AHCC07

Precision Medicine in Liver Cancer across an Asia-Pacific Network

ADDRESSING AN URGENT UNMET CLINICAL NEED: the NMRC Flagship Program in Liver Cancer

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NMRC AWARDS CEREMONY AND RESEARCH SYMPOSIUM 2021

"Scientific Paradigm Shifts"

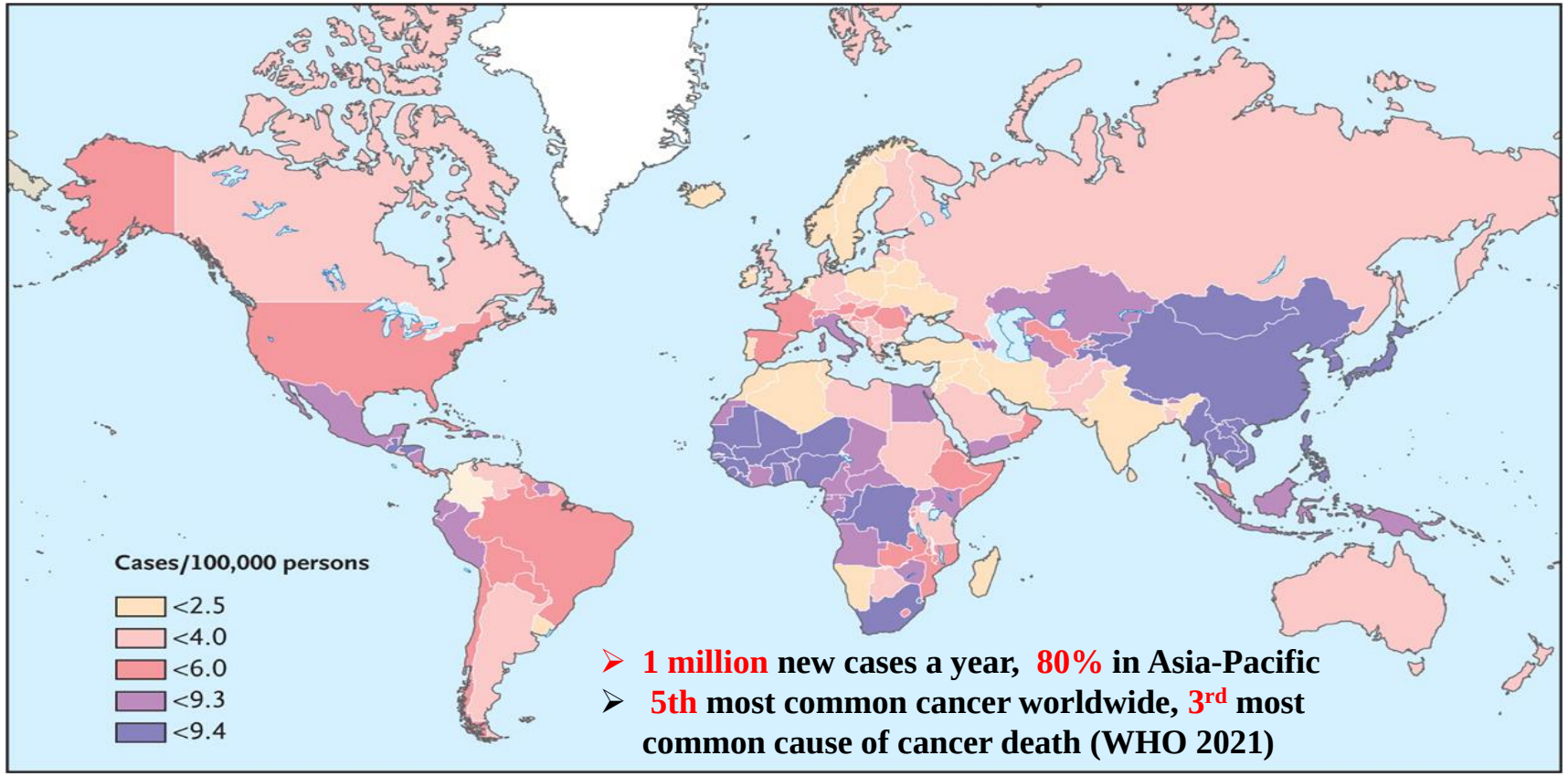
6th December 2021

National Cancer Centre Singapore SingHealth | Singapore General Hospital SingHealth | NUH National University Hospital | NUS National University of Singapore | SingHealth RESEARCH Translational Immunology and Inflammation Centre | A*STAR Genome Institute of Singapore

THE Asia-Pacific Hepatocellular Carcinoma Trials Group | The Medical City Where Patients are Partners | NCI | University of Malaya UM Medical Centre | DukeHealth | Lee Kong Chian School of Medicine

PATIENTS. AT THE HEART OF ALL WE DO.

Regional Variation in the Estimated Age-Standardized Incidence Rates of Hepatocellular carcinoma.



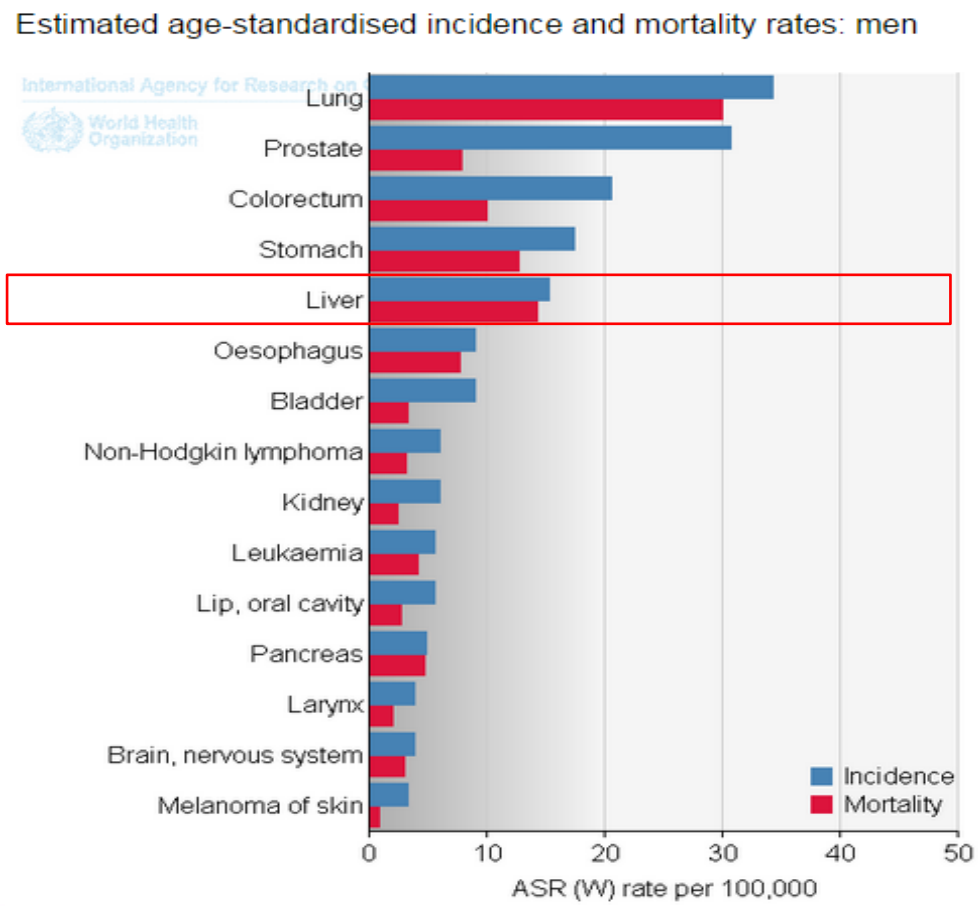
- **1 million new cases a year, 80% in Asia-Pacific**
- **5th most common cancer worldwide, 3rd most common cause of cancer death (WHO 2021)**

El-Serag HB. N Engl J Med 2011;365:1118-1127.

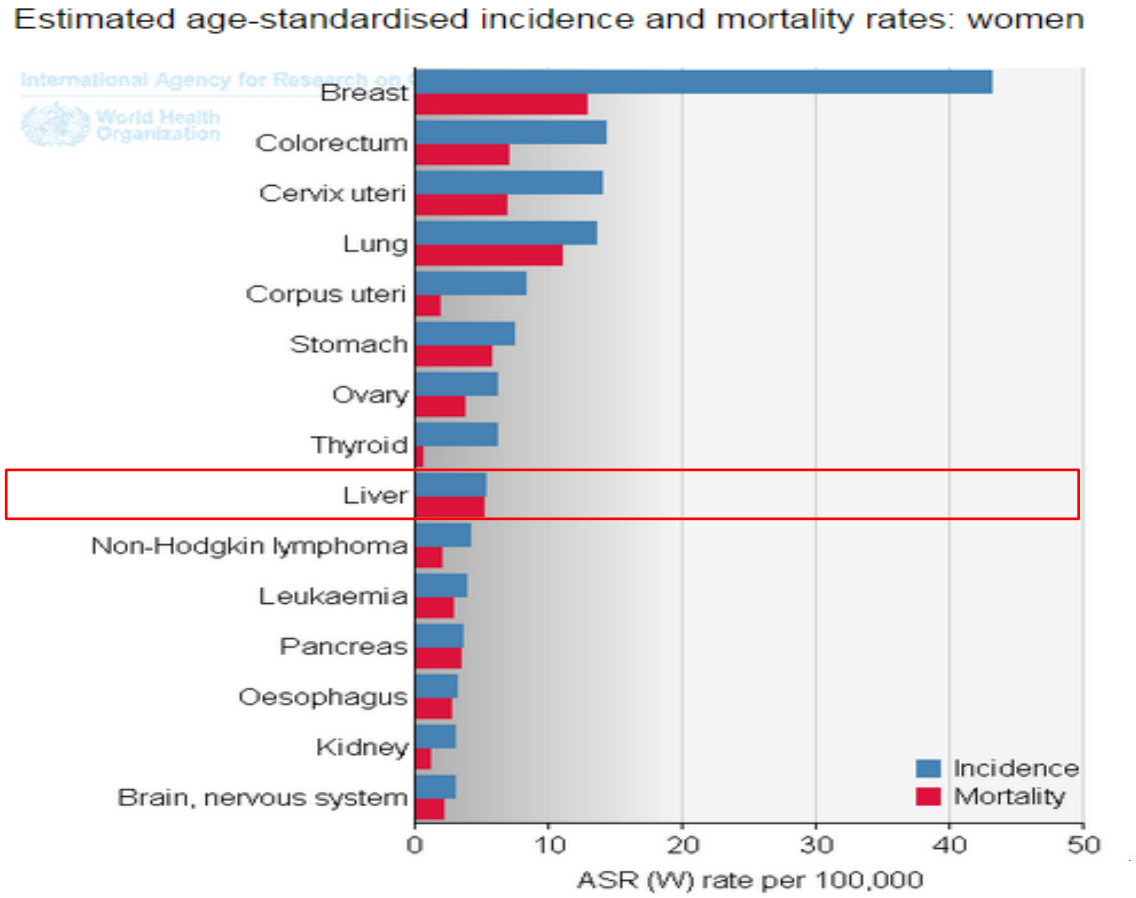
HCC: A Global Un-met Clinical Need

mortality-to-incidence ratio of 0.98

Men: 2nd cause of cancer deaths (previously 3rd)



Women: 5th cause of cancer deaths (previously 6th)

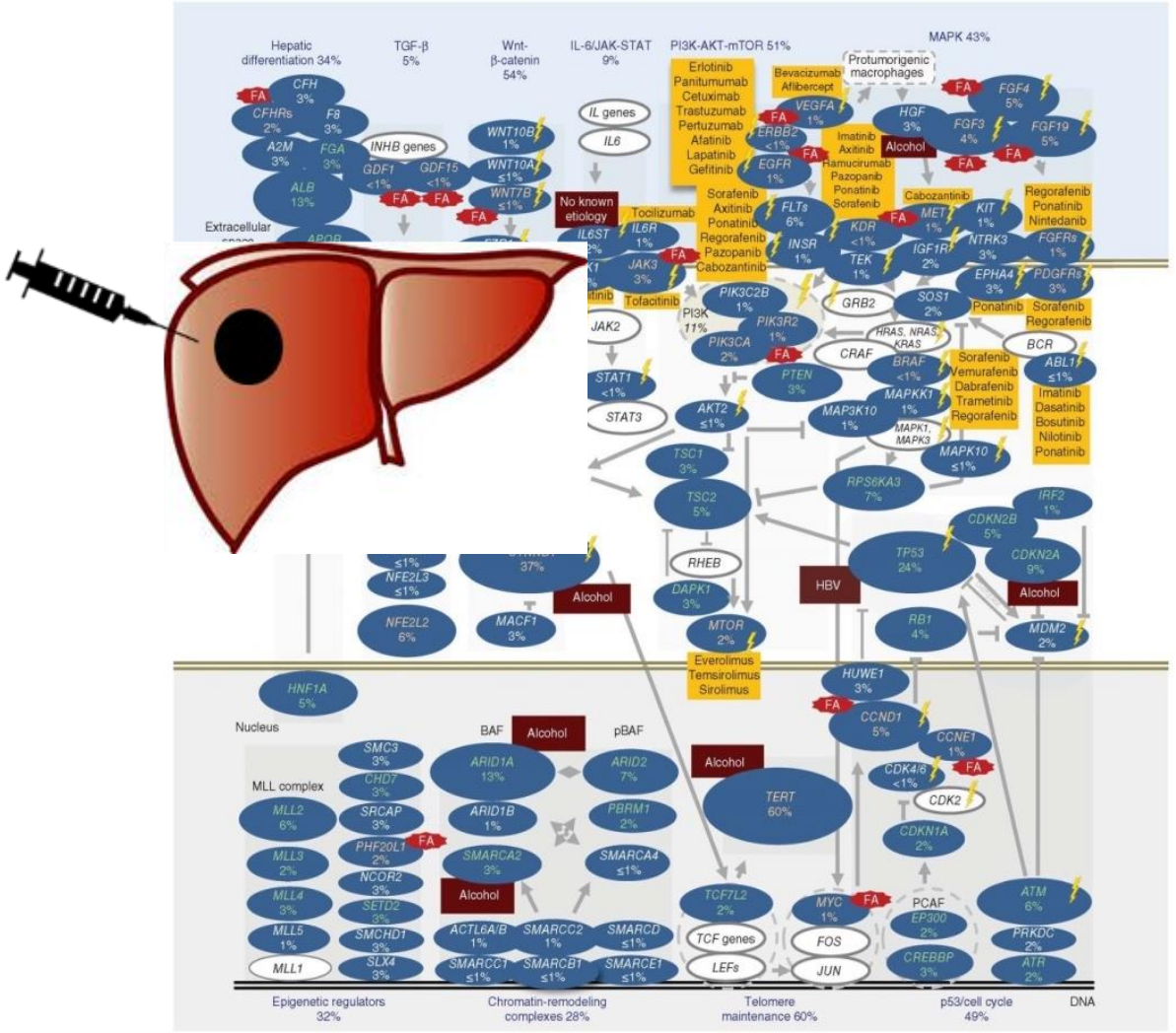


Central challenge in HCC currently: poorly efficacious systemic therapy

- More than **1 million new cases** a year, 80% in the Asia-Pacific, but **few efficacious systemic therapies**
  - **20%** of patients are diagnosed at an early stage and benefit from potentially curative therapies – *resection, transplantation, radiofrequency ablation* - recurrences common because of absence of efficacious adjuvant therapy that limits long term survival
- Poorly efficacious systemic therapy for advanced HCC because there are still **no validated predictive bio-markers**
  - best response rate in 2016 first-line < 10% (sorafenib then standard- of-care)
  - best response rate in 2021 first-line 30% (Atezo+ Bev current standard- of-care)
  - No useful adjuvant therapy after surgery in early/intermediate HCC. High recurrence rates
    - 5-year survival of 67% for early stage
    - 5-year survival of 38% in intermediate stage
  - Highly **heterogeneous genome**

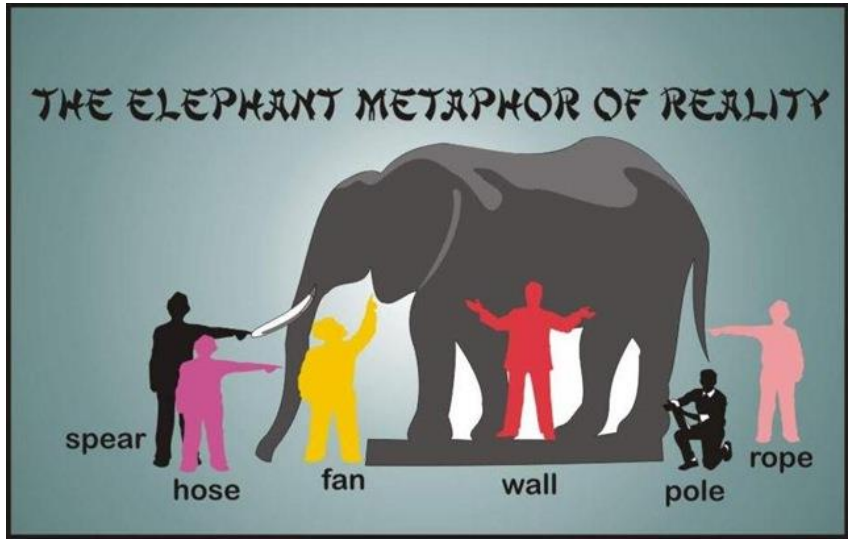
Standard approach to drug development in HCC has not been useful

- Most drug development programs depends on single samples to elucidate molecular mechanisms:
  - assumes tumor is homogenous
  - only considers the ***presence/ absence*** of a driver alteration, not their clonal/sub-clonal dominance. *(Swanton 2015)*

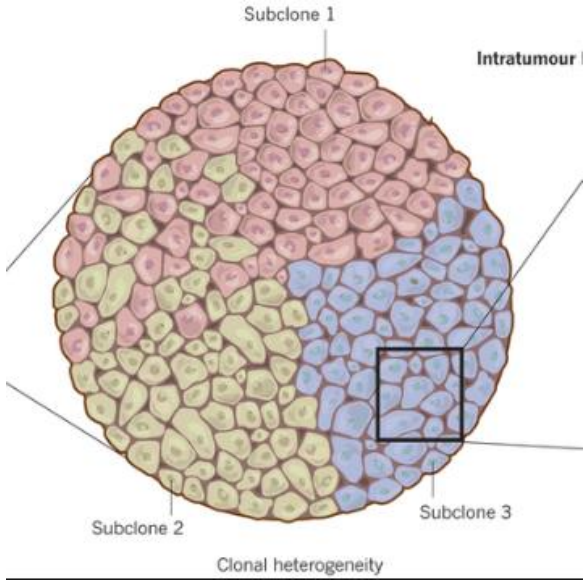


Schulze Nat Gen 2015

The importance of intra-tumor heterogeneity(ITH)



Solid tumors and their metastases are intrinsically complex. Single biopsy often reflects part of the tumor.



Tumor heterogeneity

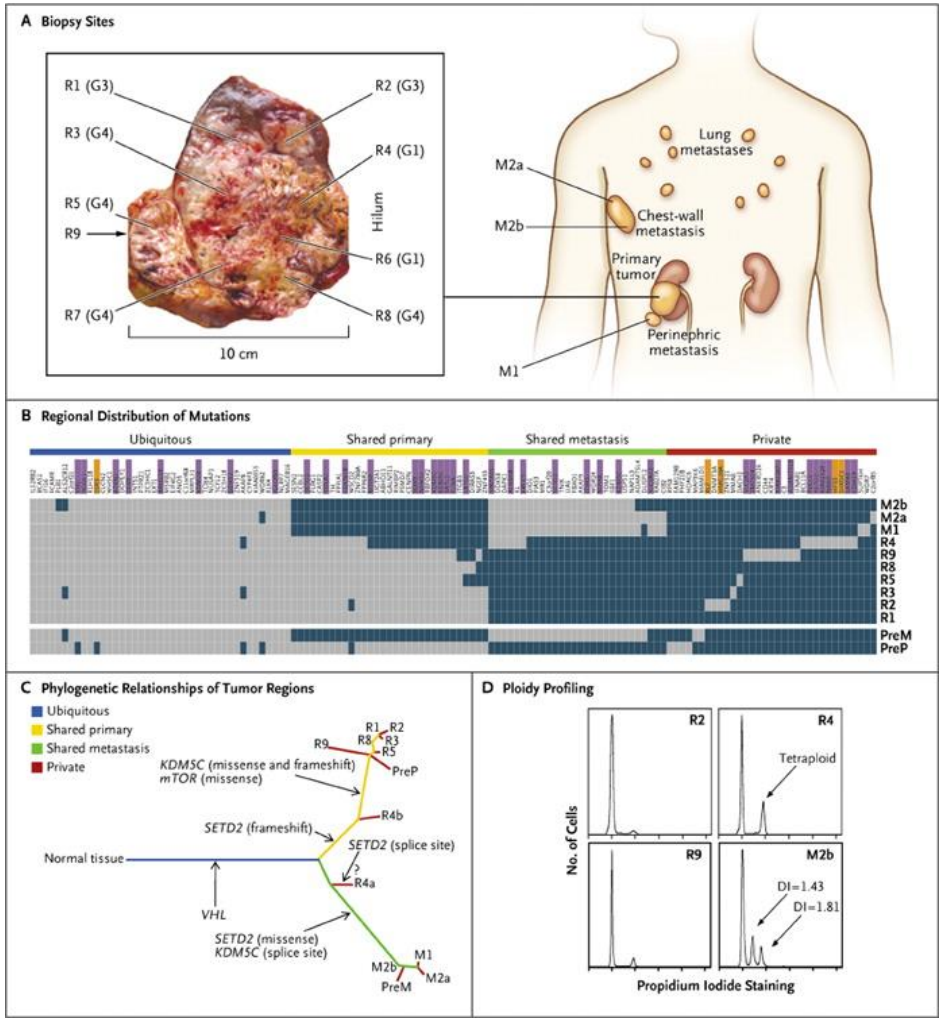
Understanding tumor heterogeneity can provide a more holistic picture of the tumor.

Tumor heterogeneity is the genetic basis of tumor evolution, treatment resistance and metastasis.

Courtesy: Zhai WW

Example: Renal Cell Carcinoma

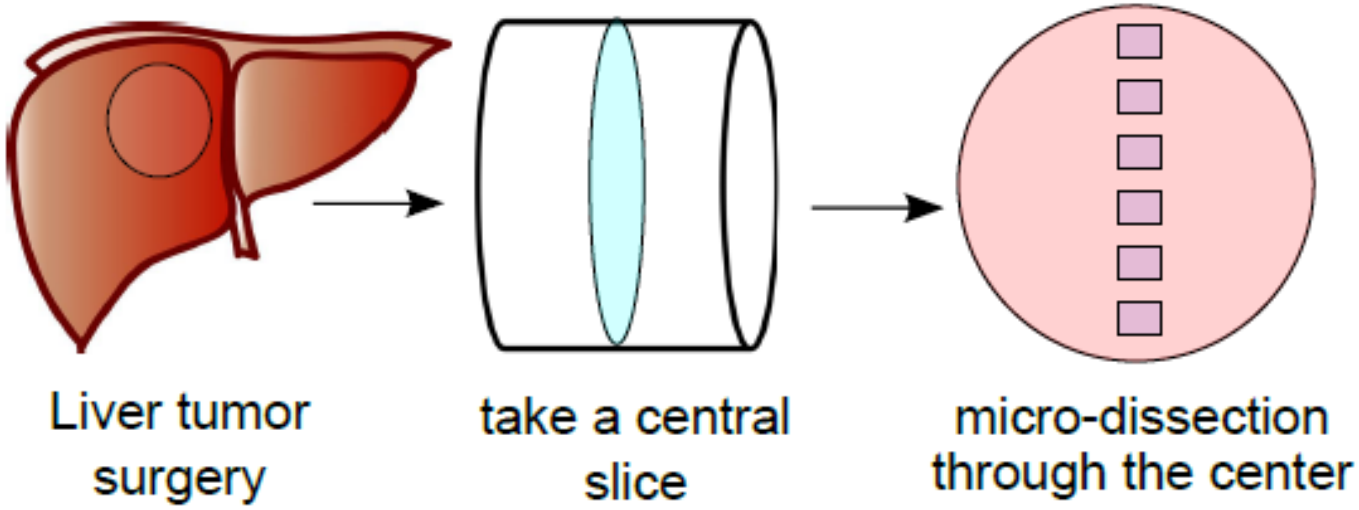
Genetic Intra-tumor Heterogeneity and Phylogeny: multi-region sampling.



Gerlinger M et al. N Engl J Med 2012;366:883-892.

few cancers are homogeneous

A more rational approach to HCC



- multi-region sampling
- Whole exome/whole genome sequencing

Surgical Cohort:

AJCC Stages I and II HCC

- Followed up longitudinally

nature COMMUNICATIONS

ARTICLE

Received 11 Oct 2016 | Accepted 12 Jan 2017 | Published 27 Feb 2017

DOI: 10.1038/ncomms14565 OPEN

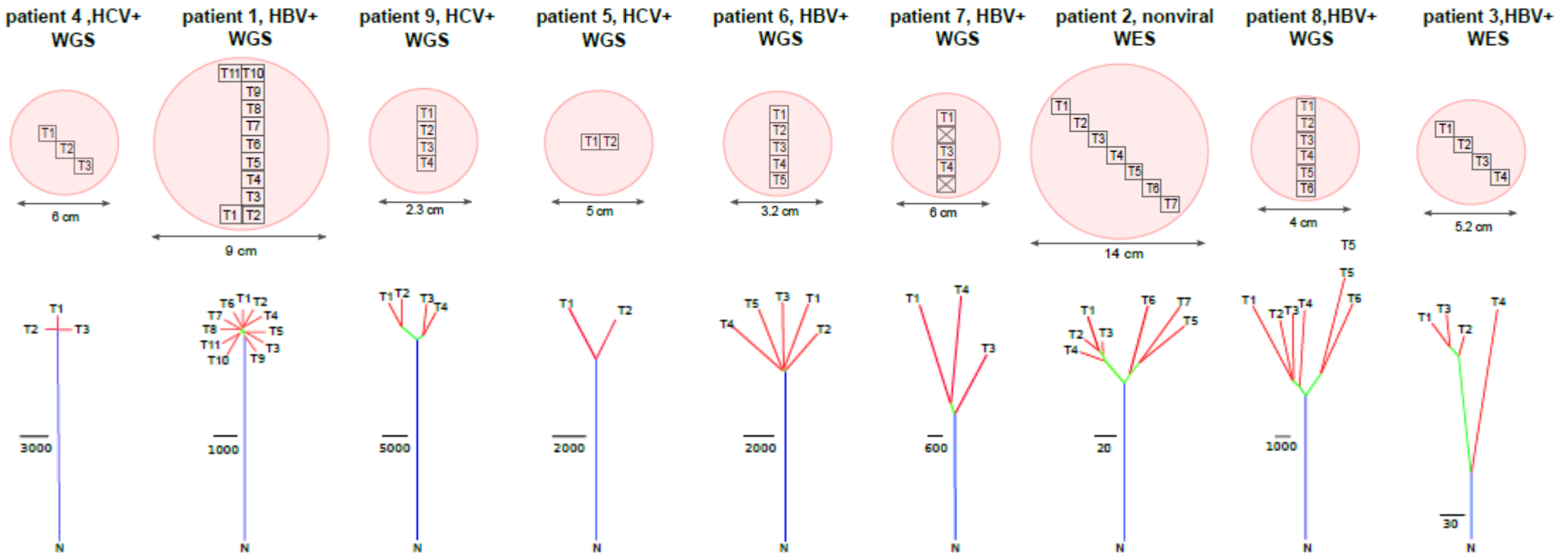
The spatial organization of intra-tumour heterogeneity and evolutionary trajectories of metastases in hepatocellular carcinoma

Weiwei Zhai[1,*,**], Tony Kiat-Hon Lim[2,*], Tong Zhang[1,*], Su-Ting Phang[3], Zenia Tiang[1], Peiyong Guan[1], Ming-Hwee Ng[1,4], Jia Qi Lim[1,4], Fei Yao[1], Zheng Li[1], Poh Yong Ng[1], Jie Yan[1], Brian K. Goh[5], Alexander Yaw-Fui Chung[5], Su-Pin Choo[6], Chiea Chuen Khor[1], Wendy Wei-Jia Soon[1], Ken Wing-Kin Sung[1,7], Roger Sik-Yin Foo[1,8,**] & Pierce Kah-Hoe Chow[3,5,9,**]

Zhai Nat Comm 2017

A*STAR Genome Institute of Singapore

Prospective data - Evolutionary Patterns in HCC

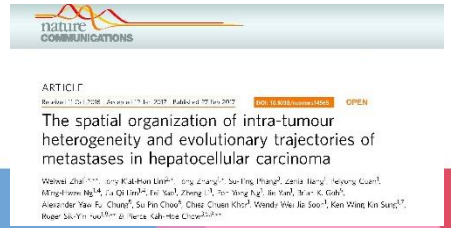


Palm tree
(low tumor heterogeneity)

A wide spectrum of ITH

Bushy tree
(high tumor heterogeneity)

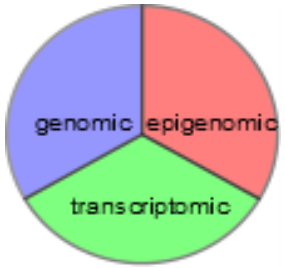
Zhai Nat Comm 2017

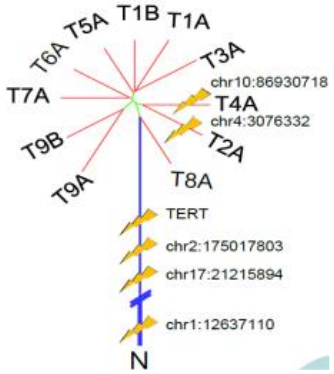


Precision Medicine in Liver Cancer Asia-Pacific Network

Epigenomics
(Parallel CS-IRG grant)

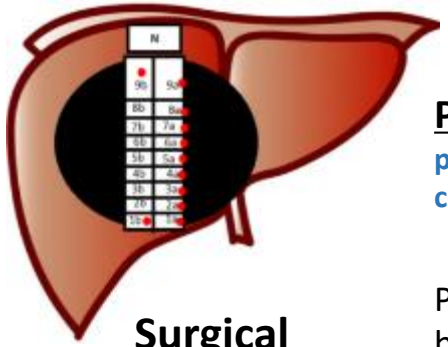
Genomics





AIMS: To meet the pressing need for **efficacious drugs** in HCC

To bring **Precision Medicine** to patients with HCC



Surgical Resection

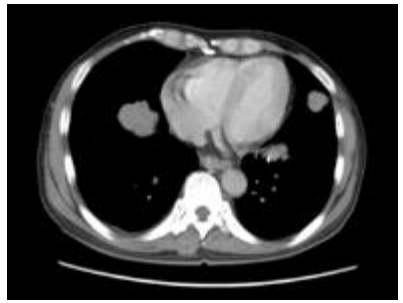
Phase 1: 100 (147) patients, 6 Asia-Pac centers, 1 USA center

Pre-op scans, bloods, multi-region tissue samples, cfDNA, CTC

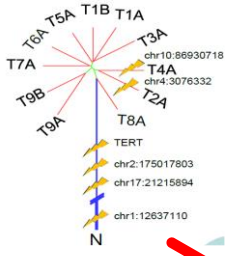
Clinical Trajectory and Translational Clinical Trial

3-monthly follow-up: scans, bloods, cfDNA, CTC

Creation of representative pre-clinical models

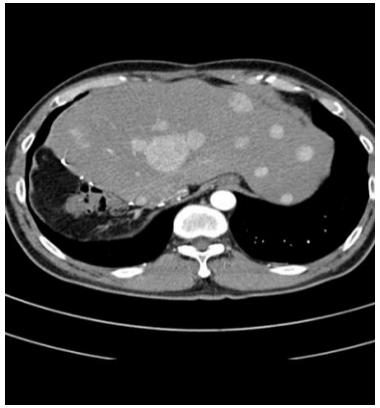


Recurrence
Biopsy or resection tissue samples, cfDNA, CTC

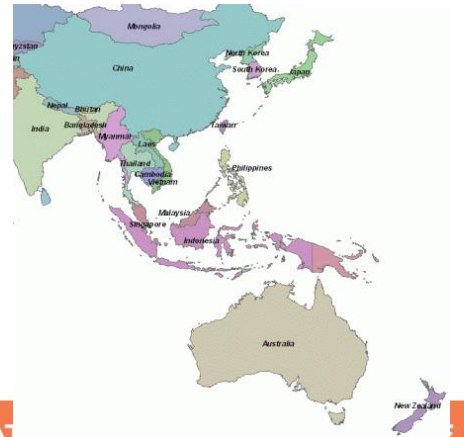


Phase 2:

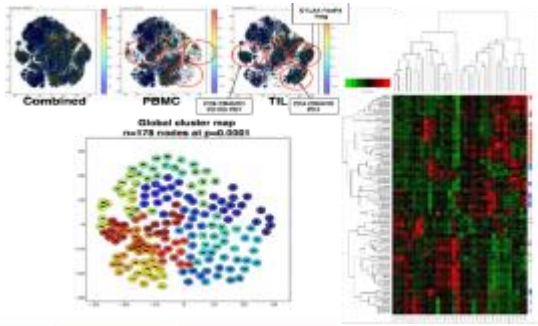
Future Therapeutic trial
basis of our grant renewal



Asia-Pacific HCC Trials Group

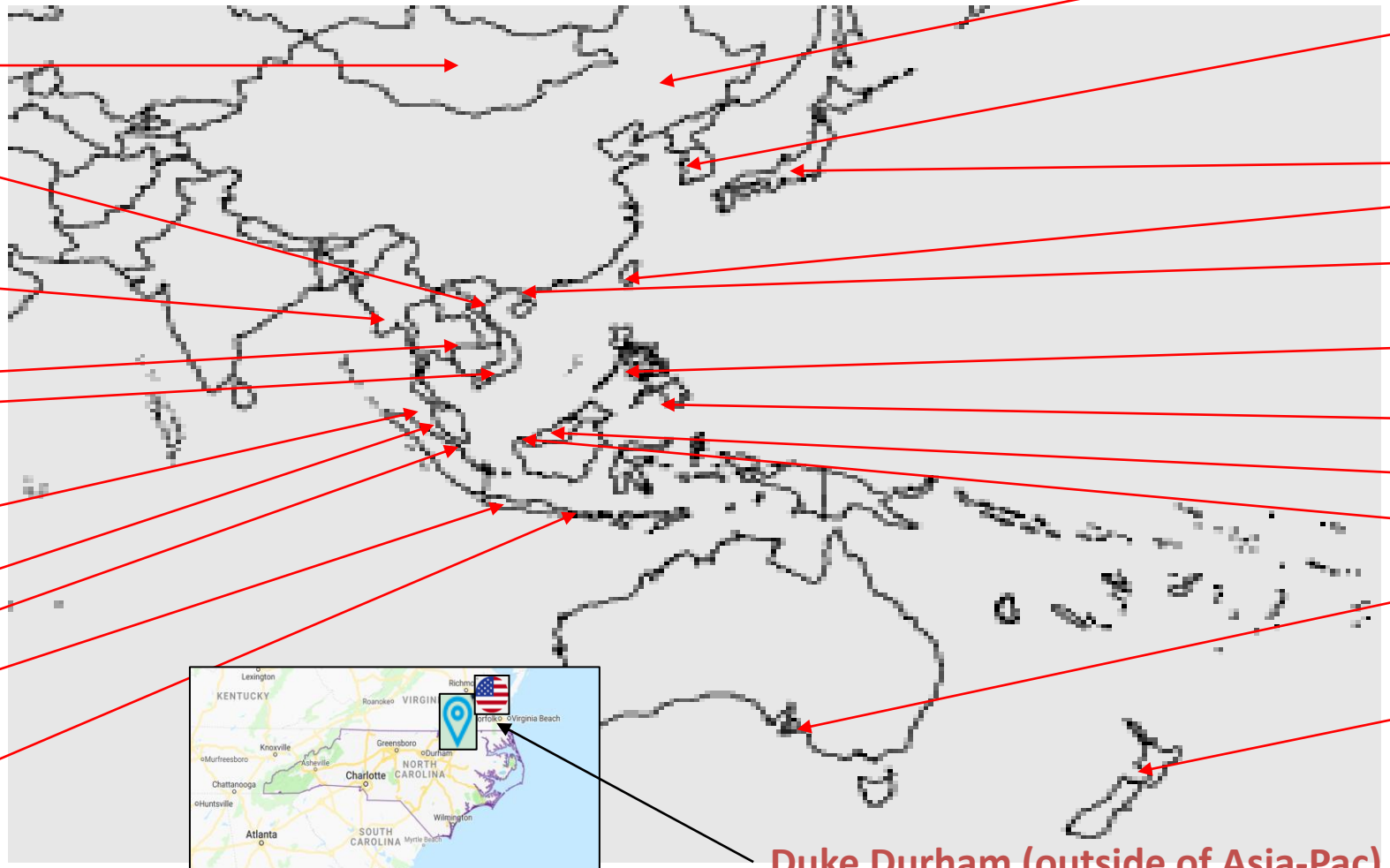


Translational Immunomics



Metabolomics
(Parallel CS-IRG grant)

AHCC07 - The PLANet Study: Asia-Pacific HCC Trials Group



China

Seoul

Ulaan Baator

Hanoi

Japan

Taipei

Yangon

Hong Kong

Manila

Bangkok (NCI)

Davao City

HCMC

Brunei

Penang

Kuching

Kuala Lumpur

Melbourne

Singapore (3)

Jakarta

Auckland

Bali

Duke Durham (outside of Asia-Pac)

Precision Medicine in Liver Cancer across the Asia-Pacific Network

Multi-national study: Inter-ethnic heterogeneity

- National Cancer Centre Singapore (Prof Pierce Chow)
- Singapore General Hospital (Prof Brian Goh)
- National University Hospital (Dr Glenn Bonney)
- University Malaya Medical Centre /University Malaya Specialist Centre (Dr Yoong Boon Koon)
- The Medical City, Philippines (Dr Vanessa De Villa)
- National Cancer Institute, Thailand (Dr Rawisak Chanwat)
- Duke University Hospital, Durham, USA (Dr Sabino Zani)

Lead PI: Prof Pierce Chow

Steering Committee
1. Prof Pierce Chow (NCCS) - Chair
2. Prof Patrick Tan (GIS)
3. Prof KK Madhavan (NUH)
4. Prof Dan Yock Young (NUH)
5. Prof Salvatore Albani (STIIC)
6. Dr Tam Wai Leong (GIS)
7. Dr Toh Han Chong (NCCS)

Project Management
Project Manager:
Dr Chew Sin Chi (NCCS)

Site Coordinators:
1 at each site

- Monitoring and overseeing of **overseas sites: IQVIA**
- Clinical data storage and analysis: **SCRI**
- Centralised data storage platform: **IHPC** (Institute of High Performance Computing, A*STAR)

Theme 1
Genomic evolution in HCC and the discovery of novel drug targets
Theme lead: Dr Liu Jiajun (GIS)

Theme 2
Translational Immunomics: Immune-phenotyping, monitoring and discovery of novel immunotherapy in HCC
Theme lead: Prof Salvatore Albani (STIIC)

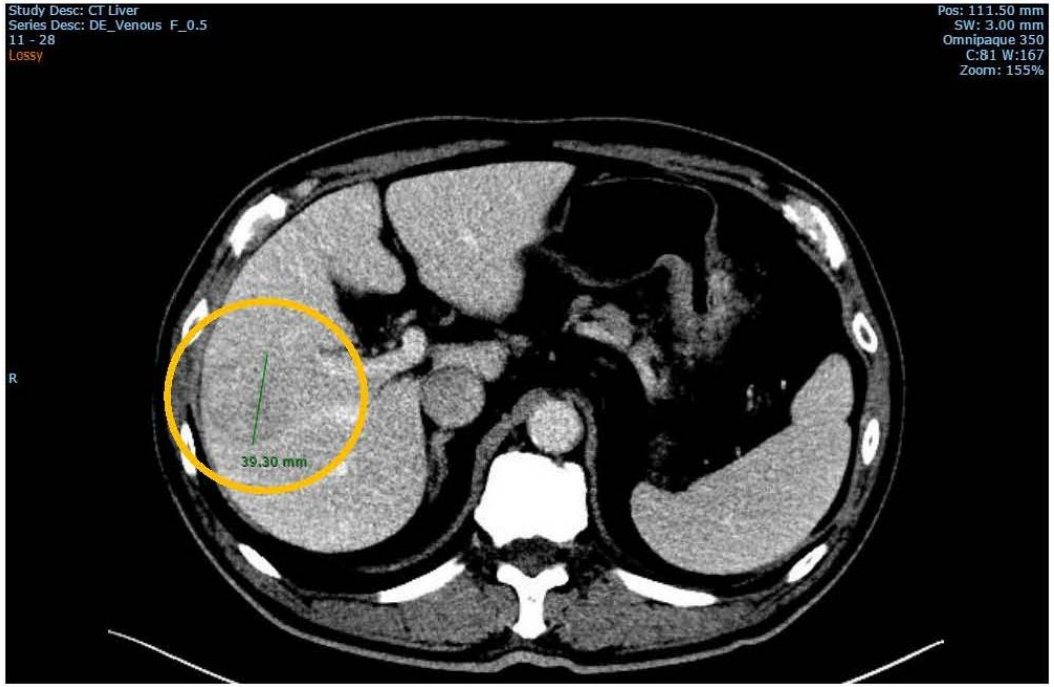
Theme 3
Clinical Trajectory and Translational Therapeutic Clinical Trials
Theme lead: Prof Pierce Chow (NCCS)

Patient-derived cell lines
Dr Tam Wai Leong (GIS)
Genome Institute of Singapore (A*STAR)

Patient-derived mouse models
Prof Edward Chow (NUS-CSI)

Multi-region sampling of HCC tumor

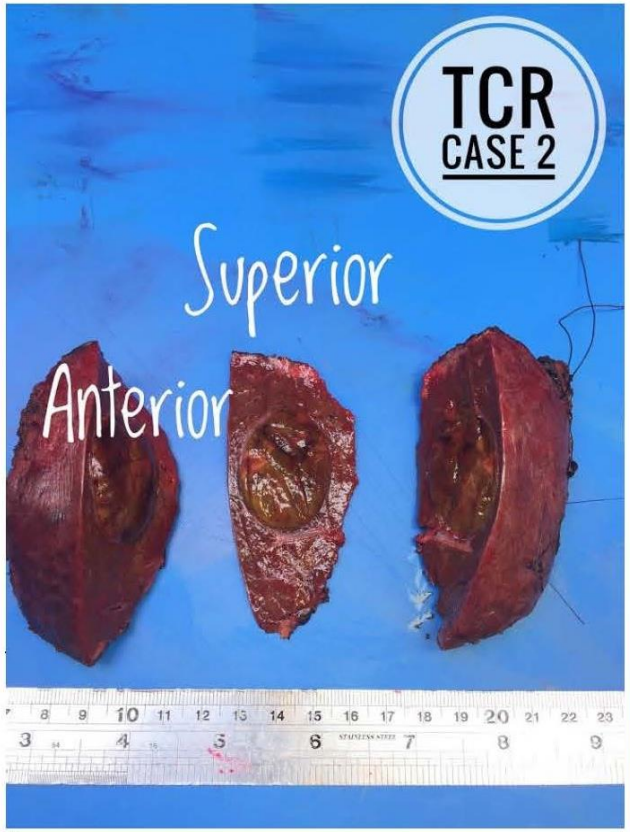
Tumour (transverse); Venous phase 11-28

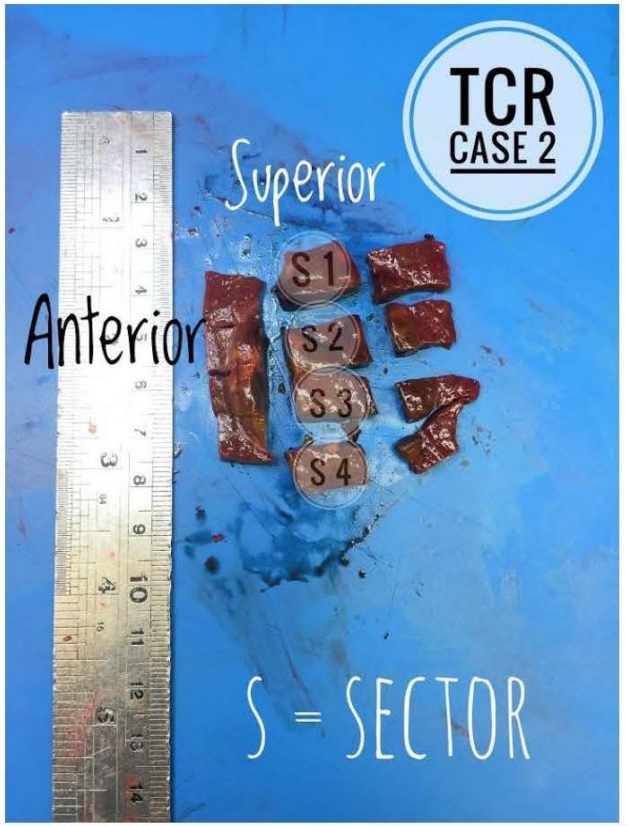


Version 1.0
2016

High logistical and cultural barrier to entry

Highly integrated process – sample collection involves surgeons, anesthetists, clinical coordinators, pathologists, couriers, RAs, post-docs, PIs – **about 15 people** from **5 institutions** involved

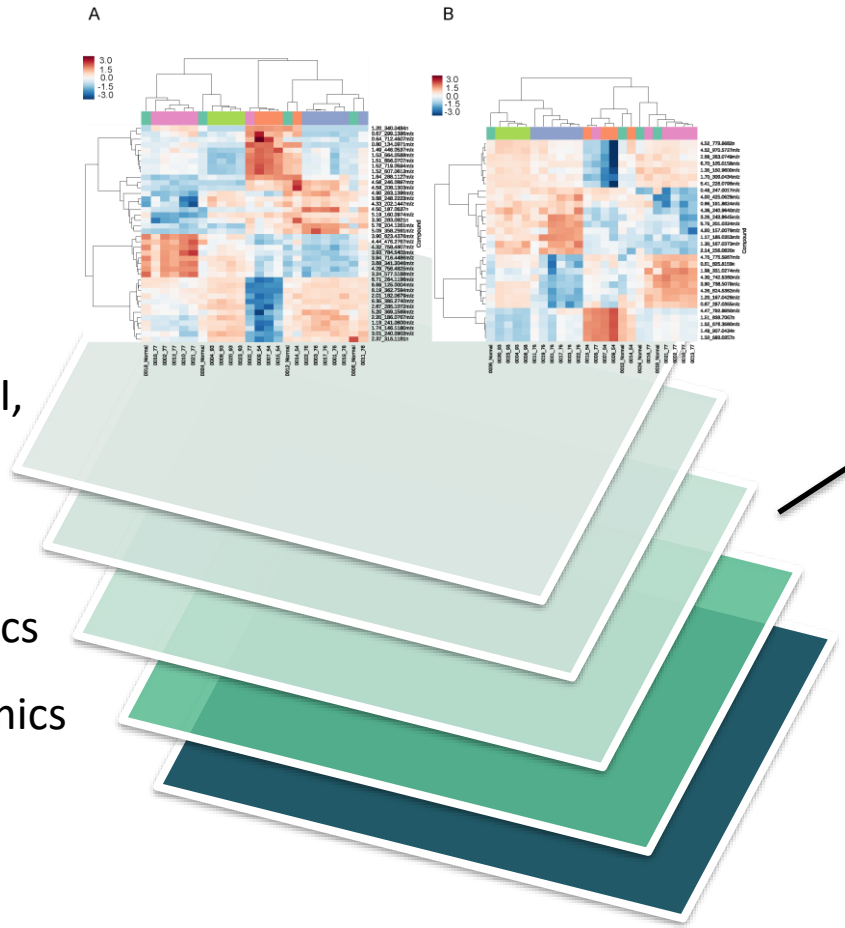




opportunity for Vertical and Horizontal integration

additional grants:

- NMRC CSA : metabolomics
- NMRC CS-IRG: epigenomics



Imaging data (CT scans, MRI, etc)

Clinical data

Metabolomics

Immunomics

Epigenomics/Genomics

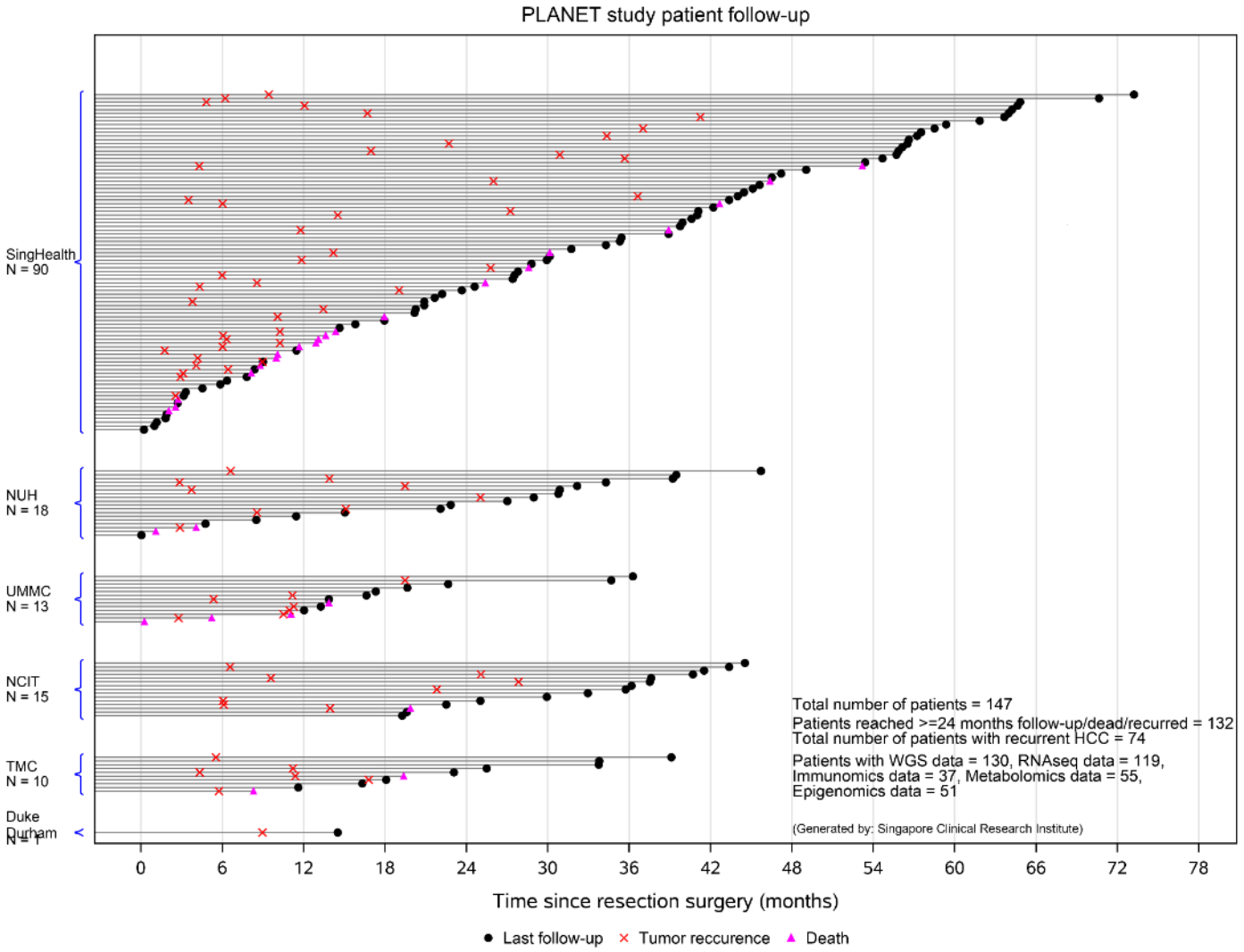
Bioinformatics integration

Thematic pathways

Relationships

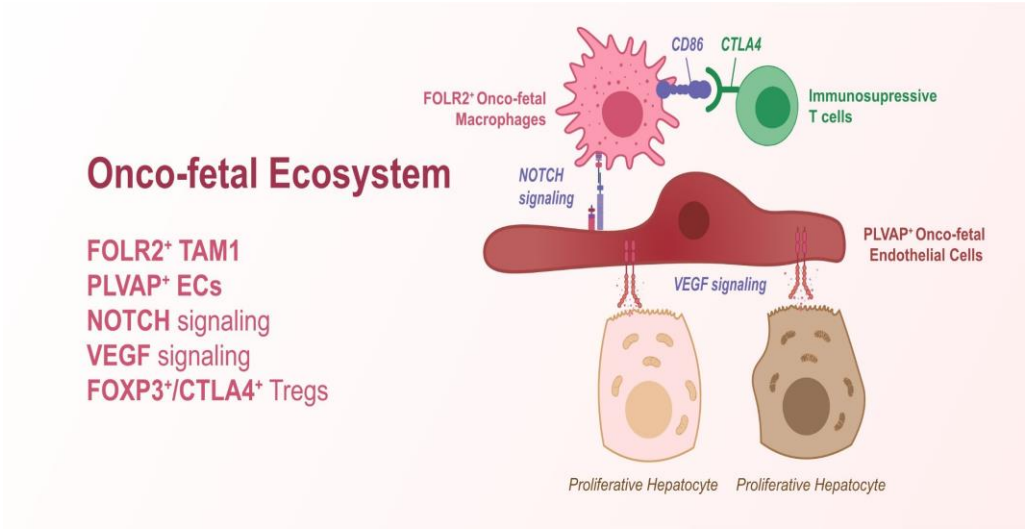
Integration of Data from the same patient/sample

PLANet 1.0 Cohort and the wealth of resources generated



- ✓ Matched recurrent samples were collected in 35 out of 74 recurrent patients.
- ✓ No. of patients with WGS data: 130
- ✓ No. of patients with RNAseq data: 119
- ✓ No. of patients with Immunomics data: 37
- ✓ No. of patients with Metabolomics data: 55
- ✓ No. of patients with Epigenomics data: 51
- ✓ No. of PDP lines successfully established: 24 lines from 16 patients (Success rate of 20%)
- ✓ No. of PDX lines successfully established: 38 lines from 20 patients (Success rate of HCC-PDX: 11.2% ; Success rate of CCA-PDX xenograft: 28.5%).

Discoveries in the TCR PLANET - Onco-fetal Reprogramming confers immune-escape in HCC (Theme 1)



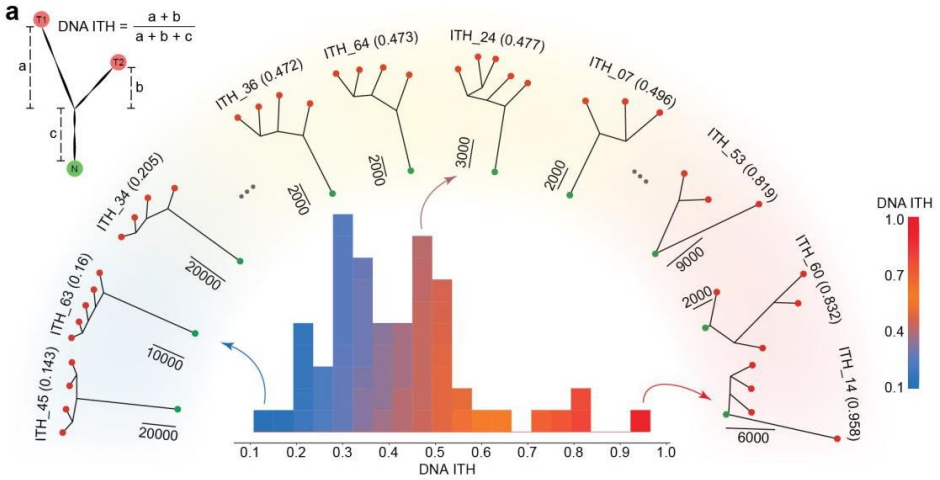
Sharma 2020 *Cell*

- Re-emergence of fetal-associated PLVAP+/VEGFR2+ endothelial cells (EC) and embryonic-like FOLR2+/CD163+ tumour-associated macrophages (TAMs)
- immune suppressive environment maintained by VEGF/NOTCH Signaling
- **Hypothesis**: key is niched co-localization of cells and molecular pathways and density

- **Provide insights on the immune-escape mechanisms targeted by PD-L1 inhibitor atezolizumab and anti-VEGF antibody bevacizumab (Atezo+Bev).**
- **Potential value of using onco-fetal profiles to correlate with clinical outcomes with systemic therapeutics and the development of predictive biomarkers in HCC.**

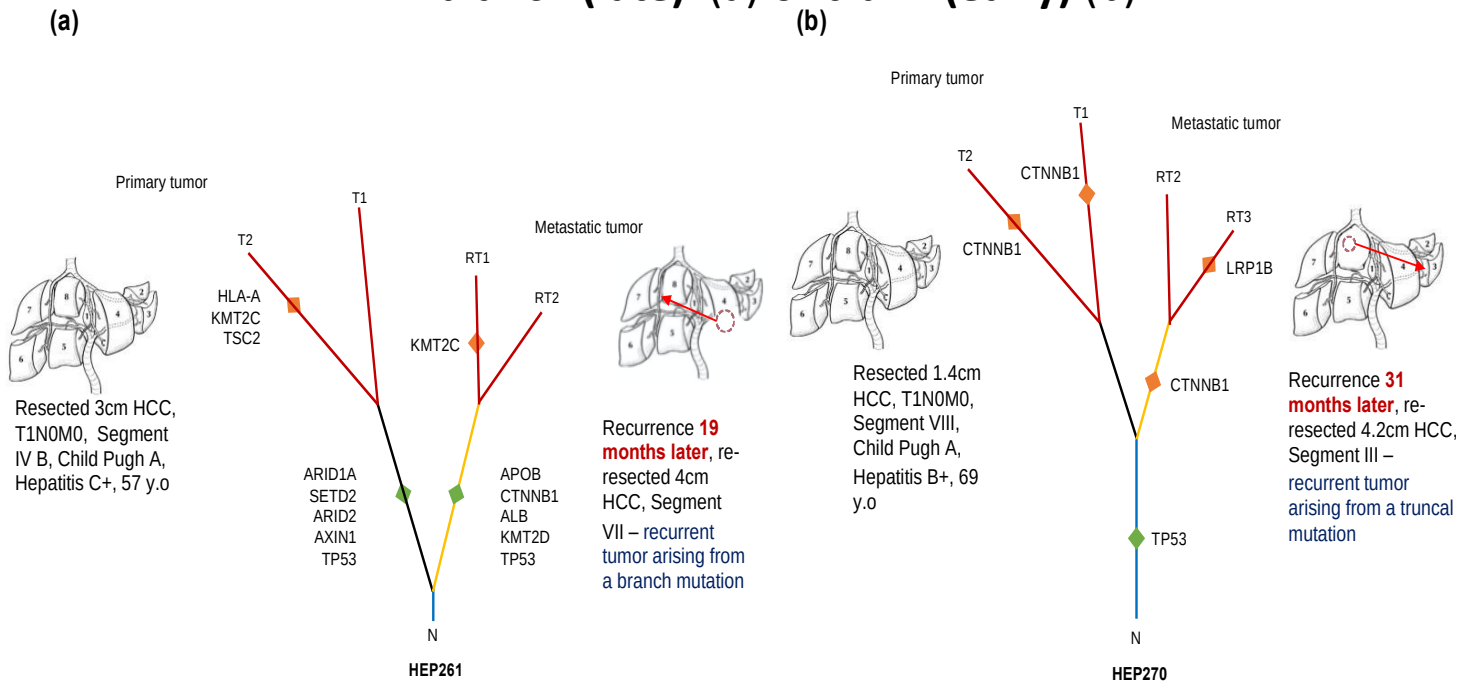
Discoveries in the TCR PLANET – DNA ITH vary a lot across patients and there are diverse evolutionary routes to metastatic tumour (Theme 1)

Wide range of Genomic ITH in primary tumour



Zhai et al. Under minor revision in National Science Review

Recurrent tumours can arise from driver mutations from either **branch (late)** (a) or **trunk (early)** (b).

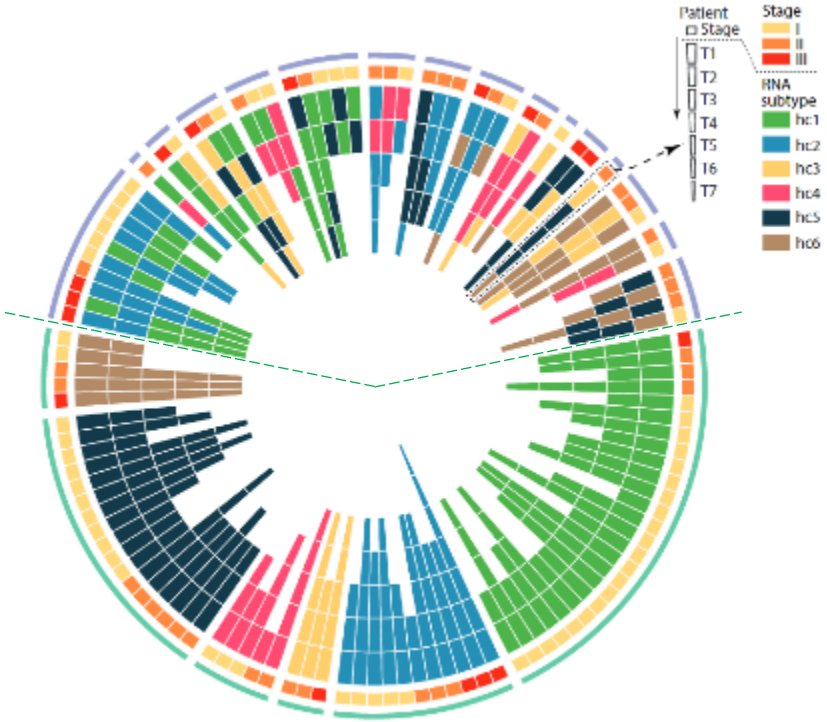


Chen et al. Manuscript in Preparation

- **Intra-tumour heterogeneity (ITH) of HCC is a major challenge to the treatment of metastatic tumour.**

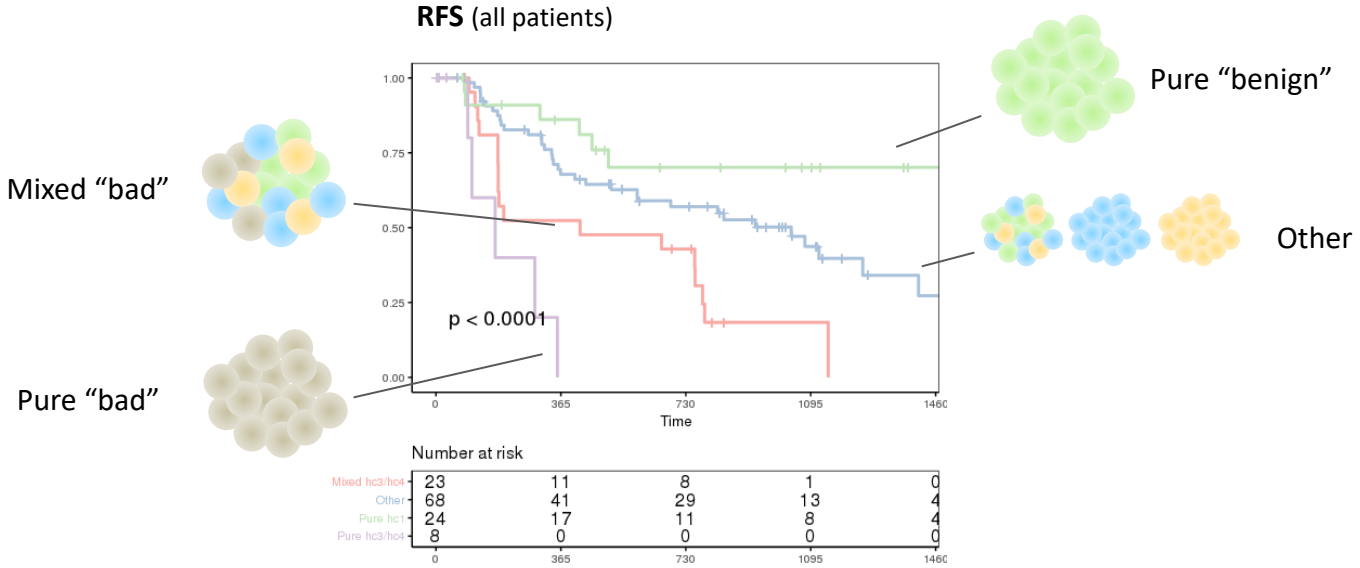
Discoveries in the TCR PLANET – Co-existence of multiple transcriptomic sub-types in 1/2 HCCs and clinical trajectory driven by "Bad Apples" (Theme 1)

Mixed RNA subtypes found in **half** of the patients



Zhai et al. Under minor revision in National Science Review

In HCC with mixed subtypes, clinical outcomes are determined by the subtype with the worst prognosis ("**bad apple**" in the barrel)

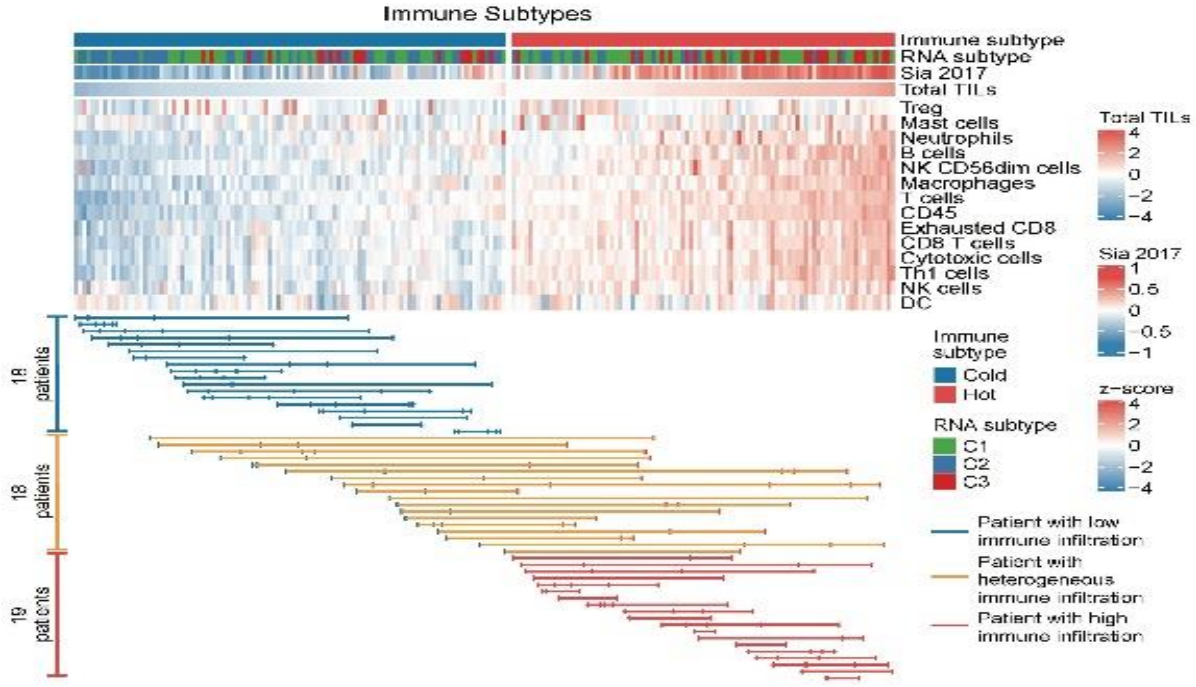


Chen et al. Manuscript in Preparation

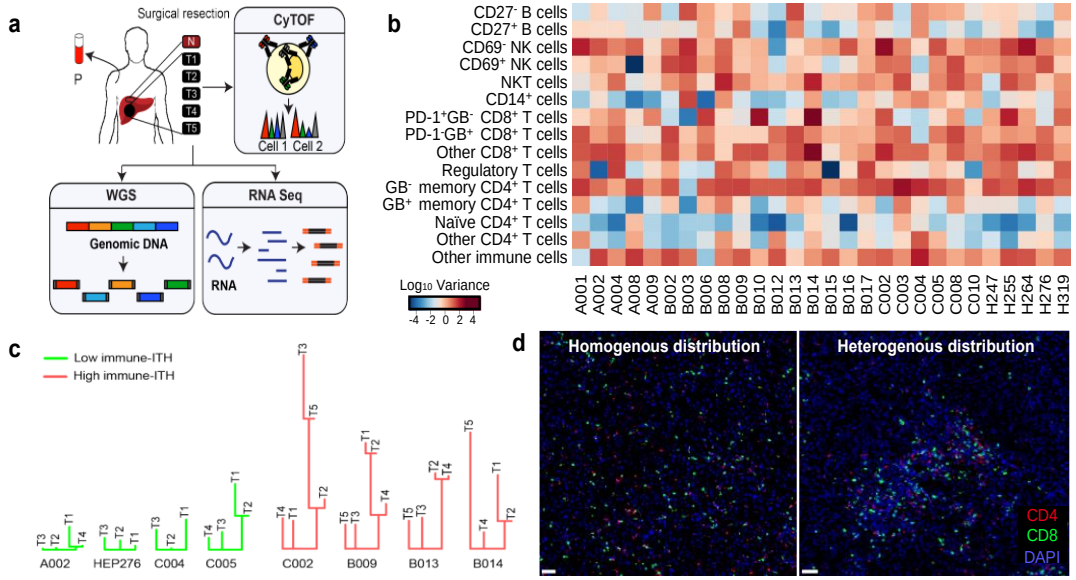
➢ **Potential predictive biomarkers based on "bad apples" signature**

Discoveries in the TCR PLANET – High immune heterogeneity within and between patient tumours (Theme 1 and 2)

While the majority of the tumours were immunologically hot (35%) or cold (33%), a significant proportion (n=18, proportion=33%) of the patients were **immunologically mixed**.



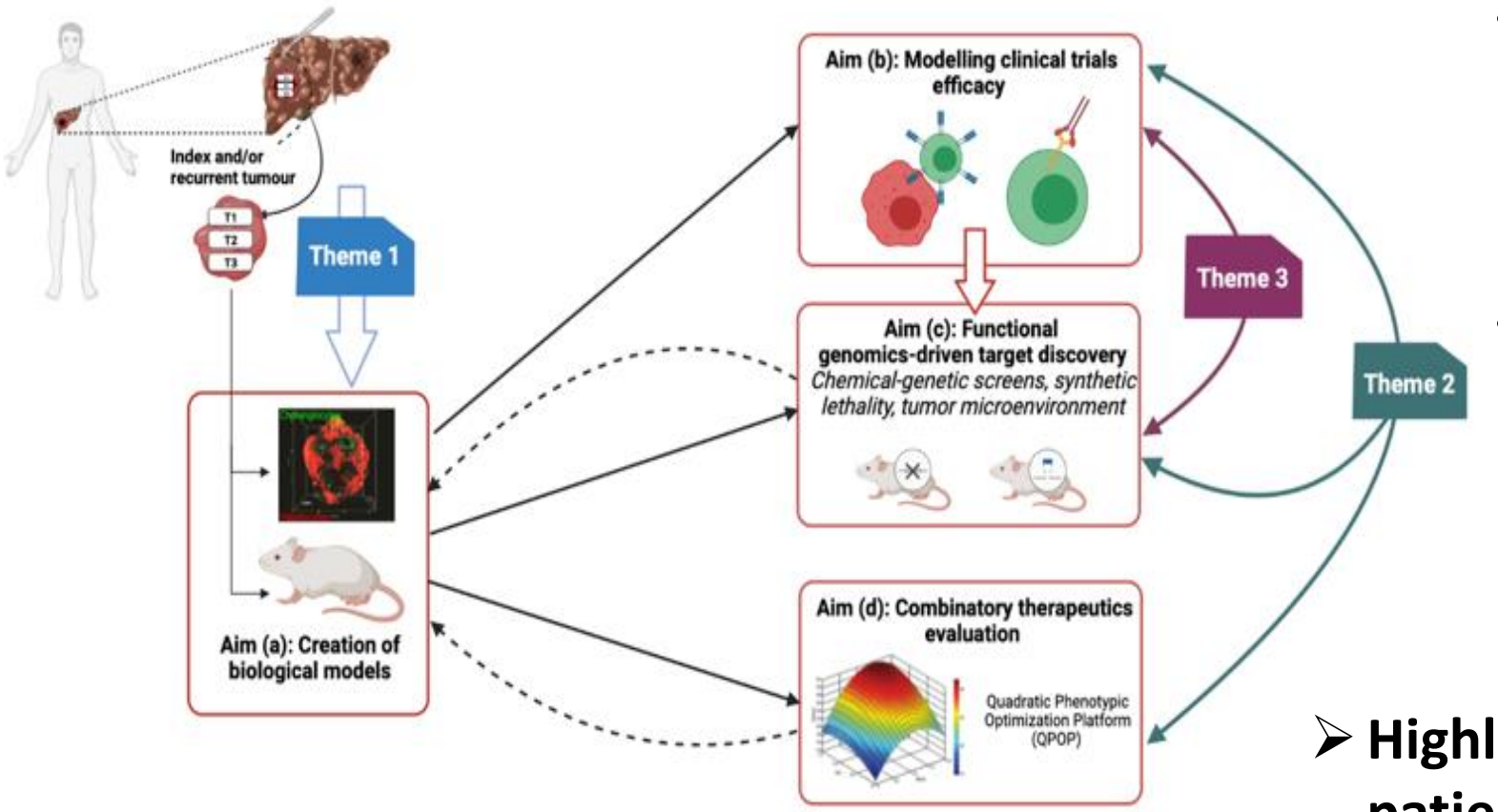
Zhai et al. Under minor revision in National Science Review



Nguyen et al. (2020) Nat Communications

➢ **High immune ITH in HCC may account for the differential response to immuno-therapy**

Discoveries in the TCR PLANET – Establishment of individualized patient-derived cellular models facilitate downstream drug discovery and clinical translation (Theme 3)



- Identification of NAD metabolism as a therapeutic vulnerability in a subset of liver cancer (*Theme 3 PI: Tam WL*).
- Application of QPOP across PDOs to identify effective treatment combinations (*Theme 3 PI: Chow E*)

➢ **Highlight the translational value of patient-derived cellular models that properly reflect the heterogeneity of HCC**

Tan et al. (2019) Gastroenterology, 157(6):1615-29
Rashid et al. (2018) Sci. Transl. Med., 10(43).

A regional and whole-of-nationeffort

NMRC Grants

Clinical Collaborators

SGH (Brian Goh)
NUH (Glenn Bonney)
UMMC (Yoong BK)
NCIT (Rawisak)
TMC (Vanessa)
Duke Durham (Sabino)

Bench Collaborators

GIS (Patrick Tan, Roger Foo, Tam WL, Zhai WW, Chen JB, Ankur Sharma)
STIIC (Valerie Chew)
NUS (Edward Chow, Tan Boon)
NTU (Yulan Wang)
SIgN (Florent Ginhoux)

PLANet patients and their families

TCR 1st Investigator Meeting, 2016

TCR 2nd Investigator Meeting, 2017

TCR 3rd Investigator Meeting, 2018

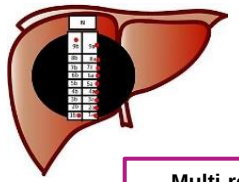
TCR 4th Investigator Meeting, 2019

Main scientific discoveries to date

From the large cohort of resected HCC patients annotated with comprehensive clinical trajectory, multi-omics data and representative PDP/PDX models, we have shown that

- ✓ Evolutionary routes to **metastatic tumour** are highly diversed and recurrence can emerge early/late from the index tumor.
- ✓ Significant proportion of HCCs have **mixed transcriptomics subtypes** and the worst subtype drives clinical trajectory.
- ✓ Onco-fetal reprogramming is a novel immune-escape mechanism in HCC
  - ✓ importance of co-localization of molecular pathways

Going forward: PLANet2.0



Multi-region sampling or biopsy (if recurrence)

Multi-region sampling, Blood, Urine

3-monthly Scans, Blood, Urine

3-monthly Scans, Blood, Urine

3-monthly Scans, Blood, Urine

3-monthly Scans, Blood, Urine

3-monthly Scans, Blood, Urine

Clinical Study 1

Adjuvant Therapy for early HCC following surgical resection

Translational studies

Theme 1: Deep Phenotyping and Correlation with Clinical Responses to Therapy
Pierce Chow, Patrick Tan, Roger Foo, Wang Yulan, Jianbin, Ah-Jung, Lingyan

Theme 2: Elucidating Spatial Distribution of Biomarkers at single-cell resolution
Vinay, Florent, Ankur, Matias

Theme 3: Translational and Functional immunomics
Toh Han Chong, Timothy

Theme 4: Pre-clinical Disease Modelling and Target Discovery
Tam Wai Leong, Edward Chow

Theme 5: Data Architecture, Data Security and Data Science Applications
Roger Daniel Vaughan

Clinical Study 2
- randomized phase II trial

Loco-regional Therapy (Y90) for intermediate/advanced* HCC +/- systemic therapy

3-monthly Scans, Blood, Urine

3-monthly Scans, Blood, Urine

3-monthly Scans, Blood, Urine

3-monthly Scans, Blood, Urine

3-monthly Scans, Blood, Urine

3-monthly Scans, Blood, Urine

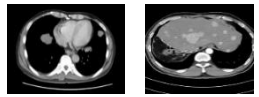
Multi-region sampling

Clinical Outcomes (Proof of Principle)

Follow-up until point of recurrence or end of study

combination immunotherapy (30)
- Recurrence
- No recurrence

Natural trajectory (30)
- Recurrence
- No recurrence



Aim: To build on insights of PLANet 1.0 and leverage on 2 Clinical Studies to identify and validate predictive biomarkers in HCC

Follow-up until death or 18 months (end of study)

Atezo-Bev immunotherapy (88)
- Regression
- No regression

Placebo (88)
- Regression
- No regression

Potential surgical resection

Restricted, Non-Sensitive

*Advanced HCC includes patients with portal-vein thrombosis but with the absence of extra-hepatic mets