A Computational Chemistry approach to fighting cancer and rare diseases

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Cancer and rare diseases

Focus / Capacities

Computational modeling physical-chemical systems of biological and pharmacological interest

Ligand-based or structure based approaches

Provide models for mechanism determination, hit discovery and hit to lead development

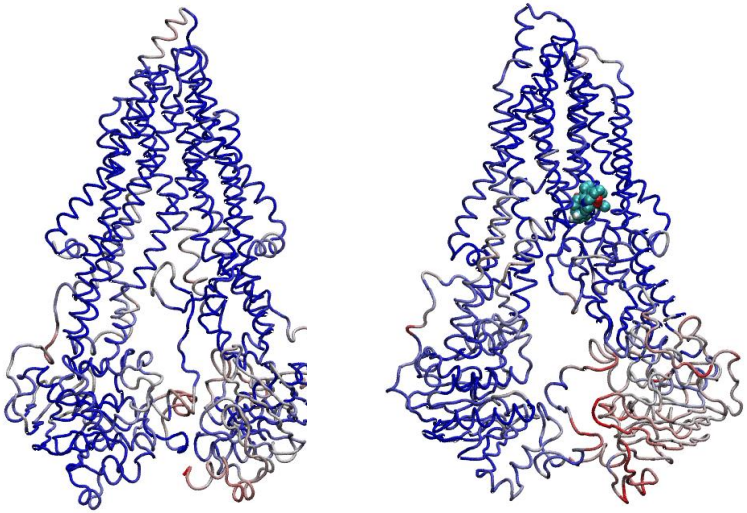
Classical & quantum mechanics, statistical models,… machine learning

- **Cancer**
- ATP binding cassette (**ABC) transporters** (P-glycoprotein, ABCB1 and Breast Cancer Resistance Protein, ABCG2) → multidrug resistance
- **MDM2/4-P53** protein-protein interactions dual inhibitors
- **Protein kinases** (PKC delta **activators**)

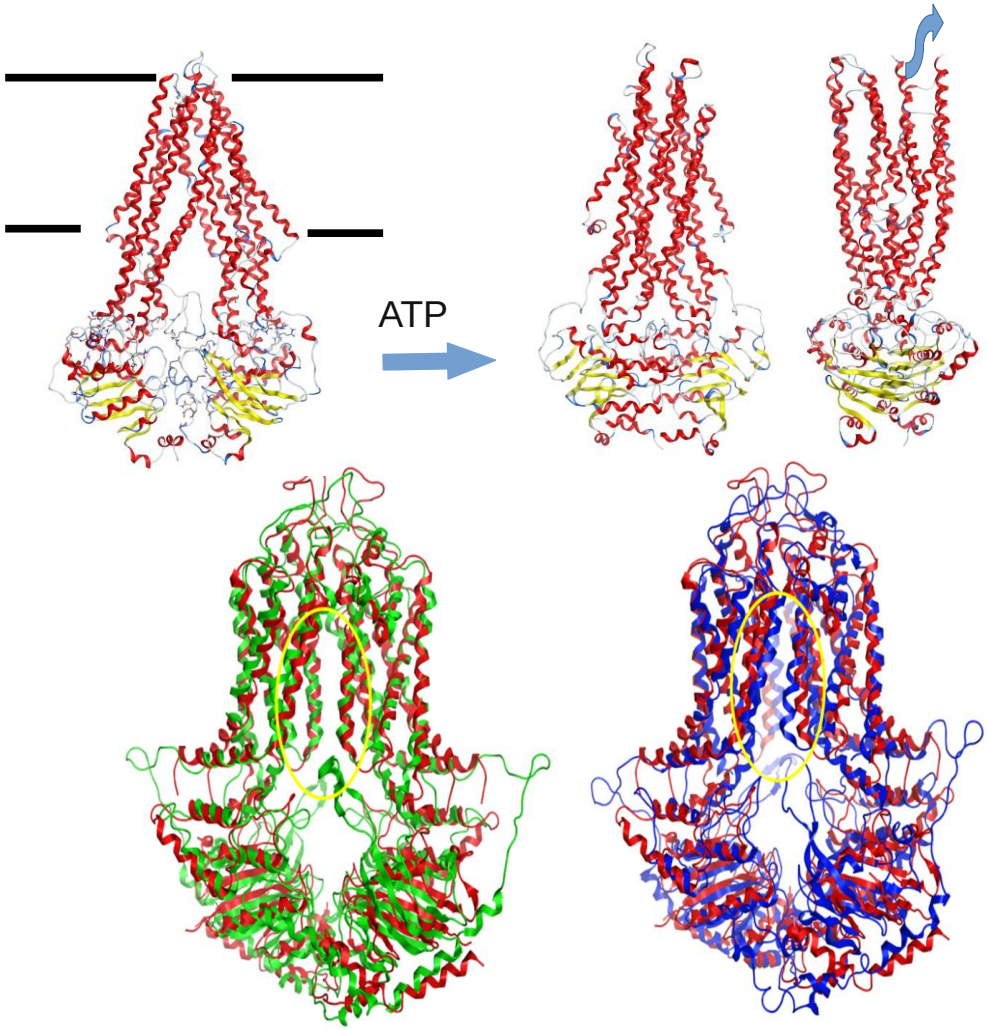
- **Rare diseases**
- **CFTR ion channel** (ABCC7) → Cystic fibrosis
- Medium-chain acyl-CoA dehydrogenase deficiency (**MCADD**) most common inherited metabolic disease

Cancer: over-expression of pumps

- Over-expression of efflux transporters is related to multidrug resistance (MDR) in cancer cells.
- P-glycoprotein (P-gp, ABCB1), the most studied, is capable to extrude a wide range of neutral and charged hydrophobic compounds through an ATP-dependent mechanism.
- Understand **mechanism** and d**evelopment of modulators** (to modulate, not to stop).



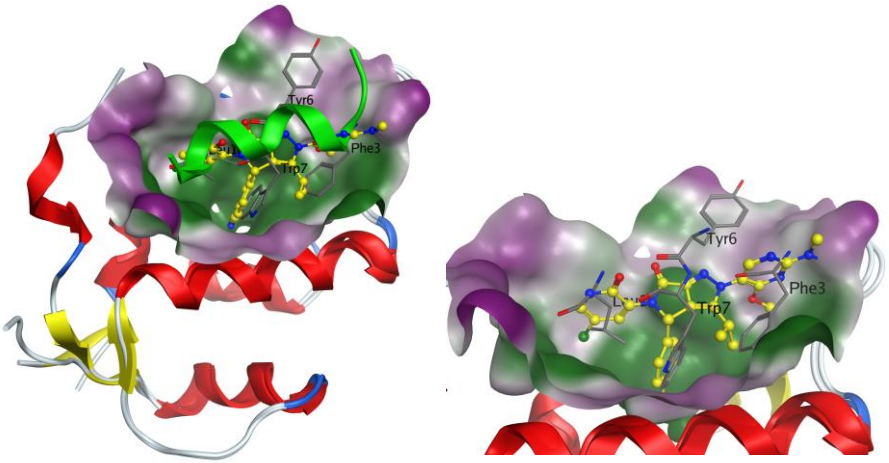
- P-gp: **normal** and **gate-induced motion** patterns; With Prof. Maria JU Ferreira, FFUL
- P-gp: mechanism and new **Pgp activators,** PhD student (Jéssica Matos); With Prof. Fernando Remião, FFUP



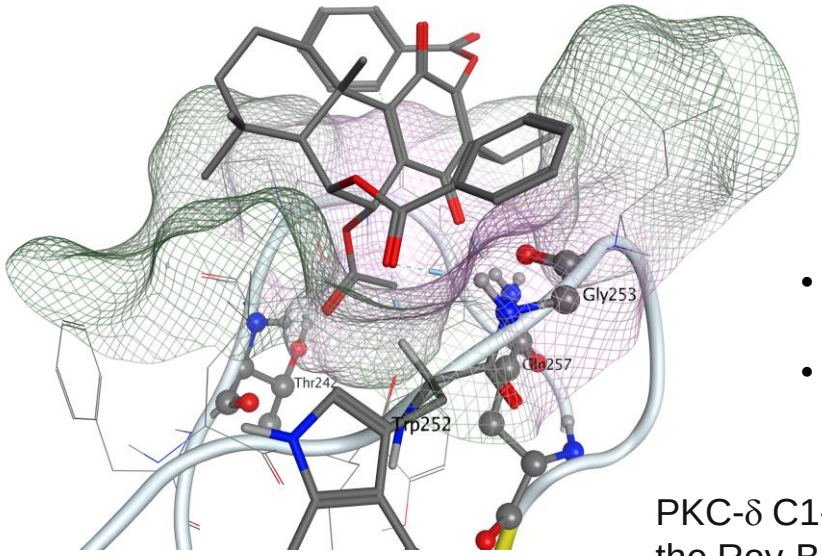
BCRP: **homology model** produced **before experimental structure**. Before and after equilibration; With Prof. Maria JU Ferreira, FFUL

Cancer: MDM2/4-P53 & PKC-δ

- **MDM2 and MDM4: two major downregulators of p53**, a protein involved in several cell processes (e.g. cell cycle and apoptosis).
- Tumors over-expressing these proteins, the **p53 tumor suppressor function is inactivated.**
- MDM2 and MDM4 are considered important therapeutic targets for an effective **reactivation of the p53 function**.



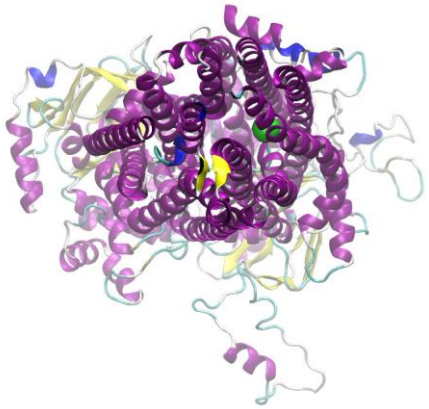
MDM2/4-P53 interaction inhibition
One dual inhibitor hit found (repositioning): being synthesized; With Prof. Maria Santos, FFUL

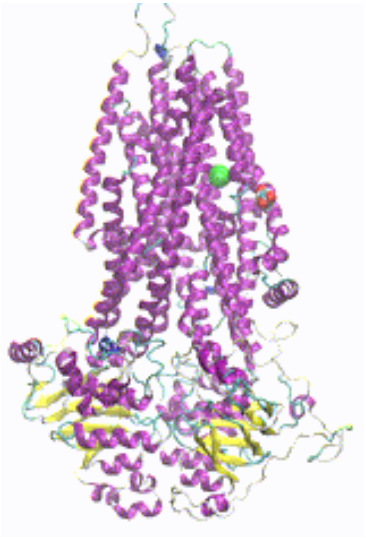


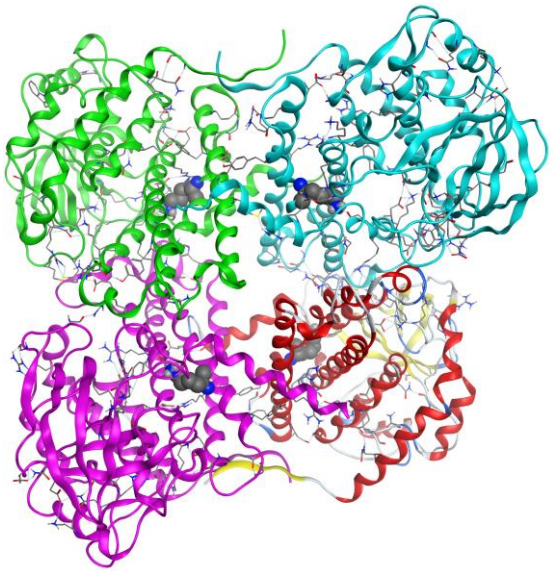
- protein kinase isozymes induce **anti-proliferative or pro-apoptotic** effects in cancer cells **upon activation.**
- Discovery of a small-molecule PKC-δ **selective activator with promising application in colon cancer therapy**

PKC-δ C1-domain and the **binding mode prediction** for the Roy-Bz molecule; With Prof. Patrícia Rijo, CBIOS

Rare diseases: Cystic fibrosis & MCADD



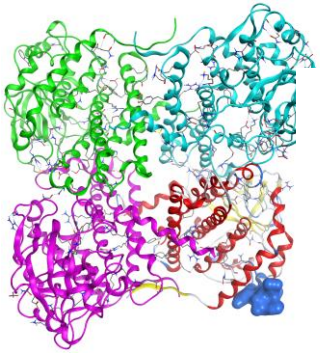


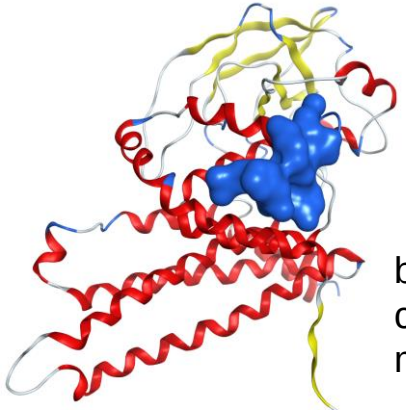


CFTR: **G85E mutation changes ion channel penetration**;
With Prof. Margarida Amaral, BioISI-FCUL

Medium-chain acyl-CoA dehydrogenase deficiency (**MCADD**) is the most common inherited **metabolic disease of mitochondrial fatty acid beta-oxidation** (mFAO), a crucial pathway in **energy** needs

MCADD deficiency: **Reverting mutation effects**;
With Prof. Fátima Ventura, FFUL





a)
~2 million
molecules
screened

b) First assay: 3/5 actives
c) Doing final selection: 20-30 molecules to buy and assay

Acknowledgments

- *The results were developed through the FCT financed projects:*

- PTDC/MED-QUI/30591/2017— Multidrug resistance reversal in cancer: natural compounds as P-glycoprotein and breast cancer resistance protein modulators;
- PTDC/MED-QUI/28800/2017— iDrugCF: Identification of New Drugs for Cystic Fibrosis;
- PTDC/BIA-BQM/29570/2017— Understand to treat: Combining in vitro and in silico strategies to explore new therapeutic approaches to the most common mitochondrial fatty acid beta-oxidation disorder (mFAOD).
- FCT: PTDC/QUI-QOR/29664/2017— Drug Discovery for p53 PPI-targets

- *We also acknowledge and appreciate the possibility of using super-computer infrastructures of FCT/RNCA through projects:*

- 2021.09821.CPCA— Studies on the human Pgp folding;
- CPCA/A00/7319/2020— Exploring the efflux and modulation mechanism of Human BCRP through Molecular Dynamics Simulations;
- CPCA/A0/7304/2020— Fighting multidrugresistance in cancer by targeting P-glycoprotein
- CPCA/A00/7312/2020— Insights on the CFTR ion gating mechanism provided by computer simulations
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- PhD grant to Cátia Bonito, 2017
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