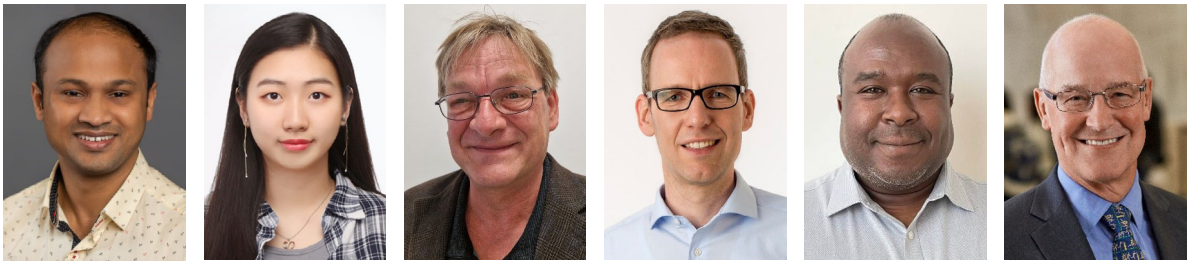
Chemistry–A European Journal
Cover Profile
doi.org/10.1002/chem.202201698
Chemistry Europe
European Chemical Societies Publishing
www.chemeurj.org

Cucurbit[7]uril Inhibits Islet Amyloid Polypeptide Aggregation by Targeting N Terminus Hot Segments and Attenuates Cytotoxicity



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Invited for the cover of this issue is the group of Prof. Hamilton at New York University. The image depicts how cucurbit[7]-uril inhibits islet amyloid polypeptide self-assembly that rescues rat insulinoma cells (a pancreatic β-cell model) from assembly-associated cytotoxicity. Read the full text of the article at 10.1002/chem.202200456.

What is the most significant result of this study?

Islet amyloid polypeptide (IAPP) and amyloid-beta ($A\beta_{42}$) are two intrinsically disordered peptides, whose amyloid aggregation is implicated in type 2 diabetes and Alzheimer's disease, respectively. The two peptides share a high degree of sequence similarity in their major nucleation sites for amyloidogenesis. An earlier report showed that more than 500 equivalents of cucurbit[7]uril (CB[7]) are required for complete inhibition of $A\beta_{42}$ aggregation. Here, we have extended this approach toward IAPP aggregation. Our studies demonstrate that CB[7] is a much more potent disruptor of IAPP self-assembly, with only 10 equivalents of the macrocycle proving sufficient for complete inhibition of de novo and membrane-catalyzed IAPP aggregation, and the associated downstream toxic effects. Our work, therefore, outlines a potential supramolecular-based therapeutic strategy for type 2 diabetes.

Who designed the cover?

Khulood Alawadi, Lecturer in Engineering Design, New York University Abu Dhabi, designed the cover image with suggestions from D.M.

What prompted you to investigate this topic/problem?

Protein misfolding often leads to the formation of β-sheet-rich amyloid plaques, which are associated with the progression of a wide range of diseases. As IAPP is implicated in the development of type 2 diabetes, modulation of this peptide's aggregation is critical from a therapeutic point of view. Crucially, aggregation of these so-called amyloid proteins is primarily driven by hydrophobic interactions. Recently, different macrocycles have been used for selective encapsulation of hydrophobic amino acids. We, therefore, explored whether the CB[7] macrocycle can interact with hydrophobic amino acids in IAPP and effectively disrupt its amyloid aggregation.

How did each team member/collaborator contribute to the work?

D.M. and A.D.H. conceptualized the project. L.G. and W.H. synthesized the ^{15}N-IAPP. D.M. performed all biophysical studies and HSQC NMR. Y.O. and M.M. designed and performed all the cytotoxicity assays. D.M. and A.D.H wrote the manuscript with contributions from all of the co-authors.