Non-alcoholic fatty liver disease (NAFLD) is a public health crisis:
- Costs $103 billion/year
- Affects ~30% of the population

Diverse environmental exposures during development can program NAFLD in later life, and epigenetic mechanisms have been proposed as key mediators. Imprinted genes are a unique set of genes expressed from only one allele and are important in developmental programming because:
- Their dynamic nature of epigenetic regulation in development
- The persistence of their epigenetic state throughout life
- The critical roles they play in liver metabolism

We aim to determine whether the imprinted gene Zac1 plays a role in developmental Cd-induced NAFLD and study the underlying epigenetic mechanisms. Cd exposure is of concern because:
- It is one of the World Health Organization’s top ten toxicants of major public health concern
- It is released into the atmosphere at ~8,000 tons/year

Zac1 overexpression in vivo is independent of its methylation and imprinting status.

Zac1 is upregulated in our model of developmental Cd-induced NAFLD as are genes relevant to steatosis and fibrosis.

Figure 1. Histological analyses of control and CdCl2-exposed liver sections (A). Arrows indicate lipids in ORO and collagen in Sirius Red sections. The 50 ppm group showed significantly increased levels of triacylglycerides (B) and hydroxyproline (C) in the liver. Proportional liver mass was significantly increased for the 50 ppm group (D).

Figure 2. Genes relevant to the Zac1 network (A), steatosis (B), and fibrosis (C) pathways were upregulated in the 50 ppm group.

Conclusions
Overall, the data suggest:
- Cd exposure significantly increases liver weight in the high dose group at 3 weeks of age and leads to a NAFLD phenotype.
- Zac1 and pathways relevant to steatosis and fibrosis are up-regulated at 3 weeks of age.
- Zac1 dysregulation is independent of its epigenetic state.
- The transcription factor Zac1 may regulate genes relevant to steatosis.

Ongoing Work
Future goals are to:
- Determine if the application of Ppara or Ppara antagonists abrogate AML12 cell phenotype.
- Determine if Ppara and Ppara are directly controlled by Zac1 via ChIP.

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References