# Rationnal Design of small-molecules inhibitors of human Cyclophilins and HCV replication by Structure Based Drug Design.

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**Résumé**

The hepatitis C virus (HCV) is the leading cause of chronic hepatitis, of liver cirrhosis and hepatocellular carcinoma. Roughly 170 millions individuals are infected in the whole world and the infection by HCV causes approximately 280.000 deaths per year. The study of the complex of replication made it possible to highlight the crucial role of cellular partners, in particular the cyclophilins1, in the driving process with the synthesis of new viral genomes and inhibition of these enzymes lead to new anti-viral agents. The Cyclophilins are enzymes that have been observed abundantly and ubiquitously in a wide range of tissue types and organisms. They are characterized by the ability to catalyse the cis-trans isomerisation of peptidylprolyl bonds2 (PPIases) which was identified as the rate-limiting step in protein folding. To design news Cyps inhibitors with low molecular mass, we applied a fragment-based screening approach on Cyclophilin D (CypD). We used X-ray crystallography and NMR that are well adapted to identify weak affinity fragments (mM). We solved 14 crystallographic structures of CypD in complex with fragments (2,00 - 0,97Å). Based on the fragments binding modes, we designed and optimized a new Cyps inhibitors family (proline mimetic). Our lead compound have an IC50 of 10 nM on CypD and CypA in vitro and an EC50 of 15 nM for the HCV replication in cellulo. The presentation will show the used of X-ray crystallography for the discovery of news human Cyps and HCV inhibitors.

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**Mots-Clés:** HCV, cyclophilin, fragment based drug design, infectious diseases

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