Estrogens are well known to promote the growth of Estrogen Receptor (ER) ?-positive breast cancers. However, emerging clinical data suggest that estrogens could also impact tumor progression and treatment of unexpected cancers that are not reported to express ER?.

In this study, we show that stromal ER? contributes to mediate a pro-tumoral effect of 17ß-estradiol (E2) observed on ER-negative tumors subcutaneously grafted to ovariectomized immunocompetent mice. By this way, E2 is able to potentiate the progression of tumor previously categorized as E2-insensitive. This is supported by a multidisciplinary approach showing that: 1) E2-accelerated tumor growth is completely abrogated in ER?-deficient mice, 2) in WT mice, E2 increases the different steps of tumor angiogenesis and improves tumor oxygenation, these effects are lost in ER?-deficient mice, 3) ER? expressed by Tie2-positive stromal cells is necessary to mediate E2-accelerated tumor growth of ER-negative tumors, 4) the activation of ER?-associated genomic effects are necessary to mediate the E2 impact. Our results demonstrate that, in a context of ER?-negative tumors, E2-induced growth relies on ER?-mediated enhanced host angiogenesis.

In conclusion, we demonstrated that ER? expressed by Tie2-positive stromal cells is a key actor contributing to mediate a pro-tumoral effect of E2 observed on ER-negative tumors. In this case, E2 accelerates tumor progression by improving tumor angiogenesis and oxygenation. Thus, both estrogenic status and stromal ER? expression should be considered to improve the management of patients with ER-negative tumor.