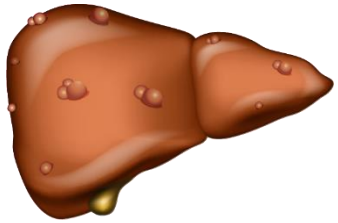
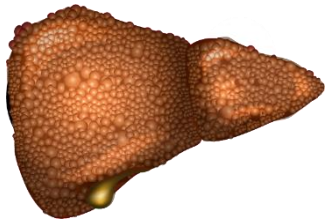
SELECTED OPPORTUNITY IN NASH

BIO17600 – METHODS AND COMPOSITIONS FOR TREATING LIVER DISESASES

NASH, AT-A-GLANCE

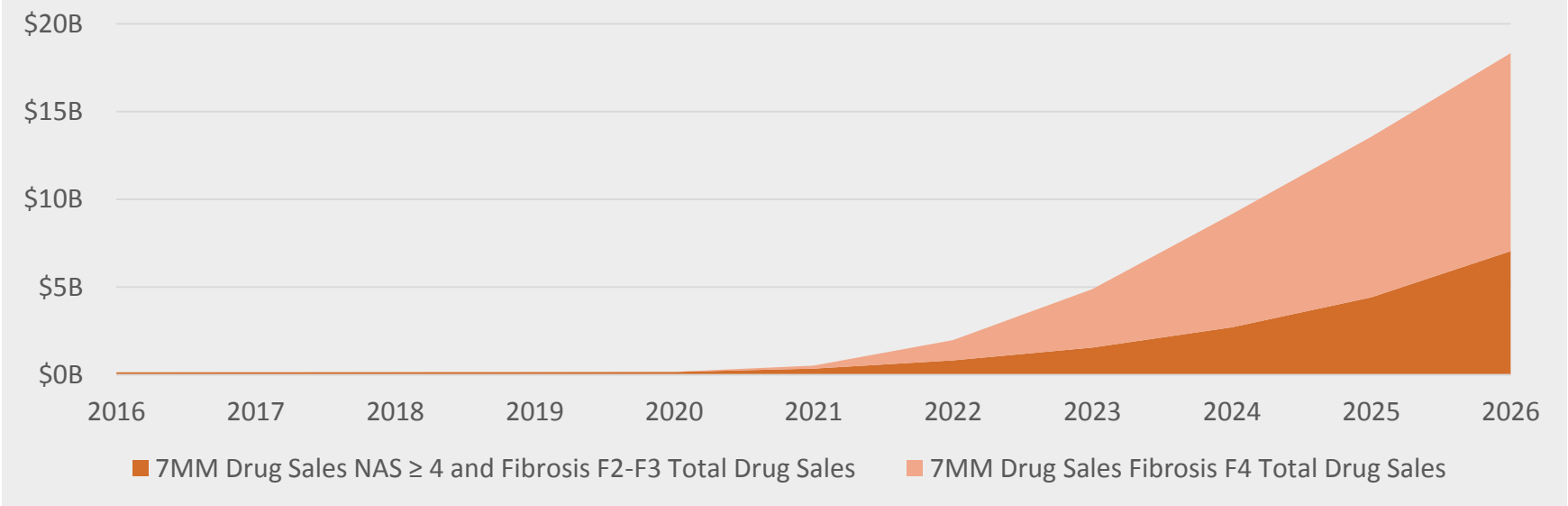
NAFLD	NASH	CIRRHOSIS
		
Deposits of fat cause liver enlargement.	Scar tissue forms. More liver cell injury occurs.	Scar tissue makes liver hard and unable to work property.
80 Million Americans	16 Million Americans	1 to 3 Million Americans
Lifestyle and dietary rules	No treatment approved	Transplantation

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

InsermTransfert
Your partner in health innovation

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

InsermTransfert
Your partner in health innovation

BIO17600 – METHODS AND COMPOSITIONS FOR TREATING LIVER DISESASES

Product factsheet

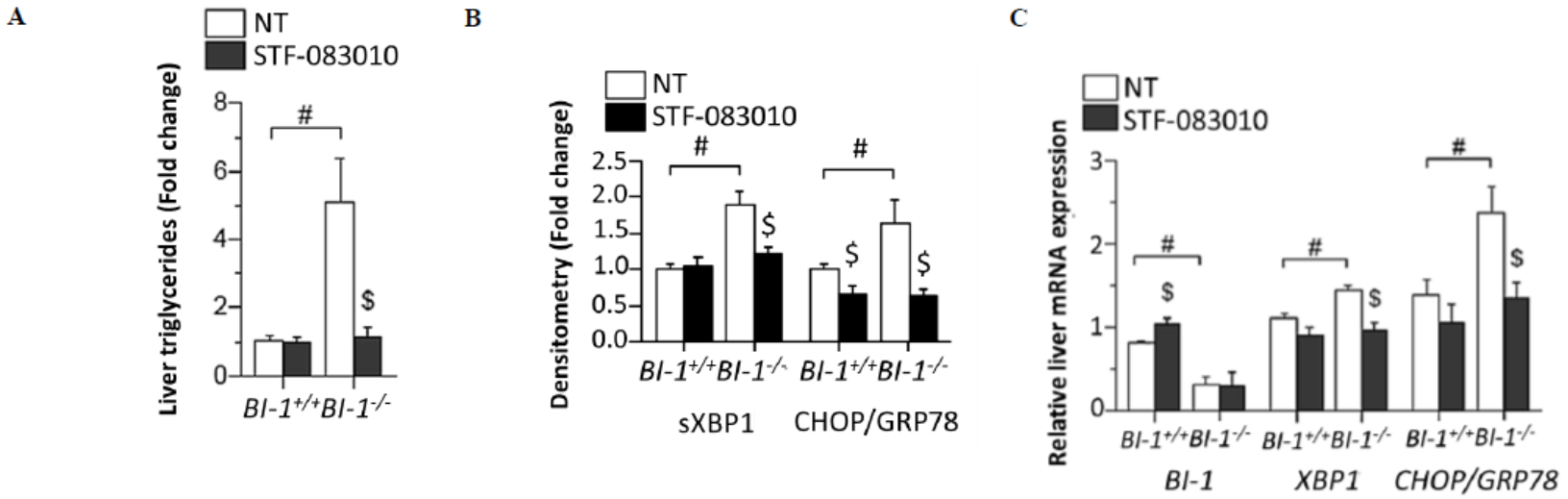
PoC in vivo

- **Target:**
  - IRE1α (endoribonuclease activity)
- **Product:**
  - STF03010 (tool compound)
- **Application:**
  - Nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), fibrotic NASH or liver cancer
- **Technology:**
  - Peptides, peptidomimetic, small molecule
- **Rational / POC:**
  - Endoplasmic reticulum (ER) stress is activated in nonalcoholic fatty liver disease;
  - B-cell lymphoma 2 (BCL2)-associated X protein (Bax) inhibitor-1 (BI-1) is a negative regulator of the ER stress sensor, inositol-requiring enzyme 1 alpha (IRE1α);
  - In livers of tunicamycin-treated BI-1-/- mice a IRE1α-dependent NLRP3 inflammasome activation, a hepatocyte death, a fibrosis and a dysregulated lipid homeostasis that led to liver failure within a week are observed;
  - Human NAFLD liver biopsies revealed that BI-1 downregulation parallel to the upregulation of IRE1'α RNase signaling;
  - The pharmacological inhibition of IRE1α endoribonuclease activity counteracted IRE1α endoribonuclease activity, improving glucose tolerance and rescuing from NASH in BI-1-/- mice.
  - Thus, targeting IRE1α-dependent NLRP3 inflammasomesignaling with pharmacological agents or via BI-1 may represent a tangible therapeutic target for NASH.
- **Patent and publication:**
  - PCT/EP2019/053807: METHODS AND COMPOSITIONS FOR TREATING LIVER DISESASES
  - Lebeaupin C, Vallée D, Rousseau D, Patouraux S, Bonnafous S, Adam G, Luciano F, Luci C, Anty R, Iannelli A, Marchetti S, Kroemer G, Lacas-Gervais S, Tran A, Gual P, Bailly-Maitre B. *Bax inhibitor-1 protects from nonalcoholic steatohepatitis by limiting inositol-requiring enzyme 1 alpha signaling in mice*. Hepatology. 2018 Aug;68(2):515-532.

BIO17600 – METHODS AND COMPOSITIONS FOR TREATING LIVER DISESASES

Proof of concept

Early into HFD feeding, limiting the ER stress response by inhibiting IRE1α RNase activity protects from steatosis and hyperglycemia

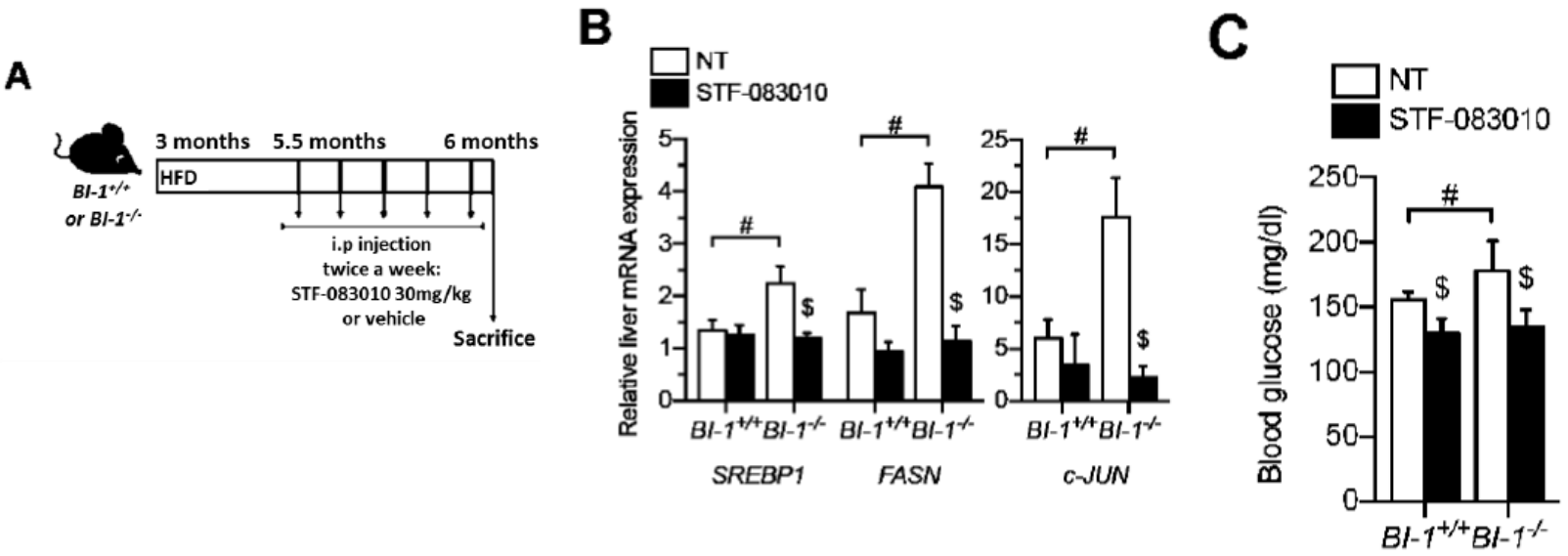


*Starting 2.5 months after HFD feeding, BI-1+/+ and BI-1-/- mice were treated with STF-083010 (30 mg/kg) or vehicle (NT, Kolliphor 16%) twice a week for 2 weeks before sacrifice. (**A**) Relative liver triglyceride levels. Analysis of ER stress markers by (**B**) immunoblot with respect to the loading control HSP90, and (**C**) qPCR, genes significantly (#p < 0.05) different in expression comparing NT HFD-fed BI-1+/+ and BI-1-/- mice. n = 6; $p < 0.05 when comparing treated to untreated counterpart.*

BIO17600 – METHODS AND COMPOSITIONS FOR TREATING LIVER DISESASES

Proof of concept

Blocking IRE1α RNase activity in HFD-fed mice limits lipogenesis priming, hyperglycemia and collagen accumulation in livers of BI-1-deficient mice and does not affect liver appearance in ND-fed mice.

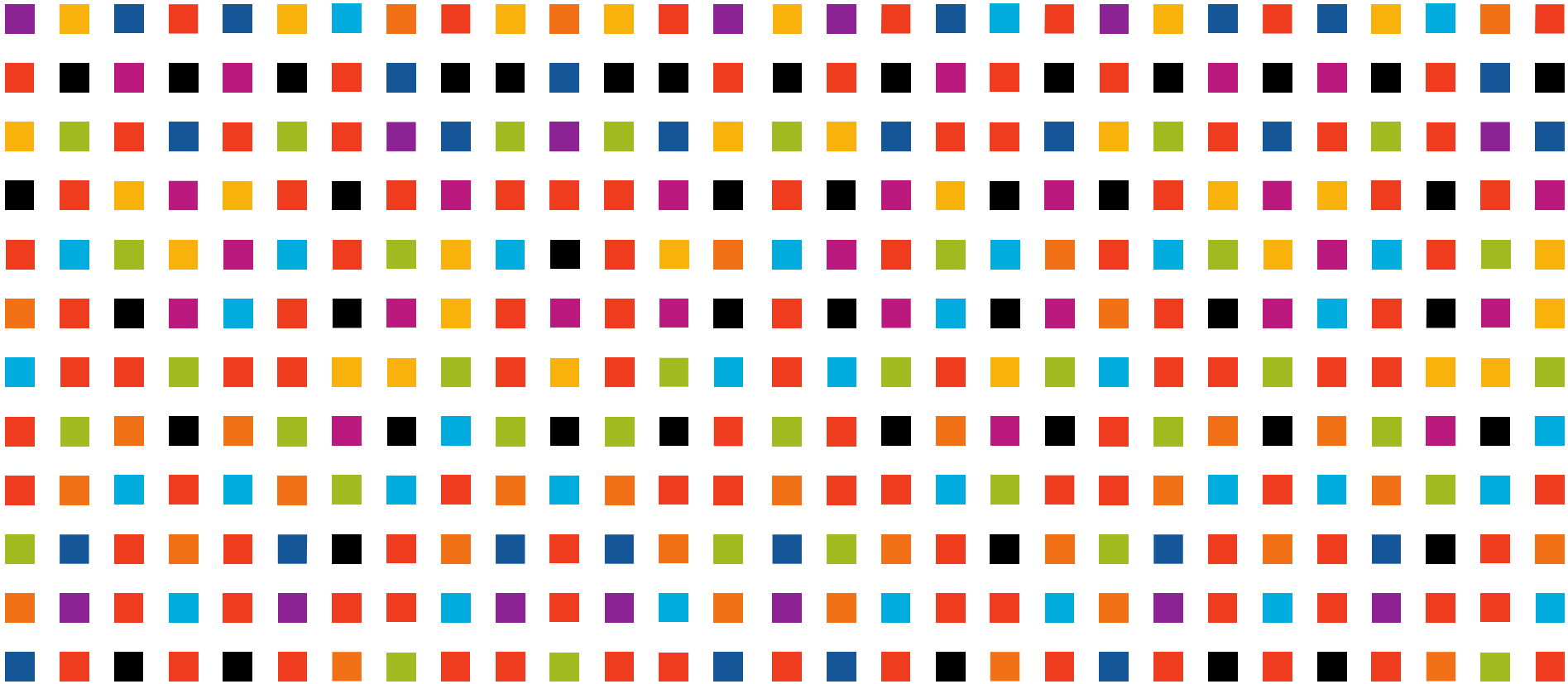


*(**A**) Protocol timeline for vehicle (NT,Kolliphor 16%) or STF-083010 (30 mg/kg) injections in HFD-fed BI-1+/+ and BI-1-/- mice. (**B**) qPCR analysis of hepatic genes involved in lipid synthesis and metabolism (n = 3). Genes are significantly (#p < 0.05) different in expression comparing NT HFD-fed BI-1+/+ and BI-1- /- mice. $p < 0.05 when comparing treated to untreated counterpart. (**C**) Blood glucose concentrations in fed BI-1+/+ and BI-1-/- mice (n = 6).*

BIO17600 – METHODS AND COMPOSITIONS FOR TREATING LIVER DISESASES

Business Opportunity

- **Collaboration:**
  - Test your Ire1-Alpha inhibitor in NASH model.
- **Licensing:**
  - Develop your Ire1-Alpha inhibitor in NASH indication.
- **Team:**
  - Work with Dr. Bailly-Maitre, member of Philippe Gual's team "Hepatic Complications in obesity (NAFLD)" at C3M-Nice (UMR1065).
  - http://www.unice.fr/c3m/index.php/research-teams/philippe-gual-albert-tran/
- **Interest:**
  - Extend the scope of your drug.



AYMERIC.EMPEREUR@INSERM-TRANSFERT.FR

Inserm Transfert - Paris Biopark
7 Rue Watt - 75013 Paris
Tel: +33 1 55 03 01 00 / Fax: +33 55 03 01 60
www.inserm-transfert.fr

InsermTransfert
Your partner in health innovation