Preclinical CRO services for drugs targeting metabolic disorders

- Obesity
- Diabetes
- NASH
- Fibrosis
- Dyslipidemia
- Atherosclerosis
- Diabetic nephropathy
- Immuno
- Metabolism
- Nutraceuticals
- Covid-19

Physiogenex
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

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

Diabetes  
Cardiovascular  
NASH  
Obesity  
Hyperlipidemia
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).

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 (NCT03300070) 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 PPAR-alpha agonist pioglitazone.

2-Materials/Methods

Golden syrian Hamsters under free choice diet (free choice between a chow diet with normal tap water or a high fat/cholesteric diet (Safe Diet) with 30% 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/E’ ratio as well as in isovolumic relaxation time (IVRT).

3-RESULTS

Metabolic parameters: glucose and lipids

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

Inflammatory and fibrosis genes

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

Diastolic dysfunction

Diasstolic 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/E’ ratio as well as the isovolumic relaxation time and tended 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 PPAR-alpha activation alone for the treatment of NASH-related liver features. Lanifibranor also markedly and significantly improved diastolic dysfunction similarly to pioglitazone. Activation of PPAR-alpha 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 PPAR 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.
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
Emmanuel Brousseau – team manager
Marjolaine Quinsat – team manager
Sura Setau – quality department manager
Julie Arasse – administrative department manager
Pr. Rémy Burcelin – Scientific expert consultant

DRUG DISCOVERY | PRECLINICAL DEVELOPMENT
Drug efficacy testing pipeline

**In vitro/ex vivo**
- Your small molecules/peptides/nutraceuticals
- **In vitro/Ex vivo** platform: classical cell lines and human organoids
- Ex vivo platform: isolated tissues (adipose, muscle)

**In vivo**
- **In vivo drug screening:** normal or disease animal models
- **In vivo efficacy:** obese/type 2 diabetic/NASH/nephropathy/HFpEF animal models

- 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
- In vivo lipogenesis
- Hyperinsulinemic euglycemic clamp
- Kidney glomerular filtration rate
- Echocardiography
- Liver/kidney/heart histology
Translational data: Derisk your drug efficiently and early.

- Diet-induced metabolic diseases for in vivo drug efficacy studies
- Original & human-like animal models Translatable efficacy parameters
- Marketed therapies
  - Obesity
  - T2D
  - Hypertension
  - Dyslipidemia
  - NASH
  - Nephropathy
  - HFrEF
New innovative animal models developed to best adapt to your lead candidate efficacy studies

<table>
<thead>
<tr>
<th>Diet-induced Metabolic diseases</th>
<th>Obesity Insulin resistance</th>
<th>Type 2 diabetes</th>
<th>NASH</th>
<th>Diabetic nephropathy</th>
<th>Heart failure with preserved ejection fraction</th>
<th>Severe COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>db/db</td>
<td>C57BL6/JRj</td>
<td>db/db</td>
<td>Lund MetS</td>
<td>C57BL6/JRj</td>
<td>Lund MetS</td>
<td>DIO Golden Syrian</td>
</tr>
<tr>
<td>Lund MetS</td>
<td>Sprague Dawley (DIO) rat</td>
<td>Lund MetS</td>
<td>Lund MetS</td>
<td>C57BL6/JRj</td>
<td>Lund MetS</td>
<td>DIO Golden Syrian</td>
</tr>
<tr>
<td>Sprague Dawley</td>
<td></td>
<td></td>
<td>Lund MetS</td>
<td>db/db</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Golden Syrian</td>
<td></td>
<td></td>
<td>Lund MetS</td>
<td>db/db</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIO Golden Syrian</td>
<td></td>
<td></td>
<td>Lund MetS</td>
<td>db/db</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIO Golden Syrian</td>
<td></td>
<td></td>
<td>Lund MetS</td>
<td>db/db</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C57BL6/JRj: C57 Black 6/JRij mouse
DIO: Diet-Induced Obesity
Lund MetS: Lund Metabolic Syndrome
db/db: db/db mouse
Sprague Dawley: Sprague Dawley rat
Golden Syrian: Golden Syrian rat

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 fibrosis) Nephropathy histopathology scoring (glomerulosclerosis interstitial fibrosis, etc.)
+ 25 publications demonstrating Physiogenex expertise in high impact scientific journals.
+ **80 POSTERS and TALKS**

in international conferences

To make our innovative new services and models known for your drug evaluation success, early.
High success rate customer satisfaction in 2021: 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

“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 during the study plan and execution Very co-operative” – India Pharma 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

“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

CONFIMATION
- Price
- Timeline (study start)
- Study plan

STUDY RUN
- Data production
- Project management

STUDY REPORT
- Data
- Interpretation
- Scientific & strategic recommendations

STUDY REPEAT?
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)
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

Obesity - Type 2 diabetes - Dyslipidemia
Inflammation - Diabetic nephropathy - NASH - Fibrosis and cardiovascular complications

- Over 20 years of experience/expertise in drug development with major pharmas & biotechs
- 97.5% customer satisfaction rate
- 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

www.physiogenex.com