**Building AI-enabled cancer diagnostic model with ligand-receptor interaction biomarkers through spatial transcriptome**

**(建構基於空間轉錄組的配體-受體互作生物標記的人工智能癌症診斷模型)**

PI: Prof. Lingxi CHEN

Co-PI: Prof. Mengsu YANG

**Summary of the Proposal**

Cancers represent a formidable challenge to global health, necessitating innovative approaches for early detection and targeted therapies [1]. Presently, hospitals rely on a meticulous visual assessment conducted by specialized pathologists for cancer diagnosis [2]. Utilizing digital whole-slide images, derived from either formalin-fixed paraffin-embedded (FFPE) or frozen tissues stained with hematoxylin and eosin (HE), diagnoses are formulated through detailed examination. Histology-based cancer diagnostics, while invaluable, often pose challenges due to their inherent time-consuming and labor-intensive nature [2]. Recognizing the need for more efficient processes, there is a growing imperative to develop automatic pipelines to expedite diagnostic workflows. Contemporary approaches leverage the power of artificial intelligence (AI) to assist medical professionals in decision-making [3, 4]. However, the existing methodologies predominantly rely on morphological features extracted from HE images, overlooking the wealth of information available at the molecular level, specifically in the realm of transcriptomics, which captures the most nuanced dynamics of tumors.

Featured as the Method of the Year 2020 by the journal Nature [5], recent advancements in Spatial Transcriptome (ST) protocol, now allow for the profiling of spatially resolved gene expression directly from Hematoxylin and Eosin (HE) stained FFPE or frozen tissues [6–9]. This breakthrough opens up new avenues for more accurate and automated cancer diagnostic processes by delving into the molecular RNA landscape of cells within the specimen. Unlike traditional methods that rely solely on morphological cues, this ST approach provides a comprehensive understanding of the intricate dynamics at the molecular RNA level. Currently, tumor diagnostics based on ST data rely heavily on inferred copy number variation or gene signatures. While the copy number signature approach is effective for tumors with copy number variations [10], it faces limitations when dealing with copy number-neutral tumors. RNA signatures, which predominantly provide information on gene expression levels, are widely employed in pan-cancer analyses [11]. However, their applicability is constrained by a

lack of details regarding the functional consequences of these expression patterns, thereby limiting their interpretability.

A crucial aspect often overlooked by many existing ST gene signature methodologies is the intricate landscape of cell-cell communication, particularly within immune-infiltrated tumor microenvironments [12]. In such complex contexts, the interplay of ligands and receptors between immune and tumor cells emerges as a significant signature. This nuanced ligandreceptor interaction (LRI) not only assists in distinguishing specimens containing malignant cells but also holds vast potential for predicting a tumor's prognosis, treatment response, and understanding its immune escape capabilities. Recognizing the pivotal role of LRIs as distinctive molecular biomarkers and establishing an automated, AI-enabled cancer diagnostic model provides a more comprehensive and contextually rich foundation for advancing the precision of spatial transcriptomic-based tumor diagnostics.