

IECRN National Leadership Forum
May 31, 2006
NIH Roadmap Update

Presenter:

Elias A. Zerhouni, MD

Director, NIH

DR. ZERHOUNI: Thank you, Steve. First of all, I would like to thank Steve Katz for his leadership. He has recognized many of the key participants in this effort and I would like to join him in thanking them all, Jim Kiley from NHLBI and, also, Dr. Barbara Alving, who is really carrying the effort internally, the Trans-NIH Steering Committee members, who have worked across all institutes, as well as the external Advisory Committee to the IECRN.

Let me just give you a context, because I think it is important to see why this meeting is occurring now. When I became NIH Director, there were lots of drivers of the biomedical research enterprise which needed to be addressed.

First and foremost was the sense that had developed over 20 years that there was a loss of energy in the translational clinical science areas of our enterprise.

Second, there was a sense that translation was more difficult. If you look at the time it takes to develop, for example, a drug from inception to implementation, it is lengthened to 17 years now and the cost is enormous.

If you look at the evolution of academic health centers, and I came from one, what was really remarkable was the loss of focus away from translational clinical sciences due to the exploding demand in clinical services.

I will give you an anecdote. I used to go around the campus and ask chairs, current chairs and former chairs, what their attention was directed to and I asked Dr. Victor McKusick, who was the head of medicine in my institution in the '70s, and I said, "In your time, how much time did you spend training, developing the next generation of clinician scientists and scientists in your department versus administrative affairs and clinical services," and he said, "Oh, I spent 80 percent of my time thinking about the next generation."

And as you know, he was one of the founders of genetics, and he spent all his time doing that.

Then I asked his successor at the time, Dr. Ed Benz, and then Dr. Mike Weisfeld, and I said, "How much time do you spend," and the answer was, "Oh, I spend 80 percent of my time on administrative issues and making sure the clinics are served and that the young faculty members are really recruited to ensure the services."

If you talk to any young scientist at the beginning of their career, you realize how difficult it is for them to see a

career in this area, very important area of our science.

And science has to be strong across all links. Otherwise, the weakest link drives the effectiveness of the whole system.

The second driver was the sense that the doubling had already gone through four years, when I became director, and, obviously, as you know, expectations are created by increases like this, and Congress was asking, "Where is NIH going? What are the fundamentals of science that we need to worry about, rather than just doubling the budget for doing exactly the same thing twice over?"

I had to really explain to Congress and to all of our constituencies that we, as an institution of 27 institutes and centers, could, in fact, come very strongly together to address what Steve was talking about, the roadblocks to science.

When you asked the question, you realized that there were three fundamental issues that came up through this process called the roadmap, which we launched in 2003.

And the roadmap is not one initiative. You have to understand that as the community was consulted, almost 96 different topics were identified, of which 28 were chosen. Today, there are almost 400 individual grants that cover the entire spectrum of what the roadmap is about.

So the three areas that came up, if I can summarize them for you, are, one, in basic science, and basic science is about 40 percent of the funding of the roadmap.

The roadmap itself, by the way, is about one percent of the total budget. People talk about the roadmap like it has taken the whole NIH, but really what the roadmap is is an incubator space.

To me, the concept is how do you bring together -- it's like in your departments at your institution. How do you bring together people around the same table to think about problems that fall through the cracks or opportunities that need to be taken or pilots, experimental pilots that need to be conducted?

And that is how you dedicated the small portion of your resources to make sure that you don't fall behind in terms of science.

So the three main areas that were identified as very important is, one, in basic science, the sense that biological systems have emerged as very complex entities.

When you look at molecular pathways and you are trying to validate a target, you realize that molecular pathways are really embedded in very complex networks, interacting networks.

For example, if you look at signaling as a module, if

you will, of cell biology, you realize that signaling really affects multiple systems, with multiple levels of crosstalk, across diseases and across organs and across tissues and across cell types. Cell signaling, in fact, is very similar across different types of cells.

So how do you really identify, tease out what you will call the hub molecules, those that really are controlling the behavior of the system versus not.

This is the era of what we would call and others have called systems biology. That was one driver. The second driver is the fact that we are not suffering, as a population, as much from acute diseases as we do from chronic diseases.

And if you look at chronic diseases, which are 75-80 percent of the disease burden today, the types of analysis and the types of studies, including clinical epidemiology, clinical trials, observational trials, have, obviously, a time line that is different.

At the same time, you realize that for you to perform experiments that are statistically valid and observationally solid, you really need to have long clinical trial times, because you are not looking at the outcome of Alzheimer's disease research in two years or one year, like you would do in an infectious disease or cancer.

Therefore, you needed to really understand how that was conducted and if you treated a disease for long periods of time, that raised different questions in terms of appropriate bio markers, appropriate predictive toxicology end points.

At the same time, at the very fundamental level, there was a gap in our understanding of what you would call molecular recognition. How is information really transferred at the biological level?

So those led to investments in structural biology, in systems biology, and in molecular libraries, which is to give tools to the research community that are easily accessible to conduct very fundamental research.

The second area that was identified as a core roadblock that NIH needed to experiment with was this notion that the scale and scope of complexity of science had reached such a level that you really needed to think of science no longer as the lone ranger experiment, but often you needed to an interdisciplinary team; often, you needed to collaborate much more with computer scientists, with physical scientists; and, across the life scientists themselves.

How did you really stimulate that and how did you not prevent that from happening? So this is what led to the concept of the research teams of the future. More importantly,

underlying all of that was the notion of how do you then -- because you have to worry about models of science that are so complicated that it stifles innovation.

How do you prevent the agency from becoming too conservative in its ideas, in its peer review? So we tried to do some experiment of what we called high risk, high impact research.

A good example is the Pioneer Award, which is a completely different review mechanism to identify really far out ideas that need to be tested. Interdisciplinary research is also a difficult issue, because you really want to create collaborations, but you don't want to force them. You want to allow them to self-assemble.

So that was the second topic and took about 20 percent of the budget.

Then the other fundamental roadblock was this one that was identified as the loss of attention, the loss of energy, and the potential loss of a full generation of clinician scientists in clinical research, and that is what the third topic is which we are addressing the part of re-engineering the clinical research enterprise.

As we looked at that, what became obvious is that NIH has tried to respond to the issues. The loan repayment program

is a good example. Everybody said, you know, students have too many lows and, therefore, they go to clinical service, they don't do clinical research. That was one. And career awards, all the case that came out, mentoring awards.

Mentoring was seen as lacking. Lack of support for career development was seen as lacking. Lack of loan repayment was seen as lacking. And every time you looked at it, every idea made sense, except that it didn't really look at the sociology of how we conduct clinical research, both within institutions or within networks.

And this is when we realized that what was needed really was for NIH to create a stimulus for change, to really challenge the community and say, "Is there a better way to really do translational and clinical science and how to train the new generation of clinician scientists," and this is where the concept of clinical and translational institutional work came about, whereby we said, "Look, instead of having all these fragmented resources, the K-12s, the K-30s, the K awards, the T-32s, the GCRCs, why don't we stimulate change toward more of an academic focus for clinician scientists, a real home, something that will define a career path that is just as defined as when you have a joint appointment in molecular biology and medicine or a joint appointment in biochemistry and some other speciality

of medicine."

Translational science, clinical science is not something that you can learn on the job the way we did 30-35 years ago.

I remember when I did my first research, basically. I was just appointed. I had a letter, "You're an assistant professor today. Welcome to the club. You are now an academic research," and I learned everything I had to learn later and with a lot of difficulty.

The complexity of regulation, the complexity of experimental design, the complexity of bio statistics requires support infrastructure that is not just a utility support, just beds and nurses. It really needs an intellectual environment to support these individuals.

And, at the end, continue to do research on research, because if you really think about what the roadmap is, and this exercise today is a good example of it, what we are doing is science and science.

As you heard from Steve Katz, clinical research networks were a puzzling issue for the roadmap work groups, because we knew there were hundreds of them, how they operated, how efficiently they were integrated, how interoperable they were rose to the top of our concerns.

And the first thing was instead of coming up with a blueprint out of a small work group, perhaps some science should be done, some real evaluation, some real inventory, so that the result, at the end, would not be something that all of us here would feel was basically superficial.

This is really the idea of this meeting and I am looking forward to seeing how you can improve the tools used by clinical and translational scientists, but at the same time, not just tools, create perhaps a new vision of how you make sure that when you want to do human-oriented research, patient-oriented research, and you do it effectively, you do it appropriately, and that the rigidity of the system doesn't stand in the way.

That is why, for example, as part of the roadmap, we created, at the recommendation of many of our advisors, a work group called Harmonization of Clinical Research Regulation

This is a trans-governmental effort that we are leading out of my office to look at IRBs and the need for central IRBs, the ethical issues that relate to that, privacy and its impact on science, the different rules between FDA, NIH and other federal agencies.

The other concept that came up was the sense that the footprints of clinical research and translational research had

to change, especially when you look at diseases, as I said, that are chronic in nature. It is obvious that those patients are going to be seen in their own community. They are not going to be seen at the academic center.

So how do you develop the partnerships around the academic center so that you have a representation or at least a presence within the community with trusted intermediaries?

And you can't really conduct some of the trials that have been thought about without a strong community-based infrastructure, and that means a good information system, an appropriate way of training and developing constant leadership, trusted leadership around the issues of whatever network you are participating in.

That ecosystem, if you will, is one issue that I would like to ask the group to think about. How do you maintain an appropriate ecosystem in clinical research in the context of the changing landscape of disease and changing priorities, whether it be from the understanding of basic biological networks, their translation and validation into appropriate targets, their implementation with appropriate bio markers and appropriate survey instruments or phenotyping strategies.

These issues really led to the launch of this particular proposal. There is another proposal, called NECTAR,

which has also gone through an evaluation, called National Electronic Clinical Trial and Research Network, because it is clear that information technology is going to play a major role, in addition to the creation of partnerships that are open.

I have to agree with Steve that the report, at least the summary that I saw, was very enlightening in the sense that much of it was expected, but in totality, when you see, for example, that 60 percent of the clinical research is still paper-driven, when you look at best practices, it is really not in that range, when you see the use of interoperable dictionaries is still not adopted across.

I think there are lots of things we can learn here. When you read about the best practices of how to govern clinical research in complex environments and how to conduct that over time, the finding, for example, that NIH, after all, doesn't fund all networks and that partnerships with industry and other players are going to be key and how you assemble these partnerships and create a governance mechanism that allows these things to happen without too much obstacles and rigidity.

How do you then integrate this in the training, the training and development of appropriate teams, both at the level of study design and study implementation?

How do we, as an institution, knowing how expensive

clinical trials have to be, given the fact that our clinical care costs are rising eight, nine percent a year, how do you manage that?

How is it that we can make sure that we don't have many delays in recruitment and many trials that go overtime, if you will, which increases the cost, obviously?

So this is the issue. We have an enriched pipeline of biomedical discoveries. Everybody recognizes that.

In fact, the thing that is amazing to me is that the doubling of NIH has created a huge boom in capacity-building for research in our country.

We have twice as much capacity in terms of lab space, in terms of facilities, in terms of number of scientists.

This year, for example, we have more scientists applying to NIH than ever before. In fact, after 2002-2003, the number of scientists who applied, the incremental number was much larger than the total increase during the doubling, which is really due to all these buildings that you have seen on your campuses and new faculty positions that have been created.

So there is huge demand for a branch, which is outstanding. There is, obviously, a larger base of research that we are supporting, but it also means that we are going to have to be very mindful of this demand-supply equation over time

and improve it as much as we can, so that we don't lose the new investigators.

This is where I think you have to also think of how to integrate new investigators in this clinician scientist pathway, where there is a validation and an empowerment of this career path within the institutions, which themselves are suffering from the explosion of clinical services.

So that is the point I started with. That is the point I want to leave you with.

I am really looking forward to see how this effort can contribute to the creation of a robust force of clinical investigators, which will make it possible to test the new therapeutic and preventive strategies and larger numbers of patients for sooner than currently possibly; will allow us to have data-driven evaluations of impact on whatever best practice strategy is implemented in the community

And we have had some examples of that with the practical clinical trials, for example, in mental health, with the mental health networks, or the practical clinical trials on hypertension that NHLBI ran with the ALLHAT trial in 600 community-based practices.

These large studies cannot be conducted unless you have a clear sense of what is the capability of our country in

establishing efficient clinical research networks.

So I am looking very, very much forward to your deliberations. I'm sorry that I couldn't attend much of it, but I really want to congratulate all of you for being here. I'm really pleased by the attendance and, also, your commitment to that.

I don't know if we have time for a few questions, but Steve always tell me don't go without getting some bad questions.

Thank you.

[Applause.]

DR. ZERHOUNI: There is a microphone there, if you want to ask a question or two.

DR. KATZ: This is your chance, folks.

DR. ZERHOUNI: Right. If not, three, two, one.

DR. CAMARGO: On the buzzer.

DR. ZERHOUNI: All right.

DR. CAMARGO: Carlos Camargo, from Boston, Mass.

General Hospital.

DR. ZERHOUNI: Yes.

DR. CAMARGO: Just I would appreciate your comments.

Very often we hear the phrase "bench to bedside."

DR. ZERHOUNI: I haven't pronounced that.

DR. CAMARGO: I know.

DR. ZERHOUNI: I haven't used that phrase, if you noticed.

DR. CAMARGO: Over and over, and I'm always concerned whenever I hear that, that that academic medical center bedside is actually very far from our country's needs.

I'd appreciate your comments on just the idea of bench to bedside to population, because I think that really speaks to the issues you raised in your talk.

DR. ZERHOUNI: I think I would like to echo that. I think it is really -- Steve Straus, who is not here today, would say "bench to bedside and back" and I would say, "Wait a minute. Science is good science, whether it is population, whether it is bench to bedside, basic."

The key thing is you can't rigidify our enterprise. I mean, after all, we have made progress in medical sciences even when NIH didn't exist, because what you want to sustain is the creative, innovative models that people can come up with.

So my view is that progress can come from any area of science and you have to have a balanced view of that, including the other end of the so-called pipeline, and you have seen that with many examples.

The Framingham study is the one that always comes to

mind, but there are many others.

Yes, sir?

DR. PETERSON: Kevin Peterson, the University of Minnesota. I completely agree with that, the bench to bedside. We used to sometimes call it from bedside to bookshelf.

DR. ZERHOUNI: Bedside to what?

DR. PETERSON: From bedside to bookshelf. I also really like the comments you have about involving the community and bringing some of this information out into the community.

I might suggest that some of -- we actually set up a demonstration across the hall of some of those new tools that we are using in networking and I would encourage -- I would be happy to show you around some of those tools.

I think you might be interested in that.

DR. ZERHOUNI: That was not a question. That was advertising.

[Laughter.]

DR. ZERHOUNI: That was propaganda 101. Good. All right.

DR. MORRIS: Can I ask one more question?

DR. ZERHOUNI: I'm sorry. I don't see you.

DR. MORRIS: You don't see me.

DR. ZERHOUNI: Oh, yes. Hi.

DR. MORRIS: I'm hidden here behind the stage. Alan Morris, University of Utah.

You point out in your very nice emphasis on translational research the need to move back and forth, and I am glad you didn't use bench to bedside as the model.

But the bio directional movement across scales of research, for example, from bedside to bench, is largely dependent upon the quality of research conducted at the bedside.

We usually think of so-called reductionist or bench research as very high quality scientific research and then when we get to medical research and intact patients, we think in much more fuzzy terms.

So my question to you has to do with the generation of tools to make the inquiry at the clinical level more scientifically robust.

We don't have mechanisms right now to establish replicable methods across different community and academic clinical institutions.

Do you think it would help the roadmap, which I think is a terrific movement, if it also embraced the inclusion of tools that focused on the clinician-patient encounter and on the decision support that would be necessary to make clinicians do replicable things in different environments?

DR. ZERHOUNI: Well, actually, I totally agree with your view and, actually, the roadmap does do that. There is a program in the roadmap called "PROMIS." It is patient reported outcome medical information system.

That is to address the fact that when you have survey instruments and you are trying to record the outcome so that you can have a measurable end point, the tools are out there, are just all over the map.

There is no one body of validated tools that you can use in all communities, in all cultural environments, with the appropriate language. So that was one example.

The other point that you make, which is absolutely on target, is this need for bidirectional exchange, constant bidirectional exchange, but that means that you have to have a cadre of scientists who are absolutely trained to be able to bridge all the worlds of science that are needed.

For example, if you look at proteomics or you look at genomics and you look at the tools that have been developed in the laboratory and how you need to translate that into population research, you have seen, for example, the genome-wide association studies that are ongoing right now in many areas of science.

Just this past year, there were a 100 discoveries

related to that. One of the main stumbling blocks is you don't really have good phenotyping tools.

So the development of understood, standardized phenotyping strategies, environmental measures is a good example of a lack of that, as well.

If you think about just a simple problem, obesity, how do you measure food intake and caloric intake? Just think about this. We do not have a good measure of that right now. There isn't a strategy to measure the environmental impact of just caloric intake at an individual level, so that you can correlate that against any particular trial, and on and on.

I mean, if you look at individual measures of exposure for particular agents at the individual level, you can do it.

So you can do it at the regional level, you can do it at a local level. So those are tool developments that need to occur, in addition to what you talked about; that is, the concept that the whole is greater than the sum of the parts.

So that you can, in fact, exchange and analyze, in the meta form, through registries, for example, events that occur in large populations. You have seen an example of that with the detection of adverse events, cardiovascular events in the use of Vioxx through the mining of the database at the Kaiser Permanente network in California, and this is what picked up the

finding and drew the attention of people to that, in part.

If you don't have that, if you don't have a strategy to look at large populations almost online, in the next 10 to 15 years, I would say that the efficiency of our current model is just not sustainable.

So we have to do all of that and I will look forward to your recommendations in that regard.

One more, and then I'm leaving.

DR. FOX: Chet Fox, at the University of Buffalo, part of a practice-based research network, where our questions are not really the "what" questions, what works, but how.

One thing is I think we need to keep focus on, whatever we are doing, how is this going to benefit the patient, not maybe 10 years, 20 years, 30 years, but how is it going to benefit the patient.

But the question I have is in this age of evidence-based medicine and standards and other things like that, the randomized control trial has become sort of the gold standard of how we do things, but as we work out in the field, creating research, patients are not interested in being randomized. They are interested in being improved.

Wouldn't studies that looked more rigorously at longitudinal observation over time, looking at quality

improvement or patient improvement, maybe, rather than quality improvement, be a better model for studying?

DR. ZERHOUNI: Right. Very good question. Again, this is something that relates to the fact that when I say do science and science, that is what I mean. I mean, do research on research.

In fact, when you look at translational clinical sciences, a lot of the fundamental concepts haven't been researched in their own ways in terms of validation in the context of a changing landscape of disease.

The randomized double-blind clinical trial, prospective clinical trial is a gold standard, no question about it. You can look at mathematically at it.

But as you deal with chronic diseases that last a long time, where you have patient loss, you have multiple diseases and morbidities at the same time, we need to engage the research community in thinking about different models.

For example Bayesian statistics is getting now the sort of treatment that I would like to see more of in both information systems and other bio statistical areas, and that can change, in fact, the way you look at what some people call population surveillance strategies, where you really accumulate data.

Like one original idea I heard was the analogy to the Nielsen ratings for TV. What you do is you take a cohort, a randomly selected cohort and you track it with great detail and that can tell you sometimes a lot more than the trials, which are difficult to conduct in the kind of pathologies that we are dealing with.

DR. FOX: The partners that we have, like we build community collaboratives and there are a lot more partners out there. HMOs have huge databases, as you mentioned with Kaiser that can help us with research without having us rebuild it.

But, also, when you get patients involved, if something works, they want it now. They don't want to wait.

DR. ZERHOUNI: Yes. And they want something now that they heard about, which may or may not work, too.

Thank you very much.