## HBKU Thematic Research Grant 3rd Cycle– Project Highlight

**Project Title:** Small molecule targeting of R-Ras, a neglected member of the Ras GTPase subfamily, as a novel Wnt pathway component and cancer driver

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**Executive Summary (limit to 200 words)**

Development of targeted anti-TNBC (triple-negative breast cancer) therapies will bring hope for millions of patients worldwide currently having no other therapeutic options than to undergo conventional chemotherapy regimens. The oncogenic Wnt signaling pathway is the key target to develop the missing therapies, but no Wnt pathway inhibitors currently exist on the market. TNBC and other Wnt-dependent cancers thus represent a huge unmet medical need. Translational research performed by our team led to identification of an innovative, effective and safe small-molecule FSA scaffold targeting the Wnt pathway in TNBC. Target deconvolution and validation experiments identified FSA compounds to act on a novel and unexpected target – R-Ras, the neglected member of the Ras subfamily of small GTPases. The current project aims at identifying the mode of action of FSA compounds on R-Ras using biochemical, biophysical, and cell biological techniques, and at resolving the structure of R-Ras in complex with the compounds. This structural elucidation will permit rational design of new FSA analogs with improved potency and selectivity, laying the ground for future industrial developments of a first-in-class small molecule anti-Wnt and anti-cancer drug candidate.

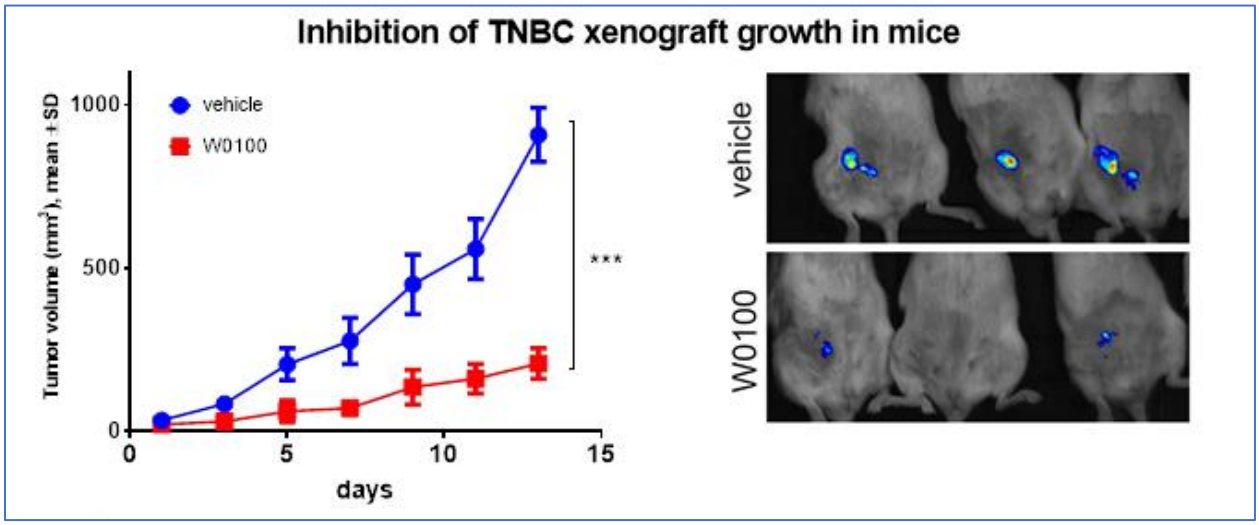
**Expected Outcome (limit to 100 words)**

The discoveries we anticipate making in the run of this project will advance the basic understanding of the oncogenic Wnt signaling pathway and will lay the ground for the rational design of improved small molecule compounds inhibiting the Wnt pathway through R-Ras, ultimately delivering first-in-class small molecule drug candidates for the treatment of TNBC and other Wnt-dependent cancers. The beneficiaries of these discoveries will be i) fundamental cell biology scientists across the globe; ii) industry players interested in novel drug candidates to invest in; iii) ultimately – cancer patients urgently in need for novel targeted therapies.

**Collaborating HBKU entities:**

QBRI and QEERI

**Photos –** please insert photos, schematics, graphs…etc. relevant to the project




**The FSA compound W0100 reveals a strong anti-tumor effect in a mouse xenograft model of human triple-negative breast cancer (TNBC).**