Diabetes Mellitus Interagency Coordinating Meeting: Use of Special Funds for Type 1 Diabetes Research April 14, 2003

Building 31, Conference Room 6C
National Institutes of Health (NIH)
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Summary Minutes

Dr. Saul Malozowski, Executive Secretary of the Diabetes Mellitus Interagency Coordinating Committee (DMICC) and Senior Advisor for Clinical Trials and Diabetes Translation, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), opened the meeting, welcomed the Committee members and their guests from the Juvenile Diabetes Research Foundation International (JDRF), and introduced Dr. Allen Spiegel, Director, NIDDK.

Dr. Spiegel welcomed the attendees and explained that DMICC is the venue for coordination of a number of diabetes functions. DMICC includes members from the major NIH institutes and centers (ICs), the Centers for Disease Control and Prevention (CDC), and other U.S. Department of Health and Human Services (DHHS) agencies. Dr. Spiegel acknowledged the phenomenal support from Congress for type 1 diabetes research. The 107th Congress not only extended the initial special statutory funding program for type 1 diabetes research from FY 2004 to FY 2008 but also increased the funds to $150 million per year. This poses both an opportunity and a challenge.

Dr. Spiegel announced that an evaluation report on the original funding will be published in April or May. The original January 2003 due date for this report was changed by the latest bill to January 2007; however, NIDDK felt the report was of such value and interest that it will issue it. In addition to presenting the results accomplished from projects supported from FY 1998–2002, the report includes an Office of Management and Budget (OMB) approved survey of all the investigators supported through these funds. This survey, as well as an analysis of the grants funded, documents that the special statutory funds were instrumental in bringing new investigators into type 1 diabetes research efforts as well as established investigators who had not previously worked in this area. Dr. Spiegel stressed that with this new stream of funding, it is critical to examine carefully each of the commitments made for initiatives, consortia, and networks that have been so productive and define milestones and criteria for how they should be renewed. At the same time, the best possible new initiatives need to be identified to move forward. Dr. Spiegel then turned the meeting over to Dr. Judith Fradkin, Director of NIDDK's Division of Diabetes, Endocrinology, and Metabolic Diseases, who has spearheaded the management of this special statutory funding program and crafted an ambitious program to respond to this dual obligation for use of the new funds.

Six Major Goals

- Identify Genetic and Environmental Causes of Type 1 Diabetes
- Prevent or Reverse Type 1 Diabetes
- Develop Cell Replacement Therapy
- Prevent or Reduce Hypoglycemia
- Prevent or Reduce Complications
- Attract New Talent

Dr. Fradkin summarized the legislative history of the type 1 special statutory funds, which have grown from the original $30 million a year in 1998 to $150 million a year for FY 2004–2008, for a total of $1.14 billion for FY 1998–2008. This funding is intended for use in trans-DHHS research efforts. Flexibility to provide for a rapid response to emerging scientific opportunities will be preserved through use of pilot and feasibility grants and short-term commitments that could roll over to subsequent initiatives. Research and voluntary communities are actively involved in the planning and evaluation of the use of the funds. Most importantly the funds are not to supplant research funded by regular NIH appropriations, but rather to

augment and go beyond these efforts to fund opportunities that would not ordinarily be addressed with regular funds. Based on these principles, six major goals have been defined (see box). To date the funds have established a large-scale, collaborative, infrastructure of intensive initiatives that could not be pursued through R01s (i.e., investigator-initiated research); promoted innovative, high-risk, high-impact research, particularly through pilot feasibility grants; brought in new talent; and fostered state-of-the-art technologies.

On May 16, 2002, an Advisory Panel of scientific and lay experts met and evaluated the research efforts funded to date. The panel strongly endorsed the six major goals noted above and the initiatives resulting from them. They were also asked to identify new and highly promising opportunities for research on type 1 diabetes. At the time the advisors met, it was not known that Congress would be providing additional funding to support these opportunities. Their recommendations will form the foundation for use of the newly appropriated funds. These recommendations included:

- Continue support for investigator-initiated projects.
- Continue support of the consortia and the resources that have been developed.
- Pursue development and application of new technologies.
- Encourage coordinated trans-DHHS and multidisciplinary approaches.
- Re-issue targeted Requests for Applications (RFAs) to create ongoing research opportunities.
- Continue to attract new research talent to type 1 diabetes research.

In addition there were specific recommendations for each of the six major goals that will be presented in more detail. These recommendations from the May meeting will be supplemented by focused meetings on the major goals or subcomponents of the goals.

Dr. Fradkin elaborated on the May 2002 Advisory Panel's recommendations based on the six major goals and sought the opinions and comments of today's participants.

Goals 1 and 2: *Identify Genetic and Environmental Causes and Prevent or Reverse Type 1 Diabetes*

To date, substantial resources have been used to develop strong consortia. The Advisory Panel recommended promoting interactions, data sharing, and coordination among these groups. They wanted to see common bioinformatics platforms; ability to integrate data; common consent forms, particularly as samples are being put into repositories for use by future scientists; and standardized assays, for instance for measuring HLA genotypes, antibodies, and C-peptides as outcomes. The panel encouraged support and interaction within the consortia for ancillary studies such as the immune response studies from the Immune Tolerance Network (ITN) in conjunction with TrialNet clinical trials, as well as partnerships with industry and academia. It was felt that fast-track mechanisms were needed to facilitate preclinical development and mechanisms for bench-to-bedside support (e.g., production of biologics when there is good preclinical data to suggest these would be efficacious in a clinical trial, access to GMP (good manufacturing practice) facilities to make materials for use in humans, and support and access to animal tests for safety, toxicology, immunoactivity, and efficacy).

Dr. Fradkin emphasized that close coordination is essential, given the number of consortia and the fact that they will be recruiting from the same population, as well as to promote the panel's recommendations for common bioinformatics platforms, standardization of assays, and partnerships. This will mean coordinating recruitment and enrollment. Particularly where multiple studies are recruiting in a common geographic area, information exchange and joint approaches to referring physicians will maximize access to patients. Cross-identification of families is needed to avoid duplication in submitting specimens to repositories. Standardization of assays, phenotyping, and consent forms will also be needed. Dr. Fradkin said that NIDDK and the National Institute of Allergy and Infectious Diseases (NIAID) have already

identified an individual who will be asked take the lead in developing a coordination mechanism. Other DHHS components responsible for consortia will be asked to participate in this effort.

At Dr. Spiegel's suggestion, the attendees described the various consortia. TrialNet is a joint effort of NIDDK, NIAID, the National Institute of Child Health and Human Development (NICHD), and JDRF to test methods to delay or prevent type 1 diabetes in patients with new onset diabetes or at high risk for diabetes. It also has a natural history component allied with NIAID's Immune Tolerance Network for mechanistic assays to understand the ongoing pathogenesis of type 1 diabetes. ITN is a joint effort of NIAID, NIDDK, and JDRF. Its mission includes conduct of clinical trials to test therapies and to develop assays to monitor the induction, maintenance, and loss of tolerance. The areas covered are kidney and islet transplantation, liver transplantation, and asthma, allergies, and autoimmune diseases among which type 1 diabetes is the major focus of proposals to the ITN. To date, about 28 percent of ITN funds have been directed to type 1 diabetes activities.

Dr. Fradkin said that ITN, TrialNet, and the Diabetes Prevention Trial for Type 1 Diabetes (DPT-1), which was the precursor of TrialNet, are good examples of efforts, originally undertaken by the Institutes with regular funds, where type 1 funds allowed expansion of the research in ways that would not have been permissible under regular funds.

The Autoimmunity Centers of Excellent (ACE), also an NIAID initiative co-sponsored by NIDDK, is a basic or preclinical research program, with clinical components, in four centers that conduct trials with the major focus on diabetes, although they work with potentially more than 80 autoimmune diseases. NICHD's Trial to Reduce the Incidence of Type 1 Diabetes in the Genetically at Risk (TRIGR) is an international clinical trial in which children at high genetic risk for type 1 diabetes are randomized at time of weaning to regular formula or Nutramigen®, a partial hydrolysate of casein produced by Mead Johnson. The outcome is the development of autoimmune antibodies to pancreatic antigens and eventually, if the children are followed long enough, onset of type 1 diabetes. A preliminary trial about 5 years ago with approximately 200 children indicated that those who were put on Nutramigen® versus regular formula had a slightly smaller incidence of diabetes, although the data are not stable or statistically significant. The goal of the Triggers and Environmental Determinants of Diabetes in the Young (TEDDY) initiative is to organize international efforts to identify infectious agents, dietary factors, or other environmental factors that trigger type 1 diabetes in genetically susceptible individuals. The TRIGR and TEDDY studies will have overlap in the sense that they are both recruiting neonates at high genetic risk at birth.

The Centers for Disease Control and Prevention's SEARCH is an effort to look at childhood diabetes, particularly type 1, but also type 2, to acquire more accurate knowledge of the incidence and prevalence of the diseases and to identify characteristics that might clinically and epidemiologically distinguish between traditional type 1 and so-called type 2 diabetes in children. SEARCH will also follow these children to examine quality of care. SEARCH's six centers are jointly funded by CDC and by type 1 special statutory funds.

CDC's Genetics of Kidneys in Diabetes (GoKinD) is an international effort to study the genetic risk factors for renal disease of type 1 diabetes and is complementary to NIDDK's Family Investigation of Nephropathy and Diabetes (FIND). GoKinD is a joint effort by CDC and, JDRF. FIND is a large consortia of seven clinical centers and a genetics coordinating center that is undertaking two studies on the susceptibility to diabetic nephropathy. About 85 percent of the patients being recruited have type 2 diabetes and about 15 percent have type 1. One strategy is to look at concordant and discordant sibling pairs. The other strategy, called mapping by admixture linkage disequilibrium, is recruiting case controls to look at genetic loci with regard to racial admixture. FIND has been working closely with GoKinD in the informatics aspects, with the long-term goal of integrating the two databases so the identified susceptibility loci can be looked at in both databases. The original goal was to look only at nephropathy susceptibility, but with the support of the National Eye Institute and some type 1 money, retinal

photographs have been added and analysis will be done of retinopathy susceptibility as well. NIDDK's Epidemiology of Diabetes Interventions and Complications (EDIC) study is also collecting genetic samples from subjects and their family members for analyzing susceptibility to complications in a particularly well characterized clinical cohort. It will complement FIND and GoKinD.

The International Type 1 Diabetes Genetic Consortium (T1DGC), composed of three clinical networks and a data coordinating center, is studying genes that influence the pathogenesis of type 1 diabetes. It will generate a large standardized family collection of genetic and phenotypic data. The NIAID's International Histocompatibility Working Group (IHWG) is a multi-institute sponsored activity that includes the Office of the Director. IHWG is looking at genetic components of a number of diseases, including the genetics of transplantation. It includes more than 100 international programs and has received some type 1 statutory funds for SNP (single nucleotide polymorphism) identification in 100 genes presumed to be possibly related to type 1 diabetes.

The Diabetes Research on Children Network (DirecNet) is conducting studies of new glucose monitoring devices to determine their accuracy and utility in improving diabetes control and avoiding hypoglycemia in children with type 1 diabetes. It is led by NICHD with NIDDK participation.

Discussion

Dr. Fradkin asked everyone to be thinking about who from their consortia should represent them on the consortia coordinating committee. There may be multiple representatives so that subcommittees can be formed on specific issues, such as standardization of consent forms, phenotyping, assays, and so forth.

Dr. Fradkin explained that a Web site dedicated to the type 1 special statutory funds program will include information from each of the consortia on their resources that will become available and when they will be available. Type 1 funding will include a requirement for public access by the general scientific community to these resources. The NIDDK is creating a repository that will store and distribute samples from clinical studies for use by the broader community. A requirement to deposit specimens into this repository is written into TrialNet and the TEDDY grant awards. The Diabetes Control and Complications Trial (DCCT) has developed a process for access to samples from that study. DPT-1 will soon have finished its second randomized trial and plans are being made to share available samples from their studies with the larger scientific community.

Dr. Daniel Rotrosen, Director, Division of Allergy, Immunology, and Transplantation, NIAID, explained that if ITN has sufficient material, samples will be in the public domain along with data and protocols. He pointed out that one problem, which also may be true of other trials, is the availability of sufficient materials from young children due to mechanistic studies already planned within the ITN protocols. Material such as DNA that is readily available and can be amplified is not a problem, but serum is quite limited. This is also true of ACE. NIAID has not yet established a mechanism for soliciting requests for samples or distributing them. He suggested the consortia would benefit from a central repository with a standard mechanism to receive requests and to distribute materials.

Dr. Gilman Grave, Chief, Endocrinology, Nutrition, and Growth Branch, NICHD, said that since TRIGR is looking at neonates, there are not many specimens available, although a predecessor study has been collecting samples in Finland for 10 years. They have also not addressed a distribution mechanism yet, but will probably ask other consortia members for submission of specific information on what they have in place for distribution.

Dr. Patricia Mueller, Chief, Diabetes and Molecular Risk Assessment, CDC, explained that GoKinD was designed to be a collection of samples that will be in a CDC repository, so the collaborating investigators can do additional studies. Then they will be made available to the broader research community, probably

through a modified Framingham model. Proposals will be reviewed by a JDRF-appointed committee of independent investigators.

SEARCH, according to Dr. Frank Vinicor, Director, Division of Diabetes Translation, CDC, has established a repository and is willing to share data with other investigators but does not have a mechanism in place yet. Currently, CDC's standard approach is that investigators must submit a proposal that is then reviewed by the SEARCH Executive Committee. The SEARCH Executive Committee will be looking at the challenge of how to strike a balance between making the samples publicly available for studies that have an appropriate scientific base without using them up.

Dr. Fradkin said that peer review can be very useful in that regard. EDIC has two peer-reviewed program project (P01) grants that will use EDIC samples and are funded with separate NIH funds. One is an NHLBI-supported P01 at the University of South Carolina and the other is an NIDDK-supported P01 at the University of Washington.

Dr. Fradkin recommended that in making samples available to the broader community, it is better if those who collect the samples are not the sole determinants of who may use them. If the collection of the samples has been supported by substantial type 1 diabetes special statutory funding resources, there is a real obligation to share them, not just by making them available among the collaborating investigators, but by placing them in the public domain. What is needed is an in-place mechanism to provide support to those who will do ancillary studies with the samples, independent of the control of the investigators. She urged everyone to be aware of the importance of this. In EDIC, for example, some of the review committee members are from EDIC, but it is not an EDIC committee. This provides insights into the use of the samples that derive from the knowledge of EDIC investigators who know the study design in detail, but does not give the study group exclusive use of the samples. Ideally, the terms and conditions of the notice of grant award or the RFA should include this understanding to prevent any difficulty in acquiring access to the samples or data. Under contracts or U01s (cooperative agreements), there is more ability to influence the process than under an R01. Dr. Fradkin explained that agreeing to share the samples and associated de-identified information will be a factor in deciding support for type 1 activities.

Dr. Vinicor brought up the related issue of the HIPPA (Health Insurance Portability and Accountability Act of 1996) rules and regulations regarding patient privacy of personal health information that will also affect the sharing of samples and data. The administrative and legal processes affected by the HIPPA rules do not have to be a major barrier but it is important to be aware of them as a potential impediment. Dr. Fradkin agreed that the consortia coordinating group needs to look at HIPPA, particularly with regard to consent forms. While these investigations are ongoing and there is regular contact with the subjects is the best time to get proper consents for sharing of data and samples.

Dr. Peter Savage, Director, Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute (NHLBI) remarked that NHLBI, through its considerable recent experience in sharing data and samples, has noticed people interpret fairly clear statements in a wide variety of ways. He urged the group to have a standardized procedure for securing data or samples and one that certainly includes the legal implications of the HIPPA regulations. He also stressed the importance of the agreement's not being so broad that later, because of commercial interest or some other consideration, there is a lot of opposition to it. Dr. Fradkin added that it would also be important to proactively talk with people about the language in the Notice of Grant Award, since there is a tendency among investigators not to read the detailed award provisions. The meaning of the terms and conditions should be discussed and clarified to ensure they are agreed to and clearly understood. Dr. Mueller also expressed support for a consistent mechanism for making the samples available. The consensus was that this would be advantageous to everyone.

Dr. Robert Goldstein, Chief Scientific Officer, JDRF, agreed with the type 1 Advisory Panel's recommendation that coordination among the consortia (and he included the DCCT/EDIC) was extremely

important and offered untold opportunities for the future, especially regarding the data centers and sample repositories. He said the international community would welcome a standard procedure for sharing these resources across borders. In all JDRF grant awards where sample collection takes place and has value, JDRF has made ultimate sharing mandatory and the notion of a public resource preeminent, despite variations in international rules and guidelines. The lack of a standard consent form and standardization of sample collecting and measurement across international borders is a barrier to providing resources from these studies to U.S. researchers. Dr. Goldstein added that once rules and guidelines are established, the clinical trials funded by JDRF could contribute to a centralized effort other populations and materials that do not duplicate those from NIH. Dr. Fradkin remarked that many of the type 1 diabetes consortia are international in scope. Making funding contingent on willingness to supply the samples has been an issue with the type 1 genetic consortia because of the lack of standardization of consent processes internationally.

Dr. Goldstein also urged that industry be granted access at some point in time to some of the resources from this phenotypically valuable patient population, which is too small in number compared to those populations with other diseases to be assessed in this way by industry. However, if industry is presented with a well-documented population, regardless of size, it is then commercially attractive for them to study that group.

Dr. Goldstein commented that it would be extremely helpful to his organization, and surely to others, including Congress, to have a summary of the amount of money the NIH ICs spend on type 1 research as a whole, since this will not be included in the type 1 special statutory funds' evaluation report. Dr. Spiegel replied that to do what Dr. Goldstein requested would require a special mechanism to collect the information across all ICs, which is being done for the special statutory funding program for type 1 diabetes research. He explained that Dr. Elias A. Zerhouni, NIH Director, in his addresses to Congress presents overarching themes for all the diseases within the ICs areas of responsibility, rather than specific diseases. However, NIDDK and the other institutes publish many documents each year covering their advances and opportunities in intramural and extramural research.

Dr. Rotrosen said that due to the strong interactions he has had with NIDDK over the years, he is confident that NIAID and NIDDK have good mechanisms for addressing overlap. He suggested that CDC, the other ICs, and multiple partners meet more frequently to ensure the same level of communication. Dr. Fradkin assured him that CDC's funded research, for instance, is very discrete from what is happening at NIH. GoKinD and FIND are complementary, but recruiting different populations. SEARCH is not duplicated by any NIH projects she is aware of. She agreed that meetings facilitated communication and added that a coordination mechanism for the consortia will also provide DHHS staff with a forum to obtain progress reports and hear about events in which they are not directly involved.

Goal 3: *Develop Cell Replacement Therapy*

Dr. Fradkin noted that the May 2002 Advisory Panel was very enthusiastic about the Beta Cell Biology Consortium (BCBC). The panel strongly recommended expanding the BCBC, involving new researchers, and integrating the research with other consortia's efforts to identify markers for imaging beta cells and for assessing the quality of islets for transplantation. This is ongoing.

In transplantation, there are several coordinated efforts, including the ITN, that are looking at immunomodulation and tolerance. There is also a primate consortia that is looking at a number of transplantation-related issues. The Advisory Panel felt that in addition to these, there were other areas that needed to be developed. These included:

- Improving harvesting, isolation, assessment, and preservation.
- Improving engraftment (insights from angiogenesis) and function.

- Conducting clinical trials other than for tolerance (i.e., site and method of transplant, less toxic immunosuppression).
- Looking at xenotransplantation (islets, reagents).
- Expanding animal and pre-clinical research.

NIDDK is planning an advisory meeting on May 30, 2003, with the National Center for Research Resources (NCRR), NIAID, and JDRF to discuss transplantation initiatives such as expanding the primate consortia. The date for the meeting was selected to coincide with a meeting in the metropolitan Washington, D.C. area, of the American Society of Transplantation.

Discussion

The discussion on transplantation included the following points:

- Multiple groups are discussing the issues, including a trans-NIH coordinating committee and an Executive Committee from Secretary Tommy Thompson's office at DHHS. Close coordination among these groups is needed.
- The trans-NIH committee has largely focused on major organ transplantation but will include islets, but not the full pancreas, in its FY 2004 initiatives. It will be FY 2005 or beyond before they address xenotransplantation.
- The Secretary's office is aware of some high profile advances in transplantation, including islet transplantation, and of third-party payer issues for kidney transplantation.
- Key issues in islet transplantation are new approaches to genomic assessment of the quality of the islets; possibly the use of xeno islets or islets derived from stem cells; and development of better tolerance or immunosuppressive approaches.
- The Secretary's office also has an advisory committee on xenotransplantation, largely taking a very broad view and focusing on scientific feasibility and industry interaction with the Food and Drug Administration.
- Although xenotransplantation research goes back about 20 years, it has not had the success anticipated. Now that transgenic pigs engineered to prevent hyperacute rejection are available, funding may attract new investigators and encourage research in this area as an alternative approach to treat type 1 diabetes.
- Encapsulation is an area that also has not had significant success so far, but if it is de-coupled from xenotransplantation, small businesses might be interested in the two fields separately. Currently, there is confusion about their relationship.
- NIDDK provided additional funding through its diabetes centers in 2002 to promote research in encapsulation and attract new talent in this area of research.
- To propel the technology forward, Small Business Innovation Research (SBIR) programs were recommended as a possible approach, subject to peer review, to getting small businesses, possibly in the bioengineering community, interested in encapsulation and in xenotransplantation as separate endeavors. In addition non-SBIR funds still may be needed to involve the right people in investigating the xenotransplantation and encapsulation issues.
- Prior to FY 2001, there was no set-aside for small business from the type 1 special statutory funds. Currently the NIDDK funds the small business commitments generated by the special statutory type 1 diabetes funding from its appropriated funds. Beginning in 2004 special statutory type 1 funds will be used for this set-aside.

Goal 4: *Prevent or Reduce Hypoglycemia in Type 1 Diabetes*

Dr. Fradkin noted that hypoglycemia is a major problem for those living with type 1 diabetes. The May 2002 Advisory Panel identified several new opportunities for research, particularly to bring in some of the latest technologies from neuroscience and neuro-imaging to prevent or reduce hypoglycemia. Their recommendations included the following:

- Study the mechanism of restoration of hypoglycemia unawareness and counter-regulation in new transplant recipients.
- Recruit neuroscientists and brain-imaging specialists to study glucose-sensing mechanisms in the brain, islets, and other glucose-sensing tissues (e.g., muscle, liver).
- Understand the brain effects of recurrent hypoglycemia (especially in young children) using brain imaging technology (PET) and assessment of glucose metabolism.
- Foster application of discovery of sensors for brain substrates and neurotransmitters to type 1 diabetes.
- Identify transporters that may be involved in hypoglycemia.
- Understand how sleep promotes hypoglycemia.

Dr. Fradkin complimented Dr. Grave for how quickly DirecNet became established. It has already initiated and completed studies on the GlucoWatch and the Minimed Medtronic continuous sensor. Dr. Grave credited the data coordinating center and DirecNet's five clinical centers. Investigators at the centers have already issued about eight abstracts and some papers.

Goal 5: *Prevent or Reduce Complications in Type 1 Diabetes*

An overall recommendation from the May 2002 Advisory Panel that Dr. Fradkin noted was the need to bring together those working on different complications in order to share information and ensure maximum use of the information acquired, for instance from existing animal models. While the Animal Models of Diabetic Complications Consortium (AMDCC) has been helpful in doing this, there are potential expansions of this effort to advance the understanding of complications. The Advisory Panel recommended facilitating animal research that addresses multiple complications and evaluates multiple tissues. They also suggested developing resources for distributing animals with prolonged hyperglycemia and developing a mechanism for preclinical pharmaceutical testing of animal models. Development of animal models provides a means of testing concepts from basic research to identify the best places to invest funds for clinical research.

In addition to those from the May 2002 Advisory Panel, Dr. Fradkin brought recommendations from the April 10–11, 2003, DCCT/EDIC 20th anniversary meeting. The participants at this meeting had focused on the concept of a possible "metabolic memory" resulting from early intensive glycemic control. In the tight control group, the onset of complications tended to be delayed long after the tight control was ended, even though the subjects' glycemic levels became approximately the same as those of subjects in the standard treatment group. Following the main meeting, the group met with DMICC to contribute suggestions for further research on complications in type 1 diabetes (see box). Animal models were a major subject of discussion. It was suggested that the animal model consortium be a venue for bringing researchers of different disciplines together through regular conferences and symposia. It was con-

Recommendations To Prevent/Reduce Complications
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- Animal models:
  - Knockout (KO) and transgenics to define pathophysiology
  - Explore genetic differences among strains re development of complications after prolonged hyperglycemia
  - Need models that fully develop complications (e.g., no models of macular edema)
  - Cores for standardized assessment
- Identify cell types important in specific complications
- Multiple potential mechanisms of complications (e.g., glycation, lipoxidation, inflammation, apoptosis, angiogenesis) require multidisciplinary teams
- More efficient trials:
  - Reliable, practical biomarkers
  - Correlate subclinical disease with events
  - New technology (e.g., MRI, proteomics)
  - Discovery-based studies (as opposed to mechanistic)
- Bench to bedside
  - Exploratory results-driven projects
  - Assays to determine which agents to carry forward to clinical trials

sidered important to bring the trans-NIH and trans-DHHS groups together with the consortium to ensure that all of the complications are being considered and to develop strategies to coordinate, expand, and broaden the joint efforts. Currently NIDDK provides coordination for the consortium, and NHLBI administers a number of the awards.

Dr. Fradkin briefly spoke of the other recommendations, including expanding the cores as a resource so that those with expertise in one organ could send their animals to be characterized in terms of other organs. Standardized characterization would help to not only find genes but to identify animals that have a higher innate susceptibility, which is important in deciding which animals to use to create knockouts that are potentially susceptible to complications.

Other key areas are to learn which cell types are involved in the development of complications and to take advantage of the progress in integrating the potential mechanisms of complications by expanding multidisciplinary approaches that involve inflammatory expertise and so forth. Clinical trials still need reliable biomarkers to make them more efficient. Finally, the goal of moving from bench to bedside requires exploratory results-driven projects and assays to determine which agents should be carried forward to clinical trials so funds are not spent pursuing ultimately unfruitful things.

Discussion

Dr. Josephine Briggs, Director, Division of Kidney, Urologic, and Hematologic Diseases, NIDDK, spoke of the value of NIDDK's partnership with NHLBI. The current animal model consortium includes three projects on large animal models and a group of investigators who are coordinating efforts on the mouse. The mouse group is focusing on genetically engineering target genes to identify cell types specific for complications and on other genetic strategies to make the mouse more susceptible. The consortium has made substantial progress in developing agreement on assessment protocols for the mouse and overcoming the sizable technical problems in doing this assessment in the mouse. The nephropathic and neuropathic groups within the consortium are reasonably well advanced; there was no retinopathy proposal originally, but a group of investigators who will be looking at retinopathy is being brought in. This is an area where the consortium would like to see substantially more effort.

Dr. Briggs explained that some things in the broad area of animal models are not being addressed yet. The group has not undertaken extensive investment in the genetics susceptibility of loci to be able to translate them into the mouse to see if they have impact. It also does not include any rat studies. People in the field report that since the rat is being used and the protocols for identifying diabetic complications vary wildly from laboratory to laboratory, more standardization of protocols is needed. What needs to be understood is that the genetic manipulation to develop animal models is not an enormously rapid process. It takes about a year to make a knockout, and this group is just reaching the point where they have models that it makes sense to talk about distributing. The consortium meets every 2 to 3 months, but these have not been meetings open to others. Dr. Briggs heard a strong message at the April 11 meeting that to open these meetings and expand their dialog would be valuable both to those within the consortium and to the broader community.

Dr. Goldstein agreed that it would be valuable to use such a venue to bring together in one place people concerned about eye disease and nerve disease and kidney disease. To date, there has been no common forum or place to have such discussions. If this can be done around animal model discussions, it would help everybody. Dr. Spiegel added that it is important to involve the National Eye Institute (NEI) and the National Institute of Neurological Disorders and Stroke (NINDS).

Dr. Savage said that a NHLBI working group is going to be exploring opportunities to better understand the causes of macrovascular disease in type 1 diabetes. Dr. Paul Nichols, Program Director, Systems and Cognitive Neuroscience Program, NINDS, added that there is an interest in his group to study various aspects related to diabetes such as pain mechanisms, stroke, cognitive deficits in type 1 diabetes, and

sleep research, particularly its relationship to hypoglycemia. They are interested in doing a diabetes initiative or preclinical trial involving neurological complications, which they feel would not require a great deal of money.

Dr. Goldstein commented on the compelling discussion at the April 11 DMICC meeting about providing funds for a program to encourage high-risk, innovative studies of novel therapeutics for complications and immunomodulation. Such a program would require a different review process. It might also attract researchers who are not currently involved in diabetes, but who have expertise to contribute.

Dr. Fradkin replied that the bench-to-bedside RFA, supported across multiple institutes, addressed that type of focused preliminary studies. The RFA, which encourages collaboration between basic research scientists and clinical scientists, has been successful and probably will be issued annually as an impetus and path for innovative studies. However, additional mechanisms are needed to move new agents forward into trials. A mechanism similar to that of the National Cancer Institute's (NCI's) Rapid Access to Intervention Development (RAID) is also being considered. (RAID is a mechanism to provide investigators with access to drug development resources in order to bring therapeutic applications that originate in an academic laboratory through preclinical development.)

Dr. Fradkin agreed with Dr. Goldstein that a special peer review process for applications for use of the RAID mechanism will be essential, both to foster a rapid response and because such efforts tend to be very expensive. It is important to invest the type 1 funds in development of the most promising agents. In addition to proposals for new therapeutics for complications, there are some proposals coming out of ITN and TrialNet that need preclinical development, mouse studies, toxicological studies, and such that the individual consortia members are not equipped to do; the consortia could benefit from such a mechanism. In addition, availability of an impartial review for access to this type of preclinical development mechanism might challenge the broader community to develop new therapeutics.

Goal 6: *Attract New Talent to Research in Type 1 Diabetes*

In introducing Goal 6, Dr. Fradkin said that the Advisory Panel clearly recommended major bold new initiatives with these funds. Complications may be a good area to pilot these since relatively fewer resources have been directed to them in the previous funding years and, even though there are excellent investigators in the area, it is a fairly small field and one that needs new talent. This might be a place for a mechanism to attract those who would not be typically attracted by an R01 award. The Panel recommended encouraging multidisciplinary teams and novel technologies, supporting high-impact goals, and, most importantly, making continued funding contingent on milestones.

A DARPA-like review was also recommended. Such a review was discussed at a recent JDRF scientific advisory board meeting. It assesses a researcher's capabilities, track record, and the novelty of the proposal being offered, rather than focusing on the technical aspects that are central to an R01 review. For example, it does not require the level of preliminary data required for an R01. The idea is for the review to be flexible and examine where opportunities lie in the applications. Because acceptance is based primarily on potential, it is essential to have specific milestones and ongoing evaluations. (DARPA is the Defense Advanced Research Projects Administration. DARPA projects are intended to develop a specified application driven by a pre-defined outcome. They usually have a lifetime of 3-5 years and a large budget of $5-10 million.)

Challenging topics might include new animal models focused on complications, surrogate markers, angiogenesis, and endothelial biology. The challenge will be to take on a difficult problem such as developing surrogate markers or a high throughput assay that could be used to move things from the bench to the bedside. Hopefully this will bring in people, such as endothelial developmental biologists, cell biologists, or those with expertise in angiogenesis, who are not currently focused on diabetes and its

complications. This has worked well for cancer research. If this is successful in attracting the right people to the field, then it could be expanded in subsequent years to other goals.

Discussion

Dr. Rotrosen cautioned that the challenge opportunities be well-defined, since most investigators believe their project is innovative and challenging. Also, a useful technique that NIAID had for their challenge grant initiatives was to not require matching funds from industry and to provide multiyear funding in one year, which is atypical, but got the attention of companies and academic investigators who otherwise might not have been interested.

Dr. Spiegel was impressed at the April 10–11, 2003, DCCT/EDIC meeting by the amount of important talent that has largely focused on the cancer area, but not on diabetes. Angiogenesis, for instance, has burgeoned dramatically in the cancer field. He said it will be important to find an inducement for these researchers to shift their focus and apply their abilities in the diabetes field. He urged the group to seize the opportunity this year to tap into the tremendous talent pool that is available—to attract those who have successfully solved problems in one area and have them focus now on diabetes—both with regular appropriations and the special statutory type 1 funds. Integrating industry also is an issue for which an appropriate program is needed.

Dr. Fradkin asked if there was interest in a pilot program to identify one or two areas of focus regarding fundamental biology related to complications. Understanding the biology might then provide the opportunity to develop biomarkers, surrogate outcomes, and other measures to move novel therapeutics forward. Before looking for therapies, it is necessary to have a reliable assay that will accurately measure the outcome of the intervention process; this is not presently available for complications. That could be the focus of the challenge.

Dr. Charles Queenan, Chair of Research, JDRF, suggested that, rather than an all-or-nothing approach, portions of innovative proposals could be approved or applications could be combined, particularly with a DARPA-like review mechanism.

Dr. Savage thought that seed funding might be the best approach to take at the present time rather than soliciting large multidisciplinary projects since many areas related to diabetes complications are still relatively primitive. For instance, there are some very specific things to be defined in the area of biomarkers, which are needed for clinical trials. Another area of interest would be to try to identify those who are at risk, and those who appear to be protected, by studying people who have diabetes for 20 or 30 years and do not develop complications versus others who develop them very early.

Seeding Collaborative Research Supplements for Shared Resources

Dr. Fradkin proposed providing supplements to regular NIH grants in a new mechanism to seed multidisciplinary collaborative research. The supplements would enable a person in one area to seek out others whose expertise, along with core or shared resources, would benefit collaborative research funded through a peer-reviewed mechanism. There would be very clear definitions on how the supplements could be used. They could not be used for merely continuing the investigator's ongoing research projects. The seed money would be expected to "jump start" important collaborative research efforts, bring in new talent, and lead to other beneficial consortia. Potentially, it would foster the following types of initiatives:

- Establishment of research consortia among researchers in complementary fields to investigate:
  - Multiple issues affected by vascular disease.
  - Inflammation, immunology, and endothelial biology.
- Sharing of unique reagents, technology, or complementary expertise.
- Funding two to five researchers, each with independent peer-reviewed support.

- Supporting a collaborative project within the scope of individual grants.

Projects would be peer-reviewed by senior NIH staff, both initially and through ongoing evaluations. The projects would be assessed on their novelty or uniqueness, the added value they will bring to underlying research, and their potential benefit to type 1 diabetes research.

Report on Consortia and Resources

The current consortia will be reporting in May 2003 on the special statutory type 1 funds they have been awarded to date. Their reports will include the following topics:

- Goals and structure (i.e., steering committee, sites, Web sites).
- Accomplishments to date.
- Milestones for future accomplishments.
- Evaluations (e.g., by External Advisory Committee, reports, recommendations).
- Coordination efforts with other consortia.
- Materials, products, and samples that will be made available to the scientific community.
- Future support requested.

With the exception of the budgets, the reports will be posted on the type 1 diabetes special statutory funds Web site that is in the process of being created. The Web site will describe the consortia and the resources available through the consortia. It will provide a central resource for people seeking information on type 1 diabetes research, including links to non-special statutory funded research as well as links to the individual consortia Web sites. Opportunities for funding will also be listed.

Dr. Fradkin said that the recommendations by the May 2002 Advisory Panel have been carefully reviewed and mechanisms are being put into place to fund these in the FY 2004 budget.

New or Re-Issued Solicitations

Goals that the Advisory Panel members were enthusiastic about will be supported by re-issued and new solicitations, including the following:

- Innovative Grants Immune Tolerance
- Bench-to-Bedside Research
- Innovative Partnerships for Type 1 Diabetes
- Ancillary Studies to Type 1 Diabetes Consortia
- Expand Beta Cell Biology Consortium
- Expand Non-Human Primate Consortium
- Hypoglycemia.

It is also likely that additional solicitations may be issued based on recommendations from upcoming meetings on the role of inflammation in CVD complications, beta cell imaging, and proteomics and islet transplantation.

Dr. Fradkin explained that these will be similar to previously issued solicitations in these areas of opportunity but will be amended based on the May 2002 Advisory Panel and other advisory committee and scientific meetings. The innovative partnerships RFA serves as a “talent scout” by fostering collaboration between researchers with expertise in type 1 diabetes and researchers whose expertise, while not in type 1 diabetes, is relevant to it. A draft of the innovative partnerships RFA has been circulated to the ICs, and NIDDK has received suggestions from individual ICs on topics that are within the mission of the IC. This is not what the Institute is looking for with this RFA. It is intended to focus on opportunities identified by the external Advisory Panel, including cross-cutting topics that would involve

multiple ICs, particularly with regard to complications and studies looking at various tissues and organs. The RFA will be re-circulated based on the recommendation from the April 11, 2003, meeting to create a mechanism for paired grants in order to attract new talent. All ICs were invited to contact Dr. James Hyde, NIDDK, if they wished to participate.

SBIR and STTR Potential Program Announcement Topics

NIDDK is required to set-aside a portion of the type 1 special statutory funds for small business. For FY 2004, the following areas will be available for development through SBIR or Small Business Technology Transfer (STTR) programs:

- Drugs or protocols to induce tolerance or reduce autoimmunity.
- Methods to assess progression and immune modulation in type 1 diabetes such as:
  - Imaging/tracking of autoimmune cells
  - Proteomic approaches
- Genetic, proteomic, or other improved tests for identifying individuals at risk.
- Islet transplantation:
  - Enhance islet survival, engraftment, *in vivo* regeneration
  - Improve islet isolation methodologies: media, collagenase
  - Islet encapsulation
- Development of a closed-loop artificial pancreas.
- Application of new technology to complications research, such as:
  - Chips for assessment of tissues and organs involved in complications
  - Biomarkers
- Improved animal models of type 1 diabetes and complications for testing new therapies such as embryonic stem cells from a NOD (non-obese diabetic) mouse.

NIDDK will be putting together an SBIR solicitation that will be a multi-IC solicitation. Dr. Fradkin invited those present to send her other suggestions for discrete areas where small businesses could make a contribution and to indicate their interest in participating in this solicitation.

Asked if companies working with human embryonic stem cells would be eligible, Dr. Spiegel answered that the funds could only be used to support those with cell lines already on the registry, which is the same restriction that applies to academic investigators. For SBIRs/STTRs, the companies must be U.S. owned and there is a limitation on the number of employees and on gross revenues. Dr. Goldstein added that the ones with approved cell lines are already being heavily solicited by NIH. The majority are not eligible for SBIR funds. Dr. Goldstein urged that new therapies be sought for the complications of type 1 diabetes.

Schedule of Advisory Meetings To Inform the Planning Process

Dr. Fradkin concluded her presentation with a slide listing the advisory meetings that would be contributing to the type 1 special statutory funds planning process. These include:

- DMICC Meeting on Complications of Type 1 Diabetes, April 11, appended to the DCCT/EDIC 20th Anniversary Meeting, April 10–11, 2003
- Inflammation and Cardiovascular Disease, April 27–28 (with NHLBI and JDRF)
- Beta Cell Imaging, April 21–22
- Proteomics and Diabetes, April 24–25
- Transplantation, May 30 (with NIAID, NCRR, and JDRF)
- Integration of Clinical Consortia, June 2003

- External Advisory Committee (EAC) Meetings of Ongoing Consortia
  - Beta Cell Biology Consortium, May 4–6
  - International Type 1 Diabetes Genetics Consortium, July 15
  - TEDDY, October 2003

Dr. Fradkin welcomed all those present to attend these meetings and urged those who are leading other consortia to notify the other members of the EAC meetings coming up for their groups and where they are being held. Dr. Goldstein announced that an NIH stem cell meeting is being held June 12, that some might be interested in. Dr. Spiegel added that there would be a symposium in the morning and workshops in the afternoon. There are a number of related activities taking place that week. The NIH event will be preceded by a meeting of the new Stem Cell Society that will be held in Washington, D.C., and it will be followed on June 13 by a joint NCRR–NIDDK meeting of the infrastructure board.

Dr. Fradkin thanked those present for their participation. She emphasized that she is looking forward to working in partnership with them in these exciting times to carry out the responsibilities and challenges to use the type 1 special statutory funds in promising ways and to do so wisely.

The meeting was adjourned at 11:05 a.m.