NMRC Symposium, 24 February 2016

SGCC

Singapore Gastric Cancer Consortium

RE-DEFINING THE MANAGEMENT OF GASTRIC CANCER

YEOH Khay Guan, Patrick **TAN**
Yoshiaki **ITO**, **YONG** Wei Peng, Jimmy **SO**

A National Translational & Clinical Research Flagship Programme

NUHS National University Health System

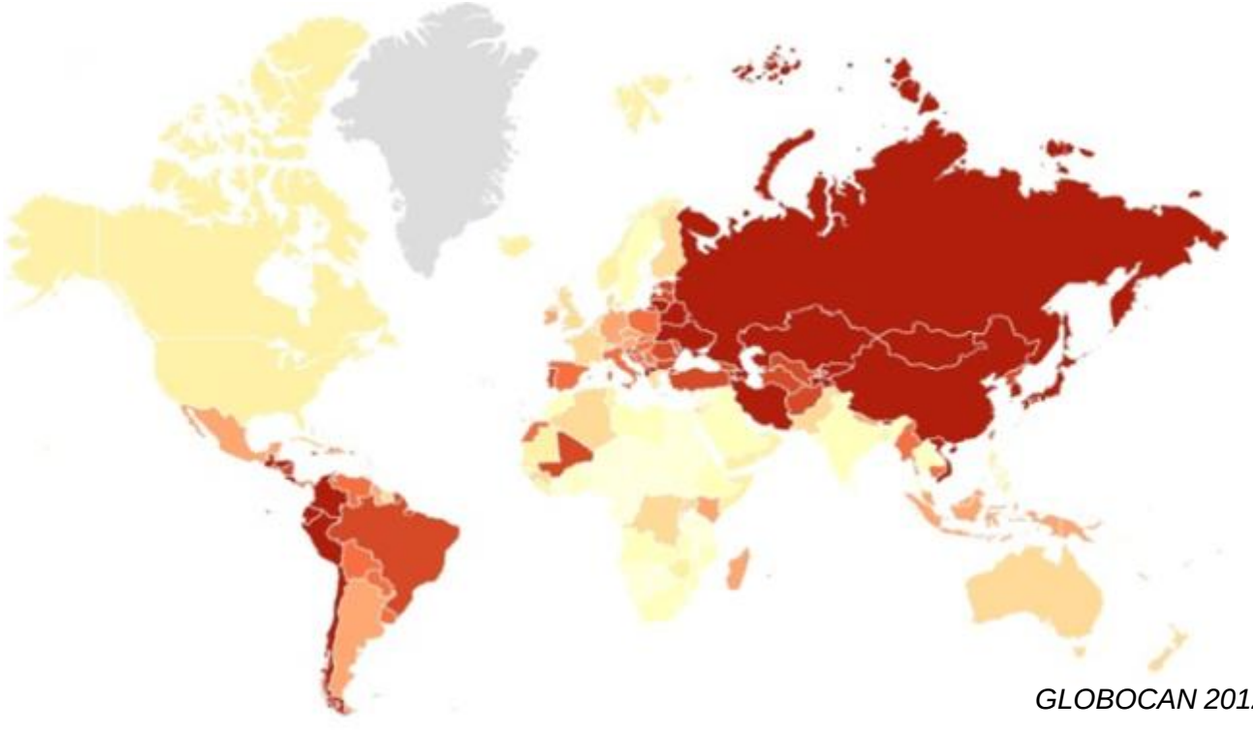
NUH National University Hospital

NUS National University of Singapore

DUKE NUS GRADUATE MEDICAL SCHOOL SINGAPORE

CSI SINGAPORE

Importance of Gastric Cancer Research



- **3rd leading cause of cancer death worldwide**
- 700,000 deaths annually, **majority of cases in Asia**

GLOBOCAN 2012 v1.0, International Agency for Research on Cancer

In the Singapore population

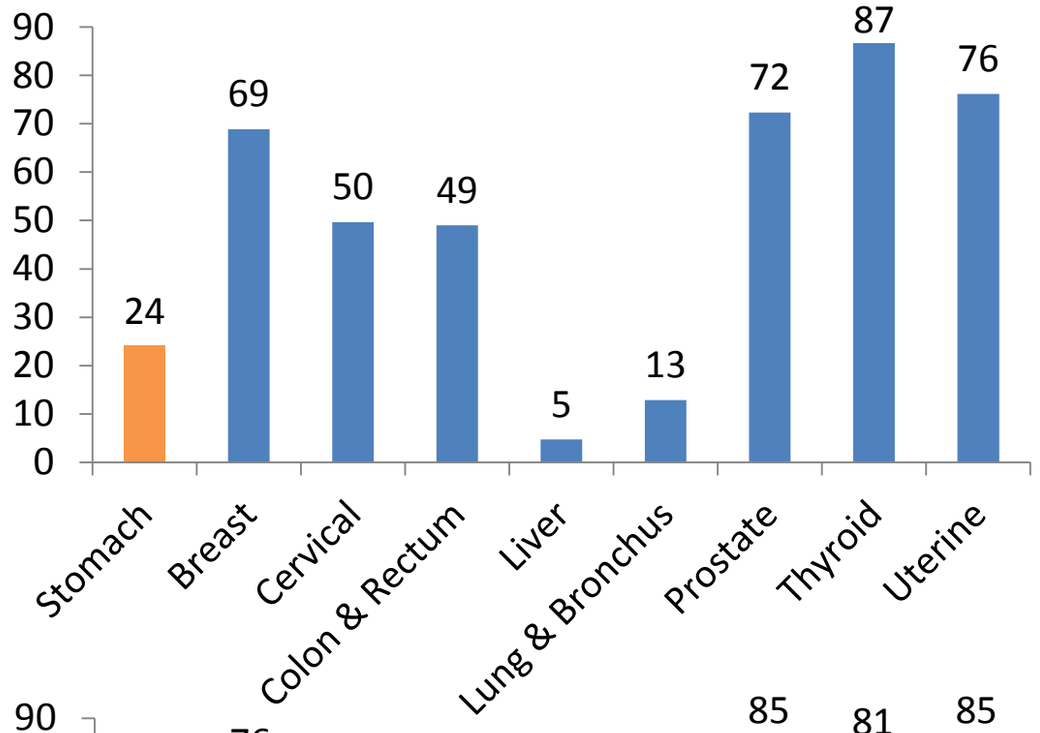
- ~300 deaths every year
- Incidence: 7th most common in men and 9th most common in women
- **1 in 100 Chinese men** develop the disease in their lifetime

Singapore Cancer Registry, Trends in Cancer Incidence in Singapore, 2010-2014

Survival for Gastric Cancer is Poor

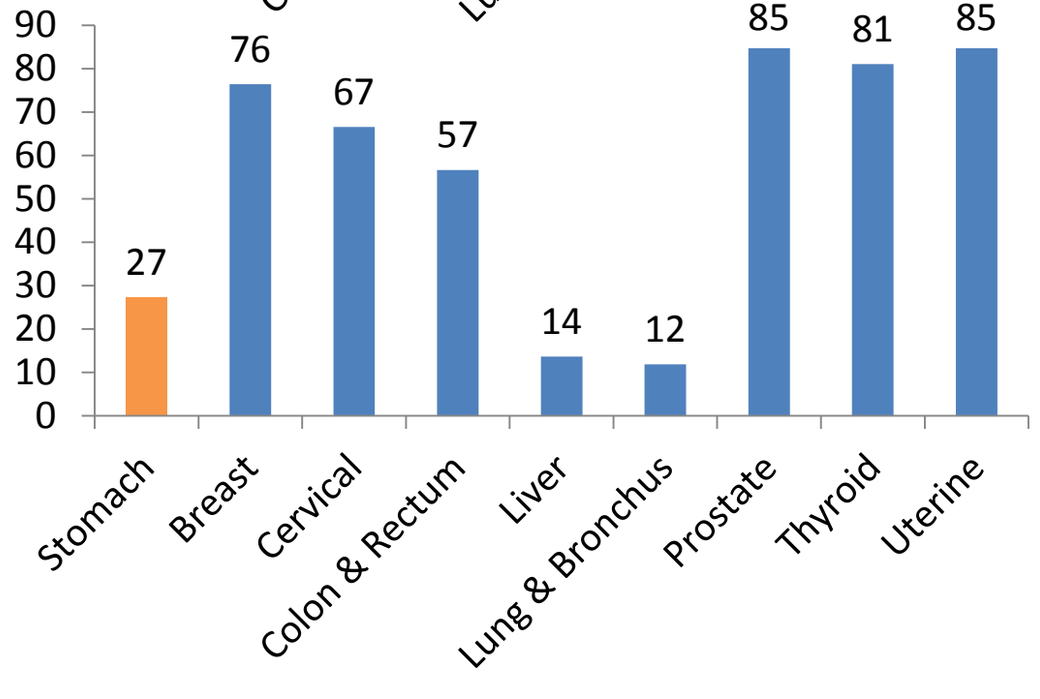
5 year Survival,
International

GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11.



5 year Survival,
Singapore

Singapore Cancer Registry. Cancer Survival in Singapore 1968-2007



- Gastric cancer is **curable if diagnosed at an early stage**
- but it is traditionally associated with poor prognosis
- because of **late presentation**

Singapore Gastric Cancer Consortium

a national effort in translating science to benefit patient care

1st Translational and Clinical Research (TCR) Flagship Grant awarded in 2007
1st TCR grant renewal awarded in 2013

Universities

- NUS National University of Singapore
- Duke-NUS Graduate Medical School Singapore
- Nanyang Technological University

Research Institutes

- NUS National University of Singapore | CSI Singapore
- A*STAR Experimental Therapeutics Centre
- A*STAR Genome Institute of Singapore
- A*STAR Singapore Immunology Network
- A*STAR Institute of Medical Biology
- A*STAR Bioprocessing Technology Institute

RE-DEFINING THE MANAGEMENT OF GASTRIC CANCER

Strongly Facilitated by

- NMRC National Medical Research Council, Singapore
- National Research Foundation
- Ministry of Health Singapore
- EDB Singapore
- A*STAR

Hospitals

- National University Hospital
- Singapore General Hospital, SingHealth
- Tan Tock Seng Hospital
- Changi General Hospital, SingHealth

Industry

- sengenics
- illumina
- Novartis
- Sanofi
- MiRXES
- Taiho Pharma Singapore
- Bayer

International Collaborators

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RE-DEFINING THE MANAGEMENT OF GASTRIC CANCER

3 Themes	Aims & Target
(1) Early Detection →	**Screening strategy** based on identifying high risk groups **+ biomarker**
(2) Improve Treatment →	**Genomic profiling to guide chemotherapy**
(3) Biology of Gastric Ca →	**Model of gastric carcinogenesis,** critical events, **gatekeeper gene,** biomarkers.

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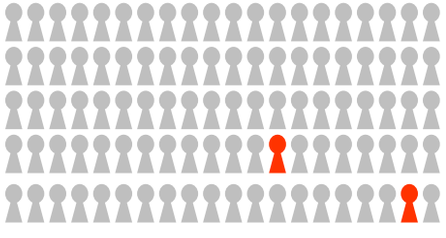
How can We Detect Gastric Cancer Earlier?

Current problem: Gastric cancer (GC) is a silent disease, and 80% of GC presents at a late stage. The challenge is to detect it early, so it can be cured.

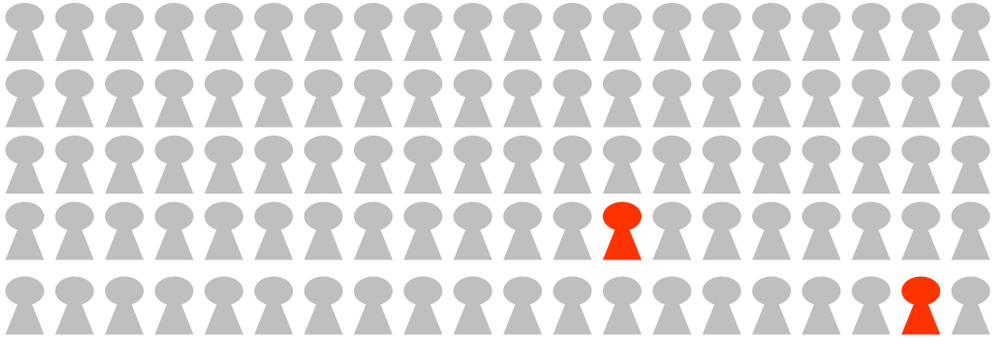


Risk- profiling

Blood Test

Imaging

Identifying High Risk for Gastric Cancer



Population Risk Stratification for Gastric Cancer

*"Combining established clinical parameters & emerging molecular information to create preventive, diagnostic & therapeutic solutions tailored to **individual patient requirements**"*

Global Agenda Council on Personalized & Precision Medicine 2012-2014, World Economic Forum

Gastric Cancer Epidemiology Programme (GCEP)

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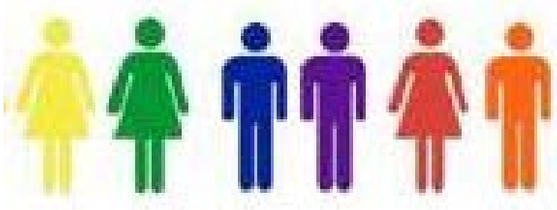
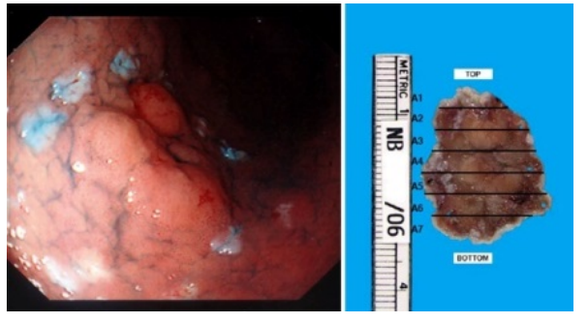
Prospective Study of Endoscopic surveillance for Gastric Cancer

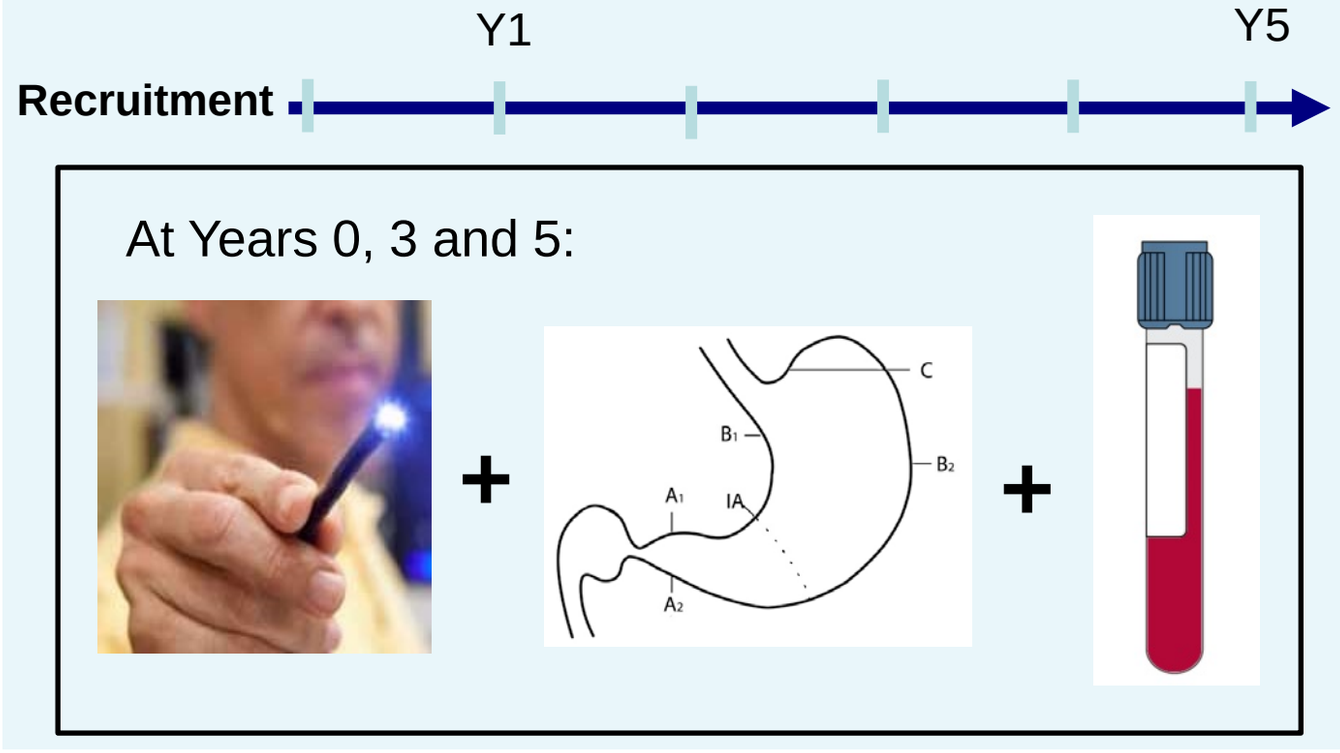


- High-risk" cohort
- n=3000
- Chinese, age >50

Quality control
Reference pathologist
All endoscopies videoed
Web-based Oracle database

Endpoint: early neoplasia defined as high grade dysplasia, adenocarcinoma





- Compliance rate of **85%**
- **2400** out of 3000 enrolled patients have completed 5 years of surveillance
- Total person-years = **9980**
- Average years of f/u per person = **4.12**
- **21** screen-detected early gastric cancers

Risk factors for gastric cancer

Risk factors by logistic regression: age ≥70, smoking, serum PG and serum Hp

Risk Category	No. of Risk Factors	No. of subjects n=2649	Prevalence of EGN n=21	Odds Ratio (95%CI)
Average risk	0	662 (25%)	0 (0%)	Ref
Moderate risk	1	1338 (50%)	9 (43%)	4.4 (0.6-36)
High risk	**≥2**	**663 (25%)**	**12 (57%)**	**11.9 (1.5 – 91.6)**

Individuals with >2 of 4 RF (age ≥70, smoking, serum PG and serum Hp) comprised 25% of the cohort and were at 12-fold increased risk of EGN

The high-risk group comprises 25% of the cohort and includes 6 of 10 cases of early neoplasia.

Serum miRNA test for Gastric Cancer Detection (1)


Too Heng-Phon
Biochemistry,NUS


Zhou Lihan,
MiRXES


Celestial YAP,
Physiology,NUS


Jimmy SO
Surgery,NUHS


WP Yong
Oncology,NUHS


KG YEOH,
Gastro,NUHS

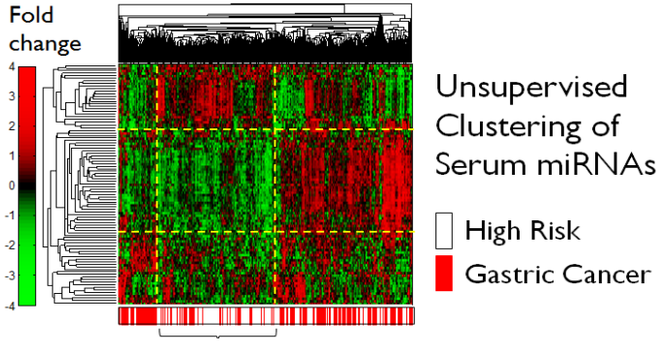

YY Teo,
Epi,NUS


Joanne Yoong,
Health Econs,NUS

Aim : Blood-based test that can detect early GC with sensitivity >90%

Discovery → **24-miR Serum Biomarker Panel** → **Validation**

N=472 (236 GC)



clear distinction of GC vs Control

2 blinded, independent cohorts (SG, Korea)
N=275 (96 GC)

Sensitivity = 0.9
Specificity = 0.73-0.8

Serum miRNA test for Gastric Cancer Detection (2)

Next Steps

Further Validation sets

pre-, post-resection.

T2 prospective study, Singapore n=5000.

International validation study.

Regulatory standards CE- IVD, HSA.

Economics, Cost-effectiveness,

Health Technology Assessment

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ETPL A*STAR

Diagnostics Development Hub, Biopolis

Imaging Research to Improve Detection of Early Gastric Cancer

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RAMAN Spectroscopy

Raman spectroscopy is an optical method which probes the biophysical changes associated with cancer.

Aim: to use Raman spectroscopy for identifying cancerous from normal gastric mucosa tissue, during real time endoscopy.

Publications :

JF Wang et al. Anal Bioanal Chem (2015)
MS Bergholt et al. Gastroenterology (2014)
MS Bergholt et al. J Biophotonics (2013)
MS Bergholt et al. J Biomed Opt (2012)
MS Bergholt et al. Biosens Bioelectron (2011)
SK Teh et al. Int J Cancer (2010)
Z Huang et al. Optics Letters (2009)
SK Teh et al. Brit J Surgery (2009)

Zhi-Wei HUANG

Lawrence HO

KG Yeoh

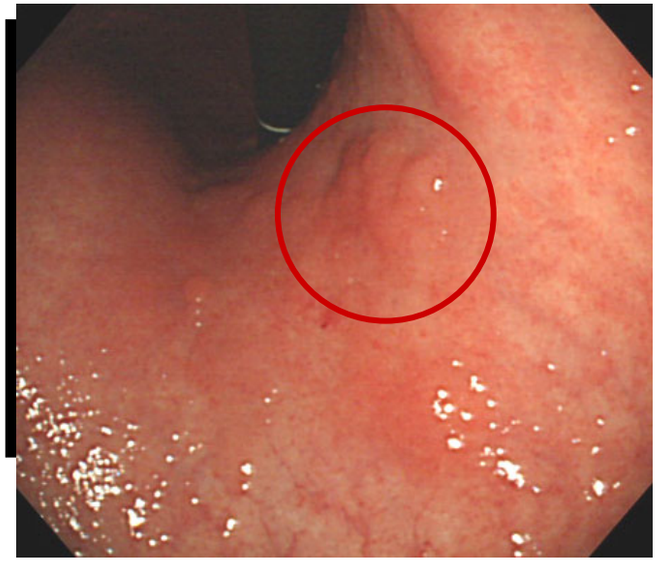
Scientists at NUS develop new cancer screening tool

Probe's new technology makes diagnosis of tissues less subjective

The Straits Times, pB6, 11 Feb 2014

Improving Imaging to detect early gastric cancer

White Light Endoscopy



Suspicious area on white light endoscopy

Simultaneous Raman

Live, real-time, in-vivo feedback
high sensitivity (94.6%) and specificity (97.8%)
for cancer and dysplasia

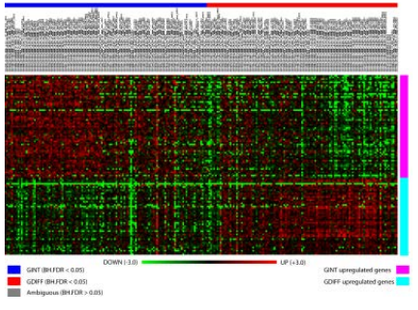
High risk

Low risk

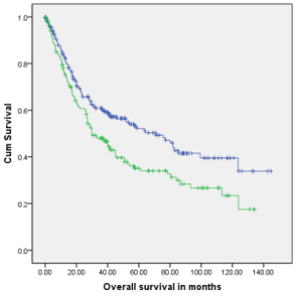
borderline

How can Treatment be Improved?

Robot endoscope



Genomic classification



Clinical Trials

Robot-Assisted Endoscope to Remove Early-Stage Gastrointestinal Cancer - *made in Singapore !*

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MASTER

A novel flexible robot-assisted endoscopic system that enables intricate surgical procedures to be performed without the need for external incisions

Aim: To ensure safe and efficient removal of early-stage cancer in the gastric and colorectal system through endoscopy.

Publications :

- **S.J. Phee et al. Robotics and Computer-Integrated Manufacturing (2015)**
- **S.J. Phee et al. Surgical Endoscopy (2014)**
- **K.Y Ho et al. Minimally Invasive Therapy & Allied Technologies (2014)**
- **K.Y Ho et al. Gastrointestinal Intervention (2013)**
- **S.J. Phee et al. Surgical Endoscopy (2013)**
- **K.Y Ho et al. Gastrointestinal Intervention (2010)**

Professor Louis Phee Soo Jay &
Professor Lawrence Ho Khek Yu
President's Technology Award 2012

THE HINDU Business Line

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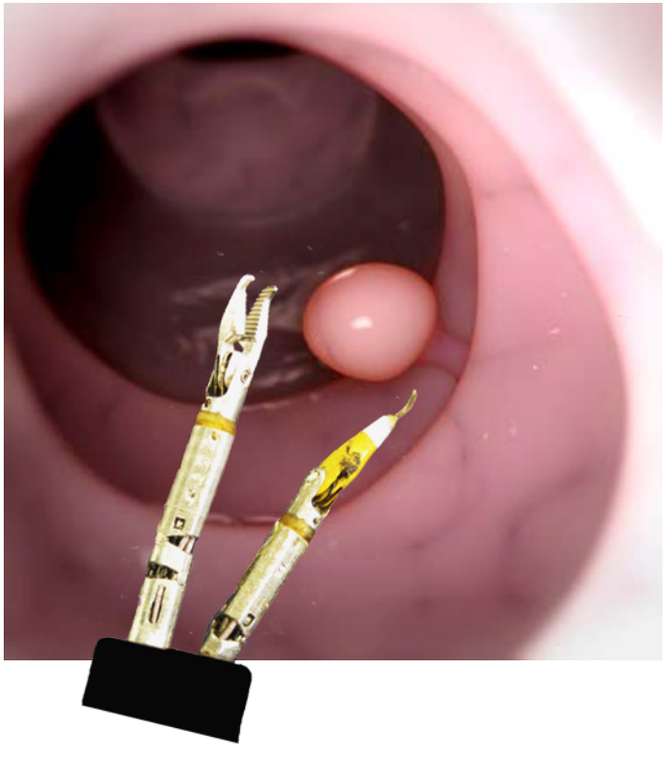
Economy Info-Tech Agri-Biz Banking Logistics Marketing Government & Policy Shipping News

AIG doctors perform world's 'first' robotic endoscopy surgery

OUR BUREAU SHARE · PRINT · T+

Dr Pradeep (left), Dr Duvvuru Nageshwar Reddy (centre), Director and Chief of Gastroenterology and Therapeutic Endoscopy in the Asian Institute of Gastroenterology; Dr Louis Phee from Singapore, explaining the world's first robotic flexible endoscopy surgery at AIG in Hyderabad on Sunday. — Photo: Surya Sridhar Business Line



New Genomic Classification of Gastric Cancer

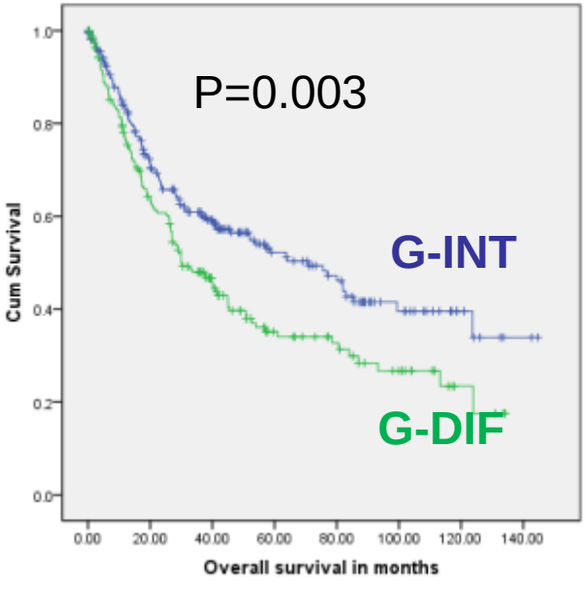
Gastroenterology. 2011 Aug;141(2):476-85
Gastroenterology. 2013 Sep;145(3):554-65.

- **Prognostically relevant** for patient survival,
- **Predictive of responses** to 5-FU and PIK3CA Inhibitors

Completely new ways of classifying gastric cancer, prognostically superior to the classic Lauren classification and diagnostically more robust

Prof Patrick TAN
Duke-NUS

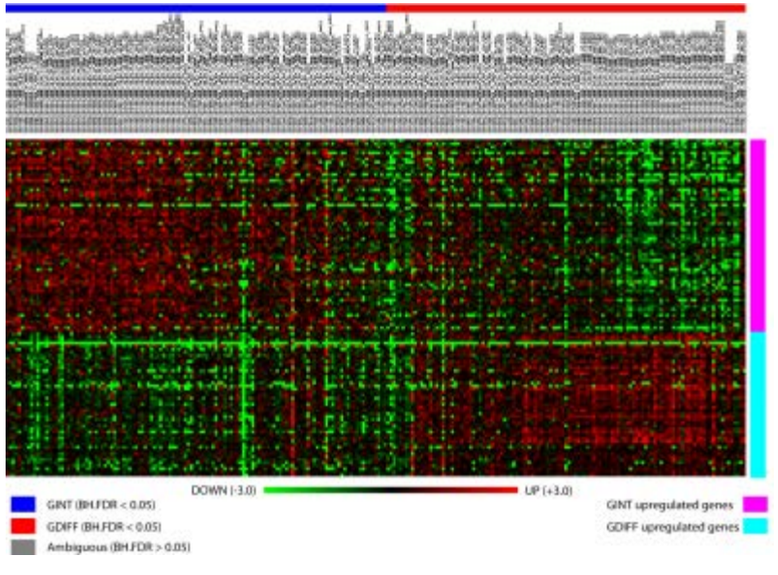
***Gastroenterology*, 2011.**



Singapore/ Australia/ UK/ HK/ S Korea/ MD Anderson Cohort (~550 patients)

"A reliable classification of biological and clinical significance."

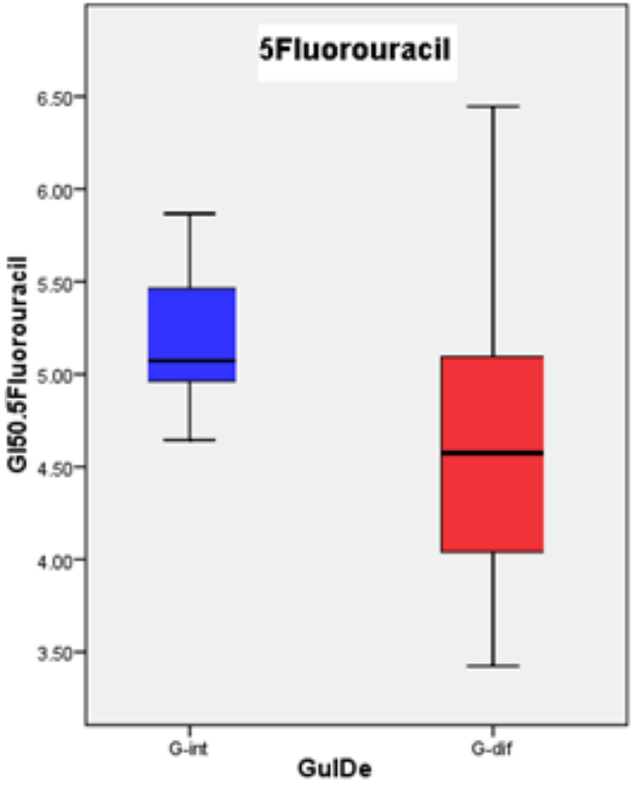
P Correa, Faculty of 1000



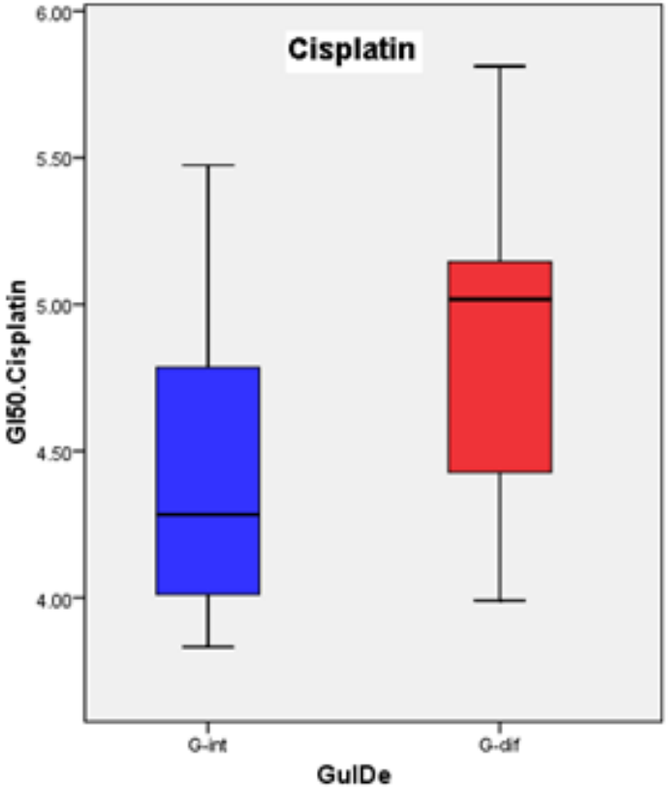
Genomic Subtypes in MAGIC, a Phase III Clinical Trial

Singapore Gastric Cancer Consortium

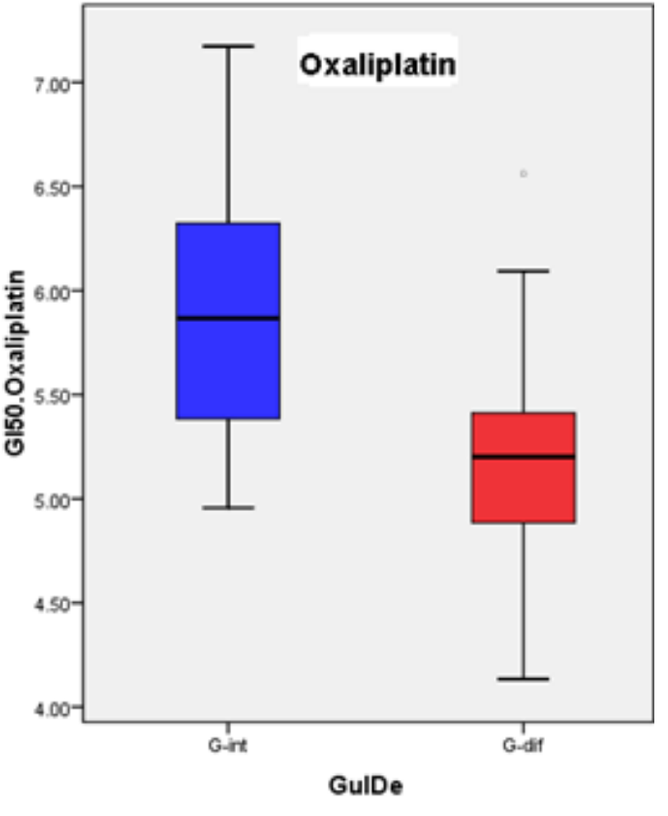
G1 and G2 Cell Lines Respond Differently to Chemotherapy Treatment



5-FU
P=0.04



Cisplatin
P=0.03



Oxaliplatin
P=0.02

G1

G2

Gastroenterology. 2011 Aug;141(2):476-85

Clinical Trial:
Guided by Genomics in Gastric Cancer (3G)

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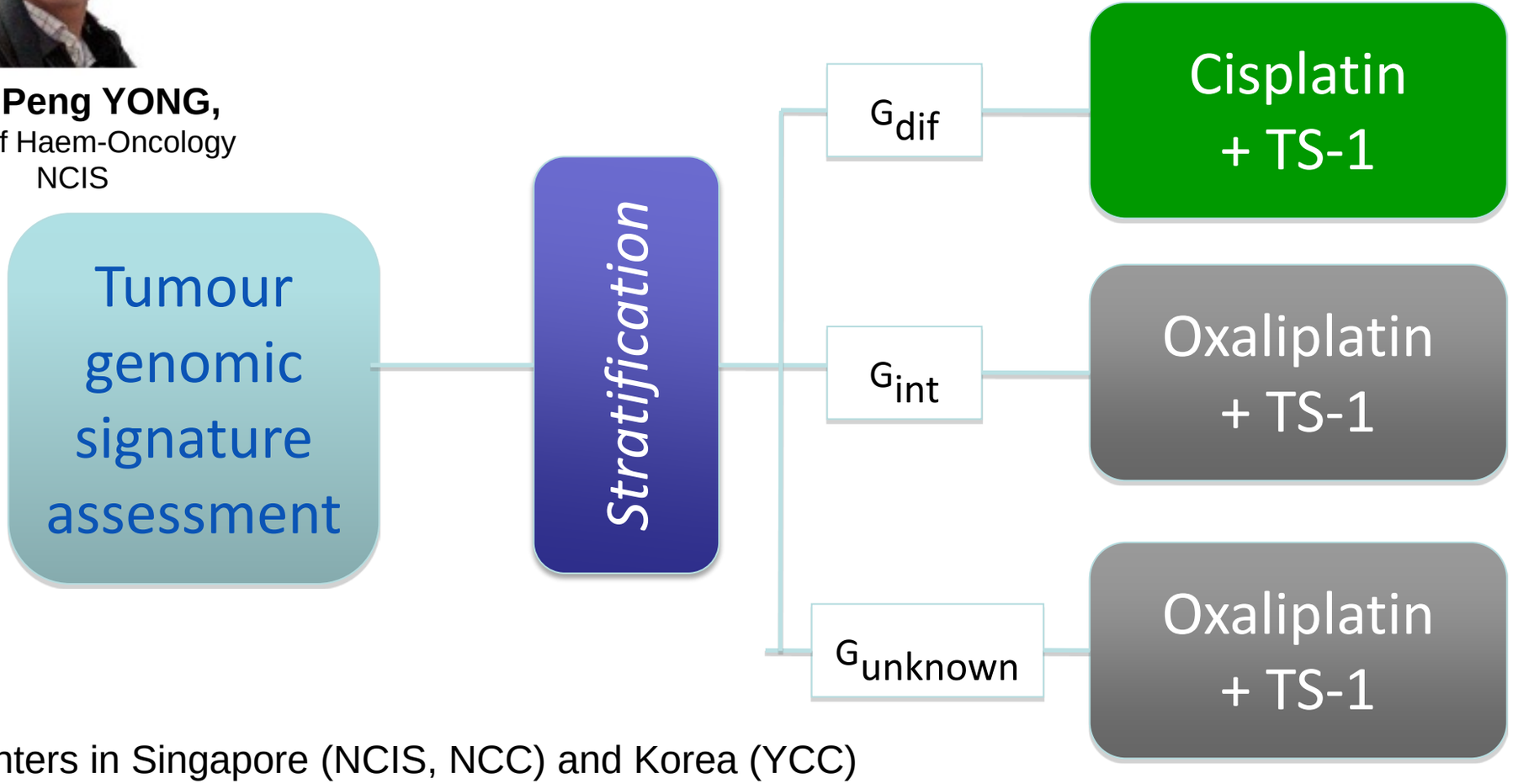
Wei-Peng YONG,
Dept of Haem-Oncology
NCIS

A Phase II study of genomic-guided chemotherapy in advanced gastric cancer patients



3 centers in Singapore (NCIS, NCC) and Korea (YCC)

n=30 per arm, detect 30% improvement in RR from 40%

79 patients (out of target n=90) recruited, as at July 2015

How Does Gastric Cancer Arise?

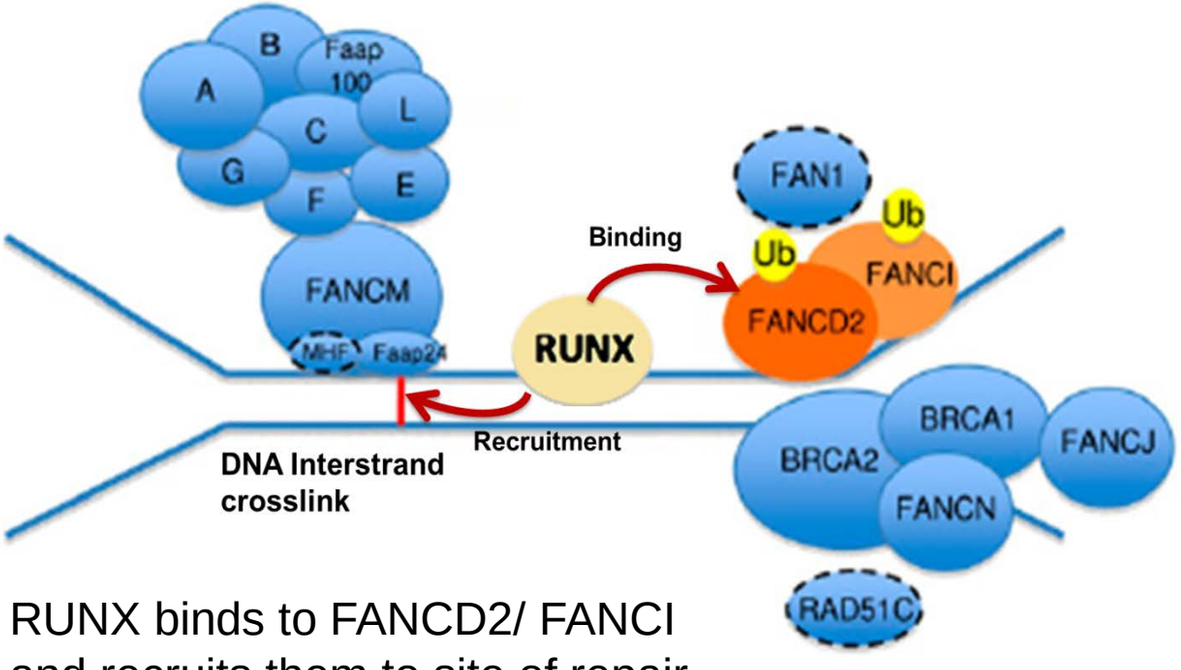
Identification of stomach stem cells by molecular marker

Prof Yoshiaki ITO,
CSI, NUS

- Lack of knowledge of stem cells is a major reason why gastric carcinogenesis is poorly understood
- Identified stomach corpus isthmus stem cells using molecular markers.
- Now able to genetically manipulate genes of interest in stem cells, to study step-wise development of gastric cancer

RUNX genes and DNA damage repair in carcinogenesis

Role of RUNX protein in Fanconi/BRCA pathway



RUNX binds to FANCD2/ FANCI and recruits them to site of repair

- Fanconi anemia (FA) pathway is dedicated to the repair of DNA inter-strand crosslinks, which are highly mutagenic DNA damaging lesions
- 18 known genes of the FA pathway include BRCA1 and BRCA2
- RUNX protein is directly involved in recruitment of FA pathway proteins to DNA damage site
- Explain findings that RUNX impairment is related to leukemia and other cancers, including gastric cancer

Cell Reports. 2014 Aug 7;8(3):767-82

Singapore Gastric Cancer Consortium

NUS National University of Singapore

microRNA test

Blood test for GC
>90% accuracy

Raman Optical bx

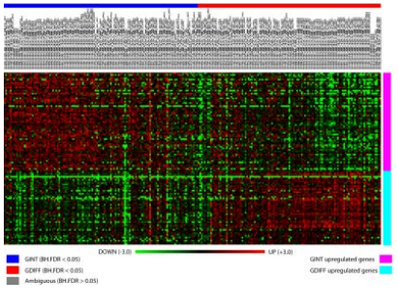
Live, real-time,
in-vivo feedback

Robot

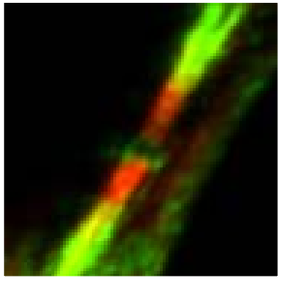
First-in-the-world
Endoscopic robot

Genomic classification

Guiding treatment,
Right drug,
right person



Gatekeeper Gene



Runx3 inactivation
leads to cancer

RE-DEFINING THE MANAGEMENT OF GASTRIC CANCER

Singapore Gastric Cancer Consortium

Our achievements at a glance

Academic Record

Employed **46** Post-doc staff

Trained **28** Masters and PhD students

>180 Peer-reviewed papers;

Awarded **$74mil** in 20 competitive grants

40 local and int'l academic collaborations

Unique Resources

GCEP cohort and other clinical studies

Gastric tissue and cancer cell line database

Novel bio-imaging techniques, robotics and endoscopic expertise

Genomics expertise

Unique animal models

Health & Society

Prevented advanced disease in 21 screen-detected early cancers; $425K in healthcare savings

H. pylori eradication in 22% of cohort reduces GC risk

Identified Risk factors for gastric cancer in SG population

New genomic classification for personalized treatment

Enhanced endoscopic and imaging technology to improve patient outcomes

Economic Value

43 patents and invention disclosures

Spin-offs:
EndoMaster Pte Ltd
Endofotonics Pte Ltd

>$22million in industry funding from 16 companies

Key Publications (>180 since 2007)

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		Impact Factor
nature medicine	Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. ***Nature Medicine 2015*** ;21(5):449-56.	**27.14**
Gut	Signatures of tumor immunity distinguish Asian and non-Asian gastric adenocarcinomas. ***Gut 2014*** doi:10.1136/gutjnl-2014-308252 [epub ahead of print]	**12.55**
nature COMMUNICATIONS	Nanoscale chromatin profiling of gastric adenocarcinoma reveals cancer-associated cryptic promoters and somatically acquired regulatory elements**.** ***Nature Communications* 2014**; 5:4361	**10.02**
JCI	mTORC1 inhibition restricts inflammation-associated gastrointestinal tumorigenesis in mice. ***Journal of Clinical Investigation* 2013** Feb 1;123(2):767-81.	**15.43**
Gastroenterology	Identification of molecular subtypes of gastric cancer with different responses to PI3-kinase inhibitors and 5-fluorouracil. ***Gastroenterology* 2013**;145(3):554-65	**12.82**
nature genetics	Exome Sequencing of Gastric Adenocarcinoma Reveals Recurrent Somatic Mutations in Cell Adhesion and Chromatin Remodeling Genes. ***Nature Genetics* 2012**; 44(5):570-4.	**35.21**
Cancer Cell	STAT3-driven upregulation of TLR2 promotes gastric tumorigenesis independent of tumor inflammation. ***Cancer Cell* 2012**; 22(4):466-78.	**26.57**
	Loss of Runx3 is a key event in inducing precancerous state of the stomach. ***Gastroenterology* 2011**;140(5):1536-1546**.**	**12.82**

Industry Collaborations

Area of Collaboration	Industry Partner
Biomarkers for Early Gastric Cancer	Illumina
Biomarkers & Treatment	Bayer
Vaccine Study	Onco Therapy & Tokyo University
3G Study	Taiho
Avagast	Roche
First-in-man Clinical Trial	Novartis
SB939	S*Bio Pte Ltd
Gastric Cancer Gene Expression	Genentech
Saladax	Saladax Biomedical
Pharmacokinetics	Novartis
Antibody	Kyowa Hakko Kirin
Multispectral imaging	Perkin Elmer

Total industry funding of >S$22 million from 16 companies

Recognition of the Consortium's work

"Gastric cancer is considered an "Asian disease", and Chinese men are especially susceptible. We established the **Singapore Gastric Cancer Consortium** comprising multiple universities, research institutes and hospitals. The Consortium has identified two sub-types of gastric cancer using genetic profiling, and is currently conducting clinical trials to improve treatments for gastric cancer."

-- Prime Minister Lee Hsien Loong, at the World Health Summit Regional Meeting, 8th April 2013

Singapore Gastric Cancer Consortium

Principal Investigators & Co-Investigators

KG YEOH	*NUS*	**Boon Huat BAY**	*NUS*	**KM FOCK**	*CGH*	**Yijun RUAN**	*GIS*
Yoshiaki ITO	*CSI*	**Shing Leng CHAN**	*CSI*	**A JEYASEKHARAN**	*NUHS*	**Iain TAN**	*NCCS*
Patrick TAN	*Duke-NUS*	**Chung King CHIA**	*TTSH*	**Matiullah KHAN**	*NUS*	**Bin Tean TEH**	*NCCS*
Wei Peng YONG	*NUHS*	**Kee Seng CHIA**	*NUS*	**Koji KONO**	*NUHS*	**Ming TEH**	*NUS*
Jimmy SO	*NUHS*	**Su-Pin CHOO**	*NCCS*	**Yoon-Pin LIM**	*NUS*	**Christopher WONG**	*GIS*
Lawrence HO	*NUHS*	**Maxey CHUNG**	*NUS*	**Khoon Lin LING**	*SGH*	**Wai Keong WONG**	*SGH*
Richie SOONG	*CSI*	**Horst FLOTOW**	*ETC*	**Chris KHOR**	*SGH*	**Celestial YAP**	*NUS*
Tiing Leong ANG	*CGH*	**Liang Kee GOH**	*Duke-NUS*	**Brendan PANG**	*NUHS*	**David ONG**	*NUHS*
Nicholas BARKER	*IMB*	**Axel HILLMER**	*GIS*	**Louis PHEE**	*NTU*	**Lee Guan LIM**	*NUHS*
		Zhi Wei HUANG	*NUS*	**Jaideepraj RAO**	*TTSH*		

Collaborators

Heng Phon TOO	*NUS*
Lihan ZHOU	*NUS*
Ruiyang ZOU	*NUS*
Yik Ying TEO	*NUS*
Woon Puay KOH	*Duke-NUS*
Ai Zhen JIN	*HPB*
Sethi SUNIL	*NUS*
Supriya SRIVASTAVA	*NUS*
Chon Boon ENG	*NUHS*
Rajeev SINGH	*NUHS*

SGCC 7th Annual Meeting, 23-24 July 2014

Funding agencies

National Medical Research Council

National Research Foundation

SGCC
Singapore Gastric Cancer Consortium

9th ANNUAL SCIENTIFIC MEETING

LATEST ADVANCES IN GASTRIC CANCER RESEARCH

FIRST ANNOUNCEMENT

20 - 21 JULY 2016

NUHS TOWER BLOCK AUDITORIUM
NATIONAL UNIVERSITY HEALTH SYSTEM
SINGAPORE

faculty (as of January 2016)

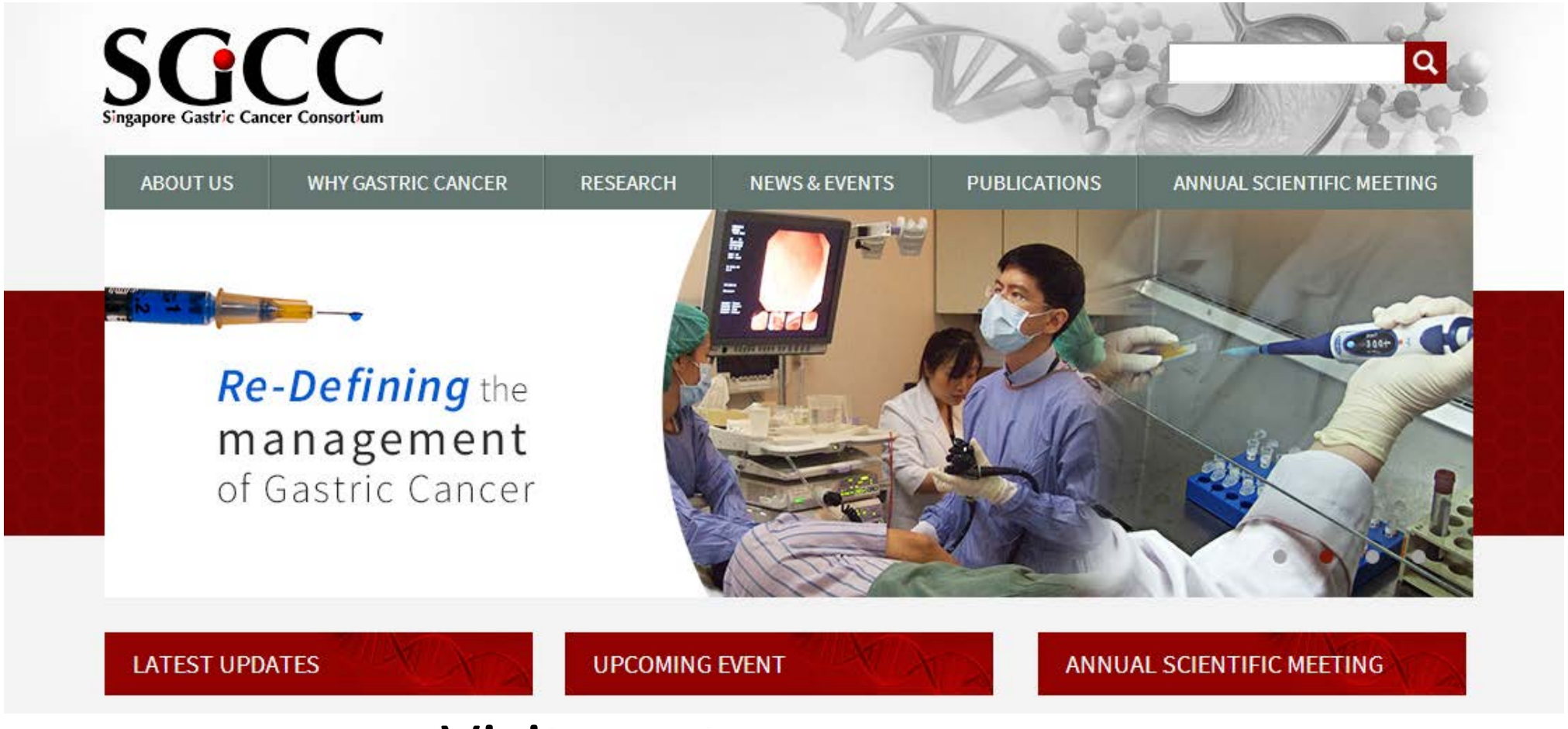
- Fatima CARNEIRO, Portugal
- Ramanuj DASGUPTA, Singapore
- Emad EL-OMAR, Australia
- Jim GOLDENRING, USA
- Masanori HATAKEYAMA, Japan
- Yoshiaki ITO, Singapore
- Koji KONO, Japan
- Tatsuhiro SHIBATA, Japan
- Jimmy SO, Singapore
- Toshio SUDA, Singapore
- Iain TAN, Singapore
- Ker Kan TAN, Singapore
- Patrick TAN, Singapore
- Toshikazu USHIJIMA, Japan
- Timothy WANG, USA
- Yoshio YAMAOKA, Japan
- Han Kwang YANG, Korea
- Khay Guan YEOH, Singapore
- Wei Peng YONG, Singapore

topics

- Epidemiology, Risk Prediction and H. pylori
- Carcinogenesis, Stem Cells and Organoids
- Genomics, Pathology and Biomarkers
- Clinical Research, Clinical Trials and Therapeutics
- Special Session: Colorectal Cancer

www.sgcc.sg/asm

Thank you!



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