DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health
National Institute of Neurological Disorders and Stroke

SPINAL MUSCULAR ATROPHY RESEARCH

Elias A. Zerhouni, M.D.
Director, NIH

April 2004

Department of Health and Human Services
National Institutes of Health
National Institute of Neurological Disorders and Stroke
SPINAL MUSCULAR ATROPHY RESEARCH

Table of Contents

Executive Summary 1

Introduction 4

Background 6
- Description of the Spinal Muscular Atrophies 6
- Current understanding 7
- Recent scientific advances in SMA research 9

SMA Research Programs 10
- Translational research in SMA 12
- SMA contract-based translational research program. 13
- Selection of SMA for contract-based program 15
- Intramural research 15

Providing information about SMA 15

Spinal Muscular Atrophy Research

Executive Summary

In House Report No. 108-188, pp. 69-70, and Senate Report No. 108-81, p.124, the Committees on Appropriations requested that the NIH prepare and submit a report on the progress of all aspects of spinal muscular atrophy (SMA) translational research. The following is submitted in response to the request.

SMA refers to a group of inherited neurological disorders that cause motor neurons of the spinal cord and brainstem to progressively degenerate. Because motor neurons are the nerve cells that activate muscles for voluntary movement, their loss leads to weakness, to muscle wasting, and, in severe forms of the disease, to paralysis and death. The several types of SMA vary in age of onset, severity, pattern of inheritance, muscles affected, and genes involved. No treatments are yet available to slow or stop the course of SMA.

In the most severe type of SMA, infants have widespread muscle weakness and lack of muscle tone; usually develop problems with breathing, feeding, and swallowing; are never are able to sit or stand; and usually die before age 2 years. Milder forms of SMA become apparent later in children or in adults and may be compatible with a normal life span.

In 1995, researchers discovered that loss of the SMN1 gene ("survival motor neuron"), or mutations that inactivate this gene, cause childhood SMA. Although the normal physiological functions of the SMN1 gene are still a matter of active investigation, the gene findings have led to improved diagnostic tests, to insights about why the severity of SMA varies so much, to animal models that mimic human SMA and greatly facilitate therapy development, and to promising strategies for developing treatments. The gene defects responsible for other forms of SMA have also been identified.

The National Institute of Neurological Disorders and Stroke (NINDS) leads NIH research on SMA. The NINDS supports basic studies to understand the underlying causes of SMA, translational research to develop treatments in cell culture and animal models of the disease, and clinical studies in people with SMA, as well as extensive research in cross cutting areas such as neurological

drug discovery, gene therapy, stem cells, and nervous system development that may have an impact on the disease.

The responsiveness of the NINDS research support strategy to the increasing scientific opportunities for research on SMA is evident in the growth of funding for research on SMA. The NINDS funding for SMA research grew by more than 500 percent from fiscal year (FY) 1998 ($945,000) to FY 2002 ($5.6 million), far greater than the overall budget growth of the Institute. The NINDS funding for FY 2003, including the obligated amount for a novel contract- based SMA translational research program, is $12.5 million. The overall FY 2002 NIH funding for SMA, the first year that NIH totals for SMA research were compiled, was $6.1 million and the FY 2003 NIH total was $12.9 million.

The NINDS supports research relevant to SMA through the Institute's broad basic, translational, and clinical research programs; a new contract-based program focused on SMA; and the NINDS intramural research program. Based on a convergence of factors, including the impact of the disease and opportunities for developing therapies arising from scientific progress, the NINDS selected SMA as the disease of focus for the novel performance-based contract approach to expedite development of therapies. In this translational research program, the primary contractor provides overall scientific and organizational support. A Steering Committee, whose membership is drawn from academia, the NIH, the U.S. Food and Drug Administration (FDA), and the biotechnology and pharmaceutical industries, guides the scientific direction. To meet specific goals highlighted by the Steering Committee, the contractor issues highly targeted solicitations for subcontract research projects. Awards are made rapidly, within 4 months of proposal submission, and progress is monitored with structured performance milestones and quarterly meetings to discuss results.

The NINDS awarded the primary contract for the SMA translational program in September 2003. The Steering Committee held an intensive meeting on September 17, 2003, at which they developed a research plan and identified priorities for the research projects to be conducted under the contract. The research plan and the first solicitation for research subcontracts were publicized in December 2003. The NINDS expects that the first of these projects will be funded during March 2004.

The NIH efforts to provide information about SMA complement the activities of private organizations focused on this disease, including web based information sources targeted to the needs of the public and to researchers.

Spinal Muscular Atrophy Research

Introduction

In its report on the Fiscal Year 2004 budget for the Department of Health and Human Services, the Committee on Appropriations stated:

> ***Spinal muscular atrophy (SMA)*** - SMA is the most common genetic killer of infants and toddlers and is the most prevalent genetic motor neuron disease. While there is currently no cure for the disease, the research outlook is promising. Researchers have already identified the genes involved in SMA as well as compounds that may lead to potential treatments. The Committee understands that the severity of the disease, its relatively high incidence, and the possibility of imminent treatments have led the NINDS to select SMA as a model for a new approach to funding translational research. The Committee encourages NINDS to sponsor and convene a scientific and clinical workshop on SMA with a focus on implementing SMA translational research, and to employ existing mechanisms such as websites, publications, and participation in conferences to promote awareness of funding opportunities. The Director is also encouraged to work with other Institutes and Federal agencies to develop formal programs that increase public and professional awareness of the disease. The Committee requests NINDS to submit a report by March, 2004 on progress on all aspects of SSMA [sic] translational research. (House Report No. 108-188, pages 69-70)
>
> ***Spinal Muscular Atrophy [SMA]***– . . . In addition, the Committee strongly urges the Institute to increase funding for basic and translation SMA research by aggressively soliciting grant applications. The Committee encourages the Institute to employ existing mechanisms such as websites, publications, workshops, and conferences to promote awareness of funding opportunities. In addition, the Committee encourages the Institute to further develop opportunities for upcoming clinical trials and to help make available all ongoing patient care options. Lastly, the Institute is encouraged to work with other Institutes and Federal agencies to develop formal programs that increase public and professional awareness of the disease. The Committee requests that NIH report back to

> the Committee, no later than April 2004 with a progress report on all aspects of SMA translational research. (Senate Report No. 108-81, p.124)

The following report has been prepared by the National Institutes of Health of the Department of Health and Human Services in response to this request.

Background

Description of the Spinal Muscular Atrophies:
Spinal muscular atrophy (SMA) refers to a group of inherited neurological disorders that cause motor neurons of the spinal cord and brainstem to progressively degenerate. Because motor neurons are the nerve cells that activate muscles for voluntary movement, their loss leads to weakness, to muscle wasting, and, in severe forms of the disease, to paralysis and death. The several types of SMA vary in age of onset, severity, pattern of inheritance, muscles affected, and genes involved. No treatments are yet available to slow or stop the course of SMA.

The childhood forms of SMA vary in age of onset and in severity, but all show an autosomal recessive pattern of inheritance. That is, to be affected by the disease, a child must inherit a defective or missing copy of the relevant gene from each parent. "Carriers," who have one bad copy of the gene, generally do not show signs of the disease.

Childhood SMA is usually divided into three types based on the course of the disease. Type I SMA, also called Werdnig-Hoffman disease, becomes evident in the first 6 months of life, with severe and widespread muscle weakness and lack of muscle tone, sometimes described as a "floppy infant syndrome." Affected children usually develop problems breathing, feeding, and swallowing, and never are able to sit or stand. About 85 percent of infants with type I SMA die before the age of 2 years. Type II SMA becomes apparent slightly later in infancy. These children may learn to sit, but never stand or walk. Life expectancy varies. Type III SMA, also called Kugelberg-Welander syndrome, is usually first noticed in childhood or adolescence with problems in walking, running, climbing steps, or rising from a chair, followed by development of arm weakness and wasting. This condition is less severe, and many people with type III SMA live a normal life span. Although these discrete categories are useful, the clinical severity of childhood SMA varies more gradually from extremely severe to very mild.

Childhood recessive SMA is a rare disorder, although it is the most common single gene cause of infant mortality. As with all uncommon disorders, it is difficult to accurately determine how frequently recessive SMA occurs. Although estimates vary considerably, expert reviewers who have examined published evidence suggest that approximately 1 in 20,000 infants die of severe childhood

SMA, which suggests approximately 200 new cases per year in the United States. Less severe recessive SMA is about equally common, for a total of about 1 in 10,000 births for the recessive forms of SMA together. The extensive NINDS efforts focused on SMA reflect the Institute's strong commitment to finding ways to prevent or to cure rare diseases of the nervous system, and the potential of SMA programs to serve as a model for progress against other rare diseases.

Spinobulbar muscular atrophy (SBMA), or Kennedy disease, is the most common X-linked recessive form of SMA. SBMA affects approximately 1 in 40,000 men worldwide. In recessive diseases, one good copy of a gene from either parent is protective. X-linked recessive diseases reflect the involvement of a gene on the X chromosome. So, males, who have one X chromosome from their mother and a Y chromosome from their father, may be affected. Females have two X chromosomes, usually only one of which is defective, so they may be carriers. The symptoms of SBMA include weakness of muscles in the tongue and face, difficulty swallowing, speech impairment, and excessive development of the mammary glands. Problems usually begin after 40 years of age, though they may become apparent in adolescence. There are also less common X-linked forms of SMA that are evident at birth, very severe, and fatal.

Several other less common forms of SMA have been described by clinicians, including adult recessive types and several dominantly inherited forms that affect adults. In dominantly inherited diseases, a single defective gene from either parent can cause the disease.

Current understanding:

Childhood SMA:

In 1995, researchers discovered that loss of the SMN1 gene ("survival motor neuron"), or mutations that inactivate this gene, cause childhood recessive SMA. Although the normal physiological functions of the SMN1 gene are still a matter of active investigation, the gene findings led to improved diagnostic tests, to insights about why the severity of SMA varies so much, to animal models that mimic SMA and facilitate therapy development, and to promising strategies for developing treatments.

One of the most important findings that followed the identification of the SMN1 gene was the discovery that people have a nearly identical gene, called the SMN2 gene. SMN protein made from the SMN2 gene can help compensate for loss of

protein from the SMN1 gene. In fact, the severity of SMA depends strongly on how much active SMN protein a person makes from the SMN2 gene. However, most of the SMN protein made from the SMN2 gene is incomplete and unstable, so the compensation is far from adequate in most children with SMA.

To explain the relationship of SMN1 and SMN2, and the implications for developing treatments for SMA, a brief description of how cells make proteins is necessary. To make a protein, cells "transcribe" the DNA code that makes up a gene into a similar molecule called RNA. Machinery in the cell then uses each three letter "word" of the code in the RNA as a guide to select one of the twenty chemical components, called amino acids, that build up each unique type of protein chain. Within most genes, interspersed among the lengths of DNA that code for amino acids, called "exons," are DNA regions that do not code for protein, called "introns." In transcribing the DNA to RNA, cells cut out the non-coding introns and "splice" together the exons to form the blueprint for the protein itself. The small difference between the SMN2 gene and SMN1 causes one of the exons (exon 7) to be left out most of the time when the SMN2 gene is used to make the SMN protein. So, only a small amount of the protein made from the SMN2 gene is the full length, but most is a shorter version of the protein, missing the amino acids coded by exon 7, and is inactive or unstable. Understanding this scenario is crucial for developing therapies for SMA. One of the major strategies under development for treating SMA focuses on finding drugs, or other interventions, that influence splicing, thus increasing the amount of full length SMN protein made from the SMN2 gene, and thereby ameliorating the disease.

SBMA:

In 1992, NIH supported scientists discovered the gene defect responsible for spinal bulbar muscular atrophy (SBMA), the most common X-linked type of SMA. SBMA results from a type of gene defect called a "triplet repeat expansion" in which a three letter "word" (CAG) of the genetic code is repeated an abnormally high number of times in a row. In SBMA, the affected gene normally codes for a protein, called the androgen receptor, by which cells respond to a type of hormone that controls masculine characteristics. The repeated CAG word specifies the amino acid glutamine, one of the protein building blocks, causing the androgen receptor protein to be made with abnormally long stretches of glutamines.

Since the discovery of the gene defect in SBMA, several other neurological disorders have been found that have the same type of gene defect, but in different genes. Scientists have determined that the "polyglutamines" resulting from the abnormal triplet repeats are toxic to cells. Many laboratories are investigating ways to counteract the harmful effects of the polyglutamines. Recently, researchers have also created animal models of human SBMA, including mice and fruit flies, that are helping them test potential therapies for the disease.

Recent scientific advances in SMA research:
The following illustrate recent scientific advances NIH-supported scientists have made in understanding SMA and moving toward effective treatment:

- Through genetic engineering, researchers have developed strains of mice that mimic essential aspects of human childhood SMA and SBMA. These animal models facilitate studies to understand the underlying disease process and to develop treatments. Scientists have also developed SMA models in simpler organisms. Zebrafish, which are transparent, present advantages for studying development of motor neurons. Fruit flies present opportunities to manipulate genes much more easily than mice, thus expediting studies about underlying mechanisms and potential therapeutic strategies.

- Investigators have determined that a single "letter" difference in the gene SMN2 (from normal SMN1) is responsible for the skipping of exon 7, producing a truncated and rapidly degraded version of the SMN protein, which cells are lacking in SMA. Other researchers have discovered how this small change, through its effect on a regulatory protein, causes this effect. Preventing this skipping, and thereby increasing the level of full length SMN protein from the SMN2 gene, is one strategy for ameliorating SMA.

- NIH intramural scientists have found that the drug valproic acid can increase the amount of full length SMN protein made by cells cultured from people with SMA. Valproic acid is commonly used for epilepsy. Other researchers have also found treatments, such as alcarubicin and sodium vanadate, that appear to increase the amount of SMN protein made by the SMN2 gene and may serve as leads for developing drug therapy.

- A consortium of investigators has, with NINDS support, developed quantitative muscle testing, lung function evaluations, gross motor activity assessment tools, and quality of life measures that can be applied with high reliability to children with SMA. This is important groundwork to prepare for clinical trials when therapeutic strategies reach readiness for testing.

- Scientists have determined the genetic cause of distal spinal muscular atrophy type V, a dominantly inherited form of adult SMA. Mutations in the gene that codes for the enzyme glycl tRNA synthetase are responsible, the first time that this type of enzyme, which plays an important role in protein synthesis, has been implicated in human disease.

- Several laboratories have made progress in understanding the normal functions of the SMN protein, which is lacking in people with childhood recessive SMA, by studying how this protein interacts with other proteins in cells. Studies suggest that SMN protein has important roles in regulating apoptosis, or "cell suicide," and in the splicing machinery that cells use in processing DNA to make RNA for protein production. Other studies have found that SMN interacts directly with p53, a protein that is important in cancer biology, and with the protein coilin, which is important in bringing SMN protein to its proper place in the cell.

SMA Research Programs and NINDS Program Activities

The National Institute of Neurological Disorders and Stroke (NINDS) leads NIH research on SMA. The NINDS supports basic, translational, and clinical studies focused on SMA, as well as extensive research in cross cutting areas such as neurological drug discovery, gene therapy, stem cells, and nervous system development that may have an impact on the disease. The NINDS supports research relevant to SMA through the Institute's broad basic, translational, and clinical research programs, a new contract-based program focused on SMA, and the NINDS intramural research program.

Basic research, supported by NIH and others, identified the genes that cause childhood forms of SMA, SBMA, and other types of SMA, which revolutionized study of these disorders. Continued basic studies are essential to explore the

normal functions of the proteins implicated in SMA, how gene defects lead to disease, and why motor neurons are uniquely susceptible to the disorder. Translational research uses cell culture and animal models of human SMA to develop therapies and gather evidence to support testing in people with the disease. Clinical investigations are studying people with the disease and developing valid and reliable measures that can be used in clinical trials when interventions become ready for testing in human patients.

With the guidance of the National Advisory Neurological Disorders and Stroke (NANDS) Council, the NINDS extramural research programs for SMA and other disorders rely heavily on the collective wisdom of scientists and physicians throughout the U.S. to seek out opportunities for progress against neurological disorders, propose research studies, evaluate which projects are scientifically meritorious, and carry out the research itself. This strategy of investigator-initiated research, which engages the scientific community, is especially appropriate to the NINDS mission because hundreds of disorders affect the nervous system and widely disparate areas of science contribute to progress. When public health needs dictate, special resources or mechanisms are needed, or extraordinary opportunities arise, the Institute catalyzes research through workshops or solicitations for grant or contract proposals. Several of these efforts are directed at SMA.

In March 2000, NINDS released a Request for Applications (RFA) on "Spinal Muscular Atrophy, Amyotrophic Lateral Sclerosis, and Other Motor Neuron Disorders" (RFA-NS-01-004), for funding of grants beginning in FY 2001. To encourage development of drug therapies for motor neuron diseases, in April 2000, the NINDS, working with private SMA and ALS organizations, held a workshop on "Assays for High-Throughput Screening of Drug Candidates for Amyotrophic Lateral Sclerosis and Spinal Muscular Atrophy." The workshop brought together experts on motor neuron diseases and on drug screening from academia, industry and government to review current knowledge about SMA and ALS, which also affects motor neurons, and to discuss potential strategies for developing drugs. Several other workshops and solicitations have potential relevance to SMA. These focus on cross-cutting areas relevant to many neurological disorders, such as gene therapy, stem cells, pediatric neurology, and drug screening for neurological disorders. SMA was also recently added to the diseases designated for inclusion in the NINDS Human Genetics Repository. This contract-based facility promotes sharing among researchers by receiving,

processing, and storing blood samples from investigators, creating cell lines from this material, and providing samples and derived cell lines to the scientific community.

Before the gene defects responsible for SMA were discovered, the underlying causes of the disease were obscure and prospects for developing therapies were dim. In the time since, productive avenues for studying the disease process and developing treatments have improved dramatically. The responsiveness of the NINDS research support strategy to the increasing opportunities for research on SMA is evident in the growth of funding for research on SMA. The NINDS funding for SMA research grew by more than 500 percent from fiscal year (FY) 1998 ($945,000) to FY 2002 ($5.6 million), far greater than the overall budget growth of the Institute. These funding levels are continuing to grow rapidly as the NINDS translational research programs for SMA are implemented. The NINDS total for FY 2003, including the obligated amount for the contract-based SMA translational research program is $12.5 million, representing more than a 10-fold increase in SMA research funding since FY 1998. Although NINDS is the lead for SMA research, other components of NIH support relevant research as well. The overall FY 2002 NIH funding for SMA, the first year that NIH totals for SMA research were compiled, was $6.1 million, and for FY 2003, the NIH total for SMA was $12.9.

Translational research in SMA:
Translational research encompasses the many steps that are needed to move from basic research insights to a therapy that is ready for human testing in clinical trials. The NINDS has a long history of programs in this arena, but basic scientific progress in understanding many diseases, such as SMA, is increasing opportunities for translational research. The NINDS has responded by developing a comprehensive research program, with peer review criteria tailored to the needs of translational research and milestone-driven funding, which is common in industry. The Institute has also undertaken cross-cutting efforts in translational areas such as drug discovery, which are relevant to SMA. The following examples illustrate:

In May 2001, NINDS issued a notice that developed a consortium of 26 investigators to screen a set of 1040 chemical compounds in 29 assays (simple laboratory tests) for neurodegenerative diseases ["NINDS Administrative Supplements: FDA - Approved Compound" (NOT NS-01-009)]. There is

compelling evidence that different neurodegenerative disorders share common underlying mechanisms, so comparing results across multiple assays that reflect specific disorders and common mechanisms is an important aspect of the consortium approach. Most of the chemicals in the set are approved by the U.S. Food and Drug Administration (FDA) for other uses, so there is considerable data on safety for these drugs, and so they might move more quickly toward clinical trials than other chemicals. An assay specific to SMA was among those tested by the consortium. The NINDS and private organizations are supporting the next step in developing the leads emerging from this project. This entails further testing of the most promising drug candidates for SMA therapy in more definitive mouse models of the disease.

In November 2002, NINDS announced (NOT-NS-03-004) that the Institute had awarded a contract for a high throughput drug screening (HTS) service for neurodegeneration investigators, and called for proposals to develop assays. SMA was among the diseases specifically listed in the call for proposals. High throughput screening employs robotics and miniaturized assays (laboratory tests) to rapidly screen libraries of many thousands of chemical compounds. The "hits" serve as research tools and as starting points for developing drugs; drugs developed for one neurodegenerative disease may be useful for others as well. The NINDS drug development efforts in general pay special attention to disorders, such as SMA, that are not sufficiently common to attract drug industry screening efforts. The Institute is also working with other components of NIH, through the Roadmap process, to develop chemical libraries, databases, and other tools to expedite drug discovery in general.

SMA contract-based translational research program:
In addition to the broad NINDS translational research programs that include SMA, the NINDS has selected SMA as the disease of focus for an innovative contract-based approach to expedite translational research. This SMA translational program is not just a novel program for SMA, but differs in important respects from any program NINDS has undertaken. Specifically, this program for therapy development uses a performance-based, milestone driven, contract mechanism that accelerates the cycle time from the point of recognition of a need or opportunity for research, through solicitation and review, to the award and funding of targeted research subprojects, with guidance by an expert steering committee that takes a very active role in driving the process.

Because the program is a model that may apply to other diseases, and because the aim is to develop treatments that will be tested in people, the Institute took considerable care in developing the process. The Request for Proposals (RFP-NIH-NIND-03-03) "Collaborative Program to Accelerate Therapeutics Development for Spinal Muscular Atrophy" was published in the NIH Guide on April 22, 2003. The NINDS awarded the primary contract in September 2003 to Science Applications International Corporation (SAIC).

In this performance based program, the primary contractor provides overall scientific and organizational support. A Steering Committee, whose membership is drawn from academia, the NIH, the FDA, and the biotechnology and pharmaceutical industries, guides the scientific direction. To meet specific goals highlighted by the Steering Committee, the contractor issues highly targeted solicitations for subcontract research projects. Awards will be made rapidly, within four months of proposal submission, and progress will be monitored with structured performance milestones and quarterly meetings to discuss results.

The Steering Committee held an intensive meeting on September 17, 2003, and developed a research plan and priorities for the research projects conducted under the contract. The Committee set immediate goals to develop:

- A 'flow plan', or series of validation steps, that the program's lead optimization teams can use for evaluating therapeutic candidates;
- An inducible mouse model of SMA to determine when increased SMN can be beneficial. In an inducible model, the experimenter can turn on and off the production of the critical SMN protein;
- A motor neuron cell culture model of SMA for identifying and testing drugs. Although cell culture models are available, motor neurons appear to be uniquely susceptible to SMA; and
- A standardized method for measuring SMN levels that can be widely used in laboratory and clinical research.

The research plan and first solicitation for research subcontracts were publicized in December 2003. The NINDS expects that the first of these projects will be funded during March 2004.

Selection of SMA for contract program
The NINDS developed the performance based contract program to determine whether this approach might expedite development of treatments for neurological disorders. The Institute selected SMA as the first disease of focus for the program because of the impact of SMA on children and families, the state of the science for developing therapies, and the expertise and enthusiasm of scientists in the Institute's extramural and intramural programs. In particular, the gene defects responsible for SMA have been identified; the biology of the protein involved is understood well enough to suggest plausible therapeutic approaches; animal models that mimic essential aspects of the disease have been developed to facilitate testing candidate therapies; some promising therapies have been identified in cell culture; and essential groundwork has been laid for measuring outcomes in clinical trials. When the concept for the SMA contract program was presented to the NANDS Council, the Council supported the program and the choice of SMA. Furthermore, the NINDS has a strong commitment to fostering research on rare diseases, which are unlikely to be the focus of industry efforts. If the SMA program is successful, this model might be applied to other diseases.

Intramural research
The NINDS intramural research program on the NIH Bethesda, Maryland, campus is heavily engaged in SMA research, including basic, translational, and clinical studies, and has made important contributions to the study of SBMA, childhood SMA and other forms of SMA. These include, for example, discovery of the gene defects responsible for SBMA and for an dominant form of SMA, and promising laboratory experiments on valproic acid as a potential treatment for childhood SMA. The intramural program also presents unique advantages for expediting early phase clinical studies of potential therapies, when laboratory studies warrant human testing. Intramural researchers played an integral role in developing the contract-based SMA translational research program, and continue their involvement in implementing this effort.

Providing information about SMA

Several voluntary health organizations focus exclusively on SMA, or include SMA within their mandate. These organizations have undertaken extensive and effective efforts to educate the general public about SMA and to promote and support research. The NIH, whenever appropriate, works together with these groups, including joint sponsorship of workshops and research solicitations. The

NIH efforts to provide information about SMA to scientists and the public complement the activities of private groups. The NINDS webpage (http://www.ninds.nih.gov/) provides information for researchers and the public about funding opportunities, and the NINDS SMA Information page (http://www.ninds.nih.gov/health_and_medical/disorders/sma.htm) provides information to the public about SMA, with links to the information provided by voluntary health organizations as well. The DHHS Healthfinder website (http://healthfinder.gov/) also provides such links. The National Library of Medicine, a component of NIH, collects many useful sources of information on its at the heavily used Medlineplus.gov site (http://medlineplus.gov/) including a spinal muscular atrophy information page (http://www.nlm.nih.gov/medlineplus/spinalmuscularatrophy.html). MedlinePlus also links to the NIH Clinicaltrials.gov site which provides information about clinical studies supported by the U.S. government and industry, and to PubMed, which provides free access to the world's largest biomedical bibliographic database, with citations to more than 14 million articles in biomedical journals, many with free summaries and full text links. The NINDS and NIH also provide extensive information for researchers about funding opportunities, through general programs and targeted solicitations, on their websites, at scientific meetings, through informal staff contacts, and via interactions with voluntary health organizations.