

ALS Alert

A NEWSLETTER FROM THE ROBERT PACKARD CENTER FOR ALS RESEARCH AT JOHNS HOPKINS

www.alscenter.org

- 2 Due Recognition
- 3 Old Drug, New News
- 4 From Broadway to Packard

Spring 2009

Vantage Point

In the end, what defeats ALS will probably come from putting ego in the right place.

You want scientists with some ego, to be a little competitive. That gives a push. It encourages focus and helps ride out research's tedious stretches. But those same scientists must be able to damp down ego when the only way to speed up ALS therapy means relying a lot on others. We don't deny that there's self-interest; we know that sharing helps our own research! But the good results are the same.

As for any organization that brings scientists together—and we know of one—there's no room at all for swagger.

This issue of *Alert* reflects all that.

Catherina Becker, for example, (opposite) brought her research skills from her native Germany to Scotland, where, at the University of Edinburgh, she's made her lab a stronghold on zebrafish nervous system development and repair. That takes a certain confidence. But in the few months she's been a Packard scientist, she's shared her unpublished progress, as her first talk at our annual symposium told us clearly. At the same time, she's able to pick the scientific equivalent of low-hanging fruit that the Center offers.

Our page three shows how Packard as a whole works with this country's ALS research community. After we first suggested that glutamate could kill motor neurons and then later explained how, the glutamate pathway became a target for potential drug therapy. And that led to Packard scientists sharing expertise with NEALS, a national group bent on making ALS clinical trials better. Our ties with NEALS are strong. Our sitting at their planning table makes everybody's trials stronger, including those at Hopkins.

The more therapy comes into view, the more determined our efforts become. That, in turn, makes us the easiest-to-work-with ALS organization we know.

Jeffrey D. Rothstein
Jeffrey D. Rothstein
Director

Piera Pasinelli
Piera Pasinelli
Scientific Director

The Robert Packard Center for
ALS Research at Johns Hopkins



A "terribly pleased" Catherina Becker finds herself the Packard Center's first joint grantee with Scotland's Euan MacDonald Centre for Motor Neurone Disease Research. The union adds clout to research on spinal cord repair.

Fishing for a Good Way to Heal

Oh, to be a zebrafish. The adult animals can take a blow to their miniature spinal cords that would paralyze a human forever. But within six weeks you'd never know anything had happened to them. "They're the pros," says newest Packard grantee **Catherina Becker**. "Clearly, they can do something we cannot but want to be able to do."

At last month's ninth annual Packard symposium in Baltimore, not an eye strayed from Becker's video of zebrafish before-and-afters. Researchers' questions tumbled out at the end of her talk—also a good sign.

Becker was tapped by Packard because hers is some of the most progressive research anywhere on nervous system regeneration. Having found this incredible trick in zebrafish—she's documented their motor neuron replacement—she's now proving the animals' worth as models of recovery.

"They should also help us greatly in testing ALS therapy," she adds.

Becker's fish studies started some 12 years ago, first by exploring the particulars of their nervous systems and how they develop. What appears when? What role do stem cells play? That, in turn, has prompted her work at the University of Edinburgh on spinal repair—with its focus on motor neurons—and understanding the underlying chemical pathways.

Meanwhile, Becker's also searching for small, potent agents that can turn on the neural stem cells that mend

the fish. Her biggest tool here is an easy, low-cost screening system she devised, one that works because zebrafish embryos are clear as glass.

When the hangnail-size embryos are the right age, at just over two days old, a lab tech slips a plastic plate with a grid of small depressions under the stereomicroscope. Each depression holds about 20 embryos. In some 10 percent of the fish, motor neurons start to clock in as a greenish stripe down the back. Six hours later, however,

90 percent show motor neuron stripes. "So we have this system that can quickly tell us if what we're testing speeds up or slows down the motor neuron process," says Becker. So far, she's identified compounds that do one or the other and apparently do it well.

The discoveries move the work closer to the therapy-exploring pipeline.

An especially bright spot, Becker says, is that spinal cord repair in zebrafish takes place seamlessly in fully adult fish. Molecular studies by her lab team show that the animals are turning on embryonic pathways shut off in adulthood. What remains is to see if repair still holds for ALS. "It's not enough," she confirms, "that zebrafish are vertebrates. We need to see if the repair process that works so well in cut fish spinal cords applies to the complex changes in ALS."

Work with Packard colleague Linda Greensmith in London on mammal models closer to the disease are under way, an optimistic Becker says. ■

"So we have this system that can quickly tell us if what we're testing speeds up or slows down the motor neuron process."

Philanthropy Partners

What a celebration! More than 100 guests gathered on April 1 for our annual Partners in Collaboration reception and awards presentation, held this year at the Marriott Inner Harbor Camden Yards hotel in Baltimore.

Packard Center supporters, scientists, patients, volunteers, clinicians, event planners, and staff were on hand to honor some very special friends of the Packard Center: Mid-Atlantic Waterproofing, Bully Entertainment, Bruce Thompson, and Charlotte Hetterick.

Mid-Atlantic Waterproofing, the nation's largest privately owned waterproofing organization, received the award for designating the Center as its charity of choice last year. For every waterproofing contract signed during a set 60-day period in 2008, Mid-Atlantic donated a portion to the Center's research program.

Bully Entertainment, a commercial and entertainment media production firm in Federal Hill, was honored for its creative contributions to the Fiesta 5K. Carlson

Bull, one of the firm's principals, was recruited to help design materials for the inaugural race two years ago. He and his team created Pepper Pete, the Fiesta 5K's colorful mascot, as well as TV spots and print pieces that continue to promote what has become a signature fundraiser for the Center.

Bruce Thompson, a well-known developer in the Virginia Beach area, was recognized for all that he and his family contributed to the ALS Association's Walk to Defeat ALS event in Virginia Beach last fall. The JT Walk Team—3,600-plus members strong—was formed to honor Thompson's son Josh, diagnosed with ALS at the age of 33. Not only was the JT Walk Team the largest group of its kind, but it also raised a record-breaking \$575,000, 40 percent of which Thompson designated for the Center.

Before announcing the Volunteer

of the Year, Packard Center Director Jeffrey Rothstein spoke on the importance of personal philanthropy. "The selflessness of the philanthropist is the same as that found in the volunteer," he stated. "The philanthropist supplies the resources; the volunteer supplies the heart—and often the philanthropist and the volunteer are one and the same person."

Such is the case with the 2009 Packard Center Volunteer of the

Year Charlotte Hetterick, fitness instructor and owner of Interactive Fitness in Timonium. She became involved with the Center after her close friend Eric Navarro was diagnosed with ALS. Hetterick organized her own fundraisers and threw her full support behind the inaugural Fiesta 5K. Passionate about fitness and finding a cure for ALS, she continues to secure all levels of support for the annual race and the Center. ■



Proud partners: From left, volunteer extraordinaire Charlotte Hetterick, Mid-Atlantic Waterproofing exec Ed Fennell, Center Director Jeffrey Rothstein, Scientific Director Piera Pasinelli, and Virginia Beach Walk gurus Chris Thompson and Kathy Thompson, both representing Bruce Thompson.

Fiesta 5K: This Year a Record-Breaker

Our third annual Fiesta 5K and Fun Run, held on May 2 in Baltimore, set some joy-making new records, thanks to our dedicated supporters and volunteers. The event attracted more than 1,400 participants—a 70 percent increase from 2008. To date, we've raised more than \$183,000, far surpassing our \$150,000 goal.

Special thanks to this year's honorary chair, O.J. Brigance, director of player development for the Baltimore Ravens. The former Ravens linebacker returned for his second year as chair, accompanied by more than 150 members of the Baltimore Ravens organization. The Brigance Brigade, which included head coach John Harbaugh and safety Ed Reed, was our largest running team this year.

Bouchelle and Friends, organized by the daughter of ALS patient William Bouchelle, M.D., of Baltimore, raised the most money, bringing in more than \$30,000. "Our family friends are always asking, *What can we do?* Forming a team gave people the chance to really lend their support," says Zoe Bouchelle. "To see my dad out there that morning, surrounded by so many people who love him so very much, was such a gift. We can't wait for next year!"

Thank you, Sponsors!

PLATINUM

AEGON
Baltimore Ravens
Packard Center for ALS Research

GOLD

Bully! Entertainment
The Saer Family
98 Rock
My 24 WUTB-TV Baltimore
WBAL-TV Baltimore
WBAL AM 1090
Baltimore Smart CEO magazine
McCormick & Company Inc.
Powerade

SILVER

Fandango
One Rock Studio
Pride Mobility

BRONZE

Anonymous (2)
Jeremiah A. Barondess, M.D.
Jay Brodie – In memory of
Georgene Gonzoles Brodie
InAppreciation Corporate Gifts
Richard E. McCready
Ridge Printing Corporation
Yuhus Consulting Group LLC



Save the Date for Next Year's 5K:
Saturday, May 1, 2010!

Going to the Principle

A new look at old data surprises all.



“Pulling something new from topiramate data is exactly why we make results available long after a study’s finished,” says Cudkowicz. “It’s good science.”

The trial looked like a failure and that was that.” When Center director **Jeff Rothstein** saw the results of the first ALS clinical trial of the drug topiramate a decade ago, disappointment crossed his face. No matter how preliminary a therapy study is, there’s a feeling—not always rational—that some benefit will surface like so much cream rising to the top.

But not this time. Things had looked good. Topiramate was picked for a trial enrolling some 300 ALS patients because the drug likely blocks a specific glutamate receptor, keeping a toxic flood of the neurotransmitter from binding to vulnerable motor neurons. Clinicians have used topiramate for epilepsy because it acts on those receptors in the brain.

Also, the trial itself was under the auspices of the Northeast ALS Consortium (NEALS), a body of university clinician-scientists who run high-quality ALS clinical research nationwide. (The Packard Center helps support NEALS with expertise and funding.)

Unfortunately, says **Merit Cudkowicz**, NEALS’ co-director, subjects given topiramate lost more weight than those on a placebo. “And though the drug showed no effect on survival or breathing ability,” she adds, “those taking it

also lost arm strength more quickly.”

“Simply having a bad side effect like weight loss ended further consideration,” says Rothstein. And as important, the overall result cast doubts on the rationale behind the drug’s use. Though they didn’t abandon it, scientists weren’t flocking to test glutamate-receptor blockers.

Recently, though, Cudkowicz was asked to take a second look at the old study. (Any researcher can access NEALS trial data. It’s purged of patient identifiers.) Could weight loss—not topiramate—underlie the faster muscle

Could weight loss—not topiramate—underlie the faster muscle weakening?

weakening? Cudkowicz’s team began a more sophisticated analysis of the numbers than previously possible.

The results made them blink: Compared with those on the placebo who’d lost the same amount of weight, those on topiramate had a 25 percent longer (median) survival.

The caution in interpreting this, however, is real, say Cudkowicz and Rothstein. The study is preliminary and needs the review of other scientists that comes with publishing.

“This doesn’t necessarily prove topiramate is a good therapy for ALS,” says Rothstein, “but it does bring drugs that work on certain glutamate receptors back into the picture.”

The analysis to settle what *did* cause the weight loss has just finished. An explanation should appear soon. ■

The Latest on Trials

Packard added a daylong session to its annual symposium this year—an update on clinical trials. Here’s the latest on three drugs in the therapy pipeline that the Northeast ALS Consortium has dubbed especially worth watching:

- Eyed by researchers for being at the top of a massive drug screening in 2004, the antibiotic **ceftriaxone** increases cells’ ability to mop up a toxic excess of the molecule glutamate. In ALS mice, ceftriaxone delays loss of grip and increases survival. Recent human trials have taken a streamlined turn, with the study that tells how the body processes the drug atypically moving right into one to see if it’s safe and tolerable. Now completed, the trials clear the way for an upcoming larger one to see if ceftriaxone is useful therapy.



- **Talampanel** is a benzodiazepine (same family as Valium) that shows benefits in animal models of epilepsy and brain inflammation. Researchers think its action could be useful in ALS—it can tie up vulnerable (AMPA) glutamate receptors and perhaps shield neurons from toxic overstimulation. A small, earlier human trial at one dosage showed that talampanel

slowed the drop in scores on the traditional functional tests of ALS patients by nearly a third. A new year-long, worldwide pharma-sponsored study of 540 subjects has just begun. It’s a phase III trial, one that looks for any slowing in disease progress.

- When a 2008 journal article described a clinical trial testing **lithium** as an ALS drug, excitement ran high. Benefits were clear, the researchers in Italy said, with some patients surviving longer. The find surprised scientists worldwide, though; lithium wasn’t in the ALS pipeline. Because such a positive study demands duplicating, designers of a new, novel clinical trial run by NEALS and its Canadian counterpart are enrolling selected patients at 37 sites. It’s an unusual safety and efficacy trial—that’s because of a proviso for switching those in the placebo (control) group to lithium. ■

Variations on a Theme

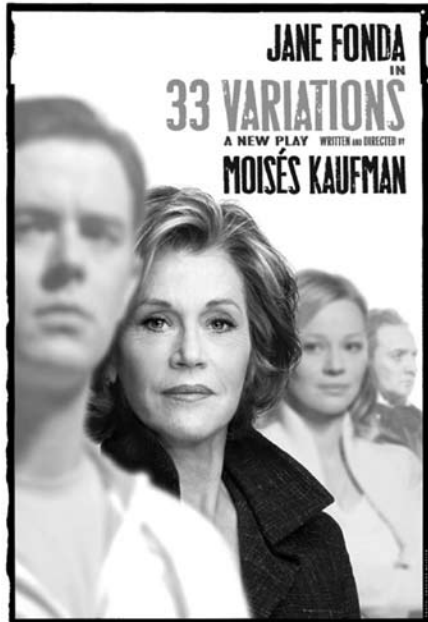
When Liz Angell Brand set out to connect the dots between Broadway and Baltimore last fall, she knew the producer of *33 Variations*, a Broadway play starring Jane Fonda as a woman battling ALS. Brand also knew, as an insider, how vital special events are to keep Packard Center research going. What she hadn't figured out was how best to link the two.

Brand's own life mixes New York savvy and Packard service. She's a busy senior editor at *Allure* magazine in Manhattan, but as the daughter of Center board members Chris and Jean Angell, she's been active in fundraising for ALS research.

So when she e-mailed Emily Eehalt on Packard's development team, a plan began to take shape. "When someone has an idea and just needs steps filled in," Eehalt explains, "we're here to help."

The two women worked closely for the next several months on everything from invitations to catering. Then, on April 8: show time! Roughly 100 guests arrived at the Century Association in New York City for an elegant cocktail reception hosted by Brand and her parents, along with Packard Center board member John Saer and wife Shelby.

After mingling with Center supporters and staff, guests took their seats at the Eugene O'Neill Theater to see Fonda's compelling performance in a play spangled with five Tony Award nominations this May. The event raised more than \$45,000 for the Packard Center's ALS research. ■



Liz Angell Brand's bridge from Baltimore to Broadway makes a cure more sure.

Good Man in the Middle

Thornley Hart and William Adams, rising professionals in the pre-boom financial industry of the mid-1970s, became fast friends when first introduced. Their business acumen and common background—both were University of North Carolina Tarheels—were the initial glue. Then 30-plus years of joint family gatherings became the cement, despite the distance between their East and West Coast addresses.

After Adams was diagnosed with ALS in 2007, he asked Hart to join the board of the newly established William H. Adams Foundation for ALS Research. Hart, willing to do whatever he could to help his friend, travelled to California for the foundation's first meeting. There he met Packard Center Director Jeffrey Rothstein.

Soon there was talk of Hart becoming a coast-to-coast liaison between the foundation and the Packard Center, whose research the foundation strongly supports. It was a role Hart didn't hesitate to accept. Now, as the only person who sits on the board of both the Packard Center and the Adams Foundation, he is a pivotal tie between the two entities.

Having joined the Packard Center board in March, Hart has already learned a great deal about ALS and the caliber and commitment of the Packard Center team. "What impresses me is the number of people on the board who are affected firsthand by ALS, starting with Chris Angell—one terrific, inspirational guy," Hart comments.



Thornley Hart: Friendship triggered activism.

"Everyone's touched by ALS, and I feel like it's my role to get out there and educate people. If we can help with ALS, then we can help with Alzheimer's, muscular dystrophy, any neurological disease," he says. "I don't have unlimited funds. I just want to try to raise people's awareness and contribute where I can, mostly with my time."

Born in New York City, Hart grew up in Cedarhurst, Long Island. After graduating from UNC, he was drafted into the Army and stationed at the Chaplain School for two years. Following in the footsteps of his father, an investment advisor at Fahnestock & Co. in New York, Hart spent more than a decade with the firm, working out of offices in New York and London. He joined Legg Mason in Baltimore in 1988 and since 2006 has been with the Baltimore office of Smith Barney, where he now serves as first vice president for wealth management. Hart lives in Owings Mills, Md., with his wife and 17-year-old son. ■

We're Going Green

With a nod to conservation, this is our penultimate hard-copy newsletter. After the October *ALS Alert* goes out, we'll publicize our news exclusively on our Web site, alscenter.org. To ensure that you stay in the loop, please visit our site and enter your current e-mail address in the "STAY INFORMED!" column on the bottom right side of the home page, below the press release listings.

ALSAlert

The Robert Packard Center for ALS Research at Johns Hopkins
5801 Smith Ave., McAuley Suite 110
Baltimore, MD 21209
410-735-7677/FAX 410-735-7680
www.alscenter.org; E-mail: alscenter@jhmi.edu

This newsletter is published for the The Robert Packard Center for ALS Research at Johns Hopkins by Johns Hopkins Medicine Marketing and Communications. It is distributed to the scientific community, patients and friends of the Center.

Some of the research in this newsletter has corporate ties. For full disclosure information, call the Office of Policy Coordination at 410-516-5560.

© 2009 The Johns Hopkins University and The Johns Hopkins Health System Corporation.

Jeffrey D. Rothstein, M.D., Ph.D.

Director, The Robert Packard Center for ALS Research
The Johns Hopkins University School of Medicine

Marketing and Communications

Dalal Haldeman, Ph.D., Vice President; Patrick Gilbert, Director of Editorial Services;
Judith Minkove, Features Editor/Writer and Managing Editor; Marjorie Centofanti,
Science Editor/Writer; Marlene England, Guest Writer; Max Boam, Designer;
Rich Riggins, Photography
Editorial Office: 901 S. Bond Street, Suite 550, Baltimore, MD 21231

Non-Profit Org
U.S. Postage
PAID
Permit No. 5415
Baltimore, MD