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# The Alzheimer's Hope

Tufts neuroscientist Philip Haydon is testing a promising treatment based on groundbreaking insights into how the brain works

Some of Philip Haydon's most promising work over the past decade concerns his quest to modify glia on the surface of the human brain to create a bold new treatment for the scourge of Alzheimer's disease. Illustration: Davide Bonazzi

By Bruce Morgan

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*A few years ago, I was out in Denver visiting my mother in her condo, sitting at the end of her couch in the living room, working through the day's newspaper. It was late afternoon. I noticed my mother, still in her bathrobe and seated beside my younger brother, Gary, in an adjacent kitchen area, perhaps 15 feet away. She was peering in my direction. "My," she said finally in a stage whisper to my brother, "our neighbor is being awfully quiet today." Gary, who was used to this sort of thing, corrected her. "That's not your neighbor," he told her quietly. "That's your son, Bruce."*

The excitement began on a small scale, with unexpected signals coming from a laboratory dish in the middle of Iowa. The dish held brain cells. Phil Haydon, a neuroscientist conducting research at Iowa State University in Ames, had killed off the neurons in the dish and left the glia—long considered by scientists to be little more than glorified packing material for the brain's all-powerful neuronal networks. He expected that the glia would fall silent along with the neurons.

But they did not. Instead, the glia kept emitting chemical signals. The year was 1994, and these signals were one half of a conversation that the world had never seen before. The glia, Haydon was shocked to discover, were not passive or inert, as they had been thought to be by medicine for more than a century. Rather, they were active participants of some kind in the brain's functioning.

"We were off on one path in science, and there was an observation we could not explain," Haydon later told a Tufts audience. "Over the course of two or three months, we figured out what was going on, changed the direction of research in the lab 180 degrees and said, 'It's time to take a risk.'"

Those faint signals in the dish raised big, immediate questions. What was the precise nature of glial involvement, and what might the implications of their role be for optimal human health?

Some of Haydon's most promising work over the past decade concerns his quest to modify glia on the surface of the human brain to create a bold new treatment for the scourge of Alzheimer's disease, which afflicts one-third of Americans over age 85 and some 50 million people around the world. Haydon's revolutionary approach, derived from his expertise in a still-obscure area of brain science and—in stark contrast to all other comparable trails to date—already tested successfully on human subjects, may upend the Alzheimer's apple cart for good.

## Neurons and Glia

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Haydon, who is now the Annetta and Gustav Grisard Professor and chair of neuroscience at Tufts School of Medicine, after seven years on faculty at the University of Pennsylvania, likes a good analogy as well as the next person. He says that when you picture the brain, imagine it as a dense bush with cables running through it. The cables are the neuronal system; the bush represents the glia, spidery filaments of connective tissue. Glia, meaning "glue," make up as much as 80 or 90 percent of the human brain by volume.

Neurons and glia "speak different languages," says Haydon, with the former brain components reliant on electrical and the latter on chemical signaling methods. They differ in other ways as well. Neurons need physical connections resembling a plug in a socket to function properly, whereas glia merely require being in the vicinity of their recipients to get their signals through.

R. Douglas Fields, a senior investigator in neuroscience at NIH who wrote a 2011 book on glia called *The Other Brain: From Dementia to Schizophrenia, How New Discoveries About the Brain Are Revolutionizing Medicine and Science*, and has also collaborated with Haydon on a number of occasions in the relatively small field they share, likens the twin signaling methods to cell phones (glia) and land lines (neurons).

How exactly are the two systems talking to each other? This is an area where Haydon may know the answers better than anyone. "Phil's pioneering work has to do with glial influence on synapses," Fields told me, speaking in technical terms and leaving me a bit confused. "Imagine a car race," Haydon explained later, offering another analogy. "The cars [neurons] get all the attention, but the car needs a pit crew. That pit crew is the glia. They are tuning the brain for peak performance."

That's fine when all systems are working well—but what happens when they malfunction? Broken or frayed connections within the brain are now known to be significant contributing factors in a host of human ailments, including multiple sclerosis, epilepsy, depression, schizophrenia, ALS, and Parkinson's and Alzheimer's diseases, among others. Over the past 25 years, Haydon has been working to understand the role that glia play not just in these ailments, but in normal, healthy human functioning as well.

Take sleep as one example. In 2009, Haydon and his team published the results of a study in the journal *Neuron* showing that glia are involved in creating sleepiness. To do this, the researchers blocked the effects of glia in a group of sleep-deprived mice and found that these mice did not require as much catch-up sleep as expected, while retaining the full memory function of well-rested mice. "Glia are altering sleep," Haydon concluded.

Every brain function has its glial contributor, as Haydon sees things. Talking with him on the subject can entail a sudden, dizzying drop into philosophy or cosmology or God knows what. "How is it that you can bring your thoughts to focus on a given task?" he inquires at one point, suggesting it may have to do with glia controlling the strength or weakness of signals at certain neuronal junctions. Then, a moment later, he muses aloud: "Some memories may be created in the glia."

**Against the Grain**

The limitations on what glia may or may not do in the human brain are yet unknown—or, rather, in the process of becoming known. When asked to specify the nature of any substantive criticism that he has drawn from colleagues in his fast-emerging field, Haydon compares it to people disputing the color of the wall in his office. "Is that wall off-white, gray or beige?" he asks with an irritated wave of his hand. "That's the kind of argument we're having these days: Exactly how much control do the glia have in the system?"

In fact, many of the early reactions Haydon heard at professional gatherings were blunt and dismissive. "There is no way that glia do anything of importance," one colleague told him to his face. "What are you trying to do," another scientist asked Haydon rather plaintively, "make our understanding of the brain more complicated?"

The answer to that one was yes**.** A study that Haydon published in *Nature Neuroscience* in May 2010 showed that a reaction that occurs in glial cells in a variety of brain diseases such as epilepsy hinders their interaction with neurons, likely contributing to the cognition, learning and memory impairments that often accompany neurological dysfunction.

Several decades ago, the problem likely would have been seen to be purely neuronal; now, with Haydon's series of findings, the problem is more precisely understood as a breakdown in glia-neuronal signaling, like a conversation between two people that all too suddenly fades away.

His field may be opening up more and more with each new discovery—and Haydon is quick to point out that there are known to be four main types of glia, with multiple subtypes waiting to be found, so the work is just beginning.

But he concedes it has not been an easy professional path for anyone leading the charge. “Twenty or so years ago, it was not in vogue,” Haydon observes. In fact, he admits he initially hesitated to submit any of his findings to established journals for fear of ridicule.

### Overlooking Half the Brain

The NIH’s R. Douglas Fields explains that there was a self-reinforcing loop of obscurity at play in the 1990s that made general acceptance difficult. People hadn’t heard of glia, so funding for glia research was hard to come by. Because there was no funding, little got published; because little was published, no one knew about glia, and so on. “This is what always happens in new fields of science,” Fields says. “The new area becomes a backwater. But the field has been transformed lately as people are realizing that we had overlooked half the brain.”

Even observers in a position to know weren’t necessarily aware of this radical shift. Fields relates that when he submitted a general-interest feature on glia to *Scientific American* in 2004—where it ended up being the cover story for April that year—the editors called him and said, “This sounds interesting, but what is this ‘glia’ you talk about?” As Fields points out, “People didn’t even know the word.”

Over the past 10 or 15 years, glial research has quietly caught fire, generating excitement, “especially among young people who want to come into an area that’s unexplored,” Fields suggests. As one example, Fikri Birey, now a postdoctoral research fellow in psychiatry at Stanford Medical School, gave a 2013 TEDx talk (http://tedxtalks.ted.com/video/Mood-disorders-are-glial-disord) that crackled with impatience.

Birey began by reviewing the conventional medical understanding of the human brain. “Glia, 90 percent of your brain, was reduced to being bubble wrap, just lifeless glue holding neurons together, or an uninspiring scaffold to hold the evolutionary wonder that is neurons,” he said near the start of his talk, an edge of sarcasm coloring those last six words. “But things are changing, and they’re changing fast. Today we realize that age-old disorders of the brain such as ALS, Alzheimer’s, MS, epilepsy, even brain cancers all have an imprint of glial dysfunction on them.”

Alzheimer’s presents a special case. In good health, the body produces protein fragments called amyloid that collect on the brain, where they are broken down and eliminated. However, the volume of amyloid produced in a person with Alzheimer’s overwhelms the brain’s regular maintenance system, with the result that protein fragments accumulate to form hard, insoluble plaques. These plaques block cell-to-cell signaling and often trigger damaging inflammation as well. With time, cognition—the ability to think clearly, function and make sense of the world—steadily declines.

### The Breakthrough Moment

Haydon's breakthrough came from a chance remark at a professional conference in 2008, when he heard a colleague say that he had identified a protein that caused certain glia cells to remove the brain's unwanted surface accumulations.

This was a moment that Haydon was primed and ready for. He reasoned that if he stimulated the protein in question, it might help clear the excessive levels of amyloid plaque found in Alzheimer's. "What we did was realize we could recruit a natural process to our benefit," says Haydon. He promptly tested the idea on mice and found that it worked.

Haydon used a small molecule dubbed GC021109 that brought two simultaneous benefits. It sped up plaque removal from the brain's surface, while also tamping down inflammation that hampered the ability of glia to function efficiently in their regular maintenance role. That was fine for the mice, but would the approach work on people, too?

*About 30 years ago, Mom was driving us through the high Rockies on twisting roads in good weather. We were looking for the highest local peak, a favorite of hers. We got stopped at one spot where a gang of mountain goats came clambering down a ledge-filled cliff and picked their way across the road in a waterfall of hooves and horns. Moments later, my mom and I descended the mountain through a sudden blinding snowstorm that's common at that altitude, a jagged rock wall on one side, a 1,000-foot drop on the other. Mom, hunched over the steering wheel, never flinching, said out of the side of her mouth, without turning her head, "We're having an adventure, kid."*

*I don't think I ever loved my mother more than right then; her comment was so much the way she lived her life.*

*On a subsequent visit, 15 years later, I caught a first glimpse of something new. We were tooling along a major highway on our way to lunch when she abruptly pulled off the road into the grid of a suburban neighborhood, made a few quick turns and stopped the car. We were facing a chain-link fence surrounding a small airport. We sat there a while. "Mom?" I said quietly. Her hands hadn't left the steering wheel. "What's this place?" she asked me in total confusion. "How do I get back on that road we were on?" Step by step—"OK, first back up the car, now go straight to the corner, turn the wheel left, now left again"—I led her around the block, tracing our return to the general flow of traffic.*

## Cleansing the Plaque

Bridging the gap between animal and human models has been the insurmountable obstacle for anyone pursuing a therapy for Alzheimer's, says Peter Reinhart, founding director of the Institute for Applied Life Sciences at UMass-Amherst. Formerly a tenured professor in neuroscience at Duke University Medical Center, Reinhart has held senior roles in research at pharmaceutical giants Pfizer and Wyeth and most recently served as chief scientific officer and head of corporate development and new products at Alzehon, a biotech company focused on brain health, memory and aging, and development of treatments for Alzheimer's disease and other neurodegenerative disorders.

Reinhart explains that the prevailing pharmaceutical approach has been to try to prevent amyloid plaque from forming and accruing on the brain in the first place—to head off what he calls, rather poetically for such a terrible process, "the amyloid cascade." Haydon, in contrast, is coming at things from the other side, intervening once the amyloid has already formed. "His approach has put him in a unique position," says Reinhart, who knows Haydon personally and has followed his career with great interest for some time.

The Proof of Concept Phase 1b clinical trial for Haydon's idea began in February 2015, and included 36 human patients with mild to moderate Alzheimer's disease. In the form of multiple increasing doses, the subjects each were given daily pills that resembled something you might come across in the multivitamin section of your local pharmacy. I've seen a sample, and the pill's modest size, oblong shape and light beige coloration left me feeling shortchanged. Could this small, nondescript pill really represent a milestone along the road toward relieving so much personal and familial and societal misery? It's possible.

**The Initial Results**

After nearly a year, the results were in. According to the usual biomarkers' readout, patients with Alzheimer's disease saw rapid reversal of the amyloid cascade. "Although this was a small sample size, we are highly encouraged by the results," Haydon said, speaking for his research team, in the official press release last Dec. 14. (Less formally, in our conversation a week or two later: "Lots of beer was consumed that night.") Reinhart considers the test results "extremely promising."

Levels of brain amyloid—readily determined through the amount of amyloid present in a subject's cerebrospinal fluid—changed to a "statistically significant" degree, according to the statement from GliaCure, the privately held biotechnology company Haydon has formed and with which Tufts University holds exclusive licensing arrangements for the GC21109 compound and related technology.

There's still some distance to go, of course. Haydon is busy raising funds for a Phase II trial of his Alzheimer's treatment that will involve 240 people and take two years. With any luck, he says, his company could have an Alzheimer's pill on the market by 2022-23, less than a decade from now.

*Once, when I was little, my mother, brother and I spent an afternoon on the eastern shore of Lake Michigan. The sand dunes were bigger than I had ever seen. My older brother Craig and I had to go up them as soon as the family car came to a stop in the parking lot, and we did, eagerly climbing, pawing with our hands as the sand gave way under us. At the top of the dune, I turned—Craig already having raced ahead to where he disappeared over a rise—and glanced back down. My mother was a small, distant figure, waving up at me. Then I turned again, back toward the lake, took one grainy, sinking step, and she was gone.*

*Wind off the dark lake blew over me atop the dunes. I couldn't see anyone; it was just me, I was seven or eight years old, and the wind was in my face, and all at once I felt like crying. Years later, my mother told me she had felt it, too, the immense, piercing loneliness of the place. "When I couldn't*

*see you, that was as frightened as I've ever been," she said with a small shudder.*

*Now she has gone over the lip of her own personal, late-life dune, reached the crest and taken one step more, the known world, cloaked in wind and sky, falling off behind her.*

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