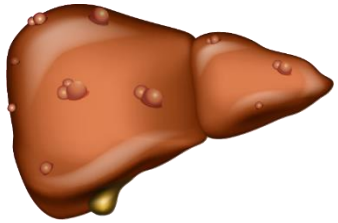
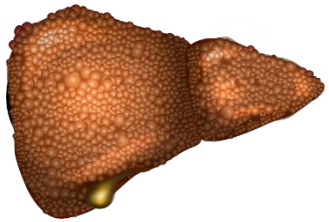
SELECTED OPPORTUNITY IN NASH

BIO13410 – Monoacylglycerol lipase as target for the treatment of fibrosis

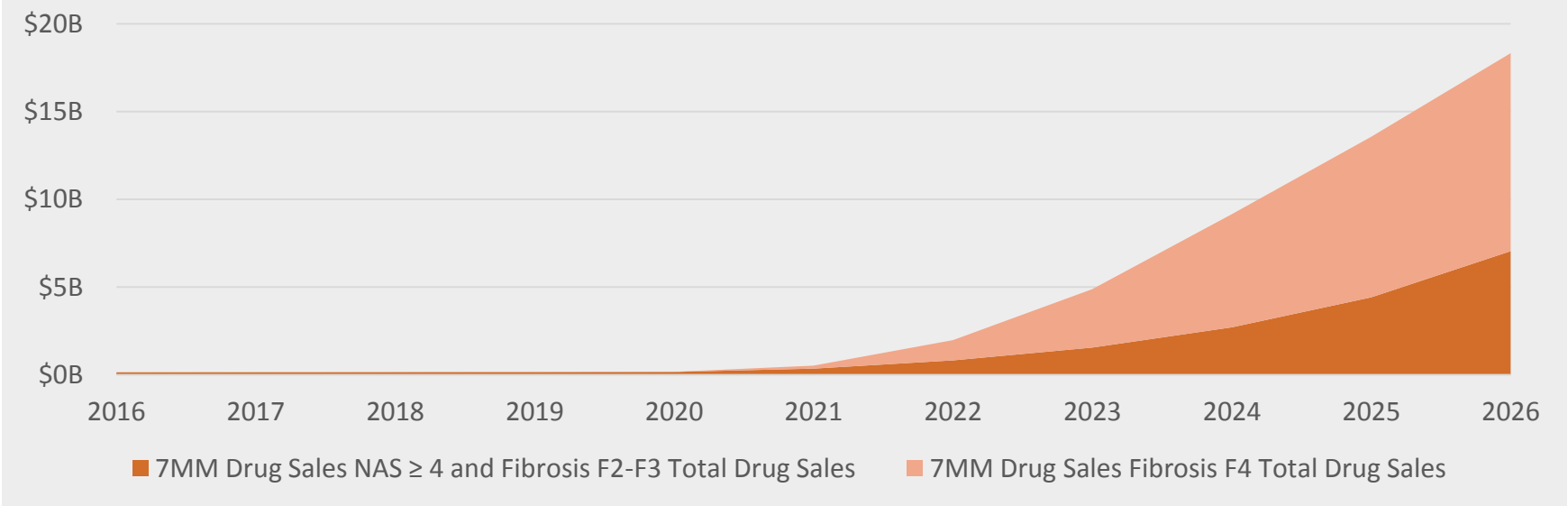
NASH, AT-A-GLANCE

NAFLD	NASH	CIRRHOSIS
		
Deposits of fat cause liver enlargement.	Scar tissue forms. More liver cell injury occurs.	Scar tissue makes liver hard and unable to work property.
80 Million Americans	16 Million Americans	1 to 3 Million Americans
Lifestyle and dietary rules	No treatment approved	Transplantation

NASH is a leading cause of liver transplantation (US + Europe)

NASH Market

Forecast Global NASH Sales (7MM) by Patient Segment



Key Global Metrics (2026)

1,42M	$11,3B	62%
Number of F4 NASH patients to be prescribed a therapeutic	Projected sales for NASH F4	Projected total proportion of sales for F4 patients

*Global Data (September 2018), 7MM = US, Germany, France, Italy, Spain, UK and Japan

BIO13410 – MONOACYLGLYCEROL LIPASE AS TARGET FOR THE TREATMENT OF FIBROSIS

Product factsheet

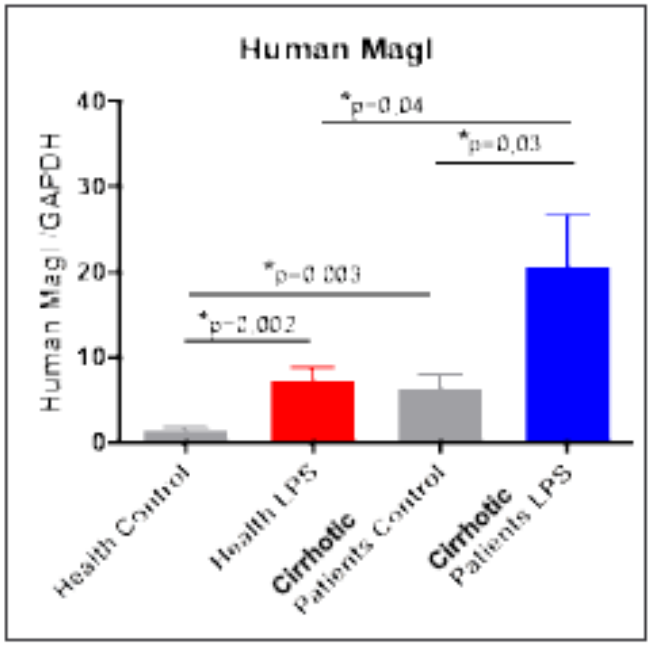
PoC in vivo

- **Target:**
  - Monoacylglycerol lipase
- **Product:**
  - Only monoacylglycerol lipase (MAGL) inhibitors (tool compounds)
- **Application:**
  - Treatment of liver fibrosis
- **Rational / POC:**
  - MAGL is expressed in adipocytes, where it functions together with hormonesensitive lipase (LIPE) to hydrolyze intracellular triglyceride stores, and in the intestine, where it is largely responsible for cleaving monoacyglycerols to form free fatty acids and glycerol;
  - These observations implicate MGL in metabolic diseases and suggest that MAGL inhibitors will have beneficial effects on metabolic disorders, including obesity, hyperphagia and diabetes;
  - This work demonstrates that MAGL is an immunometabolic target in the liver and MAGL inhibitors may show promising antifibrogenic effects during chronic liver injury.
- **Patent and publication:**
  - WO2016046130: METHODS AND PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF FIBROSIS
  - Tardelli M, Bruschi FV, Claudel T, Fuchs CD, Auer N, Kunczer V, Stojakovic T, Scharnagl H, Habib A, Grabner GF, Zimmermann R, Lotersztajn S, Trauner M. *Lack of monoacylglycerol lipase prevents hepatic steatosis by favoring lipid storage in adipose tissue and intestinal malabsorption*. J Lipid Res. 2019 May 2. pii: jlr.M093369.
  - Habib A, Chokr D, Wan J, Hegde P, Mabire M, Siebert M, Ribeiro-Parenti L, Le Gall M, Lettéron P, Pilard N, Mansouri A, Brouillet A, Tardelli M, Weiss E, Le Faouder P, Guillou H, Cravatt BF, Moreau R, Trauner M, Lotersztajn S. *Inhibition of monoacylglycerol lipase, an anti-inflammatory and antifibrogenic strategy in the liver*. Gut. 2018 Oct 9. pii: gutjnl-2018-316137.

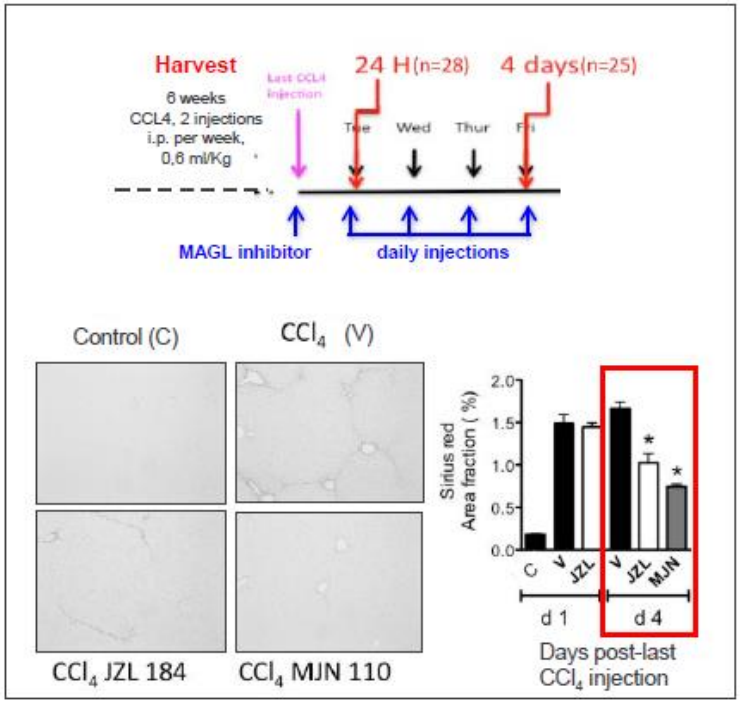
BIO13410 – MONOACYLGLYCEROL LIPASE AS TARGET FOR THE TREATMENT OF FIBROSIS

Proof of concept

MAGL is increased in cirrhotic patients and its inhibition accelerates fibrosis regression in mice



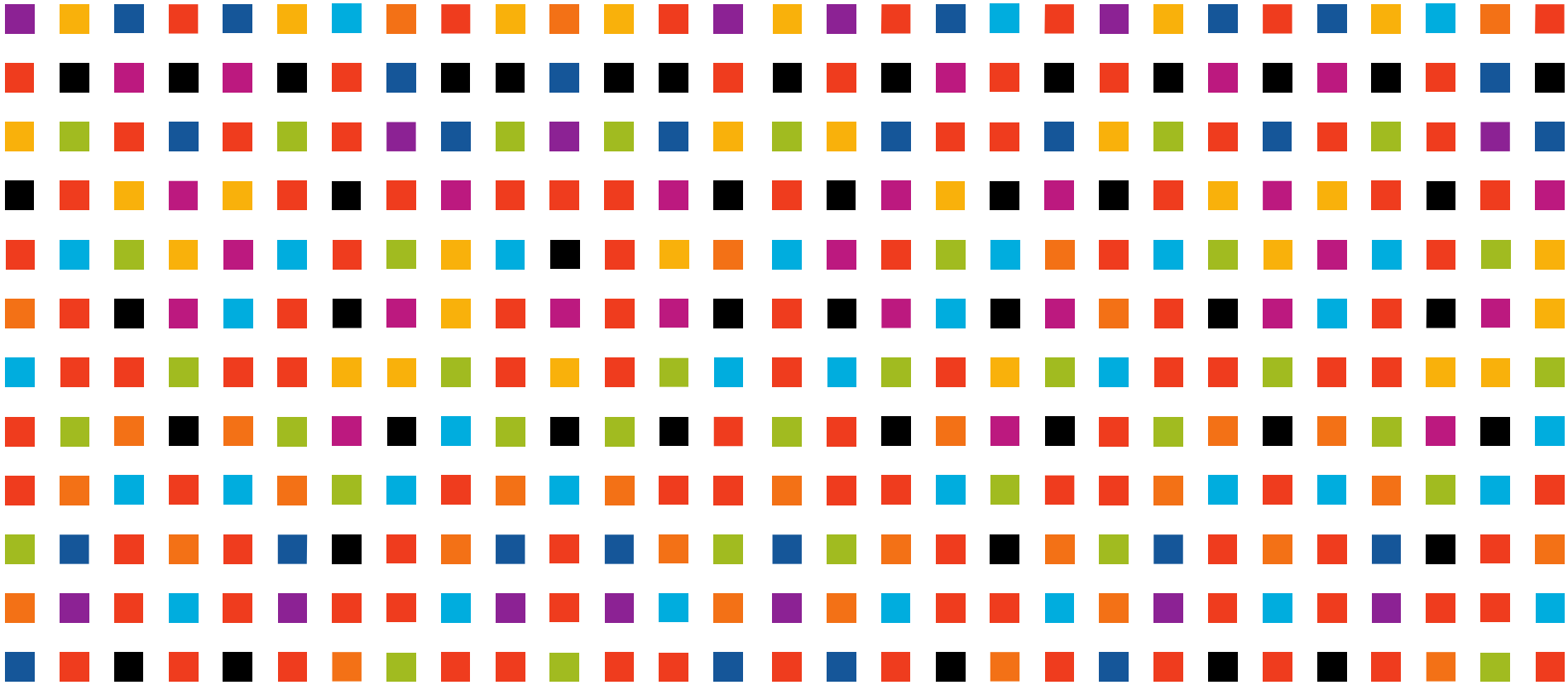
Both MAGL level and induction of MAGL by LPS are increased in PBMC cirrhotic patients.



PHARMACOLOGICAL INHIBITORS OF MAGL ACCELERATES LIVER FIBROSIS REGRESSION IN CCL4 FIBROSIS REGRESSION MODEL. PICROSIRIUS RED STAINING (lower right). Representative image of picrosirius-red stained liver tissue sections from mice treated with MAGL inhibitors or vehicle for 4 days (lower left: Morphometric analysis)

Business Opportunity

- **Collaboration:**
  - Test your MAGL inhibitor in NASH model.
- **Licensing:**
  - Develop your MAGL inhibitor in NASH indication.
- **Team:**
  - Work with Dr. Lotersztajn, Head of the team "Inflammatory responses in chronic liver diseases" and Deputy Director at Center for Research in Inflammation (CRI, Inserm U1149).
- **Interest:**
  - Extend the scope of your drug.



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