

MS. HORN: It's a Yale grant. (Multiple conversations)

DR. KRAUSE: Okay, so, what was the question? I'm sorry.

DR. HART: The question is a reviewer brings up that they're in competition with some big

Baltimore group, and I'm unaware of what they're talking about.

DR. KRAUSE: Yeah, so, I didn't read this grant, but I know about the clinical trials that are ongoing.

DR. HART: That's exactly what I wanted.

DR. KRAUSE: And, so, there are CARs, which stands for Chimeric Antigen Receptors, that have been designed, based on T cell receptors, that you can put into a patient's own T cells, and then you put those T cells back in, and they attack the cancer, and those have been developed for melanoma and are in clinical trials.

DR. GENEL: Well that's, essentially, you know --

DR. KRAUSE: If he has a better CAR, then, you know, that's going to be the competition, but they're already pretty far along in clinical trials.

DR. HART: So that's the concern. They're competing against an established group, that's maybe farther along.

DR. KRAUSE: There are lots of people at Johns Hopkins, who are trying to develop better CARs.

MS. ENGLE: Are you against taking -- not

too heavily, right? This is always to the clinic is a horse race, and just because you start out fast does not mean you finish and does not mean that, when you start out with a good horse, that it will go the whole distance, so I think one always has to have multiple horses in the race, otherwise, we wouldn't run them.

And, so, just because they may seem behind at this point does not mean that they do not have something that will be better, or long-lasting, or more useful, so I would argue against using the, well, you started late, so, therefore, you have no hope, that that is not a good argument.

DR. GENEL: There's also a strong collaboration with Anthony Rebass(phonetic) at UCLA. All of these things I would put it on the yes list.

MS. HORN: We have a motion to put it on the yes list. Do we have a second? Okay. Any further discussion? All in favor of putting this on the yes list, please signify by saying aye.

VOICES: Aye.

MS. HORN: Anybody opposed?

MS. ENGLE: If we say opposed, it will go on the maybe list, right?

MS. HORN: Yes.

MS. ENGLE: I oppose.

MS. HORN: Okay, so, it's going on maybe.

MR. STRAUSS: The next up is UCHC 01 with Mike and James.

DR. GENEL: Go ahead. I'm shuffling paper.

DR. HUGHES: Well this grant is addressed to the use of mesenchymal cells and nanoscaffolding for tendon repair. I was very impressed with the proximity to clinical application. The PI has worked on translational projects with UConn Center for Science and Technology Commercialization.

One of the reviewers questions, if the transplantation, this kind of a tissue, would be an appropriate therapy for rotator cuff injury, but I think that, as the project makes clear, this kind of innovation would have tissue engineering applicability, and I was also impressed with the use of nanoscaffolding in this, because I think it has the collaboration potential with bioengineering and nanomaterials has a broad implication for innovation in other fields, so I would recommend the funding of this project.

DR. GENEL: Well there is a discordance between the two reviewers, quite a bit of discordance.

The first reviewer has reviewed it as 1.25, and the second reviewer as a 4.

I'm more inclined to support the second reviewer, because -- and the comment here is that it's not clear if this type of injury, this rotator cuff injury, is best served with stem cell transplant. It seems unlikely to fill a huge need, and doctors will be hesitant to use stem cells in a non-life threatening condition.

Given the competition, I would probably not fund it, but, at the very least, I'll put it in the hold category.

MS. HORN: We have a motion to put it in the maybe category. Do we have a second?

A MALE VOICE: Second.

MS. HORN: Okay. Further discussion?

DR. KIESSLING: You never had a rotator cuff injury.

MS. HORN: Okay. All in favor of placing this grant in the maybe category, please signify by saying aye.

VOICES: Aye.

MS. HORN: It's in the maybe category.

MR. STRAUSS: Okay. Next up, UCHC 15,

with Treena and Paul.

DR. ARINZEH: You start.

DR. PESCATELLO: So this is about the mechanisms of Prader-Willi syndrome. The reviewers are well organized. There's a bunch of criticisms, how much of a clinical connection. He described it as complex and high-risk and some issues with the PI's expertise in this field or in gene targeting.

My reading of it was that, especially the complexity and the risk profile, this is what we're supposed to be doing, so I ended up in the pro category.

DR. ARINZEH: Yeah, so, they are linking this Prader-Willi, well, they're saying this Prader-Willi syndrome is, you know, causes this life-threatening obesity in children, and, so, they're going to be looking -- I'm just going to give a little bit. They're looking at the iPS. They're comparing neurons derived from these patients and the iPS from these patients to normal iPS cells and looking at all the gene abnormalities.

I mean I thought this was interesting, and I think this investigator has that expertise. My only concern was that looks like, is it a he or she, I'm not sure, already has just received a 2012 seed grant in this area. It looks very similar, but, again, you only have

like a title.

So that would be my only concern there, but if it's going to extend that work, then that's fine.

MS. HORN: Do we have a motion?

DR. PESCATELLO: Yes.

DR. ARINZEH: I say yes. Yes.

MS. HORN: A motion for a yes. Further discussion?

DR. FISHBONE: I have a question. My question is that we've been funding a lot of basic research over these years that we've been giving out money, a lot of it in conditions that are extremely rare. This is another one that is extremely rare, and I'm just wondering, with limited sums of money, should we be looking more at things that have a more practical application?

COURT REPORTER: One moment, please.

DR. ARINZEH: Prader-Willi is a genetic -- well, it's an imprinting disorder, and it's about one in 10,000 live births, so that is considered a rare orphan genetic disorder.

DR. HART: I think you should keep in mind that it's an outstanding example of a genetic condition. It's probably the best way to study that genetic

condition. It's this imprinting issue, and, so, it shouldn't be considered only in the context of that one disease. It's a way of getting at a genetic process you can't get at with any other disease.

DR. KIESSLING: Rare diseases are frequently really good models.

DR. PESCATELLO: I know we want to get beyond basic research, but there's sort of no substitute for basic research, and this is good basic research.

MS. ENGLE: That said, I do want to make a point, that I don't know if this specific investigator is connected with Marc Lalande, but it comes from a very well-funded effort at Yale to study both Prader-Willi and Angelman Syndrome. UConn. Excuse me. Sorry about that.

So it comes from a very well-funded effort already in this area. I don't know, you know, there's a certain argument levering the state expertise in that, but, that said and done, it's a very well-funded group and organization, and would this just be piling on?

And we have already had some conversations about sort of over-funding certain laboratories, whereas we might have an idea that it would be better to spread the money around to generate new ideas.

MS. HORN: Okay. Further discussion? All

in favor of placing this grant in the yes category, please signify by saying aye.

VOICES: Aye.

MS. HORN: Anybody opposed?

MS. ENGLE: I'm opposed.

MS. HORN: It goes in the maybe.

MR. STRAUSS: Next up, David and Milt on Yale 13.

DR. WALLACK: The grant seems to be a well-designed study. As far as I can tell, it's aimed at gaining a greater understanding of the epigenetic mechanisms that control the ability of the embryonic stem cells and iPS cells to be maintained and to differentiate.

The investigator has an excellent track record and experience in the area, and his results are excellent, from what I gather, of collaboration with Dr. Mizner(phonetic) from Harvard and MIT.

I'd be inclined to consider funding this, but not at the amount requested, $750,000. If we look at page 13 of the grant application, there's an indication that the project would be completed in about three and a half years, and that the last six months or so would be devoted to writing papers about the grant.

I would, therefore, think that, especially with the consideration of limited funding that we have, that we're faced with, that perhaps we fund the project for three years and reduce the amount requested by $200,000 to $550,000, especially since, as I was starting to discuss with David, the idea that I've been over it appears to be the principal investigator only for the first two years.

I see somebody shaking your head, but that's what I'm reading, so if there's a clarification, in that I don't understand, so I would be inclined to fund it, but as a lesser amount for the reasons I've just indicated. David, can you sort of expand on it?

DR. GOLDHAMER: So a couple of comments. It's a very interesting grant. The investigator --

CHAIRPERSON MULLEN: I'll ask people to leave, if necessary. We'll ask people to leave, if necessary.

A FEMALE VOICE: Yeah, I understand.

CHAIRPERSON MULLEN: And I mean it.

A FEMALE VOICE: No, that was my fault.

CHAIRPERSON MULLEN: That's okay. It takes two to communicate. I really feel that we owe it to everyone to have everybody walk out of here and feel

that this was a fair process, and I feel that you all owe it one another in the discussions.

DR. GOLDHAMER: All right, so, let me just say a few words about the grant. The investigator is interested in epigenetic mechanisms responsible for maintaining the pluripotent state and how epigenetic marks are reset when cells are reprogrammed from fibroblast, and she's studying a particular protein, Dppa2, which plays a role in this process, and she has -- and it's also true that sometimes, particularly it's documented in mouse cells, with results in human cells, where there's not complete reprogramming, where epigenetic marks from the cell type of origin are maintained in the iPS cells, and those iPS cells, then, have a greater ability, capacity to re-differentiate into the original cell type than to other cell types, and they don't maintain complete or obtain complete pluripotency.

So it's an interesting problem. One reviewer was concerned that this idea of maintaining an epigenetic mark and having a greater propensity towards redifferentiation into the original cell type hasn't been shown in humans, at least -- actually, I did a search, and there are examples that this is a case, where it may not be as prevalent as a mouse, or it might just not be a

study that's in mouse, so that is one possible concern.

I will say that the reviewers were close-knit on the score. One gave it a one, and one gave it a 3.75, and the one, who gave it a 3.75, was concerned that the basic premise that I just described may not be as true in human cells.

Now my overall take is that it's a well-written grant and an interesting grant, but I will say that the first two aims are an extension of preliminary data and deal with mouse embryonic stem cells. The third aim has to do with human fibroblast reprogramming to iPS cells.

And although I'm a very strong proponent of using mouse cells, when they are the best model, because of genetics, or because for whatever reason human cells can't be used, I didn't see in here any reason why this couldn't be done in human cells.

And, so, given our directive to support and encourage work on human tissue, I wanted to see a very clear and specific comment of why mouse cells were being used and human cells weren't.

Now, that being said, part of the grant, the third aim, does use human cells, so I was a little ambivalent on this. It's an important problem. It's an

interesting protein, but I would have been more enthusiastic if human tissue had been used throughout, and there was no, as one reviewer commented, no substantial preliminary data using human tissue.

My, despite the good score, my initial inclination was to say no to this grant, without a firm justification for why mouse ES cells were being used, as one of the major issues that I have.

MS. HORN: So do we have a motion?

DR. GOLDHAMER: My motion is to not fund this grant.

MS. ENGLE: I second that motion.

MS. HORN: Further discussion?

DR. HART: David, can you say anything about the productivity of this lab?

DR. GOLDHAMER: She is an assistant professor since 2008. She's very well-trained. She does have other money from the state, but on different projects. She has an established investigator grant that was funded last year to follow-up to a seed grant funded prior to that, and those two grants are related to each other, but, as far as I can tell, not directly related to this effort.

DR. DEES: But it is a lab we're currently

funding.

DR. GOLDHAMER: It is a currently funded lab, and, in terms of the question about productivity, I'd have to go back. She's a very good investigator, but I specifically don't recall what the publication record - -

DR. HART: Just looking it up quickly on PubMed, it's a little low for the time and the money involved.

DR. FISHBONE: She also has another grant. That's the next one.

DR. GOLDHAMER: The next grant is also hers, and that does deal with human tissue. It's entirely separate from, a different subject than this grant.

MS. HORN: So we have a motion for a no. All in favor of placing this grant in the no column, please signify by saying aye.

VOICES: Aye.

MS. HORN: Anybody opposed? That's in the no column.

MR. STRAUSS: Yale 14, Treena and Paul.

DR. ARINZEH: Okay, so, this is an established investigator four-year grant, and it's

looking at the -- to try to understand the cell lineages, I guess, in the human blastocyst that form, so they're looking at the three areas, trying to get molecular profiles of the epi or epiblast, the trophectoderm, and then extra embryonic endoderm cells, directly from the blastocyst stage of the human embryos, and then to use this knowledge to establish stem cell lines for these three lineages.

So they have three specific aims. They're going to be looking at high-resolution transcriptome profiles. They will determine molecular identity DNAs of these three different lineages.

Aim three is replicate blastocyst cell fates, so they're using a high level of microbiology techniques here.

The reviewers gave a mixed score. The scores, initially, they were very different from each other, then they were corrected.

The primary reviewer gave it the lowest score, and it had several weaknesses mentioned on that. They felt that the number of embryos, or it wasn't clear about how many embryos were actually going to be used.

There were a wide range of studies being suggested, and the work proposed may not be able to be

accomplished in the time frame.

Also, that the aim three was potentially problematic, where the embryonic, the ESCs may not differentiate into these extra embryonic tissues in the iPS human embryos with abnormal morphology might not provide the necessary information, so a fair amount of weaknesses there.

Again, the PI is the assistant professor at Yale, collaborators there at Yale, with appropriate expertise, so there are no weaknesses there with the investigators.

So I'm leaning towards a maybe, only because there is, I thought, substantial weaknesses that were presented there by the reviewers.

DR. PESCATELLO: That was a good summary. I'm between yes and a maybe. I thought that the weaknesses were, this goes to my bias for basic research, were related, so that it was really good basic research, with some risk associated with it, so I give it a strong maybe.

DR. ARINZEH: This is not my area, so I don't know how difficult it is to generate these additional. I guess there's concern there, that that's high risk, making these extra embryonic endoderm tissue

and things like that. I don't know if you guys are familiar with --

DR. PESCATELLO: I'll make the comment, too, that this is an established researcher, who we've seen before, and has a track record with us.

MS. HORN: Do we have a motion for a maybe?

DR. PESCATELLO: Yes.

MS. HORN: Yes, we have a motion for maybe. Second for maybe?

DR. ARINZEH: Yes.

MS. HORN: Okay. Further discussion?

MS. ENGLE: I think this still goes back to the comment that was made previously, is that she hasn't had a lot of publication. She has had money from the state of Connecticut, and, you know, has she been productive with what she's currently had?

MS. HORN: Any further discussion? All in favor of supporting this motion to the maybe column, please signify by saying aye.

VOICES: Aye.

MR. STRAUSS: Okay. UCHC 17, Diane and Mike.

DR. KRAUSE: Shall I start? Do you want

me to start?

DR. GENEL: Yeah, go ahead.

DR. KRAUSE: So this is a grant to work in spinal muscular atrophy, which is a relatively common genetic disease. These kids are born normal, and then rapidly lose their neural tone, so it's really disastrous for the families, and it's difficult to predict whether they're going to have one of the children that will die before the age of one or just be in a wheelchair for the rest of their lives.

The problem is the gene, called SMN1, and there's a splice variant that's effected, and they end up making too much of a truncated protein.

So this investigator has knocked down the full-length gene in human embryonic stem cells and shown that the motor neurons that develop initially look good, and then lose -- don't develop fully all of the appropriate outgrowths, so that it's actually a model of the disease developed from the knock down in human ES cells.

He or she has also published that these neurons have elevated reactive oxygen species, and if they treat with something that breaks that down, N-ACETYL Cysteine, then the cells do better.

So it's a strong investigator, with nice preliminary data. Those data were obtained with the previous established investigator award from '08 to 2012, from which this one publication resulted.

The problems are, and this is what the reviewers were saying, there's no mention of iPS from the actual patients, and one of their aims is to look at whether this is a disease that is intrinsic to the neurons or involves the other cell types, as well, because in these patients every cell type is effected by the mutation. Every cell type has the mutation.

I completely agree with the reviewers, that the problem is iPS cells have already been made from patients with SMA. They've already been shown, in 2008, to make defective neurons, so the data that she published were actually confirmatory of what's already known for iPS for patients with SMA.

It really somewhat -- the field has moved along quite far, and this investigator doesn't seem to address that in the grant. There was just a paper in 2013 on other, you know, spinal muscular atrophy type neurons and are similarly showing that it's a disease that's intrinsic to the neurons, even though the mutation is in all of the cell types.

The question is why, and that might have to do with RNA splicing, etcetera. So my bias is that the reviewers are writing that this is not one of the best top grants.

DR. GENEL: I would agree. A couple other points is this investigator has not only had a seed grant, but also had an established investigator grant and is, subsequently, is a co-investigator on schizophrenia culture from another application that I think is further down on our list.

Despite the 27.5 score, the second reviewer was certainly much less enthusiastic than the first.

MS. HORN: Do we have a motion?

DR. GENEL: Not fund.

DR. KRAUSE: I have trouble with that. I have trouble with the whole idea of us rearranging the scores after the peer reviewers have already scored it, so while it was not -- while I really think that there are tremendous weaknesses in the grant, I think that to say that it goes to a no, when there are grants that got worse scores, it's difficult. I'll say maybe.

DR. GENEL: I'm happy with it under maybe.

DR. KRAUSE: Maybe somebody can help me

with this, but I just have trouble in the whole thing, when we go through these grants, and then we --

DR. GENEL: I'm happy with it on the maybe list. It's okay.

MS. HORN: So we have a motion for maybe. Second?

DR. GENEL: Yes.

MS. HORN: All in favor? Or any further discussion about it?

MS. ENGLE: I will point out that I agree with your assessment, that the authors of this grant did not take into account where the current state of the field is. It is well-established that there's intrinsic issues with the neurons.

There have already been screening studies done. There are already compounds in clinic or moving towards clinic-based on screens and iPS-derived SMA motor neurons. All of that would argue that this is not necessarily current stem cell biology.

DR. DEES: I would just add that we're going to draw a line somewhere. It's not going to be far from where we are. It's probably going to be above where we are now.

DR. KRAUSE: All right, so, I move that we

change it to a no.

MS. HORN: Okay, so, you're making a motion to withdraw your motion to put it in the maybe? Is there a second, withdrawing the motion to put it in the maybe category?

DR. KRAUSE: Yes. I withdraw my motion to put it in the maybe category and second Mike's motion to put it in the no.

MS. HORN: Oh, okay. Sorry. Okay, so, we have a motion now to put it in the no category, seconded by Dr. Genel. Further discussion? Okay, the grant -- everybody in favor of placing this grant in the no category, please signify by saying aye.

VOICES: Aye.

MS. HORN: Opposed? It's in the no.

MR. STRAUSS: Yale 05, Sandy and Gerry.

MS. ENGLE: Do you want to go first? Do you want to go?

DR. FISHBONE: No, you go.

MS. ENGLE: Okay, so, this grant is looking at the genomic regions that control the making of RNA in human embryonic stem cells.

The interesting part of this is that the PI has already generated a library of enhancer elements

for stem cells, and then the purpose of this grant is to actually characterize those transcriptional enhancers, those things that help the cells make RNA, which then makes protein.

They want to test them in multiple lines, and then try a nest of deletions to find out exactly what the active component is, and then they'd like to make constructs and make transgenic animals, so inject animals with these transcription enhancer elements to see if they still function the way that they thought they functioned in the dish, and they have what they call a timer reporter system to do that.

And, then, they want to use circularized chromosome conformation capture, which is another technology to identify genes that are regulated by these enhancers.

They propose to do this over a four-year period. The comment by the reviewers, and I certainly concur, is that this is somewhat ill-defined, and they are very unclear about how much they can really accomplish, so they literally have dozens and dozens, if not, hundreds of these transcription elements, and they are unclear about how many they will really truly be able to evaluate, based upon the time and the money that they

requested.

That said and done, it also gets very confusing once they start to go into animal models and try to understand what's going on, and it can be quite difficult to progress forward.

So that's sort of my take on it. Did you want to have any -- add anything else?

DR. FISHBONE: Well I was looking at the investigator's background, and he's an M.D., Ph.D. He's done fellowships in infectious diseases, now an associate professor at Yale of infectious diseases, has an NIH grant to deal with HIV. I mean it seems to me that his main interest is infectious diseases.

MS. ENGLE: And I will point out that one of the criticisms was that this investigator had received a previous grant and has not published, and he has not published on this particular topic at all.

DR. FISHBONE: I just wondered whether his background would allow him to be able to complete what he wants to do.

MS. ENGLE: So I would recommend that we do not fund this particular grant.

DR. FISHBONE: I would second that.

MS. HORN: We have a motion for no and a

second for no. Further discussion? All in favor of placing the grant in the no category, please signify by saying aye.

VOICES: Aye.

MS. HORN: Anybody opposed? The grant is placed in the no category.

MR. STRAUSS: Okay, the next six grants you'll be looking at are the final six. They're all ranked with a score of 30. The first three on this page had the final score changed during the study section. Yale 01 is the first one, Ann and Richard.

DR. KIESSLING: So this is -- the investigator is Rizzolo, and we had funded him -- let me go back. So this is a grant to try to understand a better approach to age-related macular degeneration, which they cite as the leading cause of impaired vision. I guess that's true.

There have been a number of attempts to deal with this, and, for some reason, some of the therapies that exist aren't working, so this particular investigator has developed what he thinks is a three-dimensional model of the retina in a dish, and that's kind of an interesting thing. He is using nanofibers to do this.

The three-dimensional model claims it can either be used to transplant directly into retinas in the future, perhaps, or it will serve as a good test system for pharmacological agents to kind of delay the blindness that comes from macular degeneration.

We previously funded him or her, I don't know, we previously funded this investigator, and one of the criticisms of one of the reviewers -- this is an example of a review that doesn't match the score, so one of the reviewers gave this grant a score of four, but has no criticisms of the grant. Seems to think it's an important problem. This is a good proposal by an investigator, who focuses on tissue interactions that regulate epithelial function in the retina.

The only criticism of this score four is that there's a moderate publication record, but if you look at this investigator's publication, he's published three what look to me like very nice papers from his previous Connecticut Stem Cell Fund Award, which is studying exactly the same thing.

So this is a career investigator, who has really targeted on this particular issue of epithelial junction interaction. He's using human embryonic stem cells to do this. He's deriving retinal epithelium and

retinal progenitor cells.

The second reviewer was very enthusiastic and gave this a score of two, and, when they got together to reconcile the scores, the reviewers and the co-Chair highlighted a number of deficiencies related to the differentiation method suggested for generation of mature retinal cells.

So I guess the problem here is that the investigator, the reviewer that gave it a score of four, although he doesn't say this in his review, thought that there was going to be a better way to differentiate these cells in vitro than this investigator proposed.

So I don't know if three nice papers is a moderate publication record from our previous work, but it's the papers that seem to be really targeted to what he's working on. This seems to be, to me, a perfect stem cell-related grant, and I was more enthusiastic about this than a 3.0.

DR. DEES: This was a hard one to make sense of what was going on. Ann described the study pretty well. It's clearly related to (indiscernible) disease, at least some sense life-threatening, but it's a serious disease.

The reviewers thought the studies were

well-designed, but they're kind of all over the place. There was a two and a four. The initial was a score of a three. The two reviewers got together to decide on a 2.5, then they talked to the co-Chair, and it got moved back to 30, so it's kind of all over the place.

And what's right is we're not getting the whole story from the reviewer, who is giving it a four.

DR. KIESSLING: Right.

DR. DEES: Since I'm not a scientist, I'm not going to second-guess them, so I was willing to defer to that.

DR. KIESSLING: I think this is an example of some of the primary reviewers were trying to use one to nine.

DR. DEES: Yeah.

DR. KIESSLING: And not realizing that a score of four was probably not even possible to be funded. I don't know.

DR. DEES: I was inclined to say this is just too far down on the list.

MS. HORN: Rick has offered to provide a little clarification on the process.

MR. STRAUSS: Yeah. I just want to make sure everybody understands. We don't have a primary and

a secondary reviewer this year. There are two equal reviews, and, in this grant, what did happen is it went to reconciliation, because the scores were more than one point apart, and this is a grant that was then discussed in the study section, and the study section, not the co-Chair, because the co-Chair did not make the decision that the scores should be changed, the final scores should be changed to a 30.

The initial reconciliation was done by the two reviewers. The final study section review was a result of the consensus of the study section, and that's why it was a 30, and then there's a write-up that justifies why they thought the score should be changed to a 30, just so you're clear on the process that was used.

DR. DEES: Here's what they said in the final reconciliation, reviewers, the co-chair highlighted a number of deficiencies related to differentiation method suggested for the innervation of mature retinal cells and the inappropriate choice of models included in the proposal.

DR. KIESSLING: It clearly says that there's a lead reviewer.

MR. STRAUSS: The lead reviewer is designated to write the reconciliation, but they're two

equal reviews. Last year, there was a primary reviewer that looked at the whole grant and a secondary reviewer that only looked at certain aspects of the proposal, not a full review, so, this year, there are two full reviews.

The lead reviewer writes the reconciliation, based upon their discussions and negotiations if the score is more than one point apart.

The study section review, if the score is changed, is written by either reviewer, in some cases the lead reviewer, and, in some cases, it might be the co-Chair, but it is the -- the statement is the consensus of the peer review committee.

DR. KIESSLING: Can I read a couple of comments from the reviewer that thought this was a great project?

One of the comments was that this provides a complete study, where it characterizes in vitro, the incorporation of scaffold in cells, and then uses in vivo rodent models that are in mid to late-stage of the disease to observe the effect of the cell-based scaffold, so, evidently, not all the reviewers thought that the rodent model was appropriate.

The innovation about this application is that the use of scaffold to help in cell transplantation

is fairly normal of this particular field.

I don't know. I move that this be put in the maybe category, because I think this is kind of a good proposal on a really important problem.

MS. HORN: Do we have a second?

DR. WALLACK: Second.

MS. HORN: Further discussion?

MS. ENGLE: So I would just like to point out that there are currently ongoing clinical trials with human stem cell-derived retinal pigment epithelial cells, that the preferred model is pig, and that, you know, it seems to be working. People are starting to regain their sight. I'm not sure how novel this truly is.

DR. GOLDHAMER: I'd like to make one comment about the score of four, the reviewer's score of four. It's true that there's very little information that tells us why that score was given, except in the narrative. It does say that the experiments are well-designed, though lack critical preliminary data on generating and characterizing human ES cell-derived IBE, IBC and photoreceptors.

So that's really the main criticism that resulted in the four, so the question is how compelling was the preliminary data showing cell types?

DR. KIESSLING: But that peer reviewer also says tools generated will be of use for the larger community.

DR. GOLDHAMER: The tools generated, well, tools once generated, or tools generated. I mean the question is have they generated tools? Can they move forward? Where are they in the process? And that really comes down to where they are with the preliminary data. I mean that was the reviewer's main concern.

MS. ENGLE: And I would say my concern is that I'm not seeing what is novel about this. The science has already moved quite past this, and, so, I don't see anything that makes me think, wow, this has got something that we haven't already seen or people haven't already thought about.

MS. HORN: Okay, unless there's some reconsideration of the motion, we'll call the motion.

DR. DEES: I'll move that we put it in the no category.

MS. HORN: Okay, so, we have a motion was drawn to put it in the maybe.

DR. DEES: Withdrew.

MS. HORN: Seconded? Ann, do you move to withdraw your motion to put it into the maybe category?

DR. KIESSLING: I don't know.

DR. DEES: It's going to be in the maybe category, so why don't we just leave it there?

MS. HORN: We have a motion for maybe. All in favor of putting it in the maybe, signify by saying aye.

VOICES: Aye.

MS. HORN: It goes in the maybe.

MR. STRAUSS: Next up, we have 02 with Ron and Milt.

DR. WALLACK: I had a hard time with this grant. I thought there was a questionable design of the study. I was not clear about the goals, especially the goal of creating, as I understand it, a platform for future, more efficient therapies for heart disease.

I don't see this as being a grant that indicated any transformational movement in this area of cardiovascular regenerative medicine.

I believe that the study is also based upon some hypotheticals that might not be accurate, as far as I understand them.

I believe that the investigator has strengths in other areas, like ovarian cancer, but not specifically in this particular area.

I believe that we could recommend, for example, that the investigator could possibly come back in the future, actually, perhaps, as a seed grant, so I wasn't that impressed with it, and I'm not in favor of moving forward on it.

DR. HART: So just to give it a fair hearing, the topic is actually quite novel and interesting. She's identified a long non-coding RNA that appears to function endogenously as a MicroRNA sponge, which is just a novel mechanism. Other people have proposed other mechanisms for these long non-coding RNAs. This is the first one I've seen that it falls antagonizing MicroRNA activity.

There have been several problems. One of them is that all the preliminary data are in cells, skeletal muscle cells, other than cardiac muscle cells, and, so, it seems to be kind of manufactured into a cardiac project of whole cloth, almost.

Again, to be fair, she previously had a seed award on a somewhat related topic, Lin 28 regulation, and she was very productive on that project, mostly in kind of middle tier journals, but at least one really outstanding high-impact publication from that seed project.

So, you know, I think she certainly is qualified to work, and has found something very interesting. The reviewers kind of pounce on her for the preliminary data in a different system and a few other details. The line variability among the cardiac cells she did examine, for example, and, so, I think, at this time, with this highly-competitive environment, I would suggest no.

DR. WALLACK: Which is consistent with what I was saying.

DR. HART: Right.

MS. HORN: So, Dr. Hart, you're making a motion to place it in the no category?

DR. HART: That's right.

DR. WALLACK: Second.

MS. HORN: Any further discussion? All in favor of placing this grant in the no, please signify by saying aye.

VOICES: Aye.

MS. HORN: Opposed? It's in the no.

MR. STRAUSS: Next up, Yale 04, David and James.

DR. GOLDHAMER: So this is a grant by Karen Hirschi from Yale, and it's entitled endothelial

cell differentiation and hemogenic specification. So Dr. Hirschi is a professor in the Department of Medicine, and she has a long-standing interest, and is an expert in studying various aspects of blood vessel formation.

So the focus of this grant is to try to understand some of the molecules and signals that are involved in directing human embryonic stem cells and human iPS cells to the endothelial lineage.

This is very important for, applicable for vascular disease therapies, and a lot of people are working on this. The reviewers thought that this was an important problem.

In preliminary data, she has found that the signals required by ES cells and iPS cells are actually quite distinct and surprisingly so, and, so, she has proposed to try to delve deeper into this and try to understand the pathways involved in getting iPS cells to take on their epithelial state and ESCs to take on their epithelial state.

The major concern of the reviewers was that they didn't necessarily believe the underlying premise, that there's an inherent difference between iPS cells and ES cells in its capacity, and they argue that it could be inefficient or incomplete reprogramming of

the iPS cells, perhaps maintenance of epigenetic marks, for instances, that accounts for this difference.

The investigator did bring up this idea of incompletely programming, but it wasn't something that was developed fully.

Now I will say that this is a resubmission from a grant from last year that scored about the same. I think it scored slightly better last year. The grant is essentially identical to last year's grant, not just the aims, but the actual text. I found maybe two or three sentences that were different, and one of the criticisms from last time was that the investigator only used three iPS lines, and the reviewers were worried about variability between those lines and whether they can make any firm conclusions about iPS and ES cell differences, based on such a small sample size, and, so, the investigator has now proposed an additional iPS line, so I think it's up to 10 now.

Now, surprisingly, the investigator did not propose to use as a starting point endothelial cells to reprogram them to iPSCs to directly test the idea that there might be epigenetic marks or incomplete reprogramming that accounts for iPSCs being more efficient in making endothelial cells than ES cells.

But, anyway, the grant has improved somewhat by the inclusion of additional iPSCs. From my personal standpoint, I thought that the grant had some other issues with it that were in last year's grant, because it was identical and weren't addressed this year.

I think it's quite narrowly focused on one molecule, called 19a(phonetic), which a great -- at least half of the grant is focused on this one molecule, and there's really no evidence, direct evidence for the involvement of 19a, except that it's upregulated when cells are induced to differentiating to endothelial cells.

To me, that's not a sufficient criteria for spending half a grant, without some additional data that suggests some involvement. There's probably thousands of genes that are upregulated during this process.

So it's a very important area that I thought there was sufficient reviewer concern, and the fact that it's kind of stayed in its exact form from last year, with very kind of minor improvements, I was not compelled.

I should also say one last thing. There's another kind of discovery approach, where she is looking

for new molecules that may promote endothelial differentiation, and she has some -- she's in the process of finding RNAs that are upregulated during this process, and she's going to, then, test the functions of these RNAs in promoting endothelial differentiation.

Same criticism. First of all, there's only about one paragraph on this discovery approach, so we don't really know what is intended, and, secondly, there's no real prioritization to really know. You know, there could be hundreds or thousands of genes that change, and it just was, to me, not a compelling grant, and, so, my recommendation was it's a no for this one.

COURT REPORTER: One moment, please.

DR. HUGHES: I didn't have the benefit of comparison with the previous grant when that was eliminated. I thought that the reviewers' comments were quite troubling, and they raised a number of methodological and scientific issues that I thought merited that this not be approved.

MS. HORN: Do we have a motion to place it in the no category?

DR. GOLDHAMER: I'll make that motion.

MS. HORN: Okay and a second?

DR. HUGHES: Second.

MS. HORN: Any further discussion? All in favor of placing this grant in the no category, please indicate by saying aye.

VOICES: Aye.

MS. HORN: Anybody opposed? It goes in the no category.

MR. STRAUSS: UCHC 18, Sandy and Mike.

DR. GENEL: Go ahead.

MS. ENGLE: Do you want me to go? Okay. So this grant looks at essentially the role of Kalirin in schizophrenia, and they base it on the hypothesis that Kalirin is important in what is called spine formation, so on neurons, these little spines form, and it's thought the more dense your spines are, the better you're going to be at forming them and functioning.

And, so, they want to look at spine formation in schizophrenic patients, using iPS cells from schizophrenic patients and differentiating them into the neurons that are thought to be involved in schizophrenia, and they want to use a co-culture treatment, where they actually generate different kinds of cells and put them together in a dish, and that was one of the major concerns of the reviewers, is that not only is it really hard to measure spine density when you have just a neuron

there, but it gets extremely difficult when you have multiple different kinds of cells in a dish.

And, so, a lot of the concerns of the reviewers and a lot of concerns that I have, as well, is that it was not well-described on how they plan to account for that, or how they plan to account for the fact that there's just lots of variability between normal people, let alone people with schizophrenia and normal, and the fact that you're generating them from iPS cells, and that there wasn't much discussion of exactly how they would measure them, and how they would do the math associated with that and the sort of imaging necessary, so, overall, they were very concerned about the methodologies associated with that.

I will say that this investigator has previously received Connecticut funding and a stem cell grant or a seed grant in this area, and this would be moving him from a seed grant to an established investigator grant. Would you like to add anything more?

DR. GENEL: Yeah. This might have been better suited for a seed grant, actually, and the budget is almost close to a seed grant. They only asked for $495,000, in part, because of the methodological concerns, which is too bad.

I mean I'm inclined to be supportive, only because I think, as the second reviewer indicated, the enthusiasm is high, because it may provide a valuable screening method for new schizophrenia treatment.

In that sense, I think I find a lot of this very attractive. I suspect I know what we would do, but I'd like to keep it on the hold list until we look at everything.

MS. ENGLE: I'm okay with that, actually, because I think that schizophrenia has a huge unmet clinical need. I think the grant speaks to developing tools and methods for assessment.

I think the big concern is that it's high risk. It may all blow up, but, that said and done, it's an interesting concept and idea, so I would recommend a maybe.

MS. HORN: Okay, do we have a second?

DR. GENEL: That was the second. I made the motion.

MS. HORN: Okay. You made the motion, we have a second. Any further discussion?

DR. HART: How many subject iPS cells would be involved?

MS. ENGLE: They are very unclear on many

of the details, and that is one of them, so I will say that they were unclear, as to the number of lines they would use or would need to use, and I think that's a difficult calculation.

They were unclear, as to exactly how they would measure it. They were unclear about the statistics they would use to understand that they got there, but there's an interesting premise in there.

DR. GENEL: That's why it's high risk.

MS. ENGLE: Yeah, that's high risk. It may blow up.

DR. HART: And the problem with the schizophrenia not being a single-gene disease it's going to be very difficult to address with the small numbers you could possible do with stem cells.

MS. ENGLE: That is true.

DR. WALLACK: So can I just say why are we putting it on the maybe list, if I'm hearing, you know, all these negatives about it?

MS. ENGLE: It's an interesting idea. I think the premise was it's an interesting idea. It goes back to is it more appropriate for a seed grant?

Yes, I know they've received a previous seed grant, but could the funding be reduced to, say, you

know, let's think harder about this, but I realize that we have a funding situation that's untenable here, so it could easily be moved to the no.

DR. GENEL: I would rather not dismiss it.

MS. ENGLE: -- probably not have money to fund it, but we want to give it an endorsement if you were thinking in the right direction.

MS. HORN: Okay, so, it's remaining in the maybe. Any further discussion? All in favor of having this grant placed in the maybe, please signify by saying aye.

VOICES: Aye.

MS. HORN: It's in the maybe. Final one.

MR. STRAUSS: UCHC 08, with Diane and Gerry.

DR. KRAUSE: All right, this is a grant, called chromatin interaction network in neurocristopathy syndromes, and it's from an associate professor at UCHC, Dr. Bayarsaihan, who has for many years studied TF2I or TF21 transcription factors, which are just general transcription factors.

He has 11 publications on these TF2I or TF2 -- does anybody know what that's called? TF2I transcription factors. They're all somewhat general.

It's not a specific question of this transcription factor family, because it's a general transcription factor family, but what's interesting is, that he's getting at here, is that, in some diseases, specifically in Williams syndrome and others, where there's a problem with a neural crest cells, you actually have mutations in the chromosomes overlapping one of the genes in the TF2I category, so that's the gene GTF2I.

So the plan here is to use their expertise to map the chromatin and try to figure out how these mutations in this region, when they knock down the TF2I gene, are effected.

And it's very descriptive, but descriptive of chromatin confirmation, so what they're going to do is ChIA-PET, which is a way of identifying all the ways that the chromatin moves around a specific region.

They're going to do chromatin confirmation analysis, which is a similar kind of approach. They're going to do RNA deep seq, and all of this they're going to do normal iPS or iPS from healthy normal donors and iPS I think from patients, if I got that right. Is that right, Gerry?

Yeah, iPS from patients and iPS from normal donors, and they're going to compare this

chromatin confirmation in mesenchymal stromal cells derived from these iPS and in neural crest cells derived from these iPS.

So the reviewers were somewhat enthusiastic, just saying they hadn't taken, that maybe it didn't take into account all of the alternative approaches.

My concern was really what they're going to do with the information once they get it, because it seems like a very, very large descriptive study, so the main concerns of the reviewers were that the technical hurdles were not addressed, the controls were not described, the expected results were not described, potential pitfalls not described.

My concern was more, even if they succeed, what are they going to do with the information?

DR. FISHBONE: I would agree with you. This was a little sort of out of my category for understanding what they were trying to do. I don't know, from what you're describing, that this is something --

DR. KRAUSE: My only hesitancy in saying no is this person is well-funded to study TF2I, has been studying it for years, and maybe there's something I didn't get, but if we just go with what the reviewer

said, the reviewers both gave it a three and felt that technical hurdles and alternative approaches were not addressed adequately.

So I think, with that, rather than my expertise, because I don't have it, I would recommend no.

MS. HORN: Do we have a second?

DR. FISHBONE: I second it.

MS. HORN: Any further discussion? Okay. All those in favor of placing this grant in the no category, please signify by saying aye.

VOICES: Aye.

MS. HORN: Anybody opposed? It goes into the no.

MR. STRAUSS: Okay. The last one, the category Yale 03, with Ann and Richard.

DR. DEES: So this is a grant that proposes to understand the mechanisms by which embryonic stem cell-derived neural stem cells either self-renew or differentiate into other kinds of cells.

The group will first seek to replicate in human stem cells what they've already established in mouse studies, and then go on to look for other means of proteins that may be crucial to the mechanism by which they either self-replicate or differentiate.

The goal is that understanding these mechanisms will help us understand why stem cells ordinarily repair damaged tissue beyond that the way normal and wear and tear, the idea that you if don't get radical repair, then you'll get wear and tear repair, and the question is is there something they can do that would generate something different?

The results are mostly about understanding the basic cell mechanisms here, but they clearly have some long-term implications for the therapies. The grant calls for some mouse studies, the rationale for which nobody seemed to understand. The two peer reviewers really had really radically different takes, one being a 1.5, the other giving it a seven.

On reconciliation, they agree the results can lead to some important findings in cell biology, but the rationale for using the embryonic stem cells is weak, and the PI had little experience in the area.

DR. KIESSLING: The only thing I'll add is that this was an interesting asymmetrical cell division project, and I think asymmetrical cell division is fascination.

This investigator actually published a nice paper that talked about linking that to the Golgi

apparatus.

One of the big concerns I think, which was the publication record of this investigator, this person took over a grant when the original PI left, and, so, they were funded by Connecticut from ’07 to ’10, I think, and the PI went to San Francisco.

I don’t see any publications from that grant effort, and, in about the last four years or five years, this investigator has only written reviews or commentaries, lists three, two manuscripts in preparation and one in revision, but the one in revision doesn’t appear to be a report. It appears to be another review, so I’m very concerned that this person was sort of stuck in a numb-like asymmetric niche and really needs to get some experience with human embryonic stem cells.

They’ve done a lot with mouse, and that’s interesting, but the reviewer, who seemed to really think that the method that they’ve used from the mouse cells were not going to work on human cells, I can’t really speak to that, but was very concerned, and that’s the reviewer that gave it a seven, and they thought they needed some different tools to go from mouse to human.

It appears to be this investigator needs to get some work done.

MS. HORN: Do we have a motion?

DR. DEES: Move not to fund.

DR. KIESSLING: Yeah, not to fund.

MS. HORN: Seconded by Ann. Okay, further discussion? All in favor of moving this grant into the no column, please signify by saying aye.

VOICES: Aye.

MS. HORN: Anybody opposed? It goes into the no.

MR. STRAUSS: So, at this point, what we've done is we've got two grants that you said yes for funding, eight grants in the maybe category, and seven in the no category.

DR. KIESSLING: And nobody wanted to move anything from the below three level to a discussion level?

DR. GENEL: We have some very prominent names that are below the three.

MS. HORN: So, at this point, we can reconsider the maybes and see if there's anything that we would like to move either to yes or to the no. We have a little bit of time before lunch.

DR. KRAUSE: Rick, would you just say the names of the authors of the maybes, because I can't read

that very well.

MR. STRAUSS: Well I think you all have that in front of you, and I'm going to totally botch the names. If somebody else wants to try that? The first one is --

DR. KRAUSE: Never mind. She has it.

MR. STRAUSS: I'll tell you the numbers.

DR. KRAUSE: No, that's all right. I got it. I got it.

MR. STRAUSS: Is everybody else okay? If you make this smaller, then you can't see them all.

MS. HORN: So let's just start at the top and run down the seven maybes?

MR. STRAUSS: Eight maybes.

MS. HORN: Eight maybes, okay.

MS. ENGLE: I move that we start from the bottom and go up.

MR. STRAUSS: There's two at 30, and the UCHC 18 is the first one.

MS. ENGLE: Right, so, I move that we move, as much as I love that grant, I move Ma into the no pile. No funding at all, given what we have left, that we have seven grants that are -- I move it to the no pile.

MS. HORN: So we have a second on that, Dr. Dees?

DR. DEES: Yes.

MS. HORN: Okay.

DR. WALLACK: So is this UCHC 03 we're talking about?

MS. ENGLE: No, 18.

DR. WALLACK: 18?

MS. ENGLE: The Ma grant on schizophrenia iPS cells and spine density.

DR. WALLACK: Okay.

MS. HORN: Any further discussion? All in favor of moving this from the maybe to the no category, please signify by saying aye.

VOICES: Aye.

MS. HORN: Anybody opposed? Move to the no.

MR. STRAUSS: Okay. Next up, Yale 01, Rizzolo.

DR. KIESSLING: So this is the macular degeneration grant, and I just looked up on Clinical Trials.gov, and I can't find anything, except for one, where they're actually transplanting what look like retinal cells.

MS. ENGLE: There's already been ACT. Advanced Stem Cell Technologies is doing the clinical trial. It may be in Europe, but it's being run.

DR. KIESSLING: And it wouldn't be listed on Clinical Trials.gov?

MS. ENGLE: No, because it's European and not U.S.

MS. HORN: I'll just remind people, who have an interest in one of the grants that are a conflict, not to comment at all on any of the grants that are being discussed.

MS. ENGLE: But there is a clinical ongoing. If it's privately funded, it wouldn't be -- well it should be, but if it's in Europe, it doesn't necessarily go there, but there is an ongoing clinical trial.

DR. GOLDHAMER: I'd like to make a comment about this grant. So, Sandy, you made the argument before, that having a clinical trial ongoing should not influence --

MS. ENGLE: I would argue that, but I would argue that, even on that basis, my concern is that their science is behind. I agree with the reviewers, that some of their science is not currently up to speed.

DR. GOLDHAMER: That's a different story.

MS. ENGLE: Yes.

DR. GOLDHAMER: I just wanted to make sure that a decision --

MS. ENGLE: So I agree that you can start the race late and still have a chance at winning, but if you start with poor science, then you still have a challenge ahead of you.

DR. KIESSLING: They didn't say the science was behind, that I can find. I mean this was weird. The reviewer that gave this a score of four had no weaknesses, except for the fact that there were some details in the description, but the strengths were his expertise, and they thought that it was a moderate publication record, but I didn't see that it was moderate.

Considering some of the other PIs, I think he had three publications out.

DR. DEES: As David pointed out, there was -- I mean the criticisms are in the narrative.

DR. KIESSLING: No.

DR. DEES: (indiscernible)

DR. KIESSLING: The reviewer that gave this a score of four said almost nothing (indiscernible)

and the reviewer that gave it a score of two had lots of confidence.

DR. DEES: The reviewer that gave it a four in the narrative says (indiscernible) a lack of critical preliminary data are generating (indiscernible)

DR. KIESSLING: Right. The tools generated will be of use for the larger (indiscernible) I think this is a really hard one to not fund at all.

MS. HORN: Okay, so, is there a consensus, that we leave it in the maybe category for now?

MS. ENGLE: I would like to move that we put it in the no category.

DR. GOLDHAMER: It's kind of too far down the list, is the problem. Once there are preliminary data that shows that they can make these cells or not and if not provided by the investigator is, or evidence from the literature that they can make these cells, I'd say --

DR. KIESSLING: This preliminary data I thought was convincing, and I don't make these cells. Now if this science is just way out of touch, I guess I'm not so impressed with --

MS. HORN: Okay, so, we have a motion to move it to the no. Do we have a second?

DR. GOLDHAMER: I'll second.

MS. HORN: Okay, further discussion? All in favor of moving this grant to the no, please signify by saying aye.

VOICES: Aye.

DR. WALLACK: So if you have a no to the motion, you keep it in the maybe?

MS. HORN: We'll keep it in the maybe, and we'll have to revisit it.

DR. WALLACK: I'll vote no.

DR. HART: I'll also vote no.

MS. HORN: That stays in the maybe.

DR. HART: It stays in the maybe?

MS. HORN: It stays in the maybe.

DR. GENEL: I'm going to draw the line here. Are you on the next one?

MS. HORN: Well we can do that, or we can take a break, if we don't think we're going to change anything above this line here.

DR. GENEL: Well I think we have to see where everything folds out at the end before we can make those decisions.

MS. HORN: Okay, now, there was some discussion about moving our room, so that we are not next to the people, who are noisy, so I will let you know, but

please go ahead and have lunch. Leave your things here, and I will let you know if you need to come and transport them to the next room.

They do quiet down periodically, but, then, they get enthusiastic. It's going to be a long afternoon if that continues.

(Lunch recess)

MS. HORN: So moving onto seeds, and, Rick, how many seeds do we have to review?

MR. STRAUSS: I think it's 28.

MS. HORN: Twenty-eight, so everybody get their coffee and away we go.

MR. STRAUSS: Okay, are you ready?

MS. HORN: Ready.

MR. STRAUSS: So Yale 04 with Ron and Milt.

DR. HART: Can I ask what's the order logic here, because it seems like the scores are very --

MR. STRAUSS: Well the final score is the column that's in yellow here.

DR. HART: Okay, because that's not what's on the other Excel sheet.

MR. STRAUSS: I'm sorry?

DR. HART: The original --

MR. STRAUSS: The score on the left (multiple conversations) is the final score.

DR. HART: The Excel sheet.

MR. STRAUSS: So this proposal had a score of 12.5.

DR. HART: Okay.

DR. WALLACK: Let me start, then. So I found this grant to be an excellent, well-organized, well-designed grant, based upon previous work that this group has been involved with.

The project intends to explore the capacity of vascular endothelial growth factors and the receptors to promote human neural stem cells, which could impact cognitive disorders associated with aging.

The investigator has a very strong track record, and, from my perspective, has a real chance of achieving significant goals.

I strongly recommend funding of this particular grant.

DR. HART: Okay, so, this is the investigator -- I think we saw this person last year for a different reason, if I remember correctly, but recently moved from France to Yale, a very senior, relatively senior person for a seed award, is, therefore, very

accomplished and very polished, in terms of the grant presentation, was very highly reviewed.

It's actually, when you look at it in the context of this person's career and accomplishments and what is being proposed in the grants and the review statements that were made versus the funds being requested for a seed project, it's a great bang for the buck, so I think it's very supportable.

DR. WALLACK: I'll move that we fund it.

DR. HART: I second that.

MS. HORN: Further discussion? All in favor of moving this grant into the yes column, please signify by saying aye.

VOICES: Aye.

MS. HORN: Anybody opposed? Next grant?

MR. STRAUSS: Okay, next, UCHC 11, with James and Diane.

DR. HUGHES: This grant is about using iPSCs for cartilage regeneration, and it's investigating the epigenetic differences between iPSC-generated cells from skin fibroblast versus (indiscernible)

I thought that this was great, because of its proximity to clinical application. It's a widespread medical problem. The researcher in the lab both received

high reviews and have experience with the methods, and, so, I recommend that it be approved.

DR. KRAUSE: I'll just add that it got excellent scores. It's a very strong post-doc, though, at Yale. That person wouldn't be called a post-doc after 10 years, but she clearly is very talented and doing great research.

She already had a seed award, from which she published the data showing the differences between the chondrocyte-derived iPS and skin iPS, and now will be going into that in more depth, and I support it for funding.

MS. HORN: Okay. I'll take that as a motion. And a second? Okay. All in favor of -- is there any further discussion about it? All in favor?

DR. FISHBONE: I have a question. It seems to me that a number of the seeds are continuing work that they were doing previously on the seed grant. Is that what the seeds are supposed to be for? In other words, should they be moving into another category if they're not changing, they're not learning something different, or doing something different?

MS. HORN: Not up to the scientists for a seed grant.

MS. ENGLE: I actually think that's a fair comment, because if the point of the seed grants is, as stated, to allow you to do something new and different and a little risky, something you may not have a background in, in theory, at the end of the two-year period, you should have enough information to apply for more traditional forms of funding, be it an NIH grant, etcetera.

I did notice, as well as you did, that there were several folks that were continuing on in the seed grant program on the same topic. I don't have a history here to understand how the group as a whole feels about it, but I did notice it was a trend.

DR. HART: And if you notice, under our checklist, it says intended to support the early stages of a project not yet ready for larger scale funding. You could read that either way.

DR. FISHBONE: I mean it's an inexpensive way to have somebody do the research, but I'm wondering if it's a little different from what was established as a seed grant.

DR. KRAUSE: I think it's a fair comment. I'm not sure, given that this person is no longer really early stage, but she couldn't write for an established

investigator award, because she's not a PI, so it's an interesting -- that's an important question.

I don't know the answer. Should we put this as a maybe, because of that?

DR. FISHBONE: No.

DR. KRAUSE: Okay.

DR. FISHBONE: I'm just wondering if we're deviating from what the seeds were established for.

DR. HART: That certainly speaks to the prioritization. You would imagine prioritizing a new investigator. We truly do investigator hire, based on that alone.

DR. WALLACK: So, Marianne, I would think that this discussion would be very appropriate as we go on into the next season of funding, and you might want to put it on the agenda at some point to have a discussion about it.

MS. HORN: Yes. I know we've had the similar discussion about who was an established investigator and when an established investigator can come in and do research on a seed grant.

Okay, so, we have this one, a motion and second for funding. Any further discussion? All in favor of placing this in the yes category, please signify

by saying aye.

VOICES: Aye.

MS. HORN: Anybody opposed? It's in the funding category.

MR. STRAUSS: Okay, next, Yale 38, Ann and Richard.

DR. DEES: This is a grant that attempts to use human embryonic stem cell-derived neuronal cells to investigate the mechanisms by which West Nile virus affects brain cells and to test the possible therapies (indiscernible) RNA in vitro.

The grant essentially funds a collaboration between a researcher primarily interested in the West Nile virus with one who develops neurons from embryonic stem cells, noticing the primary work done by a post-doc and a grad student.

(indiscernible) human disease is quite obvious, and studies being done in vitro establish the possibility of therapy.

The peer reviewer is really quite enthusiastic. It's 15. Though it concerned the lack of experience to a PI working in stem cell, there is (indiscernible) such experience, and some concerns about whether the use of (indiscernible) RNAs would be as

straightforward as she thinks, so there have been several models used in HIV research, so I recommend that we fund this.

DR. KIESSLING: I wasn't so enthusiastic about this as the reviewers were, and I think my concerns are this is basically an SIR (indiscernible) expert and has previously done work and is currently doing work on HIV disease (indiscernible)

The West Nile virus is not a very big deal. People usually recover from it, as opposed to some of the other encephalitis viruses, where people always die, although they say it's a category B bioterrorism agent, I don't know what a category B bioterrorism agent is, but I don't know.

I'm not a West Nile virus expert, but I'm not even sure that infecting neurons is how this (indiscernible) encephalitis.

The reviewers were very enthusiastic about this, because they thought that this is some nice, straightforward science that might be able to do this, but I don't see it as a very big deal, a human problem.

CHAIRPERSON MULLEN: It's a national problem. Can I just say it is? Yes. It's a national problem.

A FEMALE VOICE: People die from it.

DR. KIESSLING: Well, but most people don't die from it. Most people recover, and it's an epidemic that's swept across the county, but it's over.

CHAIRPERSON MULLEN: Case fatality rate last year, particularly in places like Texas and Oklahoma, was striking.

DR. KIESSLING: But --

CHAIRPERSON MULLEN: Can I just say, though, now that we've talked about Prader-Willi and a lot of other conditions, and when we think about the reality, that a lot of the other threats that the country and world face are related to infectious disease, it would be really wise of us to consider the contributions of this work, the potential contributions, especially as infections also continue to be more virulent for reasons that perhaps the science hasn't been able to explain to us yet, but particularly how they worked really hard last year and seeing a confirmation from my colleague in Texas, that they've already had their first case of West Nile.

After what they encountered last year, I respectfully ask you to let us at least tell you more about it, since you say you don't know a lot about it,

because there's probably a lot that you might have said a little bit differently.

DR. KIESSLING: I actually have a pretty strong virus background. (indiscernible) The West Nile virus is not a killer, and it kills a few of the people it infects, but it only kills like I think five or six percent of the people that it infects.

CHAIRPERSON MULLEN: Except that we really don't know that, because we actually can't even tell everybody who is infected, since the condition is not actually manifest in everyone, so I have to insert that. I just have to insert that, and then you all figure out the merits, but I have to insert that.

DR. KIESSLING: The biggest problem that they have and the strongest, the reviewers really liked this grant, mostly because they were going to switch from the mouse models and the non-neuronal cell models that have (coughing) into human ES cell models.

I don't even see in this grant very much indication that they can actually infect any of the hES cell-derived stem cells. They want to see if they can do that. If they can't do aim one, they don't have a grant.

I was just not as enthusiastic as the reviewers or as Richard, obviously.

DR. DEES: I move to fund.

MS. HORN: Okay. We have a motion to fund. Do we have a second? We have a second?

CHAIRPERSON MULLEN: Don't be influenced by my comments.

MS. HORN: Further discussion?

MS. ENGLE: I'll add my two cents' worth. I actually think this is a phenomenally-good use of stem cell-derived cells, because, as you pointed out, infectious disease is actually the thing that's killing a lot of people in the world.

We have very, very bad models for this. Most of the things we're interested in studying now only infect human tissue, and it's very difficult to get human tissue in a dish in the quantities you need to do good drug discovery, so I think this is a perfect concept. I'd like to see more of these kinds of things, because it really does speak to a large human health problem.

You say it's only five percent, well, five percent deaths, those five percent who die, it's significant, right? So I think that this is a great use of a stem cell-derived model.

It will have a clear and immediate impact if it does work, because it will prove that you can

actually develop a test in a dish, which will start making it amenable to drug discovery, so there's a huge possibility of a great future if this actually works.

MS. HORN: Okay. Further discussion? Okay, all in favor of moving this into the fund category, please signify by saying aye.

VOICES: Aye.

MS. HORN: Anybody opposed? Okay, it will be in the funding category.

MR. STRAUSS: Next up is Yale 27, with Richard and James.

DR. DEES: So this grant proposes to investigate the ways that vessels are generated and regenerated, by looking at the role of adipocytes, the role they have in this process, even though they're in vitro in mouse models.

The project has the potential for helping patients with lymphedema, relatively calling for surgical complication.

The grant essentially funds the collaboration between the established researcher on limb(phonetic) systems with an expert on epicyte precursors. There's no preliminary work here, but the peer reviewers thought it was a good project for a seed

grant.

The peer reviewers were pretty enthusiastic. Individual scores, if you look in here, were actually worse than the final score. In their discussion, what they talked about, the reason for the lower scores is basically there's no preliminary data.

What they agreed was that this sounds like an interesting project, and realized that there was no preliminary data. It's the reason why it's a decent seed grant, so peer review 15, move to funding.

DR. HUGHES: Having never experienced lymphedema, I probably don't appreciate its clinical significance, but I found it harder to rationalize the clinical utility of this project compared to some of the others, so I would recommend that it be in the hold category.

But I will say that it got higher marks for use of multiple methods in vitro, in vivo, and in vivo lineage tracing methods.

MS. HORN: Do we have a motion?

DR. FISHBONE: I move it.

MS. HORN: Okay, so, you move to fund. Do we have a second?

DR. FISHBONE: I'll second it.

MS. HORN: Okay. Further discussion?

DR. FISHBONE: I do think lymphedema is a very serious problem, and it's very common in women, who have had mastectomies and other problems, so I think it would be worthwhile to investigate it.

MS. HORN: Any other discussion? We have a motion to fund. All those in favor of placing it in the fund category, please signify by saying aye.

VOICES: Aye.

MS. HORN: Anybody opposed?

DR. HUGHES: You've convinced me.

MS. ENGLE: I still think it should go into the maybe. I'm still having some questions about it.

MS. HORN: Hearing that, we will place it in the maybe.

MR. STRAUSS: Okay, next up, UCHC 01, with Diane and Gerry.

DR. KRAUSE: Shall I start?

DR. FISHBONE: If you want, you start.

DR. KRAUSE: So this is a grant to look at bone repair, using MSC, and what's novel here it's a combination of MSC and a small molecule or drug, called Phenamil, which is FDA approved.

Somebody else had already shown that Phenamil promotes bone differentiation. What's novel here is putting together -- from MSC. What's novel here is that they are also biomedical engineers, so they're putting together a biodegradable scaffold that will release the Phenamil into the cells.

They're going to test that in vitro and in vivo. It got quite high scores. The person, who is senior, is the senior PI, Dr. Lo(phonetic), is actually a new assistant professor as of 2012 in residence. What does that mean, in residence?

Okay, assistant professor in residence at the Institute for Regenerative Engineering at UCHC. So it seems like a straightforward proposal to look at this biomedical, look at this scaffold and the cells and the drug in vivo and in vitro and an appropriate seed grant.

DR. FISHBONE: I would agree. What is in residence? What does that mean?

DR. KRAUSE: Non-tenure track.

DR. FISHBONE: Non-tenure. Okay. We had the Ph.D. from (indiscernible) University of Virginia (indiscernible) post-doc fellow at UConn Health Center 2012. Now he's an assistant professor. He has Dr. Kumbar as a collaborator, who we just saw in his own

grant, and it seemed like a worthwhile project that we should consider funding.

MS. HORN: Do we have a motion?

DR. KRAUSE: I motion to fund.

MS. HORN: Do we have a second?

DR. FISHBONE: Second.

MS. HORN: Any further discussion? We have a motion to fund. All those in favor, please indicate by saying aye.

VOICES: Aye.

MS. HORN: Anybody opposed? Okay, we'll move this into the fund category.

MR. STRAUSS: Okay. Yale 20 with James and Milt.

DR. WALLACK: I found this project to be a very exciting, well-designed study, aimed at understanding the role of stem cell, that stem cells play in carcinogenesis.

The investigator will utilize real-time imaging techniques, an approach, which the investigator is very slow at doing himself.

The study can, therefore, potentially have a high impact in cancer therapeutics. It's one of the strongest proposals that I've read in this round, and I,

therefore, strongly recommend funding.

DR. HUGHES: I was impressed with the proposal and the review remarks about its innovative use of technology, and, also, its (papers on microphone). I also recommend funding.

MS. HORN: So we have a motion to recommend to fund, and a second? Further discussion?

DR. FISHBONE: I have a question. I'm not familiar with pilomatricoma. Could you tell what it is from the grant? I've never heard of that.

A MALE VOICE: I'm a sociologist.

(Laughter)

DR. FISHBONE: I mean is it a good model for studying that would tell you something about the usual skin cancers, squamous?

DR. WALLACK: The model, Gerry, that the individual is using is involved with hair follicles, and, as I understand it, the reason for it is that there's an opportunity, since it regenerates as it does, to test some of the theories that the individual wants to pursue.

So, in reading the model, I was, in fact, impressed with the methodology that was being used for this project. It's also what made me say what I did, about it's one of the strongest proposals that I've read.

It seems very simple, very elegant, and hopefully doable.

MS. HORN: Okay, any further discussion? All those in favor of placing this in the yes category for funding, please signify by saying aye.

VOICES: Aye.

MS. HORN: Is anybody opposed? Move it to yes.

MR. STRAUSS: Okay. Next up is Yale 23, with Richard and James.

COURT REPORTER: One moment, please.

DR. DEES: The grant generates (indiscernible) neurons from (indiscernible) patients with (indiscernible) syndrome (indiscernible) in vitro model for (indiscernible)

The grant it's got really good scores (indiscernible) it's to an established researcher, and I guess I would have thought the more logical person to (indiscernible) who is actually applying for another grant. This grant fund in 100 percent (indiscernible) so I'm not quite sure how that works.

This is a grant that is apparently related to human disease. As I said, the peer reviews were very favorable. Less enthusiastic (indiscernible) and not particularly innovative, but they did score very high, so

I would recommend funding.

DR. HUGHES: I was very enthusiastic about this grant, because it addresses something that I understand is very hard (indiscernible) and it also addresses the development of techniques for the acceleration of innovation in pharmaceuticals, which is pretty important, so I give this a very high mark.

MS. HORN: Do we have a motion to fund? Motion and second.

DR. HUGHES: Second.

DR. FISHBONE: I had a question about this. I can't find the other grant, but the second grant uses exactly identical words for this whole discussion, only he's looking at 1.8, instead of 1.7. I don't know what either of them are, and I wish I could find the other grant.

MS. ENGLE: It's Yang, Yale 39, is the other grant.

DR. FISHBONE: Yale 39? Yeah, so, is he somebody, who is on the same grant?

DR. DEES: Yeah.

MS. ENGLE: Yeah.

DR. DEES: That's the post-doc, who actually did more work on this grant.

DR. FISHBONE: Right, but he has his own proposal?

MS. ENGLE: Yes. Just vaguely confusing.

DR. DEES: From what I fear, we can't fund both, because (static on microphone).

MS. HORN: This is a Yale grant.

DR. KRAUSE: In general, I think, in the future, we need to make sure, I'm just saying this on the record, I had told you off record, we have to make sure that investigators address their pending proposals and potential overlap with existing proposals, so that we don't have to guess.

MS. HORN: I wrote it down in my post-lunch piece of paper.

DR. WALLACK: I think that this is a very interesting situation and they say it in a positive way. Investigator Waxman is a very experienced investigator, but this is his first entry into the stem cell world.

And, to Gerry's question and to Sandy's point before, about what makes it applicable for a seed grant, an experienced investigator, new to the field, is what we want to see happen, and this absolutely does it.

I know we have a motion to fund, and I enthusiastically support that motion.

MS. HORN: Any further discussion? All in favor of moving this into the yes category, please indicate by saying aye.

VOICES: Aye.

MS. HORN: Anybody opposed? Okay, we'll move it into the yes.

MR. STRAUSS: Okay. Yale 32 with Milt and Richard.

DR. DEES: This grant is to investigate the possible therapeutic effects of (indiscernible) cardiac precursor cell, with studies designed to (indiscernible) type of cell, human embryonic stem cells, and they've already been done (indiscernible) tissues in both, and then if you use both in (indiscernible) heart disease to see if they can repair damage.

That would fund a recent post-doc on a project (indiscernible) disease. The two reviewers here were pretty far apart. The less enthusiastic one thought it was too ambitious and not original, with an inexperience of well-supervised researcher, while the other thought it was clearly designed and highly promising.

Oddly, the less-enthusiastic view also mischaracterized his study, I thought, as involving iPSCs

when it doesn't.

In the study section, the scores are much closer, with the resulting score at a favorable 17.5, so I would tend to fund it.

DR. WALLACK: I would support funding. I found it to be a well-constructed project by a very capable young researcher, exactly the kind of situation that we want to see going forward.

Strong collaboration and good mentorship is also associated with this researcher's team. I, therefore, feel that the goal of understanding how to develop the engineered heart tissues for implantation, in order to enhance repair, is potentially achievable, because of the background and the associations and collaborations, and, as I said, I, therefore, strongly recommend, also, funding.

MS. HORN: Okay. Do I have a motion and a second to place this in the funding category?

DR. WALLACK: Yes.

MS. HORN: Any further discussion?

MS. ENGLE: So I would like to raise the point that their preliminary data was generated in mouse. Their plan is to move to human, and then transplant into rat. Is there some concern, that that's a lot of species

involved and how transferable this all is?

DR. KIESSLING: Why are they using rat?

MS. ENGLE: They mentioned, well, it's just easier to do rat, but, to me, they've just got a lot of cross-species going on, and I'm concerned that that's going to be a challenge as they try to make this all work, because human into rat is going to involve some rejection issues, as well, right?

Rats don't like human tissue implanted in them, unless they're immuno-compromised, so I'm a little concerned about how this is all going to truly work, especially since all of their preliminary data is based on mouse, and now they're saying, well, we're going to do it to human, when mouse to rat might be a little bit more straightforward.

To me, it seems like they're just doing it in human, because then it makes it applicable to this granting and this funding opportunity. To me, I'm just very confused by this whole premise, so if anybody has any clarity on that?

DR. DEES: I don't, unfortunately.

A MALE VOICE: Sandy, which premise is this? Human into rat?

MS. ENGLE: Right, so, all of their

preliminary work is done in mouse, and now they're saying, well, we're just going to do it in human, and we're going to transplant it back into rat, when they could easily just transplant their rat or their mouse into rat, if their argument was the rat was a better model than the mouse.

I'm having some of the concerns that the reviewers were having, is that it's a little bit confusing on why they're doing what they're doing. I'm not at all clear.

DR. WALLACK: Sandy, I don't know.

MS. ENGLE: I guess I'm leaning on the side of the reviewer, if he felt it was a three, and I'm not seeing what's raising this to the level of funding.

DR. WALLACK: So I don't know the answer to your question personally, but in reading one of the reviewers, the person makes reference to the rat and feels it's a logically-designed study that will be important for validating this approach for therapeutic application.

Now I'm assuming, by that comment, that the reviewer, at least, who has more knowledge about this than I do, feels that it's an appropriate route to take. I can't answer.

MS. HORN: Any further discussion? The motion is to move this into the yes category for funding. Please indicate support for that by saying aye.

VOICES: Aye.

MS. HORN: And opposed?

MS. ENGLE: Aye.

MS. HORN: Okay, move it into the maybe.

MR. STRAUSS: Okay. Next up is Yale 36, James and Milt.

DR. HUGHES: Briefly, this is a project to generate mesenchymal cells from iPSC cells and embryonic stem cells, with the objective of repopulating a scaffold of one connective tissue, and I thought this was a great, an easily-explainable, clinically-applicable project, with applicability to three-dimensional tissue engineering and organ engineering in the future, so I was very enthusiastic about this one.

DR. WALLACK: I agree. I also feel that the PI has experience in working in this field and has the additional benefit of working in a very strong lab with excellent leadership, and I think that there's a possibility, an excellent chance, I should say, of achieving stated goals, and that's why I agree with you, Jim, that we should fund. I would move to fund it.

DR. HUGHES: Second.

MS. HORN: So we have a motion to fund and a second. Further discussion? All those in favor of placing this in the yes category for funding, signify by saying aye.

VOICES: Aye.

MS. HORN: Anybody opposed? Okay, move this in the funding category.

MR. STRAUSS: The next is Yale 12. It's Sandy and Richard.

MS. ENGLE: So this grant is looking at mitochondrial defects in neurodegenerative disease. Specifically, they are looking at a single type of mutation in PARK7 or DJ-1, as the gene is known, and what they really want to do is investigate mitochondrial function, and mitochondria are the sort of energy house of the cell, and it has been implicated that mitochondrial dysfunction is part of Parkinson's disease, so they would like to make iPS cells in the first year of the grant and characterize them, and then do a drug screen of about 1,000 compounds in the second year of the grant.

The reviewers were concerned about the lack of alternative strategies, and I, too, am very

concerned about this. They did not discuss what they would do if they did not see mitochondrial defects in the first year, in order to correct them.

The second thing is is that DJ-1 or PARK7 mutations are only one percent of mutations in the P.D. population, the Parkinson's disease population, and they do not have patients currently identified, so I'm very concerned.

If their whole first year is predicated on generating these iPS cells, whether they're going to find 100 patients to screen, at least, in order to find one iPS line, that makes the odds that they will not get started on time very high, and, so, I'm concerned about the doability in the two-year grant period if they do not have their patients already identified.

DR. DEES: I don't have that perspective on it, and, so, it sounded like a pretty good study to me. They're looking for -- they want to derive these iPSCs from Parkinson's patients, differentiate them to midbrain neurons, look at metabolic defects that lead to neuron death, and then test for responses to the new drugs.

There's not a whole lot of stem cell experience in this either, but it is one that could

relate clearly to some serious human disease. The peer reviewers are pretty enthusiastic.

There's some worry about where neurons will (indiscernible) they hope for and what they'll do if they don't (indiscernible).

I was inclined, on initial reading, to say yes, but I'm hearing from you (noise on microphone) I'm convinced that maybe we should say maybe at this point.

DR. KIESSLING: Do they have any other funding?

DR. HART: Not having a subject with the genotypes they want in hand is going to severely restrict the possibility of success here. It's really hard to find these patients.

MS. ENGLE: And this speaks to the reviewer's concern, that they have no other alternatives. An alternative would genetically engineer a mutation into the gene, but they didn't even propose that, which makes me think they were not thinking very hard about what they were proposing, because that would have actually been the obvious, more expedient route to generate the mutation.

Overall, I'm concerned about how much effort and thought they put into this grant.

MS. HORN: So your motion?

MS. ENGLE: I actually have a motion, at best, to a maybe, so I motion for a maybe.

DR. DEES: I second that.

MS. HORN: And Richard seconds. A maybe. Any further discussion? All in favor of placing this grant in the maybe column, please signify by saying aye.

VOICES: Aye.

MR. STRAUSS: Okay. UCHC 02, Diane and Mike.

DR. KRAUSE: Okay. This is a grant from Peter Maye, the goal of which -- let me make sure I get myself focused on this one. Differentiating human embryonic stem cells down the axial skeletal lineage.

So the idea here is we're not going to just make skeletal muscle cells or bone cells. All of these things are important, and people haven't optimized differentiation of human ES or iPS to get to the beginnings of the axial skeletal lineage, and that you can do that if you use an appropriate reporter, so they have already developed reporter mice.

They used Osterix, which was for the bone, itself, but the reporter gene here is a different gene, TBX2, and now want to go from having shown this in mouse embryonic stem cells to working with human embryonic stem

cells, make them a reporter cell line that would have the TBX2 driving a reporter gene, and then use that as a way of optimizing differentiation into this lineage.

The reviewers were generally favorable, but didn't really like that they were proposing to use a piggyback approach and wanted them to extend (indiscernible) but otherwise thought, you know, it sounds like a reasonable seed grant, and getting cells to go down the axial skeleton is a good idea, so there was moderate enthusiasm.

The PI is an assistant professor. He's been an assistant professor since 2007. During that time, he's had three senior author papers in the last six years, one of which was a review on BAC transgenesis method, so, again, making transgenic mice, so he's really had two senior author papers since '07, one in (indiscernible) to show the -- (indiscernible) mice are already out there, but not with the red fluorescent protein.

So my concern here was the productivity of the investigator and, also, that the -- if he doesn't generate these reporter lines, then he doesn't have a grant, and it somewhat depended on generating reporter lines. On the other hand, it's a seed, so I'm kind of

waffling in the maybe category.

DR. GENEL: Well he has secured an NIH grant.

DR. KRAUSE: He's had to R21s.

DR. GENEL: Oh, R21s, yeah. Okay. Excuse me.

DR. KRAUSE: But his funding is limited. Both of those R21s will be done in August of 2013. One was to make the embryonic stem cell model of the mouse, and then the other was to use that to study mesenchymal stem cells, so the mouse work has been funded with two R21s.

DR. GENEL: The other thing I heard earlier was that the (indiscernible) technology is going to be introduced at the core labs at UConn, so that would, I would presume, negate one of the criticisms of the reviewers, was the concern about the -- so that I'd put it in the maybe category. That would be my recommendation.

MS. HORN: So we have a motion for maybe and a second for maybe. Any further discussion? All in favor of placing this grant in the maybe column, signify by saying aye.

VOICES: Aye.

MS. HORN: In it goes.

MR. STRAUSS: Next is Yale 06 with Paul and David.

DR. GOLDHAMER: So this is a grant by Gerald Shadel, and what he wants to do is look at mitochondria dysfunction in the disease Ataxia-Telangiectasia, or AT. This is a severe disease affecting children, where there's neuronal cell death in the cerebellum, which results in improperly-controlled muscle movements.

Patients are wheelchair bound at an early age, and they die young. The gene mutation where AT is known (papers on microphone) DNA damage, but this investigator, who is an expert in mitochondrial function, has preliminary data that suggests that the mitochondria of the cells of these patients does not function properly, and they think that that, or they hypothesize that that may be the cause of neuronal cell death leading to these symptoms.

So this is a senior investigator. He's an expert in mitochondrial function and dysfunction. He's new to stem cell research. He's enlisted the help of another investigator, Anita Hootner(phonetic), and, also, the Yale stem cell core to do these studies.

So I thought it was a great use of seed money to bring a senior investigator, with great expertise in mitochondrial function. He has the support to do these experiments.

What he wants to do is make iPS cells from AT patients, differentiate them into cerebellar neurons, and then test mitochondrial function.

There's two cell types that are possibly effected. One, they already know how do to directed differentiation of one of them, and they acknowledge that they don't know how to do directed differentiation of the other, although it has been done in the mouse.

The reviewers were very supportive, very enthusiastic. There was one concern of the low effort of the PI, which was .6 months, although, for a seed grant for a senior investigator, .6 months to me seems like a reasonable amount of effort.

The investigator has no prior funding from the state for stem cell research. So I was very enthusiastic about this grant. It was my best seed grant, and I would recommend yes.

DR. PESCATELLO: Yes, I agree. Good summary. The reviewers put the significance as very high, so I enthusiastically support it.

MS. HORN: Okay, so, we have a motion to fund and a second to fund. Further discussion?

DR. HART: I just have one question. Since ATM is involved in DNA damage, it's been reported that it's difficult to reprogram these cells in stem cells. Was that a concern?

DR. GOLDHAMER: I don't recall that being addressed.

MS. HORN: Any further discussion? Okay, the motion is to place this into the yes fund, yes category for funding. All in favor, please say aye.

VOICE: Aye.

MS. HORN: Opposed? Okay, we'll put it in funding.

MR. STRAUSS: Next up is Yale 05 with Gerry and Ron.

DR. FISHBONE: They help hypothesize that tumor hypoxia facilitates and maintenance of cancer stem cells, and that the current approaches for examining this are not very reliable, and they have designed an innovative two-component system that would allow specific genetic labeling and subsequent lineage tracing of hypoxic cells.

And they want to determine whether cancer

cells are preferentially found in the hypoxic population in solid tumors and determine whether hypoxia affects the lineage specification into stem cells.

So I think they feel (coughing) that makes cancer worse from hypoxia. He's going to devote 15 percent of his time to the project. He has a Ph.D. from the University of Texas, is now associate professor at Yale.

DR. HART: So the project is all based upon building a very elegant reporter for a transient hypoxia exposure in cells in the tumor, so, basically, they're looking for a model of the hypoxia that occurs in the middle of a solid tumor transiently that might affect malignancy.

The reviewers were positive about the overall model. There were some complaints about which technology they chose to use for this. Not a lot. The fact that they were using randomly-integrated vectors, but that's not such a big deal. It certainly would allow the investigator to address the hypothesis, as proposed.

My only concern about this is that it's really only peripherally a true stem cell project. I mean it's looking for the hypothesized stem cells for the middle of the tumor, but it's very peripherally-related

to what we've traditionally looked for in the past.

It's a cancer grant, and it's also -- I mean one might look at it as being a seed grant to bring someone to the field. They're not coming in and learning ES or iPS technologies. They're going after cancer stem cells, which is, you know, perfectly wonderful, but they're not really developing cancer stem cells to start the project. They've already got that going at this point, or they've got their method of looking at things going.

This could make a very, very nice R21 project to NIH, so I'm a little -- I'm positive on the science for sure. If this were clearly a programmatic stem cell project, I'd be very enthusiastic. I'm just a little mixed, because I don't see it as being as good of a fit to our mission.

DR. FISHBONE: I would agree with that. He's not working with stem cells.

DR. HART: It's getting to be harder and harder to say that every year, because what one defines as stem cells, because it's very much up to interpretation, so I wouldn't go as far as saying it's not stem cells.

MS. HORN: So are you making a motion to

put it in the maybe or it's a no?

DR. HART: I want to be positive for this project, because it's a good science project, and it would develop a relatively young person in the field. Why don't we hold it as maybe for the moment? I hate to do that, but that's the only answer.

MS. HORN: We have a motion for maybe. Do we have a second for maybe?

DR. FISHBONE: Second.

MS. HORN: Okay, further discussion? All in favor of placing this grant in the maybe column, please signify by saying aye.

VOICES: Aye.

MS. HORN: It goes in the maybe. The Commissioner just had a brilliant idea, that we all sort of stand up and take a little stretch and a deep breath. We're getting maybe a little sleepy. Seventh inning stretch.

(Off the record)

MR. STRAUSS: So we're at Yale 15 with James and Ann.

DR. HUGHES: Dr. Kiessling, would you like to start?

DR. KIESSLING: So this is really, I

thought, an interesting application from a new faculty appointment at Yale. This, I believe, is, well, I'm pretty sure now is this person's very first application to the Connecticut group, the Connecticut stem cell group, and he wants to characterize the problems associated with the nuclear envelope.

This is a really interesting and very difficult area to go after. The reviewers were enthusiastic about this grant, and based on the fact that this a tough question, they've developed a really novel way to go about it.

They've come up with an enzyme that's going to mark what they're after, and then they're going to sequence it. Very heavy on the bioinformatics. That was the only criticism, is that their bioinformatics is going to force them to use some published information, which may not have been obtained exactly the way they're going to, but I think that's just the nature of the beast.

So they want to characterize human embryonic stem cell chromatin, and I thought this was a very interesting project for the young investigator, so I would recommend that this get funded.

DR. HUGHES: Well it seems that they got

very high reviews scientifically, but this one, if you characterize the grants from basic to translational or applied, this one is way over on the basic side, in terms of generating big genomic datasets, so I would recommend that this not be funded.

DR. KIESSLING: Oh, but this is a seed grant.

DR. HUGHES: I think, in terms of the general part of the program, I'm recommending that this not be funded.

MS. HORN: It's a no, and we have a yes.

DR. KIESSLING: And it's based on what? What's your recommendation based on?

DR. HUGHES: I don't see the general utility that lists particular kind of genomic data analysis, compared to some of the other projects. Again, that's a lay perspective.

DR. KIESSLING: Well the chromatin remodel we know is what makes stem cells from, say, skin cells, and we don't understand the mechanisms behind that. That's because it's so hard to do, and they've come up with a very interesting enzyme tagging approach, so they're going to be able to tag the chromatin that's actually bound to the nuclear -- I don't know.

I was as enthusiastic about this as the reviewers were.

MS. HORN: Okay, so, we have a motion for yes. We're going to take them sequentially. Do we have a second for the motion for yes?

DR. HART: I'll second.

MS. HORN: Okay, so, we're going to go with the motion for yes. Further discussion?

DR. HART: Essentially, if there's going to be a vote in the end for no, it will end up being maybe anyway.

MS. HORN: That's true. We would, yes, so we'll see how it plays out.

DR. HART: And, again, going by the guidelines, we are instructed to give priority to stem cell research with potential relevance to health, but that doesn't mean exclusive support.

MS. ENGLE: I'll just argue the opposite side, that, all things being equal, we are at the point, where we are going to have to start to make hard choices, and there may be things that more fit with what we would like to encourage in the state of Connecticut along the lines of translational science that might be -- you know, we're talking now literally about tenths of a decimal

point.

I don't think that really changes how these grants do, so we're looking at a lot of good grants that may or may not be funded, so, again, it's going to be a point of prioritization.

MS. HORN: So we have a motion for yes. All in favor of placing this in the yes column, please indicate that by saying aye.

VOICES: Aye.

MS. HORN: And opposed?

DR. HART: Opposed.

MS. HORN: So it's going in the maybe.

MR. STRAUSS: Okay, next is UCHC 04, with Gerry and Mike.

DR. GENEL: I'll go first on this one. This is a proposal by a fairly newly-admitted post-doc, who is in Carolyn Daley's laboratory, so it's a post-doc, with sponsorship by a co-recognized senior investigator, who they've generated induced pluripotent stem cells from two types of achondroplasia, spondyloepiphyseal dysplasia and achondroplasia, and they propose to identify the mechanisms of the disease model in these induced pluripotent stem cells.

The reviewers were generally positive.

One noted enthusiasm, but they also note that these are not hypothesis-driven, but are essentially exploratory, in terms of pathogenesis and so forth.

I think, in terms of the criteria that we've set for funding of seed grants, the investigator certainly fulfills them. I mean she's a post-doc in a very strong laboratory, who is proposing to do studies, where they do have some innovative material that has been generated in some patients.

The one criticism that may have validity, some validity by one of the reviewers, was that it might be far better to concentrate on one of these lines, rather than looking at both of these lines, since it's likely that the pathogenesis may not be -- may be different.

It's unanswerable, until the studies are done. We have a lot of stuff up on the board. I would like to regard this as a maybe at this point, only because there's so much up on the board.

DR. FISHBONE: I don't have much to add about the science, but she is currently on an NIH training grant, which ends this year, and she's going to be spending 24 months on the budget, so we certainly would be getting a return on our investment.

I have nothing really further to add about the science. Again, it's not leading towards any translatable --

DR. GENEL: Yeah. It's what a seed grant is designed to do.

DR. FISHBONE: Yup.

MS. HORN: So I'm hearing we have a motion to place it in the maybe. Do we have a second?

DR. FISHBONE: I'll second.

MS. HORN: Okay. Any further discussion? All those in favor of placing it in the maybe column, please signify by saying aye.

VOICES: Aye.

MS. HORN: Okay, in it goes.

MR. STRAUSS: Okay. Just as a benchmark point here, so far, you've said yes to eight, maybe to seven, so the eight yeses put you at about 1.6 million, and you have 13 to go.

The next one up is UCHC 03 with Gerry and Mike.

DR. GENEL: This is an interesting proposal from a young faculty member, who has superb training in structural biology, who has very, very strong recommendations from a number of people, including her

department Chair, which also involves collaboration from the health center with Ted Rasmussen's laboratory at Storrs.

I can't speak for the science, but it basically looks to use structural biology and her techniques to identify the genetic components that control epigenetic suppression of genes in embryonic stem cells.

I think there are some here, who are probably more versed in this technology, who can speak to it, but I think, in terms of the background and the collaboration, I would strongly support this, because I feel it fulfills everything that we set apart in establishing the seed grants; a young investigator, a promising research career, and, to some extent, institutional collaborations.

DR. FISHBONE: Yeah. I would add that what she's trying to determine is the molecular mechanism, whereby developmental genes are targeted for silencing, and she wants to use NMR spectroscopy and x-ray crystallography methods to do this.

It sounds very interesting, and I agree with everything Mike said about that. It's currently supported by the Charles Hood Foundation until 2014.

Does anybody know who that is? But, anyway, she's supported by them, and she's going to give 7.2 months of her time.

It sounds like an important subject, and she's looking at it in novel ways that she is an expert in NMR spectroscopy and x-ray crystallography.

DR. GENEL: Sandy Willer(phonetic) identifies her as a rising star, and I think this is what we were looking for when we established the seed grants, both in terms of the science and the investigator that is applying.

MS. HORN: So you're making a motion to fund?

DR. GENEL: Fund.

MS. HORN: And do we have a second? Is there a discussion?

DR. HART: One of the reviewers was saying that the scope of work was similar to an RO1, a full-scale NIH grant. Is that fair?

DR. GENEL: I can't comment on that. What do you think, Ron?

DR. HART: I didn't read the whole grant. I just saw the comment.

MS. ENGLE: I did take a look at it, and

structural biology-type activities, yeah. I think she's extremely ambitious for a two-year seed grant. I agree with that comment. It's probably over-ambitious.

DR. GENEL: I'm not concerned about that. I mean rather that than the opposite. Okay. She'll have, if she's successful, she'll be able to apply for an established investigator grant, because there will be more to do. I move funding.

MS. HORN: Okay. Any further discussion?

MS. ENGLE: So can you tell me, you know, if she is listed as rising star, why did the reviewers place her this low?

DR. GENEL: It's not that low.

MS. ENGLE: Relatively, they were willing to use one (multiple conversations) what were the concerns of the reviewers, besides the fact that it was somewhat ambitious?

DR. GENEL: I don't know. I think that one of the problems we have with this whole category is that we have any large number of grants. All of them were scored very well, and our job is to differentiate between them.

DR. KIESSLING: The reviewers vary greatly in how much they were trying to go from one to nine. One

person called a two. Somebody else might have called a one. I mean I think that's a huge problem.

DR. GENEL: Well it is, since they're all so tightly clustered.

DR. KRAUSE: I'm just pulling up the review to see if I can see what the concerns of the reviewers were listed.

The first one has no concerns at all (multiple conversations) the question overreaching. There is a lack of clarity in the proposal on the binding of SCML2, and the references to DNA binding implies binding to nucleotide sequences, rather than chromatin. Analysis of all of the nucleotide binding may not be instructed, given that SCML2 binds to --

COURT REPORTER: One moment, please.

MS. HORN: So the motion is to fund. All those in favor of placing this in the yes column, please indicate by saying aye.

VOICES: Aye.

MS. HORN: And opposed? All right.

MR. STRAUSS: Okay?

MS. HORN: Yes, okay.

MR. STRAUSS: All right. Yale 08 with Treena and Paul.

DR. ARINZEH: Okay, so, this is a two-year seed project by a junior investigator at Yale, looking at patient-derived iPS cells for coronary artery disease, and they're taking a little bit of a different spin on it, by looking at -- like I said, they're deriving these iPS cells, again, into these endothelial cells, and, again, they think that the hypothesis is that these patients, or the ones that -- patients that have or developed this coronary artery disease they have occluded -- can have these occluded coronary arteries, but some people can overcome that, by actually sprouting new blood vessels, but there's a sub-population that does not have this capability, and, so, that leads to tumor mortality.

And, so, they're going to be looking at, then, or they have two aims by generating these endothelial cells from the iPS and study their behavior from these kind of subpopulation of patients that don't develop these blood vessels, and then look at endothelial defects in these patients.

So the reviewers -- actually, I thought they would be giving a better score, because they actually were pretty enthusiastic, I felt anyway, with the proposal.

They used the term as a clever proposal to

try to understand on molecular basis of these observations in these patients.

They mentioned some weaknesses, but they didn't seem like they were major weaknesses to me. They thought there were some genetic variability in these human patients, so that may be some -- they may be larger numbers of cell lines, and they thought that, you know, minor weakness they mention about a lot of the preliminary data, which is very good pilot data, showing that they do get some observations in mouse cells, so they think that just doing it in human cells is not going to be just confirmation, but I think that's necessary, so I didn't think that was a weakness.

I thought the scores could be better, actually, so, all-in-all, yeah, so, the PI this is a junior investigator, strong preliminary data in this, and has a good collaborator, who has additional expertise. I'm actually in support of this.

DR. PESCATELLO: I'm in support of it, too. I agree. I think the description, the enthusiasm is described (background noise) especially for a seed it's worth doing. I guess the main, the most valid, the most criticism was the number of cell lines. As a non-scientist, way to go.

MS. HORN: Do we have a motion?

DR. PESCATELLO: So a motion to approve.

MS. HORN: A motion to approve.

MS. ENGLE: I second.

MS. HORN: And second. Discussion?

MS. ENGLE: So could you help me? In this grant, did they explain how they were going to model the blood flow, because the premise is they're going to take and generate iPS cells from patients, who have blood flow issues versus those that do not, and then they're going to model that in a dish, but blood flow is not just about whether cells differentiate to endothelial cells, but how the cells respond to the sheer stress associated with the blood flowing through them, so was there an actual description of how they were going to generate fluid flow model to actually test this? Otherwise, what are they proposing as their intrinsic cell defects?

DR. ARINZEH: I don't recall offhand. I don't think they're actually looking at that.

DR. KIESSLING: They're not modeling blood flow. They're modeling collateral network generation.

MS. ENGLE: Okay.

DR. KIESSLING: They're not modeling blood flow at all.

MS. ENGLE: And they don't think that that's related to actual flow?

DR. KIESSLING: Well, no. The way it's described here you're talking about that some people can do this and other people can't. Who can generate collateral networks and other people can't?

MS. ENGLE: So our premise is this is an intrinsic defect that they'll be able to recapitulate in a dish in the absence of all other biology?

DR. KIESSLING: There's a genetic compound, and I think that (indiscernible) is a possible candidate (indiscernible)

DR. ARINZEH: So do you remember did they give alternatives that this was not and if they could not get an intrinsic cell defect from their samples, because that's a huge caveat, right? If they spend the first year collecting all their samples and then they don't see a phenotype, right, or they can't generate a phenotype?

DR. ARINZEH: Yeah. They do state that they don't expect any challenges with the generation of these cells.

MS. ENGLE: Did they have any other alternatives for what they would do?

DR. HUGHES: And, you know, they argue

that the fact they've done it in mouse means that they'll be able to do it in humans.

DR. PESCATELLO: That was one of the criticisms.

DR. HUGHES: Yeah. Mice are inbred. It's a whole different deal.

MS. HORN: Do we have a motion to fund? All those in favor? (Multiple conversations)

DR. HART: They screen in different humans.

MS. ENGLE: Right, because it may not be one gene. It may be 10 genes, and it may not be just a gene. It may be how genes interact with the environment and that individual.

DR. ARINZEH: I think they recognize that. They say, actually, in their potential pitfalls, that the long-term goal is to screen a larger a number of patients, so, you know, I don't know if that requires additional funding, but that's their goal.

MS. ENGLE: So, specifically, how many lines were they going to generate in this first period?

DR. ARINZEH: I think it's three to five, something like that. Yeah.

DR. PESCATELLO: And that was one of the

criticisms.

DR. WALLACK: I'm not sure if it was just answered. Can you tell me how much time the two investigators are going to be spending on it, the principal and the investigator?

DR. ARINZEH: It looks like 80 percent.

DR. WALLACK: You're talking about Deng.

DR. ARINZEH: Let me check.

DR. WALLACK: Yang is already on a lot of other grants.

DR. ARINZEH: Eighty percent.

DR. WALLACK: Eighty?

DR. ARINZEH: Deng. That's what they said, 80 percent effort.

DR. WALLACK: You mean Yang?

DR. ARINZEH: No, Deng.

DR. WALLACK: Deng, right. Okay. I'm sorry.

DR. ARINZEH: That's the lead. That's the PI.

DR. WALLACK: Okay.

DR. HART: And the same issues we saw earlier with other applications, including more effort that could possibly be funded.

MS. HORN: We're going to call the question, because we've got a lot of other grants to get to. All those in favor of placing this in the fund category, please indicate by saying aye.

VOICES: Aye.

MS. HORN: And opposed?

VOICES: Aye.

MS. HORN: Okay, it's going in the maybe.

DR. KIESSLING: Is there a way for us to find out before we leave today who is on multiple grants?

MS. HORN: For this round of applications?

DR. KIESSLING: Yeah.

MR. STRAUSS: You mean the PIs or any investigator that may be on any grant?

DR. KIESSLING: Right.

MR. STRAUSS: Well I don't think that's possible. That's a good point for -- aren't they supposed to -- are they just indicating if they're a PI on another grant?

MS. HORN: No. They missed the other major collaborators on the grant, but I don't know how we would be able to generate that for you today.

DR. HART: The way we'll find out about it is when they reallocate their budget, come back to us and

ask permission.

MS. HORN: Okay, Rick. How about a status? How many grants do we got to go?

MR. STRAUSS: Well I think we're at 17. I think we have 11 to go.

MS. HORN: Okay.

MR. STRAUSS: So the next is Yale 19, with Paul and Sandy.

MS. ENGLE: So this grant is looking at the differentiation characterization of alveolar epithelial cells from human iPS cells to repopulate decellularized human lung matrix. We've seen this before.

The proposal was revised from a 1.5 to a 2.5, due to what they call several minor to moderate concerns raised during the discussion regarding the fidelity of the directed differentiation of the iPS cells to alveolar epithelial cells.

The aims, there are just two specific aims of this. It's to optimize differentiation of airway epithelial cells, focusing on taking them from definitive endoderm, which is an early step, to the anterior foregut endoderm, which is still not an anterior lung epithelial cell, and then looking for proximal and basal airway

progenitors to subsequently differentiate, and then they would put them onto a decellularized matrix.

It's okay. There was concerns about the differentiation, and I, too, share those concerns about the differentiation. There are several well-known laboratories, who have already differentiated to airway epithelial cells.

I'm not sure what new they are adding to that, aside from the putting the cells into a decellularized matrix. There's a lot of other funding going on for that, so I guess that's partly what made me less enthusiastic, but I'll turn it over to you for your comments.

DR. PESCATELLO: I guess I've got a somewhat more positive view. Also, I think, if I remember correctly, Laura Nickleson(phonetic) from Yale is also involved in this project. She's got a great track record.

I think, given how many things we're funding so far, I would put it in the maybe category.

DR. KIESSLING: Does this investigator have any other funds?

MS. ENGLE: I will say that we already funded another seed grant from the Nickelson laboratory.

Though we already said yes earlier on to one of those, I don't know if this particular person did.

DR. PESCATELLO: So I would make a motion for a maybe.

MS. HORN: Do we have a second?

MS. ENGLE: I would second the motion for a maybe.

MS. HORN: Okay. Is there any further discussion? All in favor of placing this grant in the maybe category, please indicate by saying aye.

VOICES: Aye.

MS. HORN: Maybe it is.

MR. STRAUSS: Next up, Yale 28, with David and Ron.

DR. HART: Why don't you go first, Dave?

DR. GOLDHAMER: This is a grant from a postdoctoral fellow, Andrew Xiao's lab. He's been a post-doc at Yale since 2010 and was a post-doc at Case Western before that.

He is interested in looking at a protein, called RIF1, and its possible role in telomere homeostasis. So telomeres are stretches of repetitive DNA chromosomes that protect chromosomes and prevent genomic instability, and telomere length is correlated

with replicative capacity in stem cells and, also, in cancer cells.

So this group has quite a bit of data that they've presented on the role of RIF1 in mouse embryonic stem cells. It seems to play a critical role in telomere length homeostasis and genomic stability in mouse cells, and they had a paper under I think tertiary review in stem cell. It hasn't been accepted yet, but they completed a body of work on this in mouse cells.

And, so, essentially, they're proposing to more or less repeat these experiments in human embryonic cells, so they want to look at RIF1's function in maintaining pluripotency of human embryonic stem cells, and, presumably, if the telomeres are not stable, they won't be able to maintain pluripotency, so they knock down expression of RIF1, and they look to see the effects to see if they maintain embryonic stem cell colonies and maintain their pluripotency, and they also plan, also, to look at the telomeres directly. Are they abnormal in length? Is there telomere loss? Is there telomere damage in these knock down cells, and they also have an aim to look at RIF1 function in reprogramming.

So the reviews were a little bit divergent. There's a 1.75 and a 3.3. The 1.75 there's

essentially no criticisms at all. The second reviewer had a couple of criticisms. One was he'd been experienced as a PI. This is a very respected, competent PI, and I didn't think that was an issue.

There was some concern that the reliance of the PI that experiments whether the mouse will be translatable to humans is uncertain, because of possible differences in the biology of telomeres.

I don't know if that's a valid concern or not. Clearly, telomere length homeostasis is a huge issue in stem cell biology and cancer biology, and, as a seed grant, it seems appropriate to me to repeat the experiments in human cells and see what the effects of RIF1 are, so I consider this to be a solid grant.

Yes, it's a repeat of experiments done in mouse, so it's not as innovative as perhaps some other grants, but I thought it was worth doing. I was between a maybe and a yes for this grant.

DR. HART: Actually, I think that's right. The second reviewer that was more negative with the scoring actually had weaknesses that I considered strengths. One was that, you know, it was not terribly siding the solid yes. I mean this is something that has been done in mouse. It really needs to be repeated in

human, nor to take it to the human model, if there's no other way around, then repeat that work. Perfectly appropriate for a seed grant.

The PI is a post-doc, with little experience. That's not true. The reviewer wrote. It's not true. He's an assistant professor and has published on his own, or at least as a senior author, not a lot, so it's appropriately junior for a seed grant, again. Little experience in human embryonic stem cell biology. Perfectly appropriate for a seed grant, so, again, I saw all the negatives as being positives for this program for this application.

He's held a previous ROOK1(phonetic) award that just ended in March and an Ellison Foundation award the current. The budget, as proposed, covers nine months of the PI's salary, and it sounds to me as though this PI would actually be doing most of the laboratory work the way it's described.

Again, perfectly appropriate for a seed grant in my mind. Based on the relative novelty of the topic that there's been so little attention placed on the telomere and RIF1 and they've got a nice model, based on their work in mouse, I was actually much more enthusiastic about this than the score reflected, and I

would have supported this for a yes. I will support this for a yes.

MS. HORN: Do we have a motion for a yes? Do we have a second?

DR. HART: I'll second it.

MS. HORN: Okay. Any further discussion? All in favor of placing this in the yes column, please indicate by saying aye.

VOICES: Aye.

MS. HORN: Anybody opposed?

A FEMALE VOICE: I am.

MS. HORN: So we'll put it in the maybe.

MR. STRAUSS: So, next up, UCHC 12, Mike and Gerry.

DR. GENEL: This is a proposal for development of a or testing of an injectable polymer, which is known as chitosan, to serve as a -- both as a matrix and as a stimulant for osteogenic stem cells for bone repair.

Dr. Nair is an assistant professor in orthopedics, has been there for several years. I believe she was part of the group that Lawrenson(phonetic) brought with him from Virginia.

She is a co-investigator on another

established investigator grant that runs, on cartilage regeneration, that runs through August 1st of 2014.

The second reviewer's comments I think might be particularly relevant, is that the studies with the chitosan have been done already, and the reviewer indicates that there is little novelty or innovation in the studies proposed.

I think, given the heavy competition that we have in this category, I would move to not fund.

DR. FISHBONE: It's interesting to read the personal statement. I have the expertise, leadership and motivation necessary to successfully carry out the work. I have an extensive background in biomaterial development, tissue engineering, training and cellular biology and in vivo evaluation in biomaterial. I serve as a principal investigator, as well as a co-investigator, on several federally-funded budgets.

Sounds like - is it a he or a she? I don't know.

DR. GENEL: It's a she.

DR. FISHBONE: Yeah. Sounds like she's doing an awful lot of work in a lot of different things, but you're saying, in this particular case, this has been already --

DR. GENEL: Well I look upon it as this is not what we would regard as a new investigator. It's not a new area, and the reviewers point out, I can't verify it, that it's not original.

And in the face of what is pretty significant competition in this category, I would say that's enough for me to move it to the no funding category, without -- irrespective of the merits, the merits, you know, I think, given the category and the conditions we've set forth.

MS. HORN: Okay, so, we have a motion to place it in the no category. Do we have a second?

DR. FISHBONE: I'll second.

MS. HORN: Okay. All in favor of placing this -- I'm sorry. Is there any further discussion?

DR. KRAUSE: I'm a little confused. I didn't read the grant. The thing that's not novel is using the hydrogel with the chitosan, but is there anything novel? Are they using that as a matrix and then putting a different drug in it, or that's the drug they're trying to --

DR. GENEL: I think that's the novelty. The novelty is the drug in the matrix. The matrix is, you know, that was my impression.

DR. KRAUSE: Where does the simvastatin come in?

DR. GENEL: That, I think, is the novelty.

DR. KRAUSE: Well that's what I'm asking.

DR. GENEL: I think so. I think so.

DR. KRAUSE: Based on reading just the review, it seems that there is novelty here, because it's the simvastatin, along with the biodegradable chitosan. I don't know enough to know whether -- I didn't read the grant, but I think there's something novel here.

DR. KRAUSE: I think the drug has been investigated in bone locally, so it's been delivered. There's some basic studies out there to show that it does seem to have an effect. I think it's that combination of the drug with the chitosan and the stem cells.

DR. GENEL: I grant that, but my other concern is in the face of a large number of seed applications still holds.

MS. ENGLE: And I would like to sort of bolster that point. They already have a patent filed on this. This seems like it's in the realm of venture capital, not in the realm of seed grant.

At this point, it's unclear how funding from this organization would somehow assist them or

provide them. Again, going into a new area, it doesn't fit.

DR. FISHBONE: I have the same feeling, that you take two substances that you know work and you put them together to see if they work better. It doesn't seem to qualify for a seed grant.

MS. ENGLE: Right. It's venture capital, especially since they already have a company formed.

MS. HORN: Okay, so, any further discussion? Do we have a motion to place this in the no category? All in favor, please indicate by saying aye.

VOICES: Aye.

MS. HORN: Anybody opposed?

MR. STRAUSS: So it's a no. Next is UConn 03, with Mike and Paul.

DR. PESCATELLO: So this is an interesting project, aimed at enhancing drug metabolizing enzyme expression in hepatocytes, with potential uses in drug screening. We were just talking about it at lunch, which is a very useful and more near term use of stem cells, so there was a wide difference in the two reviewers, one really being very pro, one not so.

There's an issue of mentorship for that, the post-doc involved, an issue of epigenetic memory

(indiscernible) so I would put it in the maybe category.

DR. GENEL: The score between the reviewers is striking. This is -- this fellow is a post-doc in Ted Rasmussen's lab. I'm moderately supportive. I mean I think I'd put it in the maybe category for the moment.

MS. HORN: We have a motion for a maybe and a second to place it in the maybe category. Any further comment?

DR. KRAUSE: I'm just looking at the reviewers' comments. I did not read the grant, but in the reconciliation statement that ended with the final score, it says reviewers agreed on the limited novelty of this proposal, particularly since there are published works, showing success in deriving hepatocytes with active P450 aromatase.

Is that relevant? I mean it sounds like somebody thought it was novel, and then, in the reconciliation statement, they said it wasn't novel. Am I wrong? I mean is he proposing deriving hepatocytes with active P450 aromatase? Is that the novelty of the proposal?

DR. KIESSLING: He's proposing to up-regulate P450.

MS. ENGLE: All right and, so, I was going to say, so, I read this one, because I thought it had an interesting premise. The idea of looking to mature hepatocytes, stem cell-derived hepatocytes, is an important one, because, currently, they do not have the levels of drug metabolizing enzymes or transporters that are comparable to the gold standard, which is -- derived hepatocytes or cryopreserved hepatocytes.

Overall, the idea is really good. I think there are several methodological issues associated with this, which I could see as the reviewers are reading this, going probably not the best way to do it.

There are transplant studies I can tell will not work right now. The idea is good, but there are some methodological issues, which they will figure out really quickly will not work, because there's already data out there to show that they will not work the way they propose.

DR. KRAUSE: They should have known?

MS. ENGLE: I would say so. They've been published by multiple well-known laboratories that show that, unless you induce liver injury, you can't get liver transplant to work with any kind of cell.

DR. KRAUSE: So would you recommend no?

MS. ENGLE: The idea is good, but I think that there are better developed options.

DR. PESCATELLO: With that ringing endorsement --

DR. GENEL: Yeah. The other comment, the other thought I had was that the two co-investigators are both well, Ted Rasmussen and (indiscernible), grants are very well-funded by the stem cell program already.

MS. HORN: So the motion on the floor is maybe.

DR. GENEL: No.

DR. HART: We need to recognize that we are well-below the grade area.

MS. HORN: All right, so, you're changing your motion and second to no. Okay. Any further discussion? All in favor of placing this grant in the no column, please indicate by saying aye.

VOICES: Aye.

MS. HORN: And anybody opposed?

MR. STRAUSS: Next up, Yale 21, with Richard and Treena.

DR. DEES: This is a study that's trying to determine the role of protein PLU1 regulating stem cell (indiscernible) this is one of those studies that,

as a non-scientist, they did not do very well explaining to me what was happening and why it was important.

It's a basic science study. Its relation to human disease is, at best, really distant. I couldn't see it. Maybe it's there, but I didn't see it.

The peer reviews were pretty good. They describe it as a high-risk, high-reward project. On the plus side, it is a grant for a young investigator. That's the kind of stuff we want to fund, but my view was this is too far down on the list.

I didn't see something that made me say let's bump it up and fund it, so I was recommending no.

DR. ARINZEH: Yeah, so, same thing. They didn't write this grant -- they just need to break it down a little bit, in terms of the technical, the way it's described technically for the relevance.

They were looking at stem cell differentiation in this RNA length. There's an RNA length change that appears to play a role, and this protein, PLU1, is associated with that.

Again, it wasn't clear how that all kind of fits together to becoming a target. They said this will be a target, then, for something, but I didn't really know what that was.

But the reviews, like I said, that first reviewer really didn't have any weaknesses, so I don't know, but the second reviewer had several weaknesses there, so I would say not to support, given where we are, as well.

MS. HORN: Okay. Do we have a motion to place it in the no column? And a second? Okay, so, further discussion? All in favor of placing this grant in the no column, please indicate by saying aye.

VOICES: Aye.

MS. HORN: Any opposed?

DR. WALLACK: So, Marianne, can I ask a question?

MS. HORN: Certainly.

DR. WALLACK: So there's a separation here from the one we just voted, the last two we voted no and the subsequent ones that are coming up. I know I have two of those grants, and I know, very clearly in my mind, that I'm going to recommend not funding. Is it possible to facilitate the time factor and so forth to ask the group if there's anybody in the subsequent grants if anybody wants to rescue any of those?

MS. HORN: I think we agreed on a process, Milt. We can go quickly through these, but I think we

should at least discuss them briefly and vote.

DR. WALLACK: Okay.

CHAIRPERSON MULLEN: If you can think of another way to make up some time later on and it doesn't go against what we -- I think the group will entertain --

DR. WALLACK: Well, no. I think Marianne's point, though, if we can really, really, from this point forward, be very, very, very brief and get right to the recommendations.

CHAIRPERSON MULLEN: That's good.

MR. STRAUSS: So, therefore, Yale 33, with Sandy and James.

MS. ENGLE: Okay. Do you want me to go quick? This grant is looking at Batten's disease, which is clearly a sad disease. That said and done, there were several methodological issues associated with this grant.

On top of that, the PI has RO1 grants, as well as established, so, again, I find it hard to believe he is truly in need of a seed grant for this, so my recommendation is no.

DR. HUGHES: My recommendation is also no. I would have been sympathetic, but the reviewers, both reviewers raised significant methodological and scientific questions.

MS. HORN: Okay. We have a motion for no and a second for no. Any further discussion? All those in favor of placing this grant in the no column, please indicate by saying aye.

VOICES: Aye.

MS. HORN: Any objections?

MR. STRAUSS: Okay. Next up is Yale 34, with David and Paul.

DR. GOLDHAMER: This is a grant by a postdoctoral fellow in Art's(phonetic) lab, and this grant is interested in modeling essentially autism in a dish, and, so, they've identified some long non-coding RNAs, that non-coding RNAs are involved in regulating gene expression, and they found in autism patients that some long non-coding RNAs are down regulated, so they hypothesize that these RNAs are involved in this condition, and, so, they establish a couple of ways to look at this.

I was not enthusiastic about this grant. I don't think there's any reason to believe that assays that they've developed for looking at differentiation in a dish have necessarily any relationship at all to autism, and they also don't have any preliminary data to suggest that these long non-coding RNAs are involved in

really any aspect of neuronal differentiation anyway.

So, for both of those reasons, I was not enthusiastic about this grant, and I would suggest a no.

DR. PESCATELLO: I would suggest no, too. There's a lot of funding, a lot of research, obviously, in autism.

MS. HORN: So the motion is to place it in the no column. All those in favor of placing it in the no, please indicate by saying aye.

VOICES: Aye.

MS. HORN: Anybody object? It's placed in the no.

MR. STRAUSS: Yale 39, with Ron and Milt.

DR. HART: This, actually, it wasn't pre-scored quite so far, or I would have been much more enthusiastic. The PI is the from the Waxman lab and is working on this (indiscernible) model. They've identified a specific sodium channel that is involved in (indiscernible), and they want to add a, knock in a GFP tag, a fluorescent protein tag to that receptor, so they can better study it.

It's a wonderful idea. They're actually in detail proposing to use what is unfortunately now a rather older technology (indiscernible) fingers, and

they're actually contracting this out to (indiscernible) and there was a complaint from the reviewer, about spending money on the contractor, but that's immaterial.

Any reasonable person would have, you know, between the time they wrote the grant and now, have gone to the newer technologies, so I don't really deem them on that.

And the reviewer, I think, was a little overly-harsh with the score, so I was trying to be as positive as I could before I say, unfortunately, based on the high competition in the field, I vote for no.

DR. WALLACK: I agree. Move no.

MS. HORN: Okay, there's a motion and a second for no. Any further discussion? All in favor of placing this in the no column, please indicate by saying aye.

VOICES: Aye.

MS. HORN: Any objection? Placed in the no column.

MR. STRAUSS: Next, Yale 16, with Ann and Milt.

DR. KIESSLING: This is another application I'm trying to find. Do you have that handy, Milt?

DR. WALLACK: Do you need the review?

DR. KIESSLING: No, I got it.

DR. WALLACK: Do you want me to go?

DR. KIESSLING: I was thinking that this was farther apart, but no. So one reviewer was 2.6 and the other was three, so this is a grant that's just going to screen 82 compounds that they have to see if it's going to make it easier to reprogram cells.

I wasn't as enthusiastic about this grant as the reviewers were, so I think the competition that we're facing here that this grant application should be put in the no category.

What I was trying to find was if there's -- what is the overall funding level for this group. This is a post-doc.

DR. WALLACK: While you're looking for that, I'll make my comment, and that is that I was not enthusiastic either about the grant. Unless I read the information wrong, I was also concerned that very little time was going to be spent by the investigator on the project. I strongly recommend not funding. I move that we not fund it.

MS. HORN: So we have a motion to not fund.

DR. KIESSLING: I'll second that.

MS. HORN: Okay, second. Any further comments? All those in favor of moving this to the not fund column, please indicate by saying aye.

VOICES: Aye.

MS. HORN: Anybody object? Okay, it's moved to the not fund column.

MR. STRAUSS: Okay. Next up is Yale 17 with Paul and Gerry.

DR. PESCATELLO: So this is a gene expression -- I'll characterize it as basic research in gene expression. I was struck by the comment about lack of novelty that mouse models would suffice and have sufficed, so we'd recommend a no.

DR. FISHBONE: I agree. I don't feel that I have anything to add.

MS. HORN: I have motion to not fund and a second. Any further discussion? All those in favor of moving this to the no column, please indicate by saying aye.

VOICES: Aye.

MS. HORN: Anybody opposed? Moved to the no column.

MR. STRAUSS: Okay and the last proposal

to discuss is UCHC 18 with Mike and Treena.

DR. ARINZEH: Okay. It's a two-year seed focusing on attention deficit hyperactivity disorder, and they're going to be using patient-derived iPS cells to differentiate them into neurons, and the two different neurons, I guess these cortical neurons and these gabaergic neurons, and they have a couple of specific aims there, looking at these co-cultures.

The reviewers are pretty -- they gave okay scores, but they cited several weaknesses there about the heterogenea of these neuronal cultures and identifying appropriate targets, appropriate target neurons in cultures, and this may not actually correlate with the disease, itself. It may only, you know, correlate or target a subset population there, so I would say not to support this grant.

DR. GENEL: This is the same investigator, who submitted an established grant, I believe, isn't it, on SCB 18? Did we fund that? It's the same last name.

A MALE VOICE: So do you want to fund it or not?

DR. GENEL: No, no, I don't think so. Just a comment. I move it into the no category.

MS. HORN: Okay. We have a motion to put

it in the no category and a second. Any further discussion?

MS. ENGLE: I agree that it should go into the no, because there were clear methodological differences, but I do want to give a -- this is the kind of grant that's actually very useful of comparing two different small nucleotide differences that may lead to phenotypes.

I think, overall, the premise is good. They needed to up the quality of their grant, but this is, you know, very important kind of work to study. It doesn't change the no, but it's the kind of stuff we should be thinking about.

DR. GENEL: No, I agree with you, and I think it's unfortunate that we don't have 20 million dollars to spend, because I think we could spend it just as wisely.

MS. ENGLE: I just didn't want to come across that it's an overall bad idea, and ADHD is clinically on that need.

DR. HART: We just hope that encouraging thought gets back to the investigator.

MS. HORN: Very good. That's good feedback. Okay, so --

DR. GENEL: I see we're at nine at this point to fund at 1.8 million dollars.

MS. HORN: We didn't vote on that. All in favor of putting it in the no column, please say aye.

VOICES: Aye.

MS. HORN: Anybody opposed? It goes in the no column.

MR. STRAUSS: Okay, therefore, you're at nine to fund so far, with 1.8 million dollars, and you have 10 maybes and nine nos.

A FEMALE VOICE: Just for the yeses?

MS. HORN: Including the yeses and the maybes.

A FEMALE VOICE: Well how much have we spent for just the yeses?

MR. STRAUSS: $4,788,229 is in the yes category.

MS. HORN: I'm going to suggest that we just take a five-minute break, and then we can come back and really --

(Off the record)

DR. HART: Can I make a quick comment before we begin the process?

MS. HORN: Sure.

DR. HART: If you look at our own criteria for funding, one of the top criteria initially constituted was to fund support on human embryonic stem cells that is not currently eligible for federal funding.

We didn't see a single one of those today, so realize that's not the issue anymore. So with this relatively-limited 10-million-dollar roughly pot of money, what can we do that will be the most effective?

We have generated for ourselves this disease-oriented direction. We've already started to discuss a balance between them and already decided that not one of them is fully formed the way we imagined it, timely imagined it, and we discussed how much we liked and how we rated all these preliminary seed grants are.

We're basically being the victim of our own success. We've drawn so many people in the field that's highly competitive to get these grants, and that's the way it's always going to be.

I would argue, then, that we try our best to balance in favor of the most effective seed projects at the expense of established grants. I've encouraged those people more toward NIH where they are now eligible and have been for several years and to consider what is realistic with the disease-oriented grants, and that's, I

think, where we ought to start, because as is often incorrectly attributed (background noise) the bank robber, that's where the money is, and if we want to give it to someone else, that's where we have to start.

So I'd like to go back to my original suggestion of taking one, or two, or maybe even less, we've discussed that, of the disease-oriented grants and giving them a reduced funding, in order to get them to the next level and have them come back and reapply for a more complete project.

DR. WALLACK: So do we want to start going back to where we started this morning and start with the cores again?

MS. HORN: I think we should get the cores dealt with, and that will take some money off the table there.

DR. HART: I forgot that those were maybes. You're right.

MS. HORN: And then, I think, if we went to the group and disease-directed, we will know what pool of money we're left dealing with, and then I like your idea of looking at the seeds, then, and, then again, seeing what money we have left for established.

DR. WALLACK: So can I move that, for

discussion purposes, that we consider funding of two cores? I'll start with the Yale core, since we started with it this morning.

MS. HORN: We have a motion. Do we have a second?

A MALE VOICE: I second.

MS. HORN: Any discussion?

MS. ENGLE: So can I ask what happens if we reduce the funding of the cores? A half a million dollars is a lot of money. If we reduce it even by half, they still have the opportunity to develop new technologies that will assist their other investigators and leverage the spending, but it will make it clear that, you know, they need to have clear plans for how are they weaning themselves off of this type of funding mechanism.

I don't think it would have, in my mind, it may not have a huge impact, because Yale didn't actually give a good justification for what new things they were bringing on.

And while UCHC or the UConn one had a clear plan for what they were bringing on, they were less descriptive of how they were going to wean themselves off the funding.

I think there should be some -- if they chose to compromise on what they were putting in the grant, then I think we could compromise potentially on the funding. Is that an option?

DR. WALLACK: I understand the argument, and I understand the argument, because when I think approximately two years ago we had the cores from both UConn and Yale appear before us, I asked those questions. Others asked the same questions.

So I totally understand that, however, at this particular point, I would feel very uncomfortable with the reduction. What I would do is what we talked about this morning, and that is fund the cores, this particular core that we're talking about.

I would also fund the next core, but that will come after this, and, as we mentioned this morning and I think Ron brought it up, send a letter, indicating our desire for them to be more sustainable on their own. If that means bringing the individuals back, the individuals, namely Haifan Lin and Marc Lalande, to have a re-discussion of this, I will be totally in favor of doing that, so that's how I would handle it.

DR. KIESSLING: We did that already.

DR. DEES: If you think of what we've done

here, we have decreased the amount of money we're willing to give, and that's what we should do next year, is we can say, no, you can't get more than. If we want to make to 250 and it's 250.

They worked within the framework we gave them. We said it's okay.

DR. HART: What was the amount last year? Do you remember?

A MALE VOICE: It was 500.

DR. KIESSLING: I think our description is we would fund new areas for the core. That's what we were interested in funding.

DR. DEES: Our little summary sheet made this application inaccurate.

MS. HORN: If you want to go through the cores one-by-one and make decisions about whether to fund them?

DR. WALLACK: Well we made a motion on the first one.

MS. HORN: Okay.

DR. WALLACK: So I think we ought to leave that motion, and we'll make another motion on the other.

MR. STRAUSS: Might you read the statement in the RFP that directed the institutions to prepare

their proposals?

DR. HART: It's highlighted in the highlight sheet here.

MR. STRAUSS: Well I know, but they responded to the RFP.

DR. HART: But this is extracted from the RFP.

MR. STRAUSS: Well, but why not at least -- if you're considering cutting, why not at least listen to the specific language in the RFP?

DR. HART: We're opposing.

MR. STRAUSS: Exactly, so the language in the RFP is important.

DR. HART: I think that, in order to -- because some of the other projects stated their dependence upon these cores, because we've been decreasing their funding over time and asking them to show us new technologies and/or directions for future funding, I think we ought to take it very slow in cutting these things, because we will have danger of losing expertise and technologies if you cut too much too quickly and unexpectedly.

If we want to cut, I think we ought to discuss cuts for next year, not this year.

DR. PESCATELLO: I would echo that. I mean we've rationed it down over the years. We got a course of dealing with each core and definitely was for new stuff, but it also was to sustain the existing cores.

MS. HORN: Okay, so, Milt, remind me of your motion.

DR. WALLACK: My first motion is to fund the Yale core at $500,000.

MS. HORN: Okay, do we have a second?

A MALE VOICE: I'll second.

MS. HORN: Any further discussion?

DR. KIESSLING: Would you consider funding it at $400,000?

DR. WALLACK: No, only because it would be inconsistent. What Ron articulated I totally agree with, and, Ann, you know that I feel not dissimilar to that, but, at this point in time, it would be inconsistent with what we have done in dealing in the cores, so, therefore, I feel compelled at this time to fund it for $500,000.

DR. GOLDHAMER: Well I would say, if you look at the budget and identify something and say this is unnecessary, then we can have a discussion, but I think it's arbitrary to say we're going to cut 50,000, 100,000, or whatever that number is.

And as I said before, so many grants are dependent on this, and I would not like to take the chance of this trickled effect of effecting all of these grants that we want to fund and are dependent on the core.

I'm speaking of Yale, because I can't speak about UConn, so a Yale core, singular. So I think that I agree with Richard's comments and other comments around the table, that, next year, we can reduce that value if we feel as if maybe that that is the direction we want to go, but, for this year, I think it's too late.

MS. HORN: Okay, any further discussion? The motion is to fund Yale at $500,000. All in favor, please signify by saying aye.

VOICES: Aye.

MS. HORN: And I think, at this point, Rick, we are doing the final funding decisions, so we'll do a roll call.

DR. KIESSLING: So if I say no, it doesn't put it in the maybe category?

MS. HORN: No. We're still with maybes, but if you have a conflict with UConn, if you have a conflict with Yale, please do not vote. Okay, so, I don't have a list here, so Sandra?

MS. ENGLE: Yes.

(Whereupon, a roll call vote was taken.)

MS. HORN: The ayes carry. Yale is funded for $500,000 Yale core. Okay.

DR. WALLACK: On the UConn core, UConn/Wesleyan core, I recommend that we fund it for $500,000. It was interesting in this particular core they did pick up on the recommendations that we put forward last year, an indication that they will listen if we talk about it, and they have expanded the area of the core's involvement more into the area of genomics, genetics and engineering of human iPS cells.

I feel strongly that we should be funding this, and I strongly recommend funding, and make the recommendation to form a motion.

A MALE VOICE: Second.

MS. HORN: Okay. Discussion? We're going to vote on funding the UConn core at $500,000. Dr. Engle?

MS. ENGLE: Yes.

(Whereupon, a roll call vote was taken.)

MS. HORN: Okay. The UConn core is funded for $500,000.

MR. STRAUSS: 5.788.229 million. Do you

want to go to the group?

MS. HORN: Yes, the singular group.

MR. STRAUSS: So your decision was to fund at 1.488.229? Thank you.

MS. HORN: Okay. We need a motion on this grant.

A FEMALE VOICE: I move that we fund this grant.

A MALE VOICE: I would second that motion.

MS. HORN: Discussion?

A MALE VOICE: What was the motion?

A FEMALE VOICE: To fund it.

DR. FISHBONE: Do we have to decide beforehand on an amount or after you've approved it?

DR. KIESSLING: Well I'm happy to discuss how much. I'm not that familiar with the budget.

MS. HORN: So the motion was to fully fund?

DR. KIESSLING: The motion was to fund it. We didn't discuss how much.

DR. GOLDHAMER: I second it if they add it to fully funded.

DR. KIESSLING: Well I'm not that familiar with the budget. Who reviewed this?

DR. GOLDHAMER: I reviewed this grant. So this is -- should I speak about budget now?

MS. HORN: Sure.

DR. GOLDHAMER: So it's about 1.5 million, which is 1.2 in direct cost. It's divided between three independent investigators, so it's a four-year project, so it's about $100,000 per year per investigator, so it's basically a seed size for each of these three investigators. Four years, per year.

Per year kind of determines the rate of progress more or less, so that's not, you know, with this team that has been working together for a long time and has reached this level of maturity of this project and has some publication record of productivity, I just wouldn't be comfortable with cutting it, because I don't think they're really asking for that much money.

MS. HORN: Any further discussion?

DR. DEES: I'm just worried about, because it's a big chunk of money, I'm really worried about (indiscernible - too far from microphone).

DR. KIESSLING: Can we do that? Can we go to funded, and then come back?

DR. PESCATELLO: So, David and Treena, you've heard everything else, so having heard all the

other seed grants you established, how do you feel about voting, recommending voting for this, given what you've heard, that we're going to be voting on all the other seed and established grants?

DR. GOLDHAMER: My enthusiasm has not been diminished by hearing all of the other grants today, if that's what you're asking.

DR. PESCATELLO: How are you weighted, relative to those? I mean are you recommending, knowing that we still have to go through the rest of these, are you still recommending --

DR. GOLDHAMER: It's kind of like apples and oranges comparing this grant to the seeds, for instance, so it's hard. It's a very high-quality kind of multi-investigator group grant.

DR. ARINZEH: And there were not major weaknesses mentioned on this, so it's a good group.

DR. KRAUSE: It sounds to me like people are mostly conflicted about committing to the money part, so I recommend or I propose that we vote just yes or maybe. I guess yes. I propose that we vote yes on funding this proposal, but we not finalize right now how much we're giving.

DR. WALLACK: I would second that motion.

DR. HART: Yeah, but you got to eventually make this decision.

DR. KRAUSE: Yes, we will, but I think that -- I, for one, am a little uncomfortable before I know what happens with these group grants.

DR. HART: Can I give you a scenario that kind of came into -- came to me before I came here today, which was if we assumed just what is possible, that we funded both cores, as we just did, we funded this group grant and funded one full two-million-dollar slot somewhere among the disease grants, three fully-funded established grants, we would have room for about 30 of the -- 30? No, I'm sorry. That's not right.

Fifteen of the seed grants, and that is actually surprisingly close to where we could be, except for the established grants.

DR. KRAUSE: I hear you, and I would be disappointed if we only funded three established investigators. That's like let's give out a bunch of R21s and not give anybody an RO1.

One of the things that, just because it's relevant at this particular junction, we used to be, or the Connecticut Stem Cell Program was, at one point, heavily favored towards human ES research that wouldn't

otherwise be federally eligible.

That's changed, and now what it's doing is it's filling in a huge funding gap for a lot of really, really good investigators throughout the state, who would be NIH-funded, except NIH funding has sunk to terribly low levels, so these are really good grants that deserve RO1 funding that aren't getting it, because the cutoff at the NIH is so low.

So I think that we need to take into consideration that funding established investigators is incredibly important right now.

DR. DEES: I think of this particular grant with the other group grants, maybe a different priority, but there's a way in which I kind of want to talk about those four grants that are still in the running together, just because they all amount sort of roughly the same amount of money, so we know how much we're taking out of the pot.

DR. KIESSLING: Another way to look at this group grant is it's essentially three established investigator grants.

DR. HART: Two. Budget-wise, it's two.

DR. KIESSLING: No, no, I know that in might, but, in value, it's three.

DR. HART: It's three for the price of two.

DR. KIESSLING: That's right. We're getting three established investigators funded for the price of two, so instead of being 2.some million, it's 1.5 million.

DR. WALLACK: So I actually think that Diane's recommendation is right on the mark, and it's consistent, I think, with what we've done in the past, because, in the past, we've had certain grants that we've accepted, and we voted yes on, but we didn't finalize on the number at that particular time, and we, then, had to find a way to slot that in, and some of the grants in established investigator may have been 600,000, for whatever reason. Usually, a financial consideration.

So I would be willing to vote yes on this grant and hold the amount, until we see where we are with all the other yeses, and I think it's an excellent recommendation and consistent with what we've done in the past.

DR. FISHBONE: I just have a question. It always bothers me in these fields that are rapidly changing that we fund for four years (coughing) two more years, unless we get more funding.

During the space of the four years, things change very dramatically, and I'm wondering if we could fund for a lesser period of time, so that the major goals of what they're each trying to do could be accomplished, but they could come back in three years, let's say, to reapply.

We're putting all of our money into funding way into the future, and we don't even know if we're going to exist after two years from now.

DR. KIESSLING: It's so hard to plan if you're going to come back with another grant in two and a half years. I understand that, and if there's a particular part of the project that you think is really iffy and it should get cut, that's one thing, but it's really hard on an established group to not know what you're getting on funding. You can't even organize your team very well.

MS. ENGLE: And I would just say, for this particular grant -- I was just going to say, for this particular grant, the four years is a necessity, because part two is predicated on part one, and part three is predicated on part two, so you can't condense the timeline, because you can't implant cells until you actually have them, and you can't characterize mice,

until you've actually implanted them.

So, for some grants, there is a necessity for these longer terms, in order to actually accomplish the amount of work.

MS. HORN: So we've had a recommendation that we approve this grant, but leave the funding amount open, and that would allow us to come back and revisit it at the end.

DR. WALLACK: If Diane makes that motion, I would second.

CHAIRPERSON MULLEN: I just wanted to reflect that I thought I heard David also make the point that there's a minimum amount of money on that, which this investigator would need to be funded, so to have a completely open-ended thought about it, without, you know, somewhat framing or anchoring something here, a dollar amount, a figure to work around, isn't really that helpful, because you can end up coming back to it and then saying, oh, yeah, but this is a meaningless, if there's any such thing as a not very meaningful amount of money when it comes time to actually doing the science, so I would just suggest, based on what you said, you wanted to suggest coming back to it, with the understanding that you think the investigators would need

this much money, that the group want to hear that and keep that.

DR. GOLDHAMER: I was going to say that I'm fine with Diane's suggestion and Milt's second, but when you do come back to it, I will express those --

DR. PESCATELLO: I would just add to that. I mean I know we've done it in the past (coughing) one back with asking for a reduction, but you would hope that people would have applied, and they need what they need.

I would hate the precedent of getting into a negotiation with people, and, then, also, setting a precedent, that people are going to up their budgets, knowing that they're going to negotiate with them.

DR. WALLACK: So, in the past, when we've done this, we have never had a situation, where people have not accepted the amount that we have put out there. I mean that's the reality.

And they can't come back for more, because they're hitting the limit as it is. I mean there may be a grant that's $25 less than the limit, but, with all due respect, I mean, they're going to that number, because the number is there, and they have never, ever, as I said, come back and argued the amount. They have

accepted the amount.

DR. GOLDHAMER: Accepting the amount does not mean that you can do the science in the same way at the same speed as at the higher amount. Of course, we accept amounts that are lower, because you accept that amount or don't accept anything.

That does not mean that there's a definite tradeoff, and the science would get done less quickly if the money value is lower.

CHAIRPERSON MULLEN: So my recommendation to the group is to vote on the amount and to consider for the rest of the discussion whether or not you are voting to fund research, or whether or not you are primarily at this point getting to the point of wanting to sprinkle the money around.

What is it going to be after many hours of going through this process to reassess a bunch of maybes? You have to land in one place or another.

DR. WALLACK: I think we will be more disciplined on these anyway, because we're going to have to do that.

CHAIRPERSON MULLEN: I'm asking for discipline in the entire process, though, in considering this financial consideration. You've got to do it.

They're going to keep going around and around. On behalf of the group.

DR. DEES: For those of you, who are proposing that we fund this fully now, you want to fund this fully now, upon all the other group grants that we have to consider. If we were going to, but we're not, fund one group grant, this is the one you'd want to fund.

DR. GOLDHAMER: I would suggest funding it fully, but I cannot comment about the other grants, so I can't address your question.

DR. KRAUSE: And I read the other five, but not this one.

A FEMALE VOICE: A lot of help you two are. (Multiple conversations)

MS. ENGLE: I would fund this one over the other grants, the other disease-oriented grants. I thought this one, actually, made no pretense to pretend that it was going to get in the clinic. It's truly what it is, which is a group grant, I, personally, I'm having no problem saying full funding now, because I agree. We're at a point, where we have to make tough decisions. I feel we have to get the big grants taken care of, because that will help us tell where we're going to fall on the smaller grants.

I'm sort of a move to the decision-making process and stop sitting around.

DR. WALLACK: So you would do the 1.4 such and such number, the whole?

MS. ENGLE: I would, yeah.

DR. KIESSLING: I would, too.

DR. WALLACK: So make the motion.

MS. ENGLE: I make a motion, that we fund this grant at 1.488229. (Multiple conversations)

MS. HORN: We have to talk just one at a time, though, please. We have a motion, and we have a second. Any further discussion? Okay. We are going to take a vote. Dr. Engle?

MS. ENGLE: I vote yes.

(Whereupon, a roll call vote was taken.)

MS. HORN: Okay. It was unanimous.

MS. ENGLE: Where are we at in the money?

MR. STRAUSS: You're still at $5,788,229. The next is disease-directed.

MS. ENGLE: How are we at five million?

MR. STRAUSS: Oh, I'm sorry. That number is comprehensive for all the things you said yes to, but if you are only counting what you voted on, then it's $2,488,429.

MS. ENGLE: Thank you.

MS. HORN: So we'll move onto the disease-directed.

MR. STRAUSS: One second.

DR. KIESSLING: Just to get the discussion going, I would like to move that we fund the disease grant -- I'm trying to come up with all the numbers. ISB grant.

MR. STRAUSS: ISB01.

DR. KIESSLING: Yes, the ISB01 grant at one million.

MS. HORN: Okay. Do we have a second?

DR. FISHBONE: I'll second that.

MS. HORN: Okay. We have Dr. Fishbone. Discussion?

DR. KRAUSE: What's your rationale for that, because I'm thinking that the main thing that he would need going forward is to prove that the human ES or iPS-derived MSC are, in fact, more immunosuppressive than bone marrow-derived MSC. Is that what you think, as well? Is that where you coming up with the one million?

DR. KIESSLING: The reason I think that this is -- this really spoke to the RFP, for one thing. I think it is doing everything that we wanted this

program to do for Connecticut, partially funding a small biotech company that's coming along that's going to do GMP work.

I think the science that they're talking about is important, but I think it's going to be expensive to get this all done --

DR. KRAUSE: I love the idea that his biotech is doing GMP, but that's not what the grant says. Biotech is a wonderful idea, and he should have a biotech, and I hope we can fund it, but the GMP was going to be done by a third party that was paid to do it, so just to clarify that.

So I think that this is basic science that is being done now. It can be done in the business, and it can be done with a million dollars, but I wanted to rationalize the million. And there's no reason to do GMP, because he's got to prove that these are the cells you want to make and put into patients.

DR. WALLACK: Ann, was there a motion on this grant for a million dollars?

DR. KIESSLING: Yes.

DR. WALLACK: Okay.

DR. GENEL: Over what time?

DR. KRAUSE: Whatever. Instead of two

million, one million.

DR. HART: They can negotiate the time.

DR. DEES: What's the rationale for doing one million, as opposed to 500,000, as opposed to 1.5 million?

DR. KRAUSE: Or 750k, like an established investigator, because isn't it along that line of what we're suggesting here that needs to be done? (Multiple conversations)

DR. KIESSLING: It's a multi-investigator project. We need to get the discussion going. I'm very excited at the quality of the disease-directed grants that we're seeing this year. I hope it just continues to improve like that.

We need to see more clinicians involved in this. You want the whole soapbox?

DR. PESCATELLO: The people who reviewed it, does the budget allow -- is it rational to take a two-million-dollar budget and make it a one-million-dollar budget?

DR. KIESSLING: I actually reviewed it.

DR. ARINZEH: I reviewed it. There's -- I don't know. I guess Wang is being -- there's a large percentage there. I guess he was a post-doc, maybe.

Six-month salary there. There's a chunk of money. It's hard to go through those.

DR. WALLACK: You have in front of you how much time Ren-He Xu is going to spend on it and Dr. Wang are going to spend on it.

DR. DEES: 3.6 months per year for Dr. Xu. Six months for Dr. Wang. Post-doc at half time. Tech at half time. Is that per year going forward?

DR. KIESSLING: This is a four-year award, as I remember. They're asking for four years of funding.

DR. ARINZEH: It's three years, and, yeah, it's six throughout. There is funding for Wang, post-doc and technician.

DR. WALLACK: If you looked at this as two established investigators and pegged it, therefore, at 1.5 million instead of the one million --

DR. KIESSLING: No. When I went through this, there was a reason I was thinking this could be done at one million.

DR. DEES: My recollection, from what you said this morning, was that you thought there was something that you could do that was about half this project, but that's what we do first before we can do anything else. (Multiple conversations)

DR. KIESSLING: -- that it might not even be the cells. It might be something that they make. I think all of that is going to happen. These are good investigators.

DR. WALLACK: So if I remember, also, what we were saying before, what's good about this grant is that, correct me if I'm wrong, is that was the comment made that it seems as though this particular project has a clean path to the clinic?

DR. KIESSLING: Well it doesn't have a clean path to the clinic, no. It doesn't have a clean path to the clinic.

DR. WALLACK: As what?

DR. KIESSLING: -- straightforward of this group.

DR. WALLACK: The third grant is what we're looking at.

DR. KRAUSE: MSC are already in clinical trials for MS, so there would have to be a reason why you would make these MSCs from an immortalized cell line, rather than from primary cells.

DR. DEES: The preliminary data we were given said that they were better.

DR. KRAUSE: Exactly, but their

preliminary data with the bone marrow MSC were not as good as others, who have already published the bone marrow MSC.

DR. KIESSLING: So you would want to fund it less?

DR. KRAUSE: So I thought that that needed to be worked out, that are bone marrow MSC, in fact, the ones that are already in clinical trials, are they, in fact, less immunosuppressive than human embryonic stem cell-derived MSC?

If the human embryonic stem cell MSC are more immunosuppressive and, thus, more effective in this autoimmune disorder, then I think that you do have a great path to the clinic, because you've proven that you have a product that's superior, and that's what I think needs to happen before they would spend all the time and money to make GMP-quality blah, blah, blah, blah, blah for a clinical trial. You have to prove that what you have is superior.

DR. PESCATELLO: Remember, this was a maybe, because of the science, not because of the money, this morning. We hadn't figured out if it was a maybe, because we hadn't included the science.

DR. WALLACK: I think that Ann liked the

science, and all Ann was talking about was the money.

DR. KIESSLING: I'm under the impression, although it's been reversed here, that the advantage to hES-derived MSCs is that you understand the population is better to much greater numbers.

I'm told here that that's not true, that the MSC technology from bone marrow has gotten much (background noise).

DR. WALLACK: Can I ask a separate question? Is Dr. Wang at UConn now? Does anybody know? Didn't Dr. Wang begin at Yale?

DR. HART: Yes.

DR. WALLACK: He did. That's what I thought.

DR. DEES: Then he went to UConn.

DR. WALLACK: What's that?

DR. DEES: Then he went to UConn.

DR. WALLACK: Okay.

DR. DEES: I guess my only question is aren't there -- the objection was, the reasons why we shouldn't be funding this at all, that they haven't done their due diligence?

DR. KRAUSE: I think, actually, I'm going back to the summary of the grant that is really quite

nice, just on page 11, aim one is basically the aim that I would like to see done and funded before moving onto aims two and aim three.

So we would have to ask the PI if he would be willing to take a reduced budget and give a reduced total and give us a revised budget of how he would do aim one, because that -- it would be, if we really followed these as contracts, it would be the step that you need to achieve before moving forward with the other ones, because aim one is specific factors are expressed in human ES MSC, but not bone marrow MSC in vitro in mice, contribute to the superior effect. That's what I'd like to see.

DR. KIESSLING: But that's like re-reviewing.

DR. KRAUSE: I know. I know at the NIH you don't do that. (Multiple conversations)

DR. KIESSLING: The reviewers were very enthusiastic about this grant. There's significant merit and innovation. The preliminary data is convincing, and the methodology is sound.

DR. KRAUSE: The reviewers also said why don't you get the effect with bone marrow MSCs that people previously got?

DR. KIESSLING: Yeah.

DR. HART: Yeah, it's clear. If that were proven, if somebody back came to you with that revised grant, showing that it was better than an efficacious MSC cell, you would be very excited about that.

DR. KRAUSE: Yes.

COURT REPORTER: One moment, please.

DR. KIESSLING: This disease-directed grant for one million (interruption in recording) that's what I move.

DR. HART: Do you have a second?

DR. FISHBONE: Which one are we talking about now?

MS. HORN: We have a second? We have a second, yes. Okay, so, we've been discussing that. The discussion started out talking about whether the million dollars was -- what that was based on, and I think that's what we've been kind of trying to get a handle on, so is it time to call the question and vote on this?

DR. HART: I just have one more comment, actually. One way to think about the problem is, again, if the thing we're stuck on is, the science is good, the direction is good, everything else is good, except that we're not so convinced about this comparison to the BM

MSC, one way to do this would be to say one year support at your current level of budget, which is $600,000, and come back next year.

DR. KIESSLING: I don't want to do that. That's too hard.

DR. HART: All right. I'm trying to make it fit in your program.

DR. KIESSLING: I remember thinking they could get a lot done --

DR. WALLACK: I like Ann's recommendation, based upon what you just said, because I'm getting four years for only 400,000 more.

MS. HORN: Paul has a comment.

DR. PESCATELLO: Two questions. So the motion is to approve the grant request, as drafted, but for one million dollars? The second question, the reviewers, who reviewed it in depth, are you confident that for half the price they can do what they said, they're going to come back to us?

MS. HORN: They would have to submit a revised budget to us for approval, indicating what they could do for the million dollars.

DR. HART: My recommendation would be let the investigator tell us what period of time would work

best for the goals we want to set for that.

DR. KIESSLING: So this is exactly what you meant, that it really needs to move forward. This is like home-grown technology that's going somewhere, and this just really needs to be supported.

DR. WALLACK: So, Ann, let me ask you a question. Would it be more realistic if we raised the amount slightly and hopefully, then, let the investigators be able to fit it into that amount?

DR. KIESSLING: I don't know, Milt. With such big science that we're not going to be able to fund, I don't know. I mean I think the two million dollars was a number we put out there, hoping that it was going to cover some clinical work, which just is not going to cover any funding for it.

I think our number for this was -- we don't have a true disease-directed project before us. This is as close as we've gotten, and I think we need to move it. Call the question.

MS. HORN: Okay, no comments? All right, we'll take a vote. The motion is to fund this -- yes?

DR. PESCATELLO: So if we go back to them for a million dollars, do they come back to us and then we vote again on whatever they propose? They get to

revise it for half?

MS. HORN: I think they have to submit a budget back to us to approve, depending approval of the budget, at our next meeting.

DR. PESCATELLO: But it's a completely different -- for half the price, somebody just said it is going to be a very different grant than what we're looking at.

DR. KIESSLING: Well it might be a year shorter.

DR. DEES: If we get approval of that, they have to come back for approval, so the committee has to approve it.

DR. WALLACK: Well, Ann, and that's exactly why I'm thinking that if we, instead of taking the million-dollar slot and put it at 1.25 million, we may have a better chance of the investigators being able to fit in the majority of that grant, so that's the only reason I'm suggesting (background noise).

It still does what you want to do. It carves out another established investigator, basically. And to make it more realistic, I would offer an amendment to your motion, and that is, for your consideration, at least, and that is to perhaps consider it at 1.25

million.

DR. KRAUSE: I think that that's missing the point, or at least the point I have. I understand that we very much want to fund disease-directed grants, and we already have, because Jan Naegele's grant that we just approved funding for is a disease-directed grant, so I think we can pat ourselves on the head, and I say that sincerely, that we are funding a disease-directed grant.

I would love for this PI to come back with a disease-directed grant with stronger preliminary data that say he has something that we should send to the clinic, we, from Connecticut, should send to the clinic.

I want to say yes now, but I think the fact that bone marrow MSCs, if bone marrow MSCs are actually better than human ES-derived MSCs for this and that his bone marrow data just weren't that strong, which is what the reviewer suggested --

DR. KIESSLING: One of them.

DR. KRAUSE: The reviewer, who knew about clinical trials for MSC, they knew about the literature.

DR. KIESSLING: It was a very minor point. Let's call the question.

DR. KRAUSE: And I'm done with that sentence.

DR. KIESSLING: I call the question.

MS. HORN: Okay. We're going to take a vote on the motion. Dr. Engle?

MS. ENGLE: Yes.

DR. FISHBONE: Could you repeat what the motion is?

MS. HORN: The motion is to fund the disease-directed group grant, ISB01, for one million dollars. And there are some conflicts on this grant, so please do not vote if you have a conflict.

(Whereupon, a roll call vote was taken.)

MS. HORN: Okay, the motion carries. We have two other disease-directed grants that are in the maybe category. Which one would you like to --

MS. ENGLE: So I'd move that we do not fund the Jackson 01 grant.

MS. HORN: Okay. Do we have a second?

DR. KIESSLING: I'll second that.

MS. HORN: Discussion?

DR. FISHBONE: Could you give us the reasons?

MS. ENGLE: This goes back to my concern, that it's really not disease-directed. It's looking at airway epithelial, using an adult stem cell, putting it

into decellularized. It misses, on a lot of boats, there's a lot of specific aims. It feels very much like multiple grants smushed together, in order to get to the two-million-dollar limit.

It didn't really meet the spirit of what we were trying to do with the disease-directed grants.

DR. DEES: Even though it scored high?

MS. ENGLE: What?

DR. DEES: Even though it scored high?

MS. ENGLE: Even though it scored higher. Again, part of our job is to understand how these grants fit into the programmatic direction that we are trying to go. It's not to say that it wasn't a good grant or a series of good grants put together, but it doesn't fit what we were trying to fund with this mechanism, in my opinion.

MS. HORN: Okay, any further discussion?

DR. KIESSLING: Who is also on another grant. Two others.

MS. HORN: Okay, we'll take a vote. Dr. Engle?

MS. ENGLE: No.

A MALE VOICE: The motion is not to fund.

MS. ENGLE: Oh, then, yes. Sorry.

(Whereupon, a roll call vote was taken.)

MS. HORN: Motion carries. Okay, the next grant is UCHC 01.

DR. KIESSLING: I don't know how we want to go about this, because I'm not convinced this is a stem cell grant. This is a cancer grant, but I'm not sure -- I'm not convinced it's a stem cell grant.

DR. HART: I'm not convinced that we were convinced that clinical research would be the next anticipated step.

MS. ENGLE: I'll second the motion to say no.

DR. HART: That's a motion to say no.

MS. ENGLE: I second the motion to say no.

MS. HORN: Do we have any further discussion? Hearing none, we'll take a roll call on UCHC 01, disease-directed. Dr. Engle?

MS. ENGLE: Yes not to fund.

(Whereupon, a roll call vote was taken.)

MS. HORN: The motion carries.

MR. STRAUSS: Okay, you're at, including the established and the seeds that you've made a decision on already, or at least tentatively, you're at 6.788229. Do you want to do the established next?

MS. HORN: So in terms of what we have asked of the voted fund, we are at --

MR. STRAUSS: Well we would be at 3.3 million less, so that would be 3.488229. Do you want established? Yes?

DR. FISHBONE: Did you vote on the ulcerative colitis grant, or is that a no?

DR. KRAUSE: We had already decided no on those other two. Do we have to officially now vote on those?

DR. KIESSLING: No, we voted on them already.

MS. HORN: They just stay in the no category.

DR. KRAUSE: Okay.

MR. STRAUSS: Do you want to start from the best scored one, or do you want to start from the bottom?

MS. HORN: The seed, correct?

MR. STRAUSS: Do you want to do the seed now or the established?

DR. KRAUSE: Established.

MS. HORN: You want to go established?

DR. KIESSLING: Yeah, because that's where

the big money is now.

MS. HORN: Okay.

MR. STRAUSS: So would you prefer to start at the --

MS. ENGLE: The lowest score, hence, the highest rated, the best rated.

MR. STRAUSS: The best rated?

MS. ENGLE: The best rated.

MR. STRAUSS: So you're at Yale 10.

CHAIRPERSON MULLEN: Do you want to just remind people how many maybes we had in this, so they can just --

MR. STRAUSS: Seven. Seven maybes, two yeses so far. The highest rated was UCHC 06.

DR. KIESSLING: Okay, so, we've already funded two of the established investigator grants and voted yes?

MR. STRAUSS: Well you have to vote on them, but we've already tentatively decided to fund.

MS. HORN: We have not officially funded any established yet. Dr. Genel wanted to make a comment.

DR. GENEL: Yeah. Remind me. How much money have we not spent yet? How much do we have left?

DR. KIESSLING: Four million and change.

DR. GENEL: Four million/eight.

MR. STRAUSS: That we haven't said yes to. We're at 4.7 million, so that means you have about five million to spend.

DR. GENEL: Okay.

MR. STRAUSS: But if you take into consideration what you've already said yes to in established and the seed, that puts you at 6.78 million, so you have about three million. Okay?

DR. GENEL: Okay. All right, well, what I was going to suggest is we go back to what we had done in previous years, and that is set a fixed number of minimum seed grants, go through that, make that determination, and then go onto discuss the established, because we have -- I think we all agree that, in many respects, our priority is to try and maintain as many seeds.

DR. WALLACK: We've done two million on the seeds. Are you suggesting that we do the two million?

DR. GENEL: That's right.

DR. WALLACK: Two million.

DR. KRAUSE: How many seeds do we already have yeses to?

MR. STRAUSS: 1.8 million.

DR. GOLDHAMER: That two million is not in the RFP. That's kind of an unofficial target we kind of shoot for, but that's not -- it's almost like giving priority to the seed to a set sum dollar value that we're shooting for that wasn't in the RFP.

DR. GENEL: Would it establish a basic minimum?

DR. GOLDHAMER: In the past. We haven't done that for three years or so.

MS. HORN: Yeah, we used to say we would fund at least two million dollars' worth of seed grants.

DR. GENEL: We're almost there anyway.

MS. HORN: Okay.

DR. WALLACK: Without doing an absolute math, could we go back to the seeds and vote on the yeses, which would be about 1.8 million, and then go to the investigator, the established investigator?

MS. HORN: We might need to take a vote on that. I think we're pretty split between wanting to do established and wanting to do seed.

DR. WALLACK: Everybody will know what they're doing by voting for the seeds. I mean they know that whatever you vote on the seeds it's going to diminish the amount for the established.

DR. KRAUSE: But we can kind of assume that, because we know it adds up to 1.8 million, if we vote yes on the nine.

MS. HORN: So it's really the battlefront right now is the established, is what you're saying.

DR. KIESSLING: Part of the confusion is how many of the seed grants are from post-docs on the established investigator grants? (Multiple conversations)

MS. HORN: I think we'll go to the established grants now. Okay, so, our first grant to look at, and Rick is going to look at everything that we funded so far? Rick, am I reading correctly, UCHC 05?

MR. STRAUSS: 06.

MS. HORN: 06, okay. I need stronger glasses. Thank you.

DR. KRAUSE: I vote that we fund this one.

A MALE VOICE: Second.

MS. HORN: Okay and we've got a second. Discussion?

DR. WALLACK: So a question to Diane. Diane, does it appear to you that we need to fund it at the 750,000?

DR. KRAUSE: I have no idea.

DR. WALLACK: Does anybody have an opinion on that?

DR. HART: This was the one grant that was rated well above all the others.

DR. WALLACK: So don't question on this one, Ron?

DR. HART: I think that's exactly it.

DR. WALLACK: Okay.

MS. HORN: I would like to remind people to keep in mind we need a reserve grant at least in the established and the seed.

CHAIRPERSON MULLEN: Any other discussion?

DR. FISHBONE: Do we know how many seeds we could fund with the 1.8 million?

MS. HORN: None.

DR. WALLACK: So can I call the question on this one?

MS. HORN: Yes.

DR. FISHBONE: How many established grants can we fund?

DR. KRAUSE: These two, plus four more.

DR. FISHBONE: These two, plus four more.

DR. WALLACK: If we don't fund anymore seeds, that's right.

MS. HORN: Okay. UCHC 06, we'll take a vote? Dr. Engle?

MS. ENGLE: I vote yes to fund.

(Whereupon, a roll call vote was taken.)

MS. HORN: The motion carries. It's funded for $750,000. The next one up is Yale 06 for 750,000.

A MALE VOICE: I'll move that we fund this at 750,000.

A MALE VOICE: Second.

DR. FISHBONE: Could we possibly repeat what they are?

MS. HORN: Sure.

DR. KIESSLING: This was the grant to do what?

MS. HORN: Yale 06, pluripotency and, oh, my gosh, chromatin topology. Does that help? Okay, any discussion? We're going to take a vote. Yes to fund?

(Whereupon, a roll call vote was taken.)

MS. HORN: Okay, the motion passes. Yale 06 is funded at 750,000.

MR. STRAUSS: Next is Yale 10 in the maybe category.

MS. HORN: Yale 10 is targeted

investigation into the causes of an amelioration of vascular proliferation disease using patient-derived induced pluripotent stem cells. Any discussion?

MS. ENGLE: It's going to be really hard to make a decision.

DR. KIESSLING: Is it a stem cell grant?

MS. ENGLE: Right, so, it's essentially a disease in a dish grant. They have iPS cells for a couple of genetic disorders that will help them understand vascular smooth muscle vascular proliferative disorder.

They want to do some mechanism of action studies, and then they want to do some testing of or treating mouse models with elastin deficiency to see if they can better -- recapitulate what they see in the dish in an actual in vivo model.

DR. DEES: I'm going to move that we not fund this grant, not because the science isn't good. The science is great, but because this investigator is currently, right at this moment, has two established investigator grants from us.

MS. ENGLE: Right. It already has a CT stem cell grant.

DR. DEES: And when do those end?

MS. ENGLE: 2016.

MS. HORN: Okay. We have a motion. Do we have a second?

MS. ENGLE: I second it.

DR. WALLACK: So can I ask a question on this? How much time of the three lead investigators is going to spend on it, because if Yang is only going to spend a limited amount of time and Kench(phonetic) and Delidis(phonetic) are going to spend a considerable amount of their own time, then it may be different.

A MALE VOICE: 1.2 months, .6 months and .3 months.

DR. WALLACK: That's Yang?

A MALE VOICE: Yang is 1.2, and the other two are 1.6 and 1.3, or 0.6 and 0.3.

DR. WALLACK: I was hoping for a different answer.

DR. FISHBONE: Does he have another proposal submitted to us for 2013 to 2017 for the treatment of aortic stenosis and Williams-Beuren syndrome?

MS. HORN: Do you have a number on that?

DR. FISHBONE: I don't.

MS. HORN: Is there a second?

MS. ENGLE: Yes, there is a second to my motion.

DR. KIESSLING: I'm going to call the question.

MS. HORN: Okay. We are voting on whether to fund Yale. (Multiple conversations)

DR. GOLDHAMER: Can I have one comment?

MS. HORN: Yes.

DR. GOLDHAMER: So this investigator has two established grants currently. I have a little problem. I mean I understand the reason behind the motion, but if having two current grants disqualifies an investigator from getting money, then this needs to be very clear in the RFP, and, so, that we don't waste the time of the investigators to apply for money that is not possible to get.

They have the third highest-scoring grant, and there was no hope, as it turns out, of them getting funded.

DR. KIESSLING: Well that's not true.

DR. GOLDHAMER: That's what we're saying, that the reason that the grant is not going to be funded, from what I understand from the conversation, is that they have two active grants. If there's other reasons,

then that's a different story, and I also think it's valuable to spread the money around.

I just have a little problem with process and not making this kind of stipulation upfront, and it takes a lot of time and energy to put together a grant.

DR. WALLACK: So, David, to follow-up on what you're saying, and that's why I asked for the amount of time, I mean, Yang certainly is involved in a lot of other work, not only the two grants that you're talking about, he's collaborating on a lot of other grants, but, on this particular grant, he's only going to be spending 1.6 months. What?

DR. GOLDHAMER: 1.2.

DR. WALLACK: 1.2. Ten percent of his time. So I'm not sure that that should disqualify him, and I'm agreeing with you on that basis. If you told me he's going to be spending half of his time, supposedly, on this grant, then I understand the argument.

I don't understand the argument -- well I'm not comfortable with the argument. I understand the argument, but I'm not comfortable with it on the basis of only 10 percent of his time.

What I like about it is he's bringing two other investigators in, who I do not, and I said this

this morning, who I don't believe we've had involved in the stem cell initiative. From what I gather, two rather accomplished individuals.

DR. GOLDHAMER: I mean I agree with you, there would be a problem if the effort was at let's say 50 percent.

DR. KIESSLING: Well the other problem with this when we discussed it is that they may or may not fund the defect. Isn't that the problem here? They're going to try to find the reason that some individuals can --

MS. ENGLE: No, they already know the reason why, so they're already basing it on the issue of mutations in the elastin gene caused super-vascular aortic stenosis, cause issues in these two genetic disorders, so they propose to use iPS cells derived from these patients for disease modeling, a screen of FDA-approved drugs identified Vinblastine as a compound that increases actin bundles and inhibited proliferation, so they want to study the mechanism of action.

They want to understand what it does in a mouse model, and then they propose to do a screen of FDA-approved compounds, which is about 2,000 compounds, and potentially another 144,000 compounds --

DR. FISHBONE: I'm just wondering how many patients will be able to find the super-vascular aortic stenosis and the Williams-Beuren syndrome.

MS. ENGLE: So their argument is that this is more applicable to the general issue of restenosis, when you do things like stent implants, so they're arguing restenosis is actually a common problem.

The genetic disorder is going to help them understand and model that, so that they have potentially some translatable information to the more common problem of vascular proliferation, or vascular smooth muscle proliferation.

DR. FISHBONE: Is that valid if they're totally different diseases?

MS. ENGLE: So it is. I think it goes back to, again, there's a lot of things we're looking at here. It's not the worse grant. There's some good science in it. It's, you know, where are we at in the funding? Was it super strong and super novel? Maybe not. And then it was a question of this particular PI is already funded in this area rather significantly, and it's a question of are we giving more money to the same effort. It's unclear how much.

DR. KIESSLING: So I was going to ask is

the overlap clearly-described?

MS. ENGLE: That is the challenge. I can't tell you off the top of my head what the overlap was, except that they were already well-funded to 2016, and, so, in the spirit of is this going to get Connecticut the bang for the buck that they're hoping for, that's the challenge here, but I understand your point, about disqualifying well-funded individuals.

That said and done, putting money where we're going to get the most out of it could be an important consideration.

DR. GOLDHAMER: I agree with you, and if there's overlap, absolutely, that it should be --

DR. DEES: I don't know whether there's overlap between the grants. Our rationale was these well-funded -- and is this something that we established as a rule? I think it depends on how this grant is. I mean this is very good. It's also really well-funded. I think it's reasonable to reject my motion.

MS. HORN: The vote on the floor is to not fund this Yale 10.

MS. ENGLE: So I vote yes to not fund.

(Whereupon, a roll call vote was taken.)

MS. HORN: The yeses to not fund carry.

Not by much, though, huh? Seven to three.

MR. STRAUSS: Next is Yale 12. David and James were the reviewers.

MS. HORN: This is improving the fidelity of human iPS cells with epigenetic and chemical genetic approaches.

DR. GOLDHAMER: So this was a grant that I had suggested a maybe on initially, and it's a very good grant, trying to understand -- of genomic instability and the role of a histone variant, and that instability would often be used for greater genomic stability in iPS reprogramming.

The concerns, just very briefly, this group has extensive data in the mouse, showing the importance of this protein and want to apply this to human cells, and the reviewer was concerned that there's no preliminary data in human cells, and there's some disagreement on the importance or the extent of genomic instability during human cell reprogramming.

So, in that sense, it's risky, and, in one sense, this is, perhaps one could argue, maybe more appropriate for lower funding or seed funding, at least because there's more preliminary data that shows a connection.

Now I think it's likely that there will be. I'm not an expert in this area, but I would guess there's going to be some connection, but it might be they ask for four years, and it might be something to consider in this case to reduce the years and give them time to show the importance, developments of their mouse findings in humans, so that would be one thing.

I think, certainly, the grants scored well, and there was enthusiasm by the reviewers. There was a little bit of disagreement between the reviewers.

One possible approach here is that it would be to fund it at a lower level, so I don't know what that lower level should be. It might be that reducing it from four to three years and proportionally cutting the budget by that amount would be an approach.

MS. HORN: Does anybody want to make a motion?

DR. GOLDHAMER: So I'll make that motion to fund this grant for three instead of four years. Three years at the proportional level, whatever that would be.

One more thing I want to bring up about this grant. Remember, there was a mistake in the budget, and the investigator had asked or budgeted in $12,000 a

year for travel and they meant $2,000, so there's $10,000 a year discrepancy, and I don't know how we want to deal with that.

DR. HART: Is that a four-year grant?

DR. GOLDHAMER: It's four-year grant.

DR. HART: So I come up with, then, 522,500 a year. That's three-quarters of the current rate, minus $40,000.

MS. HORN: Is that correct for travel?

DR. HART: Yes.

DR. GOLDHAMER: What's the number?

DR. HART: The one I got was 522,500. Three-quarters of the budget, less -- oh, it should be less $30,000.

DR. KIESSLING: So what is it now?

DR. HART: 532,500.

MS. HORN: We need a second. Is that your motion, David?

DR. GOLDHAMER: So, yes. My motion would be to fund for three years at whatever corrected dollar value that is, 532,500, is it?

DR. HART: Second.

MS. HORN: Okay, second.

DR. WALLACK: David, earlier, we were

discussing this grant in relation to the Ivanova grant, because there's some similarities, and Andrew Xu is going to be the principal investigator. It appeared that he was going to be the last two years, at least the way it was written.

DR. GOLDHAMER: I think that was a clerical error. I don't see any evidence from that grant that there's a switch in the PI in year three, and we had voted no for that grant anyway.

DR. WALLACK: Okay.

MS. HORN: So we have a motion and a second. Is there further discussion? No further discussion. We'll take a vote. This is a Yale grant. Dr. Engle?

MS. ENGLE: I vote no.

(Whereupon, a roll call vote was taken.)

DR. KIESSLING: What does no and yes mean?

MS. HORN: We are voting to fund, so Dr. Engle voted not to fund.

DR. KIESSLING: Yes.

(Whereupon, the roll call vote continued.)

MS. HORN: The ayes have it. The motion carries and the grant is funded for three years at 532,500.

MR. STRAUSS: So that puts you, including the non-seeds, at $7,350,729. Next up is UCHC 05, Ron and Mike.

DR. HART: This was the T cell differentiation with the engineered T cell receptor. A couple of quick points in favor. One is they asked for 600,000, not 750,000, so we're already cutting it by whatever percent that is.

The work is currently in press in Journal of Immunology, which is a fairly prestigious journal, suggesting that it is being accepted by the field. I go with Sandy's argument, that it's a parallel to other leading groups, but having another horse in the race in this case might be helpful, and this person had a seed award, which is currently on no-cost extension, ending probably this summer. Yeah, 8/31.

So, for all those reasons, I propose we fund this at $600,000.

DR. GENEL: I support that strongly.

DR. KRAUSE: Well the reviewer said that they didn't think that this was feasible, but you think that --

DR. KIESSLING: Which reviewer said they didn't?

DR. KRAUSE: I think it was reviewer two.

DR. KIESSLING: They gave it very high scores.

DR. GENEL: The other caveat was the concern that --

DR. HART: They said that T cell production in embryoid bodies without the thymus environment is unlikely to generate functional cells.

DR. KRAUSE: And episomal reprogramming might not work efficiently with T cells and send overs(phonetic) would be better.

DR. HART: I discounted that, because I know that that's false.

DR. KRAUSE: Okay.

DR. GENEL: The other caveat the reviewer had was about the competition with the Baltimore group, and I think the consensus was, well, you know, they may be wrong.

DR. KRAUSE: Yeah. I think that the competition is not an issue. The thing that's a bigger issue is I don't know what's in press in J.I., because I didn't read the grant, but are they functional T cells?

DR. HART: It was the T cell engineering, not the functional T cell part, but, remember, we're also

arguing they're competing with the Baltimore group, doing very similar things.

DR. KRAUSE: No, no, no. The Baltimore group uses primary T cells. Those are real T cells.

DR. HART: Okay.

DR. KRAUSE: They're already functional.

DR. HART: Okay.

DR. KRAUSE: Unless I don't know what the Baltimore group is.

MS. ENGLE: That said and done, they make gobs of functional T cells. There's a thousand ways you can use them. Even if they don't win the race with the other group, they're still --

DR. HART: The only problem, of course, is is that if they fail at making T cells from stem cells, this is not a stem cell grant.

MS. HORN: Further discussion? We have a motion on the floor to fund UCHC 05 at 600,000.

DR. KRAUSE: I have a question about that. If I voted no on that, could we, then, have the proposal to fund it for less, or is a no on that the end of this grant?

DR. HART: You can suggest an amendment, which I can choose to accept.

DR. KRAUSE: I motion that we fund -- that we vote to fund this proposal at a decreased funding level, because of the preliminary nature of their data on the functional T cells.

DR. HART: What's your number?

DR. KRAUSE: That's the hard part. I'd say 300,000. Any time we give them a new budget, they have to give us a new timeline and a new budget, right?

DR. HART: New aims, yeah. So they could choose to --

DR. GENEL: Well, Diane, they're already giving us a reduced budget to begin with at 600,000, as compared to 750.

DR. KRAUSE: They didn't give us a reduced budget. They gave us their budget.

DR. GENEL: Well they gave us their budget. If they gave us 750, we'd reduce it to 600?

DR. WALLACK: Diane, is that 300,000 something that you're comfortable with?

DR. KRAUSE: No. 300,000 right now is arbitrary. What I'm thinking is that it's the nature of a seed to show that these T cells are functional.

DR. GENEL: Well the investigator already has a seed. This is built upon the seed grant that we

already funded.

DR. PESCATELLO: I think, as a matter of policy, if we're going to reduce the funding, rather than just reduce the funding, I think we should try not to do that. We should go back not just with the reduced number, but tell them what we want them to do, or what we think they should do, and then they can accept it or not accept it.

We have to give them some direction, as to why we're reducing it and what we're expecting them to do. It sounds like, in this case, it's the first component of --

DR. KRAUSE: I'd have to read the whole grant. I take back what I said, and we'll go back to funding it fully.

DR. KIESSLING: Yeah. The reviewers were positive about it.

MS. ENGLE: And I agree with Paul. I think we need to get out of the habit of just randomly reducing people's grants, because how would you feel if you went in with what you thought was a justified budget with a clear plan, and somebody came back to you and said, yeah, we just randomly cut it by half. Let's see what you do now.

DR. KRAUSE: I completely agree. I take back my proposal. Let's vote on the full funding for this grant.

MS. HORN: Okay, we'll take a vote. Dr. Engle, the vote is to fund UCHC 05 at 600,000.

MS. ENGLE: I vote yes.

(Whereupon, a roll call vote was taken.)

MS. HORN: Okay, the motion carries. Rick, where do we stand?

MR. STRAUSS: 7,950,729. Next up is UCHC 01, and Mike and James were the reviewers on that grant.

DR. DEES: What was the number with all the ones we've said yes to?

A MALE VOICE: The nine seeds that we've already yes to.

MR. STRAUSS: That's 7.950,729.

DR. DEES: So we have two million, 1.9 million.

MS. HORN: Okay. What is next up, Rick?

MR. STRAUSS: UCHC 01 with Mike and James as the reviewers.

DR. GENEL: I need a minute to refresh my memory.

MS. HORN: This is the rotator cuff

repair.

DR. HUGHES: The principal objection to this would seem to be that rotator cuff repair would not be popular with this particular therapy, but there are lots of rotator cuff surgeries every year, and this seems like it was not only applicable to rotator cuff repair, but, also, to -- it also had cross-disciplinary implications, because it would be involved in tissue engineering with bioengineering materials, so I was supportive of funding this particular one, but we put it on the shelf.

MS. HORN: Do we have a motion to fund?

DR. GENEL: I'm equivocal. I'm equivocal on this, not so much because of the grant as it stands alone, but in review of the competition and everything else that we're dealing with.

I'm persuaded by the second reviewer's comment, questioning whether or not the injury is best served by stem cell transplant. I had a rotator cuff injury. It didn't take a stem cell transplant. Not to trivialize this, but it only would indicate, in the range of everything else that we've got over here, and we've got to make some decisions, I would say we --

DR. HART: And the concern, that people

would not want to transplant stem cells into an injury that can be reasonably treated.

DR. GENEL: Well, yeah. I'm sure we can find orthopedists, who will argue with us on that and so forth, and the argument is made in the grant.

It's only in the context of everything else that we've got, and we've only got 10 million dollars.

DR. HART: Are we making a motion now?

DR. GENEL: I'm making a motion. Regrettably, but no.

MS. HORN: Okay. Just keep in mind we need to have a reserve grant in this category.

DR. GENEL: Okay.

MS. HORN: Okay, so, we do not have a motion to fund this grant.

DR. KIESSLING: We don't have a motion to fund?

MS. HORN: We don't have a motion to fund.

DR. HART: He made a motion not to fund.

DR. GENEL: The motion is not to fund.

MS. HORN: Okay, motion not to fund. Second?

DR. HART: Second.

MS. HORN: Okay, so, we're going to vote not to fund. Is there any further discussion? Dr. Engle?

MS. ENGLE: I vote yes not to fund.

MS. HORN: A yes vote means not to fund.

(Whereupon, a roll call vote was taken.)

MS. HORN: The yeses have it. It is not funded. What's next?

MR. STRAUSS: Next up is UCHC 15, Treena and Paul.

MS. HORN: This is uncovering molecular pathways disrupted in Prader-Willi syndrome.

A FEMALE VOICE: I think the comment there was maybe already heavily funded.

DR. KIESSLING: I didn't see that when I looked at the grant. That was the comment, but I looked at the grant, I didn't see.

DR. HART: Just to be fair to the other grant that we did not fund, due to lab funding, can someone please just look it up?

DR. GENEL: Why did we put this in the hold category?

DR. KIESSLING: One of the comments about this particular application was that the lab was already

heavily funded to study this, and, when I looked at the grant budget, I didn't see that.

(Off the record)

DR. KIESSLING: So this investigator is a post-doc?

DR. KRAUSE: No.

DR. KIESSLING: This is an extension of that seed grant?

DR. KRAUSE: She was a post-doc with Marc Lalande until 2012, and, as of 2012, became an assistant professor in residence. Until the end of this year, she's on a seed grant, of which she's PI.

DR. KIESSLING: So the funding is Marc Lalande's funding, right?

DR. KRAUSE: No, she's PI. (Multiple conversations)

DR. ARINZEH: Yeah, so, they have an established investigator grant that collaborated.

DR. KIESSLING: With Chamberlin as a PI. That's all, right? The rest of it is either --

DR. KRAUSE: The other funding that exists for Chamberlin is the degenerate Prader-Willi cell lines for use in drug screening to identify potential therapeutics.

DR. KIESSLING: I don't know. This grant reviewed really well.

DR. ARINZEH: Yeah, I mean, that was the only issue. It was that, and, then, I guess there was some discussion maybe that the syndrome is a very small percentage of the population.

DR. PESCATELLO: We had a discussion, and it was actually (multiple conversations). I'll make a motion to fund.

MS. HORN: At 750? Okay. We have a motion to fund UCHC 15 at 750,000. Do we have a second?

DR. ARINZEH: Second.

MS. HORN: Second. Further discussion?

DR. DEES: We can probably leave, at most, two more of these, and that's if we don't fund anymore seed grants. We have three grants that are still open.

DR. PESCATELLO: Understanding what's left under the established, this qualitatively and I think (multiple conversations).

DR. ARINZEH: The scores are more consistent on this one, then there's other ones. There's some reviewer disagreement, I think, on -- I think at least the weaknesses appear to be heavier on some of these other ones. It was overall very positive.

MS. ENGLE: And, as you pointed out, we have to have one grant in reserve, right? Is this our bubble grant?

DR. FISHBONE: So who made the motion?

DR. KIESSLING: Well I'm the one that pushed so hard for the Rizzolo grant, and there were concerns about it. This is their retinal degeneration, macular degeneration grant or retinal model, and somebody thought that the ATC is already doing a clinical trial on this, so it seems to me like, of these three grants, the Rizzolo grant seems to be most likely to be in reserve, if we're going to fund it at all.

The last grant on here, so we've got three now that we're talking about, three maybes, and the last maybe on here is one that there were -- it's the macular degeneration grant, and they have a model for building a retina in a dish and studying, and the concern about it was that there's already a clinical trial ongoing on macular degeneration. I don't think they even mentioned it in the grant.

And, so, that maybe this particular science was not in step with what's going on, so, in view of that and in view of our funding constraints, it's possible that the Rizzolo grant should be the reserve,

and the other two should be funded.

DR. DEES: And I guess I'm not so sure of that, because, you know, I'm looking at seed grants that are better scored than these grants, and if we funded, you know, if we wanted to fund all the ones that are better scored from the seed grants, we certainly can't fund both of these. Of all three, we can only fund one of them.

MS. ENGLE: And I guess my leaning is towards funding seed grants, because, you know, if we're talking about, again, bang for the buck for the State of Connecticut, grants that have the potential to become RO1-funded grants, or to acquire venture capital, or grants from some other source in the future is really getting a return on investment that may be greater than the current return on some of the established investigator grants, who, as you pointed out or was pointed out, may be used as a substitute for RO1 funding from NIH. That's sort of a zero sum game there.

DR. HART: Let's face it. We're getting close to an NIH-style pay line here when you consider all the established investigator grants.

DR. KIESSLING: I know.

MS. HORN: We have a motion on the floor

to fund this grant, UCHC 15.

DR. HART: Paul, is there a way to fund this grant at a lesser amount? I know you'd want to arbitrarily do it, but I'm asking anything specific in the application that would indicate you can?

DR. PESCATELLO: Not that I remember. There's nothing I remember that seemed particularly that you can carve out.

DR. DEES: My proposal is let's actually move over to the seed grants and see which ones of the seed grants we really want to fund.

DR. WALLACK: Well, before we did that, I would personally want to speak to the Ivanova grant, Yale 14, so I don't know how you want to handle that, Marianne.

DR. KIESSLING: Well these two are very comparable.

A MALE VOICE: The same score.

DR. KIESSLING: Yes, exactly the same score.

A MALE VOICE: Maybe we should talk about that one first.

DR. WALLACK: And I would offer that -- I would make the recommendation that we fund the Ivanova

grant. Was it Yale 14? I think it's a really important subject. Oh, sorry. I can't talk now about this?

MS. HORN: We have a motion on the floor.

DR. WALLACK: Okay.

MS. HORN: To fund this UCHC 15, so I think we need to take a look at what we're doing there.

DR. KIESSLING: The problem is we're now trying to figure out -- I don't know if we can vote on that.

DR. PESCATELLO: We can withdraw the motion and then go on to the seed grants and then go back in the final three.

DR. GENEL: I'd suggest that's probably a good idea.

A MALE VOICE: I'd suggest you table the motion.

MS. HORN: Okay, we can do that.

A MALE VOICE: You're going down the list, so let's go back --

MS. HORN: Okay. That's a good idea. We'll just table the motion and move over to the seeds, if that is acceptable.

DR. KRAUSE: Can I clarify where we are financially? My understanding is if we fund nine seeds,

so taking that into the calculation, and of the established the --

MR. STRAUSS: Decisions so far, you're at seven million --

DR. KRAUSE: Wait. Of the established, but that's with funding for established?

MR. STRAUSS: Yes. The ones we approved.

DR. KRAUSE: Okay, so, with that, how much is left?

MR. STRAUSS: We have about 1.9 million.

DR. KRAUSE: Okay, so, that would be two established and two more seeds?

MR. STRAUSS: And we have 10 seeds on our maybe list at the moment.

DR. KRAUSE: I understand, but we also were just getting to Martins-Taylor, Ivanova, Rizzolo. Those were our three more maybes.

DR. DEES: The 10 more seeds all have higher peer review scores than any established grants.

DR. HART: That's not actually true. The bottom of the seeds have 25s.

DR. KIESSLING: Yeah. The ones that are --

DR. DEES: We've already said no to all

those, no?

DR. HART: Two of the seeds on our maybe list have 25s.

DR. KRAUSE: And, for the record, Richard, we funded Naegeley at 25 and Xu at 25, so 25 is a fundable, good. We say those are great reviews. We'll give them 3.5 million, you know?

DR. DEES: That's why I wanted to go look at the seeds, so that we could decide which of those we think we really do want to fund.

MS. HORN: I just want to say I don't think we can really take one set of grant scores and compare them to another set of grant scores. Okay, so, we are tabling. We are tabling. It is hard to make these choices. UCHC 15, we're tabling that motion to fund, and we're going to take a look at the seeds and see where we end up, and then we'll come back to the established.

DR. HART: One of the problems we're going to have is that it's going to come down to a philosophical difference. If you're in favor of spending money on seeds, we could just easily access almost 10. Of those 10 may be seeds.

If you're in favor of doing more

established grants, we could fund those and none of the seeds, so it's kind of a one or the other kind of proposition. You really can't do both. You can't do much mixing, because the remaining established grants are so close to review it would be hard to pick one out fairly from the other. That's my only point.

DR. WALLACK: And I think the point that's been made is that we owe it to the process to include the seeds to stimulate the process. Sandy, I think that was the point you were making.

MS. ENGLE: But that's, again, my opinion and --

DR. WALLACK: Philosophy, yeah.

MS. ENGLE: Right. So that's my opinion.

DR. WALLACK: So are we going to seeds now?

DR. KIESSLING: Let's do that.

MS. HORN: We're going to go to the seeds and take a look at what we have there.

DR. PESCATELLO: So do we need a motion to approve the ones we've said yes to?

MR. STRAUSS: We did already. We made a motion to table.

DR. KIESSLING: For the seeds?

DR. PESCATELLO: For the seeds. We haven't funded them.

MS. HORN: We need to go through each of those and say yes.

MR. STRAUSS: You should probably table the motion on the grant that you were --

MS. HORN: That's tabled, yes. That is tabled, and now we're moving to the seeds, and the question is does the group want to go through these ones that have been placed in the yes column to decide whether that's still their vote and vote on them one-by-one, or take the whole group that we funded? What is it, Rick, six?

MR. STRAUSS: Nine.

MS. HORN: Nine?

MR. STRAUSS: Nine.

MS. HORN: And vote to fund all of those. (Multiple conversations) Okay, so, 13 SCA Yale 04, is the first one. If you have a conflict with Yale, please do not vote. We need a motion to fund.

DR. FISHBONE: I move to fund.

MS. HORN: And Paul has seconded. Any further discussion? Okay, we'll call the question. Dr. Engle?

MS. ENGLE: I vote yes to fund.
(Whereupon, a roll call vote was taken.)
MS. HORN: The motion carries.
MR. STRAUSS: UCHC 11.
MS. HORN: UCHC 11. I need a motion to fund for 200,000.
DR. PESCATELLO: So moved.
MS. HORN: Paul?
DR. HUGHES: Second.
MS. HORN: Dr. Hughes. Okay. Dr. Engle?
MS. ENGLE: I vote yes to fund.
(Whereupon, a roll call vote was taken.)
MS. HORN: Motion carries.
MR. STRAUSS: Yale 38.
MS. HORN: Yale 38 for 200,000. I need a motion.
A MALE VOICE: Move.
A MALE VOICE: Second.
MS. ENGLE: I vote yes to fund.
(Whereupon, a roll call vote was taken.)
MS. HORN: The motion carries. UCHC 01 for 200,000. I need a motion.
A MALE VOICE: Move to fund.
MS. HORN: Second?

A MALE VOICE: Second.

MS. HORN: Okay, this is a UConn grant. Dr. Engle?

MS. ENGLE: I vote yes to fund.

(Whereupon, a roll call vote was taken.)

MS. HORN: The motion carries.

MR. STRAUSS: Yale 20.

MS. HORN: This is a Yale grant, Yale 20 for 200,000. I need a motion, please?

A MALE VOICE: Move to fund.

A MALE VOICE: Second.

MS. HORN: Dr. Engle?

MS. ENGLE: I vote yes to fund.

(Whereupon, a roll call vote was taken.)

MR. STRAUSS: Yale 23.

MS. HORN: Okay. I need a motion, please, for 200,000.

DR. PESCATELLO: So moved.

MS. HORN: Paul. And second?

A MALE VOICE: Second.

MS. HORN: Dr. Engle?

MS. ENGLE: I vote yes to fund.

(Whereupon, a roll call vote was taken.)

MS. HORN: The motion carries.

MR. STRAUSS: Yale 36.

MS. HORN: Yale 36. I need a motion, please.

DR. PESCATELLO: So moved.

MS. HORN: Paul.

DR. DEES: Second.

MS. HORN: Dr. Dees. 200,000. Dr. Engle?

MS. ENGLE: This is Yale 36? I vote no.

(Whereupon, a roll call vote was taken.)

MS. HORN: The motion carries.

MR. STRAUSS: Yale 06.

MS. HORN: We need a motion, please.

DR. GOLDHAMER: Motion to fund.

MS. HORN: David.

DR. PESCATELLO: Second.

MS. HORN: Paul. Dr. Engle?

MS. ENGLE: I vote yes to fund.

MS. HORN: Yale grant.

(Whereupon, a roll call vote was taken.)

MR. STRAUSS: Yale 06.

MS. HORN: We just did it. UCHC 03.

MR. STRAUSS: 03.

MS. HORN: For 200,000. A motion, please?

A FEMALE VOICE: A motion to fund it.

A MALE VOICE: So moved.

MS. HORN: Dr. Engle, UCHC.

MS. ENGLE: No.

(Whereupon, a roll call vote was taken.)

MS. HORN: The next grant down, Yale 27. This was placed in the maybe category.

A MALE VOICE: So we're in the maybes now, right?

MS. HORN: Yes.

DR. KIESSLING: She's going back to the top of the list to the maybes.

DR. FISHBONE: Can we be refreshed on what it is? (Multiple conversations)

MS. HORN: Richard Dees and Dr. Hughes.

A MALE VOICE: I'm lost. I thought we were at Yale 12, which is the top of my list.

A MALE VOICE: Yale 27.

A MALE VOICE: Okay, sorry.

DR. HUGHES: So this was using fat cells in lymphatic vessel differentiation, and the target was lymphedema. It received high marks for innovative use in multiple methods, in vitro differentiation, in vivo transplantation and in vivo lineage tracing methods.

I was corrected in the clinical

significance of lymphedema. That seems quite important.

MS. HORN: Do we have a motion?

DR. HUGHES: That is the motion. I move to fund.

MS. HORN: Okay. Do we have a second?

DR. DEES: Second.

MS. HORN: Discussion? No discussion. I'll call the motion, and it is a Yale grant, so please don't vote on it if you have a conflict. Dr. Engle?

MS. ENGLE: Yes to fund.

(Whereupon, a roll call vote was taken.)

MS. HORN: Okay, the motion carries. We are now at 10 seeds.

MR. STRAUSS: We are at Yale 32, which is Milt and Richard.

MS. HORN: Yes, Yale 32. Cell therapy with ISL1 plus progenitor cells for cardiac repair after myocardial infarction.

DR. KIESSLING: The criticism of this grant was that it was a multi-species project. I actually looked at the rat they're going to use, and they didn't use a rat that's an engineered rat.

MS. ENGLE: You have to have an immuno-compromised rat, in order to make the transplant work.

It's just multiple species, and, frankly, if -- human cardiomyocytes beat at 70 beats per minute, and rats and mice beat at much, much higher.

If we're going to go across species, we might as well go guinea pig, but there's no immuno-compromised guinea pig, which a guinea pig at least has a heartbeat closer to ours.

There's just -- there's some interesting science. Let's put it that way.

DR. KIESSLING: It's really hard to do heart surgery on a mouse.

MS. ENGLE: Yeah, which is why, right? But, then, my question was, if you're going to -- you could do this easily in mouse, so mouse to rat, and you totally have more compatible systems. That's my opinion.

DR. GOLDHAMER: You still have the issue of rejection mouse to rat.

MS. ENGLE: Right, but at least the cardiomyocytes would be beating at comparable rates, so there's a lot of science behind this, but, essentially, you get the two, because human cells can't deal with the rat, but they're just looking at transplant and --

A MALE VOICE: I can't hear you.

MS. ENGLE: So there's a lot of science

behind this, and, again, it's my opinion. I think you'll all just have to make a decision on your own about this one.

MS. HORN: Do we have a motion?

DR. GOLDHAMER: Let me just ask another question. Do you feel that they didn't justify well the choice of rats? Did they talk about the choice and the rationale for that choice?

MS. ENGLE: They did talk about that. I think my concern is more around the justification of why did they choose human, because they've already done the work in mouse, and they could continue on with the mouse system.

Again, it felt a little to me like they were just looking for an opportunity for funding. It's my opinion on this particular work.

A MALE VOICE: I'll move that we fund this.

MS. HORN: Do we have a second?

A MALE VOICE: I'll second it.

MS. HORN: Further discussion?

DR. KIESSLING: They're making an interesting patch. I don't know if everybody is aware of that, but they're making a patch on some kind of a dish

that lifts off at lower temperatures. Is that right? They're making a cell patch of some kind.

One of the reviewers says the cell sheet engraftment strategy and characterization of functional efficacy is logically designed and will be important for validating the approach for therapeutic application. Kind of an interesting technology that they're using, so they've got a sub-straight on the dish that adheres to the dish at 37 degrees, and when you cool it down to room temperature, it lifts off, so you don't have to disrupt the cells at all. It just kind of peels up, like Scotch tape.

MS. HORN: Okay, any further discussion, or should we take a vote?

MS. ENGLE: And the motion is yes to fund?

MS. HORN: The motion is yes to fund Yale 32.

MS. ENGLE: I vote no.

(Whereupon, a roll call vote was taken.)

MS. HORN: Okay, the motion carries.

MR. STRAUSS: Okay, we're at 8,320,729. Next up is --

DR. KRAUSE: So what's the balance?

MR. STRAUSS: 1.5. A little less than

1.5.

DR. KRAUSE: So my bias from here on is I really prefer to fund two established, so if we keep forward on this, on the seeds, we're sacrificing established investigators.

DR. KIESSLING: So how many seeds are we funding?

DR. KRAUSE: Eleven.

DR. WALLACK: Eleven seed, which is one more than we've done in the past, I think.

MS. HORN: Could you double-check that, please, Rick, how many seeds we just funded?

MR. STRAUSS: Eleven.

MS. HORN: Eleven?

DR. KIESSLING: I'm worried about not funding at least one more established investigator grant. I sort of share that concern.

DR. KRAUSE: I'm worried about not funding two more. There are three more in the maybe category.

DR. GENEL: So there are three more seeds, or two more established. Is that it?

DR. KRAUSE: No. It would be more than three more seeds, because there's 750 versus 200.

DR. WALLACK: Can I speak up for, if it's

okay with you, for the Yale? It's the Ivanova grant. It's 15. No, no. Yale 14, established investigator.

MS. HORN: What is the will of the group here? Do you want to continue going through seeds or moving back to the established?

DR. WALLACK: So my point was this, Marianne. We have three more established investigators. I think we said we wanted to fund two.

MS. ENGLE: Well I said I wanted to fund two.

DR. WALLACK: So Yale 14 I would recommend that we -- my recommendation would be, if we were to fund it, would be to fund it at 550,000.

MS. HORN: Well I think we have to make the fundamental question here, we're still on seeds, whether the group wants to go back and leave the seeds for the moment and go back and look at the established, and then we can look at the one you're suggesting.

DR. GOLDHAMER: We have seeds here with better scores than the established that are left. I don't know if they can really be compared directly, but just to be aware that we have a number that are better in the established.

DR. PESCATELLO: But we can flip back to

established maybes. We can flip back and do at least one.

DR. KIESSLING: Well they're not scored that much better.

DR. DEES: We're looking at 19s and 20s versus 25s.

DR. KIESSLING: That's well within the peer review --

DR. KRAUSE: Yeah, but we didn't say that about the group and the diseases.

DR. KIESSLING: No, I know. I'm saying that I don't think that these seed grants fund is that much better than --

DR. DEES: She's agreeing with you.

DR. KRAUSE: Oh, okay. You and I agree. Okay, good. I don't pay too much attention when you're discussing the Yale grants, because I shouldn't, and, so, then I stop listening for a second, and I apologize.

DR. WALLACK: Marianne, are those the only two seeds that we're still thinking about? Is that it? Four, six, eight. So, Marianne, those are the only two seeds we're still looking at? (Multiple conversations)

DR. KIESSLING: -- and still in the maybe.

MS. HORN: There are two on this page,

Milt, that are in the maybe column, and then six, I believe, on the next page.

DR. KIESSLING: It's just that we're down to the last million and a half, and we're worried about how we should spend it.

MS. HORN: Okay. Maybe we should have a show of hands of people, who would like to go back to the established investigator and revisit that, or ones, who would rather fund a few more seeds while we're here.

DR. KRAUSE: Actually, why don't we, because I think that's the same question, and, if it isn't, then we'll go back to your question, decide if we're doing one more established, two more established, or no more established, because by continuing with the seeds, we're at least down to only one more established.

A MALE VOICE: Well either category we fund more we're going to cut off the other.

MS. HORN: Right.

A FEMALE VOICE: Is there someone here that really feels that there's a grant here we have to fund in the established?

DR. KIESSLING: That's the better way to go.

A FEMALE VOICE: Is there a strong support

for one or two of them.

DR. KIESSLING: And we need to put one in the reserved, as well.

DR. DEES: I propose we go back to the established. If we think that we really need to fund one or both of these, the two grants that are at 25, make the case, and we'll work on that.

DR. KIESSLING: I'm willing to -- I'm the one that argued so hard for the Rizzolo grant, but I've been informed that it's behind the times.

DR. DEES: So why don't we start here? Why don't we move not to fund the Rizzolo grant?

DR. KIESSLING: Yeah, if we move not to fund the Rizzolo grant. That's painful, because macular degeneration is a big deal. It would have to be something, so I move Rizzolo --

DR. WALLACK: Why are you convinced that he's behind the times?

DR. KIESSLING: Because I'm told that there's --

DR. WALLACK: No, I understand. I heard Sandy's arguments, also, but I think one of his recent papers indicated that his methodology is an enhancement over the current techniques.

DR. KIESSLING: Yeah. They were publishing. That's right.

DR. WALLACK: Right, so, I don't think that that's a fair argument to eliminate that grant, because he's arguing, if he were here, reading from his literature, that, no, I understand that that's out there.

DR. KIESSLING: No, I know. It's painful.

DR. WALLACK: The only thing I'm saying --

DR. KIESSLING: But we don't have enough money.

DR. WALLACK: So, Ann, maybe we don't fund it, but I don't think we not fund it only on the basis that, quote, unquote, "he's behind the times." If we decide that we don't want to fund it, that's another question, but I don't think that's a fair assessment of where he's coming from.

DR. KIESSLING: Okay.

MS. HORN: Well coming back to the established, we have a motion that was tabled.

DR. FISHBONE: We just made a motion not to fund the Rizzolo.

DR. KIESSLING: So I think we should vote.

DR. FISHBONE: And I want to second that motion.

A MALE VOICE: Who made the motion?

DR. KIESSLING: I did.

MS. HORN: Discussion?

A FEMALE VOICE: We already had it.

MS. HORN: We had it. Okay, we'll vote. Dr. Engle?

MS. ENGLE: So this is a motion not to fund. I vote yes not to fund.

(Whereupon, a roll call vote was taken.)

MS. HORN: The yeses have it.

DR. HART: So now we either fund two equally-scored established grants, or we start slicing and dicing.

DR. PESCATELLO: Well, as we've last left -- (laughter). I thought we had a slight edge, because there was such uniformity in the reviewers. There was a little negative or qualification in the review.

DR. WALLACK: So can I share a thought, and that is that it's pretty clear, Marianne, that we want to fund more seed grants.

DR. DEES: I don't think that's clear either, actually. I don't think that's clear.

DR. WALLACK: All right, well, I'll contain the thought. This subject has been funded by us

in the past, but, by the same token, it's something that I think is very important and that this team has done very good work with, so if we funded it at a lesser amount, and I'm thinking of taking off $200,000, I know for a fact that I can do the same thing with the Ivanova grant, the Yale 14, because, in that grant application, it said that the grant -- the work will be done in three and a half years, so that if they're telling me the work is going to be done in three and a half years, I can hypothesize that, you know what, you can get it done in three years, I can take off the last year of funding, and I can free up almost $200,000.

So I'm trying to make an argument for funding both of these grants and still have the ability to fund two more seed grants.

DR. KIESSLING: There you go.

DR. HART: Let's not trip over our argument. Just make it.

DR. WALLACK: It's a torturous argument, but I tried.

MS. HORN: Okay. I'll go back to the motion we have that is tabled. Perhaps we can take them one at a time.

DR. WALLACK: I'll make a motion that we

fund UCHC 15.

MR. STRAUSS: Just a point of order here. You have a motion that was tabled, so, technically, you have to do something with that motion if you're going to come back to the grant before you make another motion.

DR. PESCATELLO: I would bring the motion, the Martins-Taylor.

MS. HORN: All right. Do we need a second for that, Rick?

MR. STRAUSS: I just know you've got one on the table, and I don't know how to deal with that.

MS. HORN: So you're moving to bring it off the table, back onto the floor. Treena, would you second that, just out of abundance of caution?

DR. ARINZEH: Second.

MS. HORN: We now have a motion fully back on the floor for UCHC 15, Martins-Taylor.

DR. WALLACK: I'd amend the motion to fund this grant, but fund it at $550,000.

DR. KIESSLING: Which one? Martins-Taylor?

DR. WALLACK: UConn 15.

DR. PESCATELLO: I don't remember the budget as having --

DR. KIESSLING: How many years?

DR. ARINZEH: Three years.

DR. WALLACK: Is it three years? Well that's all the more reason.

DR. KIESSLING: If I read the current funding for that lab, it's not that high this year. There's a bunch of grants that are ending in 2013.

DR. PESCATELLO: Yeah, it's a three-year.

DR. KIESSLING: Yeah, it's a three-year grant.

DR. PESCATELLO: It's a three-year, so, unless anybody else has greater wisdom than I, I'm not in favor of cutting it. It's either up or down in my mind.

MS. HORN: I think we need to call the question and take the vote on your grant for 750,000. UCHC 15. Dr. Engle?

MS. ENGLE: Okay, so, the motion on the floor is to fully fund the grant?

MS. HORN: Yes.

MS. ENGLE: I vote no.

DR. DEES: Can I pause this before we take this vote? Because this really is -- we're not voting on this grant in isolation, or maybe we are, but it's hard not to think, okay, if I wanted to fund one of these two

grants, I'd like to hear why I should fund one rather than the other, because I'd like to hear why we should or should not fund the other grant.

DR. KIESSLING: I agree with that, Richard. Our funds are so limited it's really hard.

DR. DEES: And it may be that somebody makes the case and I'll say, yes, let's fund it, but I feel like I want to hear both bases before I make a decision on either one.

DR. PESCATELLO: It was my understanding that by hearing our discussions so far since this morning, that we could be incorrect. My sense was that this one had a slight edge, in the sense that there was less negativity to this, or there were fewer criticisms, less of a critique, of a negative critique -- (multiple conversations).

DR. WALLACK: Yeah, I would dispute it. I mean, first of all, let me start by saying I'm fully ready to vote positively on UConn 15 for the lesser amount.

I would speak very favorably on behalf of Yale 14, because of the subject matter.

CHAIRPERSON MULLEN: Can I ask? I'm having a really hard time keeping track of a single train

of thought, and I don't know how we're going to get to any conclusions if we can't stay on a single train of thought.

DR. KIESSLING: We're comparing two applications.

CHAIRPERSON MULLEN: Is everybody aware of what the conversation is right now?

DR. KRAUSE: Yes. It's just that half of us can't speak, because we're talking about two grants.

MS. HORN: We have a motion that started to be voted on, and now we are discussing two grants at once.

CHAIRPERSON MULLEN: Right, so, let's be clear where we ought to be in the discussion at the moment.

DR. KIESSLING: If we vote to not fund this fully, can we get a revote to fund it partially?

MS. HORN: We tried to accept an amendment to that motion, but it was declined.

MR. STRAUSS: Okay, so, you can table the motion again, and then you can move to the next grant, discuss the next grant, and then you can move back, you can table that motion, and then you can move back to discuss whichever one you want, but because of the people

that have to abstain, it's very difficult if you are talking about both at the same time, so it's a process standpoint, because of who is on the committee. That's how you have to deal with it.

DR. PESCATELLO: Just to clarify, so, we can vote in next in line, which is the Martins-Taylor, and then go on from there to the other and debate the other established grant.

We could not go either of the established grants and go back and do the seeds. We could do four. The third option is to do one established and then use the remaining dollars for seeds for the remaining balance. Is that clear as mud is?

MS. HORN: Yeah. I just think it's important that we take these grants one at a time.

DR. PESCATELLO: Are we saying we want to do two established, or are we saying we want to do one established and fill the balance with seeds, and, if we're going to do one established, then we really have a debate between the two, because they're so close.

DR. KIESSLING: It's painful.

DR. PESCATELLO: It's really hard to say that one is --

DR. DEES: I guess, from a point of order,

I mean was your motion seconded? You made a motion to amend.

DR. PESCATELLO: I'm not sure. I'm willing to table it, if you want to table it to have a discussion, but I think, formality-wise --

DR. HART: And we've already said yes to 11 seed grants, which is one greater than we usually do. That's just an observation.

COURT REPORTER: One moment, please.

DR. HART: The last year that there's records online, I don't have my notes from last year stored, but -- (multiple conversations). That's what we did in the past. We don't do anything like that in the future, but that's what we did in the past.

MS. HORN: I'm sorry. I have a question for you, Rick. UCHC 01, is it up there?

DR. WALLACK: We got a no on that one. UCHC 01, not funded.

MS. HORN: Okay. Just to reiterate, Paul has a motion to UCHC to fully fund. Milt had made a suggestion of amending that to a lower amount. Paul declined to accept the amendment to his motion, so we were calling the question to go forward and vote.

DR. WALLACK: I'm not sure of the process.

DR. PESCATELLO: Do you want me to table my motion, so we have can have a discussion?

DR. DEES: He can propose, even if Paul doesn't accept his amendment. If he accepted the friendly amendment, he can still propose it as an amendment.

DR. WALLACK: Robert's Rules allows for me to make the amendment, and the amendment can be voted on.

DR. KIESSLING: We vote on the amendment first?

DR. WALLACK: Yeah. So, Marianne, if you would entertain it, I would, then, make an amendment to fund UConn 15, fund it at $550,000.

DR. KRAUSE: Where is that number coming from?

DR. WALLACK: What's that?

DR. KRAUSE: Where is that number coming from?

MS. HORN: We need to get --

DR. KRAUSE: Oh, I'm sorry.

MS. HORN: We have a motion. We need a second.

DR. PESCATELLO: Is there a way to do this, so that we do two, without any discussion in

between sequentially? So I'm happy to do Milt's amendment if we all know that you vote up or down on that, which is Martins-Taylor reduced to 550, everybody votes on it, knowing that if they vote against it, the next vote will be in favor of it at its full amount.

DR. HART: Right.

DR. PESCATELLO: Is that --

DR. HART: That's fine. We're voting on the amendments.

DR. PESCATELLO: But we're not going to do anything in between. (Multiple conversations)

MS. HORN: Okay, so, did we get a second?

DR. KIESSLING: And if we table both of these, then we can talk about the Ivanova grant and make a decision, based on how that conversation comes out. Is that possible? We just can't do them both at the same time.

MS. HORN: Okay, so, we have an amended motion for 550.

DR. GENEL: I'm a little confused. How did we come up with 550 instead of 600?

A MALE VOICE: It's three years.

DR. PESCATELLO: It already is three years, so if it were to go to 550, they would have to

reduce it in some unknown way to us. They'd have to do something -- (multiple conversations).

DR. HART: Second.

MS. HORN: Ron Hart seconded. Discussion?

DR. KIESSLING: Can we table this and talk about Ivanova before we vote on Martins-Taylor?

MS. HORN: Would it be helpful to have some discussion on where the 550 came from?

DR. KIESSLING: Well I think that's because Milt thinks it's a four-year grant, but it's only a three-year grant.

DR. HART: He's picking that number, because he wants to fund another seed.

DR. KIESSLING: Oh. So can we talk about the Ivanova grant first? I would really like to talk about the Ivanova grant before we vote.

MS. HORN: We have an amendment out there hanging, waiting to be voted on.

DR. HART: The amendment is whether to accept the reduced budget to the existing motion. It's not to pass the grant.

MS. HORN: Yes.

DR. HART: Whether it's the amended version of the budget or the un-amended version of the

full budget, yes.

DR. KIESSLING: Right, so, we're going to have to do that before we discuss Ivanova?

DR. HART: Let's get rid of the amendment first. We won't fund anything --

MS. HORN: Okay, further discussion on the amendment?

DR. KRAUSE: If we vote yes on the amendment, what does it mean?

DR. HART: The budget goes to 550.

DR. KRAUSE: And we've approved the budget? We approved the grant?

DR. HART: No. Just that the motion changes to 550.

DR. KRAUSE: Okay.

DR. PESCATELLO: So the next vote would be on Martins-Taylor at 550?

MS. HORN: Yes, but we could also table that and then go and discuss the --

DR. HART: Let's get rid of the amendment.

MS. HORN: Okay, so, let's vote on the amendment.

(Whereupon, a roll call vote was taken.)

MS. HORN: The nos have it.

CHAIRPERSON MULLEN: Okay, so, what did you just vote for?

DR. HART: Not to change the original motion.

DR. WALLACK: So can I call the question on the original motion?

A MALE VOICE: I'd like to table the original motion.

MS. HORN: Okay. Do we have a motion to table the Martins-Taylor original motion?

A FEMALE VOICE: Yes.

MS. HORN: Okay and second?

A MALE VOICE: Sure.

MS. HORN: Okay and second. The next grant that we were interested in discussing is Yale 14.

DR. FISHBONE: Could I just make an observation? I think it's a little hard on the people that we're looking at now. Because we're coming close to the end, we're using a whole different process than every other established grant that we've voted on.

In other words, if you want to cut one, why pick that one over any others? I think Paul makes a good point, that we should perhaps look at them all in the same way and not -- this is so close to the end. I'm

just wondering if that's fair to everybody.

DR. DEES: I think we're trying to be fair, because we want to hear the case of the Ivanova grant.

DR. KIESSLING: Right. We have two left in the maybe.

DR. DEES: We want to say yes to vote the same, we should fund them both, or, no, maybe one of those, there's a little bit of a difference between one of them, and we should fund one rather than the other.

DR. WALLACK: So, Marianne, I would talk to the Ivanova grant and support that grant, but since, as I've alluded to before, the project seems to be able to be finished in three and a half years and I can hypothesize that it can probably be finished in three years, that I fund that grant at 550,000.

I think it's an important project, mainly because it talks to the issue of the management of iPS cells, their maintenance, and, also, how they're going to be differentiated into other kinds of tissues.

So I think it is an important grant. I think it's a grant that's coming out of a lab that's run by a very, very established investigator with a track record. The individual, the woman, has a wonderful

collaborator at Harvard, Alexander Meissner.

And, by the way, one of the peer reviewers came in at I think 3.875, and I had some issues, actually, with that 3.875 and some of the points that that reviewer was making, so I'm very comfortable supporting the grant, but, also, I'm comfortable with it at $550,000.

DR. FISHBONE: Is this Yale 13 or Yale 14?

DR. KIESSLING: Yale 14.

DR. WALLACK: Yale 14.

DR. DEES: I'm wondering where you got the -- I'm looking at the wrong one. Oh, no, I'm not. It says the timeline one and two will be completed the first two years (indiscernible) if time allows. It will be initiated in (indiscernible)

DR. WALLACK: Page 13 of the grant, where it talks about timeline?

DR. DEES: Yes. Whatever I was reading.

DR. WALLACK: Right. I don't know, unless I'm reading that wrong.

DR. DEES: There are a number of additional studies that follow (indiscernible), and, if time allows, we will initiate these follow-up studies in year four. That doesn't sound like we know we can get

this done. It sounds like we haven't even thought what we'll do if we happen to finish early.

DR. WALLACK: So I'm reading all three aims will be initiated in year one, all three aims, and are expected to be completed by the middle of the fourth year.

MS. HORN: Dr. Arinzeh, I think Dr. Dees was interested in trying to understand between the two, and you reviewed both of them. I wondered if you could speak to that.

DR. ARINZEH: Yeah.

DR. DEES: Because I'm reading something different from what you're reading, and I'm trying to figure out why. I'm trying to figure out if I'm looking at the wrong grant.

DR. ARINZEH: Yeah. I don't know exactly the timeline. Say it again, the timeline issue. Say it again.

DR. DEES: He was reading something, and I have to say I was reading something else, and I thought I was -- I'm wondering if I'm just looking at the wrong grant. This is Yale 14. What page is this on that you're looking at? Do you have the page number?

DR. PESCATELLO: The question is whether

the Ivanova grant lends itself to cutting $200,000, whether you can look at it and reasonably say there's $200,000 that can somehow be carved out of it.

DR. GOLDHAMER: I'd just like to comment on this. I mean it's not uncommon for investigators to state things of that sort, that, in the last few months of the grant, they'll write up the form for publication.

On the one hand, I think that's -- is it a different grant?

DR. DEES: He's looking at 13.

DR. GOLDHAMER: Then I'll withdraw my comment.

DR. DEES: I think you're looking at Yale 13.

DR. KIESSLING: Yale 14 is the one that had a real split review. One reviewer gave it a 1.5, and the other reviewer gave it a four.

DR. DEES: Yeah, so, you're looking at 13, which is regulation of pluripotent state by chromatin-associated factor Dppa2.

DR. ARINZEH: That's 13, and that one we already said no to.

CHAIRPERSON MULLEN: 13 was a no the first time around.

DR. KIESSLING: Fourteen had a real split decision from the reviewers, and they kind of came together after they chatted about it.

DR. ARINZEH: I mean the weakness was that they were concerned about the number of embryos. Now maybe that is not -- maybe that's a minor weakness, but they thought that that was going to be an issue there, and then some of the abnormal morphology that may occur there with these IVF embryos.

DR. KIESSLING: Where do they propose to get their IVF embryos?

DR. ARINZEH: Let me just see.

DR. HUGHES: Fifteen cryopreserved human blastocyst embryos were made available for these studies.

DR. KIESSLING: Fifteen?

DR. HUGHES: Fifteen leftovers from in vitro fertilization procedures. That doesn't seem like a lot to me.

DR. KIESSLING: No, it doesn't.

DR. PESCATELLO: So they're both worthy of funding at the 750 level.

DR. KIESSLING: I don't know. I'm not sure. Let's talk about the Ivanova grant, because it had some serious problems.

DR. PESCATELLO: Earlier in the day, we had said that because the Ivanova 14 had such a disparity originally between MB, Martins-Taylor did not, we gave a slight edge. Now whether that is a valid edge, that's the question, but that's what we had said, initially, as we were first going through it.

DR. ARINZEH: But that large difference in scoring came from this primary reviewer in the Ivanova, and that major weakness was the number of embryos.

DR. PESCATELLO: Then Rick did correct us, that there isn't a primary, quote, unquote, "primary reviewer," this year. They're equal weight.

DR. ARINZEH: Right.

DR. PESCATELLO: So the question is, if we wanted to do more seeds and we were looking for an edge, that would speak to doing Taylors-Martin. If we want to do two more established, we're done, because we know which ones they are.

DR. FISHBONE: I'm concerned that we're dealing with these grants differently from all the other established grants, because we're getting near the end, and we're trying to find a little more money.

I mean it would make sense to me if you said every established grant would take away a certain

amount, or I think we should look at these on their own merits and not by the funding at this point.

DR. DEES: I don't think, Gerry, at this point anyways, proposing that we cut these two funds.

DR. FISHBONE: But we are.

DR. PESCATELLO: I thought we had decided that issue.

DR. DEES: Yeah, I thought we decided that issue.

MS. ENGLE: So can I propose that, as much fun as this discussion has been, that you probably at this point come to a decision, at the very least, of whether you believe in one established grant, two established grants, or no established grants, and if you believe in one, then you just have to, in your own mind, decided which is the better grant, and I move that we actually move to voting at this point, because endless discussion doesn't seem like it's moving us forward at this point, and it's really come down to that.

We either believe in two established grants, one established grant, or zero established grants. That will, then, set up what we do with the rest of the seed grants.

DR. KIESSLING: But that's what we're

trying to do, is figure out whether we like the Ivanova grant or the Martins-Taylor.

MS. ENGLE: Well, but, in your mind, people have already made up their mind. I don't know if you're going to change anybody's opinion at this point.

DR. PESCATELLO: There is some value going on, because the longer we go on, eventually, people will --

MS. ENGLE: Well my feeling is is that we have come to a point now, where we're reaching diminishing returns, that we are not converting anybody to anybody else's opinion, so it's really to a point of straight up or down vote, and you have to vote your conscience, and your logic is your own, and, as long as you can live with it, you must go forward, because I'm not sure we're converting anybody to anything.

DR. PESCATELLO: How about a motion for the two seeds?

MS. ENGLE: Nope. I vote it's a straight up or down. We voted on the amendment of cutting the grant, and the consensus was don't cut that grant, so to your point of don't treat these any differently, we, again, said investigators made a budget, and they felt this is how long it would take them to do the research,

and this is the money that it would take them to do it, unless we, again, are going to get in the game of second-guessing everybody's budget.

DR. PESCATELLO: But we could afford two seeds.

MS. ENGLE: Right. And I'm saying, again, we're to a point in voting.

DR. WALLACK: So, Marianne, if people are comfortable with the UCHC 15, why can't we vote to accept that grant, and then go back to the seeds after that?

DR. DEES: I don't think there's -- we vote on these two grants. I want to make sure everyone has heard all they want to hear about these two grants, you've heard all you want to hear.

MS. ENGLE: So what more would you need to hear? I mean this, to me, is, again, we're to a point of diminishing return. Unless you can tell me what you need to hear from somebody around this table, I'm not sure we're going to randomly hit that for you.

DR. DEES: I want to hear if anybody has or wants to make the case for Ivanova one way or the other, either to fund it, or to fund it instead of Martins-Taylor.

DR. KIESSLING: So the Ivanova grant is

the four-year grant, and the reviewers were really split on it, and it looks to me like it's pretty speculative.

DR. WALLACK: Can we call the question on the Taylor grant?

MS. HORN: Yeah. We need to take it off the table.

DR. WALLACK: No, no. To vote it positively.

DR. HART: We tabled that motion.

DR. WALLACK: No. I'm asking if we can bring it back and vote on it.

DR. KIESSLING: You're ready to do that? You're done talking about the Ivanova grant?

DR. WALLACK: Yes.

MS. HORN: We can do that. Paul, make a motion.

DR. PESCATELLO: Make the motion again for Martins-Taylor.

MS. HORN: Okay and second?

A MALE VOICE: Second.

MS. HORN: Okay, we're voting on UCHC 15. Dr. Engle?

MS. ENGLE: We're voting to fully fund, right? I vote no.

(Whereupon, a roll call vote was taken.)

MS. HORN: We have one that left the room, but the yeses carry. What's our total, Rick?

MR. STRAUSS: You're now at 9,070,729. Is that right?

DR. KRAUSE: No.

MR. STRAUSS: No?

DR. KRAUSE: We had enough funding for two more -- oh, yeah. Sorry. Yes.

MR. STRAUSS: Okay.

MS. ENGLE: I make a motion that we fully fund Ivanova.

MS. HORN: Second?

DR. FISHBONE: I'll second it.

MS. HORN: If we can just wait two more minutes -- Dr. Hughes back. The motion on the floor is to fully fund the Yale 14, Ivanova.

DR. HUGHES: Okay.

MS. HORN: Okay. I'm hearing that we might be a little bit over. What did we fund it for?

MS. CLARK: 729,271, exactly.

MS. HORN: Do I hear a motion to fund it for 729, whatever it is.

MS. CLARK: 729,271.

DR. FISHBONE: I just have a problem with that. Because she's the last person that we're voting on, I think we want to save some money. We could reduce all of the established across the board.

DR. WALLACK: I'm uncomfortable, because this was the last one that made the cut, also.

DR. HART: Whether you vote against it, because you don't like the budget, or you don't like the grant, it's either way.

MS. ENGLE: So we do have a motion to fully fund and seconded.

MS. HORN: We have an amendment.

DR. WALLACK: What's the amendment?

MS. HORN: Will you accept that amendment?

MS. ENGLE: It doesn't matter to me. Sure.

MS. HORN: We have a second to fund for 729,271?

DR. FISHBONE: I'll second it.

MS. HORN: Oh, you're going to second that? Okay.

DR. FISHBONE: Even though I'm against it, I'll second it.

MS. HORN: Okay. Dr. Engle?

MS. ENGLE: I vote no.

(Whereupon, a roll call vote was taken.)

MS. HORN: Okay, the no's have it.

MR. STRAUSS: Before you go back, do you want to put any established in reserve?

A MALE VOICE: I move that we put Ivanova in reserve.

MS. ENGLE: I second the motion that we put the Ivanova grant on reserve.

MS. HORN: At 729?

MS. ENGLE: At 729. Well at 750, right? It's on reserve, so if something falls out, it would be at 750.

MS. HORN: Okay. Second?

A MALE VOICE: Second.

MS. HORN: Okay.

(Whereupon, a roll call vote was taken.)

MS. HORN: Okay, it is put in reserve. Ivanova, Yale 14, is in reserve.

MR. STRAUSS: Do you want any others on reserve? Is that it?

MS. HORN: Does anybody want to recommend another one for second reserve? Hearing none, we move back to the seeds.

MR. STRAUSS: So you have 729,271. You also have that established 600 that you reduced. No? (Multiple conversations).

DR. KRAUSE: We have eight maybes on the seeds.

MR. STRAUSS: Yale 12. Sandy and Richard are the reviewers on that one. That's the first one up.

MS. ENGLE: This is one on Parkinson's disease, looking at VJ1 mutations in Parkinson's disease.

DR. HART: The worry is we wouldn't --

MS. ENGLE: Right. My concern is that they don't have their iPS cells currently in hand, and that is the whole first year of their grant. I'll make a motion not to fund.

A MALE VOICE: There was concern that they may be very difficult to get those.

MS. ENGLE: Right, and they did not plan any alternatives, such as genetic engineering, in order to generate them, which was the overall concern by the reviewers.

MS. HORN: Okay, so, the motion on Yale 12 not to fund, do we have a second?

A MALE VOICE: Second.

MS. HORN: Okay. Further discussion?

This is a Yale grant. Dr. Engle?

MS. ENGLE: I vote no, or I vote yes not to fund. Sorry.

MS. HORN: Yes not to fund.

(Whereupon, a roll call vote was taken.)

MS. HORN: The yeses have it.

MR. STRAUSS: Okay. Next up is UCHC 02.

DR. KRAUSE: This is Peter Maye. The main concerns here were the productivity of the investigator and the fact that his plan for making the reporter line was not what the reviewers thought was the best way to go forward. The other reviewer was Paul. Oh, you were the other reviewer? Oh.

DR. PESCATELLO: He was switched.

DR. KRAUSE: I'm sorry.

DR. GENEL: I think the concern about the technology was the availability of using the talin to prepare the technologies there at UConn, so I think --

DR. KRAUSE: That's not the way it works really. The talin technology is catered to each gene you want to change, so while the UConn core is optimizing their talin approach for mutation A, it doesn't mean they're working on Peter Maye's mutation B.

If they said, yes, we will develop our

technology with Peter Maye's project, you're right. It would be one in the same, but you can't assume that their technologies --

DR. GENEL: Got you.

DR. HART: Yeah, but, realistically, I mean you give somebody a sequence --

DR. KRAUSE: And it works every time.

DR. HART: No, it doesn't work every time, but among a handful of candidates you'll find one that works.

DR. KRAUSE: Right, so, I have no problems with the technology change. Zinc fingers work. We used them a bazillion times. Talins work. Those can be used through the core, but they haven't invested yet. They can absolutely change the technology.

DR. KIESSLING: The other concern was the productivity of the investigator, who is in year six and basically has two papers on reporter mice.

MS. ENGLE: That is true. That said and done, skeletal muscle is something that is, I would say, underserved in the in vitro differentiation market, and moving that technology along and being Connecticut first in that area, or Connecticut at the cutting edge, is a useful thing.

DR. KRAUSE: But his reporters have all been in bone, so this is a new direction for him.

MS. ENGLE: A new direction. It's a seed grant.

DR. KRAUSE: True.

MS. ENGLE: So I move that we fund.

MS. HORN: Do we have a second?

A MALE VOICE: Second.

MS. HORN: UCHC 02 to fund. Further discussion?

DR. KIESSLING: Why -- let's talk about his low productivity. Has he been funded by Connecticut a lot?

DR. KRAUSE: Is he the one with the two R21s? I forget. I've got to look it up. Sorry. I forget. He has one R21 that ended last year. Embryonic stem cell models to study axial skeletal lineage. He currently has one, but it ends in August. Animal models to study bone marrow mesenchymal stem cells.

So this is a new direction, where he's working with human cells and skeletal. It doesn't even necessarily have to be muscle. He's just trying to get to the early stages of differentiation of the axial skeleton.

MS. HORN: Any further discussion? We have a motion to fund.

DR. KIESSLING: Wait. I'm trying to find out. The low productivity is that he's had two R21s.

DR. KRAUSE: The productivity was based on his publications, so he's been an assistant professor since '07. He has three papers on which he's senior author. One of them is a review on back transgenesis in the mouse, and the other two are on -- well one is a reporter mouse, and I can't remember what the third one was. MSC isolation, I think. I have to go back.

Generation and characterization of Osterix-Cherry reporter mouse and isolation of murine bone marrow-derived mesenchymal stem cells using Twist2 cre transgenic mice.

DR. GENEL: Well, Diane, I would agree with your concern if this were -- it was applying for an established investigator grant. I think we have to give a little bit more leeway for a seed grant in that respect.

Whether after seven years and two publications one could have some concerns about future productivity, yeah.

MS. HORN: Dr. Kiessling, have your

concerns been addressed?

DR. KIESSLING: I don't know. He hasn't had any Connecticut money before, and this is a familiar name, so I'm assuming he's been to us before.

DR. KRAUSE: He worked in Dr. Rowe's lab.

DR. KIESSLING: Did he do a post-doc with Dr. Rowe?

DR. KRAUSE: Yes, I believe so. Now I have to go back. You're asking questions I knew the answer to, and my brain is fried. Post-doc, yes, until '07, and he is still first author on papers with Dr. Rowe in 2011. It does sometimes take a while for things to come out, but yes.

DR. HART: How long has he been in his current position there?

DR. KRAUSE: Since '07.

DR. HART: Okay. Is that after the post-doc, '07?

DR. KRAUSE: '07 was the end of the post-doc and the beginning of the job, and then, in '09, he has a first author paper with Lichtler(phonetic), which is the back recombination method to make blah, blah, blah, then he's a senior author on the bone paper for murine bone marrow-derived MSC, then he has a review,

then he's first author with Rowe, and then he just made a mouse.

So, basically, a paper in bone and a paper in genesis.

DR. DEES: The reviewers have better scores on this, because they downgraded it.

MS. HORN: Okay. UCHC 02 to fund.

(Whereupon, a roll call vote was taken.)

MS. HORN: The yeses have it. UCHC is funded at 200,000.

MR. STRAUSS: We have $529,271 left, and Yale 05 with Gerry and Ron.

DR. HART: Is this the one with the cancer stem cells and the hypoxia reporter? Elegant technology. My question was whether it was truly a stem cell grant, but giving the nod to those, who feel strongly about cancer stem cells, it's a wonderful pilot project. It may go somewhere. It may go nowhere. It's a high-risk, high-reward. I am in favor of funding.

MS. HORN: Do we have a second?

MS. ENGLE: I second it.

MS. HORN: Discussion? Dr. Engle?

MS. ENGLE: I vote yes to fund.

(Whereupon, a roll call vote was taken.)

MS. HORN: Dr. Genel recused himself. So the yeses have it.

DR. GENEL: Did I abstain?

MS. HORN: Yes, you did.

DR. GENEL: Thank you. (Laughter)

MR. STRAUSS: Next up is Yale 15 with James and Ann, and you have $329,000 left.

DR. KIESSLING: We were split on this. I was in favor of this and he was not.

DR. HUGHES: That's right.

DR. GOLDHAMER: Are you going to make your case again?

DR. HUGHES: I didn't get it. It seems really basic science, and I was going for something more --

DR. KIESSLING: Oh, yeah. Trying to understand, yeah. I'm very in favor of this grant -- sequence and describe the chromatins associated with nuclear lamina. It's key to us understanding chromatin remodeling, so I move to fund this.

DR. PESCATELLO: Second.

MS. HORN: Discussion?

MR. STRAUSS: We have 329,000. If you fund this one, you only have $129,000 left.

DR. KIESSLING: I mean $200,000 is minimal to do anything.

MS. HORN: Okay. We have a motion. Do we have a second? Oh, Paul did. Okay. Any further discussion? Dr. Engle?

MS. ENGLE: I vote yes to fund.

(Whereupon, a roll call vote was taken.)

MS. HORN: The yeses have it.

MR. STRAUSS: We have 14 seeds. We need reserve.

MS. HORN: We need a reserve, okay.

DR. WALLACK: Is it possible, Marianne, to fund the Patterson grant? What is it, 04?

MS. HORN: We need one for reserve, and that would only give you 129,000 for a seed, which I'm hearing is not really enough.

DR. WALLACK: So if you had 130,000, you need 70,000.

CHAIRPERSON MULLEN: Or you need to figure out what to do with 130,000.

DR. WALLACK: But I'd rather think in terms of trying to include another seed.

DR. KIESSLING: Right. We have to come up with 70 grand.

DR. WALLACK: So you have to come up with 70,000. One of the last two established investigators we did think of reducing those grants to some extent. I mean can we possibly take 70,000 and allow this investigator to --

MS. HORN: We also have an established that was funded up to 532, rather than 750, just to put that out there.

DR. DEES: I move that we take the 100 and whatever is left and give it to --

A MALE VOICE: Where?

DR. DEES: To the grant that we reduced, the established grant that we reduced.

DR. KIESSLING: Why did we reduce it?

DR. GOLDHAMER: I recommended a reduction, go from four to three years, because there was lack of evidence for involvement of the process in human cells, and, so, it was risky.

A MALE VOICE: That was a sound decision.

DR. GOLDHAMER: It was a four-year grant, but there was uncertainness about the importance of the work in human cells, and although I was very favorable for the grant, I thought it was a very good grant, there was risk involved, and I thought they would be able to

answer the question and know about the importance of the process in human cells in a shorter time frame, and, so, it just reduced risk somewhat by reducing the years from four to three.

DR. KIESSLING: It makes more sense to find $70,000 somewhere.

MS. HORN: We don't have any magic money, and we can fund up to 9.8. There's no obligation to fund absolutely 9.8.

DR. WALLACK: Part of what I'm looking at is a couple of things. Number one, I think some of our mission is to involve new investigators and to involve people, those people in the field.

The other thing that I'm looking at is that, in my mind, there's like a natural break there at 04 at 21,225, so even if we restored 50,000 more and brought it in at, what, 180, I would imagine that that investigator at 180 over two years it's 90,000 instead of 100,000, I would imagine that that investigator could accomplish and would be happy for the opportunity to accomplish something that the investigator couldn't otherwise accomplish, so that's why I'm saying I would offer the idea of finding that 50,000 and including Patterson in the -- in funding Patterson.

DR. HART: I think, rather than cutting someone else's budget, I'd almost rather see us give $100,000 for a either shortened or reduced seed and let them come back in a year.

DR. WALLACK: So give them 100,000 and do it for a year you mean?

DR. KIESSLING: 70,000. I mean we've given some million dollars away.

DR. WALLACK: But I would argue you don't even need the full 70, Ann. Even if you found 50. I mean I can't believe that the researcher, the investigator couldn't do it for 90,000 a year, as opposed to not being funded at all.

DR. KRAUSE: I disagree. It's really -- $10,000, when you don't have much money, is a huge amount of money. It's like where am I going to get this 10,000?

DR. WALLACK: Diane, is 90,000 more than zero?

DR. KRAUSE: I just think it would be -- my vote would be to restore funding.

CHAIRPERSON MULLEN: I'm going to go back to -- excuse me. I know I'm interrupting you, but I'm going to go back to a question I posed a little while ago, and that's whether or not you're trying to fund

research or whether or not --

COURT REPORTER: One moment.

CHAIRPERSON MULLEN: I thought the goal was just to sprinkle the money around. And I know it's late. I appreciate and respect the support that everyone has, but, you know, after a while, we're starting to sound like we're looking in our pocket and saying how can we spend this last little change that we have around?

Let me finish, please, because, after a while, sitting here, that's the way it sounds, as passionate as you might be. And I don't want to criticize that, but I mean there's actually, you know, for a year's worth of work that's gone into this, and I respect the input of people, if people are saying, and I've already heard you can't even do that much with $200,000, why push ourselves, because we have a little bit, to figure out how to give out a little bit more?

I'll be a bureaucrat and a representative of three and a half million people that live in the state and say just because the Bond Commission is authorizing this money doesn't mean we have to figure out that the state needs to borrow it all, even if it's just a little bit more.

And there might be something to be said

for the work of this Committee to think about that, because you are going to have to hope that the monies continue to flow, so just a little bit of feedback for you.

DR. KIESSLING: Dr. Mullen, I think one of the things that Milt is talking about is that there's a natural break here.

CHAIRPERSON MULLEN: I understood the natural break, and I also understand the conversation of trying to cobble together a little bit of money, when we could also say our work is done for the day, and can we logically, then, say look at the natural break, and is there somebody, who sits above it, that would also be a great backup candidate if somebody can't accept a grant.

It's just another way of looking at it, not an argument, just trying to pose another way of trying to help you conclude a lot of thinking, when some people have already said their brains are feeling a little bit fried.

DR. GENEL: Well she puts a little more background.

CHAIRPERSON MULLEN: You mean you have something to say now?

DR. GENEL: This woman is a post-doc in a

well-established laboratory. To the extent that seed grants are intended for development of young investigators is entirely compatible with what you said.

There is a natural break. The reviews are very supportive. Some caveats regarding the degree to which Dr. Dealy will be supporting the post-doc I think are -- there's no way to evaluate.

I don't think $10,000 will make a difference, as to whether or not she accepts it or not. And the research was very well-regarded. One reviewer is a very strong project in addressing a medically-important issue.

I think it fits our criteria, so I would go for funding at $190,000, if that's all we can fund. (Multiple conversations)

DR. WALLACK: We have to come up with 60,000.

MS. HORN: Or we can put this in reserve.

DR. WALLACK: Well, Ron, you were making the suggestion, that we think about it for one year?

DR. HART: I think, at this point, I think I would like to see us put Patterson in reserve. I'd like to see us put Patterson on the reserve position at 200,000.

DR. KRAUSE: Why Patterson?

DR. HART: Because that's the next one in line.

DR. KRAUSE: Well --

DR. HART: I mean, if you've got a better choice, make it.

DR. KRAUSE: Well we have one more maybe.

MS. ENGLE: And we didn't say that we were limited to one on reserve. We can certainly go through and vote on all the maybes on whether they should be on reserve or not.

MS. HORN: We've typically done a couple on reserve.

DR. PESCATELLO: We cut the disease grants in half. (Multiple conversations)

DR. KRAUSE: We also had an established investigator, who had a budget of 750.

DR. KIESSLING: But that's an interesting idea, Paul.

DR. PESCATELLO: I voted tentatively. I was very on the fence, because I thought cutting it in half --

CHAIRPERSON MULLEN: I was going to say please move it, so people don't try to figure out what to

do with 29.

MS. HORN: What is the grant number here?

DR. HART: Are you putting anything on reserve in the seed?

MR. STRAUSS: We will.

DR. HART: Do you want to wrap that up?

DR. KIESSLING: I think we should put two on reserve.

DR. HART: ISB01. (Multiple conversations). Change the budget from one million to 1,129,271.

MS. HORN: Do we have a second?

DR. PESCATELLO: I'll second it.

MS. HORN: Okay, Paul seconds. Any further discussion? Dr. Engle?

MS. ENGLE: I vote yes.

(Whereupon, a roll call vote was taken.)

MS. HORN: Okay, the motion carries. So we need to put a couple of grants now, the seed grants, on reserve, and these can be ordered.

DR. WALLACK: I would recommend the Patterson grant be on reserve.

MS. HORN: Okay, do we have a second? This is Patterson, UCHC 04. Milt has made a motion to

put that on reserve. We need a second.

A MALE VOICE: Second.

MS. HORN: Okay. Any discussion? Dr. Engle?

MS. ENGLE: I vote to put it on reserve, yes.

(Whereupon, a roll call vote was taken.)

MS. HORN: And if we could do one more?

MR. STRAUSS: The next one down the list would be Deng, Yale 08.

MS. HORN: The next one down is Yale 08. Do we have a motion?

DR. PESCATELLO: So moved.

MS. HORN: Okay, any discussion? And these would be prioritized. Patterson would be the first reserve and Deng the second. Dr. Engle?

MS. ENGLE: I vote yes to put it on reserve.

(Whereupon, a roll call vote was taken.)

DR. GENEL: I'm sorry. Why did we pick that one? There are some others that are down there that have a higher -- that are a priority score.

MS. HORN: No. We just took the next one in line.

DR. GOLDHAMER: 19 is a three. The 19 at the bottom is a three, not to fund. That's not a maybe.

DR. GENEL: As opposed to a hold. Okay. I got it.

MS. HORN: Okay. Again, Dr. Engle?

MS. ENGLE: I voted yes to put it on reserve.

(Whereupon, a roll call vote was taken.)

MS. HORN: Very good.

DR. HART: And then you have two more that are still maybes. Do you want to move those to not fund?

MS. ENGLE: Yeah, we need to move on those.

MS. HORN: Yale 19. Do we have a motion not to fund?

MS. ENGLE: I make a motion not to fund Yale 19.

MS. HORN: Second? Dr. Engle?

MS. ENGLE: I vote yes not to fund.

(Whereupon, a roll call vote was taken.)

MS. HORN: And one more.

MR. STRAUSS: That's it.

DR. HART: Yale 28.

MS. ENGLE: Yale 28, Liu.

MS. HORN: Okay. Do I have a motion not to fund Yale 28?

A MALE VOICE: With great reluctance, I move not to fund.

MS. HORN: Okay. Second?

MS. ENGLE: I second it.

MS. HORN: Any discussion? Dr. Engle?

MS. ENGLE: I vote yes not to fund.

(Whereupon, a roll call vote was taken.)

MS. HORN: I think we are done. Rick, do you want to just run the numbers and make sure, before we let these fine people go home, that we are really truly finished?

MR. STRAUSS: Yeah. I think you have a couple --

MS. HORN: We do. We do.

MR. STRAUSS: We'll check the numbers.

MS. HORN: Do we have any public comments? Yes, Dr. Lalande.

DR. MARC LALANDE: I'm Marc Lalande. I'm the head of the University of Connecticut Stem Cell Institute, and on behalf of my colleagues, Haifan Lin from the Yale Stem Cell Center, and Laura Grabel from Wesleyan University, I would like to thank you very much

for the day and the time you spent on these grants.

And on behalf of the investigators in all our universities here in Connecticut, thank you so very much. Thank you.

MS. HORN:

Does anybody else have a comment? Give them a minute to make sure that we are all set.

DR. WALLACK: I'd like to introduce you to my wife, Joan Wallack. (Laughter) Do you have a comment, Joan?

DR. FISHBONE: Your husband was very well-behaved today, Joan.

DR. HART: And, actually, while we're still on the record, can I just make one comment, in terms of public comments? I just want to note my father, who just turned 95 years old two days ago and is a University of Connecticut graduate, I'd like to wish him a happy birthday. (Applause) He still lives in Connecticut.

MS. HORN: We are all set. Okay, well, thank you so much. Our next meeting, as far as I know, will be in July, and we have lots of things coming in to review.

(Whereupon, the meeting adjourned at 5:55 p.m.)

RE: CONN. STEM CELL RESEARCH ADVISORY COMMITTEE
JUNE 10, 2013

AGENDA