Research Summary

My Ph.D. research at the Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR), under the supervision of Prof. T. Govindaraju at the New Chemistry Unit, is titled "Multipronged Strategies to Mitigate Amyloid-Associated Toxicities and Ferroptosis in Alzheimer's Disease." Traditional pharmacological strategies that focus solely on the Aβ and tau pathways in Alzheimer's disease (AD) have demonstrated limited efficacy, underscoring the need for novel insights into the aggregation mechanisms and toxicity profiles associated with this disease. My work delves into the chemical biology of AD, with a particular emphasis on understanding novel disease mechanisms and developing multifunctional therapeutic molecules to address the various etiologies implicated in AD pathology.

A significant contribution of my thesis is the establishment of a pathological nexus between ferroptosis and Alzheimer's disease, termed the GPX4-Ferroptosis-AD axis that led to the development of multifunctional therapeutic molecules capable of synergistically targeting both pathways. Specifically, we identified natural polyphenols that significantly enhance endogenous antioxidant systems, such as Nrf2-GPX4, to combat ADs pathophysiology—an approach previously unexplored. This represents the first report of a multifunctional molecule that not only activates and elevates GPX4 levels but also attenuates amyloid toxicity even under AD pathology. Another key aspect of my research involves understanding tau protein phase separation and identifying molecules capable of effectively modulating this process to address tauopathies implicated in neurodegenerative diseases. We developed polymer drug conjugates and identified polyphenols that modulate tau liquid-liquid phase separation (LLPS), inhibiting the aggregation of tau into toxic species. Conventionally, tau LLPS is believed to instigate the formation of harmful tau aggregates, making it a target for the development of inhibitory therapeutic agents. However, contrary to this popular belief, our study shows that polycatechols

promote tau LLPS while simultaneously inhibiting the formation of toxic tau aggregates. By modulating the intermolecular interactions in LLPS, we direct the metastable state towards a non-toxic pathway. This finding challenges the conventional understanding of LLPS in tau pathology and highlights that not all instances of LLPS lead to a toxic state. Our research has uncovered untapped avenues in AD therapeutics, particularly the use of macromolecules to simultaneously target amyloid toxicity and ferroptosis—an approach that has shown promise in our studies. This innovative strategy has opened new possibilities for addressing tauopathies implicated in neurodegenerative disorders. In follow-up work, we identified small-molecule polyphenols that exhibit biphasic modulation of tau phase separation, with significant therapeutic potential in targeting tauopathies. In addition to these findings, we designed and developed cyclic dipeptide-based copolymers that have demonstrated the ability to inhibit amyloid aggregation and reduce neuroinflammation. Furthermore, we synthesized intrinsically fluorescent dendrimers for RNAi therapeutics, with theranostic potential, offering implications for tackling AD and other chronic illnesses. Overall, our work has opened up new and underexplored avenues in the AD therapeutic pipeline, with significant societal relevance. Alzheimer's disease imposes a substantial burden on patients, families, and healthcare systems worldwide. By addressing the multifaceted nature of this disease, our research holds the potential to contribute to more effective therapeutic strategies, ultimately improving the quality of life for those affected.

List of publications

- Baruah, P.[+]; **Moorthy, H.[+]**; Ramesh, M.; Padhi, D.; Govindaraju, T. A Natural Polyphenol Activates and Enhances GPX4 to Mitigate Amyloid-β Induced Ferroptosis in Alzheimer's Disease. *Chem. Sci*. **2023**, *14*, 9427–9438. ([+]equal first author contributions). (*Recognized as one of the most popular chemical biology articles of 2023 in Chemical Science, Royal Society of Chemistry*).
- **Moorthy, H**.; Ramesh, M.; Padhi, D.; Baruah, P.; Govindaraju, T. Polycatechols Inhibit Ferroptosis and Modulate Tau Liquid-Liquid Phase Separation to Mitigate Alzheimer's Disease. *Mater. Horizons* **2024**, *11*, 3082–3089.
- **Moorthy, H.**; Kamala, N.; Ramesh, M.; Govindaraju, T. Biphasic Modulation of Tau Liquid-Liquid Phase Separation by Polyphenols. *Chem. Commun.* **2024**, *60*, 4334–4337.
- **Moorthy, H.[+]**; Datta, L. P.[+]; Samanta, S.; Govindaraju, T. Multifunctional Architectures of Cyclic Dipeptide Copolymers and Composites, and Modulation of Multifaceted Amyloid-β Toxicity. *ACS Appl. Mater. Interfaces* **2022**, *14*, 56535–56547. ([+]equal first author contributions).
- **Moorthy, H.**; Govindaraju, T. Dendrimer Architectonics to Treat Cancer and Neurodegenerative Diseases with Implications in Theranostics and Personalized Medicine. *ACS Appl. Bio Mater.* **2021**, *4*, 1115–1139.
- **Moorthy, H.**; Datta, L. P.; Govindaraju, T. Molecular Architectonics-Guided Design of Biomaterials. *Chem. – An Asian J*. **2021**, 16, 423–442.
- Padhi, D.; Baruah, P.; Ramesh, M.; **Moorthy, H.**; Govindaraju, T. Hybrid Molecules Synergistically Mitigate Ferroptosis and Amyloid-Associated Toxicities in Alzheimer's Disease. *Redox Biol.* **2024**, *71*, 103119.
- Maity, B.; **Moorthy, H**.; Govindaraju, T. Glucose-Responsive Self-Regulated Injectable Silk Fibroin Hydrogel for Controlled Insulin Delivery. *ACS Appl. Mater. Interfaces* **2023**, *15*, 49953–49963.
- Maity, B.; **Moorthy, H.**; Govindaraju, T. Intrinsically Disordered Ku Protein-Derived Cell-Penetrating Peptides. *ACS Bio Med Chem Au* **2023**, *3*, 471–479.

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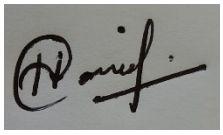

Research supervisor