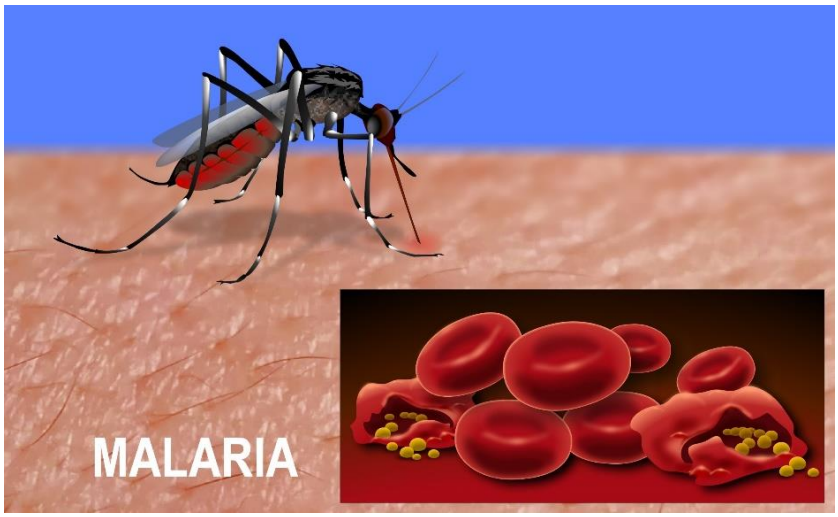
Project 4: Opening Piezo1 in red blood cells to fight malaria



In our group, Dominique Douguet develops computational methods and creates databases for virtual screening and *de novo* molecular design, drug re-purposing and knowledge-based design of drug-like compounds (LEA3D suite of tools). We are analyzing the current FDA approved drug chemical space from various dimensions: chemical structures, privileged structures, physicochemical properties, pharmacodynamic and pharmacokinetic properties (our own database e-Drug3D http://chemoinfo.ipmc.cnrs.fr/edrug3d.html; Inter Deposit Digital Number IDDN.FR.001.240001.000.S.P.2017.000.31235). Such structure-activity/property collections allow retrospective analyses of past successes and to foster the development of improved predictive methods relevant to the drug discovery and optimization process and, in particular, methods for assessing pharmacokinetic properties directly from molecular structures. These knowledge-based models and guidelines are associated with conventional ligand- and structure-based virtual screening methods (fingerprint, pharmacophore, shape-matching, docking…) to optimally identify and optimize bioactive small molecules.

S**tructural bioinformatics** studies are carried out to functionally and structurally characterize our selected protein targets by combining sequence analysis, alignments, phylogenetic analysis, fold recognition, homology modeling, electrostatic calculations and molecular dynamics. The resulting models served as a basis to devise experimental structure-function studies such as site-directed mutagenesis or protein construct design, to search for druggable cavities, to predict protein-ligand interactions and to virtually screen by docking large collections of small molecules or peptides/toxins.

The development of selective ligands makes them highly valuable as "investigational tools" or "probes" in further biological experiments. **Hit discovery, Hit-to-lead and Lead optimization** are carried out by an interdisciplinary team of computational chemistry experts, medicinal chemists, biophysicists and biologists of the group who develop biological assays for medium to high throughput screenings to identify and optimize chemical series with intellectual property.

Hereditary xerocytosis (HX) is thought to be a rare genetic condition characterized by red blood cell (RBC) dehydration with mild hemolysis. Gain-of-function (GOF) mutations in Piezo1 were identified in HX patients (*55, 57, 58*). Interestingly, **RBC dehydration is linked to reduced Plasmodium infection rates *in vitro* (*108*).** In collaboration with Ardem Patatpoutian (TSRI, La Jolla, CA, USA) and Kai Wengelnik (DIMNP, Montpellier, France) we engineered a Piezo1 mouse model of HX and show that Plasmodium infection fails to cause experimental cerebral malaria in these mice. Furthermore, we identified a novel GOF human Piezo1 variant, E756del, present in a third of African population.

Remarkably, RBCs from individuals carrying this allele are dehydrated and protected against Plasmodium infection *in vitro*. The presence of an HX-causing Piezo1 mutation at such high frequencies in African population is surprising, and suggests an association with malaria resistance (Manuscript available at: http://www.biorxiv.org/content/early/2017/07/06/159830).

We are currently developing novel Piezo1 activators (Yoda1-like molecules) with improved affinity, solubility and pharmacokinetics properties in view of fighting malaria by targeting the host red blood cells Piezo1 channels (pre-maturation grant CNRS)

References cited:

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