“Coming of Age” of Personalized Medicine

Janet Woodcock M.D.
Director, CDER, FDA
Agenda

• State of Personalized Medicine
• Current challenges
  – Scientific
  – Policy
  – Logistical
  – Value-related
• Vision for the future
STATE OF PERSONALIZED MEDICINE
Targeted Therapies have Reached the Mainstream

- Drugs in development and approved drugs in many disease areas
- Cancer, genetic diseases, and infectious disease lead the way
- Many of the “Breakthrough” request for designation are for targeted drugs
- Ever-smaller subsets of disease are being identified
Addressing disease heterogeneity

Changing paradigms in identifying disease subsets
Understanding disease on a molecular basis

Adenocarcinoma 1999
Histology-driven selection

Adenocarcinoma 2010
Targeting oncogenic drivers
# Examples of Drugs with Targeted Labels

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic Area</th>
<th>Biomarker</th>
<th>Label timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brentuximab Vedotin</td>
<td>Oncology</td>
<td>CD30</td>
<td>Pre-approval</td>
</tr>
<tr>
<td>Cetuximab, Panitumumab</td>
<td>Oncology</td>
<td>EGFR; KRAS</td>
<td>Pre-/Post-approval</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>Oncology</td>
<td>ALK</td>
<td>Pre-approval</td>
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<tr>
<td>Exemestane, Fulvestrant, Letrozole</td>
<td>Oncology</td>
<td>ER/PR</td>
<td>Pre-approval</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Oncology</td>
<td>C-Kit, PDGFR, FIP1L1</td>
<td>Pre-approval</td>
</tr>
<tr>
<td>Ivacaftor</td>
<td>Pulmonary</td>
<td>CFTR</td>
<td>Pre-approval</td>
</tr>
<tr>
<td>Lapatinib, Pertuzumab, Trastuzumab, Everolimus</td>
<td>Oncology</td>
<td>HER2</td>
<td>Pre-approval</td>
</tr>
<tr>
<td>Tositumomab</td>
<td>Oncology</td>
<td>CD20 antigen</td>
<td>Pre-approval</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>Oncology</td>
<td>BRAF</td>
<td>Pre-approval</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Hematology</td>
<td>Chromosome 5q</td>
<td>Pre-approval</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>Antivirals</td>
<td>CCR5</td>
<td>Pre-approval</td>
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<tr>
<td>Nilotinib, Dasatanib, Imatanib</td>
<td>Oncology</td>
<td>Ph Chromosome</td>
<td>Pre-approval</td>
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<tr>
<td>Arsenic Trioxide, Tretinoin</td>
<td>Oncology</td>
<td>PML/RARα</td>
<td>Pre-approval</td>
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<tr>
<td>Denileukin Diftitox</td>
<td>Oncology</td>
<td>CD25/IL2</td>
<td>Pre-approval</td>
</tr>
<tr>
<td>Capecitabine, Fluorouracil</td>
<td>Oncology</td>
<td>DPD</td>
<td>Post-approval</td>
</tr>
<tr>
<td>Pimozide, Aripiprazole, Iloperidone, Tetrabenazine, Thioridazine</td>
<td>Psychiatry, Neurology</td>
<td>CYP2D6</td>
<td>Post-approval</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>Analgesics</td>
<td>CYP2C9</td>
<td>Pre-approval</td>
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<td>Citalopram</td>
<td>Psychiatry</td>
<td>CYP2C19</td>
<td>Post-approval</td>
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<td>Rasburicase</td>
<td>Oncology</td>
<td>G6PD</td>
<td>Pre-approval</td>
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<tr>
<td>Valproic Acid</td>
<td>Psychiatry</td>
<td>UCD</td>
<td>Post-approval</td>
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</table>
Personalized Medicine Strategies: Industry Survey

Comprise 12-50% of company pipelines
Our Future

Targeting the Molecular Basis of Disease

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Predicted somatic non-silent mutations</th>
<th>Truncation mutation</th>
<th>Missense mutation</th>
<th>Clinical data</th>
<th>Copy number status</th>
<th>Mutations per Mb</th>
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</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luminal B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2-enriched</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal-like</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Luminal A</th>
<th>Luminal B</th>
<th>HER2-enriched</th>
<th>Basal-like</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>36%</td>
<td>37%</td>
<td>8%</td>
<td>4%</td>
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<tr>
<td>Luminal A</td>
<td>45%</td>
<td>12%</td>
<td>13%</td>
<td>7%</td>
</tr>
<tr>
<td>Luminal B</td>
<td>29%</td>
<td>29%</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>HER2-enriched</td>
<td>39%</td>
<td>72%</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Basal-like</td>
<td>9%</td>
<td>80%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Percentages of cases with mutation by expression subtype
Subgroup-Driven Drug Development

-------- Optimize efficacy - - - Minimize risk --------

- Restricted FIH/DDI/HV trials
- Enriched/stratified trials
- Stratified dosing
- Labeling

Nonclinical:
- Metabolism, transport
- Drug-target interactions
- Nonclinical safety

Phase 1:
- ADME
- Intrinsic/extrinsic factors
- Safety

Phase 2:
- Stratified in
- Efficacy
- Safety
- D/R, C/R

Phase 3:
- Stratified dosing
- Intrinsic/extrinsic factors

Phase 4:
- Knedle

Zineh and Pacanowski 2011 [Pharmacotherapy]
1/3 of approved NMEs contained genomic biomarker information in the original submission.
Personalizing Dose by Genotype

Tetrabenazine, a vesicular monoamine transporter 2 inhibitor indicated for the treatment of chorea associated with Huntington’s disease

- Patients who require doses of tetrabenazine greater than 50 mg per day should be first tested and genotyped to determine if they are poor metabolizers (PMs) or extensive metabolizers (EMs) by their ability to express the drug metabolizing enzyme, CYP2D6.

- The dose of tetrabenazine should then be individualized accordingly to their status as PMs or EMs.

- The maximum daily dose in PMs is 50 mg with a maximum single dose of 25 mg

- The maximum daily dose in EMs and intermediate metabolizers (IMs) 100 mg with a maximum single dose of 37.5 mg
Hepatitis C

HCV virus is a RNA virus and infects liver
Chronic infection can lead to scarring of the liver and ultimately to cirrhosis
Earlier classification according to antigenic characteristics
Currently, genotypic classification through variations in the HCV genome

Considerations in developing therapeutics for HCV: Genotypes 2 and 3 are about 3 times more likely to respond to PEG-IFN and RBV than genotype 1
Three GWAS Publications on IL28B SNP association to treatment outcome

Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance

Dongliang Ge1, Jacques Fellay1, Alexander J. Thompson2, Jason S. Simon3, Kevin V. Shianna1, Thomas J. Urban1, Erin L. Heinzen1, Ping Qiu3, Arthur H. Bertelsen1, Andrew J. Muir2, Mark Sulkowski4, John G. McHutchison2 & David B. Goldstein1

IL28B is associated with response to chronic hepatitis C interferon-α and ribavirin therapy

Vijayaparaksh Suppiah1,2, Max Moldovan3, Golo Ahlenstiel4, Thomas Berg5, Martin Weltman6, Maria Lorena Abate7, Margaret Bassendine8, Ulrich Spengler4, Gregory J Doré9,10, Elizabeth Powell11,12, Stephen Riordan13, David Sheridan9, Antonina Smedile2, Vincenzo Fragomeli8, Tobias Müller2, Melanie Bahlo3, Graeme J Stewart2, David R Booth2 & Jacob George1, for the Hepatitis C Study.14

Genome-wide association of IL28B with response to pegylated interferon-α and ribavirin therapy for chronic hepatitis C

Yasuhiro Tanaka3,18, Nao Nishida2,18, Masaya Sugiyama1, Masayuki Kurossaki2, Kentaro Matsuura1, Naoya Sakamoto4, Mina Nakagawa4, Masaaki Korenaga5, Keisuke Hino5, Shuhei Higie5, Yoshito Ito7, Eiji Mita8, Eiji Tanaka3, Satoshi Mochida10, Yoshikazu Murawaki11, Masao Honda12, Akito Sakai12, Yoichi Hiasa13, Shuhei Nishiguchi14, Asako Koike15, Isao Sakaida16, Masatoshi Imamura17, Kiyoko Ito17, Koji Yano17, Naohiko Masaki17, Fuminaka Sugauuchi2, Namiki Izumi3, Katsushi Tokunaga2 & Masashi Mizokami1,17
Hepatitis C: Further considerations

• Protease inhibitors (telaprevir, boceprevir) approved 2 years ago, for Genotype 1
• Recent development of polymerase inhibitors
• Sofosbuvir recently reported in NEJM for Genotypes 2 and 3, among others
• Looking for sustained virologic response (surrogate EP, but very plausible)
• Beginning to target both organism and host characteristics
Treatment Selection based on Individual Molecular Characteristics
Entering Mainstream

- Oncology undergoing exceeding rapid transition
- (Chronic) infectious diseases also
- Genetic disease not far behind
- Raises scientific, regulatory policy, logistical and reimbursement issues
ONGOING CHALLENGES
Scientific Issues

• “mutated gene” not site of action
• May be multiple sites where mutations occur in any given gene
• Variable functional impact: “molecular phenotype”, e.g.,
  – One mutation could drive cancer
  – A separate mutation might confer a better prognosis
  – Another mutation could confer resistance to therapy
  – Another mutation may have no impact
  – Current diagnostics may not discriminate adequately
• How to do drug development using such fine discrimination?
Scientific Issues

• Rapid evolution in diagnostic testing, particularly genomic testing
• Diagnosis is foundation of therapy—and of personalized medicine
• Need reliable diagnostics that relay understandable information to clinicians
• Making sense of large volume of information—e.g., from next-generation and beyond sequencing—will be challenging
• Other technologies will emerge that reflect a more integrated, functional view of the individual
POLICY ISSUES
FDA Policy Approach

• For over a decade, CDER has been urging adoption of pharmacogenomic strategies and pursuit of targeted therapies
• Reason: decrease variability of response; improve safety; increase size of treatment effect
• Began with proactive insertion of drug metabolizing enzyme information into existing drug dosing instructions
• For drugs under development, industry was concerned that CDER would cause delays if early genomic information was included in INDs
• Genesis of “safe harbor” concept: voluntary genomic data submission program
History of Genomics at FDA

- Early 2002: Lesko & Woodcock commit to Pgx

2002
- 1st FDA-DIA Pgx Workshop (“Safe Harbor” concept introduced)

2003
- Inception of VGDS program (later VXDS)

2004-2005
- 1st VDGS; GDS Guidance for Industry

2006
- Guiding Principles for Joint FDA/EMA VGDS

2008 to Present
- 5th FDA-DIA Workshop
- GG review infrastructure
- Genomics review “Best Practices”
- Knowledge management
- Label updates
- Investigator-initiated research
- Collaborations
**VXDS Impact on submission of novel biomarker data in INDs/NDAs/BLAs**

- Ongoing process
- More than 50 VXDSs have been received since 2004
- Led to increasing numbers of regulatory submissions with novel biomarker data
- Helped development of policy at the FDA

**Submission types**
- “-omics”
- Pharmacogenomics
- Proteomics
- Metabolomics

**Therapeutic areas**
- Alzheimer’s Disease
- Cancer
- Cardiovascular diseases
- Depression
- Diabetes
- HIV
- Obesity
- Rheumatoid Arthritis
- Sepsis
- Systemic Lupus Erythematosus

**Issues Discussed**
- Clinical/analytical
  - Clinical trial design/statistical issues
  - Genetic association to adverse events
  - Genetic variants and response to drugs
  - Use of biomarkers in stratification
  - Impact on labels
- Preclinical
  - Toxicology markers
  - Renal toxicity
  - Vascular toxicity
  - Hepatotoxicity
## Policy and Guidance

<table>
<thead>
<tr>
<th>Year</th>
<th>Guidance Titles</th>
</tr>
</thead>
</table>
| 2005 | Guidance on PG Data Submissions  
Concept Paper on Drug-Diagnostic Co-Development |
| 2007 | Companion Guidance on PG Data Submissions*  
Guidance on PG Tests and Genetic Tests for Heritable Markers |
| 2010 | ICH E16 Concept Paper on PG Biomarker Qualification: Format and Data Standards  
Guidance on Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents for Treatment  
Guidance on Qualification Process for Drug Development Tools |
| 2011 | Guidance on in vitro Companion Diagnostic Devices*  
Guidance on Clinical Trial Designs Employing Enrichment Designs* |
| 2012 | Guidance on Clinical PG: Premarketing Evaluation in Early Phase Clinical Studies |
| In Process | Guidance on Drug-Diagnostic Co-development |
FDA Guidance: Companion Diagnostics

- Defines “companion diagnostic”
  - Test essential for safe and effective drug use
  - Prediction, prognosis, selection, dosing, monitoring
- Describes FDA’s policies for approval and labeling of a therapeutic/diagnostic product pair
  - Pre-market review, risk-based regulation
  - Analytical validity of tests used for critical treatment decisions to be reviewed
- Does not describe how to co-develop products
## Principles for Biomarker Use in Targeted Drug Development

<table>
<thead>
<tr>
<th>Principle</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomarker is the major pathophysiological driver of the disease</td>
<td></td>
</tr>
<tr>
<td>Limited or adverse paradoxical activity of the drug is seen in a subgroup</td>
<td>Limited or adverse paradoxical activity of the drug is seen in a subgroup identified through in vitro or animal models (e.g., cell lines or animals).</td>
</tr>
<tr>
<td>Biomarker is the known molecular target of therapy</td>
<td></td>
</tr>
<tr>
<td>Preliminary evidence of harm from early phase clinical studies in patients</td>
<td>Preliminary evidence of harm from early phase clinical studies in patients without the biomarker</td>
</tr>
<tr>
<td>Preliminary evidence of lack of activity from early phase clinical studies</td>
<td>Preliminary evidence of lack of activity from early phase clinical studies in patients without the biomarker</td>
</tr>
<tr>
<td>Preliminary evidence of modest benefit in an unselected population, but</td>
<td>Preliminary evidence of modest benefit in an unselected population, but the drug exhibits significant toxicity</td>
</tr>
<tr>
<td>the drug exhibits significant toxicity</td>
<td></td>
</tr>
</tbody>
</table>
Need for Evaluating Marker-Negative Patients

Dx population clearly defined?

YES → Strength of Dx hypothesis

NO → B/R in all-comers

→ P2 data and assay type inform extent of P3 eval

NO → MOA

Pre-clin activity

Class effect

Λ

YES → Efficacy eval in M+ only supported?

NO → B/R in M+ only recommended
Current Unresolved Policy Issues

- How to study rare genotypes
- Incorporation of functional information ("molecular phenotype") into development plan
- Dealing with rapid evolution of diagnostic technology (compared with pace of drug development)
LOGISTICAL ISSUES
Need for New Definition of “Clinical Trial”

• Personalized therapies are aimed at subsets of conventionally defined diseases
• Doing a single trial to answer each question raised by each marker/candidate therapeutic and combinations thereof is not feasible
• Need to “turn paradigm on its head”; set up ongoing trials with broad intake and many strata based on biomarkers
• Some trials ongoing (e.g., I-SPY 2); others being set up
• Other networks (e.g., cystic fibrosis) make rapid evaluation of genetic subsets feasible
Breakthrough Therapies

• Certain targeted therapies may have startling efficacy compared to conventional drugs
• FDASIA (passed 2012) sets up a designation program for “breakthrough therapies”
• Preliminary clinical evidence in serious disease of significant improvement over existing RX
• Voluntary; sponsor requests
• We have received quite a few submissions and will be granting additional designations
Breakthrough Therapies

• Designation allows sponsor to work very closely with FDA to design most efficient development path
• Early, separate meetings on manufacturing and scale-up to meet supply, if approved
• Based on current submissions, expect to see a growing category of (mostly) targeted, highly effective drugs for serious conditions
• Potentially very rapid development programs
VALUE RELATED CHALLENGES
Value-related Issues

• Rising healthcare costs around the world are leading to increased scrutiny of medical interventions and technology

• Most targeted interventions are considered “high tech” and “expensive”

• Reimbursement for diagnostics remains a challenge in development

• Seeing increasing resistance to reimbursement in some regions
Value-related Issues

• The new field of targeted therapy needs to raise its sights—focus on adding value
• Many of these new interventions have considerably greater efficacy for at least commensurate and sometimes improved safety
• Eventually, need to combine treatments or develop effective interventions that cure or control disease
• We are only in the early stages of this therapeutic revolution, but it is important to keep in mind the ultimate goal
The Future of Personalized Medicine

• Deliver new treatments at reasonable cost that have significant impact in treating or preventing human disease, and are
  – More effective
  – Less toxic
  – More cost-effective

--Than today’s interventions
Then We can Say that Personalized Medicine is a Major Part of the Future of Healthcare