Therapeutics for Rare and Neglected Diseases Tele-Briefing
Larry Thompson, Moderator
National Human Genome Research Institute
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Operator: Good morning. Welcome to the Therapeutics for Rare and Neglected Diseases Tele-briefing hosted by the National Institutes of Health. This Tele-briefing will last approximately 60 minutes. There will be four primary speakers who will provide brief remarks and then you will be able to ask questions. To ask questions, you can press 'star' and '1' on your touchtone phone to enter the queue. To remove yourself from the queue you may press the pound key. This call will be recorded, transcribed and available on the website of the National Human Genome Research Institute at www.genome.gov. Now I'll turn over the program to moderator Larry Thompson, Chief of Communications at the National Human Genome Research Institute.

Larry Thompson: Good morning, everybody. On behalf of the National Institutes of Health I am pleased to welcome reporters to this briefing about the launch of the new NIH Therapeutics for Rare and Neglected Diseases Program or TRND, which we've been pronouncing as "trend". So you'll probably hear that throughout this discussion. I will be the moderator for today. At 11:00 AM after the briefing is over, the press release and background documents related to this announcement will go up on nih.gov, in the newsroom and at genome.gov and at the Office of Rare Diseases Research website as well.

Four speakers will talk for about 20 minutes and then we'll take questions for the rest of the hour. The speakers, in order, will be Dr. Raynard S. Kington, Acting Director of the National Institutes of Health; Dr. Stephen

Groft, Director of the NIH Office of Rare Diseases Research which is located in the Office of the NIH Director; Dr. Alan Guttmacher, Acting Director of NHGRI, the National Human Genome Research Institute at NIH; and Dr. Christopher Austin, Director of the NIH Chemical Genomic Center. So I'd like to turn this over to NIH Acting Director Dr. Kington for opening remarks. Dr. Kington?

Raynard Kington: Thank you. Good morning. My name is Raynard Kington. I am the Acting Director of NIH. As many of you know for many decades medical and congressional leaders have struggled with difficulties of adopting new treatments for rare or neglected diseases. It's distressing for physicians to have so few effective treatments for the uncommon conditions that occasionally arise among their patients, and even more distressing for patients and their families. Members of Congress and their staff have heard countless heart-rending stories from constituents pleading for help with conditions that medical science has not yet solved. This is more than a problem of anecdotes and individual patients. It's actually a major public health problem.

NIH estimates that between 25 million to 30 million Americans suffer from a rare or neglected disease. Of the estimated 6,800 rare diseases, only about 200 have effective treatments and we know that more has to be done to help our citizens with these problems. Since the 1980s, Congress has tried various approaches to stimulate development of treatments for these disorders. With the Orphan Drug Act, Congress tried to give biotech and pharmaceutical companies financial incentives to invest in the hard work of developing treatments for rare diseases. While they have the notable successes, progress has remained slow.

Now, Congress is asking us to play a more direct role. In the current budget which was just passed a few weeks ago, Congress gave NIH a down payment of $24 million to begin creating a drug development pipeline specifically to produce treatments for rare or neglected diseases, and this initiative really is new. NIH has always invested heavily in the basic science that can lead to development of new treatments, and NIH has engaged in research aimed at translating basic scientific findings into biomedical treatments, but we've never tried to directly develop medications for rare or neglected diseases, an area of drug development not actively pursued by private companies for obvious reasons.

There's a firm foundation at NIH on which to build this initiative. The NIH Roadmap for Medical Research which many of you are familiar with has created several programs over the last few years that can directly support a drug development program. For example, Roadmap funded the NIH Chemical Genomic Center, a high throughput screening center that uses a robotic system and a chemical library of more that 350,000 compounds to understand disease pathways and to potentially discover new therapeutic compounds.

Roadmap also launched the Rapid Access to Interventional Development program or the so-called RAID program which is designed to help researchers overcome obstacles in drug development as well as the Clinical and Translational Science Awards program or the CTSA program. NIH has also had an incredible clinical center where we already test medications in the earlier stages of clinical development. This program will be able to leverage all of these and other resources around the agency to directly develop treatments for rare diseases.

Let me say a few words about neglected diseases. Neglected diseases tend to be rare in the United States since they are primarily important infectious diseases that have been wiped out here but have not been wiped out worldwide. These cause havoc on poor and developing countries in particular where the population often cannot afford existing treatments and for the most part where they are neglected because private drug companies can't make enough profit developing new treatments for them. But as the recent outbreak of influenza A (H1N1) so clearly demonstrates, America is not immune from infectious agents springing up in other parts of the world. Not only is developing new treatments for neglected diseases the right thing to do, it is also in our own best interests.

This program offers a very practical and hopeful strategy for dealing with both of these important sources of pain and suffering and I'm delighted that NIH is getting directly involved. Unfortunately, I can't stay for the entire discussion here but I would like to take this opportunity to just express my personal excitement on behalf of the agency for this important program and I will now pass on to others to give you more information about the program.

Larry Thompson: Thank you, Dr. Kington. I'd now like to ask Dr. Groft who's the Director of the Office of Rare and Infectious Diseases to make some opening comments.

Stephen Groft: Thank you, Larry, and thank you all for your interest in the Therapeutics for Rare and Neglected Diseases Program. We have a rare chance here to do something really important to help many of our fellow citizens. I run the NIH Office of Rare Diseases Research which will provide governance and oversight to TRND. I know how important this effort will be. Each

year the Rare Diseases Office receives thousands of phone calls and letters from people, patients or their family members who are desperate for some relief from their condition. Too often, neither their doctors nor we have anything to offer. I believe TRND will be a critical start to changing that dynamic. This is the first time NIH is setting up a drug development program specifically for these conditions.

TRND will be a very interesting and dynamic mix of scientists working in NIH's own facilities, collaborating with researchers working at universities and in industry. TRND will be opportunistic. We will follow the science, pushing forward a new treatment for any rare or neglected disease when there is a new insight or opening that we can exploit. As much as anything, the scientific opportunities would determine what we are working on at any particular time, and of course, our available resources.

Our plan is to use strict criteria to determine what types of diseases and which drug target should be the focus of TRND. For example, TRND will not pursue a treatment already under development by someone else, especially the industry. It is not TRND's intention to compete with pharmaceutical or biotech companies. TRND will draw many of its projects from NIH-supported investigators. We will look to them for insights into the molecular causes of the disease and collaborations on pharmacological and animal models for lead optimization and preclinical testing.

We'll also be realistic. The preclinical work is hard and our resources initially are limited. Congress has appropriated $24 million for the first year. That will be enough to get us started with hiring staff, outfitting the

TRND laboratory and getting started on a couple of rare or neglected diseases. Fortunately, there's every indication that Congress will continue to provide funds each year at least through 2013. One of the biggest problems TRND will face is deciding what to work on. As Dr. Kington mentioned, there are some 6,800 rare diseases, not to mention the neglected diseases.

To make sure we are pursuing the best opportunity, TRND will have an advisory group made up of senior scientists from many of the 27 institutes and centers here at the NIH. This group will provide ongoing consultations regarding operations, advice on peer review for projects and will help integrate TRND into related efforts at the various NIH institutes and centers. TRND will also organize an external expert panel comprised of experts in drug development and rare and neglected diseases researchers from academia, industry and patient advocacy communities. Together, these two groups will help TRND decide on the best opportunities in drug discovery and development to make progress with a rare disease.

It is NIH's intention to complement and not to compete with the pharmaceutical and biotechnology industries. TRND is intended to take a promising molecule through the riskiest stages of drug development and then seek out private partners to bring the product to market. TRND will be a collaborative effort. We will be seeking relationships with a wide range of organizations, experts and advocates interested in rare and neglected diseases to help overcome the obstacles preventing these products from reaching the market.

For example, one of the problems with developing treatments for rare diseases is that they are rare. It can be challenging for researchers and even companies to find enough people with the right condition to test a new treatment. TRND plans to work with patient advocacy groups to organize collections of individuals with rare diseases to help study the condition's natural history as well as develop a pool of potential participants for clinical studies.

We've had a measure of success with these studies in our rare diseases clinical diseases network. How all of these activities will work are still in development, but this is a very exciting and very promising time. For people with rare or neglected diseases, this is also a time of hope. Thank you. Larry?

Larry Thompson: Thank you, Dr. Groft. I'd like to now ask Dr. Guttmacher, the Acting Director of the National Human Genome Research Institute, to make some opening remarks. Dr. Guttmacher?

Alan Guttmacher: Thank you, Larry. I am pleased to lend the National Human Genome Research Institute's support to TRND. This effort is a natural fit with NHGRI's mission especially as almost all rare disorders have a fundamental genetic component. Also, NHGRI is very supportive because the mission of TRND links so closely with the mission of the NIH Chemical Genomic Center or NCGC, which NHGRI operates.

Even before the human genome project was completed in 2003, NHGRI had begun to focus on finding ways to turn the hard-won knowledge about the human genome into medical advances for the direct benefit of the public. That same year, when NIH announced its Roadmap for Medical

Research, NHGRI proposed a genome-based approach to finding new molecular targets involved in health and disease. That led to the creation of NCGC which has developed a high throughput industrial-sized robotic screening system that can now test a library of more than 350,000 chemicals against molecular targets often identified through genomic studies in healthy and diseased cells and tissue.

Our early experiences quickly showed that, as had been anticipated, once NCGC discovered a promising chemical, getting from discovery to clinical trials in people is a challenging and complicated path. Many difficult basic science tests still need to be taken once the promising molecule is found. For example, the chemical needs to be modified so it can be used in the human body. It has to be put in a form that is soluble, that is not toxic, and it still acts on its target molecule in the tissue. Each step has to be tested in increasingly complex systems, in cell cultures to animals, before the Food and Drug Administration will ever grant permission to test it in people.

This preclinical stage in drug development is so difficult that it's colloquially called the "Valley of Death". That, unfortunately, is not just a metaphor. This stage of drug development can take two to four years of work, cost $10 million on average and still result in a failure rate of 80% to 90%. Therapeutics for Rare and Neglected Diseases will pick up this stage where projects such as those of NCGC currently leave off. TRND will do the hard chemical work to turn promising molecules into medicines and will perform and/or oversee the collaborative experiments needed to qualify for investigation of new drug status.

By having the opportunity to coordinate the work of these two programs, NCGC and TRND, and adding in other NIH clinical research components as well as collaborations with outside researchers and disease advocates, NIH will be organizing a powerful coalition to start making real progress on rare and neglected diseases. Larry?

Larry Thompson: Thank you, Dr. Guttmacher. Lastly, I'd like to get opening remarks from Dr. Chris Austin who runs the NIH Chemical Genomic Center and has been a driving force behind the development of TRND. Dr. Austin?

Chris Austin: Thank you, Larry. As Dr. Guttmacher said, getting a promising chemical through the preclinical stages of drug development is fraught with failure. Most molecules simply don't make it. TRND is being designed from the ground up specifically to overcome this problem. We will start with compounds discovered by either the NCGC or by NIH-supported investigators or by patient advocacy groups funding their own research, or even by industry when there are compounds that they don't want to pursue because of the risk-reward ratio not being favorable enough. TRND will get them to the point where they can be tested on people.

TRND will do this in several ways. First, it will build on what we and others have learned through the identification of promising compounds discovered so far. Second, TRND will combine the experience and lessons learned from individual projects done under the TRND initiative to develop insights into related disorders using a systems approach to biological disease problems. Third, it will focus on the science of preclinical drug development, producing new and innovative technologies and paradigms to improve success rates in this difficult stage of drug development.

In most cases, the starting point for TRND will be a compound that research has shown to be effective and in vitro or in vivo model of a rare or neglected disease. The endpoint deliverable will most often be a clinical candidate compound with a data package that is sufficient for sending an investigation on new drug or IND application to the FDA. As noted earlier, it's expected that in most cases TRND's IND candidates will be licensed to biotechnology or to pharmaceutical companies for clinical development.

Handing off the clinical development to private companies will allow TRND to focus on the most scientifically challenging stages of drug development where there's the most need. We will be "de-risking" these projects sufficiently to make them adoptable by organizations outside of NIH.

So in short, trans-scientific activities will include: first, iterative chemical modification of promising starting compounds to make them usable in the human body; second, optimizing the compounds for safety and efficacy in cells and then in animals and testing the compounds in pharmacological and toxicological models required by the FDA for testing in humans; third, development of novel technologies and paradigms to improve success rates in preclinical drug development; and fourth, receiving feedback from clinical development programs for the clinical candidates that are derived from TRND, produced by TRND, to inform and continuously improve TRND's process for future projects.

Finally, one of the things that I'm most excited about is that we will publish not only our processes and our successes, but also our failures.

Currently, journals only publish successes, science that works, and in drug development there is particularly usually a cloak of secrecy about what a company does in the preclinical space because it doesn't want to lose any competitive edge. This lack of sharing of information of what works and what doesn't work, this kind of stagnation that we've seen in the efficiency of drug development over the last decade, just as the molecular libraries program through the Roadmap created a pre-competitive space for early drug discovery, TRND will create for the first time a pre-competitive space for the science of preclinical drug development.

We're going to tell everyone what we're doing so that we can all learn from the things that don't work as well as the things that do. That alone may be revolutionary. Larry?

Larry Thompson: Thank you very much, Dr. Austin. So we have about seven or eight minutes before Dr. Kington has to leave so what I would do is I'd like to open this up for questions and if reporters could queue up and ask your initial questions for Dr. Kington. So think about what you want to hear from the Acting Director of NIH and we will then let him go and the rest of the guys who are here can provide lots of technical information for anything that you might like to know. So could we go with Jennifer Corbett, please, from Dow Jones and I guess I would ask everybody in the room since you can't see our faces to identify yourself when you're speaking and if reporters can also do the same thing. Although I'll try to tick a little bit as we go. So, Jennifer?

Jennifer Corbett: Hi, I'm Jennifer Corbett with Dow Jones. The question I have and this is really for anyone, I guess I have a broader question that you mentioned that this sort of whole project is the first time that NIH will be getting

involved directly in developing medicines. Is that true for rare and neglected diseases or is that also broader that you really haven't gone in that area for any type of disease, whether it's cancer or…?

Raynard Kington: This is Raynard Kington. I think that there have been smaller programs focused on very specific clinical challenges that have sort of ventured into this territory. The RAID program was modeled on a small program that was at the National Cancer Institute. So there have been bits and pieces of the process where we ventured in. I don't think we've ever done anything on this scale in terms of really trying to fill the entire continuum of this space that we've identified in this project and I'd welcome comments from others as well.

Jennifer Corbett: Okay and one other question I had is for the IND, if it gets to the IND process do you imagine that would be NIH filing for the IND or would you try to turn it over to a company at that point?

Chris Austin: Yes. This is Chris Austin. We're imagining that the endpoints are going to be flexible dependent on the nature of the disease, the exact prevalence of the disease and the kind of target, and the kind of organization that we're passing this off to. We're imagining that in some cases NIH will have to do the work required to acquire, to get the IND. In other cases, we can imagine that there will be other organizations who would be willing to pick up the projects with so-called IND-enabling data packages and they would actually do the IND application themselves. We really intend to be pretty flexible and again opportunistic in where that hand-off occurs.

I'll just say one other thing about the previous question. What Dr. Kington said is absolutely right. There are programs particularly for more

common diseases in cancer through the Cancer Institute, and some of the infectious diseases through NID, through the Infectious Diseases Institute, and the Neurological Institute, INDS, has a focused program in this area. The difference here is that it's focused specifically on rare diseases and neglected diseases taking a systems engineering approach to the problem as well as working on not only the individual diseases of which there are thousands but also the overall science in this area.

Larry Thompson: Okay. Can we move on to Maggie Fox? Thank you, Dr. Austin.

Maggie Fox: Hi! Thanks very much. Can you give us some for instances? I'd also like to explore this "Valley of Death" idea a bit more. Thanks.

Larry Thompson: What do you mean, Maggie, what do you mean some for instances - For instances about what?

Maggie Fox: Some diseases that are going to be part of this program.

Alan Guttmacher: This is Alan Guttmacher. I'll take that one. We can't give you for instances now. We can give you hypotheticals but we don't know yet exactly which diseases this program will take on, particularly which ones will be taken on early. It's early in the development of the program. We are going to be working with many, both experts from across the NIH but also external experts as well to develop criteria by which diseases and molecules for that matter will be accepted into TRND. Our goal is to provide medicines for people, and that is our overarching goal and one we will always be aware of, so we are going to be very opportunistic. You've heard that word before this morning. We are going to look for scientific opportunities as they arise and we have not yet developed exactly the

criteria by which specific diseases and again potential molecules will be adjudged for that.

Maggie Fox: Okay. While Dr. Guttmacher's talking, I think it was you who mentioned this "Valley of Death" idea. Can you go a bit more into that, why it's so hard to develop these drugs early on and what the costs and risks are, please?

Alan Guttmacher: Yes, I can do that. Then I might ask Chris Austin who knows more detail about this than I do to answer as well.

Larry Thompson: Can I interrupt you one second? I recognize as Dr. Kington has to leave in a minute, we can answer that question, Maggie, but let's see if there's anything else, if anybody has a burning question for Dr. Kington before he has to leave.

Raynard Kington: On this topic.

Larry Thompson: On this topic. [Laughter] Oh, there you go, setting limits again. I know how you would indicate that actually. Natasha, the operator, so I guess Dr. Kington, we thank you very much for your time and thanks for coming and being here for this. So, Chris, do you want to answer Maggie's question about the "Valley of Death"?

Chris Austin: Yes, sure. The analogy that I like to use is that the "Valley of Death" is like trying to do a Rubik's Cube and really, the process is this, that as one goes through the drug development process, a chemical has to have an increasingly long list of characteristics which are initially things that are required in the lab and then eventually required by FDA for human

testing. That list of characteristics is about twenty long. At the place where NIH stops with the molecular libraries program there are three or four of those characteristics. To get the other sixteen characteristics is really where the "Valley of Death" is. You can think about this, as I said, as a Rubik's Cube kind of exercise where as you know if you have four of the blocks of a Rubik's Cube, if you try to add the fifth usually you lose the first four, and then you get the next five and when you try to add the sixth, the first five go off.

Most people have never succeeded in completing the Rubik's Cube and there are people who work in biotechnology and pharmaceutical industries for their entire careers never getting to a project that actually gets to clinical utility. There are a lot of reasons for this but some of it has to do with the incredible complexity of the human organism and the additional complexity that is layered on top of that when the human organism is afflicted with a disease which can change the physiology that we think we understand. The other issue is that we don't really understand the rules by which those various characteristics are added on to the compound.

So it's in that whole process, the science of the "Valley of Death" if you will, is relatively poorly understood, in fact quite poorly understood, and it's something that for a variety of reasons is very hard to study in the private sector given the short-term commercial imperative that we all understand exists in that setting. So our hope is not only to work on diseases which are neglected, and those diseases might be rare or they might be tropical diseases, etcetera, that we're terming neglected in this case, but also to lift all boats by – if I can switch my analogy – by beginning to understand what the rules are, what the scientific issues are that make the "Valley of Death" such a difficult area now. We firmly

believe that there are rules which govern the science in that space; we just don't understand them and that's why it's so difficult

Alan Guttmacher: This is Alan Guttmacher. One of the other things that we're looking forward to being able to do, as Chris has referred to before, is to share information gleaned about this with others. Because our imperatives are different than those working the private sector, we come, particularly the National Human Genome Research Institute but the NIH as well, come from an imperative to share information, to share data with a cardinal feature of the human genome project and it's fairly something that we bring to our other work that as we look at steps in this process, if we notice ways to tweak them to make them better or to skip them even, that is information rather than trying to keep that to ourselves we are going to try to shout that from the rooftops, scientifically publish it in journals and other kinds of things because we really are devoted to not just developing these drugs but seeing what we can add to optimizing the process.

Maggie Fox: Thank you.

Larry Thompson: Thank you very much, Alan. So we go to Jocelyn Kaiser at Science Magazine, please.

Jocelyn Kaiser: Hi, Larry. I've got a bunch of questions, I might have to ask some after this is over, but one of them is – So the Chemical Genomic Center, is this – I've been there, it's an intramural center that also does projects for extramural scientists, and that's different from how the RAID program works, right? I think that's grants to go out to the extramural communities. So, is this is going to be a physical center somewhere in

Rockville with a whole bunch of medicinal chemists? Is it going to be sort of a service center? Is that how it's going to work?

Alan Guttmacher: This is Alan Guttmacher. That is the way it's going to work. Of the two - Adjacent of the two kinds of visions you've created there it will be much more like the NCGC vision. It will be a physical entity, it will have staff, a fair number of scientists will be working on this in radar basis, and it will, as has been the case of the NCGC, work primarily with the extramural community in terms of providing access to this kind of expertise and one-stop shopping.

There may be parts of this process that unlike NCGC will be farmed out. In other words, some of the steps in this process, it may make more sense to contract those things out and that will be done. Each step will be analyzed in sort of simplistic to think about but the areas that are really about developing new knowledge will tend to be things that TRND would do in-house but other things which are more of a question of simply perhaps some of the talks and other kinds of things might be things that will be contracted out if it's not so much a question of intellectual contribution but simply providing a service.

Jocelyn Kaiser: Okay. That was also part of my question. I wonder a lot of the work of drug development, it seems like its kind of brute force, a lot of trial and error chemistry and I just wonder if there's going to be concern from some members of the community. How many RO1s could you be funding with this $24 million? Can't companies do this better than - You're going to start from scratch doing something that companies already are very experienced at doing.

Chris Austin: Well, I think there's two ways to answer that question. One is that, as you know, companies are experienced doing it and I came from one of those companies before I came to NIH, but I don't think you'd get any disagreement from anyone in the community – public sector, private sector, biotechnology, pharma – that the process doesn't work. It has overall from beginning to end a 99% failure rate and it is exactly as you say, a brute force exercise which is horribly inefficient and expensive.

So what TRND will do is to, as the molecular libraries program did and the NCGC did, absolutely learn everything we can from our colleagues in pharma and biotech and in fact recruit those best individuals from those environments to come and work at TRND, much as NCGC did, to work on what are the causes for failure, what are the ways that we can improve the process by which this is done. That's the first answer.

The second answer is that because of the risk profile and the lack of return on investment, these projects are never worked on in the private sector, essentially never. We didn't say this at the beginning but actually where this program was initially envisioned here because of a groundswell of requests that we got from extramural investigators we were working with - disease foundations, patients, families - who came to us with the kinds of stories that Congress hears of the return on investment being low for these disorders and so the return on investment model simply not working for disorders that would affect a few hundred or a thousand people. So it's both a science issue and developing the science issue to improve success rates and working in an area which simply is not served by the typical bio-pharma model.

Larry Thompson: Did you want to add anything, Steve?

Stephen Groft: This is Steve Groft and I do want to add that as many of you know that there's been a tremendous contraction of the pharmaceutical industry in the last several years and this has resulted in a shortage of potential partners to really develop products for the rare and neglected diseases. What we've been hearing from many of the smaller companies is that they just do not have the resources and sometimes even the skills to move the potential products up to the IND stage. I think that's the basis of what we're attempting to do here is to identify those compounds that many people would potentially pick up and then sponsor, move to the new drug application stage. So that we do have products available and in such a way that there's some degree of assurance that the product is going to be relatively safe and effective for the indications that they would be studied later on in the clinical trials. So it's a major step that is missing and we've heard from a number of companies who would be willing to pick up a compound if it looked like they were again relatively safe and effective.

Larry Thompson: Okay, Jocelyn?

Jocelyn Kaiser: Sure.

Larry Thompson: You know how to reach us if you have more questions.

Chris Austin: Can we just say one other thing about this because it's a common confusion that happens even with the molecular libraries. The way that the organization works and will work is that the vast majority of the people that we work with and will work with here are in fact RO1-funded investigators at universities and medical schools. So there are - Each of these projects is a collaboration with someone who is able to do something

that their lab could never do by itself. So it's a very intimately collaborative model with those very people that you're referring to.

Jocelyn Kaiser: Could I ask one more question?

Larry Thompson: Sure.

Jocelyn Kaiser: I'm just wondering, so $24 million a year for five years, and if it's $10 million per compound, that's I guess about two compounds a year. Do you expect the $24 million to grow? And also, which institutes are funding this?

Stephen Groft: Well, we have no idea whether it will grow or not, certainly I think dependent upon how Congress views the program and how we measure success. The institutes here at the NIH have been given very appropriate increases in our budget and so funds will be taken from the individual institutes to support the $24 million per year.

Larry Thompson: And we need you to stop doing long division in your head. Just kidding. Okay, Jocelyn, we'll move on to John Reichard. John, can you tell us who you're with?

John Reichard: Sure. It's John Reichard. I had a question along the line – with Congressional Quarterly - along the lines of the one that was just asked. So in terms of the funding, is that $24 million a year or $24 million total over five years? That was one question.

Stephen Groft: Per year, each year for approximately five years.

John Reichard: Okay. So that explains why you're optimistic with 2013 because that money is already locked in?

Alan Guttmacher: This is Alan Guttmacher. It's a yearly appropriation so we know it's in FY 2009 budget obviously. As you well know, the Congress passes a budget each year and we will see with the years to come. We've been I think in conversations with Congress we understand that they have a good understanding that this is not something which within a month will produce a drug kind of thing. So there seems to be a general sense of: "Let's fund this and see how it does," and based upon how it performs, future funding decisions will be made.

John Reichard: But is the funding just guaranteed for Year One of the five years with the understanding that they'll try to do it for Years Two and Five or is it more firm than that?

Alan Guttmacher: The funding for everything the NIH does is guaranteed for one year at a time.

John Reichard: Okay.

Stephen Groft: I think what we're looking at, though, we're developing an infrastructure here that will sustain a program over a number of years and I don't think we would have been asked to develop that costly infrastructure if there wasn't some intent to continue the program over a series of years.

Alan Guttmacher: We would also, while we're talking about financing, we would also welcome opportunities to partner with potentially others in terms of this work to expand the use of these dollars and even to potentially bring other

dollars into the process, be they from foundations or philanthropic individuals or others who are interested in this same idea.

Stephen Groft: In fact - and just to extend Alan's comments a little bit - there has been a little bit of a shift with many of the patient advocacy groups really becoming the leaders of product development for their specific diseases. In doing this they, too, realize that there are certain areas that they will need help in developing other products and this isn't one of the major stages that they have a difficult time overcoming. So I think this will also be responsive to what we're starting to see within the whole patient advocacy community related to the rare and neglected diseases.

John Reichard: Thank you.

Larry Thompson: Anything else, John?

John Reichard: No.

Larry Thompson: Great. So, Bridget, would you introduce yourself, please?

Bridget Kuehn: I'm a reporter with the news section of JAMA's Medical News.

Larry Thompson: How do you pronounce your last name, Bridgette Kun?

Bridget Kuehn: "Keen".

Larry Thompson: "Keen". Excuse me. Thank you.

Bridget Kuehn: My question was if you're going to take out the hard part of drug development and then perhaps license these potential molecules, is there any opportunity for the program to profit off the licensing or to gain funding I guess from the licensing?

Alan Guttmacher: This is Alan Guttmacher. I'll be happy to take that one. Yes, I think the changing word is correct. That's right, we wouldn't be profiting from it but there is the potential that there might be eventually monies would come in from the actual drugs produced that could continue to help fund part of this, but that's not our goal. We have both the responsibility and the luxury of focusing on scientific and public health opportunity rather than the financial opportunity here. So if that does happen, that would be sort of a nice ancillary benefit to the program but the program will not be making decisions about what to do based upon the return financially of the program. We will be basing what we decide to do on the scientific opportunity and the return to patients in terms of new drugs for them.

Larry Thompson: Anything else? Any follow-up, Bridget?

Bridget Kuehn: No, thank you.

Larry Thompson: Okay. Could we go to Emily Walker, please?

Emily Walker: Hi! Thanks for taking my question. I'm sorry I came in a little bit late but could you just say again when this center is expected to be built? I think you said 2013 but I just wanted to double check. Also, kind of a basic science question here, but when you guys were talking about the Rubik's Cube analogy, when you said that usually these molecules have characteristics that stops at three or four and when you add a new one the

other ones can disappear. When you mean characteristics, does that just mean when you try to add something new into the molecule another way that it's going to interact in the body, could you explain what characteristic means a little more?

Chris Austin: To your first question, we're hoping to via some existing mechanisms begin some pilot programs actually at this fiscal year. Obviously, we're not going to have bricks and mortar in this fiscal year. We think that will probably take another year or maybe a little more, but the 2013 number I think that you heard was five years from now where we're thinking that the current funding assumption – let me put it that way - ends. So we will certainly be fully up and running long before then.

The basic science question, yes, it's exactly as you imagine it. To get into the scientific weeds here for a second, a typical problem is you have a compound which has good potency, that is it acts at a very low concentration against the target you're interested in, and now you need to add a characteristic that will make it have a relatively long life in the blood. It won't get broken down rapidly in the blood, and those are two completely different characteristics, and when you make variations you alter the molecule to make it stable in the blood, you will frequently lose the potency that you started out with. That story and if you have a potency and solubility of the compound, that is that it will dissolve in the blood for instance, if you have those two characteristics and you try to add now stability, those first two will go off and etcetera. That process continues itself.

Emily Walker: Thanks.

Larry Thompson: Okay. Can we go on to the next question from Matt Jones from Genome Web?

Matt Jones: Yes, thanks for taking my question. I appreciate it. I'd like to ask about what specific genomics research resources and technologies do you expect to use in the program and then if there's going to be a pharmacogenomic component?

Chris Austin: What a great question. The Genome Institute has always been focused on, among other things, two things. One is technologies, pushing technologies and automation, and openness of what the institute does and sharing. So this initiative will be in that tradition of pushing technologies, developing technologies, developing paradigms and opening, putting sunshine on an area of science that might not have been shared broadly before.

The other thing that the Genome Institute has always focused on is genetic disease - identifying genes for those diseases and then trying to translate those genetic discoveries into either diagnostics or treatments – so this is a very directed affirmative effort to do that in the therapeutic realm. As you probably know that through the Genome Project about 2,000 rare diseases now have their genetic bases understood and there are several new ones that are discovered every week, so the opportunity to take advantage of those discoveries and translate them into therapeutics are large.

Our current plans are really, about the pharmacogenomic realm, we don't currently have plans to focus on pharmacogenomics per se. That tends to involve the differential response of individuals to therapies and those responses are frequently genetic although not always in basis. Those

frequently have to do with complex diseases which have multiple different causes like hypertension etcetera. These diseases tend to be much more homogeneous. So these are much more uniform populations. So we don't plan on – You might view the entire initiative as a pharmacogenomic initiative if you will, but not in its conventional sense.

Matt Jones: Can I ask a follow-up?

Larry Thompson: Sure.

Matt Jones: Do you have any international collaborators yet, or do you expect that at some point in the future?

Chris Austin: We absolutely expect it. We're just in the course of thinking about the project, the first pilot projects which we're going to start with, but because the neglected and rare neglected diseases, most of those disorders are tropical disorders such as leishmaniasis, trypanosomiasis, schistosomiasis, which exist primarily in the developing world. The collaborators for more of the clinical end of those initiatives are almost always international. Molecular libraries in the NCGC in general have collaborations with people all over the world already, so that this will continue.

Stephen Groft: I would mention, too, that I think we're using our tremendous upswing in global activities related to rare diseases research and orphan product development, and this is an area that we haven't talked too much but certainly, to a few members of the international research community we've mentioned that there is something that's coming and there is a great deal of interest in hearing what it is that we're proposing. Then they

certainly have offered to be willing partners in how we move forward. So I think we do anticipate quite a bit of voluble interaction and research.

Chris Austin: Let me just add that, this is Chris again, speaking of the brute force issue, if you look at the scale of the problem, there are 6,800 rare diseases and if you add the neglected diseases on there's probably over 7,000 diseases. This problem is never going to be solved via brute force approach. We simply can't afford, the patients can't afford to wait ten years, fifteen years for every single disease to be tackled one at a time. We have to get better at understanding the causes of failure and improving the success rates and sharing data early, and sharing data with our colleagues both nationally and internationally to make this work better for the patients who so desperately need these treatments.

Larry Thompson: Cool. So Jocelyn is back in the queue to ask a question. We'll go to Jocelyn but we have about ten minutes, eight or nine, ten minutes left and so if you have any other burning questions after Jocelyn, please get in the queue. If not, we'll wrap it up shortly. Jocelyn?

Jocelyn Kaiser: Yeah so about neglected diseases, you said a lot of those are developing world diseases and infectious diseases, and I'm just wondering because there's a huge amount of money going to that already from the Gates Foundation, what this is adding. Will you be looking at diseases that are not on their list or the idea that they're funding a lot of basic research but not the "Valley of Death" stuff? How will it match with what the Gates are already funding?

Alan Guttmacher: This is Alan Guttmacher. Yes, it will complement that. We are not interested in putting resources and effort into areas where there they are

already receiving lots of resources and effort in general. So that Gates certainly has made impressive investments in working with specific diseases of the developing world, in general we probably won't involve ourselves with those, but the many other diseases for which Gates and others have not invested so heavily will be where we'd look for our opportunities.

Chris Austin: Jocelyn, you probably saw there was a really nice article on PLoS medicine about two months ago that really laid out this problem in quite a striking way, looking at the financial resources devoted to neglected diseases worldwide and the vast, vast majority, well over 95% of the financial resources went to three disorders: malaria, TB and HIV/AIDS. So one can really think about those as neither rare nor neglected any longer and because they're not neglected they are ones that, all other things being equal, we would shy away from because the need is so great in the many other tropical diseases which do not have those kinds of resources being applied to them. But that paper lays that out really quite well. It actually has studies funded by the Gates Foundation.

Jocelyn Kaiser: Okay.

Larry Thompson: I want to ask a question. Chris, could you give the reporters the example of the schistosomiasis discovery that was made a year or so, about a year ago, a year and a half ago whatever it was? This is a really nice model for how some of this stuff may work from sort of exploiting a discovery made by a researcher in academia and then working in partnership with NIH to bring forward a product that may prove to be therapeutic.

Chris Austin: Yes, sure. So this is a project that was started under the aegis of the Molecular Laboratories Roadmap Program. It's a collaboration with Dr. David Williams who at the time when we started working with him was with Illinois State. He's now at the Rush Medical University in Chicago. Dr. Williams studies schisto somiasis which is a very prevalent parasitic disease in the developing world. About 280 million people have this parasitic infection. He came to us with a basic discovery that was very interesting of an enzyme that he thought, if inhibited, would kill the parasite, and it was a theory that he had no way to test.

So working with him over the course of about a year and a half, we were able to develop an assay, do a high throughput screen, identify the target which these compounds were acting on, do some chemistry optimization, do testing in cells then worms and then in animals, and in a paper that was published in Nature Medicine last year, showed that inhibiting this enzyme is curative both of worms in dishes as well as in the worm infection in mice – the standard model of schistosomiasis in an animal model.

So this was a wonderful example of the kind of collaboration between an extramural investigator who knows an enormous amount about this disorder but doesn't have the knowledge or expertise or infrastructure to do the initially chemical probe and then drug discovery that we can do at our place, but we can't do what we do without him either. It's a three-legged race that really requires both of us.

Interestingly, when we got to this point there were no resources to carry this project forward. So this is, we think, going to be one of the first projects that we put into the TRND queue to be able to move this forward

to add that list, do that Rubik's Cube exercise we were talking about, to add the other characteristics that will be required for testing in humans.

To the point that we're making before, we investigated all the usual sources of developing world funding that you can imagine and they all said these compounds are too early. They're not developed enough. "You need to develop them more and have these other characteristics and then we will be interested in it." That's a case study that repeats itself over and over and over and over again at our Center for Rare Diseases and Neglected Diseases.

Larry Thompson: That's great, Chris. Thank you very much. So we're just about at the top of the hour so I'd like to thank everyone for participating in today's briefing. The press releases and the background information about this will be up on nhgri.gov and genome.gov shortly and the Rare Diseases Office's website. We will post the audio of this discussion as quickly as we can this afternoon and we'll follow with the transcript as soon as we can get one made, probably in a few days.

If you have follow-up questions, of course please call Kelli Marciel at the NIH Office of Rare Diseases Research or Geoff Spencer at the National Human Genome Research Institute, and they will help you get hooked up with whoever the folks who are here today that you'd like to talk to or anybody else to answer your questions. Their contact information is at the top of the press release and you probably already have it in your rolodex anyway.

So with that I'd like to bring this briefing to a close and thank you all very much for participating.

Operator: This concludes today's teleconference. You may now disconnect your lines and have a wonderful day.

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