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Rescuing proteostasis by small molecules

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Many apparently unrelated diseases, including Alzheimer's Disease (AD), Parkinson Disease (PD) and type II diabetes mellitus (T2DM), result from protein misfolding and abnormal accumulation of toxic amyloid deposits in affected tissues. According to the "Amyloid Hypothesis", targeting protein misfolding and self-assembly into toxic amyloid aggregates would prevent the diseases. However, the failure of all clinical trials focusing on anti-aggregating drugs has clearly demonstrated that a deeper understanding of the mechanisms involved in proteome maintenance is needed.
Our group focuses on the intertwined biochemical mechanisms that control protein homeostasis (proteostasis). We employ an interdisciplinary approach to screen small molecules (e.g. natural compounds, bioconjugates, and repurposed drugs) for their ability to restore proteome integrity by a multi-target strategy. Our work spans from fundamental topics related to thermodynamics of protein stability, amyloid aggregation, and ligand-protein interactions to applications in medicinal chemistry focusing on the development of bioactive compounds, involving chemically tailored contacts between lipids, proteins, nucleic acids, small molecules, and metal ions.^{1,3}

References

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