



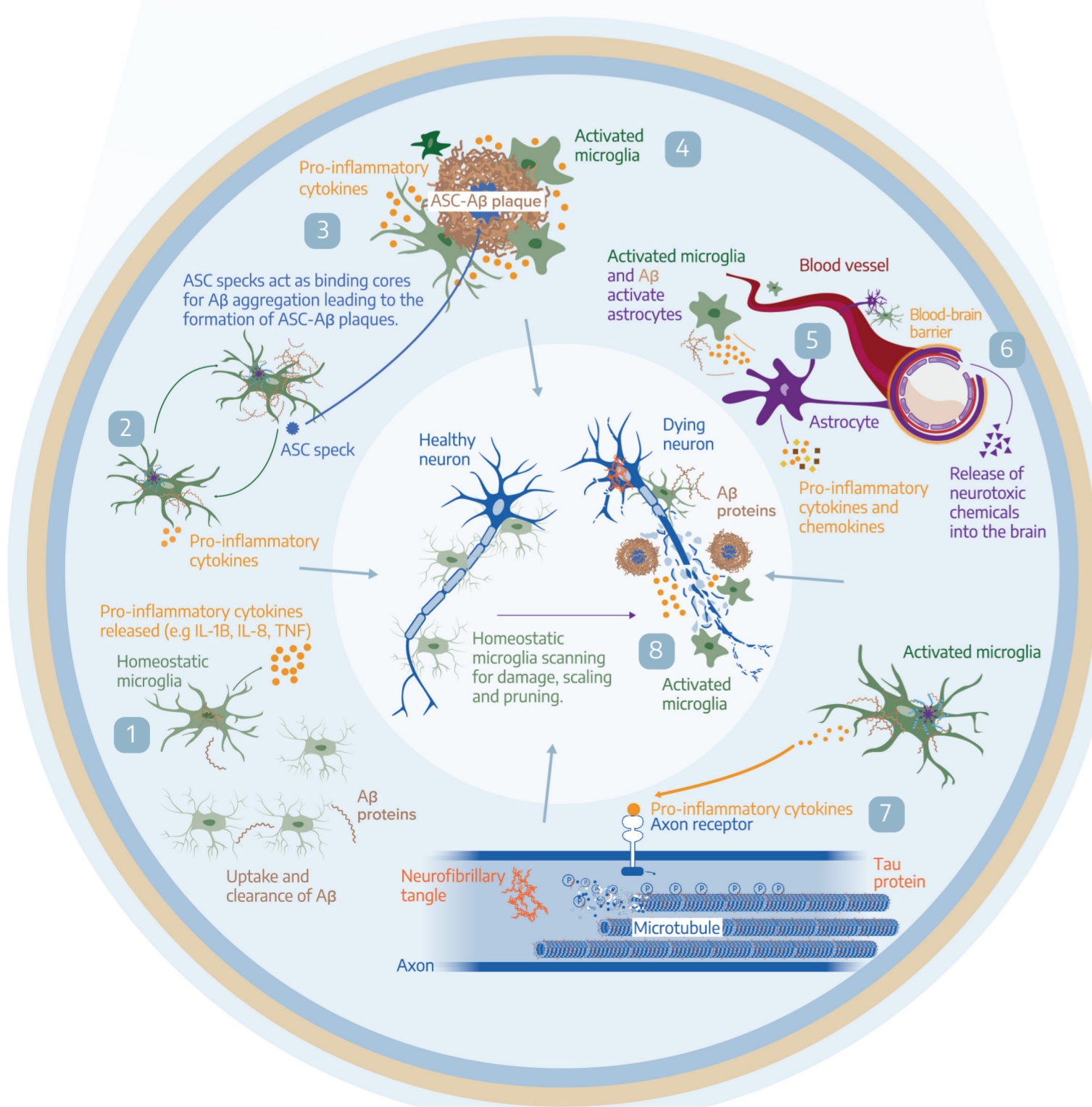
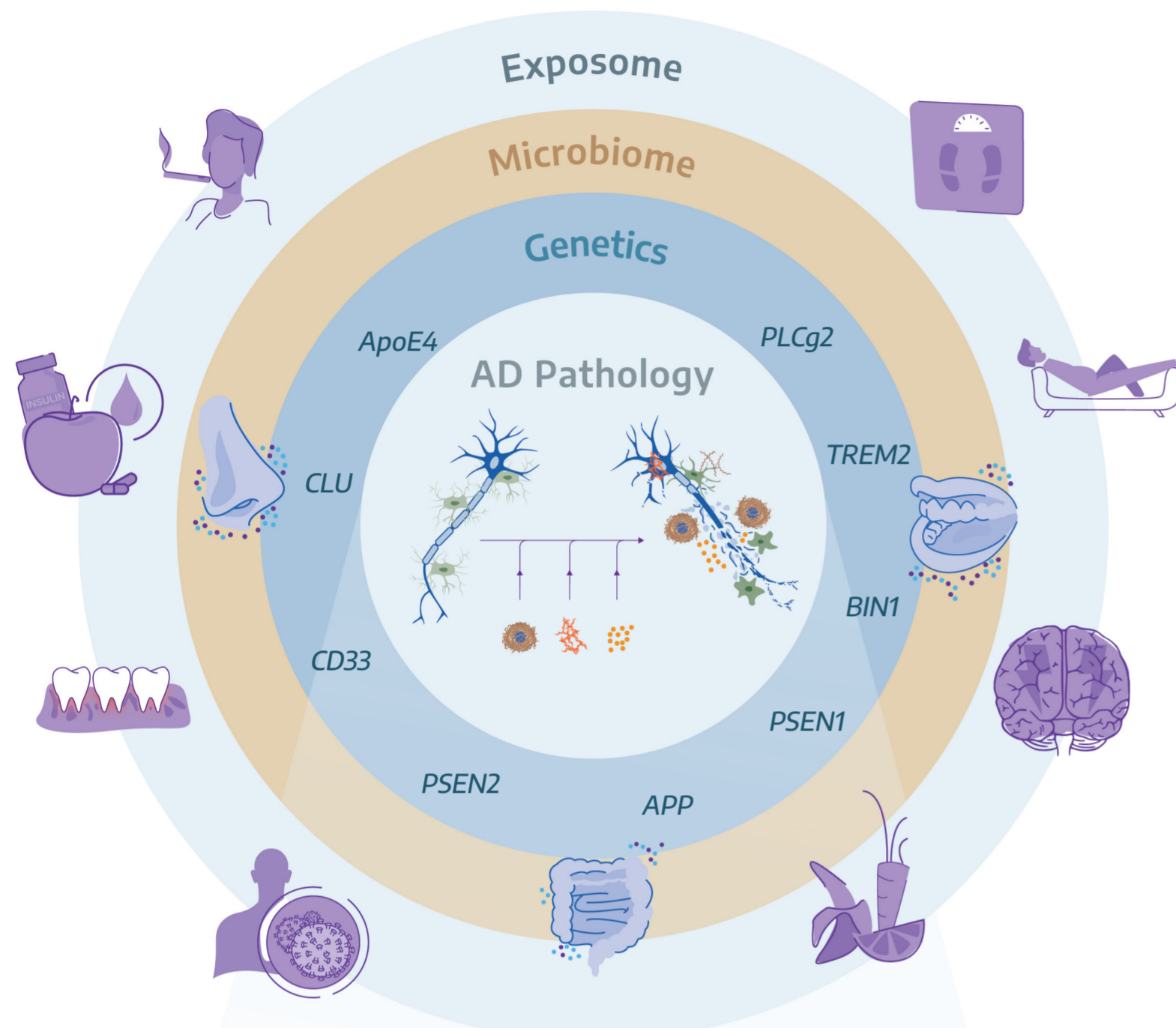
Untangling neuroinflammation in Alzheimer's disease

The past decade has witnessed tremendous efforts in Alzheimer's disease (AD) research.

Tau and A β have long been classified as the pathological hallmarks of AD, however therapeutic progress based on the tau and amyloid cascade hypotheses has remained slow.

More recently, neuroinflammation has been identified as a unifying biological principle of homeostatic destabilization affecting the risk, onset, and progression of neurodegenerative diseases. Genetic, exposome, and microbiome variation have all been found to contribute to pro-inflammatory responses.

To understand the contribution of the exposome, microbiome, and genetic factors, go to our program [website](#).



Exposome

The so-called "AD exposome" refers to lifestyle-associated risk factors for AD and associated dementias. These can contribute to an inflammatory response in the CNS that may initiate disease and exacerbate the progression of AD neuropathology.

The list of risk factors under investigation is vast, so we have only included a selection here.

Obesity >	Diabetes >	Smoking >	Infection >
Periodontitis >	Brain trauma >	Sedentary lifestyle >	Nutrition >

Microbiome

Imbalances in the human microbiota due to diet, chronic infection, environmental exposures, or the aging process are thought to lead to increased A β production and accumulation. The assessment of resident microbes in the development and progression of AD is still in its infancy.

Gastrointestinal >	Nasal >	Oral >
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Genetics

In most cases, AD does not have a single genetic cause. It can be influenced by multiple genes in combination with the lifestyle and microbiome factors mentioned above. Some of the genes currently known to increase the risk of AD are listed below.

ApoE4 >	APP >	PSEN1/PSEN2 >	TREM2 >
CD33 >	CLU >	BIN1 >	PLCg2 >

AD Pathology

<p>1</p> <p>Pattern recognition receptors on microglia detect Aβ in the vicinity. The binding of Aβ activates the microglia which engulf and breakdown Aβ releasing proinflammatory cytokines as a result.</p> <p>Under physiological conditions, Aβ is produced at high levels in the brain and cleared at an equivalent rate.</p>	<p>2</p> <p>Aggravators (described above) can modify the innate immune response caused by Aβ-exposed microglia, promoting a sustained and systemic proinflammatory state.</p>	<p>3</p> <p>Sustained microglia activation and exposure to Aβ triggers inflammasome activation and further release of pro-inflammatory cytokines and pyroptotic proteins such as ASC specks.</p>	<p>4</p> <p>Exposure to ASC-Aβ plaques further amplifies the pro-inflammatory response resulting in increased pyroptotic cell death and build-up of Aβ.</p>
<p>5</p> <p>Increased inflammatory cytokines and a buildup of Aβ also activates astrocytes which in turn release further pro-inflammatory cytokines, chemokines and other neurotoxins.</p>	<p>6</p> <p>Peripheral inflammation and reactive astrocytes reduce the expression of tight junction proteins which causes a breakdown of the blood-brain barrier and facilitates entry of neurotoxic chemicals into the brain.</p>	<p>7</p> <p>Pro-inflammatory cytokines bind to receptors on the axon which initiates an intracellular pathway leading to the hyperphosphorylation of tau causing it to disassociate from microtubules, causing their disintegration.</p> <p>Tau oligomers are toxic to neurons and cause further polymerization which results in neurofibrillary tangles.</p>	<p>8</p> <p>The sustained inflammatory state of microglia and astrocytes causes constant release of pro-inflammatory cytokines and chemokines thus resulting in neuroinflammation.</p> <p>This causes a buildup of Aβ plaques and neurofibrillary tangles leading to neuron death.</p>

As with all diseases, improved understanding of the complex mechanisms behind AD progression can highlight therapeutic targets. GLP-1 is one such target that is showing promise. To learn more visit our program [website](#).

Heneka M. et al. *Lancet Neurol* 2015; 14(4): 388-405. Heneka M. *Alzheimer's & Dementia* 2020; 16(S2): e044146

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