Pharmacogenomics: Science, Challenges and Promises

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From Shanghai to Rochester
Pharmacogenomics

- A study of the role of inheritance in variation of drug response.
- A critical component of precision medicine.
- Both tumor DNA and germline DNA can contribute to response to anticancer therapy.
Research Path

Functional characterization of SNPs in drug metabolizing enzymes

Application of cell line models and patient DNA, together with genome wide association approach and functional studies

Application of animal models and cell lines, together with high throughput omics and functional studies in PGx of anti-cancer

Pharmacogenetics. 2003 Sep;13(9):555-64;

Cancer Res. 2008 Sep 1;68(17):7050-8.
Cancer Cell. 2009 Sep 8;16(3):259-66.
Curr Opin Pharmacol. 2011 Aug;11(4):360-4
Genome Res. 2013 Sep;23(9):1363-72.

BEAUTY study
PROMOTE study
ER+ Breast Cancer Treatment

- 70-80% of all breast cancer patients are ER+
- Endocrine Therapy – AIs
- Endocrine Therapy – SERMs
- Both can be used in the prevention setting
- Third generation AIs include:
  - Irreversible steroidal inhibitors, such as exemestane
  - Non-steroidal reversible inhibitors, such as anastrozole and letrozole
Aromatase Inhibitors (AIs)

- AIs are the mainstay of treatment of ER+ breast cancer patients, which constitute 70-80% of all breast cancer patients.

Androstenedione ➔ Estrone ➔ Estrone Conjugates

Testosterone ➔ Estradiol ➔ Estradiol Conjugates

Aromatase (CYP19)

17β-HSD
Aromatase Inhibitors (AIs)

• Response to AI varies greatly, ranging from AI-induced ADE to lack of efficacy—disease recurrence.

• AI response in women with high BMI is lower relative to tamoxifen and BMI is directly associated with circulating estrogen levels.

Supports hypothesis that PD effect of AIs is a determinant of efficacy.

Does the germline genome contribute to AI response through its PD effect, i.e., reduction in estrogen level?
Clinical Studies

Mayo, MD Anderson and MSK trial: ≈800 women with primary breast cancer treated with anastrozole in the adjuvant setting

- Obtain plasma for hormone assays and blood for DNA
- GWAS genotype with Illumina Human610-Quad BeadChip
Estradiol: Baseline and on Anastrozole
n=643; Lower Limit of Quantitation, 0.625 pg/ml

**Anastrozole Concentration Quartile:**
- **Black:** Lowest
- **Red:** Second
- **Yellow:** Third
- **Green:** Highest

Ingle et al. Steroids Epub 8/24/2014
GWAS of changes in estrogen levels pre and post AI treatment

Changes in E1

Changes in E2

Changes in E1 + E2

changes in E1 + E2

Log P values

-Log P values

-Log P values
NCIC-CTG MA27

- Phase III trial comparing exemestane and anastrozole, N=4800.
- GWAS with multiple phenotypes including breast events.
Kaplan-Meier Curve for Time to Breast Event by rs6990851 Genotype

SNP association with time to distant metastasis

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<th>SNP</th>
<th>Minor Allele</th>
<th>HR</th>
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<th>U95</th>
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<td>0.111</td>
<td>Exemestane Arm</td>
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CSMD1: CUB And Sushi Multiple Domains 1

• In breast cancer, loss of CSMD1 is associated with high tumor grade and poor survival, suggesting that CSMD1 is a tumor suppressor gene.

• Promotes degradation of C4b & C3b, inhibits membrane attack complex assembly.

• SNPs within this gene associate with multiple Neuronal pathologic conditions.
**CSMD1 regulates CYP19 expression**

Expression levels corrected to the control negsiRNA

- **CYP19**
  - NegsiRNA
  - siCSMD1

- **CSMD1**
  - ZR75-1 cell
  - T47D cell

CSMD1 regulates CYP19 expression.
A. CSMD1

B. CYP19A1

rs6990851

Relative gene expression level

Anastrozole

Letrozole

Exemestane

D. WT

Non A A+An A+Let A+EXE

CYP19A1

Actin

A. CSMD1

B. CYP19A1

An.:   0      0     0     0     1    10   100  1000    (nM)

Anastrozole

Letrozole

Exemestane
Conclusions

• Response to anastrozole, but not letrozole and exemestane is SNP dependent.

• Our finding indicates additional mechanisms associated with anastrozole mechanisms of action.

• Germline genetic variation can contribute to the drug response not only by affecting pharmacokinetics genes but also pharmacodynamics genes.
PGx of Chemotherapy in Breast Cancer: Application of NextGen Sequencing Analysis and PDX Models
• Systemic chemotherapy reduces the annual odds of disease recurrence, breast cancer mortality, and all-cause mortality by 24%, 15% and 14.9% , respectively.

• There is great heterogeneity in response to chemotherapy.

• There are no specific biomarkers for anthracycline–taxane-based therapy.
BEAUTY
(Breast Cancer Genome Guided Therapy)

PIs: Matthew Goetz, Judy Boughey
   Lab PI: Liewei Wang
   Lab team: Eric Wieben, Dick Weinshilboum, James Ingle
   Bowen Gao, Jia Yu, Minetta Liu
   Pathology team: Dan Visscher, Ann Moyer
   Radiology team: Amy Conners, Katie Jones
   Genetic counselor: Marissa Ellingson
Stats team: Jeanette Eckel Passow, Vera Suman, Travis Dockter, Krishna Kalari, Steve Hart,
   Hugues Sicottes, Jason Sinnwell
Arizona team: Don Northfelt, Rick Gray
Florida team: Alvaro Moreno, Sarah McLaughlin
Breast Cancer Genome Guided Therapy Study (BEAUTY)

Women with invasive breast cancer

HER2+
Paclitaxel + Trastuzumab*
AC or EC or FEC

HER2-
Paclitaxel**
AC or EC or FEC

MRI MBI
Tumor biopsy for
1) Sequencing
2) PDX
Blood sample§

MRI MBI
Blood sample§

MRI MBI
Blood sample§

Surgery
5 year observation

Residual tumor tissue for
1) Sequencing
2) PDX

*Pertuzumab allowed for HER2+ disease after 10/18/13
**Carboplatin allowed for TN disease after 3/5/14
§For sequencing, biomarkers, CTCs, and cell-free DNA
PDX taxane response correlates with original patient response
- 4 months following completion of chemotherapy
- October 2013
- Fatigue, diffuse pain, night sweats, failure to thrive
- PET scan
- Biopsy of liver: Metastatic breast cancer: ER/PR/HER2 negative
Hypothesis: Decitabine may be effective in the treatment of breast cancer patients, especially those with high levels of DNMTs.
Conclusions

• Both germline and tumor genome can contribute to drug response.

• Integrated omics can help us to understand the drug resistance mechanisms and help us to accelerate drug development.

• Functional and mechanistic studies beyond biomarkers are crucial in the era of precision medicine.

• Team work is the key to the success.
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  BEAUT Team
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ASCPT