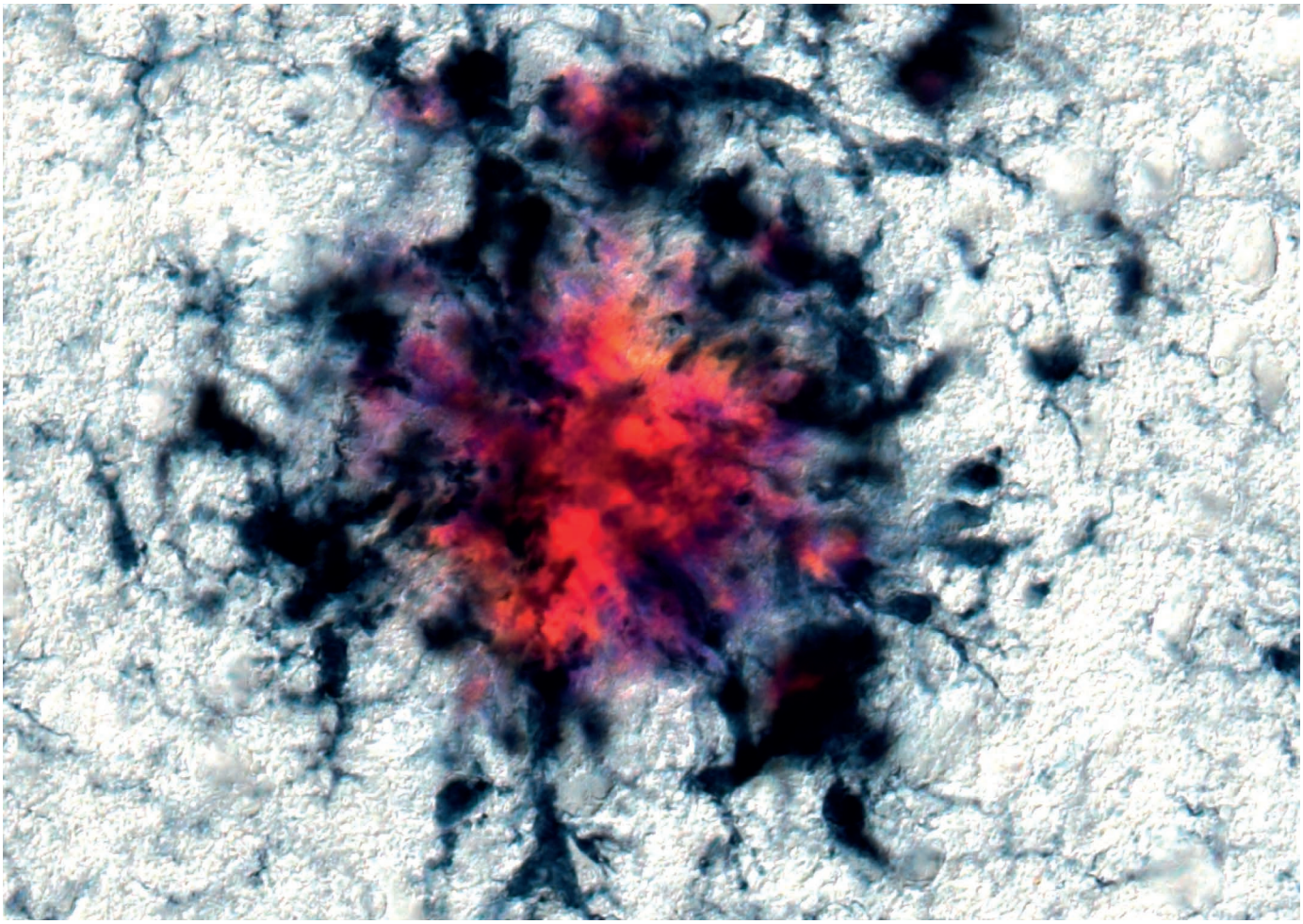

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THE BRAIN INFLAMED

The brain's immune system could be provoking Alzheimer's and other neurodegenerative diseases. Can scientists get it back in check?

BY ALISON ABBOTT

Neuroscientist Michael Heneka knows that radical ideas require convincing data. In 2010, very few colleagues shared his belief that the brain's immune system has a crucial role in dementia. So in May of that year, when a batch of new results provided the strongest evidence he had yet seen for his theory, he wanted to be excited, but instead felt nervous.

He and his team had eliminated a key inflammation gene from a strain of mouse that usually develops symptoms of Alzheimer's disease. The modified mice seemed perfectly healthy. They sailed through memory tests and showed barely a sign of the sticky protein plaques that are a hallmark of the disease. Yet Heneka knew that his colleagues would consider the results too good to be true.

Even he was surprised how well the mice fared; he had expected that removal of the gene, known as *Nlrp3*, would protect their brains a little, but not that it would come close to preventing dementia symptoms. "I thought something must have gone wrong with the experiments," says Heneka, from the German Center for Neurodegenerative Diseases in Bonn.

He reanalysed the results again and again. It was past midnight when he finally conceded that they might actually be true.

Over the next couple of years, he confirmed that nothing had gone wrong with the experiments. Together with his colleagues, he replicated and elaborated on the results[1]. Since then, numerous studies have bolstered the link between dementia and the brain's immune system, highlighting the cells and signals involved[2]. But none has managed to fully pin it down — the link seems to be slippery and dynamic, changing as the disease progresses.

Even so, the idea has sparked the interest of pharmaceutical investors, who see a large, and entirely unserved, market: an estimated 50 million people worldwide have dementia — a number the World Health Organization projects will rise to 82 million by 2030. Of the eight drug-discovery projects backed by Dementia Consortium — a UK-based group of charities and pharmaceutical companies that has

Microglia cluster around plaques in a mouse model of Alzheimer's disease.

poured £4.5 million (US$5.7 million) into the projects — four are aimed at inflammation.

But there are roadblocks ahead. Scientists don't yet agree on whether the immune system will need to be ramped up or tamped down at different stages of disease. And some of the practical problems that have dogged clinical trials in Alzheimer's disease — imperfect mouse models and difficulties in recruiting patients early enough — may plague this new approach, too. Hanging over the field like a black cloud is the fact that all clinical trials in Alzheimer's disease have so far failed.

Still, bioinformatician Martin Hofmann-Apitius at the Fraunhofer Institute for Algorithms and Scientific Computing in Sankt Augustin, Germany, who specializes in pharmaceutical research, notes that researchers have filed several patents relating to inflammation-related targets. "Soon we will see a wave of clinical trials," he predicts.

CLOGGED AND SWOLLEN

The German psychiatrist Alois Alzheimer was the first to described the symptoms and pathology of dementia, in the early twentieth century. Looking under the microscope at the brain of a woman whose cognitive decline he had witnessed, he saw — and neatly drew — the plaques, now known to contain amyloid-β, and tangles of a protein called tau that together are the signature of the disease. In those earliest depictions of the affected brain tissue, Alzheimer also sketched microglia, a type of immune cell in the brain, nestling next to neurons. "Alzheimer himself noticed the cells and drew them in abundant number alongside neurons," says Heneka.

Although the sketches made no deeper link between microglia and disease, Heneka remembered them as links between inflammation and Alzheimer's began to emerge in the mid-1990s. He had been intrigued by some epidemiological observations showing that people given some anti-inflammatory drugs (to treat rheumatoid arthritis, for instance) seemed to be at a lower risk of developing Alzheimer's disease than the general population. He became encouraged by reports that microglia gather around plaques and areas of brain degeneration, and that inflammatory molecules such as cytokines collect in the cerebrospinal fluid of patients. Most scientists assumed that these observations reflected a passive response to tissue damage. But Heneka always suspected that inflammation could be actively provoking disease.

Microglia have turned out to be central to the link between inflammation and neurodegeneration (see 'Help or hinder'). The cells have two major functions. They take care of the general health of neurons and their synapses — the junctions between neurons where they communicate with one another. And they patrol the brain, searching for threats and problems. When they detect an infectious or otherwise-aberrant molecule such as amyloid-β — or debris from damaged cells — they become activated and signal to other microglia to join them in a clean-up effort. Certain microglial proteins gather into large complexes called inflammasomes (a key component of the inflammasome is Heneka's NLRP3 protein), which churn out clean-up signals in the form of activated immune molecules. Inflammasomes usually ebb away once the job is done, but in Alzheimer's they seem to remain activated, continuing to pump out inflammatory molecules yet failing to clean up properly.

In 2013, microglia began to loom large in Alzheimer's disease research. Around the same time that Heneka's paper showed that preventing inflammation staved off Alzheimer's pathology in mice, the *New England Journal of Medicine* published two large studies of gene variants associated with the disease[3,4]. Both studies linked the risk of developing late-onset Alzheimer's to a gene called *TREM2*, which makes a protein that sits in the membrane of microglial cells.

> "WE JUST DON'T KNOW ENOUGH ABOUT THE BIOLOGY YET."

Neuroscientists started to pay attention. So did immunologists. An interdisciplinary community of neuroimmunologists burgeoned. "Suddenly, huge opportunities opened up," says neuroscientist Michela Matteoli at the University of Milan, Italy, who now runs a neuroscience programme in the immunology department at the neighbouring Humanitas Institute. At Humanitas, she found a treasure trove of mouse models lacking specific elements of the immune system, which immunologists had never had reason to use for studying brain function. "Many of the tools we need are available," she says.

HEROES AND VILLAINS

How might microglia, which evolved to keep the brain in good order, become a force for the bad in Alzheimer's? Last year, Heneka and his colleagues published evidence suggesting a plausible mechanism for the switch, at least in their mice. They found that activated microglia discard the remnants of inflammasomes in tiny clumps called specks, and that these specks go on to seed new amyloid-β clusters, spreading the disease across the brain[5]. "A perfect storm," says Heneka. "Toxic amyloid-β promotes inflammation, which promotes more toxic amyloid-β."

He is working together with immunologist Eicke Latz, at the University of Bonn, to develop a drug that can stop the inflammasome from forming. That would allow the microglia to continue their other important roles in the brain's housekeeping without conscripting other microglia to help clean up. The storm would be kept at bay.

Latz co-founded the start-up IFM Therapeutics in Boston, Massachusetts, in 2016. The company, which was acquired by the pharmaceutical firm Bristol Myers Squibb last year, already has some candidate drugs that stop inflammasomes from forming, and Latz and Heneka hope to start clinical trials in the next couple of years.

Meanwhile, neuroimmunologists around the world are trying to gain a deeper understanding of the biology of microglia, to work out whether there could be other ways to design immune-based therapies for Alzheimer's and other neurodegenerative diseases. Some scientists think that the healthy activities of microglia could be bolstered to clear toxic amyloid-β more efficiently and avoid the storm altogether.

Two studies in mice and post-mortem human brains have shown that the microglia that huddle around plaques in the brain are a very specific subset[6,7]. They express some genes at higher or lower levels than regular microglia, and those patterns tell an interesting story: the cells seem to be trying to tune up their normal housekeeping duties to combat the plaques. Some of those genes remove safeguards, or 'check-points', from the pathways that lead to the cells' activation. Others are in pathways that sense damage or encourage microglia to engulf defective molecules. In each case, the gene-expression patterns indicate that the microglia are ramping up their house-keeping duties to try to protect the brain.

Mutations in about a dozen of these genes had already been identified as risk factors for Alzheimer's in humans, says Ido Amit, an immunogeneticist at the Weizmann Institute of Science in Rehovot, Israel, who conducted one of the studies looking at the gene-expression patterns[6].

Amit says that the cells are clearly there for a reason and might therefore be harnessed to help. "The results seemed to be telling us a strong message about the biology of the system," he says. If microglia could be helped to perform their regular functions more efficiently, and kept from any overzealous cleaning efforts, they might help stave off symptoms of the disease rather than worsening its course.

If there were any doubts still lingering about the importance of microglia in mechanisms of dementia — whether they serve as heroes or villains — these papers eliminated them. What's more, microglia could even be primed for activation by inflammation elsewhere in the body. Epidemiological studies have shown that the burden of infection

during life increases the risk of cognitive impairment or dementia in later life[8,9]. And earlier this month, Jonas Neher from the German Center for Neurodegenerative Diseases in Tübingen and his colleagues showed that provoking inflammation in mice by injecting molecules called lipopolysaccharides (LPS) into their bellies led to persistent changes in gene expression in brain microglia — even though the molecules themselves didn't enter their brains. Low doses of LPS led to increased levels of amyloid-β and plaques; high doses reduced the burden[10].

Microglia could even be involved in other neurodegenerative diseases, because similar findings have been observed in models of amyotrophic lateral sclerosis (ALS) and Parkinson's disease[11]. And research from Matteoli and others suggests they could be implicated even more widely in brain disorders, such as the rare neurodevelopmental disorder known as Rett syndrome[12,13].

SHELTER FROM THE STORM

Amit is now discussing with industrial partners how the housekeeping activities of microglia might be boosted. "This would allow us to reactivate our natural defences when damage is out of control," he says.

Others worry that activating more microglia in late stages of the disease might make things worse. "We just don't know enough about the biology yet," says Oleg Butovsky, a neuroimmunologist at Harvard Medical School in Boston, who led the other study on gene expression in microglia[7] and is developing biomarkers to identify them in the brain at different stages of the disorder. He says it isn't clear whether microglia should be boosted or suppressed, or even whether different tactics could be used at different times during the progression of the disease.

And not all scientists assume that the role of the immune system in neurodegeneration stops with microglia. Neurologist Philip De Jager at Columbia University in New York is developing an Alzheimer's therapy that is based on a microglial target, but says that cells from the rest of the body's immune system, such as T cells, which are present in very low numbers in the brain, might also turn out to be relevant.

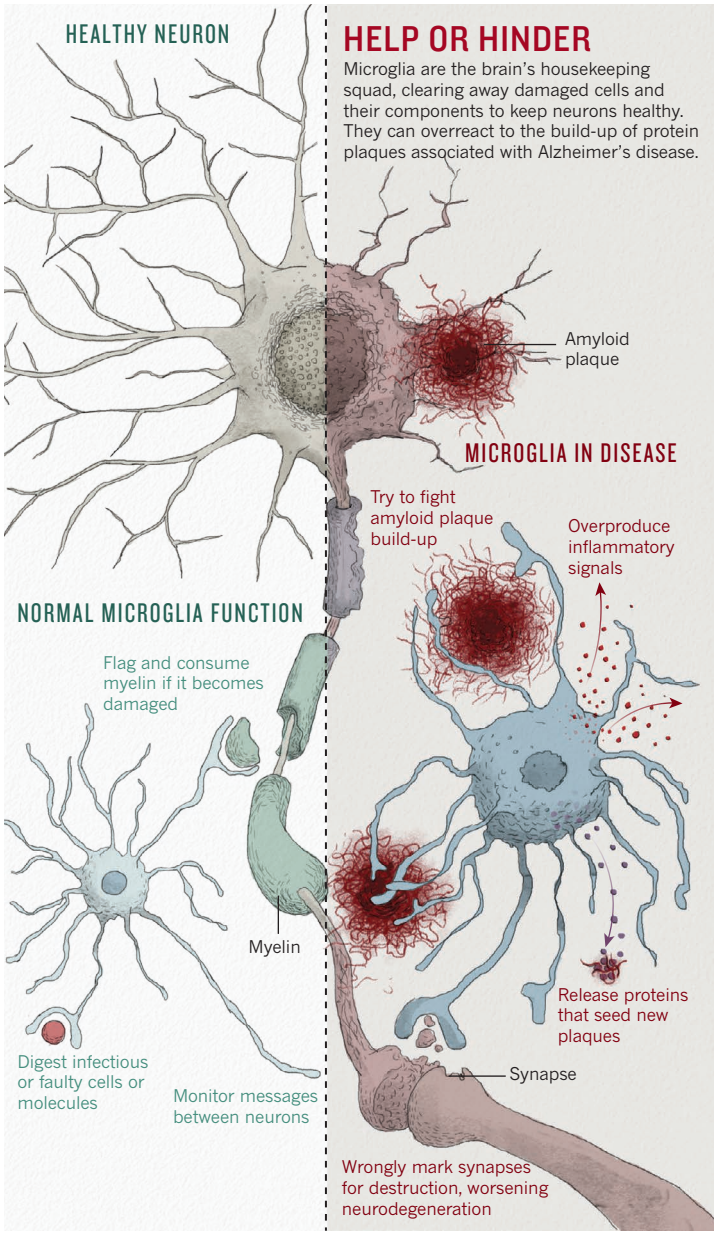
Although clinical interest is taking off, there are two stubborn elephants in the room: the mouse models used in Alzheimer's research are a poor proxy for the human condition, and it is difficult to find people who are good candidates for testing new therapies.

Mice with gene mutations that predispose them to Alzheimer's develop some realistic symptoms, but too quickly. That leaves scientists struggling to identify when treatment should be given. "Our models are just too accelerated," says Marco Colonna from Washington University School of Medicine in St. Louis, who has worked extensively on the biology of TREM2. "The field recognizes that the development of a model where amyloid accumulates more naturally is a priority."

It's also a challenge to identify people early enough in the progression of their disease for any experimental drug to have a chance of working. Alzheimer's researchers think that many of the earlier trials failed not because their hypothesis — that amyloid-β and tau are critically involved in the disease — is incorrect, but because the treatment is given too late. Patients are generally recruited to trials only after their plaque burden and neurodegeneration has advanced and the disease is probably irreversible. This could also be one reason why trials of anti-inflammatory drugs such as naproxen or rofecoxib have gone the same way as other potential treatments and shown no benefit in people with Alzheimer's, says Heneka. Biomarkers to identify people who are in a very early stage of disease are only now becoming available. Even then, the tests are very expensive and cumbersome, involving brain scans and spinal taps. And they still need to be completely validated in practice.

The many uncertainties are not damping enthusiasm. "It's been an exciting few years," says De Jager. Scientists in the field see a parallel with cancer immunotherapy, where the immune system receives a boost to attack tumours. "It seems that diseases not thought classically to be immunological may indeed have an immunological basis."

When Heneka thinks back to his experiments with the unexpectedly smart mice, he is cautiously optimistic that immune-based therapies could work for Alzheimer's disease. But the new trials need to face up to the troubles that plagued previous efforts. No one, he says, wants to see the approach fail for the wrong reasons. Then again, he had never seen a mouse that was supposed to have Alzheimer's pass a memory test with such flying colours. ■



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Alison Abbott *is* Nature*'s senior European correspondent.*

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