

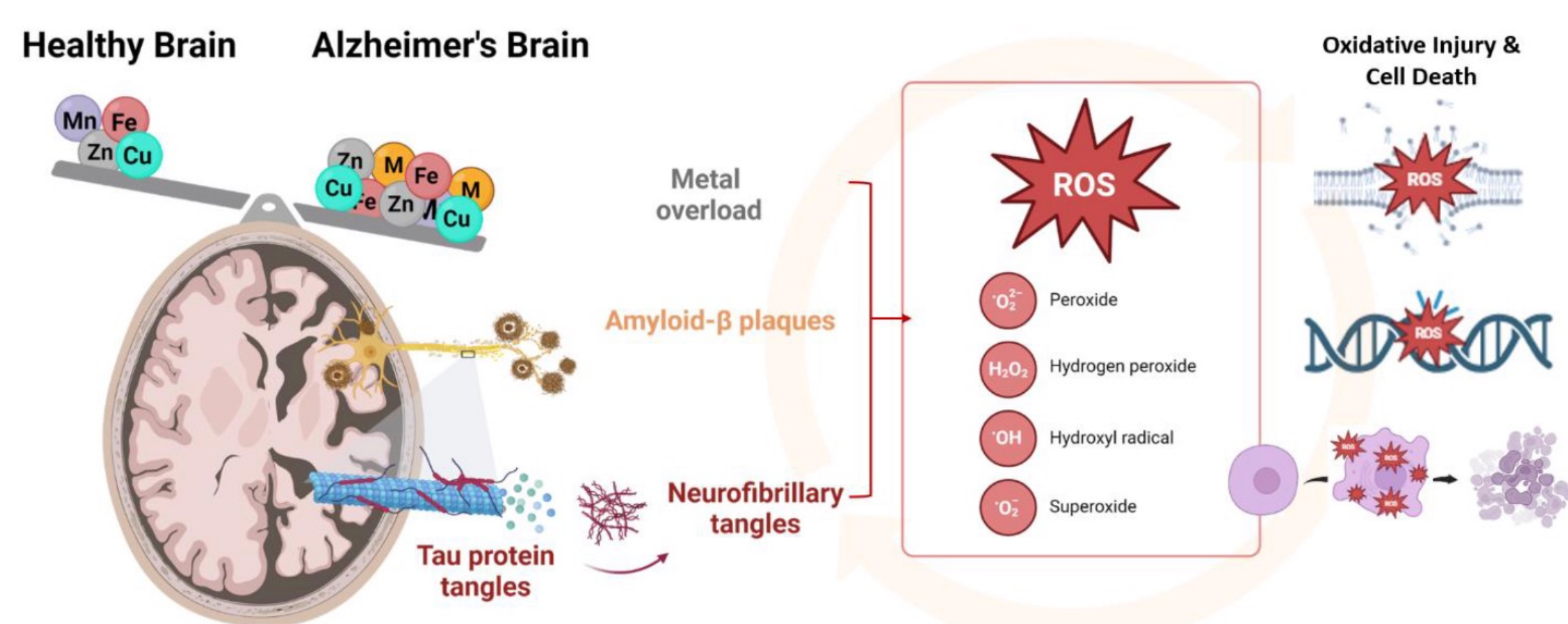
Macrocycle–Peptide Conjugates for Multifaceted Intervention in Alzheimer’s Disease Pathology



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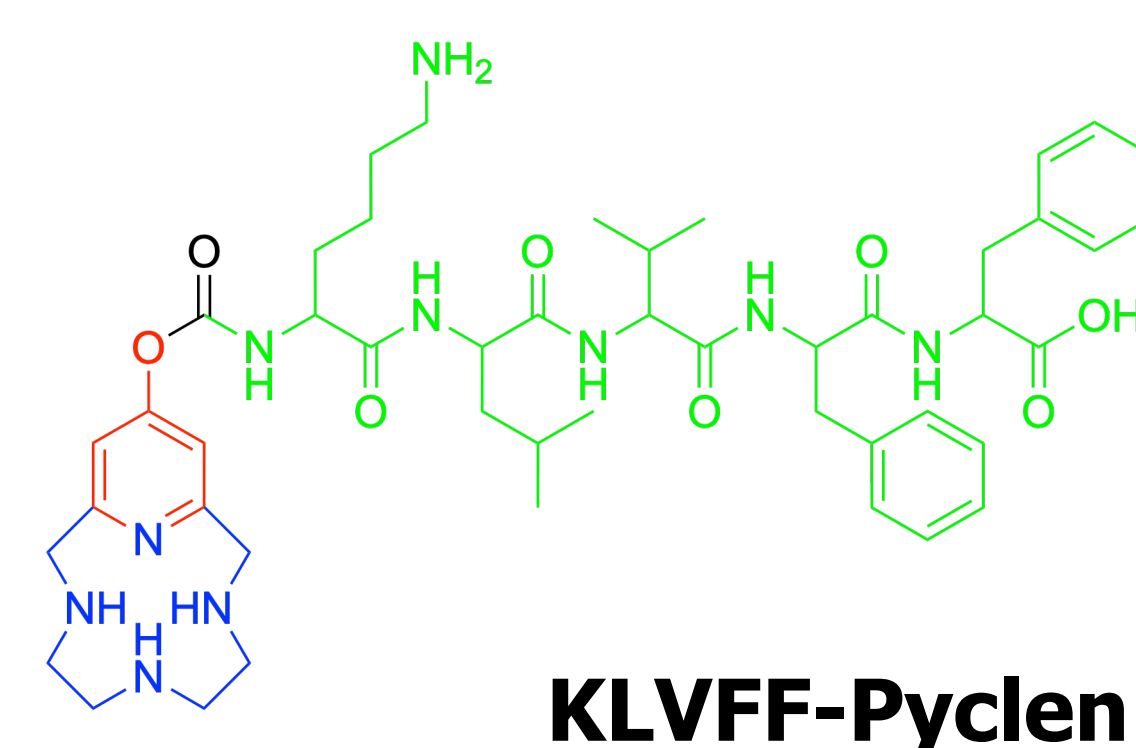
Introduction

- Alzheimer’s Disease (AD): Progressive, neurodegenerative disorder impacting millions.
- Treatments to date have largely focused on slowing the progression of symptoms.
- Hallmarks of disease progression include:



Rationale Design Strategy

- Small peptides have been shown to prevent the formation of amyloid-beta plaques.
 - Attach peptide to carboxyl group to preserve pyridine ring and 4N metal binding center
- Proposed:** Chimera molecule composed of plaque preventing KLVFF peptide with a macrocycle that has been shown to both reduce the effects of reactive oxygen species (ROS) and bind transition metal ions.
- Goal:** Three-pronged approach for the treatment of AD through prevention of amyloid plaques, ROS, and mis-regulated transition metal ions.



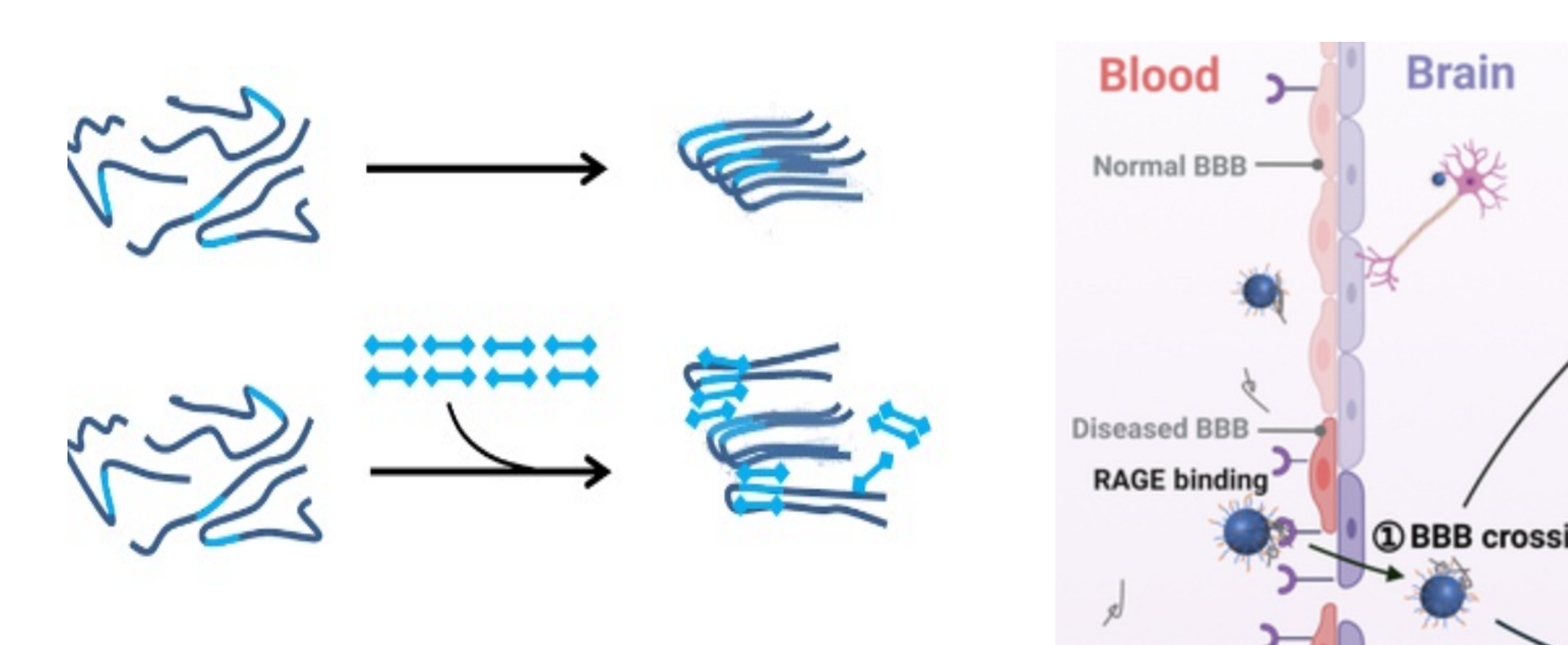
- = radical scavenger
- = metal chelator
- = amyloid plaque inhibitor

Future Testing

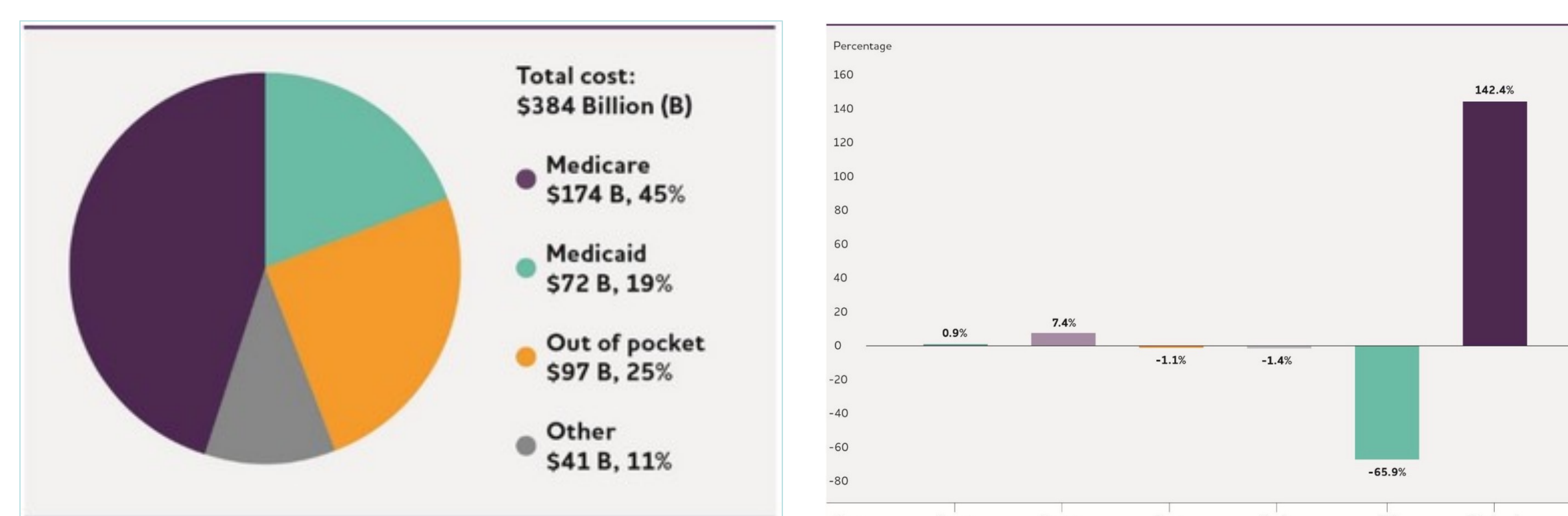
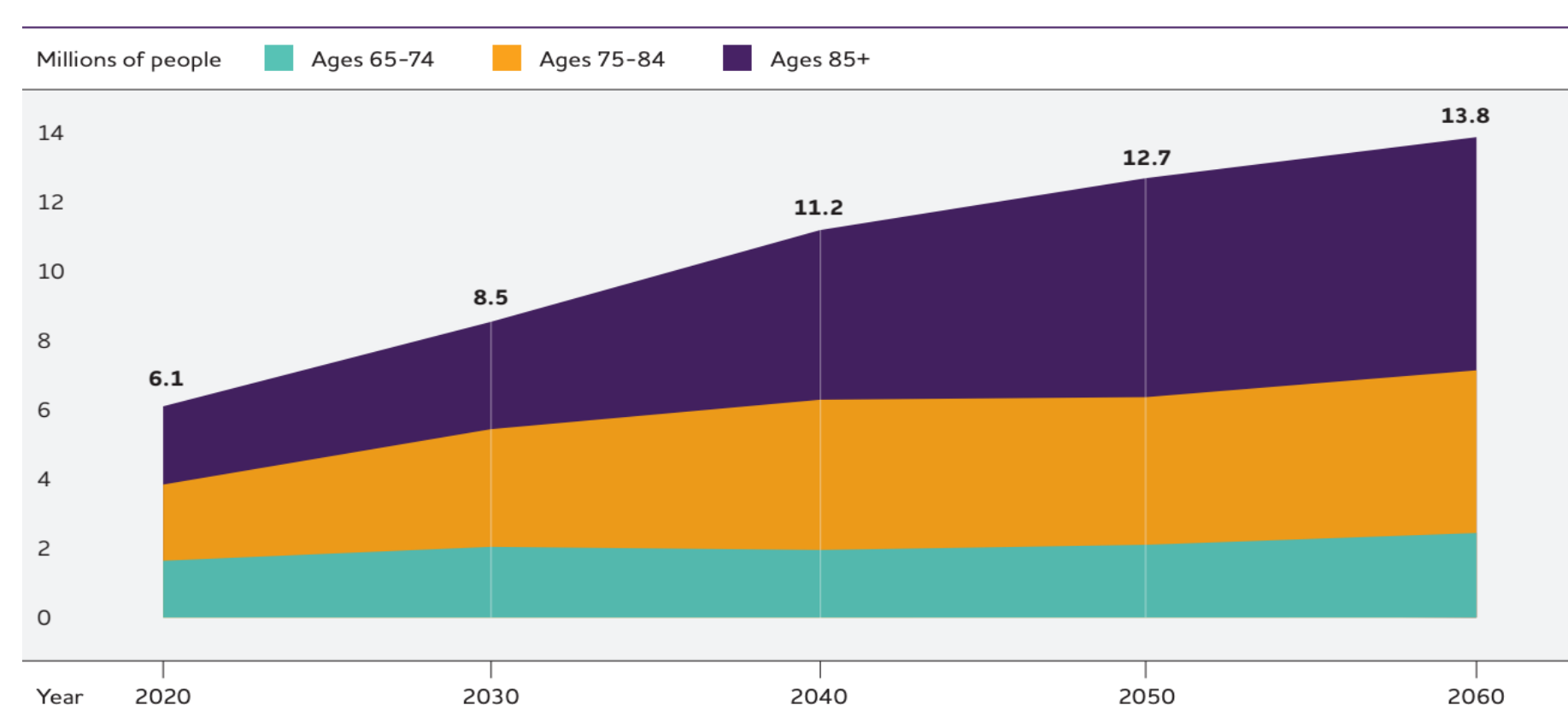
- PAMPA Assay
- DPPH Assay
- CACO-2 Assay
- Metabolic Stability

Advantages of KLVFF

- KLVFF has been shown to disrupt amyloid beta protein aggregation through interacting with regions of the amyloid beta protein
- KLVFF is amino acids 16-20 of the amyloid beta protein, allowing it to disrupt interactions in aggregation
- KLVFF has also been shown to pass the blood brain barrier through RAGE receptors, which are over expressed in AD

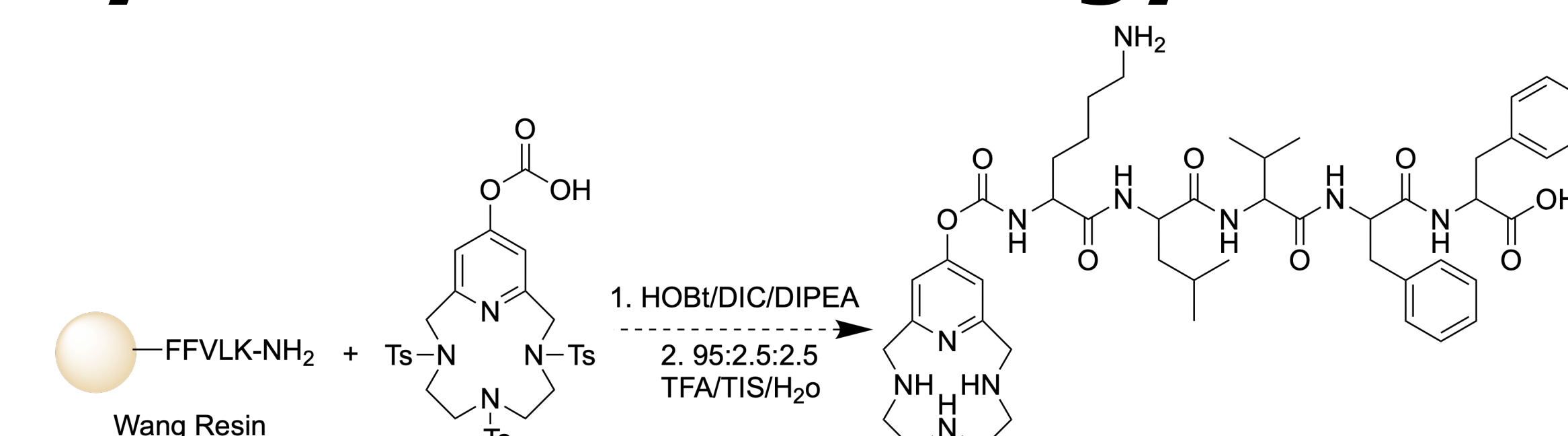


Alzheimer’s Disease: Impact



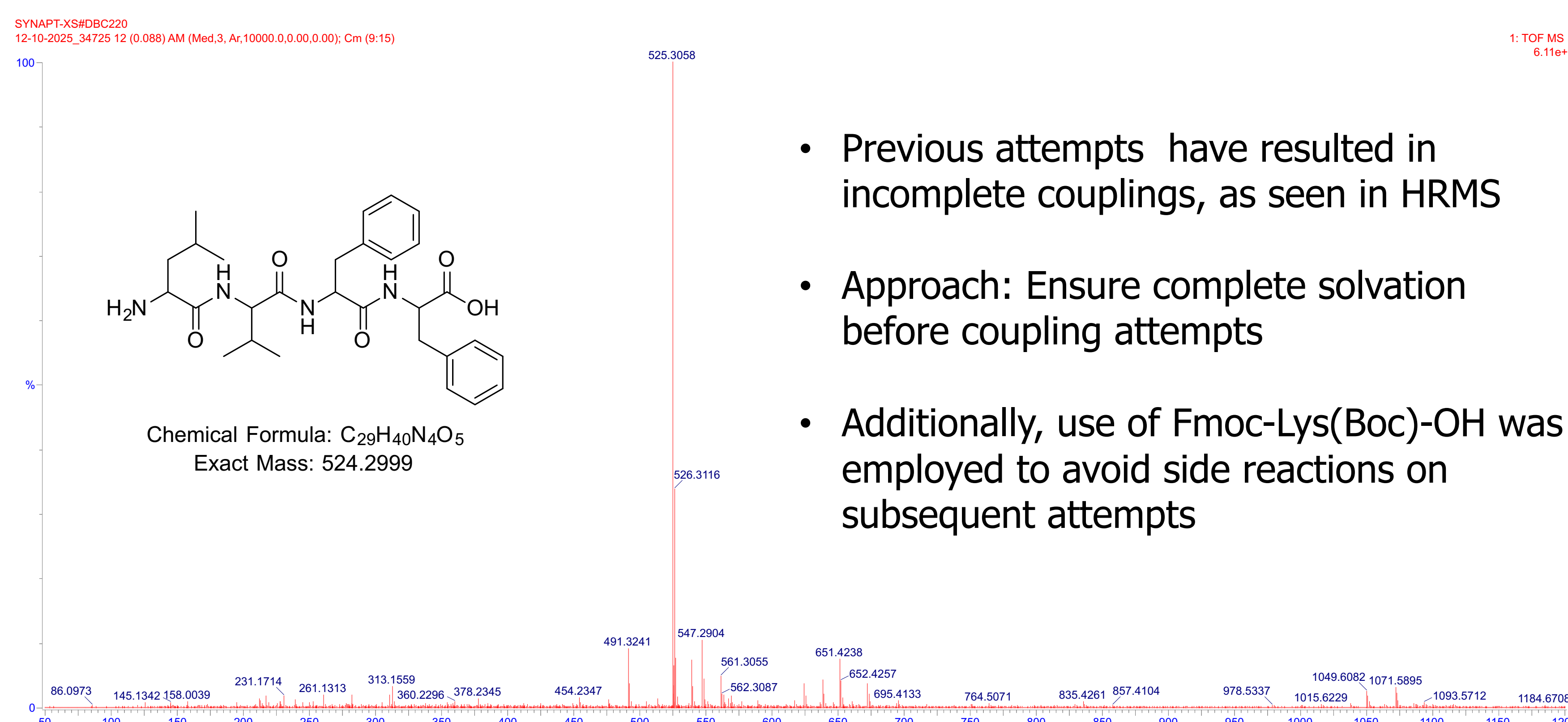
- Figures from *2025 Alzheimer’s Disease Facts and Figures*
- AD imposes both a significant personal and economic cost to the health of patients and families
- Over 13 million expected to have AD by 2050
- Research funding for AD cannot meet the clinical cost
- With the growing number of elderly individuals in America, AD will continue to be a major public health issue

Synthetic Methodology



- KLVFF: Solid Phase Peptide Synthesis
- Macrocycle coupled through –COOH with DIC

Past Work and Trouble Shooting



- Previous attempts have resulted in incomplete couplings, as seen in HRMS
- Approach: Ensure complete solvation before coupling attempts
- Additionally, use of Fmoc-Lys(Boc)-OH was employed to avoid side reactions on subsequent attempts

Future Directions

- Completion of synthesis using SPPS
- Analysis of completed product using HRMS
- Testing for metal binding capacity
- Testing for Nrf2 activation activity
- Antioxidant activity assays
- In-vivo cell studies through other labs at TCU

References

- Braymer, J. J. *et al. Int. J. Alzheimer’s Disease* **2011**, 623051.
- Huang, Q. *et al. ACS Omega* **2019**, 4(2), 4233-4242.
- Huang, Q. *et al. Research* **2023**, 6, 0180.
- 2025 Alzheimer’s Disease Facts and Figures. *J. Alzheimer’s Assc.* **2025**, 20,5, 3708-3738.

Acknowledgments

- TCU SERC Grant
- TCU Department of Chemistry & Biochemistry

