Universitat Pompeu Fabra Barcelona | Master in Bioinformatics for Health Sciences

Master project 2020-2021

Personal Information

Supervisor	Juan Fernández Recio
Email	juan.fernandezrecio@icvv.es
Institution	ICVV-CSIC
Website	http://www.icvv.es/english/3dbiowine
Group	Structural Bioinformatics for Wine Sciences

Project

Structural bioinformatics

Project Title:

Structural modeling of bitter taste receptors and their interactions

Keywords:

protein-protein interactions, computational docking, drug discovery, molecular modeling, taste receptors

Summary:

The interplay between genetics and environmental factors is critical in major non-communicable diseases (NCDs), which are the leading cause of death globally and a major cause of premature death. As an example, it is known that genetic variation can affect individual food preferences, which has impact on diet and health. Indeed, genetic sensitivity to bitter taste has been associated to different sensitivity to bitterness and/or linked to variable risk of alcohol dependence, obesity, nicotine dependence, longevity, miocardial infarction, or altered thyroid function (Duffy 2004; Mangold et al 2008; Campa et al 2012; Clark et al 2015). At the molecular level, bitter taste perception in humans is mediated by the 25 members of the Taste 2 receptor (TAS2R) gene family (Conte et al 2002). Each member of the TAS2R family can bind a range of compounds with different specificities, enabling the detection of tens of thousands of bitter molecules (Meyerhof et al 2010 Chem Senses). Therefore, knowing the atomic details of their binding capabilities would be important to understand the impact of these genetic variants in diet preferences and disease risk. In this project, we aim to contribute to the structural characterization of taste receptors to understand their functional mechanisms and the impact of genetic variants in health. We will model four bitter taste receptors that host variants associated to disease: TAS2R16, TAS2R38, TAS2R42, TAS2R50. Preliminary results using available models at www.gpcrdb.es show that critical residues for function gather around active site. However, these models still contain some structural errors that we will need to refine by molecular dynamics (MD). Then, we will model by docking the binding of around 100 bitter compounds to all TAS2R models and will compare the results with their known specificities (Meyerhof et al 2010). This will help to refine the modeling pipeline and will provide a theoretical framework for TAS2R binding to bitter compounds. We will also explore potential homomeric interactions of TAS2Rs by protein-protein docking in collaboration with Hugo Gutiérrez de Terán (Uppsala University). Finally, in collaboration with the groups of Masha Niv (Hebrew University of Jerusalem) and M. Purificación Fernández Zurbano (ICVV-UR), we will use our molecular models to test candidate compounds that are related to bitterness in wine, in order to build a functional model of taste perception in humans for the interpretation of genetic data affecting taste and hence diet preferences and health.

References:

Campa D, de Rango F, Carrai M, Crocco P, Montesanto A, Canzian F, Rose G, Rizzato G, Passarino G, Barale R (2012) PloS ONE 7,

e45232. Clark AA, Dotson CD, Elson AET, Voigt A, Boehm U, Meyerhof W, Nanette I. Steinle NI, Munger SD (2015) FASEB J. 29, 164-172. Conte C, Ebeling M, Marcuz A, Nef P, Andres-Barquin PJ (2002) Cytogenet Genome Res 98, 45–53. Duffy VB (2004) Appetite 43, 5-9. Mangold JE, Payne TJ, Ma JZ, Chen G, Li MD (2008) J. Med. Genet. 45, 578-582. Meyerhof F, Batram C, Kuhn C, Brockhoff A, Chudoba E, Bufe B, Appendino G, Behrens M (2010) Chem. Senses 35, 157-170.

Expected skills::

Linux, basic programming capabilities, motivation for structural interpretation of molecular mechanisms

Possibility of funding::

To be discussed

Possible continuity with PhD: :

Yes