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One of the world's best drug hunters went after Alzheimer's. Here's how he lost

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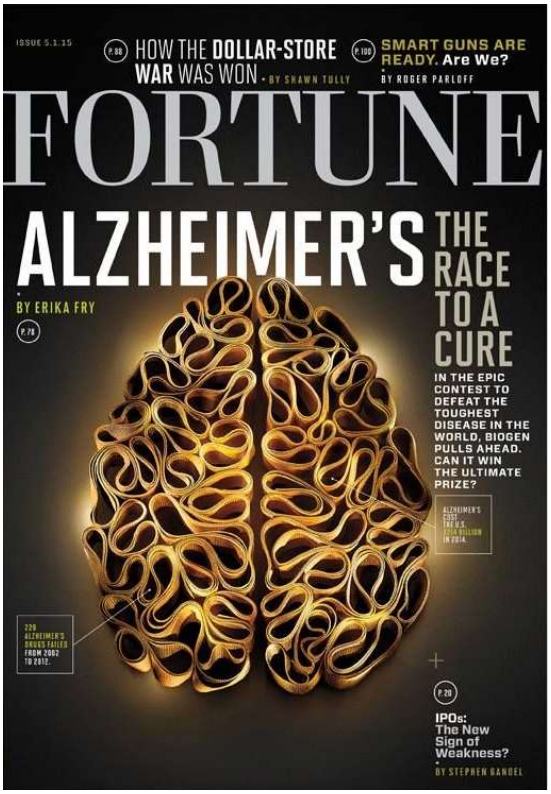
Al Sandrock, Biogen's chief medical officer, has had a knack for spotting biological clues that have eluded others. *Kayana Szymczak for STAT*

CAMBRIDGE, Mass. — The fate of the most promising Alzheimer's drug in decades was sealed with a text message.

It was sent to Al Sandrock, one of the most celebrated drug developers of his generation. He and his employer, Biogen, the pioneering biotech firm, had spent a dozen years and hundreds of millions of dollars developing the drug. It was the talk of neuroscience; it had been featured on the cover of Fortune — a sign of hope for the entire field.

The text message said his team needed to see him urgently. He didn't know why. He didn't know that Biogen's head of research was getting the same

message, and would be calling into the meeting on a secure line from an international trip.



Sandrock, the company's chief medical officer, was at the conference room in minutes; four Biogen vice presidents were waiting. "As soon as I walked in and I saw their faces, I knew it wasn't good," Sandrock said in his first interviews about the decision to stop the development of the drug. He could feel his colleagues looking at him. "I could almost tell they were feeling sorry for me, somewhat," he said. "Maybe it wasn't feeling sorry for me, it was just feeling sorry about the situation, you know? This was a very sad moment, very grave. It felt like it was very, very serious, what we were about to talk about."

In that sad, grave meeting in March, Biogen joined a grim assembly of drug developers that have failed completely and repeatedly against Alzheimer's[5]. Between 2008 and 2018, according to the IQVIA Institute, no new Alzheimer's treatment was approved, but 86 efforts were discontinued. Why has a disease that afflicts 5.8 million Americans and costs $290 billion annually proven impervious to modern medical science? New details of Biogen's Alzheimer's failure[6], as told by Sandrock himself, reveal part of the answer: The same biological detective skills that lead to successful medicines against other diseases result in only wasted money and dashed hopes in Alzheimer's, because researchers know so little about the condition that their instincts prove wrong. That is what happened to Al Sandrock.

In the room, the executives gazed at a slide deck detailing results from two ongoing clinical trials of aducanumab, the Alzheimer's drug Sandrock had championed. To guard the integrity of the study, patients, doctors, and Biogen had not been able to see the data. But as is standard practice, a committee of physicians monitored the results to make sure no dangerous side effects were emerging and that patients weren't being kept in studies that would not succeed.

A few days before, that committee had contacted the four Biogen vice presidents — in biostatistics, regulatory affairs, clinical development, and drug safety — and told them there was no hope. The vice presidents had pored over the data and reached the same conclusion. Now it fell to Sandrock and Biogen's chief scientific officer, Michael Ehlers, to make the final decision to stop the trials.

Sandrock watched the slides projected on a screen, and looked at the data in a printout in his hands. He was in a daze, and had to go over them again with the group, and on paper. "I'm not sure I quite grasped the situation," he told STAT. "I just needed another look at it, and then I looked at it a couple more times by myself, too, just to be absolutely sure."

To understand why there was so much anticipation about aducanumab, you need to understand the magnitude of Sandrock's success.

"The guy is a genius in spotting products," said Jim Mullen, who was Biogen's chief executive from 2000 until 2010. "He has personally spotted, advocated for, and successfully led more drugs through development than almost anyone in the industry."

Sandrock spent the first nine years of his life in Japan, where his father, a ship's captain in the merchant marine, met his mother, who is Japanese. He is a genial man — known for his big presence, warm emotions, and great instincts. He has been at Biogen since 1998, almost karmically joined with the company. When he was diagnosed with cancer, in 2017, he was put into remission with a Biogen drug: Rituxan, on which the company receives a royalty. But what sets him apart is his knack for spotting biological clues that have eluded others.

Sandrock identified three drugs that account for 58% of Biogen's $13.5 billion in total revenues.

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The first was Tysabri. A multiple sclerosis drug, Tysabri was being developed by Ireland's Elan Pharmaceuticals in the 1990s. But it was seen skeptically by executives at Biogen and by others in the industry; the drug had failed in one clinical trial, and there were limited data.

But Sandrock saw something different. In MS, white blood cells go rogue and attack the nerves, including the brain and spinal cord. Tysabri was being designed to try to stop the attacks. Because of work Biogen was doing in animal models, Sandrock thought it might work, despite what his then-boss, Nancy Simonian, called "an uphill battle" internally. He prevailed in his arguments, and Biogen partnered with Elan in 2000.

The next year, mid-stage data showed that the drug dramatically reduced MS relapses. It would go on to be approved by the Food and Drug Administration in November 2004 and generated $1.9 billion in sales last year.

The second was Tecfidera, also for MS. It was spotted by a colleague of Sandrock's, who mentioned to him that a German doctor had tested a pill used to treat psoriasis in 12 MS patients. Did Sandrock want to look? Once again, a big decision was going to be based on Sandrock's ability to read a small amount of data. "We had enough experience with MRI scans and MS patients to know what was unusual — and this was unusual," Sandrock remembered. Biogen purchased its maker in 2006, Tecfidera was approved in 2013, and last year it had sales of $4.3 billion.

Spinraza, Biogen's groundbreaking treatment for spinal muscular atrophy[8], the leading genetic cause of infant fatalities, came from a partnership struck with Ionis Pharmaceuticals in 2012. Sandrock heard about the animal data from the drug's inventor, Ionis' C. Frank Bennett, who he had sat with at a charity dinner. He was blown away by the data and impressed by Ionis scientists' willingness to argue with each other — the key to good science — in front of Biogen executives. Approved in 2016, the drug had sales of $1.7 billion last year.

Despite those victories, there were hard lessons along the way. Three months after the approval of Tysabri, Biogen received news that a patient taking the medicine had died. Tysabri had done its job too well, blocking white blood

cells so effectively that they allowed a dormant virus to destroy the patient's brain. More cases of the condition followed.

"I felt I had a part in that death," Sandrock recalled. Within a matter of days, Biogen had decided to withdraw the drug from the market. He felt so responsible he told his teenage children. His son shrugged, telling him that he was trying to help patients, not harm them. "It's funny, what he said made me feel better, because it's true. But I'll never forget that day."

Mullen, who was Biogen's CEO at the time, took Sandrock off all his other projects and moved him full time to figuring out what had gone wrong and how to set it right. Biogen determined that the side effect occurred only once in a thousand patients, and the FDA allowed Tysabri back on the market in July 2006, raising its price 20% to $28,400 per year because it would be used in fewer patients.

Working with Elan, Biogen developed a diagnostic test that could identify if people were infected with the brain-damaging virus, giving patients further control of the risks they took. Last year, Tysabri was taken by 84,000 people.

Sandrock's work reduced suffering and generated enormous profits for Biogen. Alzheimer's looked like an opportunity to have an even bigger impact.

The Alzheimer's Association forecasts that, by 2050, 13.8 million Americans will suffer from the disease at an annualized cost of $1.1 trillion unless researchers can develop treatments to slow or reverse it.

But drug developers have had no real success. Only four Alzheimer's drugs have ever been approved, and all temporarily improve memory without treating the underlying disease. The question was whether Sandrock's gift for drug hunting could serve him well here.

For the past 20 years, major Alzheimer's drug efforts have focused on the same thing: a protein fragment called beta-amyloid.

When German psychiatrist Alois Alzheimer first described the disease in 1906, he noticed not only memory-destroying dementia, but also a peculiar physical abnormality visible only after death: Patients' brains were filled with strange clumps and tangles. In the 1990s, scientists had realized that beta-amyloid seemed to play a key role in these tangles and might cause the disease.

Elan, Biogen's former partner on Tysabri, led the way in developing drugs based on the so-called amyloid hypothesis[9]. Its vaccine, which trained the body to attack amyloid, caused brain swelling and was discontinued in 2002. Working with Pfizer and Johnson & Johnson, it then developed an antibody drug. That failed to show a benefit in clinical trials. A similar Eli Lilly drug failed in 2012. Two antibodies licensed by Roche would go on to fail, as would numerous pills that sought to lower amyloid in the brain by other methods.

Sandrock, however, believed that these drugs had failings that made it impossible to test the amyloid hypothesis. In his view, for example, Elan's drug was underdosed to prevent side effects, and Lilly's never reduced the amount of amyloid in the brain.

"Yes, there were a lot of failed trials. But if the drug doesn't even get into the brain or doesn't engage the target or reduce amyloid, I'm not sure we really ever tested the amyloid hypothesis in the past," Sandrock posited.

Aducanumab was designed from the start to be a better drug. In 2007, Sandrock arranged a partnership with Neurimmune, a company in Zurich, Switzerland, to create the perfect antibody. The antibody they designed was based on one that occurred naturally in elderly people who did not have Alzheimer's; perhaps, the logic went, it was protecting them. And when early results from a 165-patient study were presented in 2015, they were unbelievable.

At three different doses, aducanumab seemed to lower the amount of amyloid plaque in the brain, with the result becoming stronger as the dose increased, a key sign that a drug might be effective. Moreover, two different tests designed to measure the medicine's effect on mental function seemed to show it slowed memory decline and the loss of the ability to do everyday tasks.

But there were reasons to believe that it might be a chance result. The study was small. Biogen had not compared each dose to a single placebo group, but to individual placebo groups for each dose that were then combined, which could lead to statistical artifacts. And in a middle dose, plaque was cleared from the brain according to PET scans, but the patients didn't show less of a decline in their ability to think and do tasks. That middle group "was always kind of a thorn in our side," Sandrock said. "But maybe it was telling us the truth."

For skeptics of the amyloid hypothesis, there would have been no doubt: Amyloid plaques were not destroying the brain; they were the wreckage left behind.

"If anything they're the tombstones, they're what happened earlier," argued Dr. Lon Schneider, an Alzheimer's researcher at the University of Southern California's Keck School of Medicine. "They are trailing indicators that a battle took place."

When Sandrock and the other executives gathered to review the data in March, it quickly became clear aducanumab had failed.

The two ongoing trials were to be stopped only if the chance of success had fallen below a certain threshold in both, and if no dose or subgroup showed a positive result. Sandrock said there is no doubt those criteria were met.

He and Ehlers decided in that meeting to halt the trials, and Sandrock went to tell Biogen's chief executive. He also told the researchers who had been working for him in running the trial. There were tears. It was already evening, and pizza was ordered as the next day's presentations were prepared.

Sandrock knows he ate a slice, but doesn't remember how it tasted. The next day, Biogen announced aducanumab's failure to the world. Afterward, Sandrock gave an extemporaneous speech to Biogen employees. One of his researchers approached him, telling him they had followed the science and that she would not have done anything differently.

Sandrock, after considering it, has decided he basically agreed. Some people with forms of Alzheimer's that run in families have mutations in amyloid. In those people, amyloid causes the disease. He believes it may be a trigger that can't be un-pulled. By the time patients are diagnosed with Alzheimer's it may already be too late.

He also thinks it might be worth testing amyloid drugs even earlier in the disease, but he has no idea if Biogen will decide to do that. Nor does he know if it will make sense to combine a drug like aducanumab with other medicines. He points out that Biogen was always testing would-be Alzheimer's drugs that work in other ways, such as by targeting inflammation in the brain or the protein called tau.

"We have been filling our pipeline with more shots on goal, if you will," Sandrock said. "But I also want to make sure the quality of our shots is very,

very high. I want to believe in everything we have in our pipeline."

Brian Skorney, a sell-side analyst at Baird, said he sees no reason to explore aducanumab further. "I don't think there's anything Biogen could really say compellingly to convince me to revisit the amyloid hypothesis," Skorney said.

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He feels for Sandrock and has no qualms about Biogen having run the study. "Alzheimer's was swinging for the fences," Skorney said. "And you look at their pipeline, there's a lot of swinging for the fences. There's not a lot of, OK, we're going for some base hits here. And that's where investors are frustrated."

Eisai, with which Biogen partnered on Alzheimer's drugs, has announced it is starting another trial of a new amyloid antibody, but Biogen was not on the press release as would have been expected. ("I have to say it would have been better, I think, to take some time to look at the data, personally," Sandrock said.)

When Biogen announced aducanumab's failure, Wall Street rendered its verdict. The company's stock fell 29% to $227 after the March 21 announcement, erasing some $20 billion from the company's market capitalization.

But Sandrock's first thoughts were of people he knew with Alzheimer's, the parents of people with whom he studied medicine. One had just entered an aducanumab clinical trial.

"I felt like I had been kicked in the gut," Sandrock said. "The first thing I thought about was how many people I disappointed."

Months later, he and others at Biogen continue to parse new data from the now-discontinued trials. What comes next is not clear.

Will Sandrock spot a fourth hit, or has he already done so? It's possible. Sandrock is very good, but he's also been very lucky. And in the drug business, where it is always better to be lucky than good, the hardest moments come when the luck runs out.

"One thing I remember through all of our downturns, Biogen really has this belief in science," Sandrock said. "The science will lead us to the right answer. I know that it may not seem like that now, but there's this belief here that science will show us the way. So we've got to follow the science."

It's true that science eventually leads to medicine. But sometimes the path can be fraught.

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