

17 March 2003

Dr. Elias Zerhouni
Director
National Institutes of Health
1 Center Drive
Room 126
Bethesda, MD 20892-0148

Dear Dr. Zerhouni,

We are a community of scientists and clinicians who wish to draw your attention to recent advances in research related to Spinal Muscular Atrophy, and the growing promise of treatment or cure. This genetically determined condition is comparatively common but is under-recognized. As a result, federal funding for research on this untreatable and devastating children's disease is disproportionately small.

Fortunately, despite modest federal funding for SMA research, the research community is poised to make further breakthroughs, creating the potential for treatment or cure in the near future (likely within five years). The need for additional federal funding is very apparent, and the timing is excellent. With the additional funding necessary to take the next crucial steps, development of an SMA treatment would be an example of the potential return on the tremendous investments that have been made in molecular genetics research.

Spinal muscular atrophy (SMA) is a common genetic disease that is transmitted as an autosomal recessive trait. Available information indicates that approximately one in every forty Americans is a carrier of this condition. SMA is responsible for the death and chronic disability of thousands of children and adults of all races. Though virtually unknown, the incidence of SMA approaches more publicized genetic disorders such as Cystic Fibrosis, Duchenne Muscular Dystrophy and Sickle Cell Disease. In fact, the prevalence of SMA in children and young adults is very similar to that of adults with ALS. This information, alone, cries out for a greater allocation of research dollars to conquer this dreaded disorder.

But there is an even more compelling reason for additional funding. Discoveries made over the past seven years have transformed SMA from a poorly understood condition to one in which advanced knowledge has put treatment or cure within reach. Unlike many other genetic conditions, treatment appears likely without waiting for more remote breakthroughs in gene therapy or stem cell replacement.

SMA is caused by a mutation in the survival motor neuron (SMN) gene that is located on chromosome 5, and a resulting diminished amount of critical SMN Protein. Remarkably, a second copy of the SMN gene exists (SMN2 Gene), which produces limited quantities of the SMN Protein. Ongoing research studies have provided leads on compounds which may increase the influence of this second copy of SMN. Severity of the disease corresponds

closely to levels of SMN Protein, and therefore, upregulation of this second copy should mitigate the effects of this devastating disease.

Summary of key advances in SMA research over the past seven years include:

- Defect or mutation in the SMN1 Gene on chromosome 5 has been identified as being responsible for Spinal Muscular Atrophy
- Single gene product, SMN Protein, identified as the critical factor
- SMN Protein has been found to play a critical role in RNA splicing in motor neurons, and is therefore critical to motor neuron health and survival
- Levels of SMN Protein shown to correlate with severity of SMA phenotype.
- SMN2 Gene identified, and shown to produce limited quantities of SMN Protein. Single nucleotide differential in SMN2 Gene results in transcription of unstable gene product, resulting in degradation of all but 10% of output
- Mouse models have been developed for SMA
- High throughput screens by various research teams have resulted in leads on possible compounds that may :
 - 'up regulate' production of SMN protein by SMN2 gene
 - improve transcription of SMN protein by SMN2 gene, thus improving 'yield'
- Compounds identified by the various screens include some that are already FDA approved

Given these significant advances, it is our expectation that **1) additional NIH funding of traditional investigator-initiated independent research**, supplemented by **2) additional investment in translational research** and infrastructure to accelerate development of potential treatments, will prove successful in yielding treatment.

Our most educated expectation is that with NIH funding of twenty to thirty million dollars annually, an effective therapy for spinal muscular atrophy can be achieved in the near term of five years or less. With this potential, we urge you to provide the necessary commitment and support to realize this exciting goal and to relieve our society of the burden of SMA.

Sincerely,

AMERICAN SCIENTISTS AND CLINICIANS

Bach, John

Vice Chairman and Professor, Department of Physical Medicine and Rehabilitation
Co-Director of Jerry Lewis Muscular Dystrophy Association Clinic
University of Medicine and Dentistry New Jersey

Bassell, Gary

Associate Professor , Department of Neuroscience
Associate Professor, Department of Anatomy and Structural Biology
Albert Einstein College of Medicine

Baumbach-Reardon, Lisa L.

Associate Research Professor, Department of Pediatrics
University of Miami School of Medicine

Brown Jr., Robert

Professor, Neurology
Harvard Medical School
Director, Neuromuscular Clinic
Massachusetts General Hospital

Burghes, Arthur

Professor, Molecular & Cellular Biochemistry
College Of Medicine and Public Health
Ohio State University

Conrad, Carol

Professor, Pulmonary Medicine
Stanford University

Crawford, Thomas

Associate Professor, Neurology and Pediatrics
Johns Hopkins University
Co-Director, MDA Clinic
Johns Hopkins University

Curiel, David T.

Professor, Medical Division of Human Gene Therapy
The University of Alabama at Birmingham

AMERICAN SCIENTISTS AND CLINICIANS

Darras, Dr. Basil
Associate Professor Neurology, Pediatrics
Harvard Medical School
Director, Neuromuscular Program
Boston Children's Hospital

De Vivo, Darryl C.
Director Emeritus
Pediatric Neurology Division
Columbia-Presbyterian Medical Center
Sidney Carter Professor of Neurology
College of Physicians and Surgeons
Columbia University

Di Mauro, Salvatore
Lucy G. Moses Professor, Neurology
Columbia University

Dreyfuss, Gideon
Isaac Norris Professor, Biochemistry and Biophysics
University of Pennsylvania School of Medicine
Howard Hughes Fellow
Howard Hughes Medical Center

Finkel, Richard S.
Director, Neuromuscular Program Division of Neurology
The Children's Hospital of Philadelphia

Francis, Jonathan W.
Assistant Professor, Neurology
Massachusetts General Hospital
Harvard Medical School

Hahn, Jin
Division Chief, Stanford Division of Pediatric Neurology
Stanford University

Hertel, Klemens
Assistant Professor, Microbiology & Molecular Genetics
University of California Irvine

AMERICAN SCIENTISTS AND CLINICIANS

Iannaccone, Susan T.
Director, Neuromuscular Disease and Neurorehabilitation
Texas Scottish Rite Hospital for Children
Professor, Neurology
University of Texas Southwestern Medical Center

Kerr, Douglas
Assistant Professor, Neurology and MMI
Director, John Hopkins TM Center
Johns Hopkins Hospital

Kissel, John T.
Professor and Vice-Chair, Department of Neurology
The Ohio State University

Krainer, Adrian R.
Professor
Cold Spring Harbor Laboratory and Watson School of Biological Sciences

Lorson, Chris
Assistant Professor, Veterinary Pathobiology
University Of Missouri

Manley, James
JC Levi Professor of Life Sciences, Biological Sciences
Columbia University

Matera, Greg
Associate Professor, Department of Genetics
Case Western Reserve University

Mitsumoto, Hiroshi
Wesley J. Howe Professor of Neurology
Head of the Neuromuscular Division
Columbia University

Mobley, William
Department Chair, Stanford Department of Neurology and Neurological Sciences
Stanford University

AMERICAN SCIENTISTS AND CLINICIANS

Patterson, Marc C.
Professor, Clinical Neurology and Clinical Pediatrics
Columbia University College of Physicians and Surgeons

Alan K. Percy, MD
William Bew White Jr. Professor
Pediatrics, Neurology, and Neurobiology
University of Alabama at Birmingham

Roos, Raymond P.
Marjorie and Robert E. Straus Professor, Neurological Science
Chairman, Department of Neurology Committees on Immunology, Microbiology and
Neurobiology
University of Chicago

Rowland, Lewis P.
Professor, Department of Neurology,
Columbia University

Schroth, Mary K.
Associate Professor, Pediatrics
Pediatric Pulmonary and Cystic Fibrosis Center,
University of Wisconsin Children's Hospital

So, Yuen
Professor of Neuromuscular Disorders, Department of Neurology
Stanford University

Stockwell, Brent R.
Whitehead Fellow
Whitehead Institute for Biomedical Research
Massachusetts Institute of Technology

Swoboda, Kathryn J.
Research Assistant Professor, Neurology
University of Utah School of Medicine
Director, Pediatric Neuromuscular Laboratory and Clinic
University of Utah Medical Center

AMERICAN SCIENTISTS AND CLINICIANS

Terns, Michael P.

Associate Professor, Department of Biochemistry and Molecular Biology
University of Georgia

Volpe, Joseph

Bronson Crothers Professor of Neurology
Harvard Medical School
Neurologist-in-Chief
Boston Children's Hospital

Wang, Ching

Associate Professor, Neurology
Stanford University

Watson, James

Nobel Laureate in Medicine 1962
President
Cold Spring Harbor Laboratory

Zhou, Jianhua

Assistant Professor, Department of Medicine
University of Massachusetts Medical School

Zoghbi, Huda

Professor of Pediatrics, Neuroscience and Molecular and Human Genetics
Investigator, Howard Hughes Medical Institute
Baylor College of Medicine

INTERNATIONAL SCIENTISTS AND CLINICIANS

Davies, Kay E.

Professor of Anatomy, Department of Human Anatomy and Genetics
University of Oxford
Commander of the Order of the British Empire
United Kingdom

Kothary, Rashmi

Associate Director
Ottawa Health Research Institute
Senior Scientist, Molecular Medicine Program
Ottawa, Canada

MacKenzie, Alex

Director, Children's Hospital of Eastern Ontario Research Institute
Professor, Pediatrics
University of Ottawa
Ottawa, Canada

Melki, Judith

Laboratoire de Neurogenetique Moleculaire
INSERM-Universite
France

Morris, Glenn E.

Professor, Biochemistry
North East Wales Institute
U.K.

Munnich, Arnold

Professor, Neurology
INSERM U393 Unité de Recherches sur les Handicaps Génétiques de l'Enfant Hôpital
Necker-Enfants Malades
Member of Academy of Science Institute
France

Simard, Louise R.

Associate Professor
Centre de Recherche de l'Hopital Sainte-Justine
Montreal, Canada

INTERNATIONAL SCIENTISTS AND CLINICIANS

Testi, Roberto

Professor, Immunology Laboratory of Immunology and Signal Transduction Department
of Experimental Medicine and Biochemical Sciences

University of Rome

Rome, Italy

Tizzano, Eduardo F.

Professor, Genetics and Research Institute

Hospital Pau

Barcelona, Spain

Wirth, Brunhilde

Professor

Institute of Human Genetics

Bonn, Germany