SJT MOLECULAR RESEARCH

New family of molecules with oral therapeutic potential in NASH, obesity, hypertension, dyslipidemia and type 2 diabetes

Opportunity

- Novel family of small molecules, orally applicable
- Pre-clinical stage, lead molecule (SJT4A) identified
- Potential application in a broad variety of metabolic disease indications:
  - **NAFLD (including NASH):** significant reduction in collagen gene expression (fibrosis marker) and NAS score: reduced liver steatosis, ballooning, inflammation and fibrosis
  - **Type 2 Diabetes:** greater potency compared to standard glucose lowering therapies (Metformin)
  - **Obesity:** > 40% excessive weight reduction in DIO mouse model
  - **Hypertension:** reduces systolic blood pressure
  - **Dyslipidemia and diabetes asscociated complications:** Decline of insulin resistance, reduction in blood pressure, plasma cholesterol and weight control, decrease of liver lipids in hepatic steatosis
- Encouraging safety profile from early toxicology studies
- Simple manufacturing process
- Hypothesis of MoA (FXR agonist)
- Strong IP portfolio with long expiry dates granted in major markets
- SJT is seeking a partner for the further development and commercialization of its proprietary, novel molecules

Discovery pathway to SJT's novel molecules

IBAMA

Input from local tribe elders

(1) Multiple rounds of testing on plants:
- *Anti-diabetic properties*
- *Toxicology*
- *Efficacy*

(2) Identification of active groups (alkaloids, polyphenols & glycosides)

(3) Scaffold selection
- *Addition of radicals*
- *Identification of best molecules*

AMAZON RAIN FOREST
rich source of medicinal plants

100 plants selected for further analysis *(1)*

Testing toxicology & efficacy

34 plants selected for anti-diabetic properties *(1)*

Testing in pairs

2 plants with synergistic activity *(1)*

Isolate and analyse active principles *(2)*

NASH
Obesity
Hypertension
Diabetes Type 2
Dyslipidemia

Animal testing

New family of molecules: *in vivo* screening (1 lead and 68 additional active family members)

Parent β-carboline structure

Design and synthesis of new molecules *(3)*

Herbal Product → Synthesized molecule

Company background

- SJT Molecular Research is a privately-funded biotech company based in Spain (Vitoria)
- Focus on the discovery and early development of novel molecules for metabolic disorders
- Virtual set-up with strong network of renowned public and private institutions:

Public Institutions:

- Federal University of Grande Dourados (Brazil)
- Federal University of Paraná(Brazil)
- University of Alcalá (Madrid, Spain)
- University of the Balear Islands (Spain)
- University of Vigo (Spain)

Private Institutions:

- **Eurofins**, Cerep, Panlabs (France, UK, USA, Taiwan)
- **Gubra** (Denmark)
- **Cyprotex** (UK, USA)
- **Physiogenex** (France)
- **Amylgen** (France)
- **Gentronix** (UK)
- **Sequani** (UK)
- **Softmining** (IT)

Intellectual property

Patent claims cover:

- Composition of matter for the molecules
- Intermediates and derivatives
- Pharmaceutical formulations
- Medical use
- Cosmetic, nutraceutical or functional food additive composition

Granted in:

- **USA,** US9440966 (B2)
- **Europe**, EP2691394 (B1)
- **Japan**, JP6049216 (B2)
- **Canada**, 2,831,716
- **Australia,** AU2012234230 (B2)
- **Russia,** RU2615136 (C2)
- **Israel,** 228630
- **South Korea**, 046182713
- **Mexico**, MX/a/2013/011124

National phases:

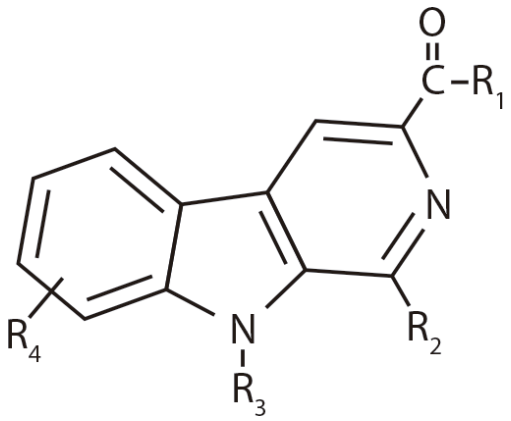
- China
- Brazil
- India

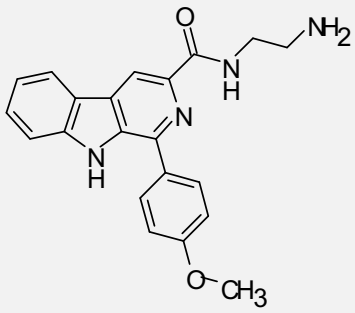
Patent filings worldwide covering novel family of molecules published as WO2012130912.

New International Patent Application No. PCT/EP2018/053990 of NAFLD and NASH

Novel family of molecules

- Data focused on the **lead** molecule (**SJT4A**)
- 2 backup modecules based on the same structure
- Intermediate and derivate compounds of the 3 molecules covered by patent applications (66 additional molecules)



SJT4A		N(-ethylamine)-1-benzosubstituted-β-carboline-3-carboxamide Mw = 360

Pharmacokinetics (PK)

- Plasma concentrations high enough to provide a therapeutic effect
- Extended bioavailability by bid administration*

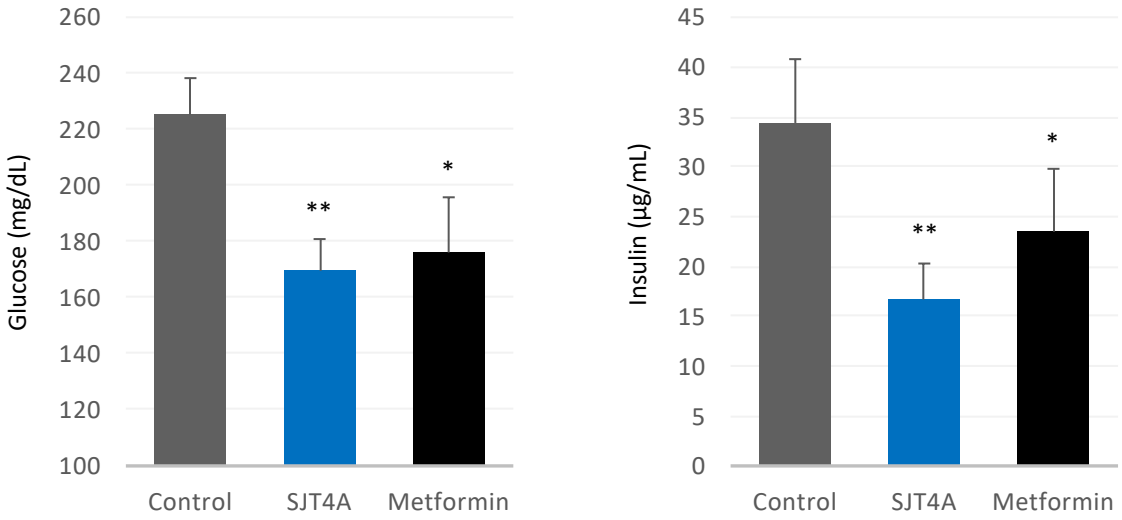
SJT4A-HCl (mice)

PK parameter	Qdx1** IV 15 mg/kg	Qdx1** PO 50 mg/kg	Qdx7** PO 50 mg/kg	Bid*x7 PO 50 mg/kg
AUC (h x ng/ml)	6229	3988	4836	8132
Last time point (AUC)	6	8	8	8
C_0 (ng/ml)	12015			
C_{max} (ng/ml)		1050	949	1524
MRT (h)	1.25	2.80	3.48	4.00
$T_{1/2}$ (h)	1.36			
T_{max} (h)		2.00	4.00	4.00
CL (ml/min/kg)	40.13			
Vss (L/kg)	3.58			
F (%)		18.87	21.81	**35.32**

* bid: 2 x daily // ** qd: once daily

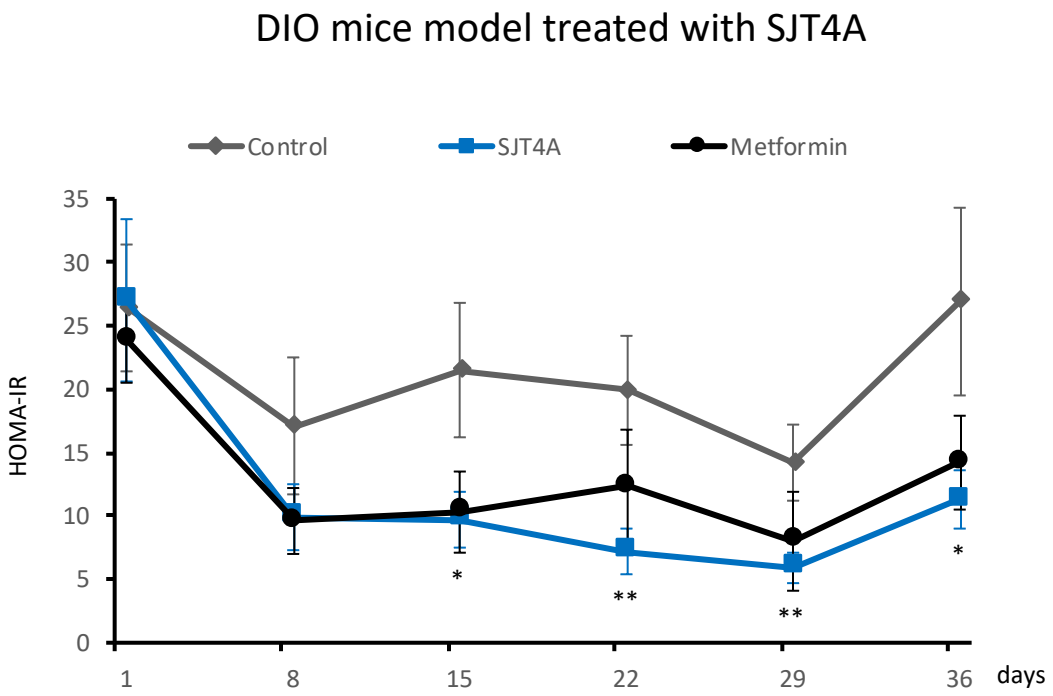
SJT4A reduces hyperglycemia and hyperinsulinemia

DIO mice model treated with SJT4A for 22 days



*Data expressed as mean ± s.e.m. values from 10 animals. *P<0.05, **P<0.01. 4A (50 mg/kg), Metformin (150 mg/kg)*

SJT4A decreases insulin resistance from the first week of treatment

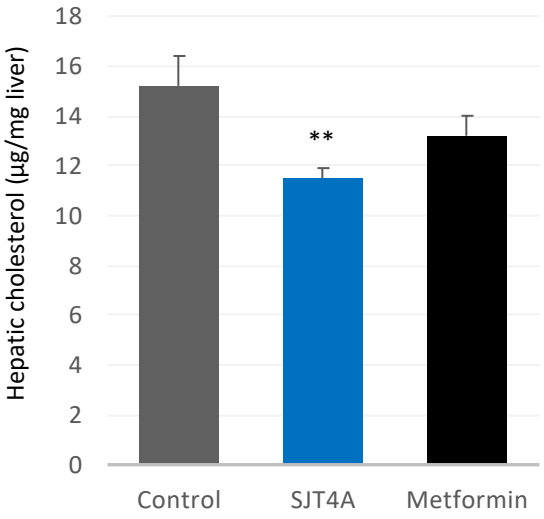


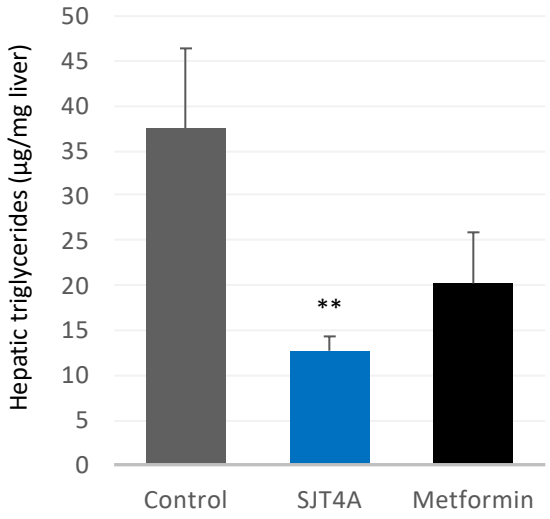
*Data expressed as mean ± s.e.m. values from 10 animals. *P<0.05, **P<0.01. 4A (50 mg/kg), Metformin (150 mg/kg)*

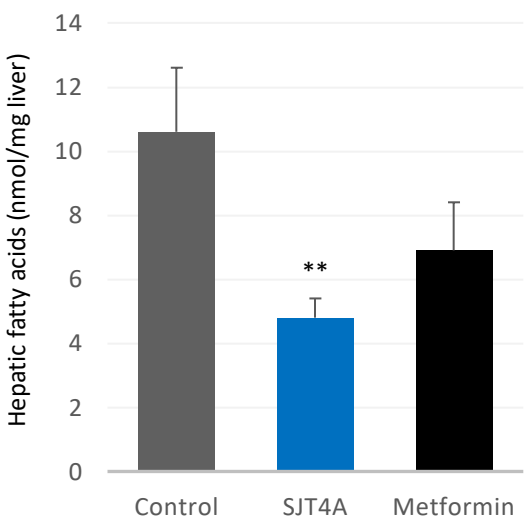
SJT4A decreases liver lipid content associated to hepatic steatosis

DIO mice model treated with SJT4A for 36 days

SJT4A decreases liver lipid content associated to hepatic steatosis



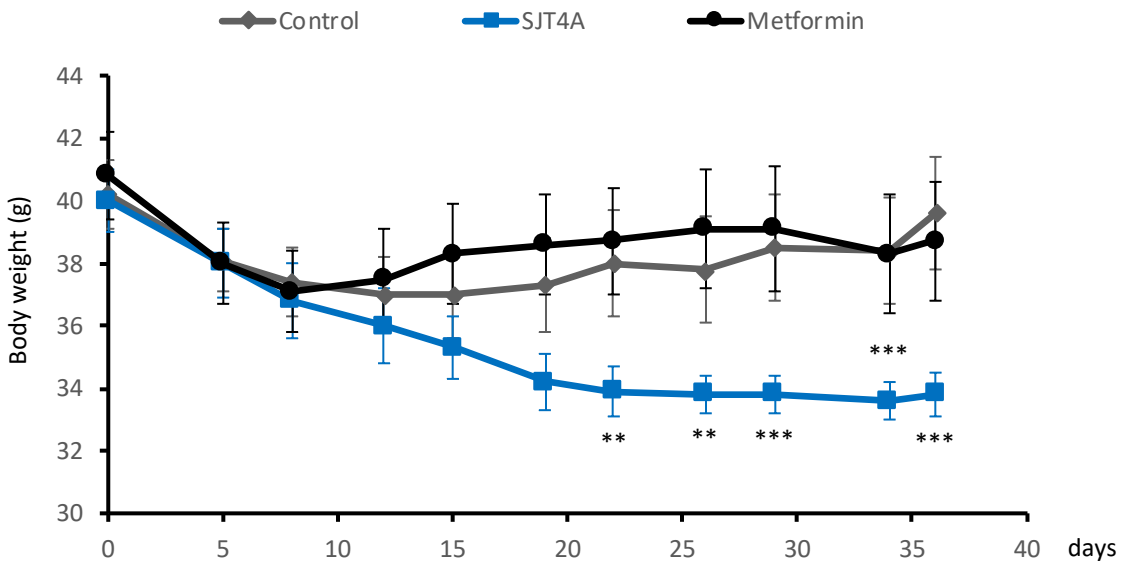




*Data expressed as mean ± s.e.m. values from 10 animals. **P<0.01. 4A (50 mg/kg), Metformin (150 mg/kg)*

SJT4A reduces the body excess weight (>47 %) and body weight by ≈15 %

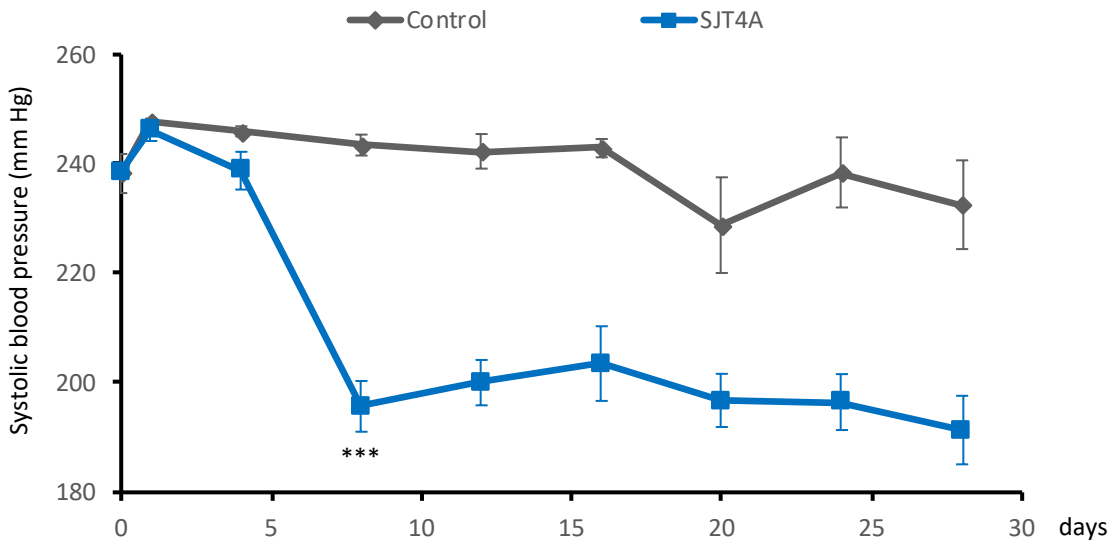
DIO mice model treated with SJT4A



*Data expressed as mean ± s.e.m. values from 10 animals. **P<0.01, ***P<0.001. 4A (50 mg/kg), Metformin (150 mg/kg)*

SJT4A reduces systolic blood pressure

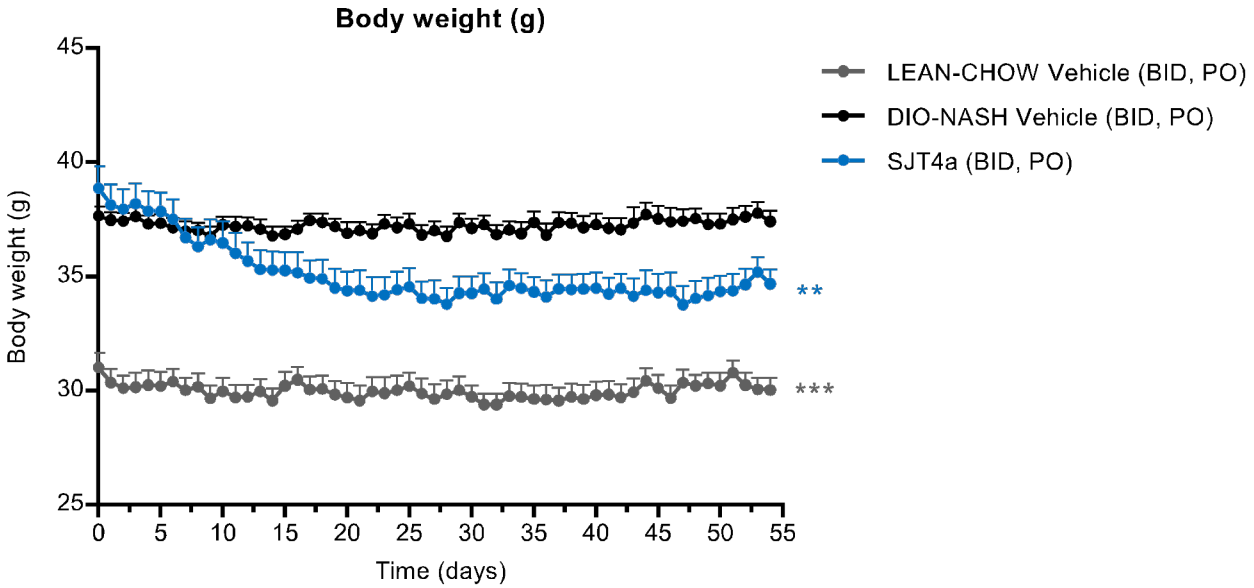
Systolic blood pressure in SHR hypertensive rat model



*Data expressed as mean ± s.e.m. values from 6 animals. ***P<0.001. 4A (15 mg/kg)*

SJT4A reduces excess weight by >40 % and body weight by ≈15 %

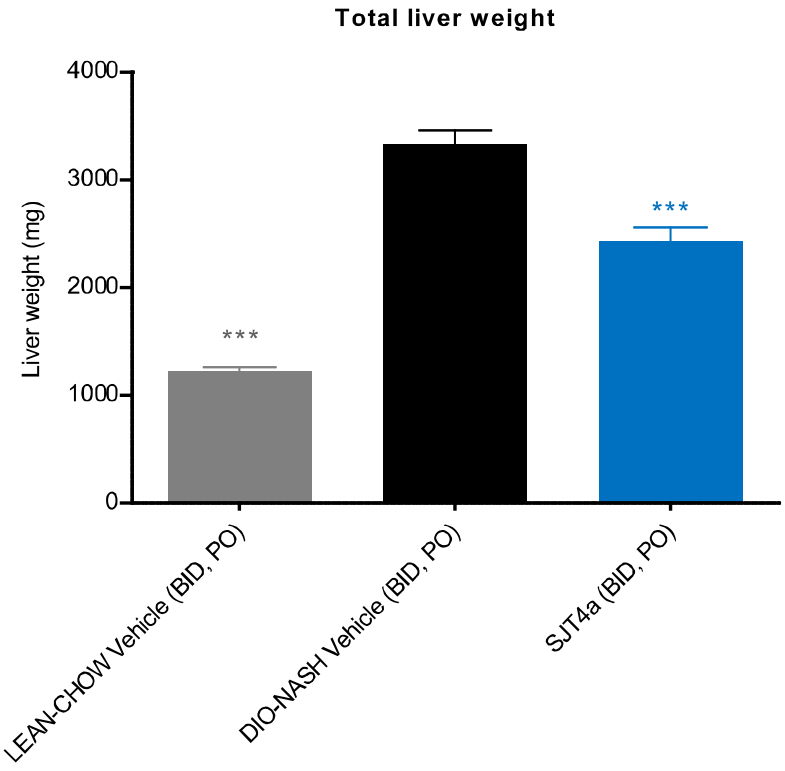
Gubra DIO-NASH mice model treated with SJT4A for 8 weeks



*Data expressed as mean ± s.e.m. values from 10-12 animals. **P<0.01, ***P<0.001. 4A (50 mg/kg)*

SJT4A reduces liver excess weight in DIO-NASH mice (>40 %)

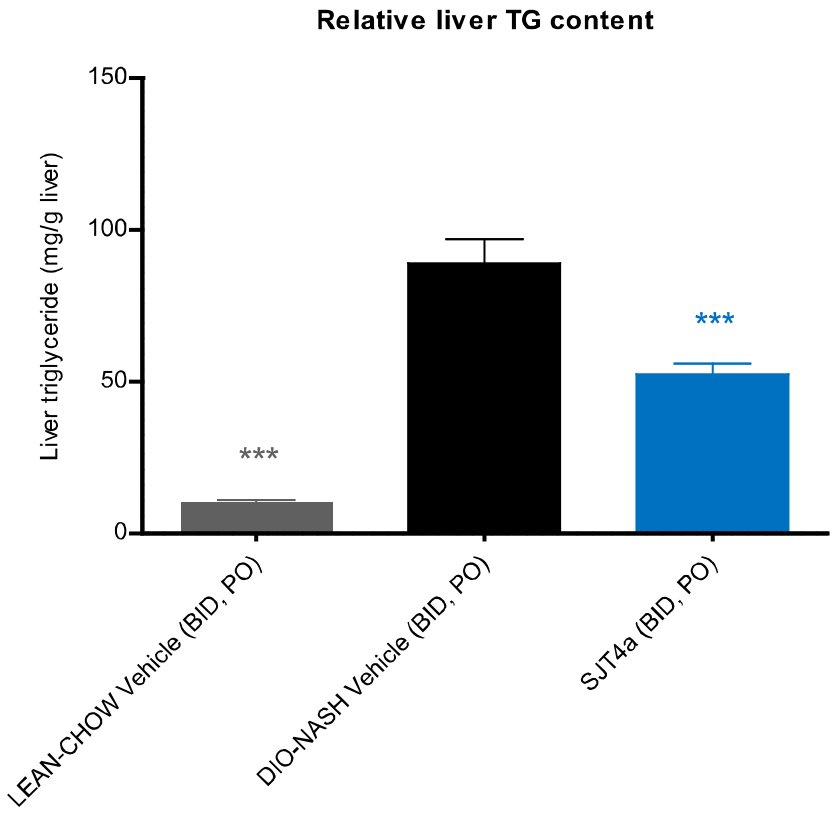
Gubra DIO-NASH mice model treated with SJT4A for 8 weeks

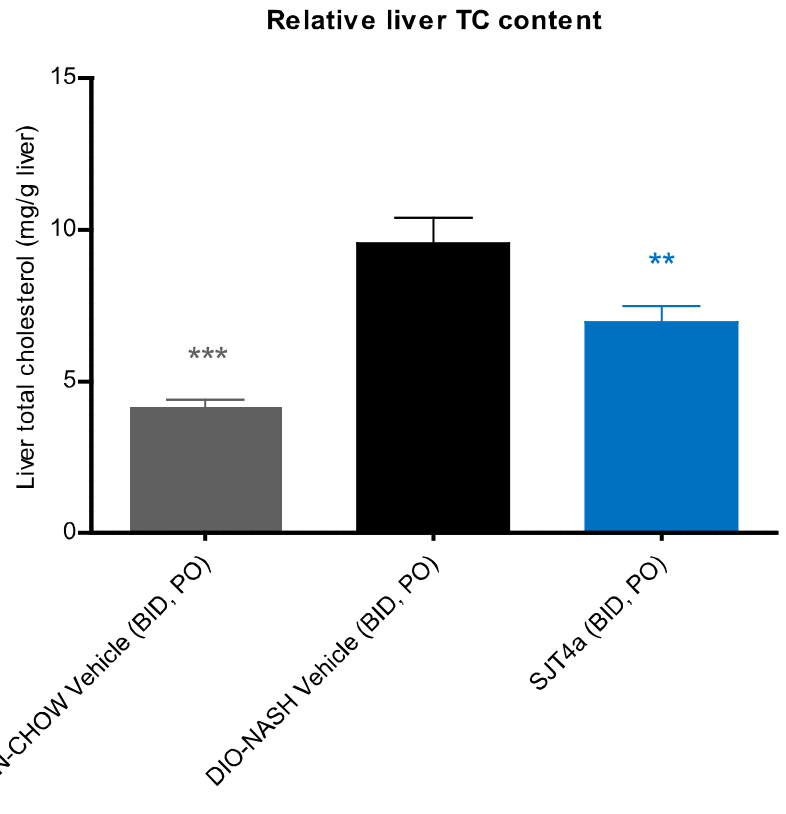


*Data expressed as mean ± s.e.m. values from 10-12 animals. **P<0.01, ***P<0.001. 4A (50 mg/kg)*

SJT4A reduces the excess of TG and TC in liver (>50 %)

Gubra DIO-NASH mice model treated with SJT4A for 8 weeks

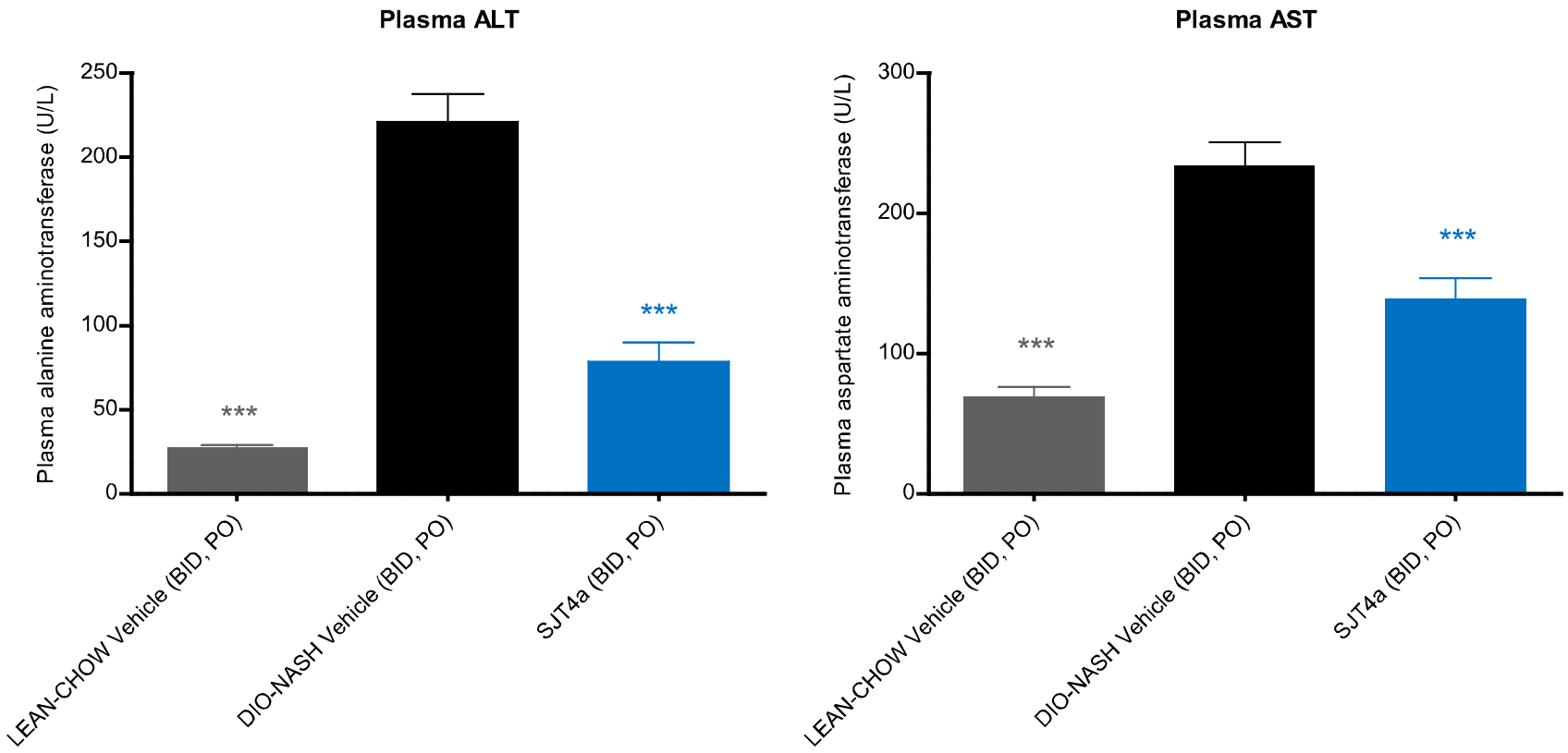




*Data expressed as mean ± s.e.m. values from 10-12 animals. **P<0.01, ***P<0.001. 4A (50 mg/kg)*

SJT4A decreases liver toxicity (77 % ALT & 65 % AST)

Gubra DIO-NASH mice model treated with SJT4A for 8 weeks



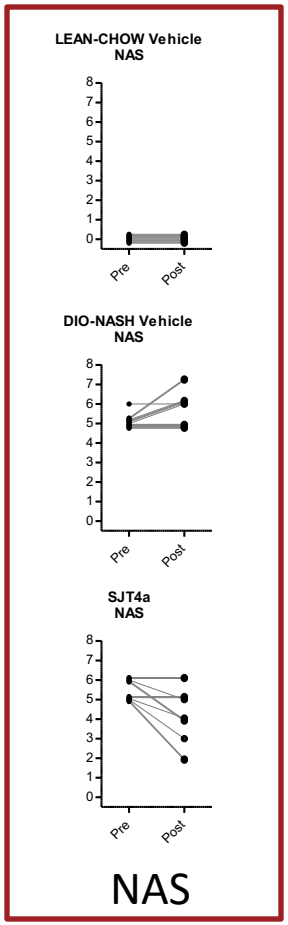
*Data expressed as mean ± s.e.m. values from 10-12 animals. ***P<0.001. 4A (50 mg/kg)*

SJT4A significantly lowers NAFLD activity score (NAS)

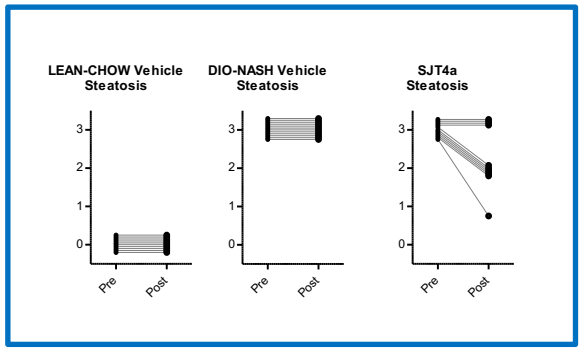
Gubra DIO-NASH mice model treated with SJT4A for 8 weeks

Significantly lower NAFLD activity score (NAS) affects steatosis and inflammation

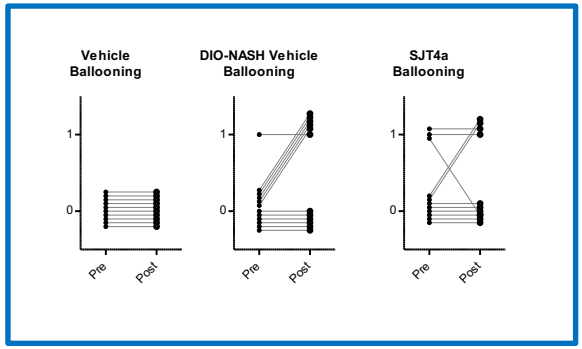
Pre and post-study biopsy comparison



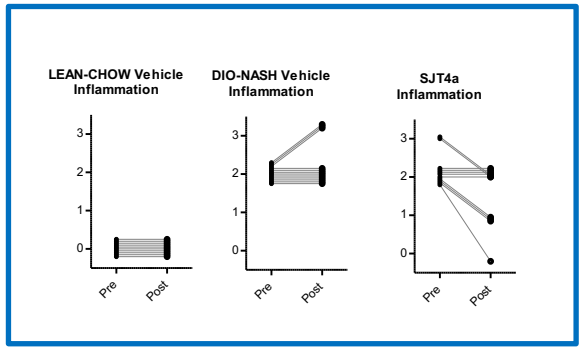
NAS



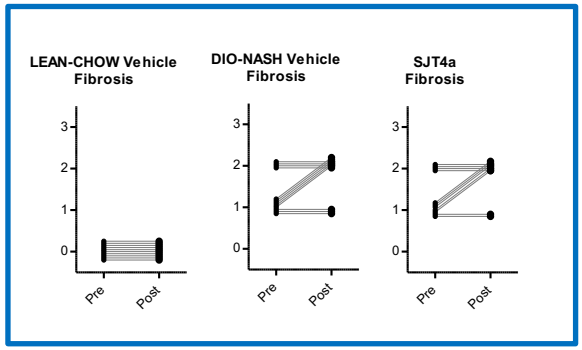
Steatosis



Ballooning



Inflammation

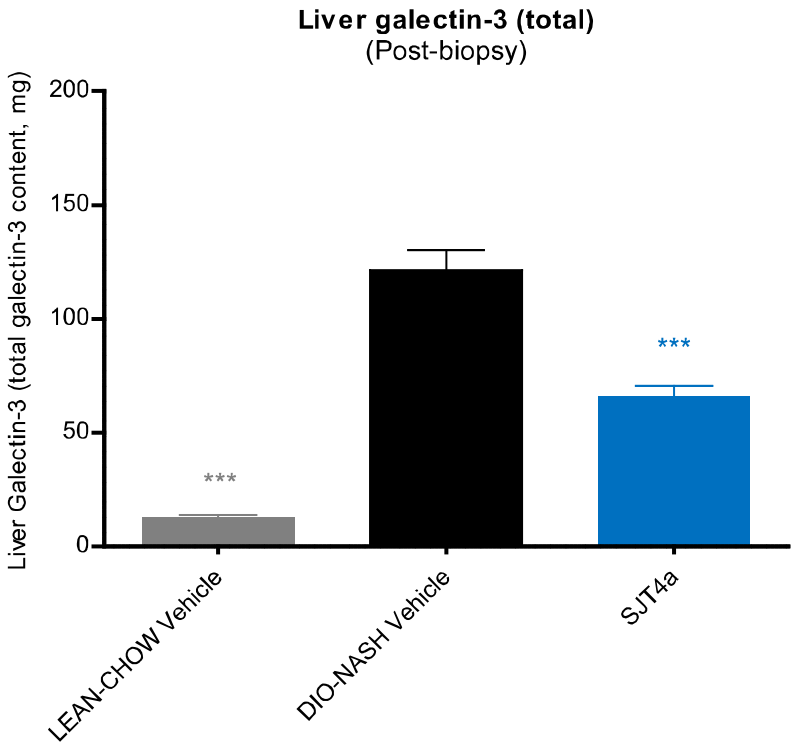


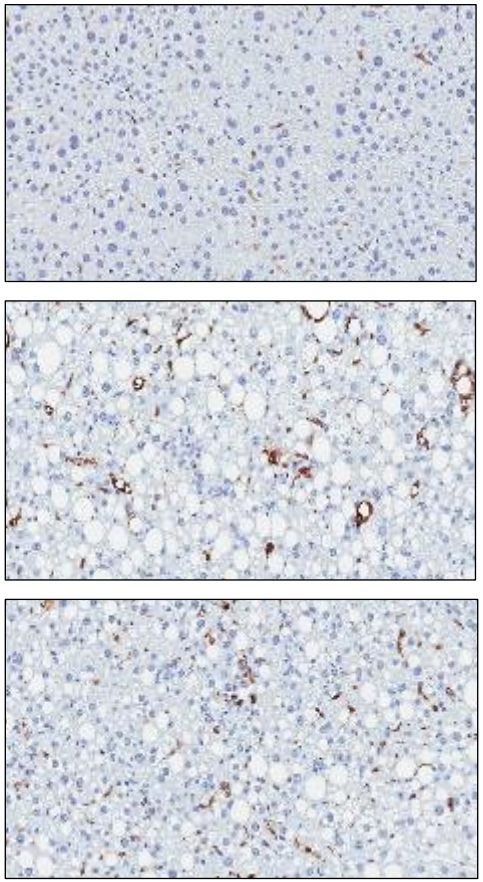
Fibrosis

SJT4A significantly reduces inflammation

Gubra DIO-NASH mice model treated with SJT4A for 8 weeks

SJT4A reduces inflammation through lowers liver galectin-3 content (inflammation marker)

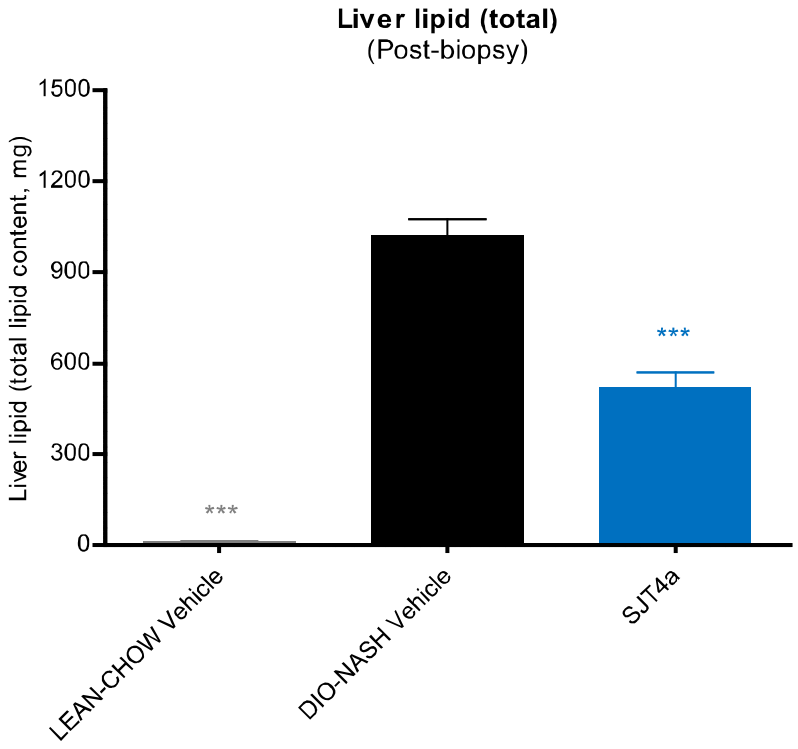


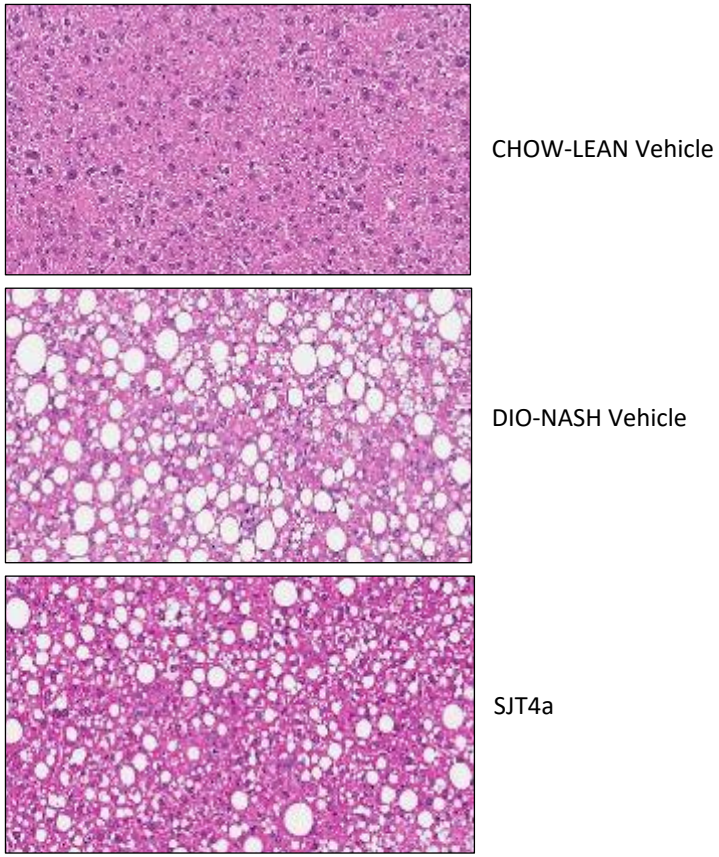


*Data expressed as mean ± s.e.m. values from 10-12 animals. ***P<0.001. 4A (50 mg/kg)*

SJT4A decreases fat accumulation in liver

Gubra DIO-NASH mice model treated with SJT4A for 8 weeks

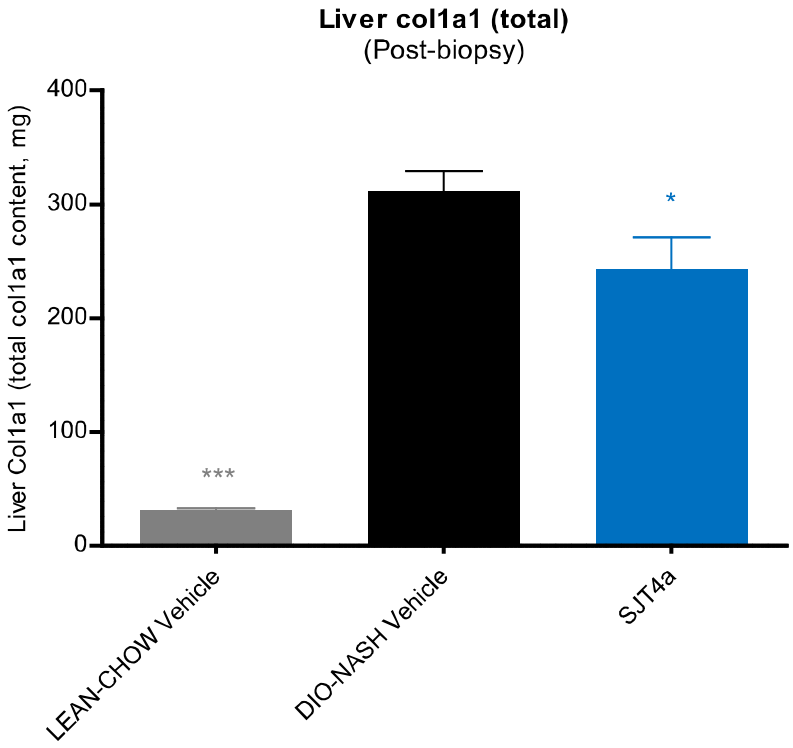


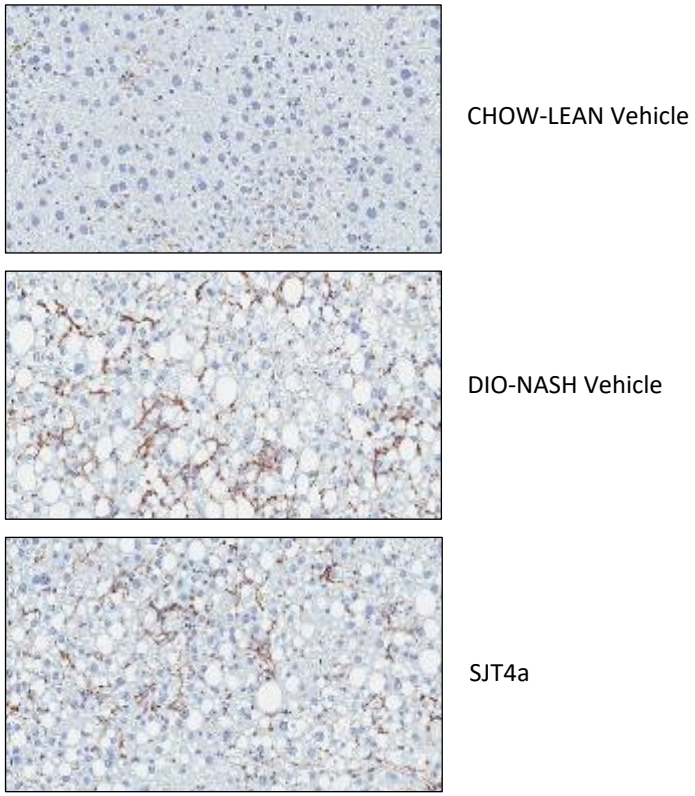


*Data expressed as mean ± s.e.m. values from 10-12 animals. ***P<0.001. 4A (50 mg/kg)*

SJT4A reduces total liver collagen type I (fibrosis marker)

Gubra DIO-NASH mice model treated with SJT4A for 8 weeks

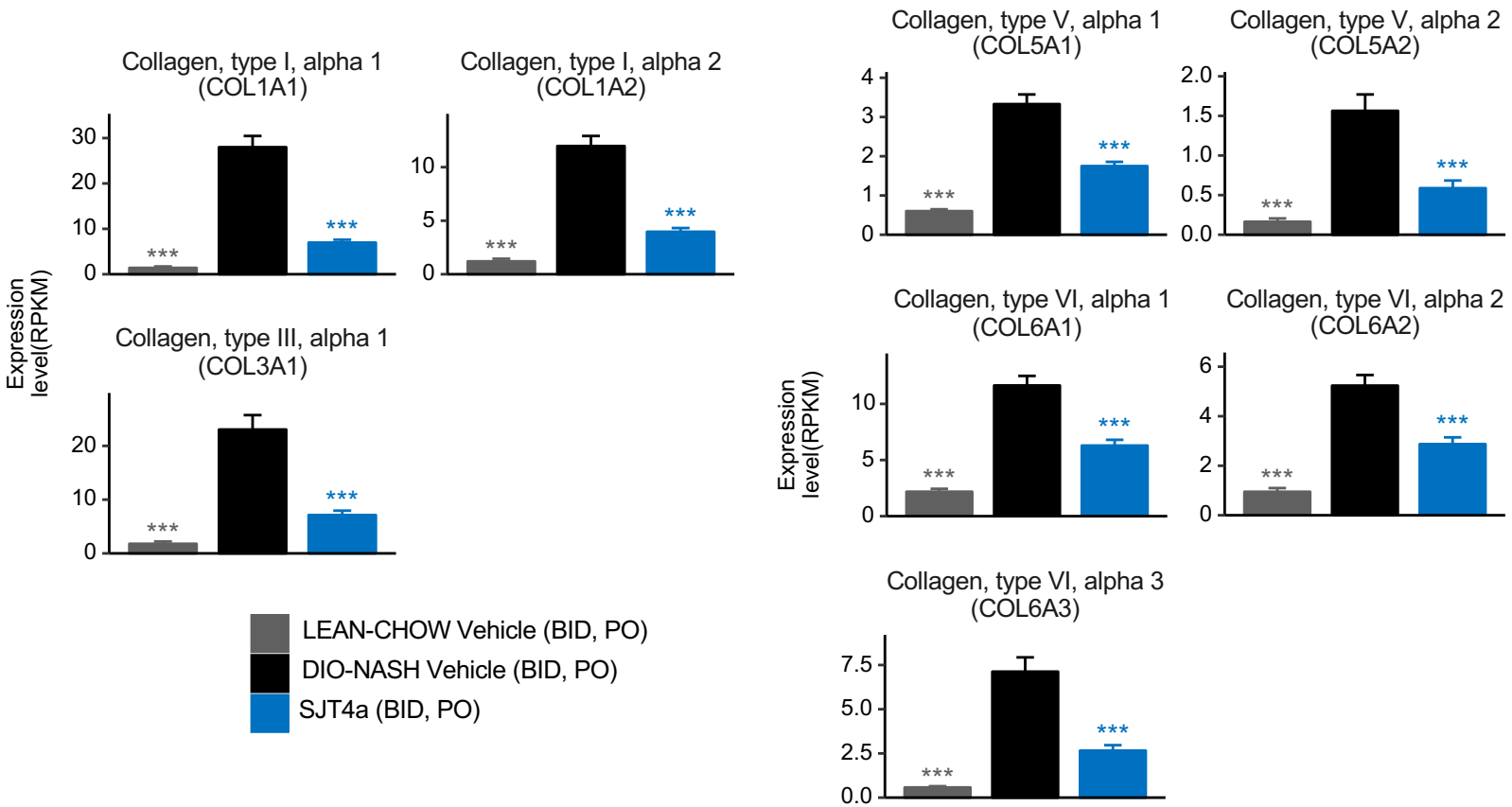




*Data expressed as mean ± s.e.m. values from 10-12 animals. *P<0.05. 4A (50 mg/kg)*

SJT4A significantly reduces collagen gene expression (RNAseq)

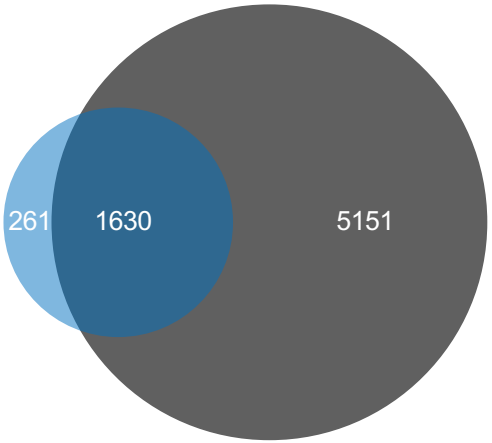
Gubra DIO-NASH mice model treated with SJT4A for 8 weeks



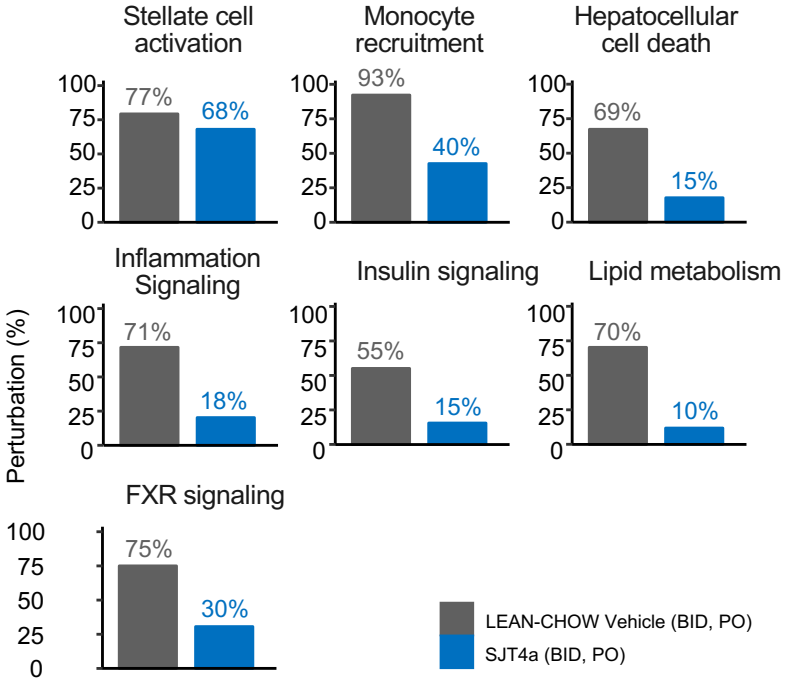
*Data expressed as mean ± s.e.m. values from 6 animals. ***P<0.001. 4A (50 mg/kg)*

SJT4A contributes to the recovery of dysregulated gene expression in DIO-NASH mice

Gubra DIO-NASH mice model treated with SJT4A for 8 weeks



Genes differentially expressed between DIO-NASH mice and lean-chow animals (grey) or DIO-NASH mice treated with SJT4A (blue)



- The majority of gene regulated by SJT4A (86.2%) were also differentially expressed between lean-chow and DIO-NASH untreated animals, indicating that SJT4A can mainly affect expression of genes associated with the disease
- Most of the pathways associated with NASH development have been affected by SJT4A, mainly the hepatic stellate cell (HSC) activation, the central driver of fibrosis in experimental and human liver injury

Gene expression regulated by SJT4A stops fibrosis development

Gubra DIO-NASH mice model treated with SJT4A for 8 weeks

Representative genes **up-regulated** in liver of DIO-NASH mice and recovered by treatment with SJT4A:

- Involved in hepatic liver metabolism (steatosis): Cidea, Cicec & Mogat1 (lipid droplet), CD36
- Involved in inflammation and macrophage recruitment: : IL members & Rc (1, 17), CCL members (MCP-1)
- Involved in fibrosis:
  - ECM components: collagens, laminins, elastin, fibrillins, fibulins, Efemps, vimentin, cytoglobin, α-SMA
  - Proteoglycans: lumican, decorin, fibromodulin, biglycan, versican, perlecan, dermapontin
  - Matrix proteases and regulators: MMPs (2,7,12,13,23) and TIMPs (1-3), ADAMs, ADAMTSs, ADAMTSLs
  - Profibrotic genes: TGFβ & Rc, IL-2R, IL-34, LOX & LOXL, annexins
  - Involved in HSC activation (fibrinogenesis): Gal-3, IL-33, PDGF, fascin

Representative genes **down-regulated** in liver of DIO-NASH mice and recovered by treatment with SJT4A:

- Involved in regulation of energy expenditure: MUPs
- Involved in inflammation and macrophage recruitment: MARCO

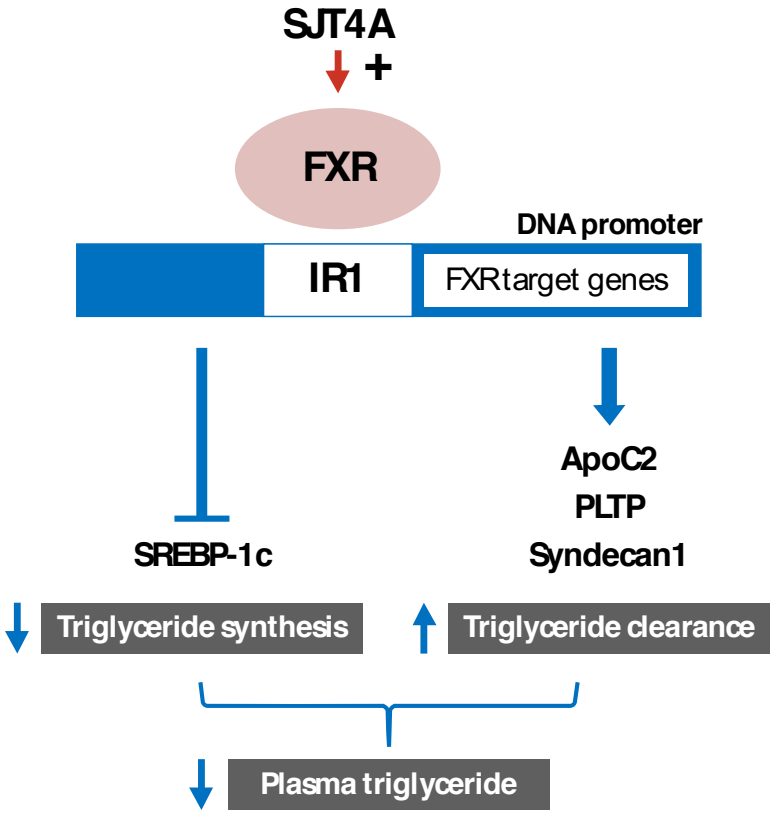
Toxicology studies

- Early toxicology studies indicate an encouraging safety profile
- Acute toxicity in male mice (Irwin test)
  - No deaths or behavioral disorders observed
- Repeat-dose toxicity in male mice
  - Repeat dose up to 250 mg/kg daily for 14 days, by oral administration
  - Neither systemic toxicity nor relevant toxicity in the major functional organs
  - No deaths at the end of treatment
  - No effects on the weight of mice
- Genotoxicity
  - No mutagenic activity detected with the bacterial reverse mutation test (Ames test)
  - No chromosomal aberrations observed with an in vivo micronucleus test in mice at concentrations up to 500 mg/kg, indicating a lack of bone marrow toxicity
  - No genotoxicity in *in vivo* bone marrow micronucleus assay
    - No evidence of clastogenicity or aneugenicity in 9 male and 9 female mice (1-2 oral administration, up to MTD* of 750 mg/kg/day in male and 500 mg/kg/day in female mice)

* MTD: Maximum tolerated dose

Hyphotesis of MoA

SJT4A, is an agonist for the FXR transcription factor



SJT4A activates FXR activity

SJT4A is an activator of the FXR transcription factor which regulates the transcription of a number of genes that contribute to NASH alleviation.

Summary

- Novel family of oral molecules
- Innovative mode of action with potential application in:
  - NAFLD (NASH)
  - Type 2 diabetes
  - Obesity
  - Hypertension
  - Dyslipidemia and diabetes associated complications
- Patent-protected molecules with long expiry dates in major markets
- Potential first in class therapeutics based on β-carboline structure
- Efficacy demonstrated in *in vivo* animal models
- Encouraging safety profile from early toxicology studies
- Hypothesis of MoA (FXR agonist)
- Simple manufacturing: 3-4 step chemical synthesis with high yield and purity (>99 %)
- Partners sought for further development and commercialisation of SJT's novel, proprietary molecules
- Flexibility in deal structuring

Contact information

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