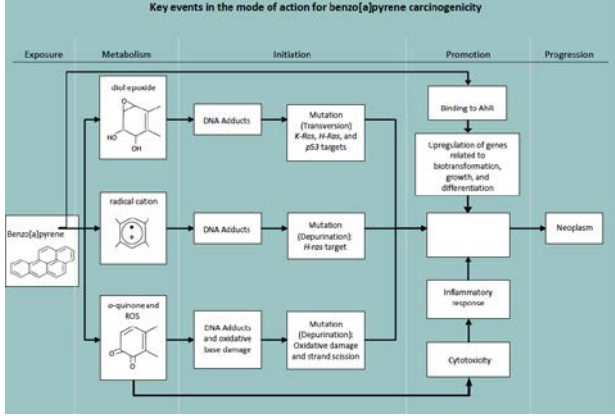
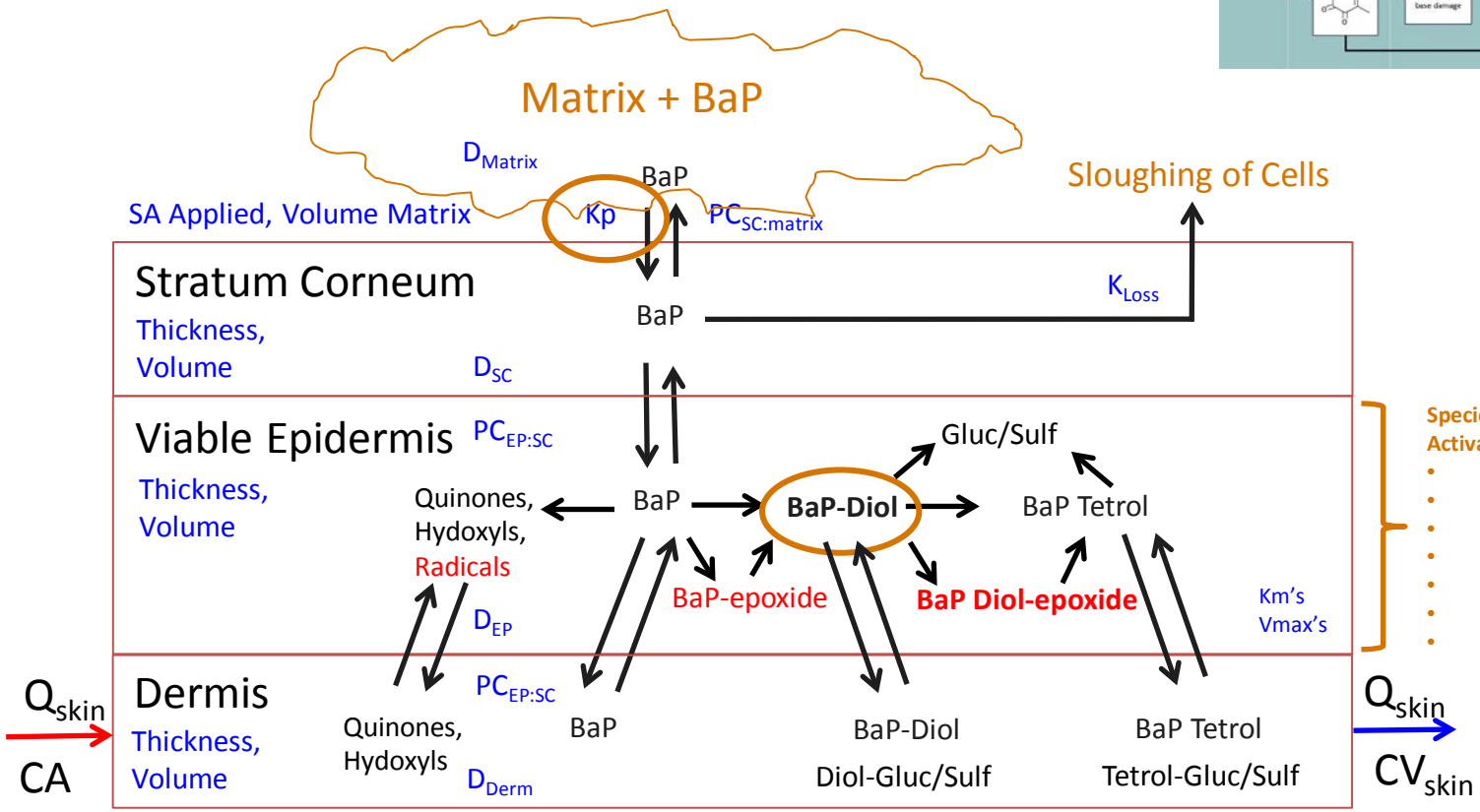
Dermal PBPK Model for BaP



EPA (2013) Fig 1-6



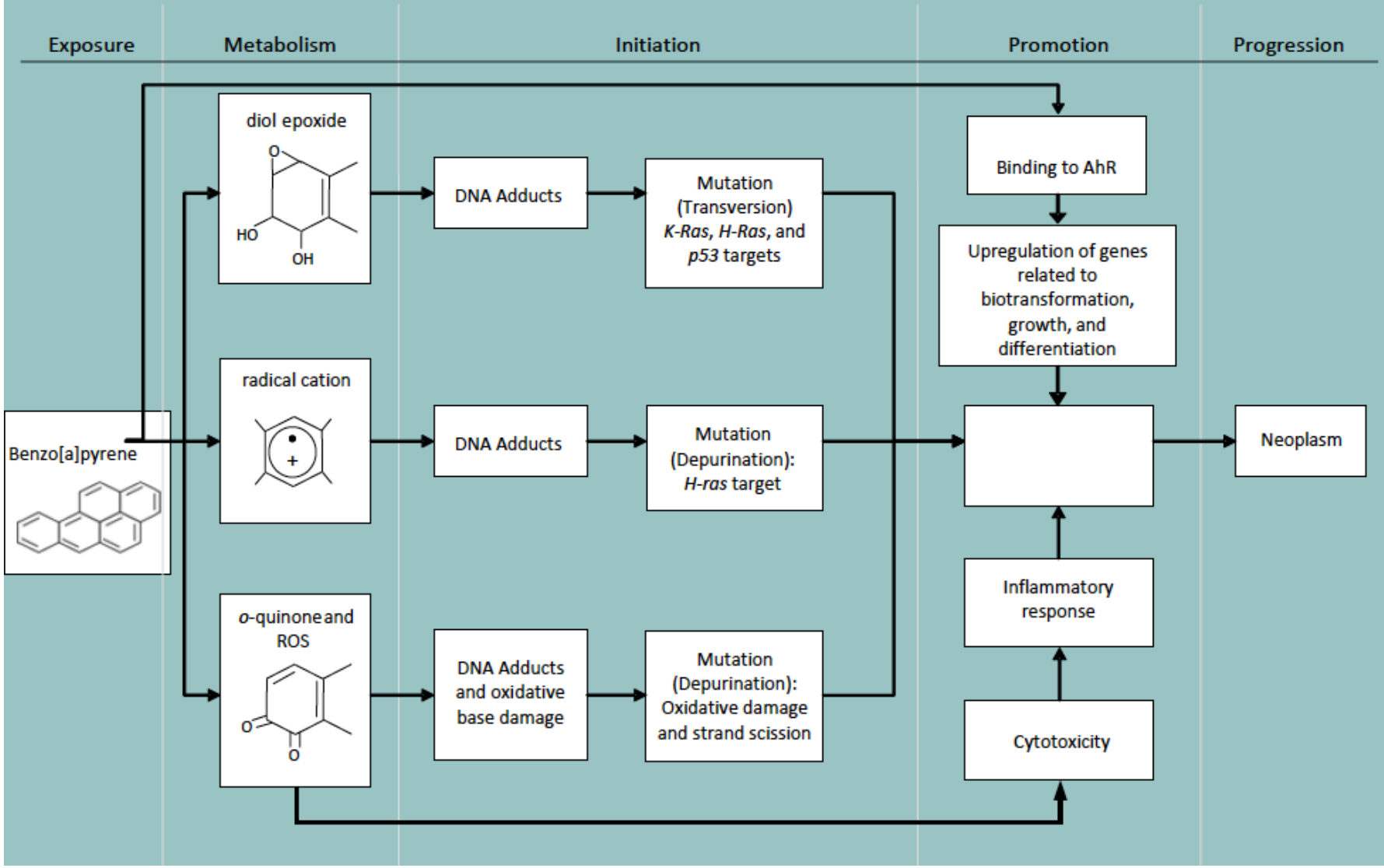
Kp is matrix-dependent

Q_{skin} increases with exercise/work conditions

LADD based upon steady-state AUC for BaP-Diol in viable epidermis
proposed internal dose surrogate

Key events in the mode of action for benzo[a]pyrene carcinogenicity

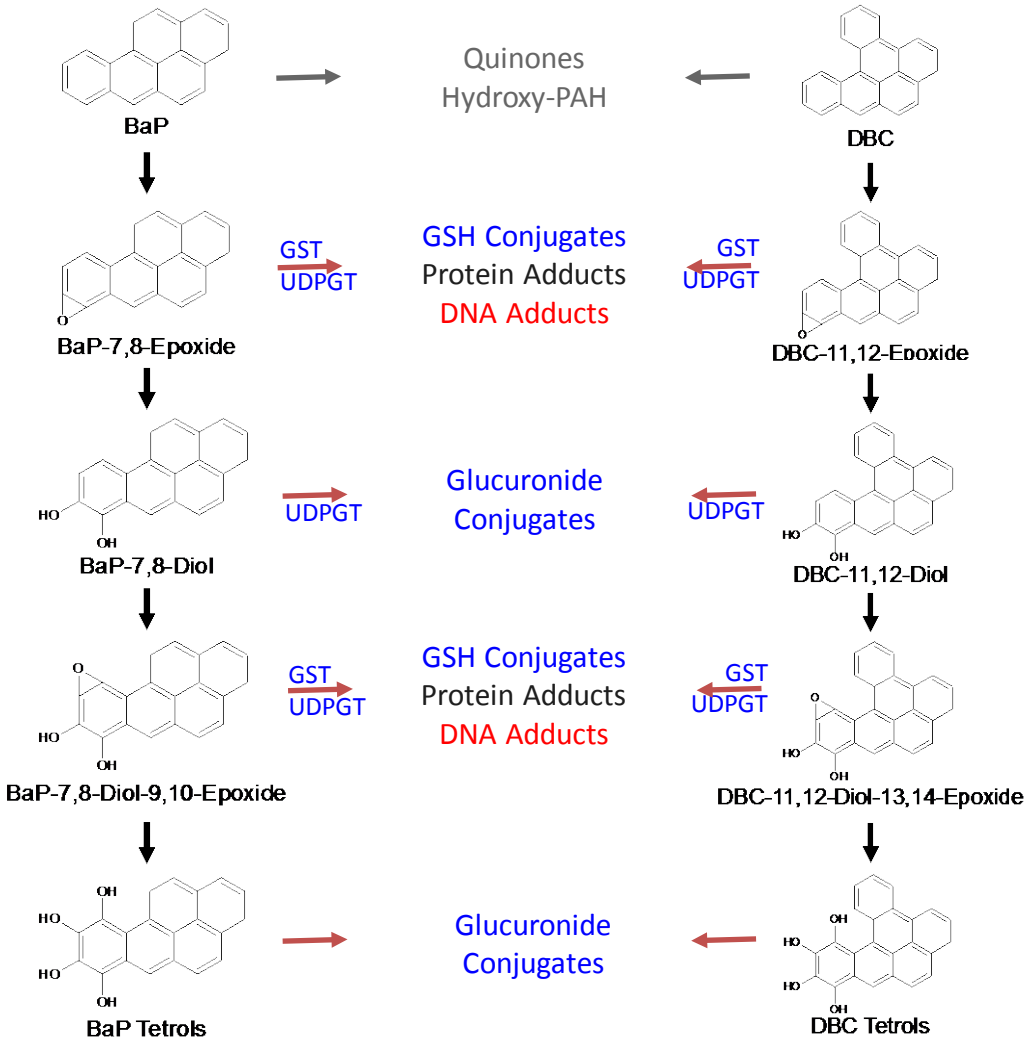
EPA (2013) Fig 1-6



NIEHS SRP Center

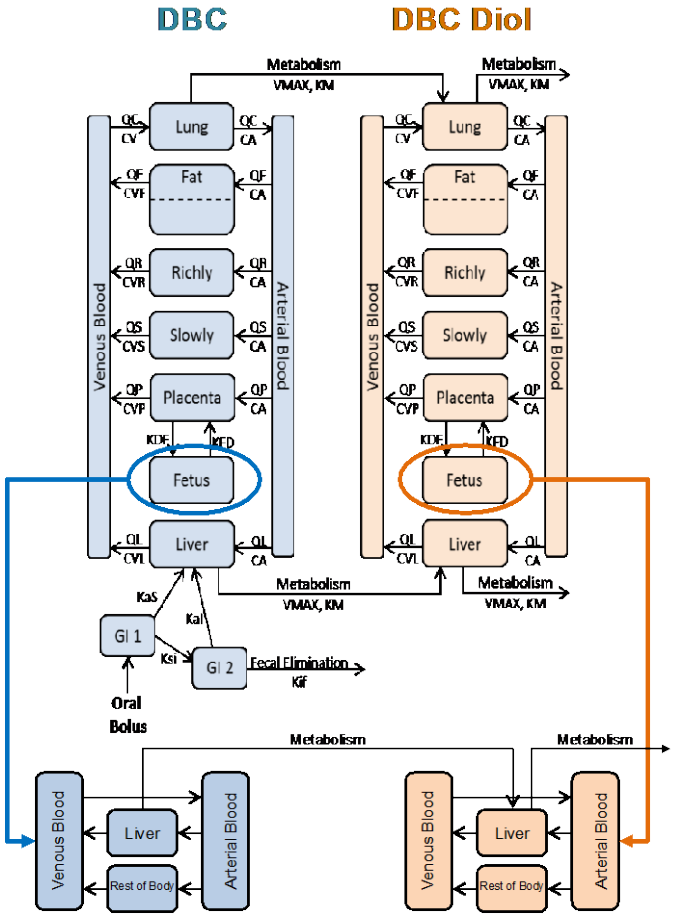
Project 2: Species & Life Stage Comparisons of PAH Dosimetry

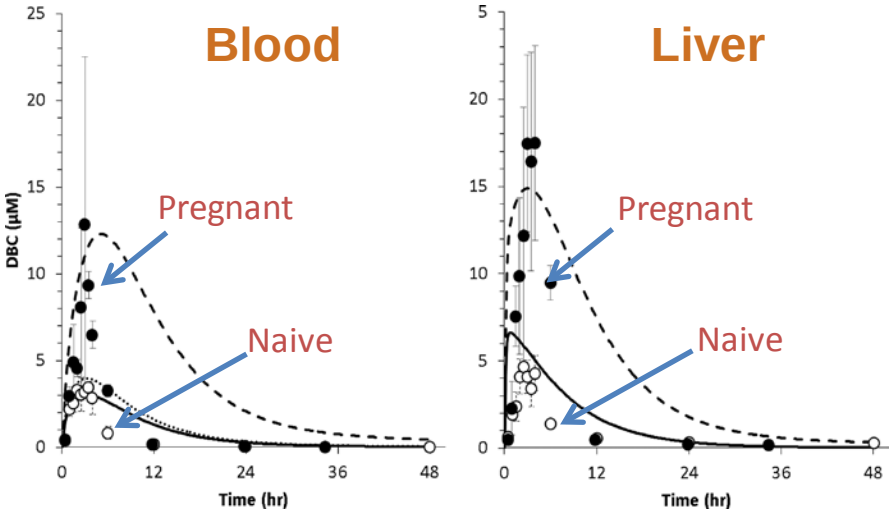
- Other than a few examples, surprisingly little is known about the toxicokinetics of high MW PAHs
  - Individually or as mixtures
  - Across species (esp. humans)
  - Across life stage
- Little is known about the ontogeny of "active" metabolic enzymes important to PAH activation vs. detoxification pathways across species
- **Goal:** Develop PBPK models that integrate species/life stage biology with PAH ADME processes to predict human dosimetry under realistic mixture exposure conditions

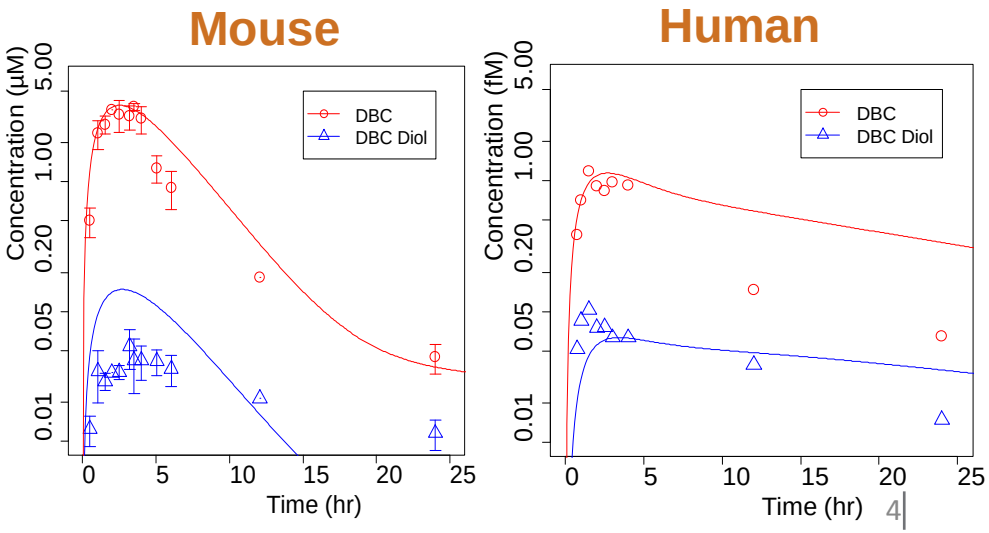


Without an integrated model, addressing the complexities of PAH metabolism is daunting

PAH PBPK Models







Crowell et al. (2013) *Toxicol. Appl. Pharmacol.* 257, 365-376
Crowell et al. (2014) *Toxicol. Sci.* 135, 48-62 (Best Paper, SOT-RASS)
Madeen et al. (2014) *Chem. Res. Toxicol*. 28, 126-134 (Editor's Choice)
Smith et al. (2016) Abst. #2234, SOT

Activity Based Protein Profiling

DNA → RNA → Protein Abundance → **Protein Activity / Function**

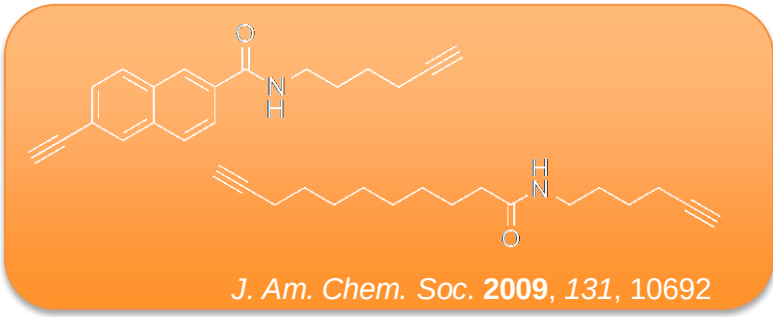
RT-PCR | *Global Proteomics* | ***Activity-Based Protein Profiling***

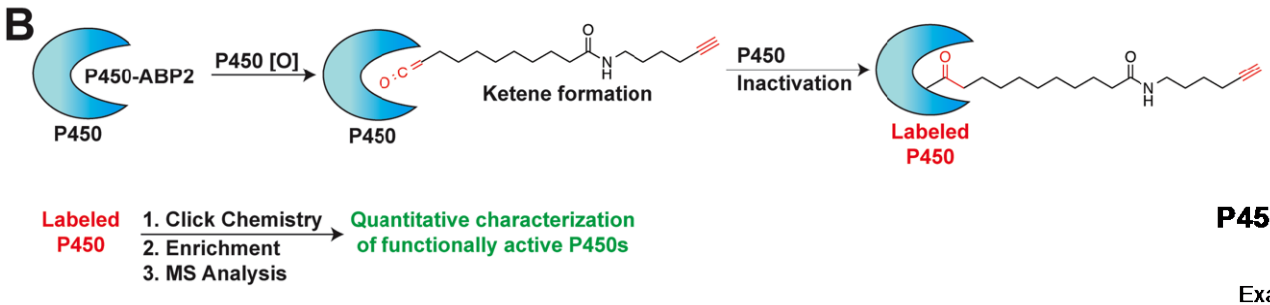
Active site directed chemical probes form irreversible covalent bonds to functionally active enzymes.

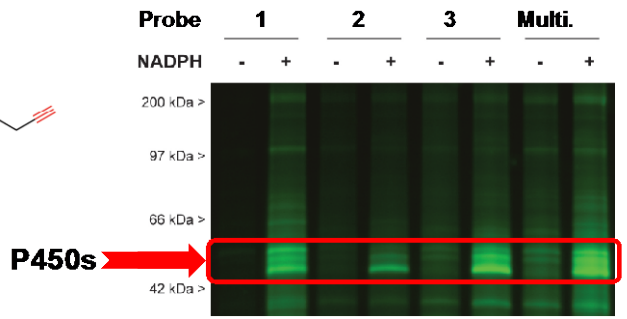
Reactive Group — **Aliphatic or Aromatic Alkyne**

Binding Region — **Polyaromatic or Aliphatic Hydrocarbon**

Reporter Tag







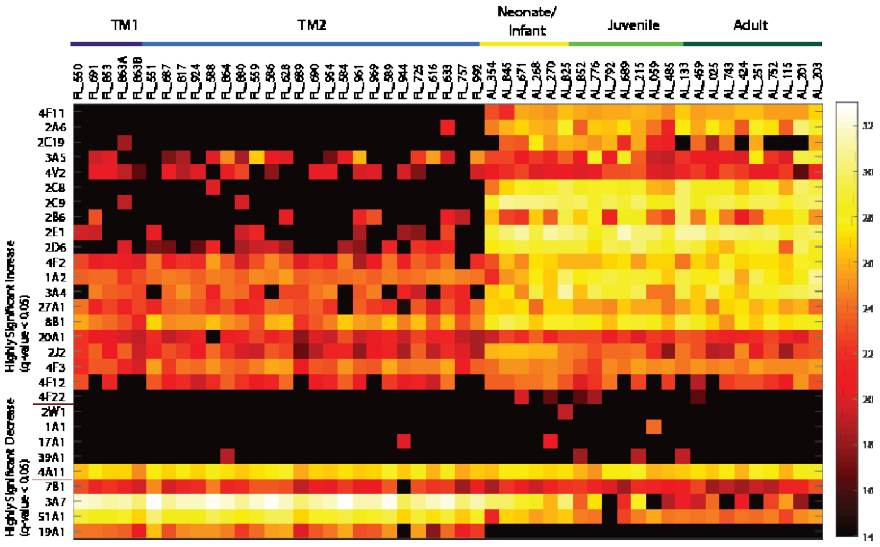
Example of labeled P450s in human liver microsomes. NADPH is required for functional activity. Multiplexing provides a thorough coverage of functional P450 space.

Major Findings

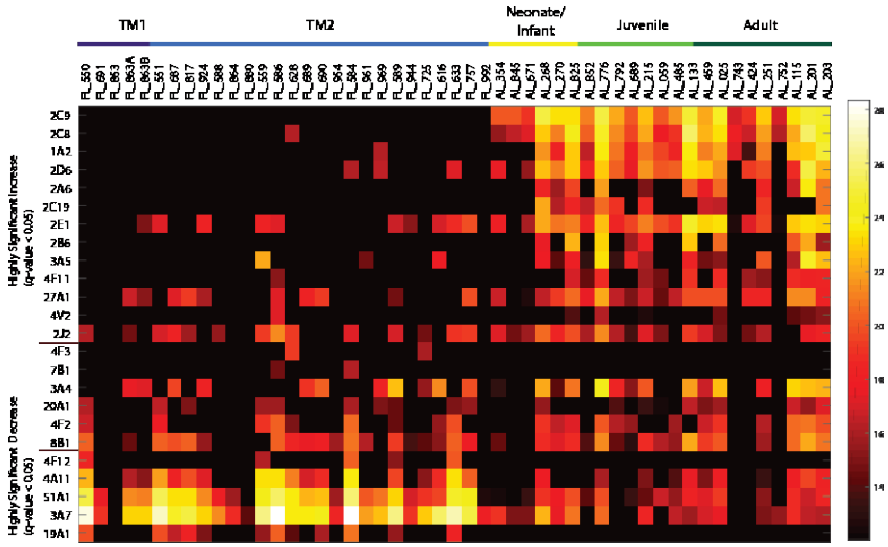
Activity Based Protein Profiling

- Human P450 ontogeny

Global Proteomics



Activity Based Proteomics



- CYP1A2 low levels of gene expression & total protein but no active protein
- CYP2D6 high gene expression but limited total and active protein
- CYP3A7 high active protein levels in fetus was replaced by 3A4/5 post-natal
- CYP1, 2, and 3 families generally low levels of active protein in fetus but higher post-natal

Sadler et al. (2016) *Drug Metab. Disp. In press*