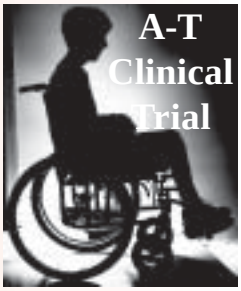
A-T CHILDREN'S® PROJECT UPDATE

For Families, Friends and Supporters

AUGUST 2004

Clinical Trial Opens at Hopkins



Funded by the A-T Children's Project, Howard Lederman, MD, PhD, Director of the A-T Clinical Center at Johns Hopkins Hospital in Baltimore, Maryland, will study how a combination of two dietary supplements, an antioxidant and a PARP-1 inhibitor, can slow the neurodegeneration and aid the pulmonary problems seen in patients with A-T.

For several years, a growing body of evidence has accumulated which suggests that oxidative stress may contribute to the pathology of ataxia-telangiectasia (A-T). Oxidative stress, which can ultimately lead

Continued on page 9

WHO WILL PARTICIPATE IN THE TRIAL?
20 confirmed A-T patients who meet the following criteria:

- Age 12 and older (during the initial phase to ensure safety with plans to include younger patients in the near future)
- Able to travel to Baltimore, Maryland monthly
- Able to swallow medicine capsules
- No nutritional supplements other than standard daily multivitamin taken within the previous 30 days
- No need for insulin or oral hypoglycemic agent
- No previous adverse reaction to alpha lipoic acid or nicotinamide
- Preference will be given to subjects who previously have been evaluated at the Johns Hopkins A-T Clinical Center

HOW LONG IS THE STUDY? 8 ½ months

WHAT DRUGS WILL BE STUDIED? An antioxidant (alpha lipoic acid) and a PARP-1 inhibitor (nicotinamide)

WHEN WILL IT START? This clinical trial will start immediately.

WHERE WILL IT BE HELD? A-T Clinical Center at Johns Hopkins Hospital in Baltimore, Maryland

WHY IS THIS CLINICAL TRIAL BEING HELD? To determine the safety and preliminary effectiveness of a combination of drugs to slow the brain cell death that occurs in patients with A-T

WHO IS FUNDING THIS STUDY? This study is being funded by the A-T Children's Project. Additional funding is currently being sought from the NIH-funded General Clinical Research Center at Johns Hopkins.

WHEN WILL THE STUDY INCLUDE MORE PATIENTS AND YOUNGER PATIENTS?
If a beneficial effect is found at the end of the study, a second trial will be planned to include a larger number of patients of a wider age range. Patients would be recruited nationally and travel reimbursement would be included in the budget.

WHOM CAN I CONTACT WITH QUESTIONS?

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Karen Rosquist, RN, Coordinator, A-T Clinical Center
Tel. 800-610-5691 E-mail: krosquis@jhmi.edu

Special Note: The safety and efficacy of these drugs for patients with A-T are unknown. While these drugs are readily available, the doses used for the clinical trial will not be made public, and these drugs are not recommended at this time for use by patients with A-T outside of this clinical trial.

Why just run when you can fly, you can fly, you can fly.

Introducing the 2005 WALT DISNEY WORLD® Marathon Weekend, January 7-9, 2005.

See related stories on pages 6-7.

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

NEW **Oxidative Stress in Patients with Ataxia-Telangiectasia**
A-T Clinical Center, Johns Hopkins Hospital

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

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

Overlapping Functions of ATM and ATX in Genome and RNA Surveillance
Robert Abraham, PhD - The Burnham Institute

NEW **Role of Atm Protein in the DNA Damage Response of Cerebellar Neuronal Cells**
Ari Barzilai, PhD - Tel Aviv University

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

Linking ATM and Breast Cancer
Kevin D. Brown, PhD - LSU Health Sciences Center

A Drosophila Model for A-T
Shelagh Diane Campbell, PhD
University of Alberta

New Mechanisms to Activate p53 Function in A-T Cells
France Carrier, PhD - University of Maryland

NEW **Gene Therapy for Ataxia-Telangiectasia**
Maria L. Cortés, PhD - Massachusetts General Hospital

Creation of a Transgenic Porcine Model of Ataxia-Telangiectasia
Christopher M. Counter, PhD - Duke University

Induction of Hematopoietic Chimerism for Treatment of Immune System Defects in Ataxia-Telangiectasia
John Iacomini, PhD - Massachusetts General Hospital

The Zebrafish as a Novel Vertebrate Model System of Ataxia-Telangiectasia
Shuji Kishi, MD, PhD - Dana-Farber Cancer Institute, Harvard Medical School

Pilot Study: Evaluating the Relative Radiation Sensitivity of ATM Functional & ATM Inactive Human Cell Lines After Treatment With Small-molecule Modulators
Keith Laderoute, PhD and Annalisa D'Andrea, PhD - SRI International

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

NEW **Generation of a Rat Model for Ataxia-Telangiectasia**
Martin Lavin, PhD - Queensland Institute of Medical Research and Michael M. Weil, PhD - Colorado State University

NEW **Mechanisms of Neurodegeneration in Ataxia-Telangiectasia**
Allen Mandir, MD, PhD - Johns Hopkins University

NEW **The Function of ATM in Neuronal Differentiation: Identification of Targets for High Throughput Screening**
Brendan D. Price, PhD - Dana-Farber Cancer Institute

ATM Modulation of CREB Phosphorylation in the Developing Thymus, Testes, and Cerebellum
Wenan Qiang, PhD - Northwestern University

Molecular Basis of Pleiotropic Phenotypes of Ataxia-Telangiectasia
Jun Qin, PhD - Baylor College of Medicine

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

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

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

Identification of Novel ATM-Rad17 Associated Proteins That Function as Regulators or Downstream Targets
Xiao-Fan Wang, PhD - Duke University Medical Center

Strain Background Effects on Atm Nullizygosity
Michael Weil, PhD - Colorado State University

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

Glucocorticoid Mimics Functional ATM Kinases to Prevent Thymic Lymphoma Development in Atm-/- Mice
Mingshan Yan, MD - University of Texas M.D. Anderson Cancer Center

Cell Cycle Events in Ataxia-Telangiectasia: Human and Mouse
Yan Yang, PhD and Karl Herrup, PhD - Case Western Reserve University

The Role of ATM in the Mitochondrial Pathway of Apoptosis
Leman Yel, MD - University of California, Irvine

Developing PARP Inhibitors that Can Penetrate the Blood Brain Barrier by Oral Dosing
Jie Zhang, PhD - Guilford Pharmaceuticals

For more information about A-TCP research grants, contact:
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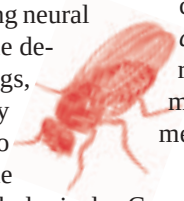
Defects Similar to Those Seen in A-T Patients Found in Fruit Flies with a Mutant A-T Gene

With a grant from the A-T Children's Project, a researcher has identified fruit flies with a mutated copy of the A-T gene. Just like humans with ataxia-telangiectasia (A-T), fruit flies with a mutation in the A-T gene (called *atm*) demonstrate ataxia or loss of motor control, genetic instability and radiation sensitivity, making this small insect a promising model for the identification of drugs that could prove beneficial for patients with A-T.

A-TCP funded investigator Shelagh Campbell of the Department of Biological Sciences at the University of Alberta in Edmonton, Canada has identified several different mutations in the *Drosophila* (fruit fly) *atm* gene. In the fruit fly, *atm* seems to be particularly important for developing neural tissues as mutant flies have variable defects in their bristles, eyes, and wings, all of which are involved in sensory perception. The *atm* mutants also have defects affecting their antennae and legs. In addition to these morphological defects, Dr. Campbell and her team found that the *atm* fly mutants demonstrated locomotor (ataxic) abnormalities. When tested for their ability to climb, both male and female *atm* mutants possessed a significantly reduced climbing ability as compared to their normal counterparts. And states Dr. Campbell, "We also noticed that [these] mutants (of both sexes) often fall down and twitch, behavior that was not seen in the control [flies]." Because this locomotor defect does not increase in severity as the flies age, Campbell and her team do not think it is a result of progressive neurodegeneration, as is the case in patients with A-T. Rather it may represent "just one aspect of a spectrum of developmental defects…affecting the nervous system [of these flies]," states Campbell. This difference, in terms of developmental versus degenerative locomotor defects, between *atm* mutant flies and A-T patients may reflect the requirement for ATM in humans during the time of brain development that occurs after birth.



Shelagh Campbell, PhD

Using their various *atm* mutants, Dr. Campbell and her lab were able to demonstrate that the *Drosophila* A-T protein (also termed ATM) is required for normal fly development, and loss of this protein can result in extensive cell death. In addition, *Drosophila atm* mutants are extremely sensitive to ionizing radiation, a phenomenon seen in cells derived from patients with A-T. Within each cell, DNA or genetic material is packaged into specialized structures called chromosomes. When Dr. Campbell's lab examined cells of the nervous system in mutant flies, they found extensive chromosomal abnormalities including chromosome instability and the fusion of chromosomal ends. All of these results are consistent with the known function of ATM in mammals, that is, regulation of the repair process in response to damaged DNA.

Dr. Campbell's work with the *atm* gene in flies will be published in the scientific journal *Current Biology* along with other research from a separate group of investigators dealing with the ATM protein in *Drosophila*. Dr. Campbell's groundbreaking research should pave the way for the use of this small model organism to screen for drugs that can help slow down or prevent disease progression in A-T patients. Additionally, Dr. Campbell's flies could be used to identify other genes that affect the severity of A-T, which would ultimately help to explain the variability in disease progression seen between different individuals with A-T.

Research Fund Named in Honor of Broadway's Priscilla Lopez

A research grant was awarded in the name of Priscilla Lopez, Tony Award winner and star of Broadway's Pulitzer Prize winning play *Anna in the Tropics*, in honor of her years of commitment and dedication to the A-T Children's Project.

The announcement of the Priscilla Lopez Research Fund was made by Brad Margus, co-founder and volunteer president of the Board of Directors of the A-T Children's Project, at The Clark Studio Theatre at the Lincoln Center during *A Very Special Evening*, an annual benefit for the A-T Children's Project.

Photo courtesy of Ginger Propper

Priscilla Lopez

Ms. Lopez, who performed at the benefit in 1995, hosted the event as she has done for the past four years. The research fund will be used for an important collaboration among international A-T researchers who are working on providing critical biological tools to the entire A-T research community (see related story page 5).

The evening spotlighted performances by *On the Town*'s Jesse Tyler Ferguson, composers Marcy Heisler and Zina Goldrich, Grammy-winning violinist Andy Stein, the Urban Ballet Theater's Amar Ramasar, and a dance piece by Lynne Taylor-Corbett. Olympia Dukakis, Louis Zorich, and Eric H. Weinberger co-chaired the event. Mr. Weinberger has volunteered his services as producer of *A Very Special Evening* for the past nine years. He wrote the one-woman show *Class Mothers '68* which starred Ms. Lopez and for which she received a Drama Desk Nomination.

Tel Aviv University Investigator Examines the Role of ATM in the Cerebellum

Research is currently underway that will hopefully contribute to treatments for the most debilitating aspect of A-T – progressive ataxia. All persons with ataxia-telangiectasia (A-T) suffer from a progressive cerebellar degeneration which results in the loss of motor control, or ataxia. Although they may initially only demonstrate a wobbly gait, children with A-T are usually wheelchair-bound by the age of ten. Unfortunately, the precise cause of this cerebellar atrophy remains unknown. However, an investigator at Tel Aviv University in Israel is planning to explore the role of ATM (the A-T protein) in the cerebellum. His research will provide us with a better understanding of how ATM functions in this part of the brain and why degeneration of the cerebellum occurs in its absence.

Ari Barzilai, PhD

To investigate the role of the A-T protein in the cerebellum, Ari Barzilai, PhD has received funding from the A-T Children's Project for his research grant entitled "Role of Atm Protein in the DNA Damage Response in Cerebellar Neuronal Cells."

The cerebellum, or area of the brain that controls learned movements, houses at least seven different types of neurons (brain cells). Mature neurons are non-dividing cells which represent some of the longest lived cells in our bodies. Diseases which affect the brain, like A-T, cause the premature death of various neurons. Two types of cerebellar neurons, the Purkinje and granule cells, appear to be particularly affected by loss or deficiency of the ATM protein, as patients with A-T possess a decreased number of Purkinje cells and an abnormally thin granule cell layer. Since ATM plays a critical role in coordinating the various cellular responses to damaged DNA, Dr. Barzilai's lab will analyze the DNA damage response of Purkinje and granule neurons using both cells in culture as well as cerebellar tissue slices from mice. Explains Dr. Barzilai, "Studying the Atm-mediated DNA damage response in cerebellar neuronal cells is expected to provide a major clue to the mechanisms responsible for cerebellar degeneration in A-T. This is a major question in the A-T field. Such knowledge may point to novel strategies for intervention in the cerebellar attrition in A-T and therapeutic approaches to the neurodegenerative aspects of this disease."

Canadian with A-T Celebrates 40th Birthday!

Dear Friends,

THANKS for the birthday cards! I am writing you this letter because a lot of you asked how I am doing.

For my birthday, I received a DVD player. I became a "real" man after the 4th remote control! In case my collection of VHS movies wasn't big enough (about 400 movies) I will now start my collection of DVD's, but they're still rather pricey. I also have a good CD music collection too. I've started a little video rental business. $1.00 per movie. Many staff and residents appreciate this service because they can't get out and purchase them on their own.

The weather here in Winnipeg has been cold! Snowing on and off for the past couple of months. Luckily I stay inside for the most part, but venture out anyway, when my companion comes. We try and go somewhere different every week. Right now I am carefully using a modified electric wheelchair to get around. I don't have the accuracy to drive a car!

I live on the young adult floor at Tache Centre, which consists of people around my age with different physical disabilities, but active minds, and healthy souls. I have a reputation for doing crazy things with my hair... The other residents on my floor never know what I'm going to do next. On Halloween I had a checkerboard shaved on my head. On Crazy hair day, I had an arrow shaved on my head. I think my personality is outgoing.

I am involved in the orientation of new staff at Tache Centre. I enjoy talking to the new staff from a resident's point of view. I educate them about the rights of the residents. For example, treating our rooms like it's our house and respecting the contents.

In closing, I would like to say to keep on going, keep your spirits up, and you've got it made! Laughter is the best medicine. I try to laugh at least 4 times a day, and sometimes even more!

Yours Truly,

Ray Kloosterman

P.S. I made it!!!

Editor's note:

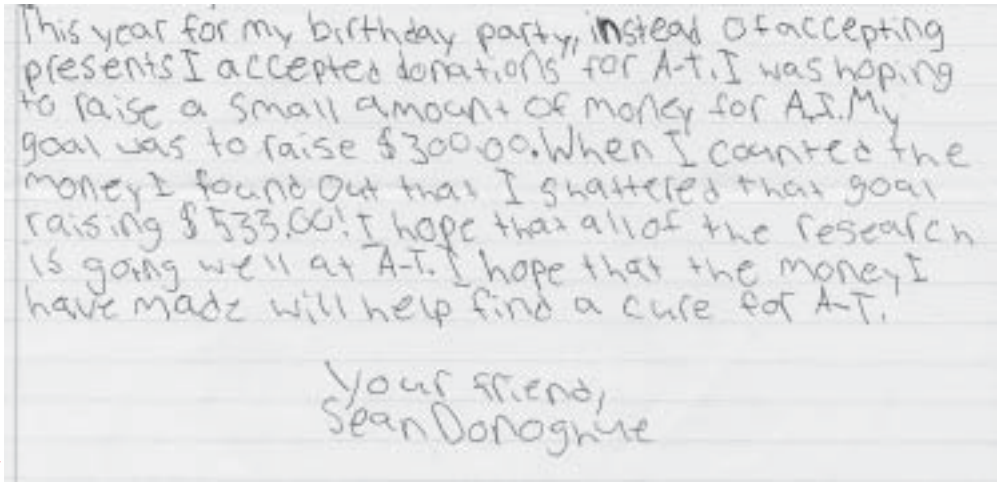
While Ray's life is an inspiration to us, he is one of the few patients with A-T to reach such a milestone. Ray's success gives us hope, but the cruel reality is that this brutal disease is not that forgiving in most cases. We pay our respects to the families and friends of the seven patients that we know of between the ages of 6 and 26 who lost their battle with A-T this year.

Sean's Birthday Wish: Donations in Lieu of Gifts

When Sean Donoghue of Darien, CT sent out invitations for his 11th birthday party, he wrote:

"**Please do not bring any presents!** Two of my friends have a terrible disease called ataxia-telangiectasia or A-T. They cannot walk, they are in wheelchairs, they have a hard time eating, and they can't talk very well....I have plenty of wonderful gifts like arms and legs that work and being able to talk well. I really don't need any presents so please consider helping me help kids with A-T. We can do something good for kids with A-T and have a great party while we are at it. I hope you can come!"

After the party, Sean sent the A-TCP this note with the money raised. ►


This year for my birthday party, instead of accepting presents I accepted donations for A-T. I was hoping to raise a small amount of money for A.T. My goal was to raise $300.00. When I counted the money I found out that I shattered that goal raising $533.00! I hope that all of the research is going well at A-T. I hope that the money I have made will help find a cure for A-T.

Your friend,
Sean Donoghue

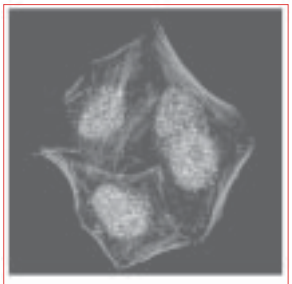
New Panel of Antibodies to be Generated against the ATM Protein

Important tools used in the search to unravel the mysteries of the A-T protein are hopefully going to gain some new, more effective additions. These tools, called antibodies, are integral to the basic science research that will one day contribute to a treatment for A-T. Currently, in the field of A-T research, there is a shortage of antibodies that can be reliably used for certain important experimental procedures, and as laboratory tests and technologies become more sophisticated, the need for such antibodies becomes more critical. Therefore, the A-T Children's Project has awarded funding for a joint research grant entitled "Generation of a Panel of Monoclonal Antibodies Against Human and Mouse ATM Proteins" submitted by Yossi Shiloh, PhD and Nechama Smorodinsky, PhD of Tel Aviv University and Susan Lees-Miller, PhD of the University of Calgary.

Antibodies are specialized proteins that literally target and bind to other proteins. In the world of science, they represent one of the most critically important reagents used to study proteins, including their structure, function and localization. Although many antibodies have been generated against ATM, the protein product of the A-T gene, the field of A-T research is still in need of effective and reliable antibodies which can be used for immunofluorescence (IF) – a technique used to visualize the ATM protein inside cells - and immunohistochemistry (IH) – a technique used to visualize ATM in preserved tissue. In addition, notes Dr. Shiloh, "Gene transfer and gene silencing methods as well as improved imaging techniques provide us with new powerful means to study protein function. However, lack of the very basic reagents – anti-ATM antibodies that can be used in conjunction with these techniques to visualize the ATM protein using immunofluorescence – is a major bottleneck in the application of these technologies to ATM research."

From Left: *Nechama Smorodinsky, PhD, Yossi Shiloh, PhD and Susan Lees-Miller, PhD*

Since progressive ataxia, due to cerebellar degeneration and atrophy, is arguably the most devastating aspect of A-T suffered by all individuals with this disease, it is vital that we gain an understanding of how ATM functions within the brain. Consequently, one of the most important issues in A-T research – which awaits the development of reliable ATM antibodies for IF and IH - is the localization and function of the ATM protein in different brain cells (neurons) under various physiological conditions. For example, we know that ATM plays a vital role in coordinating a cell's response to DNA damage, and in most cell types, ATM is located in the nucleus (which houses the cellular DNA). Interestingly, in certain neurons like the Purkinje cells of the cerebellum, the ATM protein has been shown to be located outside the nucleus, bringing into question the exact function of ATM in these cells. However, the existence of the ATM protein within the nucleus of these cells and other neurons has yet to be ruled out and will require further experimentation using techniques such as IF. Understanding the function of ATM in the brain is critical to gaining an understanding of why neurodegeneration occurs in its absence. Hopefully, this knowledge will one day contribute to a treatment for A-T.



Nuclear ATM staining

A-T Children's Project participants in the 2004 WALT DISNEY WORLD® Marathon Weekend raised:

$790,904.14

The A-Team

Special Issue

Families band together at WALT DISNEY WORLD ® Marathon 2004

Marathoners and their families carbo-load at the Pasta Party and celebrate at the Victory Party. ▼

▲ *Father and daughter team Karin and Raymond Palmieri. Karin organized $1,000 worth of cookware to be donated by Staub for the A-Team 2nd place winner.*

Marathoners Chris Runci and Cathy Martin ran for Cathy's son, Andrew (4), who was recently diagnosed with A-T. ▲

Clockwise from left: Lance Buffinga, Rick Otte, A-TCP grand prize winner Kevin Diekevers, Drew Otto ▶

A-TCP BOARD MEMBERS PUT ON THEIR RUNNING SHOES

Beth Hughes | *Conrad Van Hierden* | *Brad Margus* | *Mike Donoghue and wife Cece* | *John Feeley* | *Greg Jehlik Chicago Marathon*

◀

Not shown: *Charlie Erwin's wife Dabney who completed the half marathon and Amy Madison, who held the Madison 5 Marathon Relay in Texas.*

n Gazette

Marathon A-Team

BE A MARATHONER

Join today at www.atcp.org

Volume 1, Number 1

Join the A-T Children's Project for the WALT DISNEY WORLD® Marathon Weekend January 7-9, 2005 in Lake Buena Vista, Florida. Register online at www.atcp.org or call: 800-5-HELP-A-T.

Marathon "Fever" Spreads!

NEEDHAM, MA
"MAY"RATHON

Newman Elementary School sent the A-T Children's Project a check for over $19,000 in honor of Daniel Julien. "This is incredible for us... It just goes to show what people will do when raising money for someone near and dear to their hearts!" said event organizer Julie Minarski.

Steve Pecevich and wife Kathy

Enduring grueling heat, Steve Pecevich persevered by looking at his hands where he had written "Tate" to think of Taylor Richmond, his friend who has A-T.

Party emcee LB, with Steve and friends at "The Place."

CATCH THE FEVER IN 2005! RUN TO CURE A-T

Congressman Pete Hoekstra

Front row: *Connor Donoghue, Katie Ratay, Liam Donoghue, Mara Donoghue, Maggie Maeve Donoghue (in front of Mara), Sean Donoghue, Robbie Smarz, Mac Donoghue, Cece Donoghue, Lori Smarz.* ***Back row:*** *Gretel Turner, Matt Karon, Mike Scappaticci, Merritt Donoghue, Mike Jordan, Jason Baer, Mike Donoghue, Dave Smarz.* ***Not pictured:*** *Cathy Miller*

FAIRFIELD, CT

Mike and Cece Donoghue and Jason Baer, owner of Personal Training Professionals (PTP) spearheaded fundraising efforts for the A-TCP at the 24th annual Fairfield Half Marathon, where over $18,000 was raised through personal solicitations and sales of water bottles!

The LaSalle Bank Chicago Marathon®

The A-TCP is now an associated charity of the LaSalle Bank Chicago Marathon® 2004.
Date: October 10
Registration deadline: Sept. 1

Register online at www.atcp.org or call 800-5-HELP-A-T

A-T Clinical Center at a Glance

The Ataxia Telangiectasia Clinical Center

The A-T Clinical Center at Johns Hopkins Hospital and the Kennedy Krieger Institute in Baltimore, Maryland was established and funded by the A-T Children's Project with several goals in mind.

- Provide patients with A-T and their families with superior care and comprehensive medical evaluation
- Provide an ideal venue for staff physicians and scientists to advance much needed research on different facets of the disease.
- Serve as a centralized clearinghouse of information on the clinical and genetic aspects of ataxia-telangiectasia, as well as existing diagnostic tools and successful management strategies for doctors, caregivers and researchers around the world. As such, it is able to provide valuable consultative and support services to physicians everywhere treating patients with A-T.

The A-T Clinical Center is staffed by specialists in:

- Neurology
- Immunology
- Swallowing
- Pediatric Rehabilitation
- Speech and Language Pathology
- Occupational Therapy
- Physical Therapy

Launching Clinical Trials

The A-T Clinical Center began accepting new patients in 1995. As of 2004, the A-T Clinical Center has had more than 325 patient visits representing over 190 patients with A-T. The broad range of information gathered during visits to the center enables clinicians to provide a comprehensive clinical profile of ataxia-telangiectasia. Since the center effectively functions as a registry of patients with documented A-T, it is an ideal point from which to launch clinical trials of any potentially beneficial new therapies as they are developed.

The Johns Hopkins Tradition of Excellence

Home to the A-T Clinical Center, The Johns Hopkins Hospital has cultivated a reputation for unequalled excellence in biomedical research, clinical expertise and patient care for more than century. It has been ranked number one by *U.S. News & World Report*'s Honor Roll of American Hospitals – for 14 years. The institution's historic tradition to excellence was not the only factor on which the decision to house the clinic at Hopkins was based. Guided by a selection committee comprised of parents of patients with A-T, physicians and nurses, the directors of the A-T Children's Project chose the hospital because of the team of highly competent, compassionate specialists from relevant disciplines who could be brought together with the common goal of finding a treatment or cure for this brutal disease.

Research Progress

Since being established in 1995, the A-T Clinical Center has made significant progress in defining the clinical symptoms of A-T. The physicians there have:

- identified dysfunctional swallowing with aspiration as a critical cause of pulmonary disease,
- developed tools for assessing the long-term neurological deterioration of A-T,
- described a relatively common problem of dysgammaglobulinemia that may have important implications for understanding the immunologic perturbations of A-T,
- defined growth abnormalities in children with A-T with the aim of developing a hypothesis for their cause,
- looked at the relationship between vitamin A levels and lymphopenia in children with A-T — a study undertaken because vitamin A deficiency is a common factor linking growth failure and lymphopenia,
- identified a new hazard to older individuals with A-T: the development of progressive central nervous system vascular abnormalities, and
- collected and analyzed data on the difficulties with cognitive performance that A-T patients face as they age.

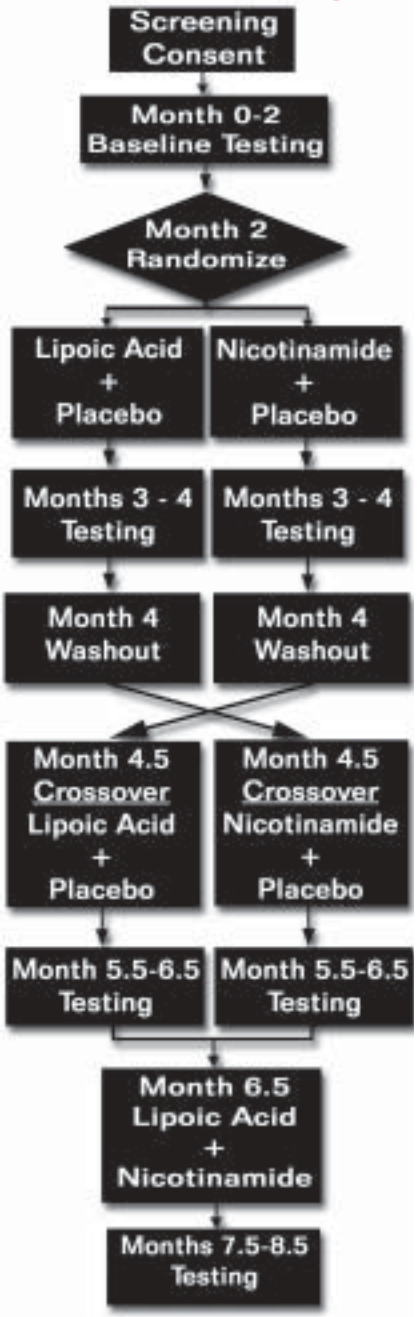
Did you know that…

- As of mid-2004, the clinic has performed over **325 comprehensive evaluations**, representing more than **190 patients with A-T**, and **countless consults** via telephone and email with families and physicians around the world.
- **Over 100 videofluoroscopic swallow studies** have been performed to help identify and prevent aspiration leading to pulmonary complications. In combination with **nutritional analysis**, these studies have helped to **recommend feeding tubes** when necessary.
- Neurological studies point **to areas of the brain outside of the cerebellum** being affected by A-T, paving the way for **possible treatment with drugs** that help other disorders.
- Early evidence indicates that the **rate of neurodegeneration slows** in the teenage years.

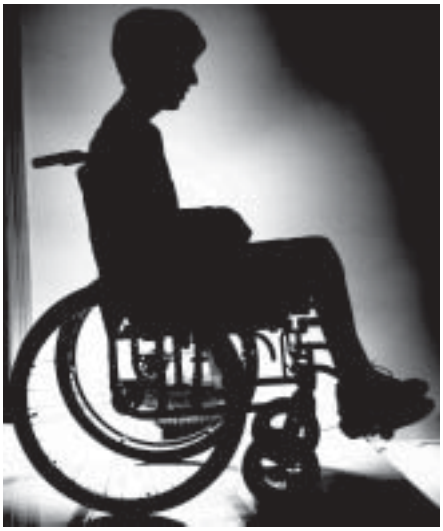
Continued from page 1

A-T Clinical Trial

Trial Design



to cell death, occurs when cells cannot properly detoxify reactive oxygen species (ROS). ROS are highly reactive chemicals which move about the interior of cells causing damage to cellular DNA (genetic material), lipids and protein. Regardless of whether oxidative stress is a primary or secondary result of ATM protein deficiency, research has shown that abnormalities exist in the oxidative state of various A-T model systems.



In addition, a recent study has also shown that in cultured A-T cells, there is an increase in the activity of the poly (ADP-ribose) polymerase (PARP-1) enzyme. Like ATM, this enzyme plays an important role in the cellular response to damaged DNA. In A-T cells, the increase in PARP-1 activity was accompanied by an observed decrease in important cellular energy stores. Treatment of the ATM deficient cells with various PARP-1 inhibitors enhanced the growth rates of these cells in culture.

As a result of the research described above, the A-T Clinical Center is preparing a trial protocol to test the efficacy of an antioxidant/PARP-1 inhibitor combination in A-T patients. To date, only anecdotal evidence exists suggesting that antioxidants have any type of positive effect in children with A-T, i.e. this evidence has come from parents who have been giving their children with A-T antioxidants such as vitamin C, E and alpha lipoic acid. The advantage of the trial at Johns Hopkins is that the combination, dosage and efficacy of the antioxidant/PARP-1 inhibitor combination will be evaluated in a clinically objective and quantitative manner. Although the ultimate goal of this trial is to determine if this treatment can slow disease progression in A-T patients, the clinical trial will also test the possibility that these compounds will have an immediate, positive effect.

A-T Clinical Trial

The clinical study will begin with a Phase I trial designed to assess the safety and toxicity of nicotinamide (a PARP inhibitor) and alpha lipoic acid (an antioxidant). During the trial, it will be important to determine if the combination of drugs used is having a biological effect in the patients that eventually might produce an overall positive result in terms of disease progression. Therefore, quantitative laboratory endpoints will be evaluated to determine the drug's biochemical efficacy. These biochemical endpoints will include specialized blood and urine tests to detect oxidative damage to cellular lipids and DNA. Tests will be performed to monitor changes in neurologic and pulmonary function, and to look for any toxicity of the combination of drugs.

The initial Phase I trial will last 8 1/2 months. Since the main objective is to determine safety and toxicity, a relatively small number of patients (20) will be enrolled, and the focus will be on teenagers and adults. If positive results are seen at the end of this trial, the study will be expanded to include more patients and a younger patient population. If, however, there are no changes in the biochemical endpoints or toxicity becomes an issue during the trial, then drug and/or dosage modifications will be made.

It is hoped that this initial trial produces positive results, leading to a much larger study investigating the treatment of A-T.

- There has been some **success treating tremors and eye movement disorders** associated with A-T with medication.
- The function of the **immune system remains the same** in A-T patients – it does not get better or worse with age.

How to Contact the A-T Clinical Center

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Antioxidant Treatment Improves Motor Performance in Mice with A-T

Recently, a new type of synthetic antioxidant compound was found to significantly improve the motor performance of mice with ataxia-telangiectasia (A-T). In the future, it is hoped that this antioxidant, or a compound like it, will be tested in a clinical trial to determine if it can slow disease progression in patients with A-T.

In humans with A-T, progressive ataxia is due primarily to degeneration of the cerebellum. The cerebellum is part of the hind brain, which also includes the spinal cord and brain stem. This wrinkled mass of tissue is responsible for motor programming and motor learning, preparation of the body for movement, coordination of ongoing movements, and the fine tuning of movements. Although mice with A-T do not show the overt ataxia seen in A-T patients, they do possess certain neurologic abnormalities as compared to their normal littermates, including a poorer performance on the accelerating rotarod. As its name suggests the accelerating rotarod is a spinning rod capable of increasing in speed. Mice are placed on this apparatus to determine how long they can stay on the moving rod. The rotarod test is typically used to assess motor impairments due to cerebellar dysfunction or the degeneration of motor neurons.

Accelerating Rotarod

Since oxidative stress may very well play a role in A-T *(please see the article A-T Clinical Trial Starts at Johns Hopkins on page 1)*, a group of A-T Children's Project funded researchers decided to investigate whether or not a special, synthetic antioxidant could improve the neurobehavioral abnormality in A-T mice as assessed by rotarod performance. The antioxidant used in this study, called EUK-189, does not simply scavenge free radicals or reactive oxygen species (the causative agents of oxidative stress in cells) but rather it is capable of mimicking certain enzymes in the body that can actually modify and thus detoxify free radicals. One member of the study team, Rod Levine, MD, PhD, notes that "EUK-189 is known to cross the blood-brain barrier and has been shown to be neuroprotective in animal models characterized by oxidative damage."

A-T mice were treated with EUK-189 at the Weill Medical College of Cornell University, in the laboratories of Susan Browne, PhD and M. Flint Beal, MD, PhD. In a paper recently published in the scientific journal *Free Radical Biology & Medicine*, the investigators were able to show that A-T mice given EUK-189 performed just like their normal littermates on the accelerating rotarod instead of more poorly, as was the case with A-T mice given a solution lacking the antioxidant.

As it is not yet able to be given orally, EUK-189 was administered to the mice via injection using a pump mechanism. This antioxidant will also have to undergo more preclinical development before it is able to be used in a human Phase 1 safety/toxicity trial. However, the A-T Children's Project is working hard to accelerate the research necessary to bring this antioxidant, or an orally available version of it, to clinical trials in humans with A-T as soon as possible.

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Tee Off for Tiffany

Sharon and Todd Myers of Katy, TX held their first golf tournament in April 2004, raising over $26,800 for A-T research. Tiffany, one of the Myers' twin daughters has A-T.

Seen here with Amanda (left) and Tiffany, Brittany Preston was a great supporter of the golf tournament, raising funds through various sororities at Texas A&M University.

Gift Gallery

A. A-T Hearts of Hope® Sterling Silver Necklace

A longtime friend of the A-TCP, Ann Partlow of Ferrari Partlow Jewelry™, designed the A-T Hearts of Hope necklace to symbolize the hope of A-T research.

Message from Ann Partlow:

A-T Hearts of Hope hearts, like children with A-T, are different. The hearts have a strong side and a vulnerable side. If you follow the curlicues of the heart from one side to the other, you'll find the symbol of unending hope in the vitality of the heart. From the bottom of the heart springs "hope eternal" that our fundraising efforts will produce a cure or improve the quality of life for children with A-T ..... **$75 ea.***

A.

B. A-T Hearts of Hope® Ring

Engraved sterling silver "A-T Hearts of Hope" ring ..... **$15 ea.***
Sizes 5, 6, 7, 8, 9

B.

C. Cookbook

Our exclusive cookbook ***Passport to Culinary Cuisine "This Ain't No Airplane Food"*** was put together by the employees of World Travel BTI and Sue Mastin, aunt of Amy Estes of Tennessee, who has A-T.
..... **$15 ea.***

C.

A-TCP Logo-Wear

D. White Polo

Pre-shrunk 100% cotton white polo, embroidered with red and black logo
Sizes: Med, Large, XL and XXL ..... **$30 ea.***

D.

E. Red Polo

Pre-shrunk 100% cotton red polo, embroidered with black logo
Sizes: Sm, Med, Large, XL, XXL and XXXL ..... **$30 ea.***

F. Sweatshirt

Lee® Heavyweight - 9.5-Ounce Sweatshirt 50/50 cotton poly Pill Free® fleece, fully coverseamed, Lycra reinforced ribbed collar, cuffs and waistband, set-in sleeves embroidered with A-TCP logo. Available only in Ash Heather ..... **$30 ea.***
Adult Sizes: Sm, Med, Large, XL and XXL

E.

G. Lapel Pin

Full color enamel lapel pin with A-TCP logo measures 1" x 3/8" and is perfect for any occasion **$6 ea.***

***Prices include shipping and handling.**

F.

Three easy ways to order. Please indicate quantities and sizes.

1. Send check or money order payable to:
   A-T Children's Project, 668 South Military Trail, Deerfield Beach, FL 33442
2. Order online at www.atcp.org
3. Call: 954-481-6611 or toll-free 800-5-HELP-A-T (800-543-5728).

We accept Visa, Mastercard, American Express and Discover Card

G.

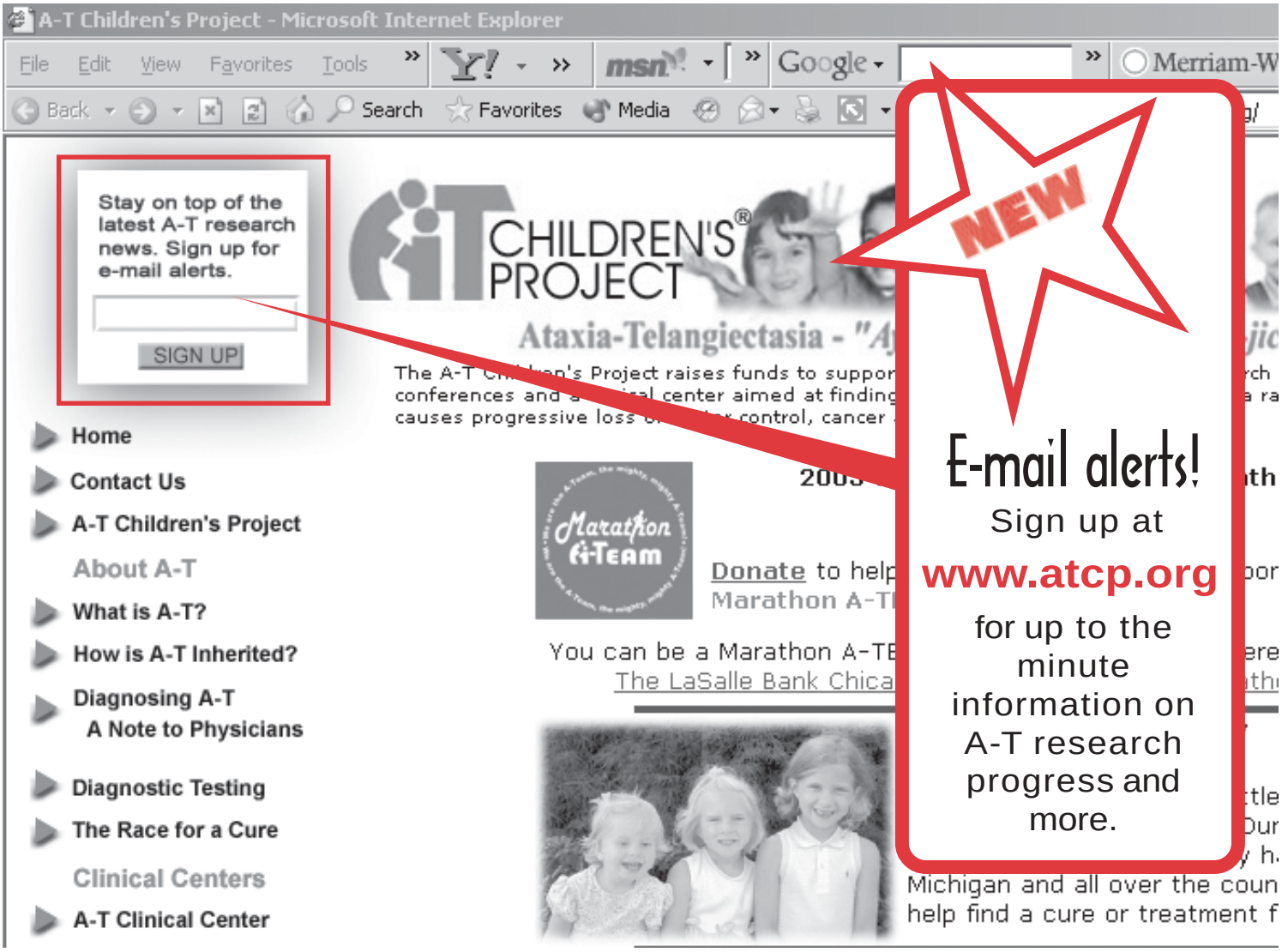
GIVE THE GIFT OF HOPE

Send a thoughtful gift card for a minimum $25 donation for someone's birthday, anniversary, a holiday, or just to say you care. You will be helping fund crucial scientific and medical research to achieve a cure or therapies for patients with A-T. The full color card spotlights children with A-T and highlights some of the promising research projects we are funding. See our website for details or call 800-5-HELP-A-T.

VEHICLE DONATION PROGRAM

DONATE any used vehicle -- cars, trucks, motorcycles or boats, to benefit the A-TCP. To learn more, go to our website, **www.atcp.org** and click on the car donation button or go directly to:

http://www.v-dac.com/org?id=650427215



The A-T Children's Project is a public 501(c)(3) non-profit organization that raises funds to support and coordinate biomedical research projects, scientific conferences and a clinical center aimed at finding a cure for ataxia-telangiectasia, a fatal genetic disease that attacks children causing progressive loss of muscle control, cancer and immune system problems.

CHILDREN'S PROJECT
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