

APPENDIX 5: SUPPLEMENTAL MATERIAL ON THE EVALUATION OF THE SPECIAL FUNDING PROGRAM

This Appendix provides methodology and detailed information for some of the approaches used to evaluate the *Special Funding Program* initially described in the “Assessment” chapter. An additional major component of this evaluation was based on the professional judgment of scientific and lay experts with expertise relevant to type 1 diabetes and its complications. Information on these expert panel meetings can be found in Appendix 3.

SURVEYS OF INVESTIGATORS SUPPORTED BY THE SPECIAL FUNDING PROGRAM

The NIDDK received approval from the Office of Management and Budget (OMB) to survey extramural scientists who received research grants supported by the *Special Funding Program*. A preliminary survey of all investigators funded by the *Special Program* from FY 1998-2000 was conducted in July 2002. The results of the preliminary survey were used in the preparation of the April 2003 Interim Report on Progress and Opportunities (see Appendix 2 of that report [pp. 154-155] at: www.niddk.nih.gov/federal/planning/type1_specialfund/appendix2.pdf).

The NIDDK launched a final survey in February 2006 to expand the respondent pool to investigators funded from 1998 through 2005 and to follow up the responses of investigators that replied to the first survey. In both surveys, potential respondents were informed of the voluntary nature of the survey and the confidentiality of their responses to the extent provided by law. Furthermore, grantees were advised that

information collected through the survey would not impact current or future decisions regarding their research grants. The response period for both surveys was 1 month.

Survey Instrument, 2006

The original instrument was developed and pilot tested with three grantees in January 2002, with OMB approval provided in June 2002. The instrument was updated and approved by OMB in December 2005 (OMB No. 0925-0503). The final survey instrument was administered via a password protected web-based platform. Investigators who took part in the 2002 survey were able to view their previous responses while completing the 2006 survey. Some investigators have multiple grants supported by the *Special Program*; grantees were requested to answer the following questions for each individual grant.

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- 1) Was this the first, independent, NIH-supported research grant for which you were the principal investigator?
Respond with "Yes" only if the specified grant was the first regular research grant (i.e., R01, U19, or other R-coded or U-coded award) that you received from any NIH institute or center for which you were designated as the principal investigator. In determining whether this was your first such grant, do not include support from training grants (i.e., NRSA, T35, or other T-coded award) or career development awards (i.e., K01 or other K-coded award).

 - 2) Was this your first grant, from any source, related to type 1 diabetes research?
Respond with "Yes" only if the specified grant was the first grant that you received in support of research applicable to the understanding, prevention, treatment, or cure of diabetes from any institute or center of NIH or any other source of research funding.

 - 3) Have you continued to pursue diabetes research?
Respond with "Yes" only if, since receiving the specified grant, you have applied for a new grant or if you have applied to renew an existing grant in either type 1 or type 2 diabetes research.

4) Did this grant permit clinically relevant research that you otherwise would not have been able to pursue?

If “Yes,” please discuss this research in your response to question 8.

5) Did this grant permit innovative or high-risk research that you otherwise would not have been able to pursue?

If “Yes,” please discuss this research in your response to question 8.

6 a) Did the research supported by this grant contribute to successful competition for funding in the same line of research?

6 b) If “Yes,” what is the source of that funding (e.g., NIH, American Diabetes Association (ADA), Juvenile Diabetes Research Foundation (JDRF), other)?

6 c) If the source of continued funding was an NIH grant, provide the grant identification number. (e.g., R01 DX123456)

7 a) Did the research supported by this grant require Institutional Review Board (IRB) approval?

7 b) Did the research supported by this grant involve large animals or non-human primates?

8 a) Identify the major accomplishment(s) resulting from the research supported by this grant that impact the understanding, prevention, treatment, or cure of type 1 diabetes or its complications.

Please respond with 3-5 sentences maximum.

8 b) Discuss new opportunities or ideas in the field of type 1 diabetes research that emerged as a result of this research.

Please respond with 3-5 sentences maximum.

8 c) Describe the diagnostic, therapeutic or clinical implications of the research and/or how this research project has contributed to the translation of fundamental new knowledge to clinical studies.

Please respond with 3-5 sentences maximum.

9) If you are working in a research partnership such as a consortium, an “Innovative Partnership” grant, or other collaboration, please describe any specific opportunities, insights, technologies or lines of research that are a direct result of collaboration with other investigators.

Responses should indicate collaborations formed in connection with this grant. Please indicate whether the research team was self-assembled or resulted from grouping determined by the granting agency (e.g., NIH, the Centers for Disease Control and Prevention [CDC], other).

10) Describe the impact of this grant on your career. Please list any awards or honors you have received since working on this grant.

Responses should indicate whether the specified grant affected the recruitment of the principal investigator or retention in the field of type 1 diabetes research in particular.

11) Please supplement this list by adding any publications, including manuscripts in press, that resulted from research supported in whole or in part by this grant. Please do NOT send abstracts or submitted papers that have not yet been accepted for publication.

Publication information should include author(s), year, title, journal, volume, and page numbers.

12) List all patents or patent applications resulting from research supported in whole or in part by this grant.

List only the title of any patents or patent applications that were based in whole or in part on research supported by the specified grant. Indicate whether that patent has been granted or is pending. Please also describe any technology transfer agreements that have resulted from this work.

13 a) Are you aware of the NIDDK website (www.T1Diabetes.nih.gov) dedicated to the *Special Funding Program*?

13 b) If you were aware of the website, have you found it useful?

14 a) Describe any new research tools or resources of value to the type 1 diabetes research community that were developed as a result of this grant.

Examples of new research tools or resources include, but are not limited to: animal models, cell lines, instrumentation, diagnostic reagents, or clinical techniques. Responses may be formatted in a “bulleted” list.

14 b) Have you used research resources developed with the *Special Funds*?

Research resources include, but are not limited to: PancChip microarrays created by the Beta Cell Biology Consortium, islet cells produced in the Islet Cell Resource Centers, animal lines from the T1D Mouse Repository, clinical trial datasets, and access to small molecule synthesis (T1D-Rapid Access to Intervention Development). For list of research resources, please see the *Special Funding Program* website resources page (www.niddk.nih.gov/fund/diabetesspecialfunds/investigator/resources.asp).

14 c) If yes, please indicate which resources were used, whether they were useful, and how you learned about them.
Please indicate whether you learned about these research resources from the *Special Funding Program* website.

14 d) What additional research resources might be helpful for your research?
Please indicate resources with general applicability to type 1 diabetes research.

15) What opportunities and/or obstacles related to type 1 diabetes research should be addressed in the future?
Responses should indicate technical barriers that prevent progress in an area of research.
THERE IS NO FUNDING ASSOCIATED WITH THIS OR ANY OTHER QUESTION ON THIS SURVEY.

16) Provide any other comments you have regarding the impact or value of this grant or funding source.

Selection Criteria for Grants Included in the Survey

The survey was targeted at independent investigators who received research project grants from the NIH through the *Special Funding Program*. The following funding mechanisms were excluded from the survey: grants that were part of a research consortium or trial network (progress on these efforts was reported for the consortium as a whole; see main text), or that initially started as investigator-initiated research but were later incorporated into a consortium; standardization programs; clinical investigator training programs; projects whose funding started in 2006 or later; grants to diabetes research centers that supported multiple projects; a grant whose funding was prematurely discontinued; administrative supplements to grants funded by regular NIH appropriations; and contracts.

The *Special Funding Program* supported 496 projects between 1998 and 2005; the survey universe included 358 projects that fit the criteria listed above. However, current contact

information could not be verified for recipients of 22 grants; also, 2 grant recipients were known to be deceased at the time of the survey. Thus, 334 surveys were distributed to grantees.

Grantee Survey Response Rate

Of the 334 projects in the survey universe, the NIDDK received 280 responses (83.5 percent response rate). Of those, 274 were complete (82 percent response rate) and used in all analyses contained in this evaluation report. The six surveys that were only partially completed were used for obtaining publication references only. Certain investigators had multiple grants supported by the *Special Program* and were asked to complete a different survey for each project. The survey covered 284 unique investigators and generated responses from 239 of them (84 percent response rate). The survey was neither biased towards investigators who received funds early in the program nor recipients with more recent grants. As noted in Figure A1, the response rate was evenly distributed among grantees funded by the *Special Funding Program* at different times over the 8 years covered by the survey.

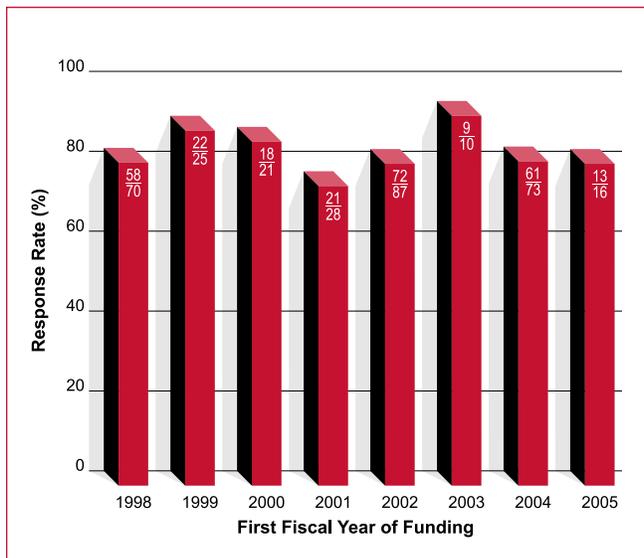


Figure A1: Distribution of survey responses.

The overall response rate of the final survey (82 percent) is a significant improvement over the 54.4 percent response rate from the 2002 survey. This improvement largely reflects the efforts of a contractor, Macro International Inc., which NIDDK retained to administer the survey. Steps taken to improve response rate included: easy-to-use, password-protected, web-

based platform that permitted investigators to save and return to the survey as often as needed; pre-survey contacts to announce the survey and verify address information; assiduous follow-up using a combination of e-mails, letters, and phone calls to request participation in the survey.

Use of Survey Data

Information collected through the survey of special type 1 diabetes grant recipients has been incorporated throughout this evaluation report. Journal citations (survey question 11) were used to supplement the list of citations collected through database searches (see next section and “Assessment” chapter). Patent information (survey question 12) is described in this Appendix. Representative comments that are generally indicative of the types of comments received regarding the impact of these grants on investigators’ research or careers (survey question 10) and the value of this funding program in general (survey question 16) are quoted verbatim, though without attribution, in the “Evaluation of Investigator-Initiated Research” sections in the Goal chapters. Other questions from the survey were used in various analyses, as cited, in the “Assessment” chapter.

METHODOLOGY FOR BIBLIOMETRIC ANALYSIS

Compendium of *Special Funding Program*-Supported Scientific Publications

As one measure of the impact of the *Special Funding Program*, the NIDDK sought to identify the scientific publications that the *Program* made possible in whole or in part. First, the names of *Special Funding Program* grantees were used to search PubMed, the National Library of Medicine's bibliographic database covering medical and pre-clinical sciences. The papers thus identified were searched for indicated grant support and were included in the analysis if they cited one or more *Special Funding Program* grants. However, authors do not always cite their grant support, and in fact some journals do not allow them to do so. Therefore, the resulting compendium was supplemented in the following two ways:

- ▶ Scientific program directors at the NIH responsible for management of the *Special Funding Program* consortia and trial networks were asked to identify any major papers produced by the consortia that had not been identified in the PubMed search.
- ▶ The grantee survey (see preceding section), which covered investigator-initiated grants not associated with the research consortia and trial networks, asked grantees to report all publications that they had produced using those grants.

The resulting collection of publications, which included only papers published between January 1, 1998, and January 1, 2006, was culled to ensure that redundant publications were removed. Publication Pool A was then restricted to those papers associated with grants awarded through initiatives, clinical trials, or consortia made possible through the *Special*

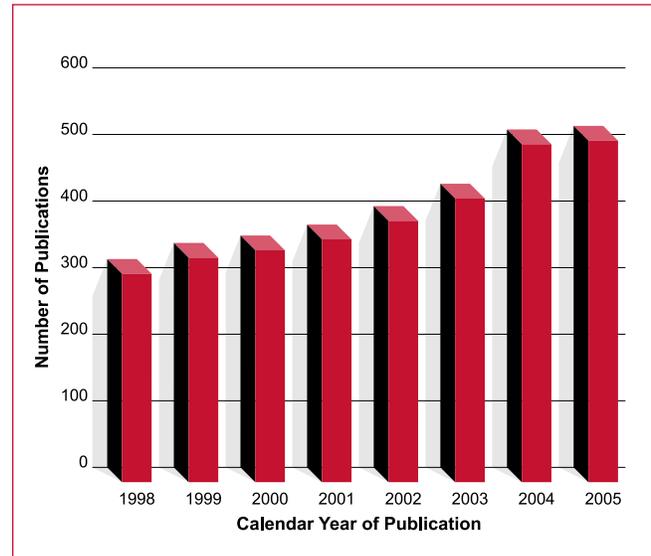


Figure A2: Publications from Pool B (*Special Fund*-augmented grants). Data only include the identified 3,203 papers published before January 1, 2006, that cite Pool B grants and do not also cite other *Special Program* grants.

Funding Program. For a complete listing of the publications in each pool, and of the groups of grants included in each pool, please see www.niddk.nih.gov/fund/diabetesspecialfunds/investigator/data.htm.

The publications in Pool B—papers associated with grants and programs that predated the *Special Funding Program* but which were augmented by it—were collected by searches using the relevant grant numbers. Thus, the Pool B library does not include papers funded under these grants if the grant numbers were not cited. The distribution of the publications from Pool B grants is represented in Figure A2. Because it is difficult to assess the relative importance of the supplementary funds compared to the original award, these papers are listed separately and were not analyzed further.

Citation Analysis

Papers in Pool A were then further analyzed in an attempt to evaluate their impact on the scientific community. The Thomson ISI Web of Knowledge database was searched to identify the number of times each paper was cited in other publications prior to January 1, 2006. The number of citations is reported in each bibliographic record (see [www.niddk.](http://www.niddk.nih.gov/fund/diabetesspecialfunds/investigator/data.htm)

[nih.gov/fund/diabetesspecialfunds/investigator/data.htm](http://www.niddk.nih.gov/fund/diabetesspecialfunds/investigator/data.htm)).

Because earlier papers have had more time to become known and to influence other researchers than more recent works, and therefore are expected to have more citations, the papers are reported by year. More recent publications will necessarily tend to have fewer citations.

METHODOLOGY FOR IDENTIFYING FILED U.S. PATENTS

In addition to collecting information on scientific publications and research accomplishments, the NIH examined data on U.S. patent applications and technology transfer agreements as another metric to assess the investigator-initiated research project grants. The following list represents the patents that were self-reported in the survey of grantees as having been derived from research supported by the *Special Funding Program*. The patent numbers were independently verified from records accessed at the U.S. Patent and Trademark Office (USPTO) website. This list only includes projects covered by the grantee survey of investigator-initiated research project grants. It therefore does not include any patents derived from research conducted by the scientific consortia or clinical trial networks, training grants, contracts, or administrative supplements. Furthermore, it is important to again underscore that not all investigators responded to the survey and, even in some cases where grantees did list patents, responses were occasionally missing information, making it impossible to unambiguously identify the patent.

Patents Issued

- ▶ “Human Pancreatic Cell Lines: Developments and Uses” Levine, F.; Wang, S.; Beattie, G.; Hayek, A. U.S. Pat. #5,723,333 (1998)
- ▶ “Development and Use of Human Pancreatic Cell Lines” Levine, F.; Wang, S.; Beattie, G.; Hayek, A. U.S. Pat. #6,110,743 (2000)
- ▶ “Implantable Sensor and System for Measurement and Control of Blood Constituent Levels” Sun, X.; Joseph, J.; Crothall, K. U.S. Pat. #6,122,536 (2000)
- ▶ “Engineered Proteins for Analyte Sensing” Lakowicz, J.; Tolosa, L.; Eichhorn, L.; Rao, G. U.S. Pat. #6,197,534 (2001)
- ▶ “Polymers From Vinylic Monomers Peroxides and Amines” Lim, D.; Gough, D.; Rourke, A. U.S. Pat. #6,348,429 (2002)
- ▶ “Inducing Insulin Gene Expression in Pancreas Cells Expressing Recombinant PDX-1” Levine, F.; Dufayet, D. U.S. Pat. #6,448,045 (2002)
- ▶ “Implant Coating for Control of Tissue/Implant Interactions” Moussy, F.; Kreutzer, D.; Burgess, D.; Koberstein, J.; Papadimitrakopoulos, F.; Huang, S. U.S. Pat. #6,497,729 (2002)
- ▶ “Polymerized Crystalline Colloidal Arrays” Asher, S. U.S. Pat. #6,544,800 (2003)
- ▶ “Photochemically Controlled Photonic Crystal Diffraction” Asher, S.; Kamenjicki, M.; Lednev, I.; Meier, V. U.S. Pat. #6,589,452 (2003)
- ▶ “Sensor Probe for Determining Hydrogen Peroxide Concentration and Method of Use Thereof” Schmid-Schoenbein, G.; Baker, D.; Gough, D. U.S. Pat. #6,592,746 (2003)
- ▶ “*In Vivo* Biosensor Apparatus and Method of Use” Saylor, G.; Simpson, M.; Applegate, B.; Ripp, S. U.S. Pat. #6,673,596 (2004)
- ▶ “Saccharide Sensing Molecules Having Enhanced Fluorescent Properties” Satcher, Jr., J.; Lane, S.; Darrow, C.; Cary, D.; Tran, J. U.S. Pat. #6,673,625 (2004)
- ▶ “Glucose Sensing Molecules Having Selected Fluorescent Properties” Satcher, Jr., J.; Lane, S.; Darrow, C.; Cary, D.; Tran, J. U.S. Pat. #6,682,938 (2004)
- ▶ “Membrane and Electrode Structure for Implantable Sensor” Gough, D. U.S. Pat. #6,721,587 (2004)
- ▶ “Polymerized Crystalline Colloidal Array Chemical Sensing Materials For Use in High Ionic Strength Solutions” Asher, S.A.; Reese, C. U.S. Pat. #6,753,191 (2004)
- ▶ “Long Wave Fluorophore Sensor Compounds and Other Fluorescent Sensor Compounds in Polymers” Walsh, J.; Heiss, A.; Noronha, G.; Vachon, D.; Lane, S.; Satcher, Jr., J.; Peyser, T.; Van Antwerp, W.; Mastrototaro, J. U.S. Pat. #6,766,183 (2004)

- ▶ “Methods and Substances for Preventing and Treating Autoimmune Disease” Langridge, W.; Arakawa, T. U.S. Pat. #6,777,546 (2004)
 - ▶ “Multivalent MHC Class II - Peptide Chimeras” Brumeanu, T.; Casares, S.; Bona, C. U.S. Pat. #6,811,785 (2004)
 - ▶ “Methods, Products and Treatments for Diabetes” Halperin, J. U.S. Pat. #6,835,545 (2004)
 - ▶ “Induction of Beta Cell Differentiation in Human Cells by Stimulation of the GLP-1 Receptor” Levine, F.; Dufayet, D. U.S. Pat. #6,884,585 (2005)
 - ▶ “Induction of Beta Cell Differentiation in Human Cells” Levine, F.; Gouty, D.; Itkin-Ansari, P. U.S. Pat. #6,911,324 (2005)
 - ▶ “Fluorescent Sensor Compounds for Detecting Saccharides” Wang, B.; Weston, B.; Yang, W. U.S. Pat. #6,916,660 (2005)
 - ▶ “Method of Use of Peptide Antagonists of Zonulin to Prevent or Delay the Onset of Diabetes” Fasano, A.; Watts, T. U.S. Pat. #7,026,294 (2006)
 - ▶ “Methods, Products and Treatments for Diabetes” Halperin, J. U.S. Pat. #7,049,082 (2006)
 - ▶ “Contact Lenses Colored With Crystalline Colloidal Array Technology” Asher, S. U.S. Pat. #7,059,719 (2006)
- In addition to the 25 U.S. patents that were issued, grantees reported 39 additional patents that had been filed with the USPTO, but had not yet been issued. A provisional patent is a 1-year intellectual property protection, often used as a preliminary step before filing a non-provisional patent. In addition, survey respondents reported eight provisional patents that had been allowed by the USPTO. In total, independent investigators responding to the survey reported 72 U.S. patent applications.

METHODOLOGY FOR RESEARCH PORTFOLIO ANALYSIS

In the “Assessment” chapter, the research portfolio analyses of *Special Funding Program* grants administered by the NIH were based on data retrieval from the NIH database of grants and applications: Information for Management, Planning, Analysis, and Coordination (IMPAC II). The Query/View/Report tool was used to search IMPAC II for archival budget and programmatic data based on the list of the NIH grant numbers for all the projects supported by the *Special Funding Program*. Separate searches were conducted for each fiscal year based on so-called “frozen records”—the finalized budget data for each fiscal year; changes incorporated after the data have been finalized are not captured in the frozen records. In these analyses, awards that spanned multiple fiscal years were only counted once, in the year that they first received *Special Funds*. Projects supported by the *Special Funding Program* that were successfully renewed for additional cycles of funding were counted again in the year that they were competitively awarded.

The analyses focused solely on research project grants (R01, R21, R24, R29, R33, R37), cooperative agreements (U01, U10, U19, U24, U42) and small business grants (R41, R43, R44). Supplements to ongoing grants were not included because it would not be possible to determine if the categorization of the research as “clinical” (an important evaluation question) related to the supplement portion of the grant or only to the primary grant. Institutional (T32) and career (K12) training programs were categorically eliminated from the analysis. Also excluded were all contracts, as well as grants to research programs and centers (P01, P30, P40, P50, P51, P60, M01).

The following methodology was used in the analyses reported in the “Assessment” chapter:

Clinical Research Portfolio: For reporting purposes, the NIH applies special codes to research grants and applications in its IMPAC II database. Several special codes are used

to designate human subjects research, ranging from human tissue sample analysis to Phase III clinical trials. In this evaluation report, clinical research was defined as all human subject research (excluding research labeled as human subject research, but that only involved human tissue samples). Sometimes, research grants in the NIH database were not flagged as clinical research in the first year of funding, but this flag was applied to the research in later years. Any research grant that met these criteria at any point in its grant history was considered “clinical research” for the first year it was funded.

New Investigators: In this evaluation report, for the purpose of review and funding, applicants were considered to be new investigators if they had not previously served as the principal investigators on any Public Health Service-supported research project other than a small grant (R03), an Academic Research Enhancement Award (R15), an exploratory/developmental grant (R21), or certain research career awards directed principally to physicians, dentists, or veterinarians at the beginning of their research careers (K01, K08, and K12). Current or past recipients of Independent Scientist and other non-mentored career awards (K02, K04) were not considered new investigators. In the IMPAC II NIH database, either the grant applicant or the Scientific Review Administrator can flag an application as “new investigator” based on these criteria. The NIH began tracking new investigators in the IMPAC II database in 1999; however, this tracking was phased in, so the reporting for 1999 is likely underestimated. Only new competing research project grants (R01 and R21) from FY 1999 to 2005 were included in this evaluation report. It is possible that an investigator received his or her first grant from the *Special Funding Program* and subsequently received an additional grant from the *Program*. This investigator would be counted as a new investigator the first time only; however, both grants would be included in the denominator of total grants analyzed. Using IMPAC II, the same search criteria were used to estimate the fraction of new investigators across

all the Institutes and Centers at the NIH: of the 37,490 new competing R01 and R21 grants awarded between FY 1999 and FY 2005, 9,528 applications had been marked as a new investigator (25.4 percent). The self-identification of new investigator status on grant applications underestimates the true number of new investigators. Hence, the NIH Office of Extramural Research (OER) uses the Consolidated Grant Applicant Files to track new investigators. These data were used as an alternate method to calculate the fraction of new investigators funded by the NIH. These data can be accessed at: http://grants.nih.gov/grants/new_investigators/New_Invest_by_Activity.xls

Continuation of Research Funding: Only R01 grants were included in this analysis. There were 100 R01 grants funded by the *Special Funding Program* with an original project end

date before September 30, 2005. Using the grant numbers for the 100 R01 grants, the IMPAC II database was searched for competitive renewal applications (application type 2). If an application is not funded after its initial submission, the investigator can amend it up to two times and resubmit it for a subsequent review cycle. Renewal applications with one or more amendments were only counted once. This query retrieved 54 applications for renewal, as of July 2006. The NIH database indicates which applications were awarded, pending, withdrawn, or not recommended for further consideration during the review process. The success rate of *Special Funding Program* grants was compared to the NIH average success rate for continuing R01 grants based on OER data for FY 2000-2005: http://grants1.nih.gov/grants/award/success/Success_ByActivity.cfm