“What we have here is a new insight into the story that may lead to new therapies down the road,” says Nicholas Seeds.

When researcher Shay Fabbro crossbred mice afflicted by Alzheimer’s disease with mice missing a key dementia-related protein, the offspring produced a quiet miracle in a University of Colorado Denver School of Medicine laboratory.

The newly bred mice in Fabbro’s study warded off the disorientation and confusion typically seen with Alzheimer’s. The results gave new hope of finding relief for a disease that affects 5.3 million Americans, incrementally robbing them of their memories and identities.

“What we have here is a new insight into the story that may lead to new therapies down the road,” says Nicholas Seeds, PhD, Fabbro’s mentor and a professor of biochemistry and molecular genetics.

“We were able to rescue a pretty specific Alzheimer’s deficit called spatial orientation,” Fabbro, a recent PhD graduate in human medical genetics, explains. “That’s where [dementia] patients sort of lose the ability to orient in three-dimensional space based on visual cues. It’s really amazing. It’s very dramatic.”

Seeds and Fabbro have focused on the protein neuroserpin, which is found at levels about 67 percent higher than normal in Alzheimer’s patients.

Neuroserpin prevents the formation of a good enzyme called plasmin by directly inhibiting a substance called tissue plasminogen activator—or tPA—that forms plasmin. Plasmin helps the body remove or minimize the formation of amyloid-beta plaques in the brain, plaques that eventually destroy brain neurons. The presence of amyloid-beta plaques is one of the hallmarks of Alzheimer’s. The activity of tPA could prove critical to Alzheimer’s patients, Seeds says.

The multi-step process Seeds and Fabbro used to stop or reduce the production of the Alzheimer’s-causing plaques in mice shows just how complex brain chemistry is and just how challenging finding a cure for Alzheimer’s will be. It took them taking several steps back from the disease to even begin to take a step forward.

But when Seeds and Fabbro found a way to take mice with Alzheimer’s and alter them genetically so that they functioned normally in a cognition test, they knew they had hit on something important.

Researchers already knew tPA played a role in learning and memory. But Seeds and Fabbro determined that tPAs activity shrinks by 50 percent in Alzheimer’s patients.

In laboratory experiments, Seeds and Fabbro found that mice lacking the ability to produce plasmin could not clear brain plaques as well as normal mice. At the same time, the researchers discovered that mice who lack the ability to make neuroserpin cleared brain plaques faster than normal mice. The findings formed a kind of double-edged sword in the fight against Alzheimer’s.

Seeds and Fabbro proved their point with a dramatic demonstration they captured on video. They trained various mice with visual cues to find a life-saving platform just beneath the surface of a pool of non-transparent liquid. Later they removed the platform.

“When you put in the normal mouse who has learned [where the platform is], he has the spatial memory and remembers,” Seeds explains, showing the video. “He will swim back and forth over where [the platform] should be.”

Mice bred solely with the Alzheimer’s gene never zeroed in on any one area.

“When you watch the Alzheimer’s mouse in the tank, he just swims all over the whole tank,” Fabbro says. “He has no clue. He doesn’t remember.”

But when a mouse with Alzheimer’s had its ability to make neuroserpin genetically removed, the Alzheimer’s mouse reacted normally, swimming in the area where the platform was.

“In fact, says Fabbro, “when you look at the Alzheimer’s neuroserpin-knockout mouse, she swims right to that quadrant. Actually, she almost finds it better than the wild-type mice.”
Seeds, a highly regarded neurobiologist whose research runs the gamut from studying brain development to neurological recovery from spinal-cord injuries, suggests that the ability to regulate neuroserpin holds promise as a potential breakthrough for preventing brain-cell death in Alzheimer’s patients.

“Where you want to go from this work is to identify potential inhibitors of neuroserpin,” he says.

This becomes even more important, Fabbro adds, because neurons damaged before Alzheimer’s is detected likely cannot be restored.

Still, Seeds cautions that similarly promising discoveries have reached research dead-ends in the past. Furthermore, even if stemming the production of neuroserpin is the answer, the pursuit of an effective therapy to relieve some of the symptoms of Alzheimer’s could take years.

Over the past 16 years, the U.S. Food and Drug Administration has approved five drugs to slow the worsening of Alzheimer’s symptoms, giving short-term relief to about half of patients but not stopping brain-cell death, according to the Alzheimer’s Association.

While medical advances have reduced the number of deaths attributed to heart disease, breast cancer and stroke, Alzheimer’s disease deaths jumped 47 percent between 2000 and 2006. As Baby Boomers grow older, the number of patients with the disease is projected to grow significantly, reaching 615,000 new cases annually by 2030.

Daniel Lawrence, a professor of cardiovascular medicine at the University of Michigan Medical School, also focuses his research on tissue plasminogen activators in the brain. Lawrence says the study by Seeds and Fabbro, published in the April 15, 2009, issue of the Journal of Neurochemistry, reveals new insight into neuroserpin’s role in the development of Alzheimer’s disease.

“Most research in Alzheimer’s disease has focused on how these harmful proteins are generated; however, it may be that it is not their generation that is harmful but their levels in the brain that are important,” Lawrence says. “This is important, as it suggests further avenues of research.”

It’s too early to tell if the discovery will be the key to unlocking the mysteries of the disease, Lawrence says, but he applauds the effort and approach.

“Nearly all research is incremental. That is how science works,” he notes. “It is clearly too early to tell if this will be an important pathway or not, but since we have not gotten as far as we would like in understanding how this disease develops, then any new leads could turn out to be important.”

For Denver neurologist Beverly Gilder, who treats patients with Alzheimer’s and other cognitive diseases, any breakthroughs that slow the decimation of the mind will be welcome.

“You can see the terror on their faces,” she says of patients diagnosed with Alzheimer’s disease. “It’s scary and very sad.”

With few other options for providing comfort, Gilder recently has softened her view on alternative therapies billed as beneficial to Alzheimer’s patients. She now advises patients that these treatments are fine as long as they don’t harm them and don’t siphon away all of their money.

“Give me something that might help or that might help even a little bit,” Gilder says. “It doesn’t have to be dramatic. It’s frustratingly slow when you have someone who’s deteriorating before your eyes. You have families and patients out there who are desperate …”

Seeds and Fabbro hold out hope that their discovery could be the first step in stemming the cognitive losses of Alzheimer’s disease, if not an outright cure.

“Really, it’s the cognitive deficit that is so tremendously bad in Alzheimer’s patients,” Fabbro says. “That’s what you really want to fix.”