VIH & Pharmacogénétique : Conclusion & Perspectives

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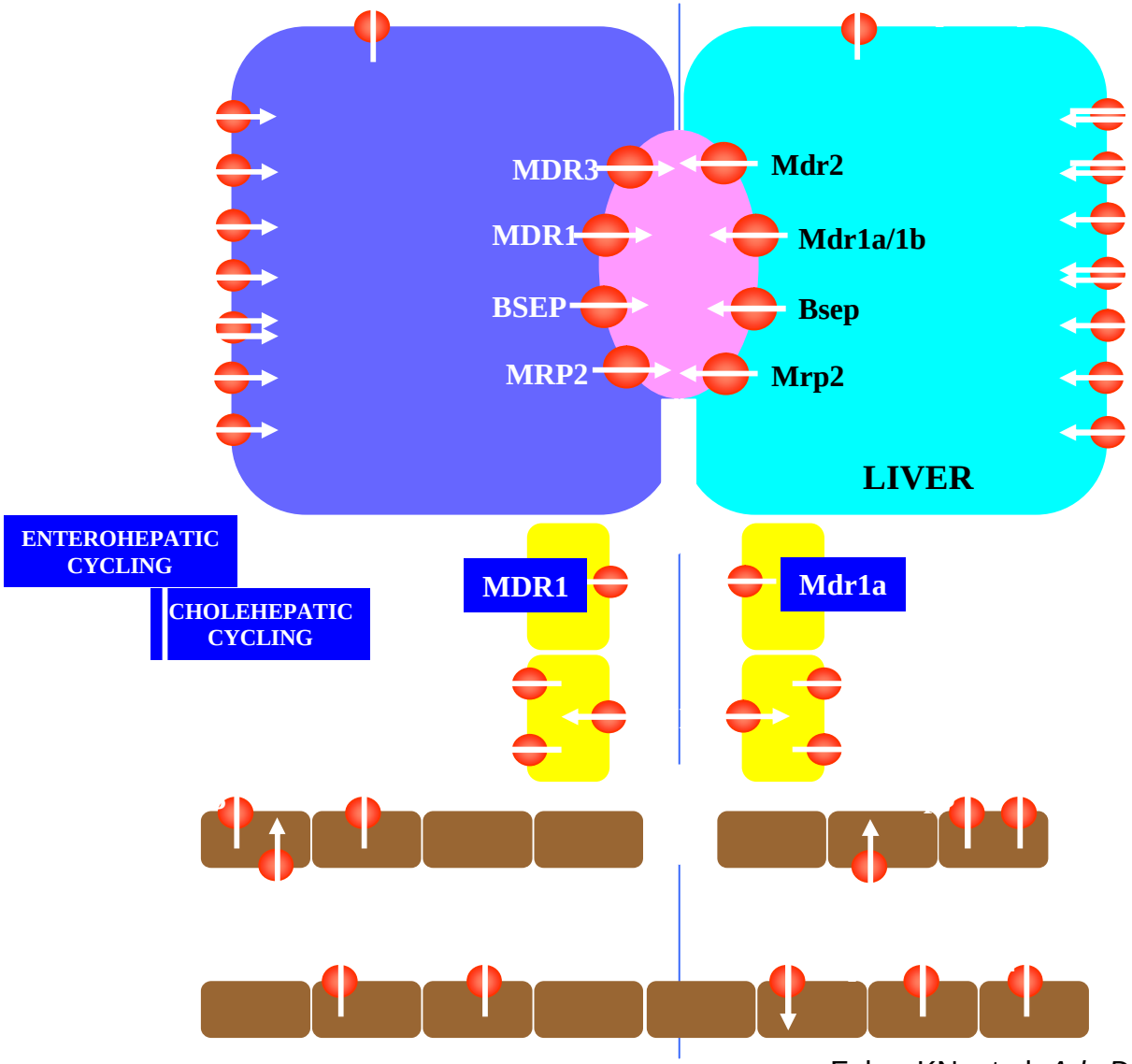
Conclusions

- Pharmaco-génétique & -génomique,
- Variabilités interindividuelles de séquences d'ADN ou du génome,
- Implications biochimiques et cliniques sur les réponses pharmaco-cinétiques ou -dynamiques,
- Différentes cibles du polymorphisme génétique :
  - Enzymes responsables du métabolisme (CYP450, UGT, NAT etc),
  - Structures cellulaires (canaux ioniques, récepteurs, transporteurs etc.)
- Conséquences pharmacodynamiques :
  - Toxicité
  - Efficacité

Transporteurs entéro-hépatocytaires



Faber KN, et al. *Adv Drug Deliv Rev 55 (2003) 107-124.*

Human genes that influence HIV-1 disease or response to treatment

Gene/genetic region	Protein function	Influence of polymorphism†
Susceptibility to infection		
CCR5	Chemokine receptor	Decreased susceptibility to infection
RANTES	Chemokine	Decreased susceptibility to infection
Natural history		
CCR5	Chemokine receptor	Delayed (Δ32), or accelerated (promoter) progression
CCR2	Chemokine receptor	Delayed progression
CX3CR1	Chemokine receptor	Controversial
SDF1	Chemokine	Controversial
MIP-1α	Chemokine	Accelerated progression
RANTES	Chemokine	Controversial
Interleukin-10	Cytokine	Accelerated progression
MBL	Manose-binding lectin	Controversial
Class I HLA	MHC	Accelerated progression (homozygosity)
HLA-B*5701	MHC	Delayed progression
HLA-B*35	MHC	Accelerated progression
HLA-Cw*04	MHC	Accelerated progression
Response to treatment		
CCR5	Chemokine receptor	Virological response
MDR1	Drug transporter (PGP)	Drug concentrations and immunological response
CYP2D6	CYP450 isoenzyme	Drug concentrations
Treatment toxicity		
SREBP-1c	Cholesterol/triglyceride regulator	Hyperlipidaemia
Haplotype HLA-B*5701, DR7, DQ3	MHC	Hypersensitivity to abacavir

†Polymorphism or allele may not exert influence directly but through linkage disequilibrium with other alleles.
MHC=major histocompatibility complex, PGP=P-glycoprotein.

Perspectives

- Complexité du « problème Pharmacogénétique »

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- Utilisation plus précoce des tests pharmacogénétiques dans le développement préclinique et clinique :
  - Sur des modèles *in vitro* et *in vivo* chez l'animal,
  - Validité des tests pharmacogénétiques appliqués à un nouveau composé,
  - Chez le volontaire sain et le patient,
  - Efficacité clinique,
  - Effets indésirables rares ou inattendus

- Respect des considérations éthiques,

Complications HIV Disease RAC Genomics Focus Group (AACTG)

- Mission: Identify genetic polymorphisms related to drug complications and toxicities,

- Areas of interest:
  - Metabolic: osteoporosis, glucose tolerance, body shape changes
  - Liver: fatty liver, hepatitis, drug toxicity
  - Cardiology: hyperlipidemia
  - Neurology: cognitive disorders and peripheral neuropathy
  - Misc: lactic acidosis, pancreatitis, cancer

Established May, 2002

Genomic issues in HIV Clinical Trials (AACTG)

NWCS 213

- Title: Role of Host Genetic Factors in Antiretroviral Drug Failure, PK, and Drug Toxicity in ACTG 384

- PI: Clifford, Degruttola, Dube, D'Aquila, Hass et al.

- Genotypes:
  - Cytochrome P450 enzymes
  - MDR1- drug transporter P-glycoprotein

- Phenotypes:
  - Nelfinavir and Efavirenz pharmacokinetics
  - First virological failure
  - Changes in CD4+ T cell count over time
  - HIV-1 reverse transcriptase and PI genotypic resistance at regimen failure
  - Peripheral neuropathy
- N= 500

Genomic issues in HIV Clinical Trials (AACTG)

NWCS 214

- Title: Relationships between Host Genetic Polymorphisms and Efavirenz Disposition, Toxicity, and Efficacy in ACTG Protocol A5097

- PI: Acosta, Gulick, Clifford, et al.

- Genotypes:
  - Cytochrome P450 enzymes
  - MDRs

- Phenotypes:
  - CNS toxicity
  - Pharmacokinetics
  - Virologic and immunologic response: viral load, CD4+ T-cell count, plasma HIV-1 RNA

- N= 180