Pharmacogenetics and the treatment of infectious diseases in the Developing World:
malaria as a translation proof of concept

José Pedro Gil
Drug Resistance Unit
Division of Pharmacogenetics
Department of Physiology and Pharmacology
Karolinska Institutet
and
Membrane Protein Disorders Unit
Center for Biodiversity, Functional and Integrative Genomics
Faculdade de Ciências da Universidade de Lisboa
Drug resistance as an extreme case in the scale of Pharmacogenetics

The concept of pharmacogenetics is a broad one. The variable degree of influence that genetic information has in the capacity of an organism to manipulate the biophysical destiny (and effect) of xenobiotics, particularly the ones with therapeutic value.

And it is not limited to human beings
Non detected association with relevant drug disposition phenotypes

Genetic does not influence relevant response phenotypes (e.g. pfmdr1 86N and Pyrimethamine)

Low resistance/Tolerance – irrelevant in terms of treatment, but influencing follow up prophylactic effect. (e.g. pfmdr1 86N and lumefantrine)

Drug resistance (associated with clinical failure, pfcr76T and CQ Pfmdr1 CNV and ACT)

Pathogen

Human host

Associated phenotype recognizable but therapeutically irrelevant

Associated phenotype significantly associated with genetic variation – (different grades)
**Infectious diseases implicates Meta-pharmacogenetics**

- **Pathogen**
  - Genetic does not influence relevant response phenotypes (e.g. *pfmdr1* 86N and Pyrimethamine)

- **Human host**
  - Low resistance/Tolerance – irrelevant in terms of treatment, but influencing follow up prophylactic effect. (e.g. *pfmdr1* 86N and lumefantrine)
  - Drug resistance (associated with clinical failure, *pfcr7 76T* and CQ *Pfmdr1* CNV and ACT)
  - Non detected association with relevant drug disposition phenotypes
  - Associated phenotype recognizable but therapeutically irrelevant
  - Associated phenotype significantly associated with genetic variation – (different grades)

---

Drug Resistance Unit (2013)
Department of Physiology and Pharmacology
Most drugs act in the therapeutically relevant intra-erythrocytic cycle

- artemether
- lumefantrine
- artesunate
- chloroquine
- mefloquine
- pyrimethamine
- atovaquone

Amodiaquine

Mainly used only as combinations

In an infectious disease the pharmacogenetic nature of the pathogen will be a factor in the pharmacodynamics of the drug – **it is a particularly complex case of “target pharmacogenetics”**. Malaria is a good study model from this perspective.

Drug Resistance Unit (2013)
Department of Physiology and Pharmacology

Amodiaquine metabolism

http://www.intechopen.com/books/howtoreference/clinical-applications-of-pharmacogenetics/the-pharmacogenetics-of-the-antimalarial-amodiaquine

Drug Resistance Unit (2013)
Department of Physiology and Pharmacology
**A P. falciparum polymorphic ABC transporter influences amodiaquine therapy outcome**

P-glycoprotein homologue located in the membrane of the food vacuole (facing the lúmen of the organelle)

Decreased transport into the food vacúole leads to Less access to the drug target (Hb processing machinery)

Reduced drug effect:

Initial frequencies ($D_0$)

- pfmdr1 86Y/184Y/1246Y frequency

- Recrudescences/ clinical failures ($D_n$)

Adapted from Bannister et al., Parasitol. Today, 16: 10 (2000)

Adapted from Sanchez et al., Int. J. Parasitol., 40: 1109 (2010)

Adapted from Holmgren et al., Genet. Inf. Evol., 7: 562 (2007)
A simple hypothesis

PGx driven changes in AQ/DEAQ disposition

Changes in drug exposure for the parasite

Changes in Pharmacodynamics

Changes in the dynamics of parasite selection
The 2005 Artesunate-Amodiaquine efficacy study

3 Day course drug administration (ASAQ)

Blood sampling

Decreasing drug concentrations (long half life partner)

Clinical follow up (6 weeks)


Drug Resistance Unit (2013)
Department of Physiology and Pharmacology
Analyzing the pharmacogenetics of the host and the pathogen

Decreasing drug concentrations (long half life partner)

Blood sampling

CYP2C8*2 and *3 (n=116, under fives)

pfmdr1 N86Y / D1246Y

from Piedade and Gil, Exp. Opin. Drug Metab. Toxicol., 7(1): 1185 (2011)
CYP2C8 status drives the selection of Amodiaquine related pfmdr1 SNPs

Extreme discordant group analysis


Drug Resistance Unit (2013)
Department of Physiology and Pharmacology
What is needed is a point of care system for fast characterization of Both the patient and the infecting pathogen

The challenge: An energetically autonomous, hand held devise of low cost and able to provide results in <20 minutes. Web connectivity for immediate communication with a central database/mission control.

NanoMal – an FP7 funded public private consortium
http://www.nanomal.org/
DNA is extracted directly through new generation disposable cartridges (3 min.) and key genes are extracted using an ultra-fast serpentine based PCR system (< 4 min). The device can analyse multiple markers simultaneously the patient and malaria parasite DNA for the pharmacogenetic characteristics of both species. Probes are attached to nanowires allowing the detection of flowing target sequences by measuring changes in electrical current (5 min).

Mock version of the near future device
Options for alternative therapy (second line, e.g. Artmether-Lumefantrine (Coartem))

Specific attention during follow up

ASAQ / Pfmdr1 86Y / CYP2C8*3

Personalized anti-malaria treatment / follow up

Drug Resistance Unit (2013)  
Department of Physiology and Pharmacology
Seasonal Malaria Chemoprevention (SMC) is arriving

Seasonal Malaria Chemoprevention in Sub-Saharan Africa (WHO, 2013)- High transmission / highly seasonal regions
Up to four monthly doses of AQ-SP (children 3-59 months old.)

http://apps.who.int/iris/bitstream/10665/85726/1/9789241504737_eng.pdf
Prof. S. Krishna, St George’s Hospital, University of London

Prof. PG Kremsner, Center of Tropical Medicine, Tubingen University

Dr. A. Martensson, Karolinska Institutet

QuantuMDx, Newcastle; Prof. Sir John Burns and Dr. J. O’Halloran on the right.

Prof. A. Djimde, University of Mali

Dr. Elaine Warburton, QuantuMDx CEO