NTP
National Toxicology Program

Lipid/Carbohydrate Breakout Group

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Breakout Group Participants

- **Sheila Collins,** CIIT Centers for Health Research **(Chair)**
- **Amy Brix,** Experimental Pathology Laboratories **(Rappateur)**
- **John Bauer,** Texas A&M University
- **Gary Boorman,** NIEHS
- **Rick Irwin,** NIEHS
- **Julian Leakey,** FDA/National Center for Toxicological Research
- **Nobuyo Maeda,** University of North Carolina at Chapel Hill
- **Kristina Thayer,** NIEHS
- **Greg Travlos,** NIEHS
- **Janice Wagner,** Wake Forest University
- **Philip Wood,** University of Alabama at Birmingham

Top 3 Recommendations

Potential Biomarkers	Useful for predicting human disease or increased risk of disease from rodent study	Detects tissue injury or altered function	Methods for human samples applicable to rodent specimens	Other Special Concerns: e.g., specific time (s) for biomarker measurement; additional animals needed	Add to routine tox screen/ special studies/ or none
Cholesterol/ triglycerides	TC – yes TGs - yes	Yes	Yes	$	Routine
Insulin	Yes	Yes	Yes, but must use rodent specific	$$$, more sensitive indicator of IR than glucose	Routine
GSH (reduced glutathione)	Yes	Yes (oxidative stress)	Yes	Assay should be done on whole blood or RBCs (EDTA?)	Routine (not specific for lipid/CHO disorders)

$ = cheap; $$ = more; $$$, $$$$ etc.

Recommendations 4 – 6

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Body composition (fat/lean) (DXA analysis)	Yes	Yes	Animals must be immobilized; can do antemortem liver fat analysis (CT)	With dxa get lean mass/fat mass and bone density, can also do microCT (faster than DXA), CT can also differentiate visceral from subcutaneous fat	Special studies or subset of routine, also consider interim time-points, ♂
Triglyceride/cholesterol/fatty acid (liver)	Yes	Yes	Yes	TG in liver more important than TC, if no change in serum cholesterol, not worth doing liver TC; FAs not very informative	Routine - Histologic analysis to separate microvesicular from macrovesicular fatty change; special studies for TG determinations
Sterol regulatory element - binding proteins -1 & 2 (SREBP -1 & 2) (liver, adipose)	Yes	Yes	Cleaved, nuclear form (molecular weight specific form); nuclear isolation would be best, immunohistochemistry would be ideal technique	Will indicate early events in cholesterol and fatty acid synthesis;SREBP -2 tends to go with cholesterol; SREBP -1 with FAs	Routine, especially if histochemistry can be developed, do liver first (before adipose tissue)

Other Recommendations

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Tumor necrosis factor alpha	Yes	Yes	Rodent specific ELISA (available)	$$$$	Special studies; could be routine
Interleukin -6	Yes	Yes	Yes	IL-6/IL-1	Special studies; could be routine
Glucose	Yes	Yes	Yes		Already there

Other recommendations or comments

- Consider using sensitive strains of mice/rats for certain studies, e.g. genetically altered mice, BL/6 mouse, B6BTBRF1 mouse
  - Use for examining the impact of environmental exposure on particular disease (e.g. obesity, insulin resistance)
  - Monogenic models, such as the Zucker/fa/fa may not be as useful for routine screening
- Consider fasting animals prior to sampling and terminal sacrifice consider drawing blood in afternoon for mice after removing feed in the morning or changing animals to different cages; fasting rats by pulling food overnight
- Consider using custom diets for specific studies (has been done for recent endocrine disruptor studies by NCTR)
  - Eliminate interference by isoflavones
- Separate macrovesicular from microvesicular fatty change during routine histopathology