GENÉTICA Y TRASPLANTES

Farmacogenética e Inmunosupresión

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Curso práctico de trasplante de órganos sólidos
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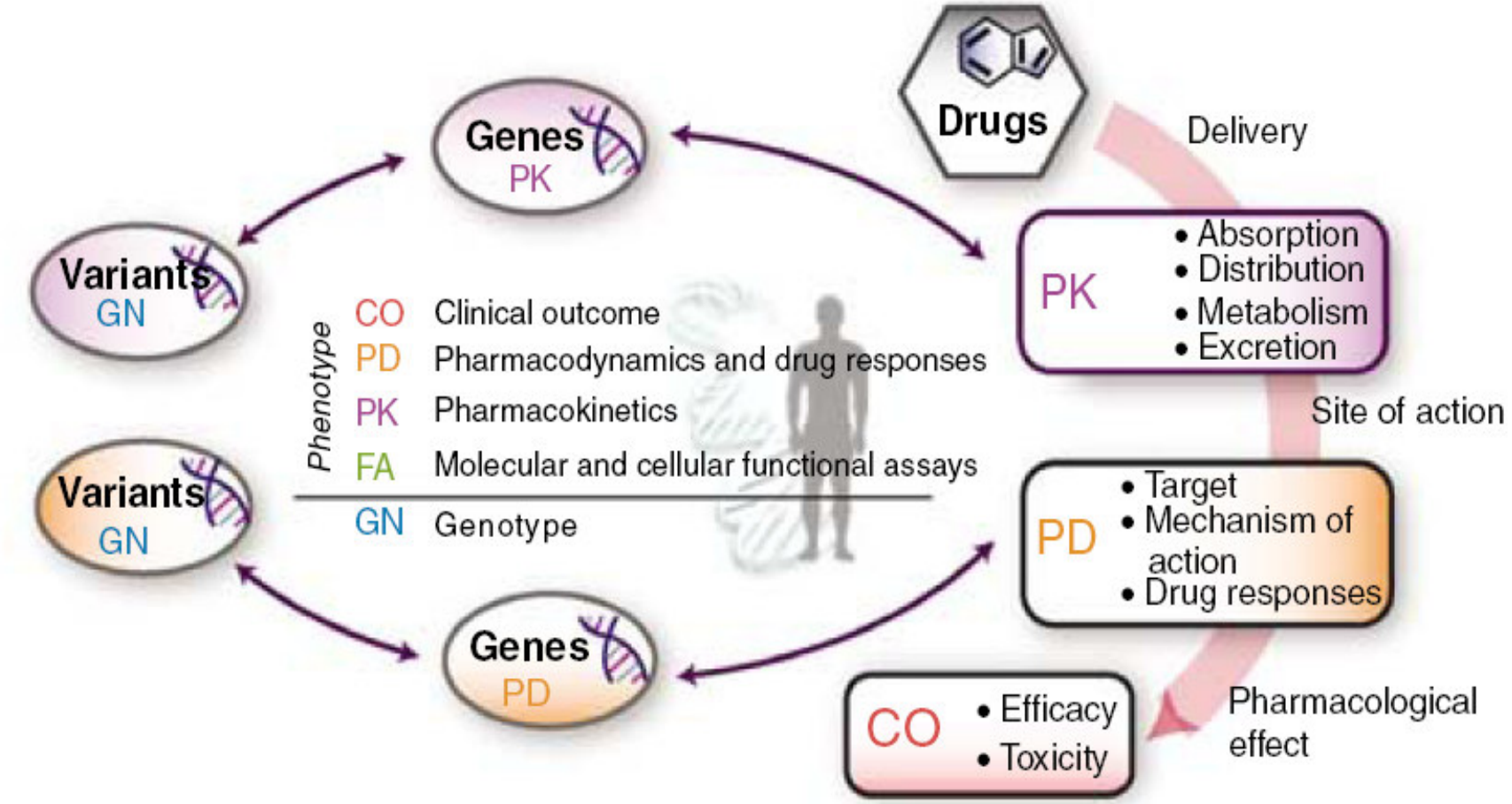
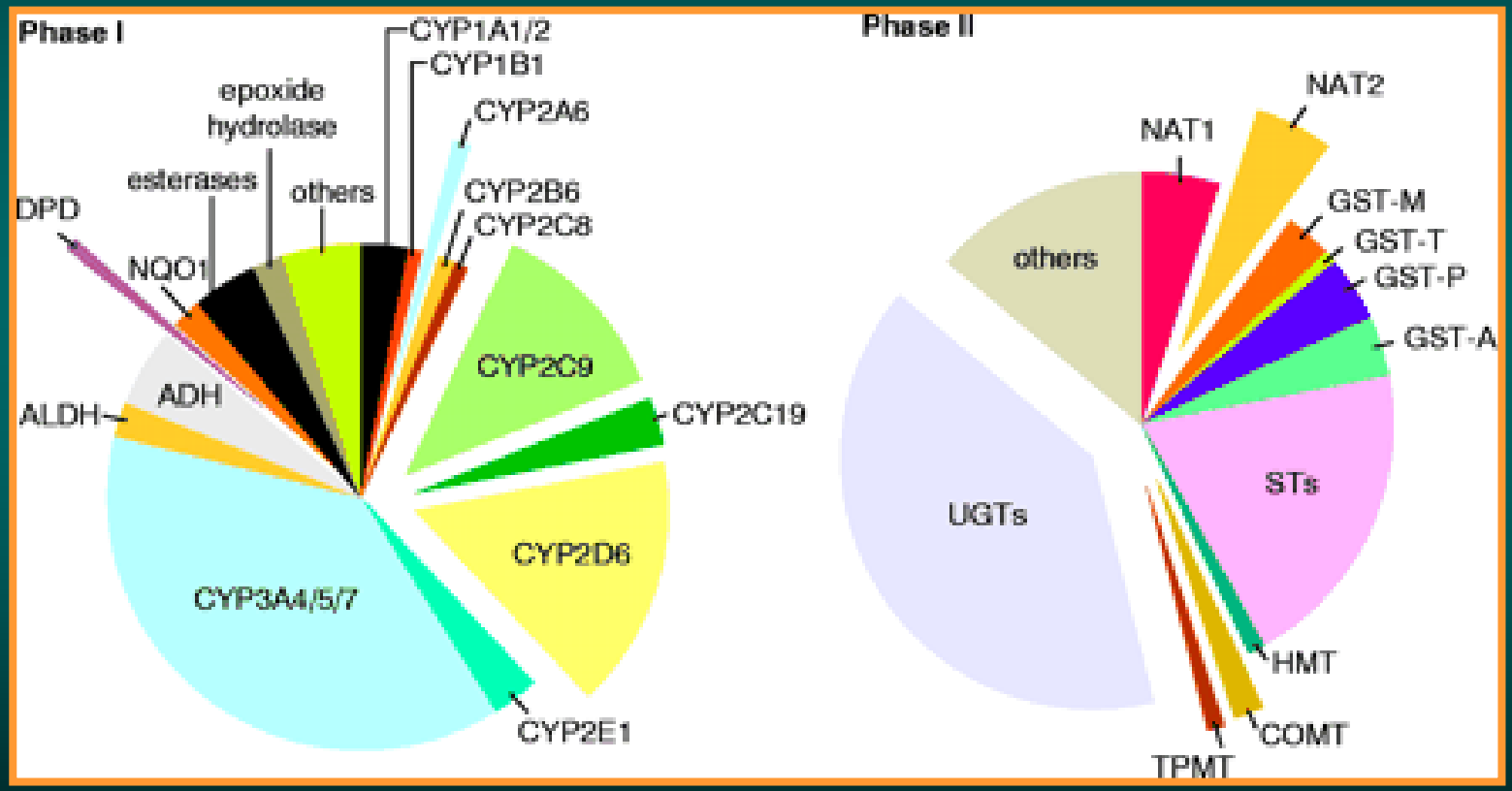
The home page of PharmGKB provides a straightforward schema for understanding pharmacogenomics.



The Pharmacogenetics Research Network: SNP Discovery to Clinical Drug Response - VOLUME 81 MARCH 2007

Principales enzimas de biotransformación que pueden estar afectados por polimorfismos genéticos que determinan su actividad enzimática



WE. Evans et al. Science 1999; 286: 487-491

Polimorfismos genéticos de interés en inmunosupresión

Enzimas de biotransformación:

- CYP3A4 y CYP3A5 (TAC, CsA, SRL, EVL)
- UGT1A9 (MPA)
- TPMT (Azatioprina ; FDA)

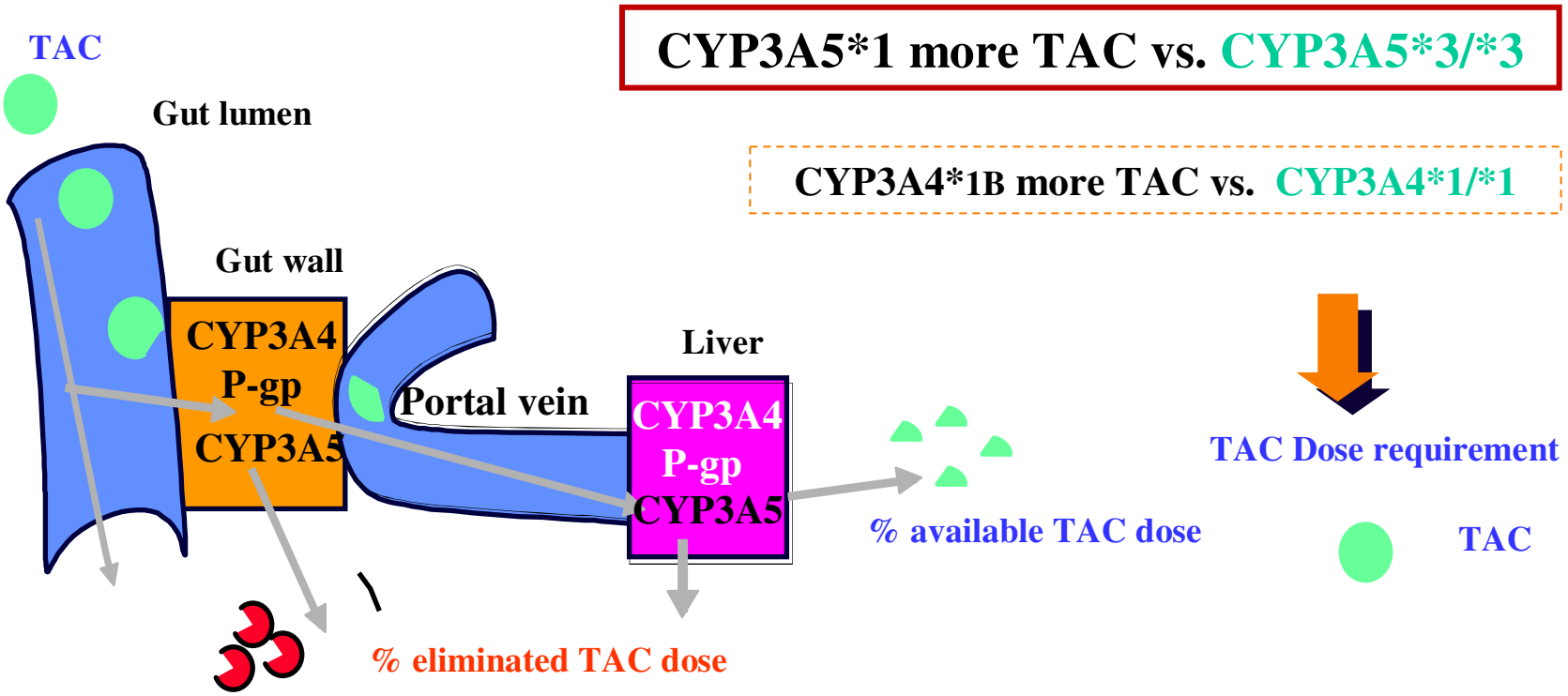
Proteínas reguladoras de transporte:

- MDR-1 or ABCB1 (nefrotoxicidad por CsA, TAC; Tx renal)
- MDR-1 (rechazo agudo; TAC,Tx hepático)

Polimorfismos de las dianas:

- IMPDH (MPA)

The role of CYP3A4, CYP3A5 genetic polymorphisms in TAC absorption

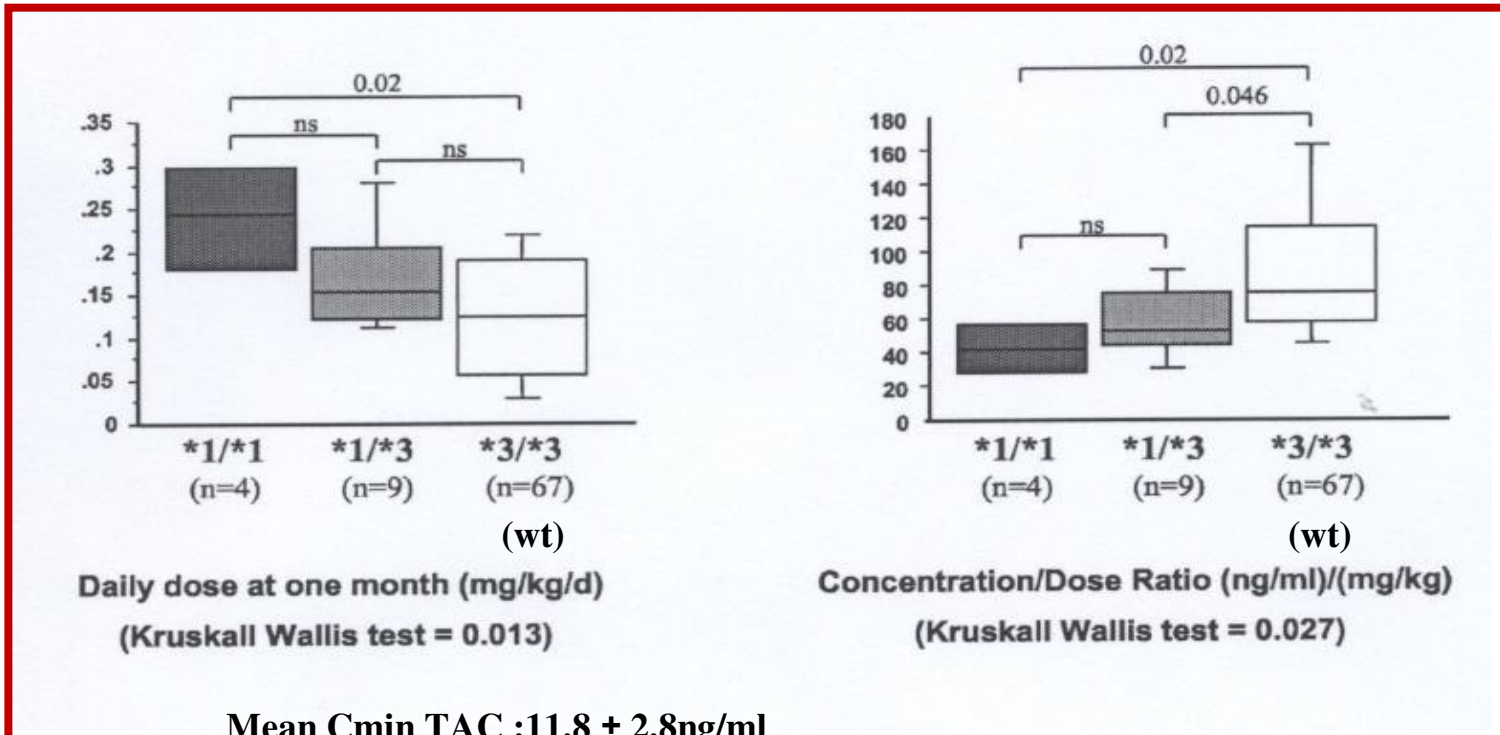


CYP3A5*1 genotype carriers require more TAC to reach target trough concentrations.

Kidney: Anglicheau D et al, Am J Transplant 2005; Hesselink DA et al, Clin Pharmacol. Therapeutics 2003; Thervet E et al, transplantation 2003; Zhang X et al, Clin Transplant 2005; Haufroid V et al, Pharmacogenetics 2004; V. Bach et al. ATC 2008

Liver: Goto M et al, Pharmacogenetics 2004; Masuda S et al, Pharmacol Therapy 2006; Yu S et al, Transplantation 2006 (CYP3A5*1 donor)

The role of CYP3A5 genetic polymorphisms in TAC absorption



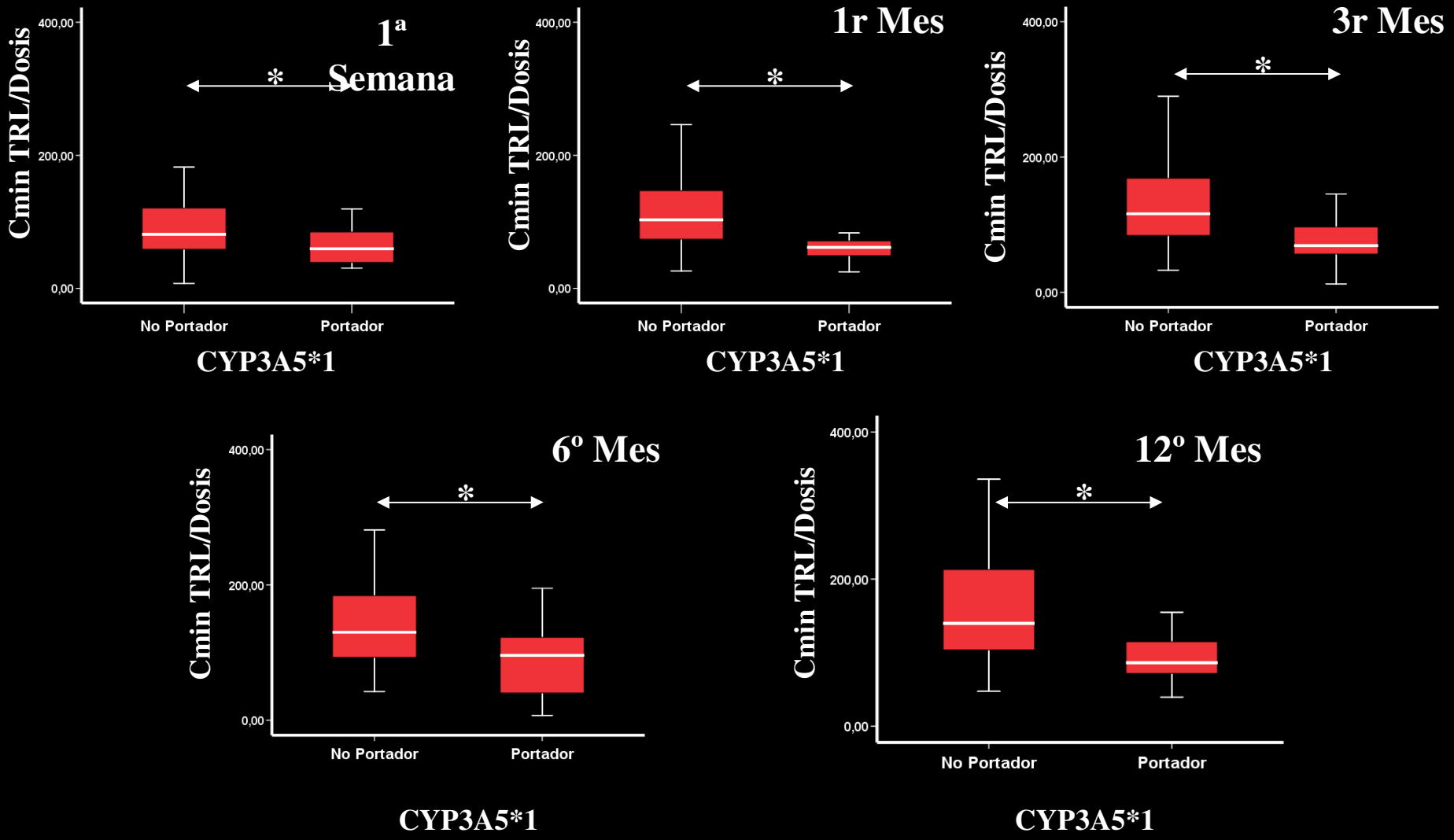
Mean Cmin TAC :11.8 ± 2.8ng/ml

No difference Cmin TAC different genotypes

Impact of Cytochrome P450 3A5 Genetic Polymorphism on Tacrolimus doses and Concentration-To_Dose Ratio in Renal Transplant Recipients.

E Thervet, D Anglicheau, B King et al, Transplantation 2003

➢ Efecto del polimorfismo CYP3A5*1 en la farmacocinética de tacrolimus



V. Bach et al. ATC 2008

Pacientes trasplantados renales; n=123

Incidence of CYP3A5*1 polymorphism

Reference	Solid Organ Transplant	Ethnic Background	n	CYP3A5*1 (%)		
				*1/*1	*1/*3	*3/*3*
Wei-lin W et al Liver Transplant 2006;12(5):775	Adult Liver	Chinese	50	13	50	37
Songfeng Y et al. Transplantation 2006;81:46	Adult Liver	Chinese	100	11.3	50.9	37.8
Goto M et al Pharmacogenetics 2004;14(7):471	Adult Liver	Japanese	70	3	38	59
Fukudo M et al. Clin Pharmacol Ther 2006;80:331	Pediatric liver	Japanese	130	3	38	58
Hesselink DA et al. Clin Pharmacol Ther 2003;74:245	Adult Kidney	Caucasian	100	1.6	17.5	81
Bach et al. Pharmacogenetics Submitted	Adult Kidney	Caucasian	125	2	18	80
Mourad M et al. Clin Chem Lab Med 2006;44(10):1192	Adult Kidney	Caucasian	90	1	19	80

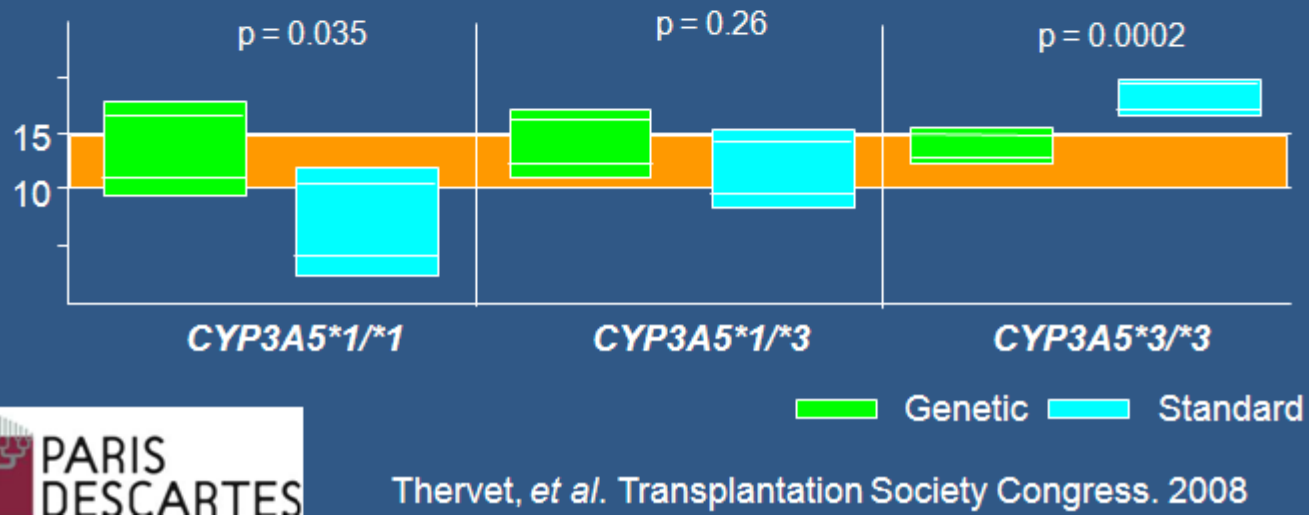
TacTic pharmacogenetic study

Renal transplants (n=280)
Tacrolimus from day 7

Randomisation

Standard dose:		0.20 mg/kg
Genetic:	CYP3A5 expresser:	0.25 mg/kg
	CYP3A5 non-expresser:	0.15 mg/kg

Tacrolimus concentration on day 10



PARIS DESCARTES

Thervet, *et al.* Transplantation Society Congress. 2008

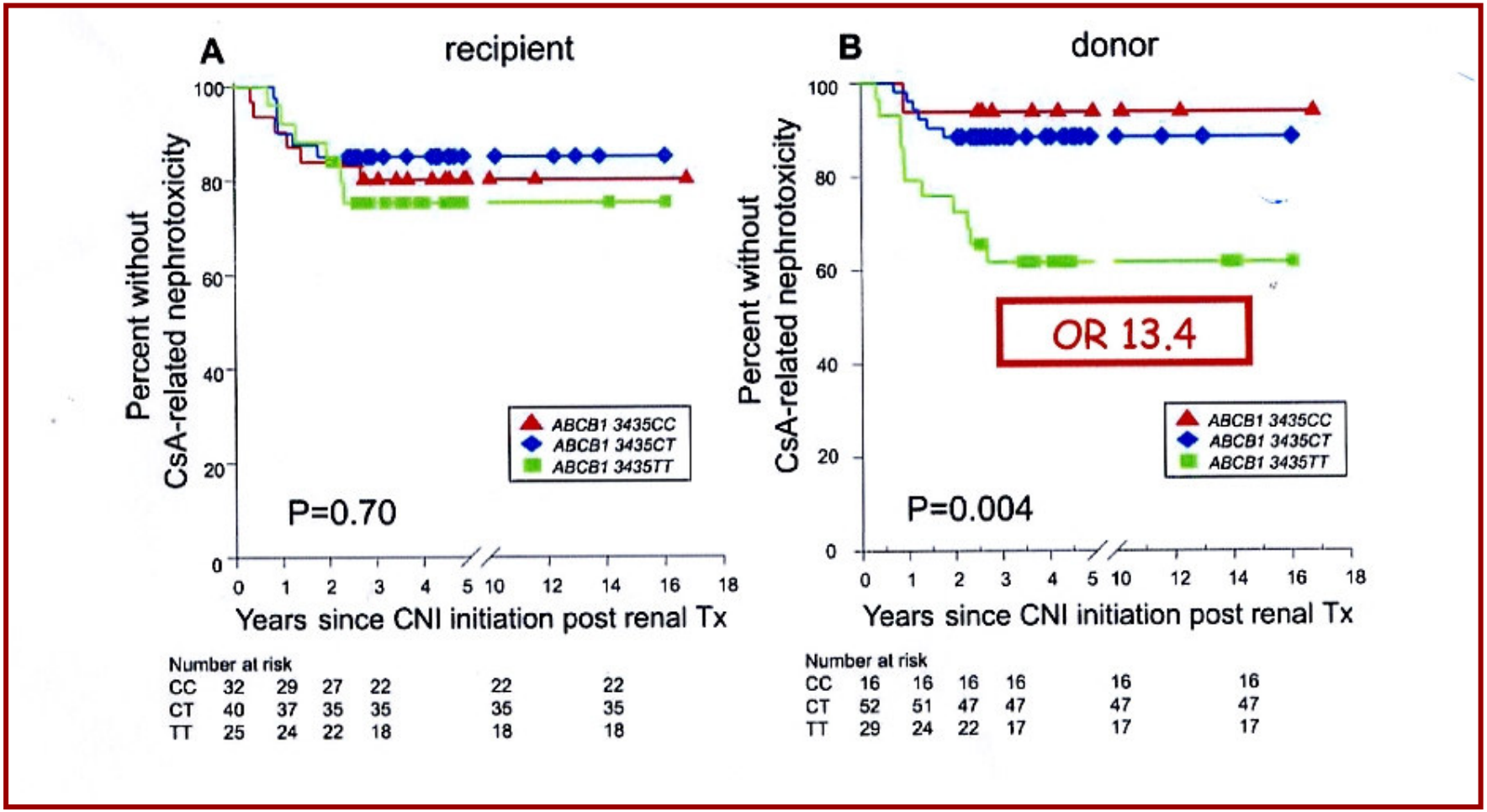
Tacrolimus

Los portadores CYP3A5*1

- Requieren 2-3 veces la dosis convencional (presentan ratios de concentración/dosis sig.inferiores).
- Sin impacto clínico en la incidencia de rechazo agudo (mayoria de estudios diversos tipos de Tx).
- Sin impacto clínico en la incidencia de nefrotoxicidad

Tx renal, hepático, cardíaco

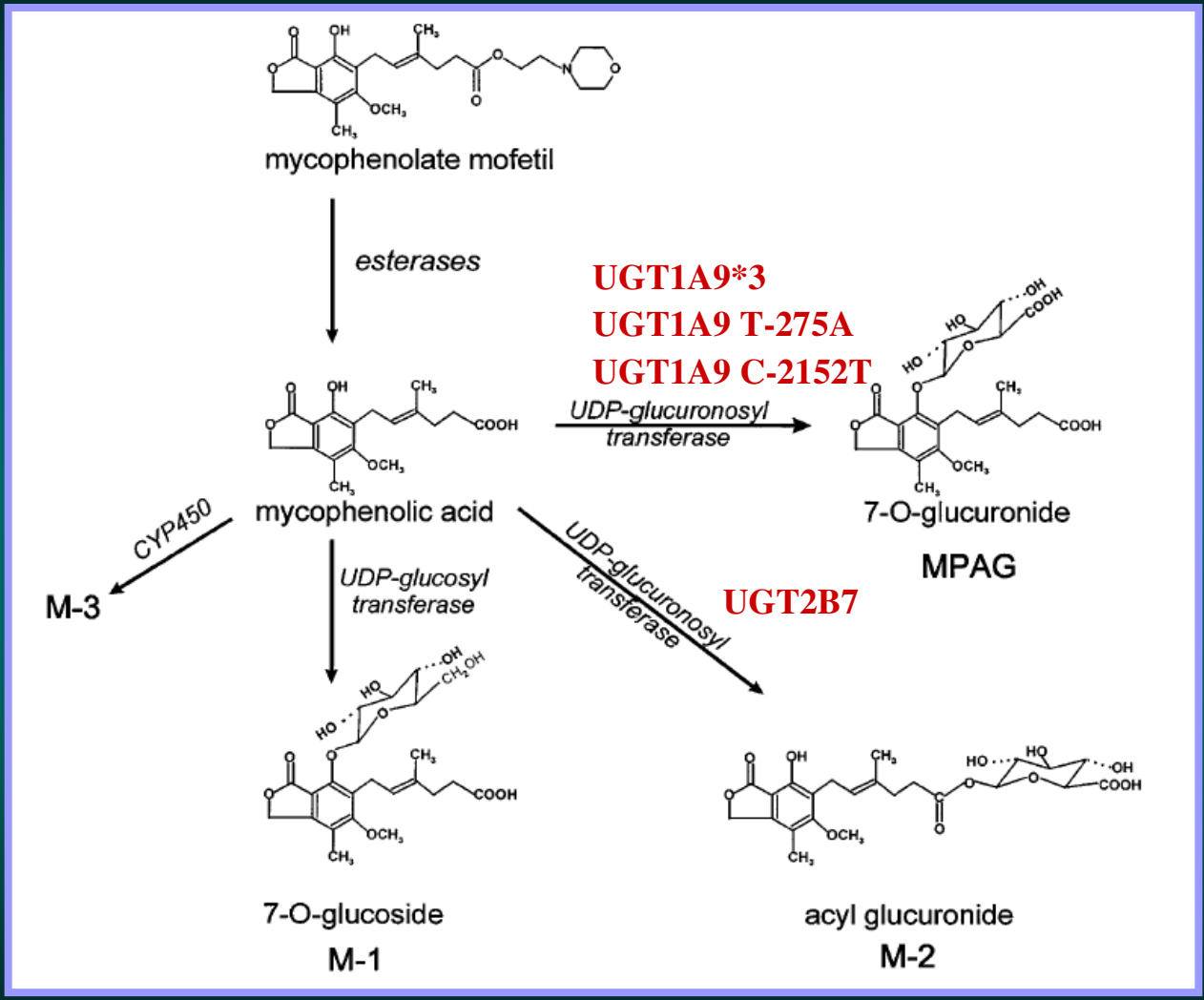
ABCB1 (MDR1) genetic polymorphisms Related to Cyclosporine (CNIs) Nephrotoxicity:



- Recipient: No consistent relationship with genetic polymorphisms in CYP3A4,CYP3A5 and ABCB1
- **DONOR ABCB1 3435C>T seems to be** correlated with nephrotoxicity

Hauser, J Am Soc Nephrol 2005;16:1501-11

Metabolismo del MPA: Polimorfismos genéticos que afectan la actividad metabólica o la expresión de los enzimas UGT



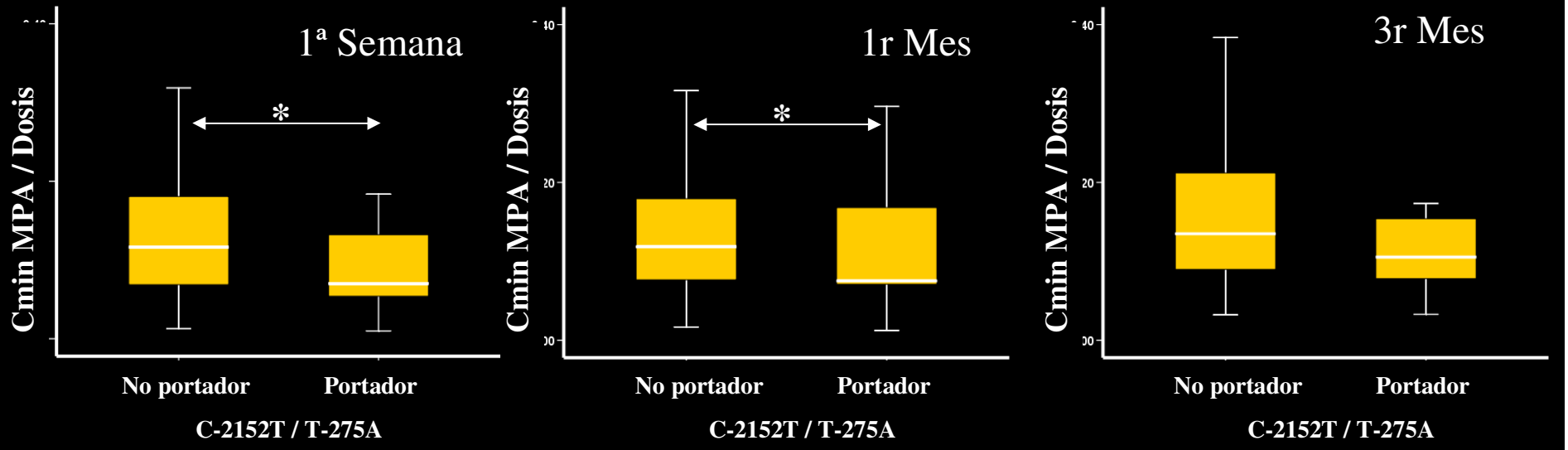
- **UGT1A9 alelo *3**
  - Exón 33
  - Incidencia población caucásica 4.4%
- **UGT1A9 C-2152T**
  - Región promotora
  - Incidencia población caucásica 12.6%
- **UGT1A9 T-275A**
  - Región promotora
  - Incidencia población caucásica 16.8%

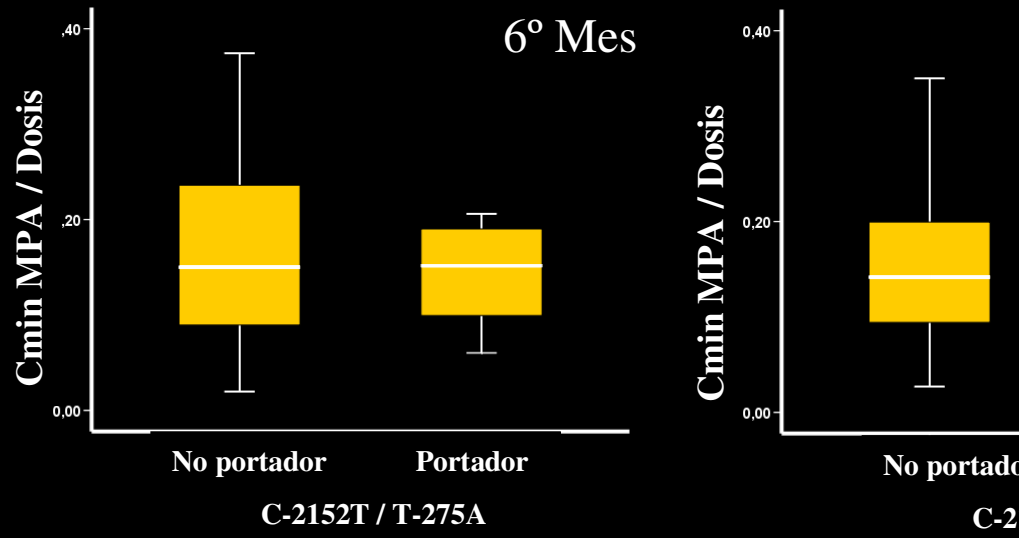
Bernard O. & Guillemette C. Drug Metab Dispos. 2004;32:775-8.

Kuypers D.R.J. et al. Clin Pharmacol Ther. 2005;78(4):351-61.

Picard N. et al. Drug Metab Dispos. 2005; 33: 139-146.

Efecto de los polimorfismos UGT1A9 -275 T>A y -2152C>T en la exposición del MPA





V. Bach et al. ATC 2008

D.R.J. Kuypers - *Clin Pharm Ther* 2005;78:351-361

Frequency of the T-275A and C-2152T SNPs

	Single-nucleotide polymorphism					
	CYP3A5*1	CYP3A4*B	UGT1A9*3	T-275A	C-2152T	T-275A and C-2152T
Noncarriers	1 (<1%)	115 (93,5%)	120 (97,5%)	105 (85,4%)	107 (87%)	NA
Total No. Of carriers	122 (99,1%)	8 (6,5%)	3 (2,4%)	18 (14,6%)	16 (13%)	14
Heterozygous carriers (1/2)	18 (14,6%)	7 (5,7%)	3 (2,4%)	18 (14,6%)	16 (13%)	14
Homozygous carriers (2/2)	104 (84,5%)	1 (<1%)	0	0	0	0

The obseved frequencies were consistent with the Hardy- Weinberg equilibrium

D.R.J. Kuypers - *Clin Pharm Ther* 2005;78:351-361.

V. Bach et al. ATC 2008

UGT1A9 -275T>A/-2152C>T Polymorphisms Correlate With Low MPA Exposure and Acute Rejection in MMF/Tacrolimus-Treated Kidney Transplant Patients.

RHN van Schaik et al. Clin. Pharmacol. Therapeutics. 2009

- **Method**

  338 adult renal transplant patients

  163 Tacrolimus + MMF (1 or 2 gr/day; 93 FD) + prednisolone

- **Carrying the UGT1A9 -275T>A and /or -2152C>T polymorphism significantly predicted acute rejection in fixed-dose (FD) MMF treated patients receiving TAC**

  Odds ratio 13.3, 95% confidence interval; $p < 0.05$.

Pharmacogenetics

Single nucleotide polymorphisms (SNPs)

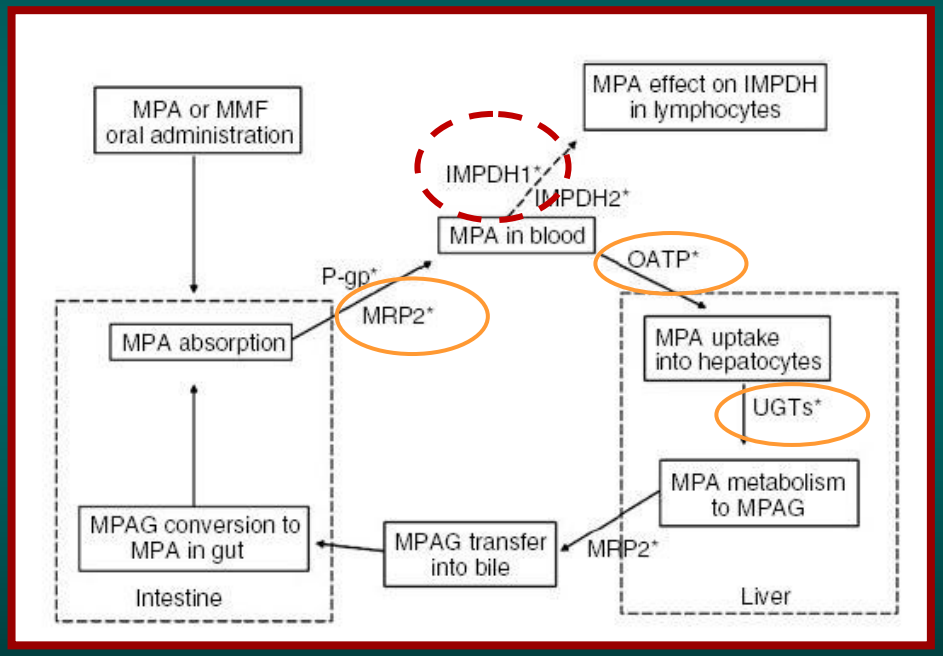
Genetic polymorphisms
Metabolizing enzymes
P-glycoproteins
MRP2

Genetic polymorphisms
Target
Cytokines
Receptors
Adhesion molecules
Growth factors

Numerous SNPs affecting drug target and drug immunomodulatory effect in organ transplant patients have been associated with acute rejection or toxicity

IMPDH1 Gene Polymorphisms and Association with Acute Rejection in Renal Transplant Patients. J Wang et al. Clin. Pharmacol. Ther. 2007

Polymorphisms in type I and II inosine monophosphate dehydrogenase genes and association with clinical outcome. O Gensburger et al. Pharmacogenetics & Genomics 2010



- 191 kidney Tx; TAC+MMF+ Pred.
- 456 kidney Tx; TAC +MMF; CsA +MMF

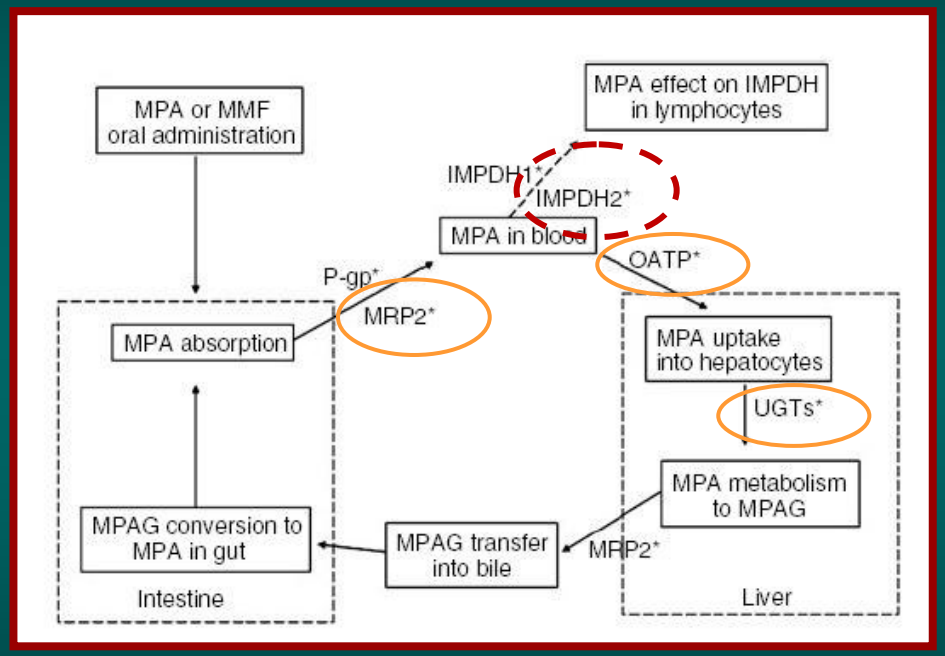
IMPDH1 Gene Polymorphism SNP rs2278293

Was associated with a lower risk of BPAR and a higher risk of leucopenia over the first year post-transplantation.

Plasma concentrations of MPA are affected by a number of gene polymorphisms*

Genetic Polymorphisms & Drug Response & Clinical Outcome

IMPDH2 Gene Polymorphisms and Association with Acute Rejection in Renal Transplant Patients



- IMPDH2 3757T>C carriers have higher IMPDH activity.

Sombogaard et al. Pharmacogenetics & Genomics 2009

- IMPDH 2 Gene Polymorphism SNP 3757 CC + CT higher incidence of BPAR (OR 3.4, p=0.006).

Caesar study Transplant Int. 2008

Genetic Polymorphisms & Drug Response & Clinical Outcome

MMF (MPA)

- UGT1A9 -275/-2152 SNPs **are associated with decreased MPA exposure.**

- In fixed-dose MMF/TACRO co-treated kidney Tx patients correlate with acute rejection (OR 13 [1.1-162])

- IMPDH 2 Gene Polymorphism SNP 3757 CC + CT was associated with higher incidence of BPAR (OR 3.4, p=0.006).

- IMPDH1 **Gene Polymorphism** SNP rs2278293 was associated with a lower risk of BPAR and a higher risk of leucopenia.

Aplicabilidad clínica

Los análisis farmacogenéticos pueden identificar a pacientes con un mayor riesgo de ineficacia o efectos adversos.

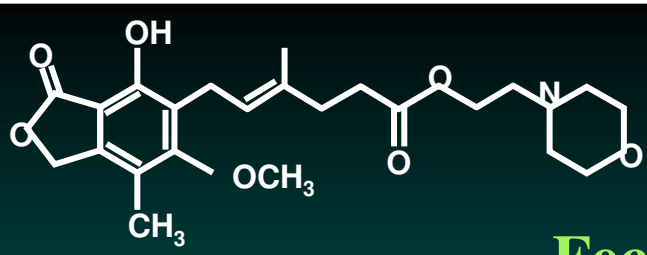
MPA: IMPDH, UGT1A9 SNPs, relevantes en la practica clínica?

Análisis "universal" No justificado (FDA, EMEA)
Si en situaciones de ineficacia o efectos adversos (IATDMCT)

1- Selección de la mejor dosis de inicio
paralelamente monitorizar FC ?
Considerar medicación concomitante?

2- En portadores de los SNPs UGT1A9 -275/-2152
Elejiríamos la mism dosis de MMFpara MMF/CsA o MMF/TAC?
Elejiriamos CsA o TAC como medicación concomitante?

Pharmacokinetics of MMF, MPA & Metabolites



Micofenolate mofetil

Intestine
Plasma

Estearase

B. albumin 97%
Tmax ≈ 30-50 min

Micophenolic Acid

Blood

2º Peak 6-12 h

Feces

Intestine

Plasma
Liver

β glucuronidasa

UDP-G transferase

Bilis

Liver

Enterohepatic Circulation

Liver
WB

MPAG
Ac MPAG

MRP2

Urine (96%)

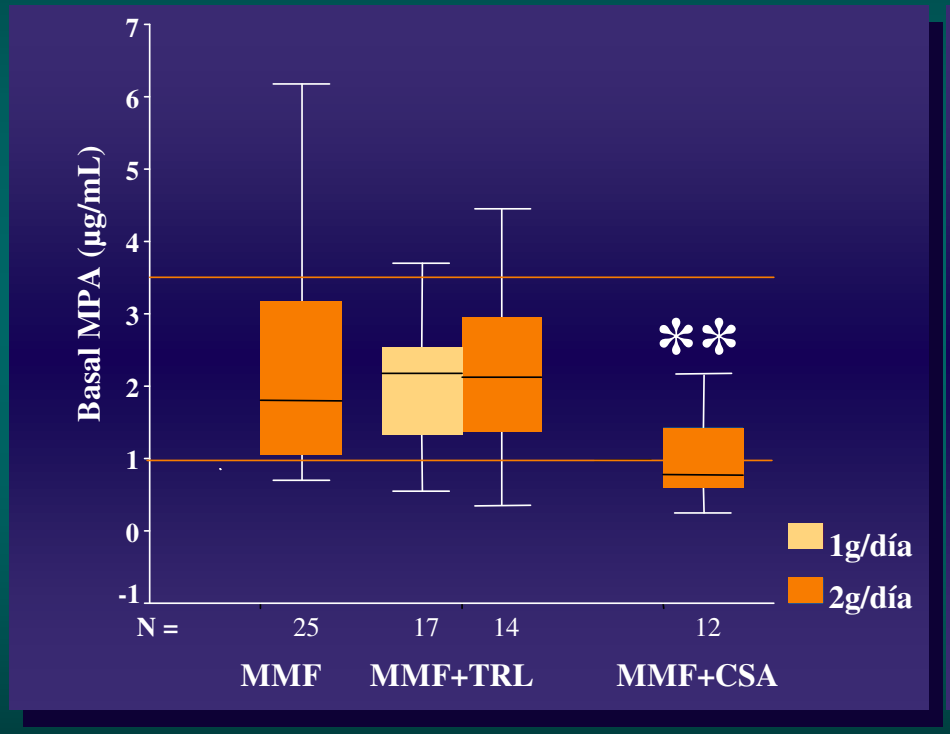
Van Gelder T. et al. 2000

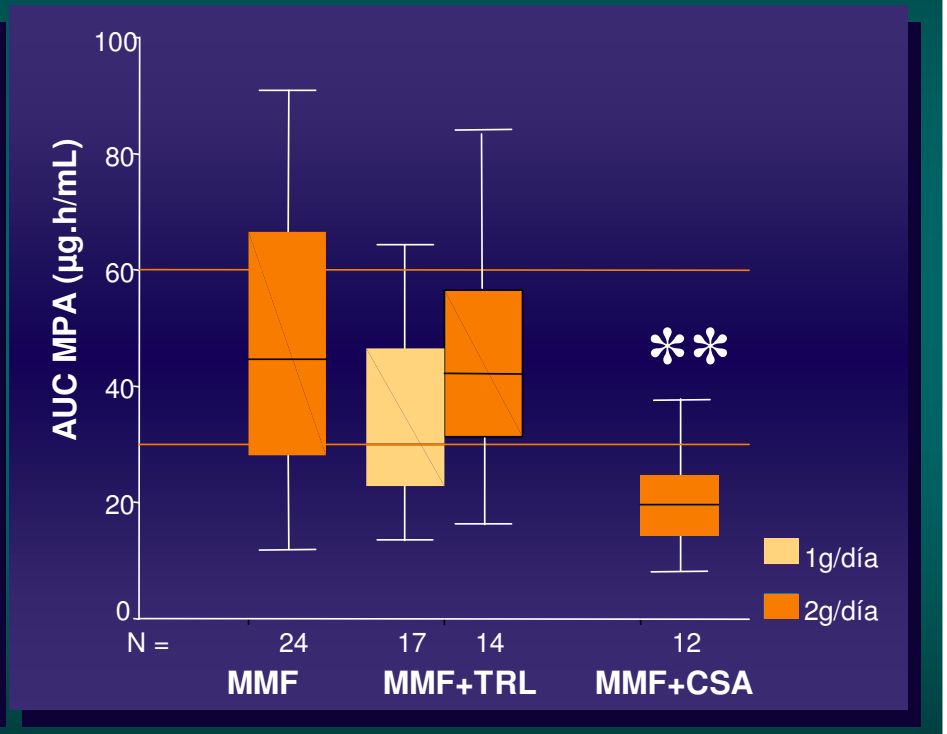
Kuypers D.R.J. et al. 2006

CsA inhibits MRP2

M. Brunet 2000

MPA & CsA
Interacciones Farmacocinéticas





MMF 2g + CsA

MMF 1g + TRL; MMF 2g + TRL

T. Van Gelder et al. 2000; M. Brunet et al. 2003; DRJ. Kuypers et al. 2006; JM. Grinyó et al. (in press)

Aplicabilidad clínica

Los análisis farmacogenéticos pueden identificar a pacientes con un mayor riesgo de ineficacia o efectos adversos.

TAC: CYP3A5, ABCB1, relevantes en la practica clínica?

Análisis "universal" No justificado (FDA, EMEA)
Si en situaciones de ineficacia o efectos adversos (IATDMCT)

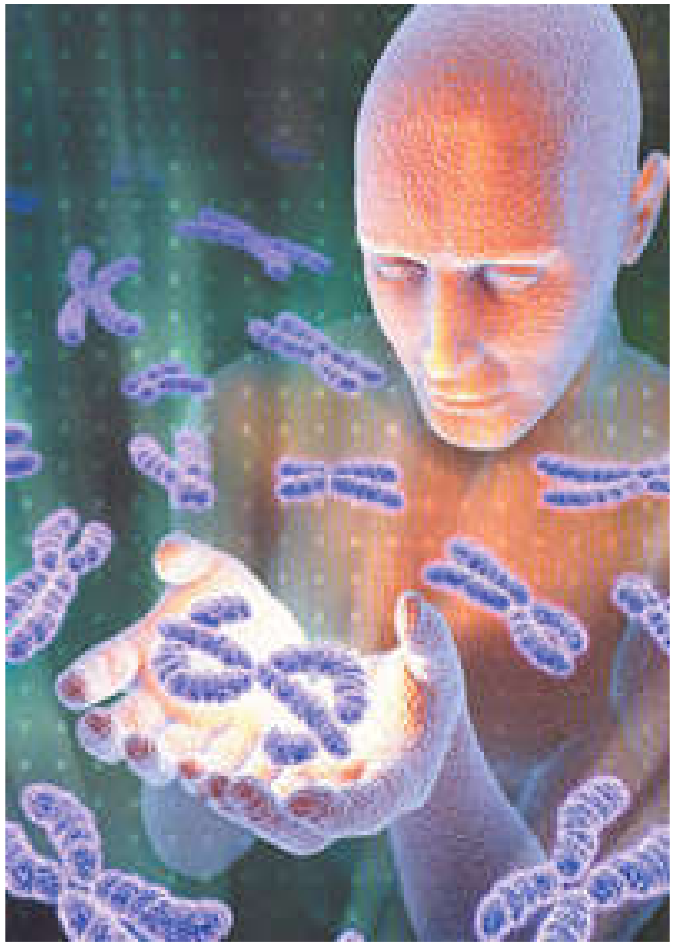
1- Selección de la mejor dosis de inicio

Portadores CYP3A5*1 (*1/*1;*1/*3), 2-3veces la dosis conven.

Considerar medicación concomitante?
Ketoconazol, Afecta a nuestra decisión referente al SNP?
Considerar función hepática?
pacientes VHC+, afecta nuestra decisión referente L SNP?

Aconsejable siempre Monitorizar FC TAC

Farmacogenética e Inmunosupresión



Gracias !

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