

DDW Wrap-Up: Liver 2013

Objectives

1. Obesity – NAFLD
2. ALD

1. Obesity/NAFLD, metabolic endotoxemia overview

2/3 of U.S. Adults are overweight or obese

1/3 of U.S. Adults have NAFLD

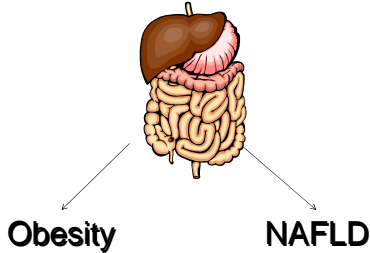
Obesity is a critical health problem in U.S.



Vastag, Obesity Is Now on Everyone's Plate, JAMA 291:1186, 2004

Gut Barrier Dysfunction

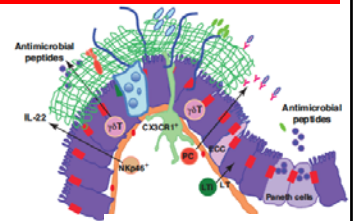
Gut:Liver Axis



Overview of Gut Barrier

Key:

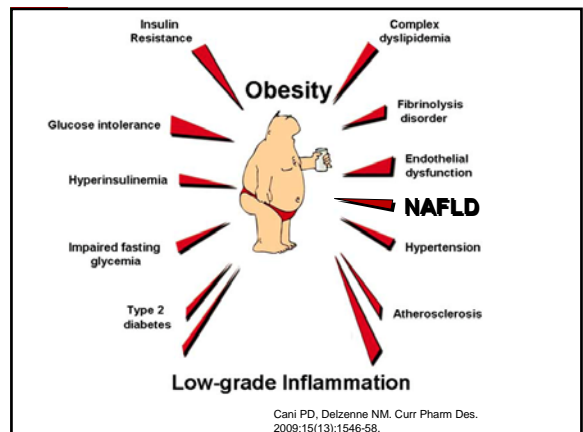
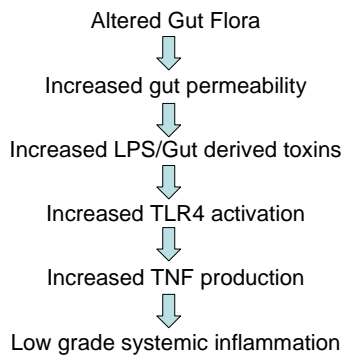
- Intercalating CX3CR1⁺ M/DC
- Epithelial cell
- Goblet cell
- Paneth cell
- Blood vessels
- Mucus
- Tight junctions
- Luminal bacteria
- Invasive bacteria
- SFB



- Gut Flora
- Mucus
- Epithelium
- Tight Junctions

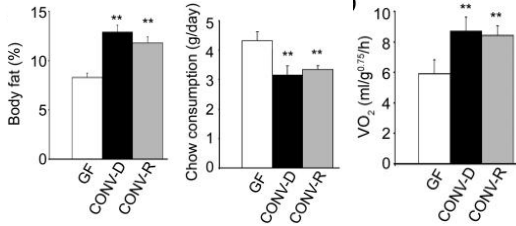
Rescigno, Trends in Immunol 32:256, 2011

Metabolic endotoxemia



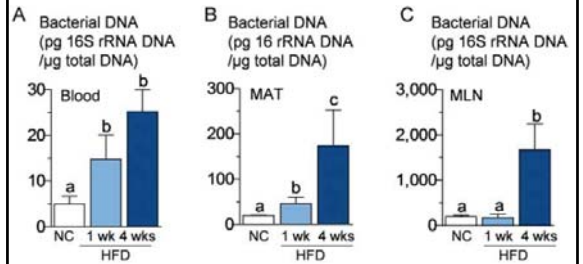
High-fat diet, gut flora, obesity, and NAFLD

Pivotal study – Germ-free mice less fat, but eat more!



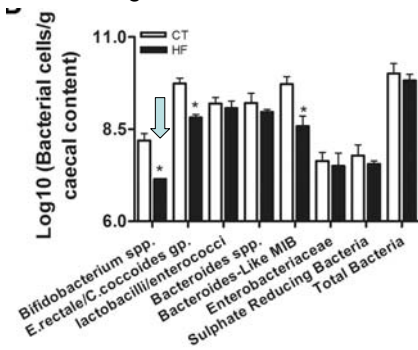
Bäckhed, et al. PNAS 2004 Nov 2;101(44):15718-23. Epub 2004 Oct 25.

Early bacterial translocation with high fat diet



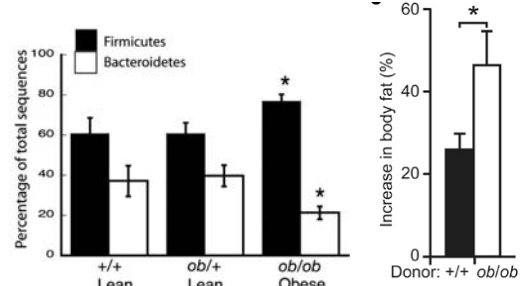
Amar, et al. Intestinal mucosal adherence and translocation of commensal bacteria at the early onset of type 2 diabetes: molecular mechanisms and probiotic treatment. EMBO Mol Med 3:559,2011

High Fat diet alters microbiota



Cani, et al. Diabetes. 2007 Jul;56(7):1761-72. Epub 2007 Apr 24.

Obese mice have altered gut flora, and transfer of gut flora induces weight gain



Ley, et al. PNAS 102(31):11070, 2005
Turnbaugh, et al. Nature 444 (21/28):1027, 2006

NASH – Human Model



	Before	At 18 days	At 21 days
BP, mmHg	110/70	150/100	---
WT, lbs	185	203	---
TChol	165	225	230
TG	60	220	263
ALT	20	290	528
AST	21	130	187

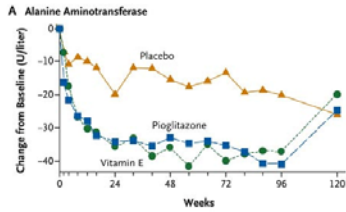
NASH Clinical Research Network (CRN)

- Adult and Pediatric NASH



Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis

- 247 adults with NASH
 - 83 placebo
 - 80 pioglitazone 30mg
 - 84 Vitamin E 800 IU

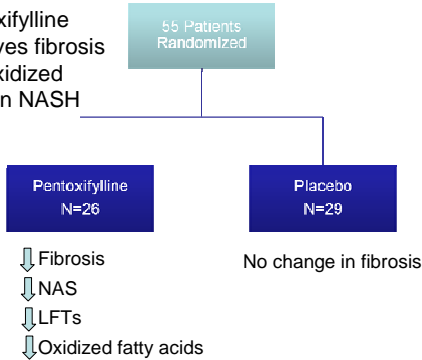


Sanyal, et al. NEJM 362:1675, 2010

New Agents

- **Pentoxifylline**
- **Probiotics**
- **Anti-LPS**
- **Bile Acid Transport Modulation**

Pentoxifylline improves fibrosis and oxidized lipids in NASH



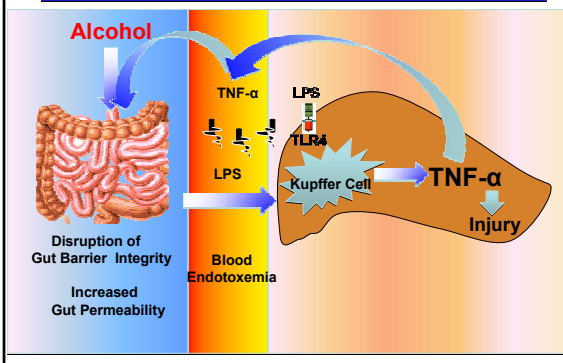
Zein, et al. Hepatology 54:1610, 2011
Zein, et al. Hepatology April 13, 2012 epub.

2. Overview of ALD

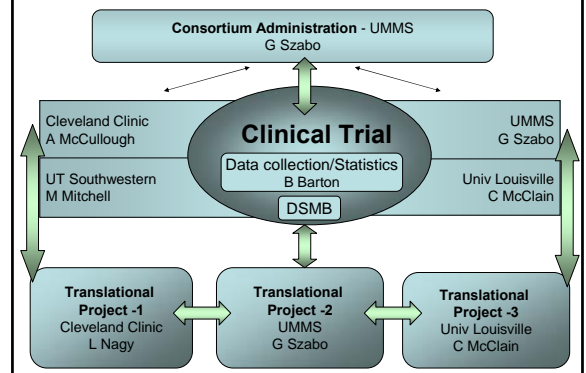
- Alcohol abuse costs U.S. \$185 billion annually
- > 2 million in U.S. with some form of ALD
- Still major form of liver-related mortality in U.S.
- Likely underestimated due to social stigma

Harwood, et al., NIAAA, 2000

ALD: Gut-Liver Axis



Novel Therapies in Alcoholic Hepatitis



UO1 Clinical Trial Specific Aims

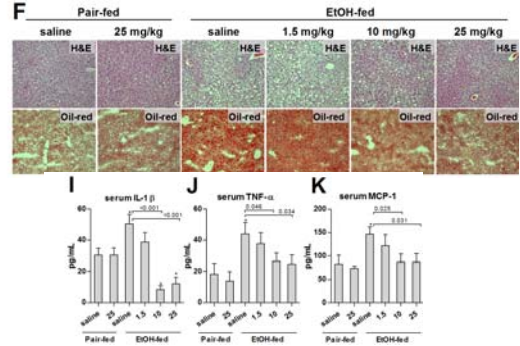
Aim 1: Evaluation of the effects of **corticosteroids** versus a combination of **interleukin-1 inhibitor** plus **pentoxifylline** plus **zinc** supplements in patients with MELD \geq 21.

Aim 2: Evaluation of the effects of **probiotic** supplements versus standard care on improvement in MELD score and gut mucosal integrity in patients with MELD $<$ 21.

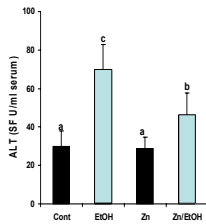
Aim 3: Develop new clinical trials for patients with alcoholic hepatitis using lead compounds identified by the translational science components of the U-01 consortium.

Aim 4: Create a data and tissue biorepository

IL-1 receptor antagonist is effective in experimental ALD

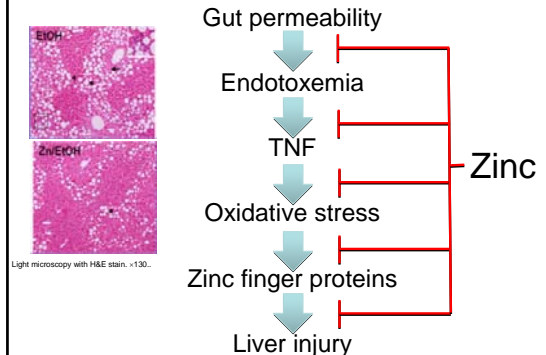


Zinc improves experimental ALD



Serum ALT activities were measured using a Sigma Diagnostic kit. Significant differences ($p < 0.05$) are identified by different letters.

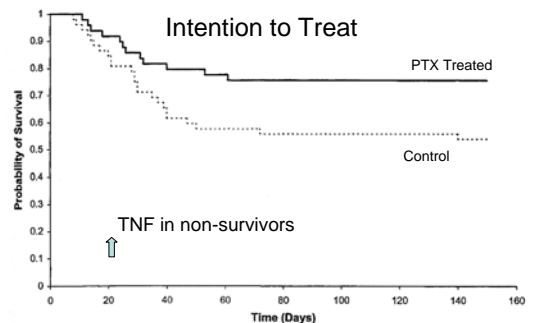
Zinc Therapy positively impacts multiple mechanisms of AH



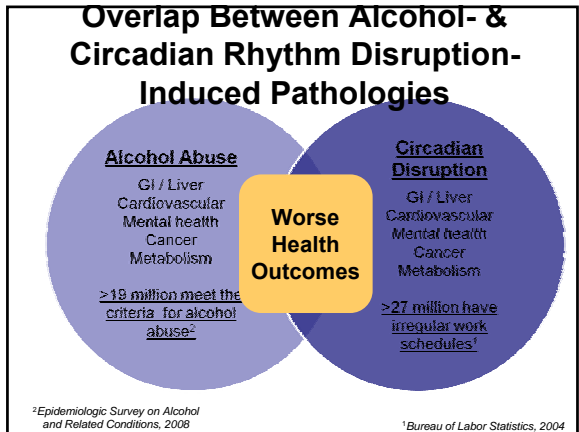
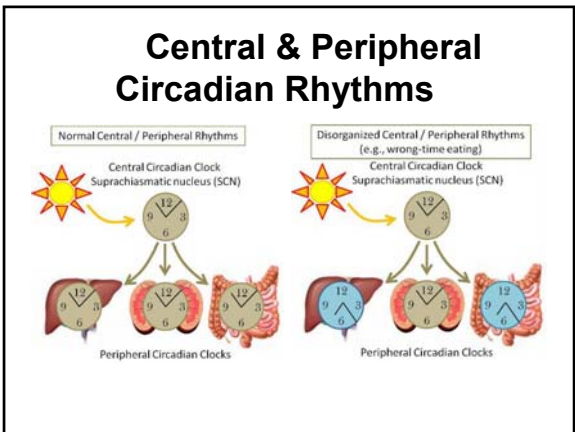
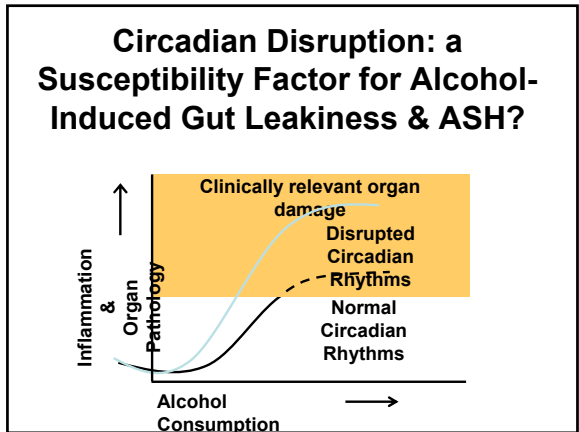
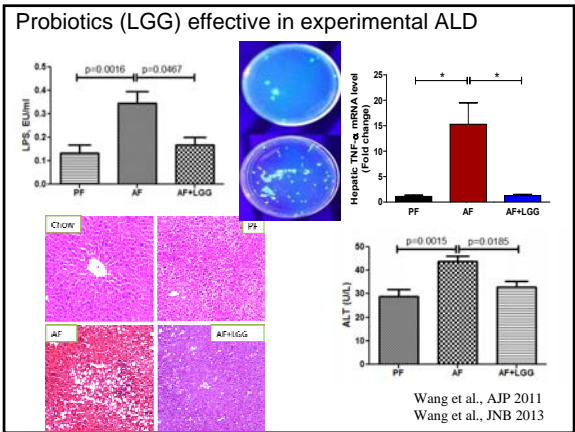
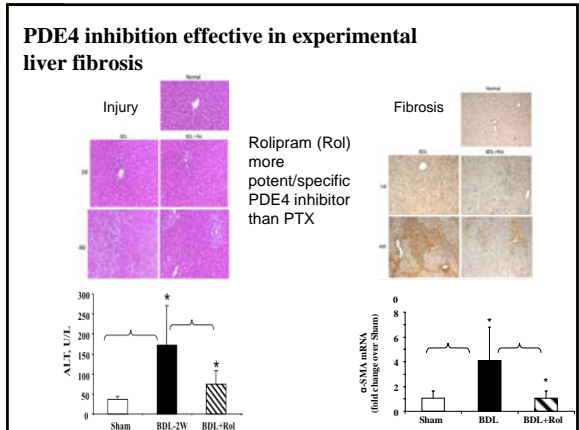
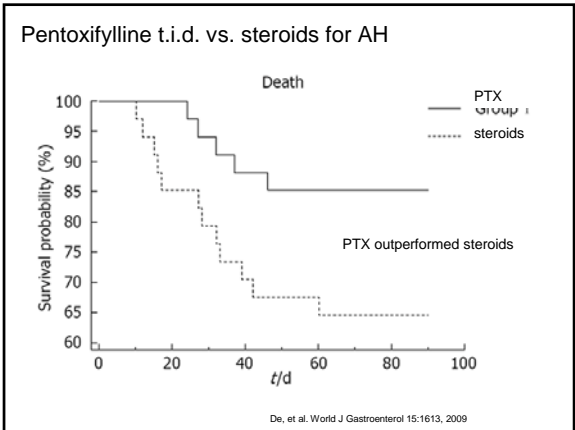
Pentoxifylline is a non-specific phosphodiesterase (PDE) inhibitor

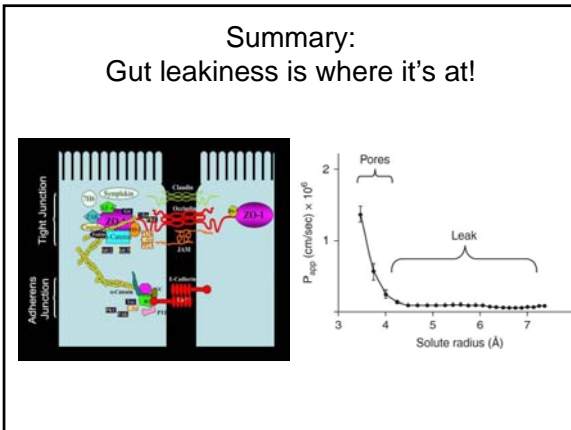
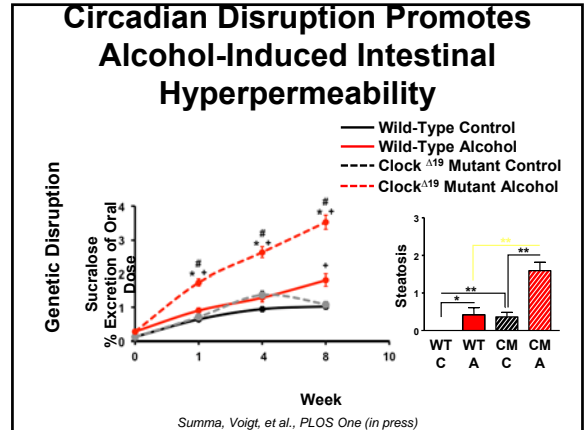
PDE4 inhibition \rightarrow \uparrow cAMP \rightarrow \downarrow proinflammatory cytokines

Pentoxifylline 400 mg TID vs placebo for AH



Akriavidis, et al. Gastroenterol 2000;119:1637





Questions?