# PHD PROJECT DESCRIPTION
**(4000 characters max., including the aims and work plan to be published online)**

**Project title:** Mapping allosteric communication networks in potassium channels for precision pharmacology

## 1.1. Project goals

The primary scientific objective of this project is to characterize how selective ligands modulate the dynamic communication within potassium channels to achieve tissue-specific effects. The specific aims are:

1. To quantify the energetics of ligand selectivity by calculating binding free energy differences (ΔΔG) across various channel isoforms using enhanced sampling methods.
2. To identify allosteric propagation pathways that transmit signals from the drug-binding site to the channel gate.
3. To pinpoint critical residues responsible for drug specificity, enabling the rational design of safer therapeutics.

## 1.2. Outline

Potassium channels are vital therapeutic targets for treating diabetes, hypertension, and cardiac arrhythmias. However, many current drugs lack tissue selectivity, leading to severe off-target effects like hypoglycemia or cardiovascular complications. This project posits that selectivity is governed not just by static binding contacts but by the unique allosteric landscapes of different channel isoforms. Using KATP channels as a primary model, the PhD candidate will employ state-of-the-art computational biophysics tools, including atomistic molecular dynamics (MD) simulations on European supercomputers, λ-based free energy calculations, and the Dynamical Nonequilibrium Molecular Dynamics (D-NEMD) framework. The research will be conducted in close synergy with experimental data (cryo-EM and electrophysiology) through active collaborations with leading international experimental research groups in the field of membrane protein structural biology.

## 1.3. Work plan

**Year 1:** Construction of atomistic models for various potassium channel isoforms in complex with selective and non-selective ligands; execution of long-timescale equilibrium MD simulations to assess system stability.
**Year 2:** Application of alchemical free energy calculations (ΔΔG) and residue-level decomposition to quantify the energetic determinants of drug selectivity.
**Year 3:** Implementation of the D-NEMD framework and dynamic network analysis to map time-dependent allosteric pathways from the binding site to the pore.
**Year 4:** Integration of computational findings with experimental results from international partners; in silico validation of predicted allosteric residues via mutagenesis simulations; finalization of the doctoral dissertation

## 1.4. Literature (max. 7 listed as a suggestion for a PhD candidate preliminary study)

1. Elsheikh et al., eLife, 2025 (AI-based discovery & cryo-EM of K channels).
2. Patton et al., Channels, 2024 (Kir6/SUR structure and function).
3. Oliveira et al., eLife, 2025 (D-NEMD framework for allostery).
4. Driggers et al., Nature Communications, 2024 (Open state K channel structures).
5. Walczewska-Szewc & Nowak, JCIM, 2023 (Role of disordered regions in KATP).
6. Nguyen et al., Current Research in Physiology, 2024 (Allosteric modulation networks).
7. Walczewska-Szewc & Rydzewski, PCCP, 2025 (Ligand dissociation pathways).

## 1.5. Required initial knowledge and skills of the PhD candidate

- Basic experience with Molecular Dynamics simulations and software (e.g., GROMACS, VMD, PyMOL)
- Proficiency in Linux environments and basic programming skills (Python) for data analysis
- A strong interest in biophysics, structural biology, and computer-aided drug discovery

## 1.6. Expected development of the PhD candidate's knowledge and skills

The candidate will become an expert in advanced biomolecular modeling and High-Performance Computing, gaining hands-on experience with the world's most powerful supercomputers. They will master cutting-edge techniques for quantifying protein energetics and allostery, which are highly valued in the pharmaceutical R&D sector. Furthermore, the student will develop professionally through collaboration with top-tier international experimentalists, contributing to high-impact publications and gaining experience in an interdisciplinary research environment.