Singapore Gastric Cancer Consortium

RE-DEFINING THE MANAGEMENT OF GASTRIC CANCER

YE OH Khay Guan, Patrick TAN
Yoshiaki ITO, YONG Wei Peng, Jimmy SO

A National Translational & Clinical Research Flagship Programme
Importance of Gastric Cancer Research

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

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
Survival for Gastric Cancer is Poor

Gastric cancer is curable if diagnosed at an early stage

but it is traditionally associated with poor prognosis

because of late presentation

5 year Survival, International

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

5 year Survival, Singapore

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

RE-DEFINING THE MANAGEMENT OF GASTRIC CANCER

Strongly Facilitated by
NMRC National Medical Research Council

Universities

Research Institutes

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

Hospitals

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

Industry

NMRC Singapore
EDB Singapore
Ministry of Health Singapore
Sanofi
Novartis
Bayer

Genome Institute of Singapore
A*STAR
Experimental Therapeutics Centre
Singapore Immunology Network
Institute of Medical Biology
Bioprocessing Technology Institute
Illumina
Sengenics
Taiho Pharma Singapore
MirXes
RE-DEFINING THE MANAGEMENT OF GASTRIC CANCER

3 Themes

(1) Early Detection

(2) Improve Treatment

(3) Biology of Gastric Ca

Aims & Target

Screening strategy based on identifying high risk groups + biomarker

Genomic profiling to guide chemotherapy

Model of gastric carcinogenesis, critical events, gatekeeper gene, biomarkers.

Singhapore Gastric Cancer Consortium
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)

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

At Years 0, 3 and 5:

• 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

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

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)

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

Discovery

N=472 (236 GC)

24-miR Serum Biomarker Panel

Validation

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

SGCC
Diagnostics
Development Hub,
Biopolis
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**:
- MS Bergholt et al. Gastroenterology (2014)
- MS Bergholt et al. Biosens Bioelectron (2011)
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
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. Surgical Endoscopy (2014)
- S.J. Phee et al. Surgical Endoscopy (2013)
New Genomic Classification of Gastric Cancer

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

- **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

"A reliable classification of biological and clinical significance."

_P Correa, Faculty of 1000

Singapore/ Australia/ UK/ HK/ S Korea/ MD Anderson Cohort (~550 patients)
G1 and G2 Cell Lines Respond Differently to Chemotherapy Treatment

5-FU
P=0.04

Cisplatin
P=0.03

Oxaliplatin
P=0.02

Gastroenterology. 2011 Aug;141(2):476-85
Clinical Trial: Guided by Genomics in Gastric Cancer (3G)

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

Wei-Peng YONG, Dept of Haem-Oncology NCIS

Tumour genomic signature assessment

Stratification

Gdif

Cisplatin + TS-1

Gint

Oxaliplatin + TS-1

Gunknown

Oxaliplatin + TS-1

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

- Fanconi anemia (FA) pathway is dedicated to the repair of DNA interstrand 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

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

Cell Reports. 2014 Aug 7;8(3):767-82
mRNA 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
<table>
<thead>
<tr>
<th>Title</th>
<th>Journal</th>
<th>Year</th>
<th>Impact Factor</th>
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<tbody>
<tr>
<td>with distinct clinical outcomes.</td>
<td>;21(5):449-56.</td>
<td></td>
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<tr>
<td>adenocarcinomas.</td>
<td>2014-308252 [epub ahead of print]</td>
<td></td>
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<td>Nanoscale chromatin profiling of gastric adenocarcinoma reveals cancer-</td>
<td><em>Nature Communications</em> 2014;</td>
<td>2014</td>
<td>10.02</td>
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<td>associated cryptic promoters and somatically acquired regulatory</td>
<td>5:4361</td>
<td></td>
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<td>elements.</td>
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<td>mTORC1 inhibition restricts inflammation-associated gastrointestinal</td>
<td><em>Journal of Clinical Investigation</em> 2013</td>
<td>2013</td>
<td>15.43</td>
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<td>tumorigenesis in mice.</td>
<td>Feb 1;123(2):767-81.</td>
<td></td>
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<tr>
<td>Identification of molecular subtypes of gastric cancer with different</td>
<td><em>Gastroenterology</em> 2013;145(3):</td>
<td>2013</td>
<td>12.82</td>
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<td>responses to PI3-kinase inhibitors and 5-fluorouracil.</td>
<td>554-65</td>
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<tr>
<td>Exome Sequencing of Gastric Adenocarcinoma Reveals Recurrent Somatic</td>
<td><em>Nature Genetics</em> 2012; 44(5):</td>
<td>2012</td>
<td>35.21</td>
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<tr>
<td>Mutations in Cell Adhesion and Chromatin Remodeling Genes.</td>
<td>570-4.</td>
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<tr>
<td>STAT3-driven upregulation of TLR2 promotes gastric tumorigenesis</td>
<td><em>Cancer Cell</em> 2012; 22(4):466-78.</td>
<td>2012</td>
<td>26.57</td>
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<td>independent of tumor inflammation.</td>
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<td>Loss of Runx3 is a key event in inducing precancerous state of the</td>
<td><em>Gastroenterology</em> 2011;140(5):</td>
<td>2011</td>
<td>12.82</td>
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<td>stomach.</td>
<td>1536-1546.</td>
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## Industry Collaborations

<table>
<thead>
<tr>
<th>Area of Collaboration</th>
<th>Industry Partner</th>
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<tbody>
<tr>
<td>Biomarkers for Early Gastric Cancer</td>
<td>Illumina</td>
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<tr>
<td>Biomarkers &amp; Treatment</td>
<td>Bayer</td>
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<tr>
<td>Vaccine Study</td>
<td>Onco Therapy &amp; Tokyo University</td>
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<td>3G Study</td>
<td>Taiho</td>
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<td>Avagast</td>
<td>Roche</td>
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<td>First-in-man Clinical Trial</td>
<td>Novartis</td>
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<td>SB939</td>
<td>S*Bio Pte Ltd</td>
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<td>Gastric Cancer Gene Expression</td>
<td>Genentech</td>
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<td>Saladax</td>
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<td>Pharmacokinetics</td>
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<td>Antibody</td>
<td>Kyowa Hakko Kirin</td>
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<td>Multispectral imaging</td>
<td>Perkin Elmer</td>
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*Total industry funding of >$22 million from 16 companies*
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

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
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<tbody>
<tr>
<td>KG YEOH</td>
<td>NUS</td>
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<tr>
<td>Yoshiaki ITO</td>
<td>CSI</td>
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<td>Patrick TAN</td>
<td>Duke-NUS</td>
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<td>Wei Peng YONG</td>
<td>NUHS</td>
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<td>Jimmy SO</td>
<td>NUHS</td>
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<td>Lawrence HO</td>
<td>NUHS</td>
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<td>Richie SOONG</td>
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<td>Tiing Leong ANG</td>
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<tr>
<td>Nicholas BARKER</td>
<td>IMB</td>
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<td>Boon Huat BAY</td>
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<td>Su-Pin CHOO</td>
<td>NCCS</td>
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<td>Maxey CHUNG</td>
<td>NUS</td>
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<td>Horst FLOTOW</td>
<td>ETC</td>
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<td>Liang Kee GOH</td>
<td>Duke-NUS</td>
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<td>Axel HILLMER</td>
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<td>Zhi Wei HUANG</td>
<td>NUS</td>
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<td>KM FOCK</td>
<td>CGH</td>
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<td>A JEYASEKHARAN</td>
<td>NUHS</td>
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<td>Matiullah KHAN</td>
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<td>Koji KONO</td>
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<td>Yoon-Pin LIM</td>
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<td>Khoon Lin LING</td>
<td>SGH</td>
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<td>Chris KHOR</td>
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<td>Louis PHEE</td>
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<td>Jaideepraj RAO</td>
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<td>Ming TEH</td>
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<td>Celestyal YAP</td>
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<td>Ruiyang ZOU</td>
<td>NUS</td>
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<td>Yik Ying TEO</td>
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<tr>
<td>Woon Puay KOH</td>
<td>Duke-NUS</td>
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<tr>
<td>Ai Zhen JIN</td>
<td>HPB</td>
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<tr>
<td>Sethi SUNIL</td>
<td>NUS</td>
</tr>
<tr>
<td>Supriya SRIVASTAVA</td>
<td>NUS</td>
</tr>
<tr>
<td>Chon Boon ENG</td>
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<tr>
<td>Rajeev SINGH</td>
<td>NUHS</td>
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</tbody>
</table>

## Funding agencies

- National Medical Research Council
- National Research Foundation

SGCC 7th Annual Meeting, 23-24 July 2014
9th ANNUAL SCIENTIFIC MEETING
LATEST ADVANCES IN GASTRIC CANCER RESEARCH

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