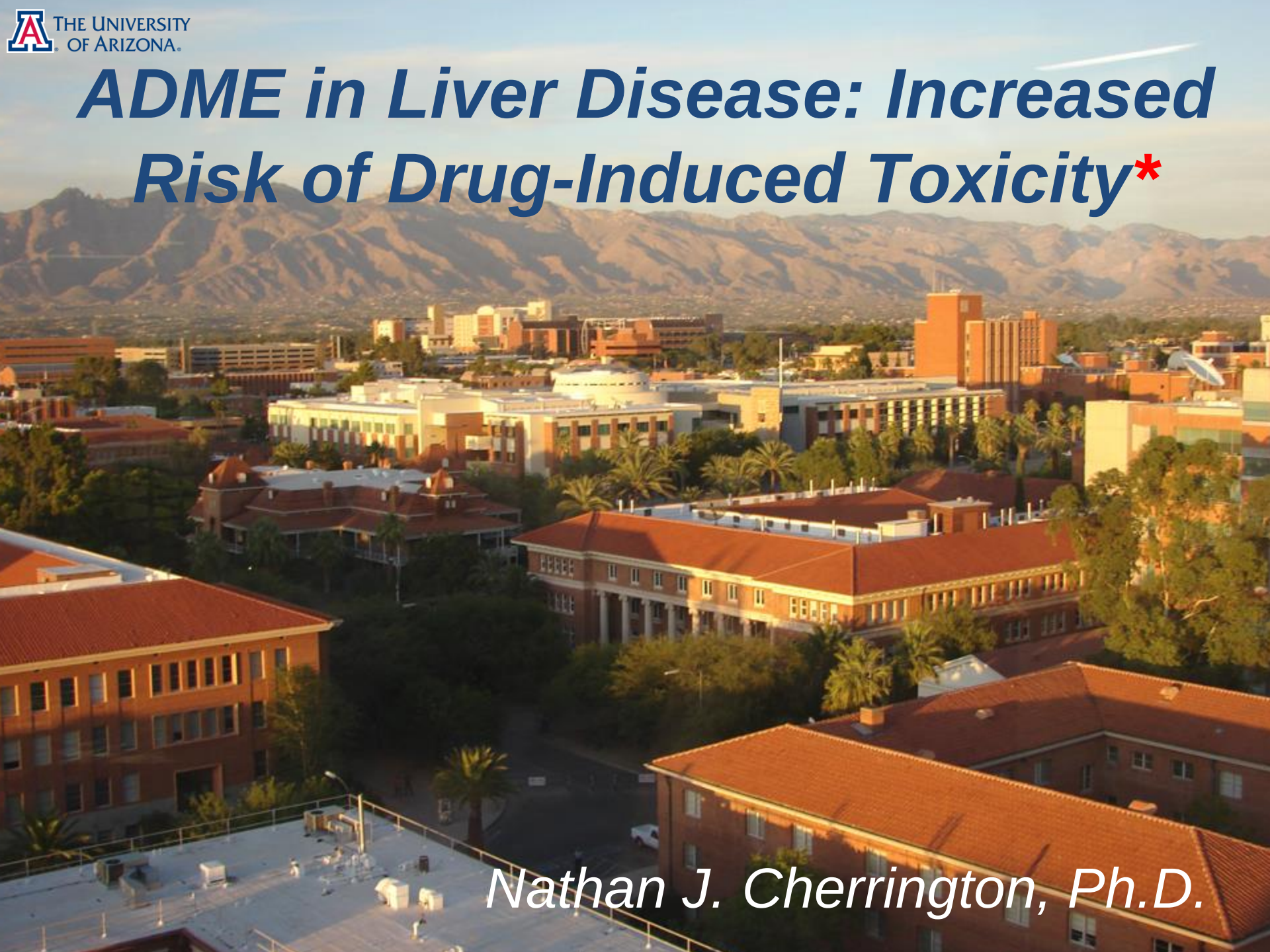
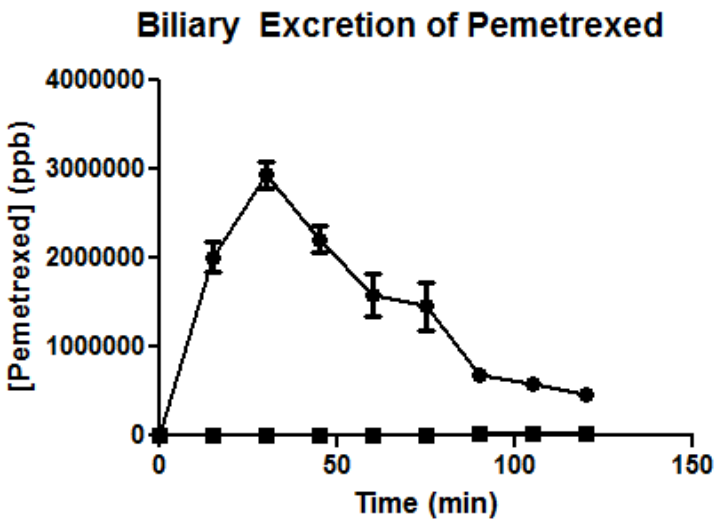
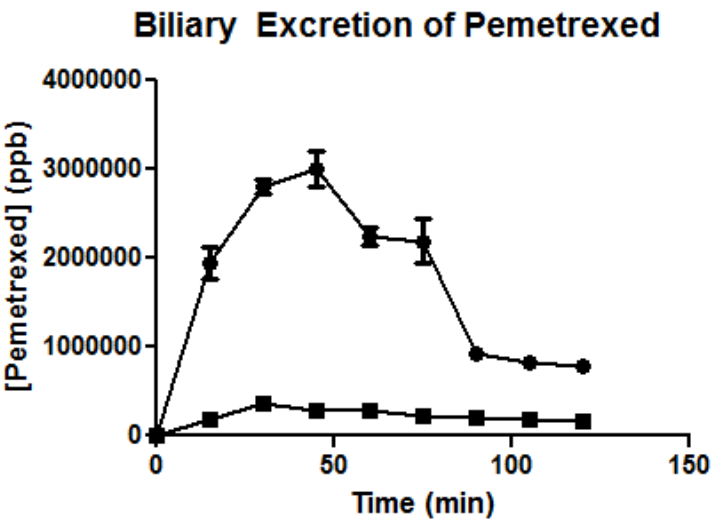

THE UNIVERSITY OF ARIZONA
ADME in Liver Disease: Increased Risk of Drug-Induced Toxicity*
Nathan J. Cherrington, Ph.D.

Phenoconversion

Genetics



Disease



Ref: Dzierlenga *et al*. DMD. 2016

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What We've Learned from the PGRN:

- Drug Metabolizing Enzymes
- Transporters
- Immune System
- Drug Receptors

Minimal Toxicity

Toxicity

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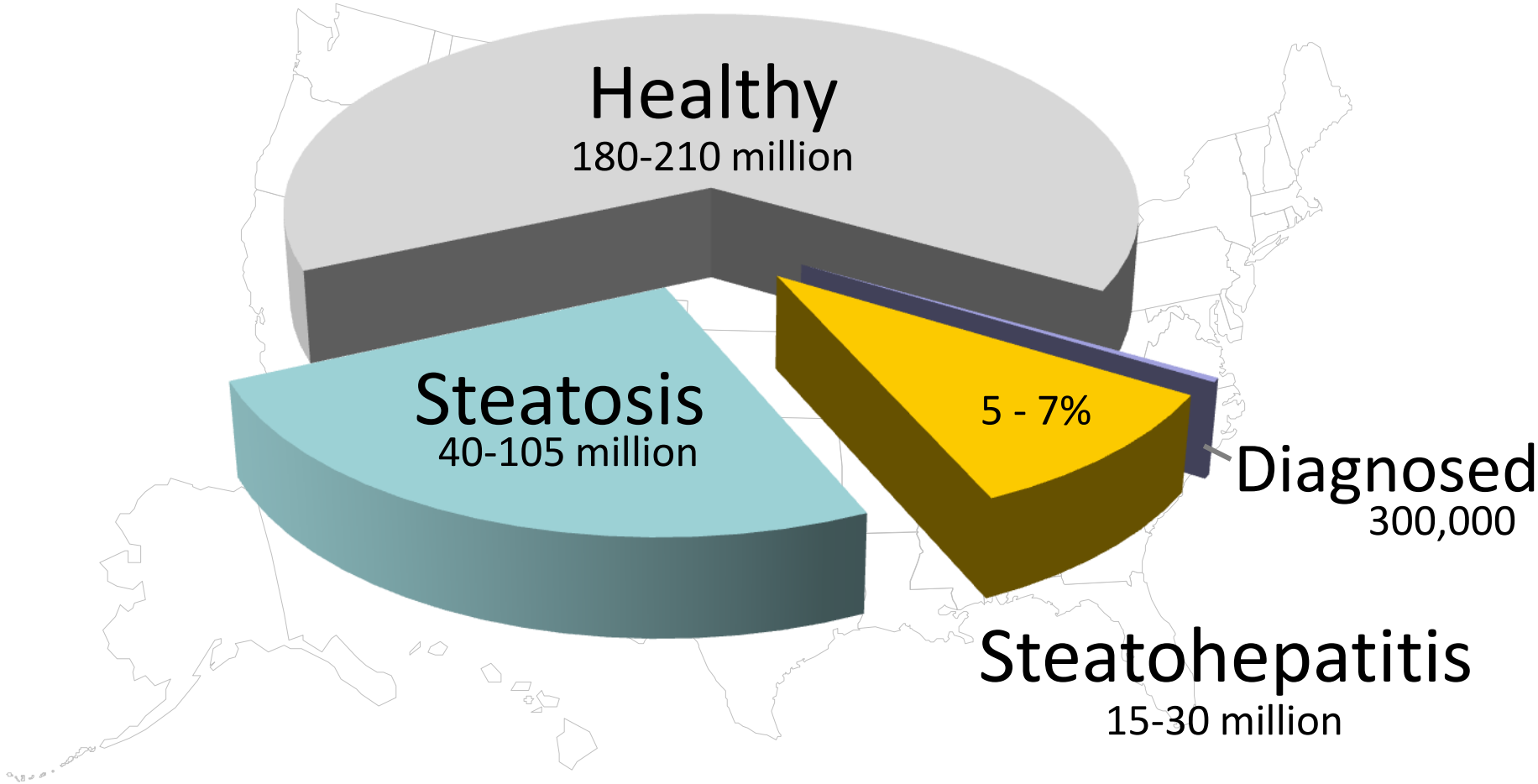
Prevalence of Nonalcoholic Fatty Liver Disease in U.S.



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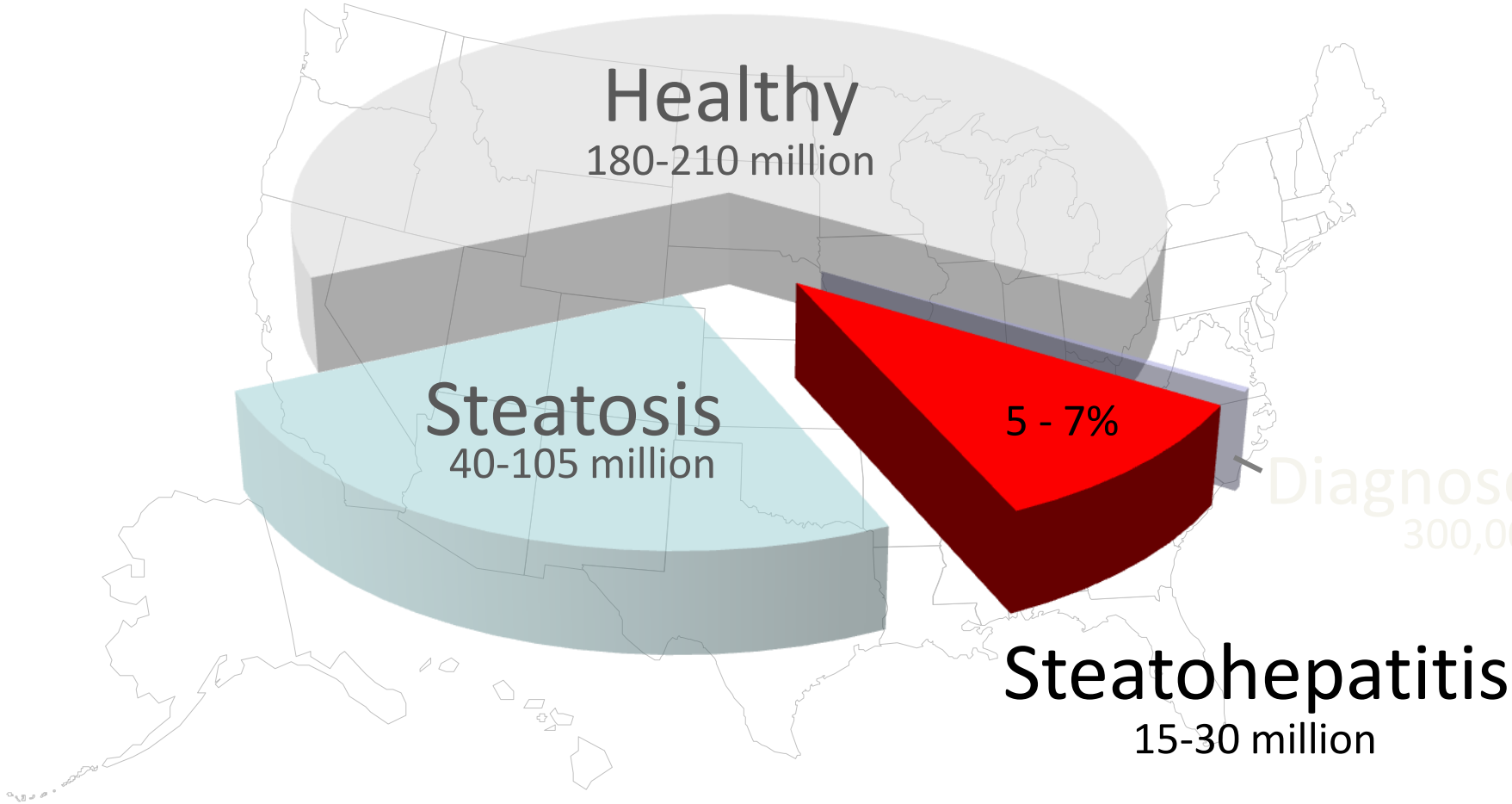
Prevalence of Nonalcoholic Fatty Liver Disease in U.S.



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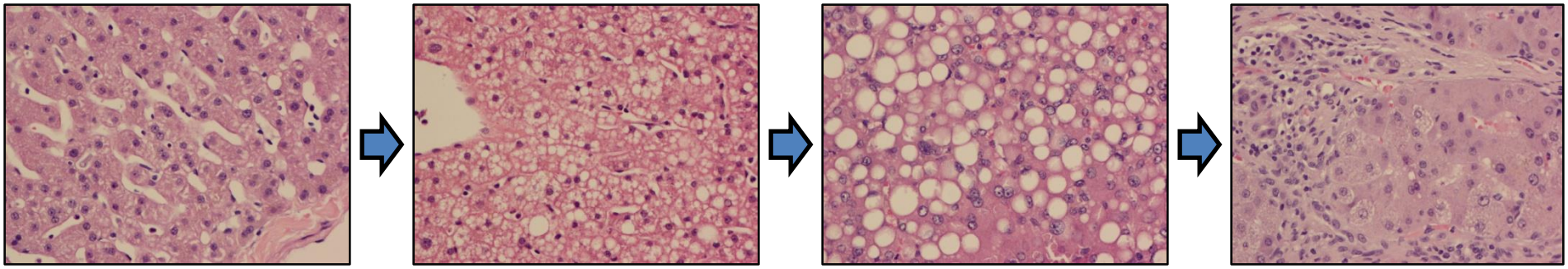
NAFLD Comprises a Spectrum of Pathologic Severity



Healthy liver	Steatosis	NASH w/fat	NASH not fatty (Cirrhosis)
	- benign - reversible	- steatosis - inflammation - progressive fibrosis	- irreversible scarring - end-stage

NAFLD = Nonalcoholic Fatty Liver Disease
NASH = Nonalcoholic Steatohepatitis

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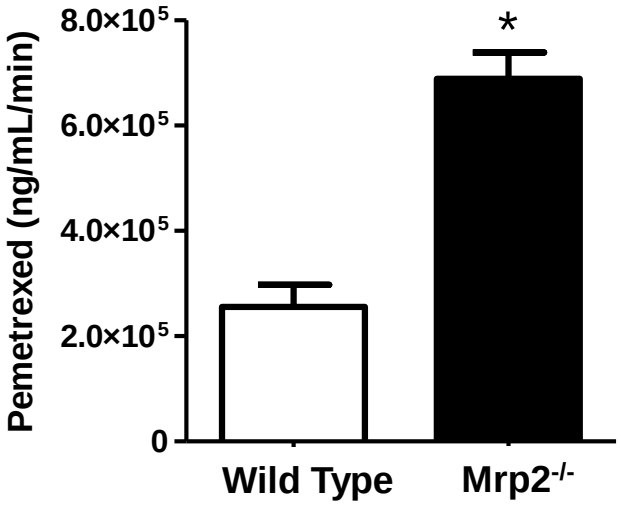
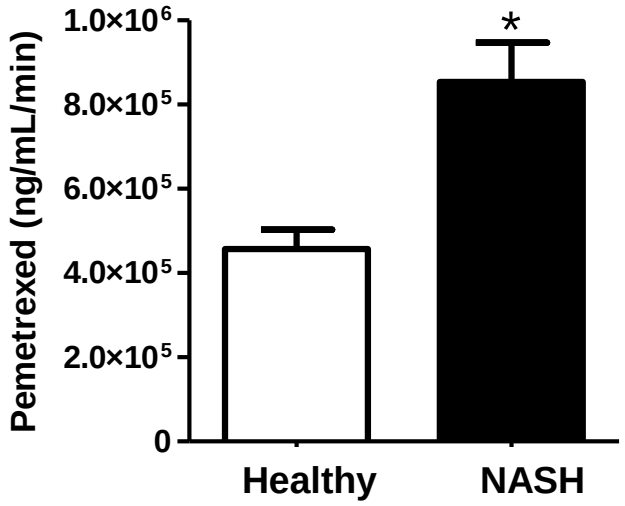
Increased Exposure in NASH





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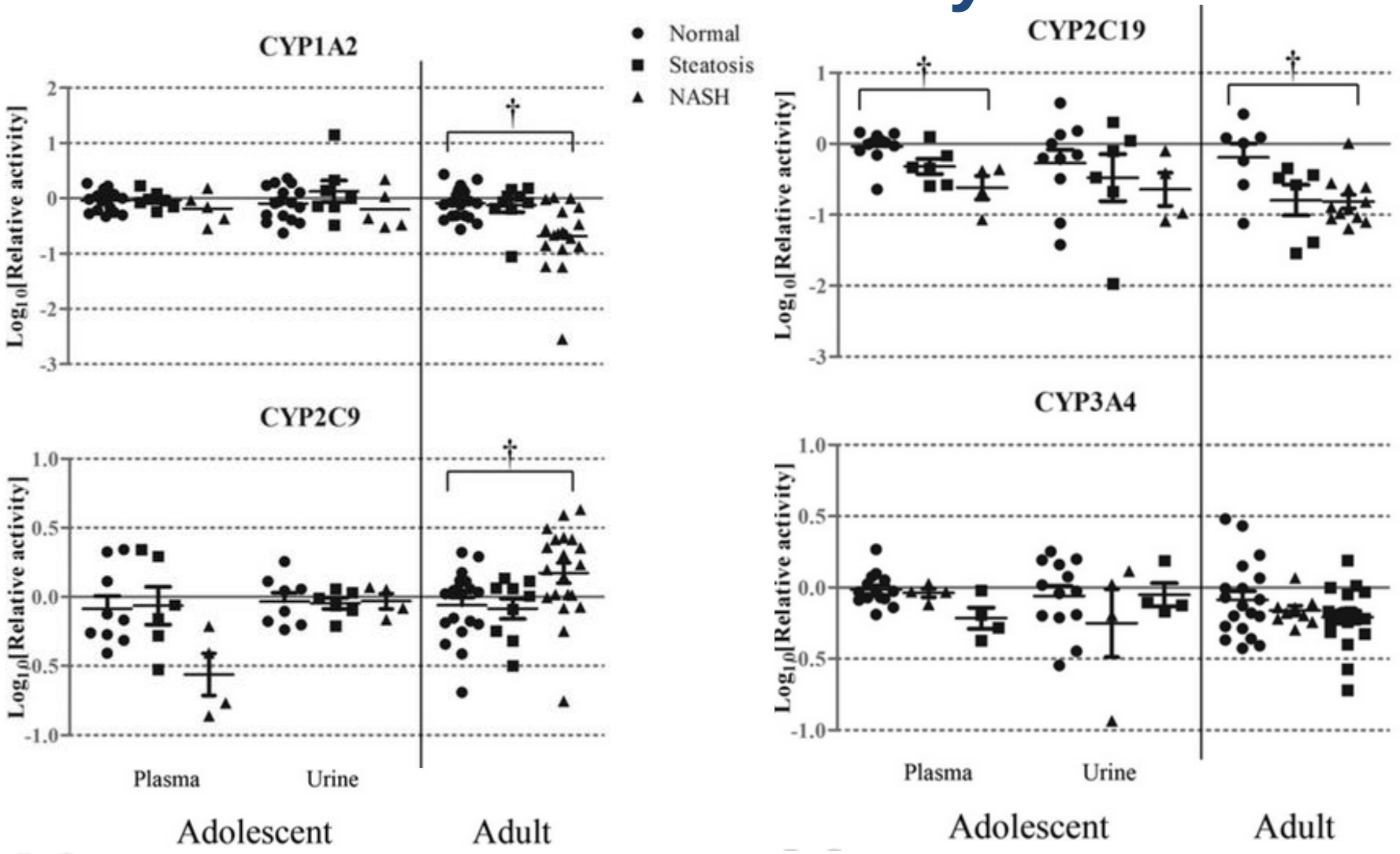
Metabolism: Pediatric P450 Activity In Vivo



Ref: Li *et al*. DMD. 2017

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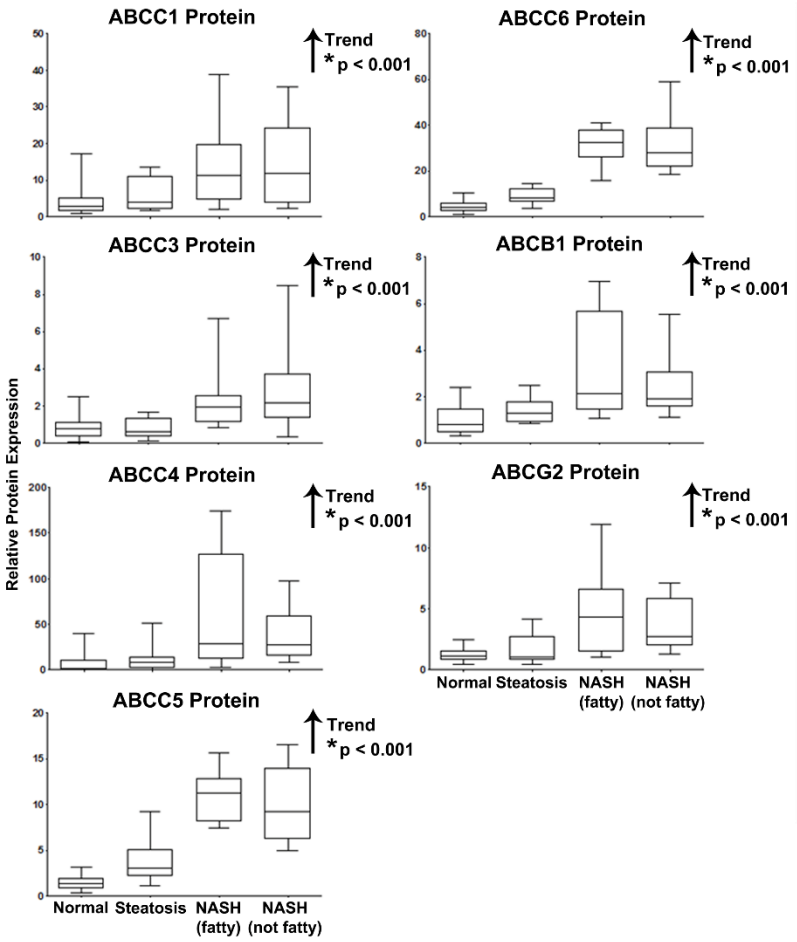
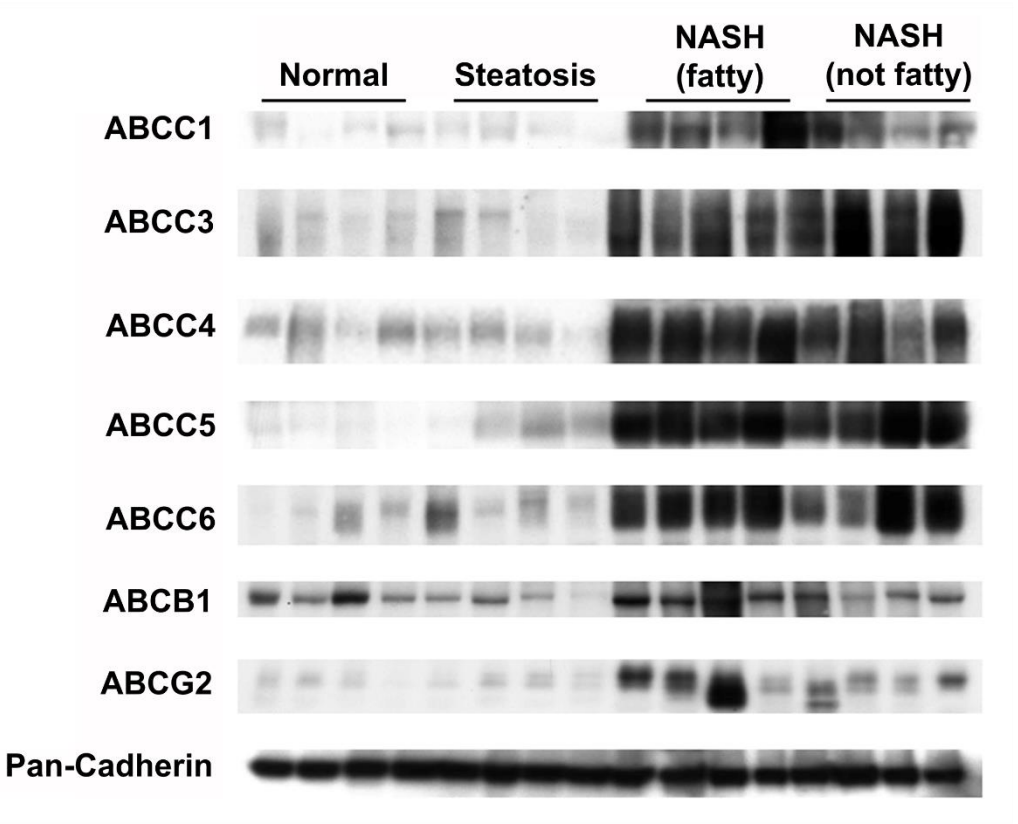
Hepatic Efflux Transporter Expression





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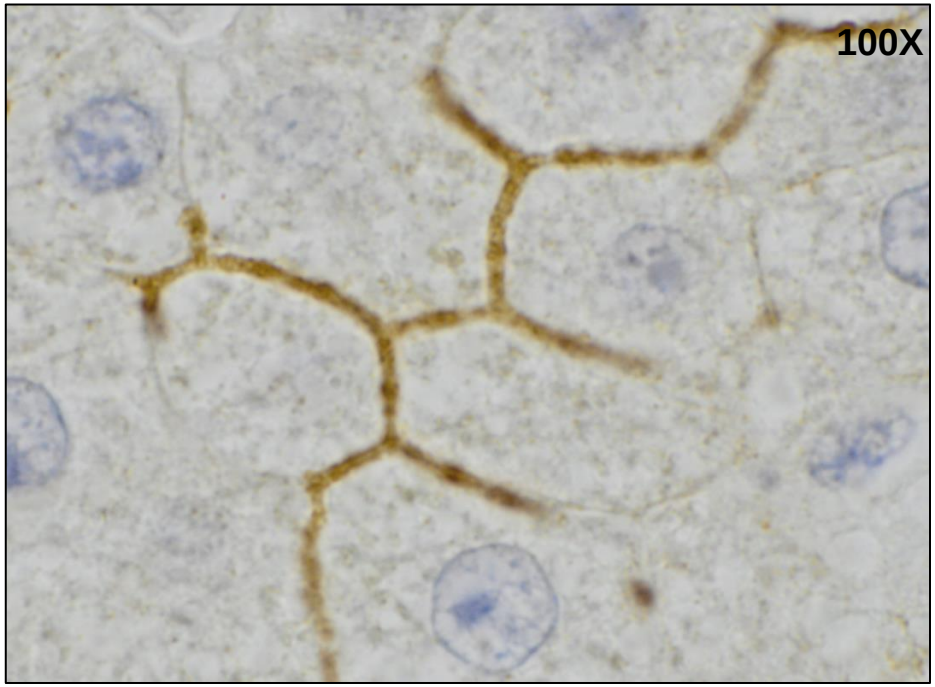
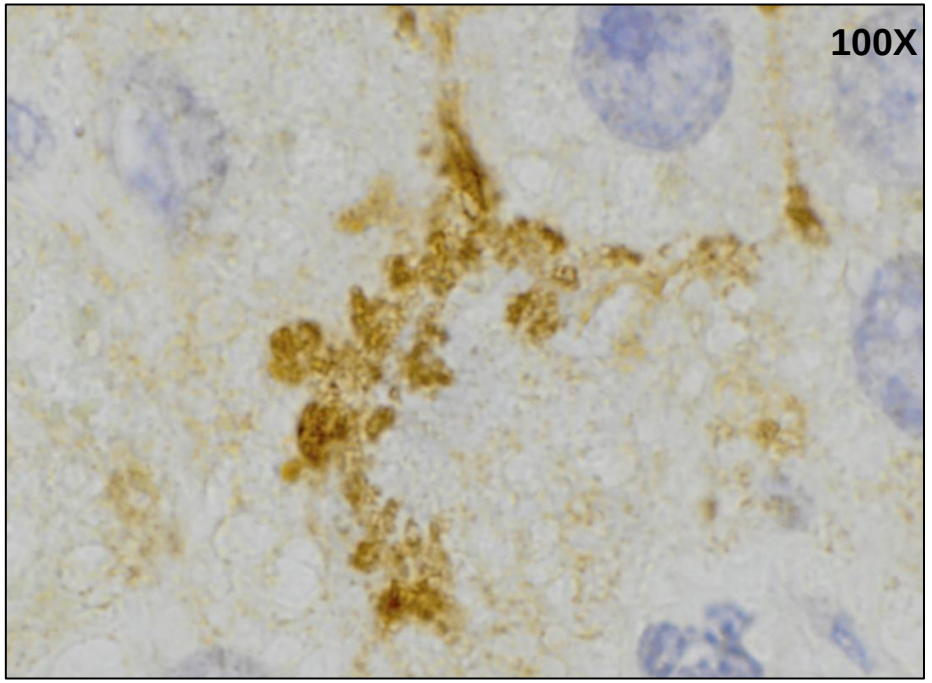
Cellular Localization of Hepatic MRP2

Normal

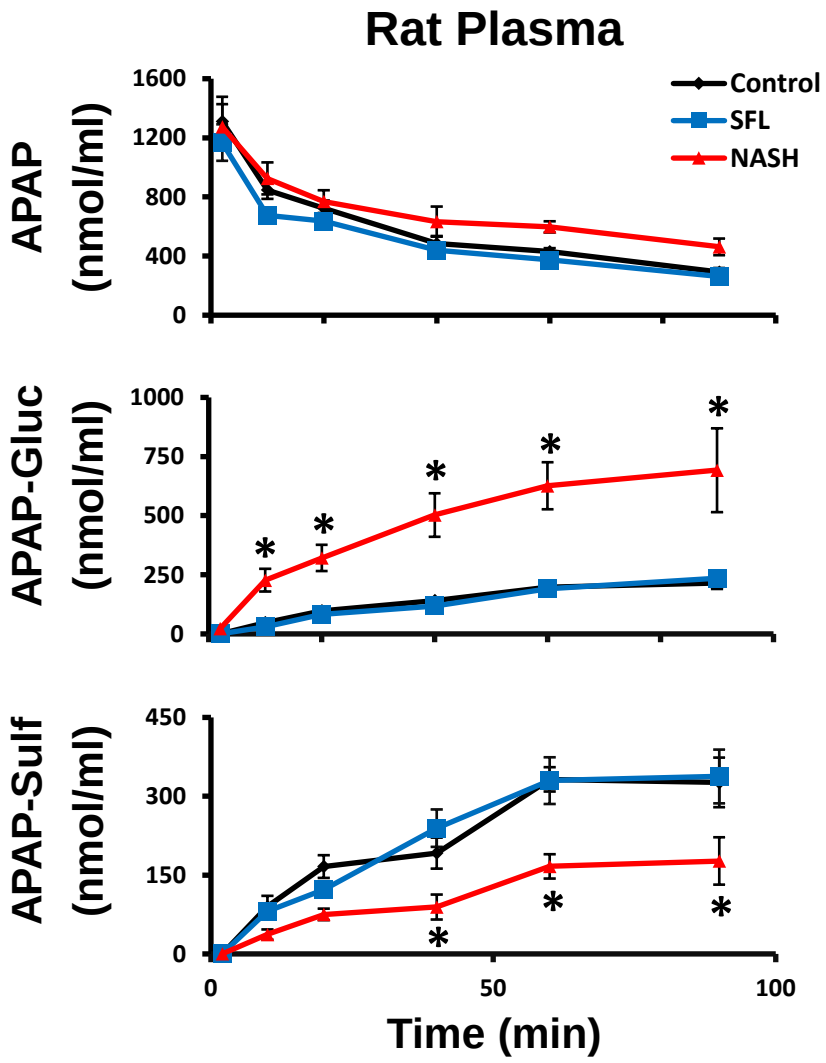


NASH (not fatty)



Ref: Hardwick *et al.* DMD. 2011

APAP Disposition



APAP = Acetaminophen

∗ *p < 0.05 significant vs. Control*

Ref: Lickteig *et al*. DMD. 2007: 35(10):1970-8

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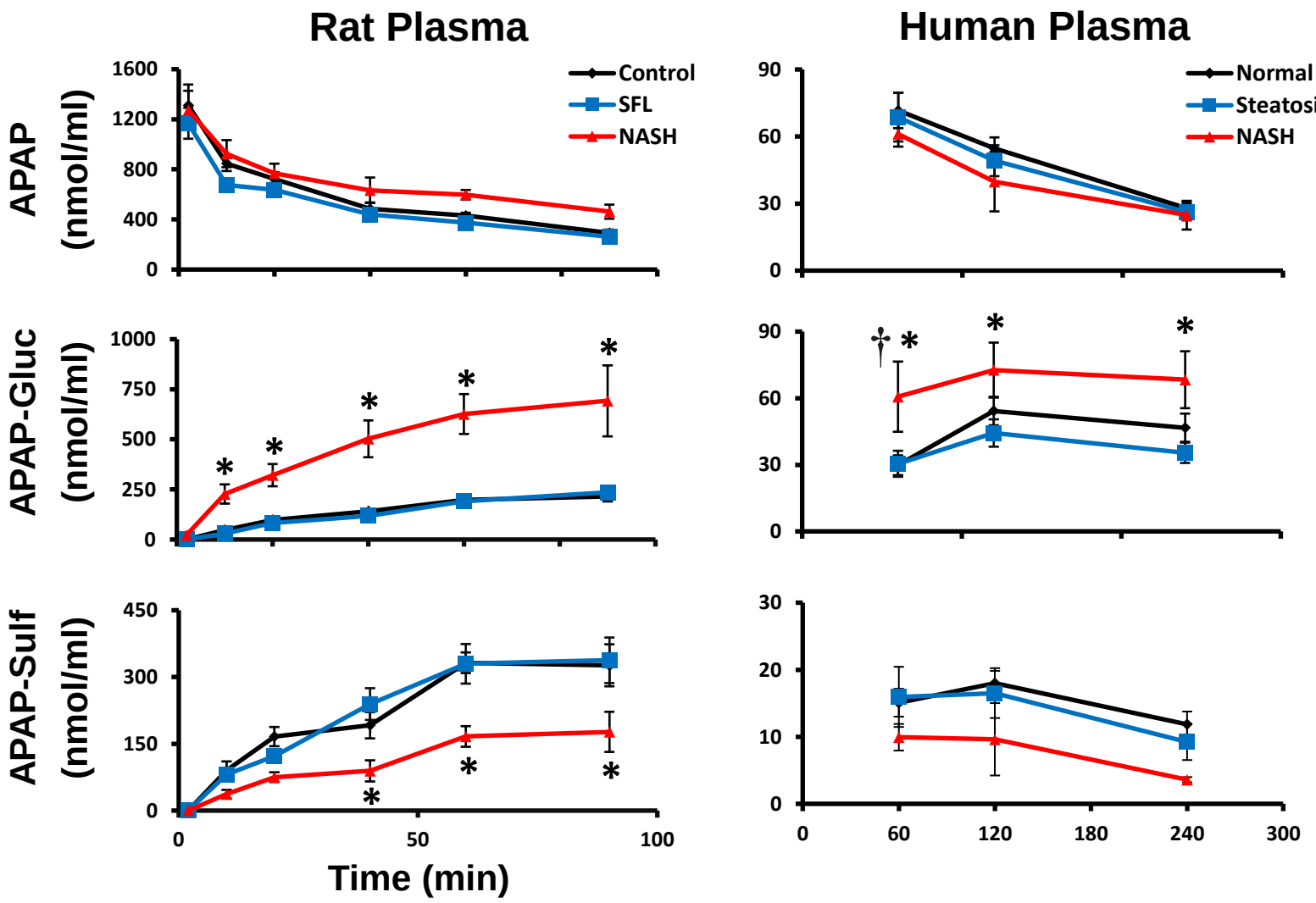
APAP Disposition



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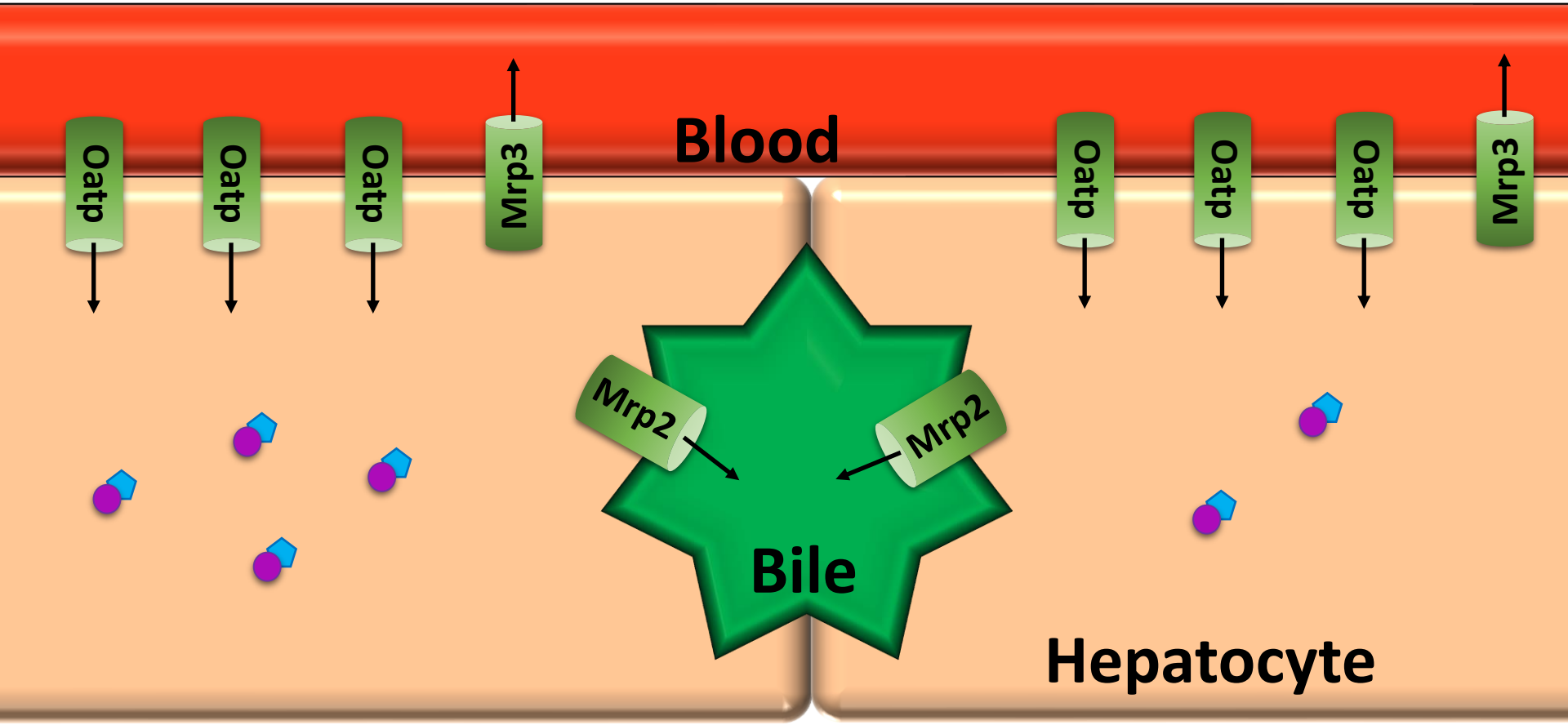
3 Mechanisms: Hepatocyte Hopping



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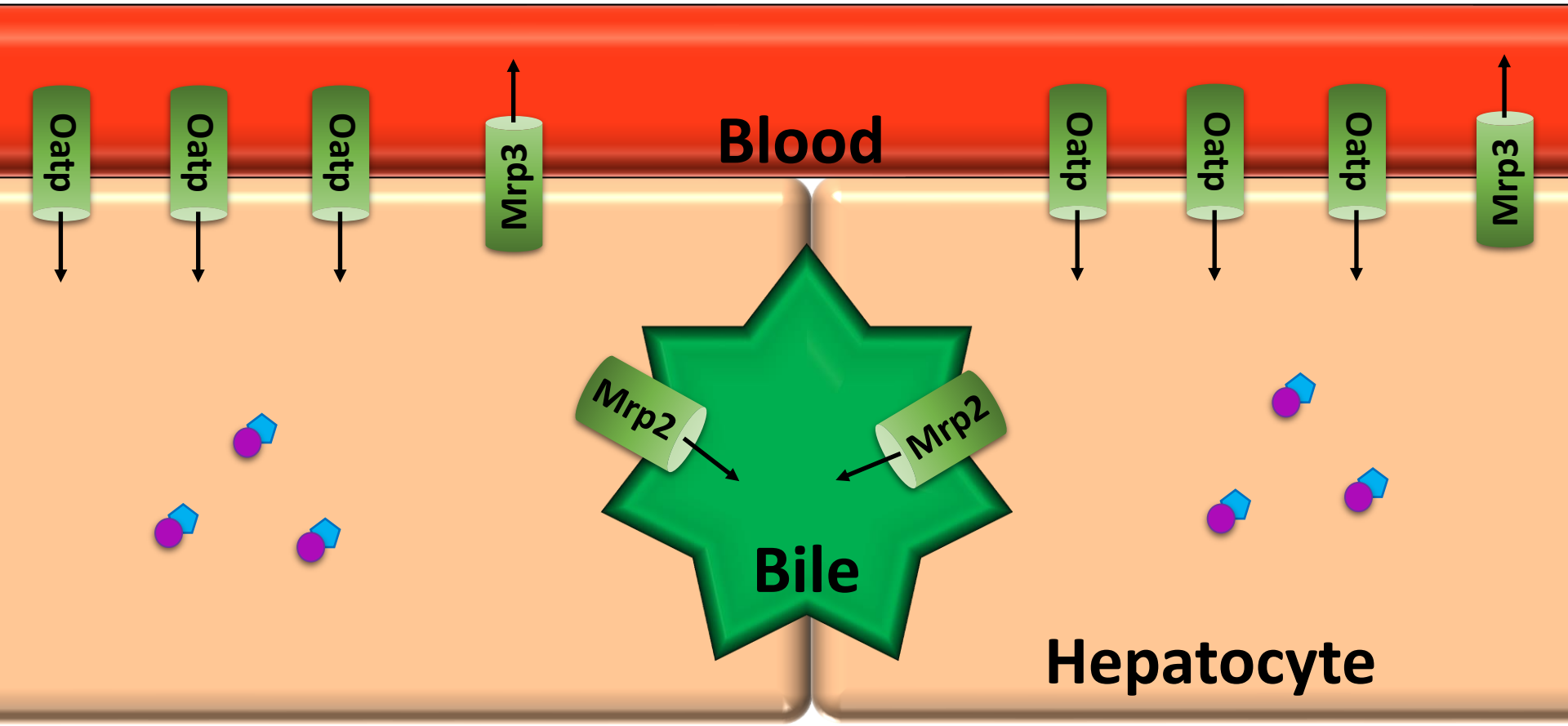
3 Mechanisms:

Hepatocyte Hopping in NASH



Altered PK in Hepatic Impairment

- **TRANSPORTER mediated**

- **Known ADRs:** ampicillin, benzypenicillin, cefadroxil, cefalexin, cefazolin, cefbuperazon, cefmetazole, cefodizime, cefoperazone, cefotaxime, cefpiramide, ceftidoren, ceftizoxime, ceftriaxone, ezetimibe, olmesartan, penicillamin, pravastatin,
- **Predicted ADRs:** adefovir, atrasentan, avibactam, benlafamab mafoditin, camptothecin, carboplatin, caspofungin, cervistatin, chlopropamide, cisplatin, digoxin, dinoprostone, eluxadoline, empaglifozin, enalapril, epirubicin, eprosartan, fexofenadine, fimasartan, folic acid, furosemide, gimatecan, glecaprevir, hydrochlorothiazide, hydroxyurea, lamivudine, levosalbutamol, liothyronine, mercapturine, mesalazine, octreotide, opicapone, oseltamivir, ouabaïne, oxaliplatine, pemetrexed, phalloidin, pralatrexate, probenicid, raloxifene, rapamycin, revefenacin, rifampicin, sulfasalazine, sumatriptan, telmisartan, temocapril, thioguanine, topotecan, vasopressin

- **TRANSPORTER and METABOLISM**

- **Known ADRs:** atorvastatin, azithromycin, canaglifozin, diclofenac, erythromycin, fluvastatin,grazoprevir, mycophenolate mofetil, paritaprevir, repaglinide, rosuvastatin, simeprevir, simvastatin, valsartan,
- **Predicted ADRs:** ambrisentan, asunaprevir, axitinib, bosentan, carbamazepin, clopidogrel, clotrimazole, cobimetinib, cyclophophamide, cyclosporin, darunavir, docetaxel, doxorubicin, elagolix, ethinylestradiol, etoposide, fluorouracil, geftinib, glibenclamide, grepafloxacin, ifosfamide, imatinib, indinavir, irinotecan, letermovir, liotrix, lopinavir, lovastatin, methotrexate, mitoxantrone, morphine, nateglinide, nelfinavir, paclitaxel, phenytoin, pitavastatin, prasterone, remdesivir, ritonavir, romidepsin, saquinavir, selexipag, sulfinpyrazone, tacrolimus, talinolol, tamoxifen, teniposide, tenofovir, testosterone, torasemide, troglitazone, ubrogepant, vinblastine, vincristine, voxilaprevir, zidovudine

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RENAL Alterations in Liver Disease?

- Are there alterations to renal ADME processes due to hepatic dysfunction
  - Untargeted Proteomics - general expression
  - Targeted Proteomics – drug transporters
- Identify appropriate rodent model
  - Extrapolation to human renal changes
- Predict toxicity
  - Identify potential toxicants due to renal ADME

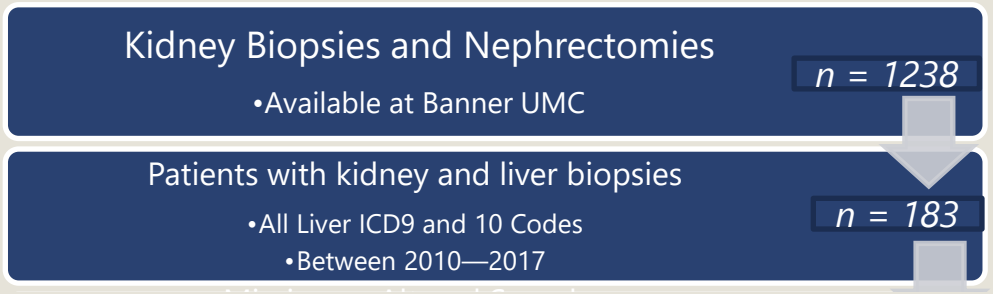
Kidneys from Patients with NASH

Kidney Biopsies and Nephrectomies

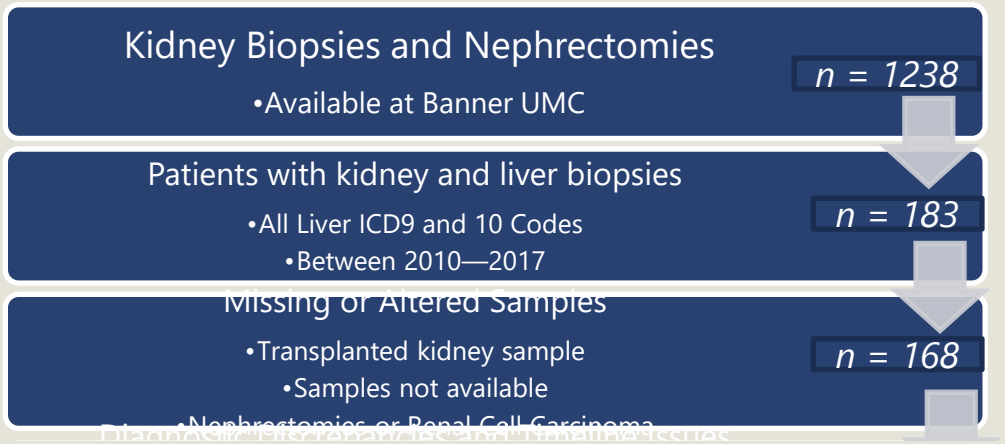
- Available at Banner UMC

n = 1238

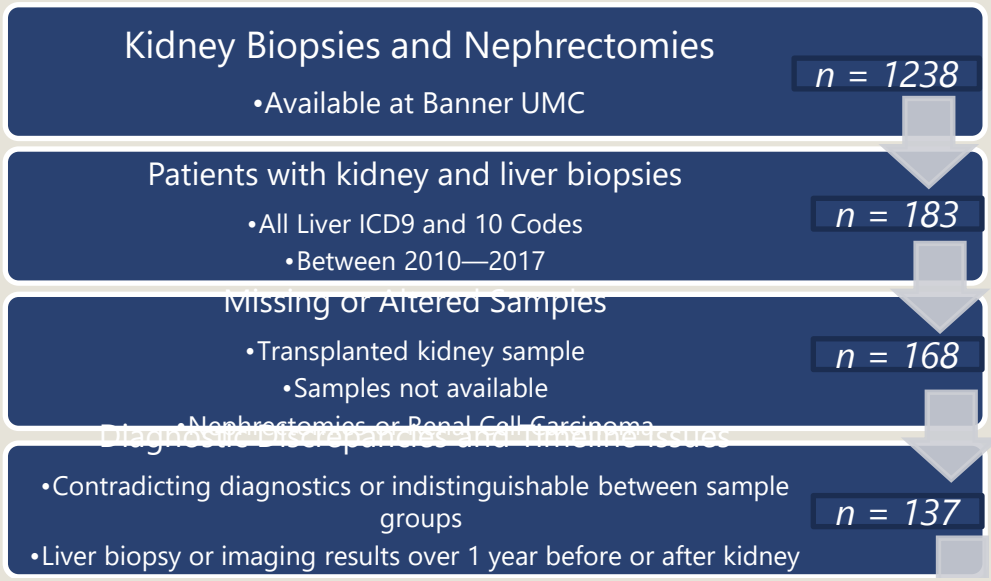
Kidneys from Patients with NASH



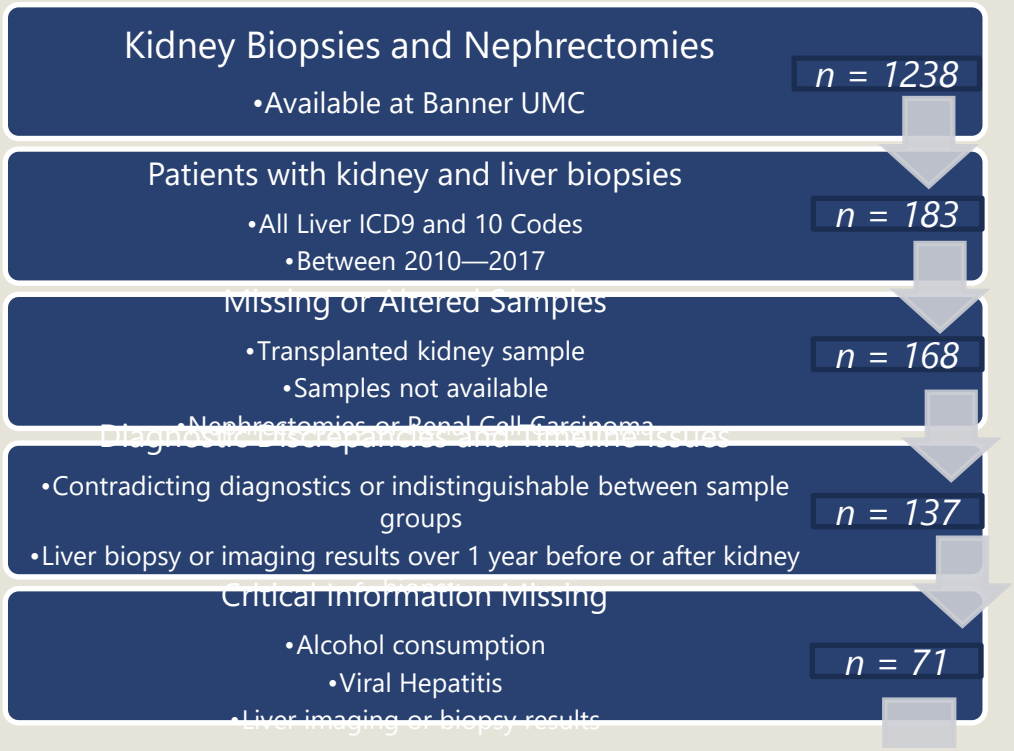
Kidneys from Patients with NASH



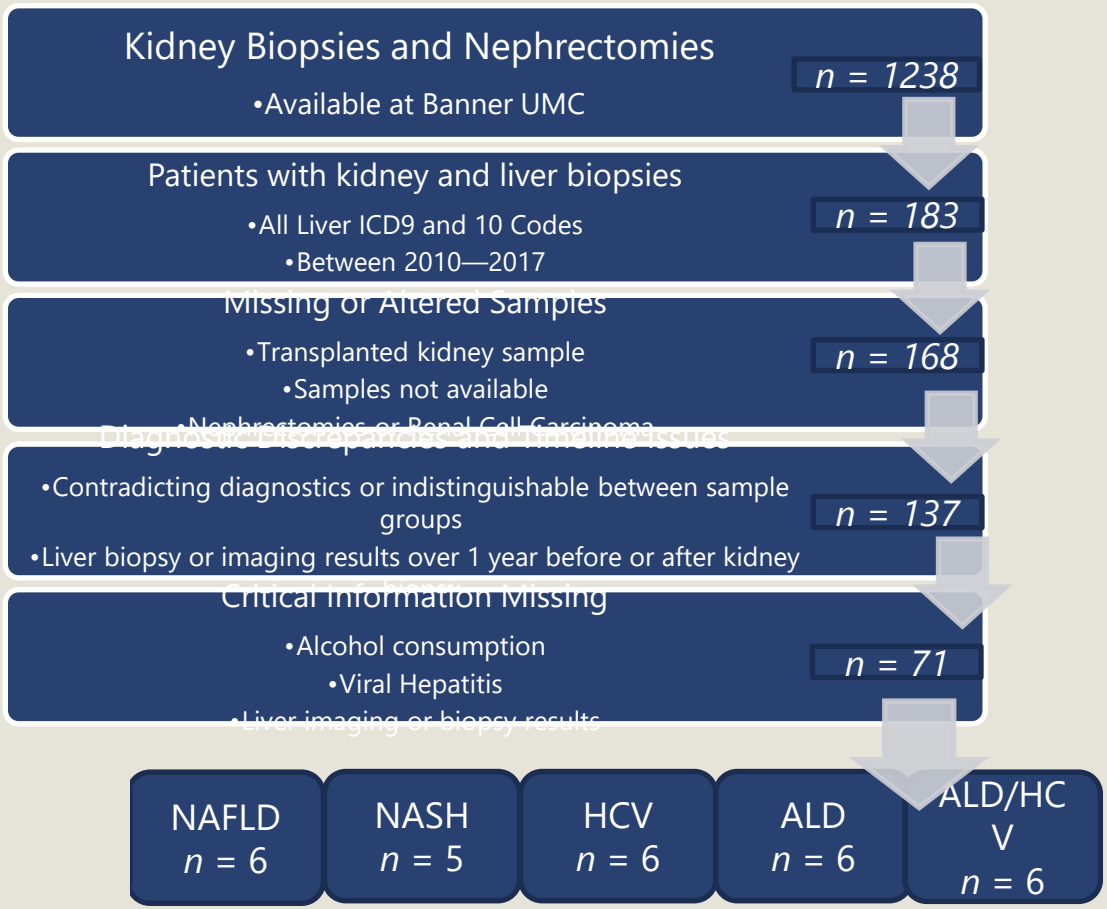
Kidneys from Patients with NASH



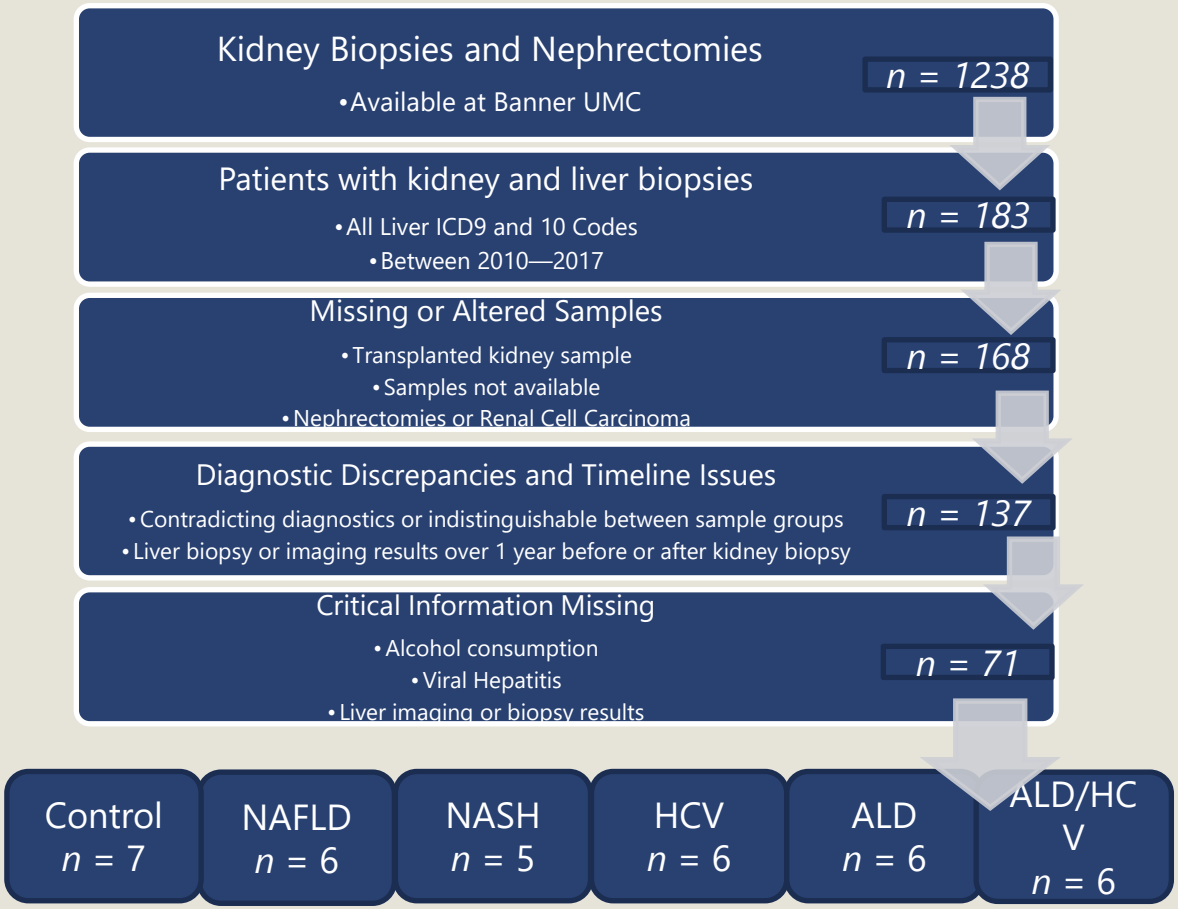
Kidneys from Patients with NASH



Kidneys from Patients with NASH



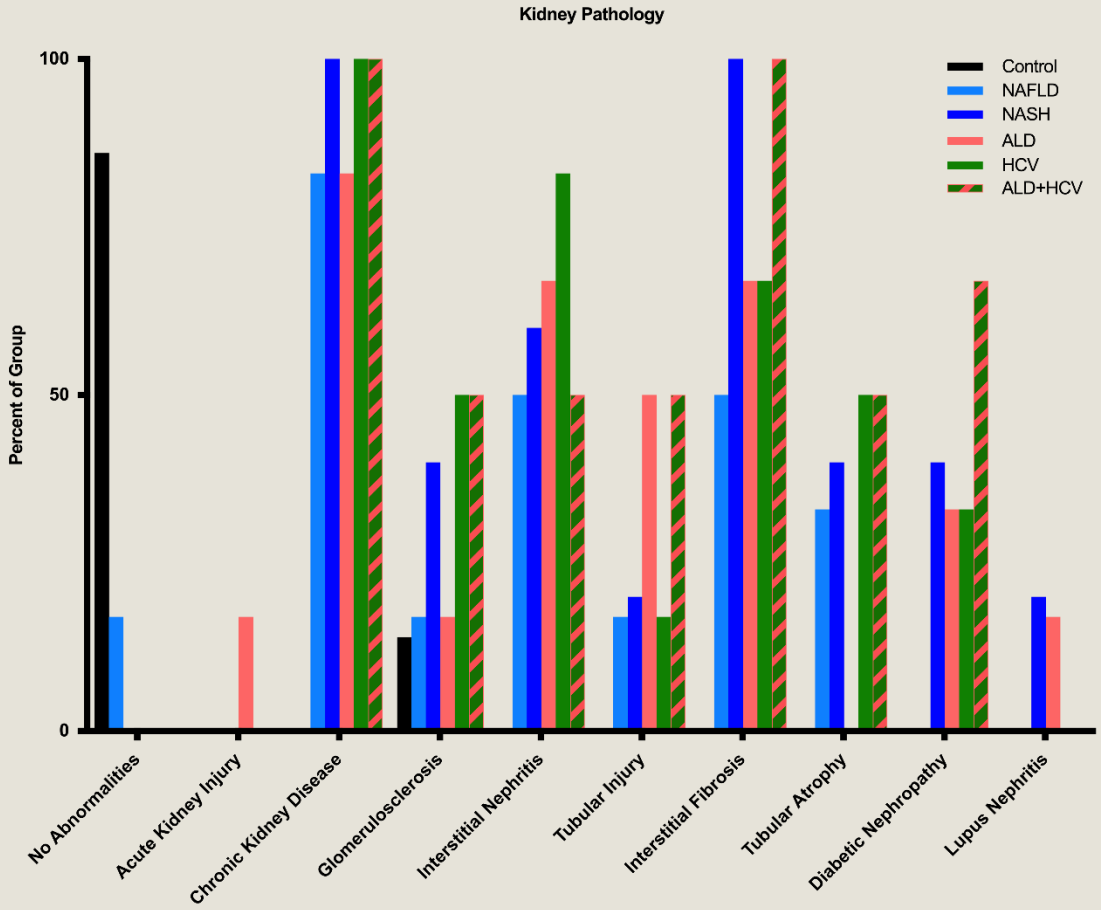
Kidneys from Patients with NASH



Demographics

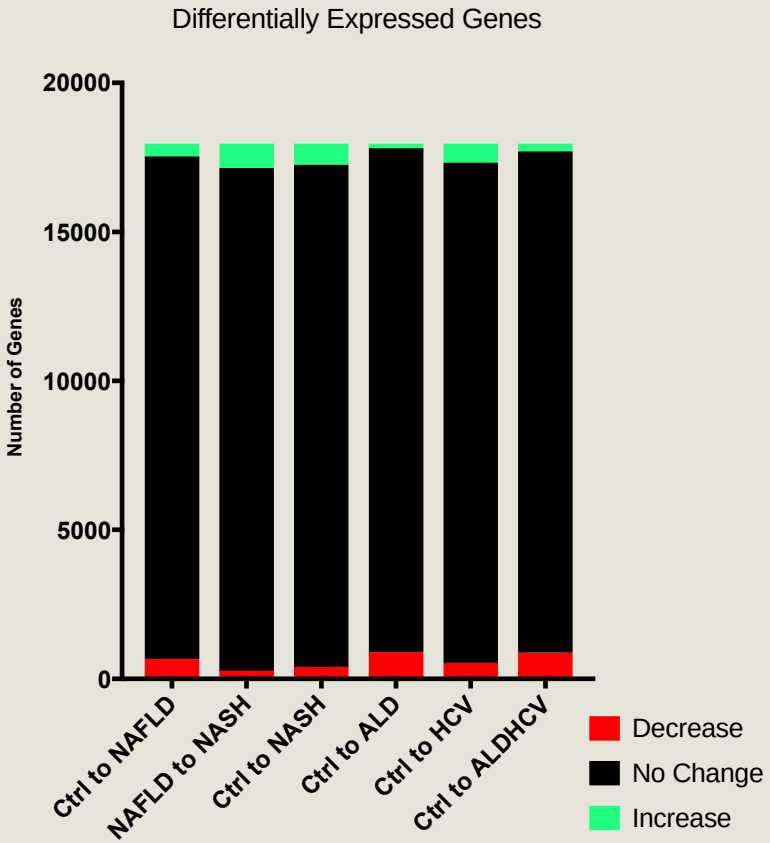
	Control (*n* = 7)	NAFLD (*n* = 6)	NASH (*n* = 5)	ALD (*n* = 6)	HCV (*n* = 6)	ALD/HCV (*n* = 6)
Age (mean ± SD years)	35.4 ± 19.4	45 ± 20.9	54.2 ± 17.3	46.2 ± 10.7	57 ± 4.8	55.7 ± 6.3
% Male	57%	50%	80%	33%	66%	50%
% Hispanic or Latino	14%	16%	40%	33%	50%	50%
% Current/Former Smoker	14%	17%	60%	50%	67%	83%
% Alcohol Consumption	0%	0%	0%	100%	16%	100%
% Obese (BMI >30 kg/m^2)	14%	100%	100%	33%	16%	0%
BMI (mean ± SD kg/m^2)	23.8 ± 3.2	35.4 ± 3.6	33.6 ± 2.9	29.7 ± 5.0	26.3 ± 4.9	27.8 ± 2.1

Kidney Pathology

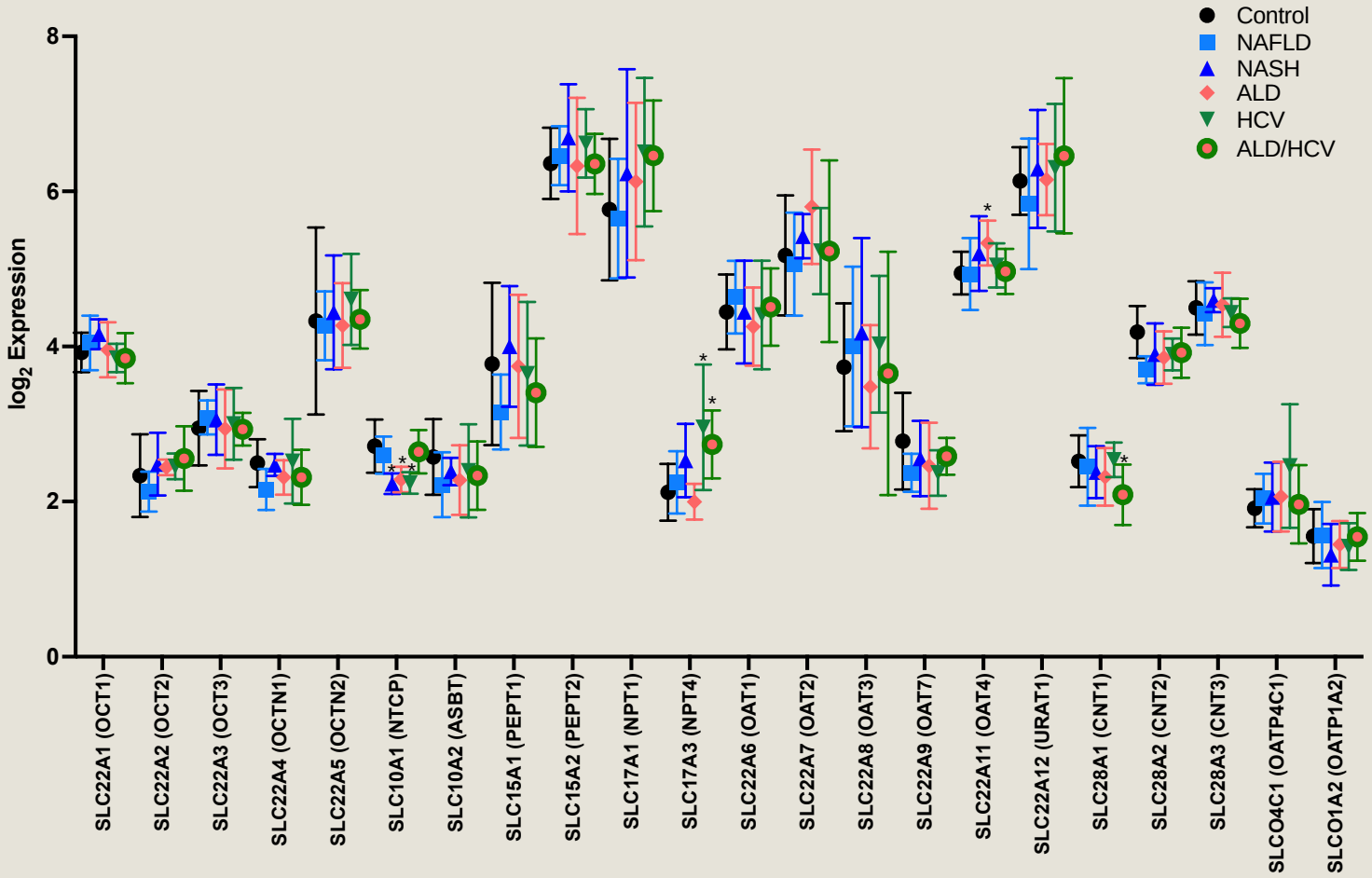


Global Transcriptomics

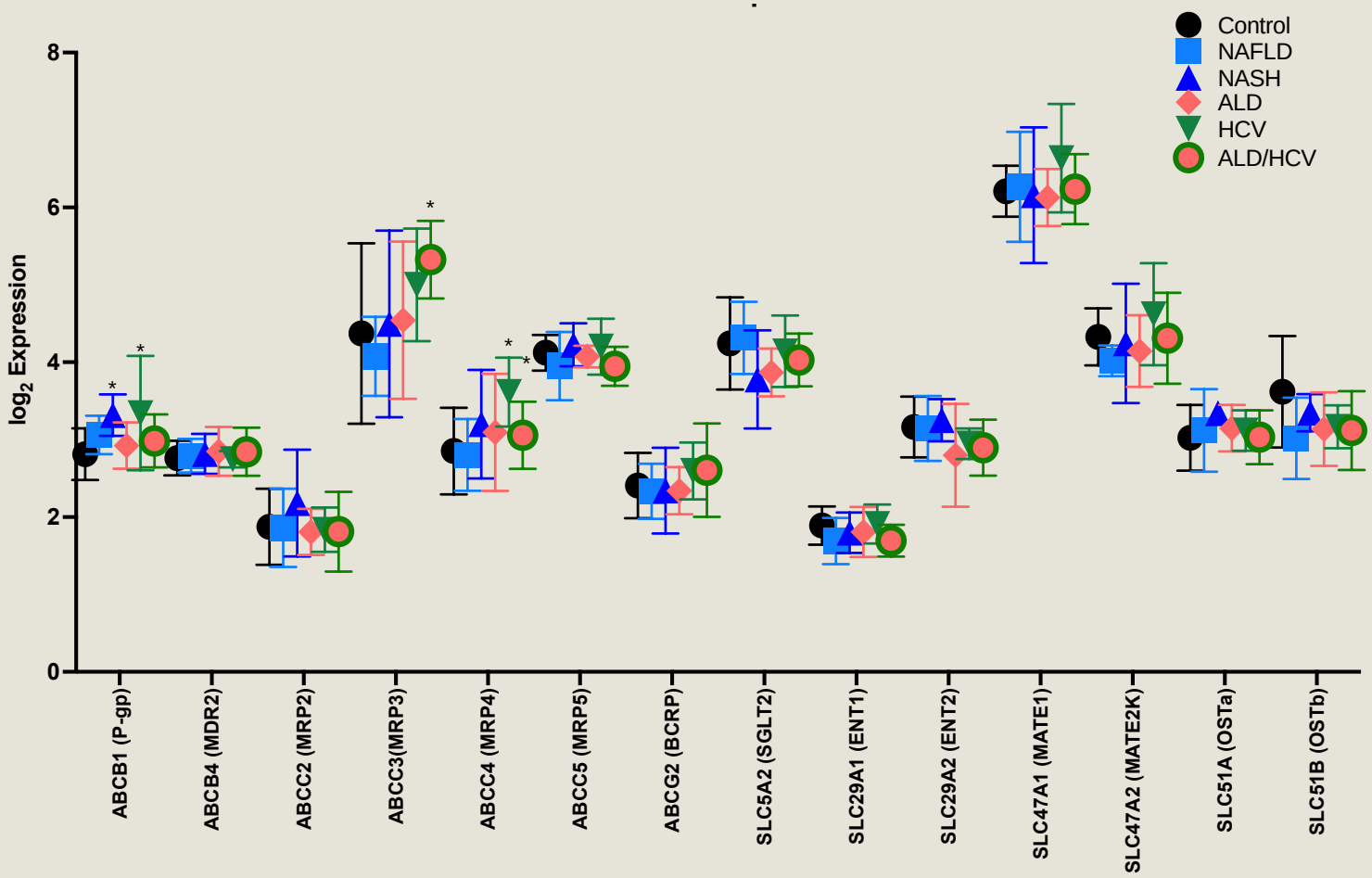
- 55 genes differentially expressed in conserved directions across NASH, ALD, HCV, and ALD/HCV
- Of the 55, immune regulators were highly represented
  - Alpha-2-macroglobulin (A2M)
  - Clusterin (CLU)
  - Complement C1qC chain (C1QC)
  - CD163
  - Joining chain of multimeric IgA and IgM (JCHAIN)



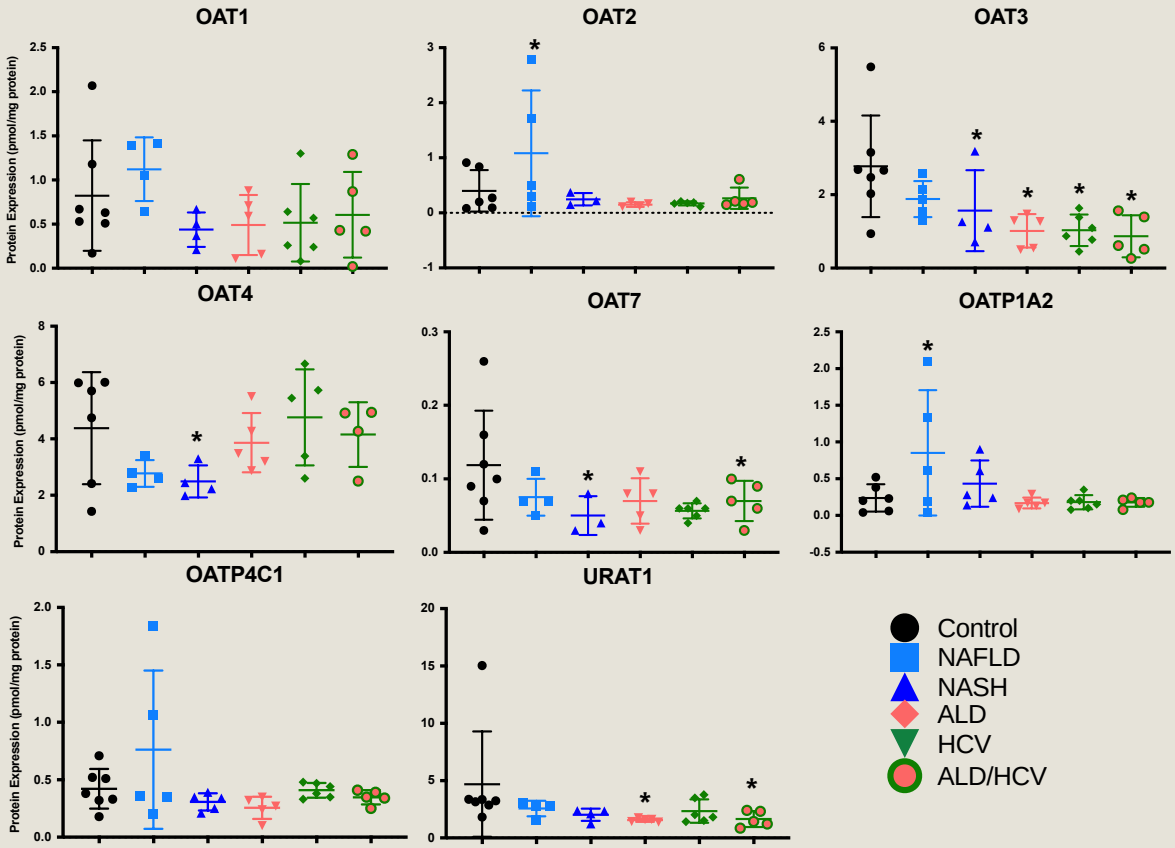
Uptake Transporters



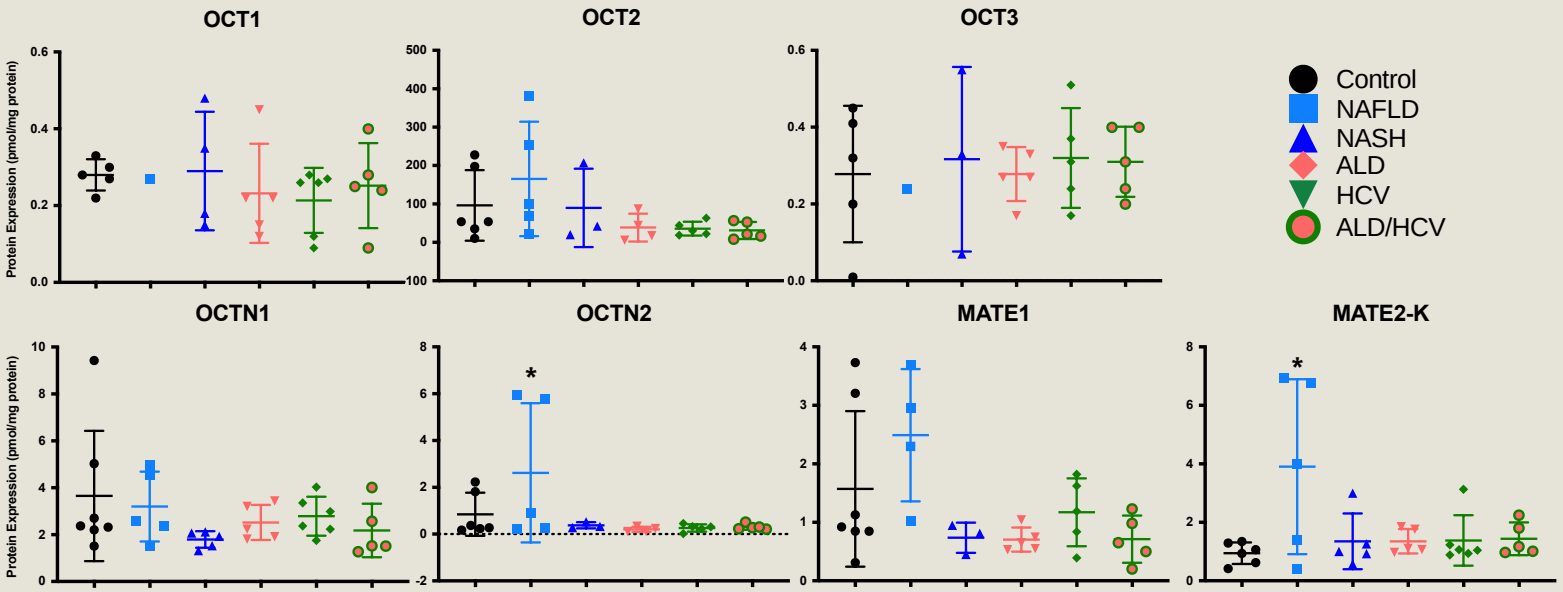
Efflux Transporters



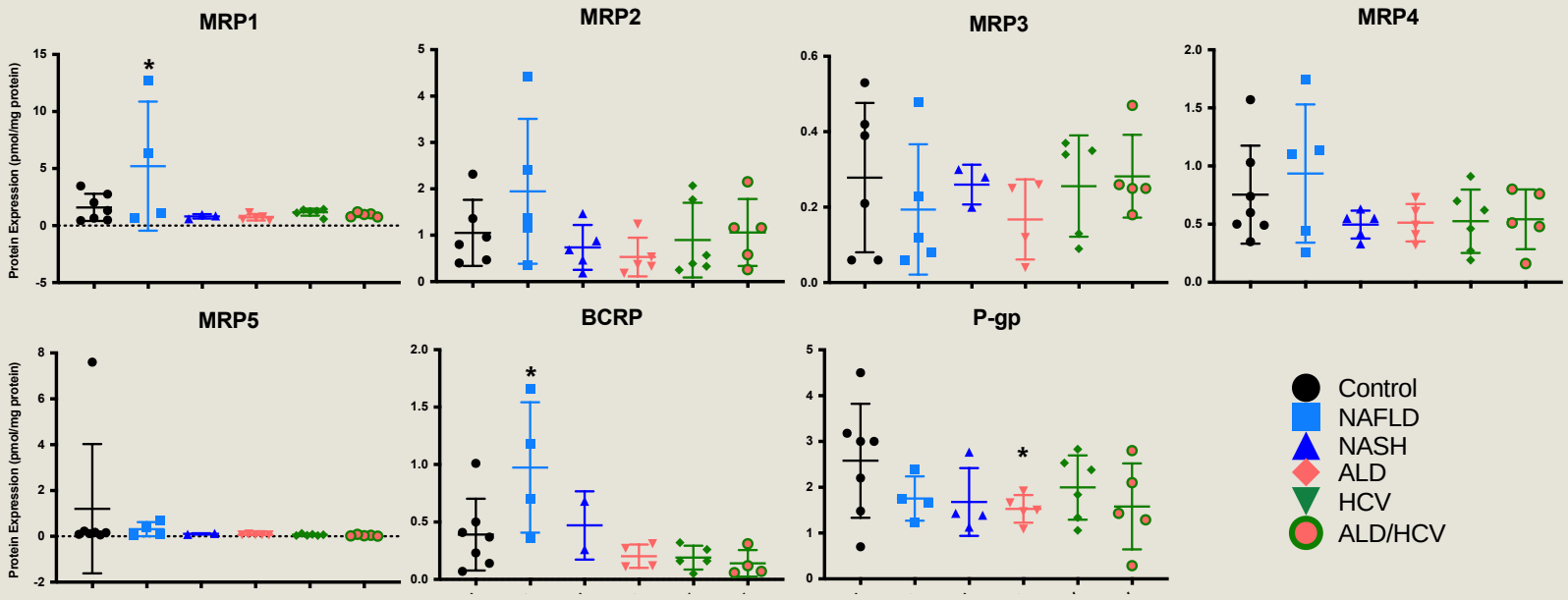
Protein Quantification: Organic Anion Transporters



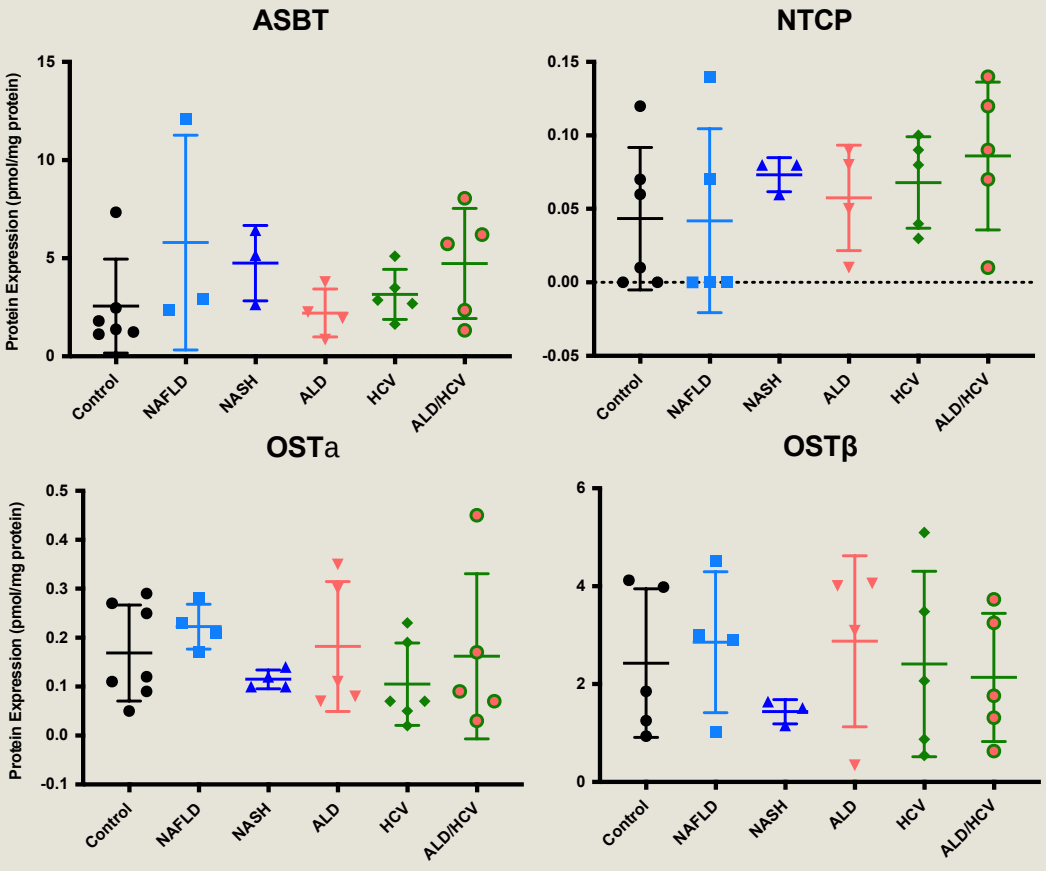
Protein Quantification: Organic Cation Transporters



Protein Quantification: ATP-binding Cassette Transporters

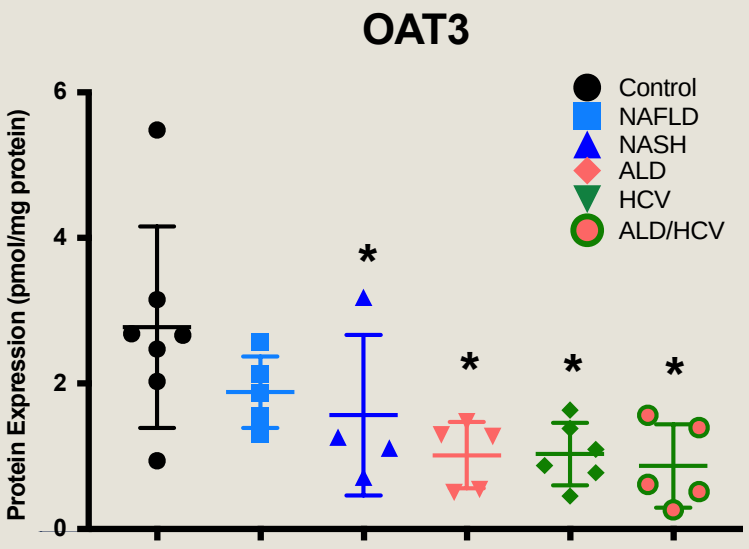


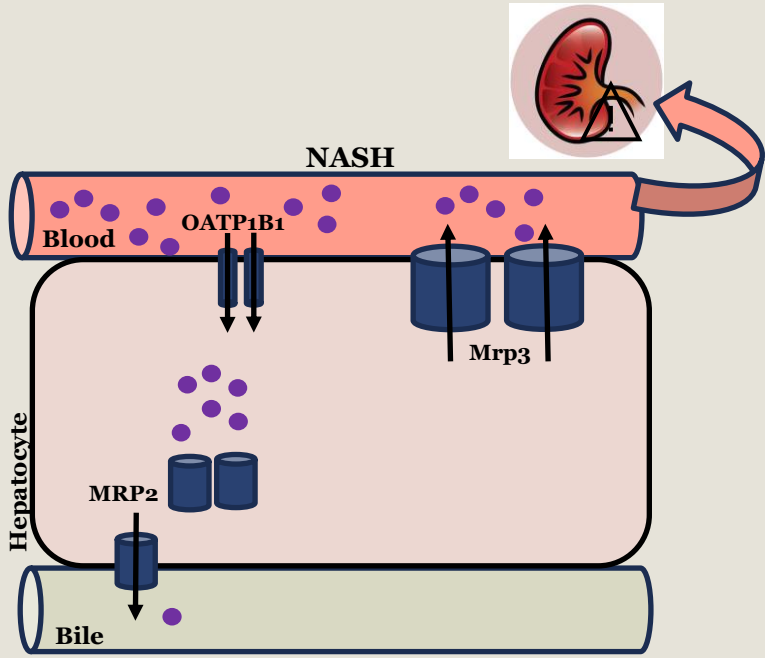
Protein Quantification: Bile-Acid Transporters



Need for Renal Elimination

- Altered disposition in NASH
  - Increased systemic concentrations
- Underestimation of systemic expos
  - Renally eliminated by OAT3/OAT4
  - Further increase systemic concent





Method Flow

Human Kidneys

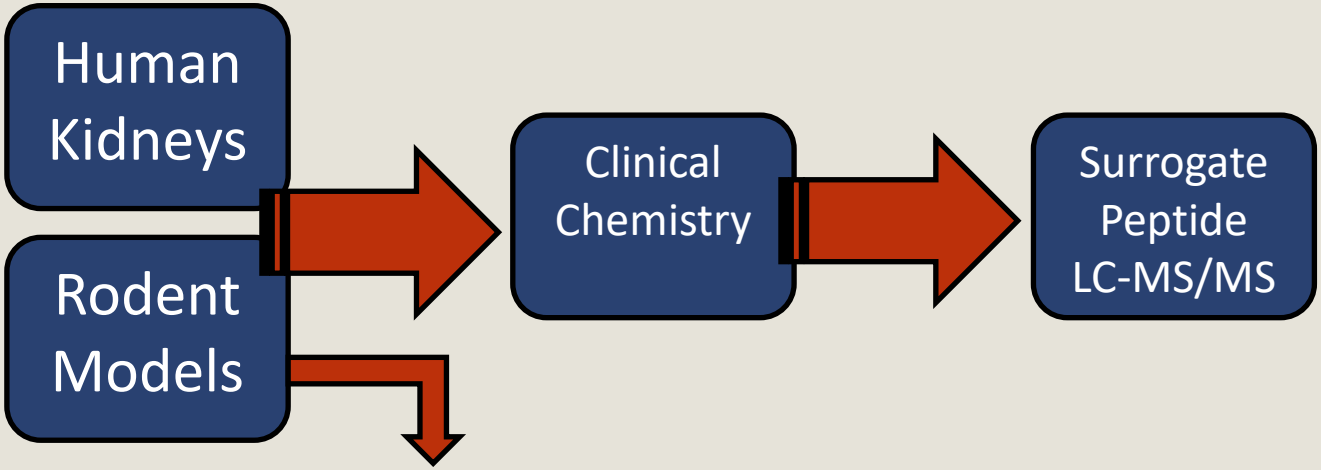
Method Flow

Human Kidneys

Rodent Models

Model	Abbreviation	Species	Strain	Duration
Leptin Deficient with Methionine and Choline Deficient Diet	**db/db**	Mouse	Leprdb/db	4 weeks
Fast Food Diet with Thioacetamide Injections	**FFDTH**	Mouse	C57BL/6J	9 weeks
American Lifestyle Induced Obesity Syndrome	**ALIOS**	Mouse	C57BL/6J	24 weeks
Control Diet	**Control Mouse**	Mouse	C57BL/6J	6 weeks
Methionine and Choline Deficient Diet	**MCD**	Rat	Sprague Dawley	8 weeks
Atherogenic Diet	**Athero**	Rat	Sprague Dawley	8 weeks
Control Diet	**Control Rat**	Rat	Sprague Dawley	8 weeks

Method Flow



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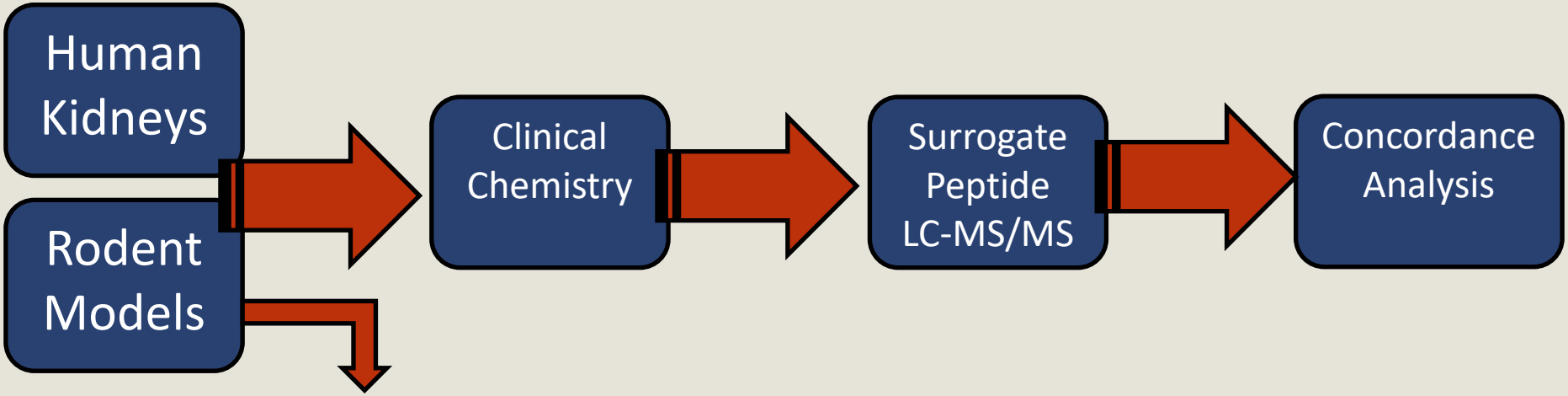
Method Flow



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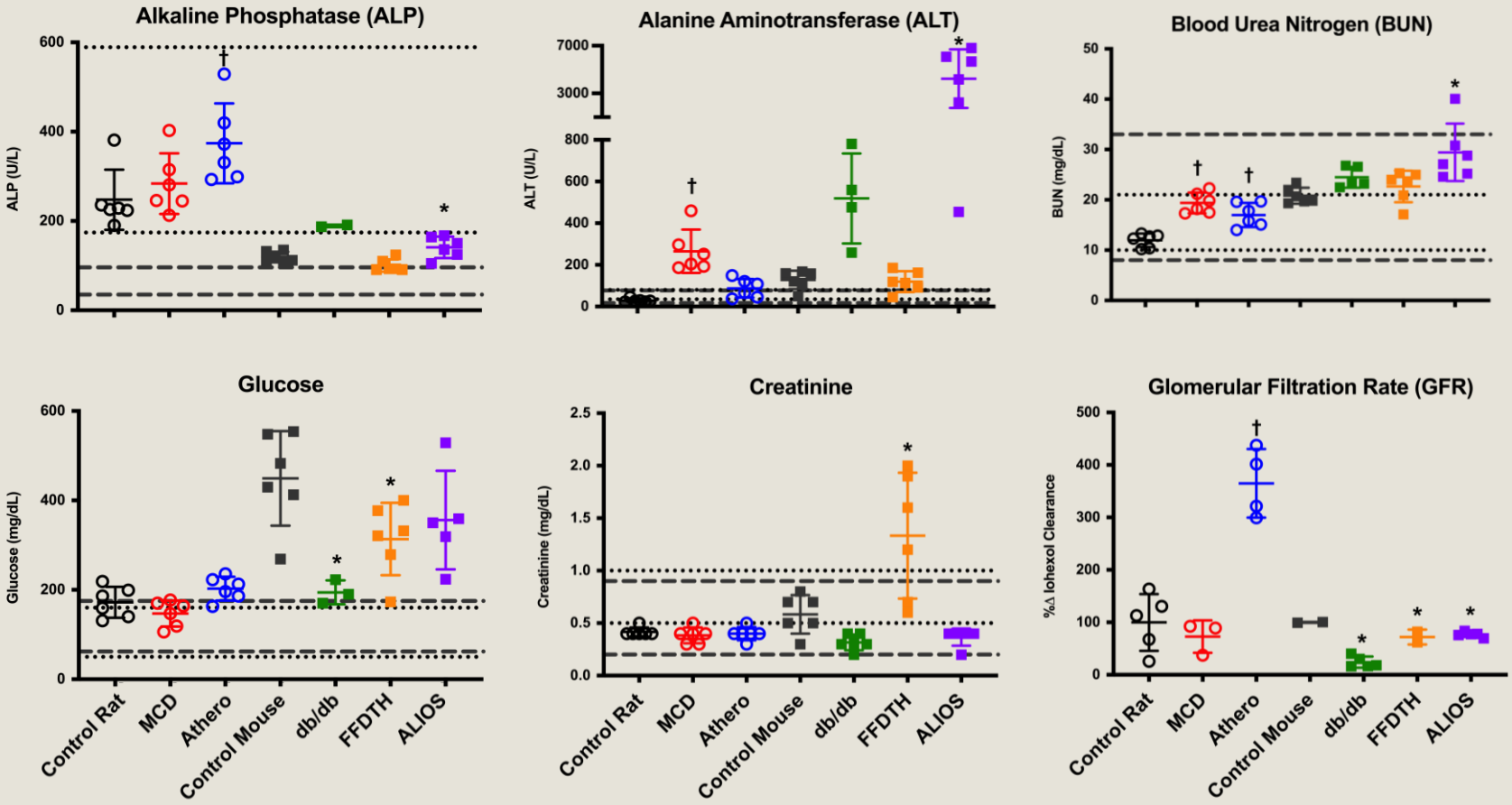
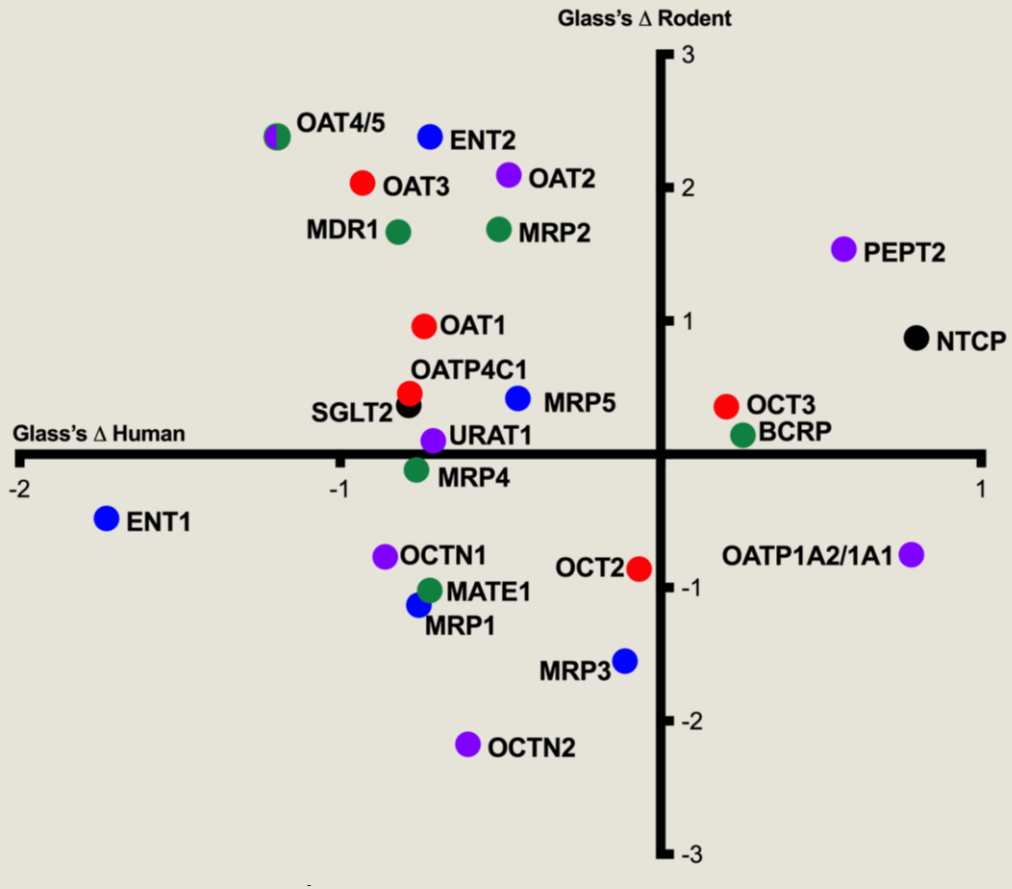
Control Diet	**Control Rat**	Rat	Sprague Dawley	8 weeks

Clinical Chemistry



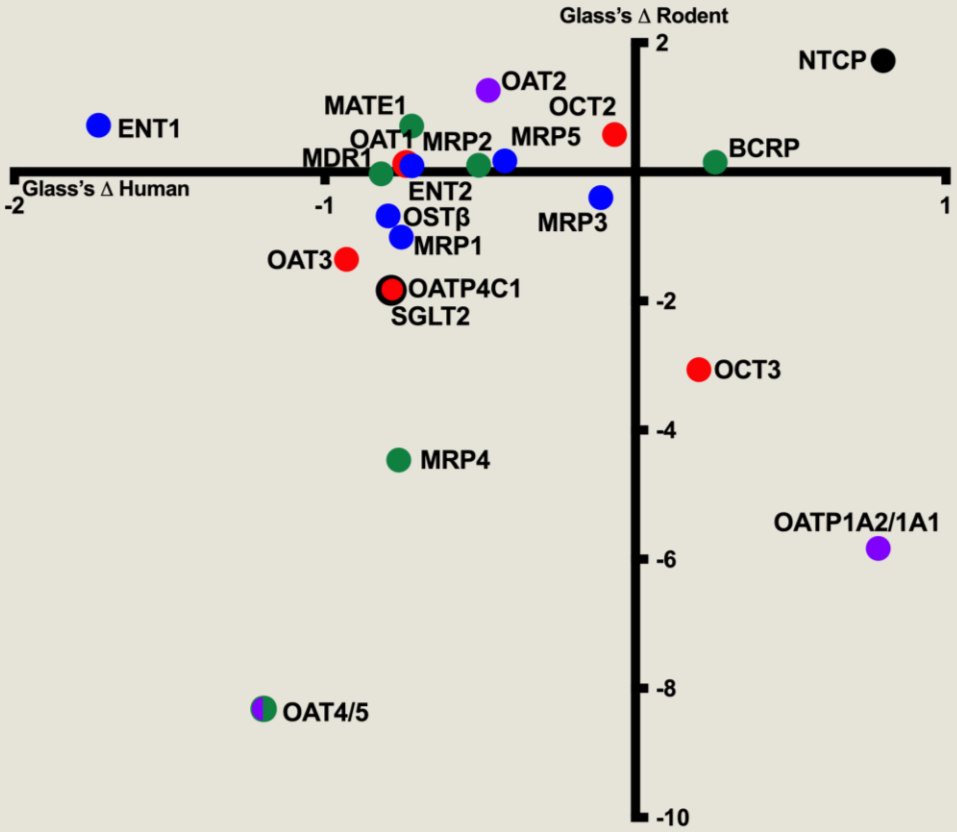
Methionine and Choline Deficient Rats (MCD)



Concordance analysis of rodent models against human renal drug transporters.

- Basolateral Uptake
- Apical Uptake
- Basolateral Efflux
- Apical Efflux

Fast Food Diet with Thioacetamide Injection Mice (FFDTH)



Concordance analysis of rodent models against human renal drug transporters.

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- Basolateral Efflux
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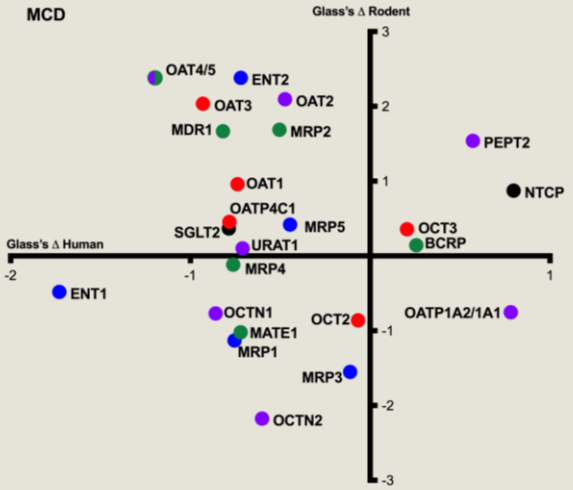
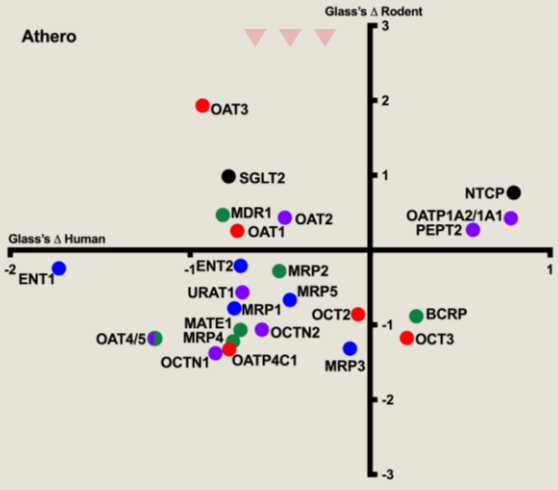
Rodent Model Concordance to Human NASH





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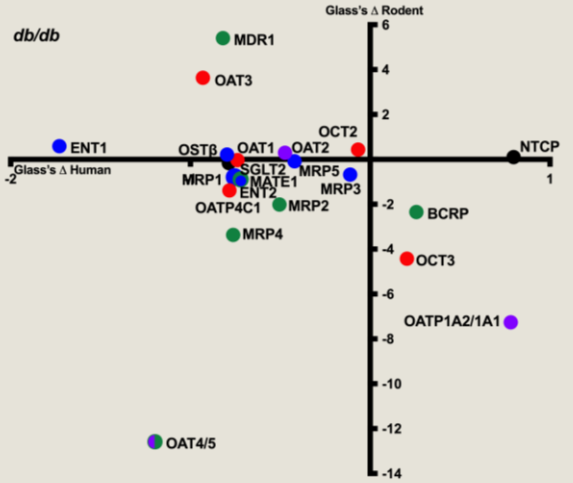
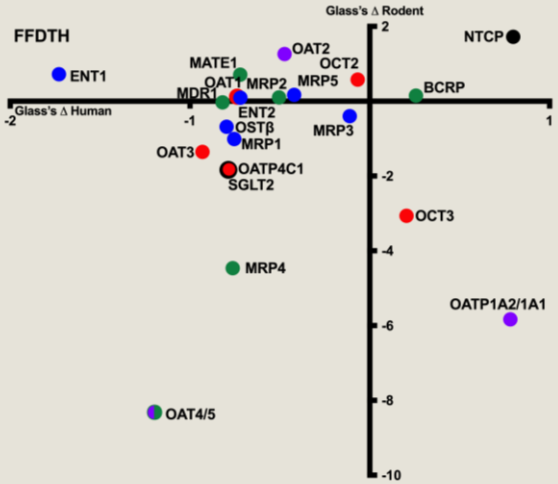
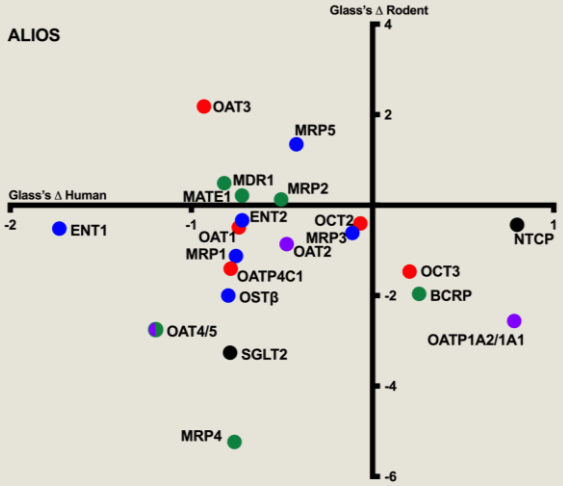
- Basolateral Efflux
- Apical Efflux

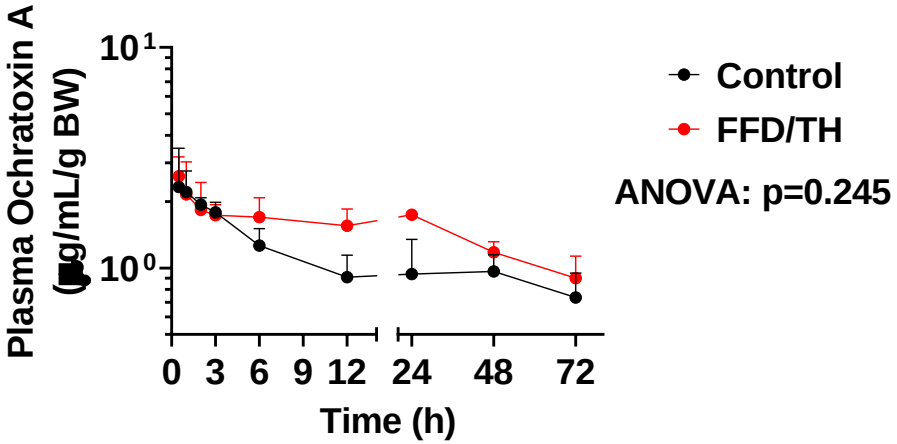


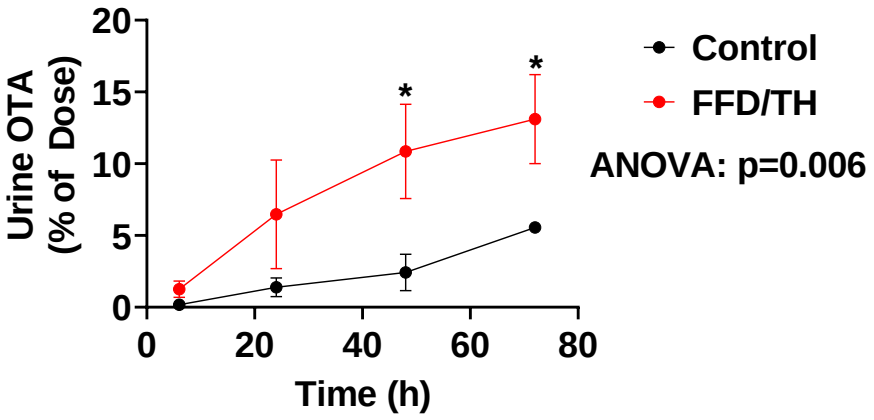




FFD/TH-Induced NASH affects Renal Organic Anion Transporter Expression and Substrate Clearance

Organic Anion Substrate: Ochratoxin A – 12.5 mg/kg bolus p.o.





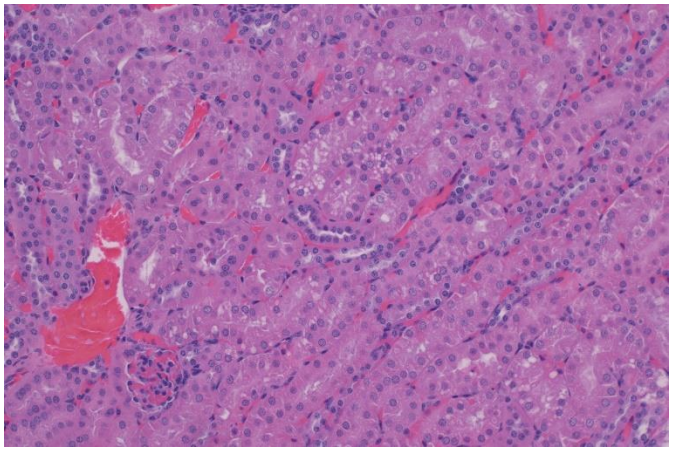
	$t_{1/2}$ h	C_{max}/D µg·mL^{-1}·mg^{-1}	AUC_{last}/D mg·h·ml^{-1}·mg^{-1}	V_z/F mL	CL/F mL·h^{-1}	A_e µg	CL_R/F mL·h^{-1}
Control	62.46 ± 17.04	199.80 ± 79.25	5.65 ± 1.10	8.28 ± 1.51	0.10 ± 0.03	24.41 ± 1.74	10.03 ± 1.45
FFD/TH	53.17 ± 19.38	196.90 ± 52.51	**7.95 ± 0.61 ***	**5.44 ± 0.41 ***	0.08 ± 0.02	**40.07 ± 9.19***	**16.72 ± 5.13***

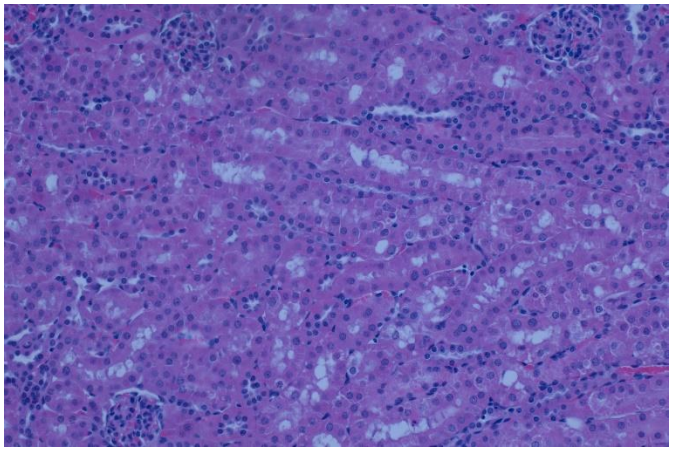
FFD/TH-Induced NASH affects Renal Organic Anion Transporter Expression and Substrate Clearance

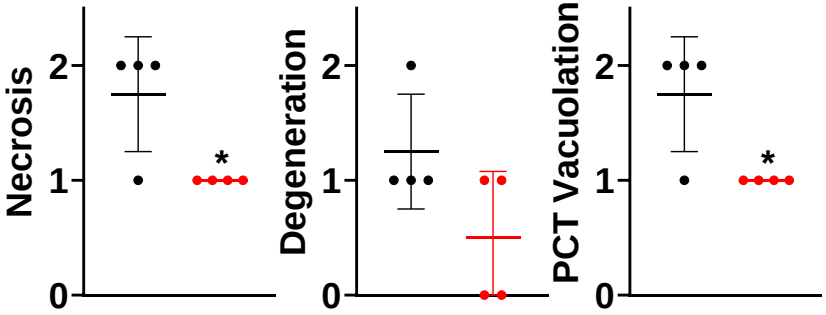
Organic Anion Substrate: Ochratoxin A – 12.5 mg/kg bolus p.o., Sac 72 h post-dose

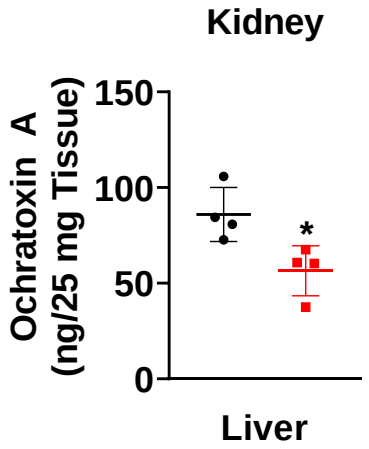
• Control

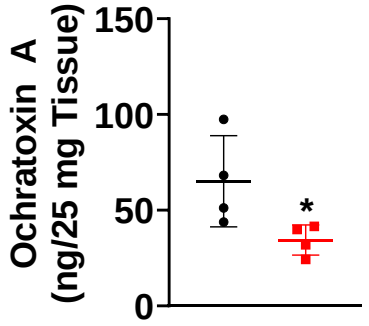
▪ FFD/TH





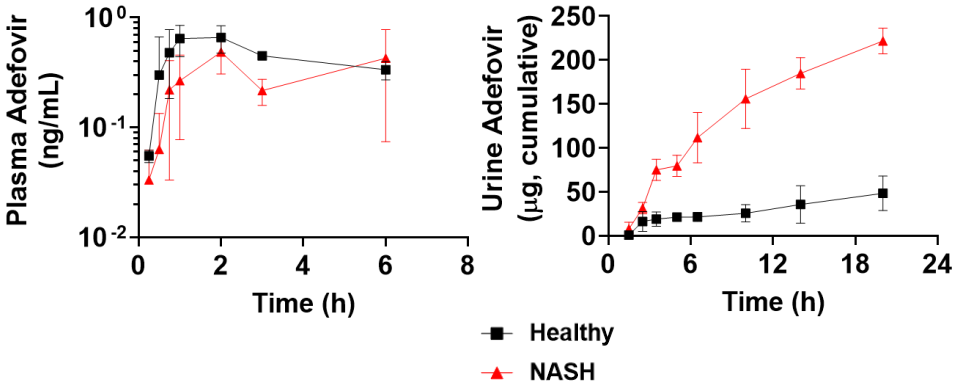


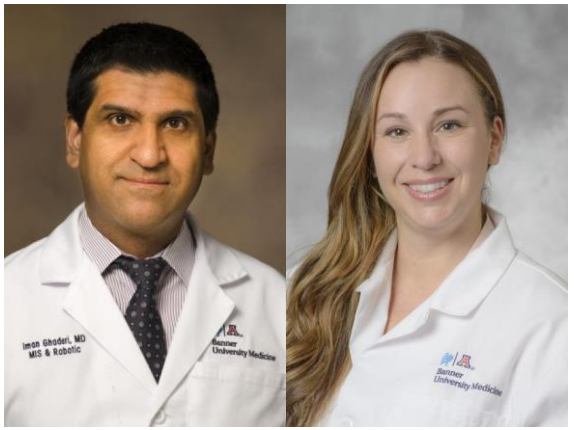




Knowledge Gaps to Fill

- Ochratoxin A
  - Unethical controlled clinical study Substrate for most OAT isoforms
  - How does the organic anion system clear Ochratoxin A?
    - Transepithelial transport via OAT4/5?
    - Other mechanisms (MRP2/4)?
- Adefovir
  - OAT1/3 substrate, high renal clearance
  - Unknown affinity for other OATs, including OAT4/5





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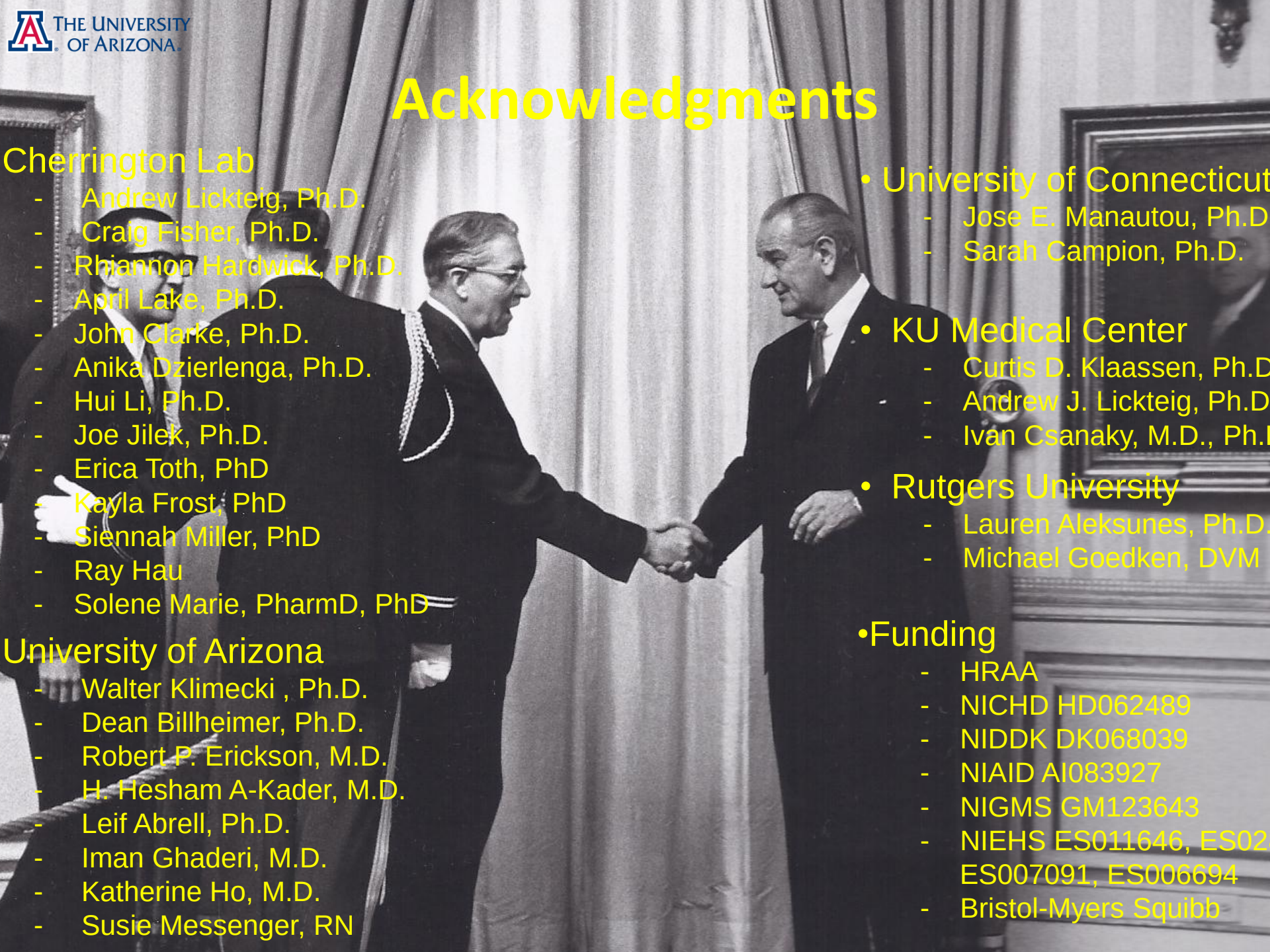
Conclusions

- Significant changes in hepatic ADME processes result in plasma retention and urinary elimination of substrates that may increase ADRs.
- Alterations in renal elimination pathways may contribute to altered ADME and potential toxicity
- The full extent of NASH-induced alterations to renal ADME processes is not fully known but could have a profound impact on patient safety.



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