A-T CHILDREN'S PROJECT℠ UPDATE

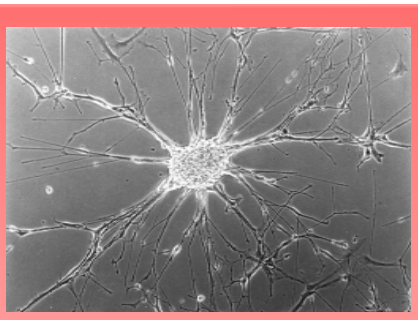
For Families, Friends and Supporters

SEPTEMBER 1999

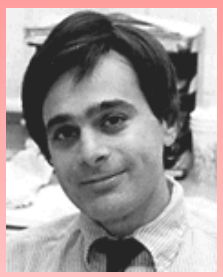
Can Brains Of A-T Children Be Re-Seeded With Stem Cells?

The A-T Children's Project has awarded a research grant to two teams of scientists associated with Harvard Medical School to try inserting recently isolated neural stem cells into the brains of A-T mice and into monkeys that have the same brain cells dying that children with A-T have. The new project is led by Evan Snyder, MD, PhD, a neurobiologist and pediatrician at Children's Hospital in Boston. Snyder's laboratory will be collaborating with the team of Richard Sidman, MD, a researcher at the New England Primate Center. Snyder is well known as a pioneer in the relatively new field of neurotransplantation of neural progenitor and stem cells, while Sidman is a highly respected neuroscientist who has made many discoveries in his career, particularly with genetically mutant mice that have neurological problems.

Last November, several groups of scientists announced that they had found a way to grow human embryonic stem cells in a lab dish. Stem cells are cells that have not yet turned into a specific tissue type and therefore have the potential to develop into any cell type in the body. While researchers have known about these cells for some time, no one had been able to grow them successfully in the laboratory. Now, by growing them in culture, scientists will have a constant source of these stem cells for research. Specializing in how brains develop and repair, Snyder succeeded in growing human neural stem cells that had the potential to become any kind of brain cell. His success has generated tremendous excitement among scientists eager to treat strokes, spinal cord injury and many neurological diseases, but as a pediatrician, Snyder is particularly interested in applying his work toward childhood disorders such as A-T.



Neural Stem Cell



Evan Snyder, MD, PhD

Richard L. Sidman, MD

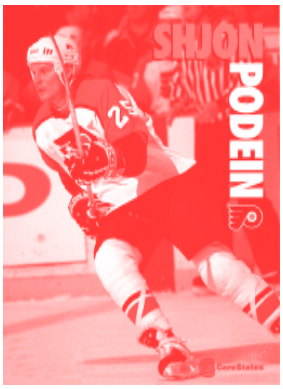
Snyder and Sidman, who have collaborated on a number of projects over the past six years, hope that they will first be able to use their stem cells to reseed the damaged brains of animal models of A-T and then eventually to replace brain cells of children with the disease. They envision being able to sprout healthy brain cells to replace the ones that are dying in A-T patients. Although this appealing therapeutic outcome may well be accomplished without having a complete understanding of why the original brain cells die, their studies may have the added advantage of yielding insights into the pathophysiology underlying the neurological defects in A-T, particularly in view of the somewhat surprising fact that the A-T knockout mice have such relatively

Continued on Page 2

PRO HOCKEY STAR HOSTS GOLF TOURNAMENT

Shjon Podein, who plays left wing for the Colorado Avalanche professional hockey team, reached out to help A-T children for the second consecutive year by hosting a celebrity golf tournament and auction on June 28 in Rochester, Minnesota.

The event was organized by the Board of Directors of the Shjon Podein Children's Foundation, an organization Podein established in 1997 to help children. Numerous volunteers helped to make the event a reality, and over 250 golfers played in the tournament which was held at the prestigious Rochester Golf and Country Club. Some of the 47 celebrities participating in the tournament included: John LeClair of the Philadelphia Fliers, Joel Otto formerly of the NHL Fliers and Mark Parrish of the Florida Panthers. Nikki Richmond, mother of nine-year-old Taylor who has A-T, spoke to the participants during the evening banquet. The A-T Children's Project is extremely grateful to Shjon Podein and his dedicated team of organizers for their commitment to helping us. A-T



Shjon Podein

continued from page 1

minimal neurological manifestations.

Already, Snyder's laboratory has discovered some intriguing characteristics about the stem cells. When inserted into the brains of animals with various types of brain injury, the cells seem to have an affinity for the

Rhesus Monkeys

damaged areas and a tendency to migrate to those areas. Then, once the stem cells have migrated to the places in the brain where they are most needed, they integrate into surrounding tissue and mature into the type of tissue that is appropriate for the particular area of the brain. While it is still unclear how well the new cells form connections with existing cells and actually function, in one type of diseased mouse that has tremors, treatment with Snyder's stem cells has alleviated the symptoms remarkably.

Nevertheless, the field of stem cell research is still very new, and much needs to be learned. For example, Snyder has realized that stem cells rely on external cues from the surrounding environment of the brain to trigger their development into specific cell types, but which of the multitude of potential cues is most critical remains an area of active investigation. And researchers concentrating on A-T have not yet determined whether the neurological problem caused by the genetic defect occurs only inside each cell or also affects the environmental cues. Snyder and Sidman have had experience in using neural stem cells in other mutants to answer precisely this type of question while at the same time replacing abnormal or missing nerve cells, including the cerebellum. The A-T Children's Project hopes that with this new grant, Snyder and Sidman may be able to answer some of these questions. AT

Board of Directors Adds Three New Members

The A-T Children's Project has added the following three members to its Board of Directors:

Carlos Rodriguez of Miami, Florida, is a long time supporter of the A-T Children's Project. Rodriguez is President of Vincam Human Resources, a large co-employment company that has just been acquired by the nation's largest human resource and payroll processing company, ADP. Rodriguez holds a Bachelors of Arts degree from Harvard College and an MBA from Harvard Business School.

Carlos Rodriguez

Amy Madison

John Feeley

Amy Madison of San Antonio, Texas, has three children with A-T. Madison has represented A-T Children's Project as a successful grant writer and public speaker. She and her husband, David, have organized several fund raising events in Florida, Texas and Oklahoma. Madison holds a bachelor's degree of Journalism/Public Relations from Phillips University and a master's degree in Mass Communication/Public Relations from Oklahoma University.

John Feeley of Scotch Plains, New Jersey, has repeatedly reached out to help A-T families even though his own seven-year-old son (third of four children), William, has a different, equally serious disease known as an undiagnosed Leukodystrophy. Feeley maintains two very separate careers, practicing law in North New Jersey and also serving as a captain in the City of Orange, NJ fire department. Feeley obtained his Juris Doctor degree from Seaton Hall University School of Law. AT

Jarrett Margus, who has A-T, meets President Clinton in the Oval Office at the White House

SALK INSTITUTE RESEARCHER AND COLLEAGUES FIND THAT PURKINJE CELLS OF A-T MICE ARE TARGETED BY OXIDATIVE STRESS

Carrolee Barlow, MD, PhD, a researcher supported by the A-T Children's Project at the Salk Institute in La Jolla, California, has been collaborating with colleagues at other institutions to use A-T knockout mice to determine if the organs affected in A-T are targets of oxidative stress. Using various tests, the group of scientists looked at tissues from the brain, thymus, testes, serum and liver. In cerebellar Purkinje cells — cells known to die in A-T patients — they found a massive overproduction of hemeoxygenas1, an enzyme induced by oxidative stress.

Carrolee Barlow, MD, PhD

The collaborating laboratories also tested for nitrotyrosines and isoprostanes. They found a significant elevation of nitrotyrosines in the brain. Looking for isoprostanes, they found a mild but not statistically significant elevation. These results seem to point to increased oxidative stress playing a major role in A-T. AT

Grant Awarded to U.K. Lab to Develop Ways to Protect Brains of A-T Patients From Free Radicals

Loss of neurons in the brain, particularly Purkinje and granule cells, is a critical mechanism in the progressive cerebellar ataxia of A-T. Reactive oxygen and nitrogen species are thought to be involved directly or indirectly in this process. Salen / transition metal complexes are catalytic antioxidant molecules that protect against these reactive species and that can be taken up by human cells.

With a grant from the A-T Children's Project, the laboratory of Michael Green, PhD at the University of Brighton in England will design a series of novel compounds, varying the ligand structure and the transition metal to produce molecules which will discriminate between superoxide dismutase-like and peroxidase-like activities or that will be effective against a wider range of reactive species. Green is Professor of Cellular Mutagenesis in the School of Pharmacy and Biomolecular Sciences.


Michael Green, PhD

Once the novel compounds have been designed, the research team will assess their ability to protect human cells, initially human fibroblasts, against reactive oxygen and nitrogen species *in vitro*, using the highly sensitive Comet assay to measure DNA damage and protection. Promising molecules will then undergo a more extensive series of tests, to characterize the scope of the protective activity, and at the same time modeling and structural studies to identify critical motifs. Green's group will measure the protection offered by these molecules in survival assays with normal and A-T primary human fibroblasts, and with apoptosis assays in transformed cells. They will then determine whether candidate molecules are effective against reactive oxygen and nitrogen species in a novel *in vitro* human neuronal culture system which will allow them to measure DNA damage and protection in human cerebellar material, in stem cells and in differentiated neurons. Similar experiments will be performed on cerebellar material from neonatal Atm knockout mice.

Green's research plan explores a class of catalytic antioxidants that are known to be effective. When such molecules are taken up by cells at risk, they offer a type of protection against cell killing which is over and above that provided by standard antioxidant supplements. Because this project coordinates the hypothesis-led synthesis of novel compounds with modeling and crystallography studies and with analyses of the specificity of biological activity, Green's group should be able to determine whether it is supplementation of dismutase or of peroxidase activity that is critical for protection and to identify novel patterns of protective activity. The structural studies may help to identify natural dietary components with similar activities, so that it would be possible to translate findings into therapy quickly.

An even more significant advance will be the combining of the Comet procedure with *in vitro* human and ATM neuronal cultures to provide an assay system that is directly relevant to neuroprotection. With this grant, Green expects his lab's work to give insights into the roles of specific damaging molecules and the processes leading to neuronal cell death, which may in turn suggest additional strategies for prevention of damage.

Fast Growth Forces the A-TCP to Relocate

In just two years, the A-T Children's Project has again outgrown its office space. With increased fundraising efforts, family support, generation of awareness, and research coordination, we were running out of space!

Please make a note of our new address and new phone numbers:

668 South Military Trail
Deerfield Beach, Florida 33442
New Phone: (954) 481-6611
New Fax: (954) 725-1153
Toll Free: 800-5-HELP-A-T

A-TCP Participates in Supermarket Chain's Community Partners Program

If you shop at Albertson's supermarkets, be sure to give us a call to request the A-T Children's Project's Albertson's Community Partners card. The card is printed with *A-T Children's Project* and an unique UPC number.

Every time you shop at Albertson's, A-TCP earns quarterly contributions. All you have to do is remind your cashier to scan the card anytime during your order. The A-TCP will benefit from your grocery shopping dollars and it won't cost you anything. Please make sure to check with your relatives, neighbors and co-workers to see if they shop at Albertson's, our Community Partner, and we will send you additional cards to pass on to them. For more information call 1-800-5-HELP-A-T.

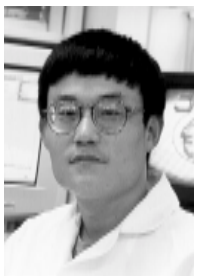
CFC Now Provides Way Federal Employees Can Support A-TCP

The Combined Federal Campaign (CFC) is the annual fund-raising drive conducted by Federal employees in their workplace each fall between Labor Day and Thanksgiving. At the start of the six week campaign, all Federal employees receive a directory and a pledge card to designate the amount they want automatically deducted from their paychecks, to contribute to the charity of their choice.

The A-T Children's Project will be listed as Ataxia-telangiectasia Children's Project with a four-digit code under the section titled: **Health and Medical Research Charities of America**. All Federal employees and military personnel wanting to make a donation to the A-TCP through a CFC pledge for payroll deduction will be able to do so by entering on their pledge cards the four digit code listed for the ATCP in the directory.

Grant Awarded to Study Protein Complexes in Which ATM Exists

Jun Qin, PhD, is an Assistant Professor in the Department of Biochemistry and Department of Cell Biology at the Baylor College of Medicine in Houston, Texas. Qin is eager to understand the molecular basis of the pleiotropic phenotypes of A-T. While scientists have demonstrated that the ATM protein exists constitutively in a protein complex of > 2 Mda, it still isn't clear whether this represents a single or multiple complexes of this size. Now, with a research grant from the A-T Children's Project, Qin's lab will seek to purify and identify (sequence and clone) constituents of the complex or complexes. His research team will use antibody-affinity chromatography together with new mass spectrometry techniques that offer unprecedented sensitivity and speed to purify and identify the protein components of the ATM complexes from cells and mouse brains.



Jun Qin, PhD

Qin hypothesizes that the pleiotropic phenotypes of A-T reflect the multiple functions of the ATM protein. Because ATM and its related kinases in yeast control so many functions, he anticipates that ATM will be integrated into a number of sensory pathways capable of detecting different types of stress such as DNA damage, replication interference, oxidative stress and possibly changes that occur specifically in neurons. These different signaling events may allow ATM to distribute information to different effector molecules. In order to unravel these complicated signaling events, it is necessary to know what proteins are contacting ATM in the tissues where it is functioning. Scientists have learned that most cell types use ATM for DNA damage responses. Therefore, Qin's group will purify ATM from Hela cells to understand this part of its function. ATM also has an important function in the brain, in particular in Purkinje cells. Because there is no Purkinje cell line model, Qin's team intends to purify ATM and its associated proteins from brain extracts.

The Scientific Advisory Board of the A-T Children's Project unanimously recommended funding this work because the biochemical purification and definition of ATM protein complexes should represent a major breakthrough in the elucidation of ATM functions. Qin's group has previously purified several large complexes and discovered many associated proteins including the human PCAF complex and the BRCA1 complex. Based on his extensive experience, Quin believes that the analysis of ATM complexes will provide more clues and targets for the investigation of ATM function. Because this planned work seeks to identify ATM asociated proteins in a much broader sense than previously attempted and is not limited by the current knowledge of ATM, the A-T Children's Project believes it may very well open new avenues in ATM research. AT

Grant Awarded to Study Activation of Cytoprotective Signaling Pathways

A-T cells are defective in their response to an oxidative challenge and, even in the absence of an external challenge, display behavior consistent with severe oxidative stress. The laboratory of Professor David S. Lawrence at the Albert Einstein College of Medicine in New York has identified a reactive oxygen intermediate (ROI)-defense mechanism that is not properly activated in A-T cells in response to oxidative stress.

David S. Lawrence, PhD

They have also shown that this defense mechanism can be switched on in A- T cells via a nonoxidative means. Dr. Lawrence's ultimate objective is to identify effective pharmacological protocols that enable A-T cells to recognize and respond to oxidative stress and damage.

With a grant from the A-T Children's Project, Dr. Lawrence aims to identify drugs and/or conditions that stimulate the up-regulation of specific stress response proteins and DNA damage-activated biochemical pathways, characterize the differences between A-T and normal cells in their response to oxidative stress using gene chip microarrays, and assess the cytoprotective effects of these drugs· AT

Grant Funding to Gene Therapy Institute Doubled

Last year, the A-T Children's Project awarded a research grant to Suming Wang, PhD at the Gene Therapy Institute of the University of Iowa School of Medicine.

Suming Wang, PhD

The goal of the funded research project was to use a viral vector (pTO-ATM) that would stably transduce the entire ATM gene into cells of A-T patients grown in a laboratory dish. Wang has succeeded at this first step. Now, with a 100 percent increase in funding from the A-T Children's Project, Wang's lab will begin work on the next steps:

- Improving the titers of HSV-1 helper free packaging. When the lab team has a large quantity of helper virus free ATM vector, they will be able to do many functional analyses.
- Injecting the pTO-ATM viral vector into rat brains.
- Transduction and expression of ATM in lymphocytes.
- Constructing a new amplicon vector that carries ATM and GFP or a Zeo gene so that they can either use a cell sorter to select ATM transduced cells or drug selection to obtain a 100 percent population of ATM expressed cells for functional analysis.
- Generating a mouse ATM cDNA clone to see if the ATM gene will work on the Atm knockout mouse model.
- Transducing the gene in the fetal liver of Atm knockout mice to determine if any of the immune system problems are corrected.

With the increased funding level from the A-T Children's Project, Wang will hire two additional scientists in his lab to accelerate this work. AT

"Help Create A Miracle" Grants Wishes to the A-T Clinical Center

The 1999 "Help Create A Miracle" fundraiser in Greenwich Connecticut made wishes come true for the A-T Clinical Center at Johns Hopkins Hospital and the Children's House in Baltimore, Maryland.

Members of the Organizing Committee, from left:
Anne and Michael Castine and Cece and Michael Donoghue

Before the event, organizers requested a wish list from the clinic's director, Dr. Howard Lederman and then appealed to their guests to make these wishes come true. Wishes included a $3,000 Panasonic Super VHS video recorder, disposable cameras, a computer, a filing cabinet, a TV-VCR, a fax machine, towels and washcloth sets, a toddler car seat and a stroller. Chairpersons for this wonderful event which raised over $203,000 included Anne and Michael Castine, Lisa and Chris Perrella, Cece and Michael Donoghue and Madeleine and Kevin Treesh. AT

Senate Appropriations Committee Hears About A-T

On May 6, 1999 Brad Margus, Co-founder and President of the A-T Children's Project, testified before the Senate Appropriations Sub-Committee on Labor, Health and Human Service and Education. In his testimony to the Senators, Brad described the status of A-T research, ways to improve NIH, the need to save clinical research centers at academic hospitals and the importance of showing the public why we need to increase the NIH budget. The full text has now been posted by the Senate at the following web site:

http://www.senate.gov/~appropriations/labor/mrgs5_6.htm

Grant Awarded to Consider ATR-Activating Therapies

The pathologic symptoms displayed by A-T patients are largely attributable to mutations in *ATM*, which encodes a member of the phosphoinositide 3-kinase (PI3K) related kinase (PIKK) superfamily of signaling proteins. The cell-cycle checkpoint and stress-protective functions of ATM are dependent on the carboxyl-terminal kinase domain. Recent studies have shown that ATM is a DNA damage-activated protein kinase that phosphorylates p53 at a critical serine residue (Ser^{15}). These results support a model which posits that ATM translates signals initiated by genotoxic stress into protein phosphorylation events that, in turn, trigger cell-cycle checkpoints and cytoprotective responses.

Robert T. Abraham, PhD

Mammalian cells express a second PIKK family member that participates in cellular responses to genotoxic stress. Biochemical and genetic evidence indicates that this *AT/Rad3* Related (ATR) kinase exhibits considerable functional overlap with ATM. Although ATR shares with ATM the ability to phosphorylate p53 at Ser^{15}, the *in vitro* kinase activity of ATR is significantly lower than that of ATM.

The A-T Children's Project has awarded a grant to Professor Robert T. Abraham, Ph.D. at the department of Pharmacology and Cancer Biology of Duke University Medical Center in Durham, North Carolina to test the hypothesis that strategies designed to activate the ATR catalytic domain will enable this protein kinase to more effectively compensate for the loss of ATM in A-T cells.

The specific aims of Dr. Abraham's proposal are: (1) to generate a panel of rationally designed ATR mutants, and to screen for mutants bearing elevated levels of protein kinase activity toward p53, and (2) to determine whether expression of activated versions of ATR will complement the cell-cycle check-point defects displayed by AT cells. If successful, these studies will provide a foundation for the development of ATR-activating therapies that may alleviate the cell-cycle checkpoint and stress-response defects displayed by A-T cells. AT

Grant Awarded to Study the Aspergillus DNA Damage Response by Suppressors of ATM Kinase Mutations

The uvsB gene in *Aspergillus nidulans*, a fungus, encodes a homologue of the ATM (Ataxia Telangiectasia Mutated) kinase that is required for multiple facets of the DNA damage response. Notably, uvsB mutants display several phenotypes in comon with A-T cells, including; 1) abrogation of cell cycle checkpoints, 2) failure to induce transcription of DNA damage-inducible genes, and 3) loss of damage-induced mutagenesis. Genetic analyses have revealed that mutations in the musN and musP genes enhance the viability and DNA damage resistance of uvsB mutants.

Steven D. Harris, PhD

Dr. Stephen D. Harris of the Department of Microbiology at the University of Connecticut Health Center proposed that MUSN and MUSP may represent attractive therapeutic targets for reducing the DNA damage susceptibility of A-T cells. With funding from the A-T Children's Project, Dr. Harris will test this notion by using a molecular genetic approach to; 1)characterize the function of MUSN and MUSP, and 2) determine how mutations in the musN and musP genes compensate for loss of UVSB function. AT

Grant for "Seed" Funding Enables Lab to Obtain Over $1 Million in Support From Other Sources

The A-T Children's Project's support of research done by Dr. Yang Xu contributed to preliminary data which recently earned the lab four grants totalling more than $1 million in direct cost for the next three years. Xu's lab is in the department of biology at the University of California, San Diego.

So there isn't an A-T Walk in your neck of the woods?

A-T Walk for a Cure T-shirts

Adult Sizes: S, M, L, XL, XXL,

Youth Sizes: S, M

$15.00 for each t-shirt (Shipping and handling included)

To order, send a check or money order payable to:

A-T Children's Project
668 S. Military Trail
Deerfield Beach, FL 33442

Please include your address and phone number.

For Visa or MasterCard orders call 1-800-543-5728 or send an e-mail to Aletia@atcp.org.

Thank You!

Our 1999 fundraisers have made funding of specific research a reality with these incredibly successful events:

1999 Events

January Charity Horse Show and Cruise - sponsored by Littlewood Farms - *Boca Raton, Florida*
January Dairy World Dinner - *Fort Macleod, Alberta, Canada*
February A Gift From the Heart - dinner dance and silent auction - *Cambridge, Massachusetts*
February Men's Night at St. Catherine's Church - dinner auction - *Cedar Grove, New Jersey*
April Help Create A Miracle - dinner dance - *Greenwich, Connecticut*.
May Softball Tournament - *Everett, Massachusetts*
May Hop-a-thon - K-4 hopping for a cure! *Carrolltown, Pennsylvania*
May American Society of Microbiology 5K Fun Run - *Chicago, Illinois*
June Barn Dinner Theatre Presents - A Tribute to Musical Legends - *Greensboro, North Carolina*
June Celebrity Golf Tournament - *Rochester, Minnesota*
August Midsummer Meltdown - Dinner dance and silent auction - *Newport, Rhode Island*

1999 Walks and Hosts

April
Seagoville, Texas - Pam Digby
May
New Braunfels, Texas - Amy Madison
Port Richey, Florida - Adrienne Zampella
Winona, Minnesota - St. Mary's University Athletic Dept. - Nikki Richmond
Carleton, Michigan - Peggy Kemeny
Romulus, Michigan - Denise Bills
Wayland, Massachusets - Cynthia Wiesniewski and Michael Sakowich
June
Buffalo City, Wisconsin - Nikki Richmond
Troy Michigan - Suzi Powell
Rensselaer, New York - Mary Broderick and Mary Cramer
St. Benedict, Pennsylvania - Melanie Mertens
Annandale, Virginia - Suzi Kindregan and Carol Lewin
July
Fort Macleod, Alberta, Canada - Conrad VanHierden
August
Chicago, Illinois - Lisa Loberg
Ozark, Missouri - Joyce Bostic and Alicia Hagen
Denver Colorado - Dennis Clark
Waterford Michigan - Mary Odle and Randy Fern
Buffalo New York - Jennifer Lane

Upcoming

Events

SEPTEMBER 12, 1999
Spaghetti Dinner to benefit ATCP - Flat Rock, Michigan. For more information please contact Peggy Kemeny 734-654-9416 or email carla@webbernet.net

NOVEMBER 4, 1999
Wine Tasting / Gourmet Extravaganza - Summit, New Jersey - A wine tasting gourmet extravaganza with live and silent auctions at the Grand Summit Hotel, sponsored by the Junior Summit Fortnightly Club. To purchase tickets, donate silent auction items, volunteer or for more information, please call Andrea Testa at 908-277-0417.

Walks and Hosts

SEPTEMBER 1999
Sat. 11 - *Atlanta, Georgia* - Heath Hamrick and Clarence and Carla Glymph
Sat. 11 - *Seattle, Washington* - Jon Jones
Sun. 12 - *Flat Rock, Michigan* - Peggy Kemeny
Sat. 18 - *Stratford, Connecticut* - Lori Smarz and Dee Jalbert
Sat. 18 - *Freedom, Wisconsin* - Mike and Sheila Smith
Sat. 18 - *Niagara, Wisconsin* - Charles and Sheila Henrichs
Sun. 19 *Hamilton, Ohio* - Prudy Kyle
Sat. 25 - *Fulton, New York* - Lisa Mahar

OCTOBER 1999
Sat. 2 *Dartmouth, Nova Scotia, Canada* - Eileen and Jerry Drohan
Sat. 9 *Scranton, Pennsylvania* - Robin Ribaudo
Sat. 2 *Los Angeles, California* - Jennifer Klein
Sat. 23 *Rochester, New York* - Lynn Bement
Sat. 16 *Burnsville, Minnesota* - Sandy Grebe
Sun. 17 *Highland, New York* - Deidre Karn and Peter and Lisa Cerniglia
Sun. 24 *Newport, Rhode Island* - Bob and Barbara Hiebner

NOVEMBER 1999
Nov 6 *Cypress, Texas* - Beth Hughes
Nov 6 *Phoenix, Arizona* - Sandy Estrella
Nov 13 *Jacksonville FL* - Jennifer Pollard and Anette Ferrell

For information to volunteer or participate in upcoming events and walks, please contact the A-T Children's Project at 1-800-5-HELP-A-T.

WANTED:
NEW WALKATHON HOSTS

As our research advances into the realms of stem cells, gene therapy, and A-T monkeys, the costs of funding these promising new explorations are rapidly increasing. To maintain and accelerate our progress, we need more volunteers to host new walks.

The A-TCP will be hosting its second annual walkathon training seminar in Fort Lauderdale, Florida the weekend of January 21-23, 2000. Contact the A-TCP if you are interested in hosting a walk and inviting your friends, neighbors, relatives and co-workers. No experience necessary!

For information contact *Aletia Patterson* at aletia@atcp.org or call 1-800-543-5728.

The A-TCP Staff Salutes our 1999 Walkathon Hosts!

1999 Walkathon Kickoff Fort Lauderdale, Florida

Walkathon hosts gathered at the 1999 Kickoff in Fort Lauderdale, Florida

The outstanding success of our 1997 and 1998 walkathon campaigns prompted our first annual walkathon training seminar in February 1999 in Fort Lauderdale, Florida for all potential walkathon hosts. All of our fundraising activities are the result of grassroots efforts of A-T families, friends, and relatives who are spearheading the fight to find a cure for A-T.

Seventy volunteers accepted our invitation and arrived with their sleeves rolled up and ready to work. Every volunteer brought their individual determination, and as the weekend came to an end, team spirit fostered new ideas and enthusiasm.

The necessary tools and supplies available from A-TCP were on display, as were examples from past walkathons such as brochures, letters, and pictures. A-TCP staff explained the basics of hosting a walk, and the veteran hosts presented their invaluable tips and support. The group broke into smaller brainstorming teams and goal setting committees, and a total of 47 walks were scheduled from April to November 1999 with a goal of raising $700,000!

Volunteers went back home with individual goals, a team goal, and renewed enthusiasm. As a result, friends, relatives, coworkers, and other local A-T families have been asked to support their local walks. To date, this team effort has resulted in four international walkathon sponsors, dozens of local tee-shirt sponsors, hundreds of corporate sponsors, thousands of individual walkers, and individual walkathon totals ranging from $1,800 to $100,000. The veteran walk hosts have significantly increased their prior income, some doubling last year's profit, and one new walk has tripled their own goal. The success of the walks is also bringing increased awareness and publicity about the A-T fight for a cure to the communities in the United States and Canada.

This small, powerful group of volunteers is achieving incredible results. Funding for specific A-T research would not be possible without the efforts from the hosts and support from the thousands of individuals who participated.

Thank You!

Sponsors Needed For A-T Walk 2000

We need international and national corporate sponsors for the 2000 "A-T Walk for a Cure" fundraiser.

Join our international campaign for the year 2000 and help us fund research.

As a sponsor you will receive recognition with your logo on the back of 20,000 "A-T Walk for a Cure" t-shirts and on 200,000 walkathon brochures.

To become a sponsor contact Aletia at 1-800-5-HELP-A-T or by e-mail at aletia@atcp.org

Thank You to Our 1999 International Corporate Walk Sponsors

AMGEN

HERBALIFE

WAL★MART

RADISSON SEVEN SEAS CRUISES

Psychological Evaluations an Important Part of A-T Clinical Center

A comprehensive visit to the Johns Hopkins Ataxia Telangiectasia (A-T) Clinical Center, funded by the A-T Children's Project, includes sessions with a rehabilitation team at the Kennedy Krieger Institute. This team includes specialists in occupational therapy, physical therapy, speech pathology, physiatry, psychology, and assistive technology (computers). They provide an integrated multi-disciplinary approach to evaluation of A-T patients and recommendations for families, schools, and therapists.

The psychological evaluation consists of a parent interview, psychological testing of the A-T patient, and a feedback session. The main goal of this evaluation is to provide specific recommendations that will help A-T patients in school.

The parent interview is conducted in order to obtain additional detail regarding history and to determine the family's specific questions in reference to psychological issues. Efforts are made to tailor the patient testing to the specific concerns of the family and the child's teachers so that the most relevant data is obtained.

Some of the tests used are commonly known as intelligence tests. It is important to understand the types of information that such tests provide and do not provide, especially in children with known neurological disorders such as A-T. Although an IQ score can be obtained from an intelligence test, this number represents an "averaging" of a number of performances and thus often does not adequately reflect a child's individual profile of strengths and weaknesses. Therefore the A-T team administers supplemental tests to sample abilities that go beyond those found on the intelligence test. Efforts are made to assess a number of separate abilities and to look for patterns in different types of psychological functions and processes.

For an appointment at the A-T Clinical Center at Johns Hopkins Hospital call 1-800-610-5691

The areas applicable to a psychological assessment include cognition (problem-solving abilities in both the language and visual/perceptual domains), memory, executive functions (attention, planning, organization), academic skills, and social/emotional functioning. The patient is given a series of standardized tests which have been selected to target brain functioning implicated by A-T research and to minimize the impact of characteristics specific to A-T. For example, tests that require motor function and timed performances are avoided. Printed material is enlarged and presented in a manner tailored to the individual's needs. This testing often requires more time than other evaluations because of efforts to provide extended time allowances and to accommodate the patient's most comfortable rate of processing information. Questions are often repeated and prompts are given. As many accommodations as possible are made within the parameters set by the standardized guidelines. However, there are limits to the extent of prompts that can be used without changing the type of processing that underlies the task or altering the validity of the results. Of course, children are consistently praised and rewarded for their efforts and cooperation.

James R. Christensen, MD

Jane C. Kunze, PhD

As a group, patients with A-T have significant variability in skills. Profiles of individual children can be very different from each other, and profiles can show differences within each child's own pattern of strengths and weaknesses. Previous research reported by Elena Boder, MD suggested that these profiles usually change over time. Thus regular monitoring of a child's abilities is necessary to provide accurate information regarding strengths and weaknesses at each point in time. It is important to understand a child's levels of functioning in order for parents and teachers to make appropriate expectations and for therapists to be most effective. Of course, the ultimate benefit is to provide an environment that enhances the child's opportunity to experience success and to ensure optimal development and achievement.

An especially relevant area related to a child's psychological profile is academic achievement. Information derived from psychological testing has been linked repeatedly in the research literature to academic performance. Thus it is crucial to understand a child's cognitive profile in order to devise the most effective educational program for him or her. Children with A-T often have unique difficulties and require different teaching strategies and techniques to "work around" their areas of weakness. Findings from the psychological evaluation have been discussed with teachers and used to obtain appropriate special interventions within the school system. In the case of older patients, findings have been used to assist in decisions regarding further education and vocational placement.

The psychological evaluation concludes with a feedback session to convey findings and discuss recommendations. The findings also are shared with the multi-disciplinary team and integrated into an inclusive summary of recommendations for the family to take with them to be used by those working with the child on a daily basis· AT

LAB FINDS NEW EVIDENCE OF OXIDATIVE STRESS IN BRAINS OF A-T MICE

Laura Dugan, MD at Washington University in St. Louis has recently been looking for oxidative stress in Atm knock-out mice with financial support from the A-T Children's Project. Scientists in her lab injected 2.5 month old mice intraperitoneally with salicylate, and then allowed the mice to do their normal mouse activities for 16 hours. Next, Dugan's team perfused and sacrificed the animals, extracted salicyate and its oxidation products from brain regions, and analyzed them using a technique known as "HPLC." The amount of the oxidation product that they follow, 2,3-dihydroxybenzoic acid, was then normalized to the weight of the tissue samples that were extracted to give pmol of 2,3-dihydroxybenzoic acid/mg tissue. Dugan's lab found that basal ganglia and cerebellum in Atm knockout mice had significantly greater levels of 2,3-dihydroxybenzoic acid than normal mice, indicating increased oxidative stress in these regions even at baseline. Levels in the basal ganglia of the Atm knockout mice were 3.5-fold higher than normal, and levels in cerebellum were 7.5-fold greater.

Laura Dugan, MD

In addition, Dugan's team injected an oxidizable fluorescent dye (dihydroethidium) into the Atm knock-out mice, and allowed them to go about their activities for several hours. After sacrificing the mice and fixing their tissues, the scientists prepared brain slices, and visualized individual cells in the cerebellum using confocal microscopy. The Purkinje cell layer in the AT mice had numerous, highly fluorescent Purkinje cells, indicating free radical dependent oxidation of dihydroethidium, while it was almost impossible to see the Purkinje cells in the normal mice due to minimal dye oxidation. Additional studies are now planned.

Funding Now Available for Research on the

Therapeutic Potential of

Neural Stem Cells

for Ataxia-Telangiectasia

- Rapid, 30-day peer-reviewed decision process
- Early start date possible
- Application process not too burdensome

Grants are now available to support efforts aimed at determining the therapeutic potential of neural stem cells for the neurodegeneration seen in patients with ataxia-telangiectasia (A-T), as well as efforts focussed on developing other mammalian models of A-T in addition to ATM knockout mice that have been made.

Competitive awards will be given to researchers for one- and two-year projects. No administrative overhead or fixed costs are supported.

Scientific excellence, originality and direct relevance to A-T neurodegeneration are the paramount criteria in award decisions. There is no formal deadline date for the submission of proposals. Decisions will be made within 30 days after proposals are received.

For grant proposal guidelines, contact the A-T Children's Project.

AT CHILDREN'S PROJECT℠

668 South Military Trail
Deerfield Beach, FL 33442 U.S.A.
Web site: www.atcp.org

Phone: 954-481-6611
Fax: 954-725-1153
E-mail: rosa@atcp.org

Here is an example of the announcements we regularly place in major scientific research journals to encourage research on A-T. After discussing research strategies with the members of our Scientific Advisory Board, we use many tactics, including announcements like this one, to engage new investigators from fields where A-T research is needed.

Basic Facts About the A-T Gene

Except for our sperm or egg cells, each cell in our bodies contains two copies of every human gene. A-T occurs when both copies of one particular gene are misspelled. If you have only one copy of this gene misspelled, then you do not have the disease but you are a carrier. Scientists have named this gene "ATM."

Special types of machinery in our cells read and follow the genetic code of the ATM gene in order to assemble together the right combination of 3,056 amino acids to form a unique protein that plays a critically important role in our bodies. Therefore, if these instructions are misspelled in someone who has A-T, his or her cells are unable to assemble a correct, functioning protein. Without the protein doing its normal job, many different body systems in people with A-T are affected.

In most tissues of our bodies, this protein is found primarily in the nucleus of the cell. In cells that have stopped dividing, such as oocytes and brain cells, however, scientists have recently found this protein located outside of the cell nucleus, in the cytoplasm between the nucleus and the membrane that encloses the cell.

Today, tremendous effort is being expended by research laboratories around the world to identify other proteins that work with the A-T protein. This will indicate what exactly the A-T protein does in different tissues (especially in the brain), and will help us to identify therapeutic techniques and drugs that might help the bodies of people with A-T compensate for the missing A-T protein.

NIH Scientist Joins Advisory Board

Rodney L. Levine, MD, PhD, has joined the Scientific Advisory Board of the A-T Children's Project. Dr. Levine is chief of the section on Protein Function in Disease, Laboratory of Biochemistry at the National Heart, Lung and Blood Institute of the National Institutes of Health (NIH). Dr. Levine is a Board certified pediatrician and neonatologist with 28 years practice. His recent work focuses on oxidative modification of proteins. His expertise will be an invaluable asset to the A-TCP in evaluating future A-T research projects.

TIME LINE of Highlights

1993

March - Jarrett and Quinn Margus are diagnosed with A-T.

June - A-T Children's Project is established. David Cox, MD, PhD, Director of Genetics at Stanford Medical School, agrees to serve as director of a multidisciplinary, objective Scientific Advisory Board.

July - Letters sent to: 12,000 alumni from several universities.

August - First announcements placed in scientific journals, *Science* and *Nature,* advertising grants available for work on A-T.

September - First A-TCP letter writing campaign to foundations and trusts in Florida, California and New York.

October - Project obtains IRS 501(c)(3) Private Foundation status making donations tax deductible.

December - First research grant of $100,000 awarded to the laboratory of Dr. Yosef Shiloh at Tel Aviv University in Israel, followed by grants to five additional research labs.

1994

January - Letters sent to every U.S. Senator; first fundraiser held: Horse Show Benefit.

June - Brad Margus testifies before the U.S. House Sub-Committee on Health.

August - A-TCP sponsors Round-Table Scientific workshop in Boca Raton, Florida. Search for A-T gene is narrowed to an area on chromosome 11 consisting of 1 megabase of DNA, and researchers begin "trapping" and analyzing candidate genes.

September - A-TCP mails announcement of A-T Physician's Registry to 20,000 physicians throughout the U.S.

November - A-T patient Cell Bank established at Coriel Institute in Camden, New Jersey.

December - Brad Margus meets President Clinton and discusses A-T.

1995

January - Conference for physicians, families and caregivers on Clinical Management of A-T is held in Chicago, Illinois.

March - A-TCP announces the selection of Johns Hopkins Hospital in Baltimore, Maryland as the site of the new A-T Clinical Center.

June - A-T gene isolated by international team led by Dr. Yosef Shiloh's laboratory at Tel Aviv University in Israel, capturing front page headline of the *New York Times* and lead-story coverage on all major television networks.

July - "Next Steps" conference in Rhode Island brings together scientists from many new fields to plan action now that the gene had been isolated.

August - Fundraising letters, hand addressed by volunteers, are sent to over 40,000 individuals.

September - Brad Margus testifies before a hearing organized by the U.S. Senate Cancer Coalition. Language about A-T is inserted in U.S. Senate appropriations bill for the first time. First grants awarded to study the A-T gene in yeast and fruit flies.

1996

April - "Unraveling the A-T Defect" scientific workshop in Philadelphia, Pennsylvania.

June - Brad Margus and David Cox, MD, PhD participate in meeting with President Clinton at the White House on genetic discrimination.

July - Development of the first mouse model of A-T announced. The mice display most symptoms seen in children with A-T, including cancer.

October - Laboratory discovers that the ends of chromosomes, called telomeres, are shortened in the cells of A-T patients.

November - Nobel Laureate David Baltimore, PhD receives grant from A-TCP to characterize A-T knockout mice.

1997

January - Researchers are able to raise a variety of antibodies against the ATM protein, important tools needed to study protein activity.

February Researchers are able to shut down the production of the ATM protein in normal cells, thereby mimicking the A-T situation.

March - Workshop on the Neurodegeneration of A-T is held in Tarrytown, New York. The ATM protein is implicated in cellular defense mechanisms against oxidative stress.

April - A-T brain bank established at Brain & Tissue Bank for Developmental Disorders at the University of Maryland.

May - Scientists produce "recombinant" ATM protein made artificially in insect and mammalian cells and introduce the recombinant protein into cultured A-T cells, thereby correcting their defects. First national fundraiser for A-TCP: 1997 "A-T Walk for A Cure" raises $235,000 with 3,500 volunteers participating in 16 walkathons.

June - Swallowing studies led by a specialist become part of the visits to the A-T Clinical Center at Johns Hopkins Hospital. These studies ultimately reveal that swallowing difficulties may cause aspiration and poor lung hygiene, contributing significantly to the serious and often fatal lung problems faced by A-T patients.

July - Researchers announce that they have purified the ATM protein to homogeneity.

Our thank you to the many celebrities, including the following, who have helped this rare, orphan disease become more known:

Tony Bennett • Olympia Dukakis
Louis Zorich • Barbara Feldman
Barbara Walters • Cokie Roberts
RosieO'Donnell • Dan Jansen
Shjon Podein • John Walsh
Sandra Bullock • Ben Affleck

August - Conference held in Baltimore, Maryland entitled Ataxia-telangiectasia and ATM: Functional, Genetic and Clinical Ramifications. Researchers in Sweden and England find that ATM gene is mutated in majority of cases of T-cell prolymphocytic leukemia (T-PLL), a rare but aggressive type of leukemia.

September - Scientists find that the ATM protein interacts with a family of proteins called adaptins in the cytoplasm of brain cells.

October - Researchers discover that poly(ADP-ribose) polymerase (PARP) is elevated in skin cells of children with A-T, and that treatment with nicotinamide, an inhibitor of PARP brings those levels back to normal.

1998

January - Research group begins using microchip technology to look at the expression of 20,000 genes simultaneously in order to compare A-T cells with normal cells.

February - Researchers find a potassium ion channel defect in A-T cells.

March - Scientific Workshop to Elucidate the Neuropathology of Ataxia-telangiectasia held at the NIH campus in Bethesda, Maryland. Scientists find evidence that dopamine-producing cells are dying in brains of A-T knockout mice and that injections of L-Dopa seem to help the mice. Brad Margus and Mohammed Ali testify before the U.S. House of Representatives' Commerce Committee's Sub-committee on Health and the Environment. Reseachers generate data indicating that the ATM protein plays an important role during fetal development of the brain.

April - Research teams find that ATM is an enzyme that can add phosphate groups onto other proteins thereby affecting their activity; one of these "targets" is identified as the famous p53 protein involved in cancer.

May - Eye studies added to protocol at the A-T Clinical Center at Johns Hopkins Hospital. Physicians conducting the studies quickly discover that some children with A-T can be helped dramatically with eye surgery.

May - Second Annual "International A-T Walk for a Cure" raises $411,608 with 6,000 volunteers participating in 27 walkathons throughout September.

June - A-T Children's Project changes from a private to a public foundation. First walkathon takes place to benefit A-TCP in Canada. Several laboratories demonstrate that the ATM protein is a protein kinase activated by DNA damage.

August - First grant awarded to explore using a virus to transfer healthy A-T gene into cells from patients — ground work for gene therapy.

October - A-TCP announces extended clinical trial of L-Dopa with 30 children at A-T Clinical Center. Scientists find that the ATM protein is involved in the development of sperm and eggs.

November - Researcher finds that ATM gene is mutated in many cases of B-cell lymphoma.

December - Brad Margus serves as ad-hoc member of Advisory Committee to the Director of the National Institutes of Health.

1999

January - A-TCP announces A-T Cancer clinic established at St. Jude Children's Research Hospital in Memphis, Tennessee.

February - Brad Margus and Jim Lewin, both fathers of A-T children, meet with President Clinton in the Oval Office. First kickoff meeting held in Florida to teach friends and families how to hold successful walkathons to benefit A-TCP.

March - Researcher finds that while ATM is predominantly located in the cell nucleus in most tissues, it seems to be accumulated in the cytoplasm of cells that have stopped dividing, such as neurons.

April - A-TCP funds grant to researchers to insert stem cells in A-T mice and monkeys. Third annual "International A-T Walk for a Cure" begins with the first of 47 walks scheduled through November 1999 with a team goal of $700,000. Over 11,000 walkers are expected to participate.

May - Brad Margus testifies before the Senate Appropriation's Sub-Committee on Labor, Health and Human Services, and Education.

June - Research teams provide experimental proof that ATM is indeed involved in defense against oxidative stress.

July - It becomes more clear that the ATM protein controls several busy intersections of biological pathways by interacting with numerous proteins tied to each other in large "complexes," explaining the large number of cellular and body systems affected by its absence in A-T patients. The pace at which new insights about ATM functions are obtained accelerates, while new teams of researchers join the field to study A-T.

Public awareness has been increased through media exposure such as:

- **CBS This Morning (TV)**
- **People Magazine**
- **Business Week Magazine**
- **CNN's Larry King Live (TV)**
- **Various alumni magazines**
- **ABC's Turning Point with Barbara Walters (TV)**
- **NBC's Today Show (TV)**
- **The Rosie O'Donnell Show (TV)**
- **Good Morning America (TV)**
- **Newspapers across the nation including:**
  - **New York Times**
  - **Washington Post**
  - **USA Today**

A day...

when kids with A-T

...walk up the steps to receive a high school diploma

...walk to the podium to graduate from college

...walk down the aisle on their wedding day

...walk with their children to their first day of school

...tell their grandchildren their story of triumph!

Another Way to Help -- United Way Fall Campaigns

As you know, the United Way begins its annual fundraising drive each fall in nearly every community in the United States. It provides a way for many charities to obtain funds by individuals contributing a small portion of their paycheck through payroll deduction. Each United Way chapter lists a variety of organizations that may be chosen for payroll deductions, most of which are locally based. The majority of United Way chapters allow individuals to write in the charity of their choice. Even though we are a national organization, our 501(c)(3) nonprofit status qualifies us for this write-in option and has provided us with much needed funds for our research budget.

To initiate a write-in campaign in your workplace, contact your company's United Way chairperson to ask if there is a write-in option and if so, the possibility of informing the rest of the employees about the special needs of A-T research. Most coworkers are eager to donate to a cause that is personally tied to a colleague. Posting a public letter or a poster asking your fellow employees to join you in our fight against A-T might be one way to reach all the employees and increase our funding.

If you or your United Way chairperson has any questions, please call us! The United Way campaigns have been a successful source of revenue for us in the past, and with your help we hope it will continue to grow.

For more information call the A-TCP at 1-800-5-HELP-A-T or visit our website at www.atcp.org

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. Visit our web site at www.atcp.org

CHILDREN'S PROJECT℠
668 South Military Trail
Deerfield Beach, FL 33442
Phone: 1-800-5-HELP-A-T

NON-PROFIT ORG.
U.S. POSTAGE
PAID
BOCA RATON, FL
PERMIT NO. 770