

The Changing Face of Biomedical Research and What This Means for the Clinician Scientist: *The Example of Liver Cancer*

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NMRC Senior Clinician Scientist

RESEARCH SYMPOSIUM 2017

8th March 2017, Grand Copthorne Singapore



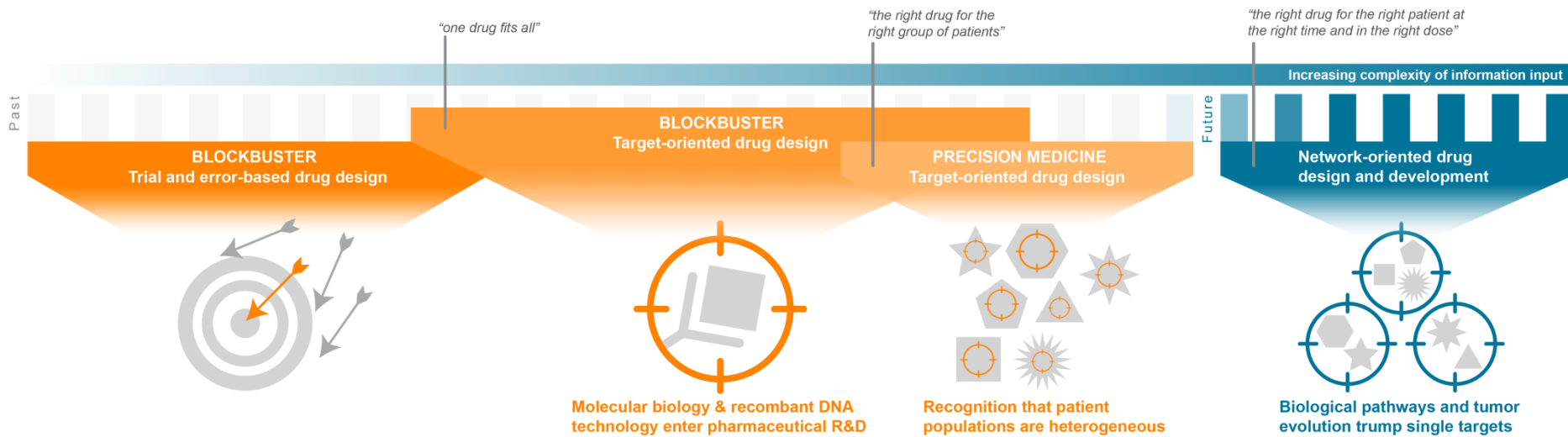
SGH – Surgery



National Cancer
Centre Singapore
SingHealth

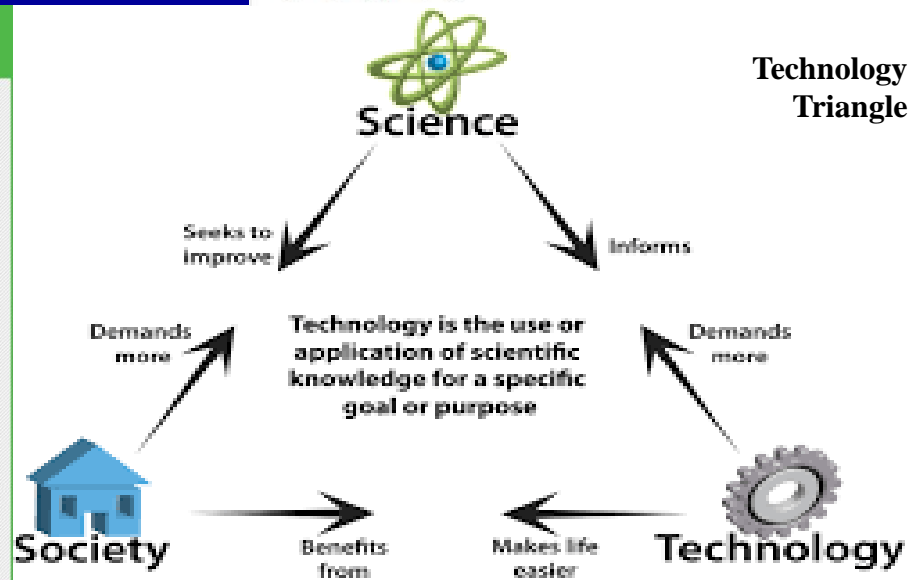
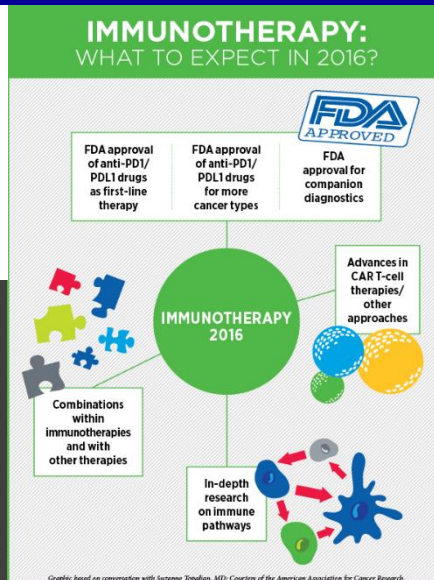
Opportunities and Challenges

- We are in a *fortunate era* in medical history
- In slightly more than a single generation, medicine has evolved from an (mostly) *intuitive art* to *empirical science* to (almost) *precision medicine*



A Vastly Changing Landscape

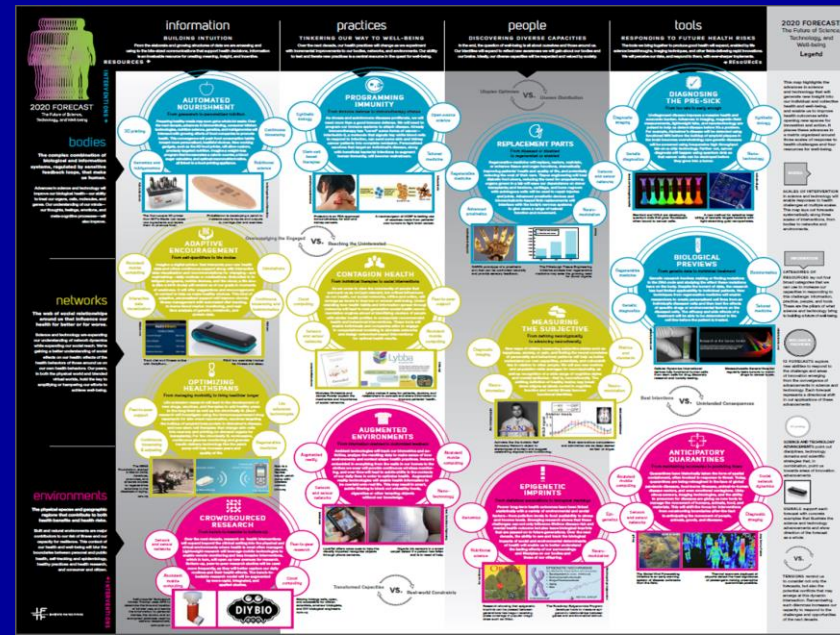
- Advances in the recent 2 decades not been only in Biomedical Science but also in the: *physical, computational, behavioral and social sciences.*
- These sciences have integrated



Transformation

- Concurrent advances in the sciences have transformed the nature of the **biomedical landscape** and impact:
 - on the way biomedical research is conducted and funded
 - on the evolving role of the clinician scientist

Will be challenging for traditionally structured research programs to adapt



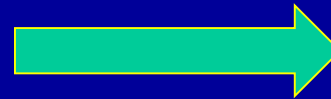
How we learnt to do research

Hypothesis-driven paradigm

**Research carried out by
PI / small research group**

- Single discipline
- Single laboratory
- Single institution

Hypothesis



Biological question

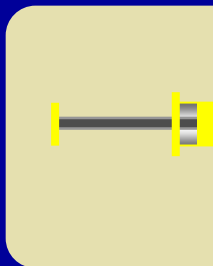
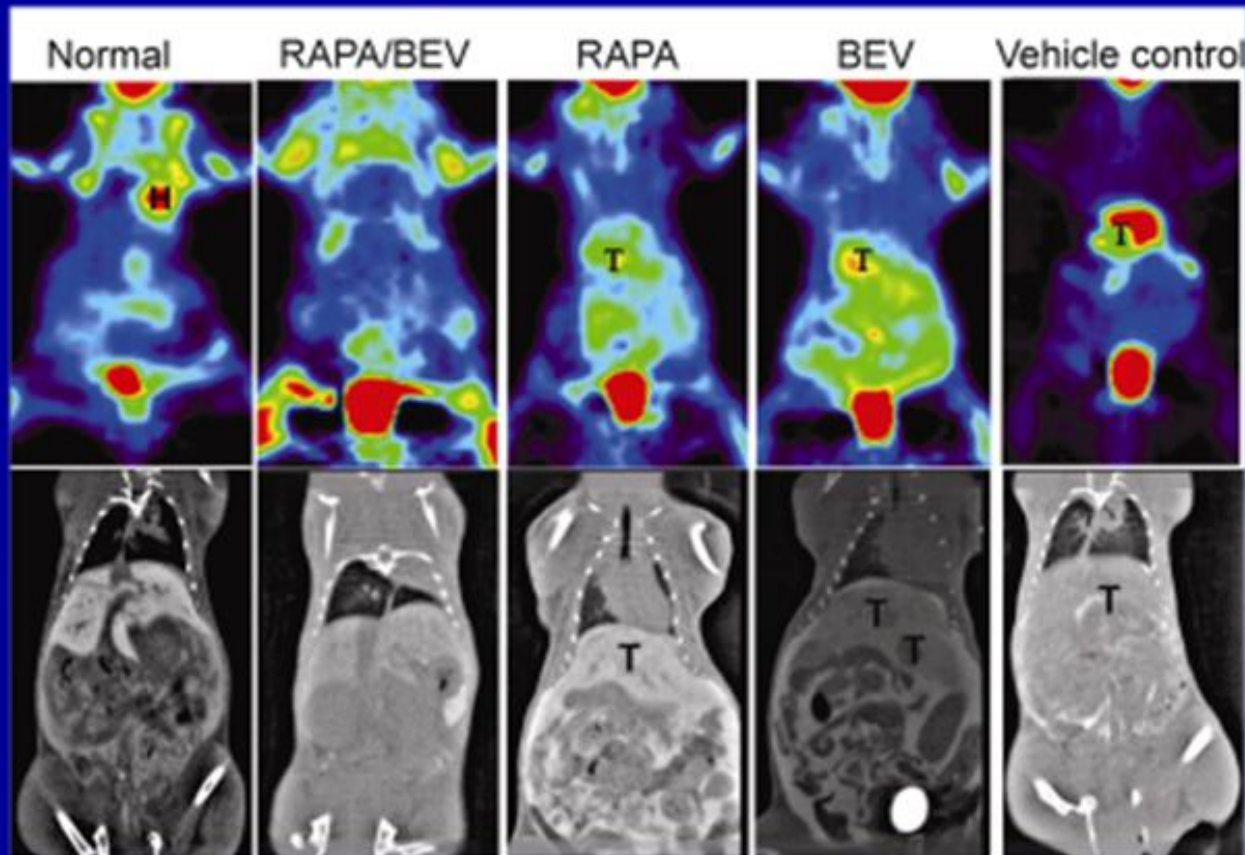
- Hypotheses come from hunches and educated guesses
- The research seeks to establish Cause and Effect
- Experiments are designed to validate hypotheses

Hypothesis Driven Research in Liver Cancer



Obtain
usually c
Bio Res

Pre-clinical study → Phase I/II Clinical Trial at NCC



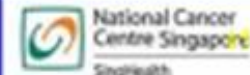
5 – 8 m
tumors



SGH – Surgery



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Experiments to Validate Hypotheses



© The Author(s), 2009
Published Online: 28 March 2009

Mol Imaging Biol (2009) 11:001–010

DOI: 10.1007/s11307-009-0001-0

Cancer Chemother Pharmacol (2009) 63:1007–1016

DOI 10.1007/s00280-008-0802-y

ORIGINAL ARTICLE

RESEARCH ARTICLE

Effective Inhibition of Xenografts of Hepatocellular Carcinoma (HepG2) by Rapamycin and Bevacizumab in an Intrahepatic Model

Lai-Chun Ong,¹ In-Chin Song,¹ Yi Jin,¹ Irene H. C. Kee,¹ Eeyan Siew,¹ Sidney Yt Choon-Hua Thng,² Hung Huynh,² Pierce K. H. Chow^{1,2,3,4}

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³Duke-NUS Graduate Medical School, Singapore, Singapore

⁴Department of General S

Research Article

Abstract
Purpose
depend
approac
tomogra
vascula
an ortho
Procedu
suspens
rapamyc
a VEGF
Results:
(F-18)-fl
uptake
marked
BEV gr
Conclus
potentia

Dovitinib demonstrates antitumor and antimetastatic activities in xenograft models of hepatocellular carcinoma

Hung Huynh^{1,*}, Pierce Kah Hoe Chow², Wai Ming Tai³, Su Pin Choo³, Alexander Yaw Fui Chung², Hock Soo Ong², Khee Chee Soo¹, Richard Ong¹, Ronald Linnartz⁴, Michael Ming Shi⁴

¹Laboratory of Molecular Endocrinology, Division of Molecular and Cellular Research, National Cancer Centre, Singapore; ²Department of General Surgery, Singapore General Hospital, Singapore; ³Department of Medical Oncology, National Cancer Centre, Singapore; ⁴Oncology Translational Medicine, Novartis Pharmaceuticals Corporation, NJ, USA

Background & Aims: Hepatocellular carcinoma (HCC) is the third leading cause of cancer death. Although sorafenib has been shown to improve survival of patients with advanced HCC, this improvement is modest and patients eventually have refractory disease. This study aims at investigating the antitumor, antian-

Introduction

HCC is the fifth most common malignancy and the third leading cause of cancer-related mortality globally [1]. More than 80% of HCCs are discovered late in stage when surgery is not an option compared to the first two groups with IC₅₀ ranges of 0.1 to >400, 131 to >400, 138 to >400 and 360.85 to >400 μM,

Studies of structure–activity relationship on plant polyphenol-induced suppression of human liver cancer cells

Jacky Loa · Pierce Chow · Kai Zhang

Received: 23 March 2008 / Accepted: 10 July 2008 / Published online: 3 September 2008
© Springer-Verlag 2008

Abstract



chalcone, 2,2'-dihydroxychalcone could induce G2/M arrest then apoptosis of the cancer cells.

clusions An analysis of structure–activity relationship showed that following structures are required for their biotory potencies on human liver cancer cells: (1) of the sub-classes of the polyphenols tested, the unique back-: structure of chalcones with a open C-ring; (2) within chalcone group, hydroxyl substitution at 2'-carbon of ng; (3) hydroxyl substitution at 3'-carbon in B-ring of ones. However, some other structures were found to ease their potencies: e.g. substitutions by sugar moie-in flavones. These data are valuable for design and ification of new polyphenols, which could be potential proliferative agents of cancer cells.

words Plant polyphenols · Liver cancer · cancer activity: apoptosis · G2/M arrest · 2,2'-hydroxychalcone

roduction

motherapy has still been an important treatment modal-or cancers. However, toxicity and poor tolerance to cur-chemotherapeutic drugs are dose-limiting factors. This led to a rising interest in developing anticancer drugs 1 relatively non-toxic sources. Plant polyphenols are one such example. They are relatively non-toxic natural products [1] found in normal diets [2] and herb medicines



SGH

How we do Clinical Trials

Hypothesis-driven paradigm

- Conventional Phase III trials:

- Study therapy versus comparator

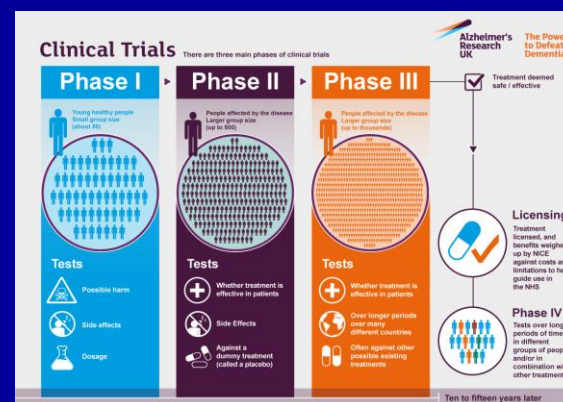
- Null-hypothesis

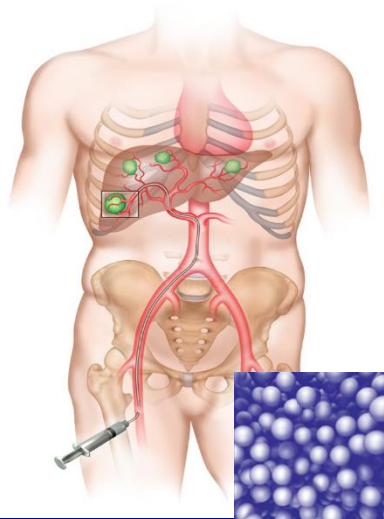
- Heterogeneous populations

- Not selected on the basis of mechanisms/biomarkers

- Depends on measuring statistical differences to elucidate meaning

- Large number of patients require





AHCC06 : SIRT versus Sorafenib in patients with locally advanced HCC (SirveNIB)

Phase III, open-label, randomised-controlled study

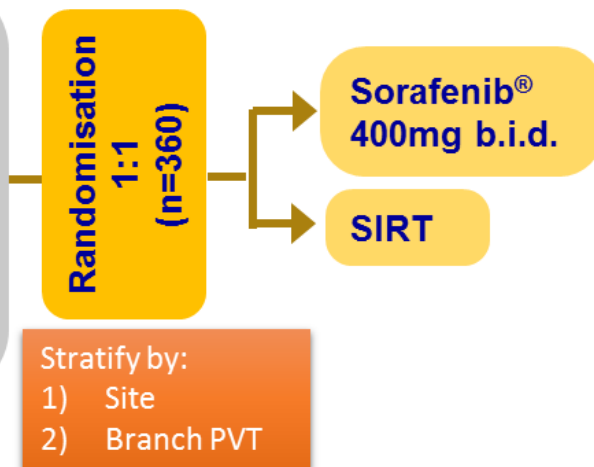


Eligibility criteria

- Locally advanced HCC
- Child-Pugh ≤ 7 pts
- ECOG PS 0 – 1

Exclusion criteria

- Distant metastases
- Main portal vein thrombosis



Endpoints

Primary

- OS

Secondary

- Progression Free Survival in Liver
- Progression Free Survival at any Site
- Tumour Response Rate (liver \pm any site)
- Toxicity and Safety
- Quality of Life
- Liver Resection Rate
- Liver Transplantation Rate
- Time to Disease Progression

ECOG PS = Eastern Cooperative Oncology Group Performance Status

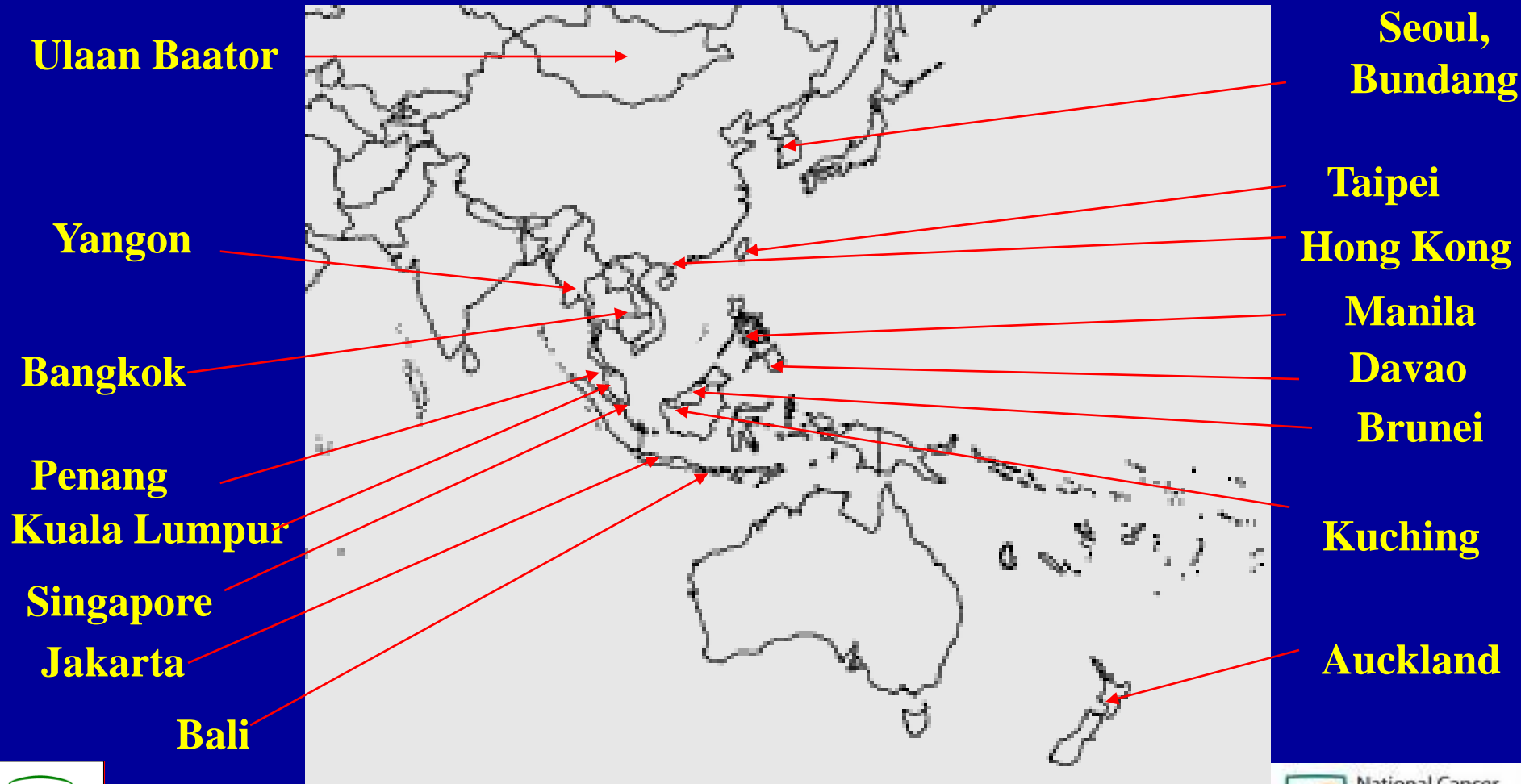
OS = overall survival; TTP = time to tumour progression

A phase III multi-center open-label randomized controlled trial that compares the efficacy of two therapies (**SIRT** versus **Sorafenib**) in the management of **locally advanced hepatocellular carcinoma**. 23 sites, 11 countries



Asia-Pacific HCC Trials Group 2016

SIRveNIB



Disruptor - High Throughput Technology

Automation

- Less manpower required
- shorter turnover time

Output

- Genomics
- Immunomics
- Proteomics
- Metabolomics
- Imaging

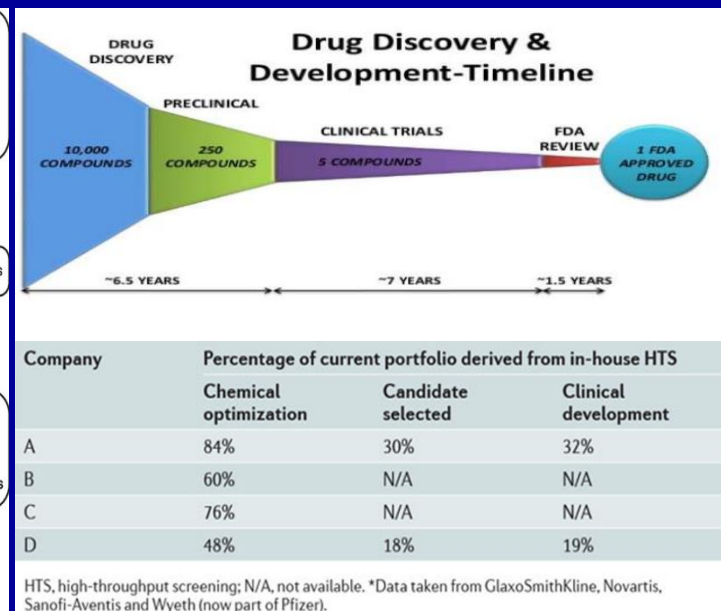
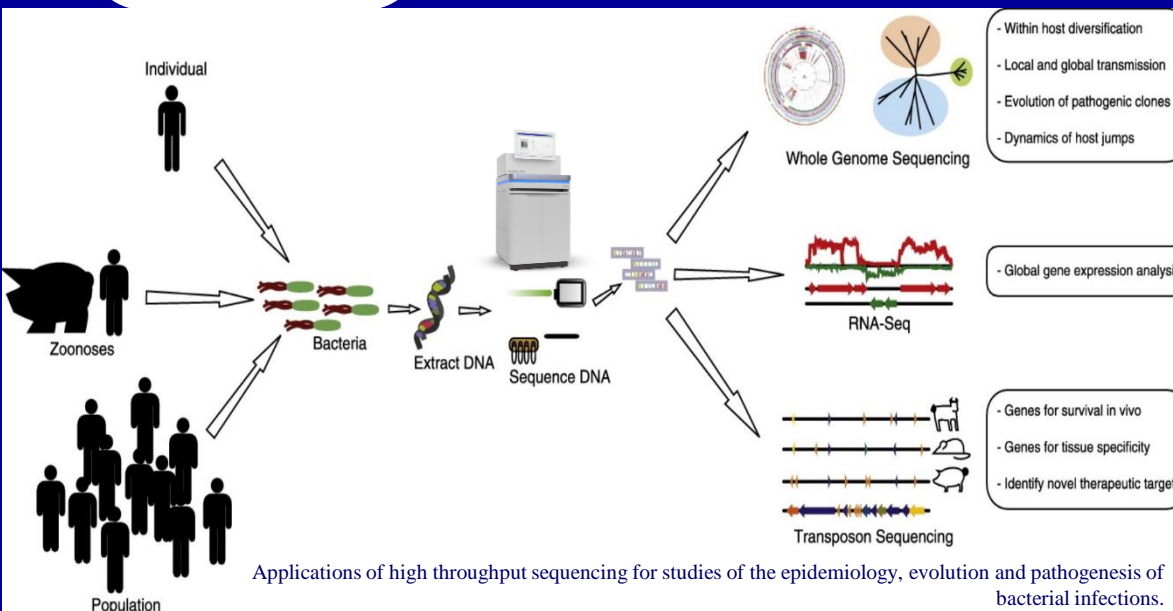
Storage of Large amount of data

Computational expertise required

Bioinformatics

Patterns

Periodicities

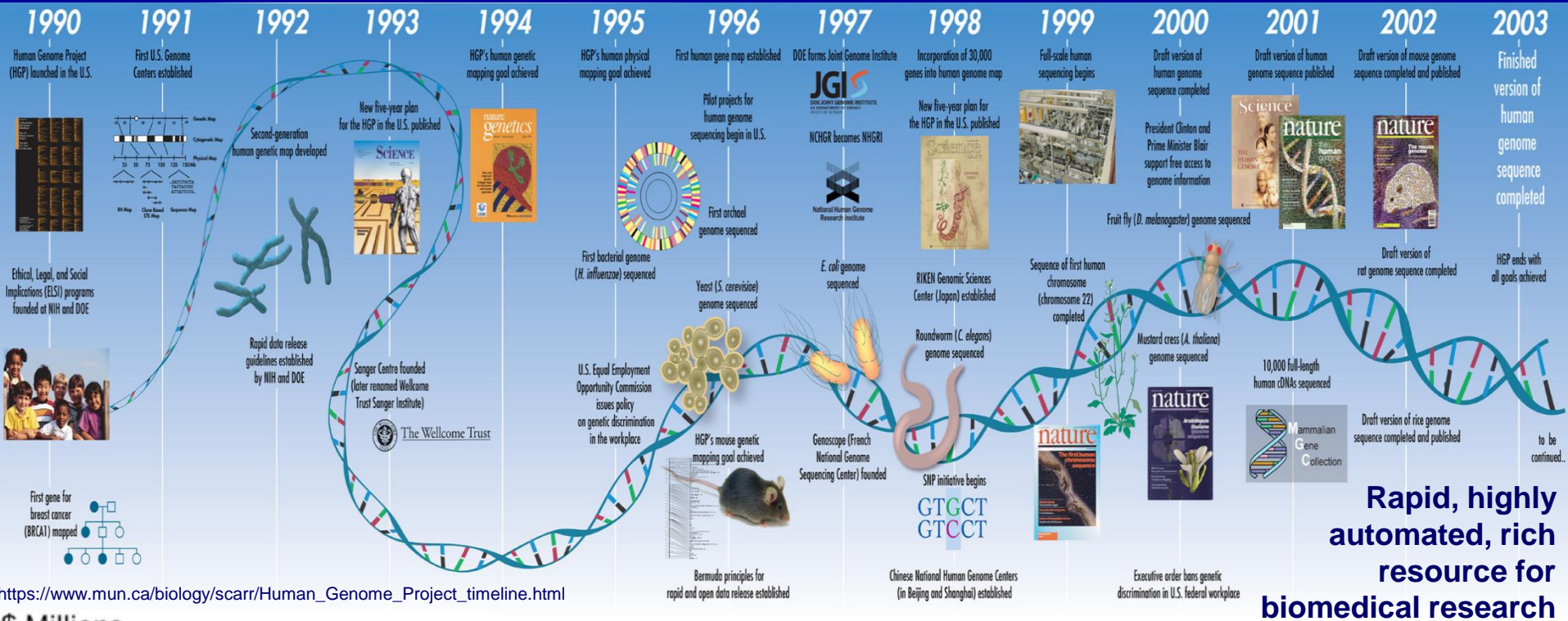


Adapted from McAdam et al. Current Opinion in Microbiology 2014, 19:106-113

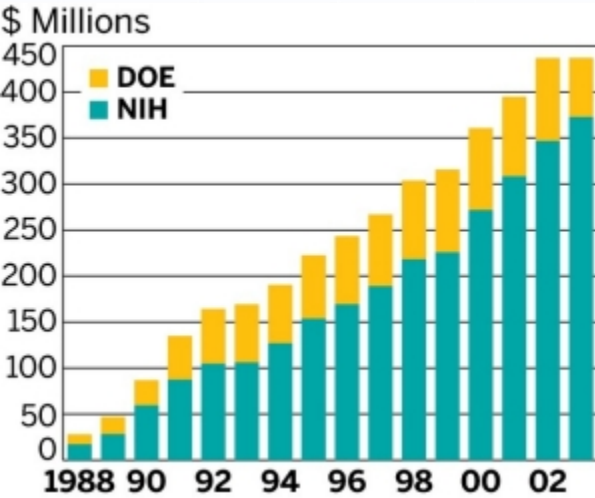
SGH - Surgery

Adapted from Macarron et al. Nature Reviews Drug Discovery 10, 188-195 (March 2011)

Human Genome Project



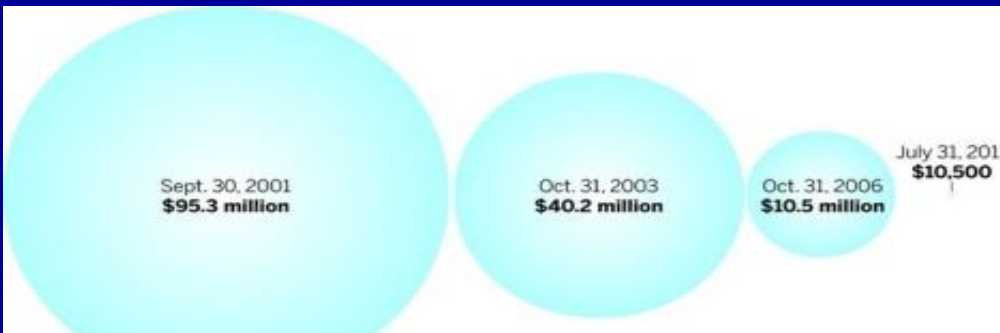
https://www.mun.ca/biology/scarr/Human_Genome_Project_timeline.html



BUDGET CLIMB
Over the course of the Human Genome Project, funding climbed steadily.

Credit: Department of Energy

PLUMMETING PRICES The cost of genomic sequencing fell sharply as the Human Genome Project advanced. - \$1000/sequence



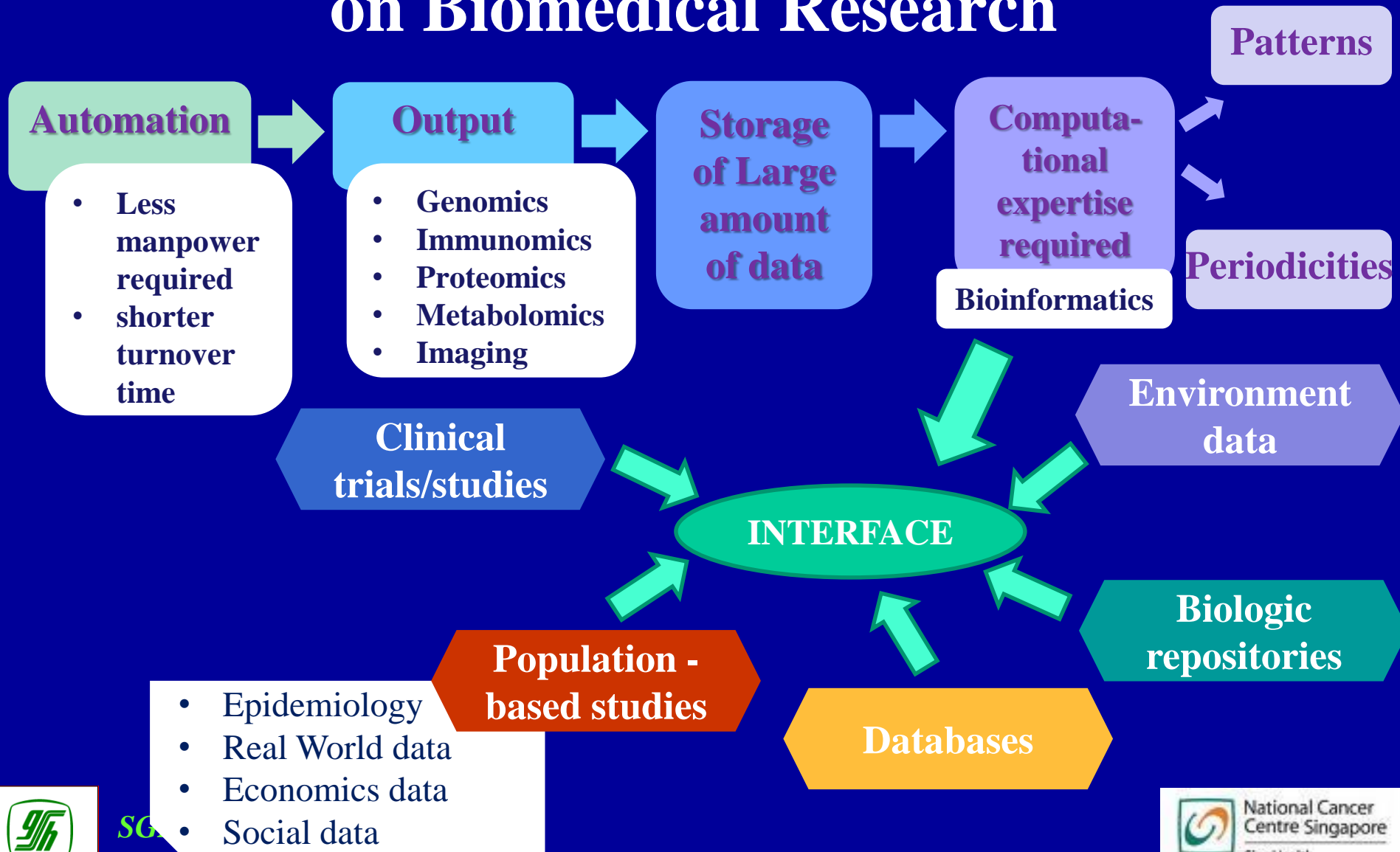
Credit: National Human Genome Research Institute

“Big Science” - Human Genome Project

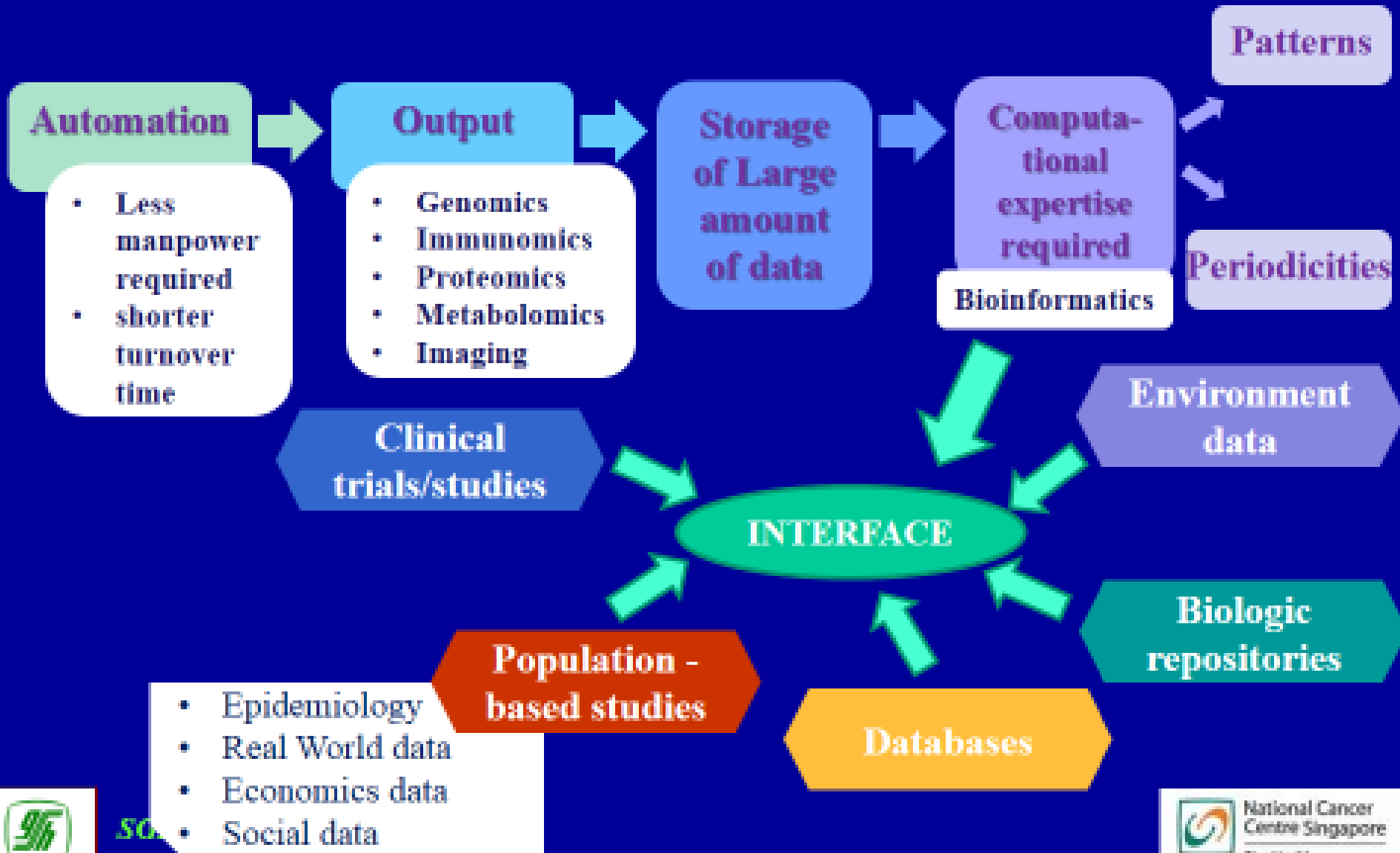
How do we transform the massive amount of information generated to biologically-meaningful discoveries?

- ↳ **Function of genes**
- ↳ **Regulatory dynamics of cells**
- ↳ **Structural genomics**
- ↳ **Proteomics**
- ↳ **Population-based studies**
 - *Epidemiology*
 - *Genotypic data*
 - *Phenotypic data*

The Impact of Technology on Biomedical Research

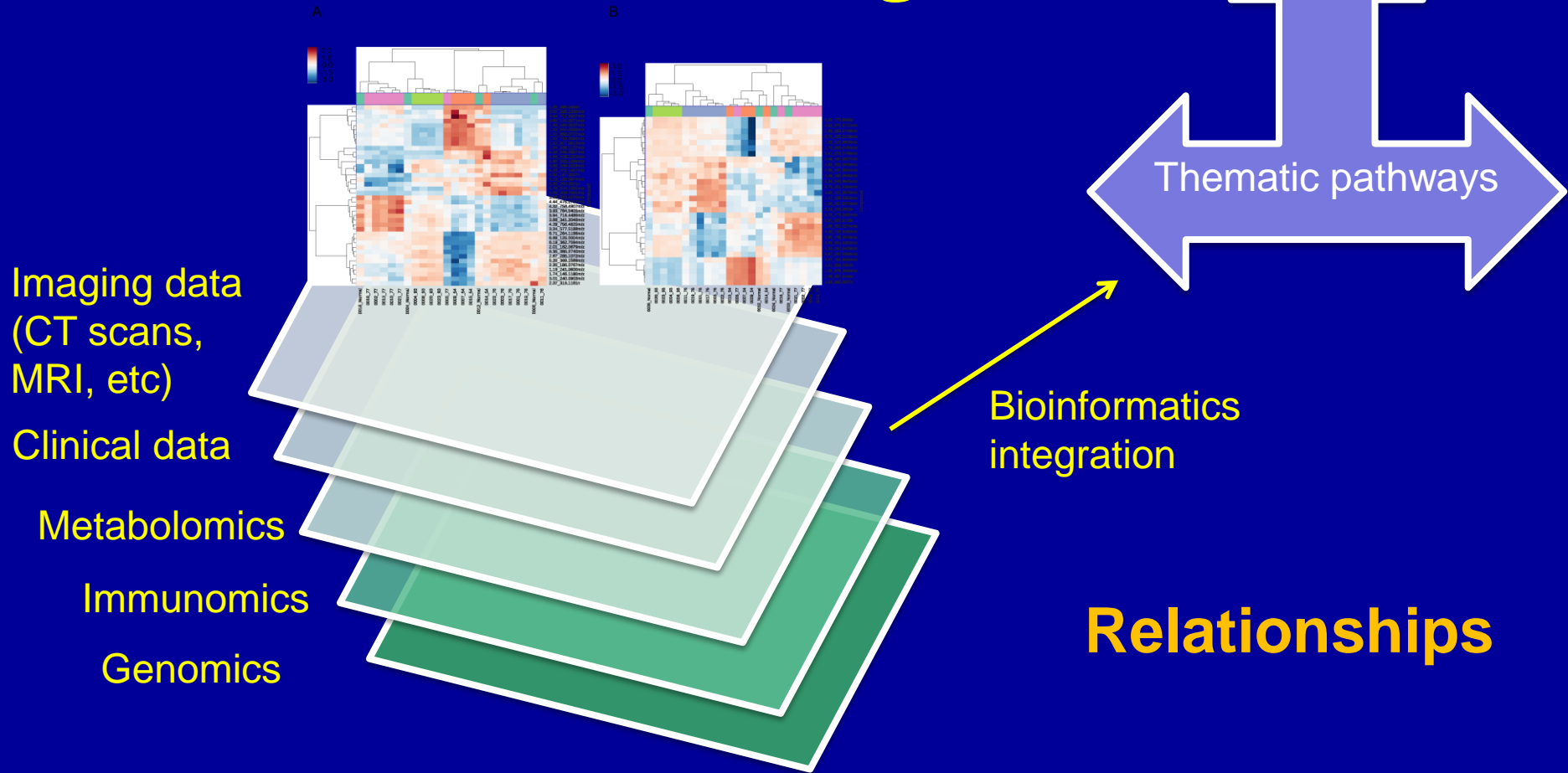


Biology is becoming an Information Science

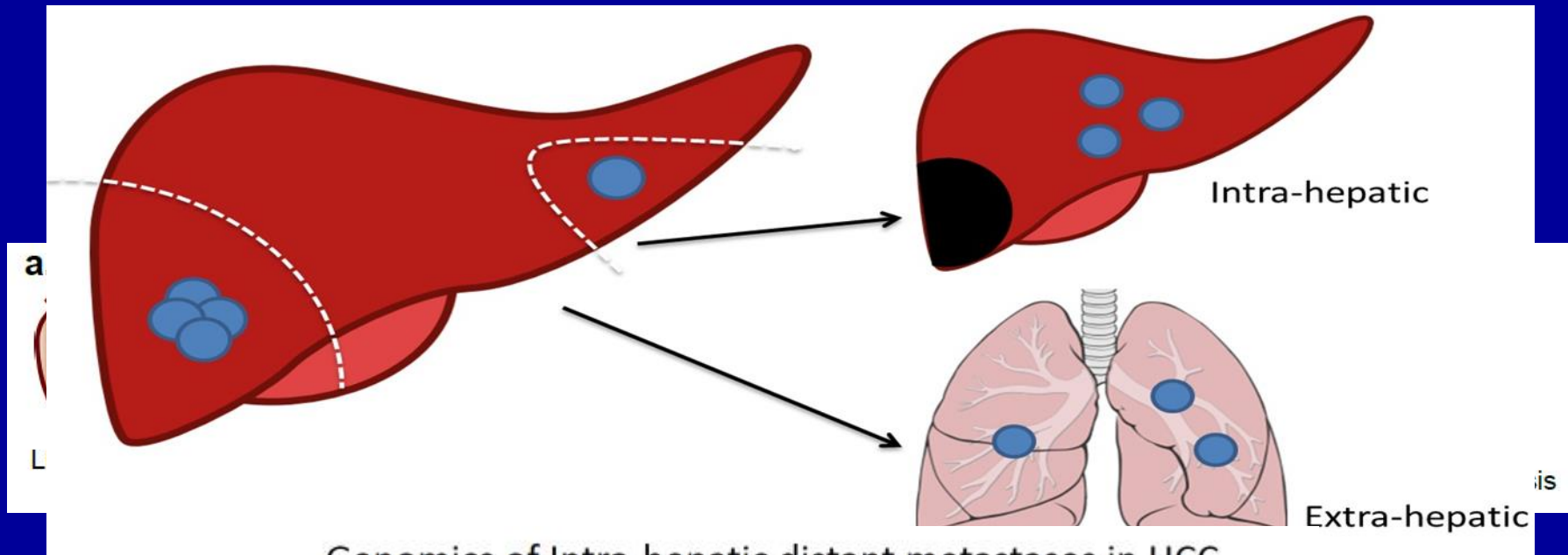


Big Data Approach

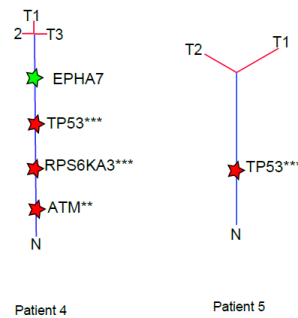
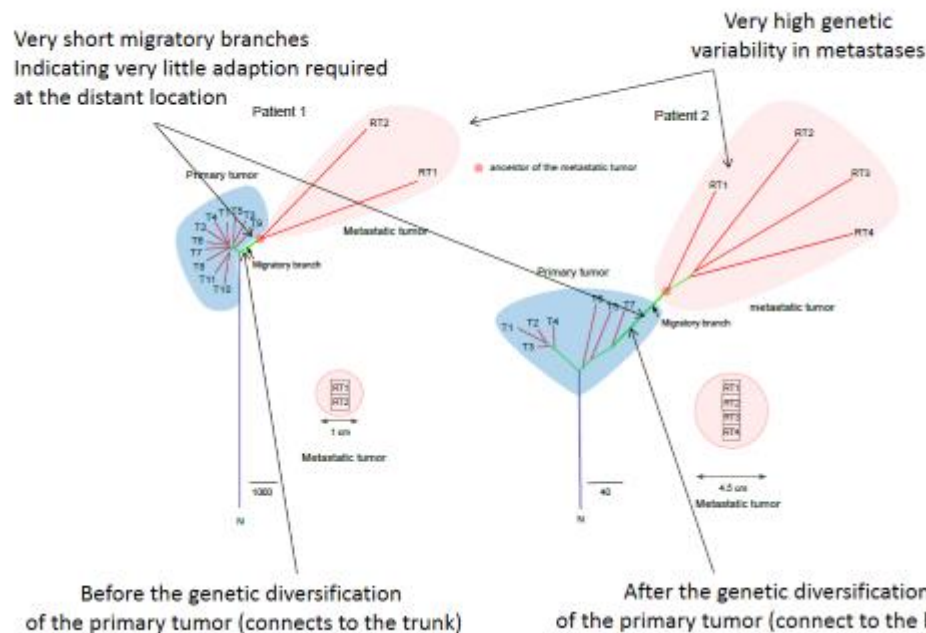
Vertical integration



Integration of Data from the same patient/sample



Genomics of Intra-hepatic distant metastases in HCC



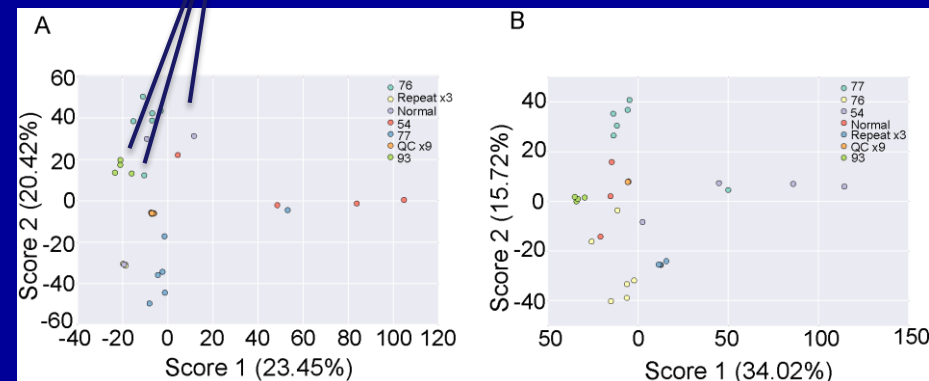
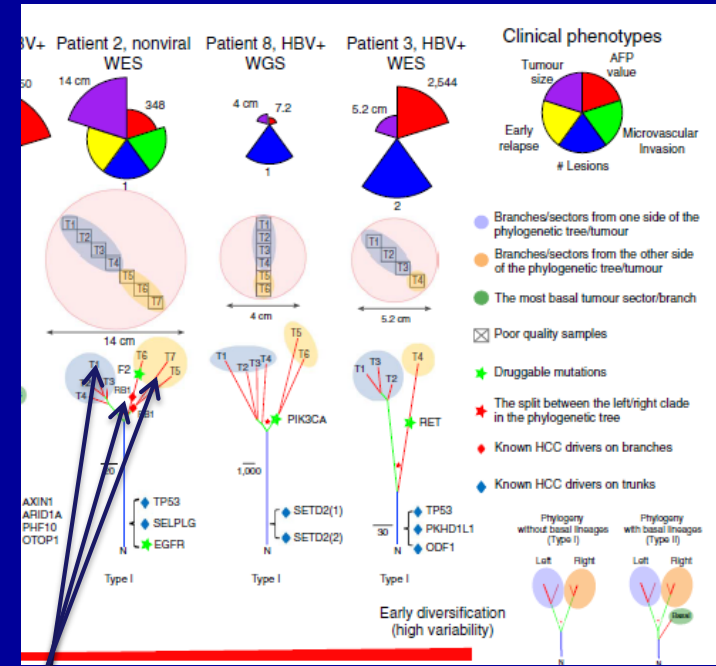
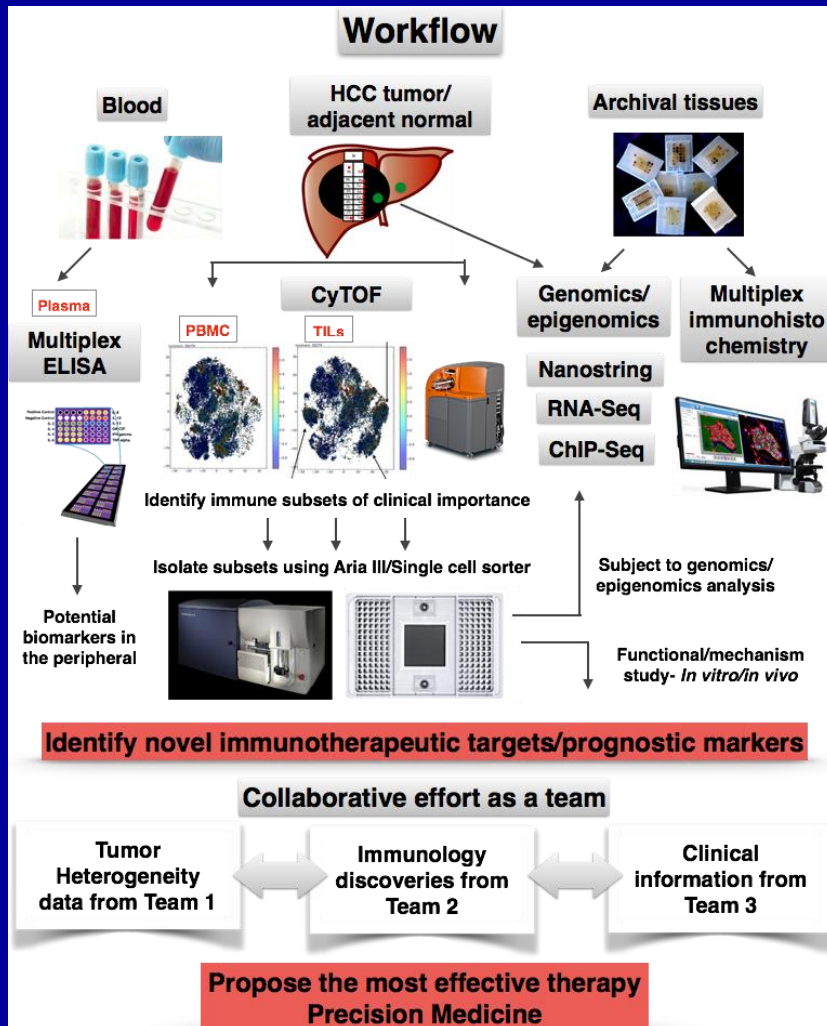
ARTICLE

Received 11 Oct 2016 |

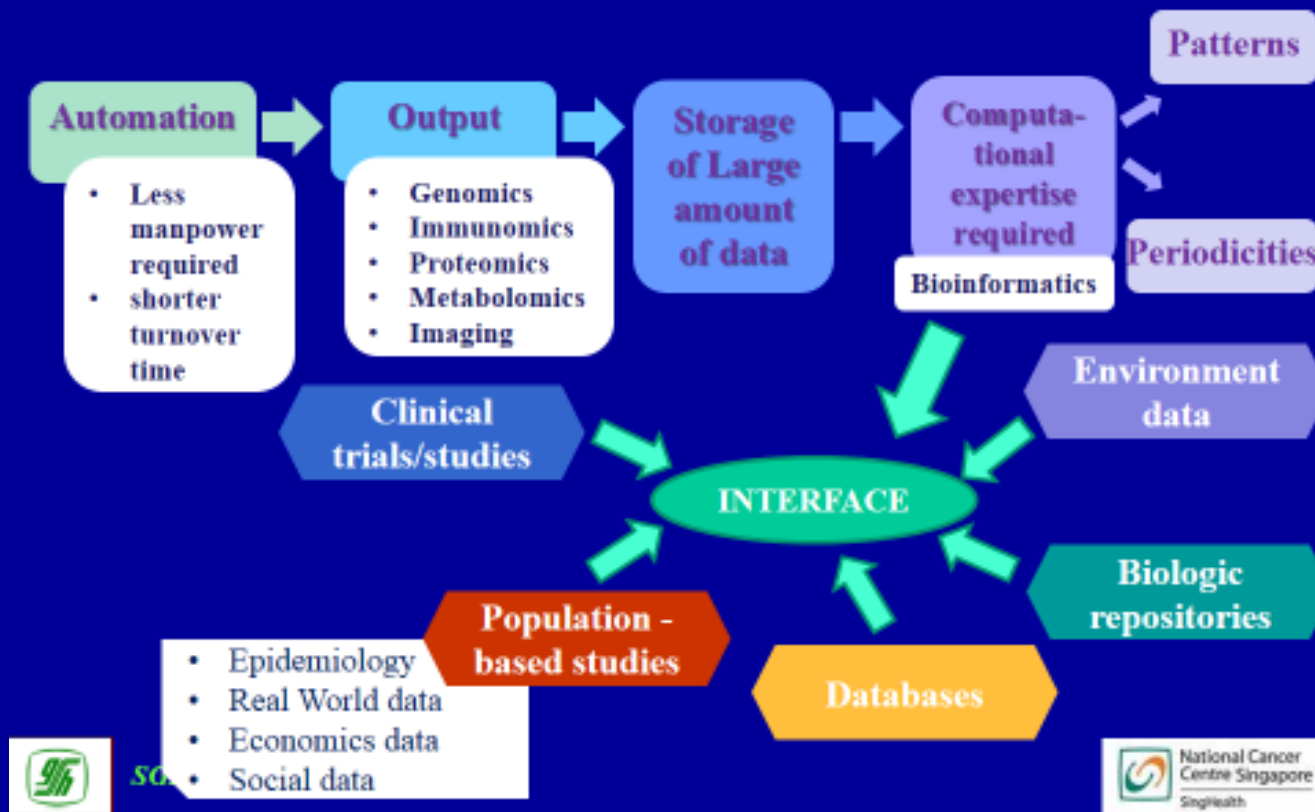
The spat heteroge metastas

Weiwei Zhai^{1,*,**},
Ming-Hwee Ng^{1,4},
Alexander Yaw-Fui
Roger Sik-Yin Foo¹

Immunomics-genomics integration in HCC



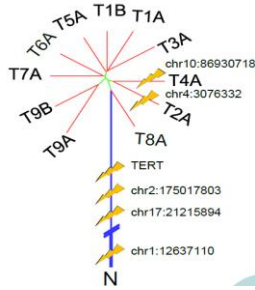
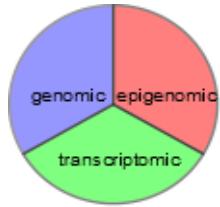
Vertical and Temporal Integration



LONGITUDINAL CLINICAL COHORT

Vertical and Temporal Integration TCR Flagship Program in Liver Cancer

Theme 1 Heterogeneity



AIMS: To meet the pressing need for **efficacious drugs** in HCC
To bring **Precision Medicine** to patients with HCC

Theme 3: Clinical Trajectory and Translational Clinical Trial

Neo-Adjuvant/Adjuvant Therapy Trial

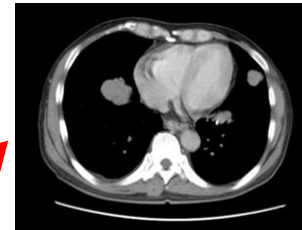
**Phase 1: 100/250
patients, 5/15 Asia-
Pac centers**

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

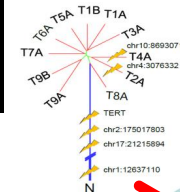
3-monthly follow-up:
scans, bloods, cfDNA, CTC



Creation of
representative
pre-clinical models

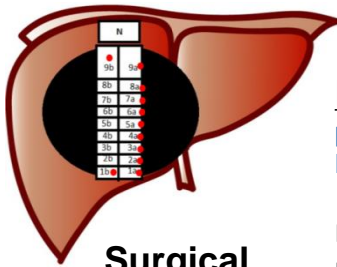
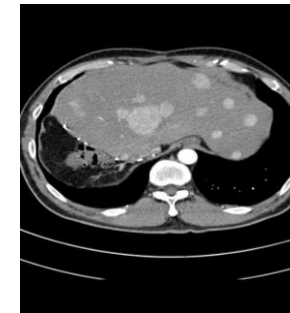
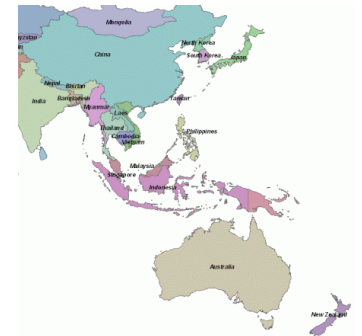


Recurrence
Biopsy or resection
tissue samples,
cfDNA, CTC

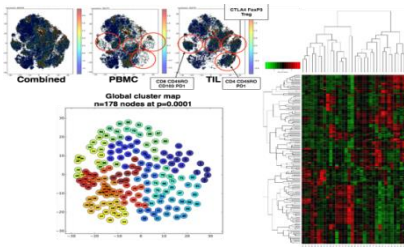


Phase 2:
Therapeutics
selected on the
basis of
discoveries in
this study

Asia-Pacific HCC Trials Group



**Surgical
Resection**



**Theme 2
Translational
Immunomics**

Precision Medicine in Liver Cancer Asia-Pacific Network

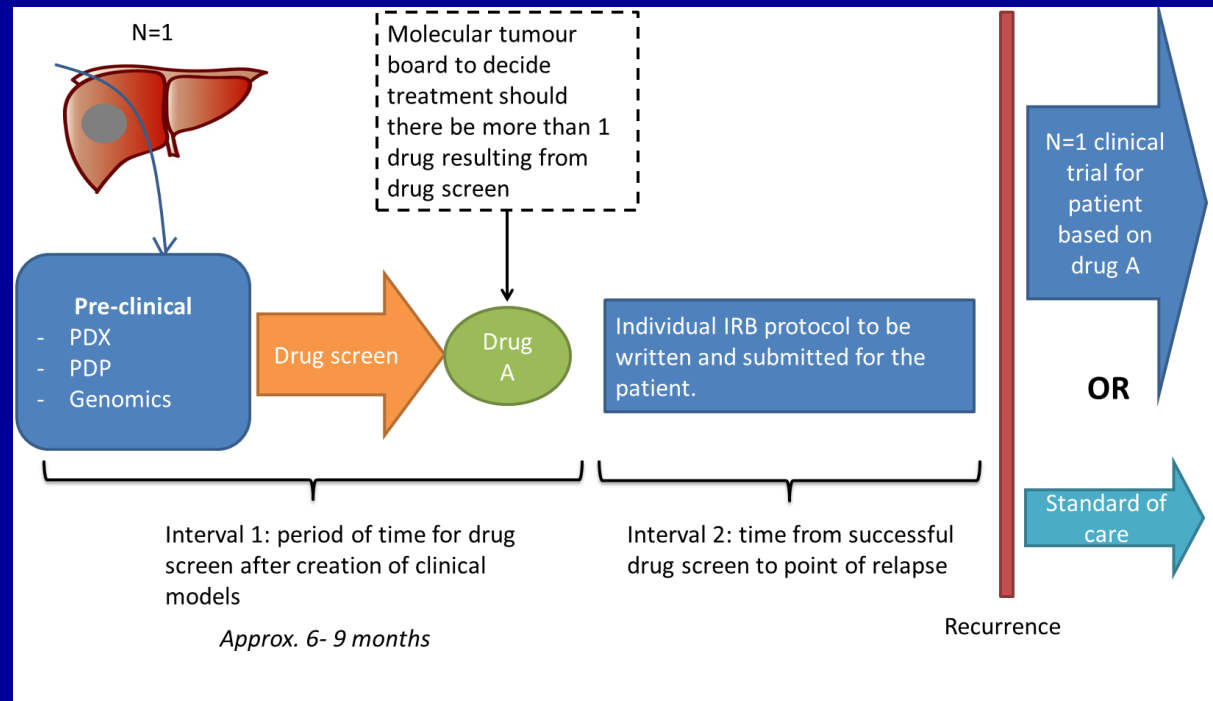
The Changing Face of Clinical Trials

- **Target enriched clinical trials**

- Biomarker selection
- Drug panels
- Possible to have N-of-1 trials

- **Patients shortlisted from**

- Biological Databases
- Electronic Medical Records (EMR)



N=1 Clinical Trial for Liver Cancer

Increasing Relevance of Real World Data: Asia-Pacific Liver Cancer Registry 2017

China

- Nanjing Bayi Hospital
- Zhongshan Hospital, Fudan University Shanghai
- Beijing Cancer Hospital
- Sun Yat Sen University Cancer Centre, Guangzhou
- Guangxi Medical University Cancer Centre
- Hunan Province Xiang Ya Hospital
- Jiangsu Cancer Centre
- Tongji Medical University, Wuhan
- Second Affiliated Hospital Zhejiang University School of Medicine
- The Eastern Hepatobiliary Surgery Hospital, Shanghai
- Third Military Medical University

Thailand

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

Singapore

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

Hong Kong

- Queen Mary Hospital

South Korea

- Ajou University Hospital
- Asan Medical Centre
- Korea University Anam Hospital
- Seoul National University Bundang Hospital

Japan

- Kyorin University School of Medicine
- University of Tokyo
- Kinki University Hospital
- National Cancer Centre

Taiwan

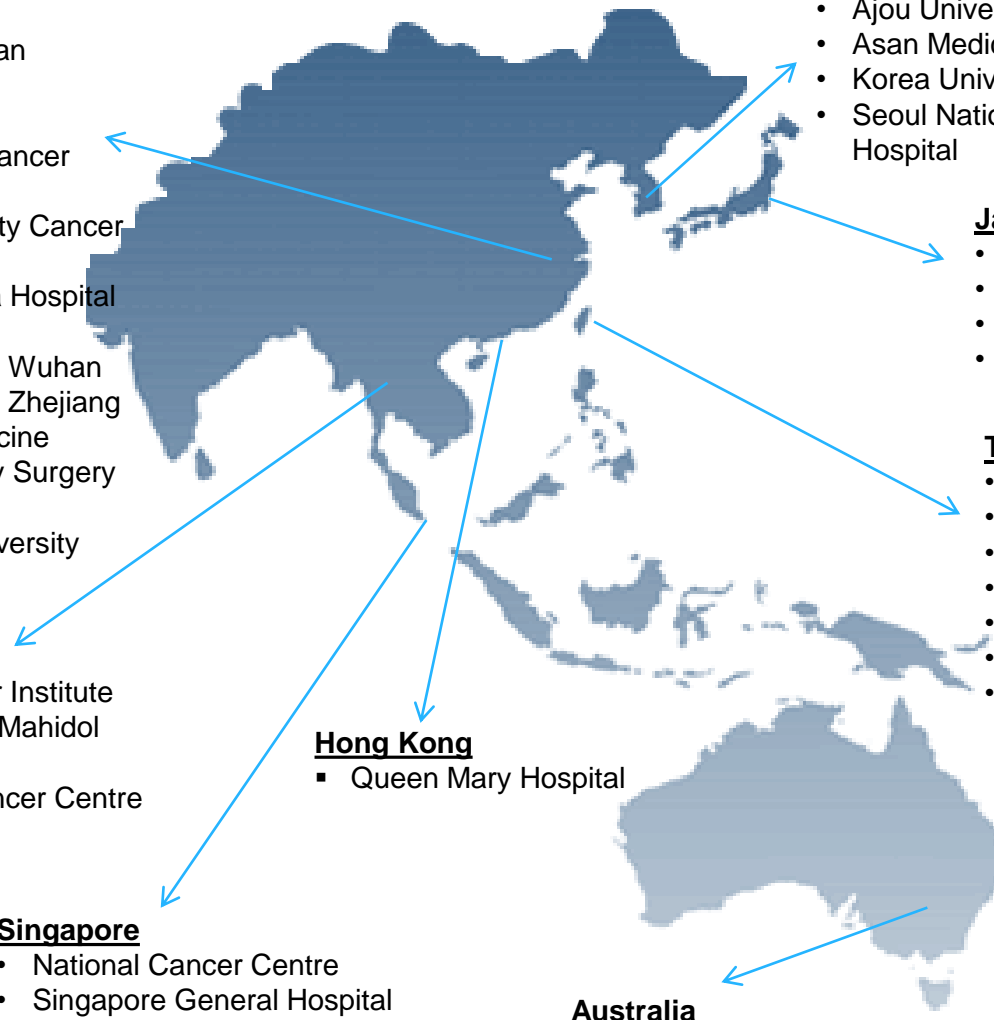
- Chang Gung Memorial Hospital
- National Taiwan University Hospital
- Taipei Veterans General Hospital
- Chang Gung Memorial Hospital – LK
- Chang Gung Memorial Hospital – KS
- China Medical University Hospital
- National Cheng Kung University Hospital

New Zealand

- Auckland City Hospital

Australia

- Royal Prince Alfred Hospital
- University of Adelaide
- Austin Hospital



From Hypothesis-Driven to Discovery-Driven Science

Still very important : Hypothesis-driven Science

PI / small research group

- Single discipline/lab
- Single institution

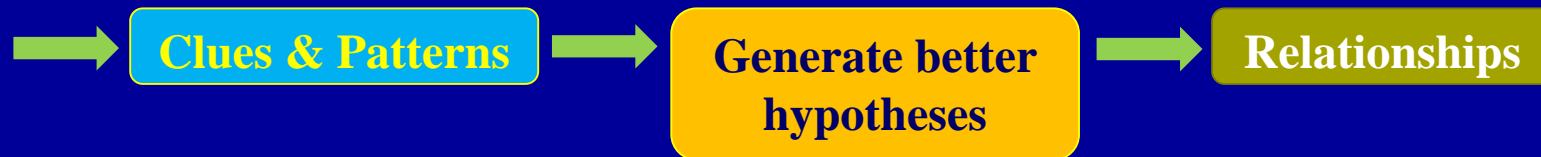
Hypothesis



Biological question

Large Funds : Discovery-driven science

Assumption: Analysis of complete data across the breadth of a disease



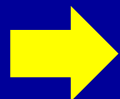
Large scale:

- *Multi-discipline*
- *Multi-institution*
- *Multi-national*

Increasing Recognition of the Need for Inter-disciplinary Research

Major Diseases

- Multi-faceted
- Share risk factors with other diseases
- Multiple etiologies e.g. diabetes mellitus, HCC



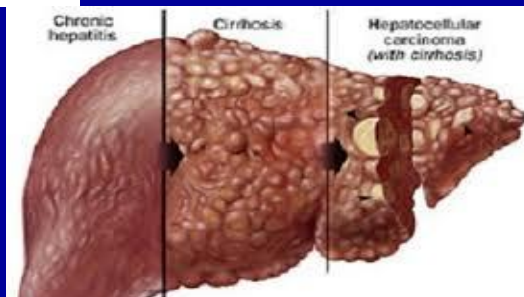
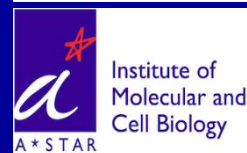
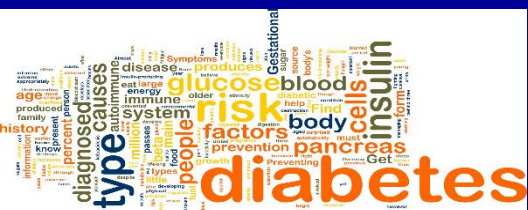
Requires

- Broad-based
- Large scale
- Trans-institutional

Challenges

(for single PI/small group)

1. No single lab has sufficient breadth
2. Logistically challenging coordination of large multi-institutional projects
3. Technology resides in different intuitions



Needed

Major Diseases

- Multi-faceted
- Share risk factors with other diseases
- Multiple etiologies e.g. diabetes mellitus, HCC



Requires

- Broad-based
- Large scale
- Trans-institutional

Challenges

(for single PI/small group)

1. Not single lab has sufficient breadth
2. Logistically challenging coordination of large project multi-institutional projects
3. Technology resides in different intuitions

Key

- Multi-disciplinary
- Multi-institution
- Large collaborative grant



- **Clinicians**
 - Medical Oncologists
 - Surgeons
 - Nuclear Med
- **Imaging**
- **Genomics**
- **Proteomics**
- **Metabolomics**
- **Immunomics**
- **Data science**

New breed of interdisciplinary
**CLINICIAN
SCIENTIST**



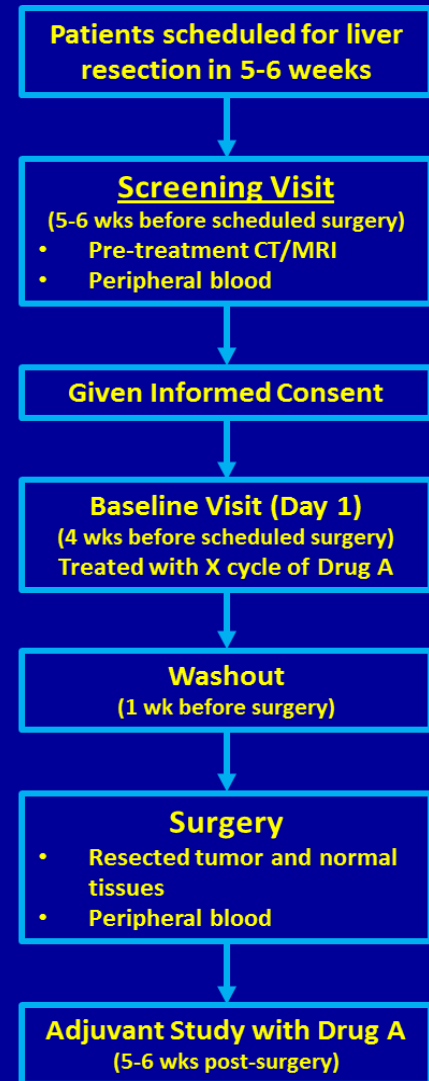
Increasing Public-Industry Collaborations

- With increasing complexity of research, industry rarely have access to all the necessary expertise
- Academia however does not manufacture therapeutics

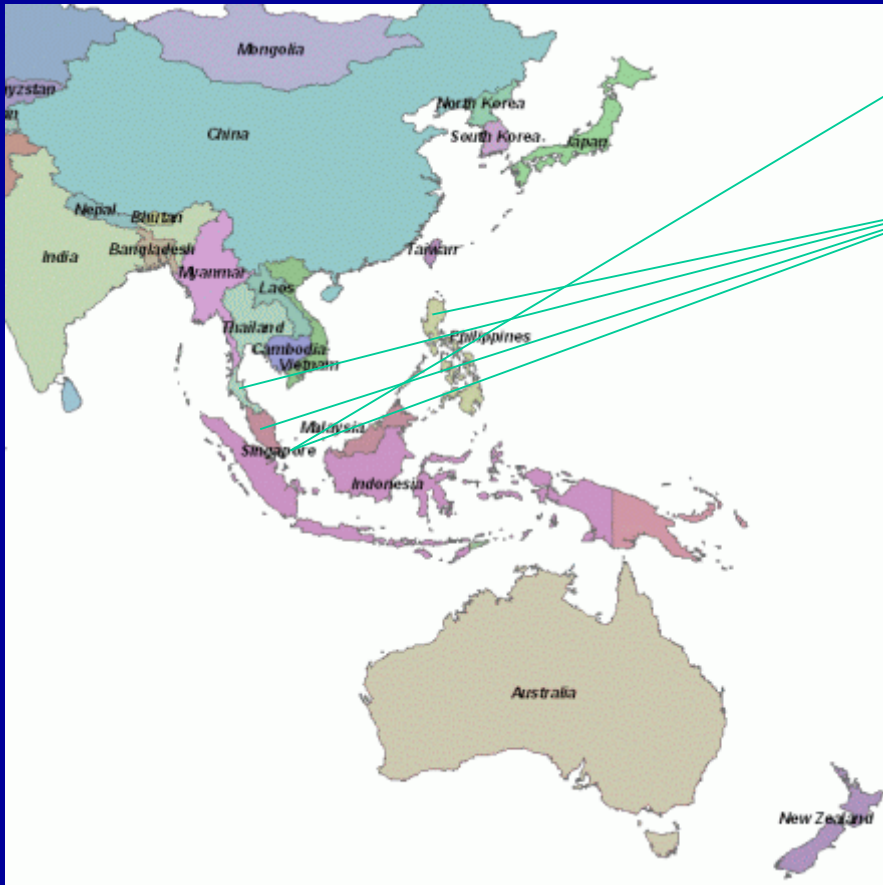
Neoadjuvant Study with Drug A

A clinico-immunomics-genomics correlative study in liver cancer

Industry-sponsored by big pharma



Increasing importance of International Collaborations in Biomedical Research



- The multi-ethnic **Asia-Pacific HCC Network** allows access to all the important **etiological and ethnic variations in HCC.**
- **Competitive Advantage** over competitors **China/Korea/Japan** where cohorts will be **overwhelmingly mono-ethnic and of single etiology**

Challenges and Opportunities in A Changing Biomedical Research Landscape

Challenges

- The ascendancy of Discovery-driven funding
- Need for large scale collaborative studies
- Need for inter-disciplinary collaborations
- Increasing Public-Private collaborations
- Increasing international research collaborations

Opportunities

- The evolution of a new breed of **uber** inter-disciplinary clinician-scientists

Its going to be cool to be a clinician –scientist





Thank You!

Acknowledgement:

- Su-Ting Pang BSc (Hon)
- Rachel Choi BSc (Hon)

