

Non-Alcoholic fatty liver disease

Peter LM Jansen



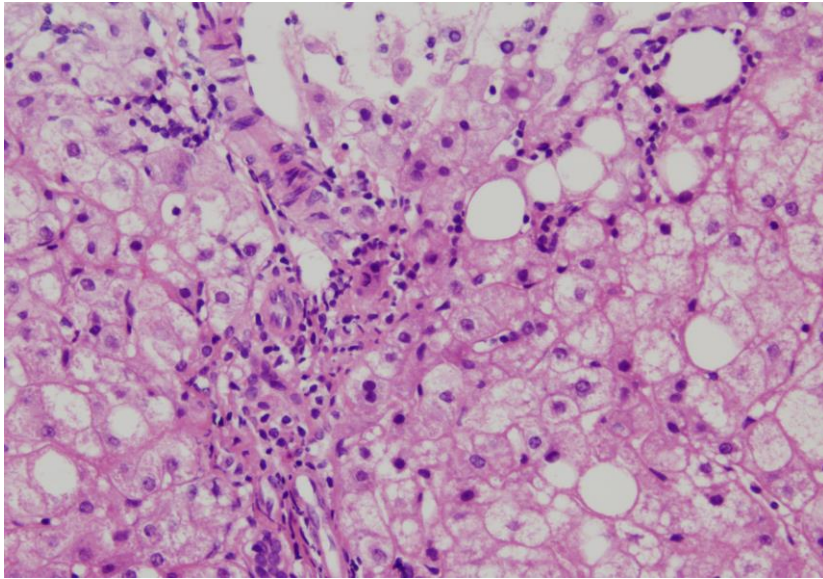
Maastricht University



LiSyM
Liver Systems Medicine

What is NAFLD/NASH?

Liver manifestation of metabolic syndrome



Prevalence in The Netherlands

NAFLD 35 %

NASH 2-3%

Koehler et al Hepatology 2016; 63:138–147.

- Hepatocytes
- Steatosis*
- Ballooning*
- Apoptosis
- Giant mitochondria

- Extracellular matrix
- Lobular inflammation*
- Fibrosis

- Kupffer cells
- OxLDL in Lysosomes

* If present: NASH

Etiology of NAFLD

Environmental factors

- Hypercaloric 'western' diet
- High fructose diet (soft drinks)
- Microbiome

Metabolic factors

- Insulin resistance
- Oxidative stress

Genome

- PNPLA3 *I148M* polymorphism (hispanics)
- APOC3 polymorphism (lean men)

Differential diagnosis

- Alcoholic fatty liver disease
- Drug-induced fatty liver disease
- CASL, chemotherapy-associated steatosis
- Volatile organic solvent exposure
- Hep C-related fatty liver disease
- Autoimmune hepatitis
- Celiac disease
- Wilson's disease
- Hemochromatosis
- Abetalipoproteinemia
- Starvation, malnutrition
- Hypothyroidism
- Lysosomal acid lipase deficiency

How to diagnose NAFLD/NASH

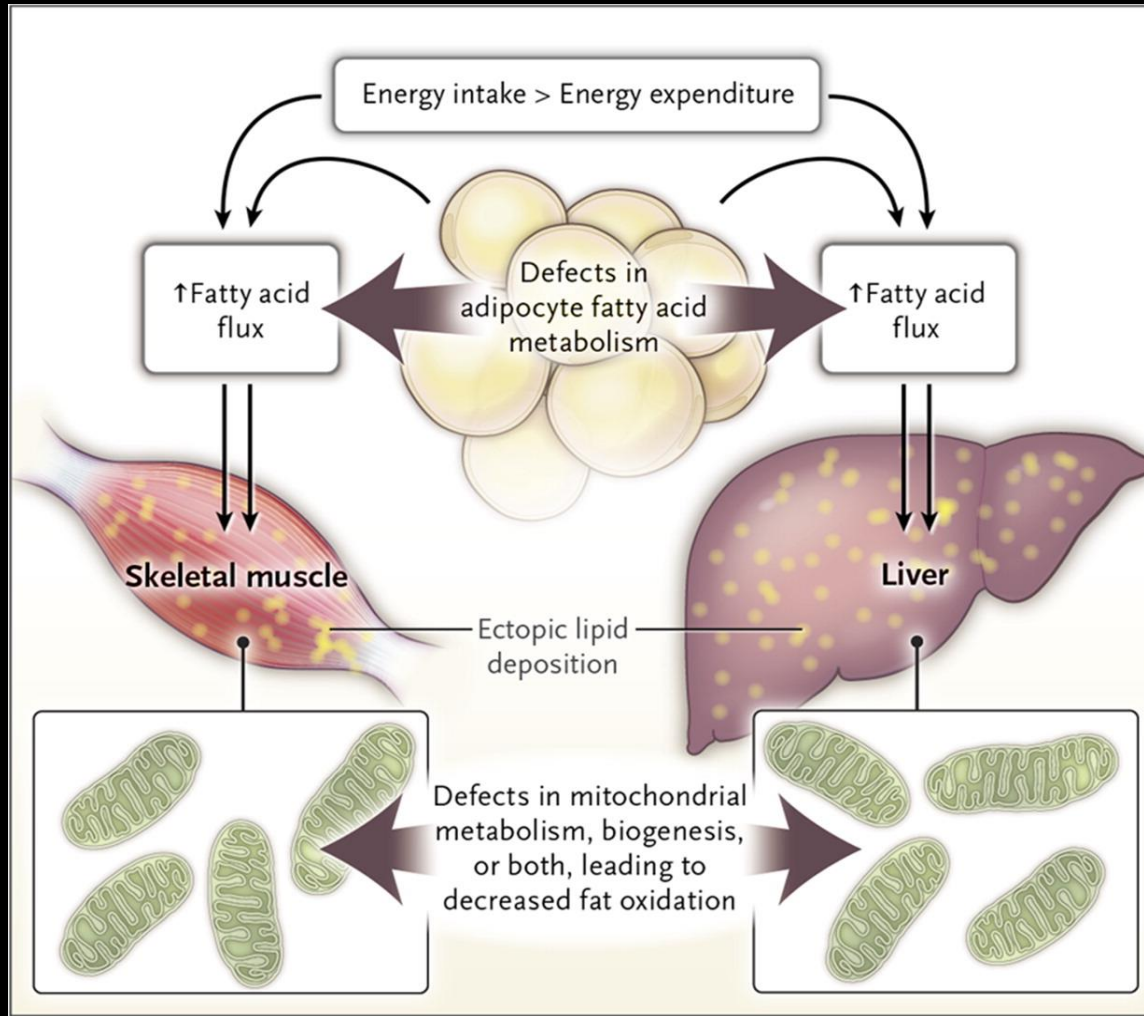
- Increased ALT (B2) (low specificity)
- Ultrasound (A1) (70% sensitivity)
- Fibroscan (C2)
- ^1HMR spectroscopy (only in trials) (A1)
- Liver biopsy (NASH suspected) (A1)

Associated diseases

- T2DM ✓
- Hypercholesterolemia ✓
- Hypertriglyceridemia ✓
- OSAS
- PCOS
- Hypertension ✓
- Cardiomyopathy, cardiac failure

Etiology

Primary defect in mitochondria

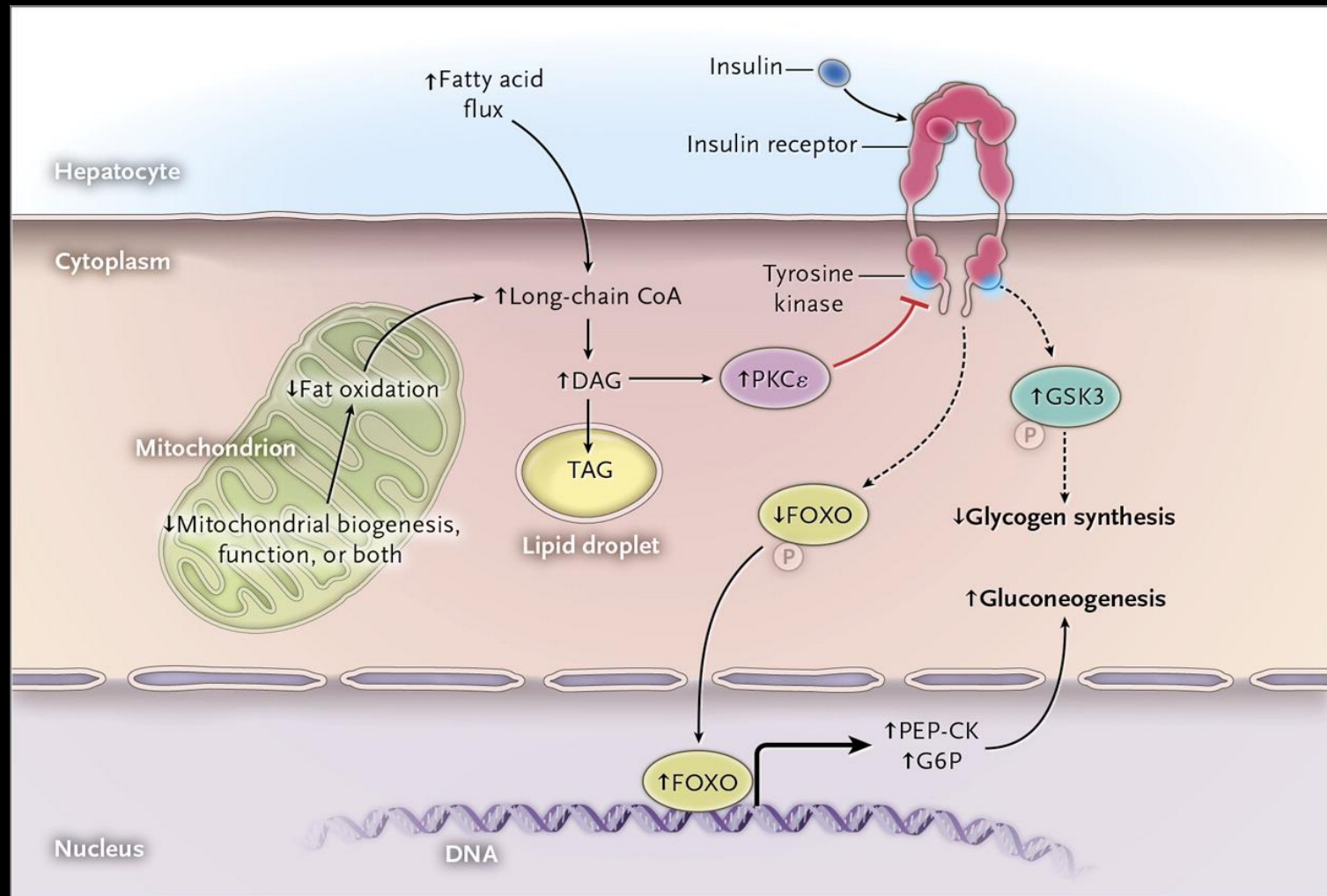


Shulman GI. *N Engl J Med* 2014;371:1131-1141.



The NEW ENGLAND
JOURNAL of MEDICINE

Hepatic insulin resistance



Shulman GI. N Engl J Med 2014;371:1131-1141.



The NEW ENGLAND
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Hepatic manifestations of NASH

- Cirrhosis
- Portal hypertension
- Hepatocellular cancer

Extrahepatic manifestations

- Metabolic syndrome
- Insulin resistance, DM T2
- Obesity
- Cardiovascular disease
- Hypertension

Therapy

- Overweight/obese 10% weight loss (B1)
- Life style intervention (C2)
 - Energy restriction (B1)
 - Increase exercise (B2)
- Correct cholesterol & lipid metabolism
- Correct insulin resistance
- Bariatric surgery (BMI > 40)

Drug therapy

Indication

- NASH and F2 fibrosis
- NAFLD and high risk of disease progression, T2DM, MetS, persistently elevated ALT

Target

- Insulin resistance
- Oxidative stress
- Steatosis

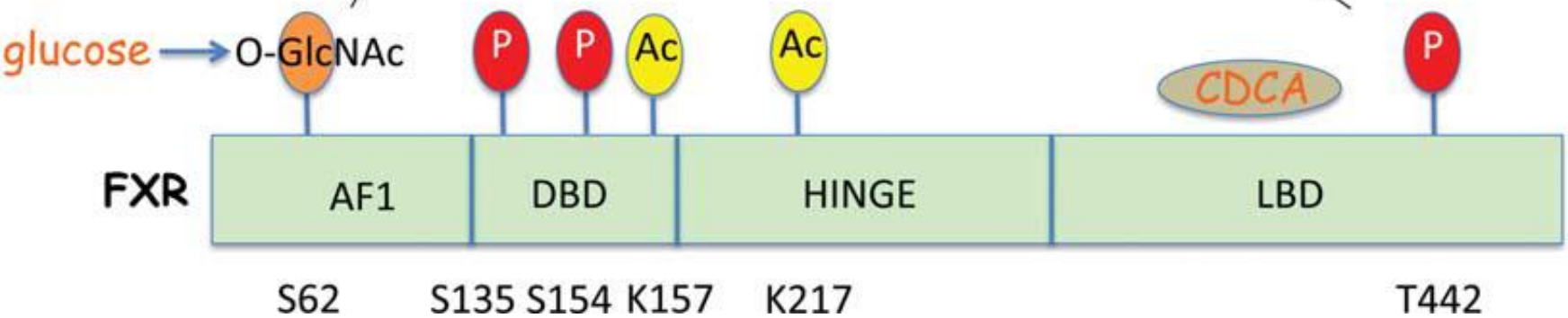
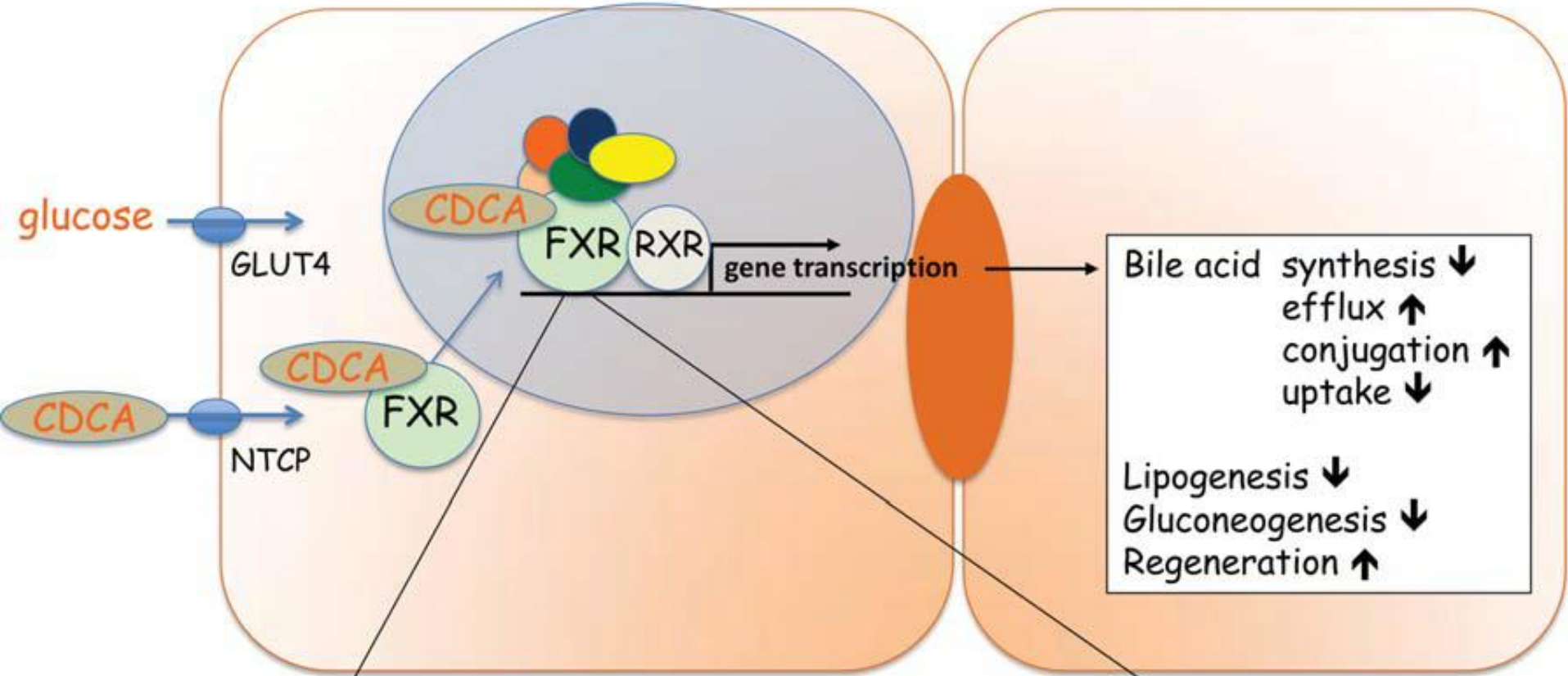
- Inflammation
- Fibrosis
- Microbiome
- LDL cholesterol

Drug

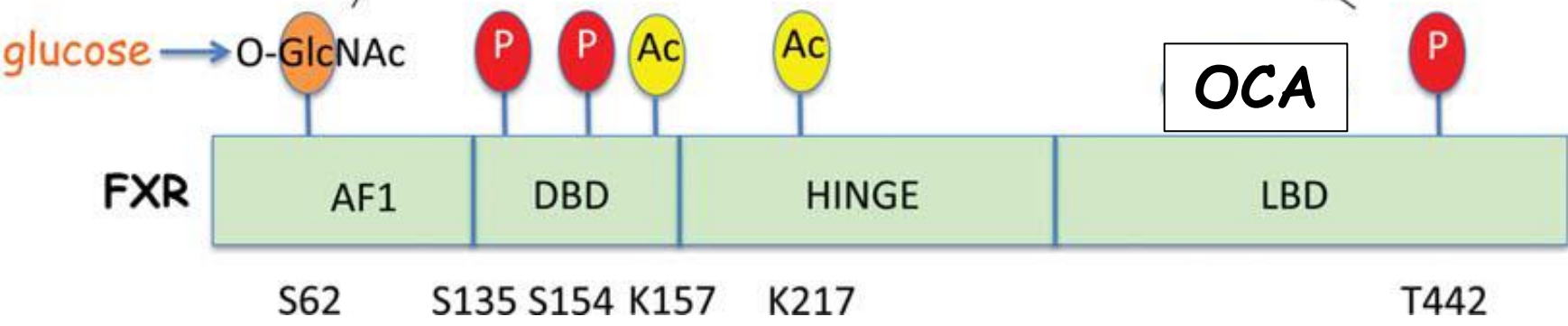
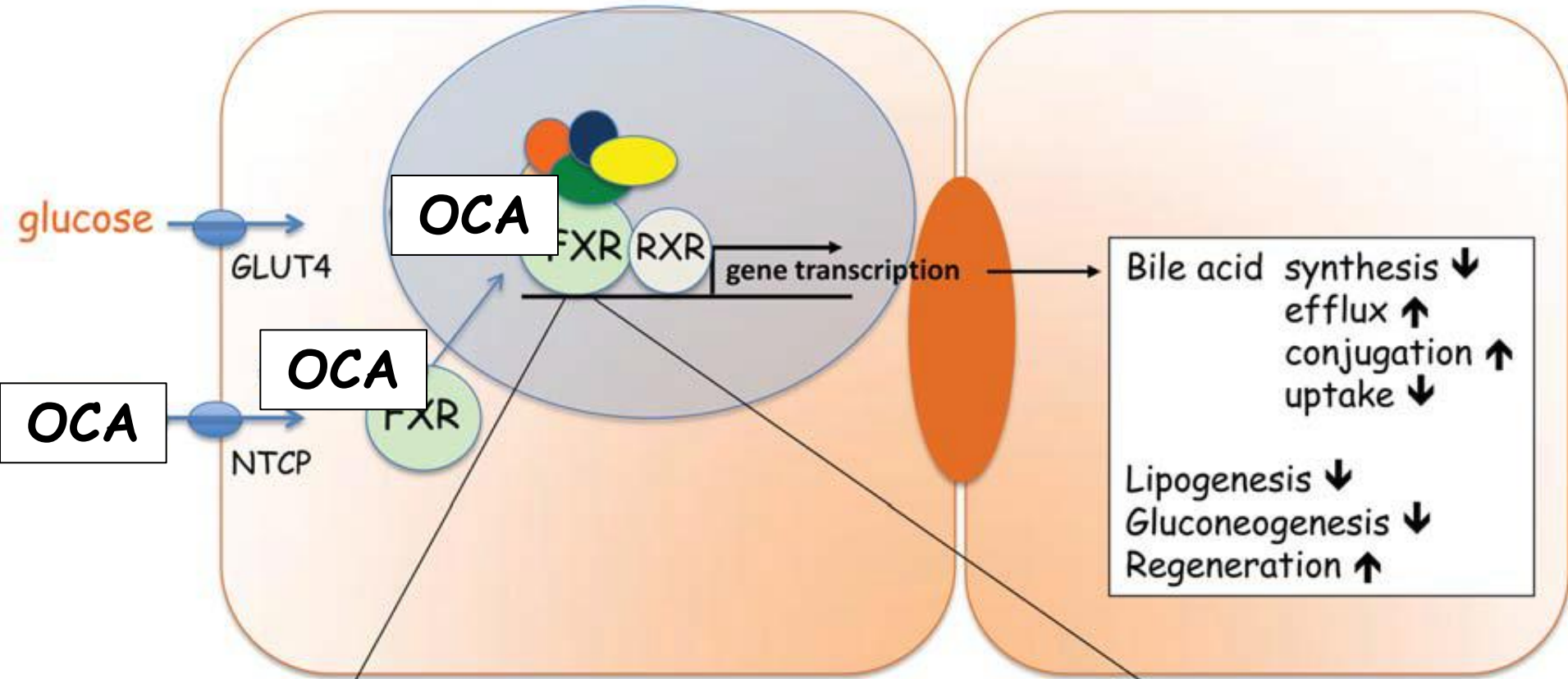
- Pioglitazone (B2)
- Vitamin E (B2)
- FXR agonist (B2)
- n-3 PUFA (B1)
- TGR5 agonist

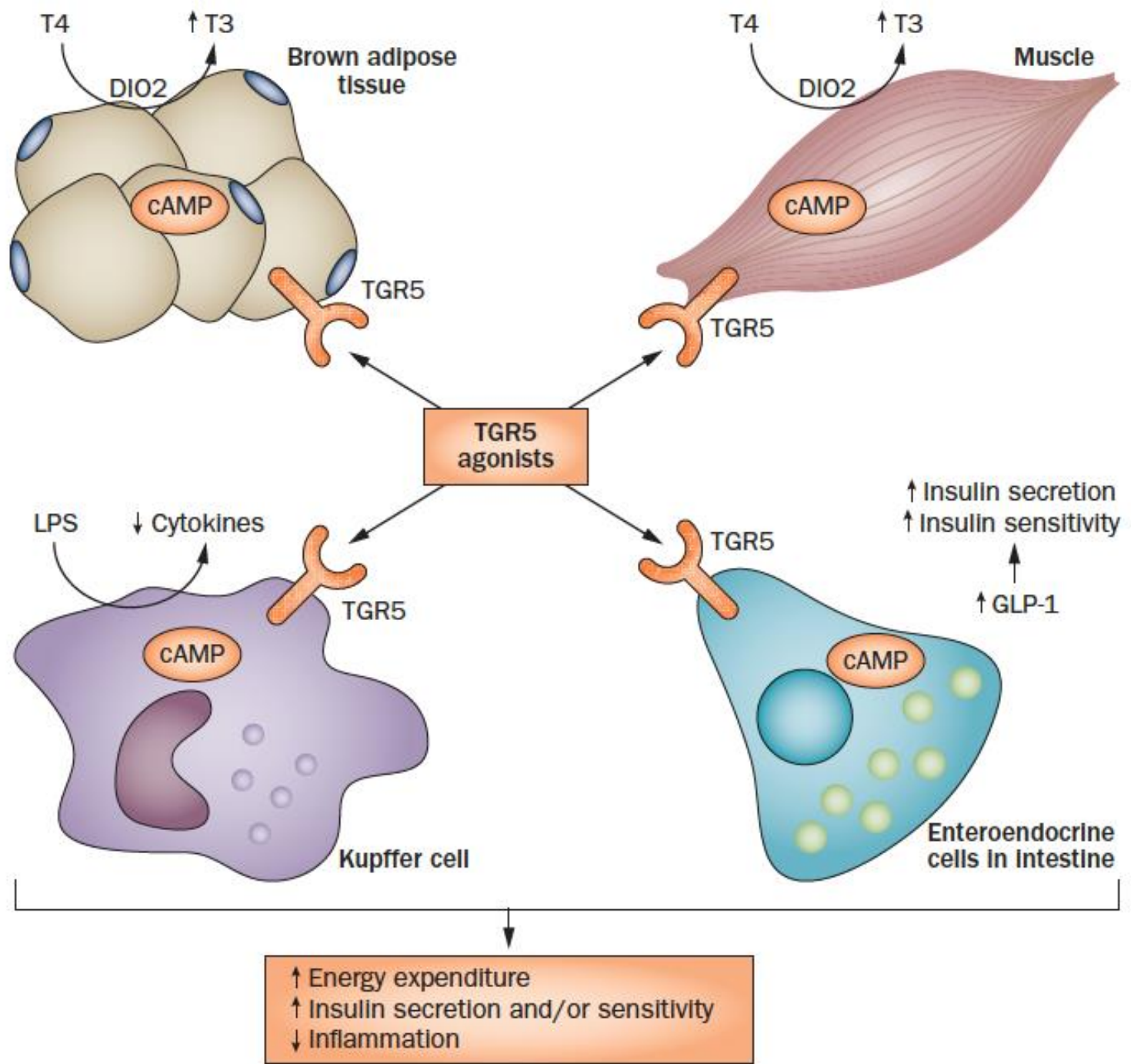
- Statins (B1)

Hepatocyte



Hepatocyte





The research agenda

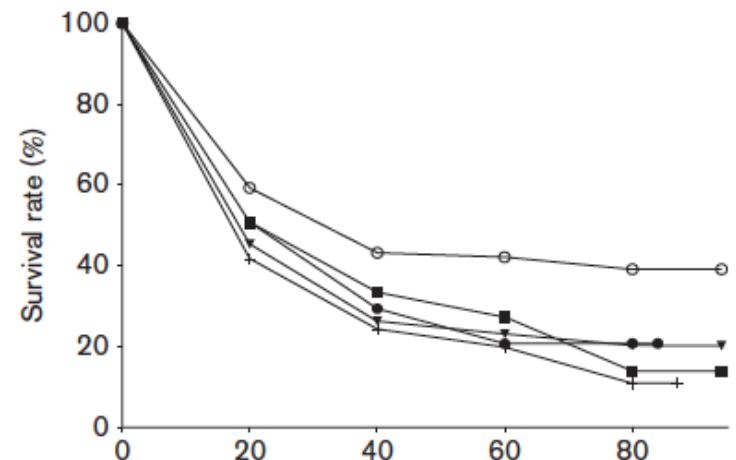
- **Non-invasive biomarkers for disease staging and for therapeutic response**
 - Serum markers (non-coding RNA)
 - Exhaled air (VOCs)
 - Mitochondrial function test
- **New Drugs**
 - TGR5 agonists (sec bile salts)
 - FXR agonists (prim bile salts)
 - Anti-fibrotic drugs
- **Preclinical research**
 - Proteomics for biomarker discovery
 - Metabolic imaging (mitochondria)
 - Role of microbiome

HCC and NAFLD

Hepatocellular carcinoma in cirrhotic versus noncirrhotic livers: results from a large cohort in the Netherlands

Suzanne van Meer^a, Karel J. van Erpecum^a, Dave Sprengers^b, Minneke J. Coenraad^d, Heinz-Josef Klümpen^e, Peter L.M. Jansen^f, Jan N.M. IJzermans^c, Joanne Verheij^g, Carin M.J. van Nieuwkerk^h, Peter D. Siersema^a and Robert A. de Man^b

Etiology	cirrhosis	no cirrhosis
HBV (16)	162	35 (17.7)
HCV (20)	236	13 (5.2)
Hemochromatosis (3)	29	8 (21.6)
NAFLD (15)	114	67 (37.0)
Alcohol (29)	312	37 (10.6)
No risk factors known (12)	73	73 (50)



	Follow-up (months)				
Number at risk	0	20	40	60	80
Hepatitis B	179	81	45	28	7
Hepatitis C	232	85	42	22	6
Alcohol	334	99	37	13	4
NAFLD	175	55	19	10	3
No risk factors	134	52	25	11	2

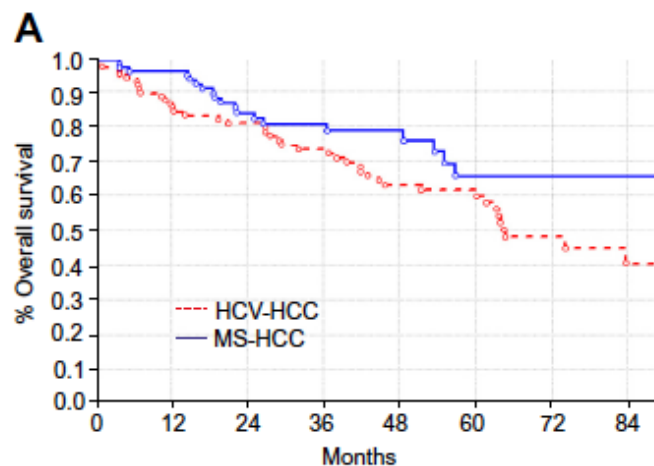
Fig. 2. Observed survival of patients with hepatocellular carcinoma with underlying hepatitis B (line with open circles), NAFLD (line with solid triangles), hepatitis C (line with solid squares), absence of risk factors (line with solid circles), or alcohol-related liver disease (line with crosses) (Kaplan-Meier survival curve; log-rank $P < 0.001$). NAFLD, nonalcoholic fatty liver disease.

Hepatocellular carcinoma in noncirrhotic livers is associated with steatosis rather than steatohepatitis: potential implications for pathogenesis

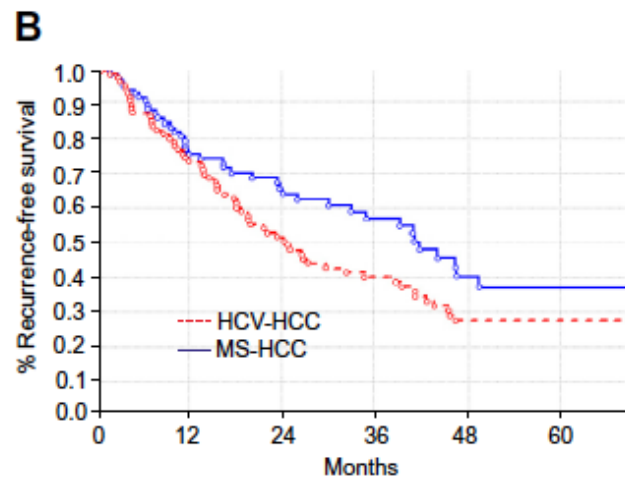
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Liver resection for hepatocellular carcinoma in patients with metabolic syndrome: A multicenter matched analysis with HCV-related HCC

Luca Viganò^{1,2,*}, Simone Conci³, Matteo Cescon⁴, Cristina Fava⁵, Paola Capelli⁶, Antonietta D'Errico⁷, Guido Torzilli¹, Luca Di Tommaso⁸, Felice Giuliani⁹, Fabio Maria Vecchio¹⁰, Mauro Salizzoni¹¹, Ezio David¹², Antonio Daniele Pinna⁴, Alfredo Guglielmi³, Lorenzo Capussotti²



Pts at risk	Total	1 yr	2 yr	3 yr	4 yr	5 yr	6 yr	7 yr
MS-HCC	96	78	55	42	29	18	12	9
HCV-HCC	96	80	69	58	45	36	17	9



Pts at risk	Total	1 yr	2 yr	3 yr	4 yr	5 yr
MS-HCC	92	61	41	29	14	10
HCV-HCC	92	64	42	30	19	14

Fig. 1. Survival curves after liver resection for HCC in the MS-HCC group and in the HCV-HCC group: (A) Overall Survival ($p = 0.031$); (B) Recurrence-free survival ($p = 0.077$). The recurrence-free survival analysis included 184 patients (92 per group) because patients with operative mortality ($n = 4$) and patients with unknown recurrence status ($n = 4$) were excluded. (This figure appears in colour on the web.)

