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## Wnt signaling in hepatocellular carcinoma, an emerging epidemic: Gene up regulation of Wnt 5a pathways with toll receptor 4 with moderated magnetic fields on human stem cells and mice and high dose vitamin D3 prevention

Liver cancer (HCC) is increasing in the USA and around the world. Although there is now effective therapy for Hepatitis C, fatty liver (NAFLD/NASH) has no recognized medical therapy other than weight loss. However, Metformin and PPAR gamma agonist have been associated with lower risk and improved prognosis of HCC. More than 95% of patients with HCC have either upregulation in the signaling protein Wnt or its receptor Frizzled, or down-regulation of Frizzled receptors making the Wnt/ $\beta$ -Catenin pathway a potential important therapeutic target according to an article in the *Journal for Cancer Research*. Current strategies for disrupting Wnt signaling include monoclonal antibodies against Wnt protein or the Frizzled receptor using soluble receptors for Frizzled to neutralize Wnt. Another approach is by using GPC3 a heparin sulfate proteoglycans that act as Wnt co-receptors of modulators. We will discuss the WNT/ $\beta$ -Catenin pathway and then review the many genes (polygenetics) in obesity and fatty liver (NAFLD/ NASH) and the epigenetics of methylation involved in NASH and HCC. Additionally the mitochondrial defects seen in the metabolic syndrome will be discussed. Until recently, this hypothesis that has received little attention and that is the mitochondrial defects seen in metabolic syndromes or diabetes 2, fatty liver and insulin resistance. In our past experiments, moderate magnetic fields of 0.5T change 2,500 gene expressions with dramatic changes in mouse morphology, liver fat and metabolism. Genes involved in Wnt signaling were down regulated in NASH but have been up-regulated in HCC. Research of the author in mice and humans will be reviewed and gene array analysis of human embryonic stem cells in another experiment of 0.23-0.28 T static magnetic fields by Wang and Yarema collaborators at JHU will be discussed. Up-regulation of genes for insulin factors genes, peroxisome proliferative activity receptor were increased, and calcium channel gene and other genes for mitochondrial ribosomal protein S, and uncoupling protein 2. Down-regulation of tumor necrosis factor alpha and up- regulation of TLR 4 via Wnt signaling and interleukin 6 were demonstrated for this transformation. A methylated gene in obesity has recently been published by Su which is also affected. Mitochondrial dysfunction in obesity, fatty liver and NASH has previously been described. Forkhead transcription factors are also up-regulated at 5 days. Of the 47 genes up regulated in NASH by a study by Bertola. 13 were identified as down-regulated by SMF and 2 up-regulated. Genes for fibrosis are also down-regulated. The use of high dose vitamin D3 in prevention will be discussed starting with the European Prospective Investigation into Cancer and Nutrition publication and then the vitamin D signaling pathways as potential for anticancer therapeutics with their potential as anticancer agents because their administration has antiproliferative effects, activation of apoptotic pathways and inhibition angiogenesis.

### Biography

Trent W Nichols Jr. MD is an internist, nutritionist, and gastroenterologist with more than 30 years of clinical experience. He is the Founder and Director of the CNDD and the Advanced Magnetic Research Institute in Hanover, Pennsylvania. He is a graduate of the University of Denver with a BS in Chemistry and Northwestern University with a MD. His Post-graduate education medicine was at Northwestern University in Internal Medicine and Fellowship in Gastroenterology and Hepatology. He has been the lead investigator in over 50 pharmaceutical trials and has worked for the Veterans Administration, Kaiser Permanente, Good Samaritan Hospital in Lebanon PA, and Sinai Hospital in Baltimore MD. He is a member of the American Gastroenterology Association, Society for Neuroscience, and Bioelectromagnetic Society. He is on the editorial panel of the *Journal of Liver OMICS* and has been active researcher in the role of mitochondrial dysfunction in liver disease and therapy with EMF.

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