Genomic Predictors of Clinical Outcome in Gastric Cancer: The Singapore Experience

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Global Leaders in Genomic Medicine Conference
Washington DC - Jan 2014
Biomedical Sciences (BMS) in Singapore (2003-2013)

Significant and increasing BMS support from Singapore government

Funding from Three Major Ministries (Trade/Industry, Education, Health)

Multiple Research Institutes (eg Biopolis) and Academic Medical Centres (eg Singhealth, National University Hospital)
Focus Area: Asian Cancers (e.g., Gastric/Stomach)

Global Cancer Mortality

Sun et al., Nature Reviews Cancer 2007

From The Scientist, Sep 22, 2003
Genomic Amplifications Highlight GC Therapeutic Targets

**TOGA Trial, Lancet 2010**

**ERBB2/HER2 Amplification**

**ERBB2 Positive (8-10%)**

**Gastric Cancer**

**OS in IHC 2+ / FISH+ or IHC 3+ (exploratory analysis)**

<table>
<thead>
<tr>
<th>Events</th>
<th>OS</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>XP/FP</td>
<td>120</td>
<td>16.0</td>
<td>0.65, 0.83</td>
</tr>
<tr>
<td>XP/FP+T</td>
<td>136</td>
<td>11.8</td>
<td>Δ 4.2</td>
</tr>
</tbody>
</table>

**Gut 2012**

=72/193 (37.3%)
Genomic Amplifications in Asian and Caucasian GCs - Concordant and Largely Similar

Singapore Cohort

TCGA Cohort (USA)
Transcriptome Clustering Identifies THREE GC Subtypes: Integration with Pathology

Consensus Clustering

250 Gastric Tumors

Consensus Subtype Matrix
### GC Genomic Subtypes: Mesenchymal, Proliferative, and Metabolic

<table>
<thead>
<tr>
<th>Genomic Subtype</th>
<th>Histological Features</th>
<th>Associated Genes/Pathways</th>
<th>Drug sensitivity (Preclinical)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mesenchymal</strong></td>
<td>• Diffuse subtype</td>
<td>• EMT pathways</td>
<td>• Sensitive to PI3K/AKT/mTOR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CSC pathways</td>
<td>inhibitors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• TGFβ</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• mTOR signalling</td>
<td></td>
</tr>
<tr>
<td><strong>Proliferative</strong></td>
<td>• Intestinal subtype</td>
<td>• Genomic instability</td>
<td>• Unresponsive to 5-FU</td>
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<tr>
<td></td>
<td></td>
<td>• TP53 mutations</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cell cycle</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• DNA replication</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Mitosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Copy number alterations</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(ERBB2/HER2 and KRAS)</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td>• Gastric subtype</td>
<td>• Metabolic processes</td>
<td>• Increased sensitivity to 5-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Digestion</td>
<td>FU</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Secretion</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• SPEM</td>
<td></td>
</tr>
</tbody>
</table>

*Gastroenterology, 2013*
Genomic Subtyping May Drive Improved Pathology

Lauren’s Classification (1960)
- Intestinal
- Diffuse

WHO Classification (2010)
- Gastric Phenotype
  - Aka Metabolic
- Intestinal Phenotype
  - Aka Proliferative

Examples of histological staining for MUC5AC, MUC6, MUC2, and CD10.
Working Roadmap for GC Carcogenesis

- Normal gastric mucosa
- Superficial gastritis (Weeks)
- Chronic atrophic gastritis (Years)
- Intestinal metaplasia
- Dysplasia (intestinal phenotype)
- Gastric adenocarcinoma (intestinal phenotype)
- Proliferative genotype?

Courtesy Fatima Carneiro, IPATIMUP
Dissecting Asian Cancers – Some Contributions from Singapore

Exome sequencing of gastric adenocarcinoma identifies recurrent somatic mutations in cell adhesion and chromatin remodeling genes

Nature Genetics (2012)

A common BIM deletion polymorphism mediates intrinsic resistance and inferior responses to tyrosine kinase inhibitors in cancer

Nature Medicine (2012)

Oncofetal Gene SALL4 in Aggressive Hepatocellular Carcinoma

The POLARIS Program – Enabling Genomic Medicine in a City-State

Funded by A-STAR (Agency for Science, Technology and Research) for 3 years

Pilot clinical use of genomic testing (cancer and genetic diseases)

National network of CAP-certified laboratories at hospitals and research institutes
Some POLARIS Operating Principles

Genomic medicine labs should be deployed _WITHIN_ existing clinical frameworks

Frameworks for GENETIC testing should exist _PRIOR_ to GENOMIC testing

Genomic tests should leverage on _EXISTING RESEARCH COMPETENCIES_

Tests providing _CLINICAL UTILITY_ will lead to clinician buy-in
POLARIS - Current Status (2013)

First POLARIS Test - **TGFBI Eye Test** (early 2014)

Genomic labs targeting **national certification** in mid 2014 (Illumina + Reflex Validation)

Test revenues are **distributed** among network partners on cost-recovery basis

Second POLARIS Test - **90 gene GI Panel** (3rd quarter 2014)
Stromal Corneal Dystrophies (SCDs) and TGFBI Testing

- Inherited disorders leading to loss of corneal transparency.
- *TGFBI* mutations underline the majority of stromal CDs.

**Clinical Utility**

- Disease Diagnosis
- Treatment Selection for Patients
- Screening of family members

**TGFBI Testing**
PARTIES INVOLVED IN POLARIS™ TGFBI TEST

**SNEC/SGH**
- Patients & Consultation
- Test Ordering
- Blood Collection

**GIS/SERI**
- Project Management
- Mutation Database

**NUHS**
- Sequencing
- Mutation Rpt

**POLARIS™ TGFBI Test**
Challenges in Developing a Singapore Framework for Genetic/Genomic Testing

Legal and licensing agreements across institutions and ministries are often complex.

Reimbursement options for genetic assays that cross medical centres.

General lack of genetic counsellors and advisors.

Official polices on patient consent, incidental findings and aggregation of genetic/genomic data.
Thanks and Questions

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