MARIE SKŁODOWSKA-CURIE INDIVIDUAL FELLOWSHIPS 2020

EXPRESSION OF INTEREST FOR HOSTING MARIE CURIE FELLOWS

HOST INSTITUTION

ITQB NOVA | Institute of Chemical and Biological Technology António Xavier
Research Unit: MOSTMICRO

RESEARCH GROUP AND URL

Cláudio M. Soares Lab - Protein Modeling
URL: https://www.itqb.unl.pt/research/biological-chemistry/protein-modelling

SUPERVISOR (NAME AND E-MAIL)

Cláudio M. Soares
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SHORT CV OF THE SUPERVISOR

Cláudio M. Soares studied Biochemistry at Universidade de Lisboa, Portugal, where he obtained his first degree in 1989. In 1990 he went to Uppsala University, Sweden where develop the research that lead to his PhD (presented in the University of Lisbon in 1994). After the PhD, he joined ITQB NOVA in 1994 and in 1999 he created and start leading the Protein Modelling Laboratory, one of the first labs in Portugal to work in this field. This Laboratory works on molecular modelling of proteins using computational biophysical methods and its members have experience in a quite large number of areas, from basic research in methods, to applications with biotechnological and biomedical interest. Along the years the Laboratory dealt with quite diverse subjects ranging from work with redox proteins (cytochromes, haem-copper oxidases, laccases, hydrogenases and others), studying electron and proton transfer, molecular mechanisms in ABC transporters, mechanisms of viral membrane fusion, enzyme engineering, among others. Besides its own research objectives, the Protein Modelling Laboratory has extensive collaborations with many experimental groups.
He is co-author of 115 published or accepted papers in peer-reviewed scientific journals and has an h-index of 37 (Scopus). He participated in 31 competitively funded projects since 1996. He was co-author of 76 invited presentations in meetings and institutions, and in 172 abstracts in poster communications. He has supervised 5 Diploma students, 5 master students, 14 research students, 14 PhD students (8 have already finished the degree) and 9 post-doctoral fellows. His present lab is composed of one Junior Investigator, one Pos-doctoral fellow, 5 PhD students and 2 master students.
He is member of the Federation of European Biochemical Societies (FEBS) Advanced Courses Committee, President of the General Assembly of the Portuguese Biochemical Society, 1st Secretary of the General Assembly of the Port. Biophys. Soc., President of the General Assembly of the Port. Biochem. Soc. and was Chairman of the Port. Biophys. Soc. (2002-2008) and member of the International Union for Pure and Applied Biophysics (IUPAB) council (2011-2017). He is member of the Scientific Council of TAGUSPARK – Parque de Ciência e Tecnologia, Portugal, since 2013.
Cláudio M. Soares is Dean of ITQB NOVA since 2013, and was Vice-Dean during the 2005-2008 and 2011-2013 periods. He is Coordinator of the Molecular, Structural and Cellular Microbiology – MOSTMICRO-ITQB Research

Unit (evaluated as Excellent) of ITQB NOVA since 2015. He has been in the organisation or in the scientific committee of 27 national and international meetings and acted as Chair in 32 symposia.
He has done extensive evaluation work for Research financing agencies from Portugal, European Commission, Argentina, Czech Republic, The Netherlands, USA, Germany, Austria, Cyprus, Poland, Romania, Israel.
He is Member the Editorial Boards of Scientific Journals i) Biophysical Reviews – From 2011-2019. ii) PLOS One – From 2012 to the present day. iii) Scientific Reports – From 2013 to the present day. iv) FEBS Open Bio – From 2018 to the present day.

5 SELECTED PUBLICATIONS

- Abreu, B, Lopes, EF, Oliveira, ASF, Soares, CM (2020) "The mutation F508del disturbs the dynamics of the nucleotide binding domains of CFTR before and after ATP hydrolysis", Proteins, 88, 113-1262;
- Kaur, H, Abreu, B, Akhmetzyanov, D, Lakatos-Karoly, A; Soares, CM, Prisner, T, Glaubitz, C (2018) "Unexplored nucleotide binding modes for the ABC exporter MsbA", JACS, 140, 14112–14125;
- Jeremias, HF, Lousa, D, Hollmann, A, Coelho, AC, Baltazar, CS, Seixas, JD, Marques, AR, Santos, NC, Romão, CC, Soares, CM (2018) "Study of the interactions of bovine serum albumin with a molybdenum(II) carbonyl complex by spectroscopic and molecular simulation methods", PLOS One, 13(9): e0204624;
- Lousa, D, Pinto, ART, Victor, BL, Laio, A, Veiga, AS, Castanho, MARB, Soares, CM (2016) "Fusing simulation and experiment: The effect of mutations on the structure and activity of the influenza fusion peptide", Sci.Rep., 6, 28099
- Victor B. L.; Lousa D.; Antunes J. M.; Soares C. M. (2015), "Self-assembly molecular dynamics simulations shed light into the interaction of the influenza fusion peptide with a membrane bilayer", JCIM, 55, 795-805.

PROJECT TITLE AND SHORT DESCRIPTION

Coronavirus spike protein: visualizing and hitting a moving target

Background:

Currently, there is no effective treatment against SARS-CoV-2 and it is urgent to develop strategies to fight the current pandemic and enable a fast response to future outbreaks by coronaviruses. This project addresses this problem using computational methods to characterize and inactivate an important therapeutic target - the spike (S) protein. This protein promotes fusion between the viral envelope and the host membrane and is a key player in the infection process and one of the main targets of the host immune system. Like all fusion proteins, the S protein experiences a large conformational change, which is initiated when the protein is cleaved by proteases, after binding to the host receptor. This releases a segment of the protein known as the fusion peptide, which inserts in the host membrane and is determinant for the fusion process.

Objectives

The vital importance of the S protein in coronavirus infections and the fact that it is exposed on the virus surface make it a privileged therapeutic target. However, to develop efficient therapeutics targeting this protein, we need to have a detailed understanding of its molecular properties and use rational strategies to inactivate this protein. The main objectives of this project are:

- To characterize the structural and dynamic properties of the S protein

-To design antiviral molecules that can inactivate the S protein, using a rational approach. The efficacy of these molecules will be experimentally validated by biophysical methods and in vitro infection assays.

Approach

Although 3D structures of the SARS-CoV-2 S protein are available, its dynamic properties remain elusive and need to be elucidated to foster the development of inhibitors targeting this protein. An important question that remains to be answered is the characterization of the molecular details of the conformational changes experienced by the S protein upon activation by proteases. This conformational change is crucial for the fusion process and its inactivation would prevent viral entry and consequently block the infection. However, the details of the transition remain elusive and current experimental methods are not able to capture the details of this transition. To answer this question, we will apply molecular dynamics and metadynamics simulations. Another relevant question is the effect of mutations on the virus transmissibility and lethality. Recently it has been shown that the D614G mutation of the S protein began spreading in Europe and rapidly became the dominant form in several regions. We aim to study the impact of this mutation by performing MD simulations of the WT and mutant proteins.

The knowledge obtained in the first part of the project will enable the identification of regions that are crucial for the S protein activity and can be inhibited by antiviral molecules. In the second part, we will design molecules that can interact with these regions and inactivate SARS-CoV-2. We will use docking calculations to identify small molecules that can bind to important pockets. Additionally, we will also design antiviral proteins that can inhibit the S protein conformational transition, using computational design methods. The designed molecules will be analysed using surface plasmon resonance (SPR), isothermal titration calorimetry (ITC) and X-ray crystallography, coupled with molecular dynamics (MD) simulations to study their interaction with the S protein. The best candidates will be evaluated in infection assays to test their inhibitory effect.

SCIENTIFIC AREA WHERE THE PROJECT FITS BEST

Life Sciences (LIF) | Biophysics