Corso di Dottorato in Biologia Cellulare e dello Sviluppo
Corso di Dottorato in Farmacologia e Tossicologia

SAPIENZA
UNIVERSITÀ DI ROMA

Aula C1
Edificio di Farmacologia, CU024

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α1-antitrypsin deficiency and the serpinopathies – pathological polymers and treatment with small molecules

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α1-antitrypsin is the most abundant circulating proteinase inhibitor. Severe deficiency typically results from homozygous inheritance of the Z allele (Glu342Lys). We showed over 30 years ago that the Z allele caused α1-antitrypsin to undergo a conformational transition to form chains of ordered polymers that are retained as inclusions within hepatocytes in association with liver disease and cirrhosis. We subsequently showed that many mutations caused α1-antitrypsin to polymerise and that there was a genotype-phenotype relationship between the severity of the mutation and the severity of both the plasma deficiency of α1-antitrypsin and liver disease, that we can explain by the rate of polymer formation. The same process of polymerisation occurs in mutants of other serine proteinase inhibitors (serpins), most notably neuroserpin in association with neuronal inclusions that underlie dementia and epilepsy. The challenge has been to define the structure of the pathological polymer that forms in vivo. Three models have been proposed with our current data supporting the C-sheet model for polymers of Z α1-antitrypsin. The results allow the rational design of novel small molecules that can block polymer formation and so ameliorate disease, whether it be the liver disease secondary to mutations in α1-antitrypsin or dementia secondary to mutants of neuroserpin. Different mutations may require different small molecules. The proof-principle of this approach is our development of orally bioavailable small molecules with GSK, and now BioMarin, that bind preferentially to Z α1-antitrypsin, block polymerisation and reverse liver disease in transgenic mice. These molecules are now in clinical trials.