Thesis subject: **Bioactive Lignans: from natural products to drugs, via stereoselective control of free radical coupling**: Study of stereoselective coupling mechanisms of radicals by auxiliary proteins for the development of biocatalysts.

Laboratory: Institut des Sciences Moléculaires de Marseille (iSm2)

Team : BiosCiences

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applications are welcome until 20/05/2020

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Context: The bioactive lignans found in plants are used in medicine as analgesic, antiviral, anti-inflammatory, anti-oxidant, etc. Natural products are also starting points for the development of new drugs or the synthesis of analogues with improved efficiency and safety. In this context, stereo- and enantio-selective catalysis has emerged as an important tool in the synthesis of active products for pharmacy, agribusiness, perfumery, cosmetics, etc.
In their environment, natural products are formed in optically pure form. Since a long time, extensive research has been conducted to understand the biogenesis of natural enantiomers but several fascinating puzzles and stereochemical anomalies still exist. For example, the transformation of a phenolic compound may involve the formation of reactive intermediate radical species which recombine in a reaction whose (stereo) control is far from being clear. Nature uses proteins to trap radicals derived from metabolism, and some of these proteins, such as DIRs, appear to have the biological function of promoting stereoselective coupling of phenoxy radicals. However, the exact mechanisms on how the radicals interact with the coupling proteins and their orientation in a stereoselective coupling reaction are not known. The end products being close to, or are themselves, drugs of interest (as is the case of pinoresinol, podophylotoxin, secoisolariciresol or matairesinol), the DIRs are prime targets for the engineering of new biocatalysts dedicated to the biosynthesis of a series of bioactive polyphenolic substances.

PhD project: The coupling of phenolic radicals and the stereoselectivity of C-C bonds by biocatalysis (mild conditions (T °, P °)) are an alternative to organic synthesis for the production of enantiopure compounds. The goal of the pHD project is to combine "dirigent" proteins, DIRs, with oxidoreductases laccases, in order to develop an efficient oxidative biocatalyst capable of specifically producing a single enantiomer of a molecule of choice. This project will allow the biosynthesis control of molecules of interest such as podophyllotoxin, a molecule used in chemotherapy.
The originality and the scientific scope of the project are visible at least on 3 levels:
- Understand how, thanks to its AA composition and its structural organization, the DIR protein not only tolerates radicals but also directs their coupling.

- Accommodate new substrates in the cavity of the DIR in order to be able to produce new reactions.
- Develop a biocatalyst associating an oxidizing entity (a laccase) with orientation properties DIR protein modules.

PhD profile: The position requires a solid at least six-month training in Biology or chimie or a student with a Master degree obtained with distinction. We are looking for a rigorous, strongly motivated and enthusiastic candidate with good knowledge in chemistry and being research dedicated and curious. Experience at chemobiological interface would be appreciated. Candidates should send a CV, a motivation letter and the contact of at least one referee.