Pharmacogenomics

Dr Howard L McLeod

Professor of Pharmacy & Medicine
Director, Institute for Pharmacogenomics and Individualized Therapy
University of North Carolina, Chapel Hill, USA
The clinical problem

• Multiple active regimens for the treatment of most diseases
• Variation in response to therapy
• Unpredictable toxicity

With choice comes decision
Hypothesis generation: Is genotype-guided therapy likely to work?
Drug effect can be heritable

Figure 1  Plasma half-lives of bis(hydroxy)coumarin (open circles) and antipyrine (filled circles) were measured in monozygotic and dizygotic twins after a single dose of each drug. An interval of 6 months separated administration of bis(hydroxy)coumarin and antipyrine. A solid line joins values within each twinship.
Pharmacogenomic examples-2004

- *bcr/abl* or 9:22 translocation—imatinib mesylate*
- HER2-*neu*—trastuzumab**
- Thiopurine S-methyltransferase—mercaptopurine and azathioprine
Pharmacogenomic examples-2007

- *bcr/abl* or 9:22 translocation—imatinib mesylate*
- HER2-*neu*—trastuzumab**
- C-kit mutations—imatinib mesylate**
- Epidermal growth factor receptor mutations—gefitinib
- Thiopurine S-methyltransferase—mercaptopurine and azathioprine*
- UGT1A1-irinotecan**
- CYP2D9/VKORC1-warfarin**
- HLA-B*5101-carbamazapine**
- Cytochrome P-450 (CYP) 2D6—5-HT3 receptor antagonists, antidepressants, ADHD drugs, and codeine derivatives, tamoxifen*

*FDA package insert information
**FDA-approved device
TABLE OF COMMONLY USED DRUGS:
ARRANGED AS P450 CYTOCHROME SUBSTRATES,
INDUCERS AND INHIBITORS

Genelex currently offers DNA Prescription Drug Reaction Profiles that test 2D6, 2C9, 1A2 and 2C19 functionality. The table below lists many commonly prescribed drugs that are metabolized through these and other pathways in the Cytochrome P-450 system. This is an abridged chart and not all pathways may be listed for all medications. If your medication is not on the list, or to obtain the most thorough information on drug metabolism, enter the medication into www.genemedrx.com.

Order DNA Prescription Drug Reaction Testing
What needs to be done to determine hope vs hype?

• Find the 'right' biomarkers
  • No published GWAS

• Validate in robust datasets

• Apply them!

• Great need for 'real' translation
Centre d’Etude du Polymorphisme Human (CEPH) Cell lines

- Large, multigeneration pedigrees widely studied
- Immortalized lymphoblastoid cell lines

CEPH/French Pedigree 35

CEPH/Utah Pedigree 1416
Methodology

Cells counted, plated at $1 \times 10^4$/ well

Cells incubated with increasing concentrations of drug

Alamar blue vital dye indicator added

Viability relative to untreated control calculated by spectrophotometry
What needs to be done to determine hope vs hype?

• Find the 'right' biomarkers
  • No published GWAS

• Validate in robust datasets
  • Many NIH studies have no blood sampling (unlike industry)

• Apply them!

• Great need for 'real' translation
U.S. Cooperative Groups

Consortia of institutions that conduct research in cancer treatment, prevention, biology and health outcomes.
<table>
<thead>
<tr>
<th><strong>ACTIVE Studies</strong></th>
<th>N</th>
<th>Short Title</th>
<th>PET Chair/PG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx Study #</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10105</td>
<td>270</td>
<td>PTK787 in MDS</td>
<td>60404/PG/McLeod</td>
</tr>
<tr>
<td>40101</td>
<td>4600</td>
<td>CA vs Taxol in node - breast</td>
<td>60202/Kroetz/PG</td>
</tr>
<tr>
<td>50303</td>
<td>580</td>
<td>RCHOP vs EPOCH-R in B-cell lymphoma</td>
<td>60405/McLeod/PG</td>
</tr>
<tr>
<td>80101</td>
<td>570</td>
<td>Adj chemo after gastric resect</td>
<td>60201/McLeod/PG</td>
</tr>
<tr>
<td>80403</td>
<td>230</td>
<td>ECF-C vs IC-C vs FOLFOX-C in mets colorectal ca</td>
<td>60601/Innocenti/PG</td>
</tr>
<tr>
<td>80405</td>
<td>2200</td>
<td>FOLFOX/FOLFIRI + bv, + C225, or + bv/C225 for mets colon ca</td>
<td>60501/McLeod/PG</td>
</tr>
<tr>
<td>90401</td>
<td>1020</td>
<td>Est/doc vs Est/doc/bev for HRPC</td>
<td>60404/McLeod/PG</td>
</tr>
<tr>
<td><strong>Closed Studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80203</td>
<td>200</td>
<td>Ph III CPT-11/5-FU/Leu or Ox/5-FU/Leu +/- C225 in colorectal ca</td>
<td>60304/McLeod/PG</td>
</tr>
<tr>
<td>80303</td>
<td>600</td>
<td>Ph III pancreatic ca</td>
<td>60401/Innocenti/PG</td>
</tr>
</tbody>
</table>
What needs to be done to determine hope vs hype?

• Find the 'right' biomarkers
  • No published GWAS

• Validate in robust datasets
  • Many NIH studies have no blood sampling (unlike industry)

• Apply them!

• Great need for 'real' translation
Phase I
In vivo Mechanism

Phase II
Biomarker assessment

Phase III
Biomarker validation

Biomarker-driven studies

Nothing
What needs to be done to determine hope vs hype?

• Find the 'right' biomarkers
  • No published GWAS

• Validate in robust datasets
  • Many NIH studies have no blood sampling (unlike industry)

• Apply them!

• Great need for 'real' translation
  • What is CYP2D6*4?
Because everybody’s therapy is not your body’s therapy.