

β -Amyloid is a Cytokine and Alzheimer's Disease is an Autoimmune Disease

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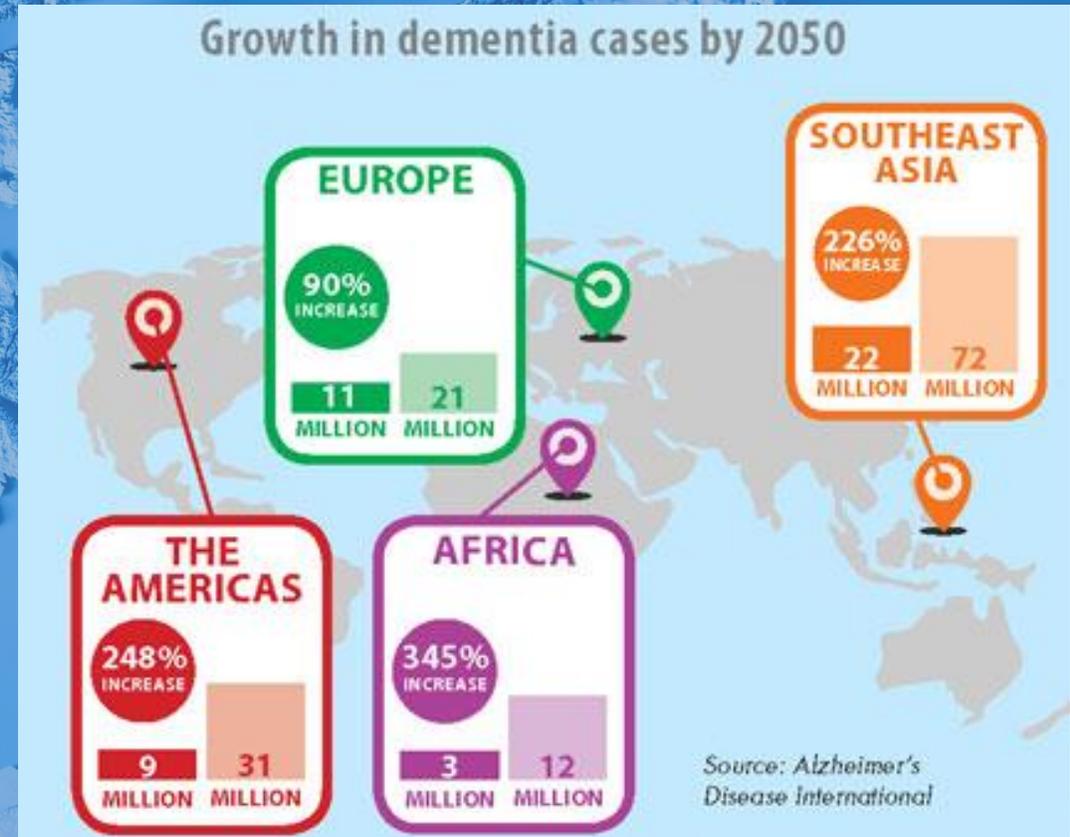
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Dementia/Alzheimer's Disease

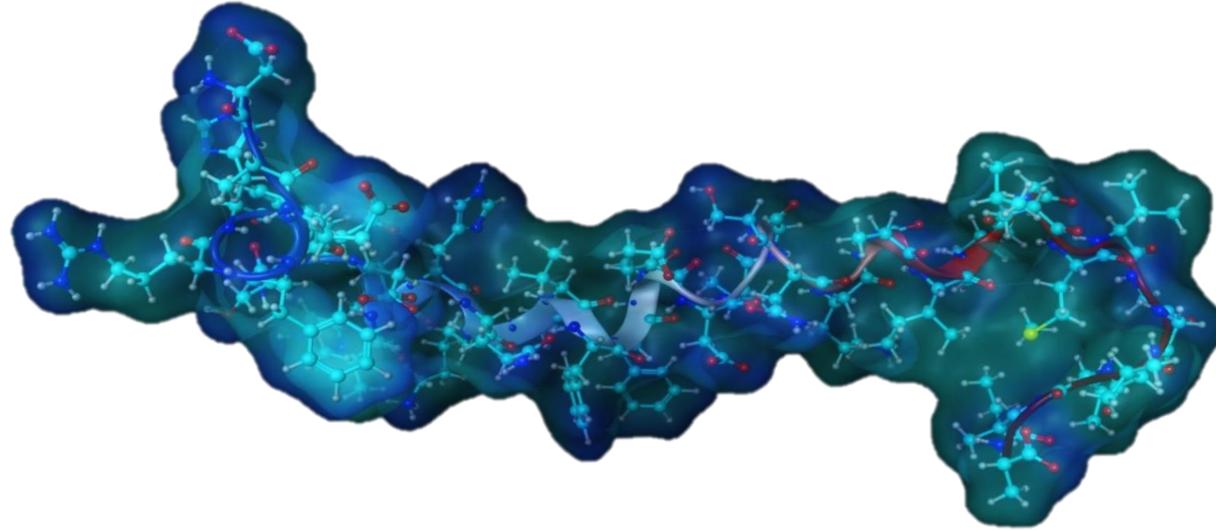
Global Problems Need Global Solutions



Afflicts 52 million people worldwide;
It will affect >150 million by 2050



β -Amyloid – Rethinking its Role?



D₁A₂E₃F₄R₅H₆D₇S₈G₉Y₁₀E₁₁V₁₂H₁₃H₁₄Q₁₅K₁₆L₁₇V₁₈F₁₉F₂₀A₂₁E₂₂D₂₃
V₂₄G₂₅S₂₆N₂₇K₂₈G₂₉A₃₀I₃₁I₃₂G₃₃L₃₄M₃₅V₃₆G₃₇G₃₈V₃₉V₄₀I₄₁A₄₂

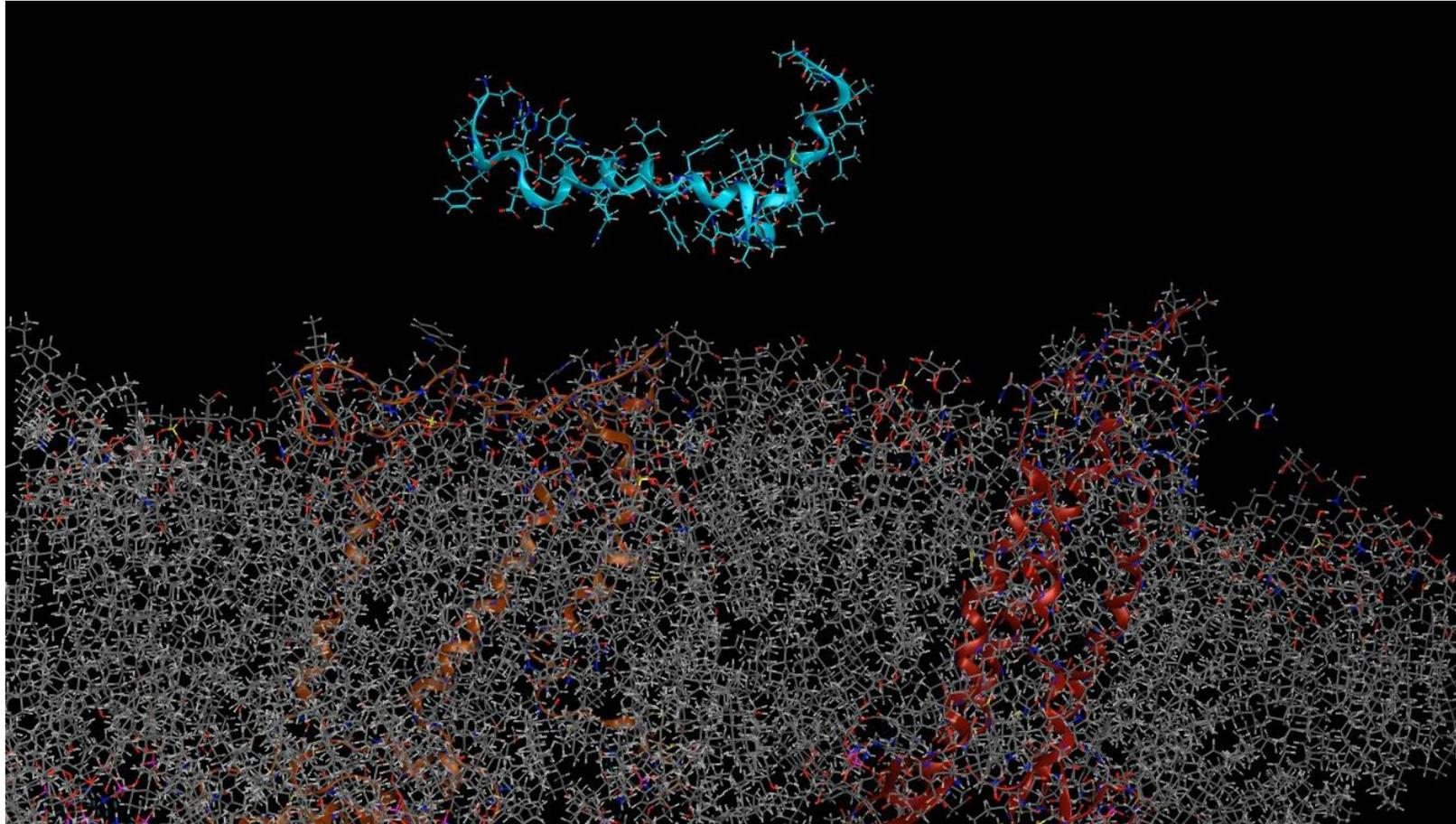
Re-evaluating the role of β -amyloid in Alzheimer's Disease

We Need New Ways to Think About this Old Disease?

“The crux of our argument is that something triggers the immune system that makes beta amyloid turn on and begin to seek and destroy bacteria. But the beta amyloid can't differentiate the bacteria from the neurons, so it starts to kill them as well. Thus, the processes of Alzheimer's begin.”

1. Weaver DF. Alzheimer's disease as an innate autoimmune disease (AD²): A new molecular paradigm. *Alzheimers Dement*. 2022 Sep 27. doi: 10.1002/alz.12789. PMID: 36165334.
2. Meier-Stephenson FS, Meier-Stephenson VC, ... Weaver DF. Alzheimer's disease as an autoimmune disorder of innate immunity endogenously modulated by tryptophan metabolites. *Alzheimers Dement (N Y)*. 2022 Apr 6;8(1):e12283. doi: 10.1002/trc2.12283. PMID: 35415204; PMCID: PMC8985489.
3. Weaver D. F. (2021). β -Amyloid is an Immunopeptide and Alzheimer's is an Autoimmune Disease. *Current Alzheimer Research*, 18(11), 849–857. <https://doi.org/10.2174/1567205018666211202141650>
4. Weaver DF. Amyloid- β is a cytokine. *Alzheimers Dement*. 2023 Sep;19(9):4237-4247. doi: 10.1002/alz.13165. PMID: 37228244.
5. Weaver DF. The Immunopathy of Alzheimer's Disease: Innate or Adaptive? *Curr Alzheimer Res*. 2023;20(2):63-70. doi: 10.2174/1567205020666230517103312. PMID: 37198985.
6. Weaver DF. Druggable targets for the immunopathy of Alzheimer's disease. *RSC Med Chem*. 2023 Jul 11;14(9):1645-1661. doi: 10.1039/d3md00096f.

A β Cannot Differentiate Bacteria from Neurons

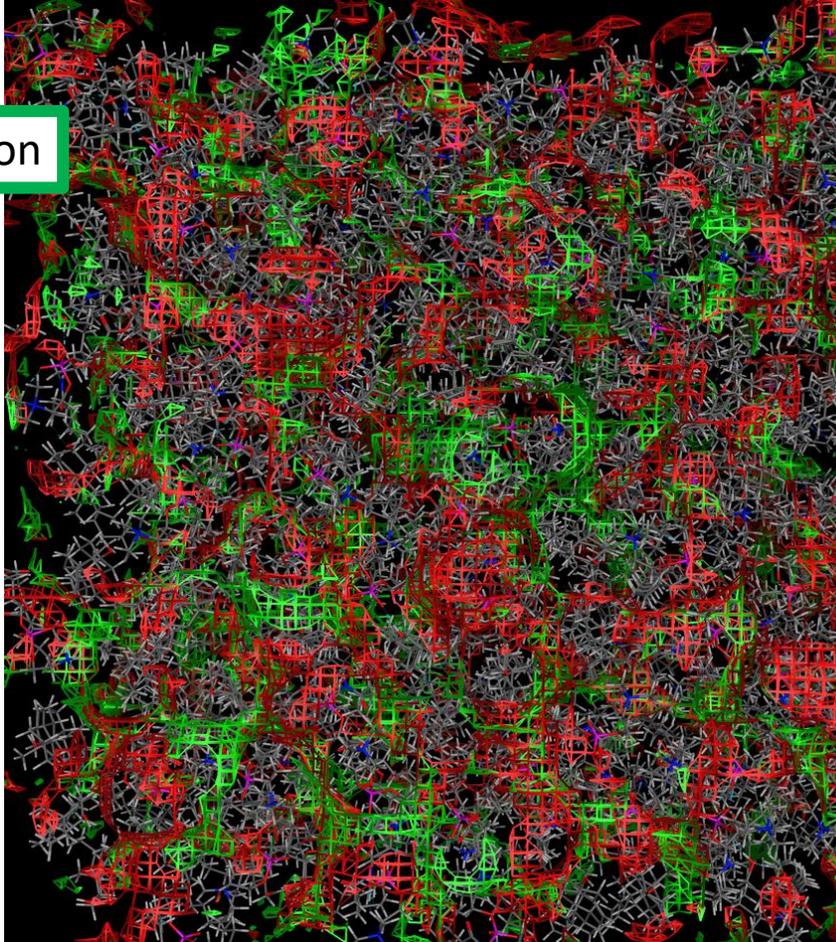


Prolonged molecular dynamics simulations of A β or AMPs attacking neuronal or bacterial membranes

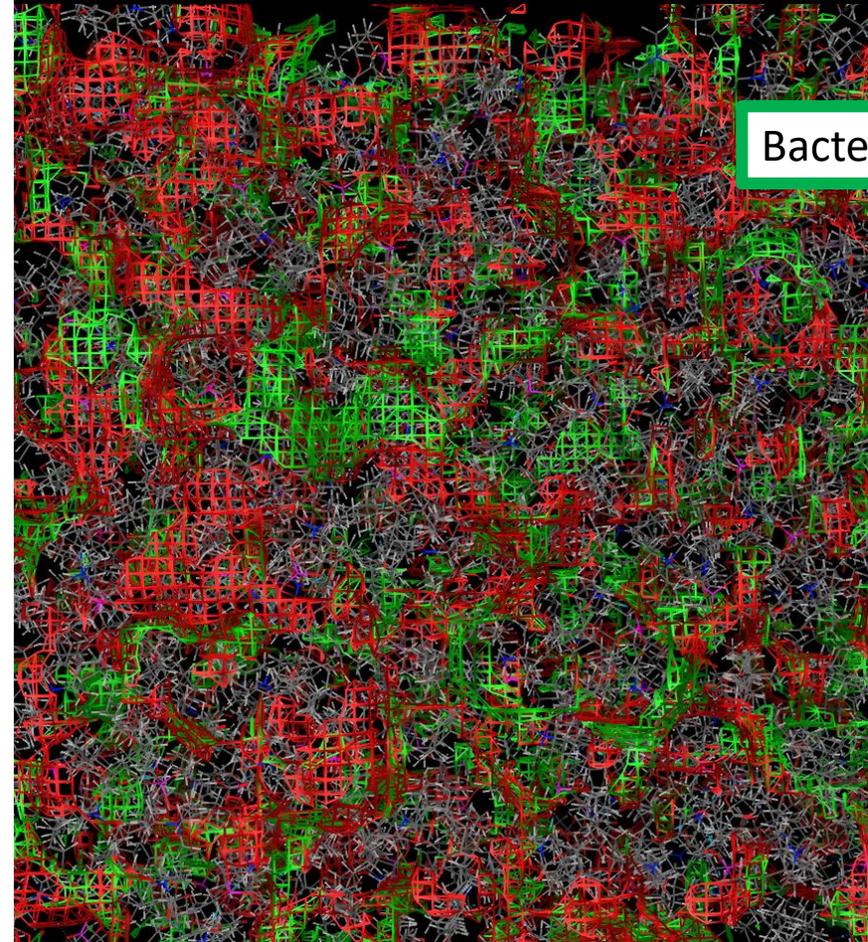
Gupta M, **Weaver DF**. Microsecond molecular dynamics studies of cholesterol-mediated myelin sheath degeneration in early Alzheimer's disease. *Phys Chem Chem Phys*. 2021;24(1):222-239. doi:10.1039/d1cp03844c

A β /AMPs Cannot Differentiate Bacteria from Neurons

Neuron



Bacteria



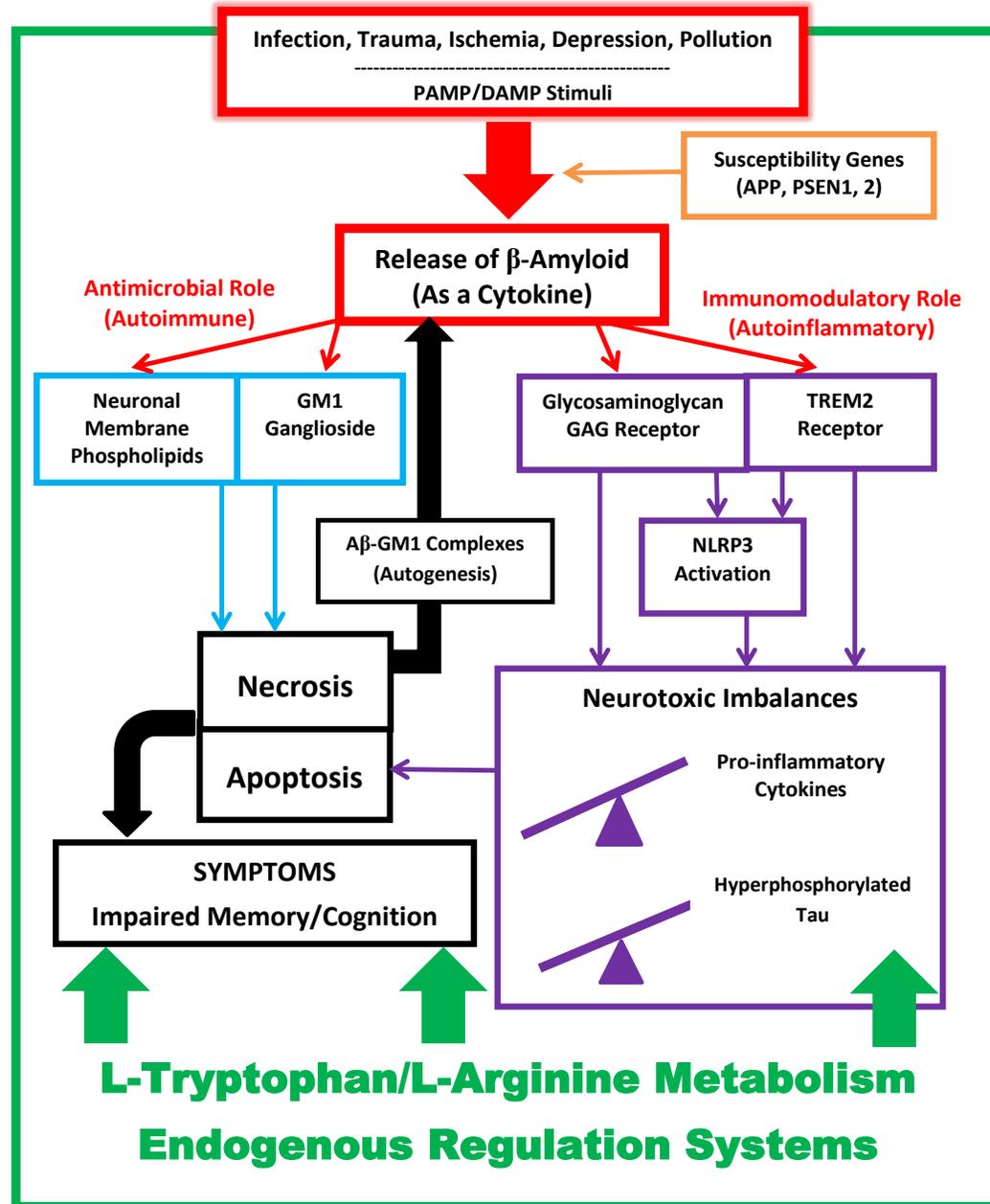
Electrotopological maps of neuronal and bacterial membrane surfaces

Alzheimer's as an Autoimmune Disease Model

In response to various stimuli (*e.g.* infection, trauma, ischaemia, air pollution, depression), A β is released as an early responder immunopeptide (cytokine) triggering an innate immunity cascade in which A β exhibits both immunomodulatory and antimicrobial properties (whether bacteria are present, or not), resulting in a misdirected attack upon 'self' neurons, arising from analogous electronegative surface topologies between neurons and bacteria, and rendering them similarly susceptible to membrane-penetrating attack by antimicrobial peptides (AMPs) such as A β . Following this self-attack, the resulting necrotic (but not apoptotic) neuronal breakdown products diffuse to adjacent neurons eliciting further release of A β , leading to a chronic self-perpetuating autoimmune cycle. AD thus emerges as a brain-centric autoimmune disorder of innate immunity.

Alzheimer's as an Autoimmune Disease Model

AD²



Key Points

- 1. β -Amyloid is an Immunopeptide/Cytokine of the Innate Immune System**
- 2. β -Amyloid Cannot Differentiate Between a Neuron and a Bacterium**
- 3. Alzheimer's Disease may be Considered an Autoimmune Disease of Innate Immunity**

1. Weaver D. F. (2021). β -Amyloid is an Immunopeptide and Alzheimer's is an Autoimmune Disease. *Current Alzheimer Research*, 18(11), 849–857. <https://doi.org/10.2174/1567205018666211202141650>

2. Weaver DF. Amyloid- β is a cytokine. *Alzheimers Dement*. 2023 Sep;19(9):4237-4247. doi: 10.1002/alz.13165. PMID: 37228244.

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