Project Title:	Development of 3D organoid models for identifying novel breast cancer therapeutics targeting tumor microenvironment and cancer stem cells 開發 3D 器官模型鑑定針對腫瘤微環境的新型乳腺癌藥物
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Triple-negative breast cancer (TNBC), an aggressive subtype of breast cancer, is restricted to conventional chemotherapy. By performing multiomic profiling, TNBC-specific super-enhancers (SEs) and one of SEs that specifically drives oncogene TCOF1 have been revealed. However, the molecular mechanisms that regulate TCOF1-SE remain to be elucidated.

In this budget period, the team collaborated with Prof Michael Yang and Prof Liang Zhang's group to identify transcription factors which bind to TCOF1-SE by combining DNA pull-down assay and bioinformatics prediction. Transcription factor FOSL1 was chosen for further study. FOSL1 depletion led to reduced TCOF1 mRNA and protein levels. Furthermore, by performing dual-luciferase reporter assays and CHIP-qPCR, it is demonstrated that FOSL1/TCOF1-SE interplay promotes the transcription of TCOF1 in TNBC cells. FOSL1 knockdown also inhibited TNBC spheroid growth and stemness properties. This work will aid in the identification of therapeutic targets to treat TNBC, and the manuscript reporting these findings has been written up for submission.

Furthermore, the identification of novel cancer-related genes in brain microenvironment has been focused. One of the genes that has been under study is TUBB2B, which is highly upregulated in brain metastasis of TNBC, compared to primary tumor or extracranial metastases. TUBB2B is overexpressed in 29% of TNBC cases, and analysis of clinical data demonstrated a significant co- relation between high expression of TUBB2B in tumor and brain relapse. The functional role of TUBB2B in the pathogenesis of cancer has not been studied. In vitro and in vivo experiments were therefore performed, which showed a critical function of TUBB2B in both primary TNBC growth and brain metastasis colonisation. The team has filed US Patent "targeting TUBB2B for cancer treatment" in December 2022.

Currently, in collaboration with Prof Liang Zhang, the team has been performing various biochemical studies to elucidate the molecular mechanisms by which TUBB2B modulates TNBC pathogenesis. Collaboration with Prof Gigi Lo has been in progress as well to deliver TUBB2B siRNA using gold nanoparticles as a potential TNBC treatment strategy.