UPDATE
A-T CHILDREN'S PROJECT®
kids. hope. cure.
November 2006
FOR FAMILIES, FRIENDS AND SUPPORTERS

A-T CLINICAL RESEARCH EXPANDS

SLEEP STUDY TO IDENTIFY POTENTIAL TREATMENT

In an important expansion of studying the lung function of patients with A-T, pulmonologist **Sharon McGrath, MD**, at the **A-T Clinical Center at Johns Hopkins Hospital** recently received funding through Hopkins' General Clinical Research Center to perform sleep studies on 12 teenagers and young adults with A-T. This will be performed to determine if children with A-T are more likely to have nighttime hypoxemia, or deficient oxygenation of the blood, when asleep compared to other people their age.


Sharon McGrath, MD

The sleep studies will allow the clinicians

Sleep Study continued on page 10

A-T CLINICAL CENTER AT JOHNS HOPKINS PLANS DRUG TRIAL TO HELP EYE MOVEMENTS AND TREMOR

The A-T Children's Project is pleased to announce funding for **Thomas O. Crawford, MD**, pediatric neurologist at the Johns Hopkins A-T Clinical Center, and **Aasef G. Shaikh, MD, PhD**, a fellow in the Department of Neurology at Johns Hopkins Hospital. Together with a team of clinician / researchers, Drs. Crawford and Shaikh will investigate ways to monitor and possibly treat certain neurological deficits associated with ataxia-telangiectasia (A-T). Results from their study will hopefully provide objective measures for the eye movement abnormalities and tremor associated with A-T. These quantitative measures will then be used in a drug trial to help treat the eye movement deficits and tremor associated with this life-threatening disease.


Thomas O. Crawford, MD and Aasef G. Shaikh, MD, PhD

Drs. Crawford and Shaikh's study contains three parts. First the Hopkins team will employ state-of-the-art, non-invasive high resolution 3D volumetric MRI to examine that part of the brain most effected by A-T, the cerebellum. "This technique," note Crawford and Shaikh, "is superior to conventional MRI because it allows visualization and objective evaluation of structural changes in relatively smaller functional units of brain." Using high resolution MRI, the Hopkins clinicians will be able to quantitatively determine the degree of atrophy (or structural loss) occurring in the cerebellum of patients. This analysis will be performed in patients with varying degrees of disease severity. Differences in the extent of cerebellar degeneration will be examined not only amongst genetically unrelated individuals but also between siblings.

Next, Crawford and Shaikh will quantitatively assess two neurological deficits experienced by patients with A-T: eye-movement abnormalities and tremors. Eye-movement abnormalities seen with A-T include periodic alternating nystagmus (rapid, involuntary eye movements),

Eye Movements continued on page 8

CLINICAL WORKSHOP EXAMINES ASSESSMENT MEASURES FOR A-T

In March 2006, an important meeting was held in Bethesda, Maryland in order to develop diagnostic and assessment measures and a minimum standard protocol for the clinical analysis of patients with ataxia-telangiectasia. Co-sponsored by the A-T Children's Project, the National Institute of Neurological Disorder and Stroke/NIH, and the Office of Rare Diseases/NIH, the workshop brought together clinicians and researchers from all over the world to help pave the way for clinical studies.

Clinical Workshop continued on page 10

UPDATE: ANTIOXIDANT CLINICAL TRIAL

The physicians at the A-T Clinical Center are encouraged by the data from a small safety trial for a combination of nicotinamide and the antioxidant alpha-lipoic acid, and they would like to establish a second, dose-finding trial for the combination of drugs to determine the effects of increasing doses of these compounds on oxidative stress markers and lymphocyte counts.

OS Clinical Trial continued on page 10

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GRANTS RECENTLY FUNDED BY THE A-TCP

A-T Clinical Center
Johns Hopkins University

ATM in Immune Responses
JESSAMYN BAGLEY, PHD - Brigham & Women's Hospital

Role of ATM in the Control and Execution of Apoptosis: Crosstalk Between ATM and Abl Kinases and Caspases
DANIELA BARILÁ, PHD - Dulbecco Telethon Institute at University of Tor Vergata

The Role of the DNA Damage Response in Cerebellar Degeneration in A-T
ARI BARZILAI, PHD - Tel Aviv University

Gene Therapy for Ataxia-Telangiectasia
MARIA LUISA CORTES, PHD - Massachusetts General Hospital

Identification and Characterization of Chemicals that Readthrough PTC Mutations in the ATM Gene
RICHARD A. GATTI, M.D. - UCLA School of Medicine

Perinatal Implantation of Human Glial Progenitor Cells as a Treatment Strategy for the Childhood Myelin Disorders
STEVEN A. GOLDMAN, PHD - Cornell University

The role of pro-apoptotic BID as an ATM effector in the DNA-damage response
ATAN GROSS, PH.D. - Weizmann Institute of Science

The Zebrafish as a Novel Model System of Ataxia-Telangiectasia and Other Related Diseases
SHUJI KISHI, MD, PHD - Harvard Medical School

Correction of the Neurological Defect in Atm Gene-Disrupted Mice by the Insoindolin Nitroxide, 5 Carbocy-1,1,3,3-Tetramethylisoindoline-2-yloxyl (CTMIO)
MARTIN F. LAVIN, PHD - Queenslands Institute of Medical Research

Generation of a Rat Model for Ataxia-Telangiectasia
MARTIN F. LAVIN, PHD - Queenslands Institute of Medical Research
and MICHAEL M. WEIL, PHD - Colorado State University

ATM Activates the Myocyte Enhancer Factor-2 (MEF2) Family of Transcription Factors Implicated in Regulation of Neuronal Differentiation and Survival
STUART LIPTON, MD, PHD - The Burnham Institute

Regulation of ATM Pathways by Oncogenic Phosphatase PPM1D
XIONGBIN LU, PHD - Baylor College of Medicine

Lung Function in Ataxia-Telangiectasia
SHARON MCGRATH, MD - Johns Hopkins School of Medicine

Relationship Between DNA Damage Detection and Signaling Revealed in Humanized Mouse Models of AT and NBS
ANDRE NUSSENZWEIG, PHD - NIH, NCI

The Function of ATM in Neuronal Differentiation: Identification of Targets for High Throughput Screening
BRENDAN PRICE, PHD - Dana-Farber Cancer Institute

Exploration of the Function of ATM in Glial Biology
PRITHI RAJAN, PHD - The Burnham Institute

Iron Chelators as a Pharmacological Treatment to Reduce Spontaneous dsDNA Breaks in Ataxia-Telangiectasia Cells
RODNEY SHACKELFORD - Louisiana State University at Shreveport

Aberrant Regulation of Mitochondrial DNA in Ataxia-Telangiectasia
GERALD S. SHADEL, PHD - Yale University School of Medicine

Understanding ATM
YOSSI SHILOH, PHD - Tel Aviv University

Multimodal Stem Cell Action in Inherited CNS Disease
EVAN SNYDER, MD, PHD - The Burnham Institute

Cell Cycle and Cell Death in atm-Deficient Neuron
YAN YANG, MD, PHD - Case Western Reserve University School of Medicine

Genome (Chromosome) Instability in the Brain and Neuronal Death in Ataxia Telangiectasia
PROF. YURI B. YUROV - Russian Academy of Medical Sciences

For more information about research grants, contact:
Cynthia Rothblum-Oviatt, PhD, Science Coordinator at cynthia@atcp.org

DISNEYLAND® INAUGURAL HALF MARATHON WEEKEND

With over 270 participants, the A-T Children's Project was by far the largest group at the Disneyland® Inaugural Half Marathon Weekend held September 15 through 17, 2006. The terrific 5K course and the 13.1 mile half marathon both wound through the Disneyland and California Adventure theme parks. The A-TCP hosted private dinners with guest appearances by Disney® characters and the presence of the A-TCP staff and A-T families at the Expo was a great way to bring awareness to A-T.

A-T Marathon participants raised over $150,000 for research.

Join us in 2007. For more information, or to register, visit our website at www.atcp.org.

Clockwise from Left:
1) Chad Wildoner and Minnie Mouse
2) Catherine Achilles with family and friends
3) A-T kids displaying the grand total raised
4) Mary Veldink and Maria Schimmer

OH, CANADA!

The A-T Children's Project – Canada has been registered with the Canada Customs and Revenue Agency since December 23, 1999. In 2006 fundraising events in Canada included: Third annual *A-T Hearts of Hope Valentine's Gala* in St. Leonard, QC; Ninth annual *A-T Walk for a Cure* in Fort Mcleod, AB; and First *A-T Golf Tournament* in Coaldale, AB

Mario Manuele joins A-TCP Canada's Board of Directors

The A-T Children's Project is pleased to announce that Mario Manuele joined the board of directors of the A-TCP Canada. Manuele has been actively involved with the A-T Children's Project since 2001 when his son, Antonio, was diagnosed with A-T. He and his wife, Diana, live in Montreal with their two sons, Antonio, age 8, and Jason, age 3.

Manuele has distinct expertise in computer networking as owner and CEO of LGIT, a privately-owned Canadian company established in 1993 that specializes in security and networking installations. In addition to hosting numerous fundraising events including galas, golf tournaments, and the marathon, Manuele has been providing computer networking volunteer services to the A-T Children's Project since he learned about the organization.

Kris Grillas raises US$45,720.78 - Wins A-T Marathoners' Grand Prize

Canadian marathon participants raised US$108,838 for the 2006 Marathon efforts.

Mark your calendars for 2007!

The 4th annual *A-T Hearts of Hope Valentine's Gala* will take place on Saturday, March 31, 2007 at *Prima Luna*. Entertainment will be provided by *The Showman*. For tickets call Mario Manuele: 514.886.1426 or email him at mmanuele@lgit.com.

A-T FACT SHEETS

The following fact sheets about A-T were prepared by Dr. Howard Lederman, Director of the A-T Clinical Center at Johns Hopkins Hospital.

- Ataxia-telangiectasia and Cancer Risk
- Ataxia-telangiectasia and Estrogen Replacement in Females
- Ataxia-telangiectasia and Immune Function
- Ataxia-telangiectasia and Swallowing Problems
- Ataxia-telangiectasia and X-Rays

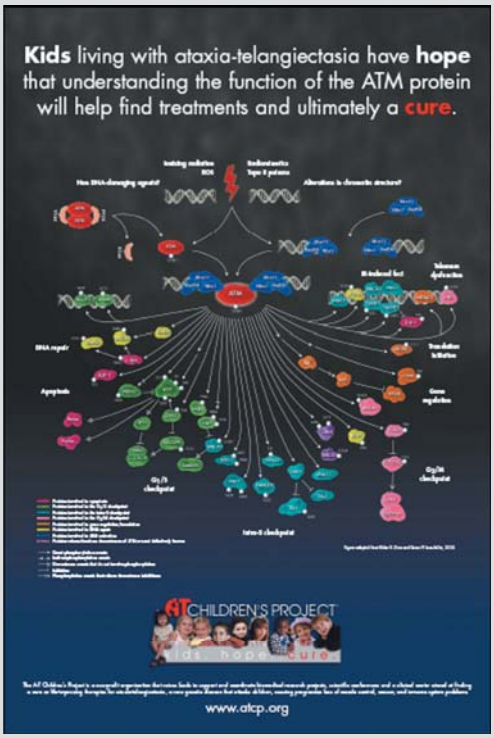

A-T Clinical Center at Johns Hopkins
IMPORTANT FACTS ABOUT:
Ataxia-Telangiectasia (A-T)
and Cancer Risk

Download the fact sheets from the A-TCP website at www.atcp.org/a-t_fact_sheets.htm or order by phone from the A-TCP at 1-800-5-HELP-A-T (800-543-5728), or from outside the US call 954-481-6611.

The 5K Run, Kids 1K and Family Fun Walk at Littleton Colorado raised nearly $50,000 in honor of Kaitlyn Leasure, a 5 year old with A-T. Her parents, Wade and Jennifer, and their friends, Craig and Laura Juran, hosted the blockbuster event in September 2006.

POSTER INSPIRES RESEARCHERS

The A-T Children's Project recently distributed a poster depicting the pathways of the ATM protein (absent in the cells of patients with A-T). The poster was mailed to researchers around the world to keep them thinking about A-T and to attract the attention of other scientists in their labs. Posters are available free of charge. To order, please email info@atcp.org.



YOU MAKE IT HAPPEN!

Join the grassroots efforts of the A-T Children's Project and help us fund critical research to find a cure or life-improving therapies for ataxia-telangiectasia.

* Marathons * Mini-Marathons * Walks * Dinner Dances * Golf Tournaments * Garage Sales * Letter Writing Campaigns * Awareness Bands *

Visit our website at www.atcp.org to find out who is hosting fundraisers in your area so that you can get involved.

A Very Special Evening

The 11th annual "A Very Special Evening" to benefit A-T Children's Project was held at the Clark Studio Theatre at Lincoln Center in New York City on January 16th, 2006. The house was full for a wonderful evening of entertainment. As they have done for so many years, actors **Priscilla Lopez** and **Louis Zorich** hosted the evening where the audience was delighted with outstanding performances by Broadway singers, **Christiane Noll** and **Doug LaBrecque**, classical guitarist, **Nadav Lev** and flutist, **Jocelyne Roy**, magicians **Darwin Ortiz** and **David Roth** and actor, **William Parry**, composer/lyricist **Beth Falcone** and singers **Heather Jane Rolff**, **Jackie Comsar**, **David A. Austin** and **Lucas Steele** and PHILADANCO dancers, **Odara Jabali-Nash** and **Tommie W. Evans** who performed a duet choreographed by **Lynne Taylor-Corbett**.

In the audience were three participants from past benefits, actress **Barbara Feldon**, singer **Margaret Wright** and World Trade Center hero, **Michael Benfante**. A special guest in the audience was Broadway great **Sheldon Harnick**, lyricist of "Fiddler On The Roof," "Fiorello" and other legendary shows.

Ms. Taylor-Corbett was honored for donating her choreography and energy to many of the previous benefits as was Lighting Designer, **Eric D. Chase**, who donates his talent every year. Research grants in Ms. Taylor-Corbett's and Mr. Chase's names will be funded with money raised at the benefit.

In addition, a research grant will be funded in memory of **Victor J. Swedosh** thanks to a most generous grant from his partner, **Richard Ennis**. Victor grew up in New York City and graduated from the University of Wisconsin. He moved to San Francisco after college where he made a success in real estate and owned a popular bar for many years. In the 70s, he produced a number of top selling disco hits and in the early 80s produced Lanford Wilson's play "Balm in Gilead" in Los Angeles. Victor was stricken with HTLV-1, a viral disease for which there is no cure, and struggled with it for seventeen years. Victor passed away in August, 2005 at the age of 55. Because he suffered many of the same symptoms that A-T children do and because he had a great love for children, Richard Ennis decided to fund an A-TCP research grant in Victor's name. The A-TCP is most grateful for his kind gesture.

Photo Courtesy of Ginger Proper

Odara Jabali-Nash and Tommie W. Evans from the Philadelphia based dance company PHILADANCO performing a duet by renowned choreographer Lynne Taylor-Corbett.

FUNDED RESEARCHER EXAMINES THE POSSIBLE ROLE OF ABNORMAL MITOCHONDRIAL DNA REGULATION IN A-T

Mitochondrial dysfunction, resulting from a variety of causes including an inappropriate amount of mitochondrial DNA, contributes to a myriad of human diseases and this may be true for ataxia-telangiectasia as well. If so, the potential for new therapeutic interventions may exist for this disease. Therefore, the A-T Children's Project is funding research to investigate this possibility.

With funding from the A-T Children's Project, **Gerald S. Shadel, PhD of Yale University School of Medicine** and his graduate student

Gerald S. Shadel, PhD and graduate student Jana Eaton of Yale University School of Medicine

Jana Eaton will be investigating the "Aberrant Regulation of Mitochondrial DNA in Ataxia-Telangiectasia." Dr. Shadel and Jana's novel research focuses on that genetic material or DNA which is housed in the mitochondria versus the nucleus of the cell. Nuclear DNA codes for the vast majority of cellular proteins; however, there is a subset of DNA that exists in the energy producing power plants of the cell – the mitochondria. Unlike nuclear DNA which is inherited from both father and mother, mitochondrial DNA (mtDNA) is inherited exclusively from the mother, and each tissue or cell contains a particular amount of mtDNA (or mt DNA copy number). The mtDNA codes for 13 proteins essential for the energy producing function of the mitochondria.

Importantly, a percentage of our nuclear DNA also codes for proteins vital to the proper functioning of the mitochondria. So mutations (or deleterious alterations) in both mitochondrial and nuclear DNA can cause dysfunction of mitochondria and disease. Indeed, Dr. Shadel's laboratory has preliminary evidence that mutations in the ATM gene (the gene mutated in A-T) may cause inappropriate changes in mtDNA copy number, and this could contribute to some of the symptoms of A-T. "Intriguingly," notes Shadel "many diseases caused by mtDNA dysfunction have as a primary component neuromuscular degeneration (including ataxia) that is often accompanied by other tissue-specific defects (e.g. diabetes and sterility), resulting from global disruption of energy metabolism or other important functions provided by mitochondria…" Also, it is thought that oxidative stress plays a role in the pathology of A-T. Because mitochondria extract chemical energy from food, they are the primary sites for the production of reactive oxygen species (ROS), the chemical entities that cause oxidative damage to cellular proteins, lipids and DNA (to include mtDNA). Therefore, mitochondrial dysfunction may be a part of the pathophysiology of A-T either as "a contributor to or a target of oxidative damage."

Dr. Shadel's preliminary evidence that ATM signaling pathways may regulate mtDNA copy number comes from research carried out in yeast. To further explore the link between ATM, mtDNA copy number and the proper functioning of mitochondria, Dr. Shadel's current A-TCP funded grant will expand his research to mouse and human cells. States Shadel, "This [grant] is based on our recent discovery of a novel function for the ATM signaling pathway in controlling mitochondrial activities by regulating the amount of mtDNA cells, suggesting a relevant new link between mtDNA and A-T. Through completion of these [studies] we will determine if the normal control of mtDNA copy number by ATM is defective in A-T and leads to important clinical manifestations of the disease from the ensuing mitochondrial dysfunction." It is hoped that Dr. Shadel's work will uncover new therapeutic targets for A-T and/or support the use of antioxidants as a treatment option for this disease.

WGRD's The FBHW Morning Show's deejays in Grand Rapids have raised over $65,000 for the A-TCP in honor of Kate and Olivia Veldink. "Free Beer," "Hot Wings," Eric Zane and "Producer Joe" are encouraging their listeners to sponsor Zane who is running the Detroit Marathon … no easy feat considering that Zane hates running!

PROGRESS REPORT

From Brigham & Women's Hospital in Boston, Massachusetts

Ten to thirty percent of patients with A-T will develop immune system-related cancers like leukemia or lymphoma, during their lifetime. Unfortunately, patients with A-T are extremely sensitive to the chemotoxic agents and radiation used to treat lymphoreticular cancer and perform bone marrow transplants.

With previous funding from the A-T Children's Project, **John Iacomini, PhD** and **Jessamyn Bagley, PhD** at **Brigham & Women's Hospital, Harvard** found that A-T mice who received normal bone marrow using a non-myeloablative, or less toxic transplantation regimen, gained restored lymphocyte development and failed to develop the aggressive thymic lymphoma normally seen in these mice.

Now, in collaboration with **Eva Guinan, MD**, Associate Director, Center for Clinical and Translational Research at the **Dana Farber Cancer Institute**, Drs, Iacomini and Bagley are "…evaluating clinically relevant bone marrow conditioning regimens that are used in syndromes such as Fanconi anemia in which patients, like A-T patients, are extremely sensitive to radiation and chemotherapy."

States Dr. Bagley, "Our collaboration with Dr. Guinan brings us substantially closer to our goal of a clinical trial of bone marrow transplantation in A-T as she will be able to lead this effort as the director of the bone marrow transplant service at the Dana Farber."

Survey of A-T F

Purpose of survey:

To **identify facets** of A-T that physicians examining patients with the disease might never detect during an office visit, but that are in fact **definite characteristics** of A-T.

To help A-T families by providing information about the **experiences of other families**. Parents observe something about their children with A-T and wonder if their observation is common or unusual for children with A-T in general, and if it is related to A-T or not.

CHILDREN'S® PROJECT
668 South Military Trail
Deerfield Beach, FL 33442 U.S.A.
Phone 954-481-6611
Toll Free: 800-5-HELP-A-T

A-T Patients:

Male ♂ 54%

Female ♀ 46%

Average age:
18 yrs. 2 mos.

Mailed to **240 Families** in USA
Received 114 Responses

Approx. 30% were diagnosed within one year; 50% within 3.5 years; 90% within 9 years.

Diagnosing A-T

- The average age at which A-T patients began walking was 16 months old.
- The average age when symptoms first appeared was 21 months.
- Nearly 95% of respondents reported symptoms by age 4.
- In over 60% a neurologist made the A-T diagnosis.
- On average, it took slightly over four years from first signs of symptoms for patients to be diagnosed with A-T.
- Almost 70% of the patients who did not receive A-T as their first diagnosis were misdiagnosed with cerebral palsy.
- The average age at diagnosis was approximately 6 years old.
- About 10% of patients did not receive a diagnosis of A-T until after the age of 10.

Activities enjoyed by people with A-T:

- Assisting with cooking and baking
- Water sports
- Weight lifting and working out
- Attending the YMCA
- Attending school athletic events
- Playing with pets
- Playing games
- Doing chores in home
- Shopping
- Working on computer
- Listening to Books on Tape
- Studying
- Programs for people with disabilities
- Volunteering eg.: college gym
- Attending physical therapy
- Helping parents with hobbies
- Listening to music
- Writing poetry
- Mowing grass
- Swimming
- Baby sitting
- Reading magazines
- Watching TV
- Playing video games
- Going to movies

Clinica

While no patients with A-T experien all of the possible symptoms, most patients experience at least a hand of the following:

- Ataxic Gait
- Telangiectasia
- Slurred Speech*
- Eyesight Problems
- Drooling
- Fatigue
- Slow to Process and Respond when
- Tremors
- Lower than Average Weight
- Other Skin Conditions
- Frequent Infections
- Graying of Hair
- Numerous Birth Marks
- Aspiration while Swallowing
- Sensitivity to Loud Noises
- Depression
- Warts
- Pain
- Allergies
- Nausea
- Gagging while Swallowing
- Sensitive to Medication
- Dizziness
- Loud Breathing when not Sick
- Unexplained Crying
- Joints that Pop Frequently
- Rapid Emotional Changes
- Trouble Controlling Bladder
- Sensitivity to Strong Smells
- Sweaty Palms

*Of those who responded that A-T reported that the slurred speech va patient's speech varies, 70% report

Families - 2006

More than two out of three patients have been **evaluated at the A-T Clinical Center** at Johns Hopkins Hospital in Baltimore, MD. Nearly all of the respondents were **interested in participating** in future clinical trials.

The most common treatments were: IgG infusion, feeding tubes, and heel cord lengthening, at nearly 20% each.

al Aspects

ce

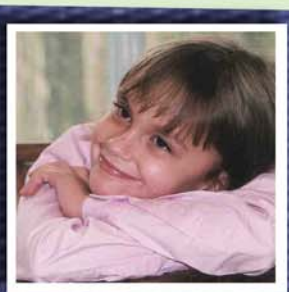
lful	Percentage Experiencing Symptoms	Average Age of Onset (in years)
	96	2
	94	5
	91	7
	80	7
	79	3
	78	7
Speaking	68	6
	61	9
	58	4
	42	8
	39	5
	37	11
	36	2
	34	14
	32	3
	28	17
	25	11
	25	11
	25	7
	25	9
	24	11
	19	14
	18	11
	17	15
	15	8
	13	14
	13	9
	13	6
	11	5
	11	12

patient experiences slurred speech, 74%
aries. Of those who responded that the
ed that slurred speech was due to fatigue.

Adjunct Therapies:

Common **therapies** that have been helpful:

- Physical therapy
- Speech therapy
- Occupational therapy
- Exercise
- Horseback riding
- Hyperbaric pressure
- Weight training
- Massage therapy
- Acupuncture
- Bike riding
- Swimming
- Stretching
- Service dog



Daily Living

- Average monthly **out of pocket cost** for coping with A-T: $228
- Three out of four report trouble **using eating utensils**
- Nearly one in three report **trouble swallowing**
- Nearly 25% of patients use manual or power **wheelchairs** most of the time

School Services

More than 85% of A-T patients who attend public school have an **Individual Education Program (IEP)**. The vast majority of respondents who have an IEP are basically or very satisfied with it. Nearly 9 out of 10 A-T patients receive full-time **classroom aide** as a part of their IEP. Approximately 3 out of 4 respondents receive **therapies**.

For complete survey results, including specific information regarding IEP services by age level, please visit the A-T Children's Project's website at **www.atcp.org**.

More than half of the respondents reported use of over-the-counter **nutritional supplements** including:

- Alpha-Lipoic Acid
- Multivitamins
- Calcium
- Ensure/Protein Shakes
- Fish Oils
- Vitamin C
- Inositol

Eye Movements continued from page 1

abnormal gaze fixation, head thrusts and the inability to track moving objects smoothly. The tremors seen in A-T patients are generally intention tremors (where goal-directed movements cause shaking) and usually follow the development of ataxia which can occur as early as the first year of life in the patient with A-T.

Using non-invasive techniques, Crawford and Shaikh will quantitatively evaluate the eye-movement deficits in approximately 30 patients and systematically correlate these deficits with the structural abnormalities observed using the high resolution MRI analysis described above. Crawford and Shaikh hypothesize that different visual abnor-malities will correlate with the atrophy of different regions of the cerebellum.

Although intention tremors are a major burden associated with A-T, to date they have not been systematically examined, quantified or correlated with overall disease status. By quantitatively assessing the deficits in eye-movements and severity of tremors, the Hopkins team hopes to use these features of A-T as disease markers not only for prognosis, but also to assess the efficacy of various therapeutic approaches.

One such therapeutic strategy or drug trial comprises the last part of Crawford and Shaikh's study. If eye-movement deficits and tremors prove to be usable primary and secondary quantitative disease markers and "important pre-therapeutic landmarks," Crawford and Shaikh will test the efficacy of a drug called *baclofen* in patients with A-T. One of the hallmarks of A-T is the loss of cerebellar Purkinje cells. These very large brain cells communicate chemically with other neurons in the brain-stem and cerebellum using an inhibitory neurotransmitter called GABA. When Purkinje cells are lost, a decrease in the production of GABA can occur, possibly resulting in deficits in motor control and eye-movements. Therefore, Crawford and Shaikh hypothesize that if the levels of GABA can be brought back to normal in the A-T cerebellum, then improvements in eye-movement and other neurological deficits may occur. Experience with Parkinson's and Alzheimer's disease has shown that functional improvements can result from treatment with drugs that mimic neurotransmitter function. Because baclofen is a drug that mimics the function of GABA in the brain, Crawford and Shaikh have decided to test this compound in patients with A-T. In addition, baclofen has been used successfully to treat eye-movement abnormalities resulting from degeneration of the cerebellum due to a variety of causes.

Importantly, in the clinical setting, baclofen has been found to be safe and well tolerated.

Regarding this comprehensive study, Drs. Crawford and Shaikh state the following: "The potential gains of this undertaking are substantial, both for the understanding and treatment of A-T. Thus, this coalition of investigators was selected for their expertise in cerebellar-motor control, neurophysiology, eye-movements, neurology, and neuro-imaging." It is hoped that this research will lay the groundwork for future imaging studies and drug trials for A-T.

Kids from all over the USA continue to raise funds and awareness for the A-T Children's Project!

Andy Sakowich and fellow students in Mr. Page's business class at **Wayland High School** ran *Chapstique, Inc.* selling custom Wayland chapsticks to the student body and local community. They earned $2,361.86 and donated it to the A-TCP in honor of Andy's brother **Keaton** who has A-T.

Kindergarten students at **Edgewood Elementary School** in Fruitport, MI participated in *Dressing for a Cause* dress down days to support their friend **Aaron Biros**. On three different Fridays, students paid a quarter to wear hats, clashed clothes, or pajamas to school.

Spirit Assembly at **Freedom Middle School** in Wisconsin raised funds in honor of Katie and Tyler Smith.

Marissa Vredeveld and Makenzie Cegard raised $100 in their neighborhood selling bead bracelets that they made.

Maddy Maurice (9) donated $30 she had saved for a trip to Chicago in honor of her best friend, **Kate Veldink**.

Cumberland Valley High School in PA held a Badminton Tournament in honor of **Douglas Fickel**.

Jonathan Rafalski, organized a bowling event for his Senior high school project and donated $638 in honor of his cousin **Bradley Bills**.

Mount Saint Charles Academy in Woonsocket, RI, organized a yard sale that raised $500 for A-T research in honor of her friends.

Jordan Juran made and sold pot holders raising over $150 for A-T in honor of **Kaitlyn Leasure**.

Matthew Smarz and Sean Craven raised $25 by organizing a "hole in one" game at a penny fair at Sterling Park Day Camp in CT. Matthew's brother **Robert** has A-T.

Waubonsie Valley High School Key Club coordinated by **Catherine McGath** raised $420 selling A-T Hearts of Hope in honor of **Rachel Kemeny**.

Edgewood Middle School Student Council raised $850 in honor of **Kyle Grand**.

Lincoln-Way High School sold Hearts of Hope and had a Jeans Day that raised $598 in honor of **Alyssa Wood**.

Ms. Gach's 4th grade class at **Barnard Elementary School** in Troy, MI picked the A-TCP to receive a donation in lieu of receiving holiday presents from their teacher. Student **Morgan Sakalian** introduced the A-TCP to the class telling them about her babysitter, Jennifer Powell, who has A-T.

Happy Birthday! The word "birthday" makes you think of parties, cake, ice-cream and... presents! How many people do you know who would turn down the opportunity of receiving gifts? Some amazing kids opted to ask for donations to the A-TCP in lieu of presents this year…

- **Meghan Hanley** (6) of Warwick, RI in honor of her classmate **Andrew Martin**
- **Emily Baker** (10) and her sister **Haley Baker** (6) honoring their cousin **Andrew Martin**
- **Mark Nuckols** (8) in honor of his cousin **Chaz Erwin**
- **Alexa Henriques** (10) and her sister **Lauren Henriques** (12) in honor of their dear friend **Andrew Martin**
- **Sydney Jordan** (9) in memory of **Tiffany Boulanger**

CFC

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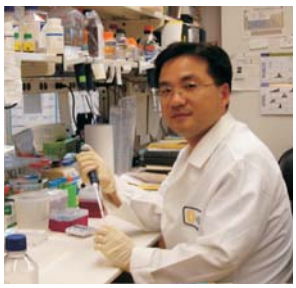
BAYLOR RESEARCHER TO DETERMINE IF INHIBITING PPM1D PROTEIN MAY HELP A-T PATIENTS

Once a normal cell has incurred and repaired damage to its genetic material or DNA, how is the repair machinery turned off? And how can understanding this process perhaps help reduce the radiation sensitivity seen in patients with A-T? **Xiongbin Lu, PhD**, an investigator at **Baylor College of Medicine** in Houston, Texas is studying the answers to these questions and, in the process, may uncover novel therapeutic targets for ataxia-telangiectasia (A-T).

To carry out different cellular functions, the proteins within a cell communicate with one another chemically. In this manner, one protein can turn "off" or "on" the function of another protein or even change its location within the cell. The addition of a phosphate group to proteins is one common means of chemical communication used within cells to alter protein activity. Proteins that transfer phosphates to other proteins are called kinases, and they represent a special type of enzyme.



Xiongbin Lu, PhD

Enzymes that remove phosphate groups from proteins are called phosphatases. For example, the A-T protein (ATM) is a kinase. When this protein is activated following DNA damage, it will halt the cell's growth cycle and promote DNA repair. Alternatively, if the damage is too extensive, the ATM protein may help induce cellular suicide. ATM carries out these functions by adding phosphates to a wide variety of other proteins involved in the processes of cell growth cycle control, DNA repair and/or programmed cell death.

Dr. Xiongbin Lu, however, is studying a phosphatase or enzyme that removes phosphates from proteins. Dr. Lu's group has shown that a phosphatase called PPM1D deactivates DNA damage response pathways – including the pathways regulated by the A-T protein – to return cells to their 'normal' state after damage has been repaired. With funding from the A-T Children's Project, Dr. Lu will now examine how silencing PPM1D in A-T cells effects cell cycle control, DNA repair and sensitivity to radiation. If PPM1D helps to deactivate, or turn off, the processes set in motion by DNA damage, then inactivating PPM1D may enhance or sustain these processes, thus attenuating some of the abnormalities seen in A-T cells. States Dr. Lu, "We propose to reduce the levels of PPM1D… to stimulate higher levels of activities of ATM targets. Our studies of PPM1D and its regulation of ATM targets may provide a potential therapeutic approach to reduce radiosensitivity [in patients with A-T]." The ability to reduce radiation sensitivity in individuals with A-T may translate into less worry about x-ray exposure and could possibly allow for more aggressive cancer therapies should this need arise.

FEAR IS NOT A FACTOR

While attending Stellent's Global User Conference in Orlando, FL, Ross Pallan, a friend of the Wood family of Lemont, IL, won $5,000 and promptly donated it to the A-T Children's Project in honor of nine-year-old Alyssa Wood, who has A-T.

Alyssa Wood

Stellent, a global provider of content management software solutions, donated the funds to Pallan's charity of choice after he beat five competitors through a series of wild events at a live showing of Fear Factor Live® at Universal Studios. His fearless stunts included:

- Hanging from a bar while suspended three stories above the ground.
- Retrieving balls from a tank full of live eels, and tossing the ball to his partner who was swinging back and forth while being sprayed with water.
- Grabbing flags while climbing a ladder up the façade of a three-story building, sliding down a fireman's pole, jumping into a convertible, and firing a water gun at a target on a building. And "one more thing…" all while being sprayed with a high-powered water jet.

In the end, Pallan proved that "Fear is not a Factor" and beat his competitor easily, which is great news for advancing A-T research. Thank you, Ross and *Stellent*!

Sleep Study continued from page 1

to stage sleep and sleep efficiency, monitor continuous oxygen saturations and end-tidal carbon dioxide levels, and measure continuous airflow to determine central and obstructive apneas. The morning after the sleep study, blood will be drawn to measure inflammatory markers. If individuals with A-T have an increase in nightime hypoxemia, it is hypothesized that this could increase oxidative stress and promote disease progression. A possible treatment for these patients could be nighttime administration of oxygen.

The community of A-T clinicians will be watching this study closely to determine if recommendations could be made for certain patients for this potentially life-improving treatment.

OS Clinical Trial Continued from page 1

Data from the safety trial demonstrated that two markers of oxidative stress were improved when participants took both alpha-lipoic acid and nicotinamide. A trend toward increased lymphocyte counts was also observed, but did not reach statistical significance. During this trial, the clinicians were also able to develop reproducible tests for neurological assessments and lung function which will be used in future clinical trials.

Clinical Workshop continued from page 1

Topics included:

- Diagnostic and Assessment Measures for Movement Disorders in Children
- Diagnostic and Assessment Measures for A-T
- Extra-Cerebellar Characteristics of A-T
- Molecular Profiling: Proteomics and Metabolomics in Clinical Research
- Developing Biomarkers for the Clinical Assessment of A-T
- The Gap between the Bench and the Bedside
- Current Clinical Trials and Assessment Measures for A-T
- Developing Critical Data Elements and a Minimal Standard Protocol for the Longitudinal Assessment of Patients with A-T
- International Registry for A-T and an A-T Clinical Listserve

The A-T Children's Project will help facilitate continuing discussions among the participants, which will be critical to finalizing the assessment protocols. And, the three groups are planning to co-sponsor a future workshop on the neurological assessment of A-T to finalize measures and cross-train clinicians from around the world.

PROGRESS REPORT

From Tel Aviv University in Israel.

For more than six years, the A-T Children's Project has provided funding for **Yossi Shiloh, PhD** at the **Tel Aviv University** in Israel. Dr. Shiloh's laboratory discovered the ATM gene in 1995 and since then has consistently performed ground-breaking research in the area of ATM biochemistry.

In his most recent progress report Dr. Shiloh writes, "Work in the A-T laboratory at Tel Aviv University is focused on understanding the physiological roles and mode of function of the ATM protein in various cell types. ATM is the primary activator of a complex network of signaling pathways in response to double-strand breaks (DSBs) in the DNA. DSBs are caused by intracellular metabolites that are formed during normal cellular metabolism, and by exogenous agents that damage the DNA, most notably, ionizing radiation (IR) and radiomimetic chemicals that mimic the action of IR on the DNA. DSBs are also formed during normal transactions of DNA, such as…maturation of the immune system genes." Dr. Shiloh states further that, "A-T is a disease that results from loss of the ATM protein. We believe that the entire spectrum of symptoms of this disorder reflects the defect in cells lacking ATM that renders them incapable of responding properly to DSBs. We obtained evidence that the cerebellar degeneration in A-T - the most important and devastating symptom of this disease - is indeed a result of the defective response of cerebellar cells to DSBs. Thus, finding the pathways that are controlled by ATM following DSB induction is critical for understanding the disease and developing new treatment modalities for A-T patients. Of special importance is the elucidation of ATM targets in the tissue that is most severely affected by ATM loss - the neurolnal tissue." The Shiloh lab thus undertook to investigate this response in a model system of human neuron-like cells (NLCs) obtained by neuronal differentiation in culture. Importantly, contrary to previous reports, ATM was largely nuclear in NLCs, and their ATM-mediated responses to DSBs were similar to those of proliferating cells. Eliminating ATM from the cells did not interfere with neuronal differentiation, but abolished ATM-mediated damage responses. The conclusion from this sudy was that nuclear ATM mediates the DSB response in NLCs similarly to in proliferating cells. Thus, attempts to understand the neurodegeneration in A-T should be directed to investigating the DSB response in the nervous system.

Dr. Shiloh's entire laboratory has been and continues to be dedicated to A-T/ATM research. We look forward to new findings from this lab as research into the function of ATM in the nervous system progresses.

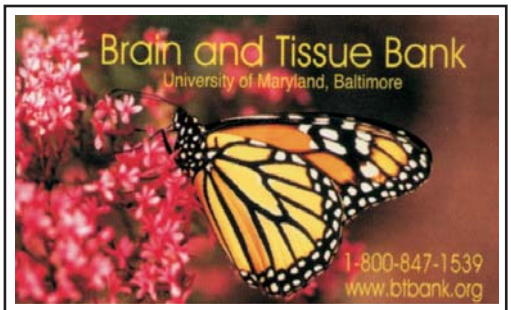
PROGRESS REPORT

From Case Western Reserve University School of Medicine in Cleveland, Ohio

With funding from the A-T Children's Project, **Karl Herrup, PhD** and **Yan Yang, MD, PhD**, from the **Case Western Reserve University School of Medicine**, were able to perform research to investigate whether or not a mechanism of cell death seen in other neurodegene-rative diseases, like Alzheimer's and ALS (amyotrophic lateral sclerosis), may also be playing a role in A-T. This cell death mechanism is the inappropriate entry of non-dividing, mature neurons back into the cell division cycle.

Herrup and Yang were, in fact, able to demonstrate that cerebellar cells from both A-T human autopsy tissue and A-T mice express proteins characteristic of the cell growth cycle. This work was published last year in the Journal of Neuroscience, a prominent scientific journal in the area of neurobiology research.

Having obtained renewed funding from the A-T Children's Project, Dr. Yang will now explore the hypothesis that in neurons from A-T mice, entry into an inappropriate cell cycle leaves them susceptible to cell death, but that the final death of the neurons requires another event. Using both whole animal mouse models of A-T and brain slice cultures derived from these animals, Dr. Yang will explore various triggers for driving A-T neurons to undergo cell death, including oxidative stress, inflammation and DNA damaging agents. "We believe", states Yang, "that his second event is an environmental insult of either chemical or physical nature and its identification would not only deepen our understanding of the neurobiology of A-T, it would offer prevention strategies of potential clinical importance."



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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.

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