

Diagram of ATM's functional connections. ATM is in the center. This is only part of the growing list of proteins that ATM modifies following its activation by DNA damage. Each box represents one protein. The colors indicate different laboratory methods used to identify these proteins as ATM targets.

Letter from Israel Ataxia-Telangiectasia: A "Systems Biology" View

Our group studies the ATM protein, the product of the gene responsible for A-T. ATM is the master controller of a complex cellular system – the one that responds to DNA damage. When the DNA is damaged, especially by ionizing radiation, ATM immediately mobilizes an intricate network of cellular responses. The further we delve into this system, the more complex it becomes: genes are turned on and turned off, proteins are modified, produced or degraded at an accelerated rate, molecules change their location, cellular processes are enhanced or shut down... ATM is in charge of all these events, controlling them by inducing tiny chemical modifications in numerous proteins.

The emerging complexity of the ATM-mediated network is typical of many

signaling systems in the cell. In the past, biologists studied one biological process at a time. But now, faced with elaborate systems like the one mediated by ATM, they had to develop new experimental methods. A new discipline emerged – "systems biology" – that employs extremely powerful methods capable of recording many cellular processes at a time, providing us with a bird's eye view of the cellular metabolic landscape. The power of these methods is mind-boggling: one experimental system called "microarrays" follows the activity of tens of thousands of genes at a time; another system monitors chemical modifications in numerous proteins simultaneously in response to a stimulus.

▶ Letter from Israel cont.

Alas, the power of these methods creates a new problem: how to digest all this information, filter out false results, and make biological sense out of the mountain of data. Here, a new science is called in to help – “bioinformatics.” This new discipline combines mathematical modeling, computer science and biology to give us the computational tools to handle massive amounts of biological data, interpret them in a short period of time, and boil them down to coherent models on which to base future studies.

We are employing several bioinformatics strategies to study the ATM-mediated response to DNA damage. We have joined forces with a superb team at our School of Computer Science, headed by Prof. Ron Shamir, one of the world's premier bioinformatics specialists. Together, we are applying computational algorithms created by Shamir's lab to our massive experiments on A-T cells and healthy cells. We know that the ATM-mediated network involves the instantaneous activity of hundreds, maybe thousands, of events set off by DNA damage. Our task now is to identify those events, determine their individual functional significance, and then see how they fit into the network as a whole. The complexity of the ATM-mediated system explains the complexity of the disease caused by the loss of ATM. We now have the tools to probe this immense biological system in our quest to understand A-T and devise for new treatments.

Yosef Shiloh, Ph.D.

Department of Human Molecular Genetics
Sackler School of Medicine, Tel Aviv University

Research Grants Currently Supported by A-T Ease Foundation

ATM in Immune Responses
Principal Investigator – Jessamyn Bagley, PhD
Brigham & Women's Hospital

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

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

Direct Research on Ataxia-Telangiectasia
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

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

A-T Ease Update: New ways to treat specific classes of ATM mutations

Now that we have finally been approved for funding our project to find better drugs for treating nonsense mutations, we can begin to address the other successful project in our laboratory that addresses patients with splicing mutations. Splicing is a complicated process but is easiest to understand if one thinks about how film is spliced. You cut out the parts of the footage that you don't need so that what you see in the projected version will be only the 'good stuff'. Biology works the same way! We all have a blueprint of our genes that is our DNA. We have about 20,000 genes. However, the portion of those genes that are actually copied into protein (called EXONS) is only about 3% of the total DNA. The rest (called INTRONS, for intervening sequences) is spliced out. "Why?" you ask. "Don't ask." The answer is unclear at this time and even what is known is very difficult to explain without diagrams. Think of the EXONS as paragraphs in a book and the INTRONS as the spaces on the page that help you keep track of where to begin and stop reading. So DNA must be sliced into RNA before it can be translated into PROTEIN. DNA > RNA > PROTEIN is what it's all about.

A-T children sometimes have mutations (mistakes) in their DNA that mess up how or where the splicing will be done. This creates either a poorly structured ATM protein or one that is so unstable that it is immediately destroyed or degraded by the cell itself – before it were to cause other problems. So when we look for ATM protein in the cells of A-T patients, we usually find none or trace amounts. Our lab is also examining why and how this happens.

Recently, in our lab, Dr. Liutao Du designed some drugs for correcting the splicing mutations in the cells of some patients. He was actually able to get the cells to start making small amounts of good ATM protein and these cells functioned as normal or near-normal cells. **That is correct: it appears that we can now "cure" A-T in the laboratory.** So how do we apply this to patients? Well, that will depend on whether we can get past certain challenges:

1) Are these drugs dangerous or toxic? Probably not. The experts in this area are quite hopeful that they will be useful for patients. They must be tested in animals. We are just about to begin such a study in mice with Muscular Dystrophy. Other labs are also working on similar trials with other genes.

2) How can we get the drug into the brain? Or more specifically, into the cerebellum? Although the Nobel Prize was given in 2006 for the discovery of

these types of drugs, called "antisense" molecules, no one has a good method for getting them into the blood stream except by direct injections. For the drugs designed by Dr. Lu for the Muscular Dystrophy mice, we are planning to inject them directly into the muscles. This also saves money because if we put them into the blood stream, this will dilute the amount of drug that actually gets to each muscle. And these drugs are very expensive at the moment. We paid about \$300 for enough to do the pilot studies. At this price, to treat a 5-year-old child just one time would cost about \$3 million. But there are some very promising experiments being done in other labs that will help to 'target' these drugs to the brain. And we are working with these other labs.

We expect that these experiments will cost about \$100,000 to fill in the details that will lead us to actual clinical trials. More than that would speed up the progress, but less will not really allow the work to reach fruition. That is the critical number as of this writing. This project requires someone to assist Dr. Lu so that he can also continue his work with the nonsense mutations. Another post-doc who is very qualified has applied to join our team. That will cost about \$50,000 per year. They will need supplies of about \$15,000 per year. They will need technical assistance: \$35,000. The project should achieve a milestone of whether this work is promising enough to compete for government grants. But getting those grants usually takes about 27 months. If the work has to stop before that time, it is almost as if we had never begun. So, I think we have a realistic target of \$300,000 for three years. If this commitment can be made, I think the project can be launched immediately.

I would like to thank all of the members of A-T Ease, past and present, for their continuing dedication to finding a treatment for ataxia-telangiectasia. It should also be pointed out that this approach to treating genetic diseases will be applicable not only to A-T but also to the other estimated 3,000 genetic diseases that are known. So we are not only working for A-T, we are helping to find drugs that will someday allow anyone to take a pill to correct a genetic mutation. Think of that!

By Richard A. Gatti, M.D.

UCLA School of Medicine

Running 26.2 miles with a Focus on the Hope

Natasha Foy: How did you first hear about the A-T Ease Foundation?

Brian Bill: Someone at work was participating in the Bike NY Tour (a 42 mile bike ride) and raising money for the A-T Ease Foundation through that event. She was doing it because, Steve Leo, who works in our company, New York Life, has 2 children, aged 9 and 8 who are afflicted with Ataxia-Telangiectasia (A-T). A-T Ease Foundation is raising money to help find treatments and a cure for this rare and fatal genetic disorder.

NF: What made you want to run the NY City Marathon for this cause?

BB: Hearing Steve's story hit home for me. I have 2 small children myself. My youngest is 2, which is about the age when A-T is generally diagnosed. Steve has done so much for me in the past, and I wanted to give back to him. Thinking of his kids, just regular everyday kids who, unfairly, are afflicted with this disease just made me want to do something to help. I have also known many people in my own life who have passed away from cancer, one of the possible effects of A-T.

I wanted to make a really big effort in order for people to make an effort in donating. I felt it was only fair to ask people to give a lot if I was asking myself to give a lot. The NY City Marathon is also a local event and A-T Ease Foundation is a local charity so I thought that would align really well and get people really interested in helping. So I ask you, dig deep when you sign up to sponsor me.

NF: Once you decided to do this how did you guarantee your spot in the marathon? 100,000 people applied and there are only 38,000 spots!

BB: Well, I jumped the gun a little and made my commitment to A-T Ease Foundation before I realized the odds of getting in were slim. There are, however, guaranteed spots for people who run for NY City Marathon-approved charities. So I agreed to raise at least \$3,000 for the Hole in the Wall Gang to gain entry. In addition, I hope to raise \$10,000 for A-T Ease Foundation. A-T Ease Foundation is now looking into becoming an official NY City Marathon-approved charity.

NF: How has the training been going?

BB: Tough, but good. It has been really challenging because I work full time and have young kids at home. We have a gym at work so that has been great. I am there in the early morning hours getting my runs in. I use Sundays for my long runs so I am out of the house at 5:30am with stern warnings from my wife to be home in time for breakfast. So that is good motivation right there for timing myself!

Brian Bill - "Marathon Man"



NF: What is the toughest part?

BB: Well, the training is grueling. It is difficult to know when to rest and slow down. Reading materials have helped – Hal Higdon's "Marathon Training Guide" has become my running bible. I am learning to be able to tell when my body needs to rest and what to eat. Balancing resting and proper eating with the workouts is so important and sometimes you get so excited about the goal you forget to rest and that can lead to injury.

The other really hard part is the long runs. Not the physical part, but the mental. Doing this for a cause makes it easier. It would be a lot harder if I weren't doing it for a cause, especially one that means so much to me. The long runs are about three hours of actual running time, but you need to think of a lot of stuff in advance. For example, the route needs to be mapped out way ahead of time. You need to prepare and take hydration packs. I think a lot about the A-T Ease Foundation logo and what it says: "Focus on the Hope". That is what I do when I am running to help me push myself right to the finish.

NF: So what's left?

BB: Well, the training is a 16-week training program. I have a half marathon next weekend, and then race day is 5 weeks from this Sunday. So I will just keep on plugging along and try to make sure I achieve my goals.

Speaking of goals, the fundraising is going extremely well. I raised about \$5,500 so far for the A-T Ease Foundation. As I said, my goal is to raise \$10,000. **So, for anyone reading this if you are interested in sponsoring me you can make a donation directly to the A-T Ease Foundation from their website.**

And if you watch the marathon look for me crossing the finish line with a huge smile and the A-T Ease Foundation Banner!!

NF:

Thanks Brian and Good Luck! We will be watching for you and rooting you on!

Upcoming Events! Please mark your calendars:

Sunday, May 4, 2008 – Join the A-T Ease Cycling Team to raise awareness and funds during the 31st Commerce Bank Five Boro Bike Tour.

Thursday, June 26, 2008 – 2nd Annual A-T Ease Foundation Golf Classic.

Fall 2008 – 7th Annual Focus on the Hope Benefit.

Information will be posted at:
www.ateasefoundation.com/events.shtml

CIBC World Markets Miracle Day – Wednesday, December 5, 2007

Each year, on the first Wednesday in December, CIBC World Markets employees and clients participate in a major effort to benefit children's charities. They have been doing so since 1984. This year's Miracle Day will take place on December 5th, when CIBC will donate 100% of their fees and commissions (less expenses) from trades made through CIBC World Markets to children's charities nominated by employees and clients and approved by the Miracle Day Committee.

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 5th.

Please remember to:

- Alert your company's traders that you will be trading for A-T Ease Foundation on Miracle Day.
- On December 5th, when you or your company trades with CIBC, mention that you are trading for A-T Ease Foundation.

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

Thank you for your help!

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

CIBC World Markets
New York Life Foundation
Peregrine Charities
Simplymad Design Studio
Steve Edge Design

A-T Ease Foundation Golf Classic Sponsors:

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Thomas Larkin, MD
White House | Black Market

Thank you.
We could not continue our quest without your help!

BAR NITE

Thursday Night. Happy Hour. McFadden's Bar. 42nd Street. Spring Time in New York City. You're probably thinking... why is this guy talking about Happy Hour in an A-T Ease Foundation Newsletter? But earlier this year I had a great opportunity to help a dear friend of mine. Joan Guadagnino, Co-President of the A-T Ease Foundation, is one of the hardest workers anyone will ever meet. Knowing that I had several years of experience bartending in Bay Ridge, Brooklyn, she asked me if I would be a guest bartender at McFadden's for Happy Hour. There was not even a second thought. I emphatically told Joan, "Of course!" The A-T Ease Foundation is totally committed to assisting children with A-T and their families and have done yeoman's work to raise money to help find a cure for this debilitating disease. I was happy to jump on the bandwagon!



The Yankees had just pulled out a great come from behind victory at the Stadium; A-Rod hit a walk-off homerun; and there was a nice holdover of fans who had been watching the game. The atmosphere was perfect for Happy Hour! I was very impressed by the turnout at McFadden's, but more impressed that the majority of people came to support a great cause! Everyone who attended was served cold beers and delicious cocktails and left the evening feeling great, not just because they had a few drinks, but because they supported the A-T Ease Foundation. So you are probably thinking right now, "How did the A-T Ease Foundation make money during Happy Hour?" The dedicated staff of the Foundation ran a 50/50 Raffle which raised money, but to top that, all of the tips collected by the bartenders went directly to the Foundation. Needless to say, everyone was a great tipper and really came to bat for the A-T Ease Foundation!

At the end of Happy Hour I told Joan how much money we had collected and she was all smiles. The smile on her face made me feel like a million dollars because I had helped make a difference for those who have been diagnosed with A-T. When I was growing up, my father gave me a note pad that had the following quote on it, "One hundred years from now, it will not matter what my bank account was, how big my house was, or what kind of car I drove. But the world may be a little better, because I was important in the life of a child." After helping the A-T Ease Foundation, I feel like I have made a difference in the lives of the children who suffer from this rare disease. If asked to tend bar for the Foundation again, I definitely would. I am glad I was given this great opportunity!

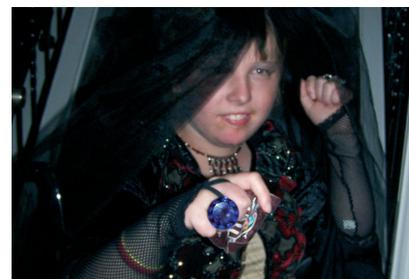
Rob Oliva

My Halloween Escape

Hi,

My name is Victoria Bement-Schramm and I LOVE Halloween. My favorite part of Halloween is getting to dress up as something or someone you are not. It is pretty cool! I got my costume in June. I am going to be a Shimmery Rose Vampire, but I am calling it a Queen of the Night costume. I like all of that weird stuff like werewolves, ghosts and witches, but my favorites are vampires. I don't know why I love them so much, but I have watched all the old monster movies since I was a little girl. It is my escape out of this disease! I also like the movie series from Disney called Halloweentown. Another favorite is also a Disney movie about twin witches called Twitches. I remember when I was little, and I could walk, my cousin Zac dressed up as Mickey Mouse and I was Minnie Mouse. We both wore Mickey ears and funny white gloves with only three fingers!!! I love to go out and see all the costumes and answer the door for Trick-or-Treaters. I could talk about Halloween all day but I'm going to stop before I take up the whole letter.

Happy Haunting,
Victoria



Inaugural A-T Ease Foundation Golf Classic

The A-T Ease Foundation's inaugural Golf Classic was a huge success. The course was filled with individuals who share a common commitment to raise money and awareness for A-T.

The outing was held on June 28, 2007 on the prestigious Private West Course at the Royce Brook Golf Club in Hillsborough, NJ. Golf Digest ranked the Private Membership West Course at Royce Brook as the "Best in New Jersey" in their 2007-2008 survey and as one of the "Four Best Places to Play" in 2007.

Our golfers were greeted with a goody bag and were sent to tee off with a boxed lunch. A variety of contests ensued throughout the afternoon's play such as a putting green contest, Beat the Pro and the Pot of Gold.

The post-play reception was held at the Club House where golfers enjoyed cocktails and a BBQ dinner. The event concluded with a drawing of an impressive array of prizes and an awards presentation by Event Chair, Dr. Victor Guadagnino.



Tim Cochrane, Jimmy Monaghan, Steve Oliver and Dan Teixeira



The A-T Ease Team Rides Again!!

May 6th, 2007 was a beautiful day. I woke up at 5:30am and headed down to lower Manhattan to meet the 2007 A-T Ease Team. We congregated in our usual spot, had a healthy breakfast together to give us strength for the ride and shared stories about everything from the most picturesque to the most physically grueling spots on the ride. At 8am we were at the starting line and ready to go! As we listened to the opening ceremonies, we thought about the children we ride for. While the NY Bike Tour is open to all individuals, many ride for a cause. Our group of nine were riding to raise funds for the A-T Ease Foundation.

I have a personal interest in this cause, as I know a family whose two young sons are both afflicted with A-T. Nick and Matt are 9 and 8 years old. Nick is in a wheelchair full time now, but both boys still play tee-ball. They have loads of friends and are two of the sweetest, and most caring boys I have ever met.

All our riders either know someone afflicted with A-T or just want to help wipe out this cruel and fatal disease. Every year we get together to support the A-T Ease Foundation in their efforts to accomplish this. And every year we know we are cycling against time, to give hope to A-T children and their families. In the face of such a monumental task, we count on the generosity of friends to support our efforts to bring hope and encouragement to families who are desperate for a breakthrough.

This year we were able to raise over \$11,000 through this event alone. Thanks to all my fellow bike riders and the donors that so generously supported them! I had a great time this year and look forward to seeing all the riders again next year. For all those reading this who didn't ride I hope you will join us too. They say "the more the merrier" and that certainly holds true here. The more riders and donations we get the better chance we have to save lives and that is definitely something to be merry about!

Natasha Foy

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

The success of our efforts will bring hope and encouragement to families who are desperate for a breakthrough.

GoodSearch

What if A-T Ease Foundation earned a penny every time you searched the Internet? Well, now we can!

GoodSearch.com is a new search engine that donates half its revenue to the charities its users designate. You use it just as you would any search engine, and it's powered by Yahoo!, so you get great results.

GoodShop.com is a new online shopping mall which donates a percentage of each purchase to your favorite cause. More than 100 great stores including The Gap, Best Buy and Barnes and Nobel have teamed up with GoodSearch and every time you place an order, you'll be supporting your favorite cause. Just go to www.goodsearch.com and be sure to enter **A-T Ease Foundation** as the charity you want to support.

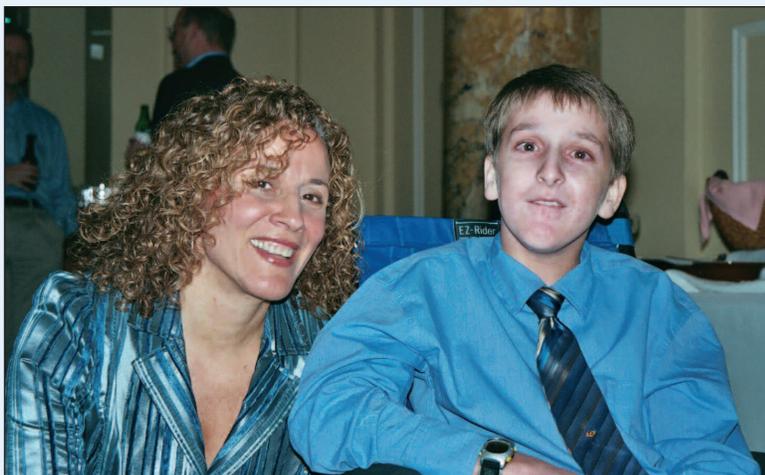
Just 500 of us searching four times a day will raise about \$7,300 in a year without anyone spending a dime!

A-T Ease Foundation's 5th Annual FOCUS ON THE HOPE BENEFIT was held on October 26, 2006 at the Midtown Executive Club in Manhattan. It was an evening of music, cocktails, and, of course, our popular silent auction.

Presentations were made by Richard Gatti, MD, the principal investigator of A-T research at UCLA Medical Center, as well as Tori Bement-Schramm, a 19 year-old woman with A-T, and Stephen Leo, the father of two boys with A-T. Dr. Gatti discussed the status of his lab's work at UCLA and reaffirmed his continued dedication into research, therapeutic treatments and eventually developing a cure for A-T. Tori spoke and read a poem she wrote about hope and finding a cure for A-T. Stephen Leo offered poignant anecdotes on family life.

The event was attended by over 100 guests and contributions were received from more than 500 individual donors. The evening raised more than \$60,000 which will be applied to continue the mission and further the initiatives of A-T Ease Foundation.

Joan Guadagnino and Robbie Smarz



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A-T Ease Foundation Inc.
532 LaGuardia Place, Suite 404
New York, New York 10012
t: 212-529-0622
f: 212-505-8031
e: info@ateasefoundation.org
w: www.ateasefoundation.org