HHS Efforts and Future Directions in Pharmacogenomics
Rochelle Long, Ph.D

DR. WINN-DEEN: We're going to ask everyone to come in and take their seats so we can start the afternoon session. We have a lot of material left to cover, and we want to try to make sure we stay on time with this session as well.

The first part of the afternoon session we're going to hear a series of three short presentations representing the different agencies within Health and Human Services that are involved in work with pharmacogenomics.

Our first speaker is Dr. Rochelle Long, who is the branch chief with NIGMS, and she currently has oversight of the Pharmacogenomics Research Network and knowledge base, and so I think is in a unique position, having looked at all the applications that have come in, as well as working with all the funded researchers within the Network, to talk to us a little bit about the state of the art in that part of the world.

Rochelle?

DR. LONG: Thank you. I thank the organizers for inviting me. I'm the first of three panelists, as I understand, talking about research that is supported within the Department of Health and Human Services, and I'll be specifically talking to you about NIH, the National Institutes of Health, which is comprised of multiple institutes. So I'll be giving you a survey of all the work supported by all the institutes, and then moving on to tell you a bit about the Pharmacogenetics Research Network, with which I'm personally involved.

What I did was start at the CRISP, which is the Computer Retrieval of Information on Scientific Projects, looked up and found over 400 different awards supported that have as their key phrases pharmacogenetics or pharmacogenomics. For today's talk, I will be just talking about extramural grants to the community outside of NIH. I will not be concentrating on the intramural program at all.

The green ones are basically training mechanisms, 40 career awards, 24 institutional training grants, and five fellowships. So this shows that people are thinking about pharmacogenetics/genomics when they comprise their training programs. The sort of peachy/orange area shows that there are 70 different cooperative agreements that list as key phrases pharmacogenetics/pharmacogenomics, and that's a relatively large proportion of 400. This includes some of the large multi-million dollar awards through the Pharmacogenetics Network, but also clinical trials, any time they're collecting materials from people and actually planning to do pharmacogenetic/genomic studies.

There also are 40 large centers and program projects that tend to be concentrated at a single institution to delve into a scientific program, as well as two facilities and centers. There are nearly 200 individual research grants. Normally this is the bread and butter of the awards made from NIH, especially from my institute, the National Institute of General Medical Sciences. So I think the relatively large proportion of these large cooperative groups shows how it takes multidisciplinary teams and large facilities to approach problems in pharmacogenetics/genomics.

There also are a few small business awards, and again a relatively large number of conference grants where people want to discuss the topic.

As I mentioned, there are many institutes at NIH, and many of the categorical disease-oriented institutes are conducting large-scale clinical trials in their disease areas, identifying the genetic contributions to complex diseases. Many are banking DNA samples for subsequent analysis. This is one thing, by the way, that is not done as a network through the Pharmacogenetics Network. They're not banking them as a group in general, but I'll get back to that.

Almost all large efforts are promoting sharing tools for researchers to enable all researchers to do better quality research, and also promoting data-sharing activities. This is definitely an activity that came to the fore in recent years at NIH, the idea being if federal government funds are being used to support the work, the results should be shared subject to privacy or HIPAA-type concerns because they're many times derived from patients or individuals, yet dating sharing is a concept that NIH wants to promote.

When I surveyed the different institutes, the National Institute of Mental Health specifically mentioned their STAR*D trial, Sequence Treatment Alternatives to Relieve Depression. Those samples are undergoing analysis for genetic predictors of who might respond to different drugs used to treat depression. They also strongly promote tissue repositories, and they do in fact have oversight for many different mental health disorders, collecting materials for subsequent human genetic studies.

The National Institute of Child Health and Human Development supports the Pediatric Pharmacology Research Units. They are clinical in nature, and they do include limited pharmacogenetic studies in some components at some sites.

The National Heart, Lung and Blood Institute is one of our major co-participants in the Pharmacogenetics Research Network. They've funded a significant number of multi-million dollar awards themselves over the last couple of years. They also have had a large program called Programs in Genomic Applications, or PGAs, that support tools for researchers to use, be they clones, be they mice, be they statistical methods. But again, the emphasis is on tools and getting that out there for researchers across the nation, or even internationally to do studies.

The Heart, Lung and Blood Institute also supports sequencing services available for researchers. These are often sequencing, resequencing and genotyping services at this time, and they also support individual research grants. This is important to recognize because not all good research takes place at good universities on the east or west coast of the United States. Again, I come from NIGMS, and research grants to individuals do matter a lot.

The National Cancer Institute, as you might suspect, has multiple large adult and child clinical trial networks ongoing. They are beginning to think more proactively about planning to do pharmacogenetic analysis of samples, and I expect their greater involvement in the Pharmacogenetics Network with the next renewal. They also have a cooperative human tissue network. They also bank samples, and they also support individual research grants.

The National Institute of Diabetes, Digestive and Kidney Disorders also, again, has several clinical trial groups particularly studying diabetes as a disease, and they have the drug-induced liver injury network of researchers setting protocols to collect materials from people who have experienced severe drug-induced liver injuries.

The National Institute of Aging supports clinical trials for Apo-E alleles and Alzheimer's correlations, sort of a classic predictor for complex disease, at least one component of it. The

Human Genome Research Institute you probably recognize, supports the HapMap Project, using SNP blocks as a tool to look at the genetic contributions that contribute to variation in responses to drugs, and also vaccines and compounds in the environment. The big effort in the HapMap is collecting and identifying the SNP blocks correctly so that investigators can go on to do these sorts of studies.

The Human Genome Institute is also the center at NIH for the Roadmap Initiative on molecular libraries and developing sets of compounds that probe molecular space.

NIDA, the National Institute of Drug Abuse, also has several tissue and cell repositories. They make services available to researchers. For example, they're part of the Microarray Consortium available through what's called the Neuroscience Blueprint or group of NIH institutes that come together to raise the research level for all.

The National Institute of General Medical Sciences, where I am based, historically has funded individual awards, most often studying drug-metabolizing enzymes because these enzyme systems are common to metabolizing many different classes of drugs. Therefore, it would be common for drug use to treat heart disease or cancer or depression, so it makes sense that the General Medical Sciences would want to support this research.

Starting around 2000, we started the Pharmacogenetics Research Network. Now, this is the way that the Pharmacogenetics Research Network looked from approximately 2001 to 2004. At this time there were six institutes participating. This initiative is undergoing renewal, and as of this summer it will come out for the next five years, starting in 2005. I'm pleased to say that we now will have nine institutes and offices contributing, so it's really becoming a trans-NIH initiative.

As I mentioned, historically NIGMS has supported research in the drug metabolism transporter area. You heard Dick Weinshilboum speak earlier. He has one of the pharmacogenetics awards to look at Phase II drug metabolizing enzymes. Another longstanding grantee of ours is Kathy Giacomini, who looks at the membrane transporters.

I'll point out that each of these groups was charged with putting together an interdisciplinary team. So here you see somebody from pharmaceutical sciences paired with somebody from a genetics background, and the very best groups that competed through this initiative brought people with pharmacological and people with genetics/genomics backgrounds together, along with people who knew statistics, along with people who could look at samples from clinical studies. You need large teams to do this kind of research.

Besides working in the metabolism and transport area, we have had groups looking in the cancer area both at breast cancer and at colorectal cancer, and at leukemia in children. Howard McLeod also works in the colorectal cancer area. We had a number of groups, as I mentioned -- NHLBI was a good supporter of ours right from the start. These researchers are looking at both cardiovascular and pulmonary diseases, looking at compounds or drugs that lower cholesterol levels in the blood, looking at anti-arrhythmic agents, looking at anti-hypertensive agents, as well as looking at drugs used to treat asthma.

It's interesting that many of the investigators coming from this side of things, again the historical NIGMS side of things, proposed what I would tend to call genotype-to-phenotype studies. They had proteins, they had families of genes, they had families of proteins of interest, they were looking at variation, and they were trying to find out what that meant functionally.

Interestingly, when we had the first competition for the Network, a lot of people also came who had very interesting patient samples. So they saw people in their research clinical situations that responded differently to drugs, and they wanted to look at the genetic contributions to that effect. So I call these more of the genotype-to-phenotype type of studies, where they're trying to find the underlying genotype or types or haplotypes that go with their clinical observations.

The Network is united by PharmGKB, which is a knowledge base. I'll tell you a little bit about that in a moment. PharmG stands for pharmacogenetics or genomics. KB, knowledge base, meaning they are trying to interpret what the functional implications, what the clinical implications, what the medical decisionmaking points ultimately might be for predicting responses to drugs. But I must emphasize that PharmGKB was and still is conceived as a research tool. It is not yet a place that a common practicing physician can just log right in and figure out which drug to give to that patient. We're not there yet. If I leave you with no other thought than this, keep in mind that there's a lot of research that needs to be done to accurately predict what the genetic contributions to predicting drug responses are.

We also supported a local informatics award that helped these groups get started to put their research results into PharmGKB, and we supported an award that specifically looked at the implications of pharmacogenetic/genomic studies for minority populations.

This is PharmGKB. This is a pretty recent slide. It shows you that any researcher can come to it, can browse through genes, can look at primary data, can look at pathway pictures -- you saw one of these earlier with Dick Weinshilboum's talk -- can enter simple queries, and they can start to pull up data. As soon as data become human data, you do actually have to have a password to access the site. For example, you need to have a valid research purpose. It's not hard to get a password. You just have to describe your research program.

I also want to emphasize that none of the information here is individually identifying. If it gets down to a granular level, that it's a person with red hair in Chicago with a certain sort of rare cancer who came into a certain study at a certain time, no. So a lot of thought has gone into this to ensure that it is ethically and legally compliant in all the most modern and appropriate ways.

The Pharmacogenetics Research Network at the present moment, their primary emphasis is on conducting cutting-edge research. You will see their papers from their individual lab groups published in both basic and clinical areas and journals. They are really working on establishing the knowledge base PharmGKB and actively depositing their data sets for genotypes and phenotypes and correlations between the two. They're working to develop pathway displays that can very easily pictorially display pathways of drug clearance and mechanisms. There are almost no drugs that I can think of that you take that just encounter one single gene as they go through the body, one single protein. It's that spaghetti diagram concept again, trying to represent research knowledge.

I do want to emphasize that this is open for scientific community submissions of data. So it's not a network-only tool. It's available to all researchers.

I think this group is still learning as a network. Early on they worked to devise policies. For example, what should you put in an informed consent for somebody whose research data ultimately will show up on a website, and is that different than just a scientific publication? They worked to develop intellectual property policies that were not encumbering. In other words, they were asked to deposit their data relatively early on, but the strategy developed was actually to encourage provisional patent applications, because people want what is important and meaningful

to be able to be commercialized, and yet that doesn't mean the research results can't be shared with others.

They are developing principles, looking at ways and comparing ways to do clinical study designs, looking at statistical analysis and ways to do more and more efficient experiments, and this is a very interesting and active area of the Network.

I'd like to point out to you that another aspect of the Network is for them to share their work with everybody in the research community. They are working right now on authoring a series of four white papers, the first one being an overview where they will discuss what are the cutting-edge problems, issues, barriers, obstacles to do pharmacogenetic studies, and have some recommendations in that paper.

The second paper is actually looking at pharmacogenetic testing and for research purposes what needs to be done, what are the considerations and, by the way, how will this fit into an ethical framework, how will this fit into a regulatory framework. But the emphasis for this group is, again, research, getting good, meaningful results.

The third paper is actually going to deal with guidelines for educating professionals in the area of pharmacogenetics/genomics. That would include physicians, but that also might include pharmacists or others who are part of the medical care team.

Each of these papers ultimately will be targeted to the appropriate journal to get the word out to the community that should be hearing some of this thought and discussion process.

The fourth white paper tentatively is in the area of doing association studies in pharmacogenetics/genomics and what is unique and different than, say, simply doing studies that might concentrate less on drugs and predicting drug effects. I've seen draft papers, I've seen draft outlines. I really expect them to be hitting the streets in good journals probably over the next couple of months or so.

This network has also worked to generate and donate sample sets to the repository. I want to particularly credit Julio for some of this work, collecting materials from individuals from Hmong Chinese communities and from Mexican Americans in greater Los Angeles. There was extensive community consultation that took place and a real effort on getting samples right and having people know they're going to be used for research purposes, and understanding they might not personally benefit but that ultimately better work could be done in the field because of it.

Finally, many members of the Network are members who do testify sometimes in front of FDA hearings. They have the knowledge, they have conducted the studies, and I feel that their work fundamentally contributes to some of the efforts at the FDA to change labels for drugs on the market and will continue beyond as they discuss ways they might interact.

So I will conclude my talk just by pointing out that it was our institute that commissioned and actually had two publications that you have as brochures out at the table. One is called "Medicines for You," the other called "Genes and Populations." These were developed to actually encourage people to understand the purposes of research and help them make decisions about joining research studies. They were just done as thoroughly as my institute thought it was possible to do. They're available free. I encourage you to take copies and go back and request more if you'd like them for any purpose.

That concludes my talk. I would be happy to take questions or delay them to the panel, however the organizers think is appropriate. Thank you.