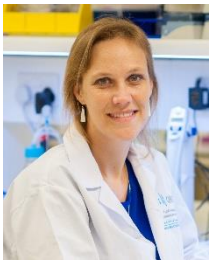
HBKU Thematic Research Grant 1st Cycle– Project Highlight

Project Title: Validation of LDHC as a novel target for precision medicine in breast cancer



LPI Name: Dr Julie Decock

Executive Summary

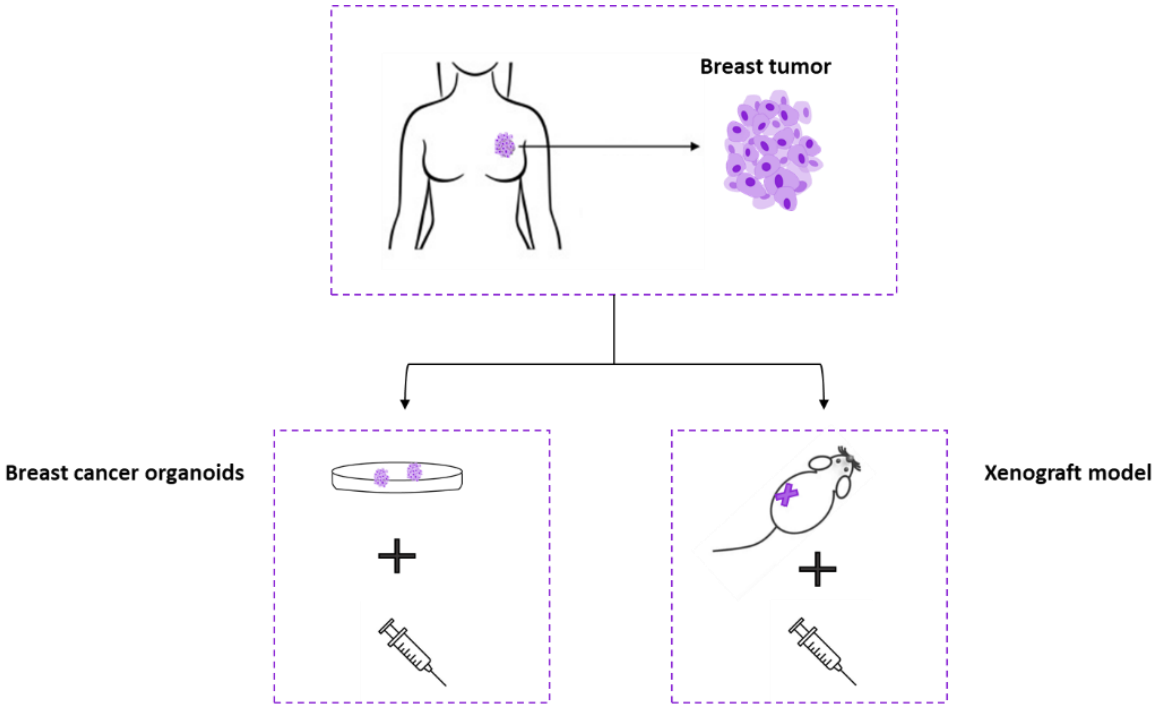
Breast cancer treatment is moving away from one-size-fits-all traditional care towards precision medicine. The lack of durable treatment responses in patients with triple negative breast cancer (TNBC) has paved the way for exploration of novel, personalized treatment approaches. Approximately 15% of these tumors harbor germline mutations in BRCA1/BRCA2, impairing DNA damage repair by homologous recombination (HR), and show clinical benefit from treatment with drugs that interfere with the DNA damage response pathway. TNBC tumors without such mutations often display HR deficiency through other mechanisms and may benefit from similar interventions. We recently demonstrated that targeting Lactate Dehydrogenase C (LDHC) promotes DNA damage accumulation in breast cancer cells through cell cycle checkpoint dysregulation, and significantly improves *in vitro* treatment response to the DNA damaging agent cisplatin and the DNA damage repair inhibitor olaparib. LDHC is a highly-tumor specific antigen, and hence could be targeted with limited to no off-target effects. In this project, we will validate its therapeutic potential in combination with cisplatin and olaparib in breast cancer organoids and xenograft mouse models. To this end, we will develop a clinically relevant, cell penetrating, peptide-assisted shRNA delivery system with tumor homing abilities to enable tumor cell-specific uptake of *LDHC* silencing molecules.

Expected Outcome (limit to 100 words)

This project builds on our previous findings where we demonstrated the therapeutic potential of targeting LDHC to resensitize breast cancer cells to anti-cancer drugs. We will design and develop a peptide-assisted *LDHC* silencing delivery system and validate its translational value in a preclinical proof-of-concept or feasibility study, which will allow us to assess the potential clinical benefit of LDHC-targeted therapy. As such, the project is expected to provide evidence to advance our current provisional patent to the next stage of the patenting process.

Collaborating HBKU entities: College of Health and Life Sciences, HBKU

Photos:



Tumor cell killing by LDHC-targeting drug alone or in combination with common anti-cancer drugs (cisplatin, olaparib)