Novel conjugation of oleic acid with an amphetamine derivative for prevention and treatment of steatohepatitis
Content

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2. The Product
   a) Target Indications
   b) Innovative mechanisms of action
   c) Differential features facing the market
   d) Current status of development
   e) IPR protection
   f) Pitfalls & Risks to be considered

3. Partnering Opportunities
The Institute of Biomedical Research in Malaga (IBIMA) is a space for multidisciplinary biomedical research that brings together:

1. The Regional and Virgen de la Victoria Malaga University Hospitals

2. The primary care units and

3. The biotechnology groups at the University of Malaga.
THE RESEARCH GROUP “NEUROPSYCHOPHARMACOLOGY”

We are a research group on pharmacology and therapeutics, focused in lipid transmitters, and with a long experience in medicinal chemistry.

We have patented 14 molecules or models for major chronic diseases

12 years of experience colaborating with pharmaceutical industry and biotechs
THE RESEARCH GROUP “NEUROPSYCHOPHARMACOLOGY”

Modelos
In silico
• Docking ligando-receptor
• Interacción de proteínas
• Dinámica Molecular
• Structure-Activity Relationships (SAR)

Modelos
In vivo
• Ingesta y metabolismo
• Locomoción, ansiedad y depresión
• Condicionamientos, memoria, autoadministración
• R. norvegicus, M. musculus

Líneas
Celulares
• Insulinoma humano (INS-IE)
• Preadipocito humano
• Hepatocitos (HepG2)
• Islotes pancreáticos R. norvegicus
• Cáncer renal Hek293

Modelos
Funcionales
• M. musculus KO
• PPAR-alfa
• IL-6
• CB1
• LPA-1

Biología
Molecular
• PCR a tiempo real
• Espectrofotometría y luminometría
• Electroforesis de ácidos nucleicos
• Análisis de imágenes
• ELISA

Bioquímica
Proteómica
• Electroforesis proteínas
• Horno de hibridación
• Geles 2D
• Escáner 2D y Software análisis proteómico
• Citoquinas

Microscopía
Histología
• Microscopía óptica y fluorescencia
• Analizador de imágenes
• Micrótomo de precisión y Criostato
• Arrayer de tejidos
• Inmunohistoquímica

Citometría
de flujo
• Citometro Cyan 3 Láseres
• Robot DISIS
• Robot EPS

Pruebas
clínicas
• Patología Dual PRISM
• Entrevista psiquiástrica DSM-IV
• Ansiedad y depresión Pfeiffer ACV-NIH, Barthei, Goldberg, Beck, GAD-7
### THE RESEARCH GROUP “NEUROPSYCHOPHARMACOLOGY”

<table>
<thead>
<tr>
<th>Año</th>
<th>Descripción</th>
<th>Identificación</th>
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<td>2011</td>
<td>Uso de derivados de sulfamidas como neuroprotectores</td>
<td>P201130486</td>
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<td>2010</td>
<td>Éteres de Hidroxitirosol</td>
<td>PCT/ES2011/070890</td>
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<td>2010</td>
<td>Derivados de oxadiazol como fármacos moduladores del receptor para el péptido GLP-1</td>
<td>PCT/ES2011/070042</td>
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<td>2009</td>
<td>Derivados de amidas de ácidos grasos con anfetaminas para el tratamiento de desordenes alimenticios</td>
<td>WO2011076966(A1)</td>
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<td>2009</td>
<td>Derivados de pirazol bivalentes como inhibidores de ingesta</td>
<td>WO2010128191(A1)</td>
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<td>2008</td>
<td>Derivados pirazólicos de amidas de ácidos grasos como activadores específicos de receptores PPAR-alfa, procedimiento de preparación y utilización</td>
<td>WO2009050318(A1)</td>
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<td>2006</td>
<td>Derivados acíclicos saturados e insaturados de cadena larga de sulfamidas como activadores específicos de receptores PPAR-alfa</td>
<td>WO2007085469(A1)</td>
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   a) Target Indications: the problem of NASH
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3. Partnering Opportunities
TARGET INDICATION: THE PROBLEM OF NASH

I. Non Alcoholic Steatohepatitis (NASH) is the most common chronic liver disease.

II. Multistep disease that progress from steatosis towards steatohepatitis, fibrosis, cirrhosis and liver cancer.

III. Its first step, Liver steatosis, has a high prevalence, ranging from Europe 28.04% (Europe), 19.24%, (East Asia) to 12.95%, in Middle East

IV. Very high incidence in kids

V. There is a clear association in between obesity, diabetes type 2 and non-alcoholic steatohepatitis (NASH).

VI. Mortality is 10x normal population

VII. No effective therapy approved
TARGET INDICATION: THE PROBLEM OF NASH

- Genetics
- Diet

Genetics leads to:
- Steatosis
- Esteatohepatitis
- Fibrosis/cirrhosis

Diet leads to:
- Obesity
- Diabetes Type 2
- Metabolic syndrome

Increased severity leads to death.
TARGET INDICATION: THE PROBLEM OF NASH

THE IDEAL DRUG:

• Reduction of liver steatosis and associated dyslipidemia

• Reduction of liver inflammation, fibrosis and prevention of cirrhosis

• Reduction of appetite and obesity

• Improvement of insulin resistance and better control of glucose homeostasis
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3. Partnering Opportunities
The natural ligand for PPAR\(\alpha\) receptor
PHARMACOLOGY OF OLEOYLETHANOLAMIDE

I. Signal for fat sensing: inductor of satiety (Food and alcohol)

II. Activator of PPARα: activation of fat oxidation and inhibition of lipogenesis

III. Visceral analgesia and anti-inflammatory actions in brain and peripheral tissues

IV. Reduces fat depots in diet induced obesity, alcohol-induced liver steatosis and leptin deficiency

V. Antifibrotic

VI. Boosts antioxidant mechanisms in liver
Oleylethanolamide, an endogenous PPAR-α ligand, attenuates liver fibrosis targeting hepatic stellate cells

Ling Chen¹,², Long Li¹,³, Junde Chen¹, Lei Li¹, Zihan Zheng¹, Jie Ren¹ and Yan Qiu¹

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² Marine Biological Resource Comprehensive Utilization Engineering Research Center of the State Oceanic Administration, The Third Institute of Oceanography of the State Oceanic Administration, Xiamen, Fujian, China
³ Xiamen Diabetes Institute, The First Affiliated Hospital of Xiamen University, Xiamen, Fujian, China
⁴ Clinical Research Institute, The First Affiliated Hospital, University of South China, Hengyang, Hunan, China
⁵ College of Arts and Sciences, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

OEA is antifibrotic in a methionine-choline Deficiency model. Activity of liver stellate cells boosted by TGF-β is attenuated by OEA through PPARα.
OLEOYLETHANOLAMIDE-MODELLED DRUGS

MEDICINAL CHEMISTRY PROGRAM DEVELOPED WITH THE GROUPS OF:

PILAR GOYA (IQM)

JESUS JOGLAR (CSIC)

RAFAEL DE LA TORRE (IMIM)
1. Analogue of oleoylethanolamide that reduces feeding
2. Small molecule that fits Lipinski’s rules.
3. PPARα agonist
4. CB1 receptor antagonist
5. Potent antioxidant
6. No HERG interaction
7. Good profile on CYP tests: non toxic
8. Easy synthesis
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INNOVATIVE MECHANISM OF ACTION: triple action

OLHHA

Reduction of feeding

Affinity for CB1

Upregulates Cb1 receptors

Affinity for PPARα similar to that of fibrates.

Antioxidant properties

Table 1. Pharmacological properties of fatty acid amides.

<table>
<thead>
<tr>
<th>Compound</th>
<th>CB₁ ( K_i ) [\text{nM}]</th>
<th>CB₁ ( pK_i )</th>
<th>PPAR-α ( EC_{50} ) [\text{nM}]^[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR141716</td>
<td>3.64 ( \times 10^{-10} )</td>
<td>9.44</td>
<td>-</td>
</tr>
<tr>
<td>anandamide</td>
<td>1.7 ( \times 10^{-7} )^[b]</td>
<td>6.77</td>
<td>&gt;10000</td>
</tr>
<tr>
<td>WIN55212-2</td>
<td>1.11 ( \times 10^{-8} )^[b]</td>
<td>7.95</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>3.65 ( \times 10^{-7} )</td>
<td>6.44</td>
<td>698 ± 102</td>
</tr>
</tbody>
</table>

[a] At a concentration of 10 μM.
INNOVATIVE MECHANISM OF ACTION

1. Reduces fat depot in the liver
2. Reduces triglycerides, leptin and transaminases
3. Reduces apoptosis in the liver
INNOVATIVE MECHANISM OF ACTION

REDUCES LIPOGENIC ENZYMES IN LIVER
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3. Partnering Opportunities
DIFFERENTIAL FEATURES FACING THE MARKET

I. No effective therapy approved

II. Many phase 2 and 3 trials are underway. Drugs hoped to be effective are obeticholic acid, elafibranor, glucagon-like peptide-1 analogues and CCR2/5 inhibitors.

III. Elafibranor is the most advanced, followed by Obeticholic (Both Phase III)

IV. GLP-1 peptide agonists well positioned with many drugs in the market for diabetes (and obesity)

V. 7 clinical trials on course on GLP-1 analogues and NASH (the only type of approved drugs with patents active on the market of obesity)

VI. All of them with potential carcinogenetic risks
Elafibranor

Fibrate: a PPARα and δ receptor agonist
Reduces inflammation, steatosis and
Does not worsen fibrosis

120 mg resolved NASH in larger proportions of patients than placebo based on the protocol definition (20% vs 11%; odds ratio ¼ 3.16; 95% confidence interval: 1.228.13; P ¼ .018)
Differential Features Facing the Market

Obeticholic Acid

A semisynthetic Farnesoid X Receptor agonist

Approved for Primary Cholangitis

Phase III clinical trial launched in 2016

Obeticholic Acid
25 mg Phase II clinical trial. 25 or 50 mg OCA for 6 weeks was well tolerated, increased insulin sensitivity, and reduced markers of liver inflammation and fibrosis in patients with type 2 diabetes mellitus and nonalcoholic fatty liver disease. ClinicalTrials.gov, Number: NCT00501592.
Differential Features Facing the Market

I. OLHHA is a multitarget drug, interacting with both PPARα and CB1 receptor and with reactive oxygen species production.

II. Synergic effects on obesity, dyslipidemia, fat depot and cell damage through multiple independent mechanisms

III. Unique profile as food intake inhibitor (Essential for prevention)

IV. No central effects observed

V. Good toxicity profile in vitro and in vivo

VI. Easy and scalable synthesis
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3. Partnering Opportunities
CURRENT STATUS OF DEVELOPMENT

I. Preclinical package being developed. Financial support for 2017-18 obtained through a ISCIII-DTS grant to IBIMA and IMIM teams

II. Two main preclinical analysis yet to be performed:
   I. Induction of fibrosis with thioacetamide
   II. Induction of fibrosis by high fat/high fructose diet

III. Backup molecule developed, protected and started to be tested (hydroxytyrosol linoleylether)

IV. DTS project included basic pharmacokinetics and toxicity in humans (Phase I)

V. Aim is to be ready for Phase II in 2018

VI. Additional studies on alcohol-induced liver disease on course
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3. Partnering Opportunities
1. Indication patent on steatosis for OLHHA:

National patent (priority date) – P201431739, 24 November, 2014.


2. Hydroxytyrosol éter patent:

Granted in Spain: ES2384852 (B1) 2013-06-04

International application (WO2012080555 (A1)) and national phases in Europe EP2666761 (A4), and EEUU: US2013267588 (A1)

The Project development plans to protect any chemical modification, formulation issues or use indication that might appear along the research course.
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3. Partnering Opportunities
PITFALLS AND RISKS TO BE CONSIDERED

I. Efficacy against liver fibrosis yet to be tested. However parent natural compound, Oleoylethanolamide, found to be effective on liver fibrosis

II. Pharmacokinetics studies in humans yet to be performed

   I. Metabolism might be different in humans

   II. Oral formulations yet to be developed. Previous IP developed for nanoemulsions for OEA

III. Competitors in phase III. Efficacy (partial) only demonstrated for elafibranor, but with limitations.

IV. The issue of carcinogenesis need to be addressed for long-term treatments (This constraint affects all Phase III studies).
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PARTNERING OPPORTUNITIES

I. Major metabolic disease without treatment: maximum interest for the main chronic liver disease.

II. Drugs being developed do not cover all the needs for solution. Good potential positioning in the market.

III. Market of alcohol-liver disease unexplored.

IV. We search a biotech/pharmaceutical company for co-development / licensing

V. Opportunities for additional IP development. Pipeline with three scaffolds active on the disease