

The Laboratory for Organic and Inorganic Chemistry

Final PhD Seminar

Monday, March 18th at 11:30 in Hall 1

Ms. Anastasia Esther Behar

Maayan Group

On the Topic of:

Peptoids and Alzheimer's: Advancing Copper Chelation Therapy

Peptoids and Alzheimer's: Advancing Copper Chelation Therapy

Alzheimer's Disease (AD), the most prevalent form of dementia, affects approximately 47.5 million people worldwide, posing significant public health challenges. The pathological role of copper (Cu) ions in AD, through their interaction with amyloid- β peptides leading to reactive oxygen species (ROS) formation and peptide aggregation, underscores the need for effective therapeutic strategies. My PhD research focused on developing peptoid-based chelators targeting Cu ions selectively, leveraging the biocompatible and efficiently synthesized peptoids as a platform for drug design.^[1]

This seminar will start with describing the development of a novel peptoid that selectively chelates Cu²⁺ ions, inhibiting ROS formation and demonstrating potential for AD therapeutics.^[2] Despite its efficacy, its solubility and selectivity prompted further optimization. Through a comprehensive peptoid library screening, we identified structural prerequisites essential for effective chelation,^[3] leading to a new peptoid with enhanced properties and introducing a novel "peptoid-cocktail" approach for improved anti-ROS outcomes.^[4]

Additionally, I will present the first example of a peptoid-based ligand that stabilizes Cu in its low oxidation state. I will demonstrate that the unique stability and selectivity for Cu⁺ ions within the peptoid sequence are achieved through the interplay of the first and second coordination spheres, mimicking protein-like behavior.^[5]

The seminar will conclude with the implications of modifying the first-coordination sphere within peptoid chelators, highlighting the discovery of **TB**, a water-soluble, highly selective chelator for Cu²⁺.^[6] **TB** represents a promising direction for peptoid-based chelators in anti-cancer therapy, emphasizing the versatility and potential of peptoid chemistry in biomedical applications.

1. **A. E. Behar**, P. Ghosh, G. Maayan. "Structure and Function of Cu-Peptoid Complexes" in Copper Bioinorganic Chemistry. From Health to Bioinspired Catalysis, *World Scientific Publishing Co Pte Ltd*, **2023**, 211-249.
2. **A. E. Behar**, L. Sabater, M. Baskin, C. Hureau, G. Maayan. A Water-Soluble Peptoid Chelator that Can Remove Cu²⁺ from Amyloid- β Peptides and Stop the Formation of Reactive Oxygen Species Associated with Alzheimer's Disease, *Angew. Chemie*, **2021**, 60(46), 24588-24597.
3. **A. E. Behar**, G. Maayan. Structure-Function Relationship within Helical Peptoids for Cu²⁺-Chelation in the Context of Alzheimer's Disease, **2024**, *in preparation*
4. **A. E. Behar**, G. Maayan. A Cocktail of Cu²⁺- and Zn²⁺-Targeting Peptoid-Based Chelators Towards Potential Application in the Context of Alzheimer's Disease, **2024**, *in preparation*
5. **A. E. Behar**, G. Maayan. The First Cu(I)-Peptoid Complex: Enabling Metal Ion Stability and Selectivity via Backbone Helicity. *Chem. – Eur J*, **2023**, 29, e202301118.
6. **A. E. Behar**, G. Maayan. A Peptoid-Chelator Selective to Cu²⁺ that can Extract Copper from Metallothionein-2 and Lead to the Production of ROS, *Antioxidants*, **2023**, 12(12), 2031.

