

## Mechanisms of Peroxisome Proliferator-Induced Hepatocarcinogenesis

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A variety of chemicals (including certain phthalate esters, chlorinated solvents, herbicides, and drugs) that have diverse structure and application cause proliferation of peroxisomes in the livers of rodents. Hepatocellular neoplasms usually develop in treated rodents following continuous administration of any of these peroxisome proliferators (PP). Because of widespread human exposure to carcinogenic PP, it is important to improve PP cancer risk assessments that rely upon extrapolation of rodent carcinogenicity data to predict human cancer risk. While the mechanism of rodent carcinogenicity is unknown, chronic modulation of cell growth and peroxisome proliferation, associated oxidative stress, and DNA damage may be involved. Research conducted at CIIT examined the importance of peroxisome proliferator-activated receptor (PPAR) activation and alteration of growth regulatory pathways for PP-induced carcinogenesis in wild-type and PPAR-knockout mice. Tumor necrosis factor (TNF) alpha and other cytokines have been hypothesized to act as mitogens in PP-induced acute liver cell proliferation and may play a role in PP-induced carcinogenesis. CIIT scientists tested this hypothesis by correlating a number of endpoints with hepatocyte growth and PP-induced carcinogenesis including (1) TNF-induced sphingolipid signaling, (2) cytokine signaling pathways, and (3) alterations in the expression of growth regulatory genes. Other studies evaluated the interaction of heat as an environmental stressor in PPAR-induced responses including induction of heat shock proteins and apoptosis. Data derived from these studies has provided key information about the most likely mechanism of PP-induced carcinogenesis in rodents and will provide appropriate endpoints to assess in human tissues. Preparation of other manuscripts associated with this project is progressing.

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### Presentations:

Anderson, S. P., Howroyd, P., Liu, J., Qian, X., Bahnemann, R., Swanson, C., Kwak, M., Kensler, T. W., and Corton, J. C. (2005). The transcriptional response to a peroxisome proliferator-activated receptor alpha agonist includes increased expression of proteome maintenance genes. *The Toxicologist* 84(S-1): 12. (Abstract 58).

Corton, J. C., Apte, U., Anderson, S. P., Limaye, P., Yoon, L., Latendresse, J., Everitt, J., Voss, K. A., Kimbrough, C., Wong, J. S., Gill, S. S., Chandraratna, R. A., Kwak, M., Kensler, T. W., Stulnig, T. M., Steffensen, K. R., Gustafsson, J., and Mehendale, H. M. (2005). Role of pparalpha in caloric restriction effects in the mouse liver. *The Toxicologist* 84(S-1): 12. (Abstract 59).

Howroyd, P., Swanson, C., Dunn, C., Cattley, R. C., and Corton, J. C. (2005). Decreased longevity and enhancement of age-dependent lesions in mice lacking the nuclear receptor peroxisome proliferator-activated receptor alpha. *The Toxicologist* 84 (S-1): 119. (Abstract 581).

Laughter, A., Anderson, S. P., Dunn, C., Yoon, L., Swanson, C., Chandraratna, R., Stulnig, T. M., Steffensen, K. R., Gustafsson, J., and Corton, J. C. (2005). Overlapping transcriptional programs regulated by the nuclear receptors peroxisome proliferator-activated receptor alpha, retinoid X receptor and liver X receptor in mouse liver. *The Toxicologist* 84(S-1): 12. (Abstract 57).

Stauber, A. J., Liu, J., Waalkes, M. P., Brown-Borg, H., Voss, K. A., Kopchick, J. J., and Corton, J. C. (2005). Constitutive expression of peroxisome proliferator-activated receptor alpha-regulated genes in dwarf mice. *The Toxicologist* 84(S-1): 119. (Abstract 582).

Xiao, S., Anderson, S. P., Swanson, C., Bahnemann, R., Voss, K. A., Stauber, A. J., and Corton, J. C. (2005). Activation of peroxisome proliferator-activated receptor alpha enhances hepatocyte apoptosis. *The Toxicologist* 84(S-1): 469. (Abstract 2286).

Anderson, S. P., Swanson, C., Everitt, J., and Corton, J. C. (2003). PPAR alpha plays a major role in determining the gene expression profile altered by caloric restriction. *The Toxicologist* 72(1): 340. (Abstract 1652).

Corton, J. C., Anderson, S. P., Stauber, A. J., Laughter, A., Swanson, C., Xiao, S., Everitt, J., and Voss, K. (2003). PPAR alpha-dependent alterations in chemical-induced stress and longevity correlates with increased expression of heat shock proteins. *The Toxicologist* 72(1): 340. (Abstract 1650).

Kinser, S., Jia, Q., Laughter, A., Cornwell, P., Corton, C., and Pestka, J. (2003). Effects of dietary omega-3 fatty acids on deoxynivalenol-induced global gene expression in vivo. *The Toxicologist* 72(1): 374. (Abstract 1816).

Voss, K., Owen, J. R., Laughter, A., Dunn, C., Anderson, S. P., Riley, R., Miller, D., and Corton, J. C. (2003). Role of the peroxisome proliferator-activated receptor alpha in modulating the effects of fumonisin B1 in mouse liver. *The Toxicologist* 72(1): 7. (Abstract 36).

Merrick, B. A., Dixon, D., Corton, C., Bushel, P., Witzmann, F. A., and Rabatin, S. (2002). Toxicity profiling of genes and proteins by toxicologists: advanced topics in toxicogenomics. *The Toxicologist* 66(1): 3. (Abstract 12).

Xiao, S., Bahnemann, R., Laughter, A., Stauber, A. J., and Corton, J. C. (2002). Peroxisome proliferator-activated receptor alpha enhances susceptibility to apoptosis inducers in mouse liver. *The Toxicologist* 66(1): 59. (Abstract 288).

Corton, J. C., Laughter, A., Lucas, J. T., Dunn, C., and Stauber, A. J. (2001). The role of the peroxisome proliferator-activated receptor alpha in mediating the effects of trichloroethylene, dichloroacetate, and trichloroacetate. *The Toxicologist* 60(1): 159. (Abstract 755).

Laughter, A., Dunn, C., Stauber, A. J., Voss, K. A., Riley, R., and Corton, J. C. (2001). The role of the peroxisome proliferator-activated receptor alpha and tumor necrosis alpha in modulating the effects of fumonisin in mouse liver. *The Toxicologist* 60(1): 159. (Abstract 756).

Rusyn, I., Denisseko, M. F., Wong, V. A., Butterworth, B. E., Cunningham, M. L., Upton, P. B., Thurman, R. G., and Swenberg, J. A. (2001). Role of oxidative stress to DNA in carcinogenicity of peroxisome proliferators: new evidence from studies of base excision repair enzymes. *The Toxicologist* 54(1): 160. (Abstract 761).

Anderson, S. P., Dunn, C. S., Cattley, R. C., and Corton, J. C. (2000). Hepatic mitogenesis and carcinogenesis induced by peroxisome proliferators is associated with alterations in IL-1b signaling pathways. *The Toxicologist* 54(1): 420. (Abstract 1976).

Chen, C., Silva, V. M., Corton, J. C., Whiteley, H., and Manautou, I. E. (2000). PPAR $\alpha$  knockout mice are not protected against acetaminophen (APAP) hepatotoxicity by clofibrate (CFB) pretreatment. *The Toxicologist* 54(1): 42. (Abstract 203).

Valles, E. G., Laughter, A., Dunn, C., Cattley, R. C., and Corton, J. C. (2000). Role of PPAR alpha in hepatic responses to diisononyl phthalate (DINP). *The Toxicologist* 54(1): 418. (Abstract 1967).

Corton, J. C., Stauber, A. J., Anderson, S. P., Fan, L. Q., and Cattley, R. C. (1999). Characterization of signaling pathways induced by peroxisome proliferators using null mouse models and cDNA arrays. *The Toxicologist* 48(1): 271. (Abstract 1280).

Lapinskas, P. J., Swanson, C., Smith, M., and Corton, J. C. (1999). Characterization of signal cross-talk between the peroxisome proliferator-activated receptor alpha and sphingomyelinase pathways. *The Toxicologist* 48(1): 250. (Abstract 1081).

Stauber, A. J., Anderson, S. P., Fan, L. Q., Conolly, R., Preston, J., and Corton, J. C. (1999). A strategy for associating peroxisome proliferator-induced hepatocellular changes with patterns of gene expression. *The Toxicologist* 48(1): 233. (Abstract 1096).

Thurman, R. G., Rose, M. L., and Cattley, R. C. (1999) Dietary glycine prevents the development of liver tumors caused by the peroxisome proliferator WY-14,643. *The Toxicologist* 48(1): 346. (Abstract 1634).

Peer-reviewed publications:

Voss, K. A., Riley, R., Dunn, C., and Corton, J. C. (2006). The role of tumor necrosis factor alpha and the peroxisome proliferator-activated receptor alpha in modulating the effects of fumonisin in mouse liver. *Toxicology* 222: 165–174.

Lapinskas, P. J., Brown, S., Leesnitzer, L. M., Blanchard, S., Swanson, C., Cattley, R. C., and Corton, J. C. (2005). Role of PPARalpha in mediating the effects of phthalates and metabolites in the liver. *Toxicology* 207: 149–163.

Stauber, A. J., Brown-Borg, H., Liu, J., Waalkes, M. P., Laughter, A., Staben, R. A., Coley, J. C., Swanson, C., Voss, K. A., Kopchick, J. J., and Corton, J. C. (2005). Constitutive expression of peroxisome proliferator-activated receptor alpha-regulated genes in dwarf mice. *Mol. Pharmacol.* 67: 681–694.

Anderson, S. P., Dunn, C., Laughter, A., Yoon, K., Swanson, C., Stulnig, T. M., Steffensen, K. R., Chandraratna, R. A. S., Gustafsson, J.-A., and Corton, J. C. (2004). Overlapping transcriptional programs regulated by the nuclear receptors peroxisome proliferator-activated receptor (alpha), retinoid X receptor, and liver X receptor in mouse liver. *Mol. Pharmacol.* 66: 1440–1452.

Andersen, S. P., Howroyd, P., Liu, J., Qian, X., Bahnemann, R., Swanson, C., Kwak, M.-K., Kensler, T. W., and Corton, J. C. (2004). The transcriptional response to a peroxisome proliferator-activated receptor alpha agonist includes increased expression of proteome maintenance genes. *J. Biol. Chem.* 279: 52390–52398.

Corton, J. C., Apte, U., Anderson, S. P., Limaye, P., Yoon, L., Latendresse, J., Dunn, C., Everitt, J. I., Voss, K. A., Swanson, C., Kimbrough, C., Wong, J. S., Gill, S. S., Chandraratna, R. A. S., Kwak, M.-K., Kensler, T. W., Stulnig, T. M., Steffensen, K. R., Gustafsson, J.-A., and Mehendale, H. M. (2004). Mimetics of caloric restriction include agonists of lipid-activated nuclear receptors. *J. Biol. Chem.* 44: 46204–46212.

Fan, L.-Q., Brown-Borg, H., Brown, S., Westin, S., Mode, A., and Corton, J. C. (2004). PPARalpha activators down-regulate CYP2C7, a retinoic acid and testosterone hydroxylase. *Toxicology* 203: 41–48.

Fan, L.-Q., You, L., Brown-Borg, J., Brown, S., Edwards, R. J., and Corton, J. C. (2004). Regulation of phase I and phase II steroid metabolism enzymes by PPARalpha activators. *Toxicology* 204: 109–121.

Howroyd, P., Swanson, C., Dunn, C., Cattley, R. C., and Corton, J. C. (2004). Decreased longevity and enhancement of age-dependent lesions in mice lacking the nuclear receptor peroxisome proliferator-activated receptor  $\alpha$  (PPAR $\alpha$ ). *Toxicol. Pathol.* 32: 591–599.

Laughter, A. R., Dunn, C. S., Swanson, C. L., Howroyd, P., Cattley, R. C., and Corton, J. C. (2004). Role of the peroxisome proliferator-activated receptor alpha (PPARalpha) in responses to trichloroethylene and metabolites, trichloroacetate and dichloroacetate in mouse liver. *Toxicology* 203: 83–98.

Stauber, A. J., Brown-Borg, H., Liu, J., Waalkes, M. P., Laughter, A., Staben, R. A., Coley, J. C., Swanson, C., Voss, K. A., Kopchick, J. J., and Corton, J. C. (2005). Constitutive expression of peroxisome proliferators-activated receptor alpha-regulated genes in dwarf mice. *Mol. Pharmacol.* 67(3): 681–694.

Fan, L-Q., Coley, J., Miller, R. T., Cattley, R. C., and Corton, J. C. (2003). Opposing mechanisms of NADPH-cytochrome P450 oxidoreductase regulation by peroxisome proliferators. *Biochem. Pharmacol.* 65(6): 949–959.

Shankar, K., Vaidya, V. S., Corton, J. C., Bucci, T. J., Liu, J., Waalkes, M. P., and Mehendale, H. M. (2003). Activation of PPAR $\alpha$  in streptozotocin-induced diabetes is essential for resistance against acetaminophen toxicity. *FASEB J.* 17(2): 1748–1750.

Valles, E. G., Laughter, A. R., Dunn, C. S., Cannelle, S., Swanson, C. L., Cattley, R. C., and Corton, J. C. (2003). Role of the peroxisome proliferators-activated receptor  $\alpha$  in responses to the hepatocarcinogenic phthalate, diisononyl phthalate (DINP). *Toxicology* 191(2–3): 211–225.

Anderson, S. P., Yoon, L., Richard, E. B., Dunn, C. S., Cattley, R. C., and Corton, J. C. (2002). Delayed liver regeneration in peroxisome proliferator-activated receptor-a-null mice. *Hepatology* 36: 544–554.

Gazouli, M., Yao, Z-X., Boujrad, N., Corton, J. C., Culty, M., and Papadopoulos, V. (2002). Effect of peroxisome proliferators on Leydig cell peripheral-type benzodiazepine receptor gene expression, hormone-stimulated cholesterol transport, and steroidogenesis: role of the peroxisome proliferator-activator receptor  $\alpha$ . *Endocrinology* 143: 2571–2583.

Muoio, D. M., MacLean, P. S., Lang, D. B., Li, S., Houmard, J. A., Way, J. M., Winegar, D. A., Corton, J. C., Dohm, G. L., and Kraus, W. E. (2002). Fatty acid homeostasis and induction of lipid regulatory genes in skeletal muscles of peroxisome proliferator-activated receptor (PPAR) a knock-out mice. Evidence for compensatory regulation by PPAR d. *J. Biol. Chem.* 277: 26089–26097.

Anderson, S. P., Dunn, C. S., Cattley, R. C., and Corton, J. C. (2001). Hepatocellular proliferation in response to a peroxisome proliferator does not require TNF $\alpha$  signaling. *Carcinogenesis* 22: 1843–1851.

Miller, R. T., Scappino, L. A., Long, S. M., and Corton, J. C. (2001). Role of thyroid hormones in hepatic effects of peroxisome proliferators. *Toxicol. Pathol.* 29: 149–155.

Poole, M., Bridgers, K., Alexson, S. E. H., and Corton, J. C. (2001). Altered expression of the carboxylesterases ES-4 and ES-10 by peroxisome proliferator chemicals. *Toxicology* 165: 109–119.

Chen, C., Henning, G. E., Whiteley, H. E., Corton, J. C., and Manautou, J. E. (2000). Peroxisome proliferator-activated receptor alpha-null mice lack resistance to acetaminophen hepatotoxicity following clofibrate exposure. *Toxicol. Sci.* 57: 338–344.

Corton, J. C., Anderson, S. P., and Stauber, A. (2000). Central role of peroxisome proliferator-activated receptors in the actions of peroxisome proliferators. *Annu. Rev. Pharmacol. Toxicol.* 40: 491–518.

Corton, J. C., Lapinskas, P. J., and Gonzalez, F. J. (2000). Central role of PPARalpha in the mechanism of action of hepatocarcinogenic peroxisome proliferators. *Mutat. Res.* 448: 139–151.

Miller, R. T., Anderson, S. P., Corton, J. C., and Cattley, R. C. (2000). Apoptosis, mitosis and cyclophilin-40 expression in regressing peroxisome proliferator-induced adenomas. *Carcinogenesis* 21: 647–652.

Other publication(s):

Lapinskas, P. J. and Corton, J. C. (1999). Molecular mechanisms of hepatocarcinogenic peroxisome proliferators. In *Molecular Biology of the Toxic Response* (Puga, A., and Wallace, K. B., editors), pp. 219–253. Taylor & Francis, Philadelphia, PA.

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