Development and Application of Precision Oncology in China

Hu Xin
Fudan University Shanghai Cancer Center (FUSCC)
Development of Precision Oncology in China
Precision Medicine Era for Oncology

Traditional Medicine | Evidence-based Medicine | Precision Medicine

Empirical Treatment | Standardized Treatment | Multi-discipline Treatment | Personal Treatment | Precise Treatment
Advances of Precision Medicine in worldwide and in China

**Human Genome Project** (1990)

I. the world's largest collaborative biological project
II. human genome map

**Precision Medicine Program in US** (2015)

I. national research cohort
II. more and better treatments for cancer
III. Regulatory modernization

**Precision Medicine Program in China** (2015)

I. ¥60 billion RMB budget
II. Listed in the 13th five-year plan

**Cancer Moonshot Program** (2016)

I. network for patients
II. data ecosystem
III. clinical trial network for immunotherapies
### The leading cancer genomic study in the world

<table>
<thead>
<tr>
<th>Year</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>Pilot</td>
</tr>
<tr>
<td>2006-2009</td>
<td>Project Expansion</td>
</tr>
<tr>
<td>2010-2014</td>
<td>Analysis Completion</td>
</tr>
<tr>
<td>2015-2016</td>
<td></td>
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</table>

- **NCAB Report**
- **GBM Report**
- **Ovarian Report**
- **Rare Projects Initiated**
- **9 tumor types closed**
- **10,000 Cases complete**

#### Data from The Cancer Genome Atlas: 2015 Update

- **12,550 cases qualified across 33 tumor types**
- **10,849 with minimum clinical data set, 8404 with at least 1 year follow-up; ~50% with treatment data**
- **155,368 samples of RNA/DNA/protein (146,950 DNA +RNA; 8418 tissue for protein)**
Next Generation Sequencing Formally Come to Clinical Practice

**FDA approved MSK-IMPACT™** for detecting mutations with evidence of clinical significance

1. Patient consent
2. Sample accessioning (Tumor, Blood)
3. Sample preparation
4. Sequencing
5. Bioinformatics (Mutations, CNV, Rearrangements)
6. Case review and sign out
7. Genomic variants database and management
8. Transitional appliance (Clinical report, Clinical trial, data mining & interpretation)

Zehir A. Nat Med. 2017
CFDA, China Food And Drug Administration; ICH, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use; CPPCC, the Chinese People's Political Consultative Conference; NDRC, National Development and Reform Commission

‘Precision Medicine’ occupies an important position of China national medicine development plans.
Grand Market for Precision Medicine in World-wide

- 2016-2020: The world-wide market for precision medicine increased at 15% per year.
- The world-wide market for precision medicine is expected to rise to 1050 billion dollars.
Gene testing industry grows rapidly in China, hoping to becoming one of biggest market for precision medicine.

2012-2017: Chinese market for precision medicine increased at 20-25% per year.
Oncogenic driver mutations (EGFR, KRAS, ERBB2, AKT1, BRAF, MEK1, NRAS, PIK3CA, ALK etc.) were found in 64% (466/733) advanced lung cancer patients.
In Chinese lung cancer patients, the major driver genes—including **EGFR, ALK, ROS1, RET, MET, HER2, BRAF, and KRAS**.
Precision Medicine of Liver Cancer in China

Targeted therapy for liver cancer

Hongyang Wang

Targeted therapy for liver cancer: Challenges and opportunities

Shuzhen Chen1,2, Jing Fu1,2, and Hongyang Wang1,2,*

Prof. Hongyang Wang
Vice President of China Anti-Cancer Association (CACA)
Advances of Breast Cancer

Precision Oncology in FUSCC
Fudan University Shanghai Cancer Center (FUSCC)

### Outpatient

<table>
<thead>
<tr>
<th>Year</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count</td>
<td>1025674</td>
<td>1127757</td>
<td>1213184</td>
<td>1279267</td>
<td>1339667</td>
<td>1447180</td>
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</table>

### Surgery

<table>
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<tr>
<th>Year</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count</td>
<td>26240</td>
<td>30621</td>
<td>34433</td>
<td>36744</td>
<td>42153</td>
<td>45017</td>
</tr>
</tbody>
</table>
Fudan University Shanghai Cancer Center (FUSCC)

240 new clinical trials (2018)

Sponsor Initiated: 87
Investigator Initiated: 153

Types of clinical trials
4 –steps strategies:

A. Patient Cohorts

B. Pan-omics profiling (Landscape)

C. Biomarkers & targets (target validation)

D. Precision treatment (clinical trials)

Jiang YZ, Shao ZM. Science Suppl, 2016
The Challenges in the precision treatment of breast cancer

- TNBC
  - Early relapse
  - No specific targeted treatment

- Anti-HER2
  - Half of patients acquire anti-HER2 resistance

- Anti-ER
  - 30-40% patients acquire anti-ER resistance
Genomic and Transcriptomic Landscape of TNBC: Subtypes and Treatment Strategies

- Genomic and transcriptomic landscape of 465 primary TNBCs (WES, CNV array and RNAseq)

- Transcriptomic data classify TNBCs into four subtypes

- Identifies potential targets within specific TNBC subtypes

- Design the clinical trials

Jiang et al Cancer Cell 2019
TNBC tumor were clearly classified into four distinct clusters according to transcriptome sequencing results.

LAR: luminal androgen receptor subtype
IM: immunomodulatory subtype
BLIS: basal-like and immune suppressed subtype
MES: mesenchymal-like subtype
Luminal Androgen Receptor Subtype

- High Androgen Receptor signaling
- High prevalence of cell cycle promoting genes: CCND1 gain and CDKN2A Loss
- Low cell cycle suppressing genes mutations prevalence: RB1
- AR antagonist or Cell cycle associated treatment: CDK4/6 inhibitor
Luminal Androgen Receptor Subtype

- HER2 non-silent mutation
  - (9% in FUSCC and 20% in TCGA)
- PIK3CA mutation
  - (0.04% in BLIS, 13% in IM, 39% in LAR and 26% in MES)
- Anti-HER2 or Anti-PI3K treatment

Jiang et al Cancer Cell 2019
Basal-like and immune suppressed subtype

- High BRCA1/2 germline mutation prevalence and genome instability
- HRD score predicts DNA damage repair pathway deficiency

- BRCA1/2 germline mutation or high HRD score: PARPi or Radiotherapy
Immune-activated cells and immuno-stimulators were enriched in the IM subtype: TILs, CD8+ T cell, M1 Microphage and activated NK cell.

Potential treatments: anti-PD1/PD-L1, anti-CTLA-4
- Tumor stem cell associated genes cluster
- High JAK/STAT pathway signaling.
- Treatment: JAK/STAT3 inhibitors?

(activated-STAT3 Signaling was defined by Sonnenblick and colleagues)
## Characterization of TNBC Subtypes

<table>
<thead>
<tr>
<th>Clinical</th>
<th>BLIS</th>
<th>IM</th>
<th>LAR</th>
<th>MES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor prognosis</td>
<td>Poor prognosis</td>
<td>Good prognosis</td>
<td>Moderate prognosis; Related to apocrine differentiation; AR positive</td>
<td>Poor prognosis</td>
</tr>
<tr>
<td>Mutation</td>
<td>High BRCA1/2 mutation prevalence</td>
<td>TP53 mut (77%) KDM5A (11%)</td>
<td>HER2 and PIK3CA mutation enrichment</td>
<td>Normal</td>
</tr>
<tr>
<td>Copy number</td>
<td>High chromosonal instability</td>
<td>Normal</td>
<td>CCND1 gain CDKN2A (p16) loss RB1 neutral</td>
<td>Normal</td>
</tr>
<tr>
<td>Potential Treatment</td>
<td>High HRD score: PARPi/DDP</td>
<td>Immune checkpoint inhibitors</td>
<td>Anti-AR Anti-HER2 CDK4/6i</td>
<td>Targeting tumor stem cell STAT3i /</td>
</tr>
</tbody>
</table>
IHC surrogates for TNBC Subtypes

*in the Department of Pathology*

- Highly expressed genes in LAR, IM and BLIS subtypes
- Microscopic images of a representative case of each FUSCC-TNBC subtype
<table>
<thead>
<tr>
<th>Mutation</th>
<th>CDK28 remains high-prevalence mutation gene</th>
</tr>
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<tbody>
<tr>
<td>CNV</td>
<td>High-prevalence mutation genes</td>
</tr>
<tr>
<td>Fusions</td>
<td>Therapeutic Actionable genes</td>
</tr>
</tbody>
</table>

**Breast cancer**

- **484 gene Panel**
- Designed for breast cancer

1. **Mutation**: 398
2. **CNV**: 109
3. **Fusions**: 25

- High-prevalence mutation genes
- Therapeutic Actionable genes
- Drug resistance associated genes
Prospective Sequencing Chinese BC Cohort: ~1500 breast cancer samples have been sequenced in PMC.

484 gene in Fudan BC Panel
Future clinical trial (FUSCC-TNBC-Umbrella)

Multi-center, Phase IB/II, open-label  (NCT03949634)

Local advanced and advanced TNBC (n=300-400)

Biopsy / Pathology validation

IHC

Gene panel screening

Algorithm

**LAR**
- HER2 mut+
  - CCND1 gain / CDKN2A loss / RB1 neutral
  - Pyrotinib + capecitabine

**IM**
- TILs/PD-L1 high
  - CDK4/6i+ARi
  - Chemo+ Immunotherapy

**BLIS**
- gBRCA mut+
  - PARPi
  - gBRCA mut-
  - CDK4/6i+ARi

**MES**
- Ki67 low / CD31 pos
  - Apatinib+ Bevacizumab
  - PI3K pathway mut+
  - mTORi

Unpublished data
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Novartis
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