

LIVER FIBROSIS RESEARCH WITH NON-LINEAR OPTICS

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- 1. LIVER FIBROSIS PROGRESSION OR REGRESSION:** Liver fibrosis/cirrhosis is a major healthcare challenge in Asia. It arises from chronic injury to liver leading to failure to disassemble the normal repair apparatus, leaving behind excessive extra-cellular matrices (ECM), activated hepatic stellate cells (HSC) and damaged parenchymal structures [1]. We focused on the key molecular and cellular events between fibrosis progression and regression. We have constructed an *in silico* model, *in vitro* co-culture of hepatocytes and HSC, and *in vivo* rat fibrosis models. We discovered a key TGF- β 1 activation switch that involves HSC and hepatocytes where HSC supports fibrosis progression while hepatocytes support regression. Hepatocytes maintain spatially dominant effects over HSC in normal liver but excessive ECM or parenchymal damages inhibit the dominant effects allowing fibrotic cores to expand to cirrhosis (connected fibrotic cores). Local administration of hepatocytes reverse the process.
- 2. QUANTITATIVE IMAGING WITH NON-LINEAR OPTICS:** We have enhanced a non-linear optical microscope with pulse-modulation to image the ECM (especially the weak ones distributed in liver parenchyma) and cellular/tissue structures [2]. We have developed image analysis algorithms to integrate the spatial relationship between ECM and cellular/tissue structures for quantification and statistical feature analysis. These allow quantification of molecular and cellular events in liver fibrosis with spatial precisions. We preliminarily demonstrate the spatially-coordinated fibrosis progression in etiology-dependent manner.
- 3. HIGH SPEED NON-LINEAR OPTICS IN LIVER FIBROSIS:** To test the hypothesis that the key molecular switch events between liver fibrosis progression and regression occur in spatially-coordinated manners highly dependent on local and global distribution of ECM and cellular/tissue structures, we are developing a high speed non-linear optical microscope for quantifying ECM and cellular/tissue structures in label-free manner on the entire liver lobe; with region-of-interest retained for subsequent molecular investigations. The multi-scale tissue informatics platform will also be applicable in redefining the diagnostic and therapeutic monitoring practices in clinical applications.
- 4. REFERENCES:**
 1. Bataller, R. and D.A. Brenner, "Liver fibrosis". *J Clin Invest*, **115**(2): p. 209-18 (2005).
 2. Tai, D.C., et al., "Fibro-C-Index: comprehensive, morphology-based quantification of liver fibrosis using second harmonic generation and two-photon microscopy". *J Biomed Opt*, **14**(4): p. 044013 (2009).