A-T CHILDREN'S® PROJECT℠ UPDATE

For Families, Friends and Supporters

SEPTEMBER 2001

Researcher at Harvard Medical School Studies Ways to Develop Successful Bone Marrow Transplantation in A-T Mice

The A-T Children's Project recently announced funding of a project at Harvard Medical School entitled "Induction of Hematopoietic Chimerism for Treatment of Immune System Defects in Ataxia-telangiectasia." John Iacomini, PhD, principal investigator on this project, proposes to conduct studies to examine whether it is possible to overcome the immune and cancer-related problems in A-T mice by using bone marrow transplantation. By using ATM deficient mice, a small animal model of A-T, the team will examine whether it may be possible to repair immune system related defects in A-T patients by replacing the ATM deficient immune system with a normal immune system through bone marrow transplantation, thereby reducing infections and malignancies such as leukemia and lymphoma.

John Iacomini, PhD

T cells are the cells of the immune system that work to provide protection from infections. There are two main steps that need to happen for the T cells to offer this protection. First, the T cells need to develop from precursors in the bone marrow. Second, they must enter the thymus and undergo further maturation in order to become fully functional. Both of these functions will be studied in A-T mice in order to confirm exactly where the problem lies with the immune system in A-T patients.

There are several hurdles in looking at using bone marrow transplantation on A-T patients. In order for transplanted bone marrow to become fully functional, the host's bone marrow must first be removed completely. Traditionally, large doses of radiation and cytotoxic drugs are used to accomplish this. Because A-T patients are extremely sensitive to radiation, these traditional methods of removing all traces of the patient's bone marrow cannot be used. Dr. Iacomini will be developing a non-toxic regimen that will allow for successful bone marrow transplantation, first in A-T mice, and later in A-T patients.

Muscle Tone Being Studied at the A-T Clinical Center

by Allen Mandir, MD, PhD

Among the primary difficulties facing patients with A-T, is the control of movement. The "when, what and where" that goes into generating a movement are easily taken for granted, but poses great hurdles to individuals with A-T. In order to address these motor difficulties, it is essential to understand the underlying mechanisms that give rise to them. There is a great need to characterize the nature of movements that occur in A-T, to understand how they manifest over time and to know the effect of potential new therapies. But how do you describe and measure motor control difficulties in A-T patients? A video picture is certainly worth a thousand words, but even that falls short in fully appreciating the spectrum of movement in A-T. In order to fully characterize motor control in A-T, we are employing the latest technology that allows objective and sensitive measures. By using these techniques, we can implicate those areas of the brain that cause these motor difficulties. This has directed us to focus on brain areas outside the cerebellum (the classical brain area thought to be involved in A-T), and will allow objective and sensitive investigations into new therapies for A-T.

A variety of movements are displayed in A-T. The classically described cerebellar "tremor" or "gait" are among but a few.

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Joey McIntyre plays *Who Wants to be a Millionaire* for A-TCP

Ben Affleck brings A-T awareness to Capitol Hill

(*Story on Page 3)*

Scientific Advisory Board

QUESTIONS OR COMMENTS:

Jennifer Thornton, Executive Director
A-T Children's Project
668 South Military Trail
Deerfield Beach, FL 33442-3023
PHONE: (954) 481-6611
TOLL FREE: 1-800-5-HELP-A-T
FAX: (954) 725-1153
WEB SITE: www.atcp.org
EMAIL: Info@atcp.org

Dr. Yossi Shiloh awarded *David and Inez Myers Chair in Cancer Genetics* at the University of Tel Aviv Sackler School of Medicine

On May 16, 2001 Dr. Yossi Shiloh was awarded the *David and Inez Myers Chair in Cancer Genetics* at the University of Tel Aviv Sackler School of Medicine.

Dr. Shiloh's group recently moved to their new lab at the university, the *Myers Genetic Research Lab*.

From Left: ***Back Row:*** Dganit Shkedy, Yael Ziv, Mali Gana-Weisz, Sharon Rashi-Elkeles, Yuval Landau, Yair Andegeko and Yossi Shiloh. ***Second Row***: Tamar Tenne, Hila Geminder, Atar Lev, Yaron Galanty and Lilach Moyal. ***Front***: Yaniv Lerenthal. *Not pictured*: Tamar Uziel, Relly Forrer, Rani Elkon, Nir Orlev, Galit Horn and Moran Finkel

Research Grants Recently Funded By The A-T Children's Project

Neurologic Pathophysiology of Ataxia-Telangiectasia
A-T Clinical Center, Johns Hopkins Hospital

Development of DNA Diagnostic Test for the Ataxia-Telangiectasia Gene
A-T Clinical Center, Johns Hopkins Hospital

ATR-Activating Therapy for Ataxia-Telangiectasia
Robert Abraham, PhD - Duke University Medical Center

Molecular Mechanisms of Cerebellar Degeneration in A-T
Ari Barzilai, PhD - Tel Aviv University

Mouse Ataxia-Telangiectasia Intervention Study
M. Flint Beal, MD - Cornell University

Experimental Gene Therapy for A-T Using HSV Amplicon Vectors
Xandra O. Breakefield, PhD - Massachusetts General Hospital

Neural Autoantibodies in the Sera of A-T Patients
Robert Darnell, MD, PhD - Rockefeller University

Ocular Manifestations of A-T, A Prospective Study
Arman Farr, MD - The Wilmer Ophthalmological Institute

DNA Damage Signaling in ATM-/- Neurons
Herbert Geller, PhD - Robert Wood Johnson Medical School

Development of Improved Protective Strategies Against Free Radical Damage in A-T
Michael Green, PhD - University of Brighton

Regulation of the Aspergillus DNA Damage Response by Suppressors of ATM Kinase Mutations
Steven Harris, PhD - University of Connecticut

Biochemical Analysis of the A-T Gene Product ATM and its Relative ATR
Stephen Jackson, PhD - Cambridge University

Role of the Extranuclear ATM Protein in Neuronal Function
Martin Lavin, PhD - Queensland Institute of Medical Research

A-T: Activation of Cytoprotective Signaling Pathways
David Lawrence, PhD - Albert Einstein College of Medicine

Telomeres, Telomerase and Lifespan of Brain Cells of Atm-Null Mice
Tej Pandita, PhD - Columbia University

Molecular Basis of Pleiotropic Phenotypes of A-T
Jun Qin, PhD - Baylor College of Medicine

Defects in Cerebellar Purkinje Cell Properties May Underlie Ataxias in A-T
Peter Reinhart, PhD - Duke University

Identification of ATM-Associated Pathways Using Gene Expression Profiles
Yossi Shiloh, PhD - Tel Aviv University

Neural Stem Cell Transplantation in Animal Models of A-T
Evan Snyder, MD, PhD - Harvard Medical School

Production of ATM Gene-Targeted Pigs and/or Cattle by Nuclear Transfer From Cultured Fibroblast Cells
Steven Stice, PhD - University of Georgia

Gene Therapy for A-T by a Novel Herpes Amplicon Vector
Suming Wang, MD, PhD - Central Iowa Health Systems

A Primate Model for Ataxia-Telangiectasia
Don P. Wolf, PhD - Oregon Health Sciences University

The Stars Come Out to Support the A-TCP

On July 11th, actor and Academy Award-winning screenwriter, Ben Affleck testified on Capitol Hill before the Senate Appropriations Subcommittee on Health and Human Services on behalf of the A-T Children's Project. The title of the hearing was "The Promise of the Genomic Revolution."

Affleck participated in a panel that included Dr. Francis Collins, Director of the National Human Genome Research Institute at The National Institutes of Health (NIH).

Affleck with Senators Arlen Specter (PA) and Tom Harkin (IA)

Brad Margus, President of the A-T Children's Project, accompanied Affleck and 13-year-old Joe Kindregan of Springfield, VA, who has A-T.

During a question and answer session, Margus was asked what he felt the federal government could do to help speed up the process of finding a cure for his two sons who have A-T. Margus asked the Committee for translational research, physicians willing and able to do clinical research, new tools and technology, and a more involved NIH.

Affleck urged the committee to support federal funding for stem cell research, for more money to be directed to the "orphan disease" slice of the pie, and to continue supporting the doubling of the NIH budget.

Later that evening, Ben Affleck and Wizard's Basketball Team owner Abe Pollin served as Honorary Co-Chairs at ***A Night Out With The Stars*** in the Capital Club of the MCI Center in Washington, D.C.

Ben Affleck, Joe Kindregan & Brad Margus

This event, co-chaired by Congressman Tony Hall (OH) and his wife Janet; Rita Norton, Sr. Vice President of Amgen; and The Hon. Don Upson, Secretary of Technology of the Commonwealth of Virginia and sponsored in part by the event's Premiere Corporate Partners Amgen, Pharmacia and Herbalife, raised over $200,000.

Continued on page 5

Muscle Tone Continued from page 1

Using miniaturized detectors of movement, much like those that are used in airbag sensors telling them to employ, we can create a digital image of movement. These transducers are so small that three can be placed together at right angles to one another to record movement in 3-dimensional space and to a degree that even a video camera could not document. An example of these types of digital "images" are displayed here. The top graph is a trace of movement from the hand at rest from a control volunteer – at rest the trace is essentially flat, representing the ability to remain perfectly still. A-T volunteers demonstrate quite a different pattern, with spontaneous movements of many different types even though they are trying to stay perfectly still (bottom graph). The "waviness" or "sharpness" of the peaks and valleys actually are quite revealing — certain parts of the nervous system are involved in producing slower types of spontaneous movement, and others produce quick, rapid changes.

(TOP) Trace of hand position over time of a control volunteer at rest. The flat line demonstrates no spontaneous movement while trying to stay still.

(BOTTOM) Example trace of hand position over time of a volunteer with A-T. Despite trying to stay still, there are many spontaneous movements including slower oscillations and some lightning fast movements.

There is yet another motor manifestation of A-T that could never be captured on videotape alone — that of increased "muscle tone." Muscle tone is the measure of baseline muscle tension or stiffness; it is normally quite low but becomes increased in many neurodegenerative diseases such as Parkinson's disease and Huntington's disease. Classically, cerebellar disorders result in "reduced" muscle tone, less muscle tension than in the control population. Using a system that is available only in a few places in the world, we objectively, sensitively and safely measure muscle tone. Muscles work much like springs do – stretching a muscle is like stretching a spring. The more you pull on a spring or muscle, the greater it pulls back. Measuring this intrinsic spring-like property of the muscle reflects resting muscle tone. The graphs in the box to the right demonstrate a plot of the force it takes to move an arm from a control volunteer (left) and an A-T volunteer (right). The oval traces represent muscle tone; the greater the slope of the oval the greater the muscle tone (the stiffer the spring).

The flat oval from the control volunteer (representing a weak spring) differs greatly from A-T volunteer traces. A-T volunteers, like in the graph from the right, mostly demonstrate increased muscle tone. This finding is unexpected as cerebellar disease decreases, not increases, muscle tone. This surprising finding points to areas of the nervous system outside the cerebellum and has led us to discover changes in non cerebellar regions of A-T patients.

These objective, sensitive measures are a great asset in directing research, understanding how AT progresses and allows us to accurately measure improvement with therapeutic intervention.

Muscle tone measured from a control volunteer is represented by a relatively flat trace of force vs arm position (left). Volunteers with A-T often have a notable slope in their trace (right) which represents a significant increase of muscle tone. Great insight comes from these findings as increased resting muscle tone is caused by neurologic involvement of specific non-cerebellar brain structures. (The extra waviness on the A-T volunteer trace reflects abnormal spontaneous movement much like that seen in the hand measures at rest, but is discounted when determining muscle tone.)

Researcher at Columbia U. Studies New Method to Suppress Neural Cell Death in A-T Mice

The A-T Children's Project recently began funding Dr. Tej Pandita at Columbia University for a research study that could lead to a treatment designed to promote the survival of neural cells in A-T patients.

Clinically, the most important feature of ataxia-telangiectasia is the progressive degeneration of Purkinje cells in the cerebellum. Why are these cells affected, and why only some of them? Programmed cell death plays an important role in the natural death of neurons during development in neurodegenerative conditions. Purkinje cell degeneration in individuals with A-T seems to be the result of aberrant programmed cell death.

Recently, Dr. Pandita and his colleagues demonstrated that vulnerability to neuronal cell death and excitotoxicity can be overcome by expressing a gene "TERT" that suppresses apoptosis induced by trophic factor withdrawal. Researchers do not know if neuronal cells of Atm null mice are deficient in telomerase activity. Dr. Pandita is examining TERT expression in neuronal cells of Atm null mice and comparing it to that of control mice. He will also determine whether expression of the TERT gene in neural cells of Atm null mice suppresses apoptosis induced by trophic factor withdrawal. If expression of the TERT gene suppresses such apoptosis, it is possible that TERT gene expression may serve a cell survival-promoting function of neural cells (specifically of Purkinje cell type) in individuals with A-T.

A-T Children Are Counting on You

U. W. - Osh Kosh Students Organize First A-T Telethon

The energy of 80 young adults, a giving community, local families and a lot of talent … all of these ingredients went into making the first A-T Telethon at U. of Wisconsin, Osh Kosh a tremendous success, raising over $10,000 toward A-T research.

The original idea for a telethon was first hatched by Osk Kosh senior Brad Carr, a Radio/TV/Film major and President of the school's National Broadcasting Society. After he learned about the A-T Children's Project from a friend who had attended Freedom's Walk for a Miracle, Carr decided to produce the telethon as the group's senior project. The team of students put together six hours of live footage, including interviews with local families and phone interviews with families from across the country.

Thank you to all of the students who worked so tireless in this project, which not only raised funds, but generated a tremendous amount of awareness in the area.

The students are planning a second live telethon on November 10, 2001 to benefit the A-TCP and the American Parkinson's Disease Foundation. For more information contact the NBS at 920-424-7037 or send an email to nbs@rtf.uwosh.edu.

The Stars Continued from Page 3

Mary Bono (CA) & Ben Affleck

Some members of Congress including, Mary Bono, (CA), Jeff Flake, (AZ), Sen. John Ensign, (NV), Melissa Hart, (PA), Steve Largent, (OK), Gary Miller, (CA), Bill Nelson, (FL), Tom Osborne, (NE), Mike Oxley, (OH), Jim Ramstad, (MN), Zach Wamp, (TN), Heather Wilson, (NM), Frank Wolf, (VA), Shelley Moore Capito, (WV) and Mike Doyle, (PA) participated in a push-up competition captained by Congressman Hall and Congresswoman Jo Ann Emerson (MO), or shot baskets on the basketball court with WNBA's Muriel Page of the Washington *Mystics* to raise money for the A-T Children's Project. The women's push-up competition, captained by Affleck, raised over $16,000 in two minutes!

Guests were also fortunate to hear from John Walsh, the host of the television show *America's Most Wanted*. Steve Buckhantz, the play-by-play announcer of the Washington Wizards emceed the evening. Suzi Kindregan and Carol Lewin, mothers of children with A-T in Virginia, led the event committee in D.C.

A Very Special Evening

The sixth annual "A Very Special Evening" was held at the Clark Studio Theatre at Lincoln Center. The standing-room-only event was organized by long-time friend of the A-TCP Eric Weinberger and hosted by actor Louis Zorich and Priscilla Lopez. This year the audience enjoyed superb performances by singer Connie Pachl; triple Tony Award winner Boyd Gaines; opera diva Madame Vera Galupe-Borszkh (Ira Siff) accompanied by Steven Blier; ballet dancers Melissa Downey, Dale Brannon and Matthew Rushing, leading dancer of the Alvin Ailey Dance Company.

Fourteen-year-old Tori Bement-Schram, who has A-T, and A-TCP friend Isabelle Russo introduced the evening winning over every single member of the audience. Actor Ben Affleck made a special appearance to draw the winning raffle ticket at the event.

Actor Boyd Gaines, star of "Contact" with Jimmy Lewin (7).

Eric Weinberger with Isabelle Russo and Tori Bement-Schram.

Tori Bement-Schram (14) receives a kiss from actor Ben Affleck.

Actor Ben Affleck and Joe Kindregan (13).

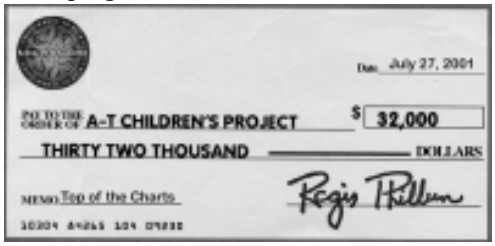
Eric Weinberger and A-TCP friend, Carolyn Seinfeld Liebling.

Photos Courtesy of Ginger Propper

Joey McIntyre plays *Who Wants to be a Millionaire* for A-TCP

Joey McIntyre, formerly of *New Kids on the Block*, became interested in helping the A-TCP after meeting several A-T families at the Shjon Podein Golf Tournament earlier this year.

McIntyre appeared on ABC's *Who Wants to be a Millionaire* on July 27, 2001 as a part of the show's "Top of the Charts" series. A-TCP president and co-founder Brad Margus spoke about A-T as Joey's on-air buddy. As a result of Joey's efforts, the A-TCP received $32,000 for research, and millions of viewers of this top-rated program learned about A-T.



Carrier Status and Cancer Risk Study Funded by the National Cancer Institute (NCI) Opens at USC

Director of Genetic Epidemiology Robert Haile, DrPH, and Project Managers Lauren Gerstmann, MPH and Laura DeJong at the Keck School of Medicine at the University of Southern California, are conducting a study funded by the National Cancer Institute to determine if carriers of the A-T gene have an increased risk for developing cancer, particularly breast cancer.

Dr. Richard Gatti at UCLA is collaborating with the USC Genetic Epidemiology research group to carry out this study, which will be the largest of its kind. Participants include families from Canada, Costa Rica, Germany, Israel, Italy, Poland, and Turkey, as well as from all over the United States. The benefit of participating in this international study is to better understand the cancer risk in A-T families in order to develop guidelines for counseling and clinical management of A-T families.

Parents of A-T patients participating in the study will be asked about their history of cancer, and any history of cancer in the grandparents, aunts, and uncles of A-T patients. Participants will also be asked to provide a blood sample. To protect the privacy of participants, results from blood tests will **not** be distributed to participants, physicians, or insurance companies. Participants interested in learning their carrier status will be referred for counseling and possible testing outside the research study at the participants' own expense.

Those interested in this study should call collect Laura DeJong at 323-865-0496 or Lauren Gerstmann at 323-865-0488 or email ldejong@hsc.usc.edu.

2001 Grassroots Events

JANUARY

22 **New York City, New York -** *A Very Special Evening*
27 **Greeneville, Tennessee -** *Twins Birthday Party*

FEBRUARY

9 **Villa Park, Illinois** - *Let's Crop Out A-T Scrapbook Party*
10 **Boston, Massachusetts** *Valentine's Day Dance*
11 **Chicago, Illinois -** *Y.E.S. Youth Ministries A-T Hearts of Hope*
16 **Villa Park, Illinois** - *Let's Crop Out A-T Scrapbook Party*
23 **Rensselaer, New York** - *Dunkin Donuts A-T Awareness Day*
27 **Cedar Grove, New Jersey** - *Men's Nite*

MARCH

10 **Fremont, California** - *Garage Sale*
24 **York, Pennsylvania** - *A-T Walk for a Cure*

APRIL

1 **Pittsburgh, Pennsylvania** - *A-T Walk for a Cure*
1 - 7 **New York, Oswego** *SUNY Students A-T Hearts of Hope*
7 - 8 **Balch Springs, Texas** - *A-T Spring Fling*
21 **Seagoville, Texas** - *A-T Walk for a Cure*
22 **Loretto, Pennsylvania** - *Flood City Rollers vs. A-Team Tip Off Challenge*
28 **Redding, California** - *A-T FundFest*
28 **Louisville, Kentucky** - *Kentucky Country Day School Karaoke*

MAY

5 **New Braunfels, Texas** - *Hope Floats in Texas*
12 **Hastings, Pennsylvania** - *Closest to the Pin*
17 **Patton, Pennsylvania** - *Cambria High School's A-T Walk for a Cure*
19 **Carleton, Michigan** - *A-T Walk for a Cure*
19 **Las Vegas, Nevada** - *Garage Sale*
20 **Wayland, Massachusetts** - *A-T Walk for a Cure*
22 **Greensboro, North Carolina** - *Hats Off to the Stars*

JUNE

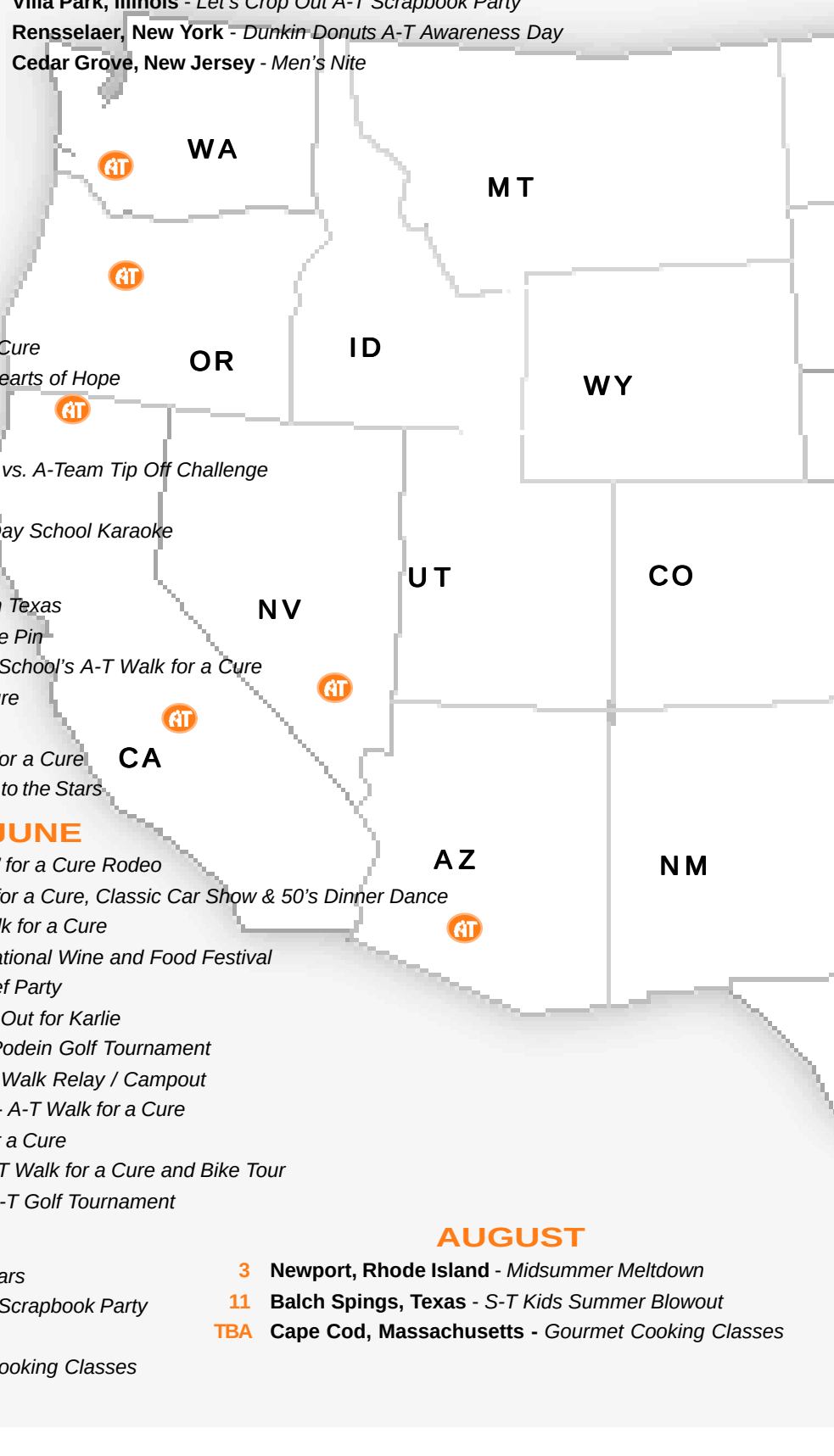
1 - 2 **Greeneville, Tennessee** - *Ropin' for a Cure Rodeo*
2 **Romulus, Michigan** - *A-T Walk for a Cure, Classic Car Show & 50's Dinner Dance*
9 **Rensselaer, New York** - *A-T Walk for a Cure*
9 **Newport, Rhode Island** - *International Wine and Food Festival*
13 **Roscoe, Illinois** - *Pampered Chef Party*
16 **Waterford, Michigan** - *Stepping Out for Karlie*
17 - 18 **Rochester, Minnesota** - *Shjon Podein Golf Tournament*
19 **Wayland, Massachusetts** - *A-T Walk Relay / Campout*
23 **Fort Macleod, Alberta, Canada** - *A-T Walk for a Cure*
23 **John Day, Oregon -** *A-T Walk for a Cure*
24 **St. Benedict, Pennsylvania** - *A-T Walk for a Cure and Bike Tour*
TBA **Houston, Texas** - *Swinging for A-T Golf Tournament*

JULY

11 **Washington, DC** - *A Night Out with the Stars*
13 **Naperville, Illinois** - *Let's Crop Out A-T - Scrapbook Party*
21-22 **Oshawa, Ontario -** *Garage Sale*
23 **Cape Cod, Massachusetts -** *Gourmet Cooking Classes*

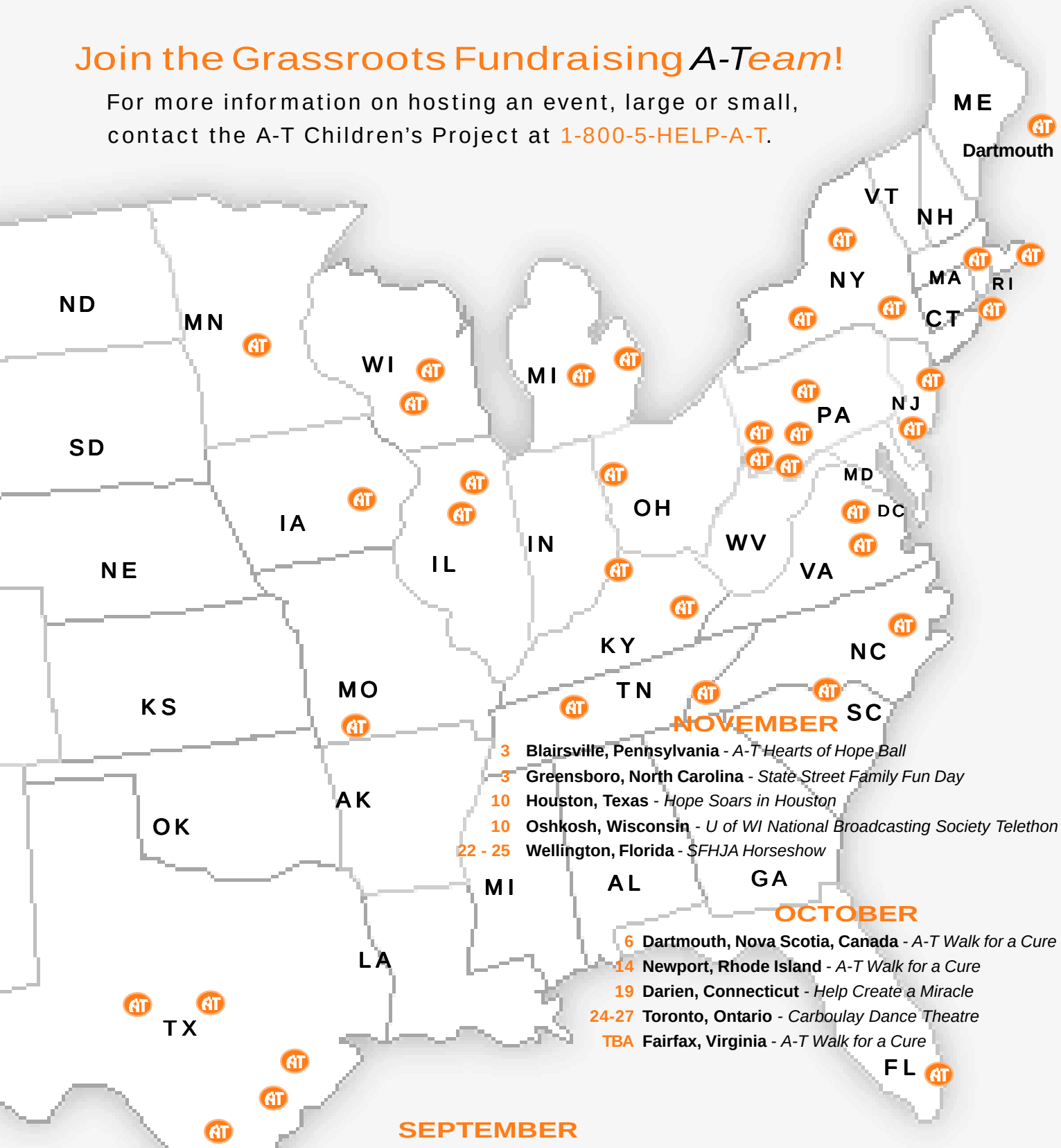
AUGUST

3 **Newport, Rhode Island** - *Midsummer Meltdown*
11 **Balch Spings, Texas** - *S-T Kids Summer Blowout*
TBA **Cape Cod, Massachusetts -** *Gourmet Cooking Classes*



Join the Grassroots Fundraising *A-Team*!

For more information on hosting an event, large or small, contact the A-T Children's Project at 1-800-5-HELP-A-T.



NOVEMBER

- 3 **Blairsville, Pennsylvania** - *A-T Hearts of Hope Ball*
- 3 **Greensboro, North Carolina** - *State Street Family Fun Day*
- 10 **Houston, Texas** - *Hope Soars in Houston*
- 10 **Oshkosh, Wisconsin** - *U of WI National Broadcasting Society Telethon*
- 22 - 25 **Wellington, Florida** - *SFHJA Horseshow*

OCTOBER

- 6 **Dartmouth, Nova Scotia, Canada** - *A-T Walk for a Cure*
- 14 **Newport, Rhode Island** - *A-T Walk for a Cure*
- 19 **Darien, Connecticut** - *Help Create a Miracle*
- 24-27 **Toronto, Ontario** - *Carboulay Dance Theatre*
- TBA **Fairfax, Virginia** - *A-T Walk for a Cure*

SEPTEMBER

- 8 **Dubuque, Iowa** - *A-T Walk for a Cure*
- 8 **Ozark, Missouri** - *A-T Walk for a Cure*
- 9 **Flat Rock, Michigan** - *Flat Rock Festival Days*
- 15 **Freedom, Wisconsin** - *Walk for a Miracle*
- 16 **Hamilton, Ohio** - *Danny's Walk for a Cure*
- 22 **John Day, Oregon** - *A-T Walk for a Cure*
- 24 **Greensboro, North Carolina** - *Golfing for Kids*
- 29 **Rochester, New York** - *A-T Walk for a Cure*
- 29 **Troy, Michigan** - *A-T Walk for a Cure*
- 29 **Nashville, Tennessee** - *Stroll in the Park*
- TBA **Cape Cod, Massachusetts** - *Gourmet Cooking Classes*
- TBA **Seattle, Washington** - *A-T Walk for a Cure*
- 30 **Friedens, Pennsylvania** - *Jonathan & Amanda's Walk for a Cure*

Causes of A-T Neurodegeneration

Herber M. Geller, PhD
UMDNJ-Robert Wood Johnson Medical School

Progress report on the A-TCP grant awarded in January 2000 to Herbert M. Geller, PhD.

Our goal is to understand the basis of neurodegeneration in A-T using the ATM knockout mouse as our test system. It has been reported that neurons from ATM knockout mice are resistant to irradiation. The first question we have addressed is whether this resistance is due to intrinsic properties of the ATM knockout neurons or whether the environment of the neurons is responsible.

To address this question, we are making cell cultures of cerebellar granule neurons from ATM knockout mice and wild-type mice and comparing their responses to DNA damaging agents. If the resistance to irradiation is due to intrinsic properties of the neurons, then we should find it in culture. If not, then cultured neurons should not be resistant.

We have built up a colony of heterozygote ATM mice capable of producing enough animals to address the question. We also put into place routine genotyping techniques to determine if mice are either ATM knockout, heterozygote or wild-type. Surprisingly, the frequency of knockout animals in our colony is less than that which would be predicted from strictly genetic factors, which suggests that there is some effect of ATM on survival. We have found that the survival of cultures of ATM knockout cerebellar granule neurons is unaffected by irradiation, while the survival of wild-type neurons is reduced. Thus, we conclude that ATM neurons have an intrinsic defect in their response to irradiation.

We have also tested the response of these neurons to two other DNA damaging agents, camptothecin and UV irradiation, and have found that there is no difference between wild-type neurons and ATM knockout neurons. This reaffirms the role of ATM in signaling apoptosis in response to damage from irradiation, but not other forms of DNA damage. We are now examining downstream events to determine whether this defect in signaling is specific for the apoptotic pathway, or extends to the DNA repair pathway as well.

A-T Clinical Center Study: Do patients with A-T exhibit abnormalities in free radical handling?

Howard Lederman, MD, PhD

A clinical study spearheaded by Howard Lederman, MD, PhD, is currently being conducted to help clinicians determine if antioxidant therapies are useful for patients with A-T.

A-T is a rare degenerative disorder caused by a mutation affecting the ATM protein. It affects many different systems in the body, particularly the brain and the immune system. Many aspects of A-T are explained by the known role of ATM in DNA repair and cell cycle regulation. Some researchers believe that cells from A-T patients are also sensitive to an internal chemical change called oxidative stress, which is thought to cause damage to tissues, including neurons. While A-T mice have shown signs of oxidative stress, oxidative stress has not been detected in A-T patients as yet.

Several researchers have hypothesized that loss of the A-T protein impairs the cell's ability to detoxify free radicals, resulting in ongoing oxidative stress. In order to test this theory, the A-T Clinical Center at Johns Hopkins Hospital has started a study designed to determine whether A-T patients exhibit oxidative stress by using acetylsalicylic acid (aspirin) as an indicator protein. Salicylic acid, oxidation to 2,3-dihydroxybenzoic acid (2,3-DHBA) has been used by a number of investigators as a general index of free radical "load" in both animal and human studies.

All A-T patients enrolled into this study will have previously been seen at the A-T Clinical Center. Age-matched controls will be recruited from among the families of clinic staff, and friends and families of A-T patients. Subjects will be given a single oral dose of acetylsalicylic acid. Two hours later, blood will be collected and shipped to Dr. Laura Dugan at Washington University School of Medicine, for analysis. The amount of salicylic acid that is oxidized to 2,3-DHBA per ml of serum will be determined and used as a measure of free radical production that could not be eliminated by the A-T patients' natural antioxidant defenses.

Results of this study will guide clinicians in their quest for therapies for A-T patients.

Hi Y'all,

My name is Clayton Donihue and I have A-T. My mommy and daddy hosted the first PRCA Sanctioned Championship *Ropin' for a Cure Rodeo* on June 1 - 2 at the Flying T Arena in Greeneville, Tennessee, to benefit the A-TCP. Rodeos are my most favorite thing.

In fact, I'm having a hard time deciding what kind of cowboy I want to be when I grow up!

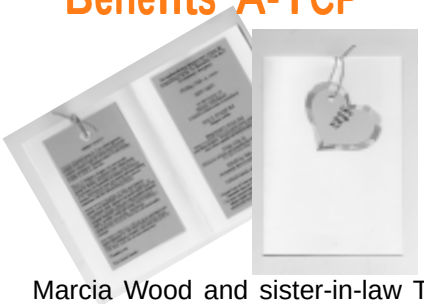
Researchers all over the world are working very hard for me and all kids with A-T. We hope that they find a cure for us soon.

The Role of DNA Damage Response Defects in Neurogenetic Diseases
Tarrytown House, Tarrytown, New York • July 29 - August 1, 2001

Researchers from around the world gathered to discuss the common mechanisms of DNA damage response defects among several diseases including A-T, Fanconi Anemia, Bloom Syndrome, and Xeroderma Pigmentosa. The National Institute of Neurological Disorders and Stroke and the A-T Children's Project co-sponsored this important workshop providing scientists an opportunity to share knowledge and set future directions for research.

From Left: ***Front Row:*** Junjie Chen, Michael Greenberg, Xandra Breakefield, Karl Herrup, Arlene Auerbach, Tej Pandita, Kathy Brumbaugh, Peter Reinhardt, Kathleen Dixon, David Lawrence, Ted Weinert, Allen Mandir, PJ Brooks, Ray Monnat, Giovanna Spinella, Pat Concannon, Rodney Levine, Carrolee Barlow ***Back Row:*** Brad Margus, Penny Jeggo, Alan Lehmann, Jerold Chun, Peter McKinnon, Jun Qin, Herbert Geller, Larry Thompson, Gene Johnson, David Park, Mike Kastan, Ellie Gallo-Hendrix, David Frohnmayer, Marisa Cortes, Nathan Ellis, Steven Harris, Martin Lavin, Tom Crawford, Yossi Shiloh, Nat Heintz. Not pictured: Alan D'Andrea, Al Fornace, Dick Gatti, James German

Let's Crop Out A-T Scrapbooking Party Benefits A-TCP



Marcia Wood and sister-in-law Teri Wood organized a scrapbooking party in Illinois this winter to benefit the A-T Children's Project. "Let's Crop Out A-T" raised over $1,200 for A-T research.

The creative invitations were handcrafted in a wonderful design featuring a brief description of A-T. Creative Memories Consultant Karen Whitezel graciously donated her time, products for a raffle, and her sale profits.

Alyssa Wood

Marcia is the mother of seven children including three-year-old Alyssa who has A-T.

Help Us Fund More Research

Participating in fundraising events is fun and it gives everyone a sense of community. But what about those who don't live anywhere near that fun event? How can they help us raise precious dollars for research?

Payroll Deductions

Many employers have payroll deduction campaigns where employees can designate the A-TCP as their charity of choice. Some of the nationwide organizations that collect these donations are United Way, Combined Federal Campaign (CFC), Health & Medical Research Charities of America and Independent Charities of America.

Tributes and Memorials

Send memorial donations in lieu of flowers and tribute donations in lieu of gifts commemorating birthdays, weddings, anniversaries or special holidays.

Used Vehicle Donations

Donate your old "clunker" -- that old car or truck that you wouldn't dare put on the market because let's face it... "Who would want to buy it?" We will issue a tax receipt for the blue book value of your car. In just minutes, you can make arrangements to have the vehicle picked up free of charge anywhere in the United States.

Adopt an Event

Collect donations among your friends and co-workers to have a "satellite" event. Call our fundraising department for ideas.

Shop, Shop, Shop

We are excited to introduce a brand new way you can support the *A-T Children's Project* at no extra cost to you or us. Buy your favorite products at our new online shopping village at *www.atcp.org* and a small portion of your purchase will be donated back to the A-TCP.

Visit our Web site at www.atcp.org, and click on **Shopping.**

Shop online at Annie's Flowers and Scents, a candle and gift shop in Milford, New Hampshire. Store Owner Anne O'Brien will donate 10% of their October through December 2001 profits to A-TCP. Go to: www.anniesflowersandscents.com/

New Catalytic Antioxidants to Prevent Neurodegeneration

Progress report on the grant awarded in September 1999 to the laboratory of Michael Green, PhD funded by the A-TCP.

In collaboration with Drs. Peter Cragg and Richard Faragher, we have been developing and testing a new class of antioxidant molecules, which are low molecular weight and can reach the brain, (like the antioxidant vitamins C or E) but which are more efficient because they can act as catalysts to remove potential harmful reactive oxygen species. The hope is that this type of molecule may delay neurodegeneration.

There is steadily increasing evidence that the loss of Purkinje cells and neurodegeneration in A-T arise from a failure to repair one particular type of DNA damage, which is caused by nitric oxide or reactive oxygen species. Nitric oxide and reactive oxygen species are formed all the time within our cells, and together with oxygen can interact to form a series of even more damaging reactive molecules. The bad news is: 1) We don't know which of these reactive molecules are important within Purkinje cells (though we can make guesses). 2) We don't know the best way to supplement defences against the key reactive molecules, to prevent them from causing harm. 3) And finally, we don't know if a protective strategy will have harmful side effects. In our project, we have mainly tried to address these last two problems: looking for agents that will be effective against specific reactive molecules, and exploring any potential harmful effects.

Our bodies have two main defensive strategies against reactive species. A number of small molecules like vitamins C and E occur in our diet and can act as scavengers. They react with a molecule of a dangerous reactive species to form a stable compound which will not cause further harm. The disadvantage is that one scavenger molecule will only protect against one harmful molecule. A big advantage is that some of these molecules are easily taken up in our diet and can reach all parts of our body, including the brain. A "good" diet, rich in fruit and vegetables, probably protects mainly in this way. The second line of defence is via enzymes which neutralize specific reactive oxygen species. Best known are the superoxide dismutases which remove superoxide, and catalase and glutathione peroxidase, which remove hydrogen peroxide. The advantage of this type of protection is that one enzyme molecule will inactivate many molecules of the reactive species. The disadvantages for therapy are that if enzymes are administered they are unlikely to reach the site where they are needed, and they may induce adverse immunological reactions. Up to now, we have been dependent on the levels of these enzymes that are already present with the cell.

Several classes of small molecule have now been identified, which can be taken up and transported round the body like vitamins, but which act as catalysts, like superoxide dismutase or catalase. We have been investigating a particular class of compounds (salen-transition metal complexes) which may have either superoxide dismutase, or catalase activity, or both. The advantage of this class of compound is that the molecules are straightforward to make, and a whole series of compounds, with subtly different protective properties can be synthesized. With a group of compounds like this, therefore, it is possible to start to understand the relationship between their function and structure. Although these particular compounds are well-known to chemists, and have been around for nearly 70 years, a number of them have been patented for therapeutic use by Eukarion Inc., most notably the salen-MnIII compound (EUK8) and the methoxysalen-MnIII compound EUK134. We have now synthesized over 100 compounds, including a number of completely novel structures. Most have some degree of biological activity, and we are making progress in trying to link the type of antioxidant activity with the structure. It is pleasing that Peter Cragg's computer modelling of the interaction between the molecule and the reactive species is tying in well with our experimental data.

Although these compounds act as catalytic antioxidants, almost any molecule that can successfully inactivate a reactive oxygen species will also have the dangerous ability to convert oxygen itself into a reactive species. (This is equally true of a natural product such as quercitin, which is found in strawberries). The compounds that we are studying do not cause damage when we use them to treat cells, and they successfully protect cells against reactive oxygen species. However, if we incubate free DNA with some of the compounds, they cause DNA damage, instead of preventing it. We find that we can greatly reduce this pro-oxidant activity by adding glutathione (or alpha-lipoic acid, which is available as a dietary supplement and which acts like glutathione). We think this may offer a clue to why the compounds do not damage cells.

Most recently, we have been using a new instrument called the quartz crystal resonant sensor (formerly known as the quartz crystal microbalance). We attach DNA strands to a quartz crystal in a small chamber (there are a few more steps to all of this). The crystal normally resonates at a specific frequency, but will do so more slowly because the DNA is attached. When we add one of these compounds (salen-MnIII, EUK8) to the supernatant, the crystal resonates even more slowly, because the compound binds to the DNA. The compound then acts as a pro-oxidant, forming reactive oxygen species which attack and cut the strands of DNA. DNA is released from the crystal, allowing it to resonate more rapidly. When we add alpha-lipoic acid together with the compound, we do not now see binding to the DNA, or strand breakage. Interestingly methoxysalen-MnIII (EUK134) seems to bind only very weakly to DNA, and does not cause strand breakage in this system.

Incidentally, a starting material for making some of these compounds can be vanilla, but sadly the connection is a little too remote for Ben and Jerry's to be a promising line of therapy.

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Coping With A-T at School

Cynthia Wisniewski and her son, eight-year-old Keaton, have compiled a booklet to help Keaton's teachers explain his unique needs to his classmates and other children. This easy-to-read booklet offers a glimpse into Keaton's day, including his need for adaptive equipment such as his wheelchair, a special wooden chair and very unique computer programs. *My Story, by Keaton Sakowich & his Mom* is a great tool for parents and teachers of children with A-T.

To receive a printed copy of this booklet, please contact Rosa Fernández at the A-T Children's Project at 800-543-5728 or send an email to MyStory@atcp.org. A printable color copy is available in Adobe Acrobat PDF format at www.atcp.org.

NASCAR Fans: Great chance to Win a Jeff Gordon/Pepsi BGN Car

The Hastings Area Industrial Development Association in Hastings, Pennsylvania is raffling a 2000 Jeff Gordon Monte Carlo Race Car to benefit the A-T Children's Project. Mary Jane Bearer, volunteer fundraiser for the A-TCP, donated the car for the raffle. Tickets are only $20 each.

The drawing will take place on November 3, 2001 at the Hearts of Hope Ball in Blairsville, Pennsylvania. The holder of the winning ticket does not need to be present to win.

To purchase raffle tickets contact Mary Jane Bearer at mjbearer@forspeed.com or call toll free 866-707-8580.

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Gift Gallery

Hearts-of-Hope Band

Engraved sterling silver "A-T Hearts of Hope" band
Sizes 5, 6, 7, 8, 9 ..... $15.00 ea.
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A-TCP Polo

Our pre-shrunk 100% cotton polos come in white with the A-TCP logo in red and black or in red with the A-TCP logo in black. ..... $30.00 ea.

Red Polo Sizes: Sm, Med, Large, XL, XXL and XXXL
White Polo Sizes: Med, Large, XL and XXL
Price includes shipping and handling.

Cookbook

Our exclusive cookbook ***Passport to Culinary Cuisine "This Ain't No Airplane Food"*** was put together by the employees of World Travel BTI at the request of Sue Mastin, aunt of Amy Estes of Tennessee, who has A-T. The 80 - page book is full of easy recipes and cooking tips. This is a great bargain that will make a wonderful holiday gift.
..... $15.00 ea.
Price includes shipping and handling.

To order, indicate quantities and sizes of the items and send a check or money order payable to:
A-T Children's Project, 668 South Military Trail, Deerfield Beach, FL 33442

Or, order by phone with your Visa, Mastercard, American Express or Discover card by calling 954-481-6611 or toll-free 800-5-HELP-A-T (800-543-5728).

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