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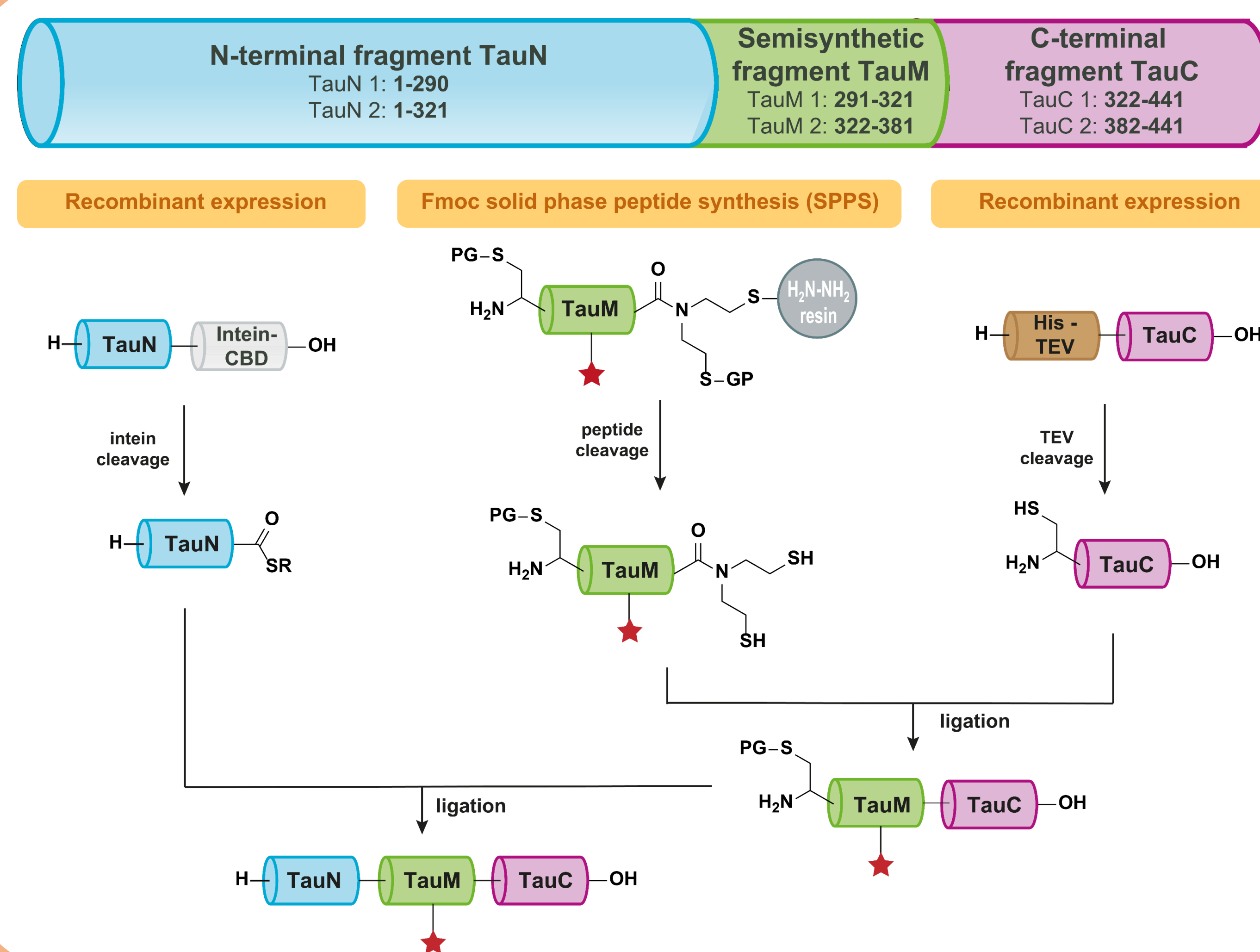
BACKGROUND

- ❖ **Molecular basis of Alzheimer's disease (AD):** proteinaceous materials of amyloid β , microtubule-associated protein tau
- ❖ **Tau fibrils are hyperphosphorylated** in AD patient's brains [1]
- ❖ **In vitro liquid-liquid phase separation (LLPS):** aberrant process may advance fibril formation *in vivo* [2]

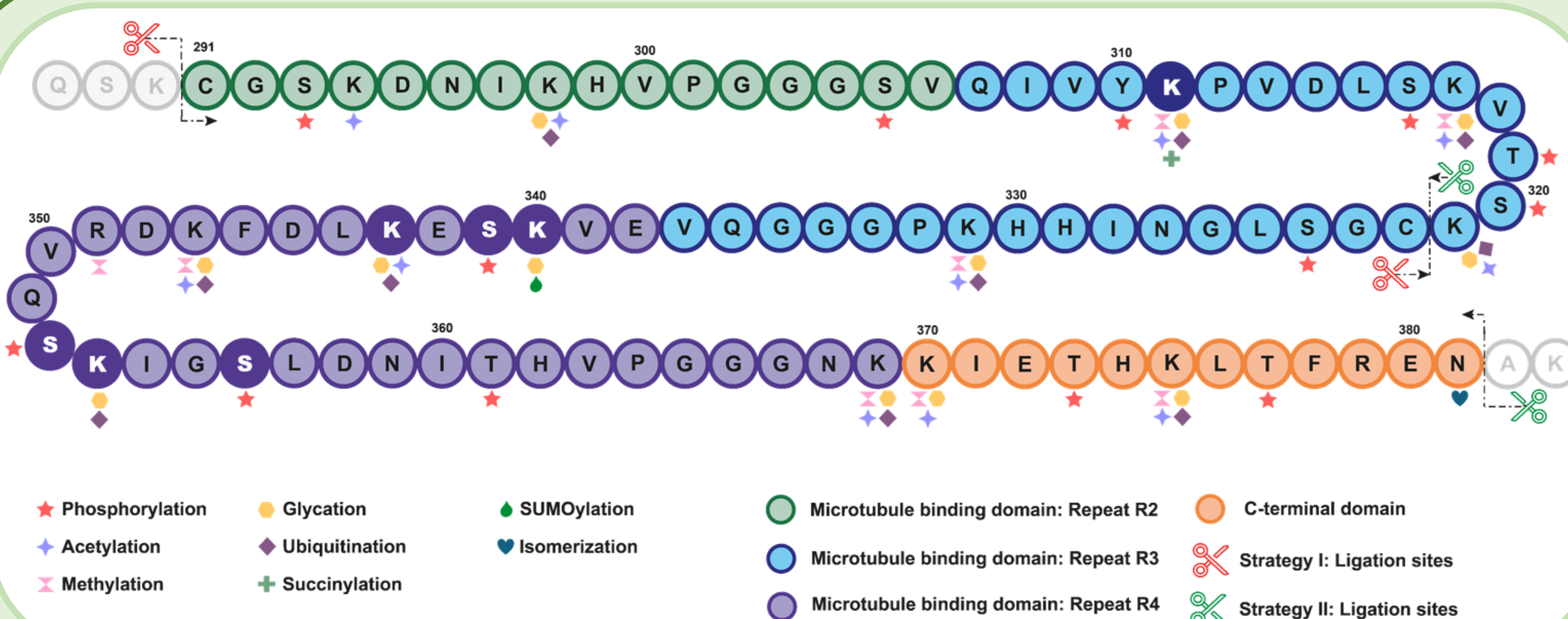
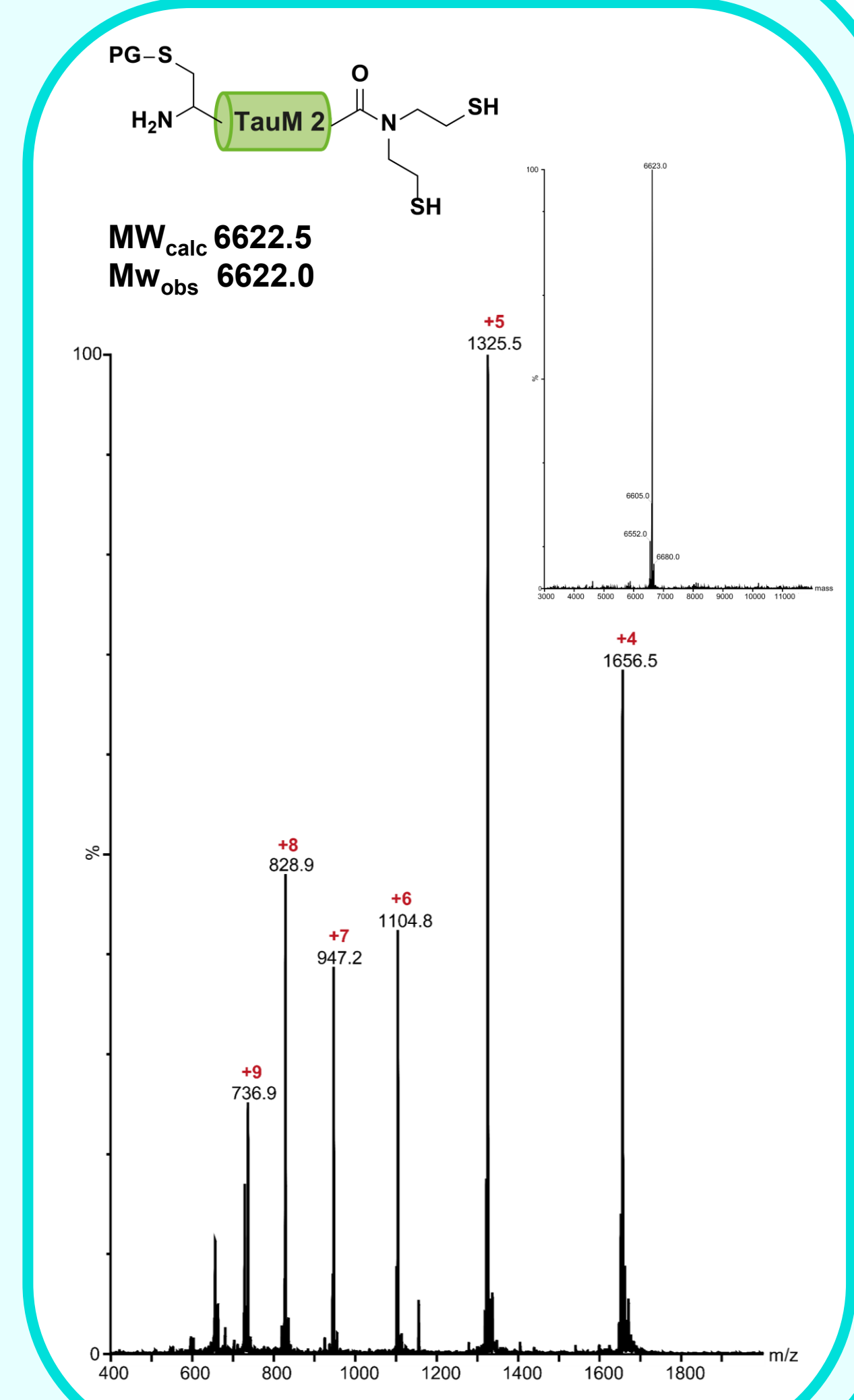
OBJECTIVES

- ❖ **Investigation of site-specific modifications** and their effects on aggregation and LLPS
- ❖ **Achieved by combination of recombinant expression and solid phase peptide synthesis (SPPS)** [3]
- ❖ **Native chemical ligation yields full length tau**

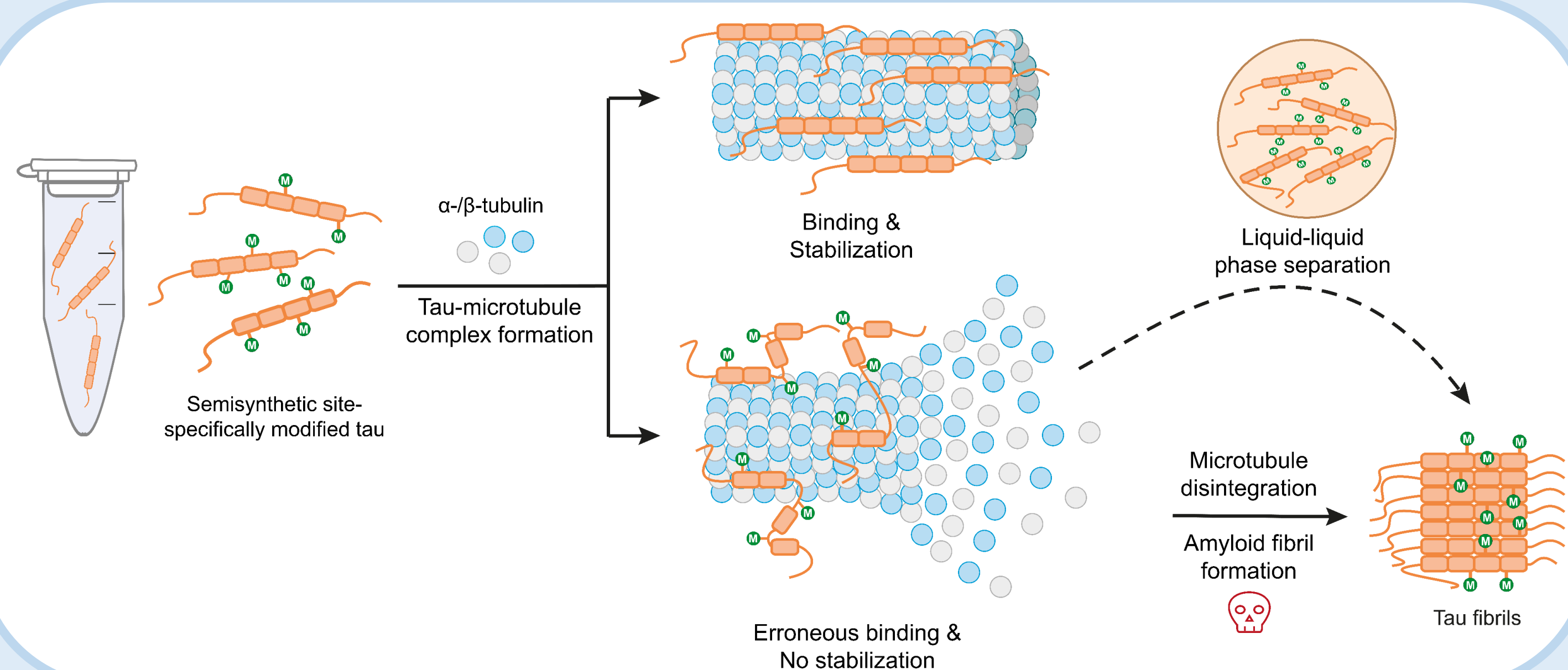
SEMISYNTHETIC STRATEGY



- ❖ **Semisynthesis of Tau 1** previously established [3]
- ❖ **TauM 2 purified**
- ❖ **TauN 2 yet to be purified**
- ❖ **Next: TauC 2, C2 + M2 ligation**



- ❖ **Longest isoform 4R2N** [1]
- ❖ **1st Semisynthetic variant**
 - ❖ Carbamylation K311
 - ❖ Succinylation K311
- ❖ **2nd Semisynthetic variant**
 - ❖ Phosphorylation S341, S352, S356
 - ❖ Acetylation K340, K343, K353



Microtubule binding & fibrillation

- ❖ **Potentially protective effect** of Ac294
- ❖ **Potentially toxic effect** of Ac311, Ac294/Ac311
- ❖ **Next:** Effects of new modified variants

LLPS

- ❖ **Modified variants to be tested:** pS341, pS341/pS352, Ac340/Ac343/Ac353, pS341/pS352/Ac340/Ac343/Sc353, CarbK311, SucK311

References:

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- [2] H. Zhang, X. Ji, P. Li, C. Liu, J. Lou, Z. Wang, W. Wen, Y. Xiao, M. Zhang, X. Zhu, *Science China Life Sciences* 2020, 63, 953-985.
- [3] D. Ellmer, M. Brehms, M. Haj-Yahya, H. A. Lashuel, C. F. W. Becker, *Angewandte Chemie International Edition* 2019, 58, 1616-1620.



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