
**Proyecto PID2022-137161OB-I00 financiado por MCIN/AEI/10.13039/501100011033/ y por FEDER Una manera de hacer Europa**

**Identificación del proyecto:**

Impulsores estructurales del sesgo de señalización de GPCR y su explotación para candidatos a fármacos más eficientes y seguros

**Descripción del proyecto:**

G protein-coupled receptors (GPCRs) are an important cell surface receptor family with more than 800 members in the human genome. They are able to sense a large variety of extracellular signals (e.g. hormones, light, neurotransmitters, mechanic stress) and in response transmit a timely adequate signal into the cell. GPCRs are virtually involved in any physiological process and therefore are highly important targets for numerous disease indications (e.g. diabetes, obesity, cancer, cardiovascular diseases, pain treatment or complex CNS diseases such as schizophrenia or Alzheimer among many others). This is reflected in the large number of approved drugs (> 30%) that target this receptor class. Recent years have been showing the complexity of GPCR signaling. This involves their ability to engage a large set of intracellular transducer proteins (e.g. G proteins and arrestins) that trigger specific downstream signaling cascades. The observation that one GPCR can selectively trigger one signaling pathway over others (called signaling bias) has created a unique opportunity to revolutionize therapeutic treatments. Engaging only disease-related pathways while sparing out others related to side effects is a promising approach to yield more efficacious and safer drugs.

Despite its therapeutic relevance, signaling bias of GPCRs and involved molecular drivers remain poorly understood. The SigBias project will tackle these challenges through a multidisciplinary approach that bridges the atomistic scale of signaling bias to cellular readouts with the final aim to provide novel strategies to target this important receptor class. To reach this main objective, we will (i) monitor signaling bias with atomistic precision at the receptor level using computer simulations and (ii) extract structural drivers for signaling bias by combining the concept of receptor allostery with large-scale cellular readouts and machine learning. A strength of this project will be a novel framework that links computer simulation directly with biophysical technologies (NMR spectroscopy and cryogenic electron microscopy) to validate mechanistic insights of signaling bias. As a proof of concept, we aim to exploit structural insights for the development of pharmacological tools with pathway selectivity. They are of great practical value for interrogating specific pathways in diverse disease conditions and at the same time serve as promising starting points for the rational design of drugs with an improved therapeutic profile. We expect that the generated knowledge and methodologies centered on GPCR signaling complexity will greatly accelerate GPCR research and drug development programs linked to a wide range of disease applications.

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**206.250,00€**

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