Physiogenex

THE METABOLIC DISEASES EXPERTS

Preclinical CRO

Efficacy

Discovery

Metabolic disorders

Innovative rodent models and tailor-made solutions

We are

An **expert preclinical CRO** delivering services for metabolic disorders and dedicated R&D studies to evaluate your drugs targeting, founded in 2003. We offer a wide range of tests to demonstrate the effectiveness of our clients' drug candidates.

ABOUT 20 YEARS OF EXPERTISE

specializing in **obesity, type 2 diabetes, NASH / Fibrosis, diabetic nephropathy, inflammation, dyslipidemia and cardiovascular diseases** for preclinical drug development, post launched studies and consulting.

We built our expertise over the years by developing innovative and predictive animal nutritional models to accelerate your drug discovery.

More than 10 of top 15 international biotech and pharma companies choose Physiogenex

and gave the best chance of success to their lead compounds

Physiogenex and Cardiomedex

Innovative twin sister-CRO companies to evaluate your drugs on cardiometabolic disorders

Physiogenex | Cardiomedex

- Physio-pathological predictive models
- Customized preclinical pharmacology studies
- *In vitro, ex vivo, in vivo* exploration

Benefits of our synergies

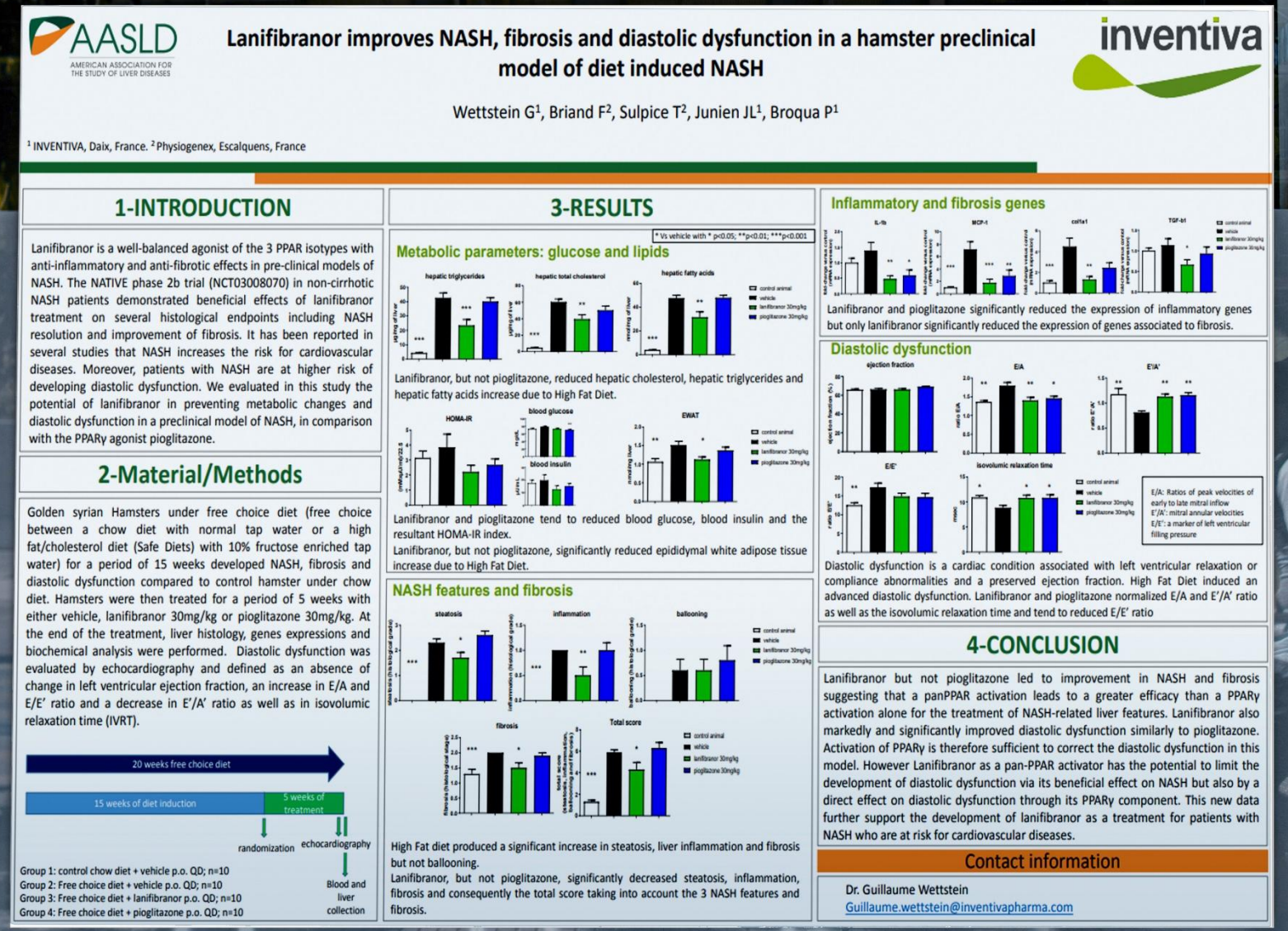
INVENTIVA AND LANIFIBRANOR:
an example of unique synergy between Physiogenex and Cardiomedex

HIGH-VALUE RESULTS

Lanifibranor improves NASH, fibrosis and diastolic dysfunction in a **Golden Syrian hamster model of diet induced obesity and NASH**.

This **new study realized at Physiogenex** generated data that further support the development of Lanifibranor as a treatment for patients with NASH who are at cardiometabolic risk.

This leading anti-NASH drug is now evaluated in phase III (NATiV3).



AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

Lanifibranor improves NASH, fibrosis and diastolic dysfunction in a hamster preclinical model of diet induced NASH

inventiva

Wettstein G[1], Briand F[2], Sulpice T[2], Junien JL[1], Broqua P[1]

[1] INVENTIVA, Daix, France. [2] Physiogenex, Escalquens, France

1-INTRODUCTION

Lanifibranor is a well-balanced agonist of the 3 PPAR isotypes with anti-inflammatory and anti-fibrotic effects in pre-clinical models of NASH. The NATIVE phase 2b trial (NCT03008070) in non-cirrhotic NASH patients demonstrated beneficial effects of lanifibranor treatment on several histological endpoints including NASH resolution and improvement of fibrosis. It has been reported in several studies that NASH increases the risk for cardiovascular diseases. Moreover, patients with NASH are at higher risk of developing diastolic dysfunction. We evaluated in this study the potential of lanifibranor in preventing metabolic changes and diastolic dysfunction in a preclinical model of NASH, in comparison with the PPARγ agonist pioglitazone.

2-Material/Methods

Golden syrian Hamsters under free choice diet (free choice between a chow diet with normal tap water or a high fat/cholesterol diet (Safe Diets) with 10% fructose enriched tap water) for a period of 15 weeks developed NASH, fibrosis and diastolic dysfunction compared to control hamster under chow diet. Hamsters were then treated for a period of 5 weeks with either vehicle, lanifibranor 30mg/kg or pioglitazone 30mg/kg. At the end of the treatment, liver histology, genes expressions and biochemical analysis were performed. Diastolic dysfunction was evaluated by echocardiography and defined as an absence of change in left ventricular ejection fraction, an increase in E/A and E/E' ratio and a decrease in E'/A' ratio as well as in isovolumic relaxation time (IVRT).

Group 1: control chow diet + vehicle p.o. QD; n=10
Group 2: Free choice diet + vehicle p.o. QD; n=10
Group 3: Free choice diet + lanifibranor p.o. QD; n=10
Group 4: Free choice diet + pioglitazone p.o. QD; n=10

3-RESULTS

* Vs vehicle with * p<0.05; **p<0.01; ***p<0.001

Metabolic parameters: glucose and lipids

Lanifibranor, but not pioglitazone, reduced hepatic cholesterol, hepatic triglycerides and hepatic fatty acids increase due to High Fat Diet.

Lanifibranor and pioglitazone tend to reduced blood glucose, blood insulin and the resultant HOMA-IR index.
Lanifibranor, but not pioglitazone, significantly reduced epididymal white adipose tissue increase due to High Fat Diet.

NASH features and fibrosis

High Fat diet produced a significant increase in steatosis, liver inflammation and fibrosis but not ballooning.
Lanifibranor, but not pioglitazone, significantly decreased steatosis, inflammation, fibrosis and consequently the total score taking into account the 3 NASH features and fibrosis.

Inflammatory and fibrosis genes

Lanifibranor and pioglitazone significantly reduced the expression of inflammatory genes but only lanifibranor significantly reduced the expression of genes associated to fibrosis.

Diastolic dysfunction

E/A: Ratios of peak velocities of early to late mitral inflow
E'/A': mitral annular velocities
E/E': a marker of left ventricular filling pressure

Diastolic dysfunction is a cardiac condition associated with left ventricular relaxation or compliance abnormalities and a preserved ejection fraction. High Fat Diet induced an advanced diastolic dysfunction. Lanifibranor and pioglitazone normalized E/A and E'/A' ratio as well as the isovolumic relaxation time and tend to reduced E/E' ratio

4-CONCLUSION

Lanifibranor but not pioglitazone led to improvement in NASH and fibrosis suggesting that a panPPAR activation leads to a greater efficacy than a PPARγ activation alone for the treatment of NASH-related liver features. Lanifibranor also markedly and significantly improved diastolic dysfunction similarly to pioglitazone. Activation of PPARγ is therefore sufficient to correct the diastolic dysfunction in this model. However Lanifibranor as a pan-PPAR activator has the potential to limit the development of diastolic dysfunction via its beneficial effect on NASH but also by a direct effect on diastolic dysfunction through its PPARγ component. This new data further support the development of lanifibranor as a treatment for patients with NASH who are at risk for cardiovascular diseases.

Contact information

Dr. Guillaume Wettstein
Guillaume.wettstein@inventivapharma.com

A management team of experience & expertise

Thierry Sulpice, Ph.D

CEO, CSO, Founder

- 9 years at Sanofi –Aventis
- In charge of drug discovery optimization and preclinical development for projects targeting the cardiometabolic syndrome.
- PhD in Physiology and Pharmacology - University of Grenoble, France.
- Founder and CEO/CSO of Cardiomedex

François Briand, Ph.D

Director,
Research and Business Development

- Expert in metabolic diseases since 2007.
- Worked with Novo Nordisk during his PhD in Nutrition and Metabolism, and with Glaxo Smith Kline and Merck as a postdoctoral fellow with Dr. Dan Rader at Upenn, Philadelphia.

Physiogenex

Highly skilled metabolic disease experts working towards innovation, client satisfaction and quality compliance

Estelle Grasset, Ph.D – Project Manager

Natalia Breyner, Ph.D – Project Manager

Claire Bigot, Ph.D, Pharm.D – Project Manager, BD

Pr. Rémy Burcelin – Scientific expert consultant

Emmanuel Brousseau – Team manager

Marjolaine Quinsat –Animal welfare manager

Sura Setau – Quality department manager

Julie Arasse – Administrative department manager

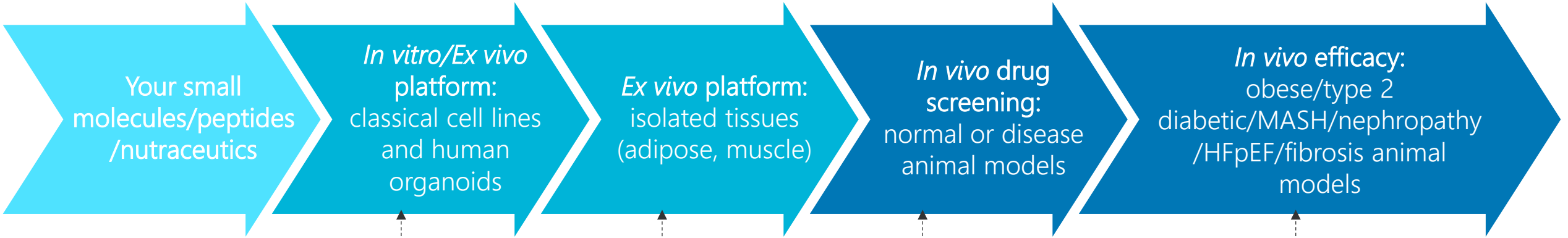
DRUG DISCOVERY I PRECLINICAL DEVELOPMENT

Physiogenex

Drug efficacy testing pipeline

In vitro/ex vivo

In vivo



- Cell viability/cytotoxicity
- Gene expression
- Protein/lipids levels

- Glucose uptake
- Fatty acids oxidation

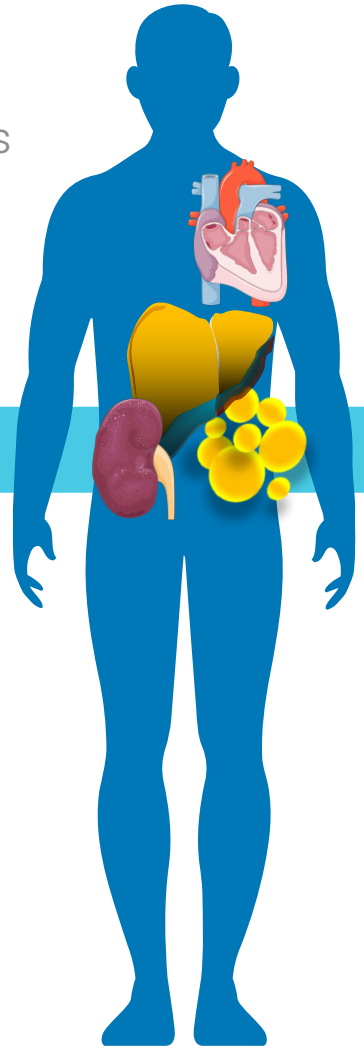
- Blood parameters
- Glucose/insulin/lipid tolerance tests
- Kidney function
- NAFLD/NASH

- Blood/tissue biochemistry
- Glucose/insulin/lipid tolerance tests
- Body composition *(Brucker Minispec)*
- Energy expenditure *(TSE Phenomaster)*
- *In vivo* lipogenesis and reverse cholesterol transport
- Hyperinsulinemic euglycemic clamp
- Kidney glomerular filtration rate
- Echocardiography
- Liver/lungs/kidney/heart histology

Translational data:
Derisk your drug efficiently and early.

Original & human-like animal models
Translatable efficacy parameters

Diet-induced metabolic diseases
for *in vivo* drug efficacy studies

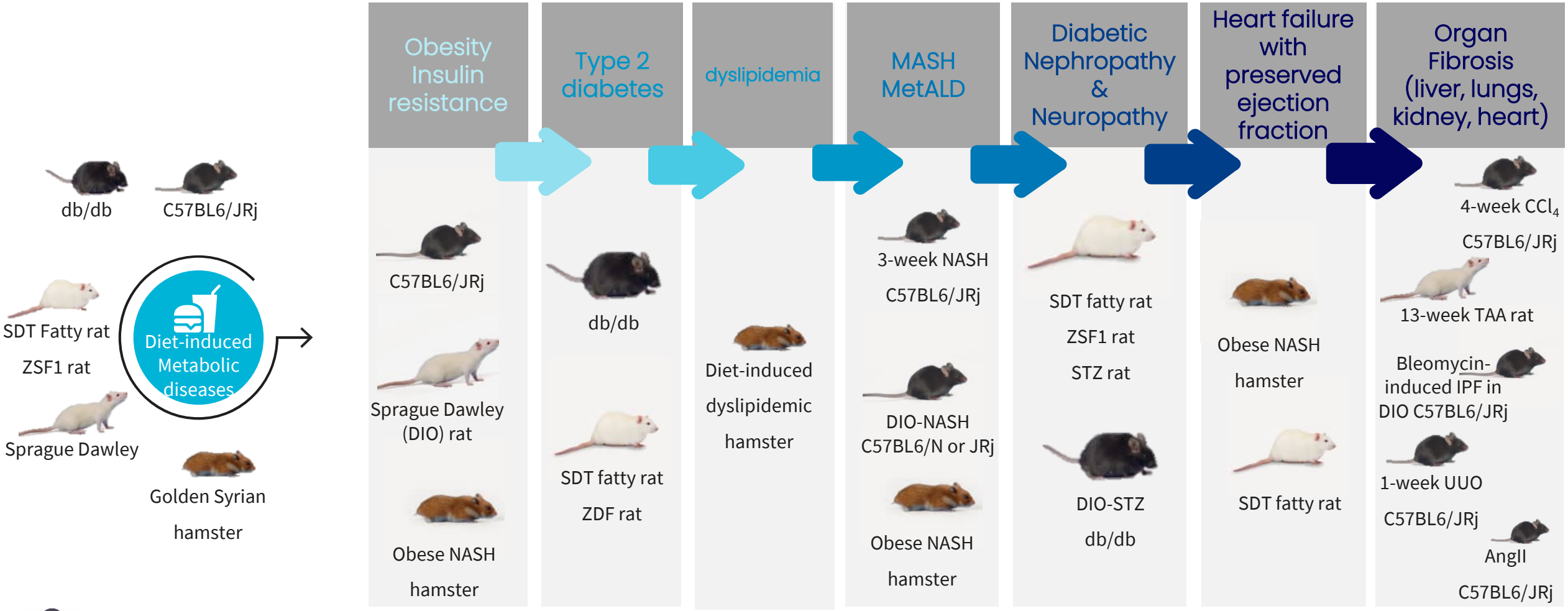


- Obesity
- T2D
- Hypertension
- Dyslipidemia
- MASH
- Nephropathy
- HFpEF

Marketed
therapies

Physiogenex

Innovative animal models developed to optimize and expedite your drug efficacy studies



Physiogenex

Platform
To fully characterize your drug candidates mechanism of action and efficacy

Colorimetric assays

- Plasma and hepatic Lipids (cholesterol, triglycerides fatty acids)
- Lipoproteins (direct LDL-C and HDL-C assays, lipoprotein FPLC profile, apo A-1, apoB)
- Plasma ALT /AST
- Total ketone bodies
- Glycerol
- Phospholipids
- Albumin
- Creatinine
- Faecal total cholesterol and bile acids

ELISA and multiplex assays:

- Hormones (insulin, glucagon, adiponectin, Leptin, etc.)
- Cytokines panel (IL-1b, IL-6, MCP-1, TNF-alpha, etc.)

Western Blot analysis

(WES technology) for any protein. on any sample/tissue.

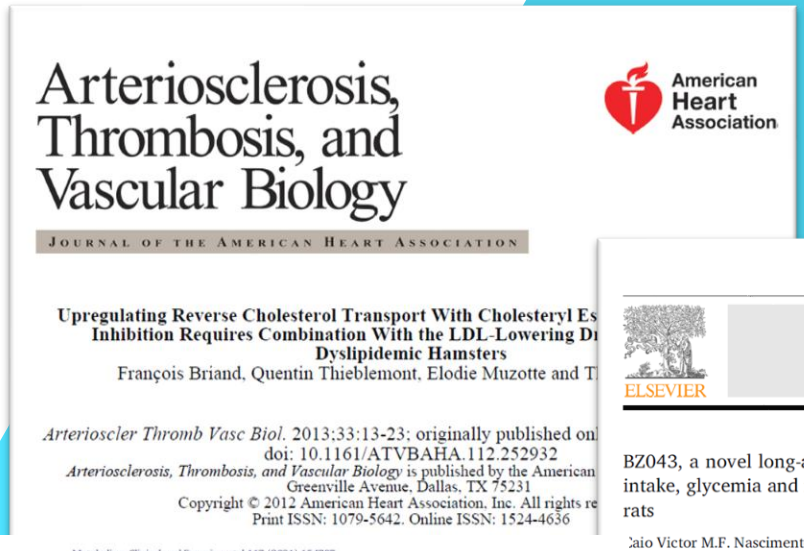
Microbiome, lipids, bile acids profiling Gene expression by qPCR on any tissue:

- Lipogenesis
- Glucose metabolism
- ER and oxidative stress
- Inflammation
- Fibrosis

Histology analysis:

- H&E
- Sirius Red
- Masson Trichrome
- ORO
- PAS staining
- Immunohistochemistry (F4/80, CD68 ED1, collagen III alpha-SMA, etc.)
- NAS scoring (steatosis, inflammation, hepatocyte ballooning tibrosis) Nephropathy histopathology scoring (glomerulosclerosis interstitial fibrosis, etc.)

+ 25 publications demonstrating Physiogenex expertise in high impact scientific journals


Arteriosclerosis, Thrombosis, and Vascular Biology

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association

Upregulating Reverse Cholesterol Transport With Cholesteryl Es
Inhibition Requires Combination With the LDL-Lowering Dr
Dyslipidemic Hamsters

François Briand, Quentin Thieblemont, Elodie Muzotte and T

Arterioscler Thromb Vasc Biol. 2013;33:13-23; originally published onl
doi: 10.1161/ATVBAHA.112.252932
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Peptides

journal homepage: www.elsevier.com/locate/peptides

ELSEVIER

BZ043, a novel long-acting amylin analog, reduces gastric emptying, food intake, glycemia and insulin requirement in streptozotocin-induced diabetic rats

Caio Victor M.F. Nascimento[a], Celimar Sinezia[b], Thayna Sisnande[b], Luís Maurício T.R. Lima[b,c,d,*], Paulo G.S. Lacativa[c,**]

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National Institute of Science and Technology for Structural Biology and Bioimaging (INBEB-INCT), Federal University of Rio de Janeiro, Rio de Janeiro 21941-590, Brazil
Laboratory for Macromolecules, (LAMAC-DIMAV)), Brazilian National Institute of Metrology, Quality and Technology – INMETRO, Rio de Janeiro, Brazil


Metabolism Clinical and Experimental 117 (2021) 154707

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journal homepage: www.metabolismjournal.com

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Metabolism


European Journal of Pharmacology 860 (2019) 172537

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

ELSEVIER

Full length article

Nephropathy in diabetic db/db mice is accelerated by
improved by the SGLT2 inhibitor dapagliflozin

Sisse Andersen Nørgaard[a,c,1,*], François Briand[b,1], Fredrik Wolfhagen
Elisabeth Douglas Galsgaard[a], Henrik Søndergaard[a], Dorte Bratbo Sø

[a] Pharmacology, Novo Nordisk A/S, Novo Nordisk Park, Måløv, Denmark
[b] Physiogenex S.A.S, Prologue Biotech, 516 rue Pierre et Marie Curie, 31670, Labège, France
[c] Department of Veterinary Disease Biology, University of Copenhagen, Grønnegårdsvej 15, 1870, Frederiksberg C, Denm

Elafibranor improves diet-induced nonalcoholic steatohepatitis associated with heart failure with preserved ejection fraction in Golden Syrian hamsters

François Briand [a,*], Julie Maupoint [b], Emmanuel Brousseau [a], Natalia Breyner [a], Mélanie Bouchet [a], Clément Costard [b], Thierry Leste-Lasserre [c], Mathieu Petitjean [d], Li Chen [d], Audrey Chabrat [e], Virgile Richard [e],


2032

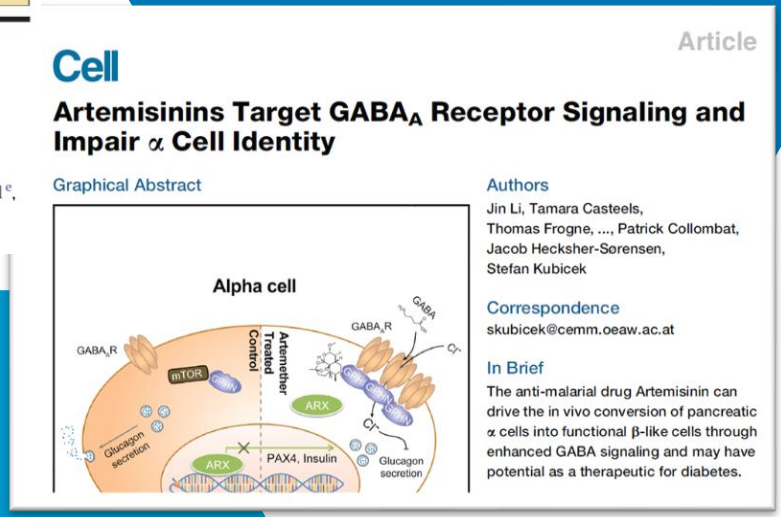
Diabetes Volume 65, July 2016

François Briand,[1] Eric Mayoux,[2] Emmanuel Brousseau,[1] Noémie Burr,[1] Isabelle Urbain,[1] Clément Costard,[1] Michael Mark,[2] and Thierry Sulpice[1]

CrossMark

Empagliflozin, via Switching Metabolism Toward Lipid Utilization, Moderately Increases LDL Cholesterol Levels Through Reduced LDL Catabolism

Diabetes 2016;65:2032–2038 | DOI: 10.2337/db16-0049


Article

Cell

Artemisinins Target $GABA_A$ Receptor Signaling and Impair α Cell Identity

Graphical Abstract

Authors

Jin Li, Tamara Casteels, Thomas Frogne, ..., Patrick Collombat, Jacob Hecksher-Sørensen, Stefan Kubicek

Correspondence

skubicek@cemm.oeaw.ac.at

In Brief

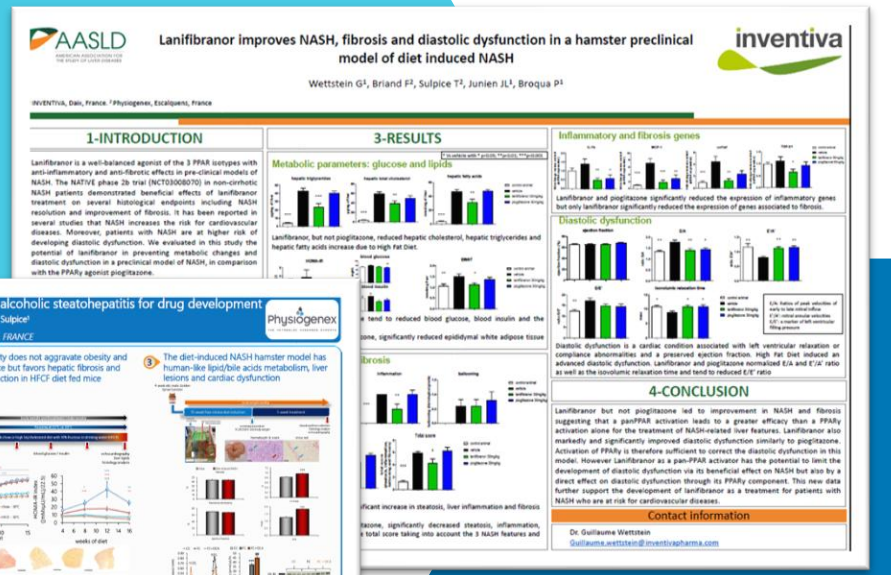
The anti-malarial drug Artemisinin can drive the in vivo conversion of pancreatic α cells into functional β-like cells through enhanced GABA signaling and may have potential as a therapeutic for diabetes.

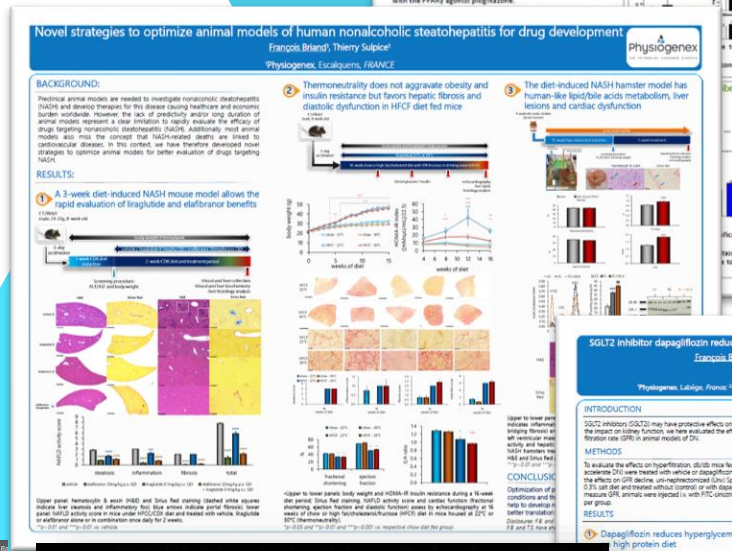
Physiogenex

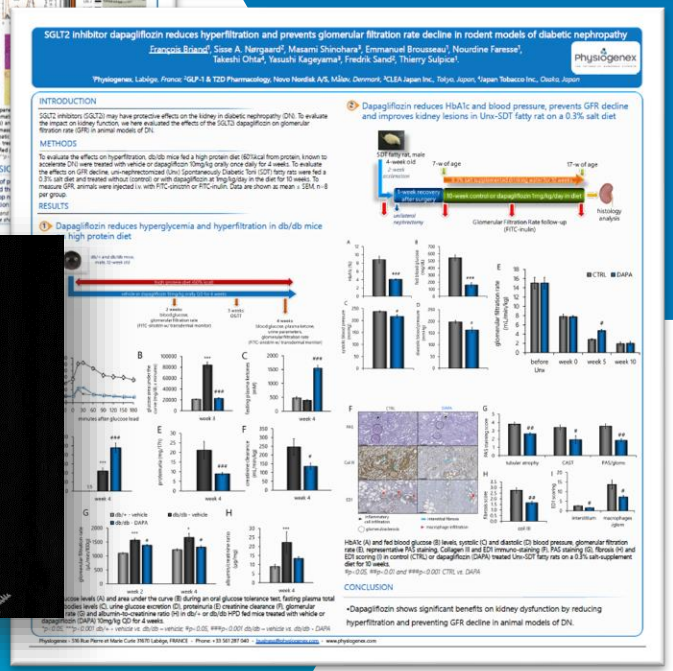
+120 POSTERS and TALKS

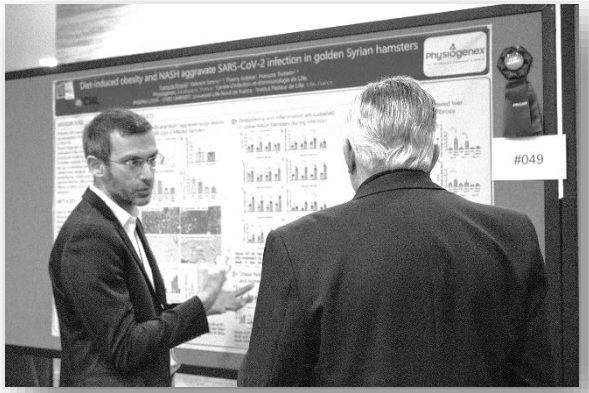
in international conferences

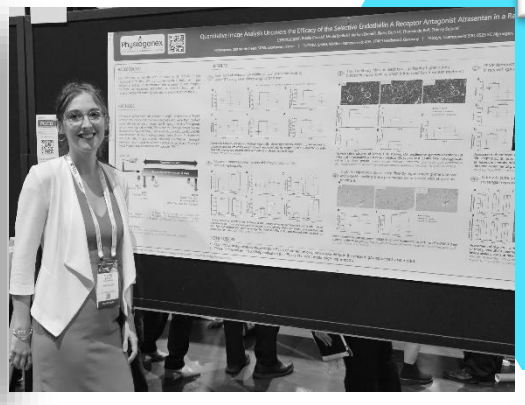
To make our innovative new services and models known for your drug evaluation success, early.

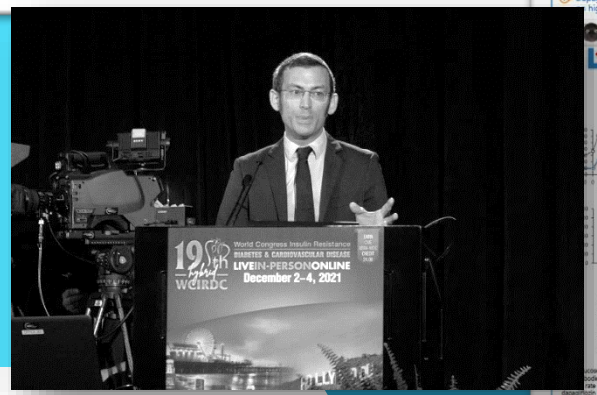












Physiogenex

They trust us

GlaxoSmithKline
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A Member of the Roche Group
ENANTA Pharmaceuticals
Debiopharm Group
WE DEVELOP FOR PATIENTS
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Nestlé
Chong Kun Dang Pharm. Seoul, Korea
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achē
AMGEN
Bionorica®
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healthcare with passion and conviction
SANOFI
SERVIER
Connexios

High success rate customer satisfaction over the last 3 years: 97.5%

« I can't thank you enough for all your great work and support! It was really nice collaborating with you all and I am very much looking forward to the next collaboration with you! »
– US Pharma customer

« Great working with Physiogenex: great competence in the area, straight answer and very good team available to support all our needs »
– European biotech customer

"Once again, I would like to appreciate for all your assistance during the study execution and all technical issues that Physiogenex experts helped us to understand. Physiogenex is a very strategic partner and in the future, we certainly will consider you to perform our preclinical studies." – South American Pharma customer

When is your turn?

"Excellent scientific advice provided for the study design. Studies tailored for small biotechs with limited budget. Timelines met, rigor in execution. Indeed a great partner for drug development in the metabolic disease area." – US biotech customer

"High level of expertise and timely discussions duringthe study plan and execution
Very co-operative" – India Pharma customer

"We really appreciate what you did for our study. A new assay development was successful. The study report was well-documented."
– Korean Pharma customer

What if we work together?
Major steps ahead

FIRST QUOTATION

- Scientific consulting
- Strategic approach
- Price
- Timeline (study start)
- Study design

CONFIRMATION

- Price
- Timeline (study start)
- Study plan

STUDY RUN

- Data production
- Project management

STUDY REPORT

- Data
- Interpretation
- Scientific & strategic recommandations

STUDY REPEAT ?

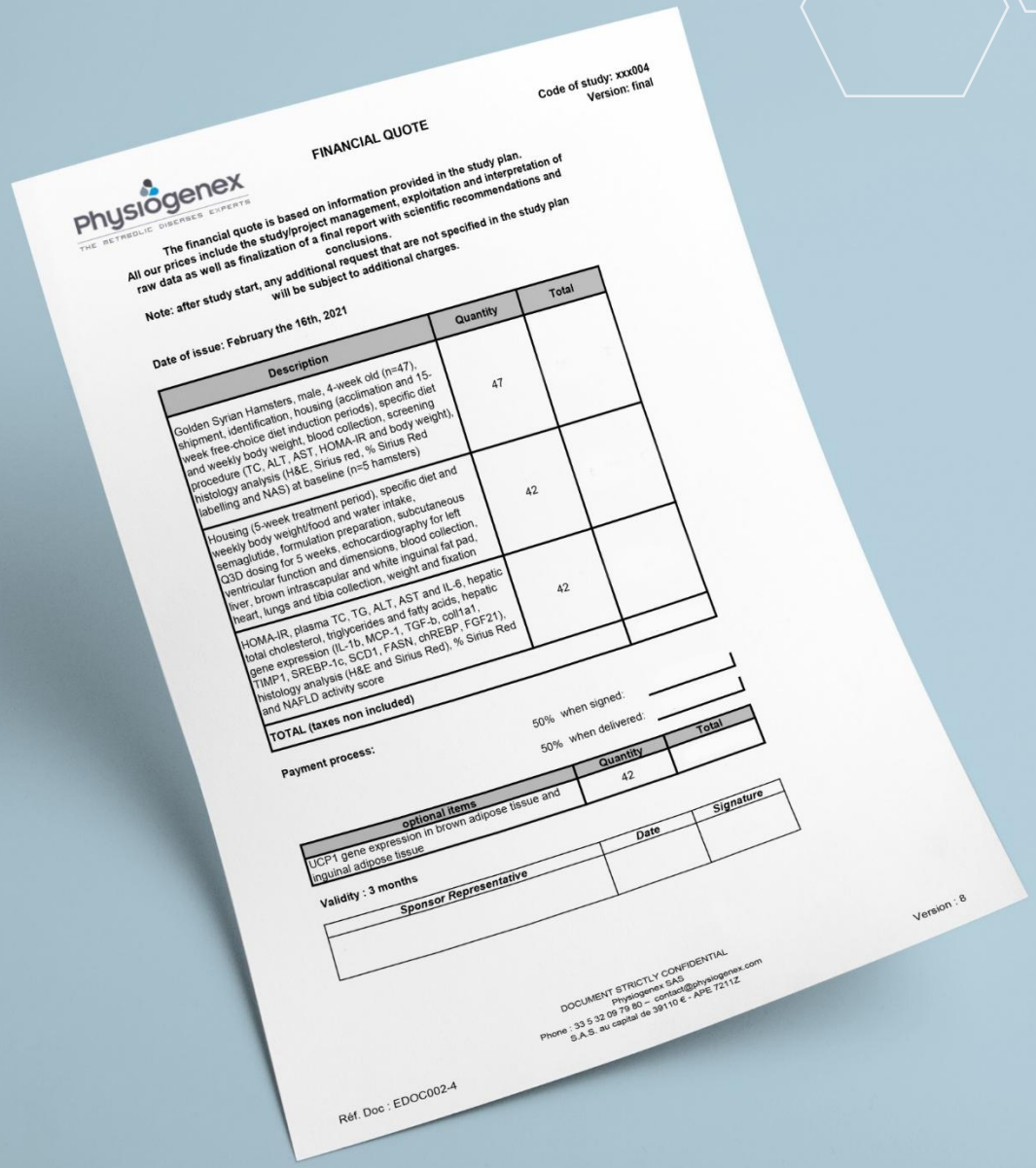
Physiogenex

Quotation and study confirmation

1. Discussion with our experts to setup the best cost-effective study design for your drug efficacy project

2. An experimental design and quotation are then proposed with study timelines

3. Upon you agreement, a study plan is issued and once signed your study starts (2-3 weeks average)



Physiogenex
THE METABOLIC DISEASES EXPERTS

FINANCIAL QUOTE

Code of study: xxx004
Version: final

The financial quote is based on information provided in the study plan.
All our prices include the study/project management, exploitation and interpretation of raw data as well as finalization of a final report with scientific recommendations and conclusions.
Note: after study start, any additional request that are not specified in the study plan will be subject to additional charges.

Date of issue: February the 16th, 2021

Description	Quantity	Total
Golden Syrian Hamsters, male, 4-week old (n=47), shipment, identification, housing (acclimation and 15-week free-choice diet induction periods), specific diet and weekly body weight, blood collection, screening procedure (TC, ALT, AST, HOMA-IR and body weight), histology analysis (H&E, Sirius red, % Sirius Red labelling and NAS) at baseline (n=5 hamsters)	47	
Housing (5-week treatment period), specific diet and weekly body weight/food and water intake, semaglutide, formulation preparation, subcutaneous Q3D dosing for 5 weeks, echocardiography for left ventricular function and dimensions, blood collection, liver, brown intrascapular and white inguinal fat pad, heart, lungs and tibia collection, weight and fixation	42	
HOMA-IR, plasma TC, TG, ALT, AST and IL-6, hepatic total cholesterol, triglycerides and fatty acids, hepatic gene expression (IL-1b, MCP-1, TGF-b, col1a1, TIMP1, SREBP-1c, SCD1, FASN, chREBP, FGF21), histology analysis (H&E and Sirius Red), % Sirius Red and NAFLD activty score	42	
TOTAL (taxes non included)		

Payment process: 50% when signed:
50% when delivered:

Optional items	Quantity	Total
UCP1 gene expression in brown adipose tissue and inguinal adipose tissue	42	

Validity : 3 months

Sponsor Representative	Date	Signature

Version : 8

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physiogenex SAS
Phone : 33 5 32 09 79 80 — contact@physiogenex.com
S.A.S. au capital de 39110 € - APE 7211Z

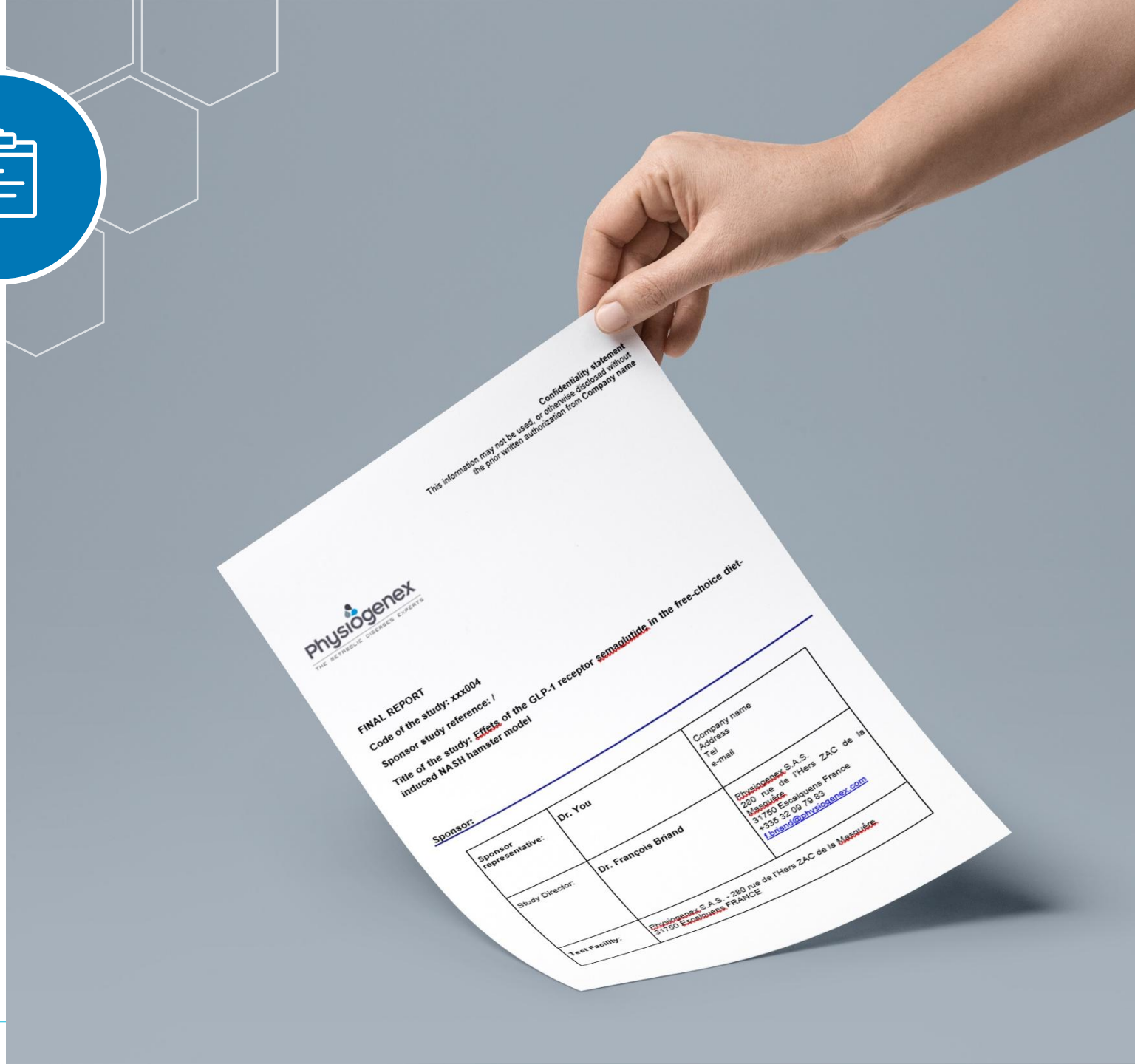
Réf. Doc : EDOC002-4

Study run

- ✓ Studies led by a dedicated project manager
- ✓ Fast and efficient communication: Weekly follow-up
- ✓ Raw data delivered as soon as available

Study report

- ✓ A clear description of your study results provided on Word format for your review
- ✓ Includes statistical analysis, data expertise and recommendations to go further with your drug development
- ✓ Reporting includes quality-controlled data on Excel format, statistics (GraphPad)



Partening with us to launch Your new therapies successfully

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Inflammation - Diabetic nephropathy – NASH -
Fibrosis and cardiovascular complications

- Over **20 years of experience/expertise** in drug development with major pharmas & biotechs
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- Unique, translational preclinical models published in **major scientific journals**
- Time and cost-effective preclinical studies to reach the clinical stage development
- **High added value partnering with Cardiomedex**
- As R&D studies providers we propose and set-up **dedicated tolls/animal models** to target your needs

Physiogenex and you

business@physiogenex.com

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