The Association for Frontotemporal Dementias

AFTD

*Opening the gateway to help and a cure*

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# Tell 10 People About FTD

## Campaign Galvanizes AFTD Families and Friends To Raise Funds and Awareness

In late September AFTD sent out more than 1,000 letters and emails, inviting FTD families and friends to help make November "Tell 10 People About FTD" month. The goal, says AFTD Executive Director Catherine Pace-Savitsky, was to generate new, fun ways for families to make a difference—and to raise funds for AFTD's ambitious new FTD Drug Discovery Program. She has been extremely pleased by the response.

"There are families and support groups across the country who clearly have wanted to do something, but didn't know how to direct their energy," she says. "As part of this larger campaign, they can design their own way to reach out to their immediate community—but at the same time feel a part of a nationwide effort to make a difference and be an advocate for FTD."

The variety of events is inspiring. Laura Michels, whose mother passed away in December, 2004 raised $1,000 from family and friends who sponsored her run in the Indianapolis Marathon. Tia Willin of Cape Coral Florida organized a "Hijack a Holiday" campaign: on Veterans Day friends and family spread throughout her community to educate people about FTD and solicit donations. Maryann Graham and her children are organizing a movie night at their school in suburban Philadelphia. In North Carolina, Paul Lester and his two children have mailed more than 400 letters to family and friends across the country. And Bill Brown, who belongs to the FTD Support Group in Dallas, is publishing a cookbook, which will contain more than 250 recipes from FTD families across the country. Profits from the cookbook (which you can order online from the AFTD website) will generate thousands of dollars for AFTD.

Both Lester and Brown have made the project a family affair by having their teenaged children play active roles in the fundraiser (in both families the wife/mother has been diagnosed with FTD). And both men state that, even just in the preliminary, planning stages, the project

*See Tell 10 People, page 6*

Inside This Issue



***Susan L-J Dickinson, MS***
***Newsletter Editor***

# Medical Advisory Council Update

## *Brad Boeve, MD, Chair*

In the spirit of keeping all interested patients, families, clinicians, and scientists abreast of progress along the research front in FTD, the following summary provides an update on some key new findings and emphasizes the importance of these findings for future drug therapy development.

First, a few words about terminology. Most experts now use the overarching term of "frontotemporal lobar degeneration" (FTLD) to represent all syndromes and disorders that relate to neurodegeneration of the frontal and/or temporal lobes of the brain. FTD, primary progressive aphasia (PPA), semantic dementia (SD), corticobasal syndrome (CBS), and other syndromes are the clinical labels used during life. The specific disorders which are well-known to cause FTLD are described below.

We have known for decades that dysfunction in the protein tau is involved in the generation of the neurofibrillary tangle – one of the pathologic hallmarks of Alzheimer's disease. Tau protein dysfunction is also involved

*See MAC Update, page 4*

Walt and Mary McKee met during their freshman year at the University of Maryland and were, as Walt says, "an item" for 52 years—including a marriage of 46 years—before Mary's death in 2004. In retrospect, Walt realizes that the symptoms of FTD (going to the store for a cake and returning with salad; having a one-car accident on a sunny day; getting lost in tall buildings) began nine years before Mary was diagnosed.

## *Spotlight On.....*

### *Walter McKee, AFTD Board member*

It took three visits to their general physician before Walt and Mary convinced him that there really was a problem, and the ensuing testing and appointments with neurologists resulted in the official diagnosis of Pick's—a disorder that neither of them had heard of before.

Walt had built a career as an engineer: first working with on fighter interceptor aircraft and later in satellite communications. "Not the kind of background to prepare for caregiving," he admits. "But we all find ways to do what seems necessary." He discovered AFTD as a valuable resource during those years; Walt especially feels he benefited from attending caregiver support group meetings and conferences, where he felt a strong connection with other caregivers who could truly understand each other's experiences and anguish.

Walt joined the AFTD Board in 2005, shortly after Mary's death. In addition to providing support to current caregivers, his main interest is to promote research to create effective treatments for FTD. He urges all afflicted families to enroll in clinical research studies and to seriously consider brain donation to help advance research. "We knew that Mary wouldn't benefit personally from participating in the extra battery of tests," he says. "But contributing to the store of knowledge so greatly needed did help to give some meaning to the bizarre journey that FTD forced upon us."

"I miss Mary," he says. "I miss reminiscing with her and together watching our wonderful family—five sons and 16 grandchildren—grow." But he is tremendously grateful for the support his family and friends provided during Mary's illness, and for the opportunity hopefully to lessen the burden for the next generation of FTD patients and caregivers.

## AFTD News

**AFTD thanks** outgoing Board members Fytie Drayton and Bob Kemp for their years of generous service, and welcomes new members Louise O'Connor and George Sidoris.

**New FTD caregiver support groups** have formed in Colorado Springs, CO, Charlotte, NC, Dallas, TX, and Sacramento, CA. Please visit the AFTD website for more details on meeting times and places.

**A new book** entitled "An Evolution of Love" by Marie Sykes and Michele Stafford is now available online at www.anevolutionoflove.com. This book, which is a tribute to Robert Sykes, their husband and father, provides support and inspiration to others who are coping with dementia and other irreversible illnesses. For each book sold, a donation will be made to AFTD.

**Drs Ian MacKenzie and Blair Leavitt** of the University of British Columbia, recipients of the 2006 AFTD Research Grant Award, have reported great success in developing a mouse model for TDP-43. A full update on the status of their research will be reported in the next newsletter.

*Board member Louise O'Connor will chair the new AFTD Advocacy Committee*

*Send us news of events in your area!*
*mmeyers@ftd-picks.org*

**Be an Advocate!** On October 7th, Senator Pete Domenici announced he will not seek reelection in 2008 due to his recent diagnosis with FTD. With the increased publicity FTD has received as a result of this announcement, now is the ideal time to write to your public officials to inform them of your own personal connection to FTD and to request their support for legislation that will increase funding and support for FTD research and programs. Watch the AFTD website for links to your legislators and template letters, to be posted this winter.

**Buy an FTD Cookbook**: Each copy contains hundreds of recipes from FTD families and friends, and all profits from sale of the $15 book will go to the FTD Drug Discovery Program.To place an order, follow the cookbook link on the AFTD home page www.ftd-picks.org.

**Please give generously** to AFTD's end-of-year fundraising appeal. See the enclosed letter for highlights of our accomplishments in 2007 and ambitious plans for 2008.

# *Caregiver Tip*: BrainGames

**Donna has found a way to re-connect with Marlyn, and to "give her a chance to shine"**

Marlyn and Donna, both retired educators, have been friends for a long time. When Marlyn was diagnosed with FTD in September, 2003, Donna tackled the problem as she would for a student who had trouble learning: she researched the disorder online and strategized ways to meet the problem head-on. The result? Something they call BrainGames, which has become the centerpiece of Marlyn and Donna's daily life during the past year.

A typical day for Donna and Marlyn includes two sessions of cognitive activities. During lunch they do a rhyming or a word-building game, multiplication flash cards, and a math or logic activity. The late afternoon session includes a picture crossword, sudoku, and an auditory game. Between sessions Marlyn does chores, writes in her journal and plays games on her computer.

"Marlyn was resistant to the BrainGames at first," Donna recalls. "Initially, it was frustrating for both of us. But as she began to have a few small successes, it ignited a spark. Now you see a special smile, and twinkle in her eye as she recognizes her progress. She's even gained enough confidence to teach friends how to play some of our games."

Although many games are available commercially, Donna has developed her own series of activities and tailored them to meet the cognitive deficits Marlyn experiences. When Marlyn developed problems recognizing friends and family, Donna created photo matching games, using pictures of the people in Marlyn's life. As Marlyn showed signs of having trouble identifying kitchen items and other common objects, Donna created a series of picture crosswords, each centered on a theme: kitchen, office, food, clothing, etc.

*Donna and Marlyn*

"During a recent appointment at the Mayo Clinic the doctor asked Marlyn to do a simple addition problem—and she couldn't do it," recalls Donna. "So we started doing flash cards every day at lunch, and we follow up later with a page of math problems." Donna reports that Marlyn is now able to multiply two-digit numbers, and has re-memorized her multiplication tables.

Donna keeps a record of Marlyn's performance each day, which charts her improvement on each type of game. Over the months the majority of problems have moved from the "failed" column, through the "correct with a hint" column, to simply "correct". And amazingly, Marlyn has now completed over 150 consecutive Sudoku puzzles without assistance and without error. But Donna reports that the benefits they both garner from BrainGames go far beyond a mere score.

The games provide a routine structure and a sense of purpose for each day. They have also brought the two women closer as friends. "I think we both derive comfort from the fact that we're a team as we battle FTD," says Donna. "We laugh together, and celebrate every little success. Some joy has returned to our lives—and that was definitely missing before."

Other changes that Donna attributes to these cognitive exercises include the fact that she and Marlyn seem to have more normal, less silly, conversations; Marlyn can complete chores (like setting the table or showering and dressing) on her own; and Donna observes an increased empathy in Marlyn, who inquires every day about Donna's back pain, and thanks her profusely for the help she provides.

Perhaps most important, Donna says, is the change she sees in Marlyn's confidence and self-esteem. "One of the cruelest things about this disease is that it builds a wall between her and the rest of the world. Out in public Marlyn tries desperately to connect with her surroundings and take part in ordinary conversations—these situations emphasize her disability and can be discouraging. But BrainGames are Marlyn's chance to shine, and they seem to give her more confidence to keep trying in all aspects of her life.

"I am determined that this disease is not going to beat us without a fight," Donna says. "We'll do everything we can to help preserve Marlyn as long as possible." *Donna is happy to share copies of her BrainGames with other caregivers: go to www. ftd-picks.org.*

## Donna's Tips for BrainGames

1. **Start slow and simple.** Pick a couple of activities to establish a routine.
2. **If the patient is resistant, pull out the prescription card.** Believing that the doctors had prescribed daily cognitive activities gave Marlyn the motivation she needed in the beginning.
3. **Reward even the smallest success.** Whoop, dance, hug—anything that will let them know they've accomplished something.
4. **Be patient.** You won't see progress every day. Stick with it.
5. **Be creative.** What works for Marlyn may not work for someone else. Adapt an activity, or create something new.
6. **Have fun.**

Photo Concentration
Hidden Pictures
Flash Cards
Word Search
Rhyme Time
Boggle

# 2007 Research Award

AFTD has awarded a $60,000 research grant to J. Paul Taylor, MD, PhD, an assistant professor at the University Of Pennsylvania School Of Medicine. Dr. Taylor will use the funds over the coming year to expand his cutting-edge work with a fruit fly model for TDP-43-related FTD.

The fruit fly is a useful system for the study of neurodegenerative diseases like FTD because the fruit fly's brain is structurally similar to that of humans, it displays complex behavior like learning and memory, and its lifespan averages just two months (a mouse, in contrast, has a lifespan of 3 years)

"Our research committee was very pleased with both the number and quality of applications we had for this year's award," says AFTD Medical Advisory Committee Chair Brad Boeve, MD. "The grant process gets more competitive each year—a hopeful sign that FTD is attracting more attention in research labs across the country."

AFTD began awarding research grants in the fall of 2005; thus far, the Association has awarded a total of $145,000 to stimulate programs investigating the causes and characteristics of FTD.

*Paul Taylor, MD, PhD*

## MAC Update *from page 1*

in the generation of the following disorders which are considered collectively as the "tauopathies."

**The "Tauopathies"**

- **Pick's disease** – the Pick bodies characteristic of the disease are comprised of abnormal tau protein
- **Corticobasal degeneration** (CBD) – the oligodendroglial coiled bodies, astrocytic plaques, and neuronal threads characteristic of the disease are comprised of abnormal tau protein
- **Progressive supranuclear palsy** (PSP) – the globose neurofibrillary tangles, tufted astrocytes, coiled bodies, astrocytic plaques, and threads characteristic of the disease are comprised of abnormal tau protein
- **Argyrophilic grain disease** (AGD) – the argyrophilic grains are comprised of abnormal tau protein
- **Multisystem tauopathy** (MST) – the inclusions of MST are comprised of abnormal tau protein
- **Frontotemporal dementia and parkinsonism linked to chromosome 17 due to mutations in the microtubule associated protein tau** (FTDP-17*MAPT*) – the inclusions are comprised of abnormal tau protein
- **Alzheimer's disease**

Since the neurofibrillary tangles of Alzheimer's disease represent abnormal accumulations of tau protein, Alzheimer's disease is also considered a form of tauopathy, although most experts feel that abnormal amyloid pathophysiology is driving the disease more than abnormal tau. Debate continues on this issue.

A major discovery occurred in the mid-1990s (published in 1998), when mutations in the tau gene located on chromosome 17 were identified by teams of researchers led by Drs. Mike Hutton of Mayo Clinic Jacksonville, Corrine Lendon of Washington University, and Patricia Rizzu of Erasmus University Rotterdam (in the scientific literature, this gene is often referred to as "microtubule associated protein tau" and abbreviated "*MAPT*"). Transgenic mouse models were developed soon thereafter, and numerous medications have and continue to be studied in the so-called "tau mice."

***Ascertaining whether a person has a tau-related disorder or a TDP-43-related disorder...may be the most important issue in determining which therapy is most likely to help each patient.***

A quandary that lasted about ten years was solved in April of 2006, and then published in July of 2006, when another major discovery in the FTD field was announced. Numerous patients and their relatives with familial frontotemporal dementia +/- parkinsonism had been "linked" to chromosome 17, but no mutations had been found in tau, nor did they have any tau-positive pathology when brain tissue was examined post-mortem. Teams of researchers led by Dr. Mike Hutton again of Mayo Clinic Jacksonville and Dr. Ian Mackenzie of University of British Columbia, Vancouver, Canada identified mutations in the gene encoding progranulin (*PGRN*) as causing FTDP, and more mutations were immediately discovered by the team led by Christine Van Broeckhoven at the University of Antwerp, Belgium. The characteristic findings at autopsy in these affected individuals were those of the pathologic entity known as frontotemporal lobar degeneration with ubiquitin-positive inclusions (abbreviated "FTLD-U"). An unlikely and startling coincidence was therefore realized – two genes, which when mutated cause amazingly similar symptoms during life, happen to reside extremely close to each other on the human DNA roadmap.

**TDP-43**

Yet a critical point was still not known – what was the dysfunctional protein that

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*AFTD is grateful for these gifts, which fund research, information and support*

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was involved in neurodegeneration? The "U" of "FTLD-U" refers to ubiquitin, which as its name implies, is a ubiquitous protein – it is not specific for any one pathophysiologic process. Researchers had been searching for many years for the protein that has specifically gone awry in FTLD-U, and this issue was solved by the team led by Drs. Virginia M-Y Lee and John Trojanowski at the University of Pennsylvania, when they announced and published in September 2006 the identification of TAR DNA binding protein-43 (TDP-43) as the critical protein. This protein is not only critical in FTLD-U, but also in amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease). More recent research has revealed that TDP-43 is involved in the following disorders, which some experts consider collectively as "TDP-43opathies."

## The "TDP-43opathies"

- **Frontotemporal lobar degeneration with ubiquitin/TDP-43-positive inclusions** (FTLD-U/TDP-43)
- **FTLD with motor neuron disease** (FTLD-MND)
- **Hippocampal sclerosis** (HS)
- **Amyotrophic lateral sclerosis** (ALS)
- **Frontotemporal dementia with parkinsonism linked to chromosome 17 due to mutations in the gene encoding progranulin** (FTDP-17*PGRN*)

While the lists of tauopathy and TDP-43opathy disorders are long, and many of the disorders may be difficult to pronounce, the key point is this—the vast majority of (though not all) patients who have an FTD-spectrum disorder have an underlying "tauopathy" or "TDP-43opathy."

Another related point should be emphasized. Clinicians have classically attempted to identify which specific disorder is causing a particular patient's symptoms with as much certainty as possible. But, as we learn more about the critical proteins – particularly tau and TDP-43 – it may actually be more important to determine which of these two dysfunctional proteins is causing a person's symptoms as opposed to the specific disorder. In other words, determining whether a person has a tau-related disorder or a TDP-43-related disorder, rather than which one of the dozen of specific disorders, may be the most important issue in order to determine which therapy is most likely to help each patient.

## Research Continues

The progranulin and TDP-43 discoveries have already had major impacts in FTD and ALS research. Research in the "test tube" has been encouraging, and animal models of progranulin/TDP-43 – related neurodegeneration are being developed. AFTD just announced the awarding of the 2007 Research Award to Dr. Paul Taylor at Penn for continuing his work in the fruit fly model of TDP-43 neurodegeneration. Drugs will soon be tested in the mouse, fruit fly, and other animal models to search for agents that may impact the disease. The National Institute of Neurologic Diseases and Stroke (NINDS) and National Institute on Aging (NIA) continue their support for funding FTD-related research, and both institutes are organizing a symposium in February of 2008 which will bring together leaders from neurology, neurodegeneration, neurogenetics, wound repair/inflammation, cancer, and other fields to share knowledge in the TDP-43 field. This will be a first such meeting of its kind.

## Looking to the Future

There is still an enormous amount of work ahead. Mutations in tau and progranulin only explain a minority of patients with familial FTD – there are clearly more genes out there For instance, there is evidence that a gene that resides on chromosome 9 may represent a critical piece of the puzzle in TDP-43-related neurodegeneration. As we find more of the genes involved in neurodegeneration, and then understand the complex interplay between these genes and the proteins they encode, we can then rigorously test various drugs for their impact on FTLD patients.

*In the next research update, Dr. Boeve will discuss drug discovery and development for FTLD in more detail.*

## Tell 10 People

*from page 1*

has brought their families a tremendous amount of community support. "My son's high school hockey team, my daughter's Junior Honor Society, even the elementary school PTA—everyone wants to help," says Brown.

"Sometimes I wonder what people will think when they read of Arnette's diagnosis," admits Lester. "But then I think: what does it matter? This is a family deal. We have to live through it together, and it feels better to be doing something about it."

The money raised from these events will go to fund the new FTD Drug Discovery program—a venture to which AFTD has pledged $100,000 for each of the next three years. AFTD's partner in this program, the Alzheimer's Drug Discovery Foundation, is matching every AFTD dollar 2:1, as well as paying all administrative costs. So every dollar raised by these families produces a total of $3 for FTD drug discovery—an impressive incentive that is helping to fuel donations.

"The response has been amazing," says Helen-Ann Comstock, Chair of AFTD. "Every new donor brings us closer to an effective treatment and also brings one more person who understands and cares about FTD. For a rare disorder, that is very important and very heartening."

"No effort is too small," says Pace-Savitsky. "Our community may be scattered across all 50 states and beyond, but it is still a vibrant and caring one. I encourage everyone to get engaged. I think we will all be amazed at what we can accomplish together."

*Interested in hosting your own "Tell 10 People" event? November may be over, but the campaign continues! On the AFTD homepage (www.ftd-picks.org) click on the campaign town crier mascot to link to a whole host of supporting materials: a list of a wide variety of event ideas—from gourmet dinners to poker tournaments; templates for letter-writing campaigns and event invitations; and a 2-page handout that provides basic information about FTD and AFTD. Call the AFTD office to discuss your idea, and AFTD will be happy to mail you brochures and donation envelopes free of charge.*

*The Lester Family, on vacation in Hawaii this summer.*

## Update on Drug Discovery Program

Twenty research proposals have been submitted by investigators for the first round of funding under the FTD Drug Discovery Program. The review committee, consisting of leading scientists and clinicians from various fields of drug discovery expertise will meet in late November to review the applications. The first round of awards recipients will be announced early in 2008.

## Matching Gifts: Double Your Donation

Wouldn't it be great if, for every dollar you give, AFTD received two? If your employer has a Matching Gift Program, you can make that happen! Many larger companies will have a program already set up: you should be able to pick up a form from your Human Resources office. They will require proof of your gift (a copy of your check) and of AFTD's status as a non-profit organization (contact the AFTD office if you need a copy of our IRS designation letter). But even if your employer does not have an established program, tell them they need to start one! Companies of all sizes have found that matching gift programs are a great way to support their employees and the community organizations that are most important to them.

**AFTD**

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