Title: **Molecular Dynamics Simulations of androgen receptor mutants linked to human disease.**

Student: Irene Rico Núñez

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Supervisor/s: Dr. Eva Estébanez-Perpiñá

Department of biochemistry and molecular biology

The androgen receptor (AR) is a ligand-dependent nuclear transcription factor and member of the steroid hormone nuclear receptor (NR) superfamily. Several point mutations in AR gene in humans are linked to prostate cancer (PCa) and androgen insensitivity syndromes (AIS), among other diseases such as spinal and bulbar muscular atrophy (SBMA) also known as Kennedy´s disease.

After solving the crystal structure of AR dimer, it was identified for the first time that many of these residues are located within or adjacent to the dimerization site. This final degree project studio has been designed to complement and further investigate the previous studies undertaken in the host laboratory, which also solved the AR dimeric structure. A series of molecular dynamic simulations (MDs) have been undertaken to study the impact of chosen point-mutations in the AR dimerization site and to analyse whether possible allosteric changes impacting the overall structure could be identified. Using the AR ligand-binding domain wild type (WT) monomer (AR-LBD from now on) and three selected AR point-mutant variants linked to PCa and AIS.

Comprehension of the structure and therefore the function of NR is crucial in order to design therapeutic treatment to solve the deregulation caused by the mutations. For the purpose studying the NRs is common the use of MDs, this allow to understand de LBD allosterism.

Allostery can be explain as a conformational change of the protein induced by the modification at one location of structure (allosteric site). This evoke a variation the behaviour of a structurally-coupled but distinct location (active site).

To achieve the objectives, first it is mandatory to ensure that the amino acid chain is complete in the used AR structure template solved by X-ray crystallography downloaded from the Protein Data Bank (PDB). Thus, one needs to localize residues that may have not been resolved during protein structure building due to poor electron density coverage and add the missing residues in the coordinates. Secondly, one needs to optimize and minimize the X-ray solved structures with the purpose of performing reliable MDs with the chosen software. The structure parameters and angles should be optimal, and the Ramachandran plot complies with all the stereochemical rules.

The protein models obtained after these optimization steps will serve as a rationalization basis to understand the impact of point-mutations on AR structure and dynamics. After running in parallel 4 MDs per each protein of study, an exhaustive analysis of the differences and impact of mutations are obtained, and comparisons are done using several variables. For instance, a detailed study of the root-mean-square deviation of atomic positions (RMSD) and the root-mean-square deviation of atomic fluctuation (RMSF) is measured and analysed.

Keywords: Androgen receptor, point mutations, prostate cancer, androgen insensitivity syndromes, dimer, monomer, RMSF, RMSD, molecular dynamic simulations, allostery.