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Drug-induced liver disease: Pathogenesis and treatment options

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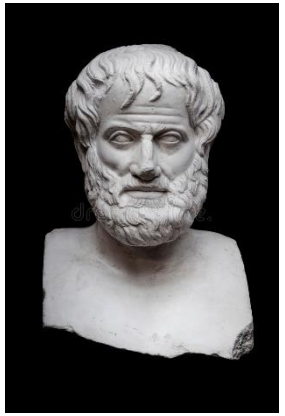
Pathogenesis: Joining the dots

- DILI acute liver injury due to a medication taken in a therapeutic dose which is not entirely explained by known pharmacological action of the drug.
  - Premise
  - Risk factors
  - Pathogenesis
  - Evidence base for interventions



Aristotle, 384-322 B.C.

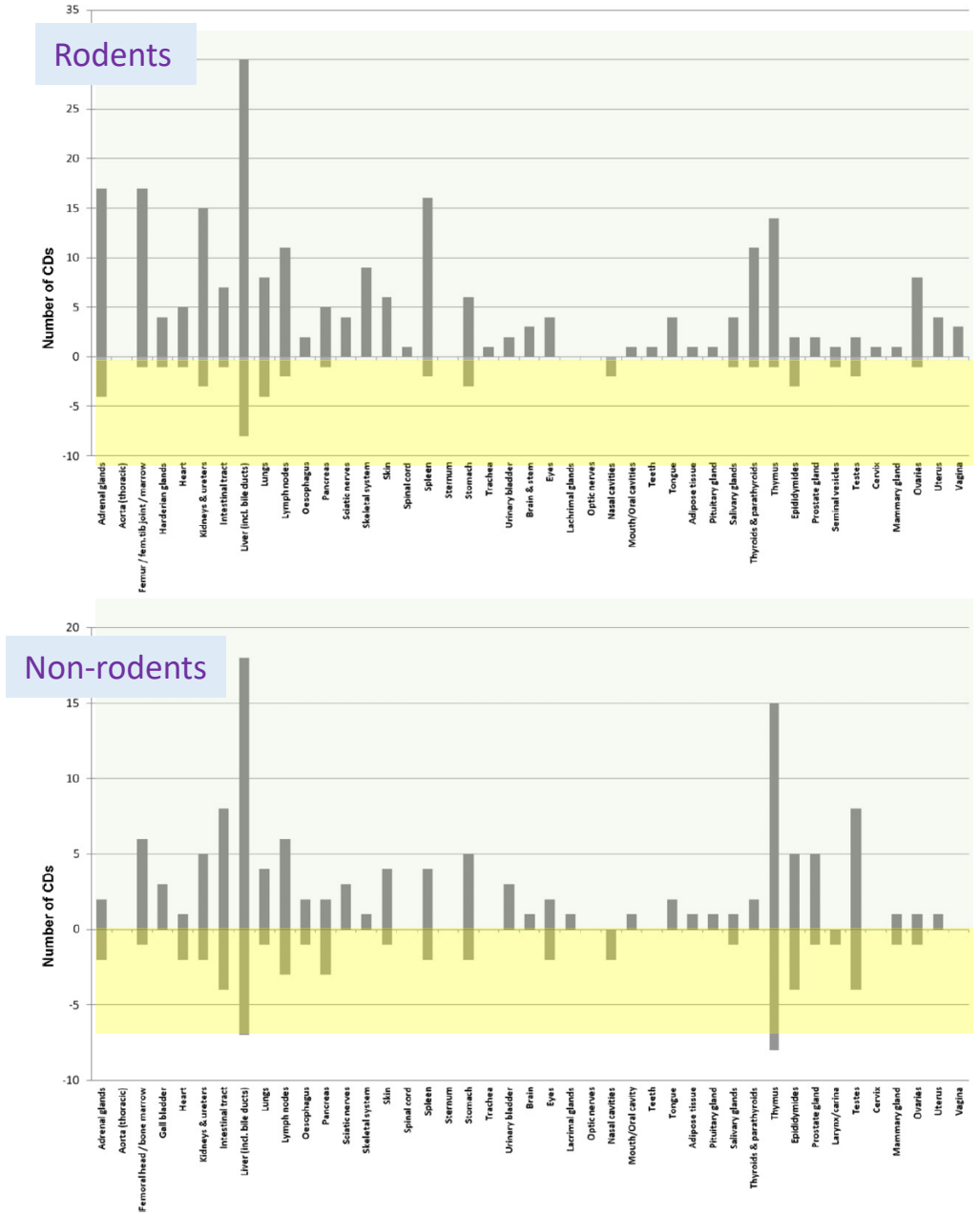
“None of the arts theorise about individual cases. Medicine, for instance, does not theorise about what will help to cure Socrates or Callias, but only about what will help to cure any or all of a given class of patients.

This alone is business: individual cases are so infinitely various that no systematic knowledge of them is possible.”

Aristotle. *Rhetoric*. book I, chapter 2: 1356b.

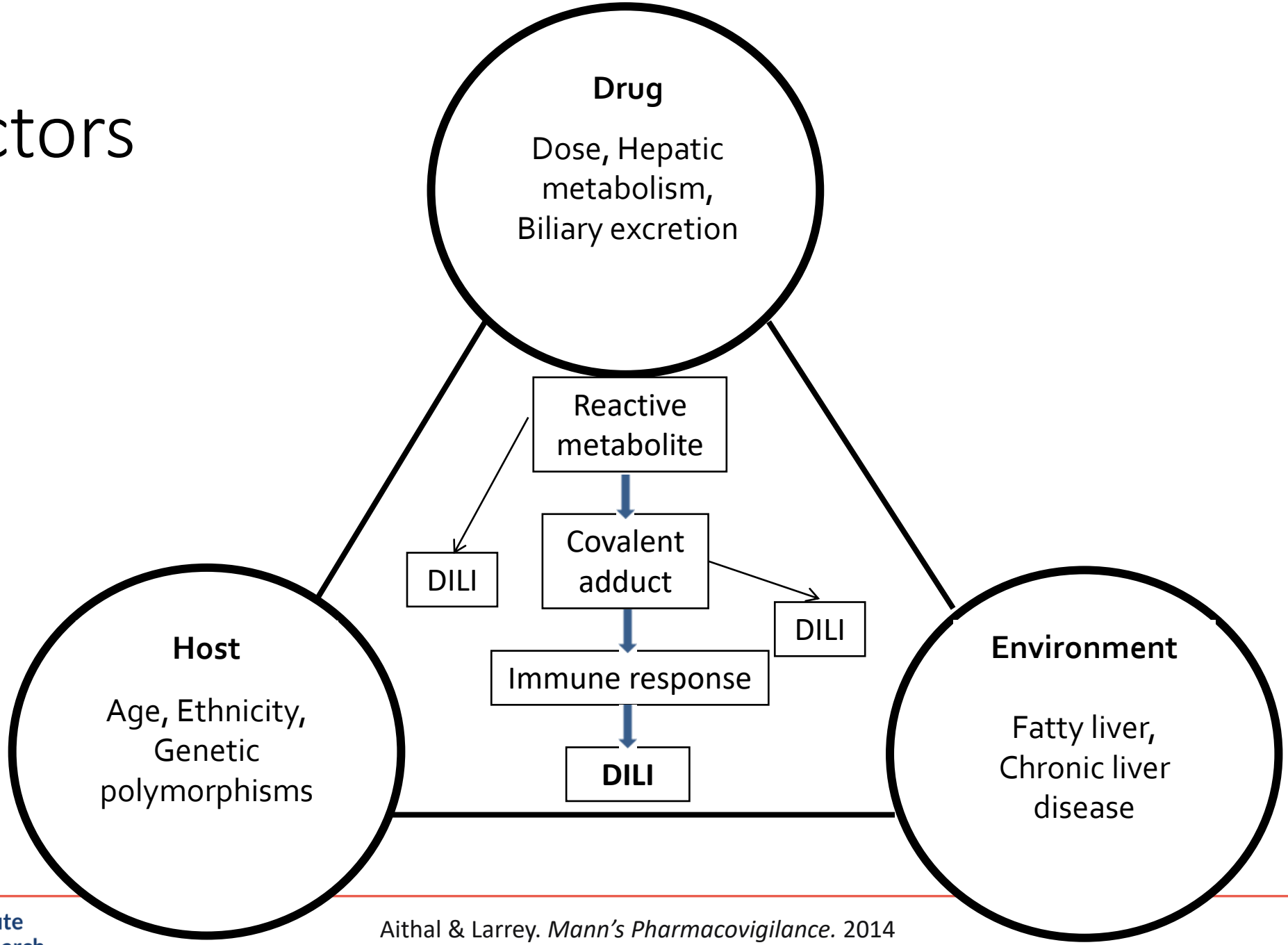
Pre-clinical toxicology

- 77 candidates:
- Liver most common target organ toxicity: 46 (61%)
  - Compound related histopathological changes
- 35% in both rodents and non rodents
- 79% (rodent) and 72% (non-rodent) with liver toxicity progressed to first in humans



Horner S. *Regulatory Toxicol Pharmacol* 2013; 65:334–343

Risk Factors



Aithal & Larrey. *Mann's Pharmacovigilance.* 2014

Does NAFLD increase the risk of DILI?

	Suspected NAFLD (n= 4837)	Control group 1 (n=61,355)	Control group 2 (n=47,869)
Age years mean	50.6	55.8	56.7
Females %	48	65	60
BMI kg/m2	32.1	31	30.4
ALT IU/L means +/-	**69 +/- 27**	19 +/- 8.2	17 +/- 5
ALP IU/L means +/-	93 +/- 41	74.5 +/- 29	73 +/- 27
Total bilirubin means +/-	0.7 +/-0.4	0.6 +/- 0.5	0.6 +/- 0.34
Type 2 DM %	34	24	24
Hypertension %	56	50	51

Lammert C. *Clin Gastroenterol Hepatol* 2019

DILI Risk in NAFLD

- Drug: amoxicillin-clavulanate, isoniazid, nitrofurantoin, minocycline, trimethoprim-sulfamethoxazole, ciprofloxacin, levofloxacin, azithromycin, cefazolin, and diclofenac.
- DILI: 0.8% (40 of 4837) in NAFLD cohort vs 0.2% in control groups
  - OR: 4.0 [95% CI, 2.8–5.8]; P < 0.001 (126 of 61,355 in group 1)
  - OR: 4.2 [95% CI, 2.9–6.0]; P < 0.001 (96 of 47,869 in group 2)
- Death/ Transplant within 6 months of DILI: 25% (10/40 in the NAFLD)
  - 16.6% (21 of 126) in control group 1 (p =0.2)
  - 13.5% (13 of 96) in control group 2 (p=0.1)

Lammert C. *Clin Gastroenterol Hepatol* 2019

Drug: Daily Dose effect

- 230 Top generic drugs by prescription volume in the US
- Grouped by average daily dose ≤10 mg (n=54), 11-49 mg (n=83) and ≥50 mg (n=93)

Out come	<10 mg	>50 mg
Median prescriptions	4,746,500	3,733,000
Jaundice	1	1.7 [0.8-3.3]
Liver failure	1	2.4 [1.03-5.5]
Death	1	3.1 [1.2-8.1]
Transplantation	1	10 [2.2-45.8]

Lammert. *Hepatology* 2008;47:2003-9

Drug: Hepatic metabolism and Biliary excretion

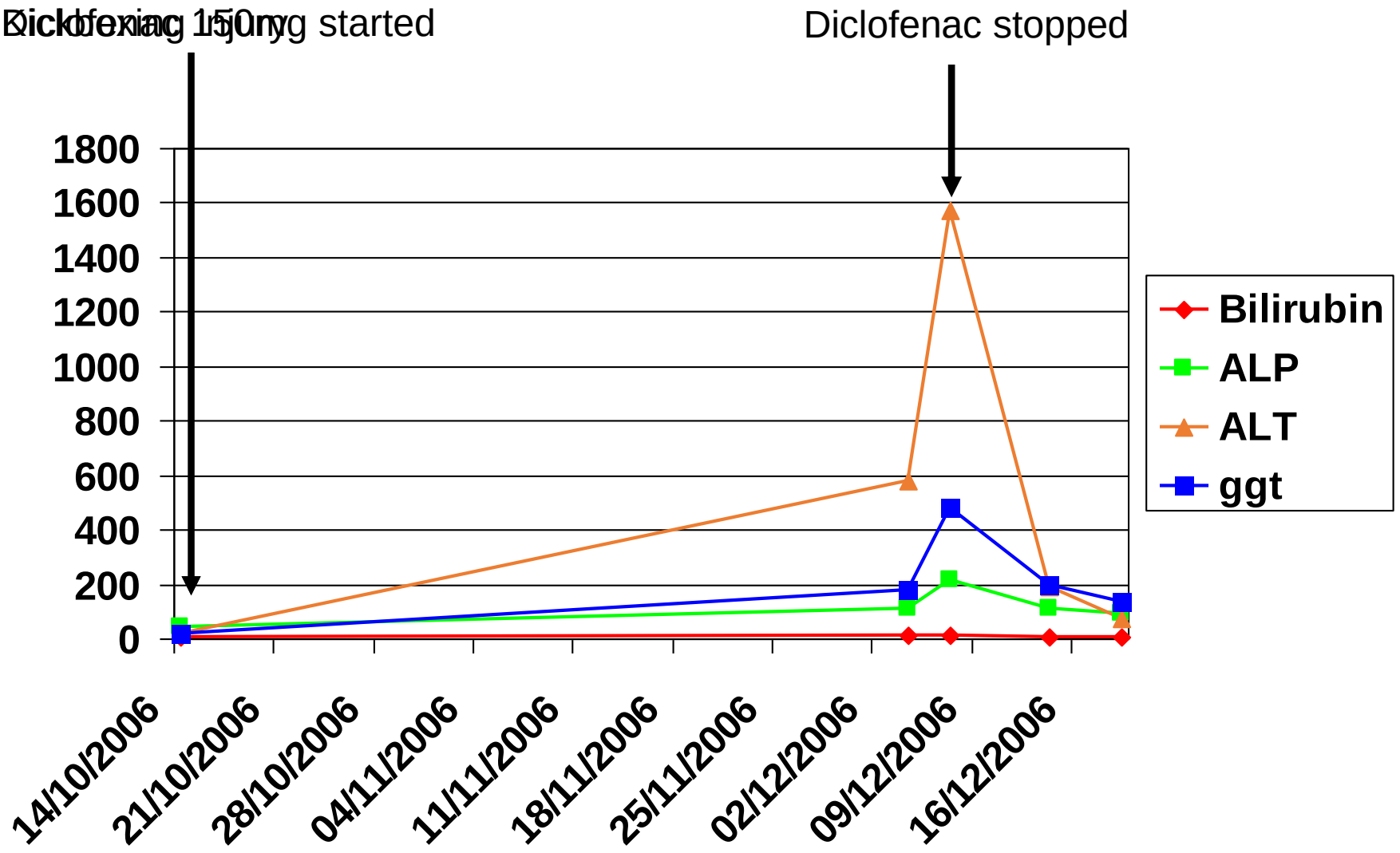
- 204 Most commonly prescribed drugs in USA

Out come (n)	<50% (n=55)	>50% (n=149)	p
>3x ULN ALT (n=58)	11%	35%	0.001
Jaundice (n=86)	35%	46%	0.2
Liver failure (n=47)	9%	28%	0.004
Death (n=36)	4%	23%	0.001
Transplantation (n=14)	2%	9%	0.1

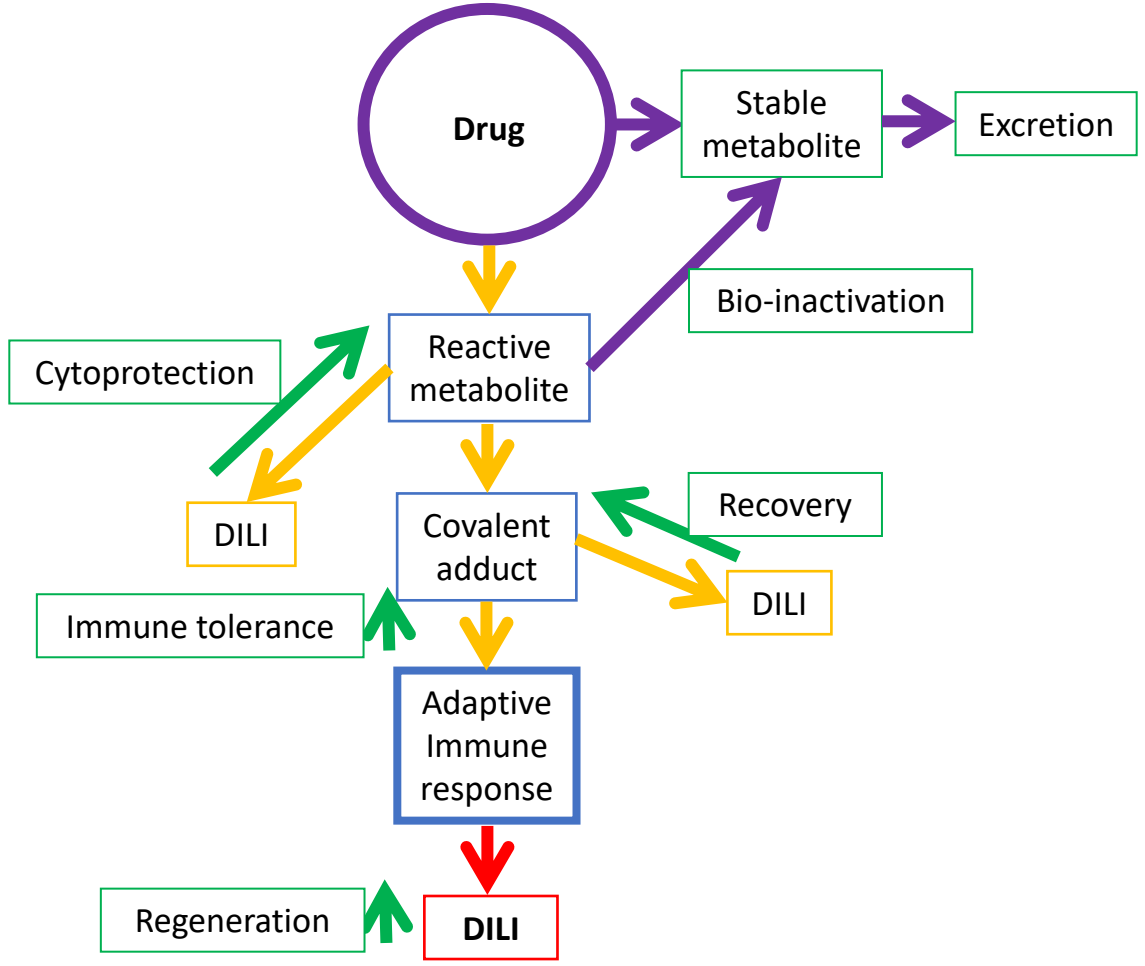
- Jaundice in 74% in drugs with biliary excretion (n=50) vs. 40% in those without (p=0.0001)

Lammert. *Hepatology* 2010;51:615-620.

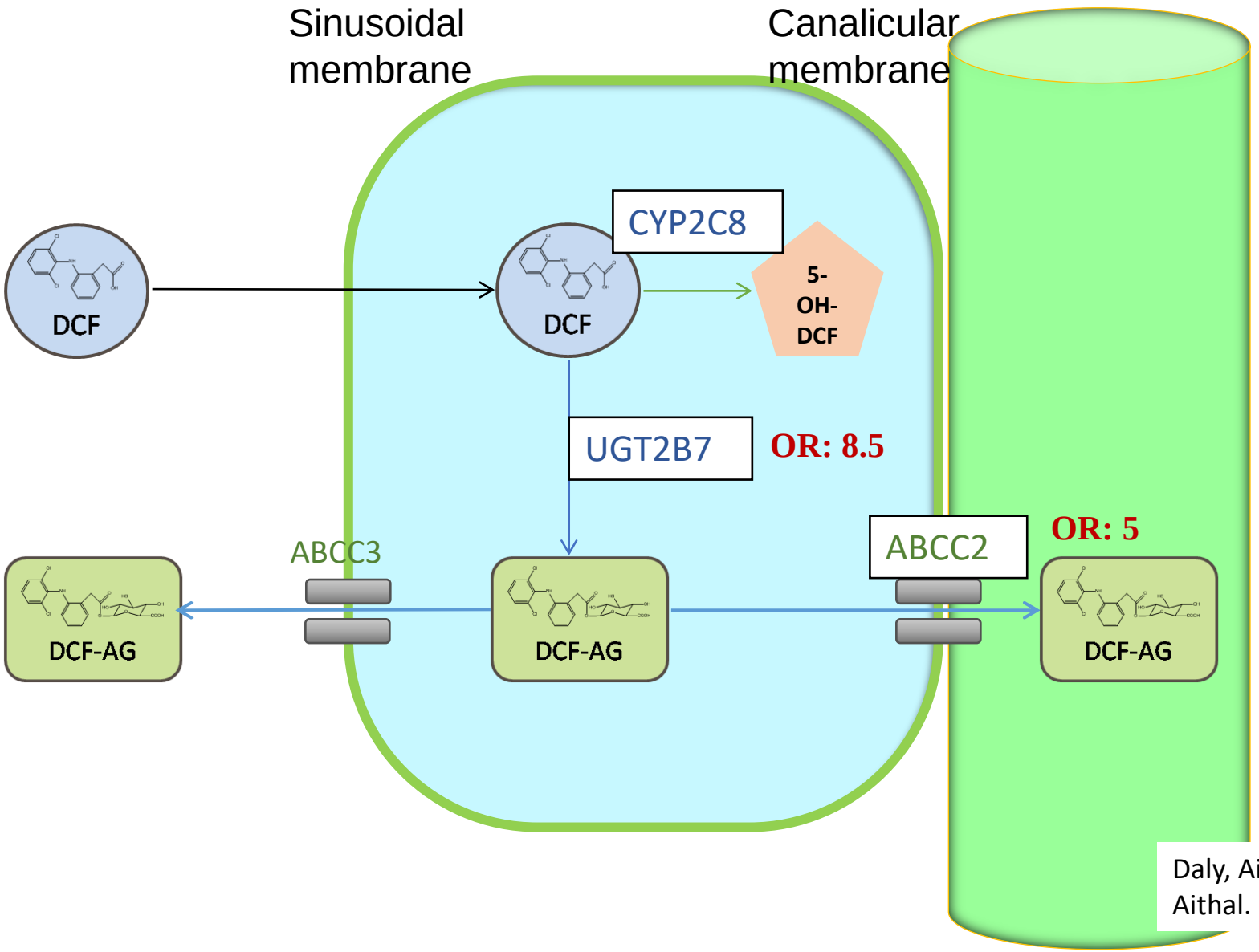
Individual


Diclofenac 150mg started
Diclofenac stopped
1800
1600
1400
1200
1000
800
600
400
200
0
14/10/2006
21/10/2006
28/10/2006
04/11/2006
11/11/2006
18/11/2006
25/11/2006
02/12/2006
09/12/2006
16/12/2006
Bilirubin
ALP
ALT
ggt

Putative pathogenesis

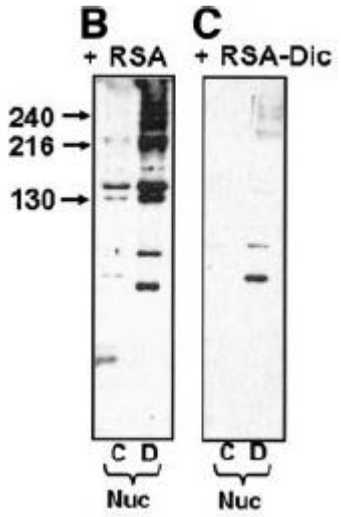


Reactive metabolite formation & retention

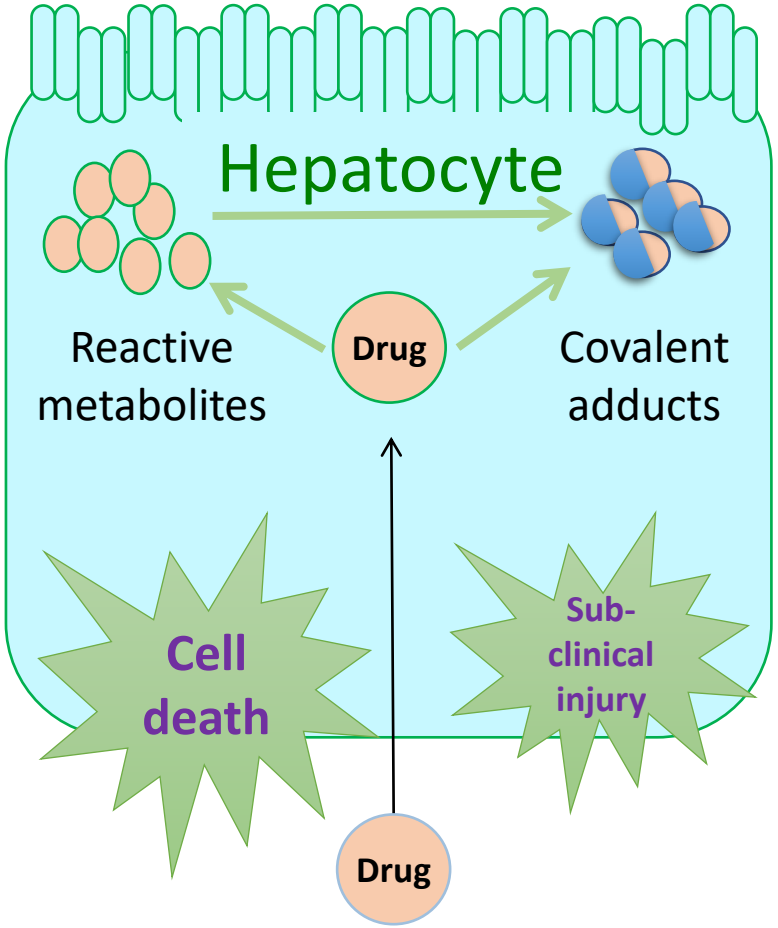


Daly, Aithal, *et al. Gastroenterology* 2007;132:272-81.
Aithal. *Nature Review Rheumatol* 2011;7:139–50.

Drug-specific ‘proximal events’



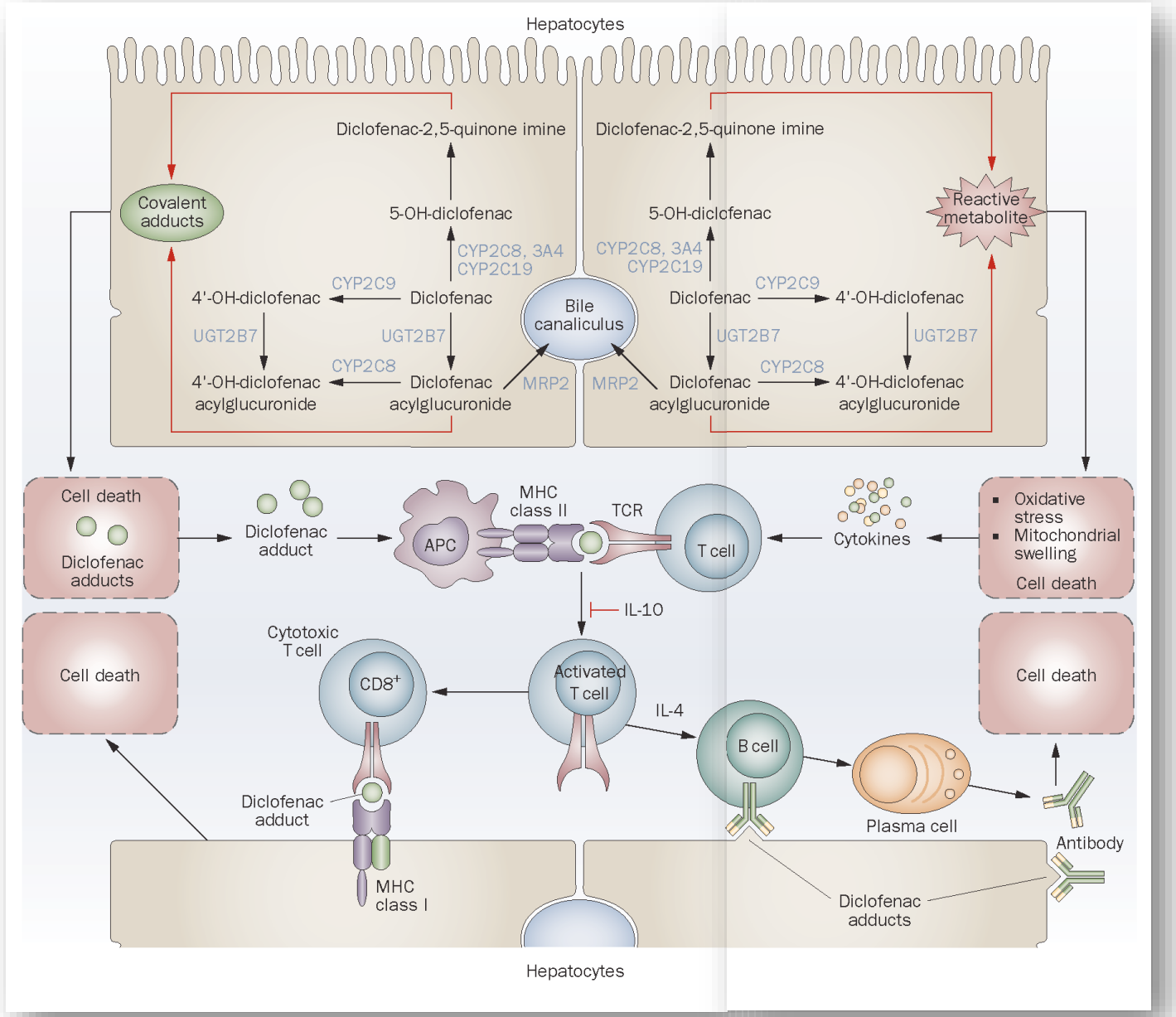
Covalent adducts in diclofenac-induced liver failure



Subclinical injury and cytokine production as a ‘**danger signal**’ for immune mediated reaction

Aithal *et al. Hepatology* 2004;39:1430–1440

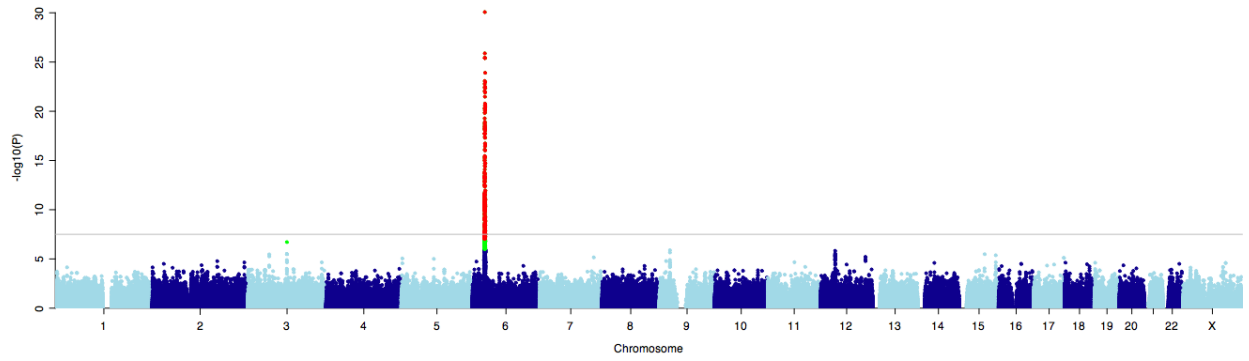
Mechanism of liver injury: proximal events



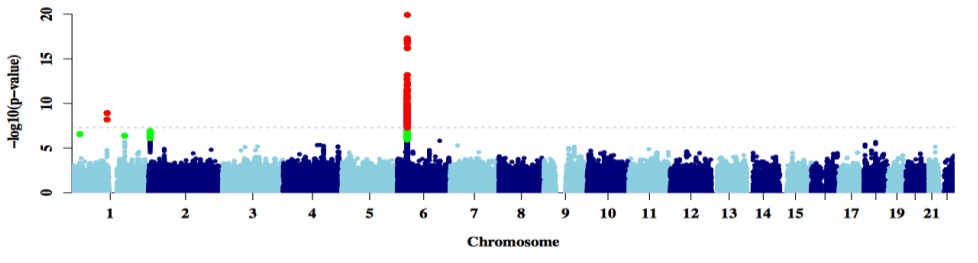
Aithal. *Nature Review Rheumatol* 2011;7:139–50.

Genome wide association studies

- 51 cases, 282 sex/ ancestry matched controls
- Rs2395029[G] ($p=8.4 \times 10^{-33}$)
  - Missense polymorphism in the *HCP5* gene= tag SNP for the HLA-*B*5701*
- 84% of cases and 5% of controls carried the risk allele G



- 2,048 cases; 12,429 population controls
  - Caucasian, Hispanics and African Americans
- Independent replication: 113 Iceland cases and 239,304 controls
- PTPN22 (rs2476601) OR = 1.44 [1.28-1.62]; $PV=1.2 \times 10^{-9}$
- Central role in regulating autoreactive T & B cell priming



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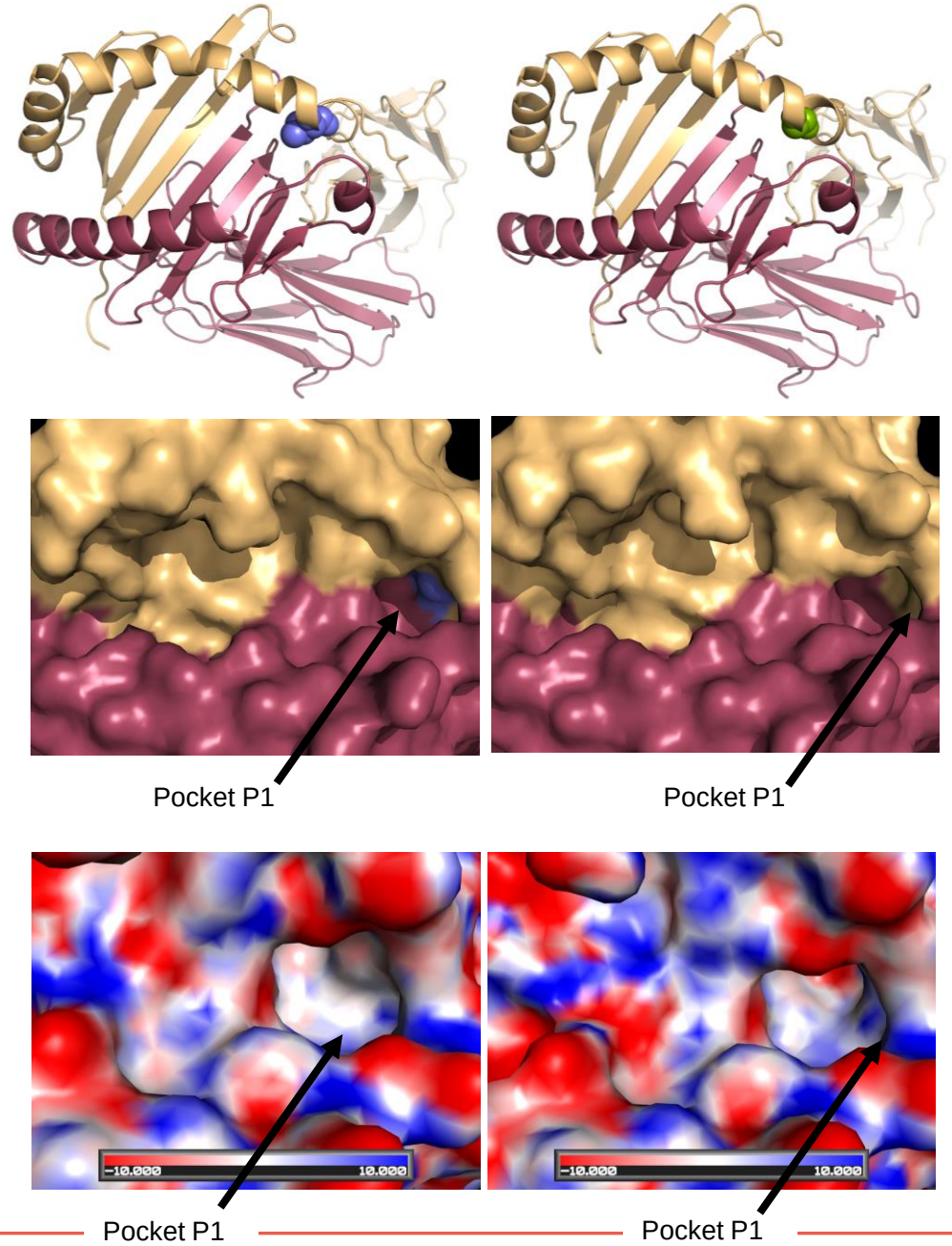
Daly, Aithal & Day. *Nat Genet.* 2009; 41:816-9.
Nicoletti, Aithal & Watkins. *Gastroenterology*. 2019;156(6):1707-16

Peptide binding grove: structure and Function

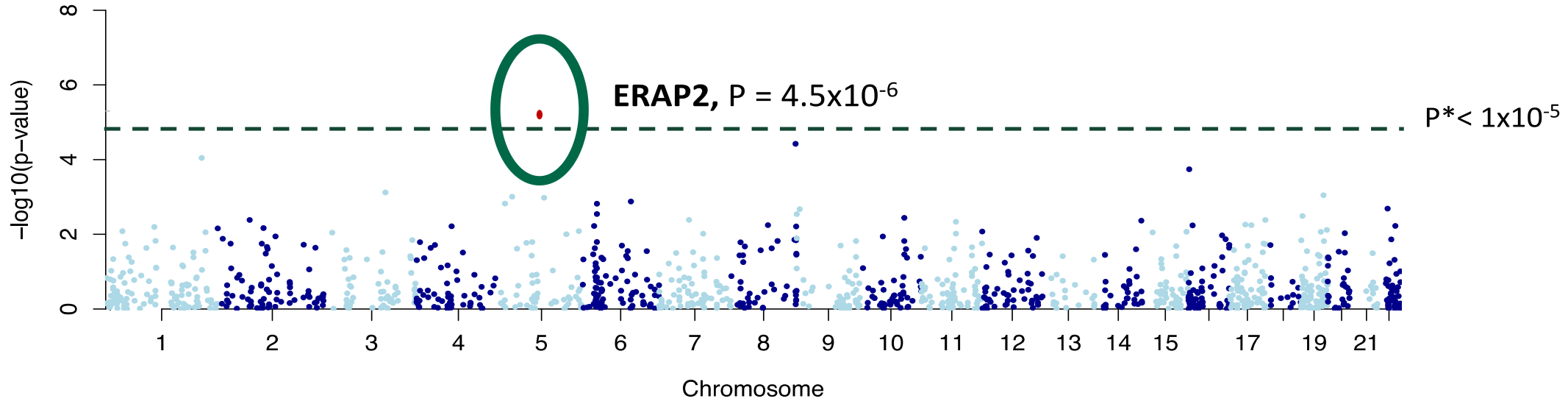
- DRB1*15:01 and DRB1*15:02 differ P1
- Residue 86 of DRB1 chain is integral in the formation of P1
  - DRB1*15:01- V (valine)
  - DRB1*15:02- G (glycine)
- Neutral in terms of electrostatic potential at P1
- DRB1*15:02 is the risk allele in Asians



Kaliyaperumal K & Aithal. *J Hepatol.* 2018; 69:948-957

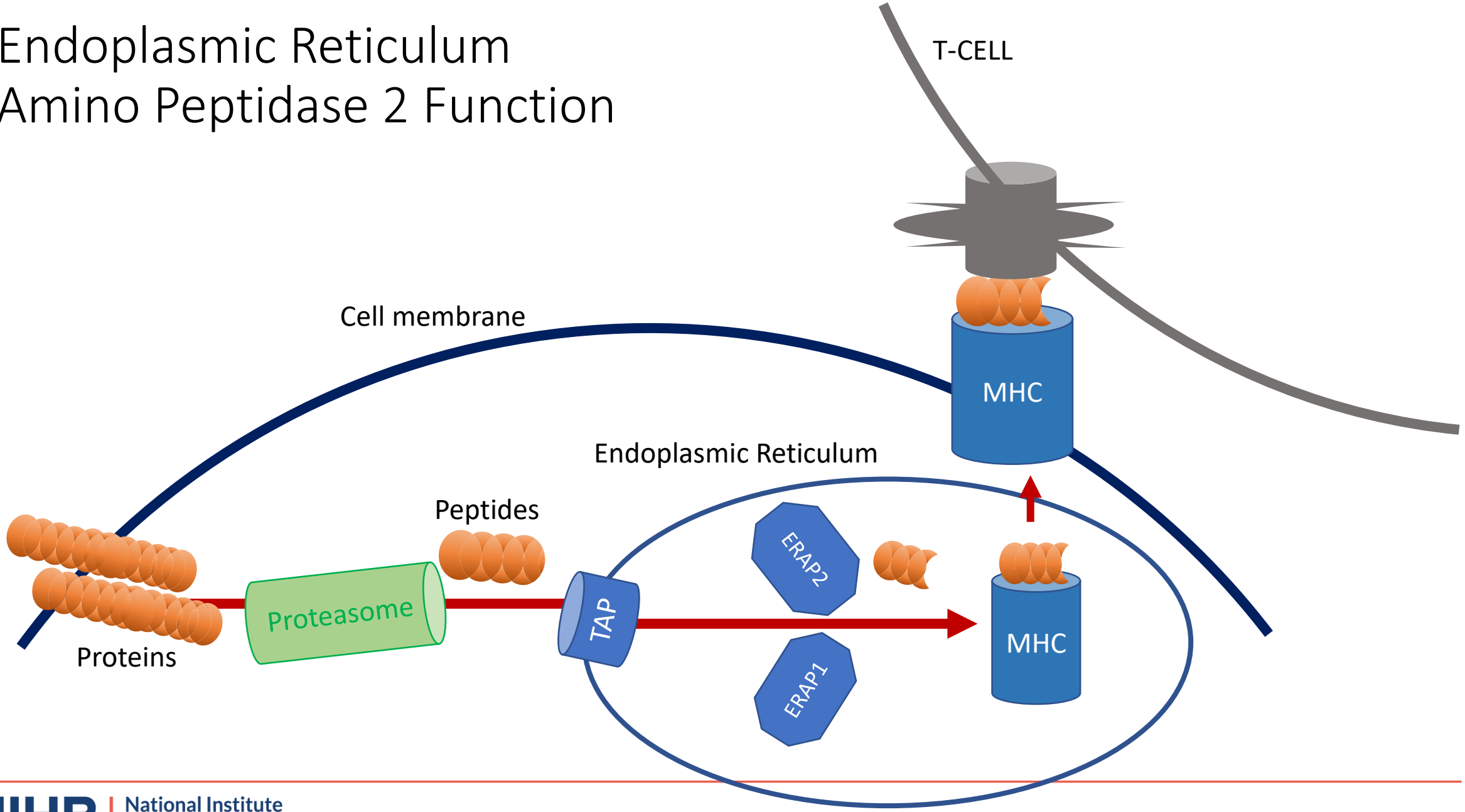
Transcriptome wide association study & GWAS

- 444 cases and 10,397 controls: The lead eQTL SNP, rs1363907 (G) associated with AC-DILI risk: OR[95%CI] = 1.68 [1.23-1.66] P=1.7x10^{-7})
  - Validation: 133 cases and 17,836 controls: OR=1.2 [1.04-2.05] P = 0.03
- TWAS: AC-DILI risk with reduced liver expression of ERAP2 (P=3.7x10^{-7})

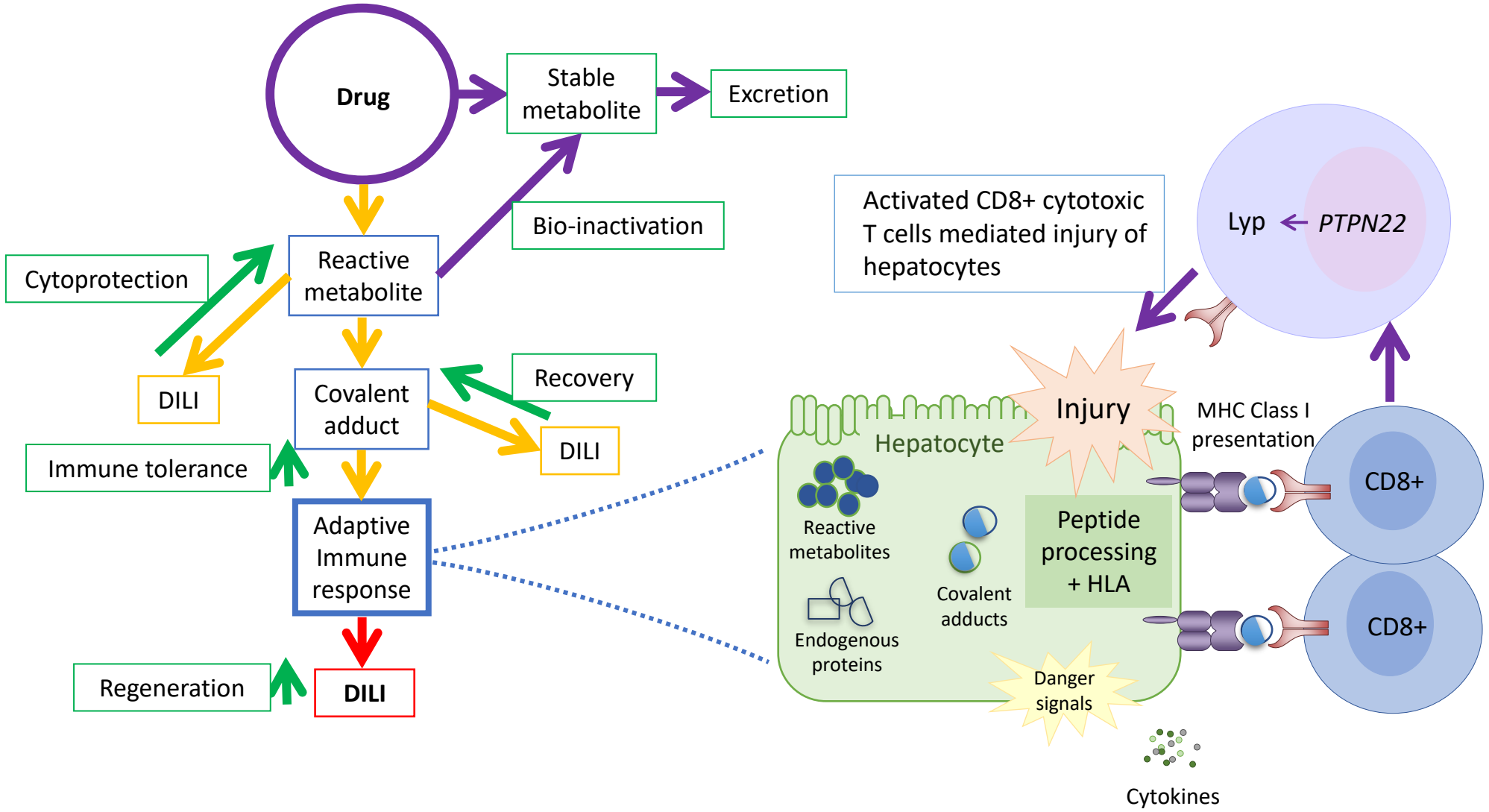


Nicoletti, Aithal, & Watkins. *Gastroenterology*. 2023;164(3):454-466.

Endoplasmic Reticulum Amino Peptidase 2 Function

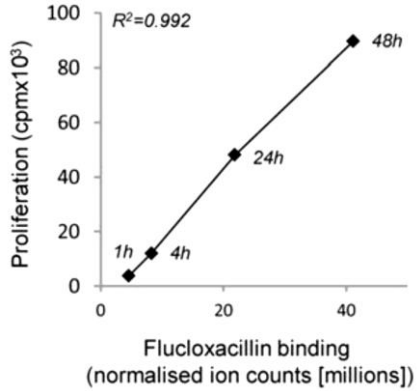


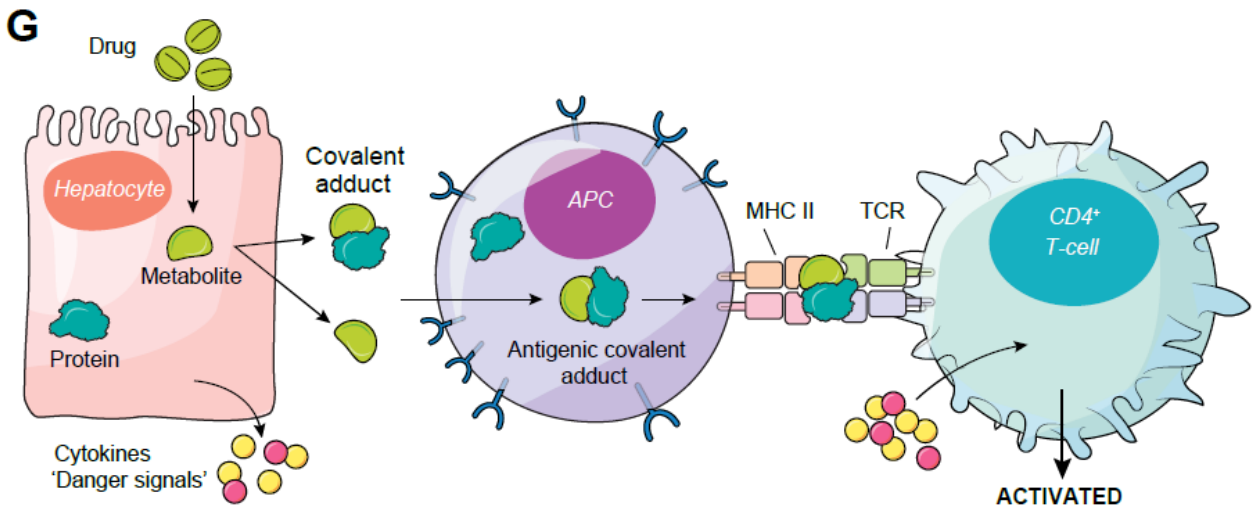
Putative mechanisms underlying DILI



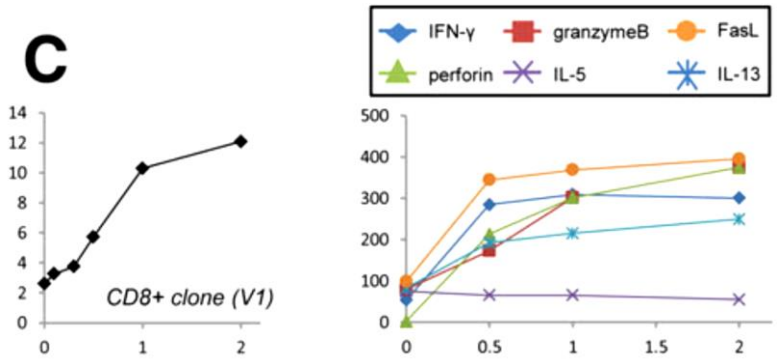
Aithal GP. *Hepatology.* 2019; 70(1):8-10.

MHC Class II molecules in DILI





Level of flucloxacillin covalent binding to albumin correlates with drug-specific T-cell response



Naive HLA-B*57:01+ive T cells primed with (dendritic cells) plus flucloxacillin proliferate and secrete cytokines/ cytolytic molecules

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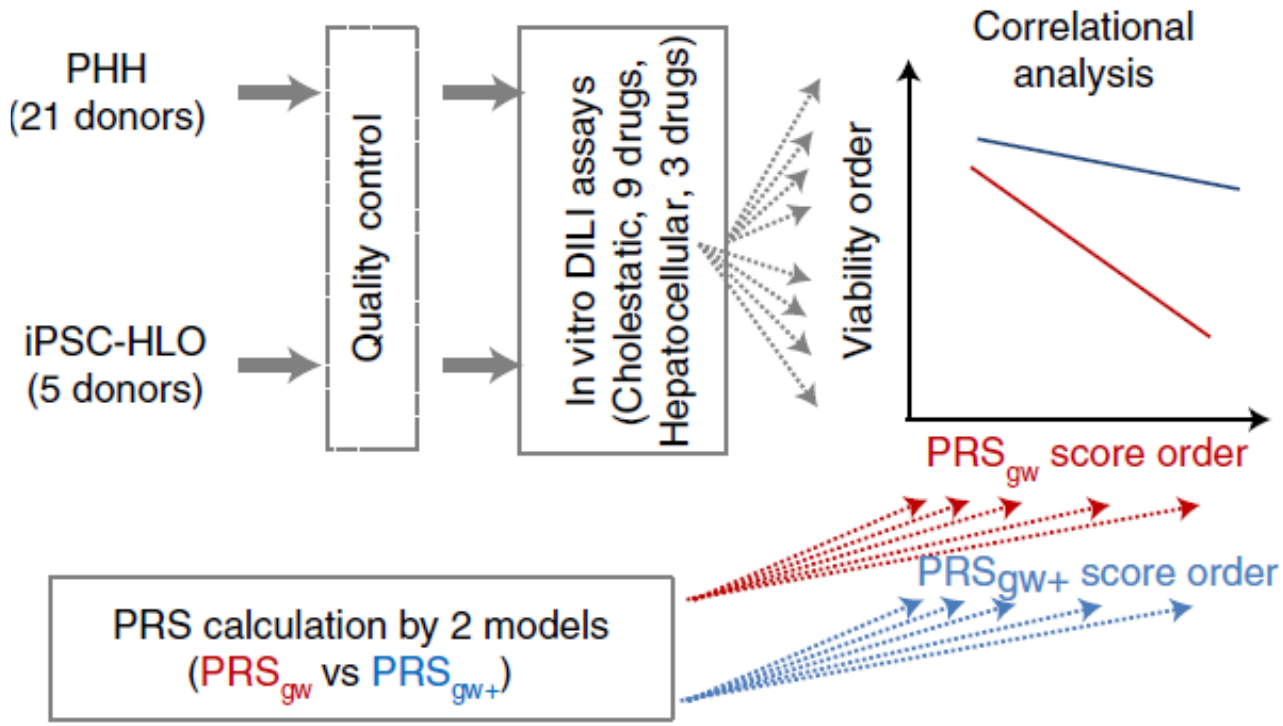
Monshi. *Hepatology* 2013;57(2):727-39.

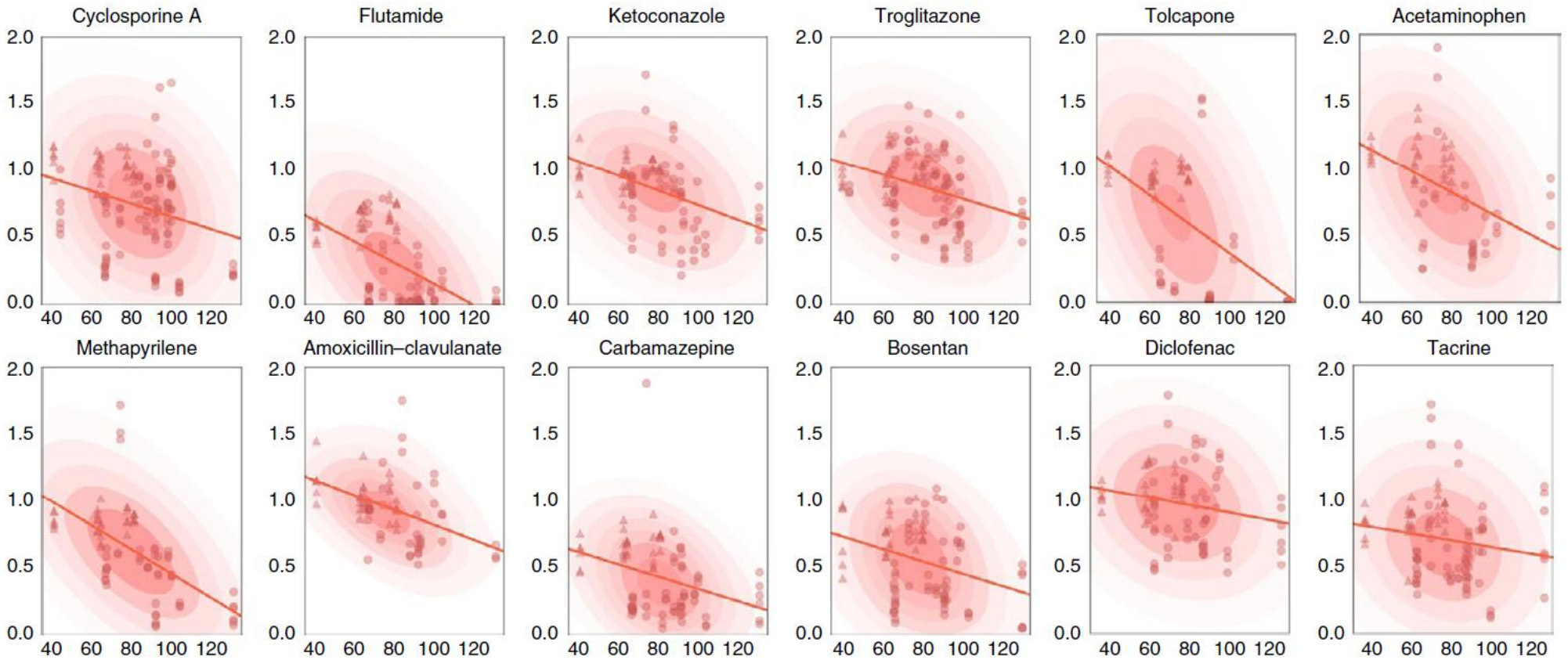
Application of PRS

- Fasiglifam (TAK-875) DILI (n=39) & controls (n=122): No signal on GWAS
- IDILIC-DILIN GWAS CM DILI shared genetic aetiology with TAK-875 DILI
  - Flucoxacillin + co-amoxiclav PRS (323 cases; 10, 588 controls, 27,740 SNPs) had the stronger correlations
- PRS correlated with DILI in vitro



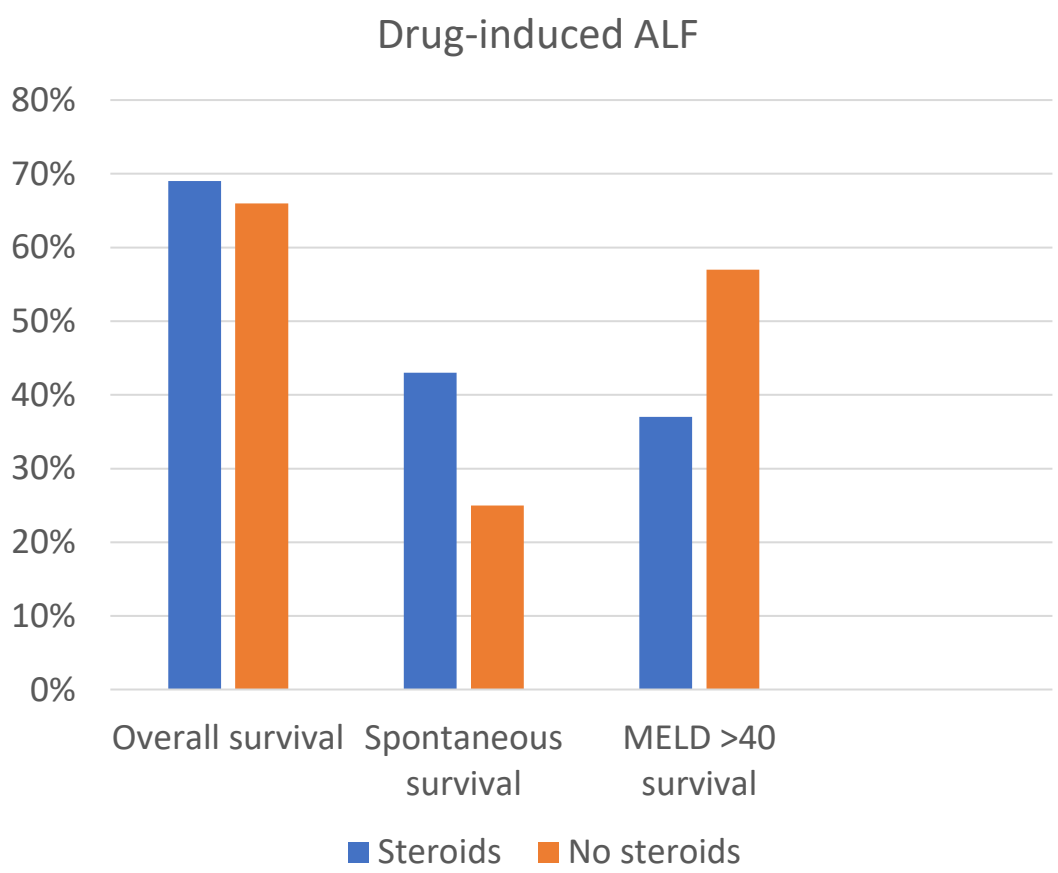
Koido. *Aithal & Takebe Nat Med* 2020; 26(10):1541-48

Drug-specific to the general



Koido. *Aithal & Takebe Nat Med* 2020; 26(10):1541-48

Consider evidence base for treatment



- 361 with acute liver failure
  - 66 AIH (25 with steroids)
  - 164 Indeterminate (21 with steroids)
  - **131 DILI (16 steroids)**
- Steroids not associated with better overall survival (61% vs 66%, P=0.41)
- Associated with diminished survival
  - MELD >40, survival 30% vs 57%, P=0.03).

Karkhanis. *Hepatology* 2014; 59(2):612-21

Drug-induced Auto-Immune like hepatitis

- Hold off steroids if spontaneously resolving
  - Follow up with 3 monthly liver enzymes
- When indistinguishable from AIH; low dose prednisolone
  - Pooled data: 91 patients from 5 case series
  - 51 (56%) treated with 20-40 mg prednisolone x 8 weeks
  - None required long-term immunosuppression in 6-77 months FU.

Devarbhavi H. *Unpublished* 2022

Open label RCT: China

- 70/ 80 completed the trial
  - 78% women
  - 78% >40 years
  - 71% hepatocellular injury
- Chronic DILI: Persistence > 6 months
- Glycyrrhizin +/ – Corticosteroid:
- 48 mg tapered over 48 weeks; 24 weeks FU

Items	Steroid group; n=40 (%)	Non-steroid group; n=40 (%)	P value
Sustained biochemical response	38/40 (95.0%, ITT) 33/35 (94.3%, PPS)	30/40 (75.0%, ITT) 25/35 (71.4%, PPS)	0.025 (ITT) 0.023 (PPS)
Histology improvement at 48 weeks			
Activity score decreased ≥2 points, n (%)	30/32 (93.8)	7/12 (58.3)	0.011
Fibrosis score decreased ≥1 point, n (%)	17/32 (53.1)	0/12 (0.0)	0.001
APRI change	-4.7(-25.8, -0.8)	-2.7(-19.9, 13.7)	0.026
FIB-4 change	-5.2(-15.5, 0.7)	-1.9(-13.4, 17.4)	0.001
Adverse effects (Grade I or II), n (%)			
Facial rounding	13/40 (32.5)	0/40	
Weight gain	10/40 (25.0)	0/40	
Impaired glucose tolerance	3/40 (7.5)	0/40	
Hypokalemia	2/40 (5.0)	1/40 (2.5)	
Acne	2/40 (5.0)	0/40	
Hypertension	1/40 (2.5)	1/40 (2.5)	
Hirsutism	1/40 (2.5)	0/40	
Dorsal hump formation	1/40 (2.5)	0/40	
Adverse effects during follow-up	0	0	

Wang, Aithal et al and Zou. *Aliment Pharmacol Ther.* 2022; 55(10):1297-1310.

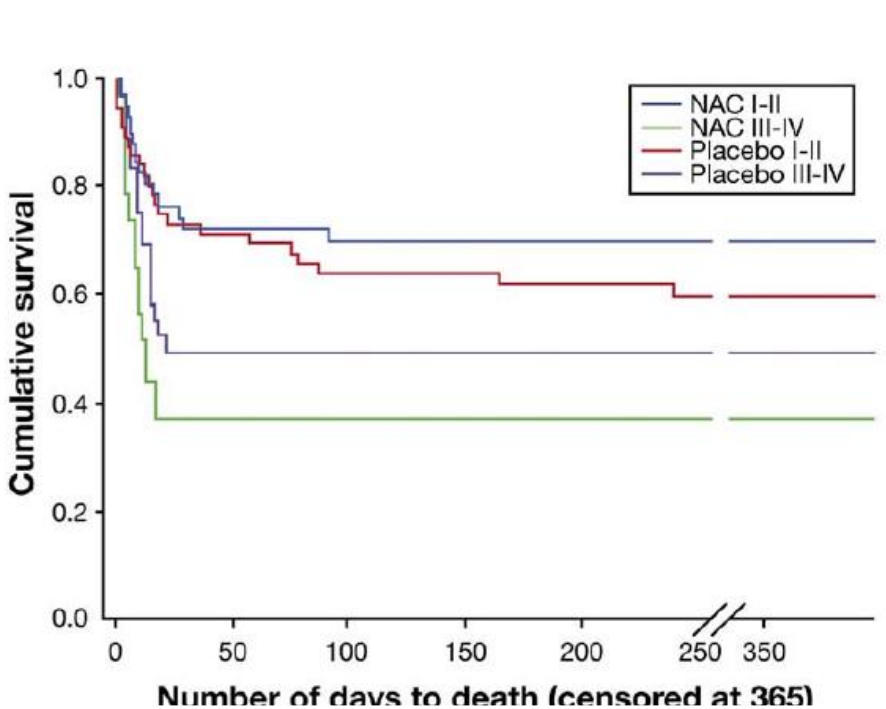
ALF: Management

	1998-2005		2006-2013		
n	989		1081		
21-Day Survival	67%		75%		<0.001
HE grade ≥ 3	48%		46%		0.48
INR	2.7 (2.0-4.3)		2.7 (2.0-3.9)		0.33
NAC Given All	49%		69%		<0.001
Paracetamol	89%		92%		0.12
Non-Paracetamol	16%		49%		<0.001
Antibiotics	37%		47%		<0.001

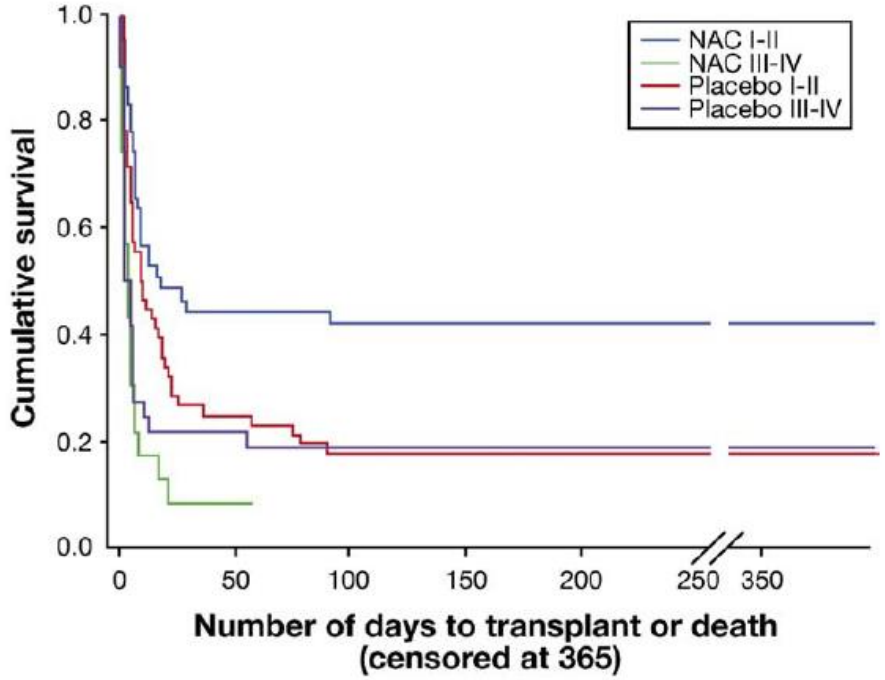
Reuben A et al. Ann Intern Med 2016 ;164:724-732

NAC in non-paracetamol ALF

- Overall survival



- Transplant free survival



Lee W. *et al* *Gastroenterology* 2009; 137:856-64

Preempting and preventing ADRs

- 50 variants in 12 gene- 41 drug pairs

- Causal, clinically relevant ADR in patients with an actionable test result: 152 (21%) of 725 in study group vs. 231 (28%) of 833 in controls
- Risk of ADR reduced by 30% (OR 0·70 [95% CI 0·61–0·79]; p <0·0001.
- During follow up, 13·7% (953 of 6944) received a second drug with an actionable genotype: ADR: OR 0.69
- All patients and all ADRs without filtering for severity and causality increased effect of pharmacogenomics intervention

Scan QR code

Swen JJ et al , Lancet. 2023 Feb 4;401(10374):347-356.

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Prospective European Drug-induced Liver Injury Network

DH Department of Health

PRO-EURO DILI REGISTRY

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DILIN
Drug-Induced Liver Injury Network

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