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Obituary

The Life and Science of Allen Roses' Lives On

In May of 2016, Duke University scientist Peter Larsen promised his mentor—neurologist Allen Roses—that he would finish a paper on their latest findings on lemurs and the TOMM40 gene that Dr. Roses had been tracking since 2009. Dr. Larsen, an evolutionary biologist who joined the Roses' team to discover genetic signals important in the development of Alzheimer's disease (AD), had a two-week respite at the end of the summer and spent it writing out the results from their study. On September 29, he sent the manuscript to a scientific journal, and emailed his mentor that the paper was submitted.

The next day, at 4 : 30 in the morning, Allen Roses penned a note to his colleague, congratulating him and laying out the next steps. Dr. Roses was sure that alternative splicing events of TOMM40 were somehow contributing to early stages of mitochondrial dysfunction that would eventually trigger the cognitive problems in AD.

Later that day, the guy who loved to say that he never bought green bananas died at the airport on the way to a medical meeting. He was 73. The neurologist had suffered a serious heart attack in 1990 and knew that another one could come at any time. He lived his life celebrating his family, science, great wine, basketball, and dance in equal measure.

Allen Roses had discovered the first and most potent risk gene for late-onset AD, APOE4 almost 25 years ago, and went on to unearth another nearby gene called TOMM40 that he believed was just as critical to the development of AD as APOE4.

His legacy is living on. The study he designed and launched to test his ideas on TOMM40 were highlighted in poster sessions this past summer at the Alzheimer's Association International Conference in England. There have been numerous publications by scientists who are carrying out the neurologist's missive to use genetics to solve the riddle of AD.

Dr. Roses held the Jefferson-Pilot professor of neurology at Duke's Bryan Alzheimer's Disease Center. Back in the early 1990s, Dr. Roses and his colleagues would turn the AD research world on its head with news that they linked the APOE gene to the disease, and that a variant of the gene—APOE4—could substantially increase a person's risk for AD. The finding sparked controversy in the field, especially since APOE is a lipid transporter and did not fit into the story that the sticky amyloid-β protein was the cause of AD. Dr. Roses spent decades refuting the amyloid hypothesis, suggesting that the protein accumulation was like a tombstone for the dead neurons and not the trigger for the disease.

Studies were quick to support APOE's link to AD and it was one of the most seminal findings of modern genetics: a common risk gene for a common disease. Still, much of the federal funding was directed to amyloid research and there was little left for other ideas. In 1996, Dr. Roses left academia for a decade to head up genetics research at GlaxoSmithKline. He continued working on his ideas and testing medicines that he believed could treat AD. In 2007, he returned to Duke to continue working on the genetics of AD and drug discovery.

Mike Lutz, PhD, a computational biologist and bioinformatics specialist who had worked with Dr. Roses at GlaxoSmithKline, joined his team at

Duke. Dr. Roses wanted to figure out why the APOE4 signal was so strong. Dr. Lutz accepted the challenge. "He thought that it had to be some other gene in that region that was also involved," said Dr. Lutz, an assistant professor of neurology. In trying to piece together the APOE story, they discovered another gene that they felt was critical to the puzzle. It was TOMM40, APOE's genetic neighbor on chromosome 19. Dr. Roses believed that TOMM40, a gene known to regulate the transport of proteins in and out of mitochondria, was tightly linked to APOE. He was convinced that a toxic mix of the two gene variants inhibit mitochondria from delivering needed energy to neurons.

"I also miss the middle of the night emails from Allen," said Dr. Lutz. "Allen thought that TOMM40 was a key aspect of the development of AD pathology, and was involved much earlier in the process than the accumulation of amyloid. He began to believe that it was the metabolic processes in the mitochondria that signaled the events that ultimately unfold in AD."

His ideas about the TOMM40 gene and problems with mitochondria led to the design and implementation of the TOMMORROW study. "Allen believed that TOMM40 would be just as important a discovery as APOE," Dr. Lutz added. At the time, Dr. Roses took out a home loan and used it to fund his research. They identified a polymorphic poly-T variant that came in various lengths and worked in association with the different APOE variants to determine the age of onset of AD. The longer lengths of the variant were associated with a higher risk for late-onset AD, and even people with an APOE3 allele and a longer version of TOMM40 developed AD seven years sooner than those with a shorter form of the variant.

Again, Dr. Roses felt that the many in the AD field met his science with more skepticism. But he did not care, and encouraged people in his laboratory, and outside, to think more broadly about basic mechanisms. AD is a complex disease, and he knew that genetics would help make sense of the disease.

"I admired Allen's out-of-the-box thinking and that he went after counter-intuitive ideas. I like that in science," said Zaven Khachaturian, PhD, a senior science advisor to the Alzheimer's Association and editor-in-chief of *Alzheimer's & Dementia*. They had been close friends for decades. "Back in the 1980s, there wasn't room for another theory outside of amyloid. The APOE finding shook the establishment." He said that Dr. Roses liked to say: I might be wrong sometimes, but I am never in doubt. "He came across confident about everything and he was not intimated by the high priests of the field," said Dr. Khachaturian. "That made him a very unpopular person because he challenged their views. It created a lot of ill feelings."

"The APOE-TOMM40 story makes it very clear that this is a complex condition that will not be explained by the amyloid hypothesis," he added.

Allen Roses brought passion and good humor to his research. He started three small companies that were named after some of his favorite wines. One of the companies, Zinfandel Pharmaceuticals, partnered with Takeda Pharmaceutical to start the TOMMORROW phase III clinical trial. The companies are testing whether TOMM40 can work as a biomarker to predict mild cognitive impairment disease risk. The study recruited 3,400 healthy older people who are being followed for five years. They are also testing the benefits of a low dose of the diabetes drug pioglitazone (Actos) to see whether it could delay the onset of the disease. Results of the study should be available in 2020.

"Allen always challenged people, hypotheses, and conventional thought," said Dr. Lutz. "He encouraged so many people." His sense of urgency is living on through his colleagues. "His dream was to find some way to make a difference in the field. He knew his time was short." He had recently become interested in ALS. Dr. Roses' last middle-of-the-night email to Dr. Lutz was about ALS.

His scientific and life partner, Ann Saunders, PhD, is now overseeing the TOMMORROW trial with Takeda. "This study is Allen's brain child," said his wife. He set up a charitable trust to help support younger scientists with novel ideas. That seed money has helped Peter Larsen move from studying the evolutionary biology of lemurs to AD. The collaboration was based on the genetic similarities between TOMM40 in lemurs and in humans.

Dr. Roses was also passionate about dance. He spent time as chairman of the board of the American Dance Festival since 2011 and was on the board since 1999. This year, the organization created a scholarship in his name that supports training young dancers. He also loved basketball and missed only two home ACC games at Duke since 1972. One of those games was when he was laid up after his first heart attack.

The neurologist had a good sense of humor about his bad heart. He had a pacemaker put in and he spent too much time in the hospital getting it to work right. His daughter Stephanie, now a medical student

at Duke, said he would get up every morning, blink three times and say: *I'm not dead yet*, and go off to fight AD.

The neurologist was the son of Jewish immigrants who fled Poland right before the Holocaust. They settled in Patterson, New Jersey. Allen was about 13 when his father suffered a fatal heart attack, and he worked to support his mother and sister. He loved to tell people that he ran numbers for mobsters. In fact, he did, and he made enough to help pay for his sister's college. In 1963, he went to medical school at the University of Pennsylvania and did his residency at Columbia University and Duke. He served as a doctor in the Air Force in Vietnam. He was drafted towards the end of the war, and directed head trauma training on ships. He was discharged as a captain. He eventually became chief of neurology at Duke and founding director of the Alzheimer's disease research center and director of the Center for Human Genetics. From 2003 to 2007, he was a member of the science board at the U.S. Food and Drug Administration and continued to consult for the agency.

Allen Roses never shook off those street-fighting days in Patterson. His close friend, Dmitry Goldgaber, PhD, a professor of neuroscience at Stony Brook University in New York, said that he shunned arrogance and was a defender of the underdog. Allen Roses was a fighter, especially in medicine. "He wanted to change the trajectory of Alzheimer's," he said.

And that he did.

Jamie Talan, MPH
Assistant Professor of Science Education
Hofstra Northwell School of Medicine
Atlantic Fellow, Global Brain Health Institute
E-mail: jtalan3k@aol.com