# Title: GTP cyclohydrolase accelerates tumor progression through interaction with angiopoietin-1 in stromal fibroblasts and activation of Tie2 on breast cancer cells

**Abstract No.** 0054

**Title** GTP cyclohydrolase accelerates tumor progression through interaction with angiopoietin-1 in stromal fibroblasts and activation of Tie2 on breast cancer cells

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**Approval** Yes

**Background**

Cancer-associated fibroblasts (CAF) play a key role in promoting tumour growth, acting through the complex paracrine regulation. GTP cyclohydrolase (GTPCH) expression for tetrahydrobiopterin (BH4) in stromal fibroblasts is implicated in tumour angiogenesis and development. However, the clinical significance of GTPCH expression in breast tumour, and the role of GTPCH/BH4 pathway in stromal fibroblast and tumour cell communication are still unknown.

**Method**

We compared levels of GTPCH expression between normal breast and breast cancer tissue microarray (TMA) using immunochemistry, and correlated GTPCH elevation with prognosis of breast cancer patients in several sets of gene microarray data. We evaluated molecular effects of ectopic expression of GTPCH in stromal fibroblasts on breast cancer development in models of cocultures or co-implants.

**Results**

We found that GTPCH was upregulated in the breast CAF and epithelia, and high GTPCH RNA was significantly correlated with big high grade tumour and worse prognosis, particularly estrogen receptor (ER)/progesterone receptor (PR)-negative patients. In cocultures, GTPCH expressing fibroblasts stimulated breast cancer cell proliferation and motility, phosphorylation of

tumour Tie2 and consequent downstream pathways. GTPCH formed a complex with angiopoietin-1 (Ang-1), which required BH4 chaperone activity and colocalized in the cytoplasm of the stromal fibroblasts. Secreted Ang-1 bound to and phosphorylated tumour Tie2. In coimplantation xenograft experiments, GTPCH accelerated tumour growth, upregulating Ang-1 and alpha-smooth muscle actin (a-SMA) mainly in fibroblast-like cells. Inhibition of GTPCH results in the attenuation of both tumour growth and angiogenesis.

**Conclusion**

This study has demonstrated that high GTPCH expression in breast tumour is a significant predictor of poor outcome in patients. Cancer-associated GTPCH expression in stromal fibroblasts favours breast cancer growth in vitro and in vivo. The underpinning oncogenic RTK Tie2 signal transduction on tumour cells was primarily mediated by GTPCH/Ang-1 interaction in stromal fibroblasts - a previously unrecognized mechanism that enhances tumour development.

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| **Theme** | The cancer cell and model systems |
| **Invivo** | Confirm |
| **Category** | Breast cancer |
| **Keyword 2** | Aetiology – Exogenous factors and cancer |
| **Presenter is available** | Yes |
| **Declaration** | Agree |
| **How do you hear** | Previous attendance |

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