Internship Proposal

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Project Title:
Characterising a potential new drug target for Triple Negative Breast Cancer

Level:

Master Student

Project Summary:

Triple Negative Breast Cancer (TNBC) shows high levels of aggressiveness and metastatic potential. Although it has been described that a retrograde transport inhibitor that specifically blocks tumour growth in multiple TNBC preclinical models, including tumor explants and xenografts, the molecular mechanisms by which this is achieved remain unknown. Using in vitro cellular models, we have previously identified a potential target protein that explains its biological effects. The goal of the current project is to determine the binding pocket of this target protein and characterise its interaction with the inhibitor. AI-based methodologies and state-of-the art bioinformatics techniques will be used to generate testable hypothesis, which will then be tested experimentally in cancer cellular lines with mutated versions of the target protein. The identification and characterization of a novel target could be a key step in the development of new therapeutic options for TNBC.

Work to be developed by the student:

The student will develop his project in close collaboration with FCUP and LAQV/REQUIMTE. In this context, the student will have the opportunity to learn how to use a wide range of bioinformatics and computational chemistry tools, including protein modelling, molecular docking, and molecular dynamics, among others. The first task will be the building of three-dimensional models of the target protein, both alone and complexed with known interacting partners. This will involve the gathering of data from several biological databases, and the use of AI tools like Alphafold, or similar. These structural models will be used for an exploratory docking of the inhibitor against the target protein, which shall highlight possible binding sites. The student will then perform molecular dynamics simulations on the most promising protein/drug complexes in order to assess the stability of the interactions. If time permits, in vitro studies will finally be used to validate the

computational predictions.

References:

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Schiefermeier, N., Teis, et al Endosomal signaling and cell migration. Curr Opin Cell Biol 23, 615–620 (2011).

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Naslavsky, N. & Caplan, S. The enigmatic endosome - sorting the ins and outs of endocytic trafficking. J Cell Sci (2018)

Frittoli, E. et al. A RAB5/RAB4 recycling circuitry induces a proteolytic invasive program and promotes tumor dissemination. J Cell Biol (2014)

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