Probing the Anti-sickling Power of Distinct Drugs in Sickle Cell Disease

Place of work: BioISI - FCUL Edificio C8, piso 5

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Sickle Cell Disease (SCD) is an autosomal recessive inherited disorder that affects hemoglobin (Hb), the protein responsible for the transport of O_2 in the red blood cells. Hb is made up of four polypeptide chains, two α chains of 141 amino acid residues each, and 2 β subunits of 146 amino acid residues each, with a Heme group. SCD is caused by a monogenic mutation in the β-globin gene that results in the substitution of glutamic acid (charge -1) for valine (neutral) at the 6th position of the β-globins of HbA. This mutation induces the polymerization of the deoxygenated hemoglobin mutant, deoxy-HbS (sickle cell hemoglobin), into 14-stranded helical fibers. The latter arrangement distorts the red blood cells into a stiff sickle-like shape, disrupting microcirculation and causing hemolysis. While several molecules have shown *in vitro* anti-sickling activity, no approved drug is currently available to boost the inhibition or delay of the polymerization process.

This project aims at designing and probing the power of new small molecules and linear and cyclic peptides, towards the aggregation inhibition of the HbS. The project will include the use of molecular docking and molecular dynamics simulations, to investigate the power of some of the designed molecules to bind to specific regions of HbS and its putative effect in the aggregation process.