

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Eunice Kennedy Shriver National Institute of Health and Human Development

Down Syndrome Research

Francis S. Collins, M.D.  
Director, NIH

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## **Down Syndrome Research**

### Executive Summary

In Senate report No. 111-66, the Committee on Appropriations requested that the National Institutes of Health prepare and submit a report on progress toward implementation of the NIH Research Plan on Down Syndrome, including the quantity and dollar amounts of each grant funded since the release of the plan, and how each grant meets the goals of the plan (p. 117). The following is submitted in response to the request.

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), in cooperation with the NIH Down Syndrome Working Group, has made substantial progress in implementing the NIH Research Plan on Down Syndrome. A complete listing of grants funded during fiscal years 2008-2009 (both with ARRA funds and regular appropriations) is provided, along with an indication of which objectives are met by each grant. In addition, the NIH issued a 2009 Request for Applications, and two large grants were funded. Other funding opportunities will become available later in 2010. The NICHD is greatly expanding resources available to researchers through a new contract for the mouse models directed to Down syndrome research, and a new contract expanding the NICHD-funded brain and tissue repository.

The NICHD is also engaged with the Down syndrome community in many ways, such as seeking input on the development of a new website, and participating in two upcoming meetings that will create a framework for a Down syndrome registry. NICHD leadership has formally updated Congress on these activities at regular intervals.

## **Down Syndrome Research**

### Introduction

In its report on the fiscal year 2010 budget for the Department of Health and Human Services, the Committee on Appropriations stated:

“The Committee commends the NIH for creating the NIH Down Syndrome Working Group to develop the NIH Research Plan for Down syndrome. However, the Committee is concerned with the implementation of the plan since its release in January 2008. The Committee requests that the NIH report to the Committees on Appropriations of the House of Representatives and the Senate by September 30, 2010, on the quantity and dollar amount of Down syndrome research grants awarded since the release of the plan, including those awarded through funds made available by the American Recovery and Reinvestment Act, and how all such grants awarded meet the short- and long-term goals of the plan. In addition, the Committee urges the NIH to pursue public-private partnerships, when available, to help leverage the overall research spent on Down syndrome.” (Senate report No. 111-66, page 117)

The following report has been prepared by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) at the National Institutes of Health (NIH) in response to this request.

### Background

Although a number of NIH Institutes and Centers have supported research related to various aspects of Down syndrome for many years, the research efforts were coordinated only informally. In 2006, the NIH Director designated the NICHD as the lead NIH Institute to organize and convene the trans-NIH Down Syndrome Working Group. This working group comprises program officers at the Institutes and Centers with portfolios of research on Down syndrome. After conducting a review of the research activities currently funded by the NIH, the Working Group embarked on several outreach activities, such as convening a meeting in July 2007 of experts in Down syndrome, including prominent researchers with far-ranging expertise on various aspects of Down syndrome, clinicians, advocates, parents, and other relevant federal agencies. In addition to recommendations made at that meeting, the Working Group also evaluated the recommendations from three earlier expert workshops, two international meetings on Chromosome 21 and an NIH-sponsored meeting on cognitive function in Down syndrome.

The Working Group synthesized the ideas culled from these many sources and formulated a draft Plan for Down syndrome research that contains short-, intermediate-, and long-term research objectives to guide the NIH’s investment in Down syndrome research over the next ten years. This Plan was made available for public comment; NIH received and responded to more than 150 comments, which were incorporated into the Plan as appropriate. The Plan was initially

posted October 2007 and is available from the NICHD Web site at [http://www.nichd.nih.gov/publications/pubs/upload/NIH\\_Downsyntaxrome\\_plan.pdf](http://www.nichd.nih.gov/publications/pubs/upload/NIH_Downsyntaxrome_plan.pdf) . It features a summary of ongoing research activities and scientific meetings, sets forth specific research goals and objectives for the NIH, and includes a bibliography of recent scientific publications on research funded by the NIH related to Down syndrome and its associated disorders.

### Progress in Implementing the NIH Research Plan on Down Syndrome

The NICHD, in cooperation with the NIH Down Syndrome Working Group, has made substantial progress in implementing the NIH Research Plan on Down Syndrome. (For reference, the Research Plan's goals and objectives are included as Appendix C.) As requested, a complete listing of grants funded by the NIH in fiscal years 2008 and 2009, including dollar amounts and references to specific objectives of the Research Plan, is included as Appendix A; a table summarizing the number of grants that meets each one of the five main goals outlined in the Research Plan is included as Appendix B. The fiscal year 2009 lists include both the grants funded by Congress through the regular appropriations process, and those funded under the American Recovery and Reinvestment Act (ARRA). All of the grants listed have been identified by the NIH as relating to Down syndrome. The Down syndrome population has been the longest studied of all of the intellectually or developmentally disabled populations, and findings from long-term research on affected families have informed natural history studies of other disorders. In addition, individuals with Down syndrome may be predisposed to comorbid conditions, such as Alzheimer's disease, or appear to be protected from other conditions, such as certain tumors.

In fiscal years 2008 and 2009, the NIH funded grants aimed at meeting all five research goals outlined in the NIH Research Plan on Down Syndrome, and the great majority of individual objectives in the Plan. The largest number of grants meets objectives listed under the first goal, Pathophysiology of Down Syndrome and Disease Progression, followed by the third goal, Treatment and Management. Appropriately, the largest number of grants (75) fits within the Plan's short-term objectives, followed by those research projects that coincide with one of the medium-term objectives (37). The two goals addressed by the fewest grants in fiscal years 2008 and 2009 were goals four and five, Living with Down Syndrome, and Research Infrastructure, respectively; in response, the NICHD has undertaken a number of additional, major activities in these areas.

### *Funding Opportunities*

Since the Plan was published, funding for Down syndrome-related research increased from approximately \$17 million in fiscal year 2008 to \$18 million in fiscal year 2009, the last year for which complete data are available. An additional \$4 million in ARRA funding for the NIH was spent on research related to Down syndrome in fiscal year 2009. Fiscal year 2009 funding reflects awards for both investigator-initiated projects and for two large grant awards to applicants in response to a 2009 Request for Applications (RFA) co-sponsored by the NICHD and the National Institute on Aging.

The RFA was written to solicit grant applications that could meet several of the Research Plan's goals, such as research on the basic pathophysiology of Down syndrome (Goal I), and better diagnostic and screening tools (Goal II). Specifically, it requested applications focused on

elucidating factors that could maximize and maintain cognitive function in adults with Down syndrome. Applications could include research projects on the development of better diagnostic tools to assess function and cognitive impairment; community-based interventions that improve individual educational, occupational, and social outcomes; and prevention or effective treatment of health disparities observed in the Down syndrome population. Seven applications were received; two scored extremely well and were funded in fiscal year 2009 (highlighted in Appendix A).

Other important research gaps identified in the Research Plan, particularly in Goals III (Treatment and Management) and IV (Living with Down Syndrome), are the range of health challenges faced by individuals with Down syndrome, especially during adolescence. Adolescence poses unique challenges for individuals with Down syndrome and other intellectual and developmental disabilities, who are already far more likely than the general population to experience emotional, behavioral, or medical disorders. The NICHD plans to issue three new Program Announcements in late fiscal year 2010 to solicit research applications addressing issues related to timely identification and treatment of these auxiliary disorders in adolescence, to improve overall functioning and quality of life.

#### *Research Resources*

One of the top priorities stated in the NIH Down Syndrome Research Plan is the availability and affordability of sufficient mouse models for study (see Goal V. Research Infrastructure). Since the 1970s, the NICHD has been supporting, under contract, the Repository of Mouse Models for Cytogenic Disorders to generate and distribute these models to members of the scientific research community. The contract has been housed at the Jackson Laboratory in Bar Harbor, Maine, where researchers breed and distribute the animals with particular emphasis on mice relevant to the study of Down syndrome. The most useful of these strains has been the Ts65Dn mouse, which exhibits many of the same characteristics as individuals with Down syndrome, including cognitive and behavioral phenotypes. Recent experimental efforts have expanded to include identifying pharmacologic interventions that improve cognitive function in these mice. After the release of the Research Plan, increasing numbers of investigators have applied to the NIH to use these mouse models to study specific aspects of the Down syndrome phenotype. The current contract was recompeted in 2010 and will be awarded before the end of the fiscal year, more fully meeting the needs of investigators conducting research on Down syndrome.

Another critical resource highlighted in the Research Plan was the NICHD-supported Brain and Tissue Bank for Developmental Disabilities. Brains and other tissues, particularly from people with conditions such as Down syndrome, are invaluable to researchers who are trying to understand the differences between what happens in the normal brain compared to a brain affected by a disease or condition. Since 1991, the NICHD has supported the Brain and Tissue Bank at the University of Maryland School of Medicine; it is now the largest repository for pediatric tissues from individuals with over 400 developmental and hereditary conditions, including a large collection of samples from those with Down syndrome. More than 700 researchers have used more than 26,000 samples from the Bank since it was established. In 2010, the University of Maryland School of Medicine won a \$7.15 million contract to substantially expand and operate the facility for the NICHD for another five years.

The Eunice Kennedy Shriver Intellectual and Developmental Disabilities Research Centers (IDDRC) Program has long supported multidisciplinary centers across the United States that provide infrastructure to support investigators, including training new investigators, who are studying the basic mechanisms, causes, diagnosis, management and treatment of intellectual and developmental disabilities, including Down syndrome. Down syndrome research supported by the IDDRC Program ranges from studies of basic neurobiology, cellular signaling, and cognition in mouse models of Down syndrome, to research on risk factors for obesity and the impact of Down syndrome on family dynamics, as well as longitudinal investigations of cognition and aging in adults with Down syndrome. The Centers Program is funded for five years on a rolling basis; three of the Centers were recently renewed (University of California at Los Angeles, Children's Hospital of Philadelphia, and the University of Massachusetts-Worcester), and a new Center was established at Washington University in St. Louis, bringing the total number of IDDRCs to 15.

#### *Reaching Out to Potential Partners*

The NICHD has continued to reach out to the Down syndrome community on a regular basis to get input into its initiatives and explore possible collaborations and partnerships.

In 2009, the Institute provided funding for the biennial conference of the International Mosaic Down Syndrome Association meeting, *Building Bridges for Down Syndrome*. The main goal of this conference was to bring together families, health care providers, educators, and researchers involved in studying this form of Down syndrome to facilitate progress in treatment, medical management, and research. NICHD representatives also made several presentations on the Research Plan to Down syndrome groups around the country to get feedback on the progress being made and to hear what additional activities might be undertaken. Among those activities is the development of the NIH Down Syndrome Web site, which will provide links and resources for researchers, clinicians, and families. The draft site is nearly complete; working with the expert NIH Library staff, the NICHD plans to seek specific input from the Down syndrome community on the proposed content later this year.

In addition, the NICHD will be participating in two Down syndrome organization-sponsored meetings in 2010 that will provide a framework and guidance for establishing a Down syndrome registry.

#### Conclusion

At the request of the Congressional Down Syndrome Caucus, NICHD leadership provided formal updates to members of the Caucus in September 2009 and January 2010. Since the release of the NIH Down Syndrome Research Plan, the NIH has made significant progress in coordinating and bolstering research on this important condition.

**APPENDIX A**

*Note: Some projects may be funded by more than one NIH Institute or Center; the lead Institute is listed.*

**FISCAL YEAR 2008 PROJECTS**

(includes all grant types funded in FY 2008)

*Goal 1: Pathophysiology of Down Syndrome and Disease Progression*

<b>Funding IC</b>	<b>Project Number</b>	<b>Obj.</b>	<b>Project Title</b>	<b>PI Name</b>	<b>Org Name</b>	<b>State</b>	<b>Amount</b>
NICHD	5R01HD0439 60-05	Long 2	The role of Mnbk in Down Syndrome Brain Development and Aging	Wegiel, Jerzy	Institute for Basic Research In Developmental Disabilities	NY	\$521,790
NIA	1R03AG0299 66-01A2	Medium 1	The Involvement of Adapt78 in Alzheimer's Disease and Down Syndrome	Crawford, Dana	Albany Medical College	NY	\$66,725
NICHD	1R21HD0543 47-01A2	Medium 2	Human Neural Precursors from CNS Developmental Disorders: Down Syndrome	Sheen, Volney	Beth Israel Deaconess Medical Center	MA	\$212,500
NICHD	5R21HD0561 95-02	Medium 3	Tau Missplicing Caused by RNA Processing Proteins Located on Chromosome 21	Andreadis, Athena	University of Massachusetts Medical School Worcester	MA	\$198,429
NIA	5F31AG02978 7-02	Medium 3	APP Metabolism in Transgenic Down Syndrome Mouse Models	Choi, Jennifer	New York University School of Medicine	NY	\$40,972
NICHD	5F32HD05574 5-02	Medium 3	Retrograde Transport at the Crossroads of Cognitive Decline and Neurodegeneration	Maloney, Michael	Stanford University	CA	\$46,826

<b>Funding IC</b>	<b>Project Number</b>	<b>Obj.</b>	<b>Project Title</b>	<b>PI Name</b>	<b>Org Name</b>	<b>State</b>	<b>Amount</b>
NIA	5R01AG0121 22-13	Medium 3	An Animal Model for Age-Related Degeneration	Granholm-Bentley, Ann-Charlotte Esther	Medical University of South Carolina	SC	\$256,328
NINDS	5K99NS05252 4-02	Medium 4	Role of Nebula/DSCR1 in Mitochondria	Chang, Karen	Indiana University Bloomington	IN	\$90,000
NICHD	5R01HD0384 66-08	Medium 4	Mitochondrial Dysfunction in Down Syndrome	Busciglio, Jorge	University of California Irvine	CA	\$188,650
NHLBI	5P50HL07472 8-05	Medium 4	Regulation of Valvuloseptal Development by Dscr1	Yutzey, Katherine	Children's Hospital Medical Center (Cincinnati)	OH	\$330,561
NIA	5P01AG0176 17-09	Medium 4	The Origins of Endosome Dysfunction in Ad Pathobiology	Mathews, Paul	New York State Council for Mental Hygiene Planning	NY	\$375,840
NIA	5P01AG0176 17-09	Medium 4	Expression Profiling Of Endosomal Pathways In Ad	Ginsberg, Stephen	New York State Council for Mental Hygiene Planning	NY	\$333,362
NINDS	5K99NS05790 6-02	Medium 5	Imaging Nerve Growth Factor Signal Transduction in Live Neurons	Cui, Bianxiao	Stanford University	CA	\$59,238
NINDS	5R01NS0482 63-05	Medium 5	Altered Glial Calcium Signaling in Neurodegeneration	Golovina, Vera	University of Maryland Baltimore	MD	\$260,490
NINDS	5R01NS0553 71-02	Medium 5	Disrupted Transport of NGF-TrKA Signaling in Mouse Models of Down Syndrome	Mobley, William	Stanford University	CA	\$369,547

<b>Funding IC</b>	<b>Project Number</b>	<b>Obj.</b>	<b>Project Title</b>	<b>PI Name</b>	<b>Org Name</b>	<b>State</b>	<b>Amount</b>
NINDS	4R00NS0579 06-03	Medium 5	Imaging NGF Signal Transduction in Live Neurons	Cui, Bianxiao	Stanford University	CA	\$247,126
NIA	5P01AG0094 64-17	Medium 5	Effects of Ab on Synaptic Transmission and Plasticity	Greengard, Paul	Rockefeller University	NY	\$327,606
NICHD	5R01HD0476 56-04	Medium 6	Age and Cognition in a Mouse Model of Down Syndrome	Wenger, Galen	University of Arkansas Medical Sciences Little Rock	AR	\$246,479
NINDS	5F31NS06038 8-02	Short 1	Differential CpG Island Methylation in Down Syndrome	Miller, Nathaniel	Hugo W. Moser Research Institute at Kennedy Kreiger	MD	\$37,092
NINDS	1F31NS06051 7-01A1	Short 2	Effects of Neural Progenitor Cell Transplantation in Neonatal Ts65Dn Mice	Rachubinski, Angela	University of Colorado Denver	CO	\$27,792
NICHD	1R01HD0554 57-01A2	Short 3	Role of PIP2 Metabolism Imbalance in Down Syndrome	Di Paolo, Gilbert	Columbia University Health Sciences	NY	\$342,125
NICHD	1R01HD0570 29-01A1	Short 3	Genome-Wide Recombination Profiles in Oocytes with Chromosome 21 Nondisjunction	Sherman, Stephanie	Emory University	GA	\$287,378
NCRR	5M01RR0080 84-15	Short 3	Blood Expression Profiles in Children with Down Syndrome	Molloy, Cynthia	Children's Hospital Medical Center (Cincinnati)	OH	\$7,803
NICHD	1R01HD0553 91-01A1	Short 4	NFAT Signaling and Down Syndrome	Crabtree, Gerald	Stanford University	CA	\$277,998

<b>Funding IC</b>	<b>Project Number</b>	<b>Obj.</b>	<b>Project Title</b>	<b>PI Name</b>	<b>Org Name</b>	<b>State</b>	<b>Amount</b>
NICHD	1R01HD0562 35-01A1	Short 4	Systems Biology for Studies of Cognition in Down Syndrome	Gardiner, Katheleen	University of Colorado Denver	CO	\$499,742
NIA	5K01AG0312 96-01	Short 4	Aging and Meiosis in the Nematode Germline	Yanowitz, Judith	Carnegie Institution of Washington, D.C.	D.C.	\$105,192

***FY 2008 Goal 1 Subtotal: \$5,757,591***

*Goal 2: Diagnosis, Screening, and Functional Measures*

<b>Funding IC</b>	<b>Project Number</b>	<b>Obj.</b>	<b>Project Title</b>	<b>PI Name</b>	<b>Org Name</b>	<b>State</b>	<b>Amount</b>
NICHD	2R01HD0356 12-10A1	Long 1	The Development of Joint Attention After Infancy	Adamson, Lauren	Georgia State University	GA	\$307,063
NICHD	5R01HD0243 56-18	Short 1	Language Development in Fragile X Syndrome	Abbeduto, Leonard	University of Wisconsin Madison	WI	\$537,773
NICHD	5R01HD0388 19-07	Short 1	Pragmatic Skills of Young Males and Females with Fragile X Syndrome	Roberts, Joanne	University of North Carolina Chapel Hill	NC	\$517,218
NICHD	2R01HD0449 35-06A1	Short 1	Speech of Young Males with Fragile X Syndrome	Roberts, Joanne	University of North Carolina Chapel Hill	NC	\$341,868
NIDCD	1R03DC0093 01-01A1	Short 1	Nonlinguistic Vocalizations in Autism: Acoustic Cry Analysis in Early Infancy	Sheinkopf, Stephen	Women and Infants Hospital-Rhode Island	RI	\$73,329

<b>Funding IC</b>	<b>Project Number</b>	<b>Obj.</b>	<b>Project Title</b>	<b>PI Name</b>	<b>Org Name</b>	<b>State</b>	<b>Amount</b>
NICHD	5P01HD02599 5-18	Short 1	Multimodal Analyses of Face Processing in Autism and Down Syndrome	Mitchell, Teresa	University of Massachusetts Medical School Worcester	MA	\$152,927
NIA	5P50AG01657 3-09	Short 3	Core--Clinical	Kawas, Claudia H.	University of California Irvine	CA	\$432,896
NIGMS	1F31GM0834 52-01	Short 5	Genome-Wide Recombination as a Risk Factor for Nondisjunction	Hollis, Natasha	Emory University	GA	\$28,062
NICHD	5R01HD0389 79-09	Short 5	Trisomy 21: Risk Factors for Chromosome Nondisjunction	Sherman, Stephanie	Emory University	GA	\$663,427
NCRR	2M01RR0010 66-31	Short 6	Comparison of Body Composition by Dexa and Bioelectrical Impedance in Adolescents	Fleming, Richard K	Massachusetts General Hospital	MA	\$324

***FY 2008 Goal 2 Subtotal: \$3,054,887***

*Goal 3: Treatment and Management of Down Syndrome*

<b>Funding IC</b>	<b>Project Number</b>	<b>Obj.</b>	<b>Project Title</b>	<b>PI Name</b>	<b>Org Name</b>	<b>State</b>	<b>Amount</b>
NIDCD	2R01DC0033 11-06A1	Long 1	Sensorimotor Control of the Human Orofacial System	Barlow, Steven	University of Kansas Lawrence	KS	\$534,917
NICHD	5P01HD02599 5-18	Long 1	Guiding Visual Attention to Enhance Discrimination Learning	Carlin, Michael	University of Massachusetts Medical School Worcester	MA	\$142,587

<b>Funding IC</b>	<b>Project Number</b>	<b>Obj.</b>	<b>Project Title</b>	<b>PI Name</b>	<b>Org Name</b>	<b>State</b>	<b>Amount</b>
NIDCD	5R01DC0086 40-02	Long 2	Treatment of Speech Disorders in Children with Down Syndrome	Camarata, Stephen	Vanderbilt University	TN	\$416,287
NIDCD	3R01DC0086 40-02S1	Long 2	Treatment of Speech Disorders in Children with Down Syndrome	Camarata, Stephen	Vanderbilt University	TN	\$83,636
NICHD	5R37HD0299 57-16	Long 3	Early Development with Williams or Down Syndrome	Mervis, Carolyn	University Of Louisville	KY	\$307,339
NICHD	5R01HD0280 88-16	Short 1	Genetic Analysis of Hirschsprung Disease	Chakravarti, Aravinda	Johns Hopkins University	MD	\$445,201
NCI	5R01CA12077 2-02	Short 1	Molecular and Pharmacologic Correlates of Acute Myeloid Leukemia in Down Syndrome	Taub, Jeffrey	Wayne State University	MI	\$406,183
NHLBI	1K08HL09329 0-01	Short 1	Genetic Modulators of Erythromegakaryocytic Development	Chou, Stella	Children's Hospital of Philadelphia	PA	\$133,920
NHLBI	1F32HL09163 9-01A1	Short 1	The Role of Dyrk1a in the Pathogenesis of Congenital Heart Disease	Twu, Karen	Stanford University	CA	\$49,646
NHLBI	5R01HL08330 0-02	Short 1	Genetic Basis for Congenital Heart Defects	Reeves, Roger	Johns Hopkins University	MD	\$1,101,599
NCI	5R01CA11177 8-04	Short 1	Molecular Studies of Down Syndrome Leukemia	Perentesis, John	Children's Hospital Medical Center (Cincinnati)	OH	\$231,698

<b>Funding IC</b>	<b>Project Number</b>	<b>Obj.</b>	<b>Project Title</b>	<b>PI Name</b>	<b>Org Name</b>	<b>State</b>	<b>Amount</b>
NCI	5R01CA11155 1-04	Short 1	Singleminded-2 in Mammary Gland and Breast Cancer	Porter, Weston	Texas A&M University System	TX	\$213,741
NICHD	5R01AG0163 81-07	Short 4	Vitamin E Trial in Persons with Down Syndrome	Dalton, Arthur	Institute for Basic Research in Developmental Disabilities	NY	\$220,500
NIA	5R01AG0163 81-07	Short 4	Vitamin E Trial in Persons with Down Syndrome	Dalton, Arthur	Institute for Basic Research in Developmental Disabilities	NY	\$662,588
NCCAM	5R01AG0163 81-07	Short 4	Vitamin E Trial in Persons with Down Syndrome	Dalton, Arthur	Institute for Basic Research in Developmental Disabilities	NV	\$196,000
NCRR	5M01RR0008 27-33	Short 4	Clinical Trial: Down Syndrome and Alzheimer Disease: Antioxidant Trial	Lott, Ira	University of California San Diego	CA	\$21,661
NICHD	1R01HD0575 64-01	Short 5	Perinatal Choline Therapy in a Mouse Model of Down Syndrome and Alzheimer's Disease	Strupp, Barbara	Cornell University Ithaca	NY	\$623,872
NIGMS	1R01GM0855 48-01	Short 6	Is Chromosome Therapy Possible for Down Syndrome and Other Karyotypic Imbalances?	Lawrence, Jeanne	University of Massachusetts Medical School Worcester	MA	\$327,083

***FY 2008 Goal 3 Subtotal: 6,118,458***

*Goal 5: Research Infrastructure*

<b>Funding I/C</b>	<b>Project Number</b>	<b>Obj.</b>	<b>Project Title</b>	<b>PI Name</b>	<b>Org Name</b>	<b>State</b>	<b>Amount</b>
NCRR	5M01RR0008 27-33	Medium 3	Diagnosis of Alzheimer Disease in Down Syndrome by Telemedicine	Lott, Ira	University of California San Diego	CA	\$6,869
NHLBI	1R01HL09151 9-01A1	Short 1	Genetic Dissection of Trisomy 21	Yu, Eugene	Roswell Park Cancer Institute Corp	NY	\$417,369
NIA	5P01AG01761 7-09	Short 1	Transgenic Core	Levy, Efrat	New York State Council for Mental Hygiene Planning	NY	\$207,945
NICHD	5R01HD0383 84-08	Short 2	Genomic Approaches to Aneuploidy	Reeves, Roger	Johns Hopkins University	MD	\$520,333
NCI	5R01HD0383 84-08	Short 2	Genomic Approaches to Aneuploidy	Reeves, Roger	Johns Hopkins University	MD	\$117,044
NIA	5R01AG0146 73-09	Short 3	Epidemiology of menopause and dementia in Down syndrome	Schupf, Nicole	Columbia University Health Sciences	NY	\$481,787

***FY 2008 Goal 5 Subtotal: 1,751,347***

**FISCAL YEAR 2009 PROJECTS (EXCLUDES ARRA-FUNDED)**

(includes all grant types funded in FY 2009)

*Goal 1: Pathophysiology of Down Syndrome and Disease Progression*

<b>Funding IC</b>	<b>Project Number</b>	<b>Obj.</b>	<b>Project Title</b>	<b>PI Name</b>	<b>Org Name</b>	<b>State</b>	<b>Amount</b>
NICHD	1R01HD0651 60-01	Long 1	Predicting Cognitive Decline in Adults with Down Syndrome	Lott, Ira	University of California Irvine	CA	\$452,809

<b>Funding IC</b>	<b>Project Number</b>	<b>Obj.</b>	<b>Project Title</b>	<b>PI Name</b>	<b>Org Name</b>	<b>State</b>	<b>Amount</b>
NIA	5R03AG0299 66-02	Medium 1	The involvement of Adapt78 in Alzheimer's Disease and Down Syndrome	Crawford, Dana	Albany Medical College	NY	\$66,725
NICHD	5R21HD0543 47-02	Medium 2	Human Neural Precursors from CNS Developmental Disorders: Down Syndrome	Sheen, Volney	Beth Israel Deaconess Medical Center	MA	\$255,000
NIA	5F31AG02978 7-03	Medium 3	APP Metabolism in Transgenic Down Syndrome Mouse Models	Choi, Jennifer	New York University School of Medicine	NY	\$41,176
NICHD	5F32HD05574 5-03	Medium 3	Retrograde Transport at the Crossroads of Cognitive Decline and Neurodegeneration	Maloney, Michael	Stanford University	CA	\$50,054
NIA	5R01AG0121 22-14	Medium 3	An Animal Model for Age-Related Degeneration	Granholm-Bentley, Ann-Charlotte Esther	Medical University of South Carolina	SC	\$256,328
NINDS	4R00NS05252 4-03	Medium 4	Role of Nebula/DSCR1 in Mitochondria	Chang, Karen	University of Southern California	CA	\$249,000
NICHD	5R01HD0384 66-09	Medium 4	Mitochondrial Dysfunction in Down Syndrome	Busciglio, Jorge	University of California Irvine	CA	\$188,650
NIA	5P01AG01761 7-10	Medium 4	The Origins of Endosome Dysfunction in Ad Pathobiology	Mathews, Paul	New York State Council for mental Hygiene Planning	NY	\$417,011
NIA	5P01AG01761 7-10	Medium 4	Expression Profiling of Endosomal Pathways in Ad	Ginsberg, Stephen	New York State Council for mental Hygiene Planning	NY	\$369,889

<b>Funding IC</b>	<b>Project Number</b>	<b>Obj.</b>	<b>Project Title</b>	<b>PI Name</b>	<b>Org Name</b>	<b>State</b>	<b>Amount</b>
NINDS	5R01NS05537 1-03	Medium 5	Disrupted Transport of NGF-TrKA Signaling in Mouse Models of Down Syndrome	Mobley, William	Stanford University	CA	\$418,666
NINDS	5R00NS05790 6-04	Medium 5	Imaging NGF Signal Transduction in Live Neurons	Cui, Bianxiao	Stanford University	CA	\$251,426
NINDS	3R00NS05790 6-04S1	Medium 5	Imaging NGF Signal Transduction in Live Neurons	Cui, Bianxiao	Stanford University	CA	\$98,000
NIA	5P01AG00946 4-18	Medium 5	Effects on Ab on Synaptic Transmission and Plasticity	Greengard, Paul	Rockefeller University	NY	\$337,177
NICHD	5R01HD0476 56-05	Medium 6	Age and Cognition in a Mouse Model of Down Syndrome	Wenger, Galen	University of Arkansas Medical Sciences Little Rock	AR	\$249,632
NINDS	5F31NS06038 8-03	Short 1	Differential CpG Island Methylation in Down Syndrome	Miller, Nathaniel	Hugo W. Moser Research Institute Kennedy Krieger	MD	\$37,296
NINDS	1F31NS06051 7-02	Short 2	Effects of Neural Progenitor Cell Transplantation in Neonatal Ts65Dn Mice	Rachubinski, Angela	University of Colorado Denver	CO	\$27,996
NICHD	5R01HD0570 29-02	Short 3	Genome-Wide Recombination Profiles in Oocytes with Chromosome 21 Nondisjunction	Sherman, Stephanie	Emory University	GA	\$501,410
NICHD	5R01HD0554 57-02	Short 3	Role of PIP2 Metabolism Imbalance in Down Syndrome	Di Paolo, Gilbert	Columbia University Health Sciences	NY	\$342,125

<b>Funding IC</b>	<b>Project Number</b>	<b>Obj.</b>	<b>Project Title</b>	<b>PI Name</b>	<b>Org Name</b>	<b>State</b>	<b>Amount</b>
NICHD	1R01HD0597 62-01	Short 4	Molecular Basis of Nuchal Edema	Hong, Young-Kwon	University of Southern California	CA	\$346,375
NICHD	5R01HD0553 91-02	Short 4	NFAT Signaling and Down Syndrome	Crabtree, Gerald	Stanford University	CA	\$278,069
NICHD	5R01HD0562 35-02	Short 4	Systems Biology for Studies of Cognition in Down Syndrome	Gardiner, Katherine	University of Colorado Denver	CO	\$510,289
NICHD	1R21HD0589 97-01A2	Short 4	MicroRNA and Down Syndrome	Elton, Terry	Ohio State University	OH	\$201,475
NCI	1R01CA11837 4-01A2	Short 4	Negative Regulation of VEGF-Mediated Angiogenesis	Ryeom, Sandra	Children's Hospital Boston	MA	\$318,409
NIA	5K01AG03129 6-02	Short 4	Aging and Meiosis in the Nematode Germline	Yanowitz, Judith	Carnegie Institution of Washington, D.C.	D.C.	\$108,118

***FY 2009 Goal 1 Subtotal: 6,373,105***

*Goal 2: Diagnosis, Screening, and Functional Measures*

<b>Funding IC</b>	<b>Project Number</b>	<b>Obj.</b>	<b>Project Title</b>	<b>PI Name</b>	<b>Org Name</b>	<b>State</b>	<b>Amount</b>
NICHD	5R01HD0356 12-11	Long 1	The Development of Joint Attention After Infancy	Adamson, Lauren	Georgia State University	GA	\$307,063
NIA	1R01AG0330 15-01	Medium 4	Glucose Metabolic, Amyloid, and Tau Brain Imaging in Down's Syndrome and Dementia	Small, Gary	University of California Los Angeles	CA	\$631,288

<b>Funding IC</b>	<b>Project Number</b>	<b>Obj.</b>	<b>Project Title</b>	<b>PI Name</b>	<b>Org Name</b>	<b>State</b>	<b>Amount</b>
NCRR	1S10RR02541 9-01	Medium 4	Purchase of a Triple Quadrupole Mass Spectrometer for Multiple Reaction Monitoring	Cotter, Robert	Johns Hopkins University	MD	\$413,070
NICHD	1R01HD0649 93-01	Medium 5	Aging of Frontal Structure and Function in Down Syndrome and Dementia	Head, Elizabeth	University of Kentucky	KY	\$499,306
NICHD	1R01HD0553 45-01A2	Short 1	Cognitive Predictors of Language Impairment in Down Syndrome	Conners, Frances	University of Alabama Tuscaloosa	AL	\$373,535
NICHD	1R03HD0572 92-01A1	Short 1	Wayfinding Skills of Persons with Down Syndrome	Merrill, Edward	University of Alabama Tuscaloosa	AL	\$69,075
NICHD	5R01HD0388 19-08	Short 1	Pragmatic Skills of Young Males and Females with Fragile X Syndrome	Losh, Molly	University of North Carolina Chapel Hill	NC	\$517,519
NICHD	5R01HD0449 35-07	Short 1	Speech of Young Males with Fragile X Syndrome	Zajac, David	University of North Carolina Chapel Hill	NC	\$345,642
NICHD	5P01HD02599 5-19	Short 1	Multimodal Analyses of Face Processing in Autism and Down Syndrome	Mitchell, Teresa	University of Massachusetts Medical School Worcester	MA	\$155,270
NIA	5P50AG01657 3-10	Short 3	Core--Clinical	Kawas, Claudia h.	University of California Irvine	CA	\$444,948
NIGMS	5F31GM0834 52-02	Short 5	Genome-Wide Recombination as a Risk Factor for Nondisjunction	Hollis, Natasha	Emory University	GA	\$28,062

***FY 2009 Goal 2 Subtotal: \$3,784,778***

***Goal 3: Treatment and Management of Down Syndrome***

<b>Funding IC</b>	<b>Project Number</b>	<b>Obj.</b>	<b>Project Title</b>	<b>PI Name</b>	<b>Org Name</b>	<b>State</b>	<b>Amount</b>
NIDCD	5R01DC0033 11-07	Long 1	Sensorimotor Control of the Human Orofacial System	Barlow, Steven	University of Kansas Lawrence	KS	\$503,549
NICHD	5P01HD02599 5-19	Long 1	Guiding Visual Attention to Enhance Discrimination Learning	Carlin, Michael	University of Massachusetts Medical School Worcester	MA	\$145,437
NIDCD	5R01DC0086 40-03	Long 2	Treatment of Speech Disorders in Children with Down Syndrome	Camarata, Stephen	Vanderbilt University	TN	\$511,260
NICHD	4R37HD0299 57-17	Long 3	Early Development with Williams or Down Syndrome	Mervis, Carolyn	University of Louisville	KY	\$370,000
NICHD	1K23HD05804 3-01A1	Short 1	Neurodevelopmental Impact of Congenital Heart Defects in Down Syndrome	Visootsak, Jeannie	Emory University	GA	\$128,250
NHLBI	5R01HL08330 0-03	Short 1	Genetic Basis for Congenital Heart Defects	Reeves, Roger	Johns Hopkins University	MD	\$1,104,989
NHLBI	1R01HL09298 1-01A1	Short 1	Copy Number Variation as a Cause of Congenital Heart Defects in Down Syndrome	Zwick, Michael	Emory University	GA	\$706,888
NHLBI	5K08HL09329 0-02	Short 1	Genetic modulators of Erythromegakaryocytic Development	Chou, Stella	Children's Hospital of Philadelphia	PA	\$133,920

<b>Funding IC</b>	<b>Project Number</b>	<b>Obj.</b>	<b>Project Title</b>	<b>PI Name</b>	<b>Org Name</b>	<b>State</b>	<b>Amount</b>
NCI	5R01CA11155 1-05	Short 1	Singleminded-2 in Mammary Gland and Breast Cancer	Porter, Weston	Texas A&M University System	TX	\$213,741
NCI	5R01CA12077 2-03	Short 1	Molecular and Pharmacologic Correlates of Acute Myeloid Leukemia in Down Syndrome	Taub, Jeffrey	Wayne State University	MI	\$417,091
NCI	5R01CA10177 4-07	Short 1	Mechanisms of Leukemogene- sis in Down Syndrome	Crispino, John	Northwestern University	IL	\$305,363
NICHD	5R01AG0163 81-08	Short 4	Vitamin E Trial in Persons with Down Syndrome	Dalton, Arthur	Institute for Basic Research In Developmental Disabilities	NY	\$196,000
NCCAM	5R01AG0163 81-08	Short 4	Vitamin E Trial in Persons with Down Syndrome	Dalton, Arthur	Institute for Basic Research In Developmental Disabilities	NY	\$196,000
NIA	5R01AG0163 81-08	Short 4	Vitamin E Trial in Persons with Down Syndrome	Dalton, Arthur	Institute for Basic Research In Developmental Disabilities	NY	\$483,473
NICHD	5R01HD0575 64-02	Short 5	Perinatal Choline Therapy in a Mouse Model of Down Syndrome and Alzheimer's Disease	Strupp, Barbara	Cornell University Ithaca	NY	\$578,030
NIGMS	5R01GM0855 48-02	Short 6	Is Chromosome Therapy Possible for Down Syndrome and Other Karyotypic Imbalances?	Lawrence, Jeanne	University of Massachusetts Medical School Worcester	MA	\$328,083

***FY 2009 Goal 3 Subtotal: \$6,322,074***

***Goal 4: Living with Down Syndrome***

<b>Funding IC</b>	<b>Project Number</b>	<b>Obj.</b>	<b>Project Title</b>	<b>PI Name</b>	<b>Org Name</b>	<b>State</b>	<b>Amount</b>
NICHD	1R03HD0598 48-01A1	Medium 1	Aging in Adults with Down Syndrome	Esbensen, Anna	University of Wisconsin Madison	WI	\$74,250
NICHD	1R13HD0621 31-01	Medium 1	Building Bridges for Down Syndrome	Lipscomb Sund, Kristen	International Mosaic Down Syndrome Association	TX	\$6,000

***FY 2009 Goal 4 Subtotal: \$80,250***

***Goal 5: Research Infrastructure***

<b>Funding IC</b>	<b>Project Number</b>	<b>Obj.</b>	<b>Project Title</b>	<b>PI Name</b>	<b>Org Name</b>	<b>State</b>	<b>Amount</b>
NHLBI	5R01HL09151 9-02	Short 1	Genetic Dissection of Trisomy 21	Yu, Eugene	Roswell Park Cancer Institute Corp	NY	\$422,174
NIA	5P01AG01761 7-10	Short 1	Transgenic Core	Levy, Efrat	New York State Cncl For Mtl Hygiene Plng	NY	\$230,728
NICHD	5R01HD0383 84-09	Short 2	Genomic Approaches to Aneuploidy	Reeves, Roger	Johns Hopkins University	MD	\$536,405
NCI	5R01HD0383 84-09	Short 2	Genomic Approaches to Aneuploidy	Reeves, Roger	Johns Hopkins University	MD	\$117,044
NIA	5R01AG0146 73-10	Short 3	Epidemiology of Menopause and Dementia in Down Syndrome	Schupf, Nicole	Columbia University Health Sciences	NY	\$495,252

***FY 2009 Goal 5 Subtotal: \$1,801,603***

**FISCAL YEAR 2009 ARRA PROJECTS**

*Goal 1: Pathophysiology of Down Syndrome and Disease Progression*

<b>Funding IC</b>	<b>Project Number</b>	<b>Obj.</b>	<b>Project Title</b>	<b>PI Name</b>	<b>Org Name</b>	<b>State</b>	<b>Amount</b>
NINDS	1R01NS0621 84-01A2	Short 2	Using Transport to Map the Brain	Bearer, Elaine	University Of New Mexico	NM	\$736,311
NICHD	1R01HD0575 80-01A2	Short 4	Forebrain Development in Down Syndrome and in Ts65Dn Model Mice	Haydar, Tarik	Children's Research Institute	DC	\$594,802
NHLBI	1RC1HL1001 68-01	Long 2	Identification of Altered Molecular Signature of Down Syndrome iPS Cells	Crispino, John	Northwestern University	IL	\$500,000

***FY 2009 Goal 1 ARRA Subtotal: 1,831,113***

*Goal 2: Diagnosis, Screening, and Functional Measures*

<b>Funding IC</b>	<b>Project Number</b>	<b>Obj.</b>	<b>Project Title</b>	<b>PI Name</b>	<b>Org Name</b>	<b>State</b>	<b>Amount</b>
NICHD	3R01HD0449 35-07S1	Short 1	Speech of Young Males with Fragile X Syndrome	Zajac, David	University of North Carolina Chapel Hill	NC	\$134,380
NICHD	3R01HD0553 45-01A2S1	Short 1	Cognitive Predictors of Language Impairment in Down Syndrome	Conners, Frances	University of Alabama Tuscaloosa	AL	\$219,390
NIA	1R21AG0306 81-01A2	Short 4	Amyloid Plaque and Tangle Imaging in Alzheimer's Disease and Down Syndrome	Nelson, Linda	University of California Los Angeles	CA	\$189,422

Funding IC	Project Number	Obj.	Project Title	PI Name	Org Name	State	Amount
NIA	1R01AG0311 10-01A1	Short 4	Natural History of Amyloid Deposition in Adults with Down Syndrome	Handen, Benjamin	University of Pittsburgh	PA	\$811,917

***FY 2009 Goal 2 ARRA Subtotal: \$1,355,109***

*Goal 3: Treatment and Management*

Funding IC	Project Number	Obj.	Project Title	PI Name	Org Name	State	Amount
NIGMS	3R01GM0855 48-02S1	Short 6	Is Chromosome Therapy Possible for Down Syndrome and Other Karyotypic Imbalances?	Lawrence, Jeanne	University of Massachusetts Medical School Worcester	MA	\$123,028
NIDCD	3R01DC0033 11-06A1S1	Long 1	Sensorimotor Control of the Human Orofacial System	Barlow, Steven	University of Kansas Lawrence	KS	\$50,000
NIDCD	3R01DC0086 40-02S2	Long 2	Treatment of Speech Disorders in Children with Down Syndrome	Camarata, Stephen	Vanderbilt University	TN	\$189,205

***FY 2009 Goal 3 ARRA Subtotal: 362,233***

*Goal 5: Research Infrastructure*

Funding IC	Project Number	Obj.	Project Title	PI Name	Org Name	State	Amount
NICHD	1R21HD0601 34-01A1	Short 2	Generation of Trisomy 21 Induced Pluripotent Stem Cells	Bhattacharya, Anita	University of Wisconsin Madison	WI	\$212,080

***FY 2009 Goal 5 Subtotal: \$212,080***

*APPENDIX B*

**NIH-FUNDED GRANTS MEETING GOALS OF DOWN SYNDROME RESEARCH  
PLAN, Fiscal Year 2008-2009 (including ARRA grants)**

	Pathophysiology	Diagnosis/Screen	Treatment	Living with DS	Research Inf.
Short-term	19	20	25	--	11
Medium-term	31	3	--	2	1
Long-term	3	2	10	--	--
TOTALS	53	25	35	2	12

## APPENDIX C

After consultation with the scientific research community and national organizations that focus on Down syndrome, and taking into account various congressional directives received by the NIH, the NIH Down Syndrome Working Group developed the NIH Research Plan for Down Syndrome ([http://www.nichd.nih.gov/publications/pubs/upload/NIH\\_Downsyndrome\\_plan.pdf](http://www.nichd.nih.gov/publications/pubs/upload/NIH_Downsyndrome_plan.pdf)). The purpose of the plan is to build upon ongoing NIH-supported research to take advantage of emerging scientific opportunities and set the stage for possible future collaborations in this area.

<b>Down Syndrome Research Area</b>	<b>Short-term Objective (0 to 3 Years)</b>	<b>Medium-term Objective (4 to 6 Years)</b>	<b>Long-term Objective (7 to 10 Years)</b>
<i>Pathophysiology of Down Syndrome and Disease Progression</i>	Continue testing cognitive and synaptic function in Down syndrome model mice.	Study whether the impact of aging on certain processes is greater than on others.	Explore genetic and environmental determinants of cognitive function in Down syndrome throughout the lifespan.
<i>Diagnosis, Screening, and Functional Measures</i>	Identify the cognitive phenotype of Down syndrome in a cohort throughout the lifespan.	Link human and mouse cognitive studies relating to Down syndrome.	Develop better measures of hippocampal and cognitive function.
<i>Treatment and Management</i>	Increase research on comorbid psychiatric and medical conditions throughout the lifespan.	Continue learning from the Alzheimer disease research community regarding the best therapeutics.	Investigate the impact of early intervention on psychomotor and cognitive development.
<i>Living with Down Syndrome</i>	Develop a more complete demographic knowledge base.	Study real-world outcomes for Down syndrome families.	Explore new intervention research, especially during transitional stages.
<i>Research Infrastructure</i>	Improve and expand availability of animal models.	Discuss the best mechanisms to use in fostering cross-disciplinary research.	Include cohorts of people with Down syndrome in longitudinal studies.

### RESEARCH AREAS AND OBJECTIVES

The NIH Down Syndrome Working Group developed the following list of research priorities to complement and guide its future efforts regarding Down syndrome. The objectives are listed according to research themes and are further grouped by the estimated, but realistic, timeframe that it could take to accomplish them. For the purposes of this document, “short-term” is defined as beginning from the date of publication of this document through approximately three years from that time, “medium-term” is approximately four to six years from that time, and “long-term” runs from seven to 10 years or beyond.

## I. PATHOPHYSIOLOGY OF DOWN SYNDROME AND DISEASE PROGRESSION

Investigators mapped the first two of several hundred genes mapped to human chromosome 21 in 1973. By 2000, a consortium of investigators published the Deoxyribonucleic Acid (DNA) sequence of chromosome 21. Once the genes on chromosome 21 were identified, it was possible to identify the effects of having an extra copy of individual genes or clusters of genes. To study these effects, researchers use animal model systems, including fully or partially trisomic mice, which have features of the human prototype not seen in other animal models.

### *Short-term Objectives*

1. Continue **testing cognitive and synaptic function** in Down syndrome model mice focusing specifically on relevant genes located on human chromosome 21.
2. **Develop mouse models to study synaptic and vesicular trafficking** (these may exist, but may not be utilized for Down syndrome research at the current time). Allow studies of other disorders associated with intellectual and developmental disabilities (Fragile X, Rett syndrome, etc.) to guide and inform directions for such studies.
3. Expand and improve proteomic, metabolomic, transcriptomics, and phenomic approaches, including:
  - Appropriate sample preparation techniques to create suitable proteomic samples from mouse brains;
  - Fractionation techniques to visualize the perhaps 100,000 proteins that exist;
  - Additional proteomic methods beyond two-dimensional gels;
  - Rigorous statistical techniques to determine whether a statistically significant change in protein levels has biologic relevance;
  - Methods to relate findings in the mouse to humans;
  - Research beyond proteins and proteomics, using emerging techniques to move into metabolites and metabolomics, and begin to examine what generates alterations in learning and memory; and
  - Linking data from transcripts to the proteome, metabolome, and phenome.
4. Study **pathways and cascades** affected in Down syndrome. These might include pathways that affect mitochondrial function (adenosine triphosphate [ATP] production), calcineurin, MAP kinases, and oxidative stress. Link up with relevant research into specific gene effects at other Institutes, and explore the effects on modulation of development in other organ systems.

### *Medium-term Objectives*

1. Study whether the **impact of aging on physiologic and cognitive processes** is greater than on others. Such research probably requires a range of longitudinal studies of more than five years' duration, with different emphases. For example, studies could include:
  - The non-demented population with Down syndrome, which is likely to be heterogeneous and may include people in the early stages of unrecognized Alzheimer disease.

- Understanding the factors that affect the risk of dementia, and what factors may be associated with not developing dementia. Some people with Down syndrome do not develop dementia by their late 60s or early 70s. To complete such studies, researchers would also need to better understand the clinical course of dementia in people with Down syndrome.
  - Consider research with different subpopulations of individuals with Down syndrome to examine variations in aging patterns. Much literature focuses on early development and on individuals older than age 40, but very little research targets people with Down syndrome during their 20s and 30s.
2. Sequence the **developmental events of abnormal spine development**, including genetics and cellular aspects (this research may interface with a common theme in developmental disabilities and could include information from other disorders, such as Fragile X and Rett syndromes).
  3. Study the biochemistry of **APP processing** in humans with Down syndrome and in animal models (including mechanisms of trafficking and Abeta production, degradation, and clearance).
  4. Describe more fully the **mitochondrial dysfunction** in Down syndrome and the exact status of mitochondrial function; develop targeted therapies for mitochondrial function in Down syndrome.
    - Assess endocytosis and endosomal trafficking *in vivo* and *in vitro*.
    - Assess failed signaling and related neurotrophic deficits to help determine the relationship between disease progression and cognitive deficits.
  5. Study **synaptic vesicle trafficking** in Down syndrome and postsynaptic mechanisms including metabotropic and ionotropic glutamate receptors and other neurotransmitter receptors.
  6. Develop a strategy to **correlate descriptive studies** of human and Down syndrome model mouse development over the lifespan. This strategy will inform the development of a cognitive phenotype for Down syndrome that will support longitudinal studies (see below).

#### *Long-term Objectives*

1. Explore **genetic and environmental determinants** of cognitive function in Down syndrome throughout the lifespan. This work may involve long-term (more than 10 years) study of existing and new cohorts of individuals.
2. Connect **cellular mechanisms** and genotype to synaptic and cognitive phenotype.

## II. DIAGNOSIS, SCREENING, AND FUNCTIONAL MEASURES

The science of assessment has evolved in recent years, and while significantly more options for diagnostic and screening measures are now available, it will be important for researchers to

capitalize on these advances in measurement. For example, utilization of more specialized measures of functioning across domains would allow more fine-grained analysis and phenotyping, which may assist in identification of biomarkers.

To proceed, the scientific community needs to focus on improving their tools, techniques, methods and measures, moving toward a minimum set of common measures for use across studies, age groups, and developmental and behavioral domains. In addition, the field may benefit from an agreement on common domains to be assessed for clinical research in Down syndrome (e.g. non-verbal problem-solving ability, language and communication skills, adaptive functioning), to allow for comparability across studies, noting that those appropriate for one stage of life may not be appropriate for others.

#### *Short-term Objectives*

1. **Identify the cognitive phenotype of Down syndrome** in a cohort throughout the lifespan, and link the phenotype to cognitive defects and developmental standards. This could include defining speech and language, behavioral, and psychological abnormalities, using magnetic resonance imaging (MRI) and functional MRI (fMRI) to examine major pathways and determining how those pathways differ in persons with Down syndrome.
2. In addition, researchers need to apply standardized instruments and criteria to **define the clinical profile of Alzheimer disease in Down syndrome**; these instruments must be sensitive to the baseline-level function of this population. Standardizing a cognitive battery in mice to help develop a core set of measures for this purpose would help researchers.
3. **Collect and bank well-characterized organs for postmortem research.** Such specimens are necessary for understanding the factors that underlie dementia in people with Down syndrome. Increasing banking of organs from individuals with Down syndrome who were older than age 40 years at the time of death would help to identify the brain correlates of clinical signs and symptoms.
4. Expand the **brain imaging project** supported by the Foundation for the NIH. This project has enrolled 400 people and might expand to include an adequate sample of people with Down syndrome. Undertake a systematic **analysis of the development of key structures in the brains** of people with Down syndrome at various developmental stages using standardized techniques and measurements. Imaging studies of normal development currently in progress and supported by the NIH could inform this endeavor.
5. **Develop new statistical approaches.** Data from partial trisomy patients can generate vectors of pathways and ways to constrain them.
6. Consider developing **additional outcome measures for use in clinical trials** to offer supplementary options for assessing change across domains of functioning.

#### *Medium-term Objectives*

1. Link human and mouse cognitive studies relating to Down syndrome to:

- Better characterize cognitive deficits in mice from the psychological/psychiatric/functional aspects;
  - Develop standardized methods to test synaptic and cognitive function in Down syndrome model mice; and
  - Develop tests that “tap” into the same “cognitive” processes in both mice and humans (such as discriminative taste aversion).
2. Establish whether and how **synaptic dysfunction correlates to abnormal cognition**, and determine the best phenotype/genotype markers for therapeutic screening.
  3. Develop **nanotechnology approaches** to enhance contrast of imaging reagents for finer resolution studies in younger populations with Down syndrome.
  4. Explore whether **magnetic resonance spectroscopy**, which can show changes much earlier than neurocognitive exams, offers another promising technology for studying neuron health in individuals with Down syndrome.
  5. **Assay specific vulnerable brain regions**, such as the hippocampus, cerebellum, and prefrontal cortex, from a prospective developmental perspective using standard measures and techniques, enhancing current cognitive batteries applicable at specific stages across the lifespan.

#### *Long-term Objectives*

1. Develop better measures of hippocampal and cognitive function in persons with Down syndrome.

### III. TREATMENT AND MANAGEMENT

For individuals with Down syndrome and their families, there is a continuing need to study clinical treatments and interventions. Moreover, at least half of all children with Down syndrome have a comorbid condition. Two conditions that have the potential to have significant impact on cognitive function during the first few years of life are the development of leukemia and the high incidence of congenital heart disease. Both of these conditions necessitate extensive medical intervention.

#### *Short-term Objectives*

1. **Expand research on comorbid psychiatric and medical conditions** that occur throughout the lifespan, including depression, dementia, and various developmental disabilities. Other comorbid conditions that could benefit from concerted interdisciplinary efforts include the following:
  - *Leukemias*—Early medical or behavioral interventions can alter the developmental trajectory in children treated for leukemias. These children have concomitant behavioral and cognitive difficulties; for example, 40 percent had an Intelligence Quotient (IQ) of less than 75 on follow-up one to three years after treatment. The extent of problems typically depends on the age of the child at treatment, its intensity, and the time lapsed

since treatment. Children with an underlying trisomic disorder that affects the brain's development who undergo this intensive treatment for leukemia are likely to face problems for at least several years. Future research could build on studies such as a new clinical trial of methotrexate and neurocognitive outcomes that may provide information on the mechanisms by which impairments occur.

- *Congenital heart disease*—As survival of children with congenital heart defects improves, clinicians increasingly recognize neurodevelopmental problems in at least half of survivors. The incidence of neurodevelopmental problems seems to increase over time. Children with congenital heart disease have a fairly characteristic neurodevelopmental signature. As adolescents, they tend to have difficulty with social cognition. However, the impact on children with Down syndrome is less clear. Neurodevelopmental outcomes vary, even in children who have the same defects and receive the same treatments and may be related to specific allelic variants of genes not located on human chromosome 21. Children with Down syndrome who are treated for heart defects probably have worse neurodevelopmental outcomes than children without Down syndrome. Possible research opportunities could include longitudinal assessments of cognitive and behavioral outcomes in relation to genetic studies.
  - *Obstructive sleep apnea (OSA)*—As with typically developing individuals, this condition may exert an impact on cognition in individuals with Down syndrome.
  - Other comorbid conditions that deserve more thorough investigation in Down syndrome individuals throughout the lifespan include:
    - o *Seizure disorders*
    - o *Psychiatric or neurobehavioral problems*
    - o *Celiac disease*
    - o *Atlanto-axial instability*
    - o *Endocrine function*
2. Review earlier literature on **understanding and improving the motor skills** of individuals with Down syndrome, with particular attention to whether and how sensory structures in persons with Down syndrome are altered. In addition, review current relevant NIH-supported research that is not specific to Down syndrome, but may be applicable.
  3. Determine whether individuals with cognitive impairment, including those with Down syndrome, could be considered as candidates for **transplantation studies**.
  4. Review findings from current **clinical trials of vitamin E and antioxidants** in individuals with Alzheimer disease, and determine whether to test these substances in persons with Down syndrome to see if they might enhance the function of circuits involved in cognition.
  5. **Test drugs** used by persons with Alzheimer disease in mouse models of Down syndrome, and eventually in other model systems, to determine their effects on cognition.
  6. Encourage **testing of “orphan drugs”** in animal and cellular models to determine potential beneficial effects on cognition in individuals with Down syndrome.

### *Medium-term Objectives*

In general, one challenge faced by researchers is how to focus on precisely targeting time windows for early therapeutics, in relation to the use of available treatments for individuals with Down syndrome, as well as the development of new agents.

1. Continue the dialog with the Alzheimer disease research community regarding the best **anti-amyloids and other agents' use as early therapeutics**.
2. Encourage studies to understand the best **use of therapeutics over time** in a Down syndrome population. For instance, few researchers have described studies of adults with Down syndrome treated with **Aricept®**. Because the progression of cognitive decline in different stages of dementia is not linear, this medication is likely to have differential efficacy depending on when in the pathological cascade it is used.
3. Explore the impact of cholesterol on dementia. People who have Down syndrome and **cholesterol levels** higher than 200 mg/dl are at substantially higher risk for dementia than people with lower cholesterol levels. However, the risk of dementia in people with high cholesterol who take **statins** is the same as in people with lower cholesterol levels.
4. Explore the specific impact of **hormone replacement therapy (HRT)** use on women with Down syndrome. Women with Down syndrome experience **menopause** at an earlier age and are at increased risk for dementia compared to women who are older at onset of menopause. Some studies show that taking HRT appears to protect episodic memory tasks in women who did not have dementia at baseline. In addition, women who took HRT had better scores on one cognitive measure over a 14- to 18-month period, but HRT had no effect on any of the other measures. Currently, the data are not sufficient to show whether HRT reduces the cumulative risk for Alzheimer disease.
5. Consider developing funding opportunities for **translational research** that applies findings from literature review **on motor skills** in individuals with Down syndrome.
6. Further investigate the **resting state hypothesis** to assess default activity. Data suggest that the resting state differs in those with Alzheimer disease or mild cognitive impairment.

### *Long-term Objectives*

Children with Down syndrome have greater deficits in auditory short-term memory than children with equivalent IQs. Researchers examining whether these deficits influence the benefits of language intervention for children with Down syndrome may be warranted, and may lead to more refinement of behavioral interventions for speech and language development.

1. Investigate the impact of **early intervention or infant stimulation** on the psychomotor and cognitive development of Down syndrome children.
2. Identify **compensatory strategies**. Children with Down syndrome need therapies that help them process available linguistic input, matching individual differences in children with Down syndrome to those therapies best suited to their profiles.

3. Develop **cross-disciplinary collaborations** (e.g., educational psychologists, psychiatrists, neurophysiologists) **and public-private partnerships** to test educational, pharmaceutical, and therapeutic interventions. Investigators should take ethical considerations into account when testing any interventions in individuals with Down syndrome.

#### IV. LIVING WITH DOWN SYNDROME

Studies of family and classroom environments may provide information that allows us to maximize biobehavioral interventions for improving daily-life function and cognition of people with Down syndrome.

##### *Short-term Objectives*

1. Develop a more complete **demographic** knowledge base of individuals with Down syndrome and their families. Surprisingly little is known about the demographics of families with a child who has Down syndrome, except that these children are more likely to have older mothers. One in eight mothers of children with Down syndrome is aged 40 years or older, compared to 1.8 percent of mothers of other children. Older mothers likely are better educated than younger mothers. The mothers of children with Down syndrome are also more likely to be white.
2. Develop a **Web page containing information on Down syndrome** and related research, similar to the condition-specific NIH Web pages for autism or other disorders. The page should include user-friendly information relevant to both the research and family communities. This page should also include links to information about pending clinical trials and diagnosis and treatment guidelines adopted by nationally recognized professional societies. (The Alzheimer Disease Education Referral site managed by the NIA may be a possible model.)
3. Examine closely the **impact of Down syndrome on families and schools**. Possible research questions include how families react to children with Down syndrome, who may have fewer maladaptive behaviors than children with other disabilities, but they do have some of the behaviors. Many families of a child with Down syndrome want integrated schooling, but there is little comparative research on whether it has beneficial effects, and many families also worry about what will happen to their children once they leave the school system.

##### *Medium-term Objectives*

1. As children with Down syndrome live longer, study **real-world outcomes** for the family. These topics include the health of the family, the lifespan of parents, sibling educational attainment, and when siblings marry and have children. Such work could include:
  - Identifying the factors that lead to positive and negative outcomes in families that have an individual member with Down syndrome.
  - Conducting research on the intergenerational transmission of caregiving responsibilities and how best to foster those transitions.
2. Research and develop and/or adapt **assistive devices** that facilitate integration into society.

### *Long-term Objectives*

1. Explore **new intervention research** in families, schools, and residential environments that integrates the transition from late adolescence to young adulthood, as well as ways to enhance physical fitness. Such research results could be disseminated for use by other agency programs and in community settings.

## V. RESEARCH INFRASTRUCTURE

### *Short-term Objectives*

1. Improve and expand availability of **animal models** for research on Down syndrome. Distribution of mouse models remains a chronic problem. Although some researchers distribute their models freely, the number of researchers who wish to use them has tripled, yet supplies of the animals are limited, the animals are expensive to purchase, and they require complex husbandry. As a result, investigators cannot afford to obtain enough of these mice for their research. Researchers need the available animal models to be inexpensive and made available as early in their development as possible. Researchers also need a central facility with several dissemination sites. However, investigators need to share the models they develop while they maintain their ability to publish their findings in high-quality journals. To achieve these goals, it would be necessary to:
  - Explore improvements to the *Tc1* model. One strategy might be to attach an intact human chromosome 21 to a mouse chromosome, which should result in more stable retention of the human chromosome, making the model much more powerful.
  - Establish a mouse “core” to create the models needed for today’s research and to also predict what mouse strains and reagents researchers are likely to need in the near future. The cores could be useful for moving from genotype to phenotype and for helping to determine the involvement of a specific gene in specific phenotypes. Increase the number of animal models and make them available (currently under a contract mechanism).
  - Find ways to reduce the cost of animal models to NIH-funded investigators.
2. Develop **other new model systems** and improve existing models, such as:
  - Develop new model systems at organismal and cellular level to study aspects of Down syndrome.
  - Add other organs (in addition to brains) as model systems.
  - Deploy studies in additional organisms such as *C. elegans* and *Drosophila* that involve perturbation of individual chromosome 21 genes, and study the effects on the differentiation and maturation of individual neurons and synapses.
3. Develop a **coherent program of analysis**. The genetic heritage of people with Down syndrome has a great deal to teach about the health of everyone. Researchers should be encouraged to analyze genetic modifiers to show how they contribute to the many phenotypes in Down syndrome and the rest of the population. Once researchers identify a region of chromosome 21 for further study and a mouse model is available, they can ask similar questions when using single-gene models.

### *Medium-term Objectives*

1. Convene a meeting of the NIH leadership (or their representatives) from the Institutes and Centers involved in the NIH Down Syndrome Working Group to discuss the **best mechanisms to use** in fostering cross-disciplinary, collaborative, and clinical research on Down syndrome, in addition to the work already being supported. To inform this discussion, the Working Group should review ongoing international collaborative efforts relating to research on Down syndrome. Further, the Working Group should follow up with more specific discussions about cost, duplication, infrastructure, and training; whether to focus on basic, translational, or clinical research; and what specific avenues of inquiry to follow.
2. Consider ways to **include participants with Down syndrome** in NIH-funded clinical trials. NIH should review existing infrastructure, such as the Clinical and Translational Science Awards or the National Children's Study, for possible inclusion of this population. NIH program scientists who write Funding Opportunity Announcements could also consider including, where relevant, individuals with Down syndrome. Some examples of possible opportunities for research studies involving individuals with Down syndrome are:
  - The impact of novel medications on cognitive enhancement, daily function, or behavioral disorders.
  - Appropriate interventions for congenital heart disease and obstructive sleep apnea.
  - Therapies used for individuals with Alzheimer disease.
3. To enhance enrollment of individuals with Down syndrome, consider using **telemedicine** to screen and enroll subjects at distant sites. (Completion of a feasibility study using telemedicine to diagnose dementia in Down syndrome enabled researchers to obtain funding to continue testing the reliability of this method.)
4. Establish a centralized **brain, cell, tissue, DNA, RNA bank**; correlate the nature and severity of cognitive deficits and age of onset and severity of dementia. (Currently, the NICHD maintains a multi-disease bank of brain and other tissue that has some Down syndrome fetal material, but the demand for tissues far outweighs availability. The major challenges are to obtain permission to collect samples and to obtain tissue prepared appropriately.)
5. Support **database development**. Determine what databases currently exist (including those already developed for other conditions, and in development internationally), and whether potential collaborations might be feasible; involve National Library of Medicine in the development of any new databases.
6. Establish or expand **training programs for clinician/scientists** in research relevant to Down syndrome. Such training is critical for moving any research plan for Down syndrome into the future.
7. Assist researchers in assembling **demographically representative samples**, to better allow scientists to determine which findings they can generalize to a larger population of people with Down syndrome in the United States, especially across their lifespans.

8. **Establish a regular collaboration** between the NIH and the larger community of parent groups and researchers. The NIH Down Syndrome Working Group should continue to meet periodically with outside groups to share progress on research and hear about pressing concerns facing families. These meetings could help the community better understand how Down syndrome research is supported across the NIH. These meetings could also serve as a sounding board for current research issues, such as the best ways to recruit participants, and to better understand the evolving needs of families and individuals with Down syndrome.
9. Support a scientific meeting to highlight and assess **best practices in the use of tests** clinical researchers currently use at different developmental stages.

*Long-term Objectives*

1. Continue to include cohorts of people with Down syndrome in appropriate **longitudinal and cross-sectional studies**, e.g. a longitudinal cohort study of children with Down syndrome with and without congenital heart disease. Investigators could study the cohort *in utero* and follow-up using structural and neural imaging.
2. To ensure applicability of research findings to all segments of the population, **expand outreach efforts to recruit** individuals who have Down syndrome and who are members of racial and ethnic minorities for clinical trials. (Lack of a diverse sample of research participants has hampered research efforts. In part, this dearth may occur because Caucasian people with Down syndrome live until their 50s and 60s, but those of other races die younger. In addition, although some parents are hesitant to involve their children in longitudinal clinical trials, others are eager to participate in research, in part, because the types of information and resources offered to parents vary widely across the United States.)