ADME in Liver Disease: Increased Risk of Drug-Induced Toxicity*

Nathan J. Cherrington, Ph.D.
Phenoconversion

**Genetics**

**Disease**

Ref: Dzierlenga et al. DMD. 2016
What We’ve Learned from the PGRN:

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

Minimal Toxicity

Toxicity
Prevalence of Nonalcoholic Fatty Liver Disease in U.S.

- Healthy: 180-210 million
- Steatosis: 40-105 million
- Steatohepatitis: 15-30 million
- Diagnosed: 300,000 (5 - 7%)
Prevalence of Nonalcoholic Fatty Liver Disease in U.S.

- Healthy: 180-210 million
- Steatosis: 40-105 million
- Steatohepatitis: 5-7% of healthy population
- Diagnosed: 15-30 million
NAFLD Comprises a Spectrum of Pathologic Severity

Healthy liver
- benign
- reversible

Steatosis
- steatosis
- inflammation
- progressive fibrosis

NASH w/fat
- irreversible scarring
- end-stage

NASH not fatty (Cirrhosis)

NAFLD = Nonalcoholic Fatty Liver Disease
NASH = Nonalcoholic Steatohepatitis
Increased Exposure in NASH

![Graph showing increased exposure in NASH](graph.png)
Metabolism: Pediatric P450 Activity In Vivo

Ref: Li et al. DMD. 2017
Hepatic Efflux Transporter Expression

- ABCC1 Protein
- ABCC6 Protein
- ABCC3 Protein
- ABCB1 Protein
- ABCC4 Protein
- ABCG2 Protein
- ABCC5 Protein

\[ \text{Relative Protein Expression} \]

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Steatosis</th>
<th>NASH (fatty)</th>
<th>NASH (not fatty)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCC1</td>
<td></td>
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<tr>
<td>ABCC3</td>
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<td>ABCC4</td>
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<td>ABCC5</td>
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<td>ABCB1</td>
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<td>ABCC6</td>
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<tr>
<td>ABCG2</td>
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</tbody>
</table>

* *p < 0.001

Pan-Cadherin
Cellular Localization of Hepatic MRP2

Normal

NASH (not fatty)

Ref: Hardwick et al. DMD. 2011
APAP Disposition

Rat Plasma

**APAP (nmol/ml)**

- Control
- SFL
- NASH

**APAP-Gluc (nmol/ml)**

- Control
- SFL
- NASH

**APAP-Sulf (nmol/ml)**

- Control
- SFL
- NASH

Time (min)


APAP = Acetaminophen

* p < 0.05 significant vs. Control
APAP Disposition

Rat Plasma

- APAP (nmol/ml)
- APAP-Gluc (nmol/ml)
- APAP-Sulf (nmol/ml)

Time (min)

Human Plasma

- Normal
- Steatosis
- NASH

APAP = Acetaminophen
* p < 0.05 significant vs. Control
3 Mechanisms: Hepatocyte Hopping
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, ceftriaxone, ezetimibe, olmesartan, penicillamine, pravastatin,
  - **Predicted ADRs:** adefovir, atrasentan, avibactam, benlafamab mafoditin, camptothecin, carboplatin, caspofungin, cervistatin, chlorpropamide, 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, ouabain, oxaliplatine, pemetrexed, phalloidin, pralatrexate, probenecid, raloxifene, rapamycin, revafenac, rifampicin, sulfasalazine, sumatriptan, telmisartan, temocapril, thioguanine, topotecan, vasopressin

• TRANSPORTER and METABOLISM
  - **Known ADRs:** atorvastatin, azithromycin, canaglifozin, diclofenac, erythromycin, fluvasatatin, grazoprevir, mycophenolate mofetil, paritaprevir, repaglinide, rosuvastatin, simprevir, simvastatin, valsartan,
  - **Predicted ADRs:** ambrisentan, asunaprevir, axitinib, bosentan, carbamazepin, clopidogrel, clotrimazole, cobimetinib, cyclophosphamide, cyclosporin, darunavir, docetaxel, doxorubicin, elagolix, ethinylestradiol, etoposide, fluorouracil, gefitinib, glibenclamide, grepafloxacin, ifosfamide, imatinib, indinavir, irinotecan, leronver, 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
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

Kidney Biopsies and Nephrectomies

n = 1,238

Kidneys from Patients with NASH
Kidneys from Patients with NASH

Kidney Biopsies and Nephrectomies
• Available at Banner UMC

Patients with kidney and liver biopsies
• All Liver ICD9 and 10 Codes
• Between 2010—2017

n = 1238

n = 183
Kidneys from Patients with NASH

Kidney Biopsies and Nephrectomies
- Available at Banner UMC
- \( n = 1238 \)

Patients with kidney and liver biopsies
- All Liver ICD9 and 10 Codes
- Between 2010—2017
- \( n = 183 \)

Missing or Altered Samples
- Transplanted kidney sample
- Samples not available
- Nephrectomies or Renal Cell Carcinoma
- \( n = 168 \)
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Nephrectomies or Renal Cell Carcinoma

Diagnostic Discrepancies and Timeline Issues
• Contradicting diagnostics or indistinguishable between sample groups
• Liver biopsy or imaging results over 1 year before or after kidney

HCV
n = 6
ALD
n = 6
ALD/HC
n = 6

NASH
n = 5
NAFLD
n = 6
Control
n = 7

n = 1238
n = 183
n = 168
n = 137
Kidneys from Patients with NASH

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Missing or Altered Samples
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Nephrectomies or Renal Cell Carcinoma
- Contradicting diagnostics or indistinguishable between sample groups
  - Liver biopsy or imaging results over 1 year before or after kidney
  - n = 137

Critical Information Missing
- Alcohol consumption
  - Viral Hepatitis
  - Liver imaging or biopsy results
  - n = 71

HCV
  - n = 6

ALD
  - n = 6

ALD/HC
  - V
  - n = 6

NASH
  - n = 5

NAFLD
  - n = 6

Control
  - n = 7

n = 1838

n = 1238

n = 168

n = 137

n = 71
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  - n = 137

Critical Information Missing
- Alcohol consumption
  - Viral Hepatitis
  - Liver imaging or biopsy results
  - n = 71

Diagnoses:
- NAFLD
  - n = 6
- NASH
  - n = 5
- HCV
  - n = 6
- ALD
  - n = 6
- ALD/HCV
  - n = 6
Kidneys from Patients with NASH

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- Contradicting diagnostics or indistinguishable between sample groups
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Critical Information Missing
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  - n = 71

Control
  - n = 7

NAFLD
  - n = 6

NASH
  - n = 5

HCV
  - n = 6

ALD
  - n = 6

ALD/HC
  - n = 6

n = 183

n = 168

n = 137

n = 71

n = 1238

n = 1238

n = 1238

n = 1238
## Demographics

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

The graph shows the percent of each group with various kidney pathologies. The pathologies include No Abnormalities, Acute Kidney Injury, Chronic Kidney Disease, Glomerulonephritis, Interstitial Nephritis, Tubular Injury, Interstitial Fibrosis, Tubular Atrophy, Diabetic Nephropathy, and Lupus Nephritis. The groups are represented by different colors and patterns:

- Control
- NAFLD
- NASH
- ALD
- HCV
- ALD+HCV

The x-axis represents different pathologies, and the y-axis represents the percent of the group with each 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

- SLC22A1 (OCT1)
- SLC22A2 (OCT2)
- SLC22A3 (OCT3)
- SLC22A4 (OCTN1)
- SLC22A5 (OCTN2)
- SLC10A1 (NTCP)
- SLC10A2 (ASBT)
- SLC15A1 (PEPT1)
- SLC17A1 (NPT1)
- SLC17A3 (NPT4)
- SLC22A6 (OAT1)
- SLC22A7 (OAT2)
- SLC22A8 (OAT3)
- SLC22A9 (OAT4)
- SLC22A11 (URAT1)
- SLC28A2 (CNT2)
- SLC28A3 (CNT3)
- SLC28A4 (OAT1A2)
- SLC28A5 (OCT1A2)

*Control
- NAFLD
- NASH
- ALD
- HCV
- ALD/HCV

**log2 Expression**

Uptake Transporters

NAFLD, NASH, ALD, HCV, ALD/HCV
Efflux Transporters

- ABCB1 (P-gp)
- ABCB4 (MDR2)
- ABCC2 (MRP2)
- ABCC4 (MRP4)
- ABCC5 (MRP5)
- ABCC3 (MRP3)
- ABCC4 (MRP4)
- ABCC5 (MRP5)
- ABCG2 (BCRP)
- SLC4A2 (SGLT2)
- SLC29A1 (ENT1)
- SLC29A2 (ENT2)
- SLC47A1 (MATE1)
- SLC47A2 (MATE2K)
- SLC5A1 (OSTa)
- SLC51B (OSTb)

Control
NAFLD
NASH
ALD
HCV
ALD/HCV

log2 Expression
Protein Quantification: Organic Anion Transporters

- **OAT1**
- **OAT2**
- **OAT3**
- **OAT4**
- **OAT7**
- **OATP4C1**
- **URAT1**

**Protein Expression (pmol/mg protein)**

- Control
- NAFLD
- NASH
- ALD
- HCV
- ALD/HCV

*Significant differences*
Protein Quantification: Organic Cation Transporters

OCT1

OCT2

OCT3

OCTN1

OCTN2

MATE1

MATE2-K

Protein Expression (pmol/mg protein)

Protein Expression (pmol/mg protein)

Protein Expression (pmol/mg protein)

Protein Expression (pmol/mg protein)
Protein Quantification: ATP-binding Cassette Transporters

MRP1
MRP2
MRP3
MRP4
MRP5
BCRP
P-gp

Protein Expression (pmol/mg protein)

Control
NAFLD
NASH
ALD
HCV
ALD/HCV

MRP5

Protein Expression (pmol/mg protein)

Control
NAFLD
NASH
ALD
HCV
ALD/HCV

MRP4

Protein Expression (pmol/mg protein)

Control
NAFLD
NASH
ALD
HCV
ALD/HCV

BCRP

Protein Expression (pmol/mg protein)

Control
NAFLD
NASH
ALD
HCV
ALD/HCV

P-gp

Protein Expression (pmol/mg protein)

Control
NAFLD
NASH
ALD
HCV
ALD/HCV

MRP3

Protein Expression (pmol/mg protein)

Control
NAFLD
NASH
ALD
HCV
ALD/HCV

MRP2

Protein Expression (pmol/mg protein)

Control
NAFLD
NASH
ALD
HCV
ALD/HCV

MRP1

Protein Expression (pmol/mg protein)

Control
NAFLD
NASH
ALD
HCV
ALD/HCV

Efflux Transporters

Control
NAFLD
NASH
ALD
HCV
ALD/HCV

*
Protein Quantification: Bile-Acid Transporters

ASBT

NTCP

OST

OSTβ

Protein Expression (pmol/mg protein)
Need for Renal Elimination

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

![Diagram showing blood flow and protein expression](image-url)

**OAT3**

- Graph showing protein expression (pmol/mg protein) for different conditions: Control, NAFLD, NASH, ALD, HCV, ALD/HCV.

- Legend: Control (black circle), NAFLD (blue triangle), NASH (blue triangle with arrow), ALD (pink diamond), HCV (green square), ALD/HCV (red circle).

- Significant differences indicated by asterisks (*) on the graph.

**Hepatocyte**

- OATP1B1: blood flow to hepatocyte.
- MRP2: export to bile.
- Mrp3: renal elimination.

**Blood**

- OATP1B1: transport proteins.

**NASH**

- Increased expression of efflux transporters.

**Protein Expression (pmol/mg protein)**

- Bar graph with data points for each condition.
## Method Flow

### Human Kidneys

<table>
<thead>
<tr>
<th>Model Abbreviation</th>
<th>Species</th>
<th>Strain</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin Deficient with Methionine and Choline Deficient Diet</td>
<td>Mouse</td>
<td>db/db</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Fast Food Diet with Thioacetamide Injections</td>
<td>Mouse</td>
<td>C57BL/6J</td>
<td>9 weeks</td>
</tr>
<tr>
<td>American Lifestyle Induced Obesity Syndrome</td>
<td>Mouse</td>
<td>C57BL/6J</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Control Diet</td>
<td>Mouse</td>
<td>C57BL/6J</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Methionine and Choline Deficient Diet</td>
<td>Rat</td>
<td>Sprague Dawley</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Atherogenic Diet</td>
<td>Rat</td>
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**Clinical Chemistry** Surrogate Peptide LC-MS/MS Concordance Analysis
### Method Flow

#### Rodent Models

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#### Human Kidneys

- Rodent Models
- Clinical Chemistry
- Surrogate Peptide
- LC-MS/MS
- Concordance Analysis
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### Method Flow

#### Rodent Models
- **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** 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** Rat, Sprague Dawley, 8 weeks

#### Human Kidneys

#### Clinical Chemistry

#### Surrogate Peptide LC-MS/MS

#### Concordance Analysis
Methionine and Choline Deficient Rats (MCD)

Concordance analysis of rodent models against human renal drug transporters.
Fast Food Diet with Thioacetamide Injection Mice (FFDTH)

Concordance analysis of rodent models against human renal drug transporters.
Concordance analysis of rodent models against human renal drug transporters.

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

**Rodent Model Concordance to Human NASH**
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.

<table>
<thead>
<tr>
<th></th>
<th>t(_{1/2}) h</th>
<th>C(_{\text{max}})/D (\mu g\cdot mL^{-1}\cdot mg^{-1})</th>
<th>AUC(_\text{last}/D) mg·h·ml(^{-1})·mg(^{-1})</th>
<th>V(_z/F) mL</th>
<th>CL/F mL·h(^{-1})</th>
<th>A(_e) µg</th>
<th>CL(_R/F) mL·h(^{-1})</th>
</tr>
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<tbody>
<tr>
<td><strong>Control</strong></td>
<td>62.46 ±</td>
<td>199.80 ±</td>
<td>5.65 ±</td>
<td>8.28 ±</td>
<td>0.10 ±</td>
<td>24.41 ±</td>
<td>10.03 ±</td>
</tr>
<tr>
<td></td>
<td>17.04</td>
<td>79.25</td>
<td>1.10</td>
<td>1.51</td>
<td>0.03</td>
<td>1.74</td>
<td>1.45</td>
</tr>
<tr>
<td><strong>FFD/TH</strong></td>
<td>53.17 ±</td>
<td>196.90 ±</td>
<td>7.95 ±</td>
<td>5.44 ±</td>
<td>0.08 ±</td>
<td>40.07 ±</td>
<td>16.72 ±</td>
</tr>
<tr>
<td></td>
<td>19.38</td>
<td>52.51</td>
<td>0.61 *</td>
<td>0.41 *</td>
<td>0.02</td>
<td>9.19*</td>
<td>5.13*</td>
</tr>
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</table>
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

![Image showing histological sections and graphs comparing Ochratoxin A levels in kidney and liver tissue between Control and FFD/TH groups.](image_url)

- Necrosis
- Degeneration
- PCT Vacuolation

Kidney

Liver
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)?

• Adeovir
  • OAT1/3 substrate, high renal clearance
  • Unknown affinity for other OATs, including OAT4/5
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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