Predict

- Select right drug
- Select right dose
- Develop new drugs

Non-Response  
Response  
Adverse Reaction
Phase I: Each Chromosome Has Many Genes...
Examples of Personalized Medicines

FDA Label Changes- Current and Planned:

- 6-Mercaptopurine: polymorphism in enzyme (TPMT) serious adverse effect (bone marrow suppression)

- Allopurinol: polymorphism in enzyme (TPMT) serious adverse effect (bone marrow suppression)

- Warfarin: polymorphism in enzyme (CYP2C9) serious adverse effect (bleeding)

- Irinotecan: polymorphism in enzyme (UGT1A1) serious adverse effect (neutropenia, profound diarrhea)

- Tamoxifen: polymorphism in enzyme (CYP2D6) may lead to non-response in women with breast cancer
Examples of Personalized Medicines: Pharmacogenomic Tests

- The Roche AmpliChip CYP450
  The world’s first pharmacogenetic microarray-based test approved for clinical use by FDA and in EU.
  - Drug Response Genes
    - Drug Metabolism Enzyme Genes

- Celera Diagnostics
  - HIV genotyping
  - Hepatitis Genotyping

- FDA Guidances
  - Pharmacogenomic Guidance
  - Pharmacogenetic Test Guidance
Some Progress But Much Research is Ongoing
Variation in Drug Response is Determined by Variation in Drug Levels

Drug Response

Intestine

Drug Levels In Blood

Liver

Drug Levels in Target

Kidney

Transporters
Organic Cation Transporter, OCT1

Metformin

Cimetidine

Pindolol

MPP⁺

MPTP

Liver
Two Stories About OCT1

OCT1 Polymorphisms: Determinant of Variation in Drug Response

Metformin

OCT1: Determinant of Anti-Cancer Drug Specificity

Oxaliplatin
Does Genetic Variation in Membrane Transporters Contribute to Variation in Drug Response?

Human Genetic Studies

Pharmacogenetic Studies

Transporter

Patients

Identify Mutant/Polymorphic Gene Mechanism

Discover Genetic Variants

Cellular Studies
Resequence Gene Regions of OCT1: Exons

n = 240-280 DNA Samples

DNA Samples

African Americans: 80-100
Asian Americans: 30-60
European Americans: 80-100
Mexican Americans: 10-50
Genetic Variants in OCT1 Identified in 247 DNA Samples from Ethnically Diverse Populations

African Americans 26%
Caucasian Americans 40%
Asian Americans 24%

3% African Americans

Non-synonymous SNP
Amino acid deletion

Extracellular

Cytoplasm
Variant Transporters Are Constructed By Site Directed Mutagenesis and Then Expressed In Oocytes or HEK293 Cells

- **Xenopus laevis oocytes**
- **HEK293 cells**
OCT1 Has Many Reduced Function Variants

Shu et al., PNAS, 2003
Metformin: A Clinically Important Drug

- Anti-diabetic agent, potential therapy for various diseases related to obesity.

\[ \text{METFORMIN IS A SUBSTRATE OF OCT1} \]
Two Stories About OCT1

OCT1 Polymorphisms: Determinant of Variation in Drug Response

Metformin

OCT1: Determinant of Anti-Cancer Drug Specificity

Oxaliplatin
Cancer Therapy: Current Status

- Cancer:
  - 2nd Killer in US
    Half a million death per year
  - Expected: 1st killer next decade

- Anticancer therapy:
  - Low cure rate
  - High toxicity
  - Poor quality of life

Change in the US Death Rates by Cause, 1950 & 2003

Anti Cancer Drug Therapy: Two Major Challenges

- Drug resistance
  - Decrease of intracellular drug levels
  - Mutation of drug targets

- Lack of tumor specificity
  - Anti-cancer drug targets are present in normal tissues and tumors
Platinum-based Anticancer Agents

• Most active anticancer agents
  • Testicular cancer (Cisplatin, cure rate > 90%)
  • Ovarian cancer, head and neck cancer

• Multiple drugs approved

  - Cisplatin
  - Carboplatin
  - Oxaliplatin
  - Nedaplatin (Japan)
  - Lobaplatin (China)
  - Heptaplatin (South Korea)

• In treatment regimens for 50% of cancer patients
Platinum Drugs Have Different Anticancer Spectra

Cisplatin
Carboplatin
Oxaliplatin: Colorectal Cancer

Similar Anticancer Spectrum

Question:
What gives platinum compounds their tumor specificity?
Platinum Drugs Share a Common Mechanism of Action

Intra-strand crosslinks

Inter-strand crosslinks
Platinum Uptake Mechanisms May Be Very Specific

• Reduced platinum uptake is the most common observation in platinum-resistant cells
OCT1 and Platinum Drug Cytotoxicity

OCT1 and Platinum-DNA Adduct Formation

- Platinum-DNA adduct formation after oxaliplatin incubation

Genomic DNA associated platinum was determined by ICP-MS

OCT2 and Oxaliplatin

Oxaliplatin Cytotoxicity

Percent of cell growth

Concentration of oxaliplatin (µM)

Oxaliplatin Uptake

Platinum uptake (pmol/mg protein/hr)

Oxaliplatin Uptake

Platinum-DNA adduct

Platinum-DNA adducts (pmol platinum/µg DNA)

Expression of OCTs in Colon Cancer

- RT-PCR study:

OCT Inhibitor Reduces Oxaliplatin Cytotoxicity in Colon Cancer Cell Lines

• Similar observations were obtained in all the six colon cancer cell lines

OCT1 Polymorphism


AA: African American; CA: Caucasian
Oxaliplatin and OCT1 Polymorphisms

- Platinum-DNA adduct formation

Patients with variant OCT1 may have an unfavorable response to oxaliplatin
Conclusions And Future: Personalized Medicines

- Predict Drug Response Based On Genetic Variation (e.g., metformin, oxaliplatin)
- Tissue Specific Drug Targeting Using Influx Transporters (e.g., platinums and OCTs)
- Pharmaceutical Scientists Should Play A Major Role
They Did It!

Shu Zhang

Yan Shu
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