UPDATE
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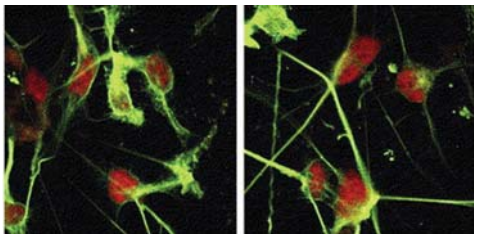
August 2007
FOR FAMILIES, FRIENDS AND SUPPORTERS

RESEARCH UPDATE:
ISRAELI SCIENTISTS REVEAL A MAJOR ROLE FOR THE A-T PROTEIN IN CEREBELLAR NEURONS

With funding from the A-T Children's Project, researchers **Yossi Shiloh, PhD** and **Ari Barzilai, PhD**, at **Tel Aviv University in Israel**, have discovered a major role for the A-T protein (ATM) in brain cells. Arguably the most prominent and devastating symptom of ataxia-telangiectasia (A-T) is relentless cerebellar degeneration, so an understanding of how ATM functions in the brain is critical for the identification of novel central nervous system (CNS) drug targets for this disease.

From the study of various proliferating (actively dividing) cell lines, it has been determined that ATM coordinates the cell's response to a particularly lethal type of damage to its genetic material called DNA double strand breaks



The A-T protein (ATM) (in red) is located in the nucleus of cultured neuron-like cells.

(DSBs). And, as one might expect, ATM was also shown to be located in the nucleus of these cells, the same compartment that houses the DNA. Unlike the actively dividing cells which have traditionally been used to study the ATM protein, mature brain cells (like neurons) do not undergo cell division. Scientists often refer to such non-dividing cells as being "post-mitotic." Because A-T is characterized by cerebellar atrophy and the loss of Purkinje and granule cells (special neurons within the cerebellum), the role of ATM in these cells has long been a question of great importance in the field of A-T research.

Several studies had previously claimed that the ATM protein is located outside the nucleus in both human and mouse neurons. This observation led some scientists to think that ATM must play a novel role in post-mitotic brain cells, other than that of mediating the response to DSBs. Therefore, a search for CNS

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RUSSIAN SCIENTIST EXAMINES GENOMIC INSTABILITY IN ATAXIA-TELANGIECTASIA BRAIN TISSUE

The A-T Children's Project has awarded grant funding to Russian scientist **Yuri B. Yurov, MD, PhD** for his grant proposal entitled "Genome instability and neuronal death in the brain in ataxia-telangiectasia.". In an attempt to better understand the cell death process in ataxia-telangiectasia (A-T) Dr. Yurov and his team are examining the link between genomic instability and brain cell death. Such research may reveal therapeutic avenues for this relentless and progressive disorder.

A-T can be described equally as a DNA-repair disorder or a genome instability syndrome because the A-T protein (ATM), a key guardian of genomic integrity, is missing or deficient in patients with this disease. Our genome or genetic material is comprised of DNA (**d**eoxyribo**n**ucleic **a**cid). Interestingly, DNA does not exist simply as long "strings" of double stranded helix, rather it is wrapped around special proteins in a particular way to form the structures known as chromosomes (see accompanying figure). "Ploidy" is the term given by scientists to describe the number of copies of chromosomes in a cell. Typical human body cells are "diploid" because they contain two copies of each chromosome (except for the sex chromosomes – females possess two X chromosomes and males possess one X and one Y chromosome per body cell). Various chromosome abnormalities can cause or contribute to disease. Describing his A-TCP funded research, Dr. Yurov states, "The present study was designed to demonstrate the presence of numerical and structural chromosome aberrations in the brain in ataxia-telangiectasia. Modern molecular-cytogenetic techniques specially elaborated for precise identification of chromosomes in the brain tissue at the single-cell resolution [examples include: fluorescence in situ hybridization (FISH) with quantification of FISH signals and

Continued on page 8

In humans, a cell nucleus contains 46 individual chromosomes or 23 pairs of chromosomes (chromosomes come in pairs, 23 X 2 = 46). Half of these chromosomes come from one parent and half come from the other parent. But not every living thing has 46 chromosomes inside of its cells. For instance, a fruit fly cell only has four chromosomes!

From: folding.stanford.edu/education/GAH/gene.html

Can a person run a marathon a day for 2 months? Turn to page 6 to find out who will attempt this feat and why.

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MY THOUGHTS ON HAVING A-T by Renate Klein, 26 years old

I've named A-T, **Anna Theresa** my evil twin because it feels really good to have someone to blame sometimes. I've known about her for about 20 years, I know her and she's part of me. It's rare to have known someone for that long and still call them a friend 20 years later. Yes, I guess I am calling A-T a friend, because ... isn't a friend someone you can cry and laugh with? ... that's basically what I do with A-T. Some days when I get really tired of dealing with Anna Theresa I'd give anything to live for just one hour like a "normal" person.

- A-T is just something I have to deal with. Just like with any illness or disease, you have your good days and your bad days. Sometimes she gets the better of me and I have to lay down, because everything feels like a chore with her. I can't ask "WHY ME" all the time because then I couldn't live and I love life even if I do have to deal with Anna Theresa.
- If someday doctors do come up with a cure, I don't know if I would take it. Because I'm happy with how my life is and I have such a mild case of A-T, I'd just as soon leave my share for someone worse off than me.
- I want to think that Anna Theresa and I are two different people. I don't know how to distinguish between the two of us ... as much as I hate her, she is part of me. But I can say with absolute certainty that without Anna Theresa I wouldn't be who I am today. I think she helped me obtain strength and will power and I think she made my heart bigger for all kinds of people and charities.
- You're not going to get Renate without A-T, I wish you could but you can't and I have to keep learning to accept it.
- Having A-T for me is like breathing, it's something you do every day and you usually don't have to think about it. In the end, everybody has some kind of disability and we all have to deal with them and go on living life.

- Anna Theresa picks out my clothing. I can't always get what is stylish or cool; I have to get what works for her, therefore what works for me. This past weekend I got some good walking shoes for riding in a wheelchair, because I wanted to. Every girl has to get something impractical in her life; I just bring a new meaning to it.
- A-T is a part of me but I am so much more than just a disease.

PROGRESS REPORT: RESEARCHER INVESTIGATES LINK BETWEEN A-T PROTEIN AND A PROTEIN KNOWN TO PLAY A ROLE IN CELL DEATH

The A-T Children's Project has provided funding for Atan Gross, PhD of the Weizmann Institute of Science in Israel. His novel research seeks to better understand the survival and development of tumors in certain types of blood cells. Dr. Gross' initial findings demonstrated that the A-T protein (ATM) targets and recruits a cell death protein to aid the arrest of cell growth and DNA repair. It is hoped that one day this research will lead to treatments for the blood cancers associated with A-T.

From Left: Galia Oberkovitz, Atan Gross, Hagit Niv and Iris Kamer

Cell suicide or programmed cell death is essential for the proper development and maintenance of tissues and organs. One protein that plays an important role in the programmed cell death process is called BID. In his own words, Dr. Gross describes the relationship between ATM and BID: "When the genetic material of the cell is damaged, the cell needs to assess the extent of the damage, and decide whether to activate the DNA repair machinery or to commit suicide to prevent the possible development of cancer. We have recently found that one prominent protein called BID lives the life of a double agent. BID plays two different roles, one in the chain of events that leads to cell suicide, and in another chain that ends in survival. BID hooks up with the ATM protein, which plays an important role in the DNA repair process and springs into action in response to toxins that induce severe damage to the DNA. We have revealed that in this process, ATM also recruits BID to join in the rescue [survival] effort. If this recruitment does not occur, then BID's cell suicide activity is activated and cells die. Thus, BID seems to play a critical "balancing act" between life and death in the ATM pathway. We are using a genetically engineered mouse model to determine the role and importance of BID for this pathway."

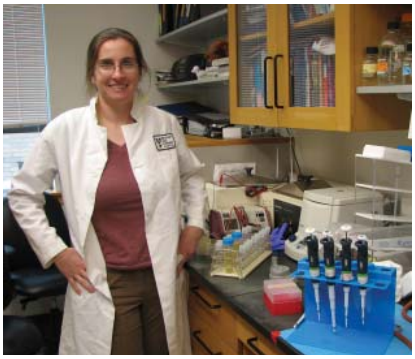
When Dr. Gross' lab exposed normal mice to irradiation, they found that BID and ATM interacted primarily in lymphoid organs (those organs that house special immune cells called lymphocytes). Since lymphocytes are especially sensitive to radiation, and patients with A-T are susceptible to two cancers that affect these cells (leukemia and lymphoma), Dr. Gross suspected that BID's life and death "balancing act" may be most critical in these immune cells. Next, Dr. Gross' team discovered that when specially designed mice which contain a BID protein that cannot bind to ATM were irradiated, these mice were actually less sensitive to lethal doses of irradiation than normal mice. Dr. Gross and his lab will continue to investigate these mice to determine if they are more prone to lymphoid tumor development than their normal counterparts.

This novel research could lead to a better understanding of cancer development in individuals lacking the ATM protein, and may guide scientists and clinicians to better cancer therapies for A-T.

A HARVARD RESEARCHER INVESTIGATES A NOVEL ROLE FOR THE A-T PROTEIN DURING IMMUNE RESPONSE

Roughly 70-80% of patients with ataxia-telangiectasia (A-T) suffer from some type of immune system abnormalities, the most common of which include deficiencies in antibody production and decreased numbers of circulating lymphocytes. Research being performed by an investigator at **Brigham & Women's Hospital, Harvard Medical School in Boston, MA**, may confirm a novel function for the A-T protein (ATM) during an immune response. This work could reveal treatment options for the immunodeficiency that can accompany A-T.

Jessamyn Bagley, PhD has received funding from the A-T Children's Project (A-TCP) to explore a new role for the ATM protein during an immune response. Our immune systems help protect us from foreign invaders such as bacteria, viruses and mold or fungi – those things we typically call "germs." One type of immune response to germs is the production of antibodies by B lymphocytes (or B cells). Scientists call any molecules capable of inducing antibody formation "antigens." However, B cells and antibodies make up just one component of our immune system. Dr. Bagley's work focuses on different immune cells called T lymphocytes or T cells. T cells can be distinguished from other immune cells by a special protein they carry on their surfaces called the T cell [antigen] receptor (TCR). The TCR allows T cells to recognize and bind to different antigens. Once the TCR has bound an antigen, it becomes "activated" or "stimulated," and the T cell will undergo rapid cell divisions to clonally reproduce itself. The resulting T cell clones will all be able to recognize and bind the particular antigen that caused the initial activation.



Jessamyn Bagley, PhD

Interestingly, Dr. Bagley has observed that in response to signals that strongly activate or stimulate the TCR, T cells from A-T mice undergo programmed cell death versus clonal proliferation. Importantly, this cell death, seen only in the absence of Atm protein, appears to be related to a burst of reactive oxygen species (ROS) that is generated following activation or stimulation of the TCR. Dr. Bagley observed further that treatment of T cells from A-T mice with the antioxidant N-acetyl-L-cysteine (NAC) during TCR stimulation could block cell death and allow the T cells to divide normally. These results lead Dr. Bagley to hypothesize that the immundeficiencies seen in A-T may be due, at least in part, to the inability of T cells to respond properly following activation of the TCR.

With her current A-TCP funding, Dr. Bagley will test this hypothesis in T lymphocytes derived from patients with A-T. In collaboration with the A-T Clinical Center at Johns Hopkins, Dr. Bagley will obtain blood samples from patients with A-T and normal controls to determine if A-T derived T cells can proliferate and produce appropriate signaling molecules following

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INTERNATIONAL MEETING ON A-T HELD IN BANFF, CANADA, SEPTEMBER 2006

A record number of A-T researchers from all over the world converged in the breathtaking mountains of Banff in Alberta, Canada this past September for the 2006 International Workshop on Ataxia-Telangiectasia and ATM. The workshop was hosted by **Susan P. Lees-Miller, PhD of the University of Calgary, Alberta, Canada**. Topics included: Clinical Aspects of A-T; ATM in the Nervous System; Activation of ATM; ATM in Tumorigenesis and Immunodeficiency and Novel ATM Signaling Pathways. This last session featured a presentation by Michael Kastan on the role of ATM in metabolic syndrome (see article on page 5).

Other highlights:

- Nuri Gueven, from Martin Lavin's laboratory in Brisbane, Australia, presented results from his A-TCP funded study demonstrating that a nitroxide antioxidant called CTMIO can not only delay the onset of thymic lymphoma in A-T mice, but also correct the neurobehavioral defects observed in these mice.
- Stacey Rimkus from David Wassarman's lab at the University of Wisconsin School of Medicine and Public Health presented her work demonstrating that alterations in certain genes can suppress eye defects in ATM-deficient fruit flies.
- Mark Ambrose from Richard Gatti's lab at UCLA found mitochondrial dysfunction in ATM-deficient lymphoblastoid cells that could be reversed by treatment with the antioxidant alpha-lipoic acid.
- P.J. Brooks from the NIAAA at the National Institutes of Health presented important data demonstrating that the A-T protein is located in the nucleus of human Purkinje neurons (for more on the significance of nuclear A-T protein localization in neurons please see article on page 1).

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John Kesseler pushes Andrew Lutzenheiser's wheelchair in the 5K

Veldink family and friends

ATTENTION LISTENERS!

"Free Beer and Hot Wings" Syndicated Morning Show's deejay, Eric Zane is challenging 100 listeners to raise $1,000 each for A-T research and join him in January 2008 at the Walt Disney World® Marathon Weekend in Orlando, Florida. Zane got involved after he met Kate and Olivia Veldink.

A LINK BETWEEN THE A-T PROTEIN AND METABOLIC SYNDROME IS DISCOVERED

Clinician/scientists studying heart disease and diabetes may need to take a close look at the A-T protein or ATM (which stands for ataxia-telangiectasia mutated). A team of researchers lead by **Clay Semenkovich, MD** at **Washington University School of Medicine** in St. Louis, MO and **Michael Kastan, MD, PhD** at **St. Jude Children's Research Hospital** in Memphis, TN have uncovered an important link between the A-T protein and metabolic syndrome.

Metabolic syndrome, which exists in roughly 25% of American adults, actually represents a group of risk factors that can lead to atherosclerosis and coronary heart disease, stroke and peripheral vascular disease. This syndrome is also associated with insulin resistance, and individuals with metabolic syndrome are predisposed to type 2 diabetes. The America Heart Association attributes the development of metabolic syndrome to three root causes: genetic factors, physical inactivity and obesity.

In the 1970's it was reported that children with ataxia-telangiectasia (A-T) can develop a form of type 2 diabetes. Research, performed in large part by Dr. Kastan, has also shown that A-T cells respond abnormally to insulin. Interestingly, when Drs Semenkovich and Kastan genetically modified a mouse model of atherosclerosis to also be deficient in the Atm protein, these mice possessed higher blood pressure, increased intra-abdominal fat, insulin resistance and accelerated atherosclerosis. So, Atm deficiency exacerbated the features of metabolic syndrome in these mice. More interesting, however, was the fact that the atherosclerotic mice showed improvement

Clay Semenkovich

Michael Kastan

Continued on page 10

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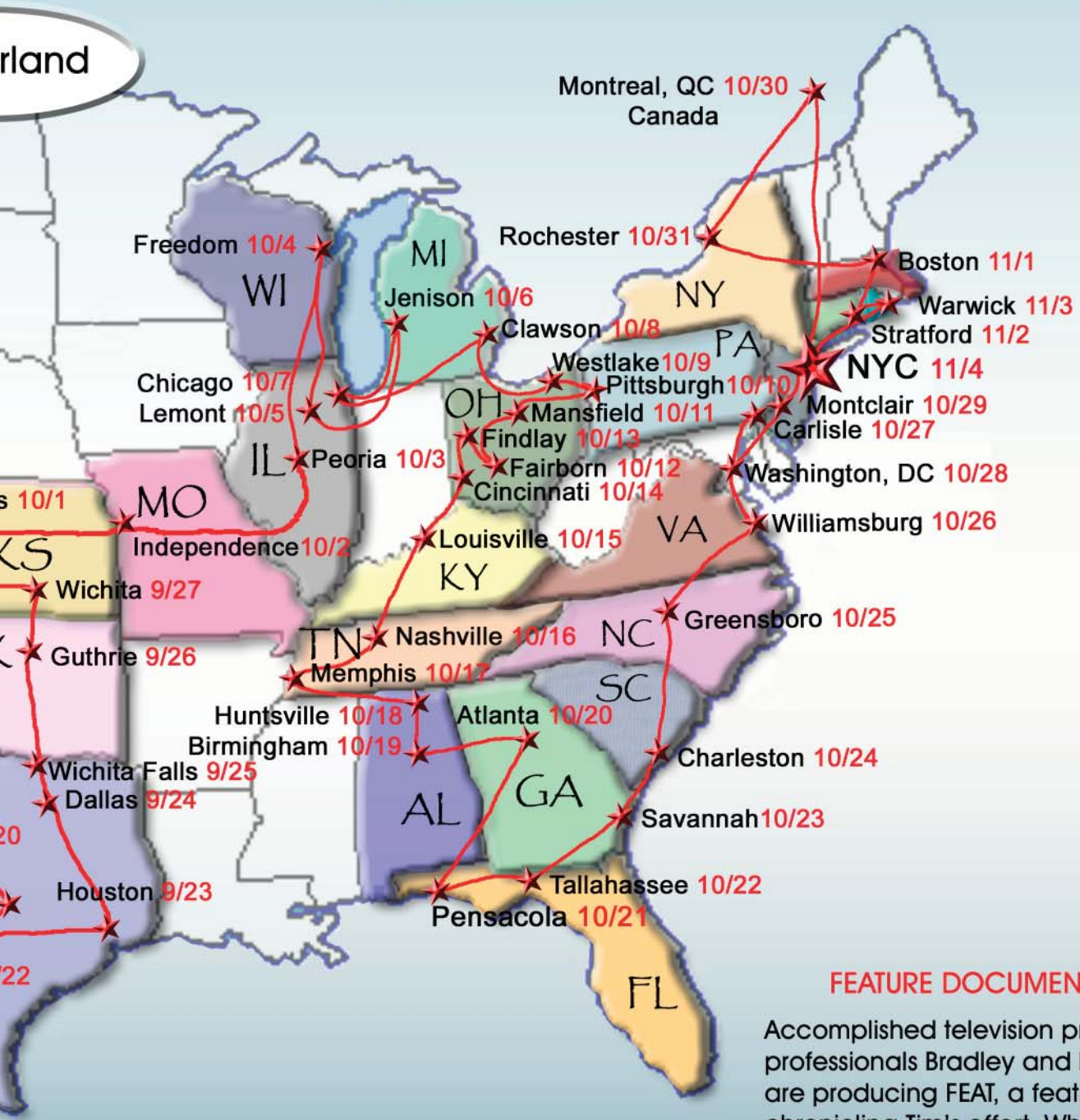


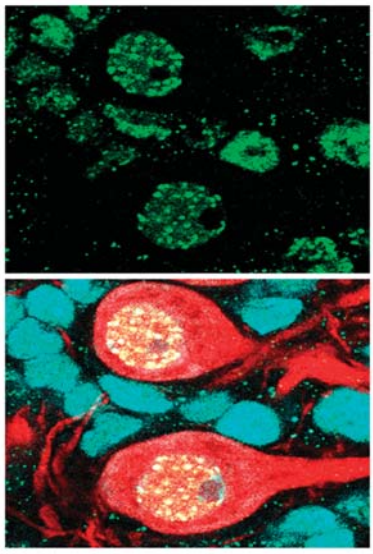
tarting at DISNEYLAND® in Anaheim,
n a full marathon (26.2 miles) a day
earch. Tim will be pushing an
in memory of a child who has passed

FEATURE DOCUMENTARY

Accomplished television production professionals Bradley and Deborah Carr are producing FEAT, a feature documentary chronicling Tim's effort. When they learned of Tim's amazing contribution to the cause, the Carrs knew that documenting this event would be one more way that they could educate audiences about A-T, inspire viewers to delve deeper into their personal potential and give A-T families hope of finding a cure or life-improving therapies.

Bagley... Continued from page 4

TCR stimulation. If patient T cells are unable to proliferate normally, and instead undergo programmed cell death following TCR stimulation, Dr. Bagley will then explore whether or not antioxidant treatment reverses this effect. In addition, Dr. Bagley will also investigate whether T cells derived from patients who took part in the recently completed antioxidant clinical trial at Johns Hopkins possess an improved capacity to respond and signal appropriately following stimulation through the TCR. Dr. Bagley does note that "…while samples from some A-T patients [may] display defects in T cell proliferation, T cells from other A-T patients [may] appear normal." If this is the case, Dr. Bagley, in collaboration with the A-T Clinical Center, will attempt to determine if patients with T cell defects have a greater degree of overall immunodeficiency. In response to the importance of her work for the treatment of A-T, Dr. Bagley states, "The results of these experiments could form the basis for using antioxidants to improve immune system function in A-T patients."



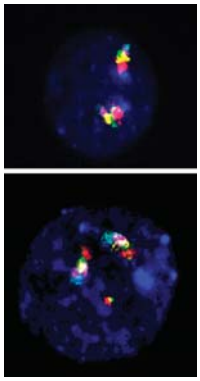
Activated A-T protein (ATM) is shown in green in the top panel. The bottom panel shows the same ATM protein localized within the nucleus of the mouse Purkinje cells (stained in red).

Yurov... Continued from page 1

Multicolor Banding (MCB)] were chosen to reveal genomic instability manifested as loss or gain of whole chromosomes (aneuploidy)." Therefore, with regards to A-T, Professor Yurov suggests that there may be a relationship between increased genomic instability, potentially leading to lethal chromosome rearrangements and neuronal (brain cell) death.

In addition, Dr. Yurov and his colleagues propose that "A-T is a disease exhibiting mosaic expression of chromosome instability that selectively affects specific tissues of the body or even specific brain areas [like the cerebellum]."

As noted above, Dr. Yurov's team will utilize state-of-the-art cytogenetics to visualize chromosome abnormalities in non-dividing neurons in post-mortem brain tissue from normal individuals and patients who succumbed to A-T. This tissue will also be analyzed for evidence of programmed cell death which may occur as a result of lethal chromosome alterations. It is hoped that Professor Yurov's research will provide new insights into the cerebellar degeneration and progressive ataxia associated with A-T.



Chromosome-specific MCB assay with multicolor DNA probe mixture for whole chromosome 14 indicates the presence of two chromosomes 14 in the nuclei (colored in blue) of two separate neurons (upper and lower panels) isolated from the cerebellum of A-T brain.

The neuronal nucleus in the lower panel contains additional structurally altered chromosome 14 (marked by red, yellow and green colored probes) and is therefore aneuploid.

Figure provided by Iourov Ivan (Moscow, Russia) with collaboration of Thomas Liehr (Jena, Germany), supported by the A-T Children's Project grant entitled "Genome instability and neuronal death in the brain in ataxia-telangiectasia."

Shiloh-Barzilai... Continued from page 1

drug therapies for A-T appeared to necessitate a focus on ATM's role outside the nucleus in brain cells. Dr. Barzilai and his graduate student Inbal Dar decided to re-examine this issue using a highly specific reagent (or substance with a particular biological activity) capable of recognizing the ATM protein under precise experimental conditions. They also utilized cultured granule cells from mouse cerebellum and cerebellar slice cultures that contained Purkinje neurons along with surrounding cells. Although they did observe trace amounts of ATM outside of the nucleus of these cultured cells, Dr. Barzilai notes that, "…our findings demonstrate that ATM is predominantly nuclear in mature cerebellar neurons and mediates the DSB response similarly to how it functions in this process in proliferating cells. Cerebellar neurons possess a sensitive and vigorous ATM-mediated DSB response which is probably critical for maintaining the main activity of their genome throughout their long lifespan." Barzilai and Dar's 2006 research was published and featured in *The Journal of Neuroscience*, a prominent journal in the field of neurobiology.

So, if ATM functions mainly in the nucleus of mouse granule and Purkinje neurons, is the same true for human neurons? Dr. Shiloh and his graduate student Sharon Biton undertook an investigation of this very important question using two types of human neuroblastoma cell lines, which can be induced to become neuron-like cells in culture. Shiloh and Biton were able to show that in human neuron-like cells ATM is nuclear and these cells do in fact undergo a nuclear, ATM-mediated DSB response. In addition, they found that this was also true of human neurons derived from stem cells in culture. Shiloh and Biton's very critical studies were published in 2006 in the *Journal of Biological Chemistry* and the journal *DNA Repair*. Collectively, Dr. Shiloh summarizes this work best when he states, "… [Our] results highlight the importance of studying the ATM-mediated network in neurons to understanding A-T. This insight into the molecular basis of A-T is expected to guide the search for novel treatment modalities to alleviate the symptoms of the disease and slow its relentless progression."

MOTOCROSS EVENT FOR A-T

Rider Ezra Lusk with Savanna Hamrick. Inset: Ricky Carmichael wears "Ride for A-T" gear.

At the fourth DMXS Charity Ride for A-T, organized by Heath Hamrick, motocross stars Ricky Carmichael and Ezra Lusk showed their support of A-T research. This incredible Motocross event and auction which took place on February 25 in Georgia. raised over $50,000 for the A-T Children's Project. Hamrick's daughter, Savanna has A-T.

PEREGRINE FOUNDATIONS' OKTOBERFEST BENEFITS A-TCP

Alyssa Wood and Jeff Kummer accepted a check for $50,000 on behalf of the A-T Children's Project at the Peregrine Foundation's annual Oktoberfest event in Chicago, IL. Standing behind Alyssa on this photo are her parents, Marcia and John Wood. Jeff is accompanied by his father, Greg Jehlik.

WE DID THE WOMEN'S 5K AT THE 2007 MINNIE MARATHON WEEKEND IN ORLANDO, FL

From Left: Rhonda VanHierden (Canada), Jamie and Amy Madison (Texas) and Francesca Mosca (Florida).

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A-T scientists and physicians are making remarkable progress, shifting their focus from basic research projects to studies aimed at specific treatments. These studies, including drug-screening technologies, drug toxicity studies, and clinical trials in children, are more costly, requiring higher levels of funding. Having a reliable source of funding over the coming months and years will enable the A-T Children's Project to plan and implement these studies. Therefore, funds that come in through this Monthly Giving Program will be earmarked for clinical and translational research.

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LONG-STANDING A-T INVESTIGATOR AND UCLA CLINICIAN/SCIENTIST SEARCHES FOR COMPOUNDS THAT CAN OVERCOME THE GENETIC DEFECT IN ROUGHLY 30% OF PATIENTS WITH A-T

Approximately 30% of patients with ataxia-telangiectasia (A-T) fail to produce the A-T protein (ATM) because of genetic defects in their ATM genes called pre-mature termination codons (PTCs) or nonsense mutations. But what if there were a drug(s) that could overcome these defects and allow production of some ATM protein? Such compounds might represent life-improving therapies for a subset of patients with A-T. In 2006, the A-T Children's Project contributed funding to the **UCLA** laboratory of **Richard Gatti, MD** to help promote research that addresses this very critical question.

The genetic code housed within our DNA is represented by four letters: A, T, G and C. To make protein, our cells first convert the DNA (deoxy-ribose nucleic acid) code into an RNA (ribose nucleic acid) code which is represented by the letters A, U, G and C. Then our cellular machinery reads triplet combinations of these letters called codons (like AUG, CAU or GGG) to produce protein. In some A-T patients, deleterious changes or mutations occur in these sequences causing a codon that would normally build protein to instead tell the cellular machinery to "STOP!" Scientists aptly named these codons "premature termination codons" because they cause protein production to halt, or terminate, before the end of the RNA message reaches the real termination codon. Prematurely terminated ATM proteins are usually unstable and are rapidly eliminated by our cells. This is why most patients with A-T have little or no ATM protein.

Dr. Gatti's laboratory has been searching for compounds that "read through" these PTCs, thus allowing some amount of full-length protein to be made. "This project," explains Gatti, "stems from our long-standing goal to treat ATM-deficiency in patients with Ataxia-Telangiectasia (A-T). We are trying to restore that protein to 15-20% of normal levels. Recently, we established that certain antibiotic aminoglycosides (AG), such as gentamicin, can partially restore ATM protein levels and correct the functions of this protein in A-T cells that carry a certain class of mutations called 'PTC mutations.' If successful, this work would affect a subset of ~30% of A-T patients. Because none of the existing aminoglycoside antibiotics presently qualifies as a good candidate for clinical trials for A-T, we developed a high throughput screening (HTS) assay to identify and characterize additional read through compounds before attempting these trials. Our goal is to make as many such compounds as possible available to the A-T research community, as quickly as possible. A mouse model carrying a PTC (nonsense) mutation in the Atm gene will be generated for animal testing of compounds, to assess availability to the brain and any possible side effects produced by the late expression of functional ATM protein in ATM-deficient animals." The A-T Children's Project hopes that Dr. Gatti's research will produce candidate drugs suitable for use in clinical trials for A-T.

Follow-up: Dr. Gatti has just been informed by the NIH that this project will be fully funded for the next five years, beginning on July 1, 2007. Dr. Gatti and his laboratory send many thanks to the ATCP for providing the "bridge funding" that kept this work in progress.

Note of Interest: PTC Therapeutics, Inc.

PTC Therapeutics, Inc. (www.ptcbio.com), a mid-sized biopharmaceutical company located in South Plainfield, New Jersey, is currently exploring the efficacy of a nonsense mutation read through compound called PTC124 in Phase 2 clinical trials for cystic fibrosis and Duchenne muscular dystrophy. Thus far PTC124 has been well tolerated among the trial participants and interim results for all trials have been favorable. The A-T Children's Project is watching the clinical assessment of PTC124 very closely as this drug may also be applicable to treating a subset of patients with A-T. However, notes Dr. Gatti, preliminary studies suggest that even this compound may not pass into the brain (i.e., cerebellum) in sufficient concentrations to be useful for A-T. This will have to be tested further, and perhaps a better drug will have to be engineered.

About PTC124*

PTC124 is an orally delivered investigational product candidate in development for the treatment of genetic disorders due to nonsense mutations. Nonsense mutations are single-point alterations in the genetic code that prematurely halt the translation process, producing a shortened, non-functional protein. PTC124 has demonstrated activity in preclinical genetic disease models harboring nonsense mutations allowing the restoration of the production of full-length, functional proteins. In Phase 1 clinical trials, PTC124 was generally well tolerated, achieved target plasma concentrations that have been associated with activity in preclinical models, and did not induce ribosomal read through of normal stop codons. Pharmacokinetic modeling of the Phase 1 results allowed development of a dosing regimen for the Phase 2 studies in cystic fibrosis (CF) and Duchenne muscular dystrophy (DMD).

*Courtesy of an April 6, 2004 Press Announcement from PTC Therapeutics, Inc.

Left to right: Julie Pollard, Liutao Du, Mark Ambrose, Bozena Cukrowska, Francesca Fike, Edyta Heropolitanska-Pliszka, Thomas Cottingham-Hodson, Alice Chang, Shareef Nahas.

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when treated with low-dose chloroquine. Chloroquine, traditionally known as an anti-malaria drug, is capable of activating the ATM protein in the absence of DNA damage. "These results", states Dr. Semenkovich, "suggest that ATM-dependent stress pathways mediate susceptibility to the metabolic syndrome and that chloroquine or related agents promoting ATM activity could modulate insulin resistance and decrease vascular disease." Currently, Dr. Semenkovich and his colleagues at Washington University are performing a clinical trial with low-dose chloroquine in patients with metabolic syndrome, the preliminary results of which are promising.

This research represents yet another example of how studying a rare disease like A-T can potentially impact health issues involving a broader population.

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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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