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SCIENTIFIC MANAGEMENT REVIEW BOARD
(SMRB)

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TUESDAY
SEPTEMBER 14, 2010

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The Scientific Management Review Board convened in Conference Room 6 of Building 31 at the NIH Campus, Bethesda, Maryland, Norman Augustine, Chair, presiding.

BOARD MEMBERS PRESENT:

NORMAN R. AUGUSTINE, Chair
JEREMY BERG, Ph.D.
JOSIE BRIGGS, M.D.
WILLIAM R. BRODY, M.D., Ph.D.
GAIL H. CASSELL, Ph.D.
ANTHONY S. FAUCI, M.D.
HON DANIEL S. GOLDIN
RICHARD J. HODES, M.D.
STEPHEN I. KATZ, M.D., Ph.D.
THOMAS J. KELLY, M.D., Ph.D.
DEBORAH E. POWELL, M.D.
GRIFFIN P. RODGERS, M.D., M.A.C.P.
WILLIAM L. ROPER, M.D., M.P.H.
ARTHUR H. RUBENSTEIN, M.B.B.Ch.
SUSAN B. SHURIN, M.D.
LAWRENCE A. TABAK, D.D.S., Ph.D.
HAROLD E. VARMUS, M.D.
A. EUGENE WASHINGTON, M.D.
HUDA Y. ZOGHBI, M.D.

EX OFFICIO MEMBERS PRESENT:
FRANCIS S. COLLINS, M.D., Ph.D.

DESIGNATED FEDERAL OFFICIAL:
AMY PATTERSON, M.D., Executive Secretary

ALSO PRESENT:

JOHN I. GALLIN, M.D., Director of NIH Clinical Center
CHARLES BAUM, M.D., Ph.D., Pfizer, Inc.
JESSE L. GOODMAN, M.D., M.P.H., US FDA
STEVEN M. ROWE, M.D., M.S.P.H., Cystic Fibrosis Foundation
RAYMOND C. BERGAN, M.D., Northwestern University
ROBERT M. CALIFF, M.D., Duke University Medical Center
GREGORY C. SIMON, J.D., Pfizer, Inc.
MARY L. DISIS, M.D., F.A.C.P., University of Washington
JAMES H. DOROSHOW, M.D., NIH
SUSAN OLD, Ph.D., NIH
THOMAS M. MILLER, Ph.D., M.B.A., NIH
MICHAEL G. KURILLA, M.D., Ph.D., NIH
BRIAN K. HALAK, Ph.D., Domain Associates
THOMAS R. INSEL, M.D., National Institute of Mental Health
WILLIAM D. MATTHEW, Ph.D., National Institute of Neurological Disorders and Stroke
JAMES F. JORKASKY, Executive Director, National Alliance for Eye and Vision Research
LYRIC JORGENSON, PhD, NIH

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8:07 a.m.

CHAIR AUGUSTINE: (presiding) Good morning, everyone. We'll call the meeting to order.

Thank you for the terrific turnout. The attendance record of this group has been, I think, better than any group I have ever served on of this size. We appreciate that.

This is the sixth meeting of the full SMRB. We don't even keep count of the number of meetings of our subgroups, but the number is significant.

I would like to welcome particularly our guests today who are going to be speaking with us, and also the visitors who come because of their interest in the topics that we are going to be addressing.

I should probably comment at the outset that, as is always the case, our meetings are being telecast to the public. So,

if you would be sure to do what I didn't do, in other words, turn on your microphone before you speak? This is a push-to-talk system. So, when you're done, you will have to push to turn it off.

I'm told that only one of our members won't be able to join us for at least most of the meeting. That's Sol Snyder. But Drs. Powell and Zoghbi and Varmus, and Kelly and Brody, will be joining us either for all day tomorrow or the last three will be arriving here very shortly, I'm told.

We have a very full agenda, as you all have undoubtedly noticed. We are now at the position -- and we'll come back to this -- where we have complied with the law that has established this Committee, so that we can start making some decisions. And as I say, we'll talk about that a little bit more later on, or perhaps I should say we should make some recommendations.

Probably the first thing we should

do, for the benefit of our guests, is go around the table and introduce ourselves.

Arthur, perhaps we could start with you?

MEMBER RUBENSTEIN: Sure. Arthur Rubenstein from the University of Pennsylvania.

MEMBER TABAK: Larry Tabak, Deputy Director, NIH.

MEMBER HODES: Richard Hodes, National Institute on Aging.

MEMBER RODGERS: Griffin Rodgers, National Institute of Diabetes and Digestive and Kidney Diseases.

MEMBER CASSELL: Gail Cassell, Eli Lilly.

MEMBER WASHINGTON: Eugene Washington, University of California, Los Angeles.

DIRECTOR COLLINS: Francis Collins, Director of NIH.

And I should have mentioned Larry

Tabak is attending this meeting now as the Principal Deputy Director of NIH, having stepped into the role previously held by Raynard Kington and already very ably taking on a whole host of important and challenging tasks.

(Applause.)

MEMBER KATZ: I'm Steve Katz, Director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

MEMBER SHURIN: Susan Shurin, the Acting Director of NHLBI.

MEMBER BERG: Jeremy Berg, Director of the National Institute of General Medical Sciences.

MEMBER BRIGGS: Josie Briggs, Director of the National Center for Complementary and Alternative Medicine.

MEMBER FAUCI: Tony Fauci, Director of NIAID.

MEMBER GOLDIN: Dan Goldin, the

Intellisis Corporation.

MEMBER ROPER: Bill Roper from the University of North Carolina.

EXECUTIVE SECRETARY PATTERSON: Amy Patterson, Office of the Director, NIH.

CHAIR AUGUSTINE: And I'm Norm Augustine. It's my privilege to chair the SMRB. I use the word "privilege" very seriously. I think all of us would view that it's a privilege to serve this great institution that has accomplished so much, and hopefully to help it accomplish even more in the future.

And I, too, should have -- Francis mentioned Larry's new responsibilities, and we look forward to working with you in both roles, as a member of this Committee and your new role.

Also, I want to point out that -- oh, there's Harold now. He's here. We did this over the telephone in our last telephone conference, but it is a particular privilege

to have Harold join this group. There are few people that know more about this institution than he.

So, welcome, Harold. We're proud to have you.

Again, we have a lot to accomplish. The meeting kind of breaks into I guess three parts.

The first part, we are going to talk about the Intramural Research work and the work of our subgroup or our group that has been dealing with that. They have focused very much on an appropriate strategy for it going into the future in terms of both usage and in terms of funding. And we will be hearing about that in just a few moments.

We will be voting on the report of that Committee this morning. As you will hear later, as with most everything we've dealt with, there are some complicating factors that we'll have to address, but we'll deal with that at the appropriate time.

Then we will turn to the latest task of the SMRB, which is the one on translational medicine and therapeutics, referred to as the TMAT Working Group. Arthur has been kind enough to agree to chair that because there is close coupling to the work that his committee was already doing. We will come to that, then, later in the day.

Tomorrow, after lunch, we will turn to the work of the Substance Use, Abuse, and Addiction Working Group. And there, too, we have a vote to take, which will, of course, be very important.

I think everybody has had a chance to read the reports of those groups. In my view, they were extraordinarily well-written. You also come away with the conclusion that these are not easy questions. They have done, I think, a good job of balancing the various perspectives. So, we should be in a very good position to vote on that issue tomorrow in terms of what we would like to recommend to

Francis and the Congress.

Before we proceed, a couple of administrative announcements. One is to the members of the public who would like to speak during the comment period this afternoon. There is a signup sheet at the registration table.

And if you would sign up, we'll take people in the order they sign up. There's obviously a limited amount of time. So, it is kind of first-come, first-serve. We will ask each of those who do speak to hold their comments to five minutes. So, you can be thinking about that.

And obviously we welcome inputs, written inputs, that are more extensive. We have a website, and you can find us all here at NIH with addresses, particularly through Dr. Patterson's office. And please feel free to share your views with us.

Secondly, the minutes for the various meetings that have been taking place

are in your package or were sent to you with your package. And I must say they're one of the most extensive minutes I've ever seen, really very well-done.

I was reminded of my lawyer friends who tell me the person who takes the most notes gets the longest deposition. But whatever the case, the minutes are extensive, and we should vote on those.

So, would there be a motion?

MEMBER FAUCI: So moved.

MEMBER CASSELL: Second.

CHAIR AUGUSTINE: Thank you very much.

All those in favor?

(Chorus of ayes.)

Opposed?

(No response.)

Okay. We have another administrative item that is very important. It has to do with our conflict of interest, the rules that we have to comply with.

Amy, would you want to brief us on that?

EXECUTIVE SECRETARY PATTERSON: Certainly. Thank you, Norm.

So, as is our protocol, at the beginning of each meeting we like to remind you about the steps we take and that you take and the loads of information that you send us to review with an eye toward identifying any potential conflicts between your private interests and the public interests in your capacity of serving on this Committee.

I just would like to remind each and every one of you that today you are a special, very special, government employee, and to be mindful of that as we carry on the discussions over the next two days, and be mindful of any potential conflicts between your private interests and the matters at hand.

Thank you.

CHAIR AUGUSTINE: Thank you, Amy.

I would be remiss if, before we go ahead, I didn't thank the members of the staff who work behind the scenes to set this meeting up. The amount of paper that has gone by and the amount of effort that has gone into it is remarkable. I hope that those who are not in this room could be thanked by those who are in the room on our behalf for all they have done to prepare for this meeting.

And before we launch into the subject matter, Francis, I would like to give you the first word, if you have anything you would like to say at this point.

DIRECTOR COLLINS: Thanks, Norm.

Very briefly, just to thank all of you for the hard work that's gone into getting us to this point and to underline what you have said about the importance of this particular meeting because of arriving at the point of taking votes and making recommendations about two major areas: the Clinical Center at NIH and the debates about

what to do with regard to two institutes, the Alcohol Institute and the Drug Abuse Institute, in terms of going forward in research on substance use, abuse, and addiction.

So, this is the culmination of a lot of hard work and deliberations. And I want to thank you and the groups that have done so, particularly the Chairs who have led that effort. And we will be hearing from them during the course of today and tomorrow.

So, Arthur Rubenstein, especially thank you for your hard work on the first of those, and Bill Roper on the second.

And also, to say that we are going to spend a big chunk of the meeting looking at this next question of whether there are opportunities to further improve the efficiency and the scientific innovative potential for translation in this new group that Arthur has agreed once again to lead – and thanks to him – the TMAT group.

And I'm going to be very interested to hear the substance of those discussions, because I think we have a real opportunity here, but it's one that needs to be addressed thoughtfully.

So, I think I would also want to echo what Norm said at the beginning about my degree of being impressed by the faithful service of all of you who have been involved in this from the beginning. This is a group of very busy people who could easily come up with excuses to be somewhere else, and yet you have faithfully attended these meetings and really put your own best ideas and thoughtfulness into this process. That's been enormously appreciated.

I found this to be an extremely valuable group for these kinds of considerations. So, thank you, and I look forward to a really interesting couple of days.

CHAIR AUGUSTINE: Well, thank you,

and, Francis, we understand that there are some hearings on the Hill on stem cell research this week. So, if you step out, we will fully understand.

DIRECTOR COLLINS: I will, unfortunately, tomorrow morning have to be involved in preparing for this Thursday's hearing in front of Senator Harkin about stem cells and the latest earthquakes that have happened in terms of federal oversight.

CHAIR AUGUSTINE: With that, we can delve into the thrust of the meeting, the first item, of course, being the work of the Intramural Research Group, which Arthur has been chairing.

So, could we turn to you?

MEMBER RUBENSTEIN: Yes.

Good morning, everyone, and thanks, Norm.

I would like to begin by thanking the members of our group for their hard work and perseverance. We had a terrific group. We

have worked very well together.

I also want to just thank Amy personally and the staff who worked with her, her colleagues. I couldn't think of a better group to deal with challenging and important problems.

To remind you, the charge to the Intramural Research Program Working Group has been to look at the Intramural Research Program and determine the changes in its organization and/or management function.

In terms of this, I hope that you all have had a chance to read the written report. This is going to give you a high-level summary of it. But I think the report itself, which we collectively did with a lot of staff support, really does spell out in very clear ways what the issues are and what some of the challenges and conclusions are.

So, this high-level summary I hope will just paint the picture, but the report itself, if you have had a chance to read it,

does indicate our deliberations and the pros and cons of the decisions we have made.

Given that the recent internal assessments have indicated an urgent need to address the fiscal vitality of the NIH Clinical Center, our group agreed to first focus its efforts on providing an analysis of and recommendations regarding the fiscal sustainability and utilization of the NIH Clinical Center.

We have a broad mandate to look at the Intramural Research Program, but realistically speaking, because of a whole variety of governance, vision, and budget issues, with the agreement of the overall committee, we decided to look at this first.

This is our group. I won't go through the names. You know them well. But I do want to just compliment them and thank you. We have worked very, very well as a group, and when there were divergent opinions, which there certainly were, we worked hard to come

to a consensus and be supportive of each other's points of views.

While our group has thought about this issue and regularly updated the SMRB regarding its process, I would like briefly to remind you of the steps that we have undertaken since April last year to try to see that we were informed by a wide variety of opinions and took into consideration alternative points of view about what might we do.

Our group has held eight teleconferences and three in-person meetings, and most recently, in May this year, we had a stakeholders' consultation. We heard opinions from informed people from all around the country as well as intramurally at the NIH.

And as you may recall, we have also had input from a whole variety of important people which are listed here: hospital administrators, external potential users of the Clinical Center. This is a really

important thing, because it is a challenging issue, and the question was the feasibility and how one would get this done in a practical sense.

The Advisory Board for Clinical Research, investigators within the Intramural Program, and the directors of the NIH, as well as the public. So, we have been open to all variety of opinions, thinking about how we might proceed with this.

Now I would like to briefly go through the findings with you.

Of course, the most important thing is to acknowledge the important strength of the Clinical Research Center here. I will not in detail today talk about all the details about why this is such an important center in the NIH as well as the country and all its great accomplishments and the important things that have made it so successful.

Here are some of them, though, just briefly, to remind you:

Investigators can put their full attention to research without much worry about budgets, although despite saying that, the budget issues have crept in. In a way, that has been the incentive for this report.

People can respond briefly and nimbly to new challenges, perhaps more so here than at other places.

Patient care is fully funded, and this is, of course, a huge advantage for patients and their family with problems who come here from around the country.

The staff has access to cutting-edge technology. And those of us who toured the Clinical Center were impressed by the up-to-date technologies and opportunities to do clinical research at the highest level.

And the opportunity to conduct high-risk trials for life-threatening diseases, sometimes which are very expensive but have very broad implications when some of the answers are discerned from beautiful

investigations.

And of course, sometimes we don't succeed. That's acceptable, too, if one's doing high-risk research. That seems more possible to do here often than at other places.

And here's a few more: critical mass of highly-skilled individuals. When we listened to the testimony given by many of the investigators who were passionately involved in studying and looking after patients here, it was extraordinarily impressive, some of the advances and reasons that they have made new discoveries.

Many are a critical role in first-in-human studies and rare disease research, which may not be able to be done, except very expensively, elsewhere.

It supports longitudinal studies. Of course, we study human biology based in basic science, which is, of course, such a beautiful thing when it works well.

And of course, there are important training opportunities which have always been a hallmark of both the Center and, of course, the NIH mission.

So, there are many reasons to think about the Clinical Center as a critically important jewel in the NIH, but also nationally, particularly at a time when there is a national view that moving discoveries from patients into a broader thing of more help for individuals around the country is important.

With that, now I would like to move through some quick review of our findings and recommendations. And it's important that, in a sense, this is a summary of what's in the report, because I'm going to give a very high-level summary. Of course, if there are questions, I or my colleagues here would be happy to answer them.

When we looked at the challenges, really we were able to break them down into

three themes. Having identified this has given us a framework to think about our report in a very specific and, I would say, focused way.

We looked at the vision and role of the Clinical Center, its governance, and the budget. They all intersect, of course, and impact on each other. Trying to move forward with each of them needed some reassessment of the other one, and we have tried to do that in a cohesive way.

In terms of the vision and role, the challenge here was really whether there was an opportunity to broaden the scope of the patients and investigators who are involved in the Clinical Center. And some of the reasons that this seemed to be worthwhile looking at in a serious way was some of the barriers and problems that investigators believed were extant in the Clinical Center at the moment.

So, there was a perceived lack of prioritization and commitment to clinical research because of some difficulties –

administratively, and particularly budgetwise – of doing it at this time, at a time it was so important from a point of view of the important mission in the country, as this is.

There were barriers to partnership, particularly between intramural and extramural collaborations and intellectual property issues. This is an understandable but difficult problem, and we thought it was really important to think about whether we could make that more streamlined and straightforward.

And there are also barriers to recruitment and retention of investigators because of a variety of salary and budget issues that are now in the purview of the government, particularly with no draft anymore, and so forth.

So, there were real issues that didn't say the Clinical Center wasn't doing well, but they were challenges as to whether it was an opportunity for it to do new and

important things in a different way.

In terms of the governance, some of the challenges were a lack of trans-NIH vision for priority-setting in the clinical research. This was particularly made worse by some of the budget issues which were quite understandable, but involved institutes disproportionately in a sense. And there were also complexities in the administrative approval process, which had grown up over time and probably, when looked at in a new way, gave opportunities for making it more straightforward and streamlined.

Here you can see the current organization of the oversight structure. I won't go through it in detail.

There were good reasons for all of these committees, subcommittees, and oversight bodies. They are spelled out in some detail in the report, but it did make many levels of oversight and perhaps delayed decision-making and made it more complex than it should be.

So, this was an opportunity to think about it as we streamlined and thought about new administrative and fiscal structures to simplify the governing structure. I think we have come up with a scheme that maintains the best of all these operations, but does it make it simpler and more streamlined?

And of course, a big driving force for all this was the projections of budgets in the next several years which were really difficult to think about in a constructive way, to both support and enhance and believe in clinical research and the utilization of the Clinical Center, but also find ways to fund it in a way that was supportive of the leadership within the NIH in a way that would be necessary to utilize the Center at its maximum.

So, all of these things, then, as you can see, were reasonable challenges for our Working Group to look at, particularly in terms of the budget. There were increasing

costs of the Clinical Center, which are now paid for proportionately by the intramural institutes, the institutes in general, which does not keep up with inflation.

The current structure is called school tax, and there's a tax on each of the institutes to pay for the Clinical Center. The cost shifts have had unintended and undesirable consequences, tending to reduce the interest and enthusiasm to use the Clinical Center by investigators in each of the institutes because of budget issues that impacted on the opportunity to do research and always had to be considered. Now that's not unusual, but some of the budget issues were disproportionately onerous on various institutes.

And the budget mechanism didn't really have an easy way, although it was possible with very great difficulty to support the involvement of investigators outside the NIH institute either collaborating or using

the Clinical Center in a straightforward way for other opportunities.

So, these were important barriers to streamlining and using the Clinical Center which we thought were worthy of review.

So, these are some of the issues that we dealt with. In a sense, we have come up with some straightforward -- I think, of course, they're always complicated to put them into practice -- but recommendations which we, as the Work Group, believe should move the Clinical Center forward within the NIH intramural community, and which we hope will maintain, of course, all the good parts without damaging them and produce new opportunities that should be, I think, advantageous.

So, we would like to suggest that we position the Clinical Center more as a national resource than just a resource within the NIH, which it should remain, of course. We hope that there will be opportunities to

prioritize clinical research both within and outside the NIH by a new mechanism of both governance and budgets.

The budget changes we hope will ensure fiscal sustainability and a stable and responsible budget without having significant impact on other areas of the NIH intramural community, as I'll describe when I talk about our recommendations.

And also, as Francis has put forward, the idea of the TMAT, that the Clinical Research Center, of course, should be a central focus and opportunity, together with other opportunities, like CTSAs and so forth, to take advantage of this new effort both at the NIH and across the country.

So this will, then, change the vision, governance, and budget, but in a way, again I stress, that maintains the best of what we have and moves the opportunities forward in each of these areas.

So, I'll stop there for a moment

and just see whether there are any questions about the setup and framework and terms, and then I'll go to the recommendations.

Any thoughts?

(No response.)

All right. So then this is what we have come up with which our Working Group would like to present to the full SMRB today.

So, first of all, we would like to advise that the committee will recommend that the Clinical Center has the potential to serve as a national resource for clinical research. It has state-of-the-art facilities and resources, and of course, we, therefore, believe it could serve the needs of both internal and external investigators and play a more significant role in supporting and making possible leading-edge clinical research and therapeutic development across the country.

Again, this will not be a simple thing to do, but we believe we could put in place a variety of rules and regulations that

would make it more straightforward than it is now.

We recommend an expanded vision and role for the Clinical Center in this regard and position it to truly function as a national resource. There are tremendous infrastructure resources, technology, and opportunities there for drug development that we do believe could really enhance investigators both intramurally and across the country.

Here are just some of them. Many of them are listed in the report. But when one asks, what are the key attributes and particular advantages of the Clinical Center, and when one goes on a tour, one is very struck by them. Here are some of the things that most places around the country don't have or do not have in the scope and expertise and excellence that are present here in the Clinical Center.

I won't go through them all, but I

would say many investigators around the country would have big thoughts about the possibility of collaborating or potentially personally using some of these resources, which are quite extraordinary.

And I think it is also true to say that some of them are underutilized. They are very expensive infrastructure facilities, and they are utilized but sometimes not at the level at which they are capable of being used.

So, this is the attractiveness of recommending the opportunity to expand the use of the Clinical Center, both to intramural and extramural investigators.

The second point we would like to recommend is a more streamlined governance structure that facilitates the development of a clear, coherent plan for the Clinical Research Center, and where the decisions made and the oversight is straightforward, answers to the Director, and makes recommendations without it being overseen by layers and layers

of a variety of committees and bureaucracy that really we felt did not add particularly to the enhancement of the Center's performance.

This is the simplified structure. The exact composition and makeup of each of these committees is detailed in your report. But, basically, there is significant input, of course, from the Intramural directors of the institutes. You can see that on the left. We would maintain the Advisory Board, the ABCR, but look to it with a variety of subcommittees that would have input into it, and they would answer directly to the director.

It is not a fundamental change. It's a simplification change and streamlining and getting rid of the layers of oversight that, I think, both intramurally and extramurally we felt did not add a lot of value to the oversight and governing structure of the clinical setting.

And equally and also very

important was the issue about the budget. When the projections were made of how the Clinical Center would be funded over the next five to ten years, it utilized a significant increase of money from the intramural budget, and this led to the disadvantages that I described to you earlier.

And so what we really wanted to do was find a stable, responsive budget transformed by a rational process of planning and priority-setting and linked to a strong planning process that would be transparent and straightforward and not lead to unintended consequences when new opportunities existed in terms of clinical research.

So, we have discussed a whole variety of options and spent a lot of time with this because, of course, when one starts changing budget allocations, there's always some people who will legitimately feel worried about what the impact is on a variety of other budgeting. Pretty much, the total budget is

unlikely to go up; otherwise, we wouldn't be having this kind of challenge.

And so we have thought very carefully about the impact of such changes, and, I think, with a lot of deliberation and input, we feel comfortable about the kind of recommendation that we are going to make.

So, we discussed a spectrum of options, analyzing in great detail the strengths and weaknesses of five particular options. These analyses are found in Appendix D of the report. And I do hope that you have either read that or will look at it, because, in a sense, the pros and cons of each of these -- of course, none of them are just obviously the best -- did consume a lot of our deliberations. And we feel quite strongly that the issues that we've come up with are worthwhile, based on that kind of analysis.

The options discussed, of course, these five, were to keep the status quo. That is the current school tax of the tax on each

of the institutes.

A second option explored was a modified version of the status quo. And this, not to snow you with details, deals with issues of fixed and variable costs which could be dissociated and which we thought about a lot but in the end did not seem to make a significant, overall, long-term advance in terms of what we wanted to accomplish.

The third and fourth and fifth options are all some version of a line-item approach to Clinical Center budgeting. This approach would result in funds for the Clinical Center to be derived from the overall NIH budget and not just from the NIH Intramural Research Program. I want to stress that is the key policy change that, if this is adopted by the full SMRB, would be the issue.

At the moment, the Clinical Center is funded from the Intramural Research Program, and we believe now it should be a mixture of both the Intramural Program and the

total NIH budget -- of course, of which the Intramural Program is a key part.

The third option would include the Center as a line item in the budget of the institutes and centers. You can see that “Fee-for-Service for Variable Costs” -- that line item on the IC budget.

The fourth would be a budget in the Office of the NIH Director, of course, who has jurisdiction over the whole NIH budget.

And the fifth and final option would be a direct congressional appropriation for the Clinical Center; the possibility way over on the right side of this slide.

Now you will see a detail -- there's also a table in the Appendix which talks about the impact of the move of the Clinical Center to be funded by the whole NIH budget. Of course, the majority of the funding would still come from the Intramural Research Program, but there would be opportunities to add funds from the total NIH budget in the

Office of the Director. And that's the key recommendation change that we are making.

Analyses and discussions have led us to recommend this fourth option, the one circled there, as the preferred funding model. They all have pros and cons, but in many, many ways this seemed to be the most advantageous one, and with little downside in terms of the amount of money that is moved in terms of the new suggestion.

The consensus view of the Working Group is that the option meets the criteria that we set and laid out in terms of what we wanted to achieve by this reformatting of the Clinical Center mission.

It would facilitate use of the Center by external investigators, provide higher visibility for the Clinical Center and its availability for enhanced clinical research, both from intramural and extramural investigators, and also put a high priority on clinical research at a time that nationally

this is assuming great importance.

And it will enhance the stability of the Clinical Center, because the funds would come from a greater pool –- the whole NIH budget -- although I want to stress again, the majority of the funds would still come from the Intramural Research Program, as was spelled out in the report in great detail.

And this, then, would give some stability going forward and not lead to unintended consequences of discouraging clinical research because of small but very real budget issues that couldn't be accommodated easily.

So, that is a summary of what we have put into the report. I think the report does spell it out in great detail, and I think I want to thank again the members, the report, and the staff.

You will hear from Norm, and I just put that forward, that this will have to be thought about in relation to the TMAT

opportunity as well. But I think our Working Group felt very strongly that this report dealt with many of the challenges that we had, and we hope that the committee, the full SMRB, would at least evaluate it carefully on that regard.

So, thank you, Norm.

CHAIR AUGUSTINE: Arthur, thank you very much and your committee as well.

The floor is open to the members who might want to comment.

Harold?

MEMBER VARMUS: Well, Arthur, thank you very much for what's gone into this report and to endorse the conclusions.

But I would like to hear a little bit more about your first recommendation. I have been a strong proponent myself of greater use of the Clinical Center by the extramural scientific community. It was one of the key elements in the Nathan report on clinical research 15 or 13 years ago.

MEMBER RUBENSTEIN: Right.

MEMBER VARMUS: And yet, it has always seemed that there's a pretty substantial reluctance of extramural clinical investigators to use the Clinical Center. There are some exceptions, the Pediatric GIST Consortium and a couple of other examples of people who came to the NIH from the extramural community and worked here on a temporary basis.

But, in general, for a variety of reasons having to do with distance, the need to hold onto one's own patients, the reluctance to collaborate with the Intramural Program, and cost considerations, there hasn't been tremendous use of the Clinical Center by the extramural clinical research community.

So, I would be curious to know what impediments to that use your group identified, what you see as ways to make Recommendation 1, which is perfectly, you know, it's kosher, but is it actually going to

be followed in reality?

MEMBER RUBENSTEIN: That's a key question we wrestled with a lot of the time. Of course, there are a lot of bureaucratic, financial, intellectual property issues that stand in the way, as you correctly say, and then there are people who have promulgated this view, as you correctly point out.

So, rather than me answer all of them, I would ask some of the people on our Work Group to weigh-in.

We have talked to a lot of extramural investigators. Of course, a lot of the issues that some of them brought up was we didn't know these things were available, like the drug development opportunities, the people who are looking at musculoskeletal involvement, and so on. And if they knew more about what the opportunities were, they would certainly be interested.

And then, of course, the issue was whether legally, budgetary-wise, and

collaborative-wise, we could make this so that it wasn't a huge barrier for people who would just throw up their arms and say, "We'd like to do it, but we can't. You know, there are no ways to get around all those bureaucratic things."

So, part of the challenge we had, which is not solved yet in our Work Group report, is if this is adopted, for Francis and his colleagues within the NIH to come up with a set of rules and regulations that would streamline the opportunity for extramural investigators to use it and then for us to publicize the opportunities available.

Perhaps one last comment I'll make, the issue of translational research has become so important and so visible around the country. And perhaps the development of the CTSAs and their restrictive funding has also led people to look for added opportunities for them to do their mission, that maybe the climate is just different in terms of people's

interest.

But it will be a challenge, as you point out, and we would have to work hard to make this a reality.

Tony, maybe you would comment?

MEMBER FAUCI: Yes, just to make a comment that relates to Harold's question and Arthur's answer, that we really need to make sure when people want to understand how this will work, that they look carefully at Table 1. Because when you're talking about what contribution from the broad NIH budget this will be, you said it's a combination of both with a majority -- it isn't the majority; it's a fraction of a fraction of a percent of the total budget.

So, the NIH Clinical Center budget will still be essentially funded by that one-time transfer of the cost to Building 1, where it will reside as an OD line item. There will either be no additional tapping out of the broad NIH budget if the increase for the NIH

is equal to or more than the increase for the cost of running the Clinical Center. Only when the increase of the cost of running the Clinical Center is greater than the increase that comes to the NIH as a whole will any money come out of a pot that's extramural. And that's very, very clearly delineated in Table 1.

And the reason why it relates in part to Harold's question and to Arthur's answer is that, yes, we need to make it more clear what the pathways are -- and that has not been clear in the past -- of how you can come in and utilize the Clinical Center.

But it's also not going to be completely free to just come in and say I want to occupy 10 beds. It won't be that way. We have to be pretty clear upfront that we'll have to work out a mechanism whereby there's money that is used from their own resources to use what the opportunities are at the Clinical Center.

So, that's what makes it a little bit confusing -- not confusing; it needs to be more clearly delineated of what those opportunities are.

MEMBER VARMUS: Can I just follow up on that?

MEMBER RUBENSTEIN: Please.

MEMBER VARMUS: I haven't seen enough of the numbers. I did appreciate Table 1. I could see that would have minimal impact.

But for the individual investigator on the outside, if you consider someone who's got a CTSA at their institution, and consider the possibility of having, say, five or so patients from that extramural site come to the NIH, what is the approximate cost to the investigator? Is cost going to be an impediment to coming?

MEMBER FAUCI: No.

MEMBER VARMUS: You think not?

MEMBER FAUCI: No, it won't. I mean, if you just want to bring a patient in,

John Gallin has discussed this in the past. There almost certainly would have to be some small amount of designation for beds for people, which would be part of the big package, not that you have to pay for it.

So, it's conceivable, Harold, that someone could come in, bring some patients in, and it comes out of the pure running of the Clinical Center. It's only when they want to come in with something that goes above and beyond what the Clinical Center has available will they be tapped for it.

MEMBER RUBENSTEIN: There is an analysis, Harold, about the underutilization of the potential of the Clinical Center in terms of bed utilization, which would not particularly increase the infrastructure cost. If the occupancy went up, someone has to staff it at a certain ratio.

So, each of these things, just like you're asking, would have to be analyzed in some detail. And this report just gives the

opportunity to do that without going through each one in detail.

Steve?

MEMBER KATZ: So, also, in answer to Harold's point, there has always been this barrier of intramural/extramural dollars. I think that we have worked it out with the lawyers that, prospectively, if someone is going to utilize a fair amount of resources, they can designate upfront that they need a certain amount of money that's going to go for paying for this over and above the occasional patient, and it's five or ten patients, a substantial study that is utilizing a lot of resources that's going to increase the budget, that budget will now be allowed.

And I think for a long time there was this barrier that we had in our heads, and it was really in our heads more so than in reality, according to the law, that you couldn't use any extramural money for intramural purposes. But I think now we've

gotten beyond that.

MEMBER RUBENSTEIN: Just if I could comment, I just want to add to what Harold said. This is not saying anything particularly new. Many of these things are actually utilized at the moment by a small number of investigators, usually in partnership with colleagues at the NIH, and so forth.

And you can see many of them are really cutting-edge issues that investigators around the country, if they had some straightforward way of accessing them, and particularly at this time, would be very interested in doing, and we heard from extramural investigators.

So, of course, the devil's in the details. How would we streamline a way that could make it work without people throwing up their hands and saying, "It's just not worth it."?

CHAIR AUGUSTINE: Gail?

MEMBER CASSELL: Yes, Arthur, as

you were presenting, I can't recall if in our committee deliberations that we discussed the potential of extramural scientists being able to access the GMP facility. The GMP facility is state-of-the-art. This is a resource that is often, most often, not available at the academic health centers.

And I just wonder...there might be a demand, even greater demand, for access to the GMP facility, but with no interest in enrolling patients in the Clinical Center. Is that possible?

MEMBER RUBENSTEIN: Yes, we did talk about that. Of course, when we toured the facility, which is beautiful and large and new, that opportunity was pretty clear, that others may not have that opportunity outside the NIH. You know, the opportunity to use that in collaboration seemed to be very real.

Would you like to comment?

DIRECTOR GALLIN: Thank you.

First, I would just like to

elaborate on the answer to Harold's question and Dr. Fauci's answer about how much would it cost.

We modeled this and came up with the idea that only the variable costs for bringing in an additional patient, for example, would be charged. And we estimated that would be about 15 percent of a patient-day's cost, and it would relate to added nursing cost and some drug costs and maybe a few other supply costs. But the essential resources of the hospital would essentially be available for use. So that's what we came up with, but there are other models that could be used.

In terms of the GMP facility, which is something we're very excited about -- and there are a number of other kinds of resources that could be accessed that would not relate necessarily to using the facility for a patient, but to some service that would enable research somewhere else -- that could

be done, but somehow we would have to come up with a mechanism to cover the cost; the added cost, for example, for formulating a new product to go into a patient.

The transfer of the dollars right now is a barrier. An investigator has come to me, for example, numerous have come and said, "Gee, I would like you to do this. Can I pay for it?" The answer is today, from an existing grant, it's not possible for us to receive or keep the funds to cover just the cost for delivering the service. That needs to be fixed.

MEMBER KATZ: But for a new grant, it is possible.

CHAIR AUGUSTINE: Harold?

MEMBER VARMUS: I would just like to make one brief comment. I don't think we should overfocus on the finances. I mean they're important, but there are a lot of other perceptual issues about working with the Intramural Program: moving your patients into

a domain where you may lose control; some sense that an institution depends on the Clinical Center; the institution itself doesn't get credit for the work that is done; the intellectual property issues that you raised.

I think all these other considerations are extremely important, and I think some work needs to be done. I strongly applaud the idea of moving in this direction, but I think we have to be very sensitive to the perceptual issues as well as the financial ones.

MEMBER FAUCI: Yes, that is a very good point, Harold, and we discussed this during some of our deliberations.

One of the points that you make is clear, and it's unfortunately a misperception, and maybe an understandable misperception. If a group comes up in -- and we just modeled a couple of examples, and you could spend a day going through all of them.

For example, by definition, just because you bring a patient into a Clinical Center, that doesn't mean that (a) you necessarily need to collaborate with anybody, and you certainly don't have to give up control of the patient or essentially responsibility for the results that come out from that patient.

There will be instances where you might want to come in and study a group of patients that are already being studied there. That, by definition, will be a collaboration. But just because you study patients at the Clinical Center doesn't mean that you give up your patients at all.

MEMBER VARMUS: I think it's important not just to write this stuff down, but Francis has been considering hiring someone to serve as an ambassador to the extramural community. This would be a very important role for someone who is carrying the NIH message out to the grantee institutions.

CHAIR AUGUSTINE: Gail?

MEMBER CASSELL: Yes, Harold, I totally agree with you. I think the perception of there being a long queue, too, is something that has perhaps precluded others from trying to access it in the past.

But, as I have said from the outset, I think the Clinical Center is an undervalued, underappreciated national and international resource.

I just had the opportunity this spring to bring in some international groups from Russia and Taiwan, and they are just blown away by the Clinical Center, the fact that you have GMP right there.

I just think we need to do a much better job, all of us, in advertising this national and international resource, much like the Rocky Mountain Laboratory in Hamilton, which, Norm, we hope that you will visit, because it really is very impressive and certainly a resource.

MEMBER VARMUS: Are there any special restrictions on bringing international patients to the Clinical Center? I've never asked that question. I don't think so, but --

MEMBER KATZ: No.

MEMBER VARMUS: Visa problems?

MEMBER RUBENSTEIN: Unfortunately, we had enough challenges, but it's an interesting thought.

CHAIR AUGUSTINE: Are there other questions or comments from the group?

(No response.)

I think, as usual, Harold, you put your finger on the problem or the challenge -- not a problem, but the challenge. Part of this is going to be how well we implement.

I have had in the back of my mind as I have listened to this debate for the past few months, and I may have even mentioned this before, a quote from Shakespeare where -- I can't even remember the character. I think it was Hotspur was bragging that "I could call

the spirits from the vasty deep." And his friend said, "Yes, but when you do call upon them, will they come?"

(Laughter.)

I think we're a little bit in that mode at this point.

So, if there are no further comments from the group, I think it would be appropriate to turn to public comments at this point in time.

And I have just been given a note that says no members of the public have signed up for comment.

So, is there anyone in the room who does want to say anything?

(No response.)

If not, let me just note for the record that the legislation that created this group asks that we seek comments from all constituencies, and certainly including the broad public. We have had many comments previously, and I guess everyone has said what

they have to say.

So, we will proceed.

Harold?

MEMBER VARMUS: Can I just ask -- we have had a lot of discussion about Recommendation 1, but to my amazement, there's been no comment on Recommendation 3, which has always been a major sticking point around the IC Directors' table.

MEMBER RUBENSTEIN: That's certainly true.

MEMBER VARMUS: Maybe we should focus for a moment on how we would pay for the Clinical Center and see. I, myself, am happy to sign up for that. I think it's a pretty good solution. But does anyone else think that?

MEMBER RUBENSTEIN: I would say, before you came, we had innumerable discussions and a lot of debate about the pros and cons of it. So, it's just you weren't here to hear about, but as you would have

predicted, it was a very, very big issue.

(Laughter.)

And I think the compromise, which we should hear people's opinion about, wasn't the only possibility or necessarily one that everyone thought was the best at the beginning.

I think in terms of what we thought we could get done and the most practical thing at this time without enormous political and other issues -- I think we all coalesced around it. But, there are opinions, both in the full SMRB and our Work Group, and I think I would advise people to respond to Harold. It was a good discussion that we have had for many, many weeks.

MEMBER FAUCI: Yes, Harold, there were five issues. The first two were either as-is or a modified version of as-is. We all agreed that was out; that didn't work.

The other three: individual institutes, in the OD, separate line item.

Individual institutes would only have a problem with pitting one against the other.

MEMBER VARMUS: And we don't want that.

MEMBER FAUCI: We don't want that. Okay.

(Laughter.)

The other one, a line item, too much at the control and manipulation of congressional issues.

The other one was OD. That's how we -- I mean it took us about five months.

(Laughter.)

MEMBER VARMUS: Thank you for the summary.

MEMBER KATZ: So, in fairness to Tom Kelly, who's not here, I think Tom repeatedly brought up the concern about this increment that came from the extramural funds. That is why we put together this table, actually, because he was very concerned, as he was concerned with the original Roadmap funds

or Common Fund, that it was going to take a lot of money from the Extramural Program, yes.

MEMBER VARMUS: Well, (a) it's not, but (b) the fact that there's some does send the signal that the extramural community is involved, and should be involved.

MEMBER KATZ: Absolutely. But I bring it up because Tom isn't here and he brought it up every single time.

(Laughter.)

And I just wanted to make sure that his view was seen at the table.

MEMBER RUBENSTEIN: I think it was always clear, as Tony very specifically said, there was confusion at the beginning when we talked about what kind of amount of money would be necessary to be added from outside the Intramural Program.

When we tried to make it exactly clear by that table and the very capable analysis, it was not a lot of money from the total NIH budget. In fact, as Tony said, it

may be a minuscule amount of money.

But, in principle, it was an important change. Of course, if the opportunity over years comes that we have to put in some more money, there was a straightforward mechanism that in the overall NIH budget was still pretty tiny. It seemed like a reasonable solution.

Gail may want to talk about her view, because we debated that a lot as well.

MEMBER CASSELL: Well, thank you, Arthur.

I guess I was the lone voice that suggested that the direct line appropriations from Congress would be a good way to go. But Tony, my friend, convinced me otherwise. It took a few meetings, but I'm in agreement with the recommendation here.

I think that we did spend an awful lot of time on the budget issue, and this is what we came up with. I really like the graphic showing the spectrum of options. I

think it is very clear now, and also the table.

And with that, I would hope that people think that this was the best decision of all the potential options.

CHAIR AUGUSTINE: Excuse me. I saw Francis and then Bill.

DIRECTOR COLLINS: So, I just wanted to ask for any more information you might be able to offer about the governance model, because we haven't talked about that.

I certainly agree that the way in which things have been overseen is complex, unnecessarily so, and potentially duplicative. And the model you put forward streamlines a lot of that effort.

I am just wondering if you have in your deliberations made any kind of inroads into what is the charge to the proposed Clinical Center Governing Board of IC Directors, since that's sort of a new entity here. I'm not asking you to get into the weeds

here, but if you have sort of a general concept of that group's role versus the ABCR?

MEMBER RUBENSTEIN: Tony, did you want to comment on that? Steve?

MEMBER KATZ: Why don't I comment on that?

MEMBER RUBENSTEIN: Yes.

MEMBER KATZ: The thought is that that group is going to serve as advisory to you. That group will serve to provide a context for what the other demands are on the NIH budget. So that, as the current Management Budget Work Group works to advise you, it's going to advise you, and in the context of what the budget allocation is anticipated from the Congress.

So, for example, the ABCR; we've actually tried to get specifically how much the ABCR has advised in the past. They have had the constraints of being told they can only advise a certain amount, because that's what the budget is going to be. But if they

advise a 15 percent increase to keep up with inflation for clinical research, and the NIH is getting a 1 percent budget increase, we felt that it would be important for you to have a group of IC directors who could put it in some context, but it will ultimately be your decision.

But, basically, what this does is it removes this financial -- this budget item from the other competing priorities of the ORS and the other central services. Basically, it sets it apart.

But the group that's advising you, the IC Directors, are advising you in the context of the total budget.

CHAIR AUGUSTINE: Bill or Tony, do you want to add anything?

MEMBER FAUCI: No. Steve said it quite well right now.

CHAIR AUGUSTINE: Bill?

MEMBER ROPER: I'm not sure this is a useful comment, but I'll make it anyway.

Harold is right to say that we shouldn't focus only on the finances; there are many other even more important issues.

But as we have been talking about the finances, I'm struck with the parallels between this and the debate that's gone on for decades around the country in various metropolitan areas about how to pay for municipal transit systems and the right balance between riders of those systems bearing the costs and whether there would be a general tax on the populace to fund the system.

The Metro system that I rode yesterday wouldn't exist if there weren't a general tax on the people of this metropolitan area, but there's always the debate.

If that's too much, then it will be bloated, and the Tea Party movement -- you don't need me to tell you what they would have us do with these kinds of things.

On the other hand, if the cost on

individual riders is too high, they will find other ways to get to work, and they will not ride Metro. So, there are a lot of parallels, it seems.

MEMBER RUBENSTEIN: Just one comment. It was also clear -- and I think, again, it is a response to a legitimate question from Harold -- that these advisory committees would be able to prioritize clinical research, because not everything can be done by everyone. That is obvious. There's just not enough money, and maybe some of it isn't worthwhile doing in terms of quality.

So, part of the input here is our oversight of the programs in the Clinical Research Center and how they would be prioritized and adjudicated in terms of investigator requests, and so on.

So, there was a really important role, and these two bodies, the ABCR, if I've got that right, and the Intramural Research Program Directors, would have significant

input in terms of advisory to you in terms of that regard, too, as well as the budget issues.

CHAIR AUGUSTINE: Any other comments?

(No response.)

Hearing none, I mentioned before we got into the topic that there are a couple of complicating factors that are probably apparent to most everyone at the table.

One of the complicating factors is the work of the TMAT group that's now underway, the Translational Medicine Group, clearly could have an impact on how you handle the Clinical Center, and particularly its budgeting.

If we take some decisive action on the recommendations we have just heard, we may in December of this year, when the TMAT group completes its work, discover that we put ourselves in a box of some type.

And in terms of the rigidity of

that box in which we could place ourselves, or more specifically place Francis and his colleagues, it is that under the law that creates the SMRB, if we make a recommendation, it triggers a number of events with specific time scales specified in the law.

For example, if Francis accepts our recommendations, he has to begin implementing them within a certain number of days and begin submitting reports as to the status of the implementation, which I know he looks forward to, but --

(Laughter.)

DIRECTOR COLLINS: That's what gets me up in the morning.

CHAIR AUGUSTINE: Yes, that's right.

But, anyway, it triggers events that we, all of us, have no control over.

Secondly, if Francis decides not to proceed with our recommendations, he then is obliged within a certain number of days to

submit an even longer report, probably -- (laughter) -- to the public and the world saying why he thinks we're off-base.

And so we kind of are in this trap where, until December, we're not really prepared, my personal view, I don't believe we're in a position to take a decisive action here. And if we attempted to do so, we would trigger a no-win circumstance, I think, in either direction. Again, that is a personal opinion, but I think it is shared by others I've talked with.

Fortunately, the way that Arthur's group has made their recommendations lends itself to a way out of this box. For example, Recommendation 2, that the current organizational structure is not adequate, that we need a new, more streamlined structure, that is not a specific enough recommendation, I'm advised by our counsel, to trigger all these events.

But the group also went to the

next step and said how you should organize, in our view, to deal with this issue. That does trigger it.

The third recommendation, where we say that the current funding approach is not viable, no problem. We say what you want is a line-item approach in the OD budget. That does trigger it.

So, one way we could handle this, if the committee chose to, would be today to vote on the report of the committee in terms of the overarching principles that it has proposed, such things as greater external use, more streamlined organization, a more viable or a viable funding approach for this new usage, and leave the specific details to be addressed in December, at the same time as we address the TMAT report, and then submit the TMAT report and this report at the same time. Fortunately, December is not that far away, and we have a meeting scheduled then.

That's one way to deal with this.

There may be other ways that are better.

So, let me just open the floor to anybody who wants to comment on that.

Steve?

MEMBER KATZ: Norm, I think your recommendation is fine, because Francis can actually implement a change in governance without actually hearing from this group at all. So, I think part of this could be implemented, if you like it, and it would not preclude what the future recommendations will be.

CHAIR AUGUSTINE: Other comments?

MEMBER VARMUS: I don't hear any disagreement with the specific recommendations that have been made. So why not endorse the report?

CHAIR AUGUSTINE: I take that as a motion?

MEMBER VARMUS: Yes.

CHAIR AUGUSTINE: Is there a second?

MEMBER FAUCI: Would it be out of form to ask, Francis, what do you think would work best for you?

DIRECTOR COLLINS: Well, I appreciated Norm's articulation of the issue. We do have this TMAT process which we're going to be talking about today and tomorrow, and which is on a short timeline, by December, to try to look more broadly at our efforts in translational medicine and therapeutics.

One possible consequence of that might be some organizational recommendations that would involve the Clinical Center, the CTSAs, perhaps what is going on with the Cures Acceleration Network, with TRND, with RAID, with our Molecular Libraries Program, and this whole pipeline for therapeutic development.

And I would think, therefore, that to make a very specific recommendation about precisely where you want the Clinical Center budget line, for instance, to land -- while it seems very thoughtful, what you have come up

with at this point, I'm not sure that without going through that process over the next three months that you would be absolutely confident that the answer is going to be the same.

So, I like the recommendations the way they are phrased because, as Norm has said, they are rather general, and they do capture the sense of the major changes that need to be made.

But I think, as Norm has also pointed out, it might present some awkwardness by triggering timelines to get down into the specifics of that in terms of exactly how the governance would be set up or exactly where the budget line for the Clinical Center would be.

I would find it easier to have those recommendations of the more specific sort delayed until December.

CHAIR AUGUSTINE: Steve, were you going to say something?

MEMBER KATZ: No, I was just going

to reiterate, if we do approve the report, then you can implement whatever part of the report you want.

CHAIR AUGUSTINE: We would approve the report in principle. We would not be saying at this point go ahead with the line-item funding, and so on.

Harold, you've got your light on there.

MEMBER VARMUS: Well, Tony was about to make a comment.

MEMBER FAUCI: I am a little bit slightly confused. And that is that we are going to approve the report but not make formal recommendations? Is that what you're saying?

CHAIR AUGUSTINE: No, I think I would word it a little differently, Tony.

MEMBER FAUCI: Okay.

CHAIR AUGUSTINE: I think I would say that we are going to approve the overarching principles cited in the report,

but we will not approve the report until December.

MEMBER FAUCI: I got it. Okay.

MEMBER VARMUS: Well, I'm still a little -- I'm not actually clear about how you imagine, Francis, that these recommendations would be changed by any of the TMAT discussion. I suppose it is conceivable, but I think the committee has done its work. There is consensus; there are some very useful recommendations. The Director does have the opportunity to disagree with them and even represent a case for not implementing them.

But it seems to me we sort of weaken our position as a group by saying, well, you know, in general, we are endorsing the report that we've done so much work on, but we don't actually endorse all the specifics.

CHAIR AUGUSTINE: Harold, so what you are arguing is your own motion here.

(Laughter.)

MEMBER VARMUS: No, I'm arguing for approving it. Yes.

MEMBER FAUCI: But, Norm, if we make the recommendation -- and again, to me, it's just what works best for Francis -- but it seems to me that, given all of our deliberations, if we make the recommendations, and what happens in December with the other group is a reason to modify them some, then since they're only recommendations to Francis, Francis can say, "I understand your recommendations, but I want to change them a little, in light of what we're talking about with the translational medicine."

Is that what you mean, Harold?

CHAIR AUGUSTINE: I think the concern is that, if we just approve the report, we trigger all these legal events that you've got to deal with that we would rather avoid until December.

DIRECTOR COLLINS: That is the concern. Let me be a little more specific.

So, for instance, suppose the TMAT recommendation is to come up with a new organizational structure that would capture what we're doing in translation. Then that would lead to the conclusion that having the Clinical Center budget line in OD is maybe not the optimum solution, once you come up with a more integrated pathway for therapeutics. I don't know if that's where TMAT may go, but it's one of the possibilities on the table, as we have talked about.

If you approve this report including the details right now, then we may have ourselves in a little bit of a pickle, or I may be in a pickle, because then I'm required, as you have heard, to go through this legal process of either agreeing or disagreeing with reports and paperwork and so on.

It would be, I think, more facile in terms of getting all of these deliberations to a good endpoint to have this group approve

the principles of your report, which I agree are superb, and that includes the recommendations themselves. Because if you look at them carefully, they're written in a general sense. But to delay approving the entire report in terms of the details until December, at which point we may have some more information that might cast some light on this -- that is the subtlety I'm trying to capture, and it doesn't look like it's been captured.

CHAIR AUGUSTINE: Excuse me. I saw Arthur, and then Harold.

MEMBER RUBENSTEIN: You know, I don't know the exact regulations, but one possibility would be just, seeing there seems to be a consensus, to delay the vote on the report until December. Then we don't have to have all this Mickey Mouse about what we are approving and what we're not.

That just seems to me -- we don't need to go back and revisit the report, because everyone seems to at least be

supportive, and just let's say in three months it will come up for a vote.

MEMBER VARMUS: Right. That's the point I was going to make. I don't know how we separate the principles from the details, because the principles are in the details.

CHAIR AUGUSTINE: I think that works fine. Okay.

Are there any further comments?

(No response.)

I assume that was your motion.

(Laughter.)

Gene, I assume that was your second.

Okay, all those in favor of tabling the motion until December, please say aye.

(Chorus of ayes.)

Those opposed?

(No response.)

That was overwhelming. Okay.

We're a little bit ahead of

schedule, and we have some people who are going to participate in the next session who won't be here for about 10 more minutes.

So, why don't we take our break at this point? We're scheduled for a 15-minute break, if everybody could be back promptly. Thank you.

(Whereupon, the foregoing matter went off the record at 9:22 a.m. and went back on the record at 9:41 a.m.)

CHAIR AUGUSTINE: If everyone would take your seats, we can begin again.

Okay. During the break, I was thinking that a week ago today I was tracking gorillas in Rwanda. The more I think about it, the better preparation for this meeting it was.

(Laughter.)

Now we'll turn to the subject for the rest of today, which is the work of the new group on translational medicine and therapeutic discovery. That group, as we have

mentioned, will be chaired by Arthur because of the close tie we have already discussed to the work he has just shared on the Clinical Center.

So, Arthur, we'll kind of turn to you to carry on here. We will have a couple of speakers just sort of introduce the topic, and then we have a terrific panel for a panel discussion. The rest of the day will be devoted to this topic.

Arthur?

MEMBER RUBENSTEIN: Thanks, Norm.

My colleagues at Penn want to know why I'm doing all this work for the NIH, and when I couldn't give them the explanation, they got rid of me.

(Laughter.)

So, I do want to say it is a labor of love, but it has consequences. So, there we are.

Anyway, it is a subject I believe in strongly, so I'm happy to do it.

We also have some colleagues from Penn here, particularly Garret FitzGerald and others.

We have thought about this subject for a very long time. Of course, with Francis' leadership and involvement in it, it does seem a very, very worthwhile issue to evaluate carefully at this time.

So, on your behalf, and particularly all the excellent invitees that we have who, I think, will be the key people to listen to, we should, I think, learn about and think about how to move this important subject forward.

So, today I would like to frame the discussion by providing you with a brief overview of the charge to the group. This charge has two principal components, and these are listed on the slides for you, and they're in your book as well.

I would ask you to look at them carefully, because it will consume our

attention for the next three or four months, because there is a short timetable, and the issues are very important.

So, we wish to identify the attributes, activities, and capabilities of a translational medicine program, particularly to advance therapeutics, which I think there is general agreement around the world that there is some lack of movement in terms of the opportunity for developing new therapeutic agents, and so on.

And broadly assessed from a high-level view, the NIH landscape for these programs, networks, incentives for inclusion in this network, and think about the optimal organization.

And of course, it is in that regard that the Clinical Center, which is or could be a key part of this, we delayed the final recommendations in that regard.

Here is the group. It involves the original group, but it expanded appropriately

to involve people with a variety of knowledge and expertise. I won't read through all their names, but, again, it is also in your book. And there will be a lot of input from outside as well as the committee group themselves.

So, the considerations that Francis has asked us to think about carefully on behalf of the SMRB is to consider how the agency could leverage and organize a wide range of resources to implement the Cures Acceleration Network, which is part of the new healthcare bill.

In addressing this change, our responsibilities are to look at the current NIH infrastructure and initiatives which may have relevance to the therapeutic development pipeline and to synergize and avoid competition with resources in the private sector.

A key part of this was to coordinate and synergize with the private sector rather than compete with them. And I

think that was made very clear in Congress in the bill and, of course, there's a mandate that we are very sensitive to.

Our Work Group in the next three or four months will consider recommendations for strengthening the Clinical Center -- we have discussed that in detail -- as well as other recommendations by a variety of informed bodies, particularly the Institute of Medicine report.

But there have been numerous reports that we actually looked at carefully as we looked at the program for the Clinical Center, and we have as well evaluated and will look at them again, so that we don't just try to reinvent the wheel.

And we would also like to have some methodology and metrics that can be used, so that we just don't come up with things that have little impact, but that we can evaluate and measure what we recommend if this group implements it and the NIH puts them into

practice.

So, this TMAT group will recommend to the full Board in their report issues related to the following big areas: The attributes, activities, and the functional capabilities of a translational medicine program.

So, are there any changes, organizational structures, or budget issues that could be modified that would make this program more streamlined, advantageous, and successful?

We would hope to come up with some recommendations to organize the existing components, to optimize their relation to each other and the organization, and then methods for evaluating successful or untoward consequences, as I have described to you before.

So, that's just a framework. The big issue is really, is there a more effective, advantageous way of organizing

translational medicine and therapeutics, starting within the NIH but involving the agencies around the country and the private sector as well, that could move this subject forward in a way that would create successes for all of us in a way that we would be pleased about?

So, we have a variety of sessions outlined here where there will be some presentations and a group of distinguished visitors. I do want to just say, on behalf of everyone -- and I know others will comment -- how pleased and delighted we are that people have made time in their busy schedules to come. And many people have given up other opportunities for the need to come here today and tomorrow, and we just want to thank you and say how pleased we are about that.

So, there will be, overall, four sessions today and tomorrow -- thinking about advice and ideas and creative thinking about this opportunity. Then, after that, the Work

Group will deliberate and think about how to proceed and advise Francis about possibilities in this area.

I think I'll stop there and answer any questions. Norm?

(No response.)

I think that's how I'll end, and if there are no questions, we could just get on with the presentations.

So, the way the program is organized, we have two talks -- the first by Charles Baum and then by Jesse Goodman. Then, after that, we have a panel discussion, and that will take the morning session. And I think there will be time for a significant input both from the SMRB and the public.

So, the first -- we have asked Charles Baum, who is the Senior Vice President for Clinical Programs at Pfizer, to talk on the current landscape of drug discovery and opportunities for new paradigms.

And we are grateful for your

coming and appreciate your comments.

DR. BAUM: Well, thank you for the invitation.

And it's a very important topic to us; the role of translational medicine and the key part that that is going to play going forward for all of us in the development of new therapeutics.

Obviously, this is a broad topic that covers a lot of ground, and we could probably spend days talking over this topic. But I'm going to focus the discussion around some of the things that we have done at our institution, at Pfizer, to try to address some of the challenges of drug discovery and development as a paradigm that we could talk about, and I welcome questions along the way on how we've done it. Certainly, we don't have all the answers, but we're looking for additional collaborations.

Someone is in my pocket.

(Laughter.)

I'm not used to that happening.

So, let's get started.

I think everyone is well aware of this topic, and there has been a tremendous amount of discussion about research and development productivity in all aspects of development, but especially in the pharmaceutical industry and how we are doing over time. Certainly, there's a number of great therapeutic advances that have occurred, but there's also, obviously, tremendous room for improvement.

And one of the indications of that room for doing better is shown here. And it indicates that, despite a huge increase in spending on our part to find new useful therapeutics, that we have ended up with roughly the same number of approvals of new molecular entities over this 20-year period, with probably a tenfold or so increase in money being expended. So, something in the model wasn't working, and we needed to change

it.

I can show you now some of the things we have done to change this, both in an organizational sense, but also in the research -- how we conduct research and the culture of how we do that work.

So, this is an obvious slide that many of you have probably seen before. The cost of bringing a program from early stages of discovery through to patients is probably on the order of $100 million. It varies somewhat, but that's probably an average for a successful program.

The problem is really on the right side, where you see that a huge amount of our expenditures are in projects that fail. So, what we need to do is really get a better sense of why those projects are failing and do a much better job of making them fail sooner rather than later.

So, we need to identify in research in Phase I and Phase II which

projects are those that are most likely to succeed and those which aren't and to kill those that aren't as early as possible. And there's a key role for translational medicine and translational research in that area.

So, just in terms of our evolution over this time period -- over the last decade, roughly, in the years up to about 2008 -- there was a great expansion in our research and development organization. We had many sites spread across a number of countries. There was a fair amount of autonomy at these sites. There were a lot of overlapping efforts and efforts that weren't coordinated together and a very bureaucratic organization that had many levels between the CEO and the bench scientists. So, a lot of the messages weren't getting through.

Obviously, there were a lot of measurements and metrics, but those were mostly metrics of activity. So that we had a large number of candidates coming through the

pipeline and a large number of Phase III programs, but that was the goal -- the numbers, to maximum the numbers -- rather than focus on the human biology, the human genetics, and really what were the most impactful projects and focus our efforts there.

The organization was made up of large groups of scientists of up to 1,000 people in some cases. Working on some of these projects are very large and bureaucratic groups. It took them a while to make decisions. They tended to be slow and bureaucratic, and that is something that slowed down progress but also slowed down decision-making.

We also had no formal scientific advisory board on the outside. That is something that was definitely a change from current expectations.

And 90 percent of our work was conducted in-house. So, Pfizer was a very

internally-focused company. We looked to the inside for all of the answers. I think that's a dramatic change there that we'll talk about in a few slides.

And probably one of the biggest changes, from all of our activity being internal to about a third of the activity is now being conducted in collaboration with external institutions, academic institutions, biotech companies, and other pharma companies. And this issue that was discussed earlier around intellectual property, how do we work with that? How do we make a more open and collaborative environment as we go forward?

So, basically, the organizational changes we made were to simplify the organization, to make decision-making easier, quicker, and make it based on the science and about validity to the patient. That could be in huge areas of unmet need, but also in rare diseases.

And there's been a new focus --

we'll mention briefly -- but ongoing, in rare diseases, and focusing not just on the overall population, but on subsets of patients that will be identified through our efforts in human genetics and translational medicine.

So, in breaking down the organization into much smaller research units, those research units are led by a Chief Scientific Officer who's local and can make decisions with a group of researchers of 100 to 200, roughly. And that group is focused entirely on a particular area of focus - a therapeutic area for the most part. They share that vision; they share ownership of the project. So, you have a much different kind of culture and a much different kind of feel -- much more like a small group, a small company, a biotech company in some cases -- that provides not just greater motivation and a different culture, but also the ability to move quicker, make decisions quicker.

And those decisions could be to go

forward, but also to cut projects. And the rewards should be there for cutting projects that are not productive, again, so that we improve our chances of success and decrease attrition in late-phase, which is where all of our expenditures of resources occur. So, the key part of this is not just structure, but how we conduct ourselves.

This is just an example of the organization. And it shows that these groups, led by CSOs in each of these areas, are focused on particular therapeutic areas and that those areas are supported by a large infrastructure that provides all of the necessary parts for drug development -- so, medicinal chemistry, a variety of approaches to biotherapeutics, and all of the parts of the organization you need to support the CSOs and these groups to be able to maximize the benefit of their science and to bring these new therapeutics forward as quickly as possible.

And I won't talk much about this, but the other part of the organization that is also changed is on the commercial side, where we have separated the business into business units, and those units are, again, specific to particular areas -- the most relevant ones, for research and development, where we feed most of our projects into primary care, specialty care, and oncology.

So, there's very close bonds between those groups. And these groups and the business units take the projects from proof-of-concept stage through Phase III and through post-marketing development.

So, in terms of how we have conducted a traditional discovery paradigm, the focus was on picking a target, picking a molecule, and optimizing the chemistry, and we became very good at that and then do the clinical testing.

But it was a linear process. So, you would go forward, generally throwing it

over the fence at each stage, and not enough interaction forward as well as backwards. So, with the interactions of research with clinical and the interactions of clinical back with research, based on the clinical outcomes, it was not what it should be.

We think that's one of the key areas that needs to occur, so that there's more interaction, more learning coming from our clinical expertise and clinical experience and the huge amount of data in those clinical trials -- even if those trials are negative -- that we can learn from in deciding the next studies and learn from in terms of patient segmentation and identifying the appropriate patient population for the next programs or modifying the population for the existing program to make it more likely to succeed.

So, the way we want to think about that process now is more of an iterative process and focusing on the best target, as defined by the best biology. So, focusing on

human biology and human genetics to help us define what the best targets are early on in the process from the very beginning, and also to focus on the human condition. What is the disease, the patient population that we're looking to study, and getting that into the lab as early as possible, so that we're addressing the right question from as early as possible.

Then we have the opportunity to design the best small or large molecule. We have a lot of expertise in chemistry and designing the small molecules, but also a large expertise not only in biotherapeutics and the ability to bring all of those different techniques to bear on a particular clinical problem, so that we find the best solution, not just the solution that's most convenient.

Another part of this is that this requires, this whole process requires extensive collaboration, and I'll mention that

as well, with both internal and external experts.

So, really, the take-home lesson here on our side of what needs to be different going forward is a focus on human biology and on human genetics to define the best patient populations and the appropriate way to treat those diseases.

So, as I mentioned, obviously, stem cell biology, cell biology in general, as well as human genetics are key components of what we believe to be a foundation for translational medicine, personalized medicine, along with all of the other attributes, molecular profiling, systems biology, and bioimaging, which all together create the right profile for the patient, selecting the right target and the right patient to increase our opportunities for success with these programs.

So, these are the areas, the key areas, of focus for us and for many other

groups. But it illustrates the need in many of these cases to focus on the right patients.

For example, we have extensive effort in immunology and inflammation. But in the past, that was focused almost entirely on rheumatoid arthritis and treating the whole population of patients. We are making significant efforts now to look at subsets of patients with rheumatoid arthritis, but also patients with lupus and with other autoimmune diseases to see if those patients will give us insight into treating subsets of patients more effectively, but also treating the larger patient population with inflammatory diseases more effectively.

So, patient segmentation, as I've already mentioned a number of times, is key to our programs going forward. So, this is an opportune time, actually, with a big emphasis in our institution, but I think across the board, in how do we better select the patients. How do we better understand the

targets, based on human genetics as well as the biology and human systems, so that we can select the best targets better sooner?

And the disease understanding is the key point to making the overall process more effective, resulting in higher probability of success, but also in terminating projects earlier. So, the better we can make decisions in Phase I and Phase II to stop programs that are not showing the kinds of effects we want to see -- because we can focus on the right patients, and if in those patients we don't see an effect, then we should move on to a different focus for that program or just stop the program. That allows us to move much more quickly, we feel, towards the real solution a more effective therapeutic.

Ultimately, it results in a better therapeutic index, a better benefit-to-risk ratio for the patients, for the payers, and for the system in general.

So, I thought I would show a couple of examples of patient selection that have been relevant to recent years here. One is in lung cancer patients, which tended to be treated as a group without looking at patient subsets very effectively.

We started a program quite a few years ago called crizotinib. It's an oral selective inhibitor of MET and ALK. And actually, our focus for the program was MET in addition, because it seemed to play a role in a number of different solid tumors.

So, we took that program forward into Phase I. During the Phase I program, we discovered, with the help of academic collaborators, that 10 percent or so of non-small cell lung cancer patients had a translocation of the ELM4 ALK, which upregulated expression. And those tumors were dependent on that mechanism.

So, we modified the clinical program. I think it's important to show that

you can do that in an iterative way, if you're keeping your eye on the literature, adding patients to that initial first Phase I, but, then, re-engineering that Phase I to focus on those patients.

And through doing that, we found a very high response rate that you could see very quickly in that small patient population, because the overall response rate was in the order of 65 percent. So, it was pretty easy to identify that quickly, see it, and act appropriately to start planning for a future, to expand the program and to move it along, but, also, to start discussions with regulators around the world to see how that could be developed collaboratively.

And in many of these cases, we found that the agency and other health authorities have been very helpful, actually, in working with us to bring these projects forward.

And this is just an example of the

data, but it illustrates why it's relatively easy to make a decision in this case -- that if you look at the line, the x-axis here, and then here is the percent change in the tumor volume, and this is a decrease -- that virtually all of the patients had a decrease in tumor size. So, it was pretty obvious early on that there was benefit.

And the other important part is that it's not just a response, but a response that lasts for a significant duration, so a durable response as well. And the toxicity of the agent was quite reasonable compared to other chemotherapeutics, especially that lung cancer patients may be treated with. So, the overall risk/benefit is very positive.

So, that program has proceeded quickly, and it is in pivotal trials now, heading towards approval, hopefully. But, again, it shows the benefit of focusing on a patient population, because if we had looked at all of lung cancer patients, treated

everyone, with benefit only coming to those 10 percent, we would have missed it; we would have missed that effect in the overall population.

Another interesting project, this is a slightly different angle, but using human genetics to define a target for a therapeutic. This is PCSK9. PCSK9 plays an important role in LDL metabolism, in that the PCSK9 molecule is secreted, it binds to the receptor, and if it does bind to the LDL receptor, the receptor is degraded. If it doesn't bind, that there is recycling of the receptor. So, that way, more cholesterol can be brought into the cell, and your cholesterol levels will go down.

So, there's a patient population that was defined by Helen Hobbs and her group at Dallas that was very interesting, a very small group, of course. But these patients had low LDL cholesterol. I don't think the low showed up, but this is a 28 percent decrease. And in terms of cardiovascular events, they

had about a 90 percent decrease in cardiovascular events. So, we know that they were relatively healthy. There were no signs that this deletion or this mutation was a problem for the patients. So, long-term therapy should be okay.

We learned a tremendous amount from these patients in developing this program, which is an antibody to that target. And it turns out that, despite the recycling that occurs, if you expose it to an antibody, you can stop the PCSK9 from downregulating the LDL receptor. And therefore, your LDL goes down. More LDL is taken up, and you can see a significant reduction in LDL cholesterol in rodents and primates. And the clinical studies are ongoing now.

But it's a very good example of using human genetics to find clinical programs, to find patients that you can look at, and the development of a therapeutic from that observation.

And that occurred relatively quickly from the first publication, because that's when the project started, was with Helen Hobbs and her publication.

So, it's not to say that patient segmentation and translational medicine is easy. It's not. Our disease understanding lags in a number of cases. We just don't know how to select the patients, how to select the best patients for benefit by a particular therapeutic.

We lack a lot of the cell models and the research models to be able to study the disease more effectively, and there are few biomarkers that are actually clinically validated or available as a surrogate endpoint that would allow you to use them in clinical trials for approval process or to move the programs along more quickly.

So, there's a lot of areas that need a tremendous amount of work. It is recognized that that needs to happen, and it's

an opportune time, since we plan to increase dramatically our focus on translational medicine, translational research, and we are very interested in collaboration with groups in that area.

I won't go through all of these things since I know a number of you are familiar with it. But there are a number of challenges for the development of biomarkers throughout the process.

But you need to begin thoughts about biomarkers right at the beginning of the research program, so that you have them available in a validated assay that can be used clinically when you start the clinical trials. You have to do that from the very beginning.

You have to then, if that program progresses into Phase III, you have to have something that's reproducible in a Phase III kind of environment. You have to work in partnership with diagnostics companies to

develop that assay and to have it available if the program is approved, if the therapeutic is approved.

So, all of these things require a tremendous amount of collaboration from both internal and external groups as well as from health authorities and agencies with this sort of co-development of a diagnostic along with patient selection markers.

So, a tremendous effort that needs to be made, and it needs to be made in collaboration between a number of different groups to make it successful.

So, one of the other points about collaboration that we want to make, partly because we were probably not the best collaborators in the world in the past -- so I think the focus on biology and improving our knowledge of biology, on using that biology across industry, but across academics and industry is really important. We realize that, and we want to put a tremendous amount of

effort in developing those partnerships.

This is just an example, but there's many partnerships that we have. We have thousands, actually, across the world, looking at various research questions. And this is an area where we think we need to collaborate extensively in order to be successful in terms of translational medicine and patient biomarkers.

So, one example that I wanted to just show that illustrates some of the changes in our thinking around intellectual property partly is an open innovation network. That is that the institution actually gets access to our compound files, both in terms of all of the scientific information there, but also the compounds themselves, so that they can look for themselves at what we have in our portfolio and evaluate whether it would work in their models and how they might be able to use it to their benefit but also eventually produce a useful therapeutic.

So, this is one example, but there's a number of them coming up now. There's a new group that we have established in Austin to focus on this area of enhancing collaboration and sharing information in this way that I think will be effective and will actually be sharing things like our antibody libraries, one of which was published in PNAS last year, but a very good antibody library that could be effective, could be helpful to a number of groups in looking for antibodies to novel targets.

And just another example, in this case a little bit different-looking for targets, but a collaboration with MGH, the Broad, and with the Lund University, to look for rare genetic variants. So, patients who have all of the risk factors for cardiovascular disease but don't have it. We have all seen them, but we don't know why.

All of the patients who are obese and diabetic, and all that just don't have

significant cardiovascular disease, what is it that is protecting them? We are trying to find out more about that through human genetic studies.

So, that has just begun in the last couple of years, but it's illustrative of a number of different efforts that we have in human genetics starting up that we want to pursue in collaboration with institutions externally.

And just one point about biologics - that biologics, I think, are coming to a new stage of development where we can do a lot of manipulation. Not just monoclonal antibodies or growth factors, but taking those basic structures and doing a lot of manipulation, almost what you might have done with small molecules in the past, so it can create biologics with biospecificity and a number of different attributes that would be useful therapeutically.

But we need the biology and the

biologic expertise that targets the appropriate patient populations to select and evaluate in these settings for these to be useful.

So, finally, I think everyone agrees that we should be focused on the right target. We need to do that from the very beginning, to know as much as we can about human genetics and human biology, to be able to do that.

Selecting the right patients, which has many challenges, but something we all have to work together to accomplish. Designing both small molecules and biologics appropriately for the right patient population eventually will lead to better, more effective therapeutics with a better risk/benefit ratio.

So, thanks for your attention. It's a very large topic. So, it's only a superficial journey, but I wanted to bring up some topics that we could discuss as part of the discussion session.

And if you have any questions now, I'm happy to entertain them as well.

MEMBER RUBENSTEIN: Thanks, Dr. Baum. We really appreciate that.

We have time for a few questions. Then we will have Dr. Goodman's presentation and then maybe a few other questions for the two of you.

But if there's some specific questions, yes, why don't we start, Bill?

DR. MATTHEW: So, one of the things in software development is open software.

DR. BAUM: That's right.

DR. MATTHEW: And you kind of alluded to that.

DR. BAUM: Yes.

DR. MATTHEW: I'm just curious as to what you think the model might be for drug development.

DR. BAUM: Yes. And so, in a similar vein, the biology is sort of the hardware, the software that we all need to

work with, and that discoveries in that area, discoveries of new targets and unique biology is something we can share with academic institutions, with biotechs, with other companies, in fact.

And then, it is how we reduce that to practice. Our ability to make small molecules or biologics to attack these issues is really where the proprietary part comes in. So, we're less worried compared to the past when we were very protective of anything.

It's like we used to stamp everything top secret, but it wasn't. You know, it wasn't needed to do that, and it kept us from doing a lot of collaborations and interacting effectively with many people. So, that needs to change. It is starting to change now, and it is something that Michael Dolston, the head of Research and Development, is very, very adamant about, that we need to change that. That's basically the model of open innovation.

So, exactly how we do it, there's a few different ideas. One is like with Washington University sharing the database about compounds. There's also something we're starting up in Cambridge with the local universities to look at actually having some dedicated people from the company who would form a real close working relationship and partnership with the university and that would basically function as one, as a way of optimizing that interaction and having a situation where we both have skin in the game. So, there's a real need for the collaboration, and both sides see it.

So, it's not just sort of some of the typical collaborations we have had in the past that really haven't been a huge benefit to either one. I think we can do much better there.

MEMBER RUBENSTEIN: And are there any others?

Gene, yes?

MEMBER WASHINGTON: First, thanks very much for a very interesting and informative presentation.

I would like to go back to the graphic that you showed regarding what percent of overall investments resulted in success.

DR. BAUM: Okay. Yes.

MEMBER WASHINGTON: So, my question, though, is looking ahead, projecting an optimistic scenario under the new paradigm, what might that graphic look like?

DR. BAUM: So, the idea is that, since less than 10 percent of our programs make it through to a therapeutic, that if you could just decrease that by a third, right, or increase, or however you look at it, if we decrease attribution by a third, that would be a tremendous amount of research that could be put towards other programs to go faster or to look for new targets.

And that 30 percent is a huge number, obviously, if you're looking at the

total R&D spent by all of the large pharma companies, since ours alone is on the order of $8 or $9 billion.

So, the amount of research is tremendous. If we can harness it better and stop programs sooner, that would suck up all those resources if they went into Phase III. So, we think that is definitely doable.

We don't think we can get to zero attrition and we shouldn't, because you want to bring some things into the clinic that you're not sure about. You want to take that risk. But you need to make the decision relatively sooner to stop something that's really not in the best interest of the patients.

MEMBER RUBENSTEIN: Steve?

MEMBER KATZ: Thank you again.

Part of the new paradigm that you talked about was a focus on rare diseases.

DR. BAUM: Yes.

MEMBER KATZ: Could you tell us a

little bit about that?

DR. BAUM: Yes.

MEMBER KATZ: I guess that fits in with your patient segment.

DR. BAUM: Yes.

MEMBER KATZ: But you made it a point specifically about rare disease.

DR. BAUM: That's right, and I think there had been some discussion about this in the past, but I think you've seen real action now, finally.

So, there is a group that has been established in Cambridge as well to focus entirely on rare diseases. And their mandate is to, for the most part, work collaboratively. There is an internal group, but, also, we recognize the need to work with the academic centers and the people that have these rare patient populations, since they are not easy to access, to focus, to help them in some cases to develop a therapeutic, but also to look for new opportunities in those for new

targets that might be effective. So, that is a huge change for Pfizer and a big change in emphasis towards those less common diseases.

And there's a good example just recently with FoldRX that we acquired. Their whole focus is in amyloidosis, a very rare condition initially.

So, it is really showing by our actions that we are very interested in those areas. We think there's lots of clinical benefit that we could bring to those patient populations.

MEMBER RUBENSTEIN: I would like, Dr. Baum, you know, agreeing that Pfizer is a worldwide company, one of the interesting things is the way you position these new or these expanded areas.

DR. BAUM: Yes.

MEMBER RUBENSTEIN: And I just wonder, from your point of view, if the climate in the United States is less positive than the United Kingdom or other places.

Because it is a thing we wrestle with a great deal, and if it is so, we need to think about that in terms of encouraging you to deal with some of the issues here.

DR. BAUM: Yes.

MEMBER RUBENSTEIN: So, you know, there's a lot going on in Cambridge, for good reasons. I just wonder what your thoughts about that are.

DR. BAUM: Yes. So, I think it depends on what aspect we're trying to focus on. So, I think in terms of biology and the deep knowledge and the innovative science, that still there's a big emphasis in the U.S. and Western Europe and other key academic centers that have that information.

But that is not to say that we are not interested in working elsewhere. So, our initial focus will be in those areas, but to expand to Asia, obviously, is one of the other greatly expanding areas now for all of us, that we need to get into more work there,

which we haven't yet. And it probably will take a bit longer to develop those kinds of relationships.

But we have existing relationships with some of the institutions in California and on the East Coast that we want to optimize. So, that is part of the reason for their location. But we are interested in looking at other opportunities. As this succeeds, we would like to see it go into a number of different places.

MEMBER RUBENSTEIN: Francis?

DIRECTOR COLLINS: I want to follow up a little bit on the question that Bill asked in terms of the open sourcing of the enterprise in a way that still protects intellectual property, but which empowers people who are doing an increasing amount of efforts to do high throughput screening for therapeutic purposes to have access to molecules that have added value, because they have already been put into circumstances where

you know a lot about them.

Your model with WashU is very interesting in that regard, but some of us might even say, why not really open that up --

DR. BAUM: Right. Yes.

DIRECTOR COLLINS: -- so that pharmaceutical companies develop relationships with high throughput screening centers, some of which NIH now funds as part of the Common Fund? So that every time a screen gets done with a target that's potentially relevant to a rare or common disease, you have a chance of getting a hit that's already well along the pathway, and you've saved a lot of money and a lot of time.

DR. BAUM: Yes.

DIRECTOR COLLINS: We're going to be running a meeting later this fall to sort of look at this question of repurposing on a broader scale.

DR. BAUM: Yes.

DIRECTOR COLLINS: And also, sort

of rescuing, perhaps, compounds that have been abandoned along the way for various reasons.

But maybe as a little foreshadowing of that conversation, do you see any barriers towards really opening up that potential, as long as careful thought is put into the IP considerations? Because companies, after all, have already invested a lot of their resources in developing information about these compounds.

DR. BAUM: Right. But I think what we also realize is that, if they sit on the shelf, there's no value, either. So, we may own it, but nothing good is happening.

So, what we need to make sure is that key parts, the composition of matter and things like that, are protected. But, then, beyond that, especially in the cases where we just don't know what to do, and there's a number of those cases, we don't know where to go, that opening it up to a lot of external sites would make sense.

And so, I think these are initial steps, but that is definitely a possibility that we have talked about, and how you would make sure that's done in a way so that it's just not everything going out in all directions and then you lose track of what's happened, and negative things can come back to you.

So, you just want to get a better system, and we don't have it now, of doing that follow-up and making sure that we know what's going on and how we can best benefit from the collaboration, so that we both share in that partnership, basically.

So, it's not worked out. We need to work on that more, but we are open to that idea, and I think it's a good discussion to have.

MEMBER RUBENSTEIN: So, let's have two more questions. Then we'll ask Dr. Goodman to give us his perspective. Then we may have time for a few more questions.

So, first, Tony?

MEMBER FAUCI: Charles, I couldn't help but think, as you were presenting this, I agree completely with the concept of fail early and fast and get out.

DR. BAUM: Yes.

MEMBER FAUCI: When you're talking about a clinical trial, sometimes that's pretty obvious. Phase I, if it doesn't happen, it doesn't happen, if it's toxic. Or if you're even in a Phase II trial, you have DSMBs looking at futility, et cetera.

DR. BAUM: Right.

MEMBER FAUCI: But since we're talking about the potential role of the NIH in translational research, how do you see in your own company, when you do research that is directed at developing something but there's a lot of other questions that might arise, as we all know who do basic research, that don't have anything to do with what your original intent is?

DR. BAUM: Right.

MEMBER FAUCI: It can be a little dangerous to drop it, because it doesn't go with your original intent.

DR. BAUM: Right.

MEMBER FAUCI: How do you see that integrating into what we're trying to do? I agree with you completely; when you are looking at a particular product, fail early, fail fast. But what about the information that might come out of a failed product but that might give you something else two years later?

DR. BAUM: Yes, absolutely. I think that's something we have done very poorly, actually, and in two ways. One, learning from those negative clinical trials and getting the information fed back into research for ourselves and for others. Why did it fail? What was the reason? Was it just a bad compound or there's some other reason?

But I think, also, the point that was mentioned earlier, that I think there are

cases where we'll have compounds that don't meet the endpoint we were looking for but that may have clinical utility elsewhere, that we could open that up to let other people investigate and find out if that's the case. But it's not something that we have the resources to do everything.

So, I think those are good cases. And then there's cases, obviously, where it is just flat failure, right, and it's not coming back in any kind of reincarnation. There's no Lazarus factor for that.

So, we can be clear about that and, I think, talk it through the different compounds with the scientists. Where was there a hint of activity or some reason to pursue it, even though the initial indication was not the appropriate one?

MEMBER RUBENSTEIN: Gail?

MEMBER CASSELL: Yes. Francis, I would say in the not-for-profit Lily TB drug discovery effort, we give full access to our

entire chemical library. Merck gives limited access. It's a partnership with NIAID, Lily, and the Infectious Disease Research Institute in Seattle, and also Academia Sinica in Taiwan, which has a library of 2 million compounds that they also share.

We have been able to work out the IP issues, the blinding of structures, the release of structures, depending on hits, quality of hits, and decisions to go forward or not.

So, I would be optimistic that maybe some of the learning from this experience since 2007 might be helpful in terms of trying to establish some of the types of collaborations I think you're suggesting could be important for the future.

MEMBER RUBENSTEIN: Let's have a comment from Harold, and then Dr. Goodman.

MEMBER VARMUS: Just a very quick comment about these extended collaborations, which seem very welcome. I hear of efforts

with academia. When you think about these extant calibrations, do you think about the NIH, the government?

DR. BAUM: Yes.

MEMBER VARMUS: And you think differently about that?

DR. BAUM: So, to be honest, I think there's a lot of history of Pfizer avoiding it. Well, it's obvious.

But now I think that's totally different, and viewing it, basically, as an academic collaboration, you know, other institutions. So, I think it is definitely something that would make a lot of sense in collaboration with the clinical --

MEMBER RUBENSTEIN: It is certainly inherent to the TMAT concept, Harold.

MEMBER VARMUS: Yes, I know, and I have an eye on that, because it is really a different set of collaborators.

MEMBER RUBENSTEIN: Right.

DR. BAUM: Yes.

MEMBER RUBENSTEIN: So, I think it is really an important question.

MEMBER KATZ: But certainly Pfizer has -- let me just add one point -- Pfizer actually played a leadership role in a public/private partnership for a pre-competitive identification of surrogate markers in the osteoarthritis initiative.

DR. BAUM: Yes.

MEMBER KATZ: And it's because of Pfizer that many companies came along without any benefit at all in an initiative that's really a true partnership.

DR. BAUM: So, we are trying to expand that to a number of other areas. I think, with your help, we can do that.

MEMBER RUBENSTEIN: Thanks, Dr. Baum.

DR. BAUM: Thank you.

MEMBER RUBENSTEIN: So, of course, there is a role of the FDA, together with NIH and other government bodies, that is

critically important. We are privileged today to have Dr. Jesse Goodman, Chief Scientist, Deputy Commissioner for Science and Public Health at the U.S. FDA Administration.

Jesse?

DR. GOODMAN: Okay. I don't think I have any slides. Okay.

Actually, I sent Amy an email. Amy promised me I wasn't giving a talk, because I only was able to free up time to do this as of yesterday, but I will try my best to say something helpful to you.

I'm really very, very excited to see what's going on here and see NIH and our colleagues in academia and industry looking at this development process.

And maybe I will just give a few broad comments first and then talk a little bit about why the timing is good with our whole regulatory science initiative at FDA.

I would also like to mention something that Tony Fauci and I have spent a

lot of time working on, because I think there are many lessons and models there, which is, what can we do to enhance development of products needed for unmet public health needs and for national defense? And I think the models we have put together for how government, industry, NIH, FDA can work together there innovatively are relevant to many of the things we are talking about here.

So, I thought I would first just react with a few things that come to mind from hearing this talk and sort of the big-picture messages and as somebody who has seen this from a number of ends.

Oh, I also want to say that I have, obviously, colleagues here previously who are at Minnesota, at Penn, and places I've been. So to thank them for all their support over time.

But, anyhow, I think the really big-picture things that I would like to mention, so I don't forget them, are that I

absolutely think that product development needs to be transformed. I think that is totally against the grain for industry, for FDA, for NIH, for everyone.

There is, sort of, nobody who wants to own that, and everybody will look at their piece and try to improve it, and they will call that transformation, but people really aren't stepping back and looking at this.

Now, in some cases the technology, like genomics and personalized medicine, will drive things that are truly transformative. But I think unless we -- and again, we tried to do this in the countermeasure initiative -- unless we really ask ourselves hard questions and say, should we be doing this completely differently, we're going to miss some opportunities.

Now, as my lab chief used to say to me, you know, it's fine for me to say something like this. It's a lot harder to do

it. And he said, you know, "If this was easy, everyone would be doing it," you know, about the work we were doing in the lab. And I said, "Well, it seems like everybody is doing it." But that didn't go very far.

In terms of big principles that really can be transformative of how we think about these things, I think one is we really need to focus not only on saying we have to do things completely differently, but on the outcome. Okay? So what is it at all times we're trying to achieve? Is it a disease? What would be the ideal outcome of an intervention in that disease? Not letting a drug or a development process drive the outcome, but having the outcome start to drive that process. It sounds very general, but I think it's not generally an operational principle.

In terms of FDA, I think the biggest message here is that we would like, to the ability of our resources, both human and scientific, and our capacities, to be engaged

in these efforts throughout, both early on and during the product development and evaluation process.

I think that what has to happen is a bringing together of two different cultures. There is a culture that people like to think of as a culture of innovation and discovery, although I would argue that much discovery is not necessarily innovative. It's discovery, and it's incremental.

But there is sort of a culture of discovery, and then there is a culture of process. FDA and industry often focus pretty well on that process discovery, that process piece. Academia and basic scientists often focus on this discovery and innovation piece.

But I think these are viewed as completely opposite cultures and in collision. I think the real challenge is to start to understand how they could be mutually-beneficial.

If you're lost all the time in

your process, which is the world I live in a lot of the time, you really risk losing innovation and, in fact, stifling it.

On the other hand, if you pay no attention to process or validation of your tools, or things like that, your discoveries really end up having much less value or certainty that they would have, which is where FDA steps in. So, I think, involve us early throughout.

And then, to build on the theme that I just heard about, information -- think about the internet -- information is totally being transformed. I mean, not just the internet, but Twitter and all information. It's now an artificial situation if information is protected or in one little place. Even the intelligence agencies can barely manage to do that anymore.

So, again, we can either fight that, which inherently innovation tries to protect its intellectual property, and that

helps drive the economics of innovation or, as I just heard Gail and Dr. Baum say -- oh, not Dr. Baum -- saying that we really need to think about ways of using the information. We have more, not less. Because, otherwise, it will happen anyhow. So this transparency.

And as an example of something that people have suggested in the drug discovery process, we have seen some sharing of unused or compounds for repurposing, as was mentioned. That's great.

But, also, we have heard about, at what point could you make data public and available for other people to analyze, other than the individual NIH scientist or innovator? So, not just the results, but the data; that could really transform how we do things.

Now a few comments about FDA and its role. What people often don't appreciate is that we are seeing not just single products, but multiple products across

multiple discovery and development efforts. So that we do have a unique place where we can learn from failure and learn from success and, in ways that protect people's intellectual property, share that information. So, I think this is a way we can help catalyze success in that area.

Now, if translational medicine is a huge gap that Dr. Zerhouni, Dr. Collins, all of you have identified -- which is going from the molecule to the patient, essentially -- what we're calling regulatory science, or going from the molecule and patient to a product that can help people and the evaluation methods that we need and the models and tools, has received even less attention. Okay?

So, what we are arguing for -- and this is where I will bring up the analogy of the countermeasure initiative -- is for FDA to have the capacity to be engaged early in this development process. In the countermeasure

initiative, for example, when HHS determines a serious public health threat or a priority need for a countermeasure, when we've looked at best practices and what has succeeded, what we have seen is when we are working closely together with our colleagues at NIH and industry from a very early point, the enterprise is much more likely to be successful.

What we plan to put in place as part of this initiative, which is being resourced significantly because it requires that on our end, is to look early on -- and again, companies do this to some degree -- and say, to go from this concept, to meet this public health outcome, what are the things, what are the gaps in our scientific knowledge base that will occur along the way?

It could be something as simple as an assay for the potency of a new vaccine. For stem cells, another promising area could be, how do we know that the stem cell we made

three months ago and the cell we make next year are going to be the same? And that's an area where we've seen many, many problems in development, where people can get something to work in a mouse or to have promising results, and then, as this is brought into a true development process, they're not sure they're making the same product or can't reproduce the results.

So this gets to the tools, the assays, the measures, things that certainly academia doesn't intrinsically think about in development. And frankly, industry thinks about them in development, but thinks about them generally in a one-off way. I have my target for getting to this point in our clinical development program by this date. How do I deal with this now? Sometimes that leads to innovation, but often that leads to pretty conservative approaches of sort of do everything. So I think we can really help by doing that. I think that's really the major

lesson.

Then the other part is collaboration, and new models of collaboration, and in some cases financing. So, in the private sector, we are hearing you talk about multiple companies getting together in certain ways. As we're trying to deal with these public health products, where the financial incentives are not there or are uncertain, we're trying to find novel ways to bring multiple people together, to get products that might have uses not just in public health but more generally, and to make it so that the enterprise is win/win for everyone. So that the government and the word "ability" can be used in the same sentence through processes that are much more innovative.

I think those are actually the major points I wanted to make. You know, a few other things is that -- and again, this was alluded to, and I know that your group and,

also, the IOM are looking at this. But we really see at FDA the challenges around clinical trials and clinical development. I think that is very worthy of a lot of attention.

On the FDA end, as Chief Scientist, what we would like to do is really change the way we do clinical trials. The clinical trials should focus on population and disease subsets to the extent possible. But where we even don't know that going in, they should be adaptable, flexible to capture that data during the clinical development process.

One of our big emphases or scientific emphasis areas -- and we're working on this with colleagues at NIH, including NCI -- is, how do we start having data systems that let us bring together data, for example, from multiple clinical trials, from multiple kinds of intervention, data on natural history of disease, both biologic and clinical data, and then, hopefully, at some point data from

the healthcare system?

Because I would estimate that right now we are not probably learning from 90 percent of the data that we collect. We are learning from it in a very narrow area of the clinical trial for drug or vaccine or product A for disease B, but we're not using that data or comparing it with other studies and products, learning about natural history of disease, or combining it with more generalizable biologic or healthcare information.

So that's why --

MEMBER RUBENSTEIN: Dr. Goodman, maybe you'll finish so we have time for a few questions?

DR. GOODMAN: Oh, yes. I will stop there. I will stop.

MEMBER RUBENSTEIN: Are you sure?

DR. GOODMAN: Yes. Yes.

So, again, we want to work with you on intent and involvement. I'm totally

convinced that the current models of development aren't working. They're not. Tweaking will help it, but we really need to do things differently, both at the very basic discovery end, where we need to encourage more creativity, and at our end, where we really need to develop better evaluation tools, so that we aren't going on and on trying to detect small benefits in very heterogenous populations.

MEMBER RUBENSTEIN: Thank you. I really appreciate your perspective. I just want to be sure we have enough time to ask you questions.

DR. GOODMAN: Sure.

MEMBER RUBENSTEIN: So, Steve?

MEMBER KATZ: Thanks, Jesse.

In terms of incorporation of new paradigms, could you tell us how the FDA is looking at patient-reported outcomes? We talked a little bit about that during the break in terms of assessment of new drugs, new

interventions.

DR. GOODMAN: Yes. I think that we need to look at clinical study outcomes in general in a very systematic way and that patient-reported outcomes can be a really important part of that. We have been working with you and various consortia on this area.

So, obviously, the part of the response to a therapy that is really most, and sometimes far more, accurate than our biologic measures is how the patient feels, how the patient reports their functional status.

This is very tricky to validate and very easy to go wrong with. But we are very enthusiastic about this. I know measures have been developed that are pretty well validated in areas like asthma that, I think, in the long-run could provide outcomes in clinical studies -- and not just in clinical studies, but in healthcare interventions -- that tell us what really works and what doesn't. You know, it doesn't matter if your

MRI shows this or that if you don't feel better. So we are very enthusiastic about that.

But I want to extend this to a broader concept of outcomes. I think the patient has been missing from the outcomes. And so, these are incredibly important efforts.

But I think, to get back to my point about meaningful benefit, you know, we really need to look at that more generally. We need better surrogate outcomes, more use of accelerated approval mechanisms for serious diseases, which is now hampered by the lack of surrogate outcomes. But then we need to follow those up and be sure we have outcomes that really are about benefit.

And frankly, I think companies are starting to look at things this way. But if a drug or another intervention do not appear to have much benefit over existing therapies, unless there's some other significant thing

that's going to make patients' lives better, I think we shouldn't be spending a lot of energy on it.

MEMBER RUBENSTEIN: Tony, did you want to comment on some of your interactions?

MEMBER FAUCI: Actually, as Jesse alluded to, we have been working on this now for it seems like months, but it's probably close to two years, on this in regard to some of the issues of emerging diseases and things. So, we already have a big head start. The question is, I think we have a long way to go, as Jesse pointed out.

MEMBER RUBENSTEIN: Yes, Gail?

MEMBER CASSELL: Jesse, a number of recent reports have emphasized the need for the science base at FDA to be strengthened in order to catch up with drug discovery and drug development, and suggesting that maybe there should be more interaction between FDA and academic health centers in terms of active collaboration.

And I wondered if you could comment on this and, as the Chief Scientific Officer, how you see this changing over the next couple of years in order to take advantage of the development of new paradigms within NIH and industry?

DR. GOODMAN: Well, I think that there are two major components or more to what we need to do at FDA. You know, right now -- and I'm always struck by this as I work with all the partner agencies very closely, like NIH and CDC -- FDA, you know, it's said all the time that FDA, for being responsible for overseeing a quarter of the country's economy, being in a world of zero-tolerance for all the challenges that we face, whether it's salmonella in eggs or getting flu vaccine in time, these are all scientific issues with science at their base.

Every decision we make is a scientific decision. Even enforcement decisions should be based on science. And the

quality of FDA's decisions is based on its scientific capacity and excellence.

So we have a big rebuilding and building job to do. FDA internally needs more scientific capacity. You know, when I came to FDA from academia, I said, gee, I deal with a dozen -- I went from running infectious disease, including on a transplant unit at a wonderful transplant center, to dealing with some of these daily public health issues, and all of them were much more complicated and challenging and had equal or more at stake than the complicated decisions we make in the academic healthcare arena.

So, we need really good people. We need to make it an attractive, independent, proud agency.

And I was delighted to see a *New Yorker* column about a month ago that was going on and on about all the broken regulatory things. It actually said there is this success at FDA, because people see themselves as

scientists and as protecting public health.

So, we need to rebuild internally, but we also, like everybody in this room, recognize that we want to and need to collaborate more. We want to really build this relationship with NIH, and Peggy and I are very excited about the work we're going to do with NIH on this Council, how we have worked with Amy in putting out a Request for Applications to try to get the academic community interested in the kind of applied regulatory science we need to have better methods and evaluation tools.

And we would also love to, and we have proposed starting, a network of Centers of Excellence in regulatory science where we could try to build training and capacity in academia that, I think, would also help NIH in the long-run gets its job done, because, you know, we just all have different perspectives and things we can bring to the table.

MEMBER RUBENSTEIN: Other questions

for Jesse or Dr. Baum?

(No response.)

If not, thank you very much.

DR. GOODMAN: You're welcome.

MEMBER RUBENSTEIN: That was very helpful.

So, we have our first panel discussion, as I mentioned. I want to thank the participants for coming today on relatively short notice.

And we have two moderators who are going to run the program, Steve Katz and Bill Brody from the SMRB.

Would you like to introduce the members, Steve or Bill, or however you would like to do that, and then moderate the session?

MEMBER BRODY: I think everybody has a list of their bios, and in the interest of time, Steve and I decided we probably would just jump right into the discussion.

I want to again thank you for

coming. I know many of you have really rearranged your schedule to be here.

I thought what we would do -- and Steve and I as moderators, neither of us is described as moderates.

(Laughter.)

But our role is simply to make sure that everybody has an opportunity to weigh in.

I think, clearly, what we have heard is that business as usual for the pharmaceutical industry and drug development is probably not the right model, and there's a new paradigm. You heard some excellent thoughts from Dr. Baum and Dr. Goodman about this, and there will be more discussion.

What I think we would like to do is just to start and kind of go through the questions and let each of you comment first. Then we will sort of work it as-is, as it comes.

But I would like to ask each of

you to comment very briefly, since we've got a large number of you. What do you think is the new paradigm? Or how do you react to what's been talked about?

And I should point out we've got everybody here from Wall Street to basic science in academia, to public policy advocates and patient advocates.

So I'm curious to hear what your thoughts are about how to fix the system or change the system that everybody, I think, agrees is in need of dramatic reform.

Shall we start with Dr. Berger, Wall Street, first?

MR. BERGER: I'm not a doctor.

(Laughter.)

This has been very illuminating for me, and I'm delighted to see that there's so much interest here at the NIH, which I respect a great, great deal.

My background is in underwriting biotech companies and then helping people

invest in biotech companies large pools of capital, and now working on Boards and with the business development. So I feel very much in the mix here.

What's happened in the real world, as much as I enjoy understanding the science, industry has already adapted to the changing reality. One of the paradigms I see is something that Bristol-Myers has taken up, and the early beginnings of the biotech industry, which is where I started following this industry in the eighties.

The companies were what some investors call specialty pharma companies, and they chose to use translational research not because of its elegant beauty and scientific merit, but because it's a better business model.

To give an example, in the multiple sclerosis business, why did Biogen succeed so well? They chose a distinct patient population that had a large unmet medical need

where the needs for a perfectly-safe drug were much less, that a relative modest improvement would be dramatically appreciated by the patients, by the society, and would be rewarded to the shareholders.

And this is what has made the small company biotechnology model successful, both commercially and scientifically. That has funded a large industry that has gone from almost no biologics to approximately $40 billion in biologics, and still growing at 20 percent. So, I think that has already happened.

Some of the bigger biotech companies, such as Amgen and others, Gilead, have experienced dramatically decelerated growth as they've gotten to larger sizes.

A couple of light-bulb moments for me that came up was listening to Dr. Goodman. The difference between a translational trial that's exciting and successful and illuminating and a registrational trial that

creates a company or allows you to develop a business model are entirely different animals.

What I heard Dr. Fauci talk about, and Dr. Collins, is creating an alliance or a point of tangency between the NIH and the FDA, so that the difference between a translational trial that's a great publication and a great clinical trial that gets you onto the market as early as possible is a real positive for me and for other investors to see that harmonization.

MEMBER KATZ: Thank you.

Dr. Duncan?

DR. DUNCAN: Ken Duncan. I'm a Senior Program Officer with the Bill and Melinda Gates Foundation.

I would just like to make a few comments relative to our position. We are investing in neglected diseases, so diseases for which there is clearly no threshold market, and that's why there are no solutions in developing countries.

And we have actually invested in a relatively small number of therapeutic areas, but we do address issues like malaria, TB, some of the neglected diseases, diarrhea. That's pretty much our portfolio.

And that touches on both the really immediate and urgent issues, which are own drug resistance, where existing therapies are failing. So, things like arythromycin resistance in malaria is the sort of thing that keeps us awake at night, but also XDR-TB and the complete failure to be able to treat TB patients today in some areas.

But we also focus on the longer-term and some of the more transformational types of medicines. So, with our malaria eradication agenda, we then stop to think about, how do you eliminate P. vivax and just treating acute disease. With TB, we have to think about how we shorten the course of therapy.

So, it is a bit of a balance

between different things. And that brings us into very close proximity with a lot of folks at NIH and other funding agencies' funds. We try to look for gaps where we can use our funding in a more catalytic sense to do things which other funders don't do, but we also try to look in partnerships.

So, some of the things that resonated with me, and which I would say are really critical, are integrating efforts much better, having the funders aligned. So funders like NIH, the Foundation, and that's both the extramural funding, intramural funding, and also bring in the pharma industry together. So, the only way we will really make serious progress in the neglected disease space is if everybody works in a much more cohesive and much more coherent way than the current sort of very disperse ways that things happen at the moment, which are both inefficient and unlikely to get us the products that we really require.

So, building multidisciplinary teams all the way through from early discovery right through to the clinic is really important. At the moment, there's an awful lot of handoffs and a lot of things which are done imperfectly. When products are getting developed, we have to actually start to go back a step and often redo things.

We work through grantees, and our major ones are some of the product development partnerships. And they have an opportunity, I think, to really work much more closely with NIH.

And I was really struck with the discussion around the Clinical Center this morning, as to how little we are actually doing in that space. A lot of people, I think, just don't realize a lot of what the capabilities are. We have accessed this to a certain extent, but not really as much as we could do.

And there are areas, I'm sure,

where some of that type of research and funding could be used in a way where the Foundation wouldn't necessarily want to fund things and really to expand the number of things that we're doing.

Because we also face the whole attrition area. We know that we don't have that many shots on goal. We know that, although we're bringing a number of products through, we're going to lose a lot of these at some stage.

And very often, choices are made at a very early stage, and that is what you are really faced with moving right away through the pipeline. Instead, it would be much more productive if we were to take many more molecules through into human trials and get some early clinical data and make the best choices from those molecules for what things to really move forward. We are often faced with just making choices based on animal data.

And what else? The issue around

pre-competitive areas is really critical to us. It is a constant frustration to me to see how much is done over and over time and time again because information isn't in the public domain. And so, trying to build the tools to allow researchers to put things in the public domain could be a real useful role.

But, also, to try to encourage people to engage in the public domain in ways in which everybody can then be working on molecules, so we have a chance of success, instead of everybody having their own little collection of molecules which they will screen over and over again.

And what comes along with that is repurposing molecules. We have tried really hard to work with pharma companies to look for ways of taking molecules that have been really advanced for one indication and turning them over to one of our indications. I think there can be a lot more integration in that in the anti-infective space.

And just two final things to finish on. One is combination studies. This is a real critical issue for us, where we may want to take some combination therapies through into the Phase III clinical trials.

There's a major effort in the TB world at the moment to look at this. There's an initiative called CPTR or Critical Path to TB Regime Development. That is being done very closely with the FDA, but it is basically making the recognition that, if we are going to get a better new combination TB therapy, the way to do that is to test the combinations upfront and not test individual products and then do replacements.

Then the final point, just to touch on this, is the biomarkers area is also very important to us. I think that's something -- we can't invest that much in biomarkers, but it's a really important issue that we recognize all the way through the projects that we do. And trying to build ways to build

on the networks of biomarker researchers at NIH would really help the Foundation tremendously.

So, I'll stop there.

MEMBER KATZ: Thank you very much.

Dr. FitzGerald?

DR. FITZGERALD: Thanks, Steve.

Well, I think this is a very timely topic for consideration. To come back to your original question, my thoughts in terms of where the future model will be is to move towards a more modular approach to drug discovery and development.

Given the highly heterogenous skill sets that are necessary to take a basic discovery through to an approved drug, it is no surprise that the best people in the world at those various components do not reside within a single company, a single university, or, indeed, a single country.

So, I think the promise and the potential of the future is that we will move

to a more plastic paradigm of, if you will, shifting coalitions of the willing around particular challenges, with modules being drawn from conventional pharmaceutical companies, biotech, and the academic sector across geographies.

I think we have nice examples of how that can work, actually, from the altruistic sector, where, driven by both altruism and perhaps the prospect of not earning much money, people have been willing to collapse the very outmoded structures of intellectual property that restrain the interactions across those sectors presently. So, I think that is really the promise.

Then, of course, a major role for the NIH is to empower and develop the capability within the academic sector to be able to play an appropriate role within such a modular approach to discovery and development.

MEMBER KATZ: Of course, one of the questions is going to be how to address some

of these challenges and catalyze moving forward. We will come back to that as the panel continues.

Eric Perakslis.

DR. PERAKSLIS: Thank you. Hi.

As an informaticist and an R&D CIO at J&J, the first thing that came to mind is I was really excited to hear the talk about open source. I think we have to be tenacious about this. This is really a big opportunity. There's a lot of things that we should be sharing.

In fact, we will be back in a few weeks. Barbara Mittleman is hosting us to look at some of the stuff that we would like to put out in the public as a company.

Similarly, I think the idea of biology getting more and more pre-competitive, I do think it's the right way to go. I think a lot of companies are taking this move themselves. And what IMI is trying to do, although they're hitting some obstacles in

Europe, I think there's some interesting notions there about drug targets possibly being pre-competitive, in many ways being pre-competitive. It's something that is important to think about.

We're also very interested in biomarkers. I spend a lot of time working on them.

I think we also have to be open, and we are thinking about what may help NIH to meet some of the challenges there. We have the risk of subsetting down to extremely expensive therapeutics that work on a very small portion of the population, having to co-develop your diagnostic and your therapeutic at the same time. It's not a reason not to do it, it is just it is something to think about.

I like the example of the rare diseases, especially about, you know, there is something really fundamentally interesting in this rare disease biologically that may be applicable back into a larger biological

setting. So, I think that's really, really important in making it meaningful.

You know, another thing I say interesting about this compound repurposing -- I've done a lot of science and technology of the literature. The interesting thing about the negative data is you can almost always believe it.

(Laughter.)

If someone ran a study and the drug didn't work and they published it, really, if the model was good, you've got a lot of biology there. There all the types of ways you can look at literature and find out that, well, if this biology is good, it could cure 20 different things. Well, maybe it could, and maybe there's some evidence for some of those statements. But if you mine the literature, a lot of the negative data is extremely powerful. So we shouldn't discard the trial that didn't work. We should be trying to learn from that.

Thank you.

MEMBER KATZ: Thank you.

Ms. Selig?

MS. SELIG: Thank you. I appreciate being here.

I'm going to give a little bit of the perspective of the nonprofit venture philanthropy trying to fill the gap in sort of the real-world model.

The Melanoma Research Alliance is very new. We are just finishing our third year and have sort of been incubated in the image of FasterCures and the Milken Institute. We have founders who have significant resource and incredible passion.

And they took a look at the existing paradigm for delivering outcomes for patients and felt that it was sorely lacking and wanted to do something about it. So we were founded, and what we do every day is look for the best translational research that we can find and fund worldwide.

And we don't care about intellectual property. All we care about is funding the most promising studies.

And in doing that, we have become the largest private funder of melanoma research in this country, having funded about $22 million in three years to 50 projects.

So, a couple of things that I was struck by, and I have a lot of synergy in what I was thinking with my colleague from the Gates Foundation. I think that, from my perspective, and I'm not a scientist, but just sitting in this incredible place, this is a time of amazing opportunity, finally, for melanoma.

So, what we would like to do is work with the NIH, with the NCI, with the FDA, with industry, with anybody out there to say, how can we accelerate the progress that maybe is finally starting to happen?

One of the things that we have done in our latest Request for Proposals -- we

generally fund academic institutions and individuals and teams -- but we have gone out to say we want to leverage the dollars that we can put on the table against what we might encourage industry to do working with these academic investigators.

So a novel kind of partnership award that we want to fund -- and again, because we don't care about intellectual property for ourselves, we really want to encourage people to just get there faster.

And the other point that was made -- and we have begun a really good dialog with FDA, and we welcome the opportunity to work with NIH and NCI -- is this issue of combinatorial therapies and how do we accelerate progress, especially when you have compounds that are in multiple companies. And obviously you have a desire, which we totally understand from the market perspective, to bring something to market as an individual agent, especially in a field where there's

been virtually nothing for decades.

But at the same time, we know that it's probably not going to be one agent that is going to be the answer for these patients. So, how do we encourage companies to work together? And are there things that the NIH can do, that the FDA can do, that we can do to break down those barriers, so that it is not a matter of a completely sequential process? But are there some things that we can do in parallel process to accelerate this?

And I'll stop there, but I have some other thoughts for later.

MEMBER KATZ: Thanks very much.

Mary Woolley?

MS. WOOLLEY: Thank you, Steve and everybody. I must say it's a delight to be here with people who aren't moderates, who are passionate about and driven to make sure that research accomplishes its promise for health. I think that, in fact, exactly encapsulates what the American public wants.

The points I thought I would make are more at the 30,000-foot level around your question for thought here about, what do we need to catalyze, implement, and sustain any new paradigm? Ultimately, what we need is the support of the American public and its elected officials and other policymakers.

We need that support so the resources are there and a positive policy environment is there. And we're only going to get it by engaging the American public every step of the way.

I think you heard perfectly well from Wendy about the value and the intelligence that the private sector patient groups, the volunteers, can add to the process. And that's entirely consistent with what the American public is saying through public opinion polls, which you may know we commission on a regular basis. So, they want to see more public participation via patients and patient groups in the science decision-

making process.

I would also say they also want to see less congressional involvement. And I think that is probably because of a negative feeling about Congress generally these days.

But I want to also just mention a few other things to keep in mind at the 30,000-foot level, some things that haven't changed and some that have. I find them quite interesting.

One is that people continue to see, overwhelmingly see the value of science and scientists. And one new thing that we have been taking a look at, we found that people see the value of what we would call in this room regulatory science, and they want Congress to find ways for academia and industry and Federal agencies to work together to accomplish this.

Now, people are very mixed in their views about what's more important, speed of regulatory approval or safety. It's been at

about 50/50 for a long, long time, and they are looking for experts to help them wend their way through deciding what's more important. Ultimately, they want both, and that's where we get back to the power of putting more evidence to work and regulatory science support.

There's strong support for cooperation and coordination among the various aspects of the science enterprise, academia, industry, and government. And this flies a little bit in the face of concerns about conflict of interest.

I personally think that those concerns boil down to people being unhappy about, angry about bad actors in the system, and of course they should be angry about it. But, ultimately, they want the various aspects, parts of the enterprise to work together.

People also say that not only do they support basic science strongly -- that

hasn't changed for 25 years at least that data has been collected -- they're also strongly supportive of clinical trials, again, a little bit in the face of some of the things we see in the media and elsewhere and so-called conventional wisdom about resistance to clinical trials.

In fact, what people say is the main reason that they haven't been engaged in clinical trials, clinical research generally, is that they haven't been asked. Only 6 percent of the population say that their medical provider, their physicians ever talk to them about research of any kind.

So, getting into the conversation, talking more, everybody involved in the science community needs to do a better job of talking about research. Sixty-three percent of the American public can't name a living scientist. A similar percentage can't name anyplace -- anyplace -- where science of any kind is conducted. Science is a little too, a

lot too invisible in our society, given the way people value it. So, it's really time to put that human face and personal story of science out there, because the public will embrace it.

So, I would say to NIH and FDA and everybody in the science enterprise that, in order to speed the day that more resources and a better policy environment is available to us, we all need to be talking more about research and development and delivery of products, i.e., outcomes and solutions and answers and better health, than only talking about research.

There's a change in my own thinking. I think it's increasingly necessary, and I think we can do it.

MEMBER KATZ: Thank you, Mary.

Bill?

MEMBER BRODY: Okay. I was going to take my moderate hat off and say, look, this is a systems problem. We have the issue that

Dr. Baum mentioned. It is not the cost of getting an approved drug through; it's the cost of all the failures that are both infant and adult mortality.

We have a problem with time to approval, and you have the FDA, which really views safety as 90 percent and is risk-averse because of the way they operate and report to Congress. I'm not being critical of the FDA. I think you get called on the carpet when things go wrong. You don't get praised as well when things go right. And it goes back to Kahneman, the economist, who said people were more worried about risk than they are about gain.

Then you have the issue where companies are going abroad to get their FDA approval. And then we have a conflict of interest.

But the topic today is really, what can the NIH do with the Cures Acceleration Network? So, we have to figure out, what are the levers that we can pull,

that we might be able to pull, that could implement what is otherwise, I think, a big systems problem which is bigger than all of us to try to solve?

So, I would like to kind of open it back up. I think the comments were all very helpful and insightful, and including Dr. Goodman and Dr. Baum, to weigh in: what should be the role of the NIH in this?

And I don't know, Arthur, do you want to intercede now or do you want to wait?

MEMBER RUBENSTEIN: I'll wait.

MEMBER BRODY: Okay.

MR. BERGER: Could I begin by asking a question? What is the interface right now with private enterprise, private companies, private pharmaceutical companies, and the NIH right now?

I know there are many interfaces and scientific meetings and presentations, but harking back on what Ms. Woolley said there, there seems to be a large possibility for the

NIH to sell itself better or interact more fully with the private industry stakeholders.

MEMBER KATZ: So, I think the answer to that question would be, could be answered by many of the institute Directors here, starting with what I mentioned with regard to partnerships in pre-competitive, building research/resources that many can use.

Other partnerships, maybe Tony and Susan can just provide examples of those.

MEMBER FAUCI: It really varies enormously, the spectrum, from very close collaboration at the clinical trial level with a product that a company is developing either for licensure or, less likely, companies tend to like to do it on their own, to how to use the combination of drugs like with HIV. That's one.

But the one that I find, I think, the most productive is something we're just beginning to accelerate more now. We have been doing it in drips and drabs. It's to try to

get a concept from one of our basic researchers who might publish a paper that they would only think: I'm going to publish it in *Nature* or *Science* and then I'll go to my next paper. It's to try to get that on a track towards translation and development by providing for them research, resources, animal models, linking them to the regulatory process.

And this is one of the things that Jesse was alluding to in his comments, is something that we're now calling the Concept Acceleration Program, of trying to have the NIH as the basic science aspect of it, even though we do a lot of clinical translational research, to try to link them to companies to ultimately develop it.

So I think that the spectrum is large, but I'm particularly attracted by that aspect of what we have been doing for the last year or so.

MEMBER SHURIN: I think that one of

the key issues is certainly the huge focus on the scientific issues and looking at mechanism. That's why the waste of information from not learning from the failures is so distressing to us.

At NHLBI, we have a lot of interactions with industry. Most drug development in recent years has been, particularly in cardiology, has been in industry and not by the NIH.

And our focus usually is on the kinds of things that industry won't be interested in. So those are often rare diseases or disorders in which there's not a huge profit margin for any of a number of reasons, including the fact that things may no longer be on patent.

And the issue that somebody mentioned about combination therapies where you have different companies is certainly one of the things that I think is of particular interest to us.

We also know that there is a tremendous amount of stuff which is of both scientific and clinical interest to us in which there have been studies that have never been published. And those create tremendous difficulties for us, because often we're asked to fund studies which we think have probably already been done for which there's an answer, but we don't know what they are.

So I think that those are the kinds of areas in which an intersection with the NIH -- we would love to provide the mechanism to both learn from the science and learn about the diseases while studying drug development.

MEMBER KATZ: So I would like to go back to the question that Bill asked in terms of how you see the NIH facilitating this type of interaction or being involved, to address some of the challenges and to catalyze the path to translation.

DR. PERAKSLIS: I can try to take

that. A few things that came to mind, you know, one, I talked about the open source thing again, right? It's very difficult for me to give data away when I want to. You know, taking support from a pharmaceutical company for certain investigators at certain universities is tough. Some companies have chosen to spin off a nonprofit, which you could do, and possibly NIH could be somewhat of a convener or an honest broker for some of that, to set up some of these consortiums. That might be a possibility.

The other one, as I think about translation, and I really focus on it, really the translation part is really going across different scientific and medical domains, right, and making decisions in pre-clinical that now become hypotheses in clinical.

You're also potentially propagating error as you go, you know, as you look at studies translational, so you're looking across those ways. So I think a lot of

biotechs and biopharmas and even pharma, when we're very therapeutically-focused, may not be seeing some of those larger areas that could be propagated in. So I think there's something there.

And the concept of patient solutions versus products, I think a lot in industry think about products, not so much solutions. So oncology products that are mixed with skin care and are mixed with a nutraceutical, you know, is an interesting thing. Or not only common with therapeutics, but, again, the combination of diagnostics with something or a device and a delivery system.

So, if you point to science, the way to translate across looks like some opportunity that came to mind.

MEMBER KATZ: Yes, Ms. Selig?

MS. SELIG: Just one thing I might add, again, from my perspective, that might be a useful thing. I know you're going to have a

session later on today, or maybe it's tomorrow, in terms of communicating with the public.

But speaking from someone inside of a nonprofit that's trying to do innovative things and isn't maybe as encumbered, in fact, isn't as encumbered at all as the NCI is or NIH or even these academic institutions that we fund, you know, I would encourage as much as possible better outreach.

Sometimes groups like ours get sort of pigeonholed into kind of the patient advocacy space, and there's sort of a certain kind of dialog that occurs, you know, a particular set of staff in a particular office.

I sit on the NCI DCLG, and I admire and I think that that's a very important function that happens. But in this space, maybe it's a little bit different. There are groups like ours -- there's a whole slew of us now out there, not just in cancer,

but across diseases -- that are doing really innovative things in terms of finding and funding research and trying to develop collaborations and break down barriers.

So, I would welcome an enhanced way to understand all the different pockets of NIH that relate to what we're doing, and, also, to know that we are really making the best use of our limited dollars to leverage what you are already doing.

I don't have a specific example to bring to mind, but I feel in my short time doing what I have been doing, I find it very confusing, all of the different programs that exist, pockets of this kind of work that are going on.

I know it's difficult. It's a big enterprise. It's trying to do a lot of things. But perhaps we can be helpful if we could expand our dialog.

MEMBER KATZ: Thank you.

Arthur and then Harold.

MEMBER RUBENSTEIN: And I wanted to ask this question, although it will sound nihilistic, I think. I just wonder, having thought about all this for a while, how possible it is that all these things we're talking about, all this money, all these collaborations, all this issue about intellectual property, actually won't make any difference in the long-run. And what actually the issue is, there are just cycles of science that allow drug development to occur, and then there are periods when it won't occur. And all these things that we process don't actually make much more than marginal difference.

And I've been impressed by looking at people looking at the economy, and they have all these views of what affects it, but then there are people who think it just goes in cycles, and these other issues do moderate it some, but they're not the critical issue in terms of long-term view of it.

And I just worry that we'll do all

these kind of things, and on the margin they may be minimally helpful. Eventually, because of all the basic science and the genome information and so on, all this will come together, and we'll have another beautiful period of drug development, and we won't have any impact on what will come out.

I hate to say it, but I would really like to hear what some of the scientists think about that kind of thing. Because we have had such an effort and so many brains and so many ideas about all this, and it seems to make rather little difference at this time. But that may just be a sign of age or something; I don't know.

MEMBER KATZ: But don't you think we have to try?

MEMBER RUBENSTEIN: I didn't say we shouldn't try. I'm just saying the try will have rather minimal effect, and eventually the science will come together to allow us to develop all these things as we always did. And

we'll say it worked.

(Laughter.)

MEMBER KATZ: Harold?

MEMBER RUBENSTEIN: I would just be interested in people's ideas about that.

MEMBER VARMUS: My hand wasn't up, but I will respond. You just think I always want to say something?

(Laughter.)

But I will say something in response to Arthur, which is that, you know, regardless of whether you think this is a cyclic phenomena that is beyond our control or not, we do have something that is on the table here that I think NIH needs to hear about from these folks. That is the Cures Acceleration Network.

There is going to be money given to us, and it will be taken out of something else rather than added on. But, nevertheless, there will be an imperative to do something. Those of us around the table who run some of

the larger institutes already have a fair amount of investment in translational and therapeutic development programs.

I'm trying to understand, and I'm not getting the message yet, what our invited experts think NIH should do with added money in this area because it's not a trivial exercise. It's likely to be $50 million in the next year's appropriation. Viewed from the perspective of any large drug company, as you have seen, that doesn't mean anything unless you invest it very, very wisely.

So, I would like to know in a more pragmatic way, and I've been listening to discussions about how academic and government scientists get involved in drug development, make connections with companies, and so forth, but we suddenly have a very specific challenge given to us by the Congress, in a sense the public. I would like to know what you think we should do in response to that.

MEMBER CASSELL: Harold, I'm not

sure they know about CAN and how much they know, maybe to answer that question. They do?

MEMBER VARMUS: I don't know.

MEMBER KATZ: Tony? And then we're going back to the panel.

MEMBER FAUCI: So I will continue to direct the question and amplify a little bit what Harold just said.

So, I'm hearing a bunch of things that I've heard a thousand times, if I might just say so. And that is there are multiple issues here, two major ones.

The problem globally, industry, academia, what have you, of getting products translated, of success in developing interventions, be they diagnostics, therapeutics, or vaccines -- that's there. That's a given.

Then there's the specific issue that we need help on. How does the NIH get involved in or improve its contribution to the translation towards these interventions?

And there's two subsets of that. There's the question that we not infrequently get asked: tell me what drug or what vaccine, or whatever, the NIH developed. Well, fundamentally, it's not our job to do that. It's our job to create the science to allow industry to do that.

So, sure, there will be an AZT that will come along that we'll develop or there will be a dengue vaccine that we develop. But, for the most part, the interventions are going to be developed by industry.

So, it would seem to me that in the issue of how we're going to use the CAN money that Harold was talking about, it is, how can we, NIH, use what we do to actually get involved in that translational process that ultimately has to involve industry?

It's fantasy to think that we're going to take $50 million, or whatever million dollars, worth of CAN money and in the

Clinical Center or someplace else we're going to develop drugs. I don't see that.

So, I would like to hear from you how you think we can work together to get the process of cures done as opposed to we develop a cure; you develop a cure.

MEMBER KATZ: Hold that thought.

Francis?

DIRECTOR COLLINS: I just want to make one friendly amendment to Harold's question to expand it a little bit beyond CAN. While CAN is the new kid on the block here, this $50 million that will probably flow next fiscal year, NIH has been developing and has actually some fairly powerful additional resources that fit into this conversation, including high throughput screening through the four centers that do that, that have the capacity of mid-sized pharmaceutical companies as far as throughput, and the ability, therefore, to train academic investigators in how to do assay development and application.

Add to that the Therapeutics for Rare and Neglected Diseases Program, TRND. Add to that, also, things like the GMP facility at the Clinical Center that we talked about earlier this morning, and the Clinical Center's capability to do Phase I and II trials, and the CTSAs which have that capacity now, some soon-to-be 60 of those across the country.

So, don't limit your answer to the question about what NIH should do just to the CAN part, which is sort of focused on the pre-clinical part. But what about this whole pipeline of opportunities? What should we do, what could we do, what might we do to be synergistic with what already exists in the private sector, but to speed up the potential here, especially with all of the new drug targets that are emerging for both rare and common diseases that are not all being followed up on right now?

So, that's the broader question,

but I sure would love to hear specificity in responses, if you can.

MEMBER KATZ: So, Garret, as a professor of translational medicine and therapeutics, do you want to start us off?

(Laughter.)

DR. FITZGERALD: So I hesitate to scoop myself as I'm stuck with giving a talk after lunch. But briefly, I will say that there are very concrete things that the NIH can do.

I really believe that there is a huge problem in terms of human capital. The number of people who practice, who pursue science nowadays in a way that straddles the translational divide, and in their own experience integrates the rigor of basic science with the practical realization of clinical research, has diminished alarmingly. And the number of those that know anything about drugs is almost down to counting on two hands.

And I think we're paying a huge price for that. Those people play a catalytic role at the point of greatest failure in drug development, which is proof-of-concept in Phase II. They are the people who understand mechanism and extrapolate the information from model systems into sophisticated science in humans.

And I think that is very pertinent to our failure to realize the potential of the great strides in basic science and translation to therapeutics. I think it's very relevant to our limitations in terms of risk detection in regulatory agencies. I think it's very relevant to the fact that our physicians get their information about new drugs from exactly the same place as our patients do, and that is from direct consumer advertising.

And I think it's extremely relevant to comparison effectiveness, where expertise in this domain plays no role in this country, but does in the UK, for example.

So I think human capital is the top of the list. It's a role that the NIH can play a central role in.

I think in terms of programmatic investment, I think a really important thing is actually aggregating the existing resources and expanding them, but in a way that is, then, bundled and visible to the relevant community, and intertwining that with initiatives to develop critical mass in TMAT, because these people have to have a career path.

And more importantly, they have to be engaged by thinking this is the really hot area of science, and that's why I'm going to sign up and train in it. And presently, that's absolutely not true.

So we have a very segmented scenario at the moment, and it is people that make things happen rather than structures. So I would really put the emphasis on people.

MEMBER VARMUS: Can we follow up on

that a little bit? I may?

Are there some very specific programs that you would view as models for the kinds of training enterprises that work well?

DR. FITZGERALD: Well, I mean, again, I'll talk about this when I talk.

MEMBER VARMUS: Okay. Fine.

DR. FITZGERALD: But I mean, just to answer specifically, for example, and as I'm sure you're aware, the Wellcome Trust launched a program about three years ago now where they funded four centers in translational medicine and therapeutics, where the academic bidders were encouraged to have close interaction with industry in their bids -- that was actually a requirement -- and where the focus was on creating this type of interdisciplinary skill set in a new workforce.

DR. DUNCAN: So maybe I can address some of the neglected disease issues. I mean, I mentioned earlier, you know, we just really

need more effort in this space, but that is not the answer you are looking for.

It's not simply just building more capacity and more projects. It's more about thinking smartly about how you pull these projects together. So, how we bring together the best of the private industry, who is not really going to invest that much in this space, with the best academic researchers.

And some of that is actually about doing things which are already being done and taking concepts and pulling them into potential products.

What has tended to happen is that you have this huge expansion of genomic information, and there's hundreds of targets here. The thing that was recognized fairly early on in the commercial markets, and this applies exactly the same in the neglected disease space, is that it's all about just a small number of well-validated targets.

And yet, trying to get the tools

and the information together to get those well-validated targets is very, very hard. It tends to be done today by individual academic investigators who are doing one target after another, and that's what they make their career. Even if it's not well-validated, they'll still continue to pursue it.

Whereas, what we really need is a more integrated, more comprehensive type of effort in some of the neglected disease space that we just do once and for all. Build the right set of tools, get the small number of validated targets, and then do a huge effort behind doors, where you know you're likely to be much more successful.

So, I think a more focused effort would help. And I think that building the teams issue for me is around saying, can you get the right expertise to work with the investigators who've got the right tools? Because, again, at the moment, it's often they're around saying we need one piece of

information. So there may well be an NIH contract. You can look to that contract, and you can be lined up, and eventually get that piece of information.

Sometimes it takes a long time. The feedback I hear is that it takes a long time, and it's not necessarily with a lot of intellectual input, which is often concerning as well.

So, in other words, without designing the right study, sometimes you get half the story because you may, for example, look for some pharmacokinetics around something, but, basically, what you can get is one type of data and not necessarily address the specific question that would help move a project forward.

So, that comes back to the issue of, I think, having fewer types of projects and more focus on things which are actually needed in the clinic and not necessarily some of the projects which are interesting, but

would never necessarily be taken up by industry or taken up by any of our current development partnerships, because they address a therapeutic need that's, quite frankly, interesting, but it is not really what is the critical need in that particular area.

DIRECTOR COLLINS: Can I just come in briefly and just ask a question? Because one of the features of the Cures Acceleration Network is to give NIH, at least a part of the funds, the ability to function in the way that DARPA does, where you bring in a project manager that is authorized to acquire resources when needed and a quick turnaround time, and also to kill projects quickly that seem not to be meeting their milestones.

Are you referring to that kind of model as something that's currently missing? Would you want to comment on that?

DR. DUNCAN: That is the sort of thing that I think is needed. Certainly from my perspective, to a certain extent, we at the

Gates Foundation are able to work that sort of way where we can move resources around a bit more easily. But I think there is that making quick decisions and moving the funds to where they're needed.

MEMBER KATZ: Go ahead, Gail, and then Jesse.

MEMBER CASSELL: I am a little bit out of my league here, but what I would suggest, Francis, is that one area that I see as a potential opportunity for NIH is perhaps a greater investment in the whole area of chemical diversity and bringing back the natural product that so many of the companies got away from.

Other countries, China, South Africa, and others, are investing heavily in building natural product libraries. But yet, we don't have good chemists, many of them, experienced in natural products.

New technology in the area of synthetic biology, like the Vintra Institute

is exploring, I think, and the possibility of being able to increase chemical diversity using that technology would go a long way.

And the other area, I think, that I see is more research in issues around bioavailability. If you look at the biggest losses, particularly in development of anti-infectives, but also oncology, and all therapeutic areas, this issue of non-oral bioavailability, new mechanisms for drug delivery, aerosol biology in particular -- I realize that some of this is controversial, but I think we still have yet to fully explore. You know, aerosol delivery is a great alternative to issues that challenge oral bioavailability as well.

MEMBER KATZ: Thank you.

Jesse?

DR. GOODMAN: The major comment I wanted to make is I think, as you do this, you should build on what is NIH and the academic community that it is most connected to. You

know, what are the strengths and how do you link those to the other parts of the system?

And this is kind of going to Garret's comment. I think you could spend -- but a little beyond it -- I think you could spend a lot of energy trying to change a horse into a giraffe, and in reality this isn't that much money. And the thing to think about would be, how can you catalyze in areas where there's promising discovery, bringing yourself together with the right people to then get the job done?

So some of that is a DARPA model, but a lot of it is about partnering with the right people and getting them to do their parts of this module and do it in a managed way.

I think a longer-term project, his comment about training is important. However, unless we create a reward system in science and academia that actually rewards the health outcome rather than the individual

accomplishment and the paper in *Science*, that ain't going to happen.

So, I mean, in the long-run, I don't have the answer, but I think we need to think about a model that rewards patient and scientific outcomes other than just publications.

I can't let Dr. Brody's comment go. Well, you said it.

You know, I need to correct a misconception around this. You know, if there are products that work and help people, they will get out of the FDA very fast. There is not a bunch of stuff sitting around that provides radically new or even substantial incremental therapies that our staff would not celebrate getting out as quickly as possible.

I think the problem is, when you have marginal benefits or diseases that aren't that serious, and then people look at risk and benefit in that context, you know the public is our customer and they are concerned about

the safety of products.

I think, as you saw with the rotavirus decision and how that was handled, when we see a product with clear benefit, we're able to look at it and try to weigh risk in a science-based way. That is part of building our scientific capacity, is to assure we make the best risk-based decisions.

But this sort of seconds Arthur's comment a little. I think there is something going on out there right now in the science cycle where there's a lot of incredibly promising science and information that hasn't yet moved forward.

But I think that's a good reason to do these activities, because maybe we're catalyzing -- you know, it's like catalyze the degradation of the oil in the ocean. Maybe we can catalyze the transition of some of these discoveries into science, into products. I think that's the interface where NIH should work.

MEMBER KATZ: Thank you.

You heard that we're not going to go into the billion dollar business of drug development, but this Cures Acceleration Network may be authorized, may be appropriated for $50 million next year, but it's authorized for up to $500 million.

And you've heard what Francis talked about in terms of some of the resources that we have at least to take something that would be more realistic as a potential product.

But I would like for you to respond to where we are with that, more than potential.

DR. BAUM: Yes. I think it's one of the areas that seems to me makes a lot of sense, is in the area of rare diseases. And where you have a clear genetic defect, maybe even if you don't, that you can do the science to evaluate that patient population, that you're sort of uniquely positioned to do that,

to get access to those small sets of patients which no one has enough of to really know exactly what to do, and to do clinical trials in a reasonable timeframe.

So, I think that's something that could be actually a near-term opportunity to show real benefit and real advance therapeutically in a short period of time.

And our company -- there's others that are interested in rare diseases. So forming some sort of consortium around that, I think, would be really a great idea and would facilitate it happening much sooner.

So, I think that's the kind of thing I see as being a unique thing that could be done in the near-term, but I think there's many others as well. And one of the key ones, I think, is around biomarkers and patient selection because, as you have seen many times, it is not always obvious what biomarkers we should be looking at. And if they are not validated ahead of time and you

don't have a diagnostic, you can't really use them in clinical trials. You have to learn through doing those trials what you can apply next time. So you almost validate the test and the drug at the same time in some of these cases.

So, is it possible, using standard of care and looking at patient populations, you could help define biomarkers that will be useful to therapeutic development for those people who are pursuing those particular approaches?

So, I think that background information is just missing in many cases. So I know in inflammation and immunology we struggle to know what to do in lupus. What are we affecting? How can we realistically follow it and know that we can make some kind of effect on a small patient population before we have to do Phase III trials? Those kinds of things, I think, are really also near-term benefits that could come out of the

collaboration with the NIH.

MEMBER KATZ: I would just reinforce one thing that Francis said. That is that, going back full circle to this morning's earlier discussion, the Clinical Center, one of the great resources is the collections of rare patients in many areas.

DR. BAUM: I think that is an incredibly unique asset, and one that you can take advantage of.

MEMBER KATZ: Francis?

DIRECTOR COLLINS: So, I think rare disease applications are, in fact, compelling, and there is the Therapeutics for Rare and Neglected Diseases Program which is already funded, which is just beginning to get started, and maybe we'll hear a little bit more about it this afternoon.

But I want to push you about the common diseases, because certainly in that category we have a lot of new targets, things that are potentially drug-able, but who knows?

If you look at the outputs from genome-wide association studies, which haven't told us very much in terms of big risk factors that are highly valuable for making predictions about future illness, but they are, after all, pointing towards pathways that must be involved in pathogenesis.

And I think most people would agree that there's probably really no linear relationship between the odds ratio of a particular variant in a particular gene and whether that actually is an interesting drug target.

After all, when you look at the cholesterol scan by genome-wide association studies, well, you find all of the known drug targets, including HMG-CoA reductase, although the odds ratio is key. It just means that the spectrum of variation that nature has tolerated or evolution has tolerated in human populations is pretty limited for really important protein products.

So, there are hundreds of these now, and I guess my sense is not only do we have rare and neglected diseases, but we have rare and neglected targets for common diseases.

So, I would be interested in your perspective from Pfizer's focus now on human genetics. Are those targets being adequately mined, or is there a need there for greater activity?

DR. BAUM: So, yes, I would say there is, and I was thinking of it more as different timeframes, and that in the near-term those rare diseases is something to show something clear quickly. But I think the real benefit is down the line.

How can we subset possibly those patient populations with hypercholesterolemia into those that should be treated with particular regimens? That would be incredibly valuable. In diabetes, I think we have similar problems. Who should we be treating and how

with these new agents? And how we might be able to use combinations in particular patients that have complementary pathways that are affected.

So, I think there's lots of that sort of work that would be a huge benefit to the community in general in sort of a pre-competitive kind of research that could be done.

So, I agree, and I think that some of the problems with not being able to show advances in many of these more common diseases is because we're looking at actually five different subsets of patients all at the same time. So the benefits are incremental.

But if we could focus on those patients that show the greatest benefit, then maybe we would have something that's more clear to the FDA. That is a benefit, making the whole process run more efficiently and more quickly for all of us. So, I think those are places that there could be benefit.

In terms of that same question, I think the combinations I brought up briefly, but the combination I think is really a key benefit, too, because you can bring together different companies or academic institutions to have a combination therapy that looks like it's really going to leapfrog over the current incremental single-agent approaches. So, to me, that's another place that the NIH could uniquely get involved and help facilitate that kind of interaction and collaboration.

DIRECTOR COLLINS: If I push a little, because it sounds like you are primarily talking about taking existing targetable pathways and figuring out smarter ways to utilize the agents that come out of that.

What about entirely new molecular --

DR. BAUM: Oh, yes, absolutely.

DIRECTOR COLLINS: -- focused on targets that we haven't previously known

about?

DR. BAUM: Yes, absolutely. Because I think the identification of targets and the biology behind those targets is probably better done by the NIH and academics than we have done. So I think there's a huge opportunity there.

And maybe some of the efforts you were talking about earlier of making that connection, so that the researchers know how to make that next step, that they actually would, and that we would see an acceleration of the wave of innovation. Maybe it will happen anyway, but if we could accelerate it, I think that would be a great accomplishment.

MEMBER VARMUS: Could I build on that just a little bit? I'm glad that Francis brought back the target issue, because it does seem to me that NIH should not be confining itself to rare diseases, and especially in the area of cancer, where the number of targets that we're identifying through the genomes is

enormous.

It seems to me there is a place where some kind of consortia relationship with industry might work, and we've had such relations before in areas, for example, CDA sequence. These are not things that are likely to be detected by IP arrangements, and validating targets is not an easy process. There are an awful lot of things on the table at the moment.

If there were some way for a major industrial firm to collaborate either intramurally or extramurally in a way that would get those targets out there on the table for the public benefit, it seems to me that this is something that we ought to be exploring a little more assiduously.

DR. BAUM: Yes, I agree completely. And one of the things that I was going to ask you, actually, was if you could meet with Jeff Kindler and the head of R&D to talk about something like that, because I think that's

really --

MEMBER VARMUS: I've only been approached by email. I'm not sure this is right for public discussion.

(Laughter.)

DR. BAUM: But I think that it's definitely something of interest, and it's the idea of this consortium. We need more interaction on that front.

MEMBER TABAK: So, just to remind everybody, there is one other asset that hasn't really been mentioned, and that's the Biomarkers Consortium, which the Foundation for NIH has convened.

At the table are NIH, FDA, and industry, including many of the companies that we have heard from today. The whole gist of it is to do things in the so-called pre-competitive space. There have been some successes. Just sitting at the table is a success.

But many of you have alluded to

the need for biomarkers. I'm just curious as to what more you think we need to do. Or is it just we need to do more?

MEMBER VARMUS: We need to do something that works well.

(Laughter.)

DR. BAUM: A lot of things we have done have been talking, but not the true sense of collaboration and where we both have skin in the game, where we really have something that we both have strong interest in. So, you're going to make sure it comes to fruition. I think that's been a problem, traditionally, that it just hasn't come to the next stage because people have discussed it, but not invested in it.

MEMBER BRODY: Dr. Rubenstein? And then I think we'll open it up to the general public.

MEMBER RUBENSTEIN: To move from being nihilistic, my colleagues in the Alzheimer's field, under the aegis of the NIMH

and our relations with industry, have, I think, moved pretty quickly in the last couple of years to develop, first, a very interactive consortium that is very broad and come up with a number of biomarkers that weren't there in the past that they feel very optimistic about.

Leaving aside exactly what one's view of that is, I actually have been impressed by both the collaboration of these individuals, the extent of the consortium, which is right across the country, and maybe it's international, and also the relationship of not-for-profit organizations, the Alzheimer's Foundation, and so on.

When I have looked at that and been to some of their meetings, I must say that many of the things we have talked about here, they seem to be well underway and very enthusiastic and collaborative about. It just may be worth -- that is already in the NIH, of course -- it just may be worth looking at some of the things that have already pushed forward

rapidly recently and taking some best-case scenarios from them. It's just an example that I have found very positive actually.

MEMBER KATZ: Dr. Hodes maybe would like to inform that as well.

MEMBER HODES: No. I am happy to comment again. That will be a topic of tomorrow morning's session when we're talking about public/private partnerships. And among the examples are some of those which have been successful in this. If you prefer some comment now, I would be happy to do it. Otherwise, we will get into it in some depth tomorrow.

MEMBER KATZ: Please identify yourself.

DR. ROWE: Sure. I'm Steven Rowe from the University of Alabama, Birmingham. I'm a CFTR, a biologist, and cystic fibrosis scientist.

I was just going to hearken back to this need for subphenotyping that Dr. Baum spoke of. One of the areas that I've been

thinking about more regularly is that of COPD or chronic obstructive pulmonary disease, and how one of the failures of those megatrials is that patients with severe bronchitis are lumped together with patients with no cough, and have severe emphysema. An improved molecular understanding of that disease could lend itself well to collaborations, both with small companies and large pharma. That could accelerate things.

The second point I would like to make is regarding the biomarkers and hearken back to the biomarkers. Perhaps NIH resources could be directed towards really improving our pre-clinical models, as we've looked, and those that are predictive of translational results.

For example, in CF science right now, there's been a new small molecule that activates CFTR. But, importantly, the pre-clinical model has been very predictive of the in vivo situation, which has facilitated much

more interest from pharma in therapies of that type. So, perhaps it's an area of resources that could be directed.

MEMBER KATZ: Thank you.

DR. BERGAN: Yes, I'm Ray Bergan. I'm one of the panelists this afternoon. I'm Director of Experimental Therapeutics for the Lurie Cancer Center at Northwestern University. I'm a medical oncologist, and I run a basic research lab.

I think it's very important to highlight the point that we don't know what to do. We don't have a clear path forward. There is universal recognition that the process of drug discovery and development is inefficient and it's highly complex, but that's universally-accepted.

I think the key issue that we need to acknowledge before we can go forward is that we don't know what to do. And that, in fact, leaves a clear role for NIH. What government does very well, and NIH does in

particular, is it recognizes large problems like this and devotes resources to them. It basically sets up incubator projects. And this is a perfect scenario to set up such incubator projects.

So, Dr. Collins, what you have done, and done very well, is through NIH, you put in the components of the existing drug discovery and development network. But, as we recognize, those components are not acceptable to us as they exist in their current form. So, basic questions are not answered.

Can the process be improved? And we don't know the answer to that. Everyone in this room, myself included, believes that they can. The facts, in fact, speak otherwise. It affects potentially new chemical entities, and times to bringing a drug from the bench to clinic haven't changed in a couple of decades, despite exponentially increasing cost.

So, I think it is a perfect opportunity to use the resources that could be

coming to CAN and the resources that NIH has to basically put out large programs, U01s, U54s, and hand it out to investigators. Put it in little incubators, and let them come up with ideas.

Put in specific parameters. These are the problems. Make it hypothesis-driven. Answer a question. Require that they interact with companies. And, as always is the case, you will be imminently surprised and amazed at some of the creative ideas that come back.

MEMBER KATZ: So, I would just say that what Francis has put in place has not really been tested yet. So we are not yet ready to talk about failure.

Yes, Rob?

DR. CALIFF: Good morning. I'm Rob Califf from Duke, and I'll be on the panel this afternoon, too. So I'll be brief.

First, I just want to reemphasize what Garret said. And I'm sure, knowing him, he will emphasize it amply in his comments

this afternoon.

I think we really do, at the basic level of person power, a lot of people are being trained to do things, but not that many are being trained to work in this future world that we are sort of describing. It is very noticeable at the level of an individual active medical center, as I travel around and talk to people.

I also agree with this concept that we sort of need -- it is sort of like a 12-step program -- we need to admit that we are fairly ignorant and we are all struggling.

Pfizer used to come to us and say, you know, "We want to buy into your discovery science, but don't tell us how to develop drugs, because we do it for a living and we're really good at it." Now they're coming saying, "We've got too many molecules, too many pathways. We don't know how to develop drugs. Can you help us do that?"

(Laughter.)

Our answer is we don't know, either, but let's try together.

But the point I wanted to make that might be a little different, I'm sure everyone realizes, but I really want to emphasize it: the really critically shortage, to me, is informatics and quantitative sciences.

My response to Arthur's cynicism, which I understand, is I think the new wave is really integrating this amazing amount of knowledge that we are overwhelmed with now that is coming from things we could measure that we just couldn't measure until very recently. And we are all overwhelmed with information coming at us, and we don't know what it means. We are lacking enough talented people who can help us arrange and structure that information to turn it into knowledge.

So, I still don't see adequate funding coming in for training programs in the very fundamental quantitative and informatics

sciences. I think that's our most critical shortage that ought to be emphasized.

MEMBER KATZ: Thanks, Rob.

MR. SIMON: I am Greg Simon from Pfizer. I'm on a panel tomorrow morning.

I wanted to talk about the two comments Dr. Rubenstein made about, "Does anything we do matter?" and what Dr. Fauci said, which was that "I've heard it all before." And what are we going to do with the $50 million or any other million that would make a difference?

I do think we have different eras in science. I think we have been leaving the small molecule blockbuster. And a lot of the failures that come out of the pipeline now were the last gasp of that kind of thinking, which is why so many failed studies now are being walked over to the people who can look at the responders retroactively, retrospectively, and say, what did we miss when we designed this trial many, many years

ago, because we weren't doing that when the trials were designed. We're doing them now when they come out and they fail.

The problem is in the era we are in now in terms of being able to target drugs based on genomic characteristics. We are still operating in a regulatory system that was built in the fifties, a disease categorization system that was designed in the 18th and 19th centuries, and a communications model to the public that came from the pre-internet era.

So, if we don't change those three things, the progress people make on the genomic personalized medicine side is always going to be swimming upriver. As an example, you heard this morning how crizotinib helps certain kinds of basically non-smoking lung cancer patients who have a particular sequence. That should be an orphan disease, but the government says, no, we're not going to treat it as an orphan disease.

We know that lung cancer is not

one thing. If Pfizer developed a drug that cured 80 percent of lung cancers, but did nothing for the other 20, wouldn't they feel orphaned in the world of lung cancer?

And yet, we know the future is not going to be curing lung cancer. It's going to be curing people with this kind of a cancer and that kind of a cancer.

And all of the incentives we have to get people to focus on orphan diseases and rare diseases are not being applied because of disease categorizations that we inherited from the Germans and the French a long time ago.

What do you do with $50 million? What is NIH's role? NIH often has a lot of these excellent consortia for one particular thing. The challenge is, how does NIH become a host of a virtual enterprise where they use that kind of money to administer programs that have begun with the end in mind? A lot of these consortia do not begin with the end in mind. They begin with a particular product in

mind or a goal to identify something in mind, but that is not the end. The end is the therapy to a patient.

So, with all of the great resources of the Intramural Program and the talent in the Extramural and Intramural Programs, if NIH were to host the virtual enterprise made up of the resources that are here on the campus and begin with the end in mind of asking the question, given these resources and given the training we have, which industry groups, which nonprofits, which other countries' resources do we need to invite in for certain kinds of therapy products to be developed? And our role is to make certain that all of those pieces come together; the right piece at the right time from the right place.

Now, that implicates a lot of things. It implicates funding models. It implicates institutes sharing. It implicates conflict-of-interest regulations.

But what are all these resources for, if not to create the base of an enterprise that, joined with the private sector, can accelerate therapy production without NIH having to fund it all? But without the seed and the coordination, if you will, from NIH, there's really nobody hosting that kind of virtual enterprise that links our government, our universities, and our industry together.

So that's what I would suggest it is. We are in an area where a lot of the things we do won't make a difference if we don't change our assumptions. And NIH has a huge future role to play as the host of this virtual enterprise, but it has to figure out, does it want to do that, and then is it willing to organize around that concept?

MEMBER BRODY: Well, we've heard --

MEMBER VARMUS: I would just make one brief comment. I agree with virtually everything that Greg just said. It was a very

useful, thoughtful statement.

But I'm a little concerned that in my earlier comment I overly focused on the $50 million in CAN money. For reasons that actually have been articulated by some of my colleagues, (a) that money, that amount is likely to grow; (b) it actually is only a small amount of what NIH, especially some of the larger institutes, are already spending in this domain of target identification, drug development, basic science that feeds drug development, drug testing, clinical trials, networks on a very large scale.

And I agree. I brought it up. I and many of my fellow institute directors are a little concerned about how the CAN initiative gets coordinated with other things that we're doing, which is a way of saying that the task that Arthur has here is a difficult one.

So I think, while the notion of NIH acting in some kind of coordinated

capacity is fair enough, there is a much bigger issue of what we do with the very large amounts of money, and the Cancer Institute alone probably has a billion dollars or more that is devoted to activities in this domain.

I think a lot of the conversation here is precipitated by the question of what we should be doing with the CAN directive that is now before us. But it raises some very complex issues that my institute, in particular, faces, because we have got so many different things operating, which you will hear about from Jim Doroshow later on.

But Heart, Lung and Diabetes and AI all have the same set of issues. I think there is a kind of strong compulsion for us now to think about new ways for us to work with industry. We think that the game has changed, as Dr. Baum's comments indicated earlier.

MEMBER FAUCI: So, Harold, thanks.

That was really the point I was trying to make about how we can best work with

industry.

CAN is a $50 million issue. If it grows, and it grows while the NIH doesn't grow, it's not going to necessarily be new money.

So what you have to look at is, what is going on? Harold mentioned the Cancer Institute. We have about $1-plus billion in the arena that Harold was talking about.

In the new response that Harold played a role in with PCAST, when he was in PCAST, about how we respond to emerging infections and the development of new drugs, there were some recommendations made about medical countermeasures. In that, there are initiatives, for example, of $33 million for that Concept Acceleration Program, $170 million for Jesse's regulatory science. So it's much, much bigger than CAN.

So I don't know, Arthur, how we are going to ultimately decide to address this, but perhaps it might be good to think in

terms of, what are the multitudinous ways beyond CAN that we can and should interact with industry, for the reasons that I articulated before?

Because, getting back to what I said, we have all heard the problems that industry has in getting products. How can we, the NIH, work with you better than we have been? I would just submit that's the major issue.

MEMBER RUBENSTEIN: It certainly seems to be consistent with Francis' charge to the Committee to look much more broadly. The CAN seems to be the catalyst, but not the end of all the possibilities out there.

MEMBER VARMUS: I would just say that I agree entirely that the emphasis is not just how does NIH work with industry. How does NIH work with itself, get itself coordinated?

(Laughter.)

And actually, it means sharing things among institutes. Some of the things,

some of the discovery units that now exist come out of the OD, the Common Fund. I think your committee has a real charge here to try to figure out how the various components of the NIH enterprise, OD-funded elements that are involved in drug discovery, the Clinical Center, which is probably going to end up under the OD, and the institutes, which have their own programs in the drug development and clinical trials, make a more powerful whole.

CHAIR AUGUSTINE: Yes, I would just like to observe, being one at this table who lives in a kind of different world from most of you, I think that the impact of DARPA, which has a very tiny budget compared to the total defense research and development budget, but it has an enormous, disproportionate impact because of certain features it has, such as investing in high-risk, high-payoff research or translation, which it does.

Another model I wanted to mention, which you probably are familiar with, is

Semtech from the semiconductor industry, which, as it happens, had $50 million a year provided by the government back when $50 million was a lot of money.

(Laughter.)

And the model there was one for pre-competitive research, sharing the research, so every company wasn't duplicating what everybody else was doing. So that when something failed, everybody knew it failed, and they didn't continue on pursuing it themselves.

They had an oversight board that had government members on it who were legitimate scientists themselves. The government contributed scientists, as did private companies.

And it just strikes me that there are a couple of models out there that we might learn from.

MEMBER BRODY: Was the semiconductor effort a success?

CHAIR AUGUSTINE: I think, by and large, it was. Yes, it is controversial, but I would say that I think the majority of people would say it was, in balance, successful.

MEMBER BRODY: We're getting towards the close, the end of the first session, but we're just beginning this discussion, which goes not only for a day and a half, but will probably go much further and, as you heard, is much more extensive.

One of the things that I throw out in jest, one of my favorite books is a book called *Moneyball*. It's ostensibly about baseball, but it's really about how to manage uncertainty.

And if you think about drug development, it's about the same as developing an MVP where, if you hit the ball three out of ten times, you're an All-Star.

And it strikes, when I talk to people in the pharmaceutical industry, that they don't have a good handle on why things

fail, and that there probably isn't a more optimal strategy.

Right now, drug development is run by a group of insiders. We all grew up in the same way. We all believe our own dogma. But I think that there are other strategies that one might consider to optimize outcomes.

I think what we should do now is to give the panelists an opportunity to make one last comment in this session, not the last comment for the meeting.

But we'll just start with Jesse on this end. Don't feel compelled to say anything.

DR. GOODMAN: I think this is a very good discussion. One comment, it's not some concluding comment, but in terms of I do think, if you consider at NIH using some of these resources to build in certain areas, like training, I would think about how you do it in terms of starting to change the paradigm in the groups of people.

For example, I think if you just put more training programs into academia but don't sort of bring other partners into that training, it won't have much impact. That's one example.

So perhaps there should be a training program around product development and evaluation, or whatever. That would also include rotations in industry, at FDA, et cetera, to really start getting people who can think across a much more complex universe than it used to be.

The other comment on information. I share with Rob the feeling that there is a tremendous amount of information out there, whether it's the basic discoveries that Tony alluded to that we're not taking advantage of or it's just the experience ever single day in the hospitals and clinics in the United States, or the experience in every clinical trial which, as I said, we're never looking at again.

So I think investing -- and NIH has made some real contributions here -- investing in working with us and others in building information platforms that can begin to let us use this information, we're really not doing it.

But, again, I think we have to do it differently. I think we have to create a generation of people who have common sense and understand clinical medicine, but also understand information. These are like ships passing in the night.

You know, there is a similar thing with epidemiology and medicine, where people, if the p-value is .05, boy, as far as they're concerned, it's true, even if I can look at it and say this makes absolutely no sense.

So, we somehow need to bring that discipline, informatics and biomedicine, together. Maybe it's too much for humans to contemplate, but I think it's worth trying.

MEMBER KATZ: Mary?

MS. WOOLLEY: Rather than trying to derail the conversation toward public engagement, which is coming up, I know, as another panel, which I can't be here for, I am just going to give some thoughts to colleagues who will be there. So I will pass right now.

MS. SELIG: I guess what I would say is this idea of -- and I want to support what Greg sort of led us to in this conversation, that $50 million is significant, and for most people very significant, when you get outside of the government structure.

But if it's just used to create another program that's not a catalyst for something bigger, which is where the conversation started to go, about getting outside the normal boundaries in NIH, and to the extent that organizations such as ours can be helpful and can be involved in those conversations, I think we would welcome an invitation.

The only other thing I wanted to

say, I didn't get a chance to say before, but with regard to subsets of patients, both within diseases, but also among diseases. So, we have a particular type of cancer in our name, but the learning that's starting to happen about pathways is leading us to think about how can we work with other types of cancers. Maybe it's a breast cancer and a melanoma, but maybe there is some way that we can work together on a pathway and getting us outside of our sort of narrow focus.

And I do think that that is something that NIH can help the community with, getting out of that sort of traditional mindset. So, I would encourage that.

DR. PERAKSLIS: To probably supplement our comment with what Dr. FitzGerald said, one thing that has occurred to me is we have talked about drug discovery costing more in the last 20 years. We haven't actually talked much about why.

It's not because of people,

because there's far fewer people doing it today, which I think is real important. So the point about we need to bring in excellent folks is important.

The other thing that goes into that cost, and I am an informaticist, is technology. I think when we talk about why things work or not, if we're being data-driven, but data-driven means we're really being technology-driven versus hypothesis-driven, there may be an opportunity for balance there.

I mean, one of the things I like to say as someone who does this, cancer is not intimidated by next-generation sequencing.

DR. FITZGERALD: I will say very little except one thing. The daunting numbers in terms of the cost of drug development tend to tear at new initiatives to move to a new model.

But, as we saw nicely this morning, most of that cost is the failure of a

model that we know is unsustainable. So building in the price of failure of a failed model should not deter people from undertaking a radically-new approach to drug discovery and development.

MEMBER KATZ: Thank you.

Dr. Duncan?

DR. DUNCAN: I don't have a lot to add, but just one reflection. Years ago, in my previous life when I was in industry, in looking at sort of programs jointly between industry and NIH, there were some efforts in the infective disease space. It was actually quite hard for us as a company to think about how we would get involved in them, just because of the way they were designed. And they weren't designed in a way that gave us the flexibility to move where we really need to move from a drug development perspective.

So I would just say, if you are thinking about ways to try to increase the way that the industry and the rest of the

community works better together, get the stakeholders together before you sit down and design the program to make sure everybody can really make a contribution.

And even sometimes industry can make interesting contributions. Something was mentioned just toward the end there around learning from failures. And in industry, you know, if a project fails, you've just got to move on. You've got to move on to the next project.

There is an opportunity cost to going back and investigating why something didn't work. Yet, there is often really interesting questions with the tools that are available from that project, but they never see the light of day because, again, the information never gets into the public domain.

So, again, taking information that's been gained in industry, taking it into the public domain, using that to really, then, teach you how to do it much better the next

time would, I think, be helpful.

MEMBER KATZ: Thank you.

MR. BERGER: I have two thoughts. One is an observation that I learned today. This organization does fabulously well when they focus on a therapeutic area. I think of HIV. I think of what is happening in oncology, which has a surfeit of targets. I think of what is beginning to happen to hepatitis C. So when you choose a therapeutic area, you seem to be able to be very efficacious.

Another is -- a second point I want to make is from my own background. When I think of the NIH, I think of them talking to Merck or Pfizer or big behemoths. I live in the small world of biotechnology. There are about 560 public companies. There are probably 400 or more private companies. I work with them. I very rarely hear the word NIH mentioned.

There may be 100 great biotech companies. Half of those are public; half of

those are private. The word NIH is mentioned only when they talk about citations.

I would love to see folks at the NIH involved on a personal level with some of these companies, and they would feel comfortable. Maybe a task force within the NIH based on a therapeutic area, exploring what's happening in the private sector, would be useful.

Thank you for my invitation.

MEMBER KATZ: Dr. Baum?

DR. BAUM: Yes, I think others have mentioned the incredible value of information exchange and that collaboration in a pre-competitive way. I think that's something that the NIH should be very strong and active.

And exchanging negative data or a forum for exchanging negative data is also very interesting because most people, you know, there's not a lot of journals that want to publish your negative data and things like that.

So, how do we get that more exposed? I think that's another thing that possibly an institution like this could help with, because I think that's very valuable information of why things fail, and we seldom pay much attention to it. So, I think that is very valuable.

And I think, also, the role, helping to bring together the FDA and public companies is also a very interesting one, because a true collaborative environment is needed, I think, to advance things more quickly and to create a better understanding of the projects more quickly on both sides.

So thanks.

MEMBER KATZ: Well, again, I wanted to join Bill and others in thanking you all for being here. I know that some of you altered your plans considerably.

This is really only the beginning of the conversation of how the NIH should really configure itself in terms of moving

therapeutics with some greater celerity and facility.

So I'll close by thanking you again, and by asking Amy to give us any groundrules that we need to know about in terms of reconvening, et cetera.

EXECUTIVE SECRETARY PATTERSON: Thank you, Steve.

Again, many thanks to all the panelists. I know you moved heaven and earth, some of you, to be here, and we're deeply grateful, and certainly hope that you can stay for the rest of today and into tomorrow, if possible. We'll adjourn now for a luncheon break and reconvene at one o'clock here in the room.

Members of the Board, you have lunch, a box lunch, provided in the room just out, down the corridor.

And for others, there is a cafeteria here on the first floor.

Please come back by one o'clock.

And also, the panelists, you, too, have your lunch here as well.

(Whereupon, the foregoing matter went off the record for lunch at 12:27 p.m. and went back on the record at 1:12 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

1:12 p.m.

CHAIR AUGUSTINE: Good afternoon, everyone. I hope you enjoyed your lunch. We are ready to begin the second phase of the discussion of TMAT.

Arthur, do you want to introduce this part of it and carry on?

MEMBER RUBENSTEIN: I'm getting more and more jobs here.

(Laughter.)

Francis, do you have a position for me here?

CHAIR AUGUSTINE: Let's see. Here it says I'm supposed to say, "Great, I would like to turn our attention to...."

(Laughter.)

It says, "Arthur, would you like to take the reins again?"

(Laughter.)

I think that's the wrong reins, though.

(Laughter.)

MEMBER RUBENSTEIN: Yes, Norm, I will.

(Laughter.)

I don't think that's helpful. For me to read Norm's comments is not that helpful.

(Laughter.)

All right. Somebody is rescuing me.

All right. On a more serious note, to build on this morning's program, I think it's obvious it's very tough and challenging, but I think everyone is trying hard to think about how to do it. I think that's very encouraging.

So, this afternoon we are going to really try to focus again on particularly what role the NIH specifically can play in translational medicine and therapeutics, related but not exclusively linked to the CAN itself or only that.

And in this regard, we have two speakers, one a very good colleague of mine who every day teaches me a lot of things at Penn, and I'm delighted he's here, and then another colleague, Mary Disis, who will also talk.

And the topic is Identifying a Role for NIH: Lessons Learned from Academic Health Centers.

First will be Garret FitzGerald, who is the McNeil Professor in Translational Medicine and Therapeutics and Associate Dean for Translational Research at Penn.

Garret?

DR. FITZGERALD: Thanks very much, Arthur. Thank you to the committee for inviting me to come along and talk to you today. I will try to stick to the assignment.

So, as came up in our discussion earlier this morning, I think we're moving to a more modular approach to drug discovery and development. Classically, we've been used to a

vertically-integrated pharmaceutical company that does everything. We are in the process of watching the disintegration of that model, currently, during the outsourcing phase of that model, but really the disintegration of the classical integrated pharmaceutical company model.

The biotech sector has been focused particularly on target identification, some proof-of-concept, and some investment in drug-ability. Whereas, the academic effort has been traditionally in target ID and a little proof-of-concept in model systems and so on.

And I think we're moving to this more sort of modular approach, where teams can assemble, different teams in different places and in different sectors, to respond to different challenges with respect to drug development. So the question is, how do we get there?

I might say that I think, to some degree, a realization of this type of model is

beginning to emerge in the not-for-profit sector.

So, I think a big issue could be NIH's, if this is where we're going, how can we empower the academic sector to play a constructive role in this type of interactive modular approach to drug discovery and development?

So, why should we care? I think what we should try to do is, as I said, enhance the capacity of the academic sector to play, and, also, to enhance the ability of the academic sector to train interdisciplinary scientists in translational medicine and therapeutics. After all, it is in the academic sector that scientists are trained, and it is with the support of the NIH that this actually happens.

So, I've been in this game, I'm somewhat scared to say, more than 30 years. Thirty years ago, there were a few exemplars of departments of clinical pharmacology, and

I've just mentioned a few of them -- the Royal Post-Graduate Medical School, Vanderbilt, Karolinska -- where clinical pharmacology as a discipline was a very sexy topic. It was a hot topic. It had charismatic leadership. And within these departments, these various types of pursuit were actually integrated within the same space.

And experts in mechanistic studies of drug action and using drugs as probes to understand physiology and disease, experts in pharmacokinetics and modeling, experts in use of proof-of-concept in model systems, what we now call systems pharmacology and physiology, the development of biomarkers, chemical biology, statistics and trial design, and toxicology all existed within divisions or departments of clinical pharmacology in a few places scattered across the world.

And that was a rich interdisciplinary environment which coincided with in some ways the Golden Age of Drug

Discovery and Development.

Now, what led to the disintegration of pharmacology, or at least that model of clinical pharmacology? Well, departments of medicine lost interest as there was a shift across centers. And what test can you apply in clinical pharmacology that can be billed for? None.

And pharmacology departments tended to lose their way a little bit in the molecular era, part of the discriminate features that mark out a department of pharmacology from a department of physiology, a department of molecular biology, or whatever, in the molecular era.

So I think, to some extent, some departments of pharmacology fused with physiology. Some disappeared altogether.

Integrated curricula did no favors for the perception of pharmacology as a discipline. It was sprinkled like pixie dust across the length of an integrated curriculum

and lost its identity as a discipline in many of our leading medical schools.

And this led to a reversion of the perception and, to some extent, the reality of clinical pharmacology as a discipline, back to rather boring pharmacokinetic studies, often in Phase I, based almost entirely in industry. So, clearly, this was unattractive for bright trainees.

So, I would contend that it's impossible to resuscitate the brand of clinical pharmacology. Essentially, it has served its purpose over time. So, if you want to resuscitate this sort of interdisciplinary skill set, it's impossible to do it under the banner of clinical pharmacology.

Now, of course, it's not just in science that we lose the ability to do things that we used to be able to do. So, when Brunelleschi was preparing his grant proposals for the guilds in Florence, trying to decide how he would portray the construction of a

freestanding dome, he was faced with the problem that at that time in the Renaissance the way you built a dome was you built a mound of earth, you built a dome over it, and you scooped the earth out.

So what he did was he went south to Rome and he sat in front of the Pantheon for two months, which had been built in the 1st century as a freestanding dome, to try to understand how it was done, so that he could recapitulate this expertise so many hundreds of years later.

So, as we discussed this morning, I think the lack of people who blend these various skill sets that I've described to you a couple of slides ago in their own experience has really come at a great cost to various parts of the pharmacokinetic industry for us in this country.

I think we have really paid a price for it in the understanding of prescribing physicians of the medicines that

they prescribe. I think we have paid a big price for it in drug discovery and development, particularly in drug development. Because I would contend that the investment in drug discovery actually has been, to some degree, cost-effective, and the whole process has been revolutionized.

And as was mentioned several times this morning, we have many potential drug targets. That's not really the issue. Where things really break down is in drug development.

I think there's a big issue in terms of regulatory science, and that needs to get re-infused with these other elements of the discipline beyond, say, pharamaco-epidemiology.

And, I think, undiscussed so far in this country is the absence of any input, never mind leadership, from expertise in pharmacology and the whole issue of comparative effectiveness.

So, what about the attempts of redemption since the disintegration of clinical pharmacology, as we used to know it? Well, many of the elements have actually matured as disciplines in their own right. So we have seen the development of chemical biology as a discipline. We have seen the development of what's called systems pharmacology.

Last week I was out at NIGMS at a meeting here, and systems pharmacology is an attempt to fuse expertise in systems biology with what is beginning to be called, in some drug companies, translational pharmacokinetics and pharmacodynamics. But for now, it is really systems biologists, often with a background in engineering or computational science, traditional pharmacokineticists and modelers, speaking different languages with no integrative glue between the two and very little understanding of human biology, frankly, never mind human pharmacology,

represented in either constituency, I would say.

Bioinformatics -- we have heard about it, and I'll come back to it.

Many drug companies have, quite understandably, recognized this challenge, have recognized the disintegration of this integrative glue, and have created a variety of structures over the last 20 years to try to address the problem.

It usually goes this way: you gather together some MD/PhDs. You brand this, according to the times, experimental medicine, molecular medicine, whatever, and you have these people superimposed on what is a conventional siloed structure of drug discovery and drug development.

You get them a little money, but relatively speaking, very little money, and then you expect them to be able to influence the behavior of the people in the traditional siloed elements of the process. And generally

speaking, those structures have lasted three to five years.

CTSAs, Clinical and Translational Science, we'll talk more about that, but that's clearly been a big initiative of NIH. And the focus here that is relevant is on so-called T1 translation, the translation that straddles the translational divide, not to be confused with the translational further down the stream. But I ask you, who will flock to the banner of T1 translation?

So, other attempts of redemption are that part of the CTSAs' remit was a focus on education, and we're going to talk about the importance of training. The difficulty here is that clinical and translational research, as a term, encompasses a very broad constituency, from the most basic science through to health services research. It includes many developed disciplines, basic science disciplines, clinical epidemiology, health services research.

T1 translational research is the orphan without a name. And yet, in some ways, it is the most cardinal point of the process.

The NIH, as Francis alluded to, has developed many relevant resources that are pertinent to this effort in terms of the translational mission, resources, and intrastructural access to, including the Clinical Center, which we have discussed this morning.

And as well as that, as has been mentioned by several of the IC directors, many of the ICs themselves have developed programs, pitched out accelerating cures or translation.

So, why can't we attract the best and the brightest of our medical students and our science undergraduates to get into this business? So, what brought any of us into what we wound up doing? It was usually charismatic leadership and the perception that this is the hot area of science.

I remember when I came to Penn, if

you'll pardon a local joke, I was staggered to find that, of the undergraduate students, 80 percent of them were opting to major in gene therapy. I rest my case.

All right. So, one of the reasons is that they can't see anything. They can't see a discipline that has an integrative mission and that has the resources and membership that render it visible. It's not perceived as a hot area. There are few training options pitched at this science. There's absolutely no career path, and there are no programmatic initiatives where they can see that these skills are actually core to the sense of the initiative.

So what can we do and what can NIH do, and what can we do in academia? Well, I would say, first of all, we need to brand this discipline. I think, obviously, translational medicine and therapeutics is a great name. It captures the excitement of translation. It puts it at the heart of medicine. It says we

are trying to discover new therapeutics.

I think we really need to adopt a unifying nomenclature. This effort has many, many different names, all of them really scattered across the landscape with very few adherents. We need to aggregate this effort under a unifying nomenclature.

As Francis mentioned, there are many initiatives, existing initiatives, funded initiatives, within the NIH that are pertinent to this, but they're scattered. And it's difficult to sort of even perceive them, if you're interested in this area, as aggregated within a tangible resource.

And similarly, within many of our academic institutions, there are many resources relevant to translational medicine and therapeutics, and they are scattered across the institution. They have not been aggregated under a visible brand.

I think we need to create training programs in TMAT. I think we have a big issue

here that actually relies on coordinated efforts by both the NIH and institutions, and perhaps the NIH, having the funding stick, can drive the institutions to reform.

But this type of research takes much longer to do than the usual performance cycles that accord with a five-year funding period. And similarly, it takes much longer to do for a conventional assessment of progress within the timeframe that leads to promotional decisions within academic centers.

To give you an example, when I was training in the Hammersmith, if we wanted to address a question in clinical research, you would ask the people in the room, your other post-doctoral fellows, would they be willing to volunteer, and you would probably do it the next morning. To do the same study now, the lead time can be a year. I'm not saying it was better then, but I'm just saying that's a changed reality.

So, this is a very different type

of science, particularly if you are trying to integrate both basic and clinical elements of this type of science. And I think we could couple training initiatives with programmatic initiatives that are actually reliant on TMAT.

So, let's talk about each of those issues in a little bit more depth. Why a unifying nomenclature? Because I think it's really important here that this should be an initiative that is coordinated across countries as well as across sectors. I mentioned earlier this morning that the Wellcome Trust has already had an initiative in this area. But right now, we have this sort of laundry list of different names for the same thing, which really fragments the exercise.

So, I think what's really important is that something like TMAT, I think, would brand the interdisciplinary integration of the knowledge, but not supplant, for example, particular expertise in

chemical biology or in systems pharmacology.

One can fly under two flags, but what this really speaks to is the interdisciplinary integration of those forms of knowledge. It begins to create a common language.

Over the last couple of years, we were putting together a highly-interdisciplinary program around the personalization of medicine. And one of the things that became clear in the course of that time was that we spoke different languages. We actually meant different things when we said the same words.

It begins to foster structures in which experts in the distinct elements commingle. So that was one of the great strengths of what clinical pharmacology used to be. You actually had an organizational structure with space and laboratories where people whose expertise was in kinetics or statistics or toxicology and human biology or

biology or large animal biology actually commingled with each other.

I think it's really important that this type of initiative should be aligned with initiatives in other countries, but also with approaches to the problem within industry.

And finally, I would say that regulatory science is the other side of the same coin. TMAT is the academic manifestation of a solution to the problem. Regulatory science is its complement in the regulatory domain.

So I think the attraction of clustering the resources in a structure is that it gives you a seat at the table. And indeed, in our experience, when we were forming the Institute many years ago now, that was exactly the objective, that there were scattered resources and people relevant to this effort who were invisible institutionally when it came to decision-making. The idea was really to aggregate those resources and to

amplify them.

So one approach to doing this within academic centers would be the following:

First of all, one could have an institute like we do. Or, secondly, one could take advantage of the clinical and translational science institutes that are beginning to proliferate and have within them a center for TMAT. The attraction of that is that it's a home for basic, for clinical scientists, for all types of scientists that might be relevant to this.

The attraction of an institute or a center is that it would be a home to a spatial and educational resource relevant to an initiative in this area.

Now, as far as physicians are concerned, the number of them interested in this type of science is likely to be very few, actually. And you run into the problem that there might be one in endocrinology and three

in pulmonary or two in cardiovascular. There's no critical mass.

So the attraction might be to have a divisional structure that actually straddled all the clinical departments, so that you picked up that two or three people in surgery and four or five in psychiatry, and you gave them a common home for clinically-qualified people who are interested in this type of discipline.

And then, finally, they might have, as appropriate, secondary appointments in basic science departments. And obviously, similarly, basic scientists who are interested in this might have secondary appointments in clinical departments.

So, that way, you take something that has a relatively small and scattered constituency and you give them an organizational home that also commands resources.

So this is not a controlled study,

but, for example, when we did cluster and aggregate resources in that domain at Penn and it became very visible and a source of distributing resources, it became very attractive. This is just showing how dense the interactions became over time across departments following the institution of the institute.

So what about training programs in TMAT? Well, I must say, I favor a master's degree as a sort of introductory basal degree that gives you the interdisciplinary exposure and then allows you to begin to focus in the area where you're likely to develop your expertise. And obviously, that can be built out of the CTSA programs.

The NIH, through the CTSA initiative, as I'm sure we'll probably hear of in T1 translational research, will become a repository for distance learning in translational research and, clearly, could be readily integrated into that type of

initiative.

I think it is important that, with any training program, there should be the option, not necessarily the compulsion, and we could discuss that, but certainly the option to rotate into industry, the FDA, and the Clinical Center. And the other option that I think we should really keep in mind is the fact that this is an international effort. There have been big initiatives in translational research in many of the countries in the developed world, and they each bring different things to the party.

I think for people who undertake that initial training, they need a career structure and they need a bridge vehicle in terms of funding. I think that one of the programs that is particularly attractive to help them to do that is a K99 type of program, where it covers some of your post-doctoral training into the early years of your junior faculty appointment.

But I think this issue of the fact that it is a long training cycle and that promotional structures need to be adjusted to reflect that, is really important. And of course, we've done that before. We did that with the MD/PhD program.

Okay. So I think, besides training, one could have programmatic initiatives that are coupled with training to raise the profile of this type of endeavor. One could use such a call to incentivize the use of existing core resources and to actually advertise them to the constituency, that they exist, and to motivate them to utilize them. And not the core resources that exist within the NIH, but, for example, analogous core resources that exist within the FDA.

I think in this type of endeavor what's really important is to allow for the flexibility to utilize money to buy services, because many of these services don't exist within institutions. And in some respects,

many of these services don't exist even in terms of what's been developed within the NIH so far.

So, for example, the types of things that I'm thinking about are toxicology, so-called blue-collar chemistry, the tedious but necessary confirmatory proof-of-concept on human primate studies, and in many schools, regulatory support.

I think what would be really nice in terms of a unifying nomenclature would be to actually adopt this brand for the many existing IC-based initiatives in the translational space, so that people begin to associate these things and think this actually is an area with momentum that I might be interested in training in.

And I think the other thing that is necessary in this business, where you really are competing with people in the real world as opposed to just in the academic world, is speed and flexibility beyond the

conventional review cycles.

So, I'll end by talking about some larger issues which I think are opportunities for NIH leadership in this domain and that are necessary and fundamental to reforming this space.

We have talked about intellectual property. We've talked about the pre-competitive space. These discussions are beginning to occur on the other side of the Atlantic as well as here.

I think the NIH could play a really leading role in beginning to address these really outmoded approaches and expectations towards intellectual property that we have both in academia and in industry.

It's been talked about before, and I think this is absolutely fundamental. If you are to move to that sort of modular structure of drug discovery and development, the infrastructure on which that model is built is the ability to share information in a

compliant and secure way, extremely heterogenous information, and to be able to integrate it and to include, obviously, clinical information as well.

And that's a sort of easy thing to say and an extraordinarily difficult thing to do. Again here, this is somewhere where the NIH at a 30,000-foot level could play a really important role.

Then, finally, I think this is another issue that surfaced this morning. That is the way the rules of the game are set by the regulatory agency. There are all sorts of contradictions in the way the rules are set right now.

So, for example, if you're developing a drug for use in arthritis, you, the sponsor, are positively disincented to explore the human biology, the human pharmacology of that drug, beyond the contextual setting of arthritis, until that drug is approved. There is a disincentive for

you to do that because, if you, for example, explore cognitive functions and get a sort of potentially negative signal, that has to be reported to the FDA, and that is not something that actually incents you to do that.

So, in the same way that we created a safe haven for pharmacogenetic studies, I think the regulatory agency can play a really important role in terms of creating a safe haven for systems pharmacology, but pre-clinically, but, more importantly, clinically, early in drug development.

So, I think these regulatory incentives can really be relevant to a comprehensive exploration of drug action, innovation, and, indeed, early risk detection. It is here that TMAT bumps up against regulatory science.

So, I think there are three areas on a larger scale where there's a real opportunity for the NIH to do something.

So my time is up, and I'll end with a comment from one of my favorite Dubliners, Oscar Wilde. He says, "It's a very sad thing that nowadays there's so little useless information."

Thank you very much.

MEMBER RUBENSTEIN: Thank you, Garret.

I think, just because we're running a little late, I would like to take the prerogative, if all of you agree, that we ask Mary Disis -- is that how you pronounce it? --

DR. DISIS: Disis.

MEMBER RUBENSTEIN: -- Disis, to give her presentation, because it's related to Garret's. Then we'll have some questions for both of them after it, if you agree.

Mary is going to talk about -- she is the Co-Chair of the T1 Translational Research Strategic Goal Committee, CTSA Awards, University of Washington. She is going

to talk about the same overall subject that Garret did, and then we'll have questions for both of them, if everyone agrees.

DR. DISIS: Thanks.

So my talk is going to be a little bit more practical, and it's going to emphasize tools and existing tools. I think one of the things that the CTSA program has really brought to bear is that there's a ton of already-developed resources for translational research, especially drug development, not only out in the community, but here at NIH. But they're just organized; in some ways, they're very outdated.

So technology and tools really drive science. That's what accelerates the pace of scientific discoveries. And technology and tools needed to advance a discipline can be physical -- I'll show you a few examples -- methodological and educational, just as Garret talked about.

The generation of these type of

transformational technology and tools in itself requires innovation, scientific rigor, expertise, and a culture change. So the development of these tools in themselves is a high-level scientific endeavor.

They are many examples of where technology really changed science and the science infrastructure and transformed intradisciplinary science within a discipline. So, for example, human genomics, I mean this is from *Nature*. They describe the big wins in human genomics. It's all around tools and the development of tools.

If you look at cancer biology, in the 1990s, the development of these mouse models transgenics to look at epidermal growth factor in knockout. You know, I'm an oncologist, so this is like the bread and butter for us. Or the study of HPV-related cervical cancers. There are actually mouse models now that almost completely recapitulate human disease.

This results in an explosion of our understanding of cancer and biological pathways that are feeding the development, but very little of this has actually ended up resulting in being used for models of translation. So that's the reason why. Why aren't these great tools not only being extrapolated into T1 drug development in a much greater way, but also why are these type of tools being developed for T1 translational research?

Part of that is due to the very big fact that translational research, instead of being intradisciplinary, is really multidisciplinary. So, there are many diverse technologies and tools that are needed for T1 research that are held by different stakeholders in silos. They are often scattered.

So, when you look at academic institutions, these tools are located all over the place. The CTSA program has taken a lot of

resource in terms of trying to gather these tools all into one place, as Garret talked about before.

And until now, translational technology and tool development has not really been a priority. People have been doing one-offs, developing tools and leaving them to be used by small groups, not available to larger groups, many times because people don't even know about them.

Multidisciplinary research, again, requires a broad array of tools. The development of those tools often takes scientific collaboration of diverse disciplines. There has to be a team approach to resource development, and that's very hard when you're talking about resources. Everyone wants to hang onto their own resources.

And finally, translational research and discovery application requires active participation by the public. Before I got involved with the CTSA program, I never

realized how big of a barrier that was. I mean, we always knew that enrollment in clinical trials is less than 7 percent or 5 percent or 8 percent of people in populations, but translational science is not a public value. People don't realize the role research plays in creating the medicines that they use.

So you have these wonderful high throughput technologies for target identification, and then they get down when you get to biologic validation. And finally, by the time you hit clinical translation, you have a huge bottleneck, not necessarily because some of the most critical tools aren't there. It's just that they're not able to be accessed. And NIH has a lot of these tools available for that type of access.

Now, what I've learned is that the CTSA program has very unique focuses that can provide lessons learned. Certainly, on a national level, through the CTSA Consortium, they are providing a lot of lessons learned

within regions and across the United States in terms of this individual program.

But I think that the CTSA lessons learned can provide some take-home messages to NIH and other very large organizations that are interested in accelerating T1 research or drug development.

So, first of all, the unique aspects of the CTSA program is that we actually had a mandate to do research about the translational research process. So the amount of data available within the CTSA program about what is needed or where the holes are is really vast and is in the process of trying to be organized.

We have a mandate to try to identify and solve barriers that we identify for the research in very innovative ways, to transform the environment, and take outdated technologies and bring them up to where they should be in terms of trying to make the pathway faster.

We have to accelerate translational science technology and tool application, make sure that tools are being used by our constituency. That means we have to foster team science and eliminate those silos, break them down in some way.

And finally, I think this is one of the few programs within NIH where we have a huge mandate to engage the community as partners. This is a big holdup in terms of getting people into clinical trials or people volunteering, enrolling their newborn babies in being able to be followed for 25 years, so that we can gain understanding about development of children.

And finally, the solutions and the lessons learned that we are developing in the CTSA have to be transportable. So, if we can't take what we're learning and give it to you as tools that you can use, then we aren't really doing our jobs. And it's through this that potentially we would be able to take these big

roadblocks away.

So, what I would like to do is give three examples. This isn't meant to be a high-level overview like Garret just gave, but drill down on just three of these things, of how you can see, and I am going to use examples from our CTSA, approaches to some of the barriers. Then, unfortunately, I am going to focus on the NCI, because that is what I know best, how some of the resources within NCI, let's say, could be retooled to become broader and accessible to lots of different people.

So, for example, we have to identify and solve barriers in innovative ways. One of the biggest problems that we tackled in the CTSA program was looking at clinical centers.

Clinical centers have been around for a long time in most institutions through the General Clinical Research Center Program. In the old days, what would happen is people

would come in and they would be in the hospital for three days, and they would participate in clinical research. But that is not how clinical research has evolved now.

People come in as outpatients. Translational research is going on in the community. We need places where we can high throughput lots of people coming in for genomics studies and places where we can accept samples that can be picked up and taken to research labs.

Certainly, the CRCs were not very business-oriented. So they were really developed on an old model from decades ago that needed to come into the way clinical research is being utilized now.

So, many CRCs or clinical centers are using business tools to try to retool the CRCs. So, for example, one of the things we found in our CRC is that we had no idea what our capacity was, but the nurses were always busy.

We use Toyota Lean as kind of a process to streamline some of these existing resources. They're running all over the place. It's taking patients three hours to have what should be a very simple visit.

In these type of business processes, you create what is your ideal state. The ideal state with all the stakeholders in the room, what would you like this to look like? Then you can map out what that ideal state is.

Once you take these complex resources and map what they should be doing, that allows you to break them off into segments and tackle those segments. Instead of trying to retool the whole resource, retool parts of it at one time. That allows people to get their heads around deconstructing enormous structures, having that type of transformation.

By teaming up with the business school and using these types of tools, we have

been able to decrease nursing overtime costs by 40 percent -- this is like a quarter-of-a-million-dollar savings -- while maintaining the same number of patient visits.

By streamlining processes, making everyone well aware of what they're supposed to be doing, we have been able to eliminate the administrative structure of the CRC. We have reduced the time of scientific review by over 50 percent. Their own review process was a major problem for investigators, kind of like IRBs. And we have been able to institute two new services during the time when we took a 40 percent reduction in the overall budget, just by streamlining the processes.

So, if you look at, let's say, the NIH RAID program, that is a fantastic program. It is desperately needed in the community. But it's not very well-utilized. In fact, there was just a recent review of the RAID program and some of the perceived problems with the program.

When I read that review, it struck me, it's almost identical to some of the things that have been said about the CRC types of reviews: slow application process, limited users, slow manufacturing or slow throughput in these clinical research centers, unclear capacity, very complex outsources, and a lack of awareness of the resource.

So, many times these resources have been developed; they have been started, but they've never gone back and been retooled for the usership. I think some of these tools that are being developed in the CTSA program would be very useful to make the resources more high throughput.

If you look at the CTSA program, there's a lot of technologies at a lot of institutions. They have come up through multiple centers. People really want to use them, and those that own them really want people to use them, so they can keep the resources going. But no one knows where they

are.

Many CTSAs, ours being one of them, create a directory of technology resources. Our CTSA covers a very large five-state region in the Pacific Northwest.

Our technology resource directory has 135 shared resources from a five-state region linked with educational material, like streaming websites or lectures or information about how you use the resource, sample preparation, things like that, and live technology consulting via PhD-level scientists.

When this resource was developed and this is data collected on the website where this resource is, most of the hits a year after the resource started came from the University of Washington. Who would have known? But after a year, most of the hits now are coming from direct links that go directly to that technology resource. And the next highest number of links are coming from search

engines outside the University across the United States, and 85 percent of those people go on to other web pages within our CTSA program.

During the time that this technology resource was launched, our membership grew 200 percent, just because there was such a need for people to get a handle on their technology. This is just a small part of a larger technology engine that is being developed within the CTSA program to link unique technologies at other CTSA institutions on a national level.

So, if you look at, again, NCI, they have an incredible, and NIH in general, amount of resources surrounding transgenic mouse models. When you look at that slide that I showed you about cervical cancer, and there is now a E6/E7 transgenic mouse where people can study the development of therapeutics for cervical cancer. Although that mouse was made in 1992, there have been 150 publications, and

the vast majority of the number of biology-based still elucidating pathways that are modulated by viral oncogenesis. Not many translational researchers in this environment are using that most relevant mouse model for testing new therapies.

When you look at the NIH website, I just clicked on a couple of the consortia surrounding transgenic mouse models. I put dot, dot, dot. There's at least 10 more, much like these different types of resources for access to these transgenic mice. And many transgenic models that are being made in other institutes have direct relevance in other disease.

If NIH could just take their playing field of transgenic mouse models and get that to a greater usability, that would be an incredible resource for people in the T1 area, and it would probably really increase their access to being able to move to the clinic faster.

And finally, I wanted to end with engaging the community as partners. I play in the T1 field, so I'm more laboratory-based. Before I took a role in the CTSA, I never really thought of this, except that when we go into Phase I clinical trials, it takes five years to enroll a 20-patient study.

But, recently, this summer, we had a summer workshop for high school science teachers. These people self-identified, so they are really into biology and science. They came and spent a week and learned about translational research. And of course, they said, you know, marvelous things.

But within all the marvelous things they said, there were comments to me that were really striking, like, "I never realized how critical research is for medicine." These are science teachers.

"I wouldn't think a researcher would be so caring, nice, and friendly." Or "I always thought research was for extremely

intelligent people who were socially inept."

(Laughter.)

You know, I laughed first. But, then, when I walked away from the presentation that showed me the comments, I thought, this is serious stuff. I mean, these were compliments to us about this. This is what our science teachers are thinking about research? They don't see the link between that.

And unless the public takes translational research as a value, we can do all we want with translational research, but we're never going to get rid of that bottleneck going into the clinic.

So, the CTSAs are interested in developing partnerships, meaningful partnerships, surrounding translational research. So, this is an example -- again, there's a bazillion examples in the CTSA program -- of WWAMI-based, this five-state area, taking clinical practices and making them a research network. It means giving them

research capacity.

So we went in. We took seven rural practices, saw a lot of patients, gave them data warehousing, put a team in there to help them address questions they were interested in. They had a townhall meeting, decided they wanted to study, based on what their patients wanted, do women taking teratogenic drugs use contraception? And what they found was they didn't and, moreover, we have no evidence that we ever told them that they should.

Now, when they finished that study, which not only are they publishing as a rural health network, but they are presenting at national meetings, it really transformed them. It's transforming their practices. It's making their patients feel that they got something out of this.

And these research practices now are coming saying, "We're really interested in being full members. Can we do clinical trials out here?"

This is the type of meaningful interaction that NIH could have a leadership role around, much like Garret says. So, for example, when you look at the NIH website and community, there's lots of stuff, numerous programs for the community. They're all over the place. There is little unification about them, and there is no common mission whatsoever.

Many programs, even within themselves, when you read about them, you're not quite sure what NIH is trying to get out of them. Many are superficial.

There really is a need for a cohesive plan to galvanize community support in translational research in many ways, and there's a need for leadership. Certainly, in cancer these are successful programs on a much smaller scale, but the Army of Women project led from the National Breast Cancer Coalition -- these are programs that have really brought to bear women going into

clinical trials in great numbers. And I think that there are some lessons to be learned from what's outside.

So, at the end of the day, the CTSA has developed many best practices and has a lot of lessons learned. NIH should use it as a resource as they go through this process of trying to figure out how they can play and have leadership in the T1 arena, especially because so many resources exist here that are not organized and not available.

These resources could contribute greatly to translational science if they were catalogued appropriately, if they weren't left in silos, and if they were operating a little bit more efficiently.

Evaluate the data collected in the CTSA program to assess potential new resources for development. There has been a huge national push on data collection in this area, and it would be great not to reinvent the wheel.

And also, encourage intramural integration around translational science. Bring those resources together, not within NIH, but also intramural participation with the extramural community in this T1 arena.

And finally, ending with Garret's slide, it's the major thing. You have the national leadership, not only in community integration, but in branding translational research and drug development, T1 research in general. You have the voice. You need the vision. We will follow and back up that vision and really galvanize the nation around this area. That's the only way they'll get the medicines and new personalized healthcare that they are so interested in, but there is a very big disconnect.

So utilize the CTSA program, and there's a lot of stuff in there that's sitting there that we want to give out.

MEMBER RUBENSTEIN: Thank you very much, Mary and Garret.

What we are going to do, in the interest of time, is have five short presentations from people from within the NIH, five minutes each. Then we will have a general discussion involving them and Garret and Mary.

So why don't we start with Jim Doroshow, who is Director, Division of Cancer Treatment and Diagnosis at NCI?

We'll try to keep it to five minutes each, if that would be acceptable.

DR. DOROSHOW: Thank you very much for the opportunity to present to this group.

I wanted to talk to you about what has gone on in the NCI's drug development program, which, as many of you know, is actually 55 years old, and as of the last few years, is clearly showing its age.

So, we have made a lot of changes -- I'm going to share some of them -- that really go the entire range, from looking at different ways to do early drug discovery through changing our early-phase clinical

therapeutics program, looking at how to improve our delivery of biological agents as well as small molecules, and how to do clinical trials more effectively.

So, this is a list you're not meant to read every line of, but, in fact, everything in black the NCI has been doing for some years and providing as resources to the experimental therapeutics community in the area of cancer. What we were not doing, and not doing very well, was providing medicinal chemistry high throughput screening and chemical biology resources.

So, about two years ago, we began a planning process to change that particular deficiency to develop something we called the Chemical Biology Consortium. This was to be, and is -- it went into operation about a year ago -- an actively-managed group, a consortium of investigators across the country. So that, instead of the NCI supporting this activity by hiring a bunch of chemists, we went out and

did a competition to try to find individuals who wanted to work together in teams to help work on high-risk projects that were not the kinds of things that, for the most part, industry was used to working on.

This is a list of investigators and institutions that are participating in this activity. It is a very good group of chemical biologists with a variety of different kinds of skills.

What we do now, and we have started as of last September, is have a quarterly process in which people put in applications for resources now in any part of the pipeline. They can ask for resources to early-phase proof-of-concept, proof-of-mechanism studies. They can ask for a high throughput screen for medicinal chemistry. They can ask for pharmacology and toxicology. This is reviewed by an outside group of special emphasis panels, either in discovery or development.

Just to give you an idea, this is our first year. We had close to 200 applications, most of them from academia and not-for-profit, some from biotech companies. Most of those applications were for early-phase therapeutics. Our level of success is around between 15 and 18 percent.

These review groups are made up of half from academia and half from industry, so that we have people who are very skilled in understanding the kinds of hurdles that need to be overcome.

And if I can spend a minute or two, I will just give you a couple examples of projects that are ongoing. One of the first is a project in the area of metabolomics from Chi Dang at Hopkins, a world authority in the area of MIC biology who discovered that LDHA is a critical downstream target, working with a chemist overseas, found a group of malarial inhibitors that are very effective in decreasing the growth of MIC-driven lymphomas,

but not very useful in terms of inhibiting the growth of non-MIC-drive pancreatic xenograms.

So, what we are doing with Dr. Dang is to develop an entire high throughput campaign to try to find a new scaffold for this particular target. And the key to this really, at least is my opinion, is that we have the chemical resources to do what he can't or it's not available at Hopkins, but he will provide the critical biological glue to provide the expertise in the area of the target that will work toward moving ahead.

In the area of development, we have for many years and continue to try to reproduce reagents and work out of our community, not only small molecules, but immunomodulatory molecules. This is a list of the top five compounds that the cancer immunotherapy community felt were critically important to move into the clinic.

We have produced clinical grade IL-15 and have an IND that has just been

approved for the first study of that compound in man. Now we're producing IL-7. And to go along with the production of these clinical grade molecules, we have just established an immunotherapy network to do Phase I trials specifically with the compounds that we have produced.

The last thing I would like to show you is a compound, and it's something that I think that only the NCI and all of the NIH can do, is to focus on a compound that has little or no -- because it's very old and it's been repurposed -- intellectual property.

This is a compound, fluorodeoxycytindine, which binds to the active pocket of DNA cytosine methyltransferase 1. It was originally developed actually at Memorial Sloan-Kettering as a pro drug of thioracil. It's of no use in that capacity. But about 10 years ago, it was found to inhibit methyltransferase and activate differentiation.

This is a patient on a Phase I study done at the Clinical Center, a woman with breast cancer on a morphine drip when she came in with a substantial amount of her liver replaced by breast cancer disease and in the skin, who had, essentially, a two-year response to this compound.

Really, it shows how you can make things, provide them to the extramural community, work with them -- and this is a trial done both at the Clinical Center and in a variety of our Phase I sites outside -- to bring things that really would be very difficult to do otherwise.

This just puts you in a schematic version, a list of our repopulated pipeline based on our recent one-year history of trying to bring things in from the extramural community. I think it's really possible to do things that are difficult to do, are high-risk, and provide resources that are not available to academic investigators.

Thank you.

MEMBER RUBENSTEIN: Thank you, Jim. I thought that was an excellent presentation. So thank you, and I appreciate that you had to do it quite quickly, but the data was really great.

Then Susan Old, the Deputy Director of Therapeutics for Rare and Neglected Disease Program at NIH, if you would proceed for five minutes, please?

DR. OLD: Thank you. I will do my best to rush through this.

I have been asked to talk about two programs that we're involved with, the Chemical Genomics Center and the Therapeutics for Rare and Neglected Diseases, which you have heard a little bit about both this morning and this afternoon. So you have seen a lot of the pipeline.

Where NCGC sits is in the discovery, sort of this, the blue, and a little bit into the probe, and where TRND sits

is from discovery through proof-of-concept in humans, which would be Phase II in the clinical trials.

So NCGC is an intramural program at the NIH. It was founded as part of the Molecular Libraries Program, which is high throughput screening program. We have about, actually, we're up closer to about 85 scientists now.

We, through the Molecular Libraries Program, bring in collaborators. Most of them are extramural. A handful are intramural, and from foundations, research, and pharma.

Our focus is on rare and neglected diseases. We come out of this program, and I don't think you're going to hear much more about Molecular Libraries, but the purpose of Molecular Libraries is take targets that have been identified in academic centers or other centers and develop high throughput assays and screen them -- you've seen this picture

several times now -- on our robots with a compound. We have several compound libraries. The Molecular Library, the Compound Library is about half a million small molecules.

Then we also do a fair amount of time in assay development, screening informatics, and paradigm development and chemistry in this area.

So the reason that we work, and just to talk a little bit about rare and neglected diseases, and this has been brought up many times over the morning, the human genome codes for many, many proteins.

The well-understood proteins are a very small portion, and these are the drug-able targets that pharma goes after for the most part. All the rest of the genome and the proteome are much more difficult to target and much less well-understood because of that. So that's a neglected area.

And the same you could say for diseases. The prevalent diseases in the

developed world are the diseases that pharma generally tackles.

So prevalent diseases in the undeveloped world are neglected, and non-prevalent diseases in the developed world or rare diseases are also neglected. So these neglected areas and rare disease areas is where TRND and NCGC focus.

So we're disease-agnostic. We are not part of a mission of any of the categorical institutes. So we do a fair amount of probe discovery just for basic research for probing, for going back in and understanding the biology.

We are somewhat nearer the NIH with cancer/infectious disease. We haven't done a lot of cardiovascular. I'm not sure why. But these seem to be the ones that come to us through the Molecular Library Program.

So what we do is we're an intramural program. We consist of a lot of chemists, biologists, robotics, compound

management, informaticians, and the vast majority, except for a handful like me, come from -- and actually, I did work in biotech for a while -- come from pharma in the biotech area. So these are people that are well-versed in drug development, and we're bringing them into NIH in sort of an academic-like setting.

So, NCGC, there is a huge number of programs under this umbrella of NCGC. So, the Molecular Libraries Program, we are a center. So, we have a grant as part of the Molecular Libraries Program, the Common Fund. We are a center in the NCI CMC program, and we get the NEXT grants to work on.

We have a large program in Tox21, which I think you've heard a bit about in playing a role in the Gulf spill. But we are mostly working in figuring out novel toxicology assays that are not model-based or cell-based.

We have an RNAi intramural program, or we support all of the intramural

programs in doing high throughput RNA screening. We have a number of intramural collaborators. We are actively working with disease foundations, and we actively work with biotechs and pharmas. These are the different types of things that we do.

So, these are our areas. So, this is mainly where NIH has played before in clinical and basic research in target identification or understanding of the biology, the mechanisms, the pathways. You can term this as translation because you are certainly translating basic knowledge, understanding of the genome and the proteome into pathways and targets. The Molecular Library takes those targets, does high throughput screening, and that is what we do.

Then our next hope is to work in the Valley of Death here and move, as we are hearing a lot from our market research, going out and talking to BCs and pharmas, that really for rare and neglected diseases, to

minimize, to reduce the risk, so it will be licensed, we are really going to have to go through proof-of-concept in humans.

So this is TRND. It's a congressionally-mandated effort. Our governance is by the Office of Rare Disease. We administratively sit in NHGRI. However, we pay our own rent. We pay for all of our utilities. We pay for all of the support staff NHGRI gives us.

We are intramural. The vast majority of our collaborators are in the extramural. You can enter TRND at sort of any stage along this pipeline.

So, our distinguishing features: we are setting collaborations and partnerships. We are an intramural program. This is not a service center. This is an in-exchange-of intellectual engagement.

We're building the laboratories and expertise infrastructure at NIH. We're out at Shady Grove by the hospital, where NCI is

going to be joining us out there shortly. We are disease-agnostics.

The big part of TRND not only is to facilitate this pipeline, but to do the science of pre-clinical development. We talked a lot about the fact this morning that the successes and the failures need to get out to the public, so that they can begin to inform the next series of studies. So, we plan to spend a large portion of our time with our intramural scientists in the biology and the chemistry, the robotics, the analytical, in understanding the pipeline and what works and what doesn't.

In addition, we're doing technology and paradigm development. We need a new process. We can't just repeat what pharma is doing. It fails 98 percent of the time or 99.8 percent of the time. We don't want to recapitulate that. We want to improve on that.

Then we are involved, actually, with speaking some with Pfizer and some with

some other groups; large-scale systematically purposing. We do the same list that you have seen from a number of other people. We do them in-house, or we are going to do them in-house.

So, we started in May 2009. We received our second funding in June of, I'm sorry, 2010, this year. We, like everyone else, are waiting for the budget to be approved to the recommended. The President's recommended was $50 million.

We are going to, even though we're intramural, we're going to solicit for our collaborative projects. We are going to use the same process that NEXT uses, because it's a very similar process. We're just bringing things in-house.

So there will be a solicitation out in about two weeks. Projects will come in. It will have an external review. It will go through a series of secondary reviews, including the trans-NIH group that we have. And we will, hopefully, be able to fund,

depending on the funds, three to five projects to get started. Then we hope that our labs are fully functional by fiscal year `12.

These are the pilot projects where we're piloting the pipeline. You can see they cross rare and neglected diseases, all different kinds of pathologies, intramural, extramural, nonprofit.

We are working with SOAR for the Niemann Pick disease and several other nonprofits. They're all at different stages and different kinds of compounds. So we're testing all the parts.

So the main thing, as you're thinking about NIH intramurally and internally, and where to go with sort of the overall collaboration, we have learned a lot in just the pilot projects that we have done in the last six months.

How do we get funding to our collaborators? We're intramural, not extramural. That's been an interesting

challenge. Collaborative agreements, CRADAs, MOUs, non-CRADAs, CRAs. How do we do this in terms of intellectual property? The government has certain rules about what our intramural scientists do and where they contribute. And then how do we partner that with the outside world?

Project management, our advisor group so far has told us this is the No. 1 key thing we need to focus on in how we move these projects along, keep them on task; go/no-go; hitting our milestones, and turning over projects that are not working well and moving them into the more science discovery realm of why isn't it working.

We have discovered huge expert advice on NIH campus. I can't tell you, in talking to people -- I've been to huge numbers of institutes, as have my colleagues. There's great stuff going on inside intramural, in the extramural side, as well as out in the pharmas and the BCs. Everyone we're talking to is very

excited about this program and seeing what NIH can do. It is sort of a small start of the intramural, but partnering with the outside, how do we tackle some of these problems?

So, I think that's it, and thank you.

MEMBER RUBENSTEIN: Thank you, Susan. We appreciate that.

Now we'll turn to Thomas Miller, Program Director, Office of Translation Research, Institute of Neurological Disorders and Stroke.

Tom?

DR. MILLER: The purpose of the NIH RAID program is to provide an opportunity for investigators to advance promising candidate therapeutics forward in the pre-clinical development pathway, particularly if a roadblock has been encountered to further development.

The application of critical development resources after the selection of

an optimized clinical candidate can help projects move quickly to IND when alternative sources of support can be really very difficult to identify.

Those of us working in this program are truly very excited about it. It fills a very important gap in the efforts that are underway outside the pharmaceutical industry to bring promising, effective candidate therapeutics to patients.

Successful applicants gain access to government expertise and therapeutics development and government contract resources to complete specific tasks in the pre-clinical development pipeline. No funds are awarded to applicant organizations. Currently, not-for-profit organizations and small businesses that meet the eligibility criteria for the NIH SBIR program are eligible to apply for support.

NIH RAID provides services for a broad set of potentially therapeutic agents, including small molecules, gene vectors, and

proteins. These services include product development planning, research grade NGMP manufacture, formulation, pharmacokinetic and ADME studies, IND-directed toxicology, and manufacture of a GMP clinical supply.

The program is led and managed by a central office that is currently at NINDS. Jamie Driscoll from NIMH and Tony Jackson, the NIH RAID Program Manager, are very important members of this office.

Our scientific staff is currently at NCI. Jim Craddock and Pramod Terse, along with a number of NCI staff, provide not only leadership, but also an enormous amount of expertise to this part of the program effort. This scientific team not only plans projects, but also implements them and manages the performance of the contractors.

Our project team and its subcommittees have been integral to our relationship with the institutes and centers at NIH and access to the disease-specific

expertise at those ICs.

We have accessed contract resources at NCI, NHLBI, and the TRND program. And our senior oversight from Dr. Katz, Dr. Landis, and the NIH Office of the Director, has been very supportive and helpful.

This is our project team, which currently has representatives from the 13 NIH ICs. This has been a truly trans-NIH effort. This team has been active and involved in the development, implementation, and growth of the program.

We established a process for consideration of NIH RAID projects that begins with electronic submission of applications using the X01 resource access mechanism. These projects are about $2 million in total cost each on average.

Applications that are responsive to the NIH RAID scope are reviewed by CSR and receive a priority score. If an application is scored in the excellent or better range in

peer review, we hold a meeting with the investigators, NIH RAID staff, and IC disease experts to formulate a development plan to advance the candidate therapeutic.

This meeting provides an opportunity to combine the expertise and experience of all the participants and leads to the development of final tasks, timeline, milestones, and budget for a project.

It's the flexibility of this process that enables NIH RAID to develop project plans that both maximize the chance of the candidate reaching the clinic and optimize the application of federal funds.

Then, after considering scientific input from the NIH disease experts, the Planning and Evaluation Subcommittee of the NIH RAID Project Team develops a funding recommendation, and that is submitted to the NIH Office of the Director for approval.

So far, the program has approved 23 projects, 11 of which have been completed.

These approved projects have led to six INDs, five clinical trials, and three development partnerships. Our approved projects span 20 different diseases, and these diseases fall within the program priorities of 11 of the NIH ICs.

There's been a very concerted effort in program outreach, and the success of those efforts is evidenced by the growth in program activity. The number of applications has nearly doubled over the last two years with 56 applications anticipated for 2010. In fact, our final receipt date for 2010 is tomorrow.

The program has a bright outlook for the future. There are apparently 14 projects with meritorious priority scores that are ready for our fiscal year 2011 starts, and we will be working together to figure out the best path forward to fund as many of these projects as we possibly can.

Thank you.

MEMBER RUBENSTEIN: Thanks a lot, Tom. That was informative and excellent.

Let's move to Michael Kurilla, Director of the Office of BioDefense Research Affairs, NIAID.

DR. KURILLA: Thank you.

I am going to describe the NIAID Product Development Program, the program's end resources that we have available to advance infectious disease product development, specifically addressing unmet public health needs, both in this country as well as throughout the world.

Just for some definitions, I know everyone puts their own different spin on these; the terminology I'll be using is you'll see how we parse out different aspects of the program. In terms of basic research, that's the generation of novel scientific concepts. It's the NIH bread and butter.

What I call translational is the exploitation of those concepts towards

practical implementations of products. It is basically looking for a product.

And then product development is the safety and efficacy testing. It is basically looking for a licensed product as a result of those efforts.

I do distinguish between an early phase -- that would be IND-enabling activities into Phase II, proof-of-concept -- late phase, which would be later stage of Phase II through licensure, which are largely the domain of commercial development activities and not something we focus much on.

We have a multifaceted approach that basically falls into general bins, directed funding, that is, funds out to investigators, be they academic or nonprofits or biotech, and we parse those out into different bins: the basic research grant area; partnership awards, which basically covers and compartmentalizes a lot of our translational efforts; and, finally, contracts, when we're

moving in later stages of product development efforts, the early product development stage.

And then a series of research services that comprises a wide array of repository capabilities, so that investigators are not hampered by having to reinvent the wheel, a number of specialized services that I'll describe, and then our clinical trial infrastructure capacity.

The direct funding mechanism with the different bins results in a series of overlapping mechanisms that allows us to basically cover the full gamut from early-stage concept generation all the way through to Phase II proof-of-concept studies. The overlap is actually desired, because that way there are no gaps that appear throughout the funding mechanism.

We do have a small aspect that should also not go unmatched, which is Phase IV, where we're looking. And I'll describe some of these activities that deal with types

of studies that would be very desirable from a public health standpoint, but would otherwise not really be considered projects that would be incentivized for the pharmaceutical industry.

The partnership program, as I described, is our fundamental program around the advancing of translational activities. It specifically calls for the exploitation of basic research, trying to reduce it into usable products. This supports a wide gamut across the field in terms of vaccines, adjuvants, therapeutics, diagnostics, as well as platforms that would support the development of all of those programs.

The focus is exclusively on product development activities, and it requires multidisciplinary approaches. We fund them in a slightly different performance-based, milestone-driven funding.

And also, a clear part of the process for obtaining these awards is to have

clearly-delineated product development plans that actually outline the future product development strategy beyond which our funding will, in fact, support, so that the reviewers have a notion that this product, beyond what they're asking funding for, actually has the capability to move forward on a licensure path.

Now, beyond the direct funding to investigators, we also lower risk for product development by providing services. We classify this under a general term of infrastructure, but it crosses the entire realm, from basic all the way through to product development.

There's two general categories. We have a series of specialized services, which is really activity-focused. This could include capabilities for doing sequencing, repositories, as I mentioned, which can supply a whole host of reagents for investigators, as well as screening capabilities, both in vivo and in vitro. Also, we have the capacity

included in the in vivo for screening in animal models, but also for the development of specific animal models.

The one unique feature of infectious disease relative to a lot of other areas is that we anticipate that there will be new and unknown diseases that will continue to emerge, and that will require the development of, in fact, new capabilities for moving those forward.

The second aspect of our gap-filling services is a product focus, and that basically is a series of contracts that provide for us a full range of pre-clinical and clinical drug development activities that would be necessary, and we provide these to individuals, either in an academic or a biotech sector to help them advance their product forward when they run up against either gaps in their available funding or limitations in their capacity to move forward.

Our clinical resources -- we have

a series of contracts that can provide capabilities in terms of bringing in products for testing or vaccine and treatment evaluation units. We have a Phase I clinical unit. We also provide clinical trial support services as well as clinical specimen repositories.

So, if you look across the entire development pipeline, we basically put together a series of various activities that can pretty much cover and allow for the capabilities to advance product development all the way forward, so that any concept should never have to be lost.

Now, in terms of development choke-points, as I outlined these before, you have seen that we have put a lot of effort into the development of translational programs into the early product development stage; a partnership program, pre-clinical services and clinical services, is deeply involved in moving this forward.

What we have begun to recognize is that the translation from the basic into the translational resources, that is, the taking advantage or exploiting these novel scientific concepts that we're seeing emerge, is sometimes rate-limiting and that these concepts can, in fact, die on the vine if they don't get correct support.

So I think this might have been mentioned earlier this morning by Tony Fauci, but we have put together now what we call a Concept Acceleration Program. This is a dedicated staff. We're assembling this staff now. The term "sherpa teams" has been used to describe them. They are focused on identifying and advancing promising, novel scientific concepts.

That is a small group of people whose effort is to identify concepts and help investigators move through the wide array of available services and funding mechanisms that we have available.

It will include in their function a tech-watch type of function, which will involve other agencies, the Department of Defense, and the Biomedical Advanced Research Development Authority at HHS, so that we can pool resources in terms of everyone looking on the outside of what concepts potentially should be exploited and can be exploited.

And finally, they will put together tightly-targeted solicitations that will specifically try to advance novel concepts that we feel are being generated that have further potential for development for products.

Thank you.

MEMBER RUBENSTEIN: Thank you, Michael. That was very informative.

Our last presentation is John Gallin, Director of NIH Clinical Center.

Maybe if you all start thinking about the questions and comments you would like to make, we will certainly have some time

for that.

So, John?

DIRECTOR GALLIN: Thank you very much.

What I would like to do is just familiarize with three GMP facilities at the Clinical Center.

One of these you've already heard about this morning. It is the Pharmaceutical Development Service that some of you have visited. The second is about our PET program, which makes radioactive ligands, and the third is the Cell Processing Service in our Department of Transfusion Medicine, which makes cells for use in patients.

So let me first tell you about the Pharmaceutical Development Section, which is in the Pharmacy Department, and it is run by George Grimes. I point out that this service has actually existed since 1956. The reason we're so excited is that just now we are opening a modern, new facility that will be

fully compliant with all FDA requirements, not that we weren't compliant in the past, but we needed to upgrade.

So, what this service does is product development, analytical and quality control, and pharmacokinetics. It's responsible for about the 1100 investigational drugs currently under study at the Clinical Center. It formulates tablets, capsules, sterile parenterals, topical products, and including placebos, which they're particularly skilled at making.

It ensures that all raw materials used in finished products are suitable for human use, and it maintains accountability records for sponsor and FDA review, and it assists all investigators that NIH has needed with IND filing.

Their output includes in an eight-hour day about 75,000 capsules, 150,000 tablets, about 220 liters of an oral suspension type of medication, preparation of

5,000 syringes for administration of drugs, and 8,000 vials which can include vaccines and biologics. And that's in an eight-hour day. We could obviously increase it by running a 24-hour day.

The Department of Positron Emission Technology, or the PET program, which is run by Peter Herschovitch. The purpose of this program is to manufacture GMP quality radiopharmaceuticals for PET scans for patients under IRB-approved protocols. Currently, there are 21 radiopharmaceuticals available, and there's a brand-new GMP facility which is going to open up in about a year, in a couple of months.

The resources include three cyclotrons. This is unusual. You probably won't find this number in many places, if any. And it can include the two types shown here.

There currently are 10 hot cells for synthesis of radiopharmaceuticals and a lab for pharmaceutical quality control and

dispensing. There are currently three scanners, whole-body scanners, PET/CT scanners, and a High Resolution Research Tomograph.

And we're, I should point out, manufacturing now, we're helping to build a new PET MRI facility as part of the Traumatic Brain Injury Initiative.

These are the various radionuclides, the standard ones and some of the more specialized ones that are available. If you're interested, we can make that available to you. These are the 21 radiopharmaceuticals that are being used and produced by this group.

The new PET GMP facility is going to be located in some space that was set aside in the new Clinical Center, which will be over 6,000 square feet, and it will increase the number of hot cells to 19. There will be a brand-new clean room and an analytical laboratory for quality control.

This will meet all the new FDA guidelines which are about to go into effect. It will double our current capacity, and we will have the capability of shipping extramurally GMP F-18 radiopharmaceuticals that have a two-hour half-life, if desired.

The last GMP facility I want to mention is the Cell Processing Section in our Department of Transfusion Medicine. That's run by David Stroncek.

The mission here is to provide cellular and gene therapy capabilities to the investigators who would like that.

The resources include a Product Development Laboratory, a GMP Lab, and a group that specializes in regulatory affairs. It supports all the hematopoietic stem cell transplant programs at the Clinical Center.

And some of the IND protocols currently in Phase I and II relate to gene therapy, the use of dendritic cells for cancer therapy, cytotoxic cells for cancer and

lymphoma therapy, and donor leukocyte infusions.

In addition, there is the NIH Bone Marrow Stromal Cell Transplant Center that is supported through this program. When we are able to advance to embryonic stem cell transplantation, this group will help do the clinical aspect of that.

So they work 12 hours a day, five days a week right now, and they do what they call 25 intense procedures and produce 8 to 12 products per week. If you ran them 24 hours a day seven days a week, we could increase their capacity.

I just want to end by saying that these three GMP facilities support the NIH Intramural Programs but could be expanded to assist outside investigators, if there were an interest, per the discussions this morning.

Thank you.

MEMBER RUBENSTEIN: Thank you, John.

So we would now open it for questions for both Garret and Mary and then the five colleagues from the NIH.

Let me just begin with one, and then we have lots of people.

So, one of my questions is, with all this wonderful work going on, why aren't we discovering a lot of drugs?

And the second question is whether reorganization, which is I think the question Francis is asking, of some of these programs enhances their success.

Those seem to be very relevant to the big questions that Francis has asked us to grapple with.

Leaving aside people on the panel could answer that, let's also ask some other people to ask a few questions, and maybe we can get some response from a variety of people of the seven of you.

So, Tom?

MEMBER KELLY: Yes, one of my

questions is related to the second issue you raised. It's pretty clear from the presentations that there is an enormous amount of capability here, and it all seems to be very high-quality.

It begs the obvious question as to how much coordination and interaction there are among all of you. Does RAID talk to TRND? Do they talk to NEXT? How do you relate to the Cancer Institute and the NIAID efforts in this area? Is there any NIH-wide mechanism for coordination now?

MEMBER RUBENSTEIN: So, why don't we get another couple of questions on the table and then the panel could respond? Who else wanted? Jeremy?

MEMBER BERG: So this is really for Garret, but with regard to training, you know, I guess I'm very worried about the career path issue with training a bunch of people to go into a career path that doesn't look very well-developed. One, it is likely to be

challenging and, two, it may not be a very good service to them.

So, I know you put some ideas about the career path, and I think you hit a lot of the issues, but it seems like that is a substantial challenge that NIH can only play a limited role in helping academic medical centers figure out how to do better.

MEMBER RUBENSTEIN: Gene?

MEMBER WASHINGTON: Yes, just a related question. First, to Tom, that was my No. 1 question, too. Is there just some council or advisory group across the institutes that at least provides a forum for discussion of all the various programs and tools and technologies that are available? So, it's related.

But to Garret -- Garret, you made the comment that you had a preference for master's, and was that just a question of practicality in terms of the length of training that we require for Ph.D. or was

there an inherent preference for master's over physician scientists, and if so, why?

MEMBER RUBENSTEIN: Sure. Is that a question or an answer?

Steve?

MEMBER WASHINGTON: It's a question.

MEMBER RUBENSTEIN: It's a question. Why don't we have a couple of questions? Then a variety of people can answer. Go ahead.

MEMBER KATZ: It's, again, a question for Garret. That is, the concept of the CTSAs was to develop this home for clinical and translational research. You made a strong point in that direction, but how does one -- you talk about having primary appointments in this home. How does one have a primary appointment in a home that is in many parts, although heavily leveraged, in many institutions dependent on NIH funding?

MEMBER RUBENSTEIN: All right.

Gail, you had a question?

MEMBER CASSELL: Well, it's again for Garret. Garret, you mentioned the importance of having an international option in terms of the training, but I wonder how you would guide NIH in terms of synergizing and capitalizing on the tremendous investments in drug discovery and drug development in China, in particular, and not missing opportunities for collaboration internationally in these efforts?

MEMBER RUBENSTEIN: All right. I think what we'll do is just put a few more questions on the table. Then we'll ask each of the panelists to respond. So, you'd better keep a list of all these questions.

Yes, go ahead.

MEMBER ROPER: Maybe this is what this whole conversation is about today and tomorrow, but I would welcome somebody drawing a Venn diagram to show what is the CTSA world, what is TMAT, what is Cares Acceleration

Network? You know, how does this all fit together? I assume that's what you're asking advice on. I think a lot of this nomenclature, Garret, sorting out would help a lot.

MEMBER RUBENSTEIN: And maybe to add to that, just to add to the questions, I just wonder how many people in the extramural community know half of what's going on here. Maybe I'll say, how many of us knew all these things were going on? So maybe that kind of highlights the problem.

Any other questions? Yes, Dan?

MEMBER GOLDIN: I would like to reserve on a comment to follow up on what Norm said. So, when the questions are over, just give me two or three minutes.

MEMBER RUBENSTEIN: Do you think we should do that, Norm?

(Laughter.)

CHAIR AUGUSTINE: I think it's safe.

MEMBER RUBENSTEIN: Okay. You got

it.

(Laughter.)

Other questions or comments?

(No response.)

So I think it was extremely informative. I mean there is an enormous amount going on. We don't know how connected it is. We don't know how visible it is outside. We don't know if it could be enhanced by collaboration or organizational change.

Maybe I still come to the thing, why isn't it as effective in terms of developing new therapeutic agents as it could be and looks like it should be?

So it would be really good to get some comments from our distinguished panelists.

So, Garret, do you want to start? And then we'll go to Mary and down the NIH group.

DR. FITZGERALD: So, as best I can remember it, I absolutely agree with you that

you can't commence a training program without linking it to a careers structure. I tried to make that point, but, obviously, not efficiently enough.

The worst thing in the world is to have an introductory degree program, which is why I favor the master's, just as a tool that has a broad-spectrum introduction to a very heterogenous discipline without having the coupled initiatives on the part of medical schools to actually enable the creation of a career structure.

And that's why this is such a challenge, because it's a challenge to many different sectors, to funders, to academia, to industry, to regulators. And the only good thing we can say is there's a crisis for all of those camps right now, and maybe that will focus the mind on coordinative action.

The reason I favor a master's as an introductory degree is because, when people begin to think about this, they come from a

thousand different angles, obviously. And what you want to introduce them to is the fact that these very apparently disparate activities are actually relevant to the one that they are trying to pursue.

I don't favor a Ph.D. in translational meds and therapeutics. I think that would be a default mechanism for the people that didn't make it into sort of kosher Ph.D. programs as things exist at the moment. But, rather, after an introductory degree, that would be the beginning of your formal education on this process. Then you could specialize in chemical biology or bioinformatics or wherever you were going, but at least you knew that these things were interrelated.

And the problem at the moment is we're developing the components of the discipline as disciplines in their own right without the ability to synthesize them across those siloed barriers, as a sort of unintended

consequence.

I think the other argument for having a sort of branding thing, which sounds trivial to an audience like this, but actually a unifying nomenclature is actually illustrated by the display of the resources on offer within the NIH. They're scattered across institutes. They are not very accessible and evident to people in the extramural community who are even interested in this.

And having a one-stop shop, where they are aggregated in a way that they are coordinately branded with initiatives to educate people, I think would be something to really argue for.

And in a sense, when we built our institute, that's what we did. We aggregated existing resources, and then we amplified them. But a lot of those resources already existed, but they were invisible as stakeholders in the process.

MEMBER RUBENSTEIN: Mary, did you

want to respond? She left. Okay.

Is Jim here? Did you want to respond to any of the questions?

DR. DOROSHOW: I don't know if I can remember them all, but I'll try in some order.

So, just so that everybody understands, the NIH RAID program really began as a road map initiative that NCI sponsored. We have been intimately involved, and I think almost certainly will continue to provide toxicology and pharmacology expertise as that grows where there are overlaps.

I sit on the TRND Trans-NIH Oversight Board, and Dr. Austin is one of the members of our CBC Consortium. So I don't know how you would have much closer interaction. He knows everything that's going on in our program, and I have a good handle on what goes on in TRND.

I think the other thing that needs to be clear is that some resources are

generalizable; some are not. Cancer models are cancer models. They don't help a lot for systemic sclerosis or hypertension.

So, there are levels of expertise that are important with regard to the specific pre-clinical models utilized. And, also, I think it's very important -- a point I would like to make is that the linkage of whatever we do pre-clinically to having the investigators who are expert at the disease bring things to proof-of-concept, proof-of-mechanism trials. If you don't have those people who are invested in high-risk ideas, who can then, in fact, translate to patients -- there is a very small breed of those individuals who really understand enough to make a difference.

I don't think, if we just only stay in the discovery space, or even if you just stay in the development space and make GMP product for people, unfortunately, in the past NCI made products for people that never

got utilized because the investigator for whom we made it didn't know to file an IND. That will never happen again. We have restructured our entire program. If we make something, it's going to go into a patient.

But you have to have, I think, one way or another, the kinds of expertise for the disease entities that you are looking at to make things actually get from the beginning of the target to usefully be studied in a proof-of-mechanism study.

MEMBER RUBENSTEIN: Thank you.

Susan, do you want to comment?

DR. OLD: Yes. Yes, we all do talk a lot, TRND and CGC. So, Chris Austin is the director of those programs, and we have met, actually, with everybody at this table and half the people around this room.

Part of our governance structure is this trans-NIH advisory group, which every institute is invited to sit on. Some send many members; some only send one. But it is more to

help us, but there is nothing to say it couldn't have a broader mission than that.

You asked a question about sort of an advisory council. So all of TRND's activities will go through the Advisory Council to the Director, Dr. Collins' Council. There's a working group that will look at sort of the bigger-picture programmatic issues as well as the TAG, the Trans-NIH Working Group.

So we do a lot of talking. We have been over to the Clinical Center. We have met with NIAID several times. We're actually very integrated with RAID. We're on NEXT. So, yes.

Now what I do want to say is that the people in the know are the people in the know. There are a lot of people that don't know that CTSAs exist.

So we go out and we give lots of talks, and we interact a lot with where we think we might get some collaboration. So that is, where do you go to find people that have these things?

I can tell you one reason TRND exists is because Molecular Libraries were so successful. People were coming out with these great probes and wanting to put them in humans and not realizing there's about four years of work to take a probe to something that FDA will give you an IND for. So that's where TRND came out of.

But how do you do that? And we thought of a number of ways that we want TRND to help do that.

MEMBER RUBENSTEIN: All right. Why don't we stop you there?

Tom? We'll just finish up quickly.

DR. MILLER: Thanks.

I'll try to tackle the "Why haven't we made a lot more drugs?" This is a really complex question. It has a lot of answers, and I can speak mainly from the perspective of the Neurology Institute, but I think my comments are somewhat general.

I think these things I'm going to

mention, sort of a laundry list I put down here, are things that we are working on very actively in a variety of ways throughout our ICs. So we really need to stimulate early-phase development. We need target identification and validation. We need assay development, screening assay development. We need the development and, very importantly, the appropriate use of animal models. And there's a whole area there. I could spend 15 minutes on it, but I won't.

We have a real hole in our expertise for optimization of small molecules, medicinal chemistry in the nonprofit and small business sectors. As I say, we're approaching this from a variety -- we're trying to solve this in a number of days. It's very, very difficult.

We need large animal model development, which are increasingly being regarded by the extramural community and the FDA as relevant.

We need to do, and are doing, a lot of coaching of extramural investigators. We need to disseminate expertise and change the mindset to applied research.

So let me move quickly to, do we talk to TRND and NCI? Oh, yes, do we ever, very much so.

So the NIH, here's the deal: applied research, by its fundamental nature, is interdisciplinary, and translational research is the applied research of human biology. When you want to combine disciplines, you need to move to a partnering paradigm.

So, what we have had in basic science is a collaboration paradigm. Collaboration is defined as working together. This is what human beings don't do very well. This is contrary to human nature.

Collaborations tend to be informal, imbalanced, to have subagendas, and they frequently fall apart due to these, as opposed to partnerships, which are documented;

they're written down. Everybody is a winner. Everybody's role and reward is defined upfront, as is defined how the parties will part ways, if they don't get along.

MEMBER RUBENSTEIN: Okay, Tom. It had better be short.

DR. MILLER: This is what we're doing in NIH RAID.

MEMBER RUBENSTEIN: I just want to keep it short. We've got to get Michael and John in, and then Dan has the last few minutes.

DR. KURILLA: All right. I would say, to your question about why aren't we making more drugs, I think, like our counterparts in vertically-integrated pharmaceutical companies, our resources are discovering lots of promising inhibitors. Whether or not they go on to become licensed drugs that are available commercially, I'm not convinced that we're doing any less success than the large pharmaceutical companies are,

and they have an overwhelming majority of "me, too" drugs which we're not focused on.

I think the other area that we face, which has been a struggle, and we're finding ways to address that, is that a lot of our concepts tend to be extremely high-risk, very novel, very innovative, and require some novel, innovative regulatory science in order to identify and craft successful strategies to actually develop those drugs.

The other component that is difficult at times is we're not going to do in general, although we can do it, if we had to do it, the commercial development activity, which means we have to transition our programs to a for-profit sector that's going to carry it forward. And in many instances, we can have products come to a Phase II proof-of-concept and not have an adequate transition partner who will take it on. The biotech entity that we have supported that has taken it that far simply doesn't have the resources and

capabilities to carry that out. They need to be able to partner. And with the ever-shrinking number of large pharmaceutical, vertically-integrated companies who have the capacity, it becomes a smaller and smaller pool from which to draw.

So, those are the two major issues I think that are unique to a lot of the programs at NIH.

MEMBER RUBENSTEIN: Thank you. That was very helpful.

John?

DIRECTOR GALLIN: Yes, I will address the first question, who speaks to whom? We have spoken, as you have heard, to TRND, but we have more than spoken with them. As a result of the discussions with Chris Austin, we actually have TRND supporting some of the bench-to-bedside award programs between intramural and extramural investigators initiated through the Clinical Center. And that's this year, and it's been, I think,

terrific.

The second group we talk to a lot are the CTSAs. A lot of the people in the Clinical Center sit on the different committees of the CTSAs, and I participate on the PI Committee. I'm a little overwhelmed with the number of committees, but there's been good communication.

Then, of course, people in the intramural programs speak to each other. The Clinical Center meets with each institute leadership once a year to plan what they are doing, and it works, but it is siloed pretty much, the planning at the institute level.

I'm still not convinced that we are as good as we should be in terms of planning across the activities among the different Institutes. It's something to work on.

MEMBER RUBENSTEIN: Thanks.

And finally, Dan, you have got three minutes from the box here and Norm.

MEMBER GOLDIN: I will follow up on what Norm said. He had talked about wind tunnels at NASA. Right after the defense industry and the aerospace industry went through a similar situation that I see with the pharmaceuticals, there was something called the Last Supper that Bill Perry held, when the peace dividend was to be paid for the defense budget, and there was a tremendous consolidation within the industry, and a lot of collaboration and sharing had to take place.

The initial NASA reaction to use the facilities: well, let's make up a lot of money from the contractors from these facilities and let's let the legal department control what was going on, and let the Congress tell us about how we ought to make money from the contractors. It didn't work.

But when the NASA leadership took charge of it, and we recognized that we were there, the taxpayers spent billions of dollars

for the agency to put up facilities, develop technologies, develop analytical tools. All the same things I'm hearing here.

And we had a realistic policy that straightened out the IP ownership that didn't charge ridiculous rates, that incentivized the NASA team to say: it's not just what you're doing; you're here to support the commercial industry.

So there are a whole variety of facilities that got used. Overhead from the industry went down. There was a real benefit to be achieved.

And I really think I'm hearing the same thing now that I heard in 1992 and `93 as we went through that transition. I encourage you, Francis, to stick with it because you have a great opportunity to help the entire pharmaceutical industry of this country.

MEMBER BRODY: It's a great idea, except we now live in this crazy conflict-of-interest world which says this is a bad thing

to do. I agree with you completely, but we have to figure out how to change the external public perception.

MEMBER GOLDIN: Well, what you need to do is you take a firm stand and you work with the Congress quietly, not at hearings. It takes lots of work with them, and then you work with the White House. It is workable.

And we worked with a White House of one party and a House and Senate of another party with incredible -- if you remember back to `94 and `95, it wasn't any easier than it is now, and you can work these things. That's my contention.

Now, you're not going to get 100 percent, but if you settle for 30-40 percent, you've made a step forward. That's my comment.

CHAIR AUGUSTINE: With that, I think what we will do is cut the break down. So, we will start the panel promptly at 3:10. That's 10 minutes from now.

Thank you all.

(Whereupon, the foregoing matter went off the record at 3:02 p.m. and went back on the record at 3:11 p.m.)

CHAIR AUGUSTINE: Okay. Before we launch into the next session, Francis has volunteered to present a chart to kind of offer an overview, an integrated overview, of some of what we have just heard.

Francis?

DIRECTOR COLLINS: So this is actually a diagram that you may remember seeing before. But given the questions about, "Wait a minute. How do all these various components fit together?", I thought it might be useful just for a quick context reminder to put this up again.

Again, this is a rather schematized and oversimplified diagram of the process of going from target identification to an FDA-approved compound with the various steps outlined there.

The NCGC is one component of the

NIH Molecular Library. So, when you heard about that from Susan Old, that is one of the four centers funded by the Common Fund that provides expertise in assay development, high throughput screening, and medicinal chemistry to go from probe to lead.

The TRND and the RAID programs sit in this space of pre-clinical to try to move you, then, from a promising compound to something that could be sent to the FDA as an IND.

And in regard to these Phase 0, I, II, and III clinical trials, there are various players here, including, of course, pharma and biotech, the Clinical Center, and the CTSAs.

The new NIH/FDA partnerships that we have developed in terms of the Leadership Council with Peggy Hamburg and the regulatory science effort fits here.

The Cures Acceleration Network, the legislation is written pretty broadly to cover a lot of this activity, but I think the

main focus is intended, again, to be in this pre-clinical space, which is often where the greatest challenges lie.

But this doesn't include anywhere near all of the components that are going on, and you have heard about many of them in the last couple of hours. These are basically the ones that are more centralized. Individual institutes, as you have heard, have vigorous programs of their own in translation, many of them having been derived a substantially longer time ago than any of the things you see here. And that is something that we should, I think, be glad about because this is an opportunity to do comparisons in terms of the effectiveness of various approaches.

The challenge, though, I think is that, while NCI and NIAID and NINDS and NIMH may have these kinds of translational programs that can actually take a rare disease or even an untouched target for a common disease and push it forward, many of the other 27

institutes and centers do not have that capability. And hence, the need for some kind of centralized ability to offer those services. I think that is what this has started to do.

And I will say that, even for those institutes that have had active involvement in this area, when you look and see the utilization of those efforts, it is clear that there is a greater need perhaps than was being met. You saw the diagram from NCGC of where their projects come from, and a lot of them, in fact, are infectious disease and cancer, just because that's where there's a lot of opportunities now.

I guess from my perspective, to sort of again call back to mind the question that we're asking the TMAT Working Group to consider here, is there an opportunity to try to coordinate this effort more effectively? The need for some kind of central approach to this does come to mind in terms of economy-of-

scale issues, and that ought to be something to think about.

I think it also comes to mind in terms of the opportunity to do process engineering of the actual pipeline, which you could imagine doing in a circumstance where that is part of the enterprise, as opposed to a number of disconnected enterprises that don't really take full advantage of the learning process that you might get by looking at the whole landscape together. So, that's another issue.

I guess another thing to think about is how training can feed into this and whether that also is being optimally met right now. I think the questions that were raised with regard to Garret's presentation are highly relevant.

And then the whole issue of project managers and the right mechanism for actually pushing projects forward to success, which may not always fit very well with the

traditional academic model of give somebody a grant and hope it all turns out well. And there again, I think one of the things that we are hoping to do with the Cures Acceleration Network encouragement is to pilot at least the effort of having more vigorously involved and empowered project managers, in addition to lots of academic investigators who are part of that team.

So, I don't think that really fills in all the answers to the questions that were raised a little bit ago, but maybe you get a little bit of sense of what's here.

There was a question raised at the break about, how many of these programs are big and how many are small? And we can get you that information.

One of my big concerns is that we have impedance mismatches here, that you have resources, but they are not really balanced in the way that you would like for what the needs are going to be. And would it actually be more

effective to do this if that was part of your plan and you weren't just hoping that the handoff worked in terms of the throughputs that were possible in each one of these steps?

So, I would just stop there, but I thought it might be useful before we go on.

CHAIR AUGUSTINE: I think it was. Francis, thank you.

Okay, let's turn to our final panel of the day. And once again, these folks have kind of turned their lives upside-down to be here. So I certainly want to thank you all for your participation.

Our two moderators are Griff and Bill. Griff, I understand you are to start.

MEMBER RODGERS: Sure. So thanks, Norm.

I am very pleased to co-moderate this part of the discussion on bridging the gaps and defining the understanding of the necessary NIH capabilities and infrastructure.

I think before the break we had a

fairly rich discussion of some of the infrastructure capabilities that exist certainly within our intramural program. We have heard about RAID, and we have heard about the TRND program and others.

Also, we heard from two outstanding colleagues on the extramural side on their concept of TMAT and how this might integrate with the CTSAs.

We now have a group of five panelists, three from the extramural side and two from intramural, who will continue this discussion and really serve as discussants to kind of advise us on how can this infrastructure capability best be utilized in this outline that Francis just quickly reviewed for us.

There are several discussion questions that were provided to the discussants moving forward. So, perhaps we can start off by just having them give a brief comment related to the first discussion

question, that is, what lessons are learned from the academic drug discovery that can be extrapolated to the NIH agency moving forward?

One of the important things about getting advice sort of in strategic planning, and obviously, it's not only what it is that you should do, but maybe also hearing what areas you should stay away from, that it may not be a profitable use of our time and effort, given what's going on in the outside, to really tackle.

So let me turn, first, to Dr. Bergan and ask him for his comments, and then I'll turn it back over to Bill to sort of field the questions.

So, Dr. Bergan?

DR. BERGAN: Yes, just comments on the first question. I don't have any great insights to that, but I would just like to point out that a lot of the confusion and misunderstanding that we are seeing with just the understanding of what is going on in the

NIH Intramural Program with all the vast resources that are available, actually, to some extent, emulates what we have seen happen in the large pharmaceutical companies. So, a major problem still relates to integration of these large and potentially very powerful resources. That needs to be altered to increase efficiency.

MEMBER ROPER: I was just -- over to you -- asking the question, should we go to the others or maybe I can add a comment?

I think that the questions posed here are interesting, but they really all devolve to what Harold and Francis and Tony earlier said. And that is, what should NIH do?

We can all agree the world would work better if the world worked better, but what are the things that NIH should do in practical terms tomorrow?

Rob, do you want to take that?

DR. BERGAN: Oh, actually, that was the question I was prepared to answer.

(Laughter.)

MEMBER ROPER: All right, go ahead.

MEMBER RODGERS: That is basically, what is it that we can optimally do and what probably should we not do?

DR. BERGAN: Yes, I think there's two broad themes that you can do. I think that the first is increase the perceived value and appreciation for someone who does research that crosses disciplines. Put whatever name you want on it, translational research, cross-disciplinary research. There is just a disincentive for people to do that.

And I would like to highlight a little anecdote. I also run a basic research lab. So I like to read general monographs on how to run a lab.

And there's one that came out of a very prominent Howard Hughes investigator, dealt with all the aspects of running the lab. This was geared to a junior investigator, but there's still some very important aspects to

it.

But there's one component that related to counseling a colleague who you were mentoring who wasn't doing so well scientifically, and here we're talking about basic science. And basically, the recommendation was to tell him to go into translational research.

(Laughter.)

And that perception actually pervades all of academia, where people who do that are perceived of lower class, not worthy. So there's a disincentive to go into that.

So, I think that one of the things that NIH needs to do is to highlight the importance of these individuals, and this has been mentioned a number of times today.

I think the second broad theme that NIH can do is increase the freedom and the resources given to individuals. And here I'm speaking mostly from the academic standpoint, to be able to accomplish two

goals.

One I mentioned at the microphone, is to re-engineer the process, to investigate the specific components of the process. Because, frankly, everything that we have seen here today and everything we see with the drugs, it is all anecdotally, anecdotally failures. Even when we get the information, they're anecdotal. And anecdotal successes, and the successes are "Gosh, gee whiz." And so it's "gosh, gee whiz science." And that's bad science.

So there are very few things that have actually been investigated that have been hypothesis-driven. Can we get a chemist and a biologist to sit down in the same room and to actually work together to design a study to use chemi-informatics to identify new biological targets? It happens very rarely, but it doesn't in the context of a large, prospectively designed program.

And then the second aspect to

that, which again relates to freedom and resources, is the theme of guidance. And we have all seen these diagrams going from bench into clinic and with all these points, and there's very few people who actually understand those points, all those points.

I do, as a physician scientist, and I would bet most of the people in this room do, but outside of this room very few people do. And even though NIH may offer the resources, they are completely clueless. They're completely lost. They don't know how to go from step 1 to step 2.

And as something to think about, I run a Phase I and Phase II chemo-prevention program out of DCP. What they did was actually really smart.

How it used to work, and these are all biomarker-driven trials. So, first-time agents in demand or Phase II agents, and you are looking at cell and molecular endpoints. So, it is a nice link between therapeutics and

the bench.

But these trials are really, really hard to run, and there's multiple pitfalls. So, what they did is they actually farmed it out to six individuals that have established track records, and they basically semi-turfed their work to individuals like me, but I deal with a smaller pool of individuals. So, they'll come to me and I help them move across the different barriers to doing this. It serves as a guidepost.

So, the single word I want to leave with is one thing you should think about is funding people or programs that can be out there and serve as guideposts for multiple other individuals to move across the program.

MEMBER ROPER: Thanks.

Rob, if we can just pose the same question, what could, should NIH do? And I encourage all of you to be as crisp as you can, please.

DR. CALIFF: It was easy with the

first assignment, what lessons have we learned for an academic drug discovery? I would say we have learned we're just as miserable at it as industry has been. Any industry with a 99.8 percent failure rate has problems.

So, then, the second question is tougher, and I'll try to be brief. I listed seven things that I'll just throw out there and not say a whole lot about, because they have all been mentioned before.

I think the most important thing when you are in any academic environment -- and I have toured most of them that are in the CTSA because of our sort of founding role -- there is a real shortage of people who actually understand the logistics of this kind of applied research. It's really quite amazing, if you take the whole faculties at major institutions. You can wander around and just get lost, and people have no idea how you go from one place to another in translation.

So, there is a massive need to

repurpose the education and training programs if there's a belief that this is a valuable societal goal.

The second thing is a little more mundane, but it's really important, I think. It is the orientation away from we give you money and come back five years later to a project management approach. It's something that industry learned. Re-import it back into academia. We are actually finding, and I think others are, that it works quite well. It takes a little bit of a cultural adaptation.

You know, my personal anecdote there, I was telling Bob Lefkowitz, as you might imagine, when we put out our pilot grants for the CTSA, the first applicant was this young investigator named Bob Lefkowitz who needed a few dollars to do some chemistry with one of his discoveries. And when we told him that he was going to be under the purview of a project manager, he was not particularly thrilled. But it has worked out quite well,

and he has founded a new company based on some of that work.

The third -- and there are three subcategories here -- missed opportunities, I call it. That is, if we had met in the 12-step program, we have a problem.

The first is that right now we are operating on a shots-on-goal environment. That is, if you fail 99.8 percent of the time, it means you've got to take a lot of shots on goal to win. And I've had a hobby of trying to find people who have successfully developed more than one drug. And there aren't many of those. And if you say, how many have really personally been at the helm of successfully developing two drugs, you get into a very select group, and most of them will readily admit for them it's also shot-on-goal.

In other words, if you ask people to predict early on what's going to succeed and what's not, we're not good at it. I think we all have a belief that, if we can measure

systems biology more effectively and get a hint as to what's going on and all the pathways that were unintended, we could get a lot better at our probabilistic assessment, but none of us know how to do that. So that's a big area we need to focus on, I think.

The second has been alluded to a lot, and that's the failed effort issue. The way this whole enterprise has worked, including in academia, is if you failed, rather than talking about your failure, you want to act like you never failed and move on to something else. So there's not a record from which to develop the evidence base for probabilistic assessment. That is absolutely critical, and I think industry and academia together, we've talked about it and need to fix it.

The third is, I think, this boundary that I heard about, early and late phase, and industry does the late phase really well, so let's don't do it. I think that's

artificial and a detrimental idea. I understand why the NIH developed that way, but I would argue it's a different time.

If you look now at what I call the "double A" of Avandia and Avastin, you know, what we have is a system where people are incentivized to work through the FDA to develop a certain kind of evidence which almost never actually tells us about the comparative balance of risk and benefit in a true sense.

And coming along doing a whole other set of clinical studies to figure out how you actually ought to use a product, I think is detrimental to our society. How can you get $12 billion in profits 15 years out from Avandia and still not know whether it kills people or helps people? And now with the vast, some of the most elegant science in history, we're in exactly the same position, and the FDA is going to have to deal with that.

So, I think the artificial boundary is incorrect. The NIH and its academic centers and the CTSAs, I think, need to figure out how to do clinical trials efficiently so it costs half as much. And rather than seeing this as a set of handoffs, even in that sphere, we see it as a synthetic whole that goes from drug discovery all the way to comparative effectiveness, and pull it together.

The last four things quickly: deal with conflict of interest. I think there was a good discussion about that already. I think when you talk to young people, and we're still sort of really dancing around what's going on out there, it's daunting for young investigators today to think about actually inventing something and developing it, because the labeling that goes on and the rules are discouraging, frankly.

The big areas, I think Garret handled well: informatics, biostatistics,

systems pharmacology, and I would add engineering, systems engineering, to that. The workforce is not what it needs to be there.

You can't forget globalization. I don't have time to talk about it, but I think a lot of the action is not going to be in the United States, for a variety of reasons, not all of which is lower cost, a lot of which has to do with governments deciding that the artificial boundary with conflict of interest and the way it is handled in the U.S. is putting us at a cultural disadvantage that they're going to take advantage of.

I'm not arguing that we shouldn't have better conflict-of-interest policies. So, we've just got to work this out.

And then I would just add, sort of related to the artificial boundary, we shouldn't forget we're also failing in clinical research itself. That is, if you look at an average outcome trial that we're demanding now to really measure risk and

benefit, $500 million will be a reasonable cost for a pharmaceutically-run outcome clinical trial. If you took $200 million out of every one of those and put it back into systems biology of early evaluation of therapeutics, we would be a lot smarter.

And anyone who knows anything about this field knows that we are wasting at least half the money that we're spending on clinical trials on useless bureaucracy that's not helping anyone.

That's a short list.

MEMBER ROPER: Thank you, sir.

Dr. Halak?

DR. HALAK: Yes. So I guess it makes sense to just briefly talk about the perspective from which I'm speaking, because it might be a little bit different than many in the room.

I work at a venture capital firm that invests in early-stage medical technology. And when I say early-stage, it

creates a whole debate, because what Domain used to do back in 1985 was roam the campuses of academia, find an interesting concept, and carry it forward, translate it into a product. We did that with things like FUZEON from Trimeris out of Duke, which was one of the first or was the first fusion inhibitor for HIV.

Because of the pressures in our business, we are less able to invest in that earliest-stage technology. And those pressures are the timeframe with which our investors are demanding their money back, and the ability for us to get their money back comes much later in development.

So, you know, I think this topic of translating science into viable therapeutics is a timely one, because I think it's never been needed more than now, because one of the traditional sources of funding and expertise for that in some of these venture-backed companies is diminishing.

So, with that as an introduction, to answer the question, I'll basically combine the questions: what can NIH do, and this first question of, what have we learned from academic drug discovery? I'll answer what we have learned from some of our successful companies that have taken early-stage science and pushed them into products.

I think there are two big things I would highlight. One is incenting and rewarding people towards that goal. Then the second is -- I guess it would qualify as project management.

So, on the incenting and rewarding side, I can tell my own anecdote that speaks to this. I was a grad student getting my Ph.D. with no intention really to go into academic medicine. I always wanted to be an industry scientist. And this is about 11 or 12 years ago, when I told one of my thesis advisors that I was going to join a venture capital firm, his response was, "Oh, what a waste."

And I think that's a real problem. So, what is the answer to that? I think you do need to elevate these people. Other programs, the Chinese I know do, I think they call it A Thousand Stars Program. There's Genius Awards that have been given, something to take the best and the brightest people and drive them and incent them to go into this area.

Now, those awards that you have heard about in other settings are often cash awards to get people to go into that area. Then, after that, the incentive system we obviously use in our company is equity stakes. So, giving people equity stakes in the outcome of what they do.

Now, I'll leave that to you to figure out with the whole conflict-of-interest issues, but that's what I think has done well in our company, is to get people focused on the goal of driving therapeutics forward.

The second area in terms of

project management, I think, again, requires a cultural shift, because it's really about finding people that can manage a product with the end goal in mind. And deciding to not necessarily do the experiment that the scientist, left to his own devices would want to do, but the experiment that's going to prove if it's worth taking this scientific discovery towards the clinic or this molecule towards the clinic. That's a very daunting thing to do, because often you can get a negative answer.

If you keep doing basic science, you will never get a negative answer. You will always just get more information.

Sometimes when you're taking a molecule -- we often do an experiment -- a second best to a positive is a true negative. The worst answer is just more information, that we are just doing a lot of experiments.

So, we will often incent people that, if you do good work and you get a clean

answer, that will be part of your bonus program. If you are good and lucky, you'll get a larger bonus, right, if you're good and lucky and it actually works?

So, I think these are the two things from our world of small biotech companies that I think the NIH should think about. One, incenting and rewarding people and, No. 2, this concept of what I would call ruthless program management to do the critical experiment that gets from point A to point B in the most efficient manner.

MEMBER ROPER: Tom?

DR. INSEL: Well, since I'm at NIH, maybe what I'll do is give you two or three ideas about what I think we shouldn't do, because that's perhaps one of the places where we want to mitigate risk.

I think it would be a real mistake for us to assume that we're ever going to be anything that looks like a pharmaceutical company or that we even want to be. We have

neither the culture, the expertise, nor the incentives for any of that.

And pharmaceutical companies don't want to be pharmaceutical companies anymore. So, this is not something that we necessarily want to emulate.

I think Francis brought up this possibility of re-engineering the system, which makes a lot of sense, to look at what works, what doesn't. We have talked a lot internally about the quick-win/fast-fail approach rather than the shots-on-goal approach that Rob just mentioned.

And thinking about, how do you really drill down on issues like proof-of-concept, and how do you really determine when it's time to pull the trigger on the biology of a new target, all of those issues that we could probably do a much better job of than has been done up until now.

Also, I would stress that one of the places that we don't talk enough about,

when we're talking about re-engineering, is the recognition that that canonical pipeline that everybody puts up on their slides is really only one way, and it's actually not the way that most drugs ever make it through.

What usually happens in terms of drug discovery and drug development, at least in the area that I work in most, is repurposing. So, that is still an area that NIH can work in and do a lot of important support, if we could get the components that we don't have access to at the current time. And there are estimates of hundreds of thousands of compounds that are out there that have been shelved by pharma that might be a really interesting sort of medicine cabinet for all of us to think about using and think about how they could be used for either rare and neglected diseases or for off-target indications.

So, don't become a pharma would be the first thing I would say. The second is, I

think we need to get out of this box that we were talking about a little bit earlier about kind of what's intramural, what's extramural? It kind of went by too quickly to see it, but some of the things we're doing currently, like the NCGC, this Molecular Libraries effort, is an intramural program which 75 percent of the research that is going on is from extramural investigators. And that's a wonderful new model which we haven't seen enough of.

So, this is a place, I think, where we want to make sure we don't get bound up too much in this intramural/extramural division, because if we are going to have a new organization, and if most of it is going to live intramurally, I would hate to see it restricted to intramural scientists as a way of pushing innovation.

The last comment is, whenever we get into these kinds of conversations, I worry. NIH is very good on process. We spend a lot of time talking about structure and how

something should be organized. But, at the end of the day, it's really the science that counts.

So, what we need to make sure is, however this goes forward, it is driven by scientific opportunity, by understanding that there are really important questions that we are ready to answer, rather than simply chasing something because we think there's a real need and because we are getting a lot of push to do it.

Those things are real, but we can spend an awful lot of time and money in areas that aren't scientifically right. So I would encourage the group, too, as we think about this, to make sure we really keep an eye on where the science is, and where it's ready and where it isn't ready.

DR. MATTHEW: So I can start by complimenting my fellow panelists for raising very good points, because as each point was raised, I had to sort of scratch something

off.

(Laughter.)

I'm left with the challenge of saying something intelligent at the end.

You asked what should NIH do tomorrow. I'll start by sort of acknowledging an effort that Amy has been working on for probably two months.

Oh, let me first say, so I came to NIH a year ago to head the Office of Translational Research at Neurologic Disorders and Stroke, and I came from industry. I bring an industry perspective to everything I do. I came from a German company. So, it was a very efficient, a very disciplined, a very goal-oriented company, and I see some differences in the government and with extramural investigators

(Laughter.)

But what I referenced was so the Office of Translational Research, I have eight programs, all run by Program Directors that

are targeted translational research.

So, we heard sort of a summary today of sort of the high-profile projects, TRND, NEXT, RAID. So, NINDS has more than 10. So, one thing that I think NIH needs to do, and they are working on it, is to do an inventory. What are all the translational efforts that are going on across the 27 Institutes, and look at where they can synergize with one another. Because, you know, I believe most of these have grown up independently within the institutes and they don't synergize very much.

We heard from Susan and others that sort of the senior people, the senior leadership talk a lot and keep themselves well-informed about different programs and what's going on. But I think where there's a gap is at the Program Director level. These are the people who run these programs. They hold portfolios of grants. They're extremely busy, and I think they may hear what's going

on, but there's sort of no facilitation of them having the ability to work together, to work out problems together.

I mean, in our translational program a big component of this is constructing annual milestones for each of the projects, assessing how they're doing against these milestones. It requires expertise in pharmacology, toxicology, all kinds of things. And we're always trying to cobble it together with the expertise in-house, and we well know that across NIH there's lots and lots of expertise at the Program Director level that really should be tapped into.

What can be consolidated amongst all these efforts? We should look at what would benefit from consolidation, what wouldn't benefit from consolidation.

But, certainly, one area that just baffled me when I came here was the whole contract mechanisms of getting things done. The idea that there could be money on the

table ready to be spent, but you can't spend because you can't get access to a contract -- that's crazy. And I know just this year our contracts have become even more complicated. So, you know, to what extent consolidation, getting access to pharmtox, medchem, all these things through contracts, I think would help a lot of the programs.

And then, ultimately, I think we need to construct an organization that -- I will go back to my six years of German training -- it has to be disciplined. It has to be focused. It has to be very proactive.

And one of the challenges I've had in helping run the translational program is sort of the mindset of these extramural investigators. Even though upfront they know that U01 is a five-year program -- the ultimate target, they must have an IND at the end of the program, five years of funding, a million dollars direct costs a year, have to hit this milestone or you're discontinued --

they miss milestones and they say, "Well, I didn't know that what's a milestone was."

(Laughter.)

So there's a lot of education. There's a lot of information that has to be passed on, and sort of a lot, actually, a lot of guidance and discipline have to be applied to these programs.

MEMBER ROPER: Thank you. Thank you all.

I think we ought to turn to the Board and ask if you want to pose questions.

Griff, do you want to facilitate this?

MEMBER RODGERS: Sure.

Harold, your hand was up?

MEMBER VARMUS: Yes. I was going to make one comment a moment ago. I would like to make it and actually three, one major, a couple of small ones, just to comment on the entire exercise we are going through today.

First, I am going to tell you

something that I think everybody in the room knows, but it disturbs me that we are not following what we know. Translational research is not just about target identification and drug development. There's a whole list of things that should be part of a translational research repertoire: imaging, radiotherapy, diagnostic testing, biological markers for monitoring disease, immune therapy, not just antibodies as drugs, but cell therapies, vaccines. Prevention strategies I'm hearing nothing about. Devices, even gene therapy, siRNAs, delivery mechanisms for drugs.

And I think we have to think about a richer repertoire of translational activities and not just we have this drug company paradigm that we're talking about, and we're massaging that, and not thinking about the many other things that NIH can do to enrich what clinical medicine does with basic research to improve healthcare. That's the main thing I want to say.

Two other just brief moments. We have mentioned conflict of interest several times here. We need to get some clarity on what those conflicts are, because there are a lot of things that even people at NIH, even people like me or Francis who are presidentially-appointed, can do interacting with drug companies or other kinds of companies. We do that all the time.

We have to distinguish between what we can do as scientists and what we can do as private entrepreneurs, working for the government. They are two very different things, and I think we need to be very clear about that if we are going to give a report.

The last comment I would make picks up on a comment that Bob Califf made about globalization. The other face of globalization, aside from the part you mentioned, is the interest that we all have, especially Francis, in global health. We put into our formula of what NIH should be doing

in the translational domain things that specifically apply to poor countries, new sets of diseases, other ways of developing new diagnostics and therapeutics that are pertinent to poor countries, and maybe some IP issues as well.

But we have a responsibility there, and I think that if we are talking about the translational research activities at the NIH, we ought to think about our mission as developers of science that is useful globally, not just nationally.

MEMBER RODGERS: Gail?

MEMBER CASSELL: I just wanted to ask, with respect to your comments, Bill, about the contracts and access to some of those services that are provided through RAID. What are the mechanisms for evaluating the quality of the services, turnaround time? And are these contractors really responsive to iterations? If you have results come back, say in a PK study or formulation studies, how well

do you think they are working?

DR. MATTHEW: I don't have any first-hand exposure to the contracts. People at NCI, they're apparently the contract gurus of NIH.

But, I mean, they work as contractors. I mean, they have very explicit this is what has to be done; this is what you do. They deliver the report.

I have a contract with the University of Utah for an anti-convulsive screening program, and it's very much that way. There's a contract that specifies how many compounds they have to screen and what assays, and the compounds are shipped and they deliver back.

But you have a more subtle nuance there of how facile are they in changing what needs to be done. Is there somebody from NCI or maybe anyone have some insight on that?

MEMBER FAUCI: I'm not from NCI, but I don't understand what you're talking,

your problem. I don't understand what the problem is. What about the contract? I'm not criticizing. I just don't understand it. What is it about dealing with contracts that puzzles your German-based --

(Laughter.)

DR. MATTHEW: So I know that RAID had six projects ready to be funded. It was coming down to the last minute. They have always had to rely on going to other institutes for capacity in contracts. That fell apart, and at the last minute it was like, where can we get contract capacity? And TRND was able to --

MEMBER FAUCI: So you're talking about the NIH-employed contract managers? Is that what you're talking about?

MEMBER CASSELL: No, no, no, no. This would be contract toxicology, pharmacology, PK studies, turnaround time, queues, how long it takes you to get an answer whether or not you'll even be able to access

them, and waiting six months to get an answer back that should take two weeks.

MEMBER FAUCI: Yes, but you could terminate a contract at the discretion of the government, if they're not performing. So, if that's the issue --

DR. MATTHEW: No, no, no. I wasn't raising this as an issue that the contractors weren't performing. It was that you need to have -- so these contracts get put in place. They have a certain dollar amount to them. They're tied to the specific institutes for this much pharmatox work.

If you rely on another institute to help you get this pharmatox work done, and they use that capacity in the contract, well, they can't help you.

And it's not easy to create new contracts. We're working on the new contracts for the Blueprint Neurotherapeutics right now, and it is a very laborious process to put a contract in place to get this work done.

DR. CALIFF: I don't know if this is helpful or not. We probably do more contract work than most research institutes because we're a clinical research institute. It's a different ball game than grants, and there are a lot more rules. You just have to know the rules, and everybody on all sides has to know the rules.

So, since everything is tied to a deliverable, the flexibility is not there, except dealing with the rules in a way which is prescribed. So, it just takes more steps.

Many academic centers or segments of academic centers aren't facile on their end --

MEMBER BRODY: Can I suggest that, although this may be a very important problem, that it's probably at a much lower level of detail than we need to do? Let's kind of move up.

MEMBER RODGERS: Richard?

MEMBER HODES: The conversation has

been interesting in many dimensions. One of them is the relative philosophies of the investigator who pursues science for the beauty of science, discovery. And the other is management of science.

And I wonder if any of you, particularly from experience, have a sense of how the ultimate reconciliation of these goes. There are a number of possibilities.

One is that the basic scientist is inspired to understand that he or she needs to be managed in order to achieve a goal, and there's an evolution. The other is to set aside a separate career path, hopefully, not a second-rate path, but a distinct path, to be sure, of somebody who is trained to be managed and part of a team. Or we work as we do now.

Are these destined to be separate tracks? Do we need to re-educate a large portion of our discovery scientific population? I mean, who has seen successes and challenges that lead them to think that one

direction or another is the path we're taking?

DR. HALAK: You know, I'm not sure there's a crisp answer about distinct or pushing them together. I think you ultimately end up getting down to the level of individuals.

I was trying to think of something that could actually be done tomorrow. Okay? So, this is a little difficult. But I would pick up the phone and call 10 entrepreneurs that have taken science forward into things that have benefitted, you know, from basic science in human health, and have them come to the NIH and talk to people, not about science, but about that process.

Maybe that already happens. Maybe you already have the founder of various companies talking, again, not about their scientific discovery, but the process, and inspiring people that that's an exciting career path to pursue.

I think when I hear you talk

about, do we have a problem in our basic science, I think there is an enormous amount of pressure -- I gave my anecdote, and I think there was another anecdote -- within the scientific community that, in fact, going translational versus basic is a second-rate career decision. So I think that is a fundamental problem.

And I don't think there is an institute you can put in place or a center or something that will magically change that. I think it is continually reinforcing that that's not the case.

DR. CALIFF: I would say, you know, we are four years into the experiment of trying to do this at an institution. And I would say the natural evolution of the science is making it so it's less of a problem now than it was.

That is, we have no shortage of previous discovery scientists who are coming to us saying, "I've got this thing, and it

needs to be translated. Can you help me do it?"

I think it is an important experiment, maybe within the CTSAs, if it can be measured to see which types of management systems and interfaces on average are most effective -- although I agree, in the end, in the individual case, some people culturally are just not capable of living in that environment, and they are really good at living in the discovery environment. Other people adapt to it right away.

And we have had a number of people that are converted. They just love it, because they hadn't thought about things. The experience of the person five years into a project who says, "I forgot about the deliverables," a lot of those people actually like it when there's a really good project manager, often with a Ph.D., who didn't want to go into the pure basic science, but likes to manage and is friendly. It can be very

positive.

DR. BERGAN: Yes, my read on that, it's all science. So, if you want to know if viruses can induce oncogenes, that's science. If you have shown that and want to make a drug to it, and you approach a chemist to make a drug that can specifically target that, that's synthetic science and then it's molecular pharmacology. And if you want to formulate that into something that the human body can tolerate, that's called formulation. That's science. If you want to give it to people in a Phase I and Phase II trial, that's science. And if you prove it in a Phase III trial, that's science, and then it's marketing.

MEMBER HODES: But, in particular, what we are hearing from a number of you is that, at the level of basic science, there's little argument that one needs to manage the scientists. As you move along the spectrum as you describe it, the requirement for management of science increases. And that's

really the dimension, I think, where there's a differential receptivity or effect culture-dependent upon individual investigators.

MEMBER RODGERS: Tony?

MEMBER FAUCI: Just a comment that may have a question associated with it. I think this is going to be relevant for what we are going to be talking about tomorrow also.

But we went through a similar experience that I will take one minute to share with you. When we went through the flu H1N1 pandemic and we didn't have vaccine ready for the peak of the infection rate, the President of the United States brought several of us down to the Situation Room, including CDC, FDA, and myself representing the NIH, and asked, "How could it be that we invest billions of dollars in the NIH, we invest billions of dollars in the CDC, hundreds of millions of dollars in the FDA, and we deal with industry, and we have this crisis, and we can't even get a vaccine?"

So, as you might imagine, that launched a thousand ships, including a weekly meeting that I had in the Situation Room for a year, meeting with the people from National Security and others.

And to make a long story short, we got a lot of groups involved, including PCAST, when Harold was out at Memorial Sloan-Kettering, and he co-chaired that with Eric Lander.

And we came up with a bunch of recommendations regarding how we can develop, they used the word "countermeasures", but it was really for everything. So you could sort of pull that out and say "drugs". Several of the things that came out were five quick ones.

One is, what can the government do to get industry more incentivized to get involved in making products that are needed for public health that they may not want to make? And they recommended hundreds of millions of dollars investment in

manufacturing capacity that the industry themselves didn't think it would be worth their while making those hundreds of millions of dollars investment.

The other was get the FDA to stop being an obstacle, but being a facilitator. And the conclusion was that they needed more investment in regulatory science. And hence, came the recommendation that Francis and Peggy Hamburg got involved with in having the NIH be closer with the FDA in bringing science to things like developing biomarkers and ways of evaluating.

The fourth was a somewhat controversial one of actually creating almost venture capital-like of an organization, so that you could support companies, not necessarily products, but companies that are willing to take the risk to make products that we need that aren't high-profit margin and to be able to support them.

And then the other one was the one

that Mike Kurilla so nicely described with the Concept Acceleration Program.

And then one was how to respond better to influenza. That was the fifth.

But the one that involved the NIH, after consultation with industry, with venture capitalist, with academia, some of which people were even involved in these deliberations today, the one recommendation that they made for the NIH was the thing that Mike Kurilla mentioned, was the Concept Acceleration Program, to be able to make sure that concepts that come out through basic science that we do so well don't die on the vine, that they actually can get shepherded or "sherpa-ed" through by giving them the reagents, the clinical trial capability, the animal models, et cetera.

The other role that the NIH was to work with the FDA, and what Francis started with Peggy Hamburg – so, just to put it into context, it was a year's worth of weekly

deliberations, and the two issues that the NIH played a role in was concept acceleration and interaction with the regulatory authority.

I just thought you might be interested in that.

DR. HALAK: What was the incentive to concept accelerate? Was there an incentive structure put in place?

MEMBER FAUCI: Someone had it all in one grant that they had a concept that was clear to people that could be translated into a product that would be useful for the public health, that it is likely that that individual -- and I think Rob may have mentioned that or Ray -- had no clue of how you take a concept and even get an IND. How do you deal with the FDA? How do you get it into a clinical trial? How do you get reagents to go to the next step?

So, money would be put into the NIH to be able to have a team of people who are very experienced in that to be able to

work either with the investigator him or herself, but to take that concept and put it in the hands of an organization that can actually take it from a concept to a product.

So, the incentive is you get a lot of help that you wouldn't get from your grant. You get reagents. You get access to clinical trial. You get to deal with the FDA for the first time by people who have done it every day. That's the incentive.

DR. HALAK: And how are the people that are doing that work incented, though, the people that are responsible?

MEMBER FAUCI: How were the NIH people that do that?

DR. HALAK: Yes. Okay. So it's a --

MEMBER FAUCI: No, these are going to be NIH people --

DR. HALAK: NIH people.

MEMBER FAUCI: -- whose job is to facilitate a concept into a product.

DR. HALAK: Got it. Okay.

DR. BERGAN: I think one aspect of that to consider is you used the word "take", and I know you didn't have time to formulate this, but, in essence, the basic researcher would then give it up. It would go somewhere else. Well, there would be links, but it would go to some central federal agency down here, and they would be out there, and you could do that.

But the point that I am trying to emphasize here is that you have to build in some maintenance of intimacy, ownership, and connectedness. If not, then it's a passing-along.

MEMBER FAUCI: That is a very good point. And we would love to have the investigator take that journey as an important part of that. If the person did not want to get involved, but wanted to get to their next *Nature* or *Science* paper, that would be fine. But if they wanted to be part of the partnership of taking it straight through,

they could do it.

DR. BERGAN: I guess what I'm saying is, no, that's not fine because then you're getting this, you know, do this little bit, and the person who knows more about that biology than anyone else in the world doesn't have much incentive and, as you allude to, is trained to just think about the next paper. So, some change in incentivation has to be built into that, so that they actually want to remain involved.

DR. CALIFF: I would argue this is a legitimate debate about which there are many opinions, but, to me, it's actually at the core of what I regard as a key conflict-of-interest issue. Because at many of the institutions now, the minute you go beyond a certain step for the inventor, if there's IP involved, to be involved at the level you're describing gets to be very tricky, actually.

DR. BERGAN: I don't think it's tricky. You just have to declare it. Yes, I

invented this. Yes, if it makes a lot of money, I, too, will make money because I filed a patent. And, yes, I'm involved in it.

MEMBER RUBENSTEIN: No, it's not that simple, believe you me.

(Laughter.)

There are rules against, as Rob is saying, people developing these things and having an economic incentive to do the clinical trial. So it is a complicated thing which one has to deal with.

MEMBER RODGERS: Gail?

MEMBER CASSELL: One thing that I would like to just remind us about, and we have talked about it before in the committee, is the development of appropriate animal models for evaluation of efficacy.

And NCI used to have a program in which it specifically provided training grants for training DVM Ph.D.s and development of animal models and also for discovery of naturally-occurring diseases in animals that,

in fact, are very good models of human disease, both genetically-inherited as well as infectious diseases, et cetera.

That program was dissolved some time ago. And I think, in fact, about five years ago, the veterinary deans got together and declared a crisis in the area of laboratory animal medicine and actually, I think, brought it to everybody's attention, but it kind of died. And I still think this is a big void and just would like to bring that up again.

MEMBER ZOGHBI: I actually would like to amplify Gail's point. Worst yet than developing animal models is having consistent and better characterization of existing models, putting on the shelf bad models that have been used in many pre-clinical trials, and unfortunately, led to expensive and failed clinical trials.

You know, I can give great details about how poor the use and characterization of

clinical models have been. So I think this is really an important point.

MEMBER CASSELL: I could just expand on that. In the area of TB drug development there are about five different animal models, and there's no consensus as to which one is best. I think you waste a lot of money, lose a lot of time because of this.

MEMBER RODGERS: Well, any other comments?

Yes, Norm?

CHAIR AUGUSTINE: I'm just going to kind of weigh-in at the end of this. If I were to kind of forecast the future, I am struck by the likelihood that the private sector industry is going to invest less and less effort in basic research because of the pressures of the marketplace to produce profits next quarter.

That being the case, I think we are heavily dependent upon our universities to conduct the research that is going to provide

the new drugs and all the other things that Harold mentioned, as funded by the government.

I have a concern, as I listen to the discussion, that a good academic researcher comes up with a great idea, would like to write a terrific paper, have it peer-reviewed and published, and then go on to the next paper, rather than to pursue this to a product that helps the public health.

The reason for that, I guess, from the discussion is that one's prestige in a community depends upon the quality of the paper rather than going out and trying to make a profit with a product. But even if this researcher is of the kind that would like to go out and make a profit with a product, I've been burned a little bit at this place myself on the subject of conflicts of interest, and it's not easy. That researcher takes a fair amount of exposure.

And that being the case, the question comes up, well, then how do you

translate basic research into products that help public health?

As I listen to the discussion, I was reminded, I was involved in a tiny way helping MIT set up a systems engineering program a few years ago. And you could have substituted that discussion for the one I heard today; just put systems engineering in for translational research. It has the quality that it cuts across all the departments, and every department considers it second-rate.

So it is very hard to get tenure. It's very hard to get your Ph.D. approved. You're viewed as second-rate if you go through this process.

And where I was headed here, trying to be a little bit constructive, one of the things that helped a great deal at MIT was that I think there are 10 University professors there, and about four of them had reached the point in their career they had become very interested in big problems that

kind of forced them to move out of their own field and look across the board.

About four of these institute professors voluntarily went into the systems engineering creation department, and it gave it instant prestige among the students and some of the faculty. And maybe I just cite that as trying to offer something constructive.

There may be here and elsewhere some really outstanding researchers with all the credentials that have reached a point that they would like to deal with some bigger issues, and maybe there's something there.

DIRECTOR COLLINS: So, Norm, since you and Dan and others have sort of pointed to historical parallels, I can't resist plunging in here, too. Because there was a time where people assumed that nobody would want to be involved in the genome project because it was mindless, because it would not give you personally much credit; you would be part of a

very large team effort. You were required to give all your data away, even before you published it. Who would want to be part of that? And yet, it eventually became a magnet for some of the best and brightest scientists because of its potential impact.

And I think we could make some of those same arguments here. I mean, why do people go into biomedical research? A whole bunch of reasons. Curiosity is a pretty good one, the chance to learn something that wasn't known before, but, also, I think particularly because it's biomedical research, a desire to try to lead to something with clinical benefit, to help somebody.

I think many basic scientists probably, when they're talking to their grandmothers, refer to their own hopes that maybe what they're doing might have some role in that kind of public benefit. And to provide that as a real possibility, in my experience, is generally welcomed as, "Oh, wow, I didn't

know that I could actually be part of going to those next steps." "I have no idea how" is usually the second part of the conversation, but to provide that capability is actually, I think, pretty well-received.

Rob has talked about this as well, and it may require, then, having a project manager who can actually make sure I don't slip back into academic mode. But there again, in the genome project we learned how to do that, and it worked pretty well, once people got over being a little ruffled by being told what to do, and that their milestones had to be met or there were going to be really serious consequences.

And the other attribute to the other resource that NIH would have in this circumstance is the funding. There again, it may be hard to herd cats, but you can always move their food.

(Laughter.)

It has an effect.

CHAIR AUGUSTINE: I like that. Not to try to one-up you, but as Vince Lombardi said, if you are not fired with enthusiasm, you will be fired with enthusiasm.

(Laughter.)

On those two philosophical notes, I think we have reached a low point.

(Laughter.)

Let me thank each of the panelists. Again, we recognize the amount of effort you went to be here. If you have thoughts as you fly home or as you go back to your facilities as to the things you wish you had said, boy, we would welcome them. So feel free to send us emails, and that applies to anybody in the room, of course.

Griff and Bill, thank you for your part here.

Oh, yes, and as Amy points out, you are very welcome to stay tomorrow, too, if you would like.

We turn to the public session

here, where we would like comments. We have one person who has signed up. So we would ask that individual to make their remarks and hold them to five minutes.

It's James Jorkasky, who is with the National Alliance for Eye and Vision Research.

So let me welcome you. There is a microphone there. Thank you for joining us.

MR. JORKASKY: I guess I'm holding everybody up from going home, but I did want to make a few comments. Thank you for your attention.

Again, I'm James Jorkasky. I'm the Executive Director of the National Alliance for Eye and Vision Research.

We are a patient and advocacy organization, also known as the Friends of the National Eye Institute. I don't speak for the NEI, but I do speak about its accomplishments.

I definitely appreciate the opportunity to listen to the discussions

today. I'm a former research scientist, and it has kind of been my chicken soup for my intellectual soul.

I had an outline for my comments. What I have done is, in between sessions, kind of scribbled in points that relate to what's been already said today to make them completely relevant.

Although I realize the TMAT discussions will continue, they're in their infancy and will continue tomorrow, I did want to inform you about clinical and translational initiatives in the vision space. I am commenting for three reasons.

None of the panelists so far represent vision research. Although the NEI is a relatively-small institute, it has conducted a number of smart translational collaborations that have effectively expanded its research dollars.

And third, NEI's translational research includes a number of what Dr.

Perakslis mentioned, patient solutions, or as Dr. Varmus said most recently, richer repertoire of translational research. That is drugs, devices, combinations thereof, diagnostics, and gene therapy.

Now, as the TMAT proceeds, I hope it works with the NIH staff to become aware of all of these novel and effective translational collaborations being conducted by all of the ICs within the NIH.

Now specifically about the NEI. Just June of this year, the NEI conducted a translational research in vision meeting, which concluded its 40th anniversary celebration. And at that event, Dr. Collins provided a keynote address where he stated that the NEI has been central to advances in translational research.

I think one of the reasons why that has been true is, as a relatively-small institute, it has really worked in collaborative ways inside the NIH, inside the

Department of Health and Human Services, with other government agencies, with private funding organizations, and internationally. Just a few examples here:

Inside the NIH, it's worked collaboratively with the NHLBI, and, of course, what has come out of that is the anti-VEGFs and the FDA approval of Lucentis to treat age-related macular degeneration.

Also within the NIH, NEI has collaborated with the NIDDK on an ongoing series of diabetic retinopathy clinical research networks, which have come up with optimal treatment for diabetic retinopathy.

I mention those two because each has now resulted in a comparative effectiveness study of one comparing Lucentis and Avastin called "the Comparison of AMD Treatment Trials", and on the diabetes side, a comparison of laser photocoagulation for diabetic edema, macular edema, alone, or laser photocoagulation along with Lucentis anti-

VEGF.

And as been mentioned earlier by a couple of the folks, there is an interesting concern about incorporating comparative effectiveness into the U.S. more completely, like it is in Europe.

Within the Department of Health and Human Services, NEI has now held a series of endpoints meetings with the Food and Drug Administration. What's really come out of this is not only the FDA better understanding NIH NEI-funded research, but how could that potentially impact upon potentially more progressive regulatory considerations.

In fact, just a week from this Friday, there will be the second of an endpoints meeting on glaucoma. It's a very exciting time in glaucoma research, because researchers are truly understanding it now as a complex neurodegenerative disease.

NEI collaborations with other government agencies include a collaboration

with the Department of Energy on an artificial retina. Essentially, folks that have been blind for 50 years are now able to see images and navigate their homes and their communities.

Also, and this is one that you kind of have to see it to believe it, is an NEI collaboration with NASA on a probe that measures light scattering within the eye. And if you're sort of a quart low on your alpha crystalline in your eye, then you are more likely to develop a cataract, in plain English.

In the private collaborations, the NEI has collaborated with the Foundation Fighting Blindness in some really earth-shattering human gene therapy trials for Leber congenital amaurosis, which is a very virulent neurodegenerative disease. Essentially, there's been very successful initial trials on that which are now being expanded to even younger children. And again, this is a disease

that usually blinds children by the time they are 20 years old. The first phase is so successful, they are now adding even younger children to that to retain vision.

And finally, in the international space, because of the breakthrough work that NEI has done with the human genome project on the genetic basis of eye disease, the NEI has formed an international AMD age-related macular degeneration gene consortium, essentially, sharing information with researchers around the world, such that the latest information can be used to then look at translation and to diagnostics and to therapies.

In fact, a week from this Thursday, my organization is sponsoring a Capitol Hill briefing to educate staffers about NEI's work on AMD, and it's got a very international flavor to it.

So, again, I just urge the TMAT in its deliberations to not only consider all of

the topics today, the cross-cutting programs within the NIH, but, of course, to take a look at the kinds of collaborations that institutes have been using to move forward translational research programs, particularly where they have had to be very smart in their use of resources.

Thank you.

CHAIR AUGUSTINE: Thank you. Thank you very much for sharing your comments with us.

I think that brings us to the end of the agenda for today.

Francis, you did mighty fine work today, heavy lifting. We appreciate that, as always.

Amy, do you want to give any instructions? Or does anyone want to give instructions for dinner tonight?

EXECUTIVE SECRETARY PATTERSON: The members are eating dinner together this evening, and Lyric has the instructions on the

location. I believe that's at 6:30, but everyone will be transported from here back to the hotel. Then the place for dinner is within walking distance of the hotel.

DR. JORGENSON: Actually, the shuttle will take you from your hotel at 6:15 to your dinner reservation.

CHAIR AUGUSTINE: Does anyone want to have anything additional to say? Francis, do you want to say anything else before we break?

DIRECTOR COLLINS: I know this has been a day that is full of an awful lot of information, and the complexity of the question that we have asked you to address through the TMAT Working Group has, no doubt, emerged full-blown, and it may be a little daunting to try to imagine exactly how to move forward.

But I have great confidence in the wisdom and experience of this group. I think, again, we are not asking you to drill down

into the details. We won't ask you to solve our contract problems.

Hopefully, you will take the sort of larger view in the context of exceptional opportunities for developing new therapeutics. How should NIH organize itself to play the most effective role? We have, as you have heard, a lot of resources already invested in various ways. How can we get the most out of this, so that we have the best chance of benefitting patients? That's what we hope you can help us with.

CHAIR AUGUSTINE: Well, that is probably a good note to close on.

We will begin tomorrow morning at eight o'clock. There will be, for the panelists, the members of our group, some breakfast there before that.

So, thank you and have a good evening.

(Whereupon, at 4:24 p.m., the above-entitled matter went off the record.)