Molecular pathways involved in nuclear membrane stress adaptation and its role in breast and prostate cancer

Breast and prostate cancers are among the ones most prevalent in Europe, accounting for nearly 30% of cancer cases in women and men. While there are various mechanisms that can drive tumour transformation and progression, cancer cells typically show **abnormal nuclear morphology: shape and size.** The nucleus is a large and stiff organelle surrounded by the nuclear membrane, a lipid bilayer that **serves as a protective cage around the nucleus.** In cancer cells, nuclear membrane is often challenged by lack of some key proteins, which was observed in both breast and prostate cancer. As the cell can be exposed to various forms of stress, especially during cancer progression, also the nuclear membrane is often subjected various stresses (known as "**nuclear membrane stress**"), including **mechanical stress (e.g. squeezing the nucleus through narrow spaces) and oxidative stress (e.g. due to massive growth and insufficient vascular irrigation)**, leading to its dysfunction and/or damaging of some of its components, which could be additionally deteriorated by the loss of some key nuclear membrane proteins in cancer. Lack of some components of the nuclear membrane could activate pathways driving cancer progression and resistance to therapy leading to patients' worse survival. The aim of this project is to extensively analyse both internal and external factors that might impact nuclear membrane stability and cell's response to stress and adaptive mechanisms.

Molecular factors influencing nuclear membrane stability and composition will be selected using **high-throughput screening** approach and cell lines without some of the nuclear membrane components will be generated and characterized with a variety of biochemical and advanced imaging methods. Then, nuclear membrane stability will be challenged by various treatments inducing **oxidative stress (chemicals, hypoxia, chemo- and radiotherapy) as well as mechanical stresses (mechano-devices)** to understand how nuclear membrane composition can affect stress response and **if there are any molecular pathways that could help the cancer cell to adapt**. Furthermore, such nuclear membrane stress adaptive pathways and their mechanisms of action and potential role will be investigated using *in vitro* 3D models and clinical material from breast and prostate cancer patients to understand their potential involvement in cancer progression and metastatic dissemination.

As nuclear membrane plays such an important role in protection of the nucleus, the results coming from the proposed project could completely change the perception of response to nuclear membrane stress and lead to discovery of **potentially novel molecular pathways** for the cell to adapt to various form of stress. Additionally, by investigating such molecular components in clinical material from cancer patients, it could help to understand nuclear membrane adaptation in tumor progression and dissemination, which would strongly influence cancer research field. By delving deeper into these areas, my project could provide **valuable insights into the role of nuclear membrane stress in cancer progression and therapy resistance**, ultimately contributing to better strategies for intervention and treatment in these cancer types.

Collectively, it is evident that the nuclear membrane plays an essential role in tumorigenesis and, advancing our knowledge of the nuclear membrane proteins, and nuclear membrane -related stress adaptation and their cellular pathways involved, will significantly **improve our understanding of tumor progression**. As most deaths from solid tumors are caused by metastases, identification of novel mechanisms that drive tumor progression and metastatic dissemination with potential druggable targets could be a **promising strategy to reduce cancer mortality**. Also, identification of cells with the highest metastatic potential that could serve as a biomarker of disease progression could facilitate **clinical decision-making**. Thus, the proposed project is yet a pioneering study and carries the potential to pave the way for precision oncology. Additionally, a potential mechanism(s) of nuclear membrane stress adaptation could be **extrapolated to other cancer types and various diseases**.