

AHCC Trials Group

Newsletter 2022

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Welcome to our AHCC Trials Group newsletter

As we are half way through 2022, we look back at the past year, which marked another exciting year of research for the AHCC Trials Group despite the ongoing COVID-19 situation. The AHCC Trials Group has demonstrated high resilience, adaptability and versatility to change as we continued to generate high scientific outputs in our ongoing PLANet Study, AHCC07 study, the Translational and Clinical Research (TCR) Flagship Program in Liver Cancer. We are happy to share that the PLANet Study has been renewed by the award of the National Medical Research Council Open Fund-Large Collaboration Grant (NMRC OF-LCG) on 1 June 2022. The study will be named as PLANet 2.0, comprising of AHCC12 and AHCC13.

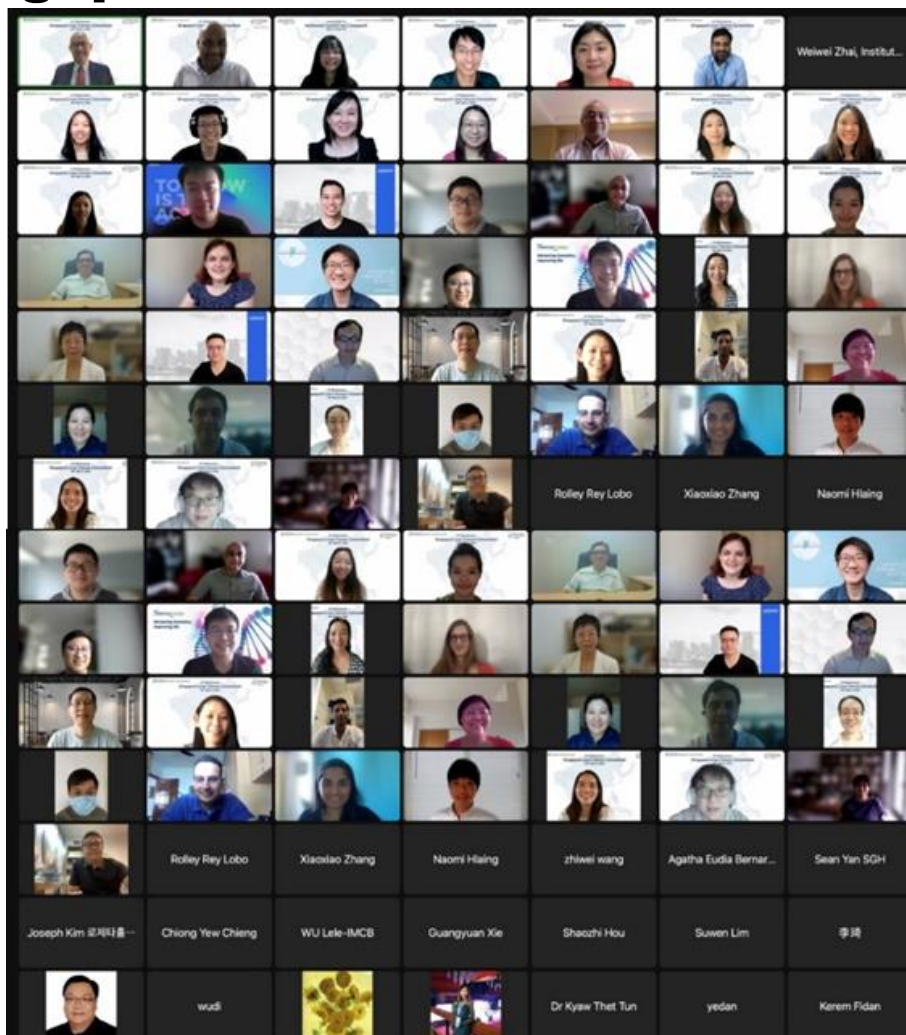
The HCC Registry in Asia (AHCC08) study was successfully concluded in July 2020 and data analysis is in progress.

The AHCC Trials Group has recently initiated 2 prospective studies, the AHCC10 ELEGANCE and the parallel AHCC11 PROSECT studies despite the challenges imposed by the pandemic. To date, we have recruited more than 1,000 patients and we are looking forward to findings from the preliminary analyses.

The Trials Group is in the midst of initiating the new AHCC09 STRATUM study in the 3rd quarter of 2022 which was approved in April 2022 and recruitment will begin later this year.

With these new developments, the Trials Group continues to thrive despite the challenging times. We would like to attribute the Trials Group's success to all the members and collaborators for their commitment and continuous support. Maintaining the close working relationship as a group for 25 years is one of the greatest feats of the AHCC Trials Group, and this is made possible with all the dedication, support and hard work of our members and study team. Thank you for pulling the AHCC Trials Group through all these years!

The 4th Symposium of the Singapore Liver Cancer Consortium



The AHCC Trials Group hosted its 4th Symposium of the Singapore Liver Cancer Consortium (SLCC) on 26 March 2022 virtually with resounding success. The last symposium was in May 2019 before the pandemic. The virtual symposium was attended by more than 150 participants including members of the AHCC Trials Group, researchers, healthcare professionals and industry collaborators. While we miss the social interactions and personal connections of a face-to-face meeting, we are glad that our online symposium was equally interactive and engaging with exchanges of knowledge between the speakers and attendees.

In this symposium, we had our esteemed speakers sharing the results of their research. The symposium started with **Dr Zhai Weiwei**, Principal Investigator, Institute of Zoology, Chinese Academy of Sciences, Beijing, China presenting “A Multi-Omic Approach for Dissecting Genotypic and Phenotypic Tumor Heterogeneity in HCC”. Leveraging the prospective observational cohort of the PLANet Study (AHCC07), Dr Zhai provided one of the most comprehensive examples how multi-layer Intra-tumor heterogeneity (ITH) can be harnessed to understand tumor evolution and patient stratification. The results were published in National Science Review in 2021 (Zhai WW, Lai H, Kaya NA, ..., Tam WL, Toh HC, Foo RSY, Chow PKH. **Dynamic phenotypic heterogeneity and the evolution of multiple RNA subtypes in Hepatocellular Carcinoma: the PLANET study**, Nat. Sci. Rev., 2021).

The 4th Symposium of the SLCC (cont'd)

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Dr Ankur Sharma, Laboratory Head, Onco-Fetal Ecosystem Laboratory, Harry Perkins Institute of Medical Research and Curtin University, Perth, Australia presented on “Oncofetal Ecosystem in HCC: Spatial Localisation and Clinical Implications”. His recent work demonstrated embryonic-like reprogramming in tumor microenvironment, indicating extraordinary cellular plasticity within the tumor microenvironment, which adds an additional layer of cellular heterogeneity. In his talk, Dr Sharma discussed the mechanisms of oncofetal reprogramming that allow tumor cells to escape from immune responses, promoting tumor growth. He also discussed the spatial organisation of oncofetal ecosystem in liver cancer and its implications in predicting response to therapy in clinic. The results were published in Cell in 2020 (Sharma A, Seow JJW, ..., Chow PKH, Ginhoux F, DasGupta R. *Onco-fetal Reprogramming of Endothelial Cells Drives Immunosuppressive Macrophages in Hepatocellular Carcinoma*. Cell. 2020).

Last but not least, **Dr Chen Jianbin**, Research Associate, Genome Institute of Singapore, presented “Prognostic Stratification by Phenotypic Subtypes Emerging from Diverse Evolutionary Paths in HCC”. Dr Chen presented his results derived from 127 patients recruited under the PLANet Study (AHCC07). Divergent evolutionary paths were identified from which transcriptomic subtypes of varying aggressiveness arise, leading to prognosis stratification. Moreover, across multiple sectors within a tumor, the most aggressive sector (“bad apple”) predicts prognosis with the highest accuracy. Interestingly, ITH showed a double-edged role in prognosis where higher transcriptomic ITH predicts better prognosis among tumors with the “bad apple” and worse prognosis among those without. This study provides a rich resource to investigate the interaction between multi-omics tumor evolution and clinical trajectory in HCC. Dr Chen is currently preparing the manuscripts for publication.

The symposium was well-received and we look forward to the next SLCC Symposium in mid of 2023.

Our Speakers



Prof Pierce Chow
 • Protocol Chair, AHCC Trials Group
 • Principal Investigator, AHCC07 PLANet Study and AHCC08 HCC Registry in Asia
Updates on Asia-Pacific Hepatocellular Carcinoma (AHCC) Trials Group



Dr Zhai Weiwei
 • Principal Investigator, Institute of Zoology, Chinese Academy of Sciences, Beijing, China
A Multi-Omic Approach for Dissecting Genotypic and Phenotypic Tumor Heterogeneity in Hepatocellular Carcinoma



Mr Alex Oh
 • Project Director, Labcorp Drug Development
 • Ph.D. Candidate in Programme in Clinical and Translational Sciences, Duke-NUS Medical School, Singapore
Survival and Cost-Effectiveness and Impact of Positive Clinical Trials in the Management of Hepatocellular Carcinoma (HCC) in Asia: The HCC Registry in Asia



Dr Timothy Wai Ho Shuen
 • Senior Research Fellow, National Cancer Centre Singapore
 • Research Manager, VICTORY Programme
Translational Analysis of Yttrium-90 Treatment in Hepatocellular Carcinoma



Dr Jeon Ah Jung
 • Bioinformatician, MIRXES
 • Adjunct Scientist, National Cancer Centre Singapore
A Genomic Enhancer Signature Associates with Hepatocellular Carcinoma Prognosis



Dr Ankur Sharma
 • Laboratory Head, Onco-Fetal Ecosystem Laboratory, Harry Perkins Institute of Medical Research and Curtin University
Oncofetal Ecosystem in Hepatocellular Carcinoma: Spatial Localisation and Clinical Implications



Dr Chen Jianbin
 • Research Associate, Genome Institute of Singapore
Prognostic Stratification by Phenotypic Subtypes Emerging from Diverse Evolutionary Paths in Hepatocellular Carcinoma

Overview of the study



- Main aims :**
 - Cataloguing consensus enhancer loci across HCC tissues
 - Identifying differential enhancer loci between T vs. adjN
 - Inferring promoter-enhancer relationship
 - Investigating downstream effect in altered gene expression
 - Investigating the patient-dependent variability
- Data analysed :**
 - H3K27ac ChIP-seq from 30 patients
 - H3K and H3K27ac ChIP-seq for a subset of patients
 - Bulk RNA-seq and clinical data from 90 patients

Translational Analysis of Yttrium-90 Treatment in Hepatocellular Carcinoma

Dr Timothy Shuen
 Senior Research Fellow
 Division of Medical Oncology, National Cancer Centre Singapore

Research Manager
 the Virus-Induced Cancer – Translational Oncology Research and Immunology (VICTORY) programme

Survival and cost-effectiveness and impact of positive clinical trials in the management of Hepatocellular Carcinoma (HCC) in Asia

– The HCC Registry in Asia between 2013 and 2019 and Real-World Data

ALEX OH YONGHO

Our esteemed speakers at the
4th Symposium of the SLCC, 26 March 2022

Dr Jeon, Dr Shuen and Mr Ho
presenting at the symposium



AHCC07 Precision Medicine in Liver Cancer across an Asia-Pacific Network

Clinicaltrials.gov identifier: NCT03267641

Protocol Chair: Prof Pierce Chow

Study Status: Completed in May 2022 and successfully renewed as PLANet 2.0 in June 2022.

Initiated in May 2016, the PLANet study has successfully recruited 147 patients from 5 countries (Malaysia, Philippines, Singapore, Thailand and USA). Within this mature cohort, 132 have reached the study end-points¹. This strategic platform has allowed us to delineate the multi-omics landscape of HCC intratumoural heterogeneity (ITH) with our results published in various high-impact journals like Cell (JIF: 41.58), Nature Cell Biol (JIF: 28.82), Natl Sci Rev (JIF: 17.725) and others.

1. as defined by recurrence or death or 2 years' follow-up from the date of surgery, whichever earlier

Significant Findings:

1. **Onco-fetal reprogramming confers immune-escape in HCC through VEGF/NOTCH signaling and niched co-localization of cells and molecular pathways.**

Results published in Cell in 2020 (Sharma A, Seow JJW, ..., Chow PKH, Ginhoux F, DasGupta R. Onco-fetal Reprogramming of Endothelial Cells Drives Immunosuppressive Macrophages in Hepatocellular Carcinoma. Cell. 2020)

2. **Most putative driver mutations are non-truncal and display high intra-tumoral heterogeneity (ITH), explaining current poor treatment responses.**

Results published in National Science Review in 2021 (Zhai WW, Lai H, Kaya NA, ..., Tam WL, Toh HC, Foo RSY, Chow PKH. Dynamic phenotypic heterogeneity and the evolution of multiple RNA subtypes in Hepatocellular Carcinoma: the PLANET study, Nat. Sci. Rev., 2021)

3. **Distinct immunological microenvironments where HBV HCC is more immunosuppressive than NBNC HCC.**

Results published in Gut in 2019 (Zhao, Y., Shuen, T.W.H., ..., Dan, Y.Y., Chow, P.K., Toh, H.C., Lim, S.G., Chen, Q. Development of a New Patient-Derived Xenograft Humanised Mouse Model to Study Human-Specific Tumour Microenvironment and Immunotherapy. Gut, 2019)

4. **Co-existence of multiple transcriptomic subtypes in half of HCC, where the worst subtype drives clinical trajectory.**

Manuscript in preparation.

Recent Publications:

- **Metabolic pathway analyses identify proline biosynthesis pathway as a promoter of liver tumorigenesis (2020); Hepatology**
Ding Z., Chow P.K.H., Han W.P., et al.
- **Intratumoral immune heterogeneity as a hallmark of tumour evolution and progression in Hepatocellular Carcinoma (2021); Nature Communications**
Nguyen P., Ma, S., Chow P.K.H., Zhai W., Chew, V., et al.
- **Pan-cancer, pervasive upregulation of 3'UTR splicing drives tumorigenesis (2022); Nature Cell Biology**
Chan J., Chow P.K.H., Tay Y. et al.
- **Trajectory of immune evasion and cancer progression in hepatocellular carcinoma (2022); Nature Communications**
Nguyen PHD, Chow PKH, Chew V. et al.
- **Hypoxia-driven immunosuppression by Treg and type-2 conventional dendritic cells in HCC (2022); Hepatology**
Suthen S, Chow PKH, Albani S, Chew V. et al.



AHCC08 Hepatocellular Carcinoma Registry in Asia

Clinicaltrials.gov identifier: NCT03233360

Protocol Chair: Prof Pierce Chow

Study Status: Completed in December 2020. Pending publications.

The study has successfully hit the recruitment target of 2,500 patients by 31 December 2019 and data lock was implemented on 30 June 2020. This is one of the biggest and most comprehensive real-world HCC patient dataset from 9 countries in Asia-Pacific, namely Australia, New Zealand, Korea, Taiwan, Thailand, Hong Kong, Japan, China. The study reflects the variation in the management of HCC from the participating countries and we are working with academic institutions to correlate variables which could possibly attribute to these differences. Data analysis is in progress and results of the registry have been presented at various conferences.

Presentations:

Presentations on the Variations in Therapeutic Decision-Making across Asia Pacific in Hepatocellular Carcinoma (HCC):

Results on all 2,533 patients from China (6 sites), Thailand (2 sites), Hong Kong (1 site), Singapore (3 sites), Taiwan (5 sites), New Zealand (1 site), Australia (2 sites), South Korea (6 sites), Japan (5 sites) until June 2020:

1. **Lecture at 4th EWALT Meeting 2022, Tokyo, Japan (virtual)**
2. **Lecture at APASL 2022, Seoul, Korea (virtual)**

Subset of the Registry Results:

3. **Online publication at ASCO 2018, Chicago** – 174 patients from China and Singapore until Dec 2017
4. **Poster presentation at ASCO GI 2019, San Francisco** – 174 patients from China and Singapore until Dec 2017
5. **E-poster presentation at ILCA 2018, London** – 174 patients from China and Singapore until Dec 2017
6. **Poster presentation at ASCO GI 2019, San Francisco** – 657 patients from China, South Korea, Singapore and Japan until Aug 2018
7. **Poster presentation at 10th APPLE Congress 2019, Hokkaido, Japan** – 951 patients from Australia, China, Japan, South Korea, Singapore and Taiwan until Apr 2019

Data analysis and publications in progress:

- Descriptive analysis of the AHCC08 Registry Demographics
- Post-study analysis and the development of suitable analytic models for the AHCC08 Registry Data
- Survival and cost-effectiveness and impact of positive clinical trials in the management of Hepatocellular Carcinoma (HCC) in Asia: The HCC Registry in Asia between 2013 and 2019

Participating Sites

Australia

- Royal Adelaide Hospital
- Royal Prince Alfred Hospital

China

- Guangxi Medical University Cancer Center
- Second Affiliated Hospital Zhejiang University School of Medicine
- Zhongshan Hospital, Fudan University
- Beijing Cancer Hospital
- Harbin Medical University Cancer Hospital
- Nanjing Bayi Hospital

Hong Kong

- Queen Mary Hospital

Japan

- Kindai University Hospital
- Kyorin University School of Medicine
- National Cancer Centre
- University of Tokyo
- National Center of Global Health and Medicine

New Zealand

- Auckland City Hospital

Singapore

- National Cancer Centre
- National University Hospital
- Singapore General Hospital

South Korea

- Asan Medical Centre
- Korea University Anam Hospital
- Samsung Medical
- Seoul National University Hospital
- St Vincents Hospital
- St. Mary's Hospital
- Ajou University Hospital
- Severance Hospital, Yonsei University College of Medicine

Taiwan

- China Medical University Hospital
- Taipei Veterans General Hospital
- KS-Chang Gung Memorial Hospital
- National Cheng Kung University Hospital
- National Taiwan University Hospital

Thailand

- National Cancer Institute
- Siriraj Hospital, Mahidol University



AHCC10 Early detection of HCC: miRNA, microbiome and imaging biomarkers in the evolution of chronic liver disease in a high-risk prospective cohort

Clinicaltrials.gov identifier: NCT04965259

Protocol Chair: Prof Pierce Chow

Study Status: Currently recruiting. Started in April 2021, the study has recruited more than 1,000 patients and plans to recruit 2,000 patients by 4th quarter of 2022.

HCC is the 7th most common cancer worldwide, but the 4th most important cause of cancer death globally with a disproportionate 80% of the disease burden shouldered by Asia. Only approximately 20% of HCC is diagnosed at an early stage where ablative therapies (surgical resection, liver transplantation, radiofrequency ablation) are potentially curative owing to the absence of diagnostic modalities with high accuracy for the detection of early stage HCC. This is the world's 1st prospective cohort study to investigate the role of miRNA, microbiome, metabolome and imaging biomarkers in the evolution of chronic liver disease and in the early detection of HCC in 2,000 high-risk patients and a parallel 100 HCC patient cohort scheduled for surgical resection (AHCC11 PROSECT study).

Study Aims:

- To develop the 1st miRNA in-vitro diagnostic (IVD) kit for HCC with higher accuracy and better ease of use compared with the extant combination of AFP and US
- To develop an AI algorithm with MRI to predict individual risks of HCC within a specific timeline.
- To stratify individual patient risks of disease progression and the development of HCC
- To identify potential therapeutic targets in the microbiome and metabolome where intervention can prevent HCC development and slow the progression of liver diseases.

Media Release: Aim to recruit 2,000 study participants by early next year, Published in The Straits Times, 2 Aug 2021

Participating Sites

Singapore

- Changi General Hospital (CGH)
- National Cancer Centre (NCC)
- National University Hospital (NUH)
- Singapore General Hospital (SGH)
- SingHealth Polyclinic
 - Bedok
 - Bukit Merah
 - Marine Parade
 - Outram
 - Pasir Ris
 - Punggol
 - Sengkang
 - Tampines
- Sengkang General Hospital (SKH)
- Tan Tock Seng Hospital (TTSH)

Aim to recruit 2,000 study participants by early next year

FROM B1

If these patients develop HCC during the monitoring period, they can receive treatment and continue contributing data to the study.

There are no costs incurred from participating in the study, unless participants develop HCC and seek treatment.

The study will include input from SGH, the National University Hospital (NUH), Changi General Hospital, Sengkang General Hospital and Tan Tock Seng Hospital.

In addition to the hospitals, eight SingHealth polyclinics will serve as recruitment sites, while academic institutions, namely Duke-NUS Medical School and the Singapore Phenome Centre, will also be collaborating.

More than 200 participants have been recruited since April. The study aims to rope in 2,000 individuals by early next year.

Early diagnosis of HCC has been challenging, given the lack of validated diagnostic, predictive and prognostic biomarkers. Diagnostic biomarkers help to determine the presence of HCC, while prognostic types provide

Non-alcoholic fatty liver disease, which has been on the rise globally, has been attributed to causes such as a more Western diet.

Some experts believe that an increased consumption of fructose (such as in soft drinks and cookies) has contributed significantly to this condition, Prof Chow said.

information on the patient's overall cancer outcome.

Predictive biomarkers identify the treatment the patient is most likely to benefit from.

Emerging data suggests that changes in the stool (microbiome), blood and urine (metabolome) may be indicative of HCC.

Building an AI algorithm that leverages magnetic resonance imaging scans may help predict the risk of developing HCC, thereby allowing for personalised surveillance and treatment.

The study has three tracks. First, it will evaluate the efficacy of a microRNA (miRNA) diagnostic kit developed by Singapore-headquartered molecular diagnostic company MIRXES for more accurate diagnosis of early-stage HCC.

Second, it will develop an AI algorithm to identify at-risk patients with digital medical technology company Perspectrum.

Third, it will determine the changes in the microbiome and metabolome that lead to HCC with precision gut microbiome company AMILL.

MIRXES had, in 2019, received approval from the Health Sciences Authority for the world's first miRNA polymerase chain reaction test for early detection of gastric cancer.

Named Gastroclear, it has since served tens of thousands of patients in Singapore, China and other countries, saving lives by identifying early-stage gastric cancer in asymptomatic patients, said Dr Zhou Lihan, co-founder and chief executive of MIRXES.

"We are very excited to be part of this study and look forward to making this innovation accessible to millions of at-risk individuals," he added.

Associate Professor Dan Yock Young, a senior consultant in the division of gastroenterology and hepatology at NUH, said: "I liver





AHCC11 Prospective Cohort Study of Changes in Circulatory MicroRNA after Surgical Resection of HCC

Clinicaltrials.gov identifier: NCT05148572

Protocol Chair: Prof Pierce Chow

Study Status: Currently recruiting. The study has recruited 10 patients out of the target recruitment of 100 patients. The expected recruitment end-date is 1st quarter of 2024 and the project end date is in February 2025.

This study will recruit 100 surgically-resected patients with histologically-proven HCC and will serve as a positive control to validate the findings in the AHCC10 ELEGANCE study. This study will determine progressive changes in the profiles of miRNA signatures pre- and post-surgical resection to identify signatures predictive of recurrence; and key metabolites that can predict recurrence of HCC.

Study Aims:

- To determine if miRNA biomarker signatures diagnostic of HCC in a high risk for HCC (AHCC10 ELEGANCE study) will revert back to signatures similar to non-HCC cohort patients in the cohort post-resection
- To understand if the same signature diagnostic of HCC in a cohort of patients at high risk for HCC cohort (AHCC10 ELEGANCE study) can be used for recurrence prediction.
- To obtain new signatures for recurrence prediction if above objectives cannot be fulfilled.
- To identify key metabolites that can predict the recurrence of HCC and to correlate changes in choline, bile acid and tryptophan metabolic pathways with changes in the composition and function of gut microbiota

Participating Sites

Singapore

- Changi General Hospital (CGH)
- National Cancer Centre (NCC)
- National University Hospital (NUH)
- Singapore General Hospital (SGH)
- Sengkang General Hospital (SKH)
- Tan Tock Seng Hospital (TTSH)

THE STRAITS TIMES
Monday, August 02, 2021

SINGAPORE 84

AWARDS GIVEN OUT AT PUBLIC SECTOR TRANSFORMATION AWARDS CEREMONY (BS)

Protecting the liver

War has been declared on a top cancer killer in Singapore – primary liver cancer. Though it is curable in the initial stages, just one in five such patients is diagnosed early. **Chae Cheng** looks at what this entails.

WHAT IS PRIMARY LIVER CANCER?

- The liver performs many important functions, such as storing glucose, regulating and filtering blood.
- Some mutations in liver cells can result in cancer.
- Mutated cells grow and divide out of control, producing extra tissue that hampers its function.
- Malignant tumours have the potential to spread to other parts of the body.
- Primary liver cancer, otherwise known as hepatocellular carcinoma (HCC), arises in the liver in those in their 50s and 60s.

Location of the liver

MAIN RISK FACTORS IN SINGAPORE

- **Non-alcoholic fatty liver disease** – A general term for liver conditions that may lead to liver cancer. It is caused by too much fat in the liver, which is linked to obesity, diabetes and high cholesterol.
- **Chronic hepatitis B and C** – Hepatitis is a viral infection that causes inflammation of the liver. It is caused by the hepatitis B virus (HBV) and hepatitis C virus (HCV). Chronic hepatitis B and C can lead to liver cancer.
- **Alcohol consumption** – Excessive alcohol consumption can lead to liver cancer.

Early detection of primary liver cancer

Early detection of primary liver cancer is crucial for better outcomes. The most common way to detect liver cancer is through a blood test called alpha-fetoprotein (AFP). AFP is a protein produced by the liver, and its levels are often elevated in people with liver cancer. However, AFP levels can also be elevated in other conditions, such as pregnancy and liver inflammation. Therefore, AFP levels should be interpreted with caution. Another way to detect liver cancer is through imaging tests, such as ultrasound, CT scan, and MRI. These tests can provide a visual view of the liver and help identify any abnormalities. However, these tests are not always accurate, and false positives and false negatives can occur. Therefore, a combination of blood tests and imaging tests is often used to detect liver cancer.

A participant's journey in the study

Visit 1: Collection of blood samples

1,000 patients will be recruited for the study. They will be asked to provide a blood sample at their local general practitioner (GP) or at a dedicated study site. The blood sample will be used for the study.

Visit 2: 3-7 (every six months)

Patients will be asked to provide a blood sample every six months for the first three years of the study. The blood sample will be used for the study.

TREATMENT

• If the liver function is good, surgery to remove the liver cancer is the best option. This is called a liver resection. It involves removing the part of the liver that contains the cancer. This can be done through a minimally invasive approach called laparoscopic surgery, or through a more traditional open surgery. The choice of surgery depends on the size and location of the cancer, and the patient's overall health.

Early-stage

• If the liver function is not good, or if the cancer is too large to be removed, then other treatment options are available. These include chemotherapy, targeted therapy, and immunotherapy. The choice of treatment depends on the patient's overall health and the stage of the cancer.

Advanced

• If the liver function is not good, and the cancer is too large to be removed, then liver transplantation may be an option. This involves replacing the liver with a healthy liver from a donor. This is a major surgery, and it carries a high risk of complications. However, it can be a life-saving procedure for some patients.

What the colours mean

• Green: Normal healthy liver tissue.

• Yellow: Fatty liver disease (steatosis).

• Red: Liver inflammation (hepatitis).

• Blue: Liver fibrosis (scarring).

• Black: Liver cancer (HCC).

Nationwide study to aid early detection of primary liver cancer

Disease among top killers here, with just 1 in 5 patients diagnosed early, when cure is possible. **Chae Cheng**

Singapore, with a worldwide study being set up to detect the disease early, when cure is possible. The study, called the Singapore Liver Cancer Cohort Study (SLCCS), is a nationwide study to aid early detection of primary liver cancer. The study will recruit 1,000 patients with primary liver cancer, and follow them for five years. The study will collect blood samples from the patients every six months, and use them to identify any changes in the levels of certain biomarkers. These biomarkers are substances that can be found in the blood, and their levels can change when there is a problem with the liver. By monitoring the levels of these biomarkers, the study hopes to detect liver cancer early, when it is still curable. The study will also collect information about the patients' lifestyle, such as their diet, exercise, and alcohol consumption. This information will be used to identify any factors that may increase the risk of liver cancer. The study is being led by a team of researchers from the National Cancer Centre Singapore, and it is expected to start in 2022.

Media Release: Nationwide study to aid early detection of primary liver cancer, Published in The Straits Times, 2 Aug 2021
Scan QR code to read article.



Media Release: Spurred by mum's death from liver cancer to take charge of health, Published in The Straits Times, 2 Aug 2021
Scan QR code to read article.



Spurred by mum's death from liver cancer to take charge of health

During a recent visit to a polyclinic, Ms Yong discovered that she has a fatty liver. The doctor informed her that she had developed non-alcoholic fatty liver disease. This means there is a build-up of extra fat in the liver cells that is not linked to alcohol consumption but which can lead to primary liver cancer. The 58-year-old IT industry freelancer, who did not want her full name to be used, is among a growing number of Singaporeans who suffer from this condition. There may be a number of causes, such as the adoption of a more Western diet. Some experts believe that the increased consumption of fructose, such as soft drinks and cookies, has contributed significantly to this condition.

Ms Yong's family has a history of primary liver disease. Her mother died of it in 2008. It was discovered at too late a stage, when a cure was no longer possible. Ms Yong, who also has hepatitis B, has been a vegetarian since 2008. She exercises regularly and goes for regular check-ups. Chronic hepatitis and non-alcoholic fatty liver disease are some of the risk factors for primary liver cancer, one of the deadliest cancers in Singapore. Ms Yong has joined the ELEGANCE study led by the National Cancer Centre Singapore. The study aims for more accurate early diagnosis, which makes a cure possible in more cases. She went for her first magnetic resonance imaging scan and blood test under the study last month. "The scan and blood tests took around an hour. The staff were very professional, there was no pain or discomfort, and it was a fast and smooth experience," she told The Straits Times. The study will be done over four years and participants will have a follow-up every six months. Their biosamples (blood, urine and stool) will be collected, and blood tests as well

AIDING IN STUDY OF DISEASE

The scan and blood tests took around an hour. The staff were very professional, there was no pain or discomfort, and it was a fast and smooth experience.





AHCC09 Multi-national, double-blind, randomized phase II trial to compare the safety and efficacy of SIRT-Y90 followed by atezolizumab plus bevacizumab versus SIRT-Y90 followed by placebo in patients with locally advanced hepatocellular carcinoma

Clinicaltrials.gov identifier: NCT05377034

Protocol chair: Prof Pierce Chow

Number of participating centres: Estimated up to 13 recruiting sites in Singapore, China, South Korea and Taiwan

Study Status: Recruitment is projected to start in the 3rd quarter of 2022.

Up to a third of patients in the Asia-Pacific and globally present with Barcelona Clinic for Liver Cancer (BCLC) intermediate-stage hepatocellular carcinoma (HCC) at diagnosis. The standard-of-care in intermediate HCC is loco-regional therapy delivered through trans-arterial chemoembolization (TACE) or Selective Internal Radiation Therapy (SIRT) with Yttrium-90, also known as radioembolization. Localized radiotherapy has been shown to induce a phenomenon known as the abscopal effect, which describes the regression of metastatic cancer located at a distance from the irradiated site. The biological mechanism underpinning this phenomenon was previously not clearly elucidated, but was believed to be mediated by immunologic mechanisms. Indeed, our own data monitoring the immune landscapes of peripheral blood and tumor microenvironment from HCC patients treated with Y90 radioembolization demonstrated a clear immune activation and subsequent exhaustion post-therapy.

We believe that the proinflammatory environment created by radiotherapies such as Y90 radioembolization (as shown by our preliminary data) and the administration of immunomodulating drugs such as atezolizumab in combination with the potential of bevacizumab to increase the infiltration of T cells into tumors will create a synergistic effect that is superior to monotherapy of either treatment modality in overcoming tumor immune evasion and improve abscopal responses. In addition, we hypothesize that by combining anti-PD1 therapy with radiotherapy and bevacizumab, this synergistic effect in increasing tumor-infiltrating immune cells may also be extended to non-PD-1/PD-L1 expressing tumors, resulting in better efficacy and response in HCC patients.

In this multi-national, phase II, parallel-arm, double-blind, placebo-controlled, two-arm study, AHCC09 STRATUM, we will assess the efficacy and safety of SIRT-Y90 followed by atezolizumab plus bevacizumab with SIRT-Y90 followed by placebo in patients with locally advanced HCC from up to 13 sites from the AHCC Trials Group (subject to feasibility studies and ethics approval). Proposed sites are in Singapore, China, South Korea, and Taiwan.

This study will enroll 176 patients randomized in a 1:1 allocation ratio (88 in each arm) to one of the two arms.

- Study arm: SIRT-Y90 + 1200mg atezolizumab + 15mg/kg bevacizumab
- Control arm: SIRT-Y90 + placebos (IV)

We hope to recruit the 1st patient by the 3rd quarter of 2022.



AHCC12 and AHCC13

Flagship Program in Liver Cancer: Precision Medicine in Liver Cancer across the Asia-Pacific Network 2.0

Protocol Chair: Prof Pierce Chow

Number of participating centres: Estimated up to 6 recruiting sites in Singapore.

Study Status: Recruitment is projected to start in the 3rd quarter of 2022.

The PLANet 2.0 team comprises of experts in different complementary fields (epigenomics, genomics, immunomics, metabolomics, proteomics, clinical trials and data science) which allows us to adopt an integrative approach. This is a whole-of-nation, multi-disciplinary collaboration with investigators from research institutions, including Genome Institute of Singapore (GIS), Institute of Molecular and Cell Biology (IMCB), Cancer Science Institute (CSI) and Duke-NUS Medical School, hospitals and specialist centres, both local and in the Asia-Pacific region.

Current therapies for hepatocellular carcinoma (HCC) are poorly efficacious as HCC has high intra-tumoral heterogeneity (ITH) and there are no validated predictive biomarkers. Our novel approach of multi-region sampling in the AHCC07 study (PLANet 1.0) confirmed the highly heterogeneous landscape of HCC and unraveled unprecedented insights including an onco-fetal immune evasion pathway. We continue these investigations in PLANet 2.0 as a natural development in progressive scientific enquiries. There are 5 themes:

Theme 1: Deep Phenotyping and Correlation with Clinical Responses to Therapy

Lead by Pierce CHOW Kah-Hoe (NCCS) and Prof Patrick TAN (GIS)

Theme 2: Elucidating Spatial Distribution of Biomarkers at single-cell resolution

Lead by Prof Vinay TERGAONKAR (IMCB)

Theme 3: Translational and Functional Immunomics

Lead by A/Prof TOH Han Chong (NCCS)

Theme 4: Pre-Clinical Disease Modelling and Target Discovery

Lead by Dr TAM Wai Leong (GIS) and Dr Edward CHOW Kai-Hua (CSI, NUS)

Theme 5: Data Architecture, Data Security and Data Science Applications

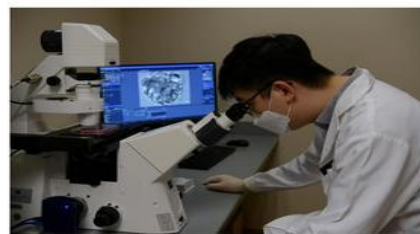
Lead by Prof Roger D. VAUGHAN (Duke-NUS)

With this integrated, multi-pronged approach, we are well-positioned to uncover and validate molecular, cellular and immunological mechanisms underpinning recurrence, response and resistance to treatment, providing an unparalleled opportunity for patient stratification and selection. These findings will directly change clinical practice and actualise precision oncology in HCC.



Media Release: 我国拨 2500 万元研究改善肝癌疗法
疗法, Published in Lianhe Zaobao, 14 Jun 2022

S'pore dedicates \$25m to liver cancer research to find targeted treatments



Media Release: S'pore dedicates \$25m to liver cancer research to find targeted treatments,

Published in The Straits Times, 14 Jun 2022

Scan QR code to read article.



Since the conception in 1997, the AHCC Trials Group led by Prof Pierce Chow, works closely with academic researchers and industry partners to leverage on complementary strengths, to design and plan clinical trials and studies that lead to a better understanding of HCC and improve clinical outcomes of patients with HCC. The secretariat has been involved in the general administration and management of the AHCC Trials Group network, while maintaining the network registry, website, social media sites and the publishing of the periodic newsletters to keep the group abreast of any developments and happenings across the network. Moving forward, the secretariat will continue to work with academic clinical trials organizations, pharmaceutical and biotech industry partners to host our annual General Meetings, Scientific Forums as well as ad-hoc meetings.

Our collaborative group

Australia

- Royal Adelaide Hospital
- Royal Prince Alfred Hospital

Brunei

- The Brunei Cancer Centre

China

- Guangxi Medical University Cancer Center
- Second Affiliated Hospital Zhejiang University School of Medicine
- Zhongshan Hospital, Fudan University
- Beijing Cancer Hospital
- Harbin Medical University Cancer Hospital
- Nanjing Bayi Hospital

Hong Kong

- Queen Mary Hospital

Indonesia

- Sanglah General Hospital
- University of Indonesia

Japan

- Kindai University Hospital
- Kyorin University School of Medicine
- National Cancer Centre
- University of Tokyo
- National Center of Global Health and Medicine

Malaysia

- Penang Adventist Hospital
- Prince Court Medical Centre
- Sarawak General Hospital
- University Malaya Medical Center

Singapore

- Changi General Hospital
- Singapore General Hospital
- Sengkang General Hospital
- SingHealth Polyclinics
- Khoo Teck Puat Hospital
- National Cancer Centre
- National University Hospital
- Tan Tock Seng Hospital

South Korea

- Asan Medical Centre
- Korea University Anam Hospital
- Samsung Medical
- Seoul National University Hospital
- St. Vincents Hospital
- St. Mary's Hospital
- Ajou University Hospital
- Severance Hospital, Yonsei University College of Medicine

Taiwan

- China Medical University Hospital
- Taipei Veterans General Hospital
- Chang Gung Memorial Hospital - Kaohsiung
- Chang Gung Memorial Hospital - Linkou
- National Cheng Kung University Hospital
- National Taiwan University Hospital

Thailand

- Chulabhorn Hospital
- National Cancer Institute
- Siriraj Hospital, Mahidol University

USA

- Duke University School of Medicine



Over the years, Singapore Clinical Research Institute (SCRI) has been our main trials coordinating partners. SCRI has played a pivotal role in the managing of the Trials Group data.

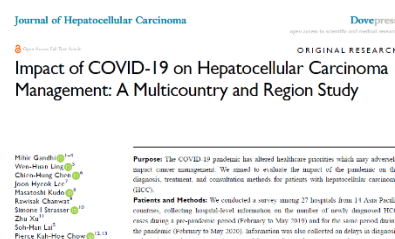
The impact of COVID-19 on the management of HCC in the Asia-Pacific

During the peak of the COVID-19 pandemic, the Trials Group collaborated with SCRI to evaluate the impact of COVID-19 on the management of HCC in the Asia-Pacific. The team conducted an online survey among 27 hospitals from 14 Asia-Pacific countries. The result was published in Journal of Hepatocellular Carcinoma and presented at the SingHealth Duke Global Health Institute (SDGHI) Global Health Series 2021.

- Gandhi M, Ling WH, Chen CH, Lee JH, Kudo M, Chanwat R, Strasser SI, Xu Z, Lai SH, Chow PKH. (2021) **Impact of COVID-19 on Hepatocellular Carcinoma Management: A Multicountry and Region Study.** *J Hepatocell Carcinoma*, 8:1159-67. <https://doi.org/10.2147/JHC.S329018>
Scan QR code to access publication on PubMed.



- 27 Aug 2021, SDGHI Global Health Series 2021: **“The Impact of COVID-19 on the Management of Hepatocellular Carcinoma in the Asia-Pacific: Lessons from the 1st Wave”**



Post Analysis of the AHCC08 Study

The AHCC08 study includes real-world data on a wide spectrum of management strategies of HCC from 9 countries in Asia-Pacific. The Trials Group will collaborate with Prof Shi Luming and Dr Julia Zhu from SCRI to conduct a post-study analysis to investigate the regional variations in the stages at diagnosis and how the clinical outcomes differ at various stage. Work has started in May 2022 and we hope to share the results soon.



[From top left] Dr Julie Zhu, Neo Shuen Kai, Sim Yu Ki, Lynette Lai, Prof Pierce Chow, Prof Shi Luming and Alex Oh at the SCRI office.

Our AHCC Secretarial Team

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[From top left] Lynette Lai, Chen Kaina, Chew Sin Chi, Sim Yu Ki, Ashley Ng, Aileen Tay, Han Qingguang, Ling Wen Huan, Chong Shay Lee, Jacelyn Chua, Wu Lingya, Pratap, Jade Goh, Fiona Ni Ni Moe, Ong Xiao Quan, Cheryl Chua and Prof Pierce Chow.

The strength of the AHCC Trials Group lies in its spread of collaborating centres and its track record of successfully completed trials. We would like to thank all our AHCC Trials Group members, the study team members and our collaborators for the support and trust in the past 25 years. We look forward to another exciting year ahead. Thank you for your support for the AHCC Trials Group.



Our members at the 3th Symposium of the SLCC on 3 May 2019.

Contact Details

For further queries, please contact the AHCC Trials Group at

Network Secretariat:

Ms Lynette Lai

Email: ahcctrialsgroup@nccs.com.sg

DID: (65) 6576 2151

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