



# Evolution of GSD1a with time in a liver-specific model of the pathology

**Gilles Mithieux-Fabienne Rajas**

Inserm u.855/Université Lyon 1

*October 2<sup>nd</sup>, 2010, Milan*

# Dysregulation of glucose homeostasis

---

## Mirror metabolic diseases

### Type 2 diabetes

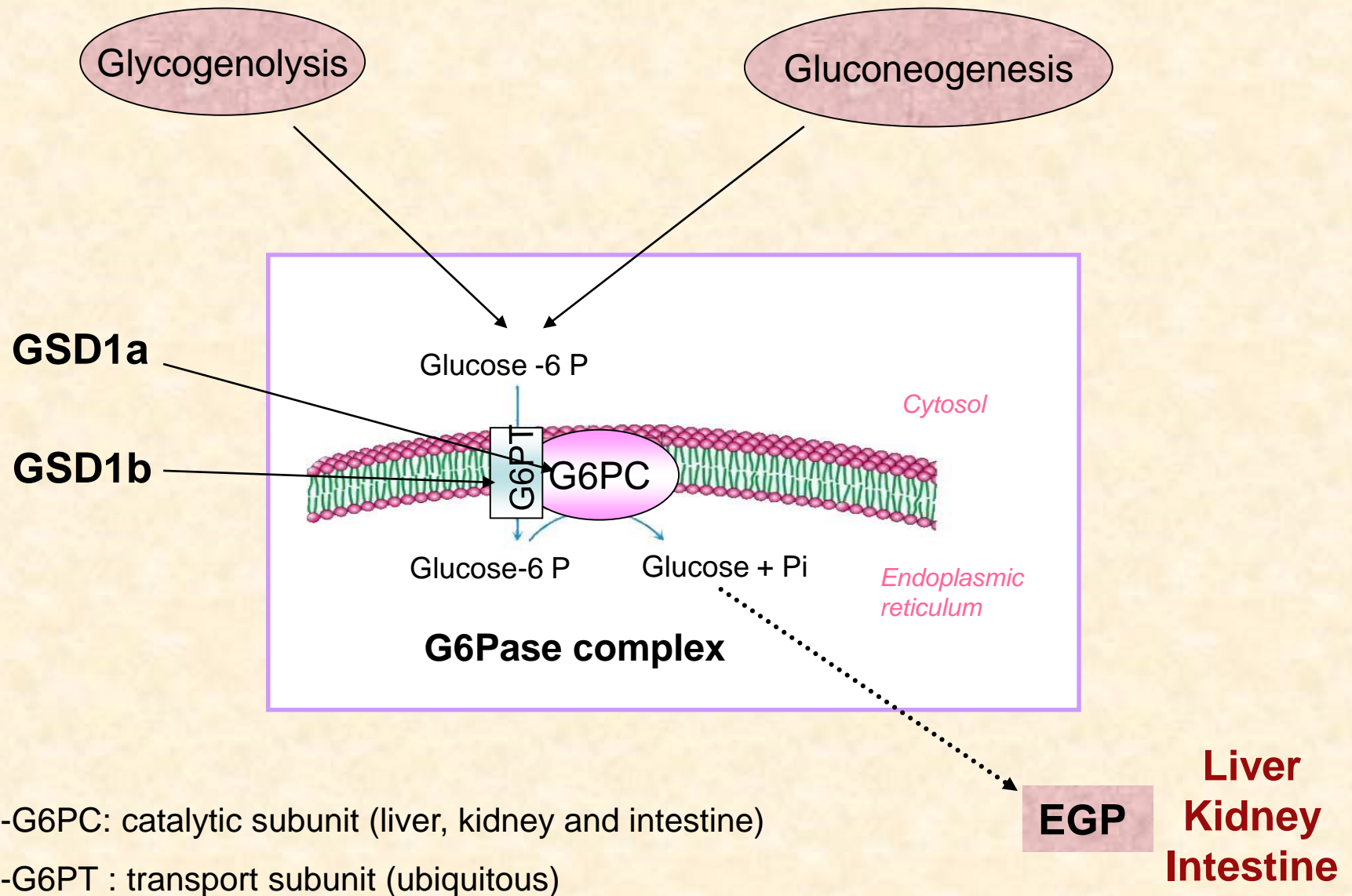
- Prevalence: 5-8%
- Epidemic
- Endogenous glucose production +++++
- HIGH glucose blood



### GSD1a

- Prevalence: 1:100 000
- Rare disease
- No endogenous glucose production
- LOW glucose blood

# Endogenous glucose production and Glucose-6 Phosphatase



# Phenotype of GSD1a

- Hypoglycemia

- Liver disease:



- Hepatomegaly with accumulation of glycogen
- Liver steatosis
- Liver adenomas (or carcinomas)

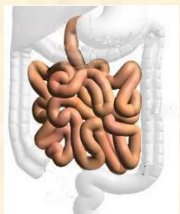


- Kidney disease:



- Nephromegaly with accumulation of glycogen
- Renal failure

- Intestinal disease (**under-estimated**):



- digestion dysfunction
- Diarrheas

# Mouse models of GSD1a

---

glucose



(Chou et al, 1999)

Total invalidation of *g6pc* :

Lethal without injection of glucose every 8 hours



(Mutel et al., J Hepatol, 2010)

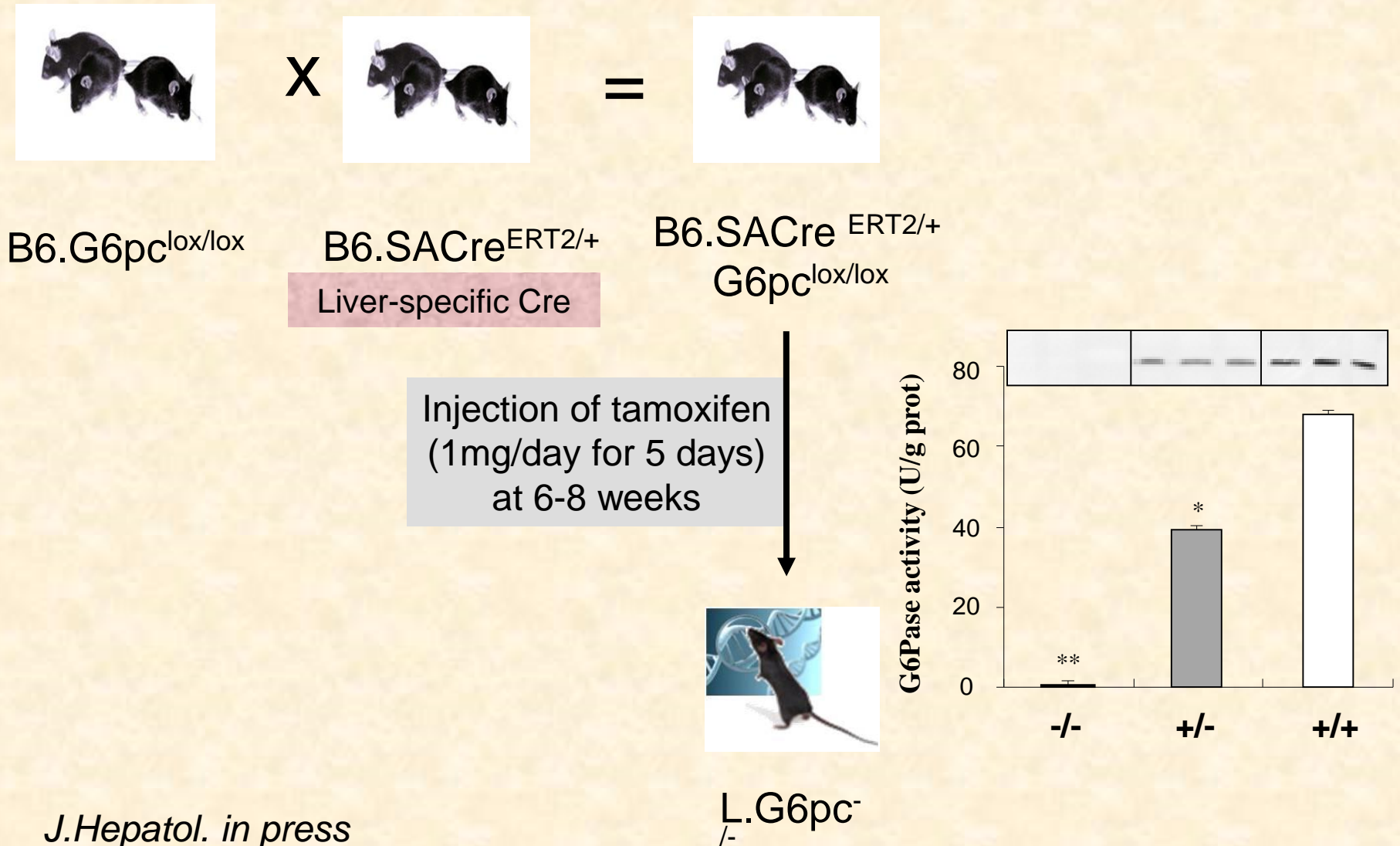
Tissue-specific invalidation of *g6pc* :

in the Liver  
and/or Intestine  
and/or Kidney

+ invalidation inducible by tamoxifen

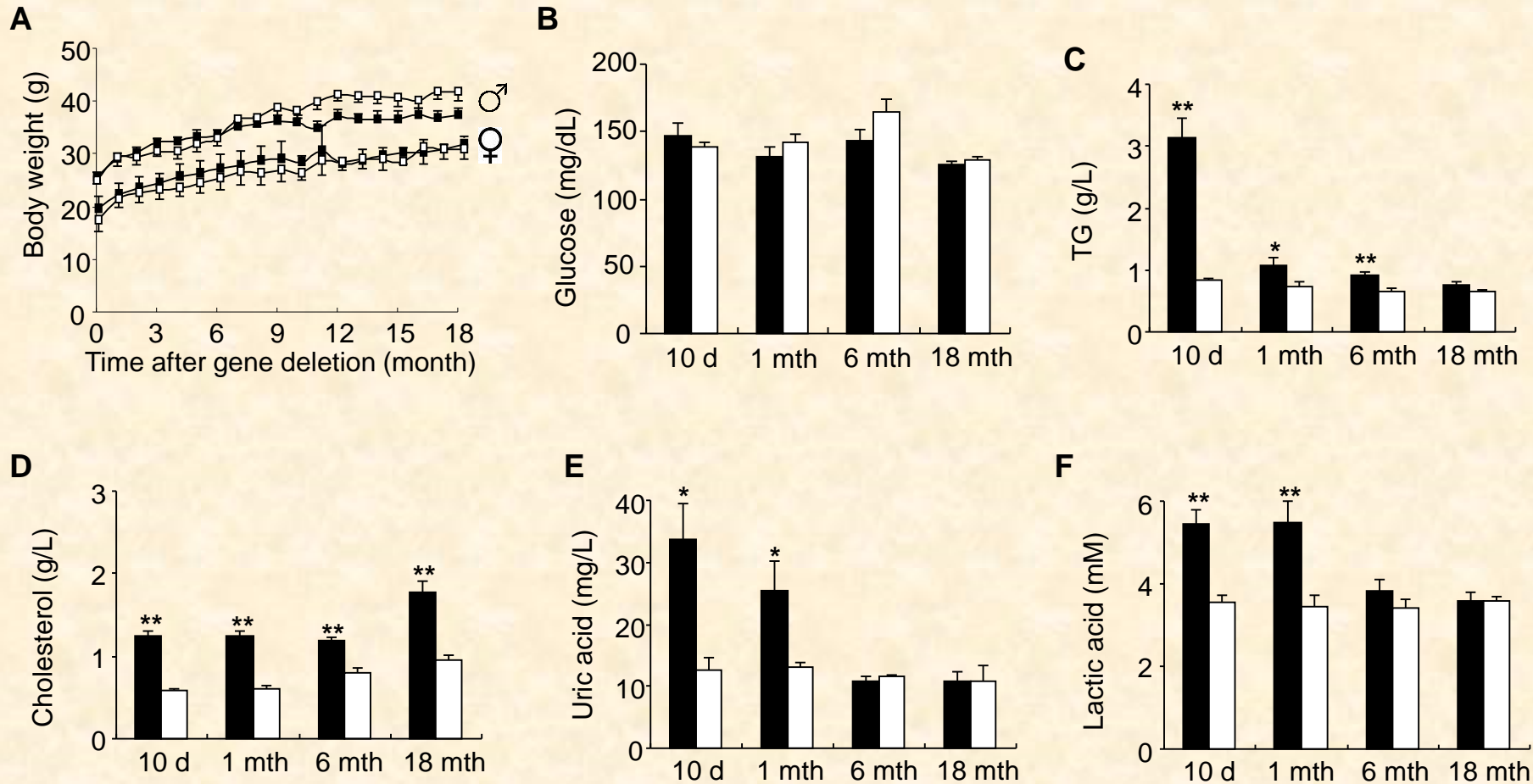
- To know if expression of G6Pase at one site is sufficient to compensate the lack of expression at the others
- To study the mechanisms of the deficiency organ by organ
- Liver gene therapy

# Targeted invalidation of G6Pase in liver of mice



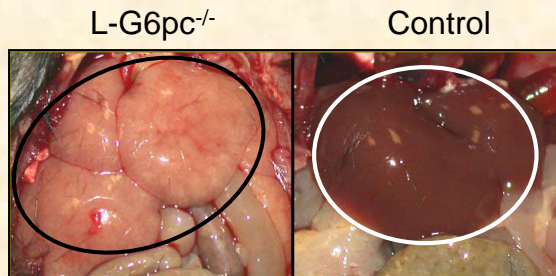
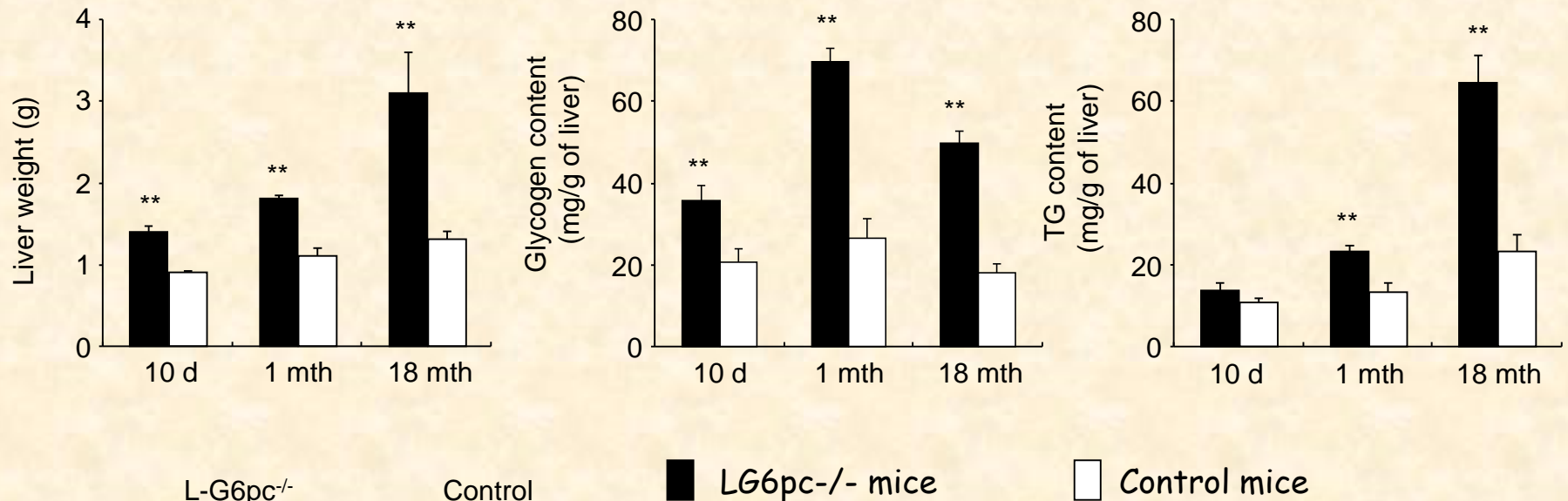
# Metabolic effects of hepatic G6pc deletion with time

■ LG6pc<sup>-/-</sup> mice      □ Control mice



Improvement of plasmatic parameters with time, except for cholesterol

# L.G6pc<sup>-/-</sup> mice develop hepatomegaly and steatosis

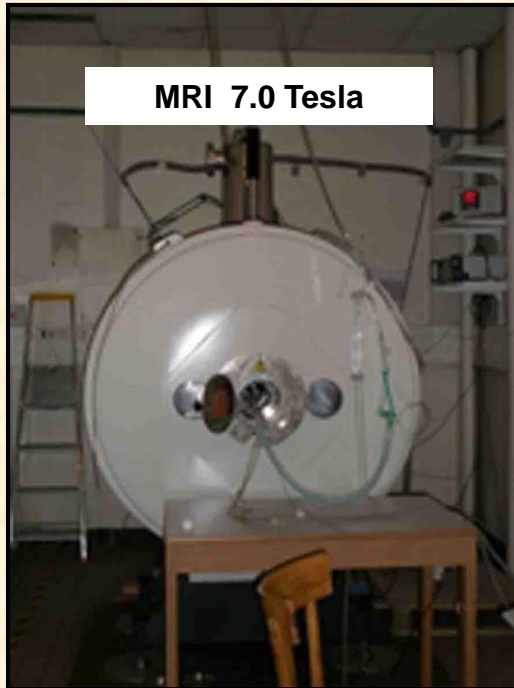


## Liver disease:

- Accumulation of glycogen in the liver of LG6pc<sup>-/-</sup> mice: HEPATOMEGALY
- Triglyceride storage in the liver of LG6pc<sup>-/-</sup> mice: STEATOSIS
- Development of hepatic adenomas with time

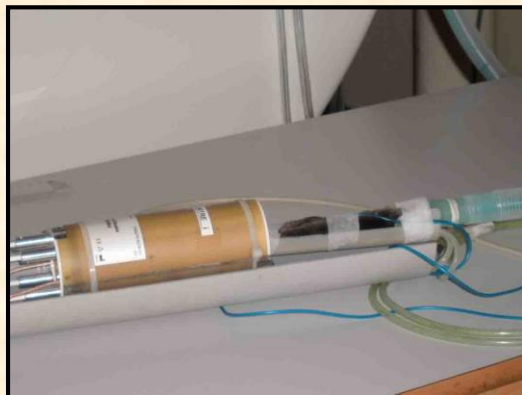
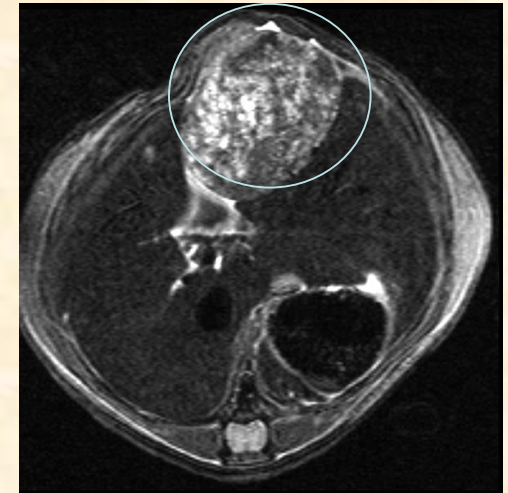
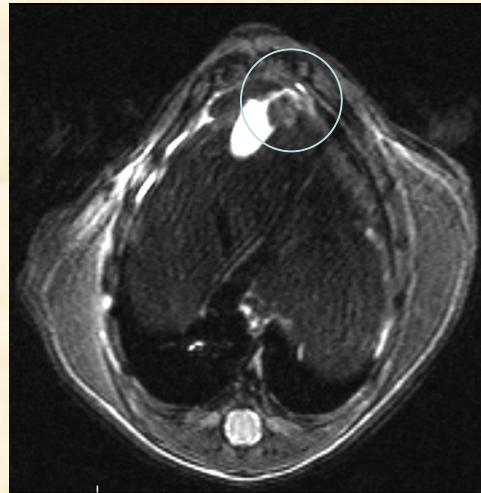
# Late appearance of hepatocellular adenoma in L.G6pc<sup>-/-</sup> mice

Follow up of mouse liver by MRI from 3 months to 18 months



*In collaboration with O. Beuf & F. Pilleul, Creatis, Lyon*

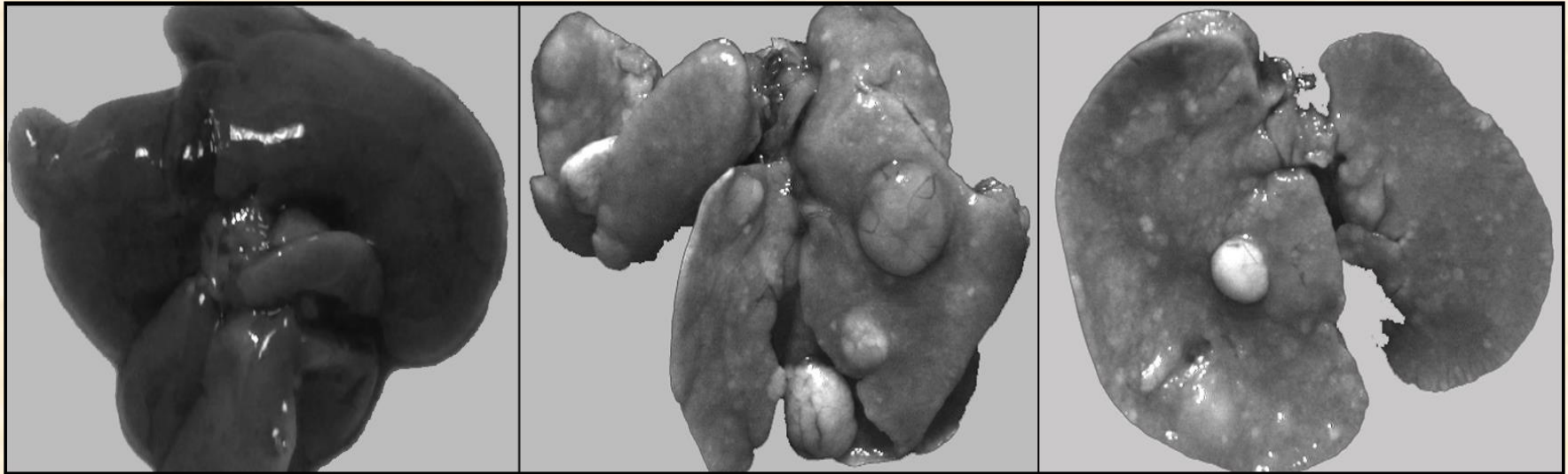
Liver of a LG6pc<sup>-/-</sup> mouse



# Late appearance of hepatocellular adenoma in L.G6pc<sup>-/-</sup> mice

Control liver

Livers of LG6pc<sup>-/-</sup> mice



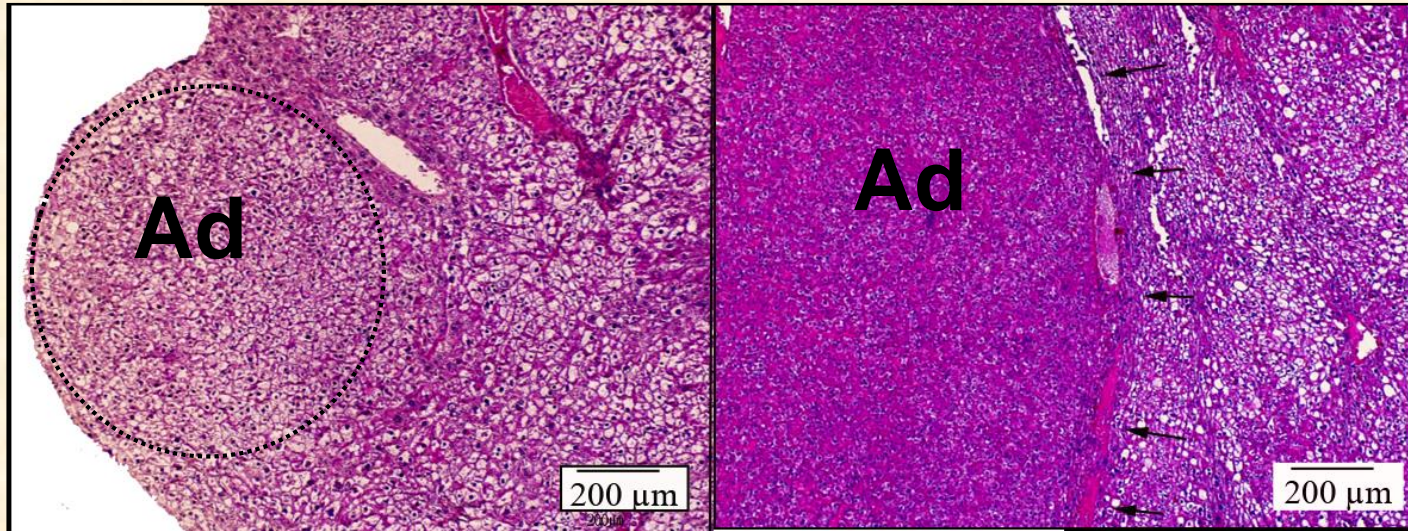
Time after G6pc deletion	% mice with lesions	Size of lesions
<6 months	0	0
9 months	15	1 mm
12 months	30	1-2 mm
15 months	40-50	1-3 mm
18 months	100	1-10 mm

# Development of adenoma in the liver of Lg6pc<sup>-/-</sup> mice

## ✓ Histology study

Liver adenomas (80%)

Liver pre-carcinomas (20%)



•Adenoma with steatosis and large hepatocytes

•Adenoma without steatosis - small hepatocytes

Loss of tissue organization  
Absence of portal space  
Necrosis and inflammation  
Glycogenic nuclei

# In conclusion

---

LG6pc<sup>-/-</sup> mice exhibit all the hepatic symptoms of the human pathology

- Viable, permitting to study the liver pathology along the mouse life
- Liver disease characteristic of GSD1a:
  - Hepatomegaly
  - Liver steatosis
  - Liver adenomas...and pre-carcinomas
- No apparent kidney disease
- No apparent intestinal disease

⇒ Excellent model to gene therapy

# Thanks to

Fabienne Rajas  
Armelle Penhoat  
Valérie Large  
Amandine Stein  
Elodie Mutel  
Aya Abdul-Wahed  
Sylvie Casteras  
Anne Stefanutti  
Isabelle Houberton  
Gilles Mithieux

**UMR Inserm u.855/UCBL, Lyon**



**MRI**

Olivier Beuf  
Frank Pilleul  
Niri Ramamonjisoa  
Sophie Cavassila  
Hélène Ratiney

**Créatis, Lyon**