Personalized medicines
Prof. dr. Irena Mlinarič-Raščan

2014 EAFP Annual Conference
Science-based pharmacy education:
Towards better medicines and patient care
Outline of the lecture

Definitions/ understandings
Life cycle of medicine
Facing the challenge
Educational challenges
PHARMACO-GENETICS/-GENOMICS is a process connecting

- Identification of variation in drug responses
- Correlation to genetic variation
- Development of screening tests
- Implementation of individualized therapy

Promises of PGX

- Focus treatment to likely to respond stratified population
- Predict and reduce adverse events
- Identify potential medicines in the pipeline for certain population
- Better understanding of drug interactions

PERSONALIZED MEDICINE

The aim: tailoring of treatment to individual characteristics, needs and preferences

Enabled by parallel advances on multiple scientific fields
- not limited to pharmaceutical therapy*

- genomics
- imaging
- comp. biology
- advanced, regener. medicine
- ITN

Drug targets HTS
PET -SCAN CT
data manege. data mining
fSC, aSC

mobile wireless sensors intraoperative devices Internet Patient monitoring

Predictive and diagnostic biomarkers

* Paving the way for Personalized Medicine; FDA, 10/2013
PM- example: Placement of the Printed Airway Splint in the Patient

Bioresorbable Airway Splint Created with Three Dimensional Printer
PERSONALIZED MEDICINES- Advanced therapies

ChondroCelect® (2009) tissue-engineered products is a suspension for implantation that contains cartilage cells

Glybera® (alipogene tiparvovec) the first gene therapy authorised in Europe (2012) approved for the treatment of lipoprotein lipase deficiency (LPLD)

MACI ®(matrix applied characterised autologous cultured chondrocytes) (2013)

PROVENGE® (sipuleucel-T) (2013) therapeutic cancer vaccine; an autologous cellular immunotherapy for metastatic prostate cancer
PESONALIZED MEDICINE (s)

Development of targeted therapeutics and diagnostic tools

What are the changes to the DDD landscape in post genome are?
THE IMPACT OF (POST) GENOM ERA ON THE LANDSCAPE OF DDD

**Basic research: target identification & validation**
- genechip expression
- microRNA expression profiling
- QRT PCR and microfluidic cards

**HIT lead:**
- identification
- validation
- optimization

**Pharmaceutical development**
- compound screening using expression profiling to evaluate efficacy and toxicity

**Pre-clinical / clinical**
- monitoring of pre-clinical trials using expression-based biomarkers
- use of genome expression signatures to analyse efficacy outcomes (prospective or retrospective studies)

**Registration / market**
- pharmacogenomics in medical practice
  - QRT PCR and microfluidic cards
  - custom microarray
  - custom microRNA quantification
  - GLP compliant toxicogenomic studies

**Patient care**
- laboratory services for health professionals
  - QRT PCR and microfluidic cards
  - custom microarray
  - custom microRNA
PHARMACOGENOMICS One of the corner stones of PM

CHANGES IN PARADIGM

- diseases delineation
- target identification
- diagnostic markers co-development: HER-ceptin, DACO, 1998
- lead identification and validation
- HTS: toxicogenomics,
- metabolism prediction
- stratification of population

## RECENT SUCCESSES WITH CO-DEVELOPMENT

<table>
<thead>
<tr>
<th>Generic name</th>
<th>US trade name</th>
<th>Indication</th>
<th>Biomarker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic trioxide</td>
<td>Trisenox</td>
<td>APL</td>
<td>PML/RARα</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Erbitux</td>
<td>Colon cancer</td>
<td>EGFR, KRAS</td>
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<tr>
<td>Crizotinib</td>
<td>Xalkori</td>
<td>Lung cancer</td>
<td>ALK</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Spryce</td>
<td>CML/Ph1+ ALL</td>
<td>Ph1/BCR-ABL</td>
</tr>
<tr>
<td>Denileukin diftitox</td>
<td>Ontak</td>
<td>Lymphoma</td>
<td>CD25</td>
</tr>
<tr>
<td>Imatinib (1)</td>
<td>Gleevec</td>
<td>CML</td>
<td>Ph1/BCR-ABL</td>
</tr>
<tr>
<td>Imatinib (2)</td>
<td>Gleevec</td>
<td>MDS/MPD</td>
<td>PDGFR</td>
</tr>
<tr>
<td>Ivacaftor</td>
<td>Kalydeco</td>
<td>Cystic fibrosis (G551D)</td>
<td>CFTR</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Tykerb</td>
<td>Breast cancer</td>
<td>Her2/neu</td>
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</thead>
<tbody>
<tr>
<td>Lenalidomide</td>
<td>Revlimind</td>
<td>Multiple myeloma</td>
<td>Chromosome 5q</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>Selzentry</td>
<td>HIV</td>
<td>CCR5</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>Tasigna</td>
<td>CML/Ph1+ ALL</td>
<td>Ph1/BCR-ABL</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>Vectibix</td>
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<tr>
<td>Pertuzumab</td>
<td>Perjeta</td>
<td>Breast cancer</td>
<td>Her2/neu</td>
</tr>
<tr>
<td>Tositumomab</td>
<td>Bexxar</td>
<td>Lymphoma</td>
<td>CD20 antigen</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Herceptin</td>
<td>Breast cancer</td>
<td>Her2/neu</td>
</tr>
<tr>
<td>Tretinoin</td>
<td>Vesanoid</td>
<td>APL</td>
<td>PML/RARα</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>Zelboraf</td>
<td>Melanoma</td>
<td>BRAF</td>
</tr>
</tbody>
</table>

Contemporary methods eg GWAs generate knowledge about associations between genomic factors and disease

PGx GUIDELINES
CLINICAL PHARMACOGENETICS IMPLEMENTATION CONSORTIUM (CPIC)

TPMT/Thiopurines (Relling et al., Clin Pharmacol Ther. 2011;89:387-91)
CYP2C19/Clopidogrel (Scott et al., Clin Pharmacol Ther. 2011;90:328-32)
CYP2C9-VKORC1/Warfarin (Johnson et al., Clin Pharmacol Ther. 2011;90:625-9)
HLA-B/Abacavir (Martin et al., Clin Pharmacol Ther. 2012; 91:734-8)
SLCO1B1/simvastatin (Wilke et al., Clin Pharmacol Ther. 2012;92:112-7)
HLA-B/carbamazepine (Leckband et al., Clin Pharmacol Ther. 2013;94:324-8)

• Others: DPYD-5FU/capecitabine, HLA-B/phenytoin, G6PD/rasburicase,
  Septra, UGT1A1/irinotecan, IL28B/peginteron, CTFR/Ivacaftor, CYP2D6/SSRIs
THE STATE of THE ART

~ 600 authorized medical products in Europe
~ 20% include genomics information
   imply personalized use of medicines (SNPs- dose, DDI)
~ 13 cases with mandatory testing prior to treatment
   targeted/personalized medicines (safety, efficacy, quality)
   + information on assays or methods
- rapid increase in understanding disease-marker associations
- affordability of genotyping, the cost of sequencing one or two genes in the past will now produce results for 225 genes
Outline of the lecture

Definitions/ understandings
Life cycle of medicine
Facing the challenge
  Societies
  Consortia
  Regulatory agencies

Educational challenges
  The role of pharmacists in PM
  UL FFA example
FACING THE CHALLENGE

Pharmacogenetics & Pharmacogenomics Research Network

Network
Pharmacogenetics and Pharmacogenomics (PGX) are emerging disciplines that focus on genetic determinants of drug response at the levels of single genes or the entire human genome, respectively. The network is the voice of the European science community in pharmacogenetics and pharmacogenomics, with the following objectives. The Network provides a platform for experts for gathering and disseminating knowledge, determining PGX-strategies, for collaboration between academic institutions and industry, for mechanisms of set up and exchange of databases, and for gatherings and promotion of knowledge about pharmacogenetics and genomics in Europe. Objectives also include to serve as a knowledge-bank for EU research programme calls, and to engage in education and training, particularly, PhD students.

Contact Point
Anke-Hilse Mattiend-van der Zee
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Mission Statement and Aims
Our mission is to be the leading European organization in the field of pharmacogenetics (PGX) and pharmacogenomics (TNG) with worldwide influence.

Aims of ESPT

- To extend the scientific boundaries of single nucleotide or single nucleotide polymorphism (SNP and TN) diffusion.
- To provide a forum for consensus, in the broadest sense, to offer a European view to the widest possible scientific and technical levels, aiming to improve quality of care for the patient.

The specific aims of ESPT are:

1. To extend the scientific boundaries of single nucleotide or single nucleotide polymorphism (SNP and TN) diffusion.
2. To provide a forum for consensus, in the broadest sense, to offer a European view to the widest possible scientific and technical levels, aiming to improve quality of care for the patient.
3. To promote and facilitate exchange of information between European and non-European researchers.
TRANSFER of pharmacogenetics testing into routine patient care

- gene-drug pairs associated with potential risks of
  - life-threatening toxicity,
  - serious adverse effects,
  - or lack of effectiveness.

- 11 genes have profound effects on 33 drugs.

**CLINICAL PHARMACOGENETICS IMPLEMENTATION CONSORTIUM (CPIC)**

**CPIC: Clinical Pharmacogenetics Implementation Consortium**

<table>
<thead>
<tr>
<th>Host Institution</th>
<th>PharmGKB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Email</td>
<td><a href="mailto:cpic@pharmgkb.org">cpic@pharmgkb.org</a></td>
</tr>
</tbody>
</table>

**Drug(s)**
- Azathioprine, Mercaptopurine, Thioguanine, Clopidogrel, Warfarin, Codeine, Capecitabine, Abacavir, Carbamazepine, Phenytoin, Allopurinol, Rasburicase, Irinotecan, Simvastatin

**Related Links**
- Publications

The Clinical Pharmacogenetics Implementation Consortium (CPIC) was formed in late 2009, as a shared project between PharmGKB and the Pharmacogenomics Research Network. CPIC guidelines are peer-reviewed and published in a leading journal (in partnership with Clinical Pharmacology and Therapeutics) with simultaneous posting to PharmGKB with supplemental information/data and updates. Anyone with clinical interests in pharmacogenetics is eligible for membership. CPIC’s goal is to address some of the barriers to implementation of pharmacogenetic tests into clinical practice.

Read an article describing CPIC’s guideline development process:
-Incorporation of Pharmacogenomics into Routine Clinical Practice: The Pharmacogenetics Implementation Consortium (CPIC) Guideline Development Process-
MEDICINES WITH PHARMACOGENETIC INFORMATION

What is the PharmGKB?
Find out how we go from extraction of gene-drug relationships in the literature to implementation of pharmacogenomics in the clinic...

Find out more

Clinically-Relevant PGx
- Well-known PGx associations
- Clinically relevant PGx summaries
- PGx drug dosing guidelines
- Drug labels with PGx info
- Genetic tests for PGx
- PGx gene haplotypes

PGx-Based Drug Dosing Guidelines
- G6PD/riboflavinase article and supplement
- CFTR/ivacaftor article and supplement
- See all CPIC guidelines
- CPIC gene-drug pairs of interest

PGx Research
- VIP: Very Important PGx gene summaries
- View PharmGKB pathways
  - Alphabetically
  - By therapeutic category
- Annotated SNPs by gene
- Drugs with genetic information
Pharmacists: Personalized Medicine Experts in Primary Care

- offering the potential for significant advances in optimizing drug therapy outcomes and minimizing adverse drug events
- aiming to equip primary care pharmacists with the knowledge and skills required to take a lead role as personalized medicine experts in the healthcare system and evaluate the impact personalized medicine has on patients’ health

Innovation in Personalized Medicine

Dr. Lisa McCarthy is the lead for a team that recently received a Canadian Foundation for Pharmacy Innovation Fund grant. “Pharmacists: Personalized Medicine in Primary Care” is a multi-phase project that will equip primary care pharmacists with the knowledge and skills required to take a lead role as personalized medicine experts in the healthcare system and evaluate the impact personalized medicine has on patients’ health outcomes. The interprofessional team working on this project includes a diverse assembly of practicing clinicians, scientists and educators partnered across three institutions - the Leslie Dan Faculty of Pharmacy, the Centre for Addiction and Mental Health, and Women's College Hospital - that includes Dr. Beth Sproule, Dr. Natalie Crown, Dr. Micheline Piquette-Miller, and Maria Bystrin.
ACTIVITIES AT THE EUROPEAN MEDICINES AGENCY

- Pharmacogenomics Working Party
  a group of European experts in pharmacogenomics that gives recommendations to the CHMP

- Specific documents
  - Key Aspects on the Use of Pharmacogenomic Methodologies in the Pharmacovigilance Evaluation of Medicinal Products (2011)
  - Reflection Paper on Pharmacogenomics in Oncology (2006)
  - Reflection Paper for Laboratories that Perform the Analysis or Evaluation of Clinical Trial Samples (2010).

NEW: EMA has opened public consultations on “Draft guideline on key aspects for the use of pharmacogenomic methodologies in the pharmacovigilance evaluation of medicinal products”
# GUIDELINES ON PHARMACOGENETICS

<table>
<thead>
<tr>
<th>Issue</th>
<th>European Medicines Agency</th>
<th>Pharmaceutical and Medical Devices Agency, Japan</th>
<th>US Food and Drug Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development phases covered in guideline or guidance</td>
<td>Preclinical and clinical development (Phases I–IV; focusing on PK)</td>
<td>Clinical development (Phases I–IV)</td>
<td>Early clinical development (Phases I and II)</td>
</tr>
<tr>
<td>Banking of DNA samples</td>
<td>Highly recommended</td>
<td>Encouraged*</td>
<td>Strongly encouraged</td>
</tr>
<tr>
<td>Genomic testing</td>
<td>Required*</td>
<td>Recommended</td>
<td>Recommended</td>
</tr>
<tr>
<td>In vitro cut-off values(^5)</td>
<td>&gt;50%</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>In vivo cut-off values(^5)</td>
<td>&gt;25%</td>
<td>None</td>
<td>None</td>
</tr>
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</table>

*Does not apply to category A (see main text for more details). \(^4\) Is a firm requirement only when in vitro (>50%) or in vivo (>25%) cut-off values are met. \(^5\) For when pharmacogenetics-related testing is required in pharmacokinetics (PK) studies.

[www.nature.com/reviews/drugdisc](http://www.nature.com/reviews/drugdisc), 2013
EDUCATIONAL CHALLENGES

THE ROLE OF THE PHARMACISTS

R&D
advance the science

Monitoring-PV

Education
Undergrad, LLL, Patients, healthcare professionals

Therapy
decision making-clinical and primary care pharmacists
EDUCATIONAL CHALLENGES

Opinion

Clinical Pharmacology & Therapeutics (2014); 95 3, 245–247. doi:10.1038/clpt.2013.184

Is There a Need to Teach Pharmacogenetics?

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Correspondence: A K Daly, (a.k.daly@ncl.ac.uk)

Abstract

Pharmacogenetics/pharmacogenomics has been subject to considerable development during the past 10 years and seems likely to advance even more rapidly in the next decade. Several surveys suggest that initial training for health-care professionals—particularly physicians and pharmacists—frequently includes education in this area, but equipping these professions more generally to deal with ongoing development of the field and to make best use of new knowledge remains an important challenge.

Development and Evaluation of a Pharmacogenomics Educational Program for Pharmacists

Design. As part of a continuing education program accredited by the Accreditation Council for Pharmacy Education (ACPE), pharmacists were provided with a fundamental pharmacogenomics education program.

PHARMACOGENOMICS AT THE UL FFA

Since 2003 an elective subject

The concept

Incorporated into other subjects

Research-based educations

- MSc research projects
  - Individualized therapy
  - Medicines Development

Professional services

- Licenced Mol diagnostics Laboratory

LLL educational program

- Laboratory Medicine Chamber
- Pharmacy chamber
PHARMACOGENOMICS AT THE UL FFA

THE CONCEPT

I. Humane genome
   Interindividual variability

II. Metodologies
   Highthroughput technologies
   microarrays, Sequencing

III. Basic bioinformatic tools

IV. Pharmacogenomics in
   individualized therapy

V. Pharmacogenomics
   incorporated in DDD proces

VI. Ethical legal and social aspects
CONCLUSIONS

Genome-era impact on all phases of drug discovery, development and utilization of medicines allowed the emergence and implementation of personalized medicines.

Pharmacists as prime drug experts should acquire key competences to both govern the concept development as well as implement the practice of personalized medicine in terms of tailoring therapeutics to individual patients.

The educators shall provide access to novelties in the interdisciplinary fields and assure the development of novel skills to be unchallenged drug therapy experts.
Thank you!