A-T CHILDREN'S® PROJECT UPDATE

For Families, Friends and Supporters

June 2003

Ataxia-Telangiectasia is Chosen as a Model for High-Throughput Drug Screening by NIH's National Institute of Neurological Disorders and Stroke

The National Institute of Neurological Disorders and Stroke (NINDS) has chosen the rare genetic disorder ataxia-telangiectasia (A-T) as a disease model for the high-throughput screening (HTS) of over 100,000 drugs to find a potential treatment for A-T and other neurodegenerative diseases. While large pharmaceutical companies have been successful in employing HTS for novel compound development, they primarily focus on common disorders that will reap significant financial benefit following drug discovery.

It is a giant step forward for a rare disease such as A-T to be chosen by the NINDS as a model disease for HTS. This acknowledgement indicates that A-T, along with the more well-known and prevalent neurodegenerative diseases such as Parkinson's and Alzheimer's, has captured the attention of an extremely important government funding agency. "Applying high-throughput drug screening to A-T is something we at the A-T Children's Project have been dreaming about for a long time," notes Brad Margus, president and co-founder of the A-TCP.

A-T has captured the attention of an extremely important government funding agency.

For years the pharmaceutical industry has been using HTS to help identify new therapeutic compounds. HTS utilizes robotic and automated systems to screen literally thousands of drugs (collectively referred to as compound or drug libraries) for those that may have some beneficial effect in the disease model being tested. To promote the use of this technology for neurodegenerative diseases, the NINDS, a part of the National Institutes of Health (NIH), recently established a High-Throughput Drug Screening Service Facility for Neurodegeneration by awarding a government contract to Southern Research Institute in Birmingham, Alabama. Southern Research is a not-for-profit contract research organization that not only has expertise in the area of HTS, but they also have established an affiliation with the University of Alabama at Birmingham, which allows them to collaborate with academic scientists in the neuroscience

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Take a peek at the A-Team's fun events on pages 6-7.

New Research Shows How the ATM Protein is Activated Following DNA Damage

Novel research performed by Christopher J. Bakkenist, PhD, a post-doctoral fellow in the laboratory of Michael B. Kastan, MD, PhD at St. Jude Children's Research Hospital in Memphis, Tennessee, has elucidated the mechanism that activates, or turns on, the ATM (A-T) protein following damage to a cell's genetic material or DNA. This landmark research was recently featured in the prominent scientific journal *Nature* and, in part, described the generation of reagents that will allow scientists and clinicians to detect and distinguish active (on) and inactive (off) ATM in our cells. Using these reagents it will be possible to determine

Continued on page 4

Christopher Bakkenist, PhD and Michael Kastan, MD, PhD, chair of St. Jude Hematology-Oncology

Photograph courtesy of Ann-Margaret Hedges of the Biomedical Communications Department at St. Jude

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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

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

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 Ataxia-Telangiectasia
Xandra O. Breakefield, PhD - Massachusetts General Hospital

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

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

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

Creation of a Transgenic Porcine Model of A-T
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 of the 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

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 - Washington University School of Medicine

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

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 - University of Texas M.D. Anderson Cancer Center

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

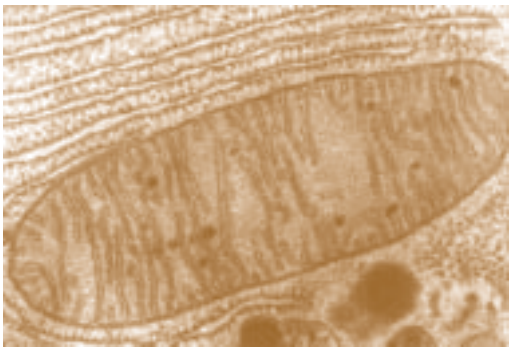
NEW **The Role of ATM in the Mitochondrial Pathway of Apoptosis**
Leman Yel, MD - University of California, Irvine

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

Investigator at University of California, Irvine to Study Possible Mitochondrial Dysfunction in A-T

An in depth study of the mitochondria from A-T cells, and their important role in the cell death process, could ultimately lead to novel drug interventions for A-T.

Therefore, the A-T Children's Project has recently awarded funding to Leman Yel, MD of the University of California, Irvine (UCI) to study the hypothesis that the energy-producing mitochondria in A-T cells could be malfunctioning.



A mitochondrion, taken from Fawcett, A Textbook of Histology, Chapman and Hall, 12th edition, 1994.

Programmed cell death (apoptosis) is the regulated process by which cells literally commit suicide. A common example of apoptosis can be seen in sunburned cells, which peel or slough off after death. UV light from the sun damages the DNA (genetic material) in our skin cells. If this damage cannot be repaired properly or is too extensive, the cells containing the mutated DNA run the risk of transforming into cancer cells. To avoid this transformation, the cells will undergo a characteristic set of internal changes that result in their death. In this case, apoptosis is beneficial. However, when apoptosis occurs inappropriately, it can be detrimental. In A-T (i.e., in the absence of the ATM protein), the process of programmed cell death is known to be altered in cells of the immune system as well as in certain developing neurons or brain cells. These alterations in the apoptotic process may result in the immunodeficiencies, immune-related cancers, and neurodegeneration characteristic of A-T.

Interestingly, mitochondria, the tiny structures (or organelles) in our cells that convert food into energy, also play a very critical role in the apoptotic or programmed cell death process. As part of her grant entitled, "The Role of ATM in the Mitochondrial Pathway of Apoptosis," Dr. Yel will examine the importance of the ATM protein in mitochondrial functioning, especially as it pertains to apoptosis.

To study the role of ATM in regulating mitochondrial function and apoptosis, Dr. Yel will utilize two different cell types taken from control patients and patients with A-T: lymphoblasts, which are a type of immune cell, and fibroblasts, or skin cells, both of which are much easier to grow and work with in the lab than most types of neuronal cells. Dr. Yel will examine how these cells undergo programmed cell death in response to a chemical that causes a special type of damage to their DNA known as double strand breaks (DSBs). The ATM protein plays an important role in a cell's response to this type of DNA lesion. Next, this UCI investigator will analyze how the cells' mitochondria function in the chemically-induced apoptotic process. It is anticipated that Dr. Yel's research will produce insight into how ATM contributes to the working environment of the mitochondria during apoptosis and as Dr. Yel notes, "[this research]

Leman Yel, MD

could serve as a model to investigate the pathogenesis of the nervous system damage [in A-T] and offer basics to establish mitochondrion-targeted therapeutic interventions [for this disease]."

A-TCP Welcomes Joshua R. Sanes to Scientific Advisory Board

The A-T Children's Project is pleased to announce the appointment of Joshua R. Sanes, PhD to its Scientific Advisory Board. Dr. Sanes is a member of the National Academy of Sciences and a professor in the Department of Anatomy and Neurobiology at Washington University School of Medicine. His interests include neuroscience and developmental biology, particularly the molecules and structures that regulate synapse formation. A graduate of Yale College and Harvard University, Dr. Sanes sits on the editorial board of several neuroscience publications, including Neuron, The Journal of Neuroscience, and Current Opinions in Neurobiology. Among his many honors is the Jacob K. Javits Neuroscience Investigator Award from the National Institutes of Health.

Joshua R. Sanes, PhD

Margus Named to HHS Secretary's Advisory Committee on Genetics, Health and Society

Brad Margus, president and co-founder of the A-T Children's Project, was one of 13 persons named to be on U.S. Secretary of Health and Human Services, Tommy G. Thompson's Advisory Committee on Genetics, Health and Society. The committee's new charge is an expansion of the mission of the Secretary's Advisory Committee on Genetic Testing to more broadly consider the impact of genetic technologies on society.

"This committee's members bring strong scientific, professional and personal backgrounds, and an understanding of the serious health and ethical issues raised by new genetic technologies," Secretary Thompson said. "...They will provide sound and thoughtful advice to the department as we weigh the impact of these advances on the health and welfare of all Americans."

At the department's request, the committee may consider the broad range of human health and societal issues involving the development, use and potential misuse of genetic technologies and make recommendations as appropriate. The committee's charge includes considering the clinical, ethical, legal and societal implications of genetic testing and other technologies, and its members include experts in each of those areas, as well as consumer representatives.

www.atcp.org

High Throughput *continued from page 1*

community. Southern Research has compiled a library of more than 100,000 drugs that have been optimized for central nervous system applications and chemical diversity, a percentage of which represent known drugs and bioactive natural products.

In order to design a protocol (or test) to screen this large collection of drugs for those that might have therapeutic value for A-T, the NINDS, in collaboration with the A-T Children's Project, held a special workshop on January 23, 2003 in Bethesda, Maryland, just one mile away from the NIH main campus. Motivation for the workshop was provided by the following individuals: Jill Heemskerk, Program Director for Technology Development at the NINDS; Giovanna Spinella, former Program Director at the NINDS and current Director of Extramural Research at NIH's Office of Rare Diseases; Carol Lewin, mother of an A-T child and fundraiser in the Washington, DC area; and Brad Margus.

To facilitate the development of a protocol for A-T that could specifically be adapted for automation, an important part of HTS, the joint NINDS/A-TCP workshop was attended by 25 scientists with expertise in the areas of A-T research, neurobiology, chemistry and drug screening. By the end of this one-day workshop, the investigators had developed a protocol for A-T, which could be adapted immediately by Southern Research for HTS. Results from this large drug screen, which represents a tremendous service for the field of A-T research, will be made available to the public by Southern Research. It is hoped that, at the very least, active compounds identified through these screens will prove to be useful research tools for A-T. At best, such compounds will lead to therapeutic drugs that could have a beneficial effect in the treatment of this rare but devastating neurodegenerative disease.

For more information on the NINDS HTS program please visit:
http://www.ninds.nih.gov/funding/technology_development/HTS_Facility.htm
To learn more about Southern Research, we invite you to visit their web site at:
www.southernresearch.org

Researcher Wins Auction at "A Night out with the Stars 2002"

After a lively auction to play a round of golf with Congressman Mike Oxley, Chairman of the House Financial Services Committee, A-T researcher Dr. Anatoly Dritschilo, Professor and Chairman of the Department of Radiation Medicine at Georgetown University, enjoyed a day of golf in Virginia this past spring.

From left: 1. Steve Buckhantz, Comcast SportsNet, Wizards Play by Play Announcer 2. Tim Jenkins, Partner, O'Connor & Hannan and Host of the game. 3.Congressman Mike Oxley 4. Dr. Anatoly Dritschilo

New Research *continued from page 1*

exactly when, where and following what insults the ATM protein is required.

Dr. Kastan has been interested in the biology of A-T for many years. He is currently the chairman of the Department of Hematology-Oncology at St. Jude, where he also oversees the A-T Cancer Clinic along with Dr. Torrey Sandlund, MD, director of the Leukemia/Lymphoma Clinic (please see related story on page 5). Perhaps it is not surprising that such a major discovery for the field of ATM research should come from his laboratory.

The ATM protein plays a very important role in our cells, the significance of which can be seen in its absence, i.e. in the multi-system disorder ataxia-telangiectasia. ATM coordinates the cell's response to a certain type of DNA damage referred to by scientists as double strand breaks (DSBs). This type of damage can be incurred following exposure to an outside agent (like irradiation) or simply by accident during the everyday, normal activities of the cell. When cells detect double strand breaks in their DNA, ATM is activated and signals to several other proteins within the cell. It does this by attaching a chemical entity known as a phosphate group to each of the proteins. This important process is termed "phosphorylation" and it can change the function and location of each of the target proteins within the cell. The various phosphorylation events carried out by ATM ultimately result in the choice between arrest of cell growth and activation of DNA repair, or if the damage is too extensive, cell death, which can prevent that cell from becoming a cancer cell.

But how does ATM itself get activated following the appearance of DSBs? Bakkenist and Kastan have demonstrated that in undamaged cells ATM exists as an inactive dimer. That is, two ATM proteins are bound together in a tight embrace with each molecule's activity restrained on its partner. Following the detection of DSBs in a cell, the ATM molecules in the dimer phosphorylate each other. This phosphorylation of the ATM molecules in the dimer breaks the embrace and pushes the two proteins apart, allowing the freed individual ATM molecules to phosphorylate their target proteins.

Subsequent experiments which examined ATM activation led to the observations that only two DSBs were needed to result in detectable ATM phosphorylation and that 18 double strand breaks caused the majority of the ATM protein within the cell to become phosphorylated. This surprising sensitivity of ATM activation led Bakkenist and Kastan to hypothesize that damage other than the breaks themselves must be capable of activating ATM. Indeed, Bakkenist was able to show that changes in the overall complex structure of the DNA, even in the absence of detectable DSBs, were sufficient to activate ATM.

Bakkenist's and Kastan's research has added significantly to our understanding of how the A-T protein works, and it is hoped that this and the distribution of the reagents they have generated to scientists worldwide will facilitate experiments that will lead to new therapeutic strategies for children suffering from A-T.

Macy's *Partners in Time* Held Their First A-T Hearts of Hope® Appeal

Employees at nineteen Macy's East stores participated in their first A-T Hearts of Hope appeal to help raise funds to develop a cure or treatment for A-T. Nancy Stanford, director of Macy's employee volunteer program, *Partners in Time*, spearheaded the appeal raising money and awareness over the month of February.

Thank you to Nancy and the *Partners in Time* leaders for making their first appeal such a success; and to all the employees who are planning to sell the A-T Hearts of Hope again next year!

Participating Macy's East Stores

Bedford, NH - Bergen Mall, Paramus, NJ - Cross Country, Yonkers, NY
Esplanade, Kenner, LA - Fashion Mall, Plantation, FL - Freehold, NJ
Hampton Bay, NY - Herald Square, NY - Hicksville, NY - Jersey City, NJ
New Orleans, LA - Oxford Valley, Langhorne, PA - Queens, NY
Rockaway, NJ - Stamford, CT - Staten Island, NY - Trumbull, CT
White Plains, NY - Woodbridge, NJ

Photo courtesy of Karen Lipman-White of Macy's Hicksville, NY

A Link Between the A-T Gene and Sporadic Breast Cancer?

Published research has shown that a special kind of alteration in the A-T gene exists in a certain type of colorectal cancer cell line. To determine if these findings are similar for breast cancer, the A-T Children's Project has awarded funding to Kevin Brown, PhD of the Louisiana State University Health Sciences Center for his research grant entitled, "Linking ATM and Breast Cancer." His research program promises to highlight a mechanism that could link ATM to sporadic breast cancer. This work will impact both our understanding of how breast cancer forms and how we treat this disease in the future.

A flurry of recent studies has shown that if A-T carriers possess a special type of mutation (or misspelling) in the altered copy of their *ATM* gene, this may significantly predispose them to breast cancer formation. Despite these recent findings, other research has failed to demonstrate an increased incidence of *ATM* gene mutations in patients with sporadic breast cancer, or breast cancer that occurs within the general population. However, Dr. Brown notes, "…several immunohistochemical studies are consistent with the notion that breast cancer cells show reduced ATM expression compared to normal breast epithelium. Thus, reduced gene expression, rather than specific genetic mutation, could explain the potential link between defective ATM function and sporadic breast cancer." So, an important question remains: In sporadic breast cancer, what contribution if any is made by alterations in ATM protein expression?

Kevin Brown, PhD

Dr. Brown's laboratory first began to consider this question when they observed that in a colorectal tumor cell line, ATM (or A-T) protein levels were decreased due to a phenomenon known as "epigenetic silencing" of the *ATM* gene. An epigenetic alteration does not occur within the sequence (or spelling) of the gene itself, but rather represents a chemical modification to the building blocks that make up the gene. In this case, an alteration has occurred in the portion of the A-T gene that controls or regulates the amount of protein to be made. This epigenetic modification results in the "silencing" of the *ATM* gene, such that significantly less A-T protein is made than would normally be the case. Now, Dr. Brown's laboratory plans to examine whether or not epigenetic silencing of the *ATM* gene plays a role in sporadic breast cancer formation.

Dr. Brown's team will analyze breast tumors that have been removed from patients using a specialized technique called Laser Capture Micro-dissection, to determine the amount of ATM expressed in these tumors. They will then determine if reduced ATM expression correlates with epigenetic silencing of the *ATM* gene. "Completion of this research…," states Brown, "will result in a greater understanding of [the role] that decreased ATM expression [plays] as a biomarker in breast tumorigenesis."

Promise: The A-T Cancer Clinic at St. Jude

The A-T Cancer Clinic was highlighted in the Spring 2003 issue of *Promise*, a publication of St. Jude Children's Research Hospital.

The article, written by Elizabeth Jane Walker, chronicles the experiences of Ricky Mahar, an eight year old with A-T who is being treated at St. Jude for non-Hodgkin lymphoma.

Because A-T patients are sensitive to traditional cancer treatments, Torrey Sandlund, MD and Michael Kastan, MD, PhD developed special protocols for A-T patients who are battling cancer. To read the story in its entirety, visit the A-TCP website at www.atcp.org.

Fundrais

Men's Night - Cedar Grove, NJ
Dance Marathon - Shippensburg, PA
Mad Dog Invitational Golf Tournament - Alto, MI
A-T Bike Run - Little Chute, WI
Poker Run - St. Benedict, PA

Working toget

Marathon
A-TEAM
Walt Disney World, Florida
January 11, 2004

Courage on the homefront

Residents
FYI

Swingin' for A-T
Golf Tournament
Houston, TX

HOP FOR A-T
CHANCELLOR SCHOOL

www.atcp.org

The Post-Crescent
Life&Style

For up-to-t
information
raising eve
area, pleas
www.atcp.or

National Broadcasting Society Telethon

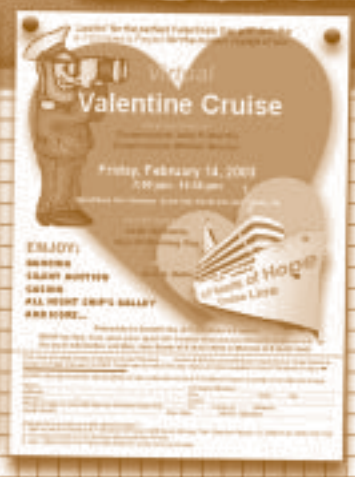
P-C EXTRA

Fight of their lives

Unrelenting disease cont
assault on bodies of two

"It's not coming fast enough for us. Realistically, I don't know. I hope to keep them
and hopefully, if not a cure, there will be a medicine that will prolong everything."

Oshkosh, WI



A Gift From The Heart

sing 2003

Cut-a-thon at Grondins - Waterford, MI
Benefit Concert - Elizabethtown, PA
Closest to the Pin - Hastings, PA
Cooking Classes - Cape Cod, MA
Dinner Dance - Bloomfield, NJ
Run for Rachel - Wayne, MI

Join the A-TEAM
HELP FUND RESEARCH NOW!

ner

FOR a cure

A-T Hearts of Hope
- Chelda Rest. Group - Greensboro, NC
- Macy's Partners in Time - Nationwide
- California Fitness Centers Challenge - Reynoldsburg, OH
- First Commonwealth Bank - Patton, PA

rally around boy with rare disease

A Night Out With the Stars 2★★3

HOME-RUN ATTITUDE

Upbeat boy inspires 1st A-T benefit

Carlisle, PA Walk for a Cure

Camp Fire Kids

Dubuque, Iowa
Wayland, Mass.
Carleton, Michigan
Romulus, Michigan
Troy, Michigan
Camp Wahkani, Missouri
Troy, Missouri
Carlisle, Pennsylvania
St. Benedict, Pennsylvania
Houston, Texas
Seagoville, Texas
Marysville, WA
CANADA
Fort Macleod, AB

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School Events

✓-Monroe School
Penny War
Monroe, CT

✓-Chancellor School
Hop for A-T
North Lauderdale, FL

✓-A-T Read-a-thon
Medway, Mass.

✓-CyFair High School's
Bike Rodeo
Cypress, TX

✓Hop for A-T
St. Benedict School
St. Benedict, PA

Memo: ← Note

More school events:

✓-O.H. Platt Middle School
Dress Down Day
Meriden, CT
✓-Airport Community Schools
Penny War
Carleton, MI
✓-JC McKenna Middle School
Fundraising Week
Evansville, WI
✓-Cambria Night's School
Penny War
Cambria Heights, PA
✓-Little Angels Pre-K
Bake Sale
Montreal, QC

Comprehensive A-T Eye Study Published in the American Journal of Ophthalmology

A recent eye study performed on patients with ataxia-telangiectasia has led to recommendations that have improved the quality of life of A-T patients through eyeglass prescriptions or surgery. The study also led to further evidence that in addition to the cerebellum, other areas of the brain may be affected by neurodegeneration as well.

The last study of ocular function in A-T patients was published more than three decades ago. Only seven individuals participated in this study, and the diagnosis of A-T in some of the participants was equivocal. In 1998, the A-T Children's Project began funding a two year comprehensive eye study to be conducted by Drs. Arman Farr and Benjamin Shalev of the Wilmer Eye Institute and their colleagues at the Johns Hopkins Hospital. The results of this study have now been published in the American Journal of Ophthalmology.

Dr. Farr and his team examined a total of 63 patients between the ages of 2 and 28 years whose diagnosis of A-T was confirmed by the A-T Clinical Center at Johns Hopkins. The average visual acuity for the study group was 20/31, near perfect. Pupillary constriction to light, visual fields, and Vestibulo-Ocular-Reflex (VOR: one of three systems in the brain that controls horizontal eye movement) were all normal. No changes were observed in the retinal blood vessels, and with the exception of one participant, no color vision abnormalities were detected.

However, Drs. Farr and Shalev's team did find that 24 of the patients (38%) had strabismus (eye misalignments) with crossed eyes being the most common (15/24). Thirty percent of the patients had apraxia of gaze (inability to quickly and/or precisely direct the eye to a different target) and every participant showed difficulty with accommodation (ability to change focus from far to near) and convergence (eyes aimed together to look at close objects). Dr. Farr's group also found the following extraocular motility anomalies:

- "abnormal response to a repetitive movement stimulus" was observed in 81% of the participants
- saccadic delay (a delay in the rapid jump of the eyes from one target to another), 76%
- jerky pursuit, 68%
- head thrust (when saccades was attempted), 30%
- nystagmus (repetitive eye oscillations) in 9%.

As is common in A-T, telangiectasia were observed on the conjunctiva (white part of the eyes) and/or the face of the vast majority of patients. These clusters of dilated blood vessels had no effect on ocular function.

Lastly, the researchers calculated an "eye severity score" for each individual in the study. This score was based upon seven abnormal ocular characteristics tested for during the eye exam. A participant was given one point for each characteristic they presented. The total score (0-7) was calculated and plotted against the respective patient's age. Interestingly, a correlation was found between eye severity score and increasing age.

What, however, is the underlying neurological cause of the visual abnormalities associated with A-T? Previous research performed by other groups has shown that certain of these abnormalities correlate with cerebellar dysfunction (e.g., strabismus and difficulty with convergence), while others (e.g., abnormal saccadic movement) are associated with disorders of the substantia nigra and basal ganglia. These findings support the increasingly popular hypothesis that A-T may involve damage to more than just one area of the brain.

Drs. Farr and Shalev's research not only represents the most up-to-date study of vision and A-T, but it also brought aid to many of the patients. The most common complaints made by participants were difficulty with reading and "poor vision at near." As a consequence of these findings, several individuals received glasses, and two others underwent successful eye surgery to correct the strabismus. Finally, the authors recommend that, "Clinicians managing these patients should attempt to assist [them] through spectacles with reading adds, base-in prism, and correction of ocular misalignment may improve their quality of life."

For more information on A-T neurology, vision, and assisitive technology, please refer to the A-TCP's "Handbook For Families and Caregivers" at www.atcp.org.

Progress Report

New Mouse Strains With the A-T Gene Being Generated

In an attempt to find genes that alter the severity of the A-T phenotype or physical outcome, Michael Weil, PhD of the MD Anderson Cancer Center in Houston, Texas has been placing a mutated version of the A-T gene into a variety of genetically diverse inbred mouse strains. Dr. Weil's research not only has the potential to generate an improved mouse model for A-T, but it may also lead to the identification of therapeutic targets that can reduce the severity of the disease.

Thus far Dr. Weil has begun transferring (or "introgressing") a nonfunctional copy of the A-T gene (*Atm*) to six genetically different mouse strains. Each of these strains is at a different point in the introgression process. It is important to note that the lines of A-T mice currently in existence, which have been studied extensively by scientists, were all made from a few closely related mouse strains. Although these mice recapitulate many of the characteristics of A-T seen in humans, they do not demonstrate the progressive neurodegeneration suffered by all A-T patients. Recalls Weil, "Studies of other disrupted genes in mice show that the symptoms they cause in the mice depend on the mouse strain in which they occur. The Ataxia-Telangiectasia Children's Project has

Continued on page 10

IMECAT SPONSORS FAMILY MEETING

Over 20 A-T families from around the United States gathered in Los Angeles for a meeting hosted by IMECAT (International Molecular and Epidemiological Consortium for A-T). Held from Sunday, February 16 - Monday, February 17 at the Sheraton Universal Hotel at Universal Studios, the meeting highlighted updates on cancer research in A-T carriers and the status of A-T clinical management and research. Speakers included Howard Lederman, MD, PhD, Director of the A-T Clinical Center at Johns Hopkins Hospital, Richard Gatti, MD at UCLA School of Medicine, Robert Haile, DrPH at USC/Norris Comprehensive Cancer Center, and Monica Alvarado, genetic counselor at USC/Norris Comprehensive Cancer Center.

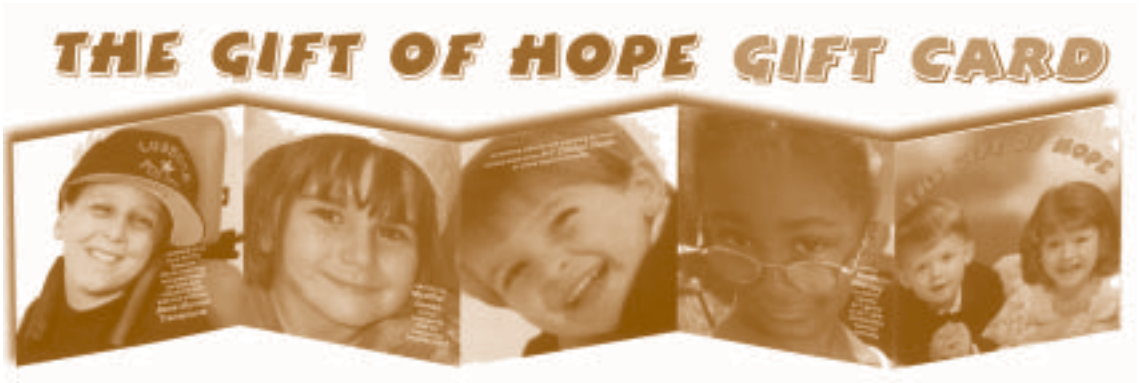
Lauren Gerstmann, MPH, IMECAT Project Manager and conference organizer, facilitated participation in the consortium's research project to study whether people who carry only one copy of an abnormal ATM gene have an excess risk of cancer compared to the general population. To participate in the study funded by the National Cancer Institute, contact Laura Dejong toll free at 866-591-9958 or via email at Ldejong@usc.edu.

Comments From Parents who Attended

"It was terrific! Thanks to doctors and staff for all their hard work and efforts for our kids. Loved it, wanted more, or course :-)"

"It was wonderful to see you all again and meet those we hadn't had the pleasure of meeting before. What a great turnout!"

"I attended the conference this weekend with my family, and I really enjoyed meeting a lot of the other families. Everyone was so amazing. I would like to thank the people who helped make the conference possible."



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New Mouse Strains *Continued from page 8*

funded us to transfer a disrupted Atm gene to…genetically diverse strains of mice in hopes that one of the strains will be useful as a model of motor coordination defects."

Dr. Weil's laboratory is also moving a copy of the knockout *Atm* gene into two other mouse strains as part of separate attempts to generate a mouse model of A-T that demonstrates motor defects. One of these specialized mouse strains lacks a thymus and mature T cells (a critical component of the immune system). This is important because the vast majority of A-T mice die at around 4-6 months of age from thymic lymphoma. Therefore, it has been hypothesized that the A-T mice may die before they ever have a chance to develop significant neuro-degeneration or overt ataxia. "The strategy here," notes Weil, "is: no T cells = no T cell lymphoma." So, athymic A-T mice may survive long enough to develop a neurodegenerative phenotype.

The second mouse strain into which Dr. Weil's laboratory will introduce a knockout *Atm* gene already has a specific genetic mutation called the X-linked Harlequin mutation. This genetic alteration causes the mice to suffer from dramatic cerebellar degeneration and overt ataxia, very similar to that seen in patients with A-T. Dr. Weil will determine if the A-T/Harlequin mice have an accelerated pace of cerebellar degeneration and ataxia. If Dr. Weil's laboratory is successful at generating an A-T mouse model with motor coordination defects, "the research community will have an animal model in which to test potential therapies for this symptom," notes Dr. Weil. An added benefit to Dr. Weil's research is that he may yet uncover new genes that not only accentuate the severity of A-T, but that also attenuate the disease phenotype. Such genes, and the proteins they code for, may be targeted therapeutically to reduce the severity of this disease.

Special note to researchers:

Dr. Weil would like to distribute breeding pairs of the new congenic Atm+/- strains to as many scientific investigators as possible. If any investigator would like more information on the strains of mice being used in the introgression process, and their state of completion, please email info@atcp.org.

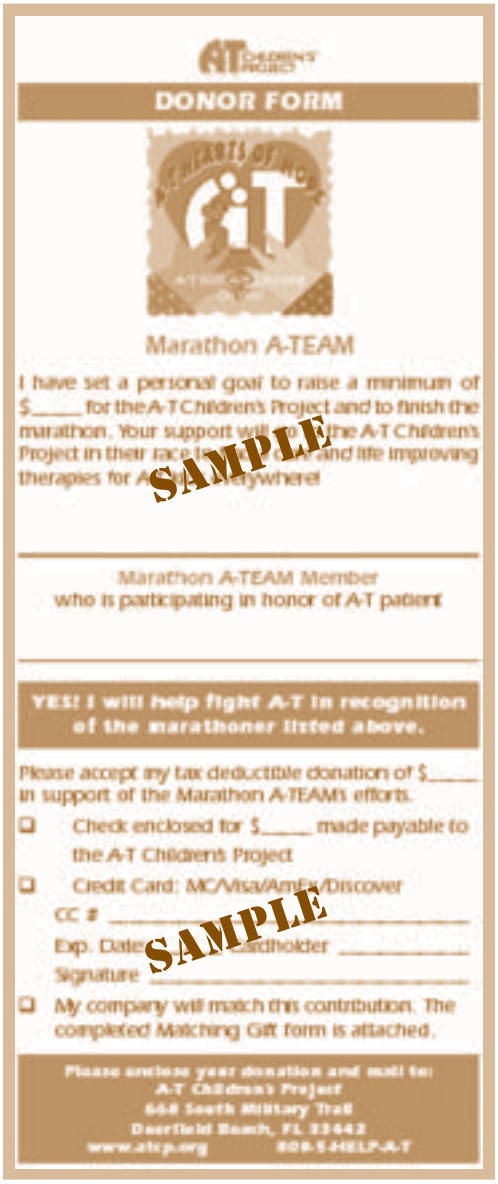
Marathon *A-Team!*

For the first time, the A-T Children's Project will have a team of runners represented at the Walt Disney World Marathon on January 11, 2004. The family and friends of Kate and Olivia Veldink, two young sisters with A-T from Hudsonville, Michigan, initiated the idea by recruiting participants to run in the 26.2 mile event. The runners are raising funds from sponsors who want to support their efforts.

The idea is spreading like wildfire among the A-T Children's Project fundraising team, and as of this printing, 99 runners are signed up for the event. Teams will have the name of patients with A-T whose families are participating. Teams as of this update are:

- Derek Baugus
- Samantha Hamrick
- Emily Hughes
- Joe Kindregan
- Jared Lane
- Jarrett and Quinn Margus
- Brooke Nelson
- Jennifer Powell
- Robbie Smarz
- Nichole Smith
- Katie and Tyler Smith
- Randy Van Hierden
- Kate and Olivia Veldink
- Alyssa Wood

Stay tuned through the website (www.atcp.org) and future issues of the Update for news on the Marathon A-Team's incredible progress! Donate online for your favorite team or marathon participant.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Marathon A-TEAM

I have set a personal goal to raise a minimum of $_____ for the A-T Children's Project and to finish the marathon. Your support will help the A-T Children's Project in their race to find [illegible] and life improving therapies for A-T everywhere!

SAMPLE

Marathon A-TEAM Member
who is participating in honor of A-T patient

YES! I will help fight A-T in recognition of the marathoner listed above.

Please accept my tax deductible donation of $_____ in support of the Marathon A-TEAM's efforts.

- ☐ Check enclosed for $_____ made payable to the A-T Children's Project
- ☐ Credit Card: MC/Visa/AmEx/Discover

CC # _____

Exp. Date _____ Cardholder _____

Signature _____

SAMPLE

- ☐ My company will match this contribution. The completed Matching Gift form is attached.

Please enclose your donation and mail to:
A-T Children's Project
668 South Military Trail
Deerfield Beach, FL 33442
www.atcp.org 800-5-HELP-AT

Progress Report

NIH Grant Awarded To Investigator at Duke University Medical Center - Preliminary Data Generated With Funds From A-TCP

An initial grant from the A-T Children's Project helped Xiao-Fan Wang, PhD of the Duke University Medical Center generate the preliminary data necessary for successful funding by the National Institutes of Health (NIH). Dr. Wang's research focuses on the regulation of the A-T protein (ATM) and some of its downstream targets. By providing a better understanding of how ATM functions, his work may help define possible targets of therapeutic intervention for ataxia-telangiectasia.

In addition to a successful NIH grant award, Dr. Wang's funding from the A-TCP has allowed him to submit a manuscript for publication based on some of his laboratory's recent findings. Dr. Wang is one of a number of scientists who are now attempting to decipher the mechanism by which the ATM protein is activated following DNA damage (See related article on ATM activation on page 1).

The A-T protein is referred to by scientists as a kinase because it transfers phosphate

Continued on page 11

NIH Grant

Continued from page 10

molecules to its target proteins or substrates. The acceptance of a phosphate group alters the activity of the substrates by either turning them on or off. This phosphorylation is a common mechanism of cellular communication and the A-T protein itself is regulated in this manner. However, Dr. Wang's laboratory now has data indicating that a dephosphorylation event (the removal of a phosphate group) may be important for switching on ATM following damage to DNA. Many cellular proteins are regulated by multiple phosphorylation/dephosphorylation events, and Dr. Wang's research indicates that ATM may be one such protein.

Dr. Wang and his team are also investigating the role of another protein, called Rad9, in an ATM-mediated signaling pathway following DNA damage. Rad9 belongs to a family of checkpoint proteins, and it forms a complex with two other such proteins, Rad1 and Hus1. Scientists refer to Rad9/Rad1/Hus1 together as the "9-1-1 complex." Checkpoint proteins ensure that the cell cycle (cell growth) does not proceed in the presence of damaged or incompletely replicated DNA. Following damage to DNA, ATM helps activate various cell cycle checkpoints to ensure that cell growth stops and DNA repair begins. Dr. Wang's new data demonstrates that the 9-1-1 complex, and specifically Rad9, may be important for mediating checkpoint signaling by ATM following irradiation-induced DNA damage.

It is hoped that novel insights such as those generated by Dr. Wang and his laboratory will help uncover new ATM-mediated pathways and specific therapeutic targets for A-T.

Funding from the A-TCP helps make discoveries such as these possible. Notes Wang, "We would like to express our appreciation to the A-T Children's Project for the generous support to this research project."

Gift Gallery

A-T Hearts of Hope® 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.

The sterling silver necklace made its first appearance in January 2003, at *A Very Special Evening*, the annual New York theater event to benefit the A-TCP. A-T mothers Lynn Bement and Suzi Kindregan presented the necklace to actress Priscilla Lopez, who hosted the event.

Message from Ann Partlow:

A-T Hearts of Hope hearts, like A-T children, 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 A-T children.

..... $75.00 ea.*

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Engraved sterling silver "A-T Hearts of Hope" ring
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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.
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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.

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*Prices include shipping and handling.

To order, send check or money order payable to:
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