

Program in Translational and Clinical HCC Research

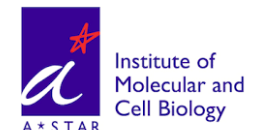
NMRC Awards Ceremony and Research Symposium 2019

3 April 2019

Avoiding Red Oceans – playing to our strengths in Liver Cancer

Prof Pierce Chow FRCSE PhD

Senior Consultant Surgeon, Division of Surgical Oncology
Professor, Duke-NUS Graduate Medical School



Red Oceans - What are they?



Definition

- Cut-throat competition in existing industries that turns the competing space into an increasingly **low-margin** market.

What is Red Ocean Strategy?

- **Centered on competition in existing markets.** As the market space gets more and more crowded, companies compete fiercely for a greater share of limited demand.
- **The competitor with the most resources eventually wins** – small players have no chance for survival unless they **innovate to make the competition irrelevant**
- Competing in red oceans = **zero-sum game**
 - A market-competing strategy that divides existing wealth between rival companies
 - As competition increases, prospects for profit and growth decline – **marginal gains**

Example of Red Ocean competition in History

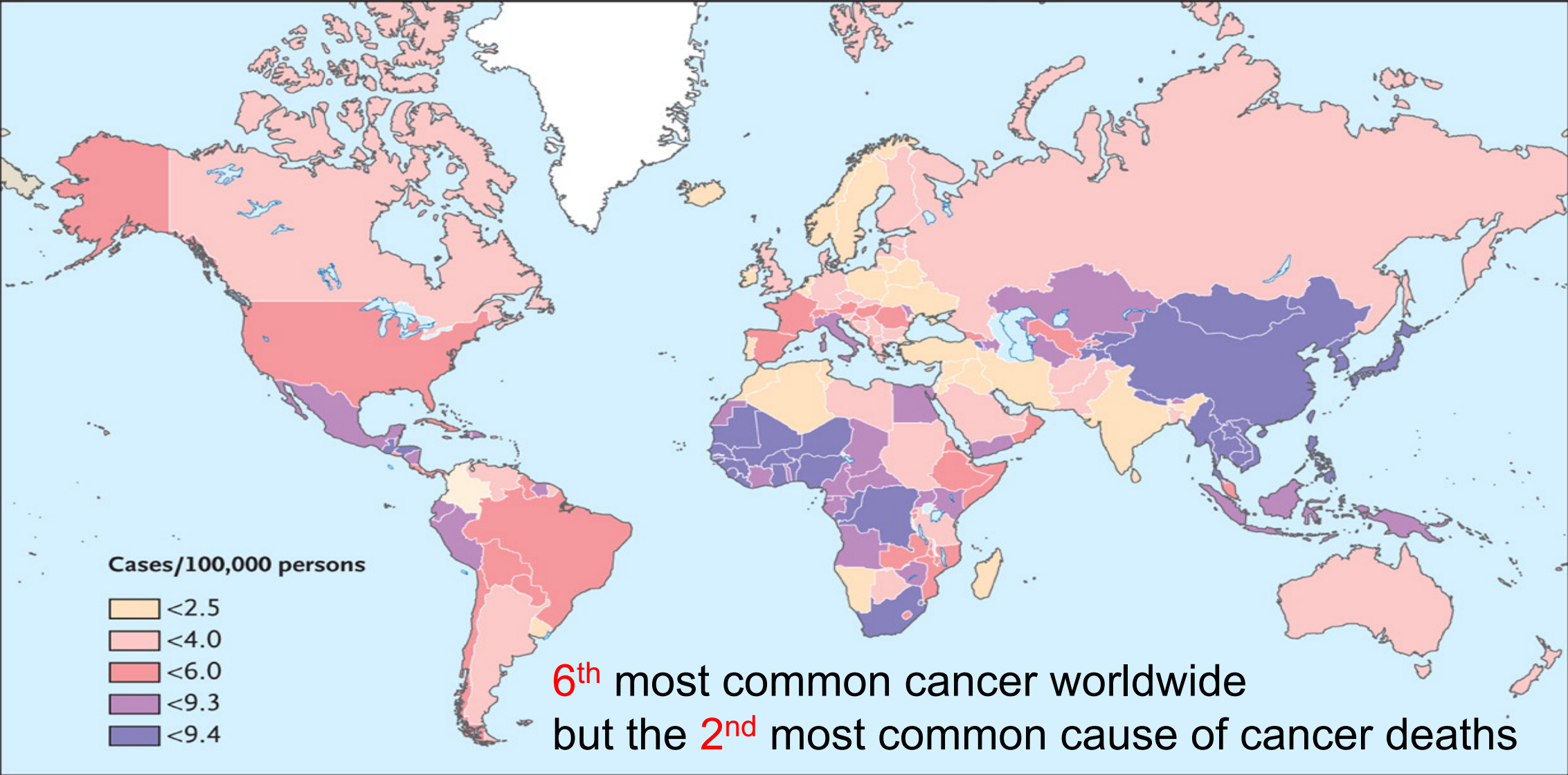


Warring States Period
221 B.C.E.



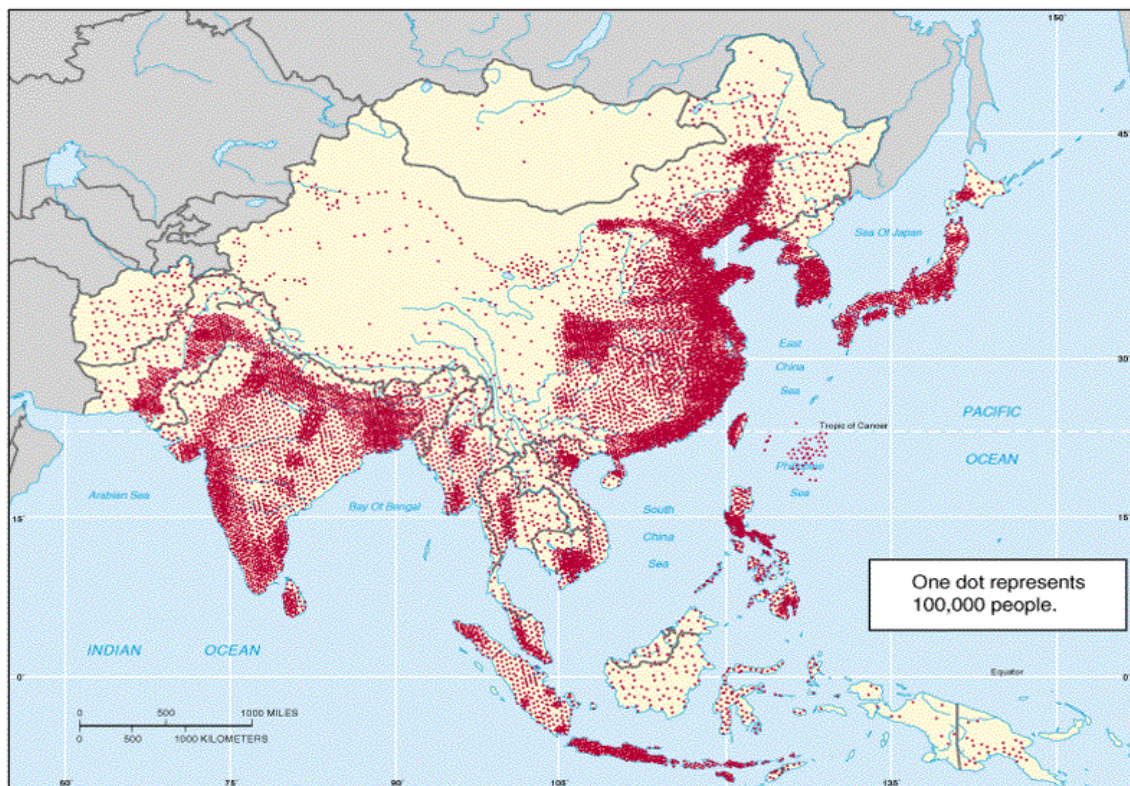
- weaker states to survive
- competing in the same **space/technology**, **weaker states** are doomed to succumb to stronger states
- after massive slaughter, **no increase in overall resources, wealth or quality of life**

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



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

Singapore is a very small country in a very big continent



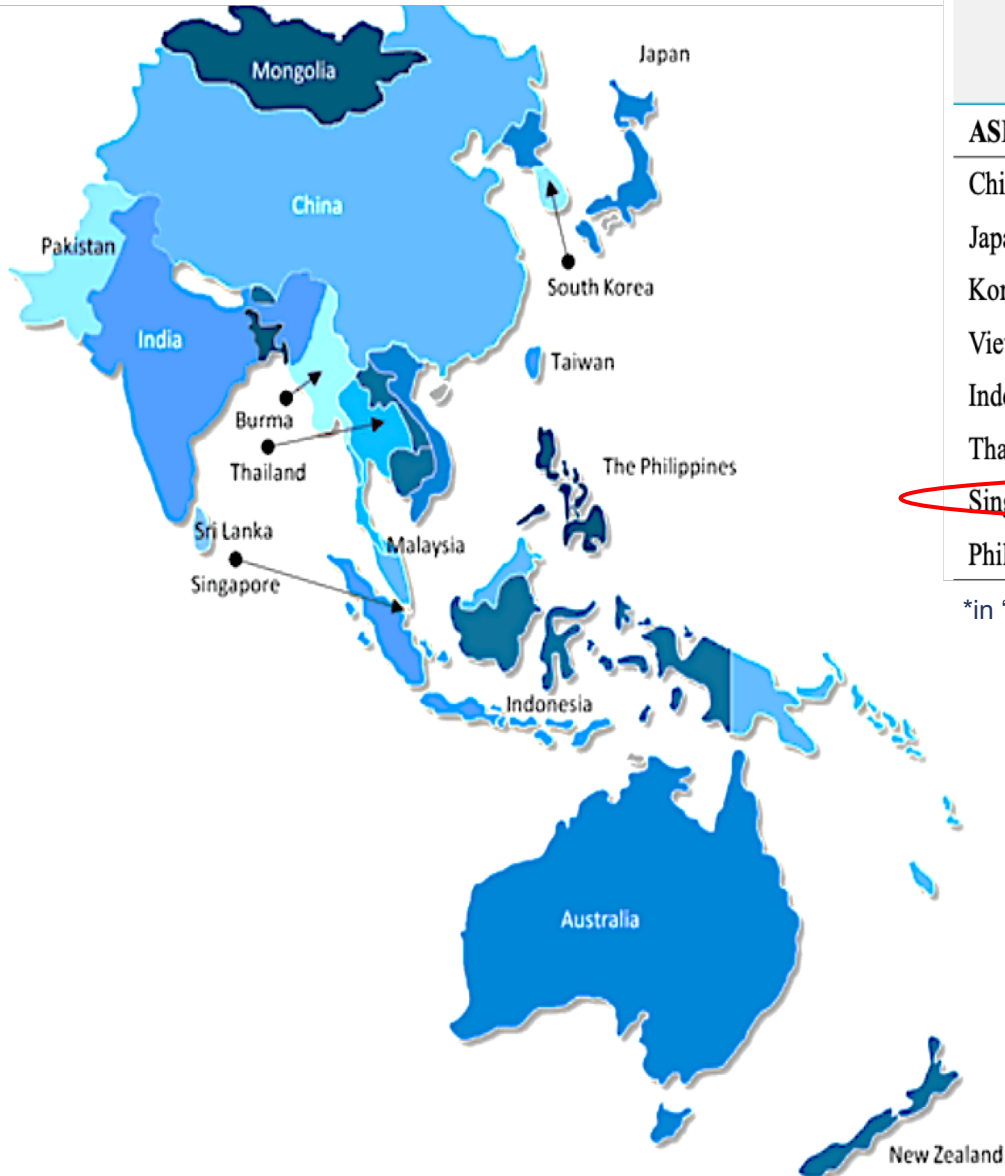
List of Asian countries by population

1	China	1,353,601,000	27	Azerbaijan	9,421,000
2	India	1,258,351,000	28	United Arab Emirates	8,106,000
3	Indonesia	244,769,000	29	Israel	7,695,000
4	Pakistan	179,951,000	30	Hong Kong (China) ^[4]	7,196,000
5	Bangladesh	152,409,000	31	Tajikistan	7,079,000
6	Japan	126,435,000	32	Jordan	6,457,000
7	Philippines	96,471,000	33	Laos	6,374,000
8	Vietnam	89,730,000	34	Kyrgyzstan	5,448,000
9	Iran	75,612,000	35	Singapore	5,256,000
10	Turkey	74,509,000	36	Turkmenistan	5,170,000
11	Thailand	69,892,000	37	Georgia	4,304,000
12	Myanmar	48,724,000	38	Lebanon	4,292,000
13	South Korea	48,588,000	39	Palestinian territories ^[5]	4,271,000
14	Iraq	33,703,000	40	Armenia	3,109,000
15	Afghanistan	33,397,000	41	Oman	2,904,000
16	Nepal	31,011,000	42	Kuwait	2,892,000
17	Malaysia	29,322,000	43	Mongolia	2,844,000
18	Saudi Arabia	28,705,000	44	Qatar	1,939,000
19	Uzbekistan	28,077,000	45	Bahrain	1,359,000
20	Yemen	25,569,000	46	Timor-Leste	1,187,000
21	North Korea	24,554,000	47	Cyprus	1,129,000
22	Taiwan	—	48	Bhutan	750,000
23	Sri Lanka	21,224,000	49	Macau (China) ^[6]	567,000
24	Syria	21,118,000	50	Brunei	413,000
25	Kazakhstan	16,381,000	51	Maldives	324,000
26	Cambodia	14,478,000		Total	4,227,067,000

*United Nations Population Division estimates for 1 Jul 2012

Hepatocellular Carcinoma (HCC) in the Asia-Pacific

Year 2016



	No. of new cases* (total)	No. of new cases* (male)	No. of new cases* (female)	ASR (total)	ASR (male)	ASR (female)
ASIA						
China	394	293	101	22.3	33.7	10.9
Japan	36	24	12	9.3	14.6	4.7
Korea	5	3	2	16.2	25.8	8.7
Vietnam	22	17	5	24.6	40.2	10.9
Indonesia	18	13	5	8.4	13.4	4.0
Thailand	21	15	6	22.3	34.8	11.3
Singapore	0.7	0.6	0.1	9.7	15.8	4.1
Philippines	7	5	2	11.4	17.1	6.5

*in '000, ASR = age-adjusted rate per 100,000

The changing epidemiology of hepatocellular carcinoma in Asia versus United States and Europe
(doi: 10.18282/amor.v3.is1.182)

On an **annual** basis, Singapore has significantly fewer HCC compared to its neighbors such as China, Japan and Thailand

- Singapore: **700** | China: **394,000** | Japan: **36,000** | Thailand: **21,000**

What should our strategy in HCC be ?

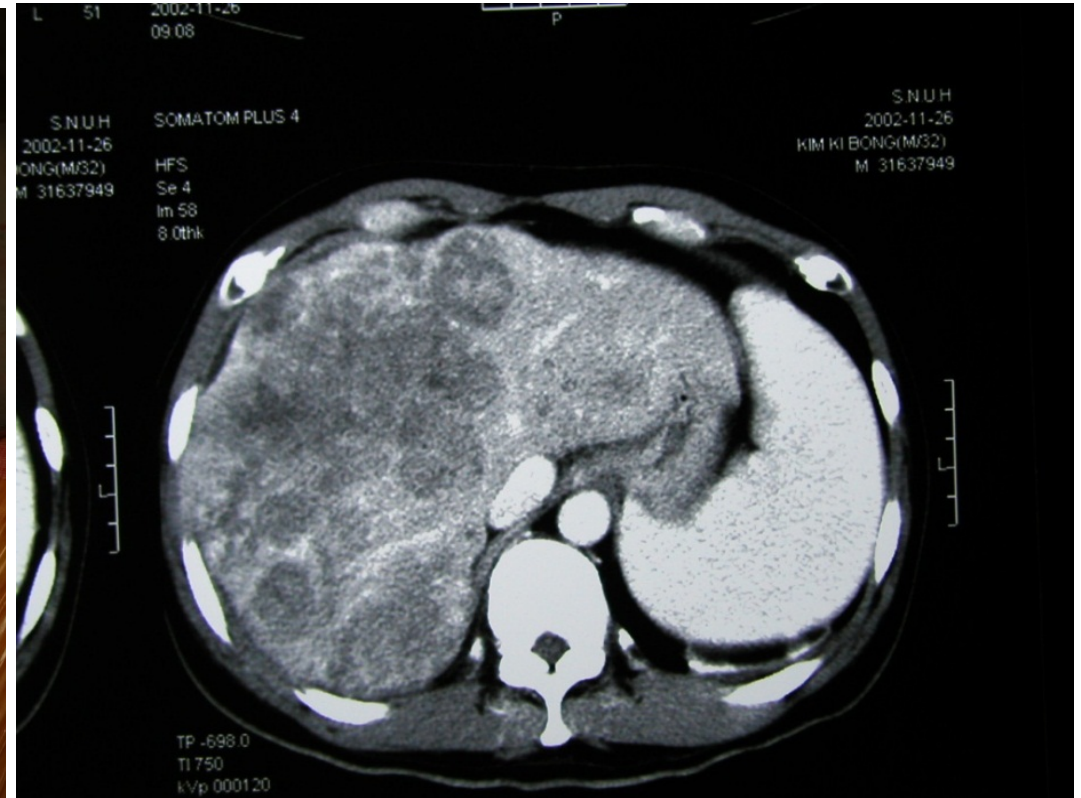
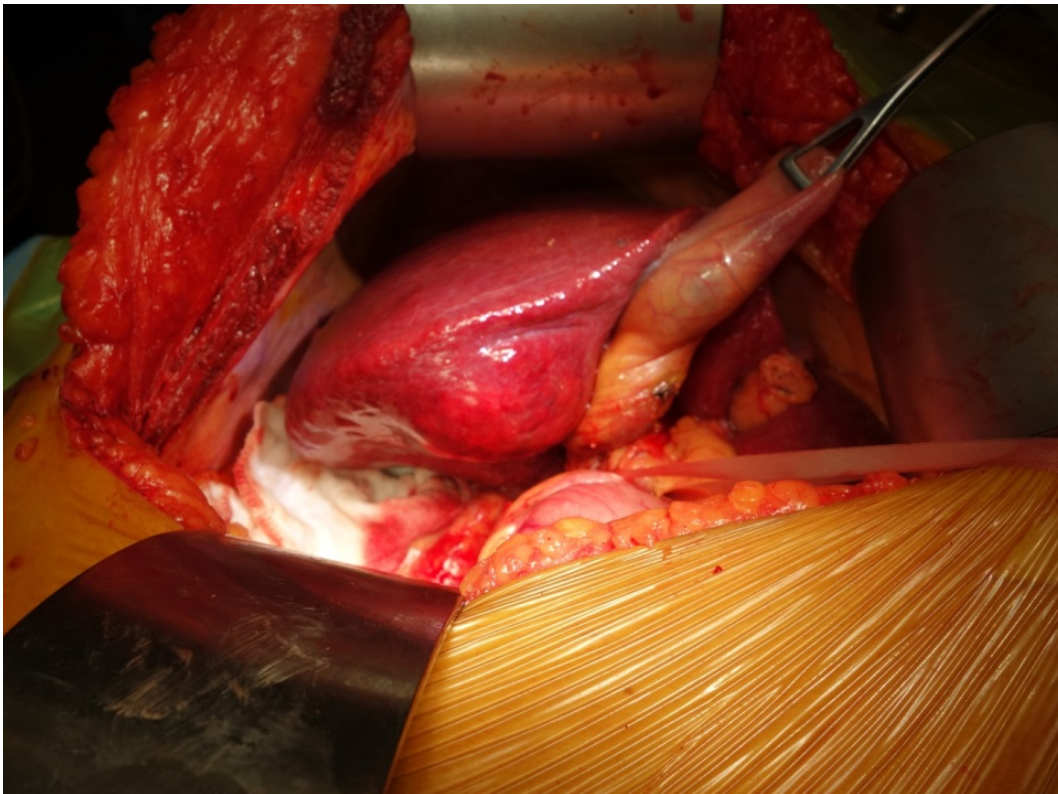
The Numbers Game in HCC – Liver Transplantation



Thinking out of the Box: More transplantation and surgical resections do not address the unmet needs of patients with HCC

Transplantation/Surgical resection is potentially curative in early stage HCC

But 80% of HCC are not transplantable/resectable at diagnosis



Brief overview of HCC

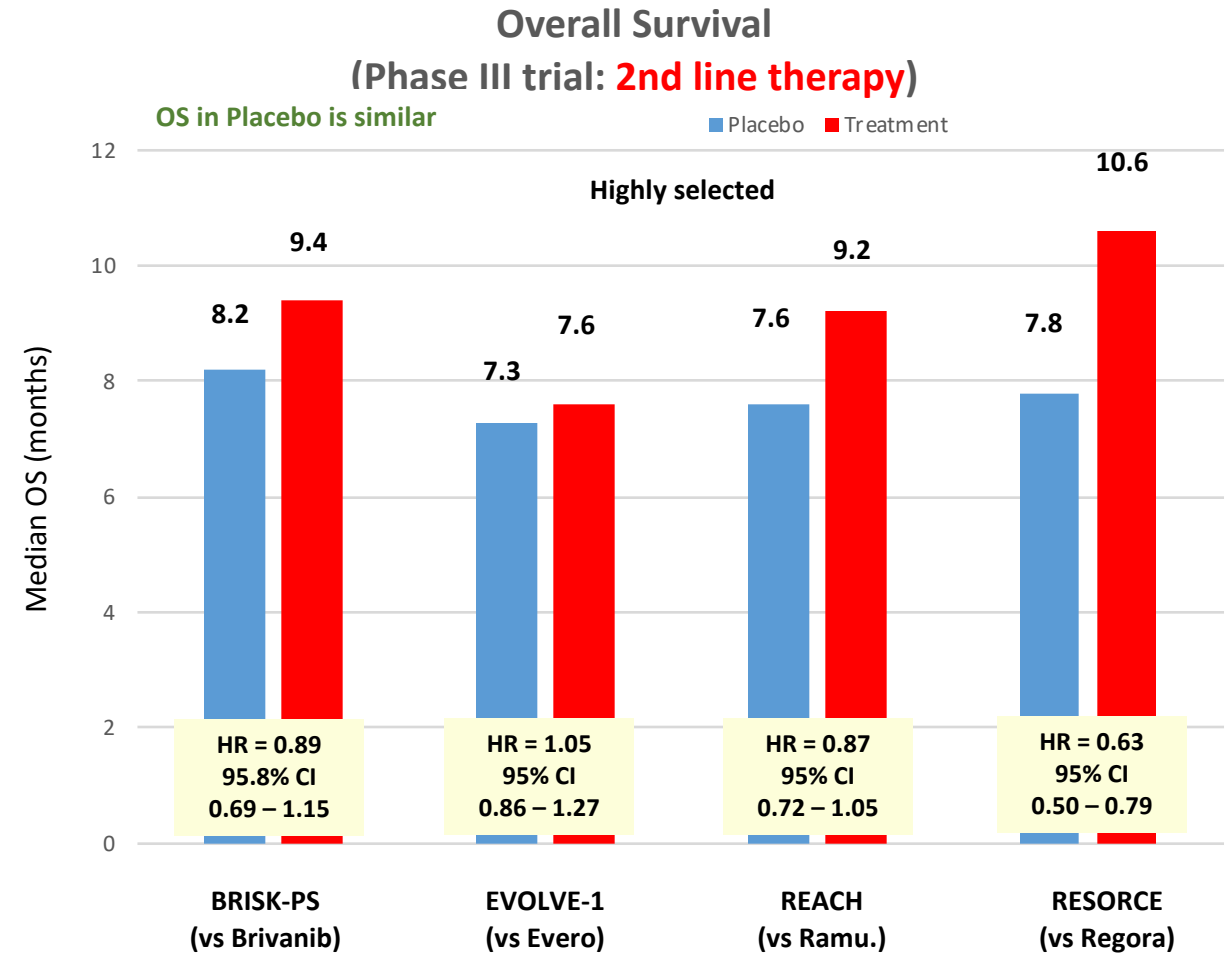
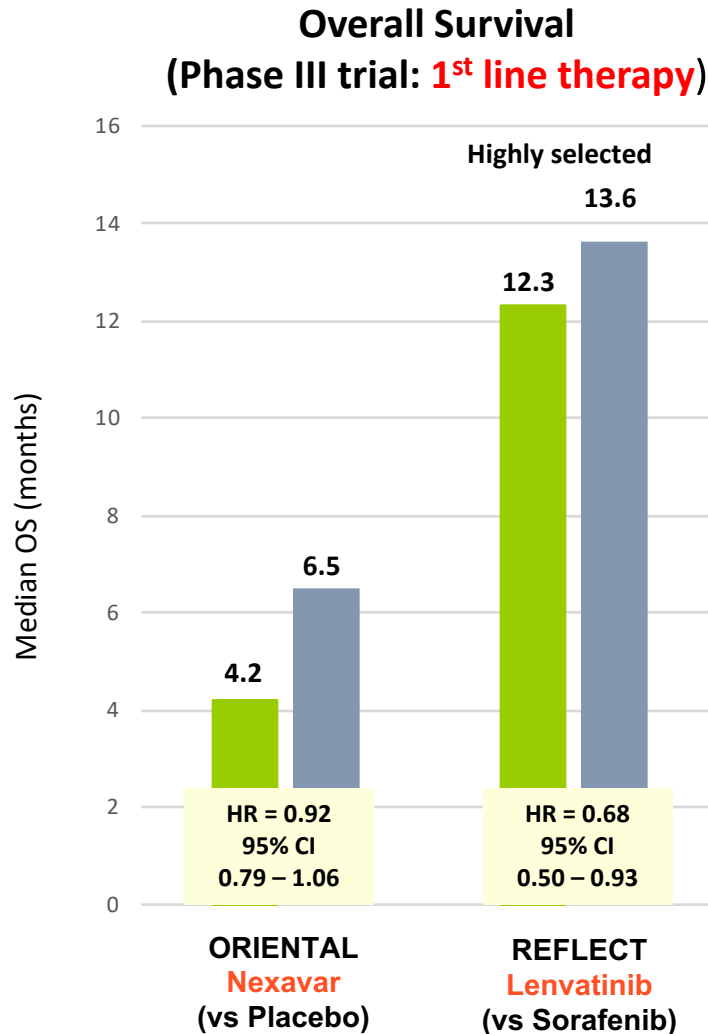
- More than **1 million new cases** a year, **80% in the Asia-Pacific**, but:
 - few efficacious therapies, **poor overall survival**
 - **20%** of patients are diagnosed at an early stage and benefit from potentially curative therapies – *resection, transplantation, radiofrequency ablation*
 - **No neo-adjuvant** or **adjuvant** therapies – recurrences are common

Huge **Unmet Needs** in HCC

1. Paucity of efficacious therapies

- Poorly efficacious systemic therapies with ORR of:
 - **2%** (*sorafenib*) **16%** (*nivolumab*) **19%** (*lenvatinib*) **5%** (*carbozatinib*) **7%** (*ramucirumab*)
- Responses to a specific treatment vary among different HCC cases – **no validated biomarker**
- No Precision Medicine in HCC

Systemic therapies have been poorly efficacious in HCC



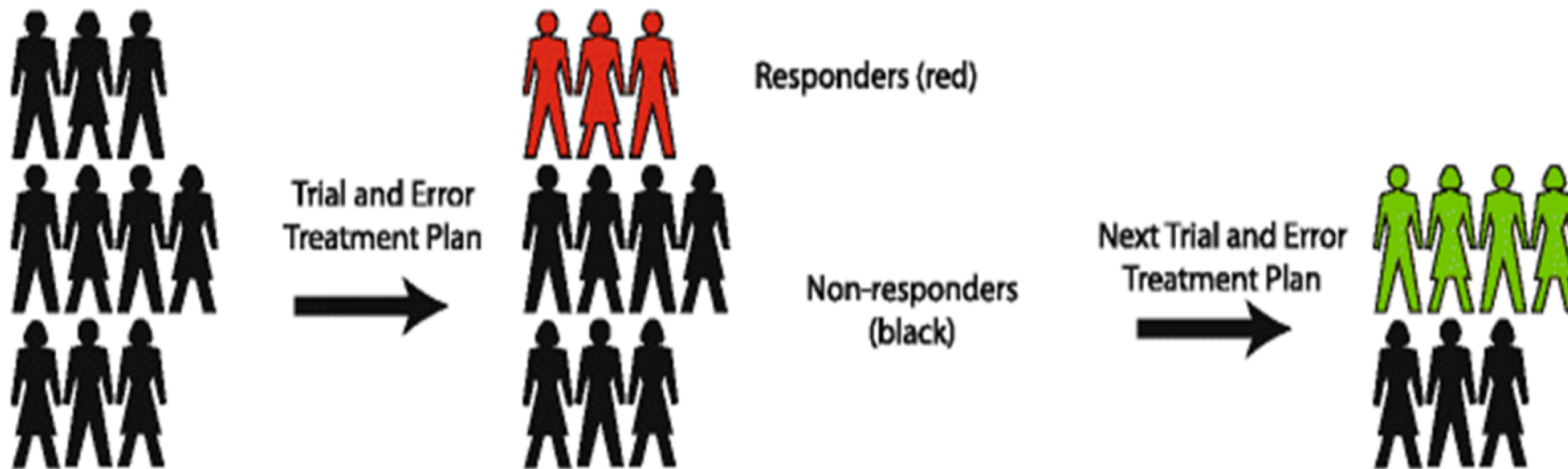
BRISK-PS: Llovet JM et al. J Clin Oncol 2013;31(28):3509-3516. EVOLVE-1: Zhu AX et al. JAMA 2014; 312(1):57-67. REACH: Zhu AX et al. Lancet Oncol. 2015 Jul;16(7):859-70. RESORCE. J Brutx et al. Lancet 2017

Overall survival in Phase III trials: **1st line therapy and 2nd line therapy**

Conventional Treatment of Liver Cancer

No validated therapeutic bio-markers

Trial and Error Approach



.....the central problem in HCC is the absence of **good systemic therapy**.....

....there is also no **validated therapeutic biomarker** in HCC.....

Huge Unmet Needs in HCC

2. Poor understanding of HCC biology

- Underlying biological mechanism(s) leading to HCC remain unclear
- Highly **heterogenous** genome, immunome and metabolome
 - between patients and within tumors
- No validated therapeutic biomarker in HCC

3. No robust Real World Data on HCC in the Asia-Pacific

- Significant limitations with the current available information
- **Sources of information: (1) national registries (very few countries), (2) some clinical trials and (3) retrospective case series**
- **Clinical trial data are idealized**
 - **Strict inclusion and exclusion criteria**
 - **Treatment limited to protocol approved therapies at stipulated doses**

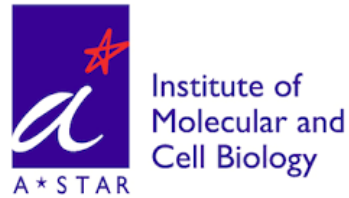
These unmet needs can only be addressed
by better **Science**.

We do not need a large number of
patients to do better science

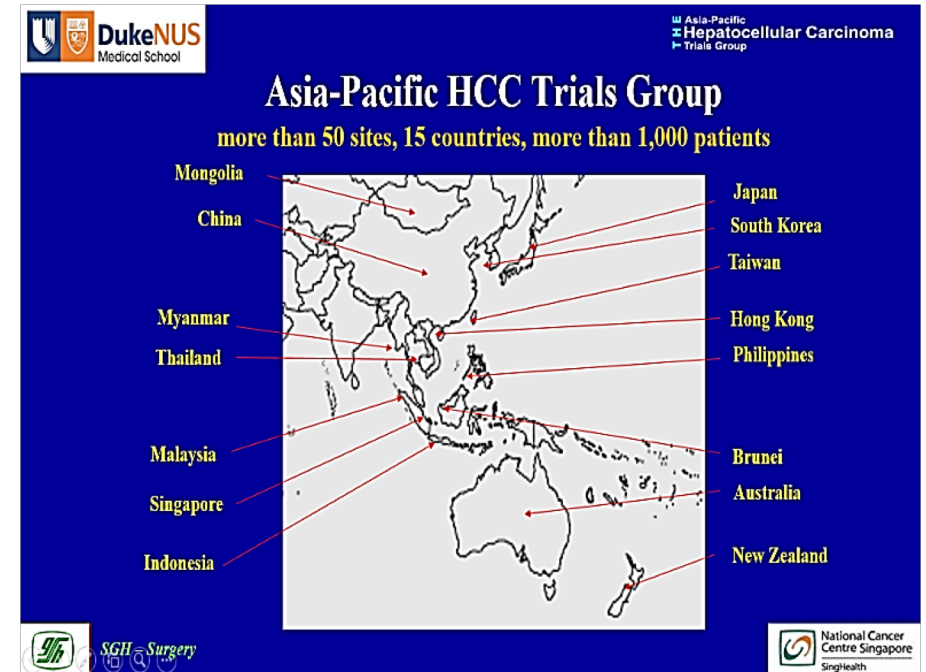
We have inherent **Strengths**

1. **research institutions** with cutting-edge
scientific capabilities within a small geography
2. leadership in a **multinational HCC trials group**
that can rapidly scale up patient numbers

These are what we leverage on



Asia-Pacific Hepatocellular Carcinoma Trials Group



A Translational-Clinical Program addressing unmet needs in HCC

Multi-disciplinary
Multi-institution

Asia-Pacific Hepatocellular Carcinoma Trials Group (AHCC)

Comprehensive Liver Cancer Clinic (CLCC) and Clinical Databases

Laboratory for Translational Liver Research

Joint Lab in IMCB

Singapore Liver Cancer Consortium (SLCC)

Translation

Application

Development of an
Bio-artificial liver
platform for drug

Poor
understanding
of HCC biology

Microbiome and
NAFLD/NASH
(with LKCSM NTU)

NMRC TCR Flagship Program in Liver Cancer: Precision Medicine in Liver CaNcer across an Asia-Pacific Network. A Clinical-Multi-omics prospective study. The PLANET Program with AHCC Trials Group (AHCC07)

Onco-metabolites (with Chugai)

Circulating miRNAs (with MiRXES)

Radiogenomics

- Holmusk
- Bioinformatics Institute
- Institute of High Performance

BMRC IAF-PP: A patient-specific diagnostic and predictive platform for precision medicine in HCC. The PuRPOSE Program with Samsung Medical Center, NUS, and A*STAR IMCB & GIS

MRI evaluation of liver health in cancer
(Perspectum Diagnostics)

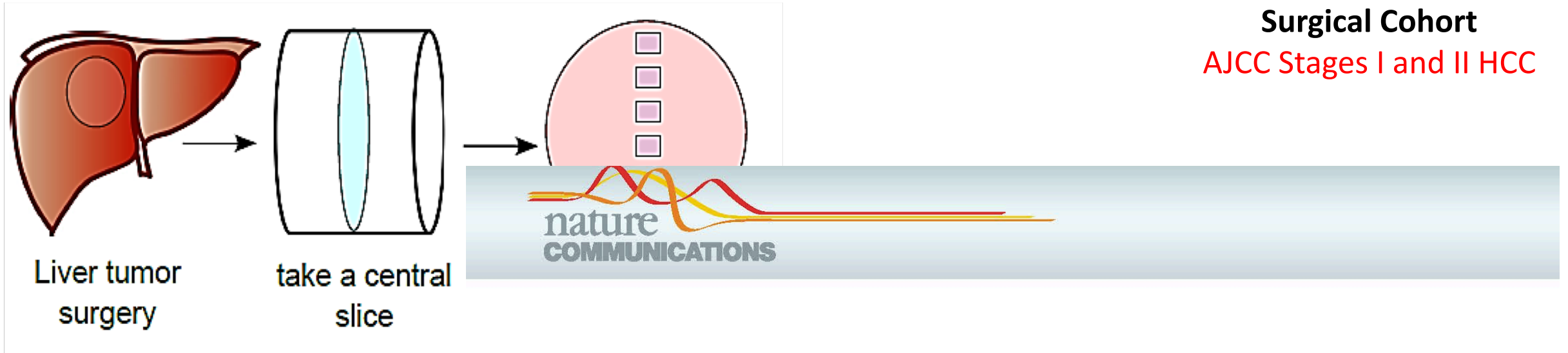
Asia Pacific HCC Registry
with AHCC Trials Group (AHCC08) and IQVIA

Branchytherapy in HCC:

- Concomitant delivery of radio-sensitizing and brachytherapeutic agents in HCC (with NTU)
- Radiation sensitization in a mouse xenograft hepatoma model (with Industry)

few cancers are homogeneous

A more rational approach to HCC



ARTICLE

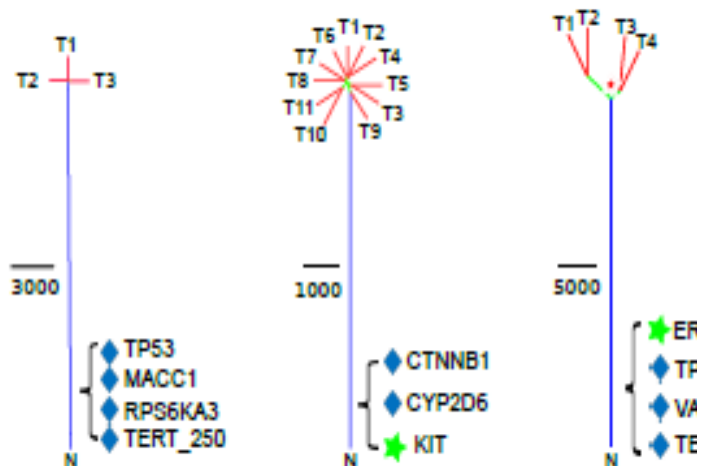
Received 11 Oct 2016 | Accepted 12 Jan 2017 | Published 27 Feb 2017

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 Phang³, Zenia Tiang¹, Peiyong Guan¹, Ming-Hwee Ng^{1,4}, Jia Qi Lim^{1,4}, Fei Yao¹, Zheng Li¹, Poh Yong Ng¹, Jie Yan¹, Brian K. Goh⁵, Alexander Yaw-Fui Chung⁵, Su-Pin Choo⁶, Chiea Chuen Khor¹, Wendy Wei-Jia Soon¹, Ken Wing-Kin Sung^{1,7}, Roger Sik-Yin Foo^{1,8,**} & Pierce Kah-Hoe Chow^{3,5,9,**}

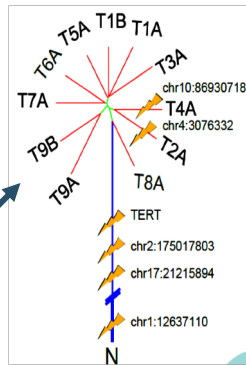
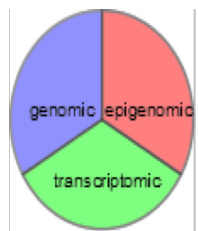


Project Title: **Precision Medicine in Liver Cancer across an Asia-Pacific NETWORK**

Collaborators

(AHCC07)

Genomic Heterogeneity



AIMS

1. To meet the pressing need for **efficacious drugs** in HCC
2. To bring **Precision Medicine** to patients with HCC

Clinical Trajectory and Translational Clinical Trial



Creation of representative pre-clinical models

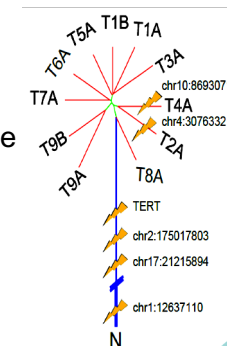
Recurrence
Biopsy or resection tissue samples, cfDNA, CTC

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



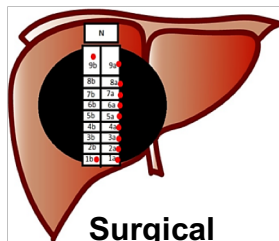
Application:

Therapeutics selected on the basis of discoveries in this study



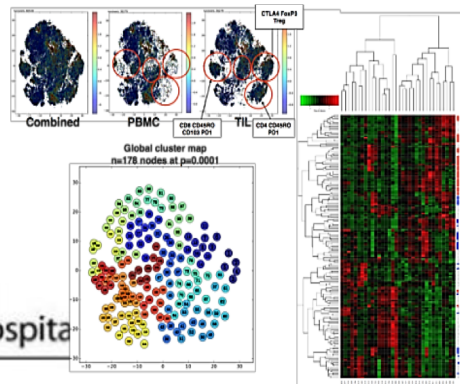
Translation: 180 patients, 6 Asia-Pacific Centers

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



Surgical Resection

Multi-region sampling



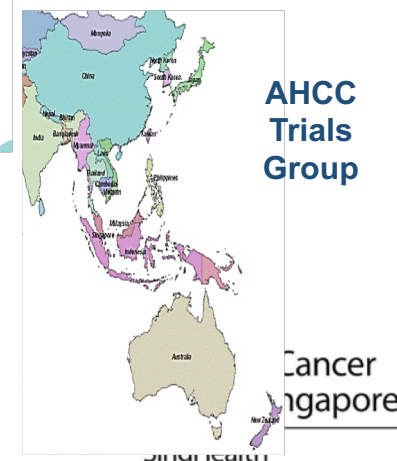
Metabolomics

Surgical resection & recurrence:
Collection of tissue, serum & urine metabolomics

Follow-up visits:
Collection of serum & urine metabolomics

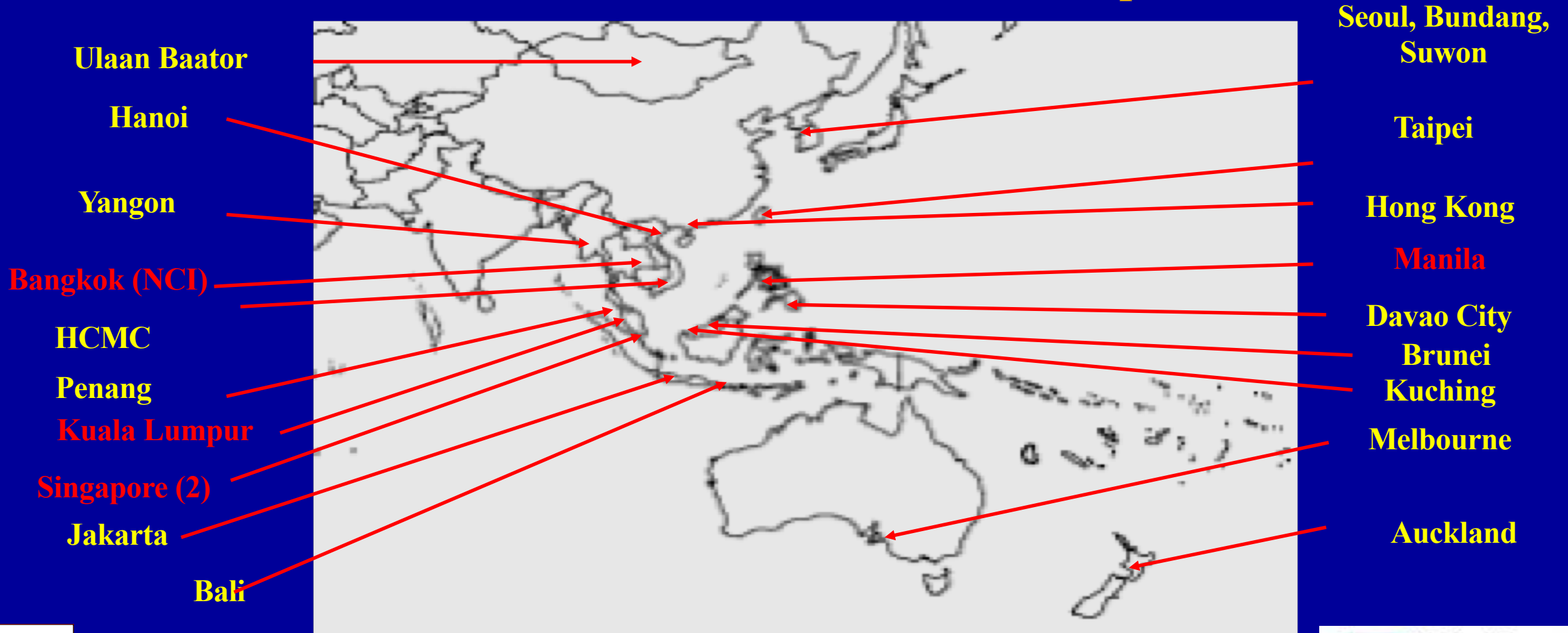
Immunomic Heterogeneity

Singapore General Hospital
SingHealth



AHCC07 - The PLANet Study 2019

Asia-Pacific HCC Trials Group



Sampling of HCC tumor

Tumour

Study Desc: CT Live
Series Desc: DE_Ver
11 - 26
Lossy

Version 1
2016

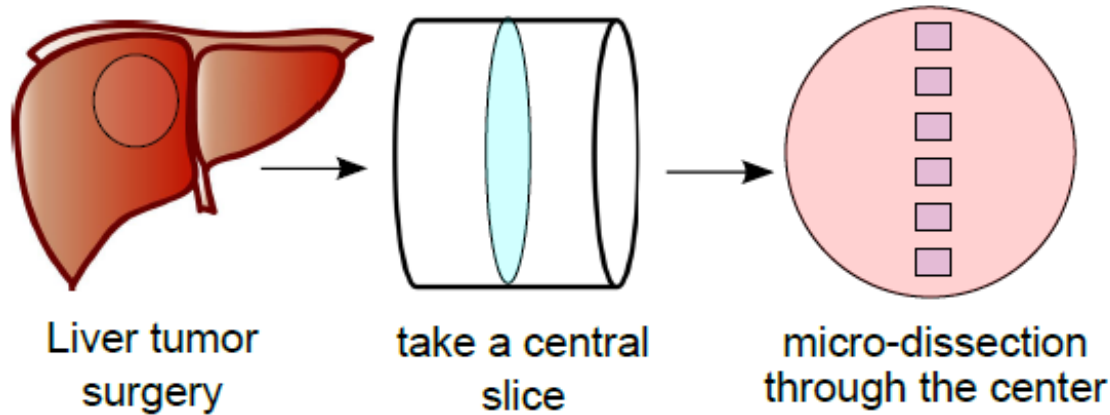


Highly integrated process
barrier to entry

Highly integrated process – sample collection involves surgeons, anesthetists, clinical oncologists, RAs, post-operative



A multi-layered –omics approach to Liver Cancer



Multi-region sampling

- **Genomics:** genome, transcriptome
- **Immunomics**
- **Epigenomics**
- **Metabolomics**
- **PDPs** and **PDX** models
- **Data integration** of the multi-omics layers

ARTICLE

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

DOI: 10.1038/ncomms14565 OPEN

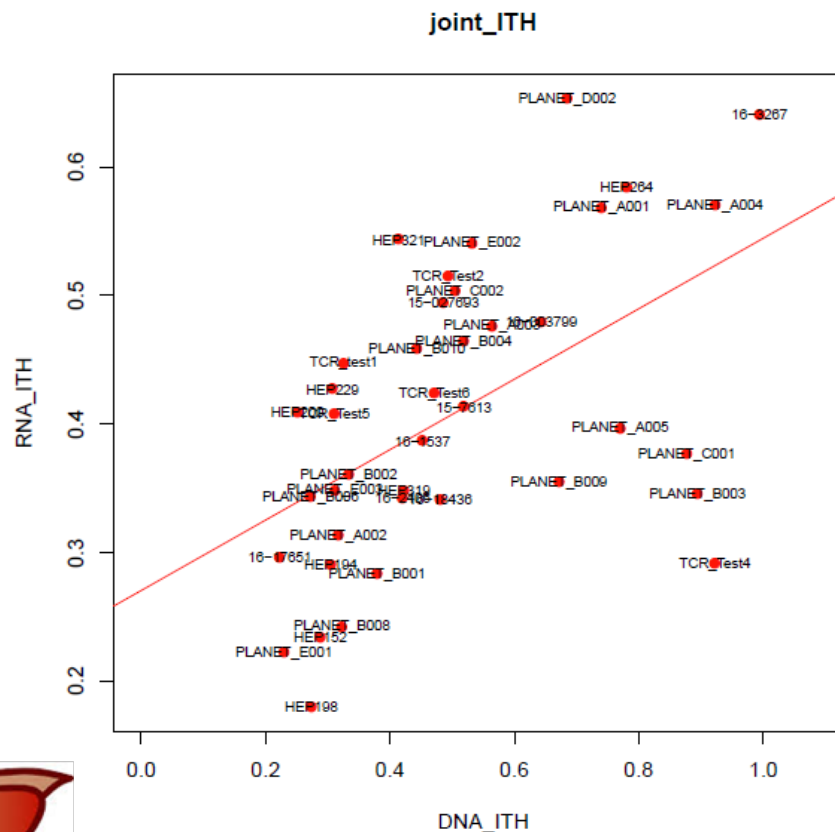
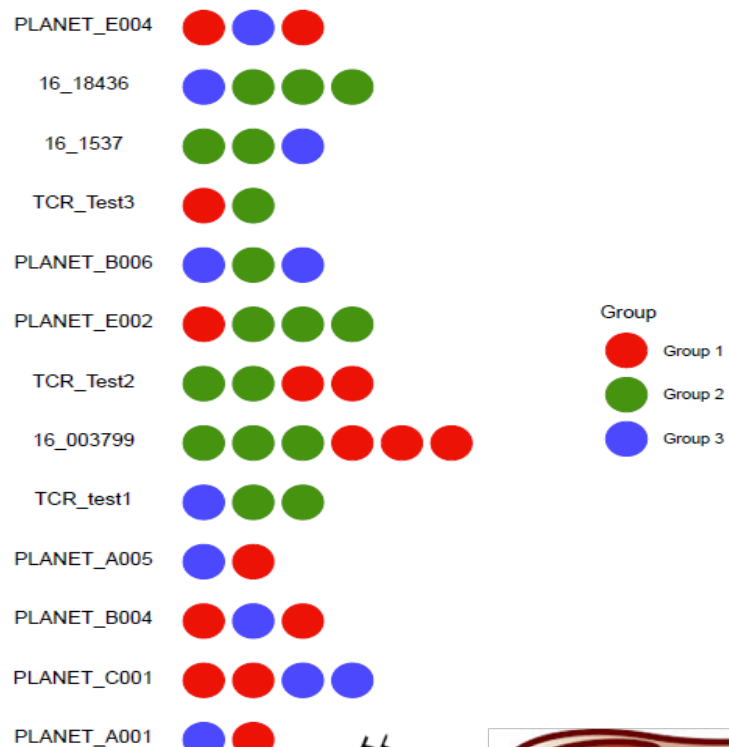
The spatial organization of intra-tumour heterogeneity and evolutionary trajectories of metastases in hepatocellular carcinoma

Weiwei Zhai^{1,***}, Tony Kiat-Hon Lim^{2,*}, Tong Zhang^{1,*}, Su-Ting Phang³, Zenia Tiang¹, Peiyong Guan¹, Ming-Hwee Ng^{1,4}, Jia Qi Lim^{1,4}, Fei Yao¹, Zheng Li¹, Poh Yong Ng¹, Jie Yan¹, Brian K. Goh⁵, Alexander Yaw-Fui Chung⁵, Su-Pin Choo⁶, Chiea Chuen Khor¹, Wendy Wei-Jia Soon¹, Ken Wing-Kin Sung^{1,7}, Roger Sik-Yin Foo^{1,8,**} & Pierce Kah-Hoe Chow^{3,5,9,**}

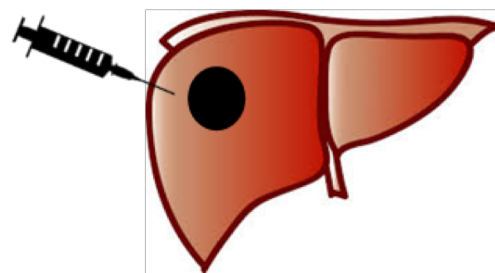
Zhai Nat Comm 2017

RNA mixed subgrouping and correlation with DNA heterogeneity

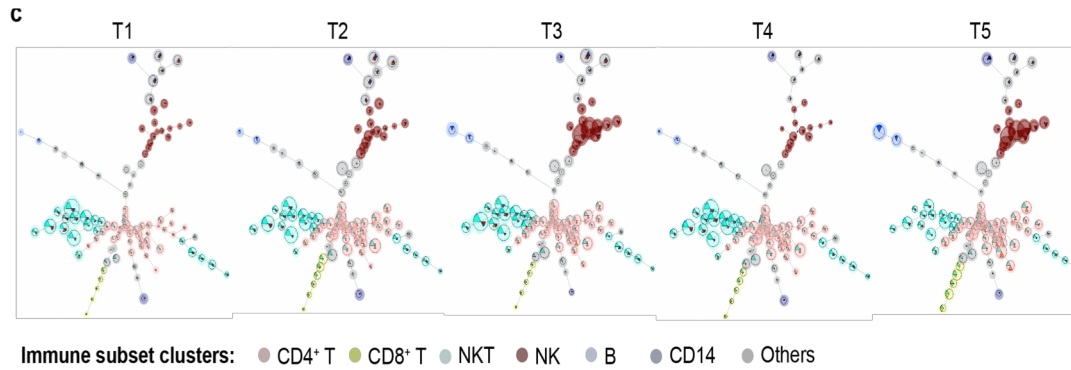
RNA subgrouping and mixing of subgroups



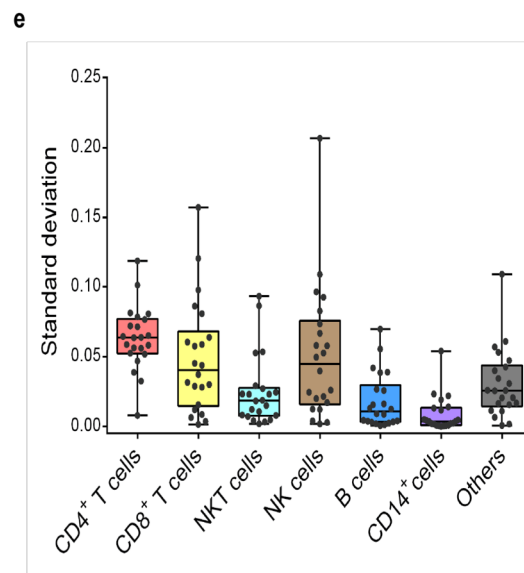
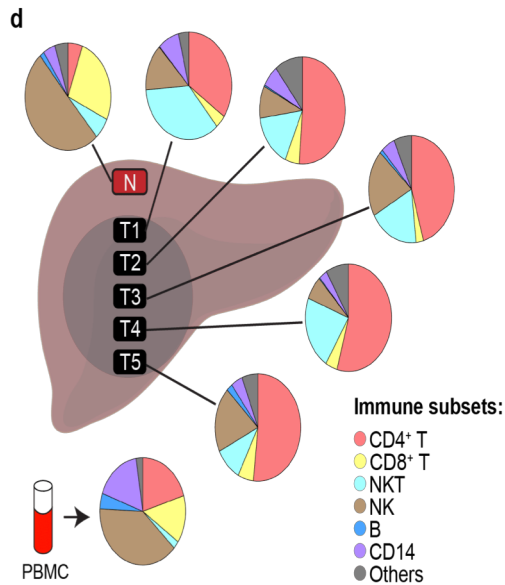
Dr Zhai Weiwei



Intra-tumoral Immunomics Heterogeneity in HCC



Intratumoral immune heterogeneity across different tumor sectors



Dr Valerie Chew



A Translational-Clinical Program addressing unmet needs in HCC

Multi-disciplinary
Multi-institution

Asia-Pacific Hepatocellular Carcinoma Trials Group (AHCC)

Comprehensive Liver Cancer Clinic (CLCC) and Clinical Databases

Laboratory for Translational Liver Research

Joint Lab in IMCB

Singapore Liver Cancer Consortium (SLCC)

Translation

Application

Development of an
Bio-artificial liver
platform for drug

Poor
understanding
of HCC biology

Microbiome and
NAFLD/NASH
(with LKCSM NTU)

NMRC TCR Flagship Program in Liver Cancer: Precision Medicine in Liver CaNcer across an Asia-Pacific Network. A Clinical-Multi-omics prospective study. The PLANET Program with AHCC Trials Group (AHCC07)

Onco-metabolites (with Chugai)

Circulating miRNAs (with MiRXES)

Radiogenomics
• Holmberg
• Bioinformatics
• Institute of High Performance

Absence of
validated
biomarkers

BMRC IAF-PP: A patient-specific diagnostic and predictive platform for precision medicine in HCC. The PuRPOSE Program with Samsung Medical Center, NUS, and A*STAR IMCB & GIS

MRI evaluation of liver health in cancer
(Perspectum Diagnostics)

Asia Pacific HCC Registry
with AHCC Trials Group (AHCC08) and IQVIA

Branchytherapy in HCC:

- Concomitant delivery of radio-sensitizing and brachytherapeutic agents in HCC (with NTU)
- Radiation sensitization in a mouse xenograft hepatoma model (with Industry)

Project Title: A patient-specific diagnostic and predictive platform for Precision Medicine in HCC
 First reliable and robust **patient-derived drug screening platform** in precision oncology

Collaborators



1) PDC Isolation and short-term culture



2) Drug response detection

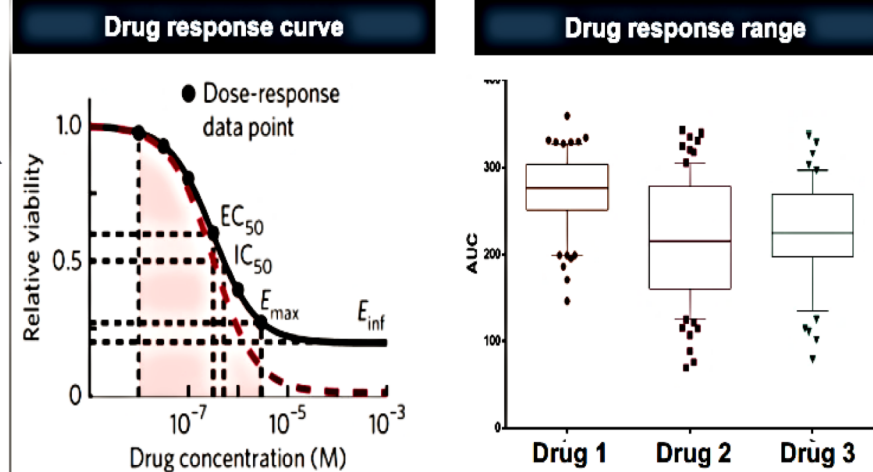


Sample ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
2	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
3	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
4	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
5	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
6	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
7	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
8	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
9	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
10	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
11	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
12	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
13	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
14	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
15	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
16	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
17	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
18	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
19	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
20	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100

Live cell detection
 >> drug response estimated

PerkinElmer 社
 EnVision (Medical device #14-1207, Korea)

3) Drug response analysis (AVATAMED)



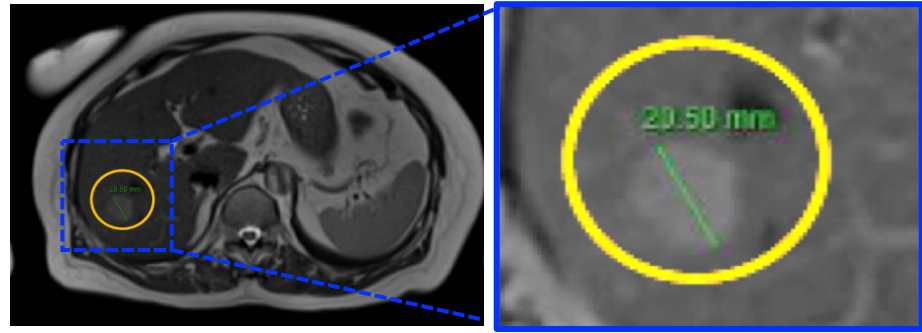
Proprietary AVATAR platform from Samsung:
 Very High throughput Platform
 – PDC Cultures and drug screens

Capabilities of the PuRPOSE Programme

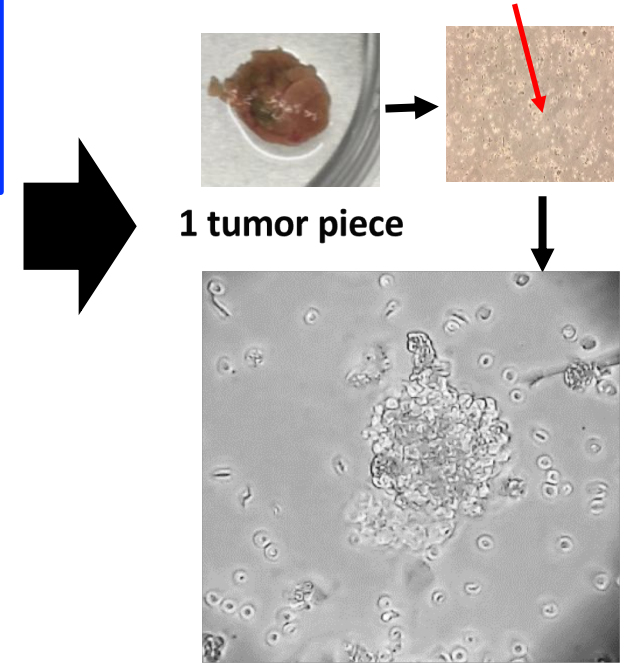
- ❖ Unique short-term cancer cell system
- ❖ Based on direct patient's cancer cells
- ❖ Streamlined sample processing
- ❖ Pharmacogenomics: Patient-Genome-Drug response
- ❖ High throughput drug screening platform
- ❖ Real-time drug response prediction
- ❖ Clinically relevant readouts of 3 to 4 weeks

CASE : AVATASCAN DATA FROM LIVER CANCER PATIENT

Nature of Operation	Case	OP Date	Code	Diabetic	HepB/C	Stage/Grade (histopathology)		Sex	Age	Tu. size (cm)	Tu Multiplicity	AFP level	Pre Treatment	PVTT	Recu.	Surgeon
						Stage	Grade									
Resection of Seg VI	HCC	04 /2018	HEP-468	Y	Non	TBA	TBA	F	70	2.0 (Seg VI)	1	248	No	No	No	Prof. Pierce Chow

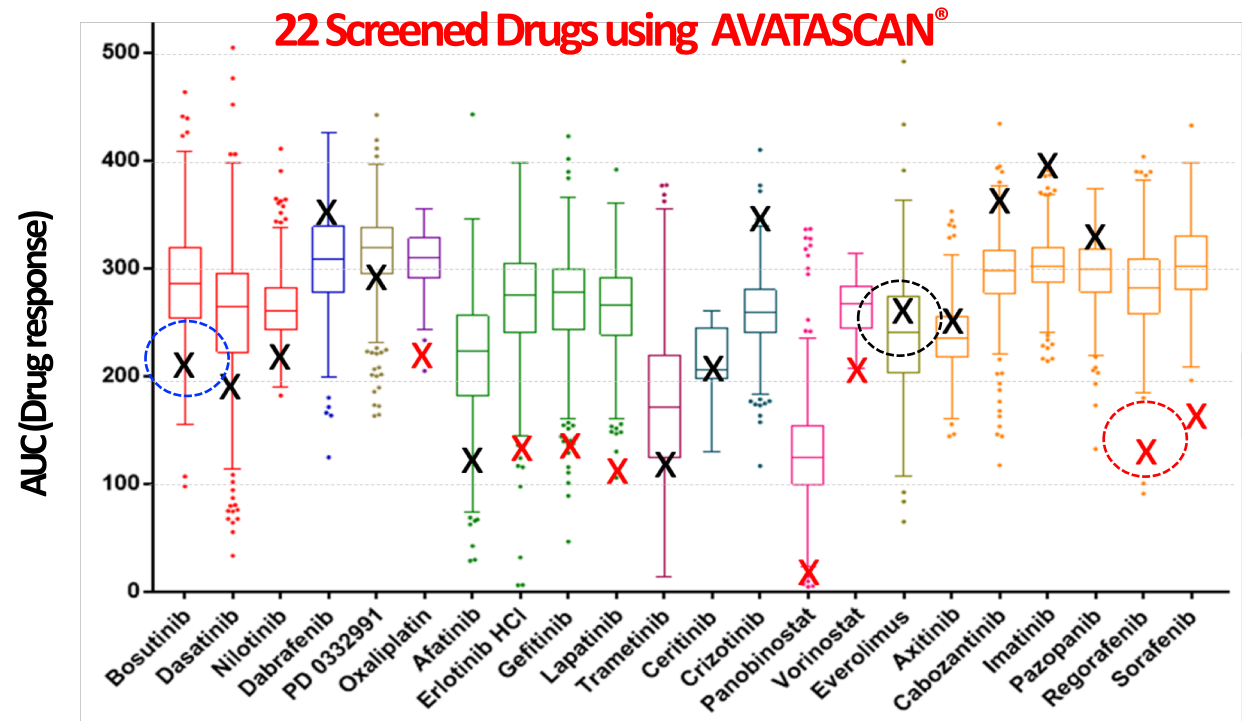


Patient derived Cancer Cells for drug screening

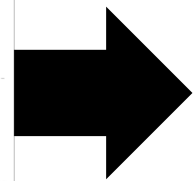


CASE 1 : AVATASCAN DATA FROM LIVER CANCER PATIENT

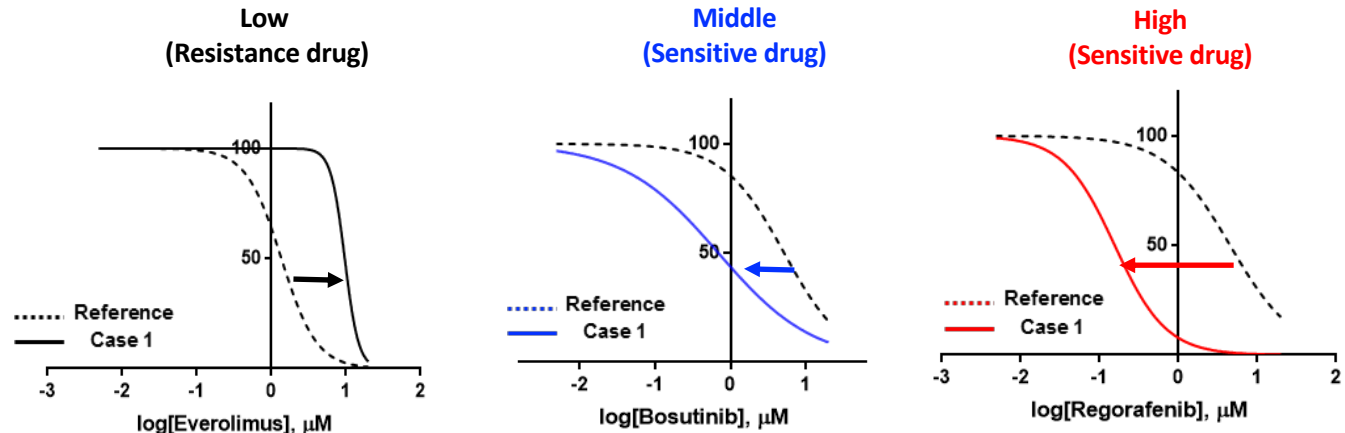
Best 8 Recommended Drugs



Ranking	Drugs	Target	FDA-approved
1	Lapatinib	EGFR	Breast cancer
2	Oxaliplatin	DNA synthesis	Colon, Rectal, Pancreatic cancer
3	Regorafenib	VEGFR/RAF-1 BRAF	Liver, Stromal tumours
4	Sorafenib	VEGFR/RAF-1 BRAF	Liver, Stromal tumours
5	Gefitinib	EGFR	Non-small cell lung cancer (NSCNC)
6	Erlotinib	EGFR	Pancreatic cancer, NSCLC
7	Panobinostat	HDAC	Multiple myeloma and other plasma cell neoplasms
8	Vorinostat	HDAC	Non-Hodgkin Lymphoma



versus Current Standard of Care for ALL liver cancer patients



Ranking	Drugs	Target	FDA-approved
1	Sorafenib	VEGFR/RAF-1 BRAF	Liver, Stromal tumours
2	Lenvatinib	VEGFR/RAF-1 BRAF	Liver, kidney

A Translational-Clinical Program addressing unmet needs in HCC

Multi-disciplinary
Multi-institution

Asia-Pacific Hepatocellular Carcinoma Trials Group (AHCC)

Comprehensive Liver Cancer Clinic (CLCC) and Clinical Databases

Laboratory for Translational Liver Research

Joint Lab in IMCB

Singapore Liver Cancer Consortium (SLCC)

Translation

Application

Development of an
Bio-artificial liver
platform for drug

Poor
understanding
of HCC biology

Microbiome and
NAFLD/NASH
(with LKCSM NTU)

NMRC TCR Flagship Program in Liver Cancer: Precision Medicine in Liver CaNcer across an Asia-Pacific Network. A Clinical-Multi-omics prospective study. The PLANET Program with AHCC Trials Group (AHCC07)

Onco-metabolites (with Chugai)

Circulating miRNAs (with MiRXES)

Radiogenomics
• Holmberg
• Bioinformatics
• Institute of High Performance

Absence of
validated
biomarkers

BMRC IAF-PP: A patient-specific diagnostic and predictive platform for precision medicine in HCC. The PuRPOSE Program with Samsung Medical Center, NUS, and A*STAR IMCB & GIS

MRI evaluation of liver health in cancer
(Perspectum Diagnostics)

Branchytherapy in HCC:

- Concomitant delivery of radio-sensitizing and brachytherapy (with NTU)
- Radiation sensitization in a mouse xenograft hepatoma

Limited HCC
data in the
Asia-Pacific

**Asia Pacific HCC Registry
with AHCC Trials Group (AHCC08) and IQVIA**



ClinicalTrials.gov identifier: NCT03233360

China

- Nanjing Baiyi Hospital, NJB
- Zhongshan Hospital, Fudan University Shanghai, ZSH
- Beijing Cancer Hospital, BCH
- Guangxi Medical University Cancer Centre, GXM
- Second Affiliated Hospital Zhejiang University School of Medicine, SAH
- Harbin Medical University Cancer Hospital, HMU

South Korea

- Samsung Medical Center, SSM
- Ajou University Hospital, AUH
- Asan Medical Centre, AMK
- Korea University Anam Hospital, KUA
- Seoul National University Bundang Hospital, SNU
- Severance Hospital, Yonsei University College of Medicine, SYH
- St Mary's Hospital, SMH
- St Vincent Hospital, Catholic University Medical College, SVH

Japan

- Kyorin University School of Medicine, KUM
- University of Tokyo, UTJ
- Kinki University Hospital, KKU
- National Cancer Centre, NCI
- National Center of Global Health and Medicine, NCM

Taiwan

- National Taiwan University Hospital, NTU
- Taipei Veterans General Hospital, TVG
- Chang Gung Memorial Hospital – KS, CGM
- China Medical University Hospital, CMU
- National Cheng Kung University Hospital, NCK

Thailand

- Siriraj Hospital, Mahidol University, SHM
- National Cancer Institute, NCI
- Chulabhorn Hospital, CHH

Singapore

- National Cancer Centre, NCS
- Singapore General Hospital, SGH
- National University Hospital, NUH

Hong Kong

- Queen Mary Hospital, QMH

Australia

- Royal Prince Alfred Hospital, RPA
- Flinders Medical Centre, FMC
- Royal Adelaide Hospital, RAH

New Zealand

- Auckland City Hospital, ACH

Aim

To address the need for a complete longitudinal picture of HCC in the real world with **clinical, associated health costs** and **patient reported outcomes** data.

Background

Significant limitations on currently available information on HCC as they **do not represent real world data** e.g.:

- *Randomized controlled trials*
- *Cases series from tertiary clinical centers*

Real world data on the presentation, clinical trajectory and management of HCC in the Asia-Pacific must be prospectively collected on the ground in order to develop effective **public health strategies** and provide direction to the **development of therapeutics**.

Design: **investigator-initiated multi-country cohort study** of patients newly diagnosed with HCC.

Sample size of **2,500** patients from **9 countries**.

Status

Total of **34 sites**.

Leveraging on our Strengths : Singapore

Hospitals

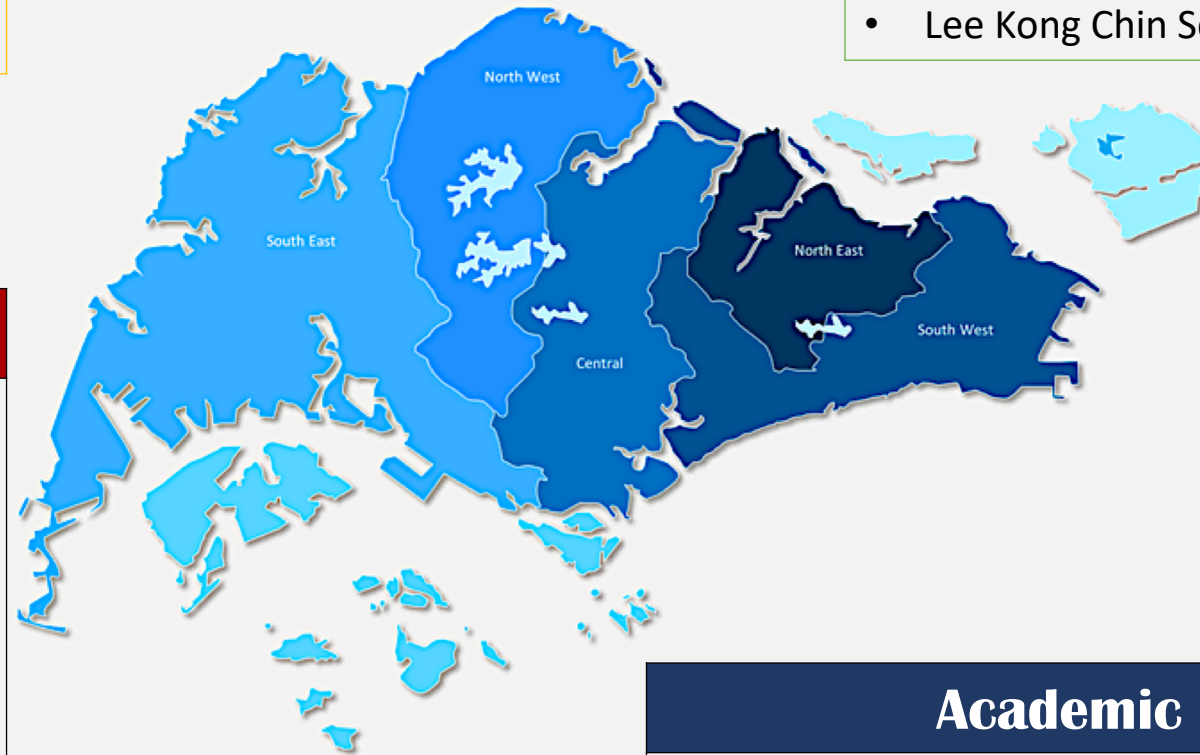
- National Cancer Centre Singapore
- Singapore General Hospital
- National University Hospital

Academic Institutions

- Duke-NUS Medical School
- Yong Loo Lin School of Medicine, NUS
- Lee Kong Chin School of Medicine, NTU

Research Institutes

- Genome Institute of Singapore
- Institute of Molecular and Cell Biology
- Singapore Bioimaging Consortium
- Bioinformatics Institute
- Institute of High Performance Computing
- SingHealth Translational Immunology Inflammation Centre
- Singapore Phenome Centre
- Cancer Science Institute of Singapore



Academic CRO

- Singapore Clinical Research Institute

Leveraging on our Strengths : Asia-Pacific



▣ Asia-Pacific
▣ Hepatocellular Carcinoma
▣ Trials Group



AHCC Trials Group's General Meeting 2018

THANK YOU!



Together
For A
Cancer-Free
Tomorrow



Contact:

Prof Pierce Chow

Pierce.chow.k.h@singhealth.com.sg

