Overview of PSC Research

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Treatments based on the concepts of pathogenesis of PSC ?

- Immunologic (Rx: immunosuppression)
- Gut bacterial toxins - (Rx: IBD, antibiotics)
- Vascular - (? Rx anti VEGF)
- Toxic Bile - (Rx: UDCA)

Medications evaluated for PSC (Silveira,M.G. and Lindor,K.D. 2008. Primary sclerosing cholangitis. *Can.J.Gastroenterol.* 22:689-698)

No benefit	Possible benefit	Under consideration
Azathioprine	Metronidazole	DHA*
Budesonide	Minocycline*	Thalidomide*
Cladribine	Silymarin	Nor-UDCA*
Colchicine	Tacrolimus	6-EDCA*
Cyclosporine		Losartan*
Etanercept		
Infliximab		
Methotrexate		
Mycophenolate mofetil		
Nicotine		
Penicillamine		
Pentoxifylline		
Pirfenidone		
UDCA (28 mg/kg/day to 30 mg/kg/day)		

*Please refer to text for references. *Unpublished or ongoing studies. 6-EDCA 6-alpha-ethyl-chenodeoxycholic acid; DHA Docosahexaenoic acid; UDCA Ursodeoxycholic acid*

New Treatments for PSC ?

- Difficulties in establishing effective Rx
  - (uncommon, long duration, variable outcomes, uncertain pathogenesis)

- UDCA monotherapy controversy
  - (EASL vs AASLD guidelines)
  - (? survival benefit; ? Toxicity of highdose UDCA)

EASL and AASLD Practice Guidelines (summary points)

Practice point	EASL guidelines	AASLD guidelines
Cholangiography	MRC recommended as initial investigation. ERC if indicated.	MRC recommended as initial investigation. ERC if indicated.
Liver biopsy—adults	Only in patients with normal cholangiography or disproportionally elevated serum transaminases.	Only in patients with normal cholangiography or disproportionally elevated serum transaminases.
Liver biopsy—children	Recommended.	Recommended.
Antibiotic prophylaxis during ERC	Recommended.	No recommendation point.
Long-term antibiotic treatment	No recommendation point.	Recommended in patients with recurrent attacks of acute cholangitis.
Endoscopic treatment	Balloon dilatation with or without stenting.	Balloon dilatation with or without stenting.
UDCA treatment in PSC	No specific recommendation made.	Not recommended
UDCA chemoprevention	In patients with longstanding IBD and family history of colorectal malignancies.	
Treatment of PSC with features of autoimmune hepatitis	UDCA and immunosuppression recommended.	Corticosteroids and other immunosuppressive agents recommended.
Treatment of IgG4-associated sclerosing cholangitis	Corticosteroids and/or azathioprine.	No specific treatment recommendation.
Liver transplantation	Treatment of choice in cirrhotic patients and should be considered in refractory bacterial cholangitis.	Treatment of choice in cirrhotic patients and should be considered in refractory bacterial cholangitis.
Surveillance colonoscopy	Every 1–2 years in IBD.	Every 1–2 years in IBD.
Surveillance ultrasound	Annually.	Annually.
Cholangiocarcinoma surveillance	No recommendation made.	No recommendation made.

Karlsen et al Dig Liver Dis ‘2010

The blind man and the elephant
(referral bias)

Goals for New Therapies for PSC

- Reduce Liver inflammation, bile duct proliferation, liver fibrosis
- Improve symptoms and quality of life and increase longevity

Candidates for New Treatment of PSC

- Novel bile acids

  A. **<u>6-ethyl-CDCA</u>**, a semi synthetic derivative of chenodeoxycholic acid;
  - A potent agonist of **FXR ,a nuclear receptor** that regulates bile acid homeostasis.
  - Improves liver function in several animal models of cholestasis;

  B. **<u>NorUDCA</u>**

- Other Nuclear receptor ligands ?

  – **PXR agonists** (regulates expression of genes involved in bile acid metabolism and detoxification) e.g. rifampicin, phenobarbital
  – **Vit D receptor agonists**
  – **Retinoid receptor agonists** (retinoic acids)
  – **PPARα and γ agonists** (Fibrates; curcumin)

NorUDCA

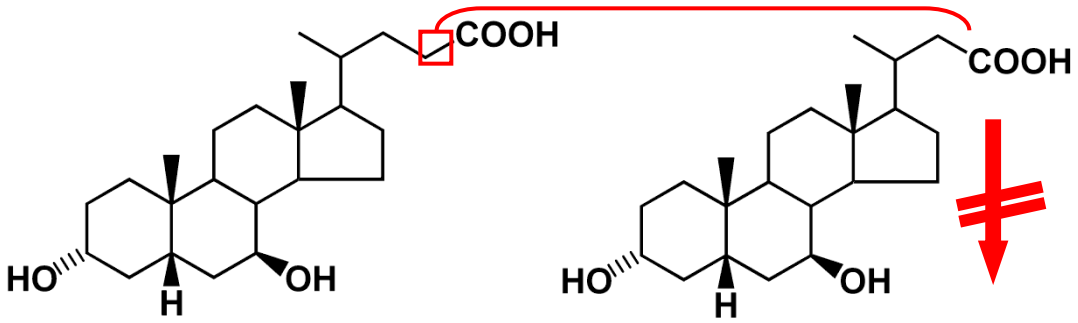
NorUDCA improves liver injury in a mouse model of PSC

(Mdr2 deficient mouse)

- norUDCA, a carbon 23 homologue of UDCA is excreted in bile mainly in uncongugated form
- Undergoes “cholehepatic” shunting from bile across the bile ducts and stimulates bile flow and bicarbonate excretion
- More effective than UDCA in improving liver tests, markers of inflammation and fibrosis and inducing bile acid detoxifying enzymes and transporters
- A promising candidate for human trials

PSC: Pathomechanisms → Rx

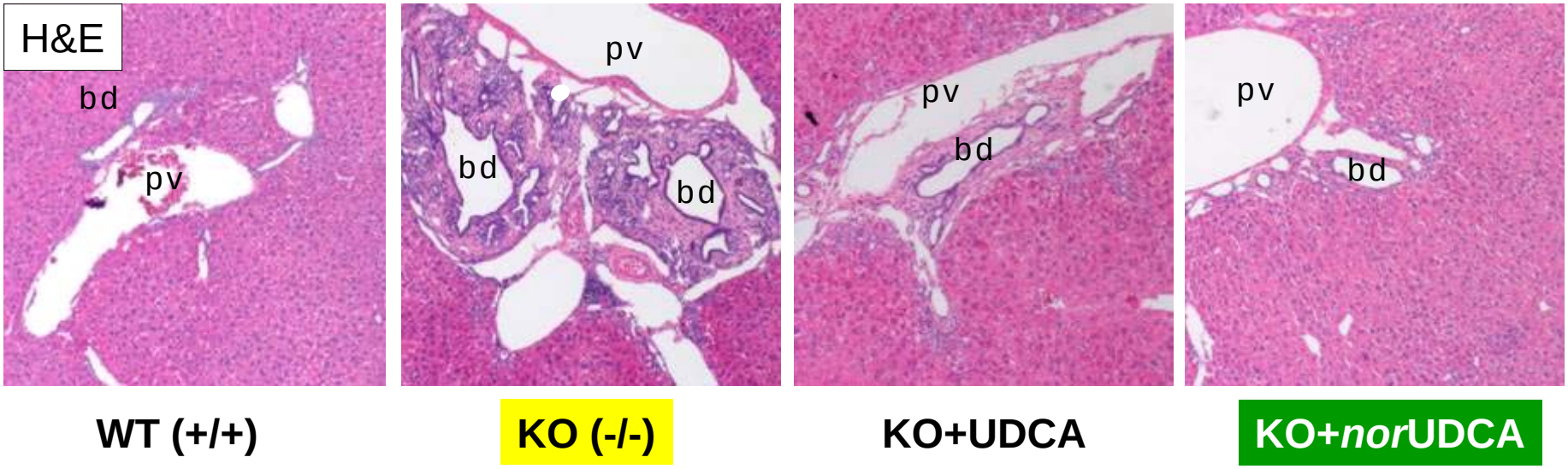
- Immunological → ~~Immunosuppressive~~
- „Gut-derived“ → ~~Rx of IBD, ABx~~
- Vascular → Angiogenesis?
- Toxic bile → UDCA?



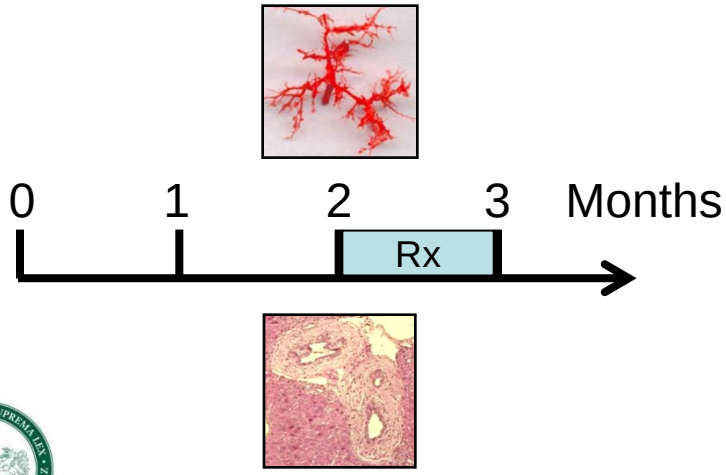
Phase 1	2010
Phase 2	2011
Phase 3	2012

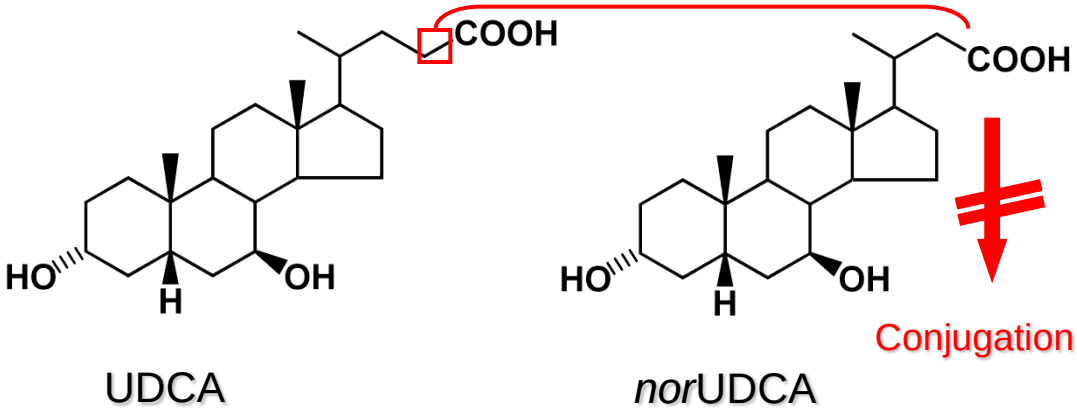
Fickert et al., *Gastroenterology* 2006; 130: 465
Halilbasic et al., *Hepatology* 2009; 49: 1972

*nor*UDCA Reverses Sclerosing Cholangitis in *Mdr2* $^{-/-}$ (KO) Mice



WT (+/+) | **KO (-/-)** | **KO+UDCA** | **KO+*nor*UDCA**

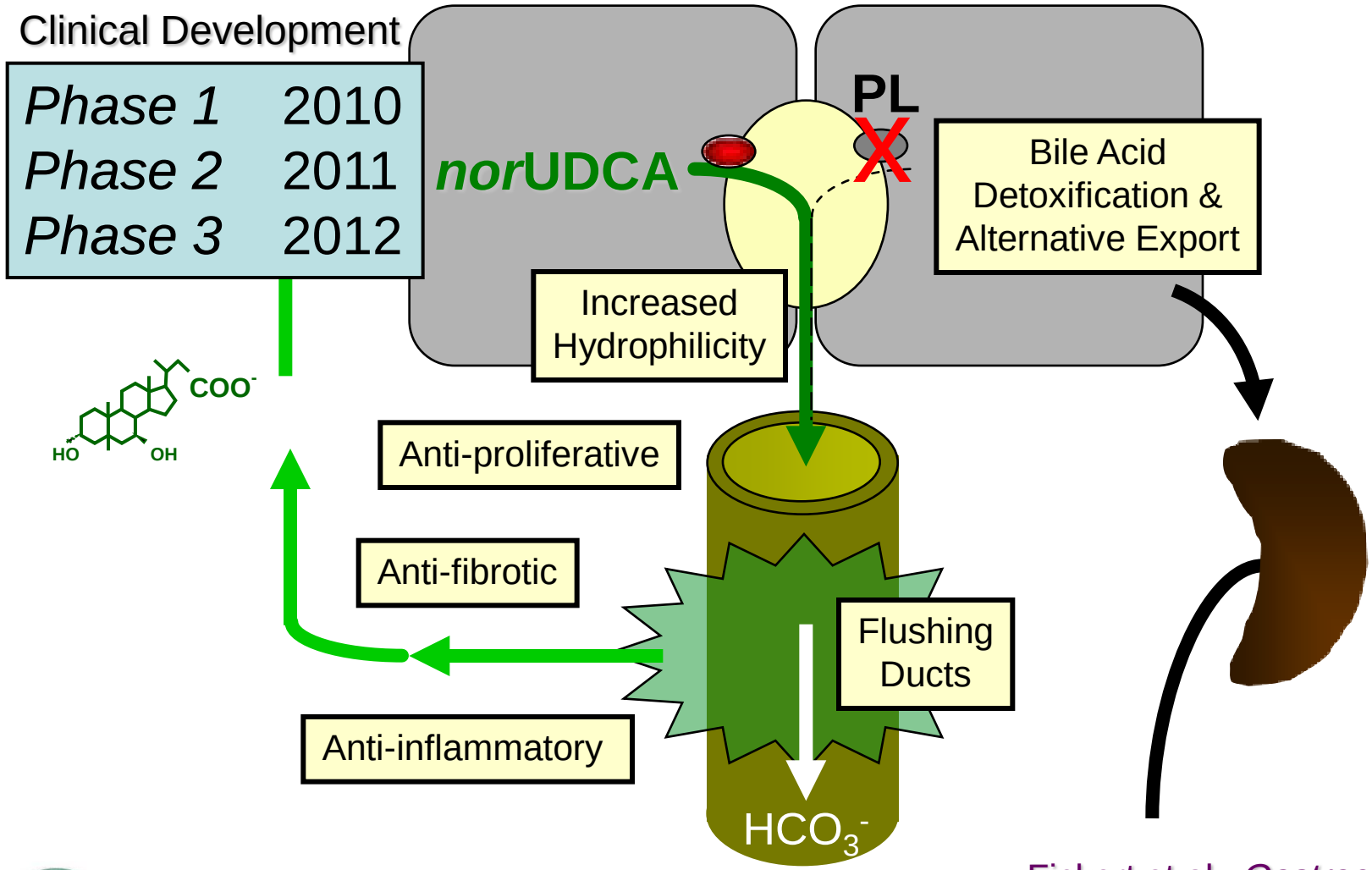




UDCA *nor*UDCA

Fickert et al., *Gastroenterology* 2006; 130: 465

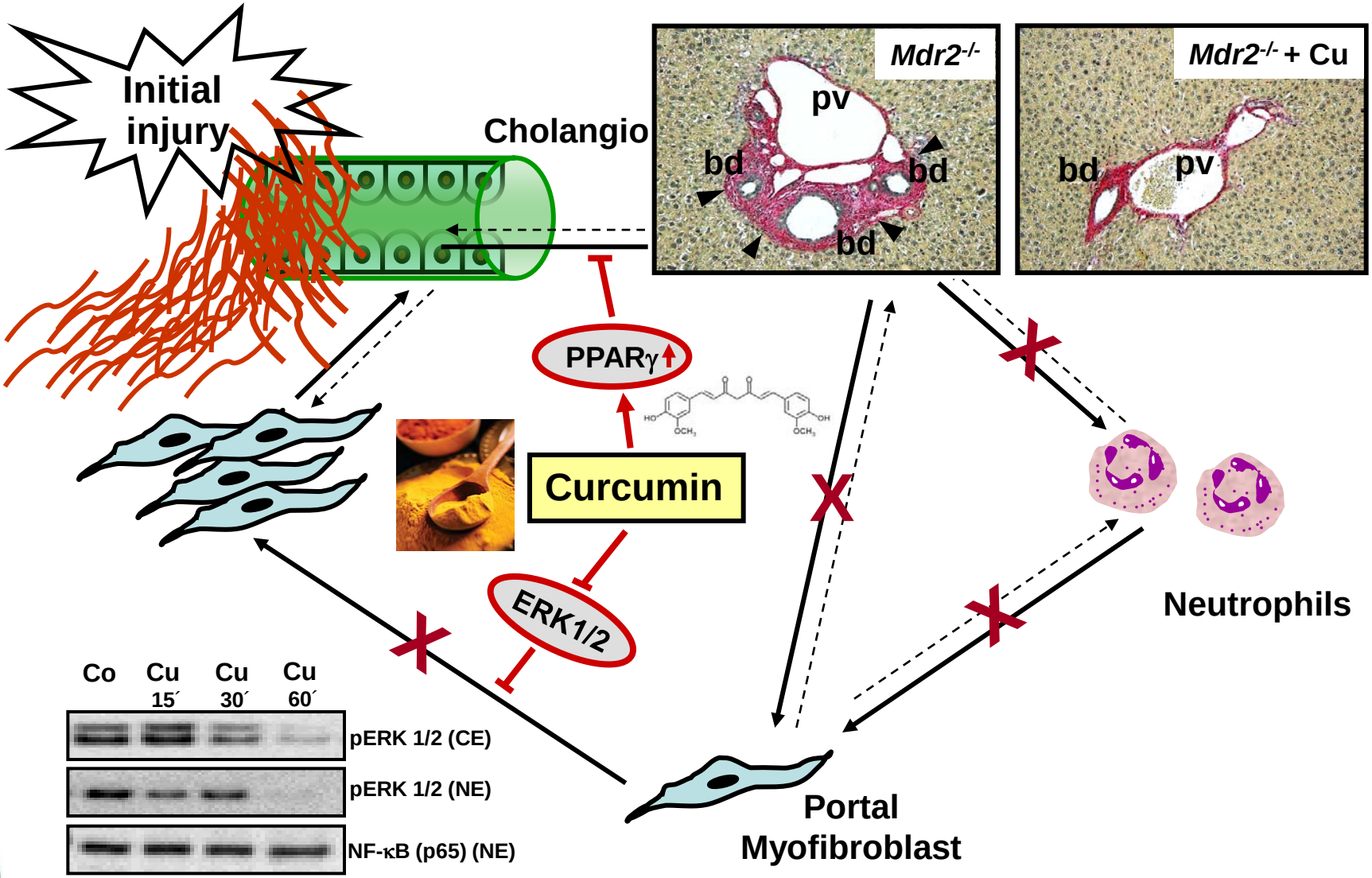
*nor*UDCA: Mechanisms of Action in *Mdr2* $^{-/-}$ Model of Sclerosing Cholangitis



Patent EP 2005 / 052178
Patent EP 2007 / 1131072

Fickert et al., *Gastroenterology* 2006
Halilbasic et al., *Hepatology* 2009
Moustafa et al., *in preparation*

Curcumin Inhibits Cholangiocyte Inflammatory Response and Portal Myofibroblast Proliferation



Baghdasaryan et al, *Gut* 2010

Summary

- Pathogenesis of PSC is still uncertain
- The infrequency of the disease and the variable clinical features make it difficult to assess effective therapies
- Novel bile acids and other modifiers of nuclear receptor activity are the most promising new agents
- NorUrso is now undergoing phase 1 clinical trials

Conclusions

Cautious optimism is warranted for more effective treatment for PSC in the near future

Thank you