Dipartimento di Chimica dell'Università di Pavia
Via Taramelli 10 – 27100 Pavia

Lunedì 7 maggio 2018, ore 15.00
Aula I - Sezione di Chimica Organica

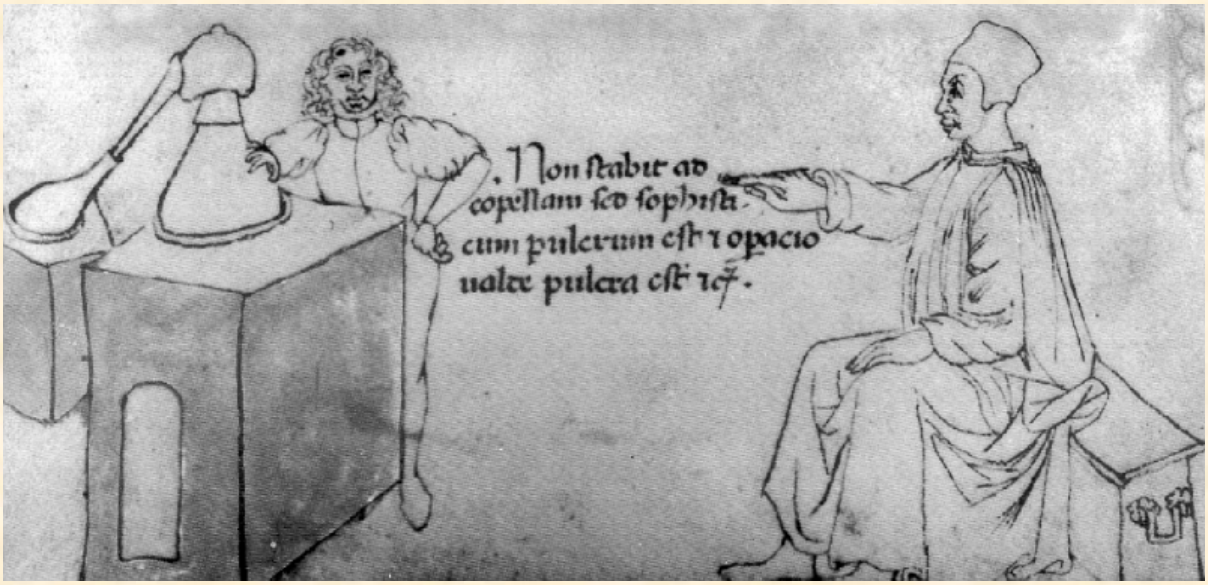
La S.V. è gentilmente invitata alla Conferenza del

Prof. Jason E. Gestwicki

UCSF, Dept. Pharmaceutical Chemistry, Institute for Neurodegen. Disease

Chemical Strategies for Treating Protein Misfolding Disease

Many inherited protein misfolding diseases, such as cataract and cystic fibrosis, are caused by mutations that destabilize the target protein. One approach to potentially treat these diseases is to identify "correctors" that bind to the mutant and restore its lost stability. In addition, such molecules can be useful probes for understanding the molecular origins of the folding defect. Our group is working to create high throughput differential scanning fluorimetry (HT-DSF) methods to rapidly identify potential correctors. In our first model, we screened a cataract-associated mutation in alpha-crystallin by HT-DSF to identify molecules that limit misfolding and aggregation. After a medicinal chemistry campaign, we found that the best molecules bound to the native, dimeric state of the alpha-crystallin and that it did not bind to the misfolded or amyloid structures. In turn, this compound partially reversed aggregation of this target in vitro and in multiple animal models. From a mechanistic perspective, we used these compounds revealed the reversible aggregation of alpha-crystallin, which is unusual amongst the amyloid-prone proteins. Inspired by this concept, we have been building next-generation HT-DSF approaches that improve sensitivity, scope and scale.



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