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A remyelinating agent remains a distant hope

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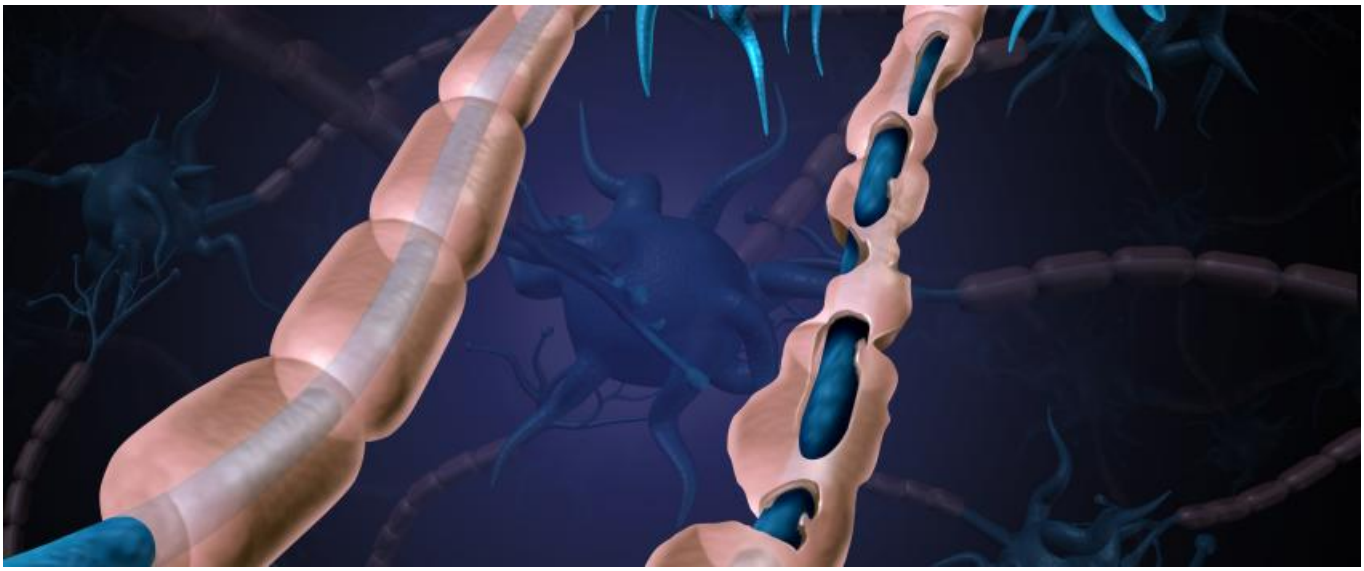

But the pipeline contains various approaches that are worth watching, with data from Abbvie possibly the next big event.

Keenly awaited early data from Atara that many hoped would show convincing evidence that ATA188 was driving the remyelination of nerves damaged by multiple sclerosis ultimately disappointed. Not that the project is being written off, but signals remain weak and hard to interpret; phase 2 data due next year will hopefully provide a clearer picture.

Remyelination is the next frontier for MS treatment, and Atara is one of a handful of companies with novel clinical projects, trying to prove that this is possible. Very varied mechanisms are being employed to achieve this end, from Abbvie's antibody elezanumab to Clene's nanotechnology; several academic groups are also exploring repurposed drugs.

Disability improvement, or at the very least stable disease, is the ultimate goal. Existing MS drugs achieve this for a while, by dampening down the immune attack that causes the damage to the myelin, and they do this very effectively. This is particularly true with some of the latest drugs to reach the market like Roche's Ocrevus and Novartis's Mayzent. There is even some suggestion that the latter might help promote remyelination.

But developing an active remyelinating agent is another matter entirely. This is not helped by the fact that the processes behind nerve degeneration in MS are still not fully understood, and that different mechanisms could cause relapsing/remitting and progressive forms of the disease.

Biggest hopes?

Biogen's opicinumab was arguably the biggest hope this field of research has seen – the antibody was thought to promote the development of oligodendrocytes, the cells that maintain the myelin coating around nerves. The project failed an important test back in 2016, and Biogen finally abandoned work a few years later.

The company has pushed on, however, and currently has a small-molecule remyelinating agent, BIIB061, due to enter phase 2 shortly. At a recent R&D day Biogen also mentioned two preclinical neuro-repair agents, although nothing has been disclosed about their mechanisms.

Abbvie also has a presence here with elezanumab, an antibody against repulsive guidance molecule A. RGMa is thought to block the growth of nerve endings and inhibit regeneration after CNS damage. The project, which is also being investigated in spinal cord injuries and stroke, has been put through two relatively large phase 2 MS trials, from which results should emerge soon.

Clene's approach has also attracted a fair amount of attention, although much remains to be proven. The company describes its lead asset, CNM-Au8, as a "bioenergetic nanocatalyst". This comprises a concentrated, aqueous suspension of clean surfaced faceted nanocrystalline gold, which is said to act as a catalyst to various intracellular biological reactions, including those involved in repairing and reversing neuronal damage.

Data from an imaging study released in August failed to excite investors, however, and strong results from ongoing larger trials, in MS and other neurodegenerative conditions like ALS, will be required to build hope.

The search for a remyelinating agent in MS: notable efforts

Company/sponsor	Project	Mechanism	Trial
Abbvie	Elezanumab (ABT-555)	Anti-RGMa MAb	2 ph2 trials, Radius-R in RRMS and Radius-P in progressive MS, due to report soon
Atara	ATA188	Epstein-Barr virus-targeted T-cell immunotherapy	Ph1/2 Embold study ongoing; interim ph2 data due H1 2022
Clene	CNM-Au8	Nanocrystalline gold	Ph2 in chronic optic neuropathy in MS (Visionary-MS), and small imaging study (Repair-MS)
Biogen	BIIB061	Oligodendrocyte progenitor cell stimulant	Ph2 +IFN +Copaxone due to start shortly
Nervgen	NVG-291	Protein tyrosine phosphatase modulator	Ph1 in healthy volunteers ongoing, plans to start ph2 MS trial in 2022
Pipeline Therapeutics	PIPE-307	M1R antagonist	Ph1 in healthy volunteers enrolling in first stage of MS programme
Acorda	rHIgM22	Remyelinating antibody	Two ph1 trials completed, development "deferred" since 2018
Rewind Therapeutics	Remyelination programme	Undisclosed	Preclinical
Convelo	Myelin repair programmes	Undisclosed (signed discovery deal with Roche in 2019)	Preclinical
Inflectis	IFB-048	ISR modulator	Research stage
Frequency Therapeutics	Remyelination programme	Undisclosed	Preclinical
Autobahn Therapeutics	ABX-003	TRβ agonist	Preclinical
Non-industry work			
US academic group	Bazedoxifene	SERM	Ph2 in women with RRMS
University of California/Moorfields Eye Hosp UK	Clemastine	Anti-histamine	Ph2 acute optic neuritis trial
MS Society	Metformin + clemastine	Type 2 diabetes medicine and anti-histamine	CCMR-two slated to start this year
Canadian academic group	Metformin	Type 2 diabetes medicine	Ph1/2 in children with MS

Source: Evaluate Pharma, clinicaltrials.gov & company statements.

Projects that more recently moved into the clinic include NVG-291 from Nervgen, being tested in healthy volunteers. It is said to work by modulating protein tyrosine phosphatase sigma, a receptor thought to be

involved in impeding the recovery of nerve cells. The small Canadian developer hopes to move into phase 2 in MS next year, as well as pushing forward in Alzheimer's and spinal cord injury, although funding would presumably need securing first.

Pipeline Therapeutics, which is working on several early-stage neuro-regenerative assets, has PIPE-307 earmarked for MS. A healthy volunteer study started this year. The company believes the project, a selective muscarinic M1 receptor antagonist, might work by driving the maturation of oligodendrocyte precursor cells into those that can produce myelin.

Academics and charities are also driving research. A few years ago a trial called CCMR-One, run by Cambridge University, found signals of remyelination with bexarotene in relapsing remitting disease. But this RXR agonist and off-patent skin cancer drug caused too many side effects to push on.

The same research unit hopes to start the CCMR-two trial this year, studying a combination of clemastine and metformin, respectively an anti-histamine and front-line diabetes medicine.

Clemastine is believed to work in MS by signalling stem cells to commence repair, and showed early promise as a remyelinating agent in the Rebuild trial. Metformin is thought to play a role in stem cell signalling, and could promote remyelination in a similar way to bexarotene. Both are also being tested in various other academic-sponsored studies and settings.

Much work is also ongoing preclinically at various small start-ups. But neurodegeneration is an incredibly tough area littered with many failures. It is encouraging to see so many different approaches in the pipeline, but it is success stories that are really needed.