A-T Ease Focus
NEWSLETTER

A-T EASE FOCUS
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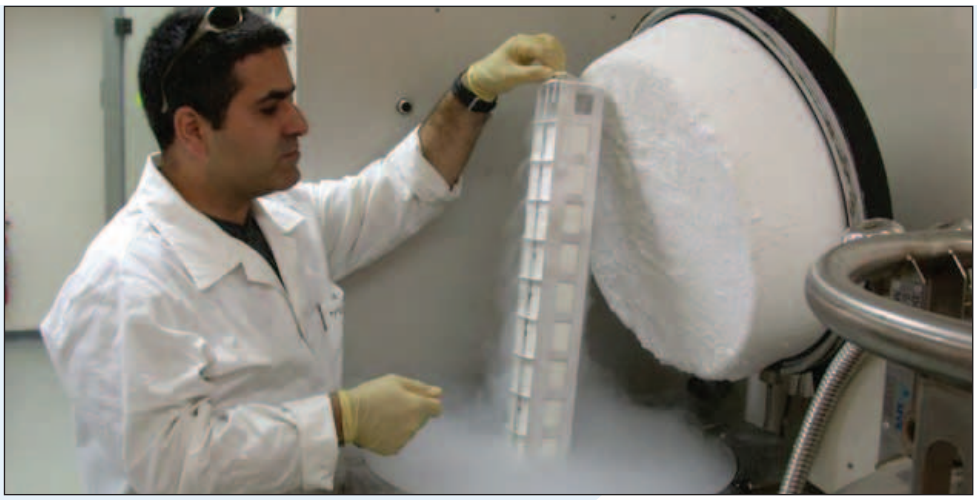

Dr. Shiloh's Lab

What is ATM's Function in Neuronal Cells?

Our group is interested in understanding the molecular and physiological bases of A-T. We believe the key to treatment lies with full understanding of the molecular defect that leads to A-T's numerous symptoms. A-T is a multisystem disease affecting many tissues and organs in the human body. Its cardinal symptom is neuronal degeneration, which affects primarily the cerebellum, leading to progressive ataxia and eventually to severe neuromotor dysfunction. Other hallmarks of A-T are immunodeficiency, cancer predisposition and extreme radiation sensitivity. This myriad of symptoms is caused by mutations in a single gene, ATM, that lead to loss or inactivation of its protein product, the ATM protein. Thus, understanding the functions of the ATM protein in unaffected individuals should explain why its loss is so devastating in A-T patients.

The identification of the ATM gene in our laboratory in 1995 paved the way to the isolation and investigation of the ATM protein in many laboratories, including ours. ATM turned out to be the chief activator of the cellular response to a specific type of DNA lesion called "double strand break" (DSB). As the name implies, the DSB is a break in the DNA molecule, making it an extremely serious lesion that must be repaired before it leads to cell death or cancer. Indeed, the long DNA thread that makes up our genome is constantly subject to chemical and physical agents that damage it and disturb its normal structure and function. Some of those agents are by-products of normal cellular activity, which means that DSBs are constantly being produced in the DNA of every cell in our body. Besides these DSBs produced by normal cell metabolism, one of the external causes of DSBs is ionizing radiations (e.g., X-rays), which explains why A-T patients are so sensitive to this radiation.

Thanks to sophisticated surveillance and repair mechanisms that exist in our cells, DSBs are usually repaired before they get a chance to cause harm. These lesions activate a vigorous network of processes collectively called "the DNA damage response", which consists of many processes that take care of the damage while the life cycle of the cell is temporarily arrested. The mobilization of this entire network is carried out by the ATM protein. ATM recognizes key players in the network and makes slight chemical modifications in them that alter their action, thereby activating the entire system. A-T patients, having no ATM protein or inactive ATM, simply fail to properly activate the ATM-mediated response to DSBs.

ATM's role in the DNA damage response readily explained the radiosensitivity of A-T patients and the high chromosomal breakage observed in A-T cells. This role of ATM was also linked to the immunodeficiency in A-T, since DNA breakage and reunion occur normally during the generation of immune system cells. But, how ATM's role in the response to DSBs was linked to neuronal degeneration continued to puzzle scientists. One reason for this conceptual difficulty stemmed from the notion that DSBs are critical mainly because they hamper the duplication of DNA prior to cell division. Since neuronal cells do not divide and therefore do not duplicate their DNA, it could be assumed that the DSB response must not be that critical in neuronal cells. Several papers even reported that ATM in neuronal cells was not located in the nucleus - its natural location in other cell types – but, rather, outside the nucleus. *cont.*

Current Developments in A-T Research at the UCLA Molecular Pathology Laboratory

The past year has been very exciting for our laboratory, as we search for chemicals that ignore or 'readthrough' mistakes in the DNA code of A-T children and correct their ATM protein defects. Our goal is to find a lead compound that warrants testing in animals, and then in clinical safety trials -- before actually trying it on children with A-T. Using a high throughput assay that we developed two years ago which screens 386 compounds every three minutes, we screened over 35,000 compounds and discovered several new classes of chemicals. We expect to have the Effective Concentration curves for over 20 new compounds completed shortly. This will allow us, for the first time, to quantitatively compare the potency of one compound over the other. We think we have at least two to three chemicals that are better than the aminoglycoside antibiotic Gentamycin. Until now, Gentamycin has been our gold standard. But Gentamycin is not really the best drug for clinical trials. Once we get past this difficult point of analyzing over 20 drugs at the same time, progress should be faster because we can then concentrate on only the best ones. In addition, we have a medicinal chemist comparing the molecular structures of this first set of active compounds, in hopes of designing a second generation of even better ones within the next two years.

We have also been setting up the genetic testing that will be important for identifying mouse embryos to work with in developing a mouse colony that carries the type of mutation that our new drugs are expected to correct. The technology is not difficult or new, it is simply a lot of work to breed mice. This has to be done with extreme care because each experiment takes over a year to complete, and a little mistake in the procedure can set us back a full year. Once we succeed in getting the new mutation established in a mouse colony, we will begin breeding enough mice to treat with different drugs and different concentrations of each. We will follow the concentrations of those drugs in different organs, such as the cerebellum - the site of greatest deterioration in A-T children.

cont.

What is ATM's Function in Neuronal Cells cont.

This notion severed ATM in neuronal cells from its well-documented function in proliferating cells – being the master controller of the DSB response. It was then assumed that ATM does something else in neuronal cells, operating in processes not necessarily connected to the DNA damage response.

This notion threw into question the relevance of the work of our and so many labs worldwide to understand ATM's role in the DNA damage response with regard to A-T's most important symptom! Clearly, in light of this concept, we were still far from "understanding A-T" based on understanding ATM's functions. This was both intriguing and frustrating to the A-T scientific community.

However, work done in our lab three years ago provided initial genetic-molecular evidence that the neuronal degeneration in A-T may, after all, be a result of defective response to DSBs. In that study we investigated another, very rare disease, called "A-T-like syndrome" (A-TLD): this disease is caused by mutations in another gene, not the ATM gene, but nevertheless closely resembles A-T. We showed that the defective protein in A-TLD is required for the activation of ATM by DNA breaks, and in its absence, ATM (itself being intact) cannot respond properly to DSBs. This meant that the neuronal degeneration in A-TLD patients, and probably in A-T patients, could still result from a defective response to DSBs! But how could this be reconciled with the localization of neuronal ATM outside of the nucleus, where it normally resides in other cell types? ATM's nuclear localization is conceivably important for its role in the response to DNA damage, since the DNA resides in the nucleus.

We decided to revisit the issue of ATM localization and function in neuronal cells. Work in our lab and in that of our close collaborator, Prof. Ari Barzilai of Tel Aviv University, led us last year to conclude unequivocally that ATM in neuronal cells in fact resides in the nucleus and carries out a similar function as in proliferating cells – activating the response to DSBs in the DNA. Using human neuron-like cell cultures and cerebellar cultures obtained from mice, and a range of microscope and biochemistry methods, our laboratories were able to show that neuronal cells possess a vigorous response to DSBs, which is mediated by ATM, itself being largely nuclear in these cells. The difference between our and other investigators' results on ATM localization in neurons probably reflects technical and methodological differences between laboratories.

Our finding that neuronal cells do possess a vigorous ATM-mediated DSB response made a lot of sense to us. Although these cells do not duplicate their DNA, maintenance of the stability and integrity of the DNA is of prime importance to them: DNA in neurons is extremely active in directing protein production in the cell, and at the same time the intensity of the metabolic activity in these cells constantly exposes their DNA to by-products of this metabolism which induce DSBs. We should also bear in mind that neuronal cells exist in finite numbers, are long lived, and go through a lot of wear and tear during our lifetime.

It was also a great relief to know that all the work done so far on the role of ATM in the DNA damage response is in fact relevant to the neuronal degeneration in A-T. Our understanding of ATM's role in this response can now be used to screen for drugs for A-T patients, since this function of ATM can now be linked to the most important clinical manifestation of A-T.

But, as often happens in science, answering one question raises new ones. After all, neuronal cells ARE different from proliferating cells, and the components of the ATM-mediated network may differ from those of proliferating cells. Therefore, our current goal is a thorough examination of the ATM-mediated DNA damage response in neuronal cells. Work in that direction has already begun, for which we enjoy the support of the A-T Ease Foundation, and others. We expect to gain new insights into what has gone awry with the neurons of A-T patients, and how they deteriorate over the years. Such understanding should serve us in our ongoing quest for new treatment modalities for A-T patients.

Yosef Shiloh, Ph.D.

The David and Inez Myers Laboratory for Genetic Research
Department of Molecular Genetics and Biochemistry
Sackler School of Medicine, Tel Aviv University, Tel Aviv 69978 Israel

Dr. Gatti and Staff Member

Current Developments in A-T Research cont.

We are also hoping that similar ongoing experiments with other mouse colonies, in other laboratories, may produce an even better background mouse model, one that would show more symptoms similar to A-T children. So far, this has been a big obstacle for animal research on A-T.

Our diagnostic testing continues at the UCLA Molecular Diagnostic Laboratory. During 2005, we diagnosed 25 new children with A-T, and we are now defining the mutations for each child. However, diagnostic testing is usually covered by medical insurance, defining the mutations is presently not covered by any insurance carriers. If this work were to discontinue, it is unlikely that any other laboratory in the country would actually pick it up since diagnostic testing for rare disorders is not profitable for commercial laboratories.

I hope this gives you a better idea of what we are doing in both the diagnostic laboratory and in research, as well as an appreciation for where the A-T Ease Foundation continues to make important contributions to the welfare of A-T children in the U.S. and abroad.

Richard A. Gatti, M.D.

Distinguished Professor, Rebecca Smith Chair for A-T Research
Department of Pathology and Laboratory Medicine, UCLA School of Medicine

The Perfect Day for a Ride Around New York

May 7th, 2006 was a beautiful day. The sun was shining down on the A-T Ease Cycling Team as they departed from the front of the pack in downtown New York City upon their aluminum horses for a 41-mile journey around the five boroughs.

The weather cooperated and the day was a great success from all perspectives. Our team did an amazing job raising funds for A-T research, and because of their efforts their sponsors contributed a total of $15,000 to A-T Ease Foundation; more than double the amount raised in 2005!!

Just wait until next year!!
Mark your calendars – Sunday, May 6th, 2007

JOIN US!

www.ateasefoundation.org
the Web Site for News and Information About A-T

Hello! I would like to introduce myself.

My name is **www.ateasefoundation.org** and I am a new resource on the internet for families and friends of children with A-T.

Feel free to visit my pages. I contain information on A-T Ease Foundation and Ataxia-Telangiectasia (including how to pronounce the name of this complicated disorder). Come look at my News and Photos, Research Articles, Upcoming Events, Newsletters, Ways to Help **and much, much more.**

Please check me out regularly –
I wouldn't want you to miss out on any news!!

Research Grants Currently Supported by A-T Ease Foundation

Experimental Gene Therapy for Ataxia-Telangiectasia
Principal Investigator - Marisa Cortes, PhD
Massachusetts General Hospital

The Function of ATM in Neuronal Differentiation: Identification of Targets for High Throughput Screening
Principal Investigator - Brendan Price, PhD
Dana-Farber Cancer Institute

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

Direct Research on Ataxia-Telangiectasia
Principal Investigator - Richard Gatti, MD
UCLA School of Medicine

Investigation of ATM's Function in Neuronal Cells
Principal Investigator - Yosef Shiloh, PhD
Sackler School of Medicine, Tel Aviv University

The Role of Pro-Apoptotic BID as an ATM Effector in the DNA-Damage Response
Principal Investigator - Atan Gross, PhD
Weizmann Institute of Science

A-T Ease Foundation Partners with the National Institutes of Health

In May 2005, representatives of A-T Ease Foundation participated in a Trans-NIH A-T working group meeting at the NIH. A-T Ease Foundation, along with representatives from two other A-T advocacy groups, met with researchers from various divisions of the NIH: the Office of Rare Diseases, the National Institute on Aging, the National Cancer Institute and National Institute of Neurological Disorders and Stroke, among others, whose mandate was to help build an A-T team to develop a strategic plan for A-T research.

The strategic plan is now in place, and in October 2006 a Program Announcement is being placed on the NIH website inviting researchers to submit proposals for A-T research programs. A-T Ease Foundation is a part of this exciting program.

We are very hopeful that this program is another promising step toward finding treatments and a cure for A-T as well as to raising awareness with a broader audience. (www.ateasefoundation.org/NIH).

We would like to extend our gratitude to the following foundations and corporations who have supported A-T Ease Foundation:

CIBC World Markets Miracle Day

Morgan Stanley Foundation

New York Life Foundation

Peregrine Charities

Rhen

Simplymad Design Studio

Steve Edge Design

We would also like to thank our families, friends, colleagues, volunteers and vendors for their continued support and faith in what we are trying to accomplish.

A-T Ease Foundation
FOCUS ON THE HOPE

"Living With A-T"

I was diagnosed with A-T when I was six years old. I really don't remember much about that time, but I do remember all the doctors that wanted to see me. Living in Rochester, NY there were many people from the University of Rochester that examined me. I didn't mind and my mom always made sure people talked about me like a normal kid with an interesting disease. We traveled to Johns Hopkins Hospital just before I turned eight years old to meet the people at the A-T Clinical Center and have the full evaluation for A-T. We have been back there every two years since then. I also was a part of the oxidative stress clinical trial at the A-T Clinical Center. During the trial my mom and I got to go to Baltimore every month for almost a year. We stayed at the Children's House and got to meet other kids with A-T and their families.

I used to be able to get around by myself, ride a bike, and even roller skate. Now I have to use a power wheelchair and have a lot of help from other people. Sometimes my A-T gets me down, but I try to be positive about things. My mom and I have traveled a lot. I have been to Florida, the Bahamas on a Disney Cruise, the Great Smoky Mountains of Tennessee, Virginia, Washington, D.C. and Hawaii. We also have a trip planned for Alaska next summer. I love to travel and I especially like to fly on planes.

Since I finished my High School program last June I have been working part of the day for the ARC and in a transition program the rest of the day. I would like to take a course at our local community college in the future. I have plans to move into a group home with 5 other young women with physical disabilities in the next year or so. I would also like to write a book, I have the perfect name too, "Just Because It Has Grab Bars Does Not Mean It Is Handicapped Accessible". When we travel I check out the facilities and especially the bathrooms. You should see my mom sometimes; it's really fun trying to get the wheelchair, her and me into a bathroom stall!!! We have gotten very creative over the years and had many laughs.

Sometimes when I feel down or discouraged about my A-T I think about all the other kids with A-T too. I would like to be the example to them and let them know they are not alone. There are so many scientists and doctors working on our disease and many people that we don't even know who are raising money for research. There have been great discoveries made that will not only help all of us with A-T, but many other people with rare diseases. Keep thinking happy thoughts and someday our dreams for a cure will come true.

Tori Bement-Schramm

Pink and White Sneakers

Blonde hair, blue eyes
A much wanted child
Infectious laugh
Smile like sunshine

Pink and white sneakers
Doctors and questions
No answers
Agony and tears in the dark

Wheels now roll where
Pink and white sneakers
Once played
Nothing to do but wait
And hope for a cure
Someday...

Lynn M. Bement
4/30/2006

"You should see my mom sometimes; it's really fun trying to get the wheelchair, her and me into a bathroom stall!!! We have gotten very creative over the years and had many laughs."

A Teacher's Perspective

Teaching is such a rewarding profession. A teacher watches the children grow as the year progresses. A teacher learns from her students. A teacher guides the children to make wise decisions. A teacher listens. A teacher teaches much more than reading, writing, math, science, social studies, art, music, technology, and health. A teacher teaches respect. A teacher learns patience. A teacher encourages. Above all, a teacher uses every opportunity to make each student feel special. This year, I experienced all these wonderful teacher qualities. Yes, I have taught before, but it wasn't until the 2005-2006 school year, that I really recognized just how lucky I am to be a teacher.

My class of 22 students is filled with different personalities, levels, emotions, and experiences. Although, every year I am presented with different students, this past year was a little different. Nicholas, an eight year old boy was in my class. He will change my life forever. Aside from being thoughtful, smart, funny, and creative, Nick has A-T. Nick tried his best whether we were illustrating a fiction book, writing a poem, reading a short story, or solving a math problem. He was always eager to participate and enjoys learning. At times, Nick tired easily, got frustrated, or had trouble expressing himself, but don't all other eight year olds experience these things too?

The children were wonderful to each other. Teaching respect last year was so easy partially because Nick demanded respect from everyone and everyone wanted to show him that they felt he was capable of doing all of the classroom activities. While Nick learned to ask for help, others learned how to help him. They knew he was capable of reading most of the work on his own, but if he asked for help – they would read to him. While Nick learned how to be a little more selfish, others learned how to be less selfish. Some students even walked Nick back to his seat before getting started on their own work. While Nick learned to speak his mind, others learned to think before they speak. While Nick learned to express himself, others learned to listen more carefully. For example, Nick asked others to speak up if he couldn't hear them; the rest of the class sat silently to listen to what Nick was saying. It was understood that Nick was speaking as loud as he could so no one would ask him to repeat an answer. After all, being a fair teacher doesn't mean being equal. It is my job to give each student the tools they need to be successful. As Dorothy Briggs said, "When children know uniqueness is respected, they are more likely to put theirs to use." Nick taught the rest of the class how to put their own uniqueness to use. For that, we will all be grateful.

Alyssa Aferiat
2nd Grade Teacher and Extraordinary Human Being

CIBC Miracle Day – December 6, 2006

Each year, on the first Wednesday in December, CIBC World Markets employees and clients participate in Miracle Day to raise funds for children's charities. They have been doing so since 1984. This year's Miracle Day will take place on December 6th, when CIBC will donate a portion of their trading commissions to designated charities.

A-T Ease Foundation is one of these designated charities!

In order to maximize our grant potential, if you are a client of CIBC World Markets, associated with a company that trades with them, or if you know anyone who is, you can make a Miracle happen for A-T Ease Foundation on December 6th.

Here's how:

- Alert your company's traders that you will be trading for A-T Ease Foundation on Miracle Day.
- On December 6th, when you or your company trades with CIBC, mention that you are trading for A-T Ease Foundation. (This is not at a cost to you or your company. CIBC will donate a portion of their commissions to designated charities.)
- The Miracle Day funds allocated by CIBC to A-T Ease Foundation will be used to raise awareness of A-T and to support important research into treatments and a cure for A-T!

If you have any questions, please call us at 212-529-0622 or email us at: info@ateasefoundation.org

Thank you for your help!

Upcoming Events!

Please mark your calendars:

Sunday, May 6, 2007 – Join the A-T Ease Cycling Team to raise awareness and funds during the Bike New York Five Borough Bike Tour

October 2007 – 6th Annual Focus on the Hope Benefit

Information will be posted at:
www.ateasefoundation.org/events

• A-T Ease Clubs •

Know an ambitious high school student? High school students and teachers are starting up A-T Ease Clubs to help raise awareness and money!

Become involved in your community.

If you know someone who is interested please have them contact **Alyssa Aferiat** at:
atclubs@ateasefoundation.org

Ways In Which You Can Help

- Donate Directly to A-T Ease Foundation
- Be a Corporate Sponsor
- Organize an A-T Ease Fundraising Event
- Spread the Word
- Remember Corporate Matching Gift Programs
- Introduce us to Organizations who Might Support our Mission
- Volunteer Your Time or Services
- Donate in Memory of Friends and Loved Ones or as a Gift for a Special Occasion

A-T Ease Foundation is a 501(c)(3), tax-exempt, not-for-profit corporation. All donations are tax deductible.

A-T Ease Foundation
FOCUS ON THE HOPE

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