FOLDAPPI Report Summary
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Final Report Summary - FOLDAPPI (Foldamers against protein-protein interactions)

The FOLDAPPI project aims to investigate the potential of aromatic amide foldamers to disrupt protein-protein interactions. The scientific goals of the project include:
- the development of synthetic methods to build foldamer libraries displaying different R-groups;
- the development of strategies to target foldamers to protein surfaces;
- measuring in vitro properties of foldamer(s) to assess ADME profiles of these molecules.

In this project we explore the use of quinoline-derived aromatic amide foldamers developed initially at the University of Bordeaux to inhibit protein-protein interactions, namely the interaction between interleukin 4 (IL-4) and its receptor. A similar task has been added in the course of the project that concerns the recognition of the surface of human carbonic anhydrase (HCA(II)) as a model system. These foldamers have a very well defined structure that lends itself to the rational design of substituents and the production of focused combinatorial libraries of foldamers capable of interacting with the IL4/IL-4R binding epitope. They are also large enough to block a protein-protein interaction, a feat that is not possible with small molecules. The cytokine IL-4 is a key regulator of the immune system determining the formation of immune cells and immunoglobulin class switching. IL-4 is critically involved in misguided immune reactions during atopic diseases as allergy and asthma. In spite of its importance as a drug target, no small molecule inhibitor of the IL-4/IL-4R has been reported so far, warranting the use of foldamers to do the same.

The work plan of the project was organized in seven work packages WPs: WP1 Molecular modelling; WP2 Foldamer chemistry; WP3 Molecular Biology and protein production; WP4 Tethering of foldamers to proteins; WP5 Biocrystallography; WP6 Assay Development and screening; WP7 Dissemination and networking activities

The project has seen such scientific achievements as:
- the development of a specific force field for the modeling of aromatic amide foldamers
- the production of specific Cysteine mutants of IL-4
- the validation of the tethering chemistry of a foldamer on IL-4
- the validation of a synthetic method for the preparation of focused libraries of quinoline tetramers
- the production of focused foldamer libraries
- the validation of an assay to tests foldamer-IL4 interaction
- the screening of foldamers for their interactions with HCA(II)
- the resolution of the crystal structure of a foldamer-HCA(II) complex

In addition to these scientific achievements, 17 scientists have been exchanged or recruited between the partners (UCB Pharma, UCB Celltech, Université de Bordeaux, and Universität Würzburg) for a cumulative duration of 85 months in secondments and 78.75 months in recruitment.
Several scientific conferences on this topic have been organized in the course of the project. The 1st one took place in Bordeaux in January 2010 and gathered over 120 scientists around the theme of foldamer chemistry. The 2nd conference took place in Würzburg in April 2011 to discuss Protein-protein interactions. A third conference was organized in Bordeaux in January 2012 and a final conference took place in Paris in April 2013 gathering over 200 scientists from all over the world. Three out of four of these conferences were organized synergistically with a European COST (cooperation for science and technology) on foldamers and were critical in assembling a diverse scientific community around the theme of foldamers.

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