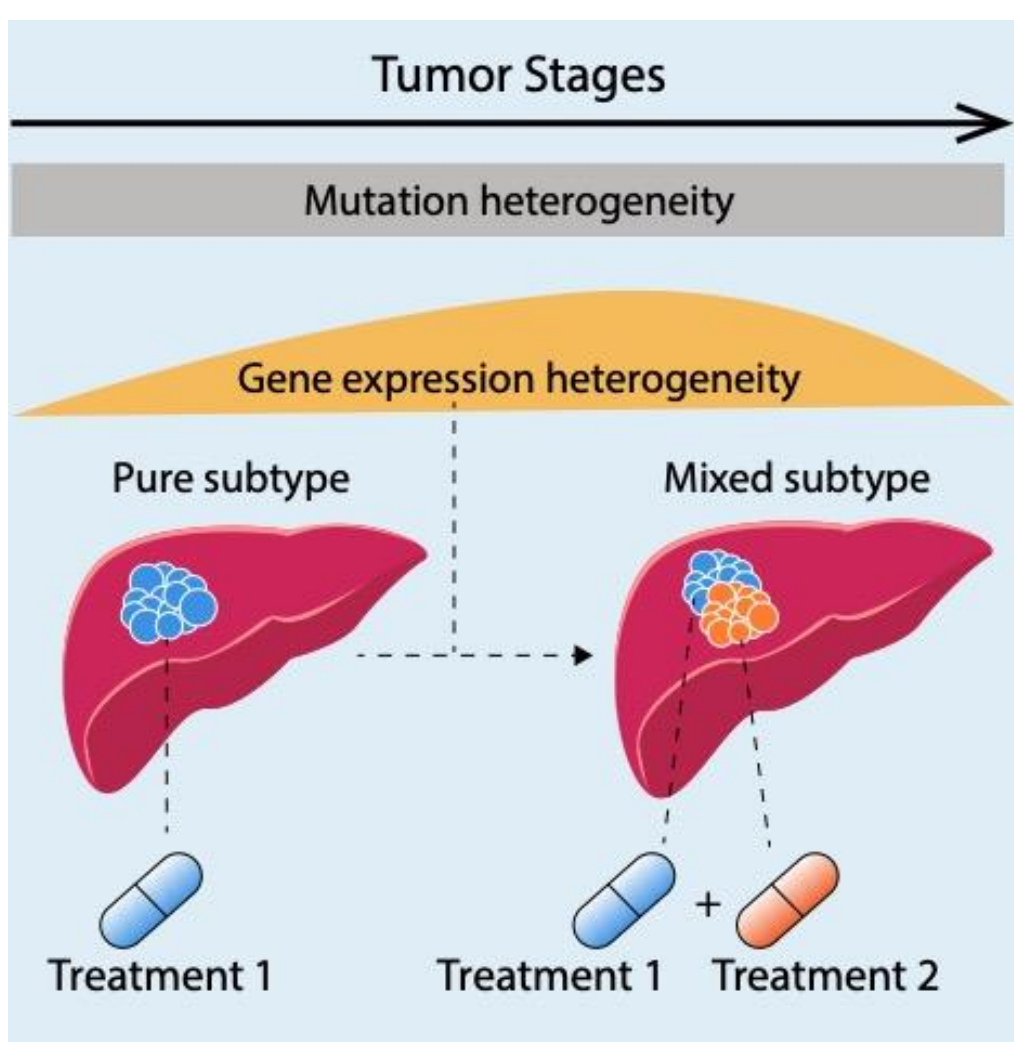


NEW STUDY IN PRIMARY LIVER CANCER CALLS FOR NOVEL STRATEGIES TARGETING A DYNAMIC LANDSCAPE OF HETEROGENEOUS TUMOURS



*HCCs diversify during tumour evolution, leading to multiple co-existing subtypes in a significant proportion of HCC that will require combination systemic therapies to treat the disease (Copyright, A*STAR's Genome Institute of Singapore)*

Singapore scientists and clinician scientists have established one of the largest prospective cohorts for HCC known as the Precision Medicine in Liver Cancer across Asia-Pacific Network (PLANet). Based on the PLANet study, scientists and clinician scientists from the A*STAR's Genome Institute of Singapore (GIS), National Cancer Center Singapore (NCCS), Singapore General Hospital, National University Health System from National University of Singapore, Duke-NUS Medical School, Nanyang Technological University, and collaborators from China, Malaysia, Thailand and Philippines, have described a dynamic genomic landscape of tumour heterogeneity in hepatocellular carcinoma (HCC). This research comes from one of the largest prospective cohorts for HCC known as the Precision Medicine in Liver Cancer across Asia-Pacific Network (PLANet) study. These novel findings from PLANet were recently published in the journal *National Science Review* (NSR)¹.

Hepatocellular carcinoma (HCC) is the seventh most common cancer worldwide, but the fourth leading cause of cancer death globally due to its high mortality rate². Strikingly, a disproportionate 80% of the disease burden is shouldered by Asian populations. Despite much effort, there is currently no validated predictive biomarker for systemic therapies in HCC and treatment efficacy remains poor. To address this unmet clinical need, a collaborative multi-disciplinary and multi-institutional team was awarded funding to establish the Translational and Clinical Research (TCR) Flagship Programme in Liver Cancer, which is supported with funding from the National Research Foundation Singapore and administered by the Singapore Ministry of Health's National Medical Research Council (NMRC)³. In this programme, the PLANet study was initiated to enroll a prospective HCC patient cohort working with the Asia-Pacific Hepatocellular Carcinoma (AHCC) Trials Group across multiple Asian countries. Specifically, this study aims to understand molecular diversities within a tumour, i.e. intra-tumour heterogeneity (ITH), as well as how we can use such understanding to guide patient stratification and treatment in HCC. In 2017, the group discovered that HCC has a wide range of genetic ITH across patients⁴.

The study and its findings

The current study is based on a cohort of 67 patients from 4 Asian countries from the PLANet study and is the first study of intra tumour heterogeneity across multi-omic data layers (genome, transcriptome, immunome) in HCC. Researchers found variations in different regions of the same tumour for both genetic (DNA mutation) and transcriptomic (RNA expression) profiles. In particular, they found that the level of such variations differs across patients and over 30% patients show a high transcriptomic ITH where a single tumour could contain multiple transcriptomic subtypes.

Such dynamic evolutionary process in HCC helps to explain the poor response to systemic therapy in HCC, where therapies addressing only a single group of molecular targets is not sufficient. Using the PLANet cohort, the authors demonstrated how combination therapies can potentially address the high ITH to increase treatment response rates for HCC. Discoveries from this research provide novel scientific rationale for the development of innovative therapies for HCC. In the next phase, the group will focus on how to improve liver cancer treatment outcome by targeting this dynamically evolving heterogeneity.

The PLANet study has also provided researchers and clinicians a complete atlas to assess the evolutionary history of liver cancer. Such genomic information will provide a solid basis for understanding how individual patients might respond differently to drug treatments, thus enabling a precision medicine approach to treat patients differently in the future. Data from this study is now publicly available via the Singapore Oncology Data Portal (OncoSG)⁵ which allows integration, visualization, analyses, and sharing of cancer genomics datasets generated in Singapore.

"This study depicted the first full landscape of tumour heterogeneity in HCC, providing a solid basis harnessing tumour evolution for patient prognosis and treatment.."

*Dr Zhai Weiwei,
former principal investigator at GIS,
who co-led this study*



"I have been treating HCC for more than 20 years and have conducted multi-national clinical trials in this cancer, but HCC remains a very challenging malignancy. Significant scientific breakthroughs are required to further improve patient outcomes and our current findings provide an important step in this direction."

*Prof Pierce Chow,
senior author of the study, overall principal investigator of PLANet,
Senior Consultant, Department of Hepato-Pancreato-
Biliary/Transplant Surgery, Division of Surgery
and Surgical Oncology at SGH and NCCS*



"GIS is honored to be part of the largest prospective cohorts for HCC, which spans across numerous institutes and countries. For the first time, we revealed an unprecedentedly dynamic landscape of phenotypic heterogeneity in HCC, highlighting the importance of studying phenotypic evolution and novel therapies contending a vibrant landscape of tumor evolution in HCC."

*Prof Patrick Tan,
Executive Director of GIS*



References:

1. Zhai, W. et al. Dynamic phenotypic heterogeneity and the evolution of multiple RNA subtypes in Hepatocellular Carcinoma: the PLANet study. *Natl. Sci. Rev.* (2021) doi:10.1093/nsr/nwab192
2. Singal, A. G., Lampertico, P. & Nahon, P. Epidemiology and surveillance for hepatocellular carcinoma: New trends. *J. Hepatol.* 72, 250–261 (2020)
3. SingHealth clinician scientists win national grant to research brain tumours, liver cancer. <http://www.sgh.com.sg:80/news/awards/singhealth-clinician-scientists-win-national-grant-to-research-brain-tumours-liver-cancer>
4. Zhai, W. et al. The spatial organization of intra-tumour heterogeneity and evolutionary trajectories of metastases in hepatocellular carcinoma. *Nat. Commun.* 8, 4565 (2017)
5. OncoSG. https://src.gisapps.org/OncoSG_public/study/summary?id=GIS041