A-T CHILDREN'S® PROJECT℠ UPDATE

For Families, Friends and Supporters

NOVEMBER 2000

New DNA Testing Service for A-T Gene to Be Developed

The Research and Development Division of the DNA Diagnostic Laboratory at Johns Hopkins University School of Medicine has begun developing a sequenced-based ATM gene mutation testing service. When established, the difficult challenge of diagnosing unclear cases of A-T will be greatly improved. In addition, families of A-T patients who want and deserve to know whether or not they are carriers or want to have prenatal diagnosis will be able to obtain these services from a CLIA-approved laboratory with a quick turn-around time and with appropriate genetic counseling.

Gary Cutting, MD, Corinne Boehme, PhD, and Heidi Tyson.

At the same time, with this service, researchers will be able to learn how different misspellings (mutations) of the A-T gene's code may correlate to different symptoms or degrees of disease severity. Using funds provided by the A-T Children's Project, the DNA Diagnostic Laboratory, under the direction of Gary Cutting, MD, will develop this new testing service in collaboration with the A-T Clinical Center at Johns Hopkins Hospital in Baltimore, Maryland.

Quite often, physicians around the world refer children to the A-T Clinical Center. These children may have some, but not all, of the typical features of A-T. For example, they may have ataxia and immune system problems but have normal levels of alphafetoprotein and normal sensitivity to radiation. As in all cases, making an accurate diagnosis is important, so that the family can know the long-term prognosis for the child and so that parents can understand the risk they carry of having another child with A-T. Particularly with younger children, there are several other diseases that can seem like A-T, and reading the exact sequence of the A-T gene's code is the one clear method for confirming the diagnosis of A-T. Studying the A-T gene in unusual cases of A-T may also be useful for increasing scientists' understanding of the disease.

As researchers study A-T, they will undoubtedly be in a position to conduct new clinical trials of drugs or other interventions such as stem cell implantation or gene therapy. A genetically confirmed diagnosis of each participant is essential for each of these projects to ensure that the evaluation of the treatment is not compromised because patients without A-T were accidentally included in the trial.

The DNA Diagnostics Laboratory at Johns Hopkins University School of Medicine possesses the expertise and experience needed to develop the testing service. It has been in operation since 1979 and received CLIA certification in 1988.

Continued on page 2

ATCP Awards Grant to Produce Bovine and Porcine Models of A-T

Steven L. Stice, PhD, Associate Professor and Senior Research Scientist at the University of Georgia, has been awarded a grant by the A-T Children's Project to knock-out the A-T gene in both pigs and cattle to create new animal models of A-T.

Steven L. Stice, PhD

Having good animal models of A-T is critical for testing potential treatments. The various mouse models that are being used do not show the same neurodegeneration as A-T patients. One of the factors in considering which animal to use is how long until an animal is born and how fast animals of a specific genotype can be multiplied. According to Dr. Stice, pigs and cattle hold the most promise for producing good A-T models.

Continued on page 2

Matt Damon Attends Fundraiser

(See story on page 5)

QUESTIONS OR COMMENTS:

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DNA Testing *Continued from page 1*

In addition to Dr. Cutting, the laboratory's efforts on the A-T genetic test will include Corinne Boehme, PhD and Heidi Tyson.

The laboratory has extensive experience in the design, development and implementation of sequence-based DNA diagnostic tests for inherited disorders. These include sickle cell disease, thalassemia, Von Hippel Lindau disease, craniofacial disorders due to defects in fibroblast growth factor genes, X-linked adrenoleukodystrophy, and cystic fibrosis. For each of these diseases, tests have been developed that can even detect a single letter of the genetic code (a single nucleotide base) missing or substituted in a gene.

Before any new samples are obtained from A-T patients or their families, the new test will be validated by analyzing blinded cell-lines from A-T patients and from healthy individuals. This format is consistent with the validation tests used by the College of American Pathology and the American Board of Medical Genetics Test of Molecular Genetic Laboratories. Once the testing service is established and validated, it will begin testing samples. The A-T Clinical Center will obtain signed, informed consent for each case. Dr. Cutting expects the test to be developed and the service up and running by June of 2001.

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Tax Write-Off for Parents Attending Medical Conferences

On May 8, 2000, the Internal Revenue Service (IRS) issued a ruling that will allow parents to deduct some of the costs associated with attending medical meetings related to their child's health condition. Congressman George Miller (D-CA) who called for the IRS decision noted that physicians, vendors, salespeople, and others can deduct the costs of attending medical meetings, but until now parents could not. The new ruling allows parents to deduct "amounts paid by an individual for expenses of admission and transportation to a medical conference relating to the chronic disease of the individual's dependent." For more information, consult the Internal Revenue Bulletin 2000-19 (May 8, 2000), Rev. Rul. 2000-24, pp 963-964.

Familes who attended the International A-T Caregiver Conference 2000 might be eligible to take a tax deduction for costs associated with their attendance.

Animal Models *Continued from page 1*

Although the technology for cloning pigs is a slower process than for cattle, with a gestation of four months and with 7-10 offspring per pregnancy, there is a definite advantage in cloning pigs for research. Cattle have a nine-month gestation period, and one offspring per pregnancy, but more is known about the embryology and genome of cattle than any other farm animal; therefore, we will probably have an A-T model of cattle first.

Working closely with Don Wolf, PhD, at the Oregon Health Sciences University, and Robert Norgren, PhD, at the University of Nebraska Medical Center, Dr. Stice will be using a combination of gene targeting and nuclear transfer technology to produce a farm animal model for A-T that closely replicates the disease in humans. Dr. Norgren is working with Dr. Stice to isolate the DNA fragment of A-T (called ATM) in cattle and pigs. The ATM gene will be disrupted. Fibroblast cells with at least one ATM gene mutation will be used as donor nuclei in efforts to produce cloned A-T pigs and cattle fetuses by nuclear transfer. The first step will be to culture embryos to the blastocyst stage in vitro. Then, when viable embryos are established, they will be transferred to surrogate pigs and cows in efforts to establish pregnancies.

Dr. Stice has over 14 years of animal cloning research experience. In 1987 he produced the first cloned rabbit and the first cloned transgenic calves in 1998. This research led to a prestigious publication in *Science* magazine and the first U.S. patents on cloning animals and cattle embryonic cells. It is anticipated that the first cattle and/or pig models for A-T will happen within the next two years. AT

WISH LIST

Your donation of items or services to the A-TCP is tax deductible. These items will help us in our mission to bring awareness. Please email info@atcp.org or call 800-543-5728 to find out how you can help.

- ❒ Printing Services
- ❒ LCD Projector
- ❒ Portable TV-VCR
- ❒ Laptop Computer
- ❒ Digital Camera
- ❒ Digital Video Camera

A-T Clinical Center Expanding Neurological Services

The A-T Children's Project recently awarded a grant to Johns Hopkins Hospital to expand the neurological testing services at the A-T Clinical Center.

Howard Lederman, MD, PhD, and Thomas Crawford, MD, have assembled a team of neurologists who will use state-of-the-art equipment and novel approaches to objectively analyze the neurology of A-T patients and answer the following questions:

What is the underlying neuropathology and neurodegenerative mechanism of A-T? More specifically, what is the underlying pathology of A-T, and what clues about cellular pathogenesis can be discerned from studies of human tissues?

The following research design was developed to study these areas of neuropathology:

- ☐ Characterization of ATM antibodies in humans
- ☐ Spatial localization of ATM within the central and peripheral nervous system

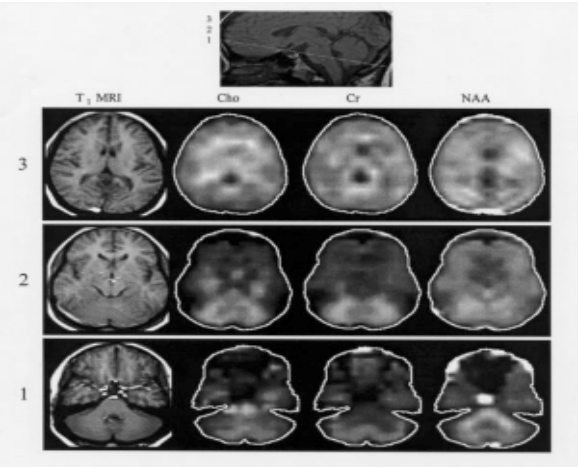


Figure illustrates 3-slice long TE (280 msec) MRSI sequence on a normal volunteer recorded on the new Kennedy Krieger Institute 1.5 Tesla Philips scanner.

- ☐ Update the neuropathology of A-T
- ☐ Additional studies to address possible abnormal brain formation in A-T
- ☐ Examining the process of ongoing neurodegeneration

Carlos Pardo, MD, will focus on the neuropathology segment of these new studies. (*See related story page 4.*)

What is the neurophysiologic basis for the abnormalities in movement and tone that characterize A-T?

Studies will be conducted that will build on the observations made in the first years of clinical evaluations of patients with A-T. Understanding the movement patterns of A-T patients will give the researchers and clinicians insight into the neurodegeneration and offer the introduction of therapies to target the specific areas of difficulty. Among other things, these studies will examine tremors, tone, reaction time, movement time, and movement persistence. Forty A-T patients will be studied under the supervision of Allen Mandir, MD, PhD.

What areas of the central nervous system demonstrate features of abnormal cellular metabolism in A-T?

Advanced neuroradiologic studies through special magnetic resonance imaging (MRI) approaches will be used to evaluate the basal ganglia and cerebellum of A-T patients. A high resolution MRSI will provide a look at which areas and how the brains of A-T patients work when they are completing certain thinking tasks. Dr. Peter Barker will conduct these studies.

Participants in these studies will be identified at regular A-T Clinical Center visits.

First Annual Skydive For A Cure

The A-T Children's Project and Skydive Space Center in Titusville, Florida joined forces on September 18, 2000 to bring awareness to A-T. Amy Madison and Rosa Fernández participated in the first annual Skydive for a Cure jumping from a perfectly good airplane in the heart of the Florida Space Coast. Tandem masters Josh Dolan and Jeremy Wilder made sure that these two daredevils made it safely to the ground while having an exhilarating experience. The freefall lasted 60 seconds, and after the parachute opened it took five minutes to get to the ground. The local newspaper did a story about the skydivers and the Madison family and made this community aware of the plight of all the families living with A-T.

Amy Madison and Jeremy Wilder freefalling above Titusville, Florida with videographer Brian Elder.

FROM LEFT: Dewey Strickland, Brian Elder, Rosa Fernández, Jeremy Wilder, Amy Madison, Margaret Strickland, Joao Fernández and Josh Dolan. NOT SHOWN: Chief Pilot Glen Gray

If you would like to participate in next year's A-T Skydive for a Cure, please contact the A-T Children's Project at 1-800-543-5728.

Rosa Fernández and Josh Dolan seconds after the "jump."

A-T Mice Brains Lose GABAergic Cells With Age

A team of researchers led by Raya Eilam, PhD, Yoram Groner, PhD, and Menahem Segal, PhD, at the Weizmann Institute in Israel recently completed a two-year research project funded by the A-T Children's Project. The project came about after Dr. Segal began pondering A-T at a scientific workshop held in Tarrytown, New York. Hearing how little scientists knew about the neurological problems of the A-T mice, Dr. Segal decided to use his expertise in brain development and structure to analyze the brains of A-T mice himself. Rather than concentrating on the cerebellum, the brain area most often considered the culprit in A-T, Dr. Segal focused his efforts on looking at the substantia nigra, an area in the brain stem where he was most experienced, and where oxidative stress was known to cause problems in other diseases. Working with the laboratories of Dr. Eilam and Dr. Groner, Dr. Segal's group used a brain cell staining technique to discover early on in the project that a certain type of nerve cell, known to produce a chemical called dopamine, was missing in five-month-old A-T mice. This finding was significant, because this was the same type of cell that was known to die in Parkinson's disease.

Menahem Segal, PhD

Next, the team compared two-month-old A-T mice with the older mice and discovered that the younger mice had not lost any of the "dopaminergic" brain cells yet. The scientists realized that they had found clear evidence of brain deterioration in A-T mice.

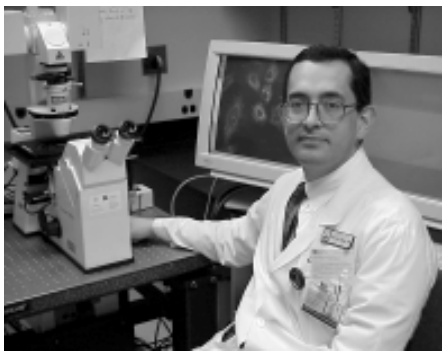
The researchers did not stop. Their subsequent step was to determine if the dopaminergic cells were dying as the mice aged because the cells had not developed correctly from the start, or because of some other factor. By showing that the dopaminergic cells had made normal-looking connections with other cells when the mice were young, the scientists concluded that the cells had formed normally and that the problem was not one of development. Instead, not having an A-T gene seemed to make the older mice more vulnerable to some stress that caused them to die.

Most recently, the three research groups have looked at other cells in the brain — this time in the striatum — by injecting A-T mice with a particular die and then examining their brains under a light microscope. They found that as A-T mice grow older, another type of cell dies. These cells produce a chemical called "glutamic acid decarboxylase." This latest finding is intriguing because these GABAergic cells are also known to die in Parkinson's disease. And, they play an important role in motor control, something all children with A-T gradually lose.

The group of Isreali scientists do not yet know why these types of cells are dying in the brains of A-T mice. Because the GABAergic cells seem to die a little later than the dopaminergic cells, there remains the possibility that the GABAergic cells are dying as a result of the dopaminergic cell death. More studies are needed to clarify the causes. But for now, it seems possible that A-T has more in common with Parkinson's disease than was previously thought.

A-T Brain Tissue Reveals Intranuclear Inclusions

Carlos Pardo, PhD, at the Johns Hopkins Hospital in Baltimore, Maryland, recently studied the brain tissue obtained from five deceased A-T patients. He found extensive pathological changes in the cerebellum and brainstem. Dr. Pardo looked at cells in the substantia nigra and the cerebellum using histological and immunocytochemical techniques. In three of the five specimens, using antibodies against ubiquitin, he found a remarkable and novel abnormality -- the presence of intranuclear inclusions in subsets of nigral cells.



Carlos Pardo, PhD

Ubiquitin-binding is one step in a pathway of protein degradation. The finding of accumulated ubiquitin positive inclusions suggests that there are insoluble or abnormal nuclear proteins in this specific cell.

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Neurodegeneration Possibly Linked to Autoimmune Response

Robert B. Darnell, MD, PhD

Neural autoantibodies are being discovered in more than 40% of A-T patients, according to the lab of Robert B. Darnell, MD, PhD, at Rockefeller University in New York. This current study used sera samples of 54 A-T patients, confirming the findings of an initial study of 10 samples. Research shows that there might be a previously unsuspected cause-effect relationship between immune dysfunction and neuronal degeneration in A-T.

Dr. Darnell's lab is continuing to receive samples from A-T patients. To participate in this study, or if you have any questions, please contact the A-TCP at 1-800-5-HELP-A-T or email info@atcp.org.

Snyder's Stem Cell Research Highlighted in *Boston Globe*

The July 4, 2000 issue of the *Boston Globe* featured Evan Snyder, MD, PhD, in an article about stem cell research entitled "The Man Who Fixes Brains." Dr. Snyder is currently funded by the A-T Children's Project to research the feasibility of transplanting neural stem cells into A-T patients to reverse neurodegeneration.

Brad Margus, president and co-founder of the A-T Children's Project, is quoted in the article as saying, "Scientists like Evan Snyder are like first-round draft picks: every disease group wants to get their hands on someone like this."

A-T research in Snyder's lab is progressing quickly. First, monkeys were treated with onconase, a drug that causes brain damage similar to that seen in A-T. Then, the same monkeys were given neural stem cells. Some of the stem cells migrated to the areas of the brain that were damaged and grew into the type of brain cells that were missing -- Purkinje cells. Snyder's team is now waiting to see if the transplanted cells begin to function.

One of the next steps will be to test neural stem cells on A-T mice to see if the stem cells have any unanticipated effects.

Snyder is already having discussions with the FDA about the necessary protocols and testing that will be required on A-T patients, paving the way for clinical trials hopefully within the next two years. AT

Johns Hopkins Hospital Heads the Honor Roll

Johns Hopkins Hospital in Baltimore, Maryland, the site of the A-T Clinical Center, was ranked the number one hospital in the United States, according to *U.S. News and World Report*'s "America's Best Hospitals." Out of 6,247 institutions analyzed, only 173 qualified to be eligible for ranking. Runners up were Mayo Clinic in Rochester, Minnesota (#2) and Massachusetts General Hospital in Boston (#3). AT

Matt Damon Auctioneer at Shjon Podein's Charity Golf Tournament

Oscar-winning screenwriter and actor Matt Damon participated at the Shjon Podein Foundation's golf tournament in Rochester, Minnesota this past June. The A-T Children's Project is one of the beneficiaries of the annual golf tournament. The organizers of the event, Colorado Avalanche hockey player Shjon Podein and Jim and Holly Renn, invited Nikki Richmond, mother of 11-year-old Taylor, to speak at the awards dinner about A-T and the research progress made possible because of funds raised at events such as this one. A-T families, including the Smiths from Wisconsin, the Richmonds and Christiansens from Minnesota, and the Kindregans from Virginia attended the event.

Katie and Trevor Smith present Matt Damon with a A-T Hearts of Hope T-Shirt

From Left: Taylor Richmond, Tyler and Katie Smith, Colorado Avlanche's Shjon Podein and Joe Kindregan

Twelve-year-old Joe Kindregan donated his script of the movie *Good Will Hunting*, autographed by Ben Affleck. Matt Damon added his signature and auctioned it to the highest bidder for $5,000. We learned recently that Damon sent Joe another copy of the script autographed by Ben Affleck, Robin Williams and himself. "This one I'm keeping," Joe said.

A Car for A Cure?

Can't sell that used car?
Would you be better off with a donation tax receipt for its blue book value ?

It's easy and hassle free. Donate your used vehicle to the A-T Children's Project. We will issue a tax receipt for your used car donation. In a matter of minutes you can make arrangements to have your vehicle picked up free of charge anywhere in the United States.

For details, please call the A-TCP at 800-543-5728.

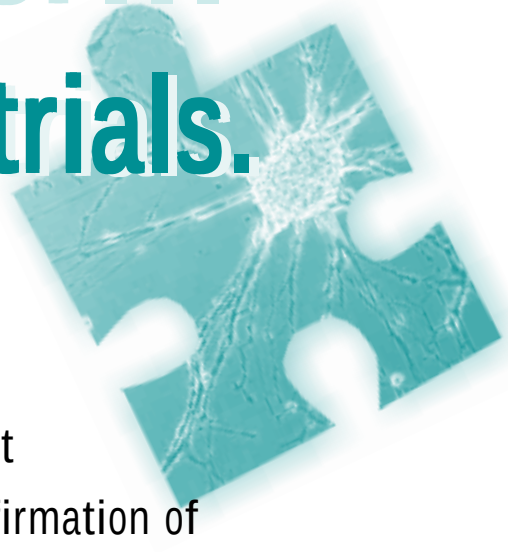
A-T CHILDREN'S PROJECT℠

Putting the Preparing

Finding Treatments

- Continuing in-depth basic molecular biology lays groundwork for applied research.
- Weakened immune system investigated as possible cause of brain cell death.
- Cattle and pigs added to mice and monkeys as A-T models for possible therapies.
- A-T mice now being tested for decreased A-T progression with new antioxidant, already shown to increase lifespan of worms by 44%.

puzzle together...
for more clinical trials.



Expanding Clinical Services

- Automated DNA sequencing machine available at the A-T Clinical Center in 2001 for genetic confirmation of A-T diagnosis, A-T carrier status and pre-natal testing.

- New state-of-the-art neurological testing equipment will improve the A-T Clinical Center's capabilities to run clinical trials.

Going for the Cure

- Two top gene therapists seek means to deliver healthy genes to A-T patients.

- Brain damaged monkeys show improvement with transplanted neural stem cells.

What's New with Fundraising...

On the Web -- Body1.com Promotes A-T Awareness

Body1.com, which bills itself as "the website where technology innovators and health consumers meet," is promoting A-T awareness. The website features excerpts from an exclusive interview with Dr. Evan Snyder, who discusses the significance of A-T research and the impact of organizations such as the A-T Children's Project. Body1.com is currently running a promotion -- for every person who registers online (for free) and references the A-T story, Body1.com will donate $1 to the A-TCP. Thanks to Chris Messina and the staff at Body1.com for making this happen.

Stamm Wins 1st Place Orange Classic

Josh Stamm entered the Orange Classic 10K road race in honor of his friend Joey Presutto (20) who died of Duchenne Muscular Dystrophy.

Josh Stamm placed first among the wheelchair participants.

I recently participated in the Orange Classic, a 10K road race in Middletown, New York, and was fortunate to place first among the wheelchair participants (there were a total of fourteen wheelchair participants registered, however, only two showed up). This turned out to be very fortunate for me, as there was a cash prize for the first place male and female finishers.

I participate in these races for the thrill of the event and just being a part of it, so I would like to donate some of the money to you in the hopes of helping me and others with A-T.

Please find a cure.

Sincerely,
Josh Stamm
Age 19

Ride for a Cure

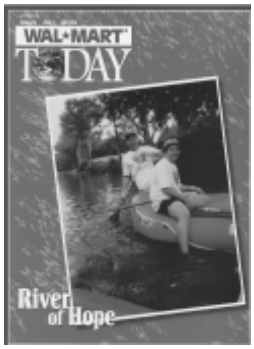
Sheila Smith of Freedom, Wisconsin, rode in style with the local bikers who volunteered their time and money on the second annual Bike Run benefiting the A-T Children's Project.

Family Reunion Turned Fundraiser

Pam Digby, from Seagoville, Texas, participated in an extended family reunion that takes place once every ten years in Alexandria, Minnesota. With about 200 family members in attendance, Pam turned the reunion into the **Lee Family A-T Walk for a Cure.** The Digbys drove to Minnesota and introduced their son, Jared, and A-T to all their relatives. The family had a great time and managed to raise quite a bit of money and awareness, too. AT

"Nite of Giving"

Bruce and Pat Beauchamp, and Steve and Sara Hiebner thanked long time supporters of Rhode Island events at an intimate summer party with dancing, dining, and an auction. Over 150 guests gathered at the Beauchamp home and tripled their original goal, raising funds for A-T research. AT

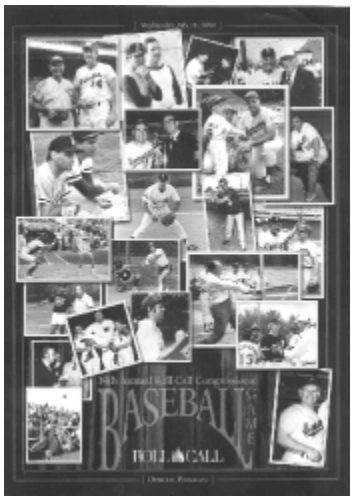


Wal-Mart Today Spotlights A-T Family

An article in *Wal-Mart Today* highlights the experiences of Dave and Amy Madison of New Braunfels, Texas, parents of three children with A-T. The magazine, with a circulation of 1.2 million, describes A-T and the hard work of hundreds of Wal-Mart and Sam's Club associates to support Dave and Amy's fundraising efforts for the A-T Children's Project over the years. The Madison family hosted Hope Floats in Texas, an event that included a float trip, 2K walk, barbecue, auction, and live entertainment. AT

The A-T Children's Project is a 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 lethal genetic disease that attacks children, causing progressive loss of motor control, cancer and immune system problems.

Congressional Baseball Game Benefits A-TCP



On July 26, 2000 a Congressional Baseball Game featuring the House Republicans versus the House Democrats was held at the Bowie Bay Sox Field in Maryland. Suzi Kindregan, Carol Lewin, and other volunteers hosted an A-TCP booth where they handed out information, hats, and shirts. This year the A-T Children's Project was chosen as one of the beneficiaries of the charity match.

A-T Hearts of Hope Ball

The Bearers and Mertens of Blairesville, Pennsylvania, held their first formal dinner dance at the beautiful *Chestnut Ridge Inn on the Green*. The event's featured speaker was Amy Madison, A-T parent and Vice President of the Board of Directors of the A-TCP. Madison compared receiving the diagnosis of A-T to jumping out of a plane. "Finding the A-T Children's Project was like opening a parachute," said Madison as she compared friends and supporters of the project to the wind under the canopy for a safe landing. (*See related story, page 3*)

Join the A-TCP Fundraising Team Call 800-Help-A-T

Cape Cod Cooking Classes

Great recipes, gracious hosts, and A-T awareness all made for a very successful series of cooking classes in Cotuit, Massachusetts. Event host Francesca Carriuolo was introduced to the A-T Children's Project by volunteer and friend, Ned Bilhuber. Classes were held at private homes and a local restaurant, and donors enjoyed trying new recipes and sipping on donated wine. One of the classes included a presentation about A-T from Bob Hiebner, an A-T grandfather. Through income generated by the classes and corporate sponsorships, the event brought in over $20,000 for A-T research and introduced many new people to the A-T Children's Project.

From Left: Edmund Bilhuber, Francesca Carriuolo, Barbara Hiebner and Robert Hiebner

Cooking Class

A-T Hearts of Hope Pop Up Everywhere

An easy way to get involved and be part of the grassroots fundraising efforts of the A-T Children's Project is selling Hearts of Hope.

To learn how you can help, contact the A-T Children's Project at 1-800-5-HELP-A-T or email info@atcp.org.

Bessie proudly displays her hearts of hope! Moo!

Rachel Kemeny and a volunteer at the Flat Rock Festival Days Parade in Michigan

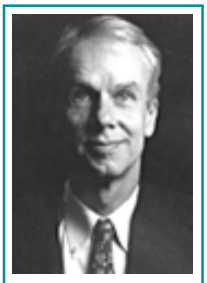
Volunteer lines road with hearts in Troy, Michigan

A-T Mice Receive Therapeutic Antioxidants

In an effort spearheaded by Rodney L. Levine of the National Institutes of Health, and supervised by M. Flint Beal, MD, chairman of the Department of Neurology and Neuroscience at Cornell University, researchers across the country are collaborating on a study to test two antioxidants, creatine and EUK-134, on A-T mice. These antioxidants have already been shown to have positive therapeutic effects on other diseases.

Creatine has been shown to have a neuroprotective effect on transgenic mice of amyotrophic lateral sclerosis, better known as Lou Gehrig's disease, a neuromuscular disorder.

EUK-134 is a low molecular weight compound shown to affect a number of acute pathophysiologic conditions, including a rather dramatic ability to lessen brain damage in a stroke model. EUK-134 has also been shown to increase the life span in the lowly worm *C-elegans* by an average of 44%. The NIH recently awarded Eukarion, the maker of EUK-134, a $1,300,000 grant to continue the development and testing of their compounds in stroke victims.


Flint Beal, MD

The A-TCP grant is entitled, "Mouse Ataxia-Telangiectasia Intervention Study." This exciting project represents a collaborative effort between many researchers and is the direct result of a brainstorming session at one of the A-T Children's Project's small scientific workshops.

The mice will be bred and housed at Cornell under the supervision of Dr. Beal's experienced staff. Carrolee Barlow, MD, PhD, at the Salk Institute for Biological Studies, provided the breeder mice and will perform the immunohistology for heme oxygenase in half of the brain from each animal. Phyllis Dennery, MD, at Stanford University School of Medicine, will assay heme oxygenase in the other half of the brain. L. Jackson Roberts II at Vanderbilt University School of Medicine, will perform F2-isoprostane assays on thymus and testes. Susan Doctrow, Eukarion's vice president of research, has agreed to supply EUK-134 at no cost for the project.

These compounds will be considered for clinical trials in A-T patients if a quantitative therapeutic effect is shown in the A-T mice.

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Multi-Year Committment to Shiloh's Lab in Israel

The A-T Children's Project has committed to fund the laboratory of Yossi Shiloh, PhD at Tel Aviv University in Israel for his grant proposal entitled, "Understanding ATM Functions by Dissection of ATM-Containing Protein Complexes." Here, Dr. Shiloh describes his laboratory's efforts.

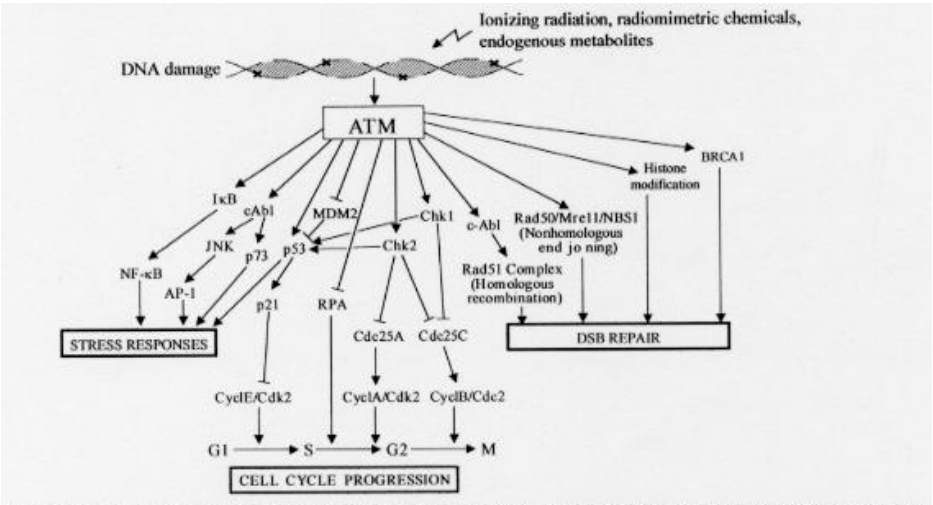
Since its establishment, our laboratory has been dedicated to understanding the biological basis of A-T. Several years ago we used the positional cloning approach to identify and clone the gene responsible for A-T, which we designated *ATM*. We then set out to investigate the functions of its protein product, the ATM protein.

ATM indeed turned out to be a master controller of many signaling pathways, by virtue of its catalytic activity and numerous interactions. Work in our and other laboratories has established ATM to be a large protein kinase that is present primarily in the nucleus but also in the cytoplasm and is involved in several high molecular weight protein complexes. While some of its substrates and interactors have been identified, it is clear that the majority remain to be elucidated. Some of ATM's targets and interactors may be tissue-specific, while others may be specific to particular physiological situations (e.g., following genotoxic stress). Their identification is central to understanding ATM's numerous roles in different tissues.

We have developed a large-scale, high throughput strategy to identify these proteins, based on our findings that ATM is embedded in protein complexes ranging in size from 500-2000 kDa. While some members of the complexes may convey signals to ATM, others may be its downstream targets. Our approach consists of the isolation of ATM-containing complexes by biochemical fractionation, and identification of individual proteins in the complexes by mass spectrometry. Initial analysis of complexes obtained from cultured cells resulted in the identification of 15 proteins, many of them known to be involved in a variety of physiological processes which can be tied to stress responses, and some that are completely novel.

Specific Aims

1. To delineate the functional relationships between ATM and selected members of the protein complexes identified in our lab to date.
2. To apply the strategy we developed, with some modifications, to the identification of additional members of ATM-containing complexes in cultured cell lines.
3. To dissect ATM-containing complexes in neuronal cell lines and tissues, and delineate the functional relationships between their members and ATM.



The Molecular Neurobiology of ATM
The Inn at Rancho Santa Fe, California

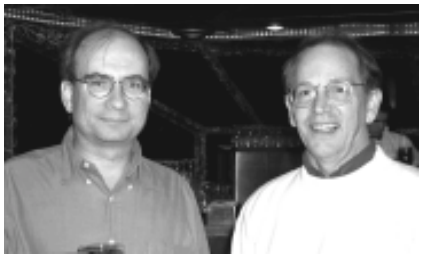
September 11 - 13, 2000


Galit Rotman


Ari Barzilai


Suming Wang


Ken-Ichi Yamamoto and Jun Qin


Robert Norgren with Don Wolf

Overview of A-T and Planned Clinical Center Activities
- Howard Lederman, MD, PhD
- Thomas Crawford, MD
- Allen Mandir, MD

New Insights on the Neuro-pathology of A-T
- Sara Becker-Catania, PhD
- Howard Mount, PhD
- Peter McKinnon, PhD

ATM Protein and Complexes
- Martin Lavin, PhD
- Ken-ichi Yamamoto, MD
- Christopher Bakkenist, PhD
- Robert Abraham, PhD
- Jun Qin, PhD
- Steven Harris, PhD

Electrophysiological Studies
- Peter Reinhart, PhD

Neural Autoantibody Levels in A-T Patients
- Robert Darnell, MD, PhD

Oxidative Stress and A-T
- Carrolee Barlow, MD, PhD
- Ari Barzilai, PhD
- Phyllis Dennery, MD
- Rodney Levine, MD, PhD

Animal Models
- Anthony Wynshaw-Boris, MD, PhD
- Robert Norgren, PhD
- Don Wolf, PhD
- Galit Rotman, PhD
- Steven Stice, PhD

Gene Transfer
- Xandra Breakefield, PhD
- Suming Wang, MD, PhD

Stem Cells
- Fred “Rusty” Gage, PhD
- Vaclav Ourednik, PhD
- Jitka Ourednik, PhD

Stem Cells
- John W. McDonald, MD, PhD

Review of Reagents and Experiments Needed


Phyllis Dennery


Peter McKinnon


Tom Crawford, Howard Lederman and Allen Mandir


Christopher Bakkenist


John McDonald


Dick Gatti


Martin Lavin and Xandra Breakefield

Margus Appointed to NIH Advisory Council

U.S. Secretary of Health and Human Services, Donna Shalala, recently announced the appointment of Brad Margus to serve a four year term on the National Advisory Neurological Disorders and Stroke Council (NANDS), the major advisory panel of the National Institute of Neurological Disorders and Stroke (NINDS). Margus, who is also the president and a co-founder of the A-T Children's Project, has two sons with A-T. The NANDS Council meets three times a year to review applications from scientists seeking financial support for biomedical research and research training on disorders of the brain and nervous system. Members also advise the Institute on research program planning and priorities. Composed of physicians, scientists, and representatives of the public, the Council oversees the distribution of over $1 billion annually from the NIH budget for research programs.

Research Grants Recently Funded By The A-T Children's Project

NEW! Neurologic Pathophysiology of Ataxia-Telangiectasia
A-T Clinical Center, Johns Hopkins Hospital

NEW! Development of DNA Diagnostic Test for the Ataxia-Telangiectasia Gene
A-T Clinical Center, Johns Hopkins Hospital

ATR-Activating Therapy for Ataxia-Telangiectasia
Robert Abraham, PhD - Duke University Medical Center

Molecular Mechanisms of Cerebellar Degeneration in A-T
Ari Barzilai, PhD - Tel Aviv University

NEW! Mouse Ataxia-Telangiectasia Intervention Study
M. Flint Beal, MD - Cornell University

Experimental Gene Therapy for A-T Using HSV Amplicon Vectors
Xandra O. Breakefield, PhD - Massachusetts General Hospital

Neural Autoantibodies in the Sera of A-T Patients
Robert Darnell, MD, PhD - Rockefeller University

Ocular Manifestations of A-T, A Prospective Study
Arman Farr, MD - The Wilmer Ophthalmological Institute

DNA Damage Signaling in ATM-/- Neurons
Herbert Geller, PhD - Robert Wood Johnson Medical School

Development of Improved Protective Strategies Against Free Radical Damage in A-T
Michael Greene, PhD - University of Brighton

Regulation of the Aspergillus DNA Damage Response by Suppressors of ATM Kinase Mutations
Steven Harris, PhD - University of Connecticut

Biochemical Analysis of the A-T Gene Product ATM and its Relative ATR
Stephen Jackson, PhD - Cambridge University

Role of the Extranuclear ATM Protein in Neuronal Function
Martin Lavin, PhD - Queensland Institute of Medical Research

A-T: Activation of Cytoprotective Signaling Pathways
David Lawrence, PhD - Albert Einstein College of Medicine

Molecular Basis of Pleiotropic Phenotypes of A-T
Jun Qin, PhD - Baylor College of Medicine

Defects in Cerebellar Purkinje Cell Properties May Underlie Ataxias in A-T Peter Reinhart, PhD - Duke University

Brain Pathology in ATM-Deficient Mouse: Correlating Structure and Functions
Menahem Segal, PhD - Weizmann Institute

Identification of ATM-Associated Pathways Using Gene Expression Profiles
Yossi Shiloh, PhD - Tel Aviv University

Neural Stem Cell Transplantation in Animal Models of A-T
Evan Snyder, MD, PhD - Harvard Medical School

NEW! Production of ATM Gene-Targeted Pigs and/or Cattle by Nuclear Transfer From Cultured Fibroblast Cells
Steven Stice, PhD - University of Georgia

Gene Therapy for A-T by a Novel Herpes Amplicon Vector
Suming Wang, MD, PhD - Central Iowa Health Systems

A Primate Model for Ataxia-Telangiectasia
Don P. Wolf, PhD - Oregon Health Sciences University

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