



New Insights Into the Blood-Brain Barrier

by David Shenk

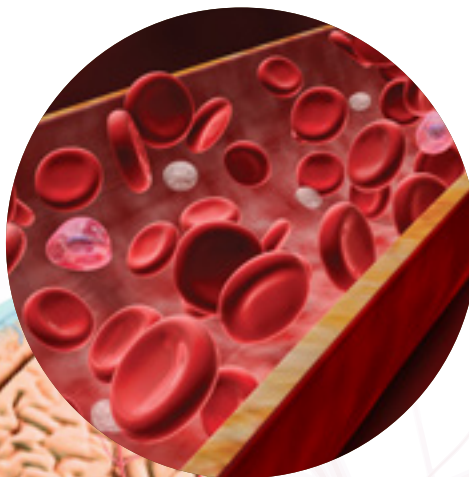
Three recent discoveries by University of Southern California neuroscientist Berislav Zlokovic, M.D., Ph.D., have clarified one of the least-understood elements of Alzheimer's disease: how the blood-brain barrier becomes compromised and contributes to the disease process.

In healthy individuals, the blood-brain barrier (BBB) is a fine mesh filter that transports only select molecules from the body's main circulatory system into the brain in a highly controlled manner, protecting the more delicate brain from a variety of dangers, and transports certain molecules back out of the brain as well. Changes to the structural components of the BBB have been known to be a normal consequence of aging for decades, but it also has been known for many years that the BBBs of Alzheimer's patients allow more harmful particles to cross into the brain than the BBBs of those without the disease do.

Precisely when and how, though, does the BBB become compromised, and does it happen as a prelude to Alzheimer's or as a cause of it? These are essential questions. Alzheimer's unfolds as a complex cascade of molecular events—one event leads to another, which leads to another, and so on. The effort to stop it rests on understanding all of the key cascade events in the correct sequence—a monumental challenge requiring a coordinated team effort.

The discoveries by Zlokovic—director of the Zilkha Neurogenetic Institute and professor and chair of the Department of Physiology

continued on page 3 »



INSIDE THIS REPORT

New Insights Into the Blood Brain Barrier

1

FEATURED RESEARCHER

Berislav V. Zlokovic, M.D., Ph.D.

2

Continued Growth Puts Focus on Research

4

Raising Awareness in North Carolina

5

International Rotary Club Meeting

5

Global Family Reunion

5

Cure Alzheimer's Fund Heroes

6

**SAVE THE DATE
Cure Alzheimer's Fund's
5th Annual Symposium
on Alzheimer's Research**

8



FEATURED RESEARCHER

Berislav V. Zlokovic, M.D., Ph.D.

*Director of the Zilkha Neurogenetic Institute,
Professor and Chair of the Department of Physiology
and Biophysics, University of Southern California,
Keck School of Medicine, Los Angeles*

Born in Belgrade, “Betza” Zlokovic grew up an only child with a passion for the arts. As a child he played violin for six years and learned to speak French, Italian and Russian in addition to his native language, Serbian. But most of all, he loved to sing. By age 19 he had performed several Italian operas and it seemed he was destined to be a professional musician. Only one thing could lure this Renaissance man from the stage—his passion for science.

Zlokovic grew up in a middle-class, cultured, intellectual family. His father was an engineer, but Zlokovic describes him as more of an “inventor” with several patents to his name. His mother spoke French and Italian and taught Betza to “think and ask questions.” Early on, Zlokovic discovered he had a natural voice for opera, as he was able to hit the high notes as a tenor—but his love for science was even stronger. When he was in high school he used to love reading his uncle’s medical books. He dreamed about one day becoming a scientist.

Education

With his passion and aptitude for science, Zlokovic earned a B.S. in science and mathematics at Belgrade College in

1970. He went on to medical school at the University of Belgrade, graduating in 1975, and stayed on to earn his Ph.D. in physiology in 1983 with a focus on membrane transport.

At medical school, he met his wife, Zora Mihailovich, a concert pianist who had been a child prodigy. While in school, Zlokovic continued to develop as an opera singer, using his voice as a creative outlet. “Opera became an inseparable part of my life. When I was studying medicine, I was a top student, so I was able to pursue some private classes in opera.”

He did his postdoctoral fellowship in England where he worked with Hugh Davson, the renowned physiologist and

co-developer of the Davson-Danielle “protein sandwich” cell membrane model. With Davson as his mentor, Zlokovic developed an interest in the blood-brain barrier field. “Davson was a legend in his field and we became great friends,” explains Zlokovic. “It was thanks to him I left the opera—I really loved singing, but I couldn’t give up my research for anything.”

In 1986, Zlokovic returned to Belgrade with his family to do his residency in clinical physiology (neurology and intensive care). But three years later Zlokovic decided to move to Los Angeles to become an associate professor at the University of Southern California. Zlokovic knew that working in the United States would provide him with the best opportunity to pursue his career as a researcher. “I knew my dream would start becoming a reality in the U.S.,” he said. “There are more resources, more opportunities to apply for grants, and it’s just paradise.” In 1991, at the age of 39, he became a fully tenured professor at USC. Four years later he achieved medical board certification in California and in 1997, he became a U.S. citizen.

Cure Alzheimer’s Fund

In 2011, Rudy Tanzi invited Zlokovic to join the Cure Alzheimer’s Fund Research Consortium and Zlokovic was awarded his first grant from CAF in 2012. Tanzi and Zlokovic had run in the same circles for years and Zlokovic had made some important discoveries about the blood-brain barrier that were linked to Alzheimer’s disease. “Rudy and I had the musical connection as well as the scientific connection,” adds Zlokovic. “I love Cure

“I love Cure Alzheimer’s Fund—it lets you test your ideas quickly and ask risky questions. It’s really a first-class organization and it has been essential for helping my colleagues and me generate preliminary data.”

Alzheimer's Fund—it lets you test your ideas quickly and ask risky questions. It's really a first-class organization and it has been essential for helping my colleagues and me generate preliminary data.”

Research

Early on Zlokovic studied molecules and peptides that influence mood and whether they can be transported over the blood-brain barrier. Currently, he uses both experimental models and the living human brain to study the role of blood vessels in the pathogenesis of Alzheimer's disease and neurological disorders. He also looks at how blood-brain barrier cellular and molecular mechanisms can cause neuronal injury and degeneration and influence our cognition and memory.

His most recent investigations seek better understanding of the underlying mechanisms by which genes that influence the risk for Alzheimer's affect the brain's vascular system through the use of transgenic models, human-induced pluripotent stem cell models and molecular and imaging studies in humans with genetic risk factors for Alzheimer's. He has won numerous honors and awards for his contributions to Alzheimer's disease research and his innovative approaches to drug discovery, both bringing us closer to a cure. His findings also have contributed to the development of a new treatment for stroke with an activated protein C analog, 3K3A-APC, which is being evaluated in ischemic stroke patients in a Phase 2 clinical trial funded by the National Institutes of Health (NIH).

Personal Life

Zlokovic and his wife have a daughter, Anna, who is a film director, writer and producer. He continues to sing whenever he can for fun, and to maintain the quality of his voice. “Music is a big part of my life, and a great creative outlet,” he says. Next March, he will appear with his wife and the Los Angeles Opera Singers in a prestigious USC series, “Vision and Voices,” to sing about and discuss memories and music, which he says have a “real connection. Besides,” he adds, “singing is a great way to cheer people up. Science requires clear and perfect language, while music is a universal language.” To find out more about Zlokovic's innovative work, don't miss our next webinar. ■

New Insights to the Blood Brain Barrier

continued from page 1 »

and Biophysics at the University of Southern California, Keck School of Medicine, Los Angeles, and a member of the Cure Alzheimer's Fund Research Consortium since 2011—bring us one step closer:

- In January, Zlokovic's team was able to use high-resolution imaging of the living brain to show, irrefutably, that the BBB becomes leaky with age, starting in the area of the hippocampus—the area responsible for memory and learning that is affected very early in Alzheimer's disease. This leakiness begins long before there are any cognitive symptoms. The discovery, published in the journal *Neuron*, suggests that specialized brain scans might, in the near future, help doctors routinely spot very early, presymptomatic warning signs of dementia. It also identified early injury to brain vascular cells called pericytes, a type of mural cell that surrounds brain capillaries and acts as a “gatekeeper” of the blood-brain barrier.
- In March, Zlokovic's team discovered that deficiency of a key BBB protein called GLUT1, which helps move glucose, a major energy substrate for the healthy brain, across the BBB, is directly connected to a compromised barrier. It also suggested that the gene regulating this protein could be an excellent drug target. The discovery was published in the journal *Nature Neuroscience*.
- In May, Zlokovic discovered the mechanism of action for an

Alzheimer's-implicated gene encoding protein known as PICALM. The PICALM-Alzheimer's connection had been studied previously by Cure Alzheimer's Research Consortium Chair Rudy Tanzi, Ph.D., and Zlokovic in a Cure Alzheimer's Fund-supported study. Zlokovic, publishing his research in *Nature Neuroscience*, showed that PICALM is crucial for clearing Abeta across the BBB. PICALM variants associated with increased risk for Alzheimer's lead to diminished expression of PICALM and faulty clearance of Abeta from the brain, leading to its accumulation both in the human brain and animal models of the disease. This suggests that, while Abeta is crucial in the subsequent cascade that leads to Alzheimer's disease, the compromise of the BBB may happen earlier in the process, and may contribute directly to the destructive excess of Abeta in the brain.

“The brain cannot function in the presence of blood-brain barrier breakdown,” said Zlokovic. “Now we know that not only is Abeta important in Alzheimer's, but also that this barrier, which is regulating transfer of molecules between the brain and blood, and vice versa blood and brain, can become leaky and dysfunctional and lead to subsequent problems likely contributing to onset and progression of dementia.”

Jeffrey Morby, chairman of Cure Alzheimer's Fund, added, “We created our Research Consortium in order to spur innovation through the speedy sharing of vital data between top researchers. Dr. Zlokovic's latest advance with PICALM is a perfect example of what we've been able to do, and it brings us that much closer to a cure.” ■

Tune In to Our Next Alzstream™ Webinar

How Leaky Brains Can Lead to Alzheimer's

Wednesday, Sept. 9, 2015, at 1 p.m. EDT

Hear from University of Southern California neuroscientist Berislav Zlokovic, M.D., Ph.D., about his work on the blood-brain barrier and how it becomes more porous with age, which can lead to Alzheimer's disease. No registration is required—simply visit curealz.org/webinar on Sept. 9 to join.

Continued Growth Puts Focus on Research

With 10 years of research behind us, Cure Alzheimer's Fund continues to grow, with the quality of our research remaining extraordinary. To build on our success, we recently welcomed four new Research Consortium members and four new employees to our organization.

Christoph Lange, Ph.D., Harvard T.H. Chan School of Public Health, assistant professor of medicine at Harvard Medical School, is highly respected for his work in statistical genetics and generalized linear models, including family-based association tests. **P. Murali Doraiswamy, M.D.**, Duke University, who heads up the Biological Psychiatry Department there, is a world leader in the fields of cognitive neuroscience and neuropsychiatry, specifically brain longevity and mental health. **Karen Duff, Ph.D.**, professor of pathology and cell biology at Columbia University, is renowned for her work on Alzheimer's disease. **Christian Haass, Ph.D.**, chair of the Metabolic Biochemistry Department at Ludwig-Maximilians-Universität München, has devoted his research to the discovery of cellular and molecular mechanisms of dementia.

The addition of these prestigious researchers further underscores our commitment to finding a cure for Alzheimer's disease as soon as possible. In order to efficiently handle our continued growth, we also have made four new strategic hires, funding for whom will be covered by our generous board members. That means 100 percent of donations will continue to go directly to research.

Barbara Chambers, our new senior engagement officer, will be our "chief story teller." She will elevate awareness of CAF's role in eradicating Alzheimer's and communicate our mission to the media, the public and our donors. She has worked with entrepreneurial

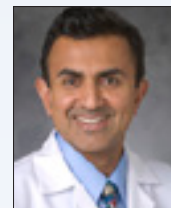
start-ups and well-established businesses in branding, marketing and PR. **Meg Smith** joins us as senior adviser for strategy and special projects to manage and coordinate research opportunities. Most recently, she was a management consultant with McKinsey & Company. **John P. Slattery Jr.** is our new senior vice president, development. He joins us to take a leadership role in fundraising and outreach. His experience includes developing innovative outreach and fundraising initiatives to drive revenue for a number of nonprofit and sports organizations. **Sara Oettinger** is our new administrative manager. She will maintain our office systems and support our staff. She served as support staff at a pharmaceutical company and venture capital firm, and as the president and general director of a Boston opera company.

In addition, **Toni Carbone**, who has served as our office manager for many years, will modify her role to continue to assist the increasing number of "heroes" who raise awareness and money for us and to help manage the growing number of research projects we are funding. Finally, Senior Vice President **Mike Curren**, who worked with us for four years, has moved on to a new organization. We are most appreciative of Mike's efforts in helping to fuel the growth CAF is now experiencing in donors, dollars and research initiatives.

We would not be where we are today without our generous donors. Thank you for your unwavering support. ■



Christoph Lange, Ph.D.



P. Murali Doraiswamy, M.D.



Karen Duff, Ph.D.



Christian Haass, Ph.D.



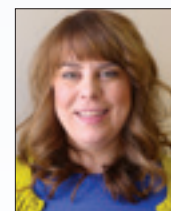
Barbara Chambers



Meg Smith



John P. Slattery Jr.



Sara Oettinger



Toni Carbone



Mike Curren



ALZHEIMER'S/DEMENTIA
ROTARIAN ACTION GROUP



International Rotary Club Meeting

To continue the momentum we've built with Rotary Club International creating awareness for Alzheimer's disease, Jeff Morby, chairman and co-founder of CAF, spoke at a June Rotary meeting in São Paulo, Brazil. He talked about the impending "tsunami" of Alzheimer's that will affect millions of people around the world in the next decade, and the urgent need to educate people about this disease and fund research to get to a cure. There was a great turnout and the attendees walked away with a sense of urgency and a clear call to action. ■

Global Family Reunion

The first Global Family Reunion was held on June 6 at the New York Hall of Science in Queens, New York. Created and spearheaded by writer A.J. Jacobs, the event brought together 3,700 people with the message that we are all "cousins" in one way or another, and together need to fight Alzheimer's disease. The event, which raised \$62,000 for research and care, featured dozens of speakers, activities, food and music, as well as a presentation on Alzheimer's by Dr. Rudy Tanzi. Jacobs plans to make this an annual event. ■

Raising Awareness in North Carolina

Cure Alzheimer's Fund board member Matthew Szulik and his wife Kyle held a gathering in early May at the Umstead Hotel in Cary, North Carolina. More than 50 people attended, including representatives from Rotary International and Alzheimer's North Carolina. Szulik spoke about the enormous impact of Alzheimer's disease on the people of North Carolina, especially given the state's popularity as a retirement destination. Dr. Rudy Tanzi shared how CAF's Research Consortium has been able to make important discoveries over the past 10 years, but underscored the need for further research. ■



(from left)
Matthew and
Kyle Szulik,
Henry
McCance



(above from left) CAF's Madeleine Adelson, Tim Armour and Sally Rosenfield greeted attendees in the CAF tent. Sister Sledge (background) performed "We Are Family" on the main stage.



(left) Organizer A.J. Jacobs stands in front of the "Tree of Family Memories." Attendees wrote favorite family memories on leaves (below) and added them to the tree.



GLOBAL FAMILY REUNION



"Your donations make a big difference in our progress toward finding a cure for Alzheimer's disease. Your passion, your energy and your generosity are an inspiration to all of us to work even harder to end this terrible disease. Thank you all for your leadership and support."

—Tim Armour, president and CEO, Cure Alzheimer's Fund

Ride for Research

On March 1, Rick Wojciak (AKA Ridin' Rick), 62, and five of his friends set out on their bicycles to ride 2,673 miles across the country—from San Diego to St. Augustine, Florida. His wife Mary Jean's mother, Ruth, has suffered from Alzheimer's for the past few years. "The vibrant, outgoing, adventurous, strong-willed woman I first met 17 years ago has turned into a shadow of what she once was," says Rick. By asking friends and family to donate a few cents per mile cycled, he raised more than \$10,000 for Alzheimer's research. He completed his journey on April 30, 2015. ■



At the end of the ride in St. Augustine.

6th Annual

running 4 answers



For the past six years, Carolyn Mastrangelo and Barbara Geiger have held their annual Running 4 Answers Race and Fun Run in Roseland, New Jersey. Carolyn's mom suffered from Alzheimer's disease, prompting Carolyn and Barbara to start the event to support research toward a cure. This year the race took place on April 25, with about 250 participants and more than 700 attendees. Since its inception, Running 4 Answers has donated more than \$200,000 to CAF. ■



(from left) Barbara Geiger and Carolyn Mastrangelo



Jonathan Minkoff
Photo by TimeLine Media

Since 2009, the a cappella festival SingStrong, founded by Jonathan Minkoff, 45, of New York City, has been bringing together groups from around the world for a weekend of world-class singing and charitable fundraising. This past spring, the festivals were held in Washington, D.C., and Chicago. At each event a capella singers joined together for five concerts and two days of classes and coaching. Kieran Daly, graphic designer for CAF, sang the Rudy Tanzi/Chris Mann composition "Remember Me" with his group Cartoon Johnny to help raise awareness of Alzheimer's disease. SingStrong raised more than \$10,000 for CAF this year and Jonathan plans to continue to support the fight against Alzheimer's disease through the SingStrong festival. ■



Kaely McDougall

Registered dietician Kaely McDougall of Huntington Beach, California, got hooked on long-distance running about 10 years ago when she and her father ran their first race together. Since then, Kaely has lost both of her paternal grandparents to Alzheimer's and she has seen the disease's impact on many other family members and friends. On May 3, she ran the Orange County Marathon in less than four hours, breaking her personal record, and raised \$670 for research. ■



For more information on our events, go to curealz.org/events.

34 Washington St., Suite 200
Wellesley Hills, MA 02481
Telephone: 877-CURE-ALZ (287-3259)
Fax: 781-658-2399
curealz.org

Centre City Tower
650 Smithfield St., Suite 2015
Pittsburgh, PA 15222

Mission

Fund research with the highest probability of preventing, slowing or reversing Alzheimer's disease.

Research Consortium

Develops and updates a "roadmap for research" for the most effective and efficient route to preventing, slowing or reversing Alzheimer's disease. Members research their own projects and recruit others whose work will hasten development of effective therapies for and prevention of Alzheimer's disease.

Rudolph E. Tanzi, Ph.D., Chairman, Research Consortium;
Harvard Medical School/Massachusetts General Hospital
P. Murali Doraiswamy, M.D., Duke University
Karen Duff, Ph.D., Columbia University
Sam Gandy, M.D., Ph.D., Icahn School of Medicine at Mount Sinai
Charles Glabe, Ph.D., University of California, Irvine
Christian Haass, Ph.D., Ludwig-Maximilians-Universität München
David Michael Holtzman, M.D., Washington University, St. Louis
Richard L. Huganir, Ph.D., The Johns Hopkins University
Christoph Lange, Ph.D., Harvard T.H. Chan School of Public Health
Virginia M.-Y. Lee, Ph.D., M.B.A., University of Pennsylvania
Roberto Malinow, M.D., Ph.D., University of California, San Diego
Eric E. Schadt, Ph.D., Icahn School of Medicine at Mount Sinai
Sangram S. Sisodia, Ph.D., University of Chicago
Robert Vassar, Ph.D., Northwestern University
Steven L. Wagner, Ph.D., University of California, San Diego
Berislav Zlokovic, M.D., Ph.D., University of Southern California

Scientific Advisory Board

Reviews individual grant proposals for science integrity and roadmap objectives. Provides advice and counsel to Cure Alzheimer's Fund regarding scientific soundness of the roadmap.

John C. Mazziotta, M.D., Ph.D., Chairman, Scientific Advisory Board; UCLA
Dennis Choi, M.D., Ph.D., Stony Brook University
Caleb Finch, Ph.D., University of Southern California
Paul Greengard, Ph.D., The Rockefeller University
John S. Lazo, Ph.D., University of Virginia
Robert C. Malenka, M.D., Ph.D., Stanford University
William Mobley, M.D., Ph.D., University of California, San Diego
Thomas C. Südhof, M.D., Stanford University
Marc Tessier-Lavigne, Ph.D., The Rockefeller University

Board of Directors

Jeffrey L. Morby*, Key Largo, Fla., Chairman
Robert F. Greenhill, New York City
Henry F. McCance*, Lake Wales, Fla.
Jacqueline C. Morby*, Key Largo, Fla.
Phyllis Rappaport*, Stuart, Fla.
Sherry Sharp, Richmond, Va.
Matthew Szulik, Boston
Tim Armour, Wellesley Hills, Mass., President
*Founder

Administration

Tim Armour, President and CEO
Madeleine Adelson, Marketing Manager
Toni Carbone, Office Manager
Barbara Chambers, Senior Engagement Officer
Laurel Lyle, Director of Fundraising Programs
Jessica Mutch, Director of Finance
Sara Oettinger, Administrative Manager
Sally Rosenfield, Senior Vice President
David Shenk, Senior Adviser
John P. Slattery Jr., Senior Vice President, Development
Meg Smith, Senior Adviser, Strategy and Special Projects
Cindy Turner, Bookkeeper
Dorothy Vacaro, Gift Processing

Contributing Writer: Patty Bovie
Copy Editor: Colleen O'Neill
Design: Winking Fish

Financial Update

	This Quarter*	YTD*	Inception to Date
Fundraising	\$763,000	\$3,275,000	\$51,417,000
Expenses paid for by the board	\$520,000	\$994,000	\$10,485,000
Funded research	\$1,347,000	\$1,647,000	\$29,668,000

*Numbers shown are preliminary for the period and are rounded to the nearest \$1,000.

Research Update

Research funded during the second quarter of 2015

Project	Researcher	Distribution Amount
Analytical and Statistical Tools for Sequence Analysis for Alzheimer's Disease	Christoph Lange, Ph.D., Harvard T.H. Chan School of Public Health	\$150,000
Long Aβ, Intraneuronal Amyloid and an Alternative Amyloid Hypothesis of Alzheimer's Disease	Charles Glabe, Ph.D., University of California, Irvine	\$100,000
The Role of Microbial Immune Responses in Alzheimer's Disease	Sangram S. Sisodia, Ph.D., University of Chicago	\$250,000
Novel Compound Therapy Blocking Endoplasmic Reticulum and Mitochondrial Stress	Amylyx Pharmaceuticals Inc.	\$150,000
Lead Optimization and Lead Evolution of Potent SGSMs for the Treatment of Alzheimer's Disease	Steven Wagner, Ph.D., University of California, San Diego Rudy Tanzi, Ph.D., Harvard Medical School/ Massachusetts General Hospital	\$476,988
PKC Mutations and Alzheimer's Disease	Alexandra Newton, Ph.D., University of California, San Diego	\$220,000
Total Distributed to Research for Q2 2015		\$1,346,988

Help us fund research with the highest probability of preventing, slowing or reversing Alzheimer's disease. Donations can be made through our website, curealz.org/donate, or sent directly to our office.

For gifts of securities or direct wire transfers, please contact Tim Armour at **877-CURE-ALZ (287-3259)** for further information.

CHARITY DESIGNATION

Cure Alzheimer's Fund® is a "doing business as" name for the Alzheimer's Disease Research Foundation, a 501(c)(3) public charity with federal tax ID #52-2396428.



Cure Alzheimer's FUND

34 Washington St., Suite 200
Wellesley Hills, MA 02481

877-CURE-ALZ (287-3259)
curealz.org

Non-Profit Org
U.S. Postage
PAID
Washington, DC
Permit No. 13



*(from left) Dora Kovacs, Ph.D.,
Julianne Moore and Rudy Tanzi, Ph.D.,
at the TIME 100 Gala this past April in New York City,
where Tanzi was named one of the Most Influential
People of 2015.*



Check out our Facebook page for our most recent posts, photos, videos and more! Go to **facebook.com/CureAlzheimers**.

JOIN US FOR OUR 5TH ANNUAL SCIENTIFIC SYMPOSIUM **From Genes to Therapies** CONVERGING ON A CURE

Save the Date

Wednesday, Oct. 14, 2015

This year's fifth annual research symposium will be held at the Harvard Club on Commonwealth Avenue in Boston on Oct. 14. The event will feature a talk on "Genes to Therapies: Converging on a Cure" by CAF Research Consortium Chair Dr. Rudy Tanzi, and the a cappella group, Cartoon Johnny, will give a live performance of the Rudy Tanzi/Chris Mann song, "Remember Me."

The symposium is free but registration is required; sign up now at **curealz.org/symposium**.