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PRESS RELEASE

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Publication in Nature advanced on line publication: researchers at the Université Libre de Bruxelles, ULB identify the cells at the origin of breast cancers.

One of the key questions in cancer biology is to understand the mechanisms that control tumor heterogeneity and to determine to which extend tumor heterogeneity influences clinical outcome.

In a study published in ***Nature***, researchers lead by **Cédric Blanpain**, MD/PhD, WELBIO investigator and Professor at the Université Libre de Bruxelles, Belgium, in collaboration with Pr Wayne Phillips, Australia and Pr Christos Sotiriou, Bordet Institute, Belgium uncovered the cellular origin of PIK3CA-induced breast tumors and demonstrated that the cancer cell of origin controls tumor heterogeneity and is associated with different breast tumors types and clinical prognosis.

Breast cancer is the most common cancer among women. Human breast cancers can be classified according to their histological and molecular features into different subtypes, including luminal, ERBB2 and basal-like tumors. PIK3CA and p53 are the two most frequently mutated genes in human breast cancer and are associated with different molecular subtypes.

In this new study published in ***Nature***, **Alexandra Van Keymeulen** and colleagues used state of the art genetic mouse models to identify the cellular origin of PIK3CA and p53 induced breast tumors. They found that depending on the cell of origin, mutations in PIK3CA and p53 induced very different types of tumors. The luminal cells generally lead to more aggressive tumors. "It was really surprizing to realize that oncogenic *Pik3ca* in basal cells induced the formation of luminal tumours, while its expression in luminal cells gave rise to

heterogeneous and more aggressive tumors including basal-like tumors", **comments Alexandra Van Keymeulen**, the first author of the paper.

By analysing the early steps that precede tumor formation, Alexandra Van Keymeulen and colleagues found that expression of oncogenic *Pik3ca* reactivates a multilineage differentiation program in adult stem cells that resembles to an immature embryonic state. Molecular characterization of the cells that undergo cell fate transition upon oncogenic *Pik3ca* expression demonstrated a profound oncogene-induced reprogramming of these newly formed cells and identified gene expression signatures, characteristic of the different cell fate switches, which was predictive of the cancer cell of origin, tumour type and clinical outcomes in women with breast cancers. "These new findings not only demonstrate the importance of the cancer cell of origin in controlling breast tumor heterogeneity, but also show that the gene expression signature found in the early steps of tumor initiation is predictive of the type of tumors that will eventually develop and the clinical prognosis of women with breast cancers" comments **Cédric Blanpain,** the senior author of the ***Nature*** paper.

In conclusion, this new study identifies the cellular origin of *Pik3ca*-induced tumours and reveals that oncogenic *Pik3ca* activates a multipotent genetic program, setting the stage for future intratumoural heterogeneity at the earliest stage of tumor development. These results have important implications for the understanding of the mechanisms controlling tumour heterogeneity and the development of new strategies to block *PIK3CA* induced breast cancer.

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Reactivation of multipotency by oncogenic PI3KCA induces breast tumor heterogeneity

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