

Harvard Researcher Plans to Develop a High Throughput Drug Screening Assay for A-T

A researcher at the Dana Farber Cancer Institute at Harvard University will develop a cell culture-based assay or test, using brain cells, for high throughput drug screening (HTS) to identify compounds that may help treat the neurodegenerative aspect of ataxia-telangiectasia (A-T). This researcher will be joining the international effort, supported by the A-T Children's Project as well as the National Institute of Neurological Disorders and Stroke at the NIH, to capitalize on high throughput technology in an attempt to identify therapeutic drugs for A-T.

High throughput screening is a powerful technique used by pharmaceutical companies to identify compounds that may prove beneficial for the treatment of a wide variety of diseases and disorders. Once identified, these so called "lead" compounds undergo further testing for efficacy and safety before entering a Phase 1 clinical trial in humans. During a high through-

put screen, thousands or even millions of drugs can be tested using a single assay that has been automated for the robotics necessary to carry out the HTS procedure. In an attempt to utilize this technology to help find a treatment for A-T, Brendan Price, PhD has been awarded funding from the A-T Children's Project to develop a HTS assay utilizing specially modified human brain cells.



Brendan Price, PhD

The cells being used by Dr. Price and his laboratory are a human neuroblastoma cell line called SH-SY5Y. The SH-SY5Y cells have been used by scientists to study other neurodegenerative diseases such as Huntington's, Parkinson's and Alzheimer's disease. These cells can be differentiated into brain cells by manipulating the growth

conditions of the cells. Differentiation is the process by which these cells cease dividing and become mature neuronal-like cells. Dr. Norvin Fernandes, a research fellow in Dr. Price's lab, has shown that the A-T protein (ATM) is necessary for the proper differentiation of SH-SY5Y cells. Dr. Price's lab demonstrated the importance of ATM to the differentiation of these cells by modifying the SH-SY5Y cells such that they no longer produce ATM protein. The ATM deficient neuroblastoma cells failed to complete the differentiation process and instead underwent programmed cell death or suicide.

These ATM null SH-SY5Y cells will be used to screen for compounds that can restore their ability to differentiate into mature neuronal-like cells. Dr. Price will develop the HTS assay in collaboration with Drs. Ross Stein and Li-An Yeh of the Laboratory for Drug Discovery in Neurodegeneration at the Harvard Center

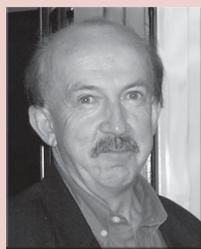
Continued on page 4

Researchers Collaborate to Generate a Rat Model for A-T

In an attempt to create an animal model that accurately represents the central nervous system dysfunction seen in patients with ataxia-telangiectasia (A-T), and which can be used to test potential treatments for these neurological abnormalities, two investigators have formed a collaboration to generate a rat model for A-T.



Michael M. Weil, PhD



Martin F. Lavin, PhD

tion in A-T mice limits the usefulness of this animal model for the study of potential treatments for this aspect of the disease. Therefore, Michael M. Weil, PhD from Colorado

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Although the mouse model of A-T mimics many of the characteristics of the human disease, it does not possess the relentless cerebellar degeneration and ataxia observed in all patients with A-T. The absence of this same type of neurodegenera-

A-T Awareness Bands are Here!



Marketplace..... p. 11

A-T MARATHON
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Join in the fun and help raise money for A-T research! Fundraisers are already signing up for the WALT DISNEY WORLD[®] Marathon in January 2006, and for other marathons around the country. For details and registration, visit our website at atcp.org.

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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

Role of Atm Protein in the DNA Damage Response of Cerebellar Neuronal Cells
Ari Barzilai, PhD - Tel Aviv University

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

Linking ATM and Breast Cancer
Kevin D. Brown, PhD - LSU Health Sciences Center

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

New Mechanisms to Activate p53 Function in A-T Cells
France Carrier, PhD - University of Maryland

Gene Therapy for Ataxia-Telangiectasia
Maria L. Cortés, PhD - Massachusetts General Hospital

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

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

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

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

Correction of the neurological defect in Atm gene-disrupted mice by the isoindolin nitroxide, 5-carbocyl-1, 1,3,3-tetramethylisoindoline-2-yloxy (CTMIO)
Martin Lavin, PhD - Queensland Institute of Medical Research

Generation of a Rat Model for A-T
Martin Lavin, PhD - Queensland Institute of Medical Research and Michael M. Weil, PhD - Colorado State University

ATM Activates the Myocyte Enhancer Factor-2 (MEF2) Family of Transcription Factors Implicated in Regulation of Neuronal Differentiation and Survival
Stuart Lipton, MD, PhD - The Burnham Institute



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

Functional Interactions between ATM, E2F1 and the M/R/N DNA repair complex.
Tanya Paull, PhD - The University of Texas at Austin

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

ATM Modulation of CREB Phosphorylation in the Developing Thymus, Testes, and Cerebellum
Wenan Qiang, PhD - Northwestern University

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

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

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 - Colorado State University

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

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

The Role of ATM in the Mitochondrial Pathway of Apoptosis
Leman Yel, MD - University of California, Irvine

Developing PARP Inhibitors that Can Penetrate the Blood Brain Barrier by Oral Dosing
Jie Zhang, PhD - Guilford Pharmaceuticals

For more information about A-TCP research grants, contact:
Cynthia Rothblum-Oviatt, PhD,
Science Coordinator
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Mario Manuele and Friends at the Montreal's Casino Night

A-T Walk 2004 in Dubuque, Iowa

Halloween Costume Party Lemont, Illinois



Co-hosts John and Marcia Wood with Lemont Mayor John Piazza and wife Karen

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and techniques to get
started.

Kemeny Meets Céline Dion



Peggy & Rachel Kemeny with Celine Dion

Rachel Kemeny, of Carleton, Michigan, dreamed of seeing international superstar Céline Dion in concert, and *Kids Wish Network* made her dream come true. In January, Rachel was flown to Las Vegas where she was taken in a limo to see Ms. Dion's show at the Colosseum at Caesars Palace. Before the show she was escorted backstage to meet Céline. "She was very kind and loving - and her show was totally awesome!" said 18-year-old Rachel, who has A-T. Peggy, Rachel's mother

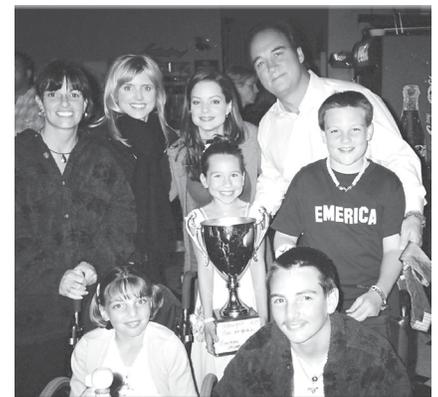
commented, "I would highly recommend *Kids Wish Network*. They truly know how to grant a wish!"

To refer a child to the wish program, visit www.kidswishnetwork.com/registerwishkids.asp

Katie Smith's cameo on "According to Jim"

Eleven-year-old Katie Smith made her television debut in a cameo on the ABC network family sitcom "According to Jim" – courtesy of actress Kimberly Williams-Paisley, who plays Dana, the sister-in-law. The actress arranged for the cameo as an auction item for the *Shjon Podein Children's Foundation* annual Golf Tournament. The donor who won the bid generously passed it on to Katie who has A-T.

Katie, her mother Sheila and her brothers Tyler (who also has A-T) and Trevor had a wonderful time at the filming of the episode titled "Father Daughter Dance" which aired on Nov. 9, 2004.



Standing from left: Sheila Smith, Courtney Thorne-Smith, Kimberly Williams-Paisley, Jim Belushi, Taylor Atelian and Trevor Smith. Sitting: Katie and Tyler Smith

A New Role for the A-T Protein in the Brain is Being Studied by Scientists at The Burnham Institute

Scientists at The Burnham Institute in California are investigating a potentially novel function for the A-T protein in the brain. This research could reveal an important aspect of the pathophysiology of A-T and may have therapeutic implications for treatment of the neurodegeneration associated with this disease.

The A-T Children's Project has awarded funding to Stuart A. Lipton, MD, PhD, Professor and Scientific Director of the Neuroscience and Aging Center at The Burnham Institute for his grant proposal entitled "ATM Activates the Myocyte Enhancer Factor-2 (MEF2) Family of Transcription Factors Implicated in Regulation of Neuronal Differentiation and Survival." The MEF2 family of proteins plays an important role in the developing nervous system. Interestingly, one of the MEF2 family members, MEF2A, is found predominately in the cerebellum. This region of the brain is greatly affected by the loss of ATM (the A-T protein), as patients with A-T suffer from a degeneration of neurons (brain cells) in the cerebellum



Stuart A. Lipton, MD, PhD

resulting in progressive cerebellar atrophy and ataxia.

Dr. Lipton, his graduate student Shing-Fai Chan, and postdoctoral fellow Jonathan Radford, PhD have found that ATM may directly regulate MEF2A function. "Taken together, our preliminary results suggest that MEF2 may act as a 'gatekeeper'... for the mediation of neuronal differentiation and survival in the ATM-dependent signaling pathway in the CNS [central nervous system]," states Dr. Lipton. A role for ATM in neuronal differentiation or maturation has been proposed by

other investigators; however, the precise function of ATM in this process remains unknown. The research performed in Dr. Lipton's laboratory may help define the exact mechanism by which ATM mediates neuronal development and cell death. Furthermore, by identifying an ATM dependent signaling pathway in the brain involving MEF2 family members, Lipton's team may reveal new therapeutic targets for the treatment of A-T. The knowledge of how ATM functions in brain cells may allow scientists to identify a drug(s) that can compensate for the loss of ATM in these cells.

A Very Special Evening

The tenth anniversary production of *A Very Special Evening* at Lincoln Center was co-hosted by Olympia Dukakis, Louis Zorich, and Priscilla Lopez. A special

appearance by Senator Bill Bradley complemented the evening's fabulous entertainers.

Funds raised at the event went to a research fund established in honor of the New York Production Crew who has worked for many years to make the event a success. The honorees were Tom Miller, Jenny Jones, Nick Leone and Suzen Poshek-Brancaccio.

Brad Margus presented event host Eric Weinberger with a plaque signed by children with A-T thanking him for all that he has done for the A-T Children's Project during the last 10 years.



Photos by Ginger Propper

Left clockwise: Senator Bill Bradley, Alton Fitzgerald White, Brad Margus, Priscilla Lopez, Louis Zorich, Olympia Dukakis, Eric Weinberger and Quinn Margus.

Drug Screening Assay for A-T *Continued from page 1*

for Neurodegeneration and Repair (HCNR). The HCNR has extensive experience screening for lead compounds that may prove therapeutic for Alzheimer's and/or Huntington's disease. Once Dr. Price and his colleagues successfully automate their cell-based assay for HTS, they will screen a library (drug collection) of approximately 60,000 compounds. The drugs in this library were chosen for their small size, low toxicity and chemical diversity. "By developing a screen for compounds which can bypass the requirement for ATM in neuronal differentiation," states Price, "we expect to identify compounds which can be used for the rational design of novel therapeutics to treat the neurodegeneration seen in [A-T] patients."

Godiva Raises Funds and Awareness for A-T



Suzi Kindregan and Brad Margus accept a check from Godiva at the A-T Children's Project "A Gift From the Heart" dinner dance in Boston.

A lucky party-of-eight won an Ebay auction to have dinner with Ben Affleck to celebrate the opening of the chocolate season and the introduction of a new line of Godiva truffles – raising over \$28,000 for the A-T Children's Project.

In an effort to help charities and introduce the new truffles, Godiva Chocolatier teamed up famous chefs, celebrities, and cities for fabulous dinners that were auctioned on Ebay, benefiting the charities of the celebrities' choices. Godiva brought together Ben Affleck, the city of Boston and chef Todd English with the Godiva Mojito truffle. Because of his long-time friendship with Joe Kindregan, who has A-T, Affleck selected the A-T Children's Project as a beneficiary of his dinner auction.

Rat Model for A-T

Continued from page 1

State University and Martin F. Lavin, PhD of The Queensland Institute of Medical Research in Australia, with funding from the A-T Children's Project, are working together to make another rodent model of A-T using the rat, which may possess neurological abnormalities similar to those seen in patients.

For years mice have been genetically manipulated in order to gain a better understanding of human disease. For example, researchers have added genes to the mouse's already existing genetic repertoire, creating so called "transgenic" mice, which produce an overabundance of a certain disease-related protein. In order to study what happens when a protein is missing, as is the case in A-T, scientists can alter or mutate a particular gene in the mouse such that it no longer makes its protein product. These mice are called "knock-out" mice. The A-T mouse is an example of a knock-out mouse because it cannot make the protein (Atm) missing in ataxia-telangiectasia. Unfortunately, the technology used to create knock-out mice does not work in rats. So, although the rat is often considered a more physiologically relevant experimental model for various human diseases, researchers have not been able to genetically manipulate it like the mouse.

In 2003, however, a group of scientists published a paper describing the generation of the first knock-out rats, which fail to produce important breast cancer associated proteins. Drs. Weil and Lavin will use the same technology described in this landmark paper to generate rats lacking Atm. The Atm deficient rats will be extensively studied. In addition to growth and lifespan, tumor incidence, immunological and reproductive function and radiosensitivity, neurological assessments will be made. These assessments will include examination of the cerebellum and certain behavioral tests to analyze motor function. The research performed by Weil and Lavin will hopefully produce an animal model which mimics the progressive neurodegeneration seen in humans, such that these animals can be used to study potential treatments for this devastating aspect of A-T.

Oxidative Stress Clinical Trial Update

Twenty patients with A-T have started the Oxidative Stress Clinical Trial at the A-T Clinical Center at Johns Hopkins Hospital, where in an effort to slow the death of brain cells associated with the disease, an antioxidant (alpha lipoic acid) and a PARP-1 inhibitor (nicotinamide) are being tested.

As of this printing, there are three spots open in the clinical trial. Limited funds are available to assist with travel expenses. Please contact Karen Rosquist, RN, A-T Clinical Center Coordinator for more information at 800-610-5691 or krosquis@jhmi.edu.



Scott Gover is evaluated at the A-T Clinical Center for participation in the Oxidative Stress Clinical Study.

Criteria for Participation in the Clinical Trial:

- Age 12 and older (during the initial phase to ensure safety with plans to include younger patients in the near future)
- Able to travel to Baltimore, Maryland monthly
- Able to swallow medicine capsules
- No nutritional supplements other than standard daily multivitamin taken within the previous 30 days
- No need for insulin or oral hypoglycemic agent
- No previous adverse reaction to alpha lipoic acid or nicotinamide

Preference will be given to patients who previously have been evaluated at the Johns Hopkins A-T Clinical Center.

One Parent's Perspective of the Clinical Trial

by Karen Knudson

From Diagnosis to Clinical Trial

When Brooke was first diagnosed in 1995, I saw Brad and Vicki Margus on a morning show talking about the discovery of the gene and the new A-T Clinical Center at Johns Hopkins. I scheduled Brooke right away for an evaluation, and she was the fifth patient to be seen at the clinic. During that visit, I decided that Brooke should have a legacy, and returning to the clinic to help with research would be a main part of her future. We have participated in as many studies as possible over the years, and with each year that passed, I knew that there would soon be drug trials such as this one.

Traveling to Baltimore

When Brooke was young, I would drive about 10 hours to get from our home in metro Detroit to the clinic in Baltimore. Now, we

always fly, which takes about 90 minutes. Travel is the most difficult part of participating in the trial because it takes a lot of planning regarding plane tickets and reserving the right seats.

Keeping Track of Medications

Brooke and I have to make sure that we get on a good schedule with the different drugs that she is taking. For the trial, she takes 12 pills during a waking day period. There is no diary to keep or specific times to take the pills. It's just important to stay organized.

Proud to Participate

Brooke, who is 14, feels good about helping to work toward a cure most days. Other times, she says she feels like a guinea pig. Overall, she is proud and feels like she is accomplishing something important.

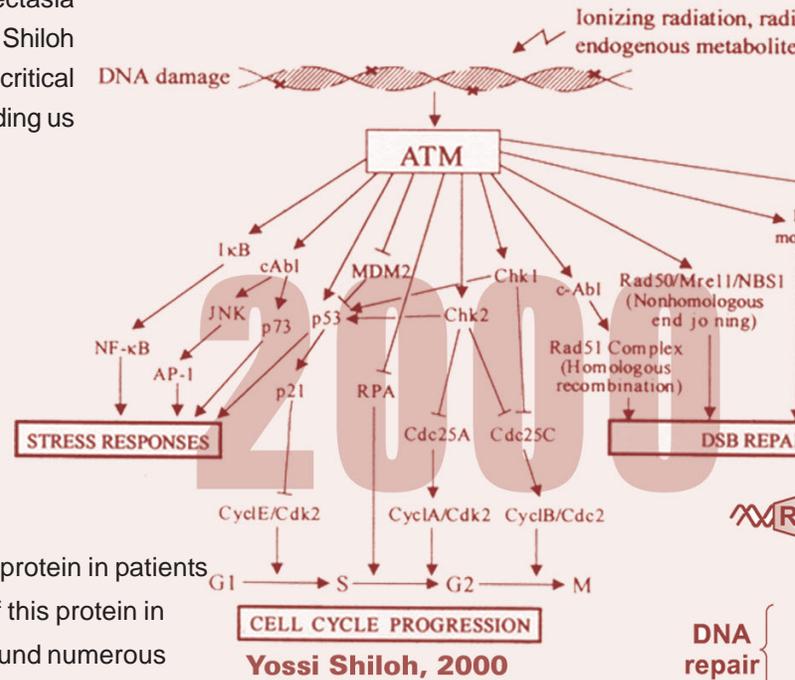
Important Research Advances Since

A-T is caused by mutations or alterations in the *ATM* (Ataxia-Telangiectasia Mutated) gene. This gene was discovered by the laboratory of Dr. Yossi Shiloh at Tel Aviv University in Israel. That discovery ten years ago has led to critical research advances that otherwise would not have been possible – leading us closer to a cure or life-improving therapies for A-T.

1995
ATM

DISCOVERY OF ATM TARGET PROTEINS

In order to find a therapy to compensate for the lack of the ATM protein in patients with A-T, it is important for researchers to understand the role of this protein in normal cells. Since the discovery of the gene, scientists have found numerous target proteins (or substrates) for ATM. ATM “talks” to these target proteins through chemical modifications and ultimately coordinates the cell’s response to a certain type of DNA damage called a double strand break. Because some ATM substrates play important roles in cancer development, A-T has also captured the interest of those scientists who perform cancer research. Examples of ATM substrates include the proteins: p53, NBS1, BRCA1 and FANCD2.



GENERATION OF ANIMAL MODELS FOR A-T

Because the gene that causes A-T was identified, researchers were able to successfully produce a mouse model and a fruit fly model for this disorder. These animal models are critical for A-T research as they enable researchers to test potential treatments before they are tried in patients.



DIAGNOSING A-T

The ability to sequence the complete ATM gene enables the definitive diagnosis of those patients who cannot be diagnosed solely by clinical and laboratory analysis.

OXIDATIVE STRESS IN A-T

Over the past several years, scientists studying ATM have accumulated evidence that oxidative stress is associated with ATM deficiency in cells and mice, as well as patients with A-T. This evidence has led researchers to believe that anti-oxidants could potentially become a life-improving therapy for patients with A-T.

ATM ACTIVATION FOLLOWING DNA DOUBLE STRAND BREAK

In normal cells, the ATM protein is activated to repair double strand breaks in DNA. In A-T, the DNA repair process is impaired, causing cellular sensitivity to certain DNA damaging agents, genomic instability and cancer susceptibility. In 2003, scientists began to uncover the mechanisms by which ATM is activated or “turned on” following DNA damage. These mechanisms involve: 1) the ‘intermolecular autophosphorylation’ of the ATM protein, wherein one ATM protein molecule chemically modifies another ATM protein

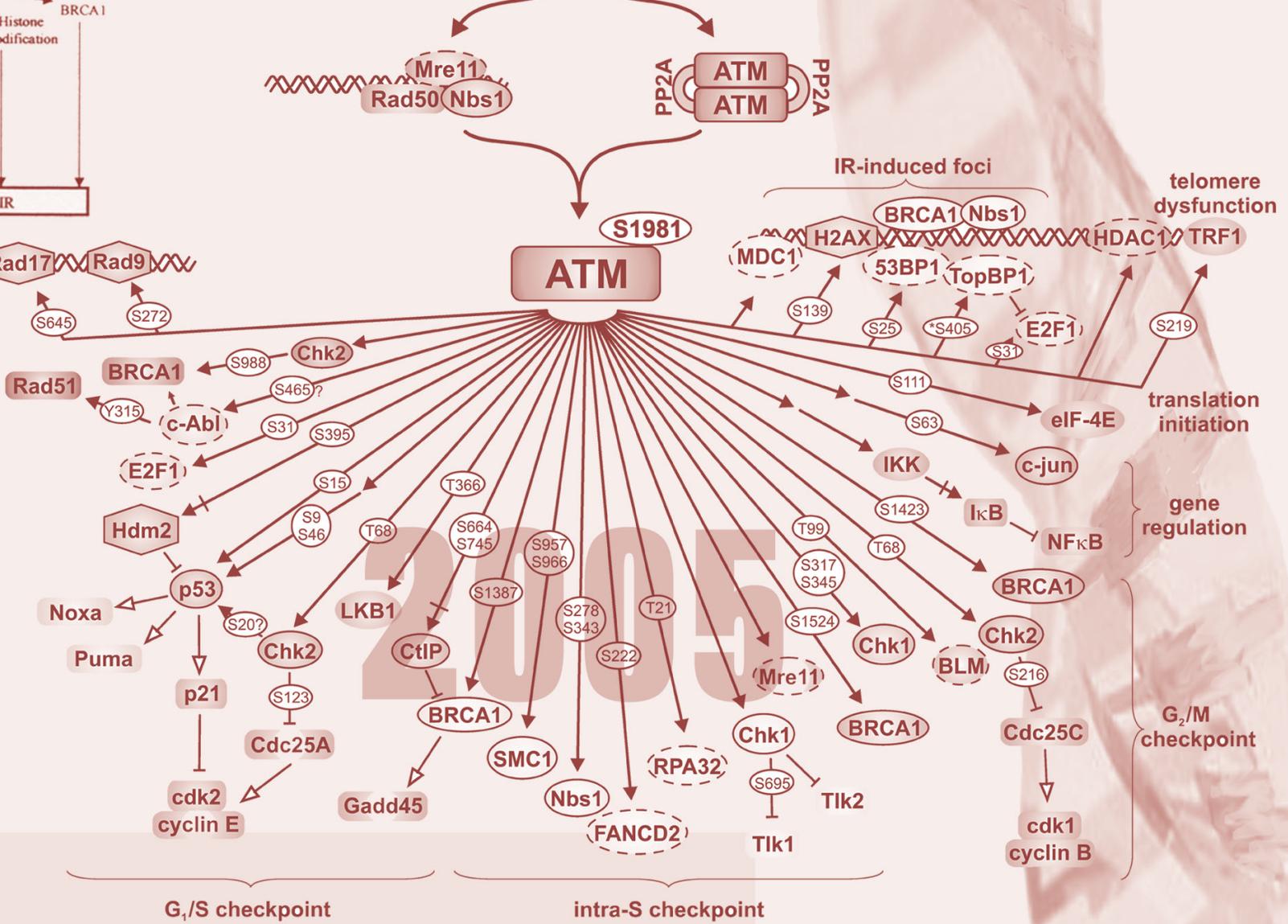
The Discovery of the Gene in 1995

radiomimetic chemicals,
topoisomerase II inhibitors

IR, ROS,
radiomimetics,
topo II poisons

alterations in
chromatin structure?

non DNA-damaging
agents?

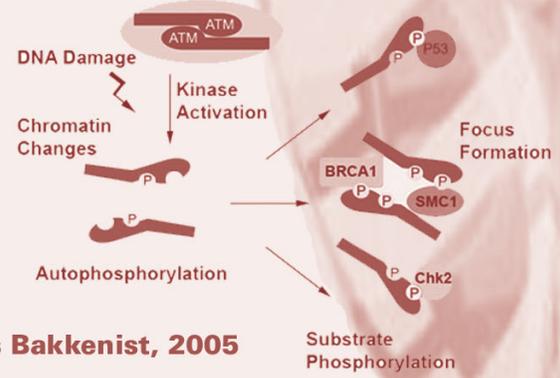


Ebba U. Kurz and Susan Lees-Miller, 2005

FACTS

Without
A
began
the ATM

molecule and 2) the MRN complex – a complex of three proteins which are also involved in the DNA repair process. Knowing how the ATM protein is activated may help reveal potential therapeutic interventions for A-T. In addition, cancer researchers are interested in finding ways of inhibiting ATM in cancer cells, making them more susceptible to DNA damage and death.



Chris Bakkenist, 2005

Washington and Hollywood Join Forces for A-T Research

At the third annual *Night out with the Stars* in Washington, DC on September 21, 2004, Washington and Hollywood friends joined forces to raise over \$268,000 for the A-T Children's Project. The 2004 Congressional Co-Chairs, Representatives Cal Dooley (CA) and Mike Oxley (OH),

were joined by co-hosts, actors Ben Affleck and Jennifer Garner. Billy Bush, co-anchor of television's *Access Hollywood* emceed the evening.

The reception was held on a rooftop terrace across the street from the U.S. Capitol. Affleck and Bush were the auctioneers for items that included a trip to the world premiere of the movie *Ocean's 12* and a *National Geographic* 10 day expedition to the Galapagos Islands donated by *National Geographic Expeditions* and longtime A-TCP friend Lynn Cutter.



Billy Bush interviews Ben Affleck for "Access Hollywood"



Representatives Calvin Dooley (CA) and Michael G. Oxley (OH) with actress Jennifer Garner

Shjon Podein, NHL's 2001 Humanitarian of the Year and 2001 Stanley Cup Winner, was honored for his foundation's continued support of A-T research when A-TCP President Brad Margus presented the *Shjon Podein Translational Research Award* to Dr. Howard Lederman, Director of the A-T Clinical Center at Johns Hopkins Hospital.

Also in attendance were Senators Tom Harkin (IA), Ben Nelson (NE), Don Nickles (OK) and John Sununu (NH). From the House side, Representatives Roy Blunt (MO), Henry Bonilla (TX), Eric Cantor (VA), Shelly Moore-Capito (WV), John Dingell (MI), Dave Hobson (OH), Jim Langevin (RI), John Shadegg (AZ), Ted Strickland (OH), Diane Watson (CA) and Anthony Weiner (NY) attended to show support for the A-T Children's Project.



the movie *Ocean's 12* and a *National Geographic* 10 day expedition to the Galapagos Islands donated by *National Geographic Expeditions* and longtime A-TCP friend Lynn Cutter.

International Conference on *The Clinical Science of Ataxia-Telangiectasia* held in Birmingham, UK

Physicians and scientists from around the world gathered in Birmingham, England in October, 2004 to discuss the clinical science of ataxia-telangiectasia (A-T) in hopes of discovering ways to improve the clinical management of A-T and thus the quality of life and length of life of patients with this disease. The conference was sponsored in part by the A-T Children's Project and was organized jointly by The Ataxia-Telangiectasia Society of the UK, the Division of Cancer Studies at the University of Birmingham and The A-T National Clinic at Nottingham City Hospital, UK.

Participants from Europe, the US and Australia first heard overviews of the various neurological and immunological aspects of A-T. Also, the relationship between A-T gene mutations, A-T protein/activity levels and the clinical presentation of the disease was discussed in general, and a study of the correlation between A-T gene mutations and clinical presentation was presented based on a cohort of Turkish patients with A-T.

Later, clinicians and researchers presented even more information about the underlying neurological and immunological defects associated with A-T. Importantly, A-T as a disease that not only affects the cerebellum but also other areas of the brain was discussed, as well as the possible mechanisms of cerebellar degeneration in this disorder. A special presentation on the eye

movement abnormalities associated with A-T was also given, and participants learned about different brain scanning technologies that can be used to study this disease.

With regards to the immunological abnormalities observed in A-T, a study of the immunodeficiencies and infections that occurred in a cohort of patients from the A-T Clinical Center at Johns Hopkins Hospital was presented. Of note, this study was recently published in *The Journal of Pediatrics*. Also of importance was a current review of the management of immune-related cancers (lymphomas and leukemias) which can occur in roughly 10-30% of patients with A-T.

Presentations were also given regarding pulmonary function and the age-related consequences associated with the progression of A-T. Other topics discussed at the conference included A-T like disorders, abnormal alpha-fetoprotein levels in A-T and A-T like disorders, and cancer risk in A-T carriers. The conference ended with a panel discussion entitled "Implications of the Clinical Science for the Management of A-T." During this discussion it was noted that the clinical problems associated with A-T are different depending upon the patient's age. In addition, questions were raised regarding the over 16 patient population. For example, should patients over 16 have annual clinical examinations and



From Left: Dr. Colin Dunkley, Dr. Susan Ritchie, Dr. Gabriel Chow, Dr. Liz McDermott, Dr. William Whitehouse and Dr. Nick Davies

should these patients receive preventative treatments with antibiotics and vaccines? The clinicians agreed that there is no one right answer. Due to the variation in disease presentation from one person to the next, an emphasis was made on taking the "individual approach" with each patient.

Maureen Poupard, Honorary Secretary for the A-T Society, commented that she "was very impressed by the enthusiasm and dedication of all the participants." Professor Malcolm Taylor of the University of Birmingham and Dr. Susan Ritchie of the UK's A-T National Clinic observed that "[the] feedback so far from many of the delegates has been excellent and new collaborations are being developed as a result. It is very likely that further meetings of this kind will take place in the future."

To download the meeting abstracts visit www.atsociety.org.uk/.

A-T Marathoners at WALT DISNEY WORLD® Marathon on January 9, 2005 raise over \$500,000



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A-T MARATHON
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Marathoners, families and friends celebrated at the Victory Party after helping raise over \$525,000 for A-T research. Over 250 marathoners participated in the WALT DISNEY WORLD® Marathon for the A-T Children's Project, giving our kids hope for a cure. And, marathon fever is spreading! Runners and walkers have already signed up to raise funds for A-T research while participating in the N. Olympic Discovery Marathon in Sequim, Washington on June 12, and in the Fort Collins Old Town Marathon in Colorado on May 8. The A-T Children's Project is an Associated Charity for the La Salle Bank Chicago Marathon, which will take place on Sunday, October 9.

Science News Featuring Ataxia-Telangiectasia

A “Hot Paper”

In July, 2004 Dr. Yosef Shiloh of the Tel Aviv University Sackler School of Medicine had his article entitled “ATM and related protein kinases: Safeguarding genome integrity,” which was published in the journal *Nature Reviews Cancer*, chosen as one of the most frequently cited papers in Clinical Medicine.

Thomson-ISIR’s Essential Science Indicators (ESI)-Special Topics* web site featured comments from Dr. Shiloh regarding his “hot” paper. The following is an excerpt of Dr. Shiloh’s comments from

<http://esi-topics.com/nhp/2004/july-04-YosefShiloh.htm>

Special Topics: Could you summarize the significance of your paper in layman’s terms?

Dr. Shiloh: Our genetic material, the DNA, which is contained in the nucleus of every cell of our body, is constantly under attack from physical and chemical agents that cause a variety of DNA lesions. While some of these agents are external, many are formed within the cell as by-products of normal metabolism. A sophisticated system has evolved to respond to these lesions—an intricate network that includes DNA repair machinery and numerous other stress responses that help the cell maintain metabolic equilibrium while its normal life cycle is temporarily halted to allow DNA repair to take place. Defects in this system lead to

severe genetic disorders involving tissue degeneration, sensitivity to specific damaging agents, genomic instability, and cancer predisposition. Furthermore, subtle defects in the DNA damage response probably underlie certain chronic diseases, cancer predisposition in the general population, and differences in the pace at which individuals age. Recent progress in our understanding of the DNA damage response has led to the discovery of many of the central players in this system. We now understand the chain of events that leads to instantaneous activation of the enormous cellular response to DNA lesions. This system is turning out to be a prime example of cellular signal transduction.

Special Topics: How did you become involved in this research?

Dr. Shiloh: My involvement in this field stems from my long-term interest in a devastating human genetic disorder called ataxia-telangiectasia (AT), an interest that began when I was a graduate student some 27 years ago and met a family with A-T. The striking phenotype of the patients led me to make the disease the subject of my Ph.D. thesis and I have remained in A-T research ever since. AT is caused by a defect in the cellular response to a specific type of DNA lesion—the double-strand break. This is the most critical DNA lesion caused by ionizing radiation. A-T patients suffer from neurodegeneration,

immunodeficiency, radiation sensitivity, genomic instability, and cancer predisposition. In 1995, our lab in Tel Aviv identified the defective gene that leads to A-T, and called it ATM (A-T, Mutated). We then shifted gears from molecular genetics to protein chemistry and began studying the ATM protein, the product of the ATM gene, in order to understand the physiological basis of A-T. Work in our lab and many other labs has elucidated the role of the ATM protein as the chief regulator and mobilizer of the cellular responses to DNA double-strand breaks. We now understand how one protein, ATM, can stir such a wide chain of reactions, sometimes in response to very few or even a single double-strand break in the DNA!

“ESI Special Topics spotlights New Hot Papers, Fast Breaking Papers, Emerging Research Fronts, and Fast Moving Fronts, all of which deal with current and emerging trends in specialized areas of research.” To learn more, please visit their web site at <http://esi-topics.com/>.

Oxidative Stress and the Immune System in A-T

In October, 2004 Dr. Toshio Suda of the Keio University School of Medicine in Tokyo, Japan and his colleagues were able to demonstrate that A-T mice greater than 6 months old suffer from progressive bone

marrow failure. Dr. Suda and his team found that this failure was the result of oxidative stress in those cells responsible for generating new blood cells, termed hematopoietic stem cells or HSCs. Oxidative stress occurs when cells produce an excess of reactive oxygen species (ROS) or free radicals, and/or they are unable to properly detoxify the ROS. Free radicals are harmful to cellular DNA, protein and lipids and can result in cell death.

Dr. Suda’s research, published in the prominent scientific journal *Nature*, contributes to the body of evidence suggesting that oxidative stress plays a role in the pathophysiology of A-T.

Overcoming a Subset of A-T Gene Mutations

In the November, 2004 issue of the scientific journal *Proceedings of the National Academy of Sciences, USA* Dr. Richard Gatti of the David Geffen School of Medicine at UCLA published a paper entitled “Correction of ATM gene function by aminoglycoside-induced read-through of premature termination codons.”

Approximately 14% of the patients with ataxia-telangiectasia possess alterations or mutations in their A-T gene called premature termination codons (PTCs). These mutations cause shortened forms of the A-T protein (ATM) to be produced which are highly unstable and readily degraded in the patients’ cells. The net result is that these individuals produce no functioning A-T protein. Dr. Gatti’s research team found that, in A-T cells possessing PTCs, the class of antibiotics known as aminoglycosides can cause the cellular machinery to “read-through” the PTCs and thus produce a certain amount of full length, functioning protein. As Dr. Gatti notes in his paper, “Because some A-T patients with 5-20% of normal levels of ATM protein show slower neurological progression, A-T may prove to be a good model for aminoglycoside-induced read-through therapy.”

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These three words encompass the mission of the A-T Children's Project. Through our grassroots efforts, we give families and **kids** living with ataxia-telangiectasia, the **hope** that all of our fundraising efforts to support scientific research will soon become the reality of a **cure**.



The A-T Children's Project is a public 501(c)(3) 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 fatal genetic disease that attacks children causing progressive loss of muscle control, cancer and immune system problems.



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