A-T CHILDREN'S® PROJECT UPDATE

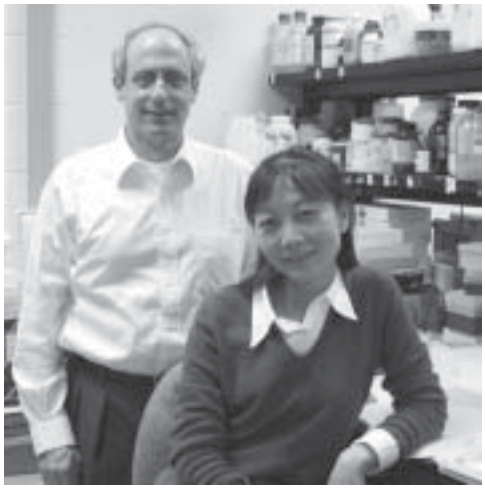
For Families, Friends and Supporters

November 2003

Alzheimer's Disease and A-T May Share Similar Cause of Brain Cell Death

Researchers in Ohio suspect that the brain cell death occurring in children with A-T may have the same cause as the brain cell death seen in more common diseases, including Alzheimer's Disease and ALS (Lou Gehrig's disease). If these scientists are correct, this cell death mechanism would reveal a new target for developing drugs to help prevent the loss of muscle control suffered in A-T. To explore this possibility, Yan Yang, PhD, in collaboration with Karl Herrup, PhD, at Case Western Reserve University School of Medicine in Ohio, has been awarded funding by the A-T Children's Project for a project entitled: *Cell Cycle Events in Ataxia Telangiectasia: Human and Mouse.*

Mature brain cells do not normally undergo cell division. When, for any reason, they enter into a cell division cycle, they will ultimately die. Studies both in vivo and in vitro show that cell division is not simply associated with neuronal death, but that it is sufficient to cause the death of brain cells.



Karl Herrup, PhD and Yan Yang, PhD of Case Western Reserve University School of Medicine

"[These] findings," states Yang, "suggest that nerve cell death and unregulated cell division are closely related phenomena: **any event that forces a post-mitotic [non-dividing] neuron back into the cell cycle will result in its death.**" Indeed Yang and her colleagues have gone so far as to explicitly speculate about this linkage (Herrup and Yang, TRENDS in Molecular Medicine Vol. 7 No.11 2001). Yang and Herrup hypothesize that, similar to AD, the loss of cerebellar neurons (known as Purkinje cells) in A-T may be the result of these cells re-entering an abortive cell division cycle which ultimately kills them, thereby contributing to the progressive ataxia associated with A-T. The link is especially compelling in A-T because of the observed predisposition towards cancer (a disease of abnormal cell cycling or proliferation) in patients with this disorder.

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New Drug May Prevent Neurodegeneration and Enhance Radiation Therapy in Patients with A-T

A brand new molecule being further developed for clinical use has been shown to be neuroprotective in a rat model of stroke and therefore may possibly help prevent neurodegeneration in patients with A-T. In addition, this molecule has been shown to prolong the survival of mice with metastatic cancer and could be a potential adjunct treatment to radiation to combat lymphoma or other predisposed cancers in A-T patients.

Researchers led by Jie Zhang, PhD at Guilford Pharmaceuticals, Inc. in Baltimore, Maryland, recently received funding from the A-T Children's Project for their grant entitled: *Developing PARP Inhibitors that Can Penetrate the Blood Brain Barrier by Oral Dosing.*

Ataxia-telangiectasia (A-T) is characterized by progressive degeneration of cerebellar neurons and predisposition for cancer. The mutation(s) in the *ATM* gene that cause A-T render cells sensitive to DNA damage, defective in DNA repair, and result in the prolonged activation of a protein called poly(ADP-ribose) polymerase-1 (PARP-1) which typically helps to repair damaged DNA. In normal cells, over-activation of PARP-1 can deplete cellular energy stores, ultimately resulting in cell death. In cancer

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The Story of the Marathon A-TEAM… or … how did they get us into this?!

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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 - The 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

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 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 - 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

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

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 - 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

NEW **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

NEW **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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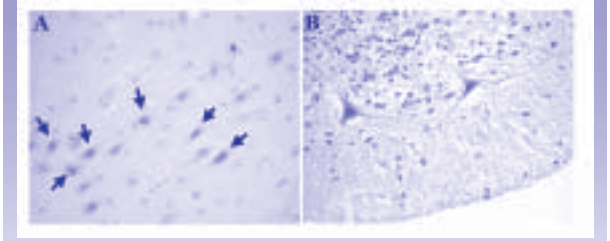
Alzheimer's... *Continued from page 1*

In support of this hypothesis, Yang and Herrup have found that Purkinje cells from mature A-T mice undergo replication of their genetic material or DNA, a hallmark characteristic of cell division. Unfortunately, these mice die from thymic lymphoma before any neuronal cell death is observed. However, A-T mice and their wildtype (normal) counterparts will be used by Yang and her colleagues to investigate the role(s) of the A-T protein in preventing an abortive cell division cycle in Purkinje cells.

In addition to the mouse model of A-T, Yang and Herrup have also observed evidence of inappropriate cell cycle re-entry in the Purkinje cells of human A-T autopsy material. When they compared cerebellar tissue from control and A-T autopsies, they found that a significant number of Purkinje cells from the A-T patients possessed an increased level of cell cycle-related proteins as compared to the control material, proof that the brain cells of patients with A-T could be inappropriately entering a cell division cycle. Yang is excited about these results as they offer a possible connection between the symptoms in dividing tissue (e.g. the immune system and predisposition to immune-related cancers) and, for the first time, the nervous system.

Yang and her colleagues will use their funding from the A-T Children's Project to confirm their preliminary data in human tissue and expand their studies using the mouse model for A-T. Should they be successful in confirming their hypothesis of neuronal cell death, blocking the re-entry of Purkinje cells into a lethal cell cycle could represent a therapeutic intervention to help alleviate the ataxia seen in patients with A-T.



Cell cycle protein (cyclin B) is expressed in the hippcampal neurons of Alzheimer's disease patient (A) and in the Purkinje cells of A-T patient (B).

A-T Children's Project Highlighted on CNN

A-T Children's Project co-founder and president Brad Margus was featured on CNN on September 17, 2003. Margus, who currently runs Perlegen Sciences, a biotech company, was profiled on Lou Dobbs' *Moneyline* during a five-part series on the extraordinary careers of select CEOs. The 4-minute spot, much of which was filmed at the A-T Children's Project's offices in Deerfield Beach, Florida brought much needed awareness to ataxia-telangiectasia.

Kemeny Honored as Volunteer of the Week in Detroit, MI

VOLUNTEER OF THE WEEK
PEGGY KEMENY

Volunteer: Peggy Kemeny, 46, of Canton.

Organization: AT Children's Project.

What she does: Kemeny started volunteering about seven years ago after one of her daughters was diagnosed with Ataxia-Telangiectasia (AT). She has organized an annual AT walkathon for seven years and has held fund-raising dinners. Kemeny makes presentations to raise awareness of the disease with local service groups.

About AT: It's a genetic disease that attacks in early childhood. It progressively affects coordination, predisposes children to cancer and severely compromises their immune systems.

Personal: Peggy and her husband, Dennis Kemeny, have two daughters, Alyson and Rachel. She is a teacher at Flat Rock Preschool.

Upcoming fund-raiser: The Kemenys will host a Hog Wild Pig Roast at 6 p.m. Saturday at the UAW Hall, 24250 Telegraph, Flat Rock. Tickets are $20 in advance or $25 at the door. For information, call 734-654-0416, anytime.

If you'd like to help: Call the AT Children's Project at 800-649-5728, 8:30-5:30 weekdays or visit www.atcp.org.

To nominate a Volunteer of the Week, call Jacksonville O. Griffith at 313-222-6000 anytime.

A-T mother and A-TCP volunteer Peggy Kemeny was featured in the *Detroit Free Press* newspaper on October 29 as ***Volunteer of the Week***. Peggy has hosted the A-T Walkathon for seven years, and along with A-TCP volunteer Carla McLaughlin hosted their second annual **HOG WILD** Pig Roast on November 1.

Congratulations, Peggy!

www.atcp.org

International A-T Workshop Held "Down Under"

On September 10, 2003, eighty researchers met in Fraser Island, Australia for a four day workshop on *The Role of ATM and Related Proteins in DNA Damage Response.*

The meeting was chaired by Martin F. Lavin, PhD of the Queensland Institute of Medical Research at the University of Queensland.

The international committee for this workshop included Patrick Concannon, PhD, Richard A. Gatti, MD, Peter J. McKinnon, PhD, Yosef Shiloh, PhD, Malcolm Taylor, PhD, Robert Ullrich, PhD and Brad Margus.

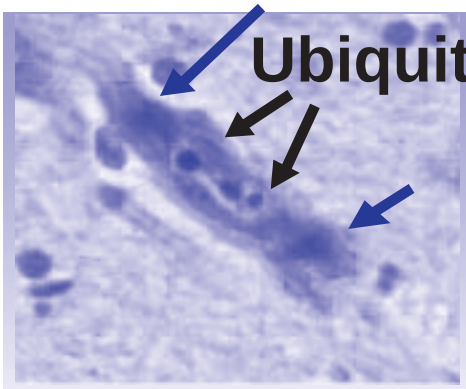
Major sponsors of the meeting were the A-T Children's Project and the A-T Medical Research Foundation.

Johns Hopkins Investigator Examines the Extra-Cerebellar Features of A-T

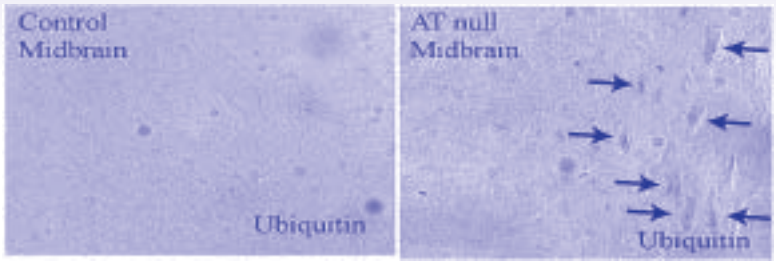
A hallmark characteristic of ataxia-telangiectasia (A-T), seen in all patients with this disease, is a progressive ataxia due to the apparent loss of Purkinje cells within the cerebellum. However, some research suggests that other areas of the brain may also be affected by A-T. Such a possibility expands the potential treatment options for individuals with this disease.

Allen Mandir, MD, PhD at Johns Hopkins University School of Medicine has been studying the extra-cerebellar features of A-T for approximately two years and has recently received funding from the A-T Children's Project to continue these studies.

Previously, Dr. Mandir performed motor control experiments on a cohort of patients who visited the A-T Clinical Center at Johns Hopkins and found that they possessed extra-cerebellar features including parkinsonian-like movement abnormalities, e.g. increased muscle tone (muscle stiffness or tension). Typically, cerebellar movement disorders result in a loss or reduction in muscle tone. Together, Dr. Mandir's physiological studies on A-T patients demonstrate that areas of the brain outside of the cerebellum appear to be involved in A-T.



A dopamine-producing neuron in the substantia nigra from human A-T post mortem tissue. Dark arrows indicate the intranuclear and perinuclear inclusion bodies that contain ubiquitin. These types of inclusions were found in 7 out of 8 A-T patient post mortem tissues.



In the control mouse midbrain (area of the substantia nigra), there is little to no ubiquitin staining (left panel). However, the A-T null mouse midbrain demonstrates an abundance of ubiquitin staining (right panel).

Interestingly, two models of Atm-deficient mice (mice that lack the A-T protein) have demonstrated a selective loss of dopamine-producing neurons, the same neurons that are lost and/or are nonfunctional in persons with Parkinson's disease.

Recently, Dr. Mandir's laboratory, along with Drs. Crawford, Lederman and Pardo, has also shown that in post mortem tissue from 7 out of 8 A-T patients, there was evidence of brain abnormalities in a region other than the cerebellum that could explain the parkinsonian-like movements of A-T patients. Dr. Mandir's lab found ubiquitin-positive intraneuronal inclusions (or inclusion bodies) in the region of the brain known as the substantia nigra, which houses the dopamine-producing (dopaminergic) neurons. No such inclusions were observed in the cerebella from these 8 patients. Ubiquitin-containing inclusions represent knots or aggregates of improperly folded, modified and/or damaged proteins. These protein aggregates can be toxic and lead to cell death.

Normally, to maintain proper functioning, cells will eliminate malformed proteins via a process scientists call ubiquitylation. During this process, the damaged proteins are tagged with molecules of ubiquitin, which marks them for degradation and elimination. Abnormalities in the protein degradation process have been found to contribute to the pathology of various neurodegenerative diseases.

Dr. Mandir and his laboratory will undertake a more in-depth study of the effects that alterations in the A-T protein have on the unfolded protein response or protein degradation process. In addition, they will continue their studies of extra-cerebellar inclusion formation. Notes Mandir, "Further understanding of the composition and mechanism of inclusion formation will lead to improved insight into neuronal degradation in A-T, and suggest novel therapeutic interventions."

Celebrity Poker Showdown

Tune in to Bravo at 9 p.m. Dec. 2 for the "**Celebrity Poker Showdown**" debut, when celebrities will play poker to benefit their favorite charities. Sources close to the show tell us that one of the celebrities will be playing for the A-T Children's Project. Hmmmm... Who could that be? Stay tuned.

A-T Gene Facts - Quiz

Q. What does "ATM" stand for?

A. Ataxia-Telangiectasia Mutated. Yossi Shiloh's lab in Israel announced the discovery of the ATM gene in June 1995.

Nelson Competes in Cerebral Palsy Games

Thirteen-year-old Brooke Nelson from Michigan participated this summer in the CP games held at Michigan State University. Brooke, who has A-T joined differently abled people of all ages to compete in bowling, softball throw, club throw, and 60 meter wheelchair dash using a manual wheelchair.

Brooke Nelson

Brooke also won 5th and 6th place ribbons for handicap horseback riding at the 4-H Fair.

Her determination and positive outlook are an inspiration to all who know her.

SUPERMARKET CHAINS' DONATION PROGRAMS

ALBERTSON'S COMMUNITY PARTNERS - Every time you shop at Albertson's, present your Albertson's Community Partners Card to the cashier for scanning, and a percentage of the dollars you spend is directed to the A-TCP. Call 1-800-543-5728 to receive your card.

FOOD LION'S "LION SHOP & SHARE" - Link your Food Lion MVP card to the A-TCP to "Shop and Share" for us. To link your MVP card to the A-TCP, go online to www.foodlion.com. Members have to re-link their cards in the fall of each year.

JC McKenna Middle School Rallies for Ethan

JC McKenna Middle School in Evansville, Wisconsin, held a great fundraiser in honor of fifteen-year-old Ethan Flood, a student with A-T. By selling A-T Hearts of Hopes, the students, teachers, and families joined together to raise thousands of dollars for research. Their efforts also raised awareness of A-T within the community. Thanks to Karen Bass and everyone who helped with this event.

Ethan Flood

The Combination of an Iron Chelator and Aspirin is Being Tested in A-T Mice

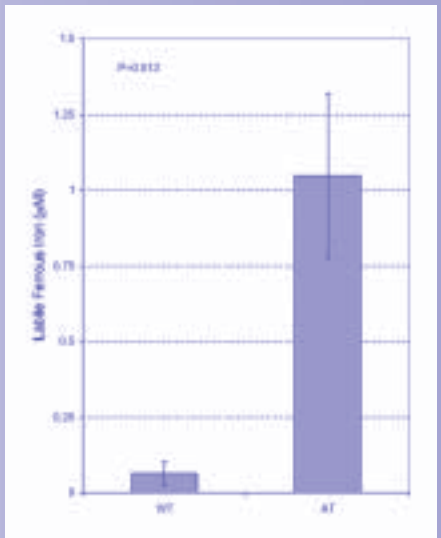
Aspirin and a compound capable of binding intracellular iron are being used in combination in an attempt to increase the overall lifespan of A-T mice.

A growing body of evidence indicates that, compared with normal cells, A-T cells appear to be in a state of chronic oxidative stress and/or exhibit an increased sensitivity to external oxidative agents. These observations imply that A-T cells have an increased level of reactive oxygen species (ROS) and/or possess a decreased ability to handle intracellular ROS and externally applied oxidants. ROS and external agents that represent oxidants or cause oxidative stress (like irradiation) can damage cellular DNA, lipids, and proteins. If not detoxified properly, external oxidants and ROS will cause cell death.

Under conditions of oxidative stress, intracellular labile iron is released and in turn can mediate the toxic effects of external oxidants. Rodney Shackelford, DO, PhD, a former post doctoral fellow in the laboratory of Dr. Suming Wang at the Stoddard Cancer Research Institute in Des Moines, Iowa, recently published data demonstrating that the iron chelator (binding agent) desferrioxamine, increased the genomic stability and improved the growth of A-T cells in culture. Treatment with desferrioxamine also protected the A-T cells against the externally applied oxidant, *t*-butyl hydroperoxide. "While preliminary, our findings suggest that A-T might be, in part, a disorder of iron metabolism and treatment of individuals with A-T with desferrioxamine might have clinical efficacy," comments Shackelford.

Rodney Shackelford, DO, PhD

Interestingly, before leaving Dr. Wang's lab, Dr. Shackelford found that A-T mice have elevated levels of iron in their serum as compared to normal mice. With new funding from the A-T Children's Project, Dr. Wang's laboratory will test the possibility that the combination of desferrioxamine and aspirin (which also possesses antioxidant capabilities and has been hypothesized to bind iron) can increase the lifespan of A-T mice. These studies could potentially lend credence to the idea that iron binding agents can affect the clinical course of A-T.



Serum labile iron concentration is significantly increased in A-T mice (AT) as compared to a wildtype (WT) or control mice.






We are the A-TEAM, the

The Story of the *Marathon A-TEAM*... or ... how did they get us into this?!

It all started with **Jodi Medina** in Ada, Michigan. After her sister-in-law's two nieces were diagnosed with A-T, she thought of a way to combine her hobby, marathon running, with fundraising to help find a cure or treatment to save **Kate and Olivia Veldink**.

Jodi and her sister-in-law **Laura Vos** spread the word about their training for the **WALT DISNEY WORLD®** Marathon in January 2004. Everyone thought Jodi was half out of her mind (especially since she delivered a baby girl in July 2003!). But, Jodi and Laura are not easily dissuaded, so the tight-knit group decided: "If you can't beat them, join them!" Now Jodi and Laura, along with Kate and Olivia's parents **Dave and Mary Veldink**, have encouraged no fewer than **55 friends and relatives** to run, walk, or crawl to the finish line, and to **raise much-needed funds** and awareness for research on ataxia-telangiectasia at the same time!

Not to let a good opportunity for a new national fundraising event slip by, our very own fundraising coordinator **Aletia Patterson** quickly mobilized the forces – and encouraged other fundraising friends and families of A-T children to join in the fun … and pain! … of marathon training.

The A-TCP now has **244 Marathoners and Half Marathoners** running in honor of **A-T patients**.









mighty, mighty A-TEAM !

To sponsor a ***Marathon A-TEAM*** member, or to check for updates on our progress, please visit our website at **www.atcp.org**. And, think of us on January 11th when we make our first appearance as a group at the **2004 WALT DISNEY WORLD® Marathon Weekend** – when the most magical miles in the world will turn into **BIG DOLLARS** to fund research to find a cure or life-improving therapies for A-T!

Starting in February 2004 you can sign up on our website at www.atcp.org to **join** the **Marathon A-TEAM** for the **2005 WALT DISNEY WORLD® Marathon**. You can also join the **A-TEAM** and help raise funds for a cure by participating in any other marathon.




A New Mechanism to Partially Compensate for the Lack of the A-T Protein in Cells

Can a method be found to speed up the delayed activation of a tumor suppressor in A-T cells, ultimately leading to a treatment that could decrease both sensitivity to radiation and predisposition to cancer in A-T patients?

To answer this question, France Carrier, PhD at the University of Maryland in Baltimore, has been awarded funding by the A-T Children's Project for her grant entitled *New mechanisms to activate p53 function in A-T cells.*

Ionizing radiation (IR) can cause cells to become cancerous. In normal cells an important protein called p53 acts as a tumor suppressor in response to IR, effectively rescuing cells from becoming cancerous.

The primary function of the A-T protein (termed ATM for Ataxia-Telangiectasia Mutated) is to chemically modify and activate the tumor suppressor p53 in response to IR. Therefore, in A-T cells – which lack the protein ATM – one might expect that the p53 protein would not be activated at all. However, in cells derived from A-T patients, the p53 response to IR is delayed, suggesting that proteins other than ATM can eventually activate p53. Unfortunately, "…for A-T patients," notes Carrier, "the delayed p53 response is detrimental and leads to several cellular aberrations that can cause cancer."

Interestingly, Carrier's lab has recently shown that a protein called nucleophosmin (NPM) can set a threshold for p53 response to ultra violet (UV) radiation mediated by the ATM-related protein ATR. Reduced levels of NPM can decrease the UV dose at which p53 can be activated. Because ATR and ATM often modify the same protein targets, and because ATR can also be activated by IR, Carrier proposes that reduced levels of NPM might also restore an earlier p53 response to IR in A-T cells. Restoration of early p53 activation could potentially allow A-T cells to suppress tumor development in a manner similar to normal cells.

The Carrier lab will also study the possibility that nucleolin, a protein that interacts with both NPM and p53, similarly affects the p53 response to IR.

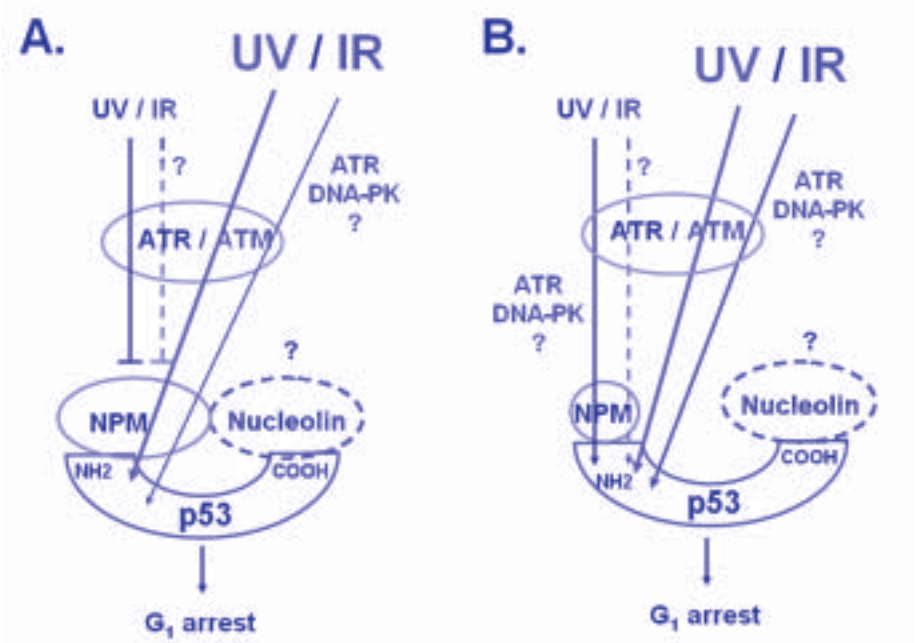


***Fig. 1**: A) At low levels of DNA damage including **UV** radiation, and possibly IR, and in the presence of NPM, p53 cannot be activated. At high levels of DNA damage (higher **UV** doses), p53 activation does occur in spite of NPM. Activation of p53 may be mediated by other kinases (ATR, DNA-PK). B) When NPM levels are reduced, the doses at which p53 can be activated are also reduced. In AT cells reduction of NPM may allow activation of p53 by other kinases at low IR doses. Nucleolin interacts with p53 and NPM. Its role in p53 activation will be explored.*

Therapeutically, it is hoped that the prompt activation of the tumor suppressor p53 will reduce the sensitivity to radiation and predisposition to tumor development observed in patients with A-T.

New York, New York
The Lincoln Center Institute
Monday, January 19, 2004

Boston, Massachusetts
The Waltham Westin
Saturday, March 6, 2004

POWELL FAMILY PUTS THE *FUN* IN *FUN*DRAISING!

Jennifer's parents, Wade and Suzi Powell of Troy, Michigan, are having fun this fall with a Euchre Tournament, a Bowling Tournament, and their annual A-T Walk for a Cure to fund research to find a cure or life-improving therapies for patients with A-T.

Jennifer Powell

Wade is also training to run the **2004 WALT DISNEY WORLD® Marathon** as part of the **A-TCP's Marathon A-TEAM**.

Good luck Wade!

O'Reilly Swims From Alcatraz to Help Raise Funds For A-T Research

Swimming competitions are not the same as marathons... nonetheless, they are a lot of work. Add strong currents, icy cold water, wind and sharks and you now have the "Swim from Alcatraz" in the San Francisco Bay.

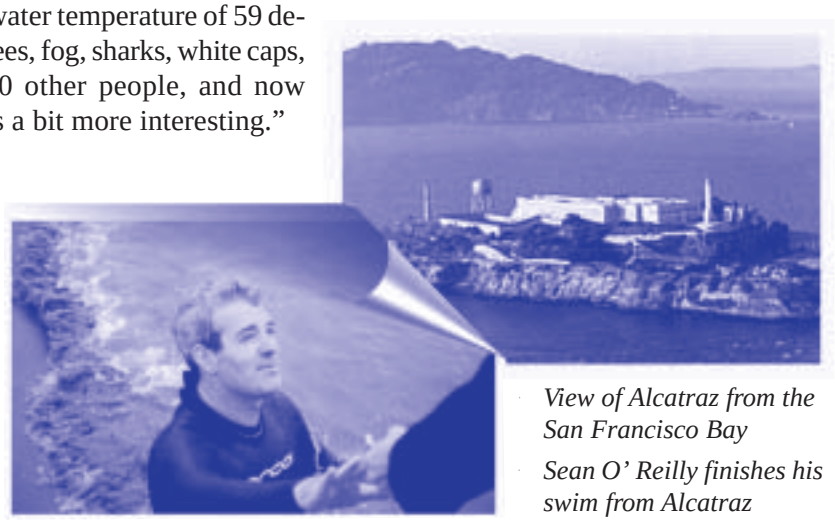
To enter, Sean O'Reilly paid $100 and joined about 400 other swimmers in the annual competition. Why? To help his friends, Dave and Mary Veldink raise funds for the A-T Children's Project.

"Dave and Mary, who are not athletes, are training for the Disney Marathon to raise money to find a cure for A-T. I have been so inspired by the Veldinks' attitude that I wanted to help in some way," O'Reilly said.

"This year I thought the swim from Alcatraz would be a way to raise money for A-T and maybe help the Veldink girls."

The swim is very challenging, O'Reilly said. "By way of a straight line, the distance is approximately 1.5 miles, but it is impossible to swim straight to shore due to the ever-changing currents and tricky tides. Throw in a water temperature of 59 degrees, fog, sharks, white caps, 400 other people, and now it's a bit more interesting."

Professional and amateur open-water swimmers from all over the world enter the race, O'Reilly said. This year the finishing times ranged from 28 minutes to one hour, 45 minutes. O'Reilly swam the distance in 40 minutes, 48 seconds, and raised $1,000 for A-T research.



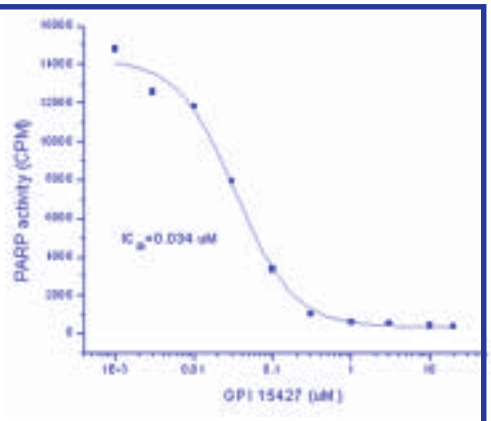
View of Alcatraz from the San Francisco Bay

Sean O' Reilly finishes his swim from Alcatraz

New drug ... *Continued from page 1*

cells, PARP activity contributes to the resistance of tumors against radiation and chemotherapy that damage DNA. Recently published data has shown that inhibition of PARP-1 can enhance the growth of non-cancerous A-T cells in culture. In addition, Zhang's laboratory has found that PARP-1 inhibition enhances the effect, and thus reduces the required doses, of radiation and chemotherapies to eradicate cancer cells.

Guilford Pharmaceuticals, Inc. is one of the leading pharmaceutical companies in developing PARP inhibitors for treating stroke and cancer. As such, Guilford has synthesized various families of potent, small molecule PARP-1 inhibitors for possible clinical development to treat these disorders. For example, one of their new drugs has demonstrated neuroprotection in a rat model of transient cerebral ischemia, or stroke, after intravenous dosing. This same PARP inhibitor also increases the survival time of mice with various types of cancer by enhancing the effect of an anti-cancer agent and radiation. Lowering doses of cancer therapy by PARP inhibitors may benefit A-T patients who are predisposed to cancer and yet cannot tolerate conventional radiation therapy.



Increasing concentrations of one of Guilford's leading PARP-1 inhibitors effectively decreases PARP enzymatic activity.

In their grant, Guilford Pharmaceuticals proposes to: 1) determine the bioavailability of leading PARP-1 inhibitors after oral dosing, 2) establish initial toxicity profiles of these compounds, and 3) test their efficacy in a mouse model of brain tumors. Currently, Guilford's PARP inhibitors have only been administered intravenously. Zhang and his collaborators believe that orally active PARP-1 inhibitors, that can penetrate the blood brain barrier with minimal side effects, will be the most suitable for further clinical development.

The A-T Children's Project hopes that PARP inhibitors will prove effective as adjuncts to radiation therapy for cancer treatment and as compounds capable of slowing down or preventing the neurodegeneration observed in A-T.

VEHICLE DONATION PROGRAM

Just in time for tax season - you can donate any used vehicle e.g. cars, trucks, motorcycles or boats, to receive a tax deduction while benefiting the A-TCP. Go to our website at **www.atcp.org** and click on the car donation button or go directly to:

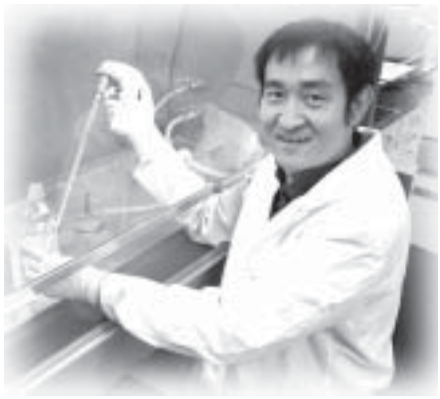
http://www.v-dac.com/org?id=650427215

A Defect in One Cellular Signaling Pathway May Underlie the Multisystem Abnormalities Observed in A-T

Potential therapeutic targets common to each of the major organ systems affected by A-T could be identified, if a hypothesis that the loss of ATM may affect a certain cellular signaling pathway critical to all these cell types proves true.

Only certain cells of the body seem to be particularly sensitive to the loss of ATM, the A-T protein. These include cells of the immune system, reproductive system and brain; hence the immunodeficiencies, immune-related cancers, gonadal atrophy and ataxia observed in patients with A-T. The A-T Children's Project is pleased to provide funding for a grant proposal submitted by Wenan Qiang, PhD, of the University of Texas MD Anderson Cancer Center entitled *ATM Modulation of CREB Phosphorylation in the Developing Thymus, Testes, and Cerebellum*. Dr. Qiang will use the mouse model of A-T to exam how the loss of ATM affects the CREB (cAMP response element binding) protein signaling pathways in these three tissues.

CREB is an important protein that binds to a special sequence in a variety of different genes, thus regulating the expression of these genes. The genes regulated by CREB play important roles in cell growth and differentiation, and research has shown that CREB is involved in the proper differentiation of T cells (cells of the immune system), germ cells (cells of the reproductive system) and neurons (brain cells). Therefore, CREB signaling pathways are critical for the proper development of those cells also affected by A-T. The objective of Dr. Qiang's research is to understand the functional role of ATM in development of T cells, germ cells and cerebellar neurons, and to determine if ATM exerts its function(s) by modification of CREB and/or its signaling pathways.



Wenan Qiang, PhD, of the University of Texas MD Anderson Cancer Center

To this end, Dr. Qiang has preliminary data demonstrating that the levels of the CREB protein, and a modified version of this protein, are significantly reduced in the thymus (organ where T cells of the immune system mature), testes, and cerebellum of Atm-deficient (A-T) mice.

Dr. Qiang will also address an as of yet unanswered question in A-T research, that is: Why don't A-T mice demonstrate the same type of cerebellar degeneration and overt ataxia seen in humans with this disease? Interestingly, mice that lack another protein involved in the CREB signaling pathway, CaMKIV (calcium/calmodulin-dependent protein kinase IV), do become ataxic and develop an altered gait and loss of motor control consistent with the cerebellar defects observed in A-T patients. Therefore, Dr. Qiang and his colleagues will test the hypothesis that the CaMKIV-CREB signaling pathway may not be dependent on Atm in the mouse cerebellum, which is perhaps why Atm-deficient mice do not appear ataxic.

"If successful," states Qiang, "insights gained from these studies may shed light on therapeutic intervention[s] targeted to the CREB pathway." It is the hope of the A-T Children's Project that Dr. Qiang's research will ultimately lead to an effective means of treating the immune, reproductive and cerebellar abnormalities characteristic of A-T.

Jehlik Runs Chicago Marathon - Raises over $13K for Research

October 25, 2003

Dear Friends & Family,

I did it! Thanks to your overwhelming support and generosity, I am happy to report that I completed the LaSalle Bank Chicago Marathon in a time of 4 hours and 1 minute! The 85 training runs that spanned four states and three counties over five months actually worked!

It is hard to describe the emotion of this amazing event. The Chicago Marathon is the largest marathon in the U.S. with 40,000 runners. In addition, there were 1,000,000 spectators along the race route! We ran on a glorious day bathed in sunshine.

It was at the 22 mile mark that I was confident I would complete the run. Yet when I made the final turn to cover the last 300 yards, running past huge crowds including my family, I was overcome with emotion. I had just run 26.2 miles, hoisted and pushed by each of you. My personal goal was to raise $7,500.00 for the A-T Children's Project. I am pleased to say that the A-T Children's Project has received over $13,000.00 for all your efforts! Almost double the goal I set.

Thanks to each and every one of you who supported me, and the A-T Children's Project. Jeff, as well as many other A-T kids will be touched by your giving. Your thoughtfulness and generosity truly pushed me through this life impacting event.

With warmest regards,

Greg Jehlik

Thanks for everything!

MAKING A LIST AND CHECKING IT TWICE? SHOP ONLINE TO BENEFIT THE A-TCP

Holiday time is here! Cooking, decorating, greeting cards and... GIFTS! Don't fight the traffic and the crowds! Buy the perfect gift for everyone on your list at the same or even better prices than the stores. Visit the mall without leaving your home -- go online to **www.atcp.org** and click on the link to GreaterGood.com (purple button at the bottom right hand side of the page) to start your holiday shopping.

Online shopping continues to gain popularity because of its convenience, and this holiday season you can help raise a lot of money for research while doing your shopping. Best of all, there's no extra cost to you or to the A-TCP.

Happy Holidays!

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 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.***

A.

B. A-T Hearts of Hope Ring

Engraved sterling silver "A-T Hearts of Hope" ring ..... **$15.00 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 at the request of Sue Mastin, aunt of Amy Estes of Tennessee, who has A-T. The 80 - page book is full of easy recipes and cooking tips. This is a great bargain that will make a wonderful holiday gift. ..... **$15.00 ea.***

C.

A-TCP Logo-Wear

D. 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.
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D.

E. White Polo

Pre-shrunk 100% cotton white polo, embroidered with red and black logo
Sizes: Med, Large, XL and XXL ..... **$30.00 ea.***

E.

F. Red Polo

Pre-shrunk 100% cotton red polo, embroidered with black logo.
Sizes: Sm, Med, Large, XL, XXL and XXXL ..... **$30.00 ea.***

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***Prices include shipping and handling.**

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

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2. Order online at www.atcp.org
3. Call: 954-481-6611 or toll-free 800-5-HELP-A-T (800-543-5728).

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A distinctive gift for special occasions and holidays, this full color card spotlights children with A-T and highlights funded research projects that can lead to a cure or life-improving therapies for ataxia-telangiectasia. It is great for holiday greetings from individuals or corporations.

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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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