

Stanford



Natalie Torok

Professor of Medicine (Gastroenterology and Hepatology)
Medicine - Gastroenterology & Hepatology

CLINICAL OFFICE (PRIMARY)

- Liver Transplant Clinic
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ACADEMIC CONTACT INFORMATION

- Alternate Contact
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Bio

BIO

Our primary research interest is in the pathomechanisms of liver fibrosis and matrix remodeling, and their role in the development of hepatocellular carcinoma. Clinically, metabolic dysfunction associated steatohepatitis (MASH) is becoming the leading cause of chronic liver disease and liver cancer, and we are interested in deciphering how dynamic changes in the liver matrix accelerate this process in certain conditions such as type 2 diabetes. Of particular interest are studies on collagen architecture and connectivity and how these are implicated in mechanosensing. We are also focusing on aging-related pathways and wound healing processes. We are exploring the age-related modulation of hepatocyte stress signals, metabolic changes, and how these intersect with innate immune responses and matrix modulation in the liver. Based on these studies we have identified targets for novel small molecule inhibitors to treat fibrosis, and are performing investigator-initiated clinical trials. As MASH is becoming the most common liver disease in the US and worldwide our ultimate goal is to target high-risk populations, and to develop novel therapeutic approaches that reverse fibrosis and improve patient outcomes.

CLINICAL FOCUS

- Gastroenterology
- Hepatology
- Liver transplant

ACADEMIC APPOINTMENTS

- Professor - University Medical Line, Medicine - Gastroenterology & Hepatology
- Member, Bio-X
- Member, Maternal & Child Health Research Institute (MCHRI)
- Member, Stanford Cancer Institute

HONORS AND AWARDS

- Fellow, American Association for Studies of Liver Diseases (2016)
- elected member, American Society for Clinical Investigation (2014)

- Boris Ruebner and John Rosenquist Excellence in Teaching Award, UC Davis (2014)

BOARDS, ADVISORY COMMITTEES, PROFESSIONAL ORGANIZATIONS

- Associate Editor, Hepatology (2021 - present)
- Associate Editor, Seminars in Liver Disease (2017 - present)
- Associate Editor, Hepatology Communications (2017 - 2021)
- Associate Editor, American Journal of Physiology Gastrointestinal and Liver Physiology (2015 - 2018)
- Data Monitoring Committee, NASH Clinical Research Network, NIH (2012 - present)
- Regular member, NIH HBPP Study Section (2012 - 2016)

PROFESSIONAL EDUCATION

- Board Certification: Gastroenterology, American Board of Internal Medicine (2003)
- Residency: Mayo Clinic Internal Medicine Residency (1999) MN
- Board Certification, American Board of Internal Medicine , Gastroenterology (2004)
- Fellowship: Mayo Clinic Gastroenterology Fellowship (2003) MN
- Medical Education: Semmelweis Univ Med School (1988) Hungary

Research & Scholarship

CURRENT RESEARCH AND SCHOLARLY INTERESTS

Our laboratory focuses on the mechanism of liver fibrosis in metabolic associated steatohepatitis (MASH), and hepatocellular carcinoma (HCC). We are particularly interested in clinical conditions that are linked to accelerated fibrosis and higher cancer risk such as aging and type 2 diabetes (T2DM). Our goal is to uncover how biomechanical changes in the extracellular matrix (ECM), in particular, viscoelasticity affect mechano-sensation, and how these pathways could ultimately be targeted. We are exploring the changes in collagen architecture and the effects on viscoelasticity, guiding cancer invasion. We are also interested in aging, dysregulation of metabolic pathways and mitochondrial function and how these intersect with matrix changes in MASH and HCC.

Our other major focus is primary sclerosing cholangitis, to define early matrix changes and mechano-sensation. Our ultimate goal is translation and to develop new treatment approaches that reverse fibrosis and improve patient outcomes. To this end we have conducted two investigator-initiated clinical trials exploring novel treatment and diagnostic strategies in MASH.

CLINICAL TRIALS

- Novel MRE Technique to Assess a Risk Factor for Liver Cancer, Not Recruiting
- Study of Oral Idebenone to Treat Non-Alcoholic Steatohepatitis, Not Recruiting

Teaching

STANFORD ADVISEES

Postdoctoral Faculty Sponsor

Petronela Buiga, Weiguo Fan, TZU HAN LO

Postdoctoral Research Mentor

Weiguo Fan

GRADUATE AND FELLOWSHIP PROGRAM AFFILIATIONS

- Gastroenterology & Hepatology (Fellowship Program)

Publications

PUBLICATIONS

- **Matrix viscoelasticity promotes liver cancer progression in the pre-cirrhotic liver.** *Nature*
Fan, W., Adebawale, K., Váncza, L., Li, Y., Rabbi, M. F., Kunimoto, K., Chen, D., Mozes, G., Chiu, D. K., Li, Y., Tao, J., Wei, Y., Adeniji, et al
2024
- **Primary sclerosing cholangitis and the path to translation.** *The Journal of clinical investigation*
Váncza, L., Torok, N. J.
2023; 133 (17)
- **Shc is implicated in calreticulin-mediated sterile inflammation in alcoholic hepatitis.** *Cellular and molecular gastroenterology and hepatology*
Li, Y., Jiang, J. X., Fan, W., Fish, S. R., Das, S., Gupta, P., Mozes, G., Vancza, L., Sarkar, S., Kunimoto, K., Chen, D., Park, H., Clemens, et al
2022
- **Non-alcoholic Fatty Liver Disease and Liver Fibrosis during Aging AGING AND DISEASE**
Li, Y., Adeniji, N. T., Fan, W., Kunimoto, K., Torok, N. J.
2022
- **Editorial: Noninvasive Fibrosis Biomarkers in Patients With NASH With Diabetes.** *Hepatology communications*
Fan, W., Torok, N. J.
2021; 5 (4): 553–55
- **NADPH oxidase 4 (Nox4) deletion accelerates liver regeneration in mice**
Herranz-Iturbié, M., Lopez-Luque, J., Gonzalez-Sánchez, E., Caballero-Díaz, D., Crosas-Molist, E., Martín-Mur, B., Gut, M., Esteve-Codina, A., Jaquet, V., Jiang, J., Torok, N. J., Fabregat, I.
ELSEVIER SCIENCE INC.2021
- **Soluble epoxide hydrolase hepatic deficiency ameliorates alcohol-associated liver disease.** *Cellular and molecular gastroenterology and hepatology*
Mello, A., Hsu, M., Koike, S., Chu, B., Cheng, J., Yang, J., Morrisseau, C., Torok, N. J., Hammock, B. D., Haj, F. G.
2020
- **Non-phagocytic Activation of NOX2 is Implicated in Progressive Non-alcoholic Steatohepatitis During Aging.** *Hepatology (Baltimore, Md.)*
Jiang, J. X., Fish, S. R., Tomilov, A. n., Li, Y. n., Fan, W. n., Dehnad, A. n., Gae, D. n., Das, S. n., Mozes, G. n., Charville, G. W., Ramsey, J. n., Cortopassi, G. n., Török, et al
2020
- **AGER1 downregulation associates with fibrosis in nonalcoholic steatohepatitis and type 2 diabetes.** *The Journal of clinical investigation*
Dehnad, A. n., Fan, W. n., Jiang, J. X., Fish, S. R., Li, Y. n., Das, S. n., Mozes, G. n., Wong, K. A., Olson, K. A., Charville, G. W., Ali, M. n., Török, N. J.
2020
- **Digoxin improves steatohepatitis with differential involvement of liver cell subsets in mice through inhibition of PKM2 transactivation.** *American journal of physiology. Gastrointestinal and liver physiology*
Zhao, P., Han, S., Arumugam, S., Yousaf, M. N., Qin, Y., Jiang, J. X., Torok, N. J., Chen, Y., Mankash, M. S., Liu, J., Li, J., Iwakiri, Y., Ouyang, et al
2019
- **P300, A New Player in Mechanosensitivity and Activation of Cancer-Associated Fibroblasts.** *Gastroenterology*
Torok, N. J.
2018; 154 (8): 2025-2026
- **Digoxin Suppresses Pyruvate Kinase M2-Promoted HIF-1# Transactivation in Steatohepatitis.** *Cell metabolism*
Ouyang, X., Han, S. N., Zhang, J. Y., Dioleitis, E., Nemeth, B. T., Pacher, P., Feng, D., Bataller, R., Cabezas, J., Stärkel, P., Caballeria, J., LePine Pongratz, R., Cai, et al
2018; 27 (5): 1156
- **Hepatocyte Nicotinamide Adenine Dinucleotide Phosphate Reduced Oxidase 4 Regulates Stress Signaling, Fibrosis, and Insulin Sensitivity During Development of Steatohepatitis in Mice GASTROENTEROLOGY**
Bettaieb, A., Jiang, J. X., Sasaki, Y., Chao, T., Kiss, Z., Chen, X., Tian, J., Katsuyama, M., Yabe-Nishimura, C., Xi, Y., Szynralewiez, C., Schroeder, K., Shah, et al

2015; 149 (2): 468-?

● **Strategies and endpoints of antifibrotic drug trials: Summary and recommendations from the AASLD Emerging Trends Conference, Chicago, June 2014 HEPATOLOGY**

Torok, N. J., Dranoff, J. A., Schuppan, D., Friedman, S. L.

2015; 62 (2): 627-634

● **Phagocytosis of apoptotic bodies by human stellate cells induces NADPH oxidase activation.**

Torok, N. J., Wu, J., Zern, M. A., Friedman, S. L., Zhan, S. S.

JOHN WILEY & SONS INC. 2004: 532A-533A

● **THE INCIDENCE OF HEPATOCELLULAR CARCINOMA IN CHRONIC HEPATITIS B VIRUS INFECTION SUBJECTS NOT MEETING CRITERIA FOR ANTIVIRAL THERAPY**

Alshuwaykh, O., Goel, A., Daugherty, T., Cheung, A., Kim, W., Kwong, A. J., Ahmed, A., Ghaziani, T., Torok, N. J., Nguyen, M. H., Dronamraju, D., Dhanasekaran, R., Kumari, et al

WILEY. 2020: 472A-473A

● **SHC INHIBITORY DRUG IDEBENONE PROTECTS MICE FROM DIET-INDUCED NASH**

Jiang, J., Tomilov, A., Torok, N. J., Cortopassi, G.

WILEY. 2020: 1036-37

● **Leptin/adiponectin ratio correlates with hepatic steatosis but not arterial stiffness in nonalcoholic fatty liver disease in Japanese population.** *Cytokine*

Mikami, K., Endo, T., Sawada, N., Igarashi, G., Kimura, M., Hasegawa, T., Iino, C., Tomita, H., Sawada, K., Nakaji, S., Matsuzaka, M., Torok, N. J., Fukuda, et al 2019; 126: 154927

● **SHC LINKS OXIDATIVE AND INFLAMMATORY SIGNALS IN ALCOHOLIC LIVER DISEASE (ALD)**

Gupta, P., Dehnad, A., Das, S., Fish, S., Jiang, J., Cortopassi, G., Torok, N. J.

WILEY. 2019: 826A-827A

● **Patterns and co-occurrence of risk factors for hepatocellular carcinoma in four Asian American communities: a cross-sectional study.** *BMJ open*

Stewart, S. L., Dang, J. H., Torok, N. J., Chen, M. S.

2019; 9 (6): e026409

● **SHC MODULATES OXIDATIVE AND INFLAMMATORY SIGNALS IN ALCOHOLIC LIVER DISEASE**

Dehnad, A., Das, S., Fish, S. R., Jiang, J. X., Torok, N. J.

WILEY. 2019: 46A

● **Macrophage Nourishment in NASH: A Novel Role for Ketone Bodies.** *Hepatology (Baltimore, Md.)*

Torok, N. J.

2019

● **Neutrophil-Hepatic Stellate Cell Interactions Promote Fibrosis in Experimental Steatohepatitis.** *Cellular and molecular gastroenterology and hepatology*

Zhou, Z., Xu, M. J., Cai, Y., Wang, W., Jiang, J. X., Varga, Z. V., Feng, D., Pacher, P., Kunos, G., Torok, N. J., Gao, B.

2018; 5 (3): 399-413

● **The NOX1 isoform of NADPH oxidase is involved in dysfunction of liver sinusoids in nonalcoholic fatty liver disease.** *Free radical biology & medicine*

Matsumoto, M. n., Zhang, J. n., Zhang, X. n., Liu, J. n., Jiang, J. X., Yamaguchi, K. n., Taruno, A. n., Katsuyama, M. n., Iwata, K. n., Ibi, M. n., Cui, W. n., Matsuno, K. n., Marunaka, et al

2018; 115: 412-20

● **AGER1/RAGE imbalance and accumulation of AGEs result in inflammation, expansion of ductular cells and fibrosis in NASH**

Dehnad, A., Wong, K. A., Fish, S., Jiang, J., Alzofon, N., Olson, K., Gui, D., Matsukuma, K., Abdi, R., Ali, M., Singh, S., Stewart, S., Angel, et al

WILEY. 2017: 210A

● **Activation of NOX2 in older mice by the aging protein p52Shc leads to accelerated fibrosis in NASH**

Fish, S., Tomilov, A., Dehnad, A., Jiang, J., Alzofon, N., Das, S., Ramsey, J., Cortopassi, G., Torok, N. J.

WILEY. 2017: 208A

● **TRIF as a Novel Modulator of Liver Inflammation and Fibrosis.** *Cellular and molecular gastroenterology and hepatology*

Török, N. J.

2017; 3 (3): 299-300

- **Galectin-3 regulates inflammasome activation in cholestatic liver injury** *FASEB JOURNAL*
Tian, J., Yang, G., Chen, H., Hsu, D. K., Tomilov, A., Olson, K. A., Dehnad, A., Fish, S. R., Cortopassi, G., Zhao, B., Liu, F., Gershwin, M. E., Torok, et al
2016; 30 (12): 4202-4213
- **Ductular reaction-on-a-chip: Microfluidic co-cultures to study stem cell fate selection during liver injury** *SCIENTIFIC REPORTS*
Haque, A., Gheibi, P., Stybayeva, G., Gao, Y., Torok, N., Revzin, A.
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- **Dysregulation of redox pathways in liver fibrosis** *AMERICAN JOURNAL OF PHYSIOLOGY-GASTROINTESTINAL AND LIVER PHYSIOLOGY*
Torok, N. J.
2016; 311 (4): G667-G674
- **Aged mice exhibit a more proinflammatory and fibrogenic NASH phenotype linked to the induction of Shc and NADPH oxidase 2**
Fish, S., Dehnad, A., Jiang, J., Tomilov, A., Ramsey, J., Cortopassi, G., Torok, N. J.
WILEY.2016: 825A
- **Advanced glycation end products and dysregulated RAGE/AGER1 induce proinflammatory and fibrogenic signaling in NASH via NOX4**
Dehnad, A., Fish, S., Jiang, J., Torok, N. J.
WILEY.2016: 830A
- **Metabolic Syndrome Post-Liver Transplant: Can We Predict?** *METABOLIC SYNDROME AND RELATED DISORDERS*
Marsano, J. G., Torok, N. J.
2016; 14 (6): 289-290
- **Extracellular vesicles and ceramide: new mediators for macrophage chemotaxis?** *JOURNAL OF LIPID RESEARCH*
Toeroek, N. J.
2016; 57 (2): 157-158
- **Update on Alcoholic Hepatitis.** *Biomolecules*
Torok, N. J.
2015; 5 (4): 2978-2986
- **Vascular adhesion protein 1 in nonalcoholic steatohepatitis: A novel biomarker?** *HEPATOLOGY*
Torok, N. J.
2015; 62 (4): 1313-1315
- **Galectin 3 regulates HCC cell invasion by RhoA and MLCK activation** *LABORATORY INVESTIGATION*
Serizawa, N., Tian, J., Fukada, H., Baghy, K., Scott, F., Chen, X., Kiss, Z., Olson, K., Hsu, D., Liu, F., Toeroek, N. J., Zhao, B., Jiang, et al
2015; 95 (10): 1145-1156
- **Calciphylaxis in a Patient With Alcoholic Cirrhosis.** *ACG case reports journal*
Akhtar, E., Parikh, D. A., Torok, N. J.
2015; 2 (4): 209-210
- **Role of intestinal myofibroblasts in HIV-associated intestinal collagen deposition and immune reconstitution following combination antiretroviral therapy** *AIDS*
Asmuth, D. M., Pinchuk, I. V., Wu, J., Vargas, G., Chen, X., Mann, S., Albanese, A., Ma, Z., Saroufeem, R., Melcher, G. P., Troia-Cancio, P., Torok, N. J., Miller, et al
2015; 29 (8): 877-888
- **MLK3 as a regulator of disease progression in Non-alcoholic steatohepatitis** *LIVER INTERNATIONAL*
Jiang, J. X., Toeroek, N. J.
2014; 34 (8): 1131-1132
- **Advanced glycation endproducts induce fibrogenic activity in nonalcoholic steatohepatitis by modulating TNF- α -converting enzyme activity in mice.** *Hepatology*
Jiang, J. X., Chen, X., Fukada, H., Serizawa, N., Devaraj, S., Török, N. J.
2013; 58 (4): 1339-1348
- **Calciphylaxis in a Patient with Alcoholic Cirrhosis**

- Akhtar, E., Parikh, D., Torok, N.
NATURE PUBLISHING GROUP.2013: S337
- **Hepatocyte NOX4 plays an important role in modulating stress response-mediated fibrogenic injury during NASH**
chao, T., Jiang, X., Fukada, H., Haj, F., Bettaieb, A., Torok, N.
WILEY-BLACKWELL.2013: 221A
 - **Liver Injury and the Activation of the Hepatic Myofibroblasts.** *Current pathobiology reports*
Jiang, J. X., Török, N. J.
2013; 1 (3): 215-223
 - **Wilson's Disease: Changes in Methionine Metabolism and Inflammation Affect Global DNA Methylation in Early Liver Disease** *HEPATOLOGY*
Medici, V., Shibata, N. M., Kharbanda, K. K., LaSalle, J. M., Woods, R., Liu, S., Engelberg, J. A., Devaraj, S., Toeroek, N. J., Jiang, J. X., Havel, P. J., Loennertdal, B., Kim, et al
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 - **Role of FNA and Core Biopsy of Primary and Metastatic Liver Disease.** *International journal of hepatology*
McGahan, J. P., Bishop, J., Webb, J., Howell, L., Torok, N., Lamba, R., Corwin, M. T.
2013; 2013: 174103-?
 - **Nox4 plays an important role in alcohol-induced hepatic oxidative stress**
Chen, X., Jiang, J., Fukada, H., Schroder, K., Brandes, R. P., Torok, N.
WILEY-BLACKWELL.2012: 1124A
 - **NADPH oxidase 4 plays a key role in hepatocyte injury and HSC activation leading to NASH progression**
Jiang, J., Chen, X., Fukada, H., Schroder, K., Brandes, R. P., Devaraj, S., Torok, N.
WILEY-BLACKWELL.2012: 258A
 - **NOX4 IS A KEY ENZYME IN ALCOHOLIC LIVER DISEASE**
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WILEY-BLACKWELL.2012: 76A
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 - **Human ESC self-renewal promoting microRNAs induce epithelial-mesenchymal transition in hepatocytes by controlling the PTEN and TGF β tumor suppressor signaling pathways.** *Molecular cancer research*
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Jiang, J. X., Chen, X., Hsu, D. K., Baghy, K., Serizawa, N., Scott, F., Takada, Y., Fukada, H., Chen, J., Devaraj, S., Adamson, R., Liu, et al
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 - **TREATMENT WITH A NOVEL NOX4 INHIBITOR ATTENUATES LIVER FIBROSIS**
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 - **NOX1/Nicotinamide Adenine Dinucleotide Phosphate, Reduced Form (NADPH) Oxidase Promotes Proliferation of Stellate Cells and Aggravates Liver Fibrosis Induced by Bile Duct Ligation** *HEPATOLOGY*

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- **Molecular Characterization of Stool Microbiota in HIV-Infected Subjects by Panbacterial and Order-Level 16S Ribosomal DNA (rDNA) Quantification and Correlations With Immune Activation** *JAIDS-JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES*
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 - **Reduced Nicotinamide Adenine Dinucleotide Phosphate Oxidase 2 Plays a Key Role in Stellate Cell Activation and Liver Fibrogenesis In Vivo** *GASTROENTEROLOGY*
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 - **Minocycline in the Treatment of Patients With Primary Sclerosing Cholangitis: Results of a Pilot Study** *AMERICAN JOURNAL OF GASTROENTEROLOGY*
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- **Nonalcoholic steatohepatitis and the metabolic syndrome.** *Metabolic syndrome and related disorders*
Jiang, J., Torok, N.
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