

Hepatic Steatosis Shifts Phase I Metabolism & Alters In Vitro Toxicant Susceptibility

P10
#2054



Tucker, NN1, Nelson GM2, Harrill JA2, Chorley BN2.

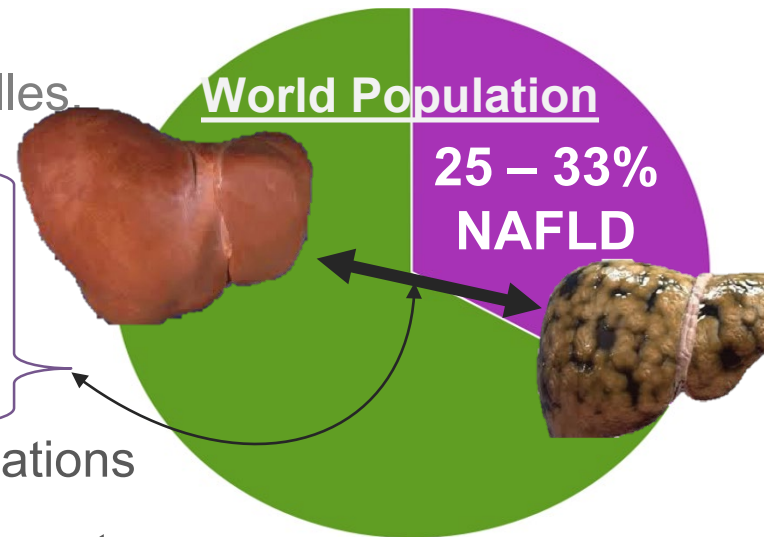
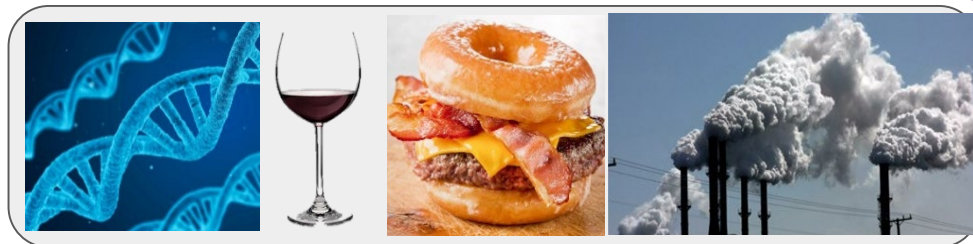
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This poster does not necessarily reflect EPA policy. Mention of trade names is not an endorsement or recommendation for use.



- **Prevalent** (~1/3rd of the world)
- **Fat builds up in liver cells:** displaces organelles, alters metabolism & cell function



- EPA is mandated to consider vulnerable populations
- Incorporate new approach methodologies & comp tox

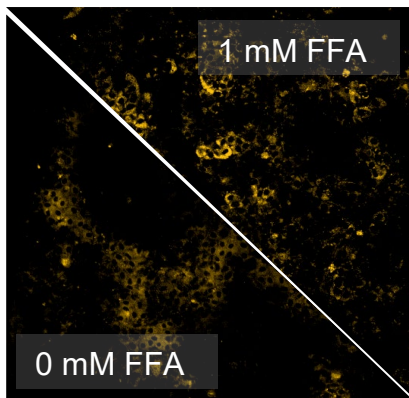
[Toxic Substances Control Act (1976) & Lautenberg Act (2016)]

Thomas et al. The Next Generation Blueprint of Computational Toxicology at the U.S. Environmental Protection Agency. *Toxicol Sci.* 2019;169(2):317-332. doi:10.1093/toxsci/kfz058

Establish an in vitro, high-throughput assay that assesses the impact of hepatic steatosis on chemical exposure susceptibility

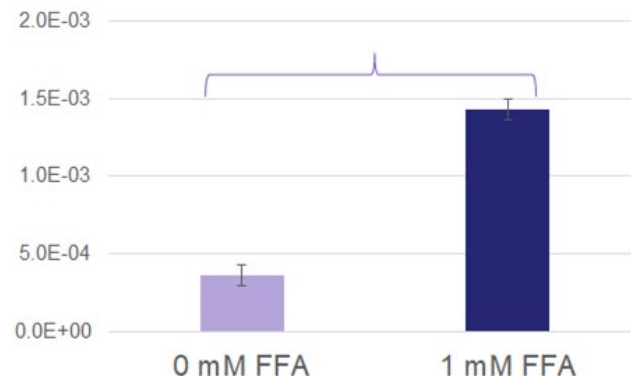
Establishing steatotic HepaRG cells

Creating steatotic HepaRG

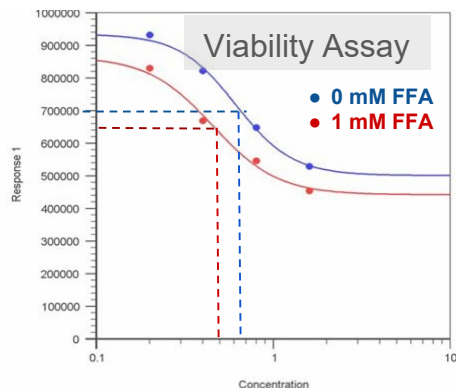


Visual comparative morphological change in steatosis, quantified. Hoechst [HO] nuclear stain and Nile Red [NR] triglyceride stain following 48h exposure to media containing 1 mM of a 1:2 oleate:palmitate free-fatty acid [FFA]. Figure on right demonstrates quantified lipid spots per cell.

Lipid Accumulation – Spot Count / Cell



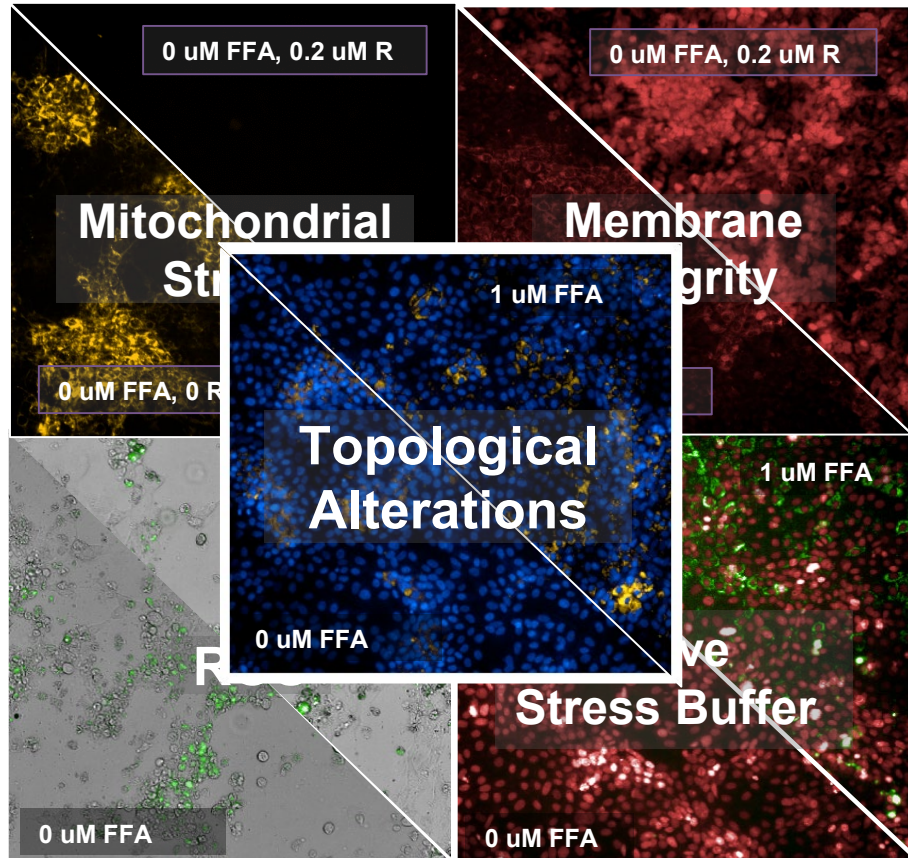
Measuring impact on chemical toxicity (Rotenone exposure)



Comparative IC50s

	ATP	LDH	Cell#
0 mM FFA	0.62	0.83	0.80
1 mM FFA	0.48	0.57	0.62

Establishing HC measurements and chemical screen



- Established steatotic HepaGR cell culture to assess high-throughput assay of chemical exposure susceptibility
- Established high-content imaging multiplexed assay to assess topological and mechanistic indicators of hepatotoxicity
- Current efforts to test chemical screen using reference panel of known CYP mediated toxicity/detoxification

The background of the slide is a composite of two fluorescence microscopy images. The left half shows a dense network of cells with bright blue nuclei and yellow cytoplasmic or extracellular staining. The right half shows a similar cellular structure but with blue nuclei and red staining, possibly indicating a different marker or a different region of the same sample.

Thank you for watching!

Visit with me for more details, or

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