A-T CHILDREN'S® PROJECT UPDATE

For Families, Friends and Supporters

NOVEMBER 2002

MERCK TO SCREEN OVER 1 MILLION COMPOUNDS TO FIND DRUGS THAT COULD HELP CHILDREN WITH A-T

Recently, at a meeting on the campus of Merck & Co. in West Point, Pennsylvania, company scientists met with A-T researchers from academia to consider applying the company's high-throughput compound screening capabilities to finding drugs that might eventually help children with ataxia-telangiectasia. The meeting concluded with Merck researchers offering to screen over a million different chemical compounds on human cells to search for drugs that will increase levels of proteins that may compensate for the loss of the ATM protein in children with A-T.

For the A-T Children's Project, interacting with a company like Merck was a huge departure from encouraging scientists at small academic and government laboratories to think about and study A-T. Merck employs 49,100 people worldwide and spends billions of dollars each year on research.

The unprecedented meeting happened because Stephen Friend, MD, PhD, Vice President of Basic Research at Merck, offered to assemble experts in medicinal chemistry, automation and neuroscience at Merck to hear from A-T researchers about biochemical tests that could be used to screen for drugs.

"This is a very special occasion where the needs of patients with a disease such as A-T line up nicely with our own internal programs in a way that there is such a great potential win for all involved," commented Dr. Friend.

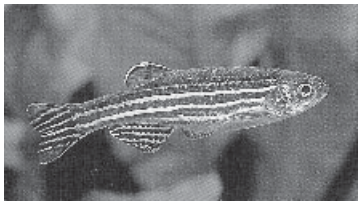
Dr. Friend's interest in helping children with A-T dates back to the mid-1990s when he was an investigator at Harvard and served on the scientific advisory board of the A-T Children's Project. Other Merck researchers who provided guidance to this project included Dennis Choi, MD, PhD - Executive V.P. of Neuroscience, Joel Huff, PhD - V.P. of Medicinal Chemistry, George Hartman, PhD - Executive Director of Medicinal Chemistry, Jerold J.M. Chun, MD, PhD - Senior Director of Molecular Neuroscience, and Berta Strulovici, PhD - Executive Director of Automated Biotechnology.

Stephen Friend, MD, PhD

(continued on page 4)

Flies and Zebrafish to Help Find Drug Treatment for A-T

Drosophila



Zebrafish

The A-T Children's Project is funding two investigators to generate small animal models of ataxia-telangiectasia for finding potential treatments for the disease.

Some small animal models, like the fruit fly, zebrafish, and nematode round worm provide certain economic and experimental advantages. They can be handled and studied in large numbers at relatively low cost and can readily be used to screen libraries of potential therapeutic compounds.

THE FRUIT FLY, DROSOPHILA may have a small brain, but it has proven to play a large role in the study of human neurodegenerative diseases. Within the past couple of years, aspects of Parkinson's, Alzheimer's, amyotropic lateral sclerosis (Lou Gherig's disease) and Huntington's disease have all been studied in Drosophila. Now, with funding from the A-T Children's Project, Shelagh Campbell, PhD of the Department of Biological Sciences at the University

(continued on page 3)

Scientific Advisory Board

Editor:
Jennifer Thornton, Executive Director
Science Editor:
Cynthia Rothblum-Oviatt, PhD
Design and Layout:
Rosa Fernández

A-T Children's Project
668 South Military Trail
Deerfield Beach, FL 33442-3023
PHONE: (954) 481-6611
TOLL FREE: 1-800-5-HELP-A-T
FAX: (954) 725-1153
WEB SITE: www.atcp.org
EMAIL: Info@atcp.org

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

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

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

Overlapping Functions of ATM and ATX in Genome and RNA Surveillance
Robert Abraham, PhD - Burnham Institute

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

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

Experimental Gene Therapy for Ataxia-Telangiectasia
Xandra O. Breakefield, PhD - Massachusetts General Hospital

NEW

A Drosophila Model for Ataxia-Telangiectasia
Shelagh Diane Campbell, PhD - University of Alberta

Creation of a Transgenic Porcine Model of A-T
Christopher M. Counter, PhD - Duke University

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

Development of Improved Protective Strategies Against Free Radical Damage in Ataxia-telangiectasia
Michael Green, PhD - University of Brighton

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

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

NEW

The Zebrafish as a Novel Vertebrate Model System of Ataxia-Telangiectasia
Shuji Kishi, MD, PhD of the Dana-Farber Cancer Institute, Harvard Medical School

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

Telomeres, Telomerase and Lifespan of Brain Cells of Atm-Null Mice
Tej Pandita, PhD - Washington University School 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

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

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

Identification of Novel ATM-Rad17 Associated Proteins That Function as Regulators or Downstream Targets
Xiao-Fan Wang, PhD - Duke University Medical Center

Strain Background Effects on Atm Nullizygosity
Michael Weil, PhD - University of Texas M.D. Anderson Cancer Center

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

Glucocorticoid Mimics Functional ATM Kinases to Prevent Thymic Lymphoma Development in Atm-/- Mice
Mingshan Yan, MD - University of Texas M.D. Anderson Cancer Center

NEW

Pilot Study: Evaluating the Relative Radiation Sensitivity of ATM Functional & ATM Inactive Human Cell Lines After Treatment With Small-molecule Modulators
Keith Laderoute, PhD and Annalisa D'Andrea, PhD - SRI International

For more information about A-TCP research grants, contact:
Cynthia Rothblum-Oviatt, PhD
Science Coordinator Cynthia@atcp.org

Flies and zebrafish - *(from page 1)*


Shelagh Campbell, PhD

of Alberta, Canada will begin to examine the genetics of *ATM* in Drosophila. Until recently, scientists thought that they had successfully identified the Drosophila *ATM* gene, which was called mei-41 in flies. However, it is now known that mei-41 really represents the Drosophila version of ATM's sister protein, ATR. Dr. Camp-bell's ultimate goal will be to use the different Drosophila *ATM* mutants she obtains to identify various genetic and environmental factors that affect the progression and/or severity of the A-T phenotype in flies.

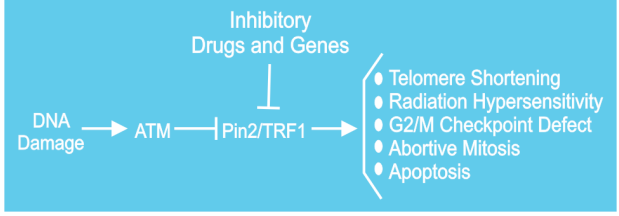
Like humans, Drosophila possess two copies of each of their genes. Each individual copy is known as an allele. Dr. Campbell's laboratory has already found several different mutant alleles of *ATM* in the fruit fly and has preliminary evidence that *ATM* mutations produce significant neurological defects that affect eye development. Interestingly, the majority of the *ATM* mutant alleles found by Dr. Campbell result in nonviable flies, and are therefore termed lethal alleles. These results suggest that, unlike humans, ATM is essential for overall viability in Drosophila. However, despite their lethality, these mutant alleles are still useful, as fly genetics allows for the development of Drosophila with eyes derived from cells containing the mutant *ATM* alleles. That is, Dr. Campbell can make otherwise normal flies that possess A-T eyes. Such animals can then be used to screen for genes or compounds that attenuate or reverse the eye defects.

In addition to these studies, Dr. Campbell's lab will utilize different genetic approaches in Drosophila to determine the contribution of oxygen free radicals (or oxidative stress) to the development of the fly A-T phenotype.

Dr. Campbell's research represents one of the first attempts to understand the role of the true *ATM* gene in fruit flies and, as Campbell herself notes, "…the startling success of Drosophila models for understanding other human neurodegenerative diseases provides a strong rationale for believing that our studies of Drosophila *ATM* mutants will similarly be relevant to understanding ataxia-telangiectasia."

ZEBRAFISH have traditionally been used as an animal model in the study of embryonic development. More recently, however, this organism has been used as a model system to examine cancer development, hematopoietic (or blood-derived) diseases, as well as cardio-vascular and neurodegenerative diseases. Now, the A-T Children's Project is funding a research grant entitled "The Zebrafish as a Novel Vertebrate Model System of Ataxia-Telangiectasia" submitted by Shuji Kishi, MD, PhD of the Dana-Farber Cancer Institute, Harvard Medical School.

Because genes cannot be disrupted or "knocked-out" in zebrafish the same way that they can be in mice, Dr. Kishi will use two relatively new approaches to disrupt, or inactivate, the A-T gene (*ATM*) in zebrafish. One of these approaches is termed target-selected muta-genesis. This technique involves treating male zebrafish with a drug that causes random mutations to occur throughout their genomic DNA. These so called "mutagenized" males are then bred to normal female zebrafish. DNA is subsequently isolated from their fertile male offspring and sequenced to identify the various mutations in their *ATM* genes. Next, through a combination of in vitro fertilization and breeding, sperm from these male offspring containing a mutant *ATM* allele, are used to generate A-T zebrafish. Dr. Kishi's lab has already started this process and is currently screening DNA from more than 3000 male zebrafish for *ATM* gene mutations.



By target-selected ATM gene inactivation and human Pin2/TRF1 trans-genesis, we will generate a zebrafish model of A-T and an A-T phenocopy, respectively. These zebrafish model systems will be utilized for high-throughput drug screening and secondary modifier gene discovery, which may in turn lead to therapeutic interventions for A-T.

The other approach being used by Dr. Kishi to generate A-T zebrafish is a popular research technique called RNA interference. Normally, the A-T protein (given the same name as the gene, ATM) is made in the following stepwise fashion: ATM gene/ DNA (deoxyribose nucleic acid) →ATM RNA (ribose nucleic acid) →ATM protein. In other words, the ATM gene codes for ATM RNA, an intermediate which in turn provides the biochemical code for generation of the ATM protein. Because RNA interference blocks the second step of this process, ATM protein cannot be generated, thus mimicking the A-T situation. As with the Drosophila A-T model system, Dr. Kishi's laboratory hopes to use their zebrafish models of A-T to screen for compounds that can reverse the disease phenotype.


From left top: Shuji Kishi, MD, PhD; Junzo Uchiyama, MD, PhD, and Stephanie Tsai
Bottom Row: Mao Lin, and Teru Goto, MD

In addition to generating A-T zebrafish by the methods described above, Dr. Kishi and his lab will also attempt to make an A-T phenocopy, or A-T like disorder, in zebrafish. Instead of mutating the ATM gene or blocking ATM protein expression, Dr. Kishi's team will over-express a protein in ze-brafish called Pin2/TRF1. Previously, Dr. Kishi observed that following DNA damage, the ATM protein phosphorylates Pin2/TRF1 and prevents Pin2-induced programmed cell death. Most interestingly, when Pin2/TRF1 is inhibited in A-T cells, these cells gain certain wild type characteristics like increased telomere length, reduced sensitivity to irradiation, and an appropriate G2/M phase cell cycle checkpoint (see figure). In other words, in the absence of ATM, inhibition of Pin2 makes cells appear more normal.

Therefore, Dr. Kishi's lab will generate zebrafish that over-express Pin2 and analyze these transgenic animals for A-T-like traits. If the Pin2/TRF1 transgenic fish exhibit A-T-like traits as expected, they will be screened for drugs that can specifically and effectively inhibit Pin2. Such compounds may one day prove useful in humans as therapeutic agents for A-T.

UPDATE

Harvard Researcher Finds Successful Bone Marrow Transplant Protocol For A-T Mice

Last year, the A-T Children's Project began funding John Iacomini, PhD, an investigator at Massachusetts General Hospital, Harvard Medical School, to develop a safe and effective bone marrow transplantation protocol in A-T mice for the prevention and/or treatment of immune abnormalities and immune cell-related cancers. Like children with A-T, affected mice cannot tolerate the doses of irradiation and cytotoxic chemicals necessary to destroy their bone marrow prior to the transplant procedure. Therefore, Dr. Iacomini's laboratory has been attempting to develop a significantly less toxic transplant protocol which utilizes specialized antibodies to destroy the host bone marrow versus irradiation and harsh chemicals. This type of pre-transplantation regime is termed "non-myeloablative host conditioning."

In their first try at a non-myeloablative protocol, Dr. Iacomini's lab was only able to replace 10-20% of host A-T mouse bone marrow with donor hematopoietic (bone marrow) cells. Dr. Iacomini then modified the initial protocol and subsequently found that 70% of the bone marrow in host A-T mice had been replaced with normal or donor bone marrow cells. In addition, approximately 100% of the A-T mice T cells (an important arm of the immune system) were found to be derived from donor marrow.

In this upcoming year of funding, Dr. Iacomini and his team will continue to refine their pre-transplantation conditioning regime to obtain *complete* replacement of A-T mouse bone marrow with normal donor marrow. They will also begin monitoring their host A-T mice for attenuation of immune abnormalities including the characteristic development of thymic lymphoma. If Dr. Iacomini's protocol for bone marrow transplantation in A-T mice is successful, it will be modified for use in humans. For the first time, A-T patients could then be safely cured of immune system deficiencies, leukemias and lymphomas. AT

800-5-HELP-A-T

NIH Steps In to Fund Primate Model of A-T

In 1999, the A-T Children's Project began funding one of their most promising and most challenging research grants, "A Primate Model of Ataxia-Telangiectasia." Don Wolf, PhD of The Oregon Regional Primate Research Center and Robert Norgren, PhD of the University of Nebraska Medical Center, the principal investigators for this project, have overcome a number of daunting technical problems in their attempt to clone primates via the process of somatic cell nuclear transfer. When this task is accomplished, Wolf and Norgren hope to be among the first group of scientists to then generate primates that recapitulate certain genetic diseases in humans, including A-T.

This summer, Dr. Wolf and Dr. Norgren were awarded funding from the NIH's National Institute of Neurological Disorders and Stroke (NINDS) to continue their ground-breaking research. The A-TCP congratulates them on this accomplishment and wishes them the utmost success in fulfilling all their research objectives. We are very grateful for their continued interest in A-T. AT

Shop And Share With Food Lion's MVP Card

When shopping at Food Lion using your MVP card, a portion of your total grocery purchase can be donated to the A-TCP. For details, inquire at your local Food Lion supermarket or call Food Lion's Customer Service Department at 800-210-9569. (Locations in North Carolina, South Carolina, Georgia, Tennessee, Florida, West Virginia, Virginia, Maryland, and Kentucky.)

Patriot cheerleaders flank Jeffrey Kummer at Wayland's A-T Walk for a Cure on June 2nd.

MERCK - *Continued from page 1*

Researchers studying A-T have known for some time that even though the disease was caused when the ATM protein was missing in children, there were other proteins that might share some of the same cellular functions. Consequently, scientists suspected that increasing the levels of these other proteins might compensate for the missing ATM protein and be therapeutic for children with A-T. But, even though drug companies have been applying automated, high-throughput drug screening technologies for years to discover compounds that change protein levels, this powerful approach had always been out of reach for A-T researchers. As a result of this meeting, however, experts at Merck will soon begin looking for compounds that increase levels of one or more of these proteins, and if they succeed, a drug may be discovered that could eventually be tested in children with A-T.

Merck has been tremendously successful in finding drugs. Today, it is a leading research-driven pharmaceutical company that discovers, develops, manufactures and markets a broad range of human and animal health products and services. Merck's research has produced vaccines and medicines to treat cardiovascular, gastrointestinal and infectious diseases, arthritis, glaucoma, and symptomatic benign prostate enlargement and products to treat animal parasites and crop pests. The A-T Children's Project is thrilled to have senior executives at this highly-respected company helping to develop and implement new research paradigms for A-T. AT

You can help fund critical research TODAY! Get involved by volunteering to host fundraising events. Choose the type of fundraiser that you want to host and we will provide materials to help customize your event. From t-shirts, sponsor brochures, invitations, flyers and technical support to networking with other volunteers -- we can provide the necessary information to put together your own fundraiser to help us fund research on A-T. Call 800-5-HELP-A-T or send an email to info@atcp.org.

April in Connecticut

The A-T Children's Project was fortunate to benefit from no fewer than three dinner dances in Connecticut during April 2002.

HELP CREATE A MIRACLE - Mike and Cece Donoghue of Darien, hosted *Help Create a Miracle* at the Westin Stamford on April 5. One of the first benefits for the A-TCP, the Donoghues' annual event has been embraced by their community. Highlights of the evening included the fulfillment of their *Wish List* to provide specialized therapy evaluations at the A-T Clinical Center when insurance denies coverage.

HOPE IS IN BLOOM - On April 6, Dave and Lori Smarz hosted *Hope is in Bloom*, a dinner dance and silent auction held at the Oronoque Country Club in Stratford. Dave and Lori's ten-year-old son, Robbie, has A-T. Family, friends and the community supported the benefit with their attendance, donation of silent auction items, and more.

FOUNTAIN OF YOUTH - Chairman Francesca Carriuolo and Co-Chairman Timothy Moynahan were joined by Honorary Chairs Helen and Harry Gray on April 27 at the *Fountain of Youth* gala in Hartford. The benefit for the A-T Children's Project and the Connecticut Children's Medical Center featured the Jimmy Dorsey Orchestra and a sumptuous dinner at the Bond. The live auction included two vacation packages to castles in Ireland. A special thanks to Mrs. Carriuolo for spearheading the benefit that introduced many new people to the A-T Children's Project.

"BREAK A LEG"

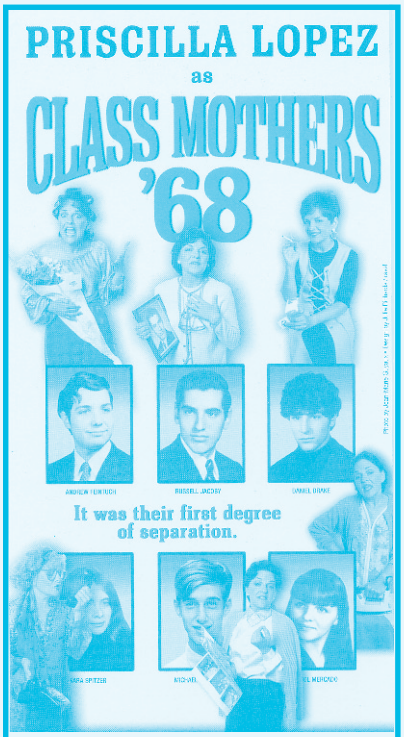
The A-T Children's Project wishes all the best to our friends, writer and producer **Eric H. Weinberger**, and Tony and Obie Award winner **Priscilla Lopez**.

Lopez will star in Weinberger's one-woman comedy, **CLASS MOTHERS '68** which makes its off-Broadway debut on Monday, November 25 at Theatre Rows' **Clurman Theatre** (410 West 42nd Street), New York.

Since 1994, Mr. Weinberger has produced and hosted ***A Very Special Evening***, the annual theater event in New York City benefiting the A-T Children's Project. Ms. Lopez has both hosted and performed at these events.

Mr. Weinberger is very busy these days with the opening of **Class Mothers '68** and planning *A Very Special Evening VIII*. Ms. Lopez will again be participating in the benefit which will take place at the Clark Theater at Lincoln Center on Monday, January 20, 2003.

For tickets to ***A Very Special Evening***, call the A-T Children's Project at 954-481-6611 or 800-5-HELP-A-T.



For tickets to **Class Mothers '68**, call Ticket Central at (212) 279-4200.

Duke University Investigator to Lead Pig Cloning Effort

Christopher M. Counter, PhD

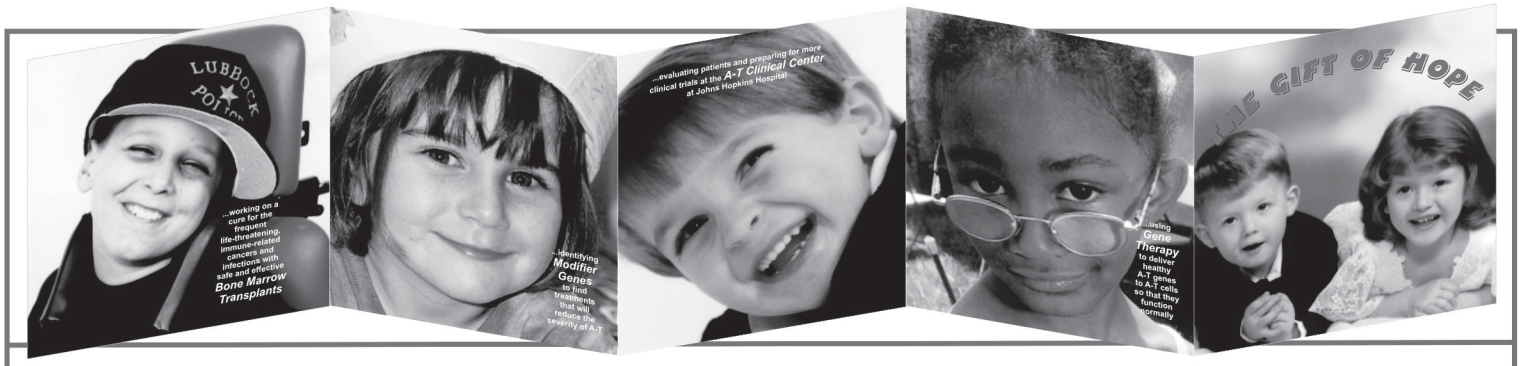
The A-T Children's Project is pleased to announce the funding of a new research grant submitted by Christopher M. Counter, PhD (Duke University, Durham, North Carolina) entitled, "Creation of a Transgenic Porcine Model of A-T." As principal investigator, Dr. Counter has brought together a group of scientists who will work to generate a model for A-T in pigs, the only other mammals besides rodents in which genes have successfully been disrupted or "knocked out."

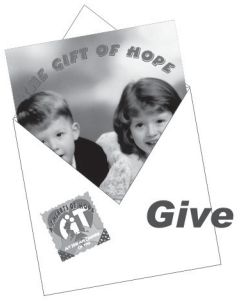
Dr. Counter's collaborative team includes: Lawrence Schook, PhD and Jonathan Beever, PhD of the University of Illinois at Urbana-Champaign; Erik Forsberg, PhD and Michael D. Bishop, PhD from Infigen Incorporated, Wisconsin; and Robert T. Abraham, PhD of the Burnham Institute in La Jolla, California. Each member of the team is "renown in their respective field," notes Counter.

To genetically engineer a pig lacking functional copies of both A-T genes, these investigators will perform a combination of targeted gene disruption, somatic cell nuclear transfer and breeding. It is hoped that this non-rodent model of ataxia-telangiectasia will effectively mimic the progressive neurodegeneration seen in humans with A-T. The A-T Children's Project is confident that the research performed by Dr. Counter's team will expedite the making of this large animal model of A-T.

this holiday season give the gift of hope

A **distinctive** new way to give a meaningful gift for special occasions and holidays, this lovely **full color Gift Card** spotlights **children with A-T** and highlights funded research projects that can lead to a **cure** or life-improving **therapies** for **ataxia-telangiectasia**. Recipients will be honored to receive your **Gift Card** and message. **Choose** how you would like your Gift Card sent. We can **mail it on your behalf within two business days** indicating a gift has been made in the recipient's honor and include your personal message. Or, we can **send you a blank card for you to personalize and mail**. When you send a Gift Card for a **minimum $25 donation,** you are giving a double gift. The recipient will be touched by your thougthfulness, and **children with A-T will benefit from crucial scientific and medical research**.





THE GIFT OF HOPE GIFT CARD

Give The Gift of Hope for special occasions and holidays.

Card folds into a 5" square; envelope and seal included.

Choose your gift level

☐ $25 ☐ $50 ☐ $100 ☐ $250 ☐ $500 ☐ $1000 ☐ Other $ _____

Please specify

FOUR WAYS TO ORDER

1. **MAIL**
   this completed order form with check or credit card information to:
   A-T Children's Project
   668 South Military Trail
   Deerfield Beach, Florida
   33442 USA

2. **ORDER ON-LINE**
   on our secure website:
   www.atcp.org

3. **FAX**
   completed order form with credit card information to:
   954-725-1153

4. **CALL**
   Monday - Friday
   8:30 - 5:30 Eastern Time
   with your credit card information:
   800-5-HELP-A-T
   (800-543-5728) or
   954-481-6611

Name _____

Address _____ City _____ State _____ Zip _____

Phone (_____) _____ Email _____

Gift Amount US$ _____ Check made payable to the A-TCP enclosed **OR** charge my credit card

☐ Visa ☐ MasterCard ☐ Discover ☐ American Express

Credit Card # _____ — _____ — _____ — _____ Exp. Date _____ / _____(mm/yy)

Signature _____

Please send me _____ (number of) gift cards (minimum $25 gift per card) **OR** send card(s) to:

Name _____

Address _____ City _____ State _____ Zip _____

Message _____

Name _____

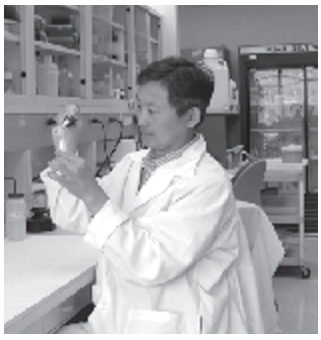
Address _____ City _____ State _____ Zip _____

Message _____

Please add any additional names with addresses and messages on a separate sheet of paper.

Drug Prevents Cancer in A-T Mice

Mingshan Yan, PhD, a researcher at the University of Texas M.D. Anderson Cancer Center, has discovered that a drug called Dexa-methasone prevents cancerous tumors that usually occur in ATM-deficient mice. Now, with a new research grant from the A-T Children's Project entitled, "Glucocorticoid Mimics Functional ATM Kinase to Prevent Thymic Lymphoma Development in Atm-/- Mice," Dr. Yan's laboratory will strive to understand how the drug works in mice and how it could be a potential treatment for children with A-T.



Mingshan Yan, PhD

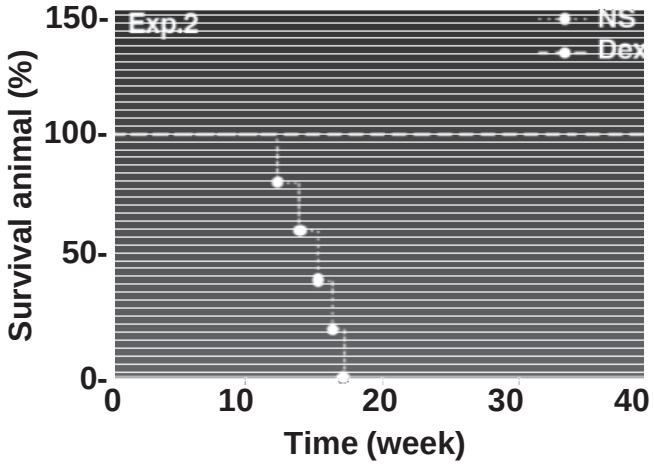
In humans, loss of ATM (the A-T protein) results in a multisystem disorder that often affects the immune system, resulting in immunodeficiency and/or an increased risk for the development of leukemia or lymphoma. Interestingly, the majority of A-T mice develop thymic lymphomas and die at around 4-5 months of age (the average life span of a mouse is normally around 2 years).

For the past year or so, Mingshan Yan and his colleagues have been busy investigating how ATM regulates T lymphocyte development in mice. The development of T cells, an extremely important component of the immune system, depends upon the thymus. T lymphocyte precursors (or progenitor cells) originate in the bone marrow and migrate to the thymus, where they then undergo differentiation into mature T cells. During this differentiation process, the immature T lymphocytes (also called thymocytes) undergo a specialized series of changes characterized by the appearance of certain cell surface molecules. These molecules can be used by scientists to monitor the differentiation process of a population of thymocytes, and as such, are termed cellular "markers."

By following the appearance of the various cell surface markers during the differentiation of thymocytes in A-T mice, Dr. Yan and his colleagues discovered that the rate of DNA synthesis and proliferation (or growth) of a certain set of thymocytes was significantly increased as compared to those of wildtype or normal mice. Dr. Yan hypothesized that this subset of immature T cells, located at a particular stage in their differentiation process, would undergo either programmed cell death or transform into cancer cells, ultimately giving rise to the observed thymic lymphoma.

Because thymocytes are sensitive to treatment with corticosteroids, Dr. Yan began treating two week old Atm-/- (A-T) mice with the glucocorticoid, Dexamethasone (Dex), to determine if it might effectively reduce the population of rapidly dividing thymocytes and decrease thymic lymphoma development. After treating A-T mice with varying doses of Dex, Dr. Yan indeed found that the abnormally proliferating population of thymocytes was reduced, and that Dex treatment completely prevented development of thymic lymphoma.

Dexamethasone Administration Prevents Thymic Lymphoma Development and Increases Survival of A-T Mice



Dr. Yan treated 2 week old Atm-/- (A-T) mice with dexamethasone (Dex) or normal saline (NS). By 20 weeks (approximately 5 months of age), the A-T mice given NS had died from thymic lymphoma. In contrast, 100% of the A-T mice treated with Dex were still alive and healthy at 10 months of age.

Based on Dr. Yan's results, it would appear that Atm plays an important role during T cell development in mice by mediating the proper differentiation of immature thymocytes.

Dr. Yan will continue to investigate the role of Atm in thymocyte development and the mechanism behind the efficacy of Dex in preventing thymoma. However, "Our long term goal," says Yan, "is to develop this tumor prevention protocol [as] an effective therapy for A-T children." AT

"I CAN'T" is NOT in their vocabulary...

Although they can no longer walk and rely on wheelchairs to get around, Arlon Maxfield (left) and Randy Van Hierden are seen here climbing a rock wall at the A-T Walk for a Cure in Fort Macleod, Alberta, Canada. Both Arlon and Randy have A-T. **Way to go, guys!**

Children with A-T to Participate in Endocrine Study

Arleen D. Auerbach, PhD

Arleen D. Auerbach, PhD at The Rockefeller University in New York and Michael Wajnrajch, MD have developed an endocrine study protocol for A-T patients to include growth hormone, glucose metabolism, thyroid function, adrenal function and pubertal function. The study will incease our current understanding of A-T and any endocrine abnormalities found amongst the participants will likely be amenable to treatment.

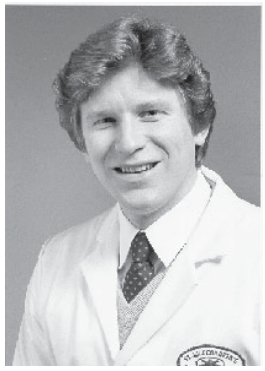
Dr. Auerbach's laboratory focuses on Fanconi anemia (FA). Like ataxia-telangiectasia (A-T), FA is a rare autosomal recessive disorder. Other similarities between FA and A-T include increased susceptibility to cancer and, at the cellular level, chromosome instability. Whereas cells from patients with A-T are sensitive to agents like irradiation that cause genetic lesions known as DNA double strand breaks, Dr. Auerbach discovered that FA cells are sensitive to DNA cross-linking agents. Just as radiation sensitivity is used as a cellular marker facilitating the diagnosis of A-T, Dr. Auerbach demostrated that this sensitivity to DNA cross-linking agents can be used as a unique pre- and postnatal marker for the diagnosis of FA.

Since 1990, Dr. Auerbach and her colleagues at the Weil Medical College of Cornell University have been conducting a comprehensive endocrine study on patients with Fanconi anemia. The goal of this study has been to gain an understanding of how to optimize the growth and development of children with FA. As such an in depth endocrine study has not yet been performed on children with A-T. The revised protocol was recently approved by the Institutional Review Board of The Rockefeller University and, with the aid of the A-T Children's Project, candidate recruitment is underway.

Upon entry into the study, participants will spend five days at The New York Presbyterian Hospital to be evaluated for adrenal and pubertal function, glucose metabolism, growth hormone and thyroid function. In addition, they will receive consultations with specialists in areas such as genetics, neurology, ENT, ophthalmology, dermatology and cardiology.

A-T Cancer Clinic Uses Specialized Protocols To Help Patients With A-T

Michael Kastan, MD, PhD



John T. Sandlund, MD

When a child with ataxia-telangiectasia (A-T) develops cancer, families are faced with the difficult decision of where to have their child treated. A-T is a rare disease, not seen by many local oncologists, and treatment options are reduced due to radiation sensitivity and immune system problems.

The recently established A-T Cancer Clinic at St. Jude Children's Research Hospital eases much of the burden of parents when their A-T children are faced with cancer. Experts at St. Jude have been developing specific protocols for cancer treatment in A-T patients to maximize the potential for remission. Families of A-T patients who develop cancer can decide if they would like treatment to take place at St. Jude, or at their local hospital with consultation from St. Jude specialists.

Vickie Mautino's son was diagnosed with Acute Lymphoblastic Leukemia (ALL) at age seven. He was originally treated at St. Jude in Memphis, Tennessee and receives follow-up care at the St. Jude Midwest Affiliate near their home in Illinois.

"The concern and care Alex received at St. Jude was outstanding. At St. Jude, pediatric cancer patients receive the very best treatment from world-renowned physicians and scientists who have revolutionized leukemia treatments. Patients receive treatment regardless of the family's ability to pay and any costs not covered by the insurance companies are waived. Many of their pediatric cancer treatment protocols are used by other hospitals. A-T does complicate treatment; however, with Alex they tailored his chemo protocol, and today he is cancer-free."

Another family coping with a diagnosis of melanoma for their 10-year-old son sought treatment at St. Jude. Melanoma is a rare cancer diagnosis for children with A-T. Typically, malignancies such as lymphoma or leukemia are more common diagnoses. The expertise available at the A-T Cancer Clinic led to special treatment protocols as this was the first time that a child with A-T was treated with Interferon at the Clinic. In addition to the special protocols, the extra care on the part of the doctors and nurses made a big difference, and the family always felt like they were at the top of the priority list.

The Clinic is overseen by Michael Kastan, MD, PhD, currently chairman of the Department of Hematology and Oncology, and John T. Sandlund, MD, director of the Leukemia/Lymphoma Clinic at St. Jude.

To contact the A-T Cancer Clinic at St. Jude Children's Research Hospital, page Dr. Sandlund at 901-594-3300 or email him at: john.sandlund@stjudge.org.

February will be upon us sooner than we think... Start planning your *Hearts of Hope* fundraiser at school, work, or through your local retailers. These symbols of hope come in red or gold. Red paper hearts sell for $1 and Gold paper hearts sell for $5.
For more details contact us by email at Hearts@atcp.org or call 800-5-HELP-A-T.

DOUBLE H RANCH

Fifteen-year-old Tori Bement had the opportunity to attend **Newman's Own** *Double H Hole In The Woods* Ranch at Lake Luzerne, New York, on the week of August 10th. The camp was like a dream come true for Tori, who was diagnosed with A-T in 1993 at the age of six. Tori has lost the ability to walk and has tremors that make doing the simplest task very difficult. She needs assistance with all aspects of her daily life. She has been attending Rotary Camps since she was seven years old, but Double H was a new and exciting experience for her.

Tori's mom, Lynn, had reservations about leaving her at camp 250 miles away. "My mind was put at ease within two minutes of our arrival at the Ranch. Counselors met us at the car and assisted with her bags and wheelchair. Tori was whisked away to registration and to get settled into her room. The facility was like a resort! She especially liked the indoor and outdoor pools. As a parent of a child with physical disabilities I am cautious about leaving my daughter just anywhere. I was so pleased that she was treated like any other camper and had the opportunity to climb the ropes in the trees, horseback ride, camp out and help in the barn with the animals. She even was awarded the title of *Queen of the Barn*. It is my hope that other kids with A-T will take advantage of the great opportunity of the Double H Ranch. I am so impressed with the Ranch I plan on volunteering next year as a nurse."

The camp is located in New York's beautiful Adirondack Mountains. It provides hope and adventure to 1,000 critically ill children each summer, 500 children through the winter skiing program, and several hundred through family based programs. Activities include indoor and outdoor swimming, high ropes, whitewater rafting, and trips to local attractions. Aside from transportation, there is NO CHARGE for any child to attend the *Double H Hole in the Woods Ranch*.

The Hole In The Wall Gang Camp, was founded by Paul Newman with Ursula Gwynne and A.E. Hotchner in 1986 with funds from Newman's Own, in addition to other generous donors. Find out more about the Hole in the Wall Gang Camp Association, and all their different camps across the nation and overseas. Visit their website at: www.newmansown.com/3c_camps.html

THANK YOU 2002 INTERNATIONAL SPONSORS

TD Securities
Bruster's Old-Fashioned Ice Cream & Yogurt
Pharmacia
Amgen — Dramatically Improving People's Lives
CIBC World Markets
Acquisition Solutions
Sara Lee
Sam's Club
Pfizer for living
Target
Wal-Mart
Morgan Stanley
Carnival Cruise Lines
Tellium
PricewaterhouseCoopers
Herbalife
The IDI Group Companies
Clark/Bardes Consulting
Robbins Gioia Inc.
Bristol-Myers Squibb Company
Body1.com — Where Technology and Health Care Meet
Instinet — A Reuters Company
Fleet
Dart Group II Foundation
TJX — The TJX Companies, Inc.
Weichert Realtors
Bank of America

For your holiday shopping, don't forget to visit our website and click on *Shopping*. The link to GreaterGood.com will let you shop at major stores, and a portion of your purchases will be donated to the A-TCP. You won't pay a higher price, and you will be helping the A-TCP to fund critical research on ataxia-telangiectasia.

FAPE

Teaches Education Rights to Familes of Children With Disabilities.

It can be difficult for families of children with A-T to know what their rights are when it comes to public education. There is an organization that can help.

The Families and Advocates Partnership for Education (FAPE) aims to improve the educational outcomes for children with disabilities. FAPE links families, advocates, and self-advocates to communicate the new focus of the Individuals with Disabilities Education Act (IDEA). The project represents the needs of six million children with disabilities in the United States.

A primary goal of IDEA '97 is to ensure that children with disabilities receive quality education. The new IDEA shifts the focus of the previous law from providing access to education to improving results for children with disabilities. For more information visit www.fape.org or call toll-free (888) 248-0822.

Rundle College Society's "Children Helping Children" Raises Over $57,000 for the A-T Children's Project in Canada

Students from Rundle College Senior High joined forces with all the Rundle College Society schools accepting the challenge of raising money for the A-T Children's Project Canada as part of their Children Helping Children community outreach program.

An alumnus of Rundle College, Aaron Goodarzi (class of '95) was one of the key event organizers. Goodarzi is currently researching A-T in his doctoral studies under the supervision of Dr. Susan Lees-Miller at the University of Calgary. Early in October, Goodarzi visited the Rundle College Society Schools and introduced the student body to A-T and the role research plays. His sister, Zahra Goodarzi, presently in grade 12 at Rundle, was also a key organizer.

Dr. Susan P. Lees-Miller (center) and graduate student Aaron A. Goodarzi (right).

The Academy student body (grades 4-12) is divided into houses (much like in Harry Potter). Together with the Elementary and Primary Schools they all had individual events throughout the month of October -- from walkathons, *Radical Rundle Relays*, *Bling-Bling* (penny wars), *and Dress Down Days* to art sales and bake sales.

On October 24, the Celebration Assembly at the High School campus was opened by A-Channel television's local hosts "Kate and Glen," who asked the students to give themselves a round of applause for making a difference. Speakers celebrating the students' efforts included headmaster Dave Hauk, co-founder of Rundle College Society and Superintendent of Schools Dr. Rodney Conklin, Dr. Lees-Miller, and Goodarzi. The students presented a check for $57,117.57 to the president of A-T Children's Project Canada, Conrad Van Hierden, his wife Rhonda, and their 18-year-old son Randy, who has A-T.

The Van Hierdens accept donation on behalf of A-TCP Canada.

Anshul Fernando, a good friend of Goodarzi and president of Lepidopteran Inc., a company that creates artwork with preserved butterflies and other insects, prepared a piece of art for the raffle, which sold hundreds of tickets. To promote the raffle, Goodarzi prepared a poster (pictured on the back cover of this *Update*) using the analogy that Fernando had in mind when he created the piece.

Goodarzi, who attended Rundle from grades 8-12 said "it was one of the best experiences of my life." This private school is dedicated to academics (math, english, science and history) with a good dose of athletics, and it is also dedicated to developing citizenship skills in their students. To that end, students support charitable causes such as this one.

The grand prize winners were eighteen-year-old Daniel Arnoldussen and thirteen-year-old Henry DeKok. They were awarded airline tickets for raising the most dollars for A-T. AT

High School students had fun with the Rundle relay races.

Happy Birthday Sweet Sixteen

Most girls look forward to their 16th birthday anticipating the party and gifts that traditionally mark this occassion. But on her sweet sixteen, Rachel Kemeny of Flat Rock, Michigan, had other plans. To celebrate this special day, Rachel, who also has A-T, went to get a haircut and chose to donate her beautiful long hair to "Wigs for Kids," a not-for-profit organization providing hair replacement solutions for children affected by hair loss due to chemotherapy, alopecia, burns and other medical conditions. Rachel's selflessness and caring are an inspiration to all of us. Happy Birthday, Rachel!



Blue is the color of hope

For almost a decade, the A-T Children's Project has fuelled research for new treatments and a possible cure for A-T. Yet still the medical breakthrough to defeat A-T eludes those who most desperately need it. Despite these challenges, A-T kids, their parents and researchers around the world have hope. The hope that one day we will discover the elusive cure for A-T, improving all of our lives.

The iridescent blue on the wings of the butterflies featured in this artwork is, in fact, one of natures great optical marvels. Not really blue at all, the specialized wing cells of these butterflies refract light in a very remarkable way, so that the blue colour that we see is only visible from certain, often elusive angles. As such, these beautiful creatures symbolize the undiscovered cure for A-T, not visible to us yet, but very much there, embodying hope to us all.

Please help us find the cure for A-T

Poster by: Aaron Goodarzi
and Anshul Fernando

LEPIDOPTERAN
Purveyors of Quality Preserved Butterflies
www. lepidopteran.com

A-T CHILDREN'S® PROJECT
668 South Military Trail
Deerfield Beach, FL 33442
U.S.A.