Cancer Pharmacogenomics Development, Science, Translation

Richard Weinshilboum, M.D.
Dasburg Professor of Cancer Genomics Research
Department of Molecular Pharmacology and Experimental Therapeutics
Mayo Clinic-Mayo Medical School
Rochester, Minnesota USA
Cancer Pharmacogenomics

- Introduction
- Present
- Promise
- Conclusions
Pharmacogenetics-Pharmacogenomics

Critical component of “personalized” or “individualized” medicine
Clinical Goals

• Avoid adverse drug reactions
• Maximize drug efficacy
• Select responsive patients
Pharmacogenetics-Pharmacogenomics

Scientific Goals

• Link variation in genotype to variation in phenotype

• Determine mechanisms responsible for that link

• Translate the link into enhanced understanding, treatment and prevention of disease
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FDA Hearings
Pharmacogenetics and Drug Labeling

• Thiopurines – TPMT*
• Irinotecan – UGT1A1*
• Warfarin – CYP2C9 and VKORC1*
• Tamoxifen – CYP2D6*

*germline polymorphisms
Childhood ALL Survival
St. Jude Experience

Pui and Evans, *NEJM*. 2006;354:166-78. Copyright © 2006 Massachusetts Medical Society. All rights reserved.
TPMT
Genetic Polymorphism
Clinical Consequences

• Low TPMT
  — Increased thiopurine toxicity
  — Increased risk for secondary neoplasm

• High TPMT
  — Decreased therapeutic effect
Selected Human TPMT Alleles

TPMT*1 (wild type)

TPMT*3A

TPMT*3B

TPMT*3C

Pharmacogenetics-Pharmacogenomics

FDA Hearings
Pharmacogenetics and Drug Labeling

- Thiopurines – *TPMT*
- Irinotecan – *UGT1A1*
- Warfarin – *CYP2C9* and *VKORC1*
- Tamoxifen – *CYP2D6*
Tamoxifen Biotransformation

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CYP2D6 Pharmacogenetics

Debrisoquine/4-Hydroxydebrisoquine Metabolic Ratio

Number of Subjects

0 10 20 30 40 50 60 70 80 90 100

0.01 0.1 1 10 100

UMs  EMs  PMs

cutoff

1011 Subjects

Tamoxifen Pharmacogenetics

Breast Cancer (190 Patients)

Relapse–Free Survival, %

Disease–Free Survival

Goetz et al., Breast Cancer Res. Treat. 2007; 101:113-121.
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Tamoxifen Pharmacogenetics

Schroth et al., JCO. 2007; 25:5187-93. Reprinted with permission. © 2010 American Society of Clinical Oncology. All rights reserved.
Pharmacogenomics

Evolution

• One gene, one or a few SNPs
• One gene, intragenic haplotypes
• PK and PD pathways and haplotypes
• Genome-wide association studies
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Pharmacogenomic Genome-wide Model System

“Human Variation Panel”
Cell Lines

• 96 CA, 96 AA, 96 HCA
• Illumina genome-wide SNPs
• Affymetrix 6.0 genome-wide SNPs
• Affymetrix U133 2.0 Plus expression data
• Affymetrix exon array data

Liewei Wang, M.D., Ph.D.
Cytidine Analogues

Ara-C

Gemcitabine
Gemcitabine "Pathway"

Deamination

SLC28A1, A2 and A3

SLC29A1 and A2

CDA

NT-5C

DCK

UMP-CMPK

Gemcitabine

RRM1

RRM2

RRM2B

NDPs

dNDPs

dNTPs

dNTPs

DNA

Nucleus
Gemcitabine-AraC
IC50 – Expression Association

Gemcitabine
IC50 vs. expression array

AraC
IC50 vs. expression array

“Biased” – pathway-based

“Unbiased” – genome-wide

Functional validation

*NT5C3*, a “pathway” gene, and *FKBP5*, a “non-pathway” gene encoding a 51 kDa immunophosphitin, were selected for functional study based on p values and QRT-PCR verification.
The Therapeutic Revolution

Goodman and Gilman’s
“The Pharmacological Basis of Therapeutics”
Functional Characterization of FKBP5
Gemcitabine

FKBP5 Functional Characterization in Caspase-3/7 Activity

Signal for Apoptotic Cells

- **Negative-siRNA**
- **FKBP5-siRNA**

**Graph 1:**
- **SU86**
- **Gemcitabine Concentration (µM)**
- **Signal for Apoptotic Cells**

**Graph 2:**
- **MD-MB-231**
- **Gemcitabine Concentration (µM)**

Reprinted with permission from Li et al. *Cancer Res.* 2008; 68:7050-7058. (Figure 4)
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• Introduction
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Pharmacogenomics
Genomic Era

Developments

• Next Gen DNA Sequencing
• 1000 Genomes Project
• ENCODE
• RNA-seq
• DTC Genomics
Pharmacogenomics

Clinical Goals

• Avoid adverse drug reactions
• Maximize drug efficacy
• Select responsive patients
Cancer Pharmacogenomics

Challenges

• Germline and/or somatic genome
• Clinical trials and/or population studies
• Translational and/or mechanistic studies
• Funding to incorporate rapidly changing, expensive technologies
• Collaboration and replication
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Primary Investigator Site
Co-Investigator Site