A-T Ease Focus
NEWSLETTER

A-T EASE FOCUS
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Understanding ATM, Understanding A-T

In the summer of 1977, I had just obtained my M.Sc. degree in Human Genetics from the Hebrew University in Jerusalem and was thinking about possible subjects for my Ph.D. thesis. A chance encounter with an A-T family made me choose this devastating disease as the subject of my thesis. At that time, it was no more than the subject for my thesis, but this decision determined the direction of the rest of my scientific career. I found myself submerged in a profound biological and human problem - trying to understand the molecular basis of a disease that affected so many systems in the human body. It was clear from the start that the elusive function which is defective in A-T patients was a very important one. A defect in this function was capable of affecting the nervous and immune systems, causing severe neuromotor impairment and immunodeficiency, and rendered A-T patients cancer-prone and extremely sensitive to X-rays. What could be the common cause of all these symptoms?

Today, some 28 years later, we know much more about the causes of A-T. Many years of research in our lab and in many labs worldwide have brought us to a point where we are seriously considering the possibility of applying the information we have accumulated over the years to seek new treatment modalities for A-T.

The first major breakthrough in our work occurred in 1995, when we identified the gene which is defective in A-T patients. A gene is one segment in our genome which is responsible for a specific function. Most of our genes contain the information for the production of proteins, the molecules that build the cell and carry out all its metabolic activity. A mutation in a gene may abolish the production or structure of the corresponding protein, thereby eradicating the function carried out by that protein. This is why genetic mutations are capable of causing devastating genetic disorders.

We designated the A-T gene "ATM" (A-T, Mutated). Its protein product is also called ATM, and we found that the ATM protein is either absent or inactive in the cells of A-T patients. The next question was, what is the role of the ATM protein in healthy cells? If we could understand the function of the ATM protein in healthy cells, we would have taken the first giant leap into understanding what exactly was missing in the cells of A-T patients. It turned out that the ATM protein has a critically important function in the cellular response to radiation damage. The DNA in each cell of our body is constantly exposed to agents that damage this molecule by modifying it chemically or simply breaking it. These agents are formed as by-products of normal metabolism or they come from the environment in the form of chemical pollutants and radiations. This constant exposure to DNA damage is a serious threat to cellular life. Furthermore, since cancer is initiated by defects in the DNA, DNA damage may lead to the actual formation of tumors. It is not surprising therefore, that cells possess sophisticated systems for monitoring the integrity of their DNA, for repairing any damage to it and for alerting other systems in the cells to the existence of a DNA lesion until it is repaired.

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Progress on A-T Research

Children with Ataxia-Telangiectasia (A-T) look normal when they are born and begin walking at a normal age. Shortly after that, however, they begin to stagger and sway. By 10 years of age, most children are confined to a wheelchair for the rest of their lives. At first, they resist using the wheelchair but then find that they can no longer protect themselves adequately from falling because their reflexes are too slow. There are other problems as well, such as slurring words (because the tongue is controlled by the same part of the brain - the cerebellum) and getting frequent infections (because their immune system is inadequate). In addition, one in three develops cancer at some time during their lifetime. Twenty years ago, most children with A-T did not survive their twentieth birthday; today many live into their forties and even fifties. The reason for this improvement is not understood. Perhaps better antibiotics and better cancer treatment has made this difference; perhaps the use of antioxidants (see below) has also helped.

Parents worry about who will take care of their A-T 'children' when they are gone because they cannot speak clearly enough to work, they cannot write clearly or quickly, they have trouble reading regular size print, and they cannot bathe themselves independently. On the other hand, most patients have learned to use a computer keyboard, and some have finished college (with the help of an aide). Many ride horses, and swim regularly. Some even bowl from their wheelchairs and a few have learned to drive light vehicles on local roads.

Despite impressive progress over the past few years with diagnosing A-T and understanding the cellular functions of the protein, the major challenges confronting A-T researchers today are to understand how the neurological symptoms develop and how to reverse this development. The neurological deterioration begins even before birth, and is most obvious in the cerebellar part of the brain; under the microscope, Purkinje cells in the cerebellum are depleted in number and seem to be attached improperly to other surrounding nerve cells. It is not clear whether the primary problem is in the Purkinje cells, or in the nerves leading to these cells, or perhaps even in the nerves leading away from them -

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Understanding ATM, Understanding A-T

Defects in this system lead to severe disorders which are usually characterized by degeneration of specific tissues and predisposition to cancer. A-T is a striking example of such a disease.

After devoting years to intensive research, we discovered that the ATM protein is the chief activator of the cellular response to the formation of breaks in the DNA by ionizing radiations and environmental chemicals. This finding explained the extreme sensitivity of A-T patients to ionizing radiation and DNA-breaking chemicals. It also explained their predisposition to cancer. It took us several more years to understand why the defect in the response to DNA breaks also affects the nervous system to such a great extent.

Work in our lab is currently focused on understanding ATM's mode of action. How can ATM, a single protein, control so many processes in the cell at the same time? Each of these processes is composed of a series of steps, and each step is carried out by a specific protein. ATM "knows" who is the key player in each process: in response to the formation of breaks in the DNA, it creates a quick contact with that protein and changes its activity, thereby altering the pace of the entire process. We are attempting to identify new branches of the ATM-mediated network in the belief that these new insights into the molecular basis of A-T will enable us and other labs to develop new treatment modalities for A-T, which will at least slow down the relentless progression of this disease.

In what specific ways do we hope this growing knowledge could help in better treatment management of A-T patients in the future? We firmly believe that by understanding ATM functions and mode of action, particularly in the nervous system, we may be in a better position to help A-T patients compensate their body for the loss of ATM. This takes us back full circle to the title of this article: understanding A-T depends on understanding ATM!

Yosef Shiloh, Ph.D.
The A-T Laboratory, Department of Molecular Genetics and Biochemistry,
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Research Grants Currently Supported by A-T Ease Foundation

Introduction of Hematopoietic Chimerism for Treatment of Immune System Defects in Ataxia-Telangiectasia
John Iacomini, PhD - Massachusetts General Hospital

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

Mechanisms of Neurodegeneration in Ataxia-Telangiectasia
Allen Mandir, MD, PhD - Johns Hopkins Hospital

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

A-T Clinical Trial – Oxidative Stress in Patients with Ataxia-Telangiectasia
Howard Lederman, MD, PhD - A-T Clinical Center at Johns Hopkins Hospital (A-T Ease has sponsored participants in this clinical trial.)

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

Direct Research on Ataxia-Telangiectasia
Yosef Shiloh, PhD - Sackler School of Medicine, Tel Aviv University

Dr. Gatti's Research Team

Progress on A-T Research cont.

much like when a light does not go on in a room when you hit the switch, you can't just assume it is the light bulb that is defective.

A-T is caused by mutations (mistakes!) in the DNA code for the ATM protein. These mutations prevent normal ATM protein from being made. This protein is required in the nucleus of all cells in the body. Its most important function is to repair broken strands of DNA. Since our DNA breaks quite often as a result of 'sparks' or oxidative free radicals that are created by normal chemical processes, there is always a lot of damaged DNA to repair in every cell every minute of the day. This takes a great deal of coordination inside the cell and this coordinated DNA repair is masterminded by the ATM protein. No wonder then that when it is absent many things can go wrong!

There is presently no proven way to prevent or even reduce the progress of the neurological deterioration. Studies are underway to minimize the DNA damage in A-T patients with antioxidants, such as Vitamin E or alpha lipoic acid. These compounds seem to slow neurological deterioration but this is not clearly established as yet, and these compounds do not make the symptoms go away. Other medications are available that reduce tremors or drooling, or prevent infections. However, none of these approaches restore the manufacture of the missing ATM protein in the cells of A-T patients.

Recently, the UCLA laboratory has spearheaded studies that are very promising in this respect. They indicate that certain aminoglycoside antibiotics can trick the cells into reading the DNA code in a way that ignores certain types of mutations in the ATM gene and encourages small amounts of functional ATM protein to be produced. In the test tube, we have been able to restore several properties of A-T cells to near normal levels of function. We are quite encouraged that this has potential as an approach to therapy for A-T children. However, we have not yet found an antibiotic that would be effective enough to be used in patients because the few chemicals that produce sufficient protein are also toxic to the cells. So we have developed a test that can be performed by robots in the laboratory to screen and identify other compounds that are active in the same way on the ATM gene. So far we have screened 13,500 chemicals and we have found four new ones that we are testing further. We are also screening another 19,000 chemicals (at a cost of about $2.10 per chemical screened).

Once we have identified a new active chemical, it has to be tested on A-T cells, and then in animals to check whether it is safe for use as a medication. Once those hurdles have been passed, the few best compounds will be evaluated for their ability to correct neurological deterioration in animals that have mutations similar to those seen in A-T children. Only then can we proceed to test that compound in patients. We hope to define some new classes of chemicals that will lead us to an effective treatment for A-T within the next 3-4 years. Since the same principles will apply to mutations of other genes, what we learn from A-T can then be used to treat other genetic disorders as well. With the help of the A-T Ease Foundation, we can keep this research moving at top speed!

Richard A. Gatti, M.D.
Distinguished Professor, Rebecca Smith Chair for A-T Research
Department of Pathology and Laboratory Medicine, UCLA School of Medicine

Letter from Gabrielle

Dear Friends,

Inspiration is a divine influence on a person. You might say my cousin Stephen is my inspiration. He has had a challenging life. What I mean when I say his life hasn't been easy, is that he lost his first wife to cancer. Moving on with her blessing, he was able to fall in love and marry again. He and his wife, Annette, were lucky to have two wonderful children, Nicholas and Matthew.

A couple of years later, my family were faced with some heart breaking news that changed our lives forever. My cousins' two precious little boys were diagnosed with Ataxia- Telangiectasia (A-T, "Ay-TACK-see-uh Teh-LAN-jick-TAY-sha"). A-T is a rare genetic disorder that attacks children. It is progressive and debilitating; causing cancers, immune system deficiencies and neurological deterioration which causes the loss of muscle control. Most children with A-T are wheelchair bound by their teens and do not live past their 20th birthday.

Now put yourself in their shoes - could you imagine waking up one day and never being able to walk again? Or, for those of you who have a younger brother or sister, could you imagine them saying to you, "why can't I do what all the other children do…?" But worst of all, can you imagine turning 18 when your life should just be beginning, but knowing in the back of your mind, it could be near the end? These are the thoughts, and questions that are faced by my cousins everyday. Everyday my cousin feels regret that he has no answers or the power to save his two little boys. *However, I admire that he still has hope - as do I.*

I am writing this letter hoping this has touched your heart and hoping you will help us save all the little angels that have been affected by Ataxia-Telangiectasia.

Sincerely,
Gabrielle G. (10th Grader)

A-T Ease Cycles the Five Boroughs!

For the second year in a row, A-T Ease Foundation organized a team of cyclists for the Bike New York Five Boro Tour.

On May 1st, 50 cyclists assembled in downtown Manhattan to join the A-T Ease Team for a 42-mile recreational bike ride around the five beautiful boroughs of New York City – traffic free! The Tour gives us the opportunity to gather with family and friends for a wonderful day of cycling while lending our support to an important cause.

Through the generosity of Pam Tice, Executive Director of Bike New York, we were able to offer our team Group Passes, allowing us to start the tour ahead of the 30,000 other cyclists from all around the world.

A-T Ease raised $8,000 through the sponsorship of our team's cyclists and we are looking to increase both the number of cyclists and funds raised at next year's Tour.

Join us next year, and secure your group pass, for the 29th Annual Five Boro Bike Tour which will be taking place on Sunday, May 7, 2006. For more information please contact us. We look forward to hearing from you!

A-T Ease Team Bike NY Tour 2005

Natasha and other A-T Team Cyclists
Having Lunch at the Brooklyn Bridge

One Cyclist's Experience

My name is Natasha Foy and I just completed my 2nd Annual Bike NY Tour, riding with, and raising money for, the A-T Ease Foundation. A very good friend at work, Steve Leo, has two children afflicted with Ataxia-Telangiectasia (A-T), a disorder I knew little about. But after learning more about A-T, I began to explore ways in which I could help. The Bike NY Tour is a great opportunity to see more of the city and have fun, and riding on the A-T Ease Team allows me to support an important cause at the same time.

When I learned that I could do the bike ride and raise money for the A-T Ease Foundation it was a no-brainer. I signed up right away. My first ride was such a great experience. Two highlights for me were riding over the Queensboro Bridge and stopping for lunch by the Brooklyn Bridge. Seeing NYC landmarks up close like that was fantastic and made me proud to be a New Yorker. Knowing I was riding for the AT-Ease Foundation made it that much more special.

I had not met Steve's two boys before my first ride, but since then I have spent some quality time with them. They are two sweet, caring, gentle boys who love soccer, boating, fishing and basically any sport you are willing to play with them. I am so happy to have the opportunity every year to help raise money to find a cure for A-T, in the hope that these boys will be able to have long happy lives and be able to share their great spirit and love of life with many more people.

I have received loads of support from family, friends, and co-workers. And I am proud to be a member of the A-T Ease Foundation Bike NY Team.

By Natasha Foy

A-T Ease Foundation's Efforts in Washington D.C.

The efforts of the A-T Ease Foundation in Washington, D.C. have been tireless and fruitful. Stephen Leo, a father of two children afflicted with Ataxia-Telangiectasia (A-T), and Tom Mooney, Washington Liaison, have made several trips to Capitol Hill over the last three years and have met with staff of several key U.S. Senators and Congressmen who serve either on the Committee on Health and Human Services, or one of its many Sub-Committees, and whose decisions may directly impact the possibility of funding for A-T research.

Our original objective was to raise awareness of A-T at the government level and to familiarize Senators and Congressmen with A-T. These strategic people now know about A-T, and are aware that there are efforts being made to find treatments and a cure.

While educating government officials about A-T, we went on to emphasize how much A-T has in common with other high-profile diseases that get automatic government funding, such as cancers, Alzheimer's, AIDS and Parkinson's. We emphasized that research into A-T will help unlock the mystery of finding a cure for other diseases that share a similar pathology, and help us at the same time.

Stephen and I have reached across both sides of the aisle. We met with the aides of Senators Corzine, Lautenberg, Clinton, Schumer, Frist, McCain, Spector, Hatch, Dodd, Kennedy and Landrieux; Congressmen Garrett, Rothman, Israel and Rangel, all of whom are members of the Health Committee and its Sub-Committee. We also had a private meeting with Dr. Story Landis, the Director of the National Institute of Neurological Disorders (NINDS), a division of the NIH that will oversee A-T research.

The meeting with Dr. Landis generated some publicity for A-T Ease Foundation as we are now included in the NIH directory of organizations supporting neurological disorders. The first benefit we experienced as a result of this listing was an invitation to a working group meeting at the NIH in May 2005. A-T Ease, 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 NINDS, among others, whose mandate was to help build an A-T team to develop a strategic plan for A-T research.

In November, if Senator Corzine, who is one of our allies in Washington, becomes Governor of the State of New Jersey, we anticipate that there will be increased support for our efforts. There seems to be new hope in stem cell research, which Mr. Corzine favors, and New Jersey is attempting to make this new technology work for those in need.

Our efforts will continue with the help of our supporters and Government funding of A-T research. We must continue to have faith that this tireless effort will continue to bear fruit. Thank you for your continued support of finding a cure for A-T.

by Thomas J. Mooney

3rd Annual Focus on the Hope Benefit

The 3rd Annual Focus on the Hope Benefit took place on October 21st, 2004 at the Midtown Executive Club in Manhattan. Over 100 of A-T Ease's family and friends were in attendance at our annual Cocktail Party and Silent Auction. Our guests enjoyed live jazz by RHEN and delicious wine and hors d'ouvres.

Some of the winning bidders in the Silent Auction took home prizes such as: a one-week stay at a resort of their choice anywhere in the world, a hot air balloon ride, a round of golf, a chef for a night, a consultation with an interior designer, and a hands-on cooking lesson.

Our heartfelt thanks go out to all those who helped and supported us that evening.

Virtually all of the funds raised went to support our programs and services.

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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