GOAT (Ghrelina-O-aciltransferasa), nuevo biomarcador en orina para el diagnóstico de cáncer de próstata

Madrid, 28th November, 2018
Content

1. The Institution and the team

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
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3. Partnering Opportunities
1. The Institution

University of Cordoba

- Established in 1972
- 11 Faculties
- Students:
  - 16,694 undergraduate students
  - 1,245 in Master’s Programmes
  - 1,384 in Doctoral Programmes
- PhD
  - 1,384 PhD candidates
  - 228 International PhD candidates
  - 125 PhD dissertations/year
  - 21% of them with European PhD award
- U-Ranking (from Ivie/BBVA fundation): **top 6 in Spain**
  **top 1 in Andalusia**; Total of 61 public and private Universities
1. The Institution

Maimónides Institute for Biomedical Research of Córdoba (IMIBIC)

- Established in 2008
- Accredited by the ISCIII since 2011
- Building opening in 2015
- 10,000 m²; 5,500 m² = laboratories; 900 m² = Experimental Animal Service
- 5 scientific programmes

Active aging and Frailty
- Immunology and senescence
- Attention and care of the chronically ill
- Fragility and quality of life in the elderly

Nutrition and endocrine and metabolic diseases
- Metabolic Syndrome
- Reproductive Health
- Pediatric and perinatal diseases
- Neuroendocrine tumors

Infectious and immunological diseases and organ transplants
- HIV + Hepatitis C Virus
- Transplants
- Multi-drug resistance

Cancer, Oncology and Oncohematology
- Lung Cancer
- Breast Cancer
- Hepatocellular Carcinoma
- Leukemias and Lymphomas
- Digestive Tumors
- Other tumors

Chronic and Inflammatory diseases
- Cardiovascular diseases
- Diseases of the locomotor system and connective tissue
- Neurological diseases
- Mental health
- Kidney and Urologic diseases
- Liver and Digestive diseases
- Chronic inflammation and signaling
1. The team

Department of Cell Biology, Physiology and Immunology (UCO)
GC27: OncObesity and Metabolism (IMIBIC)

Research topics:
* Neuro-endocrine/metabolic (dys)regulation in tumoral pathologies, including:
  - **Prostate cancer**
  - Breast cancer
  - Pituitary adenomas
  - Neuroendocrine tumors
    - Gastro-entero-pancreatic
    - Lung NETs
    - Thyroid
    - Adrenal
  - Brain tumors
  - Hepatocarcinoma

Traslational group (basic and clinical researchers)

Prize of the Spanish Society of Endocrinology and Nutrition for the research career of the group

**Team fully capable, motivated and committed with the project**

Department of Innovation (IMIBIC)

Begoña Roibas da Torre

Rosa Natera
1. The team

Other associated research groups at the HURS, UCO and IMIBIC

- Fresh samples
- Blood/Urine samples
- Collaborative projects
- Río Hortega PhD student

- Blood/Urine samples
- Collaborative projects
- Pathological analysis
- Collaborative projects
- PhD students
Background in the identification of novel tumoral biomarkers

1. The team

1. Novel biomarkers in prostate cancer
1. The team

Background in the identification of novel tumoral biomarkers

2. Novel biomarkers in other tumoral pathologies
1. The team

Experience in research transfer

Proyectos de desarrollo tecnológico en salud (DTS)

Instituto de Salud Carlos III - Acuse de recibo

<table>
<thead>
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<th>DATOS GENERALES</th>
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<tr>
<td>Asunto</td>
<td>Solicitud del expediente: DTS17/00081</td>
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<tr>
<td>Procedimiento</td>
<td>Acción Estratégica de Salud. Ayudas y Subvenciones</td>
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<td>SG de Evaluación y Fomento de la Investigación</td>
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3. Partnering Opportunities
2. The Product: a) Target Indications

### Prostate cancer

- **Stage I**
  - Urethra
  - Lymph node
  - Vas deferens
  - Bladder
  - Seminal vesicle
  - Prostate gland
  - Rectum
  - Urethra

- **Stage II**
- **Stage III**
- **Stage IV**
  - Cancer may spread to other organs

#### Appropriate diagnosis

- Early stage detection

#### Other Biomarkers & Tests

- **PCA3**: proposed as the most prominent biomarker emerging as a non-PSA-based diagnostic test for PCA. Unfortunately, PCA3 has also serious limitations (i.e. lower sensitivity than PSA).

- **4KScore**: Total PSA + free PSA + intact PSA + human Kallikrein-2 (hK2). Yet: “Concentration of hK2 was not significantly different between patients with BPH or prostate cancer”.

- **SelectMDx**: Test measures mRNA levels of two biomarkers in urine, and lets the clinician to take decisions in order to perform biopsy or not.

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3 millions of new cases in 2016

- > 330,000 cases/year *(higher incidence in Spain)*
- > Higher prevalence > 900,000 cases/5-years *(Spain)*
2. The Product: a) Target Indications

**PSA test**

- Non-invasive (plasma levels)
- Specific and sensible
- Relevant to the decision
- Prognostic biomarker

```
<table>
<thead>
<tr>
<th>Test characteristic</th>
<th>PSA (normal &lt;4 NG/ML)</th>
<th>PSA (normal &lt;3 NG/ML)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test positivity (%)</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>Cancer detection rate (%)</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>21</td>
<td>32</td>
</tr>
<tr>
<td>Sensitivity (%) for high grade cancer, i.e., Gleason score ≥8</td>
<td>51</td>
<td>68</td>
</tr>
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</table>
```

“Elevated PSA levels may be driven by benign conditions (i.e. prostatic hyperplasia or prostatitis)”

19 millions PCa screenings

4.7 millions abnormal PSA results

1.3 millions biopsies procedures (many unnecessary)

- Unnecessary biopsies
- Risks and Reduced QoL
- Associated cost
2. The Product: b) Innovative mechanisms of action

Gutierrez JA, et al. PNAS. 2008

Ghrelin

\[
\text{O}=\text{C}\cdot(\text{CH}_3)_2\cdot\text{CH}_3
\]

GOAT enzyme

- GOAT (Ghrelin-O-acyl-transferase)
- MBOAT4 (Membrane Bound O-Acyl-transferase Domain Containing 4)

Pituitary

- GH
- ACTH
- PRL

Beta-cells

- \(\beta\)-cell function
- Insulin secretion

Adipose Tissue

- Adipogenesis
- Lipolysis
- Glucose metabolism

Tumoral pathologies

Goméz-Gómez E, et al., J Cell Mol Med. 2018
2. The Product: b) Innovative mechanisms of action

Ghrelin gene products, receptors, and GOAT enzyme: biological and pathophysiological insight


Department of Cell Biology, Physiology and Immunology, Campus Universitario de Rabanales (CSIC), University of Córdoba, 14004 Córdoba; Instituto Maimónides de Investigaciones Biológicas (IMIBIC), University of Córdoba, Paterna de Córdoba, Córdoba, Spain.

In1-ghrelin, a splice variant of ghrelin gene, is overexpressed in prostate cancer, and its levels are associated with patient's metabolic status: Potential value as a non-invasive biomarker

Daniel Hormaechea-Aguila a, b, c, d, e, Enrique Gómez-Gómez a, c, f, Alejandro Ibáñez-Costa a, b, c, d, e, Julia Carrasco-Valiente a, c, f, Esther Rivero-Cortés a, b, c, d, e, Fernando L-López a, b, c, d, e, Sergio Pedraza-Arevalo a, b, c, d, e, José Valero-Rosa a, c, f, Rafael Sánchez-Sánchez a, b, c, d, e, Rosa Ortega-Salas a, b, c, d, e, María M. Moreno a, c, g, Manuel D. Gañete a, b, c, d, e, José López-Miranda a, c, d, h, María J. Requena a, c, f, Justo P. Castaño a, b, c, d, e, * and Raúl M. Luque a, b, c, d, e, *
2. The Product: b) Innovative mechanisms of action

GOAT in prostate cancer

*Hormaechea-Agulla et al. / Cancer Letters 383 (2016)*

**Benign glands (BG)**  **Tumoral glands (TG)**

**GOAT** is overexpressed in prostate cancer (tissues and cell lines) and can be secreted by prostate cancer cells.
2. The Product: b) Innovative mechanisms of action

**GOAT in prostate cancer**

GOAT levels can be detected in **plasma**, where it discriminates between prostate cancer patients and controls.

The difference was even bigger in the **non-diabetic population**.

*Hormaechea-Agulla et al. / Cancer Letters 383 (2016)*
Most importantly, **GOAT** levels can be detected in urine, where it discriminates between prostate cancer patients and controls.
2. The Product: c) Differential features facing the market

GOAT better diagnostic tool than PSA:

- **Higher sensitivity than previous methods**
  - GOAT levels in **plasma**: (cut-off 1.22 ng/mL) **81.1% sensitivity**
  - GOAT levels in **urine**: (cut-off 1.061 ng/mL) 75% sensitivity

- **PSA** levels in **plasma**:
  - cut-off 3 ng/mL: 32% sensitivity for any prostate cancer and **68%** for high-grade cancers (Gleason ≥8)

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<tr>
<td>Sensitivity (%) for High Grade Cancer, i.e., Gleason Score ≥ 8</td>
<td>51</td>
<td>68</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>91</td>
<td>85</td>
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<tr>
<td>Positive Predictive Value (%)</td>
<td>30</td>
<td>28</td>
</tr>
</tbody>
</table>

**Easy to assess**

- GOAT levels can be measured using **simple, easy to use and rapid methods**: ELISA plate reader in contrast to other assays that require qPCR or automated systems
2. The Product: c) Differential features facing the market

<table>
<thead>
<tr>
<th></th>
<th>GOAT</th>
<th>PSA</th>
<th>PCA3</th>
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<td>PCR</td>
<td>ELISA</td>
<td>PCR</td>
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<td><strong>Sample type</strong></td>
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<td>Urine (post-massage)</td>
<td>Plasma</td>
<td>Urine</td>
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<td>14 Days</td>
<td>Few days</td>
<td>Days</td>
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<tr>
<td><strong>Resources needed</strong></td>
<td>Plate reader</td>
<td>Plate reader</td>
<td>External assay</td>
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<tr>
<td><strong>Sensitivity</strong></td>
<td>81%</td>
<td>32%</td>
<td>65%</td>
<td>89%</td>
<td>–</td>
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<tr>
<td><strong>Specificity</strong></td>
<td>68%</td>
<td>85%</td>
<td>73%</td>
<td>61%</td>
<td>–</td>
</tr>
</tbody>
</table>

- Cui et al., SciRep 2017
  10.1038/srep25776
- Wolf et al., CA Cancer J Clin 2010
  10.3322/caac.20066
- http://mdxhealth.com
- http://4kscore.com
2. The Product: d) Current status of development

Novel non-invasive biomarker for prostate cancer

Proyectos de desarrollo tecnológico en salud (DTS)

Instituto de Salud Carlos III - Acuse de recibo

DATOS GENERALES

Asunto: Solicitud del expediente: DTS17/00061
Procedimiento: Acción Estratégica de Salud. Ayudas y Subvenciones
Organo destinatario: SG de Evaluación y Fomento de la Investigación
Número de expediente: IESM-2017-201207
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Resolución definitiva de la Convocatoria del segundo plazo de Ayudas de la Modalidad II: Protección de Resultados de la Investigación

III Plan Propio Gallego de Innovación y Transferencia de la Universidad de Córdoba

Tras la publicación en el Diario Oficial de la UCO, con fecha 12/10/2017, de la relación provisional del segundo plazo de ayudas de la Modalidad II: Protección de resultados de la investigación concedidas de acuerdo con los criterios establecidos en las bases de la convocatoria del III Plan Propio Gallego de Innovación y Transferencia, y una vez finalizado el plazo de presentación de adhesiones, el Consejo de Gobierno aprueba la siguiente relación de ayudas concedidas por la Comisión de Innovación y Transferencia.
2. The Product: d) Current status of development

**Valorization Strategy**

**Current Status:** Promising results

- 113 plasma samples cohort
- 113 urine samples cohort
- 64 tissue samples cohort
- Good preliminary results

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**Valorize this tool**

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**Expected Results**

1) Expand to 1000-1300 plasma/urine samples cohort

2) Perform a regulatory and transfer plan and a budget Impact study

- Generate a **STRONG PROOF OF CONCEPT** and a way for the **TRANSFERRING OF THE ASSET**

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**Goal and associated main objectives**

1. **To obtain a strong proof-of-concept** (diagnostic tool: >1,000-1,300 patients, MULTICENTER study; Explore the feasibility and validity of GOAT as **prognostic tool** compared with PSA).

2. **To develop and optimize new antibodies against GOAT** (to improve the screening ability and the sensibility of the technology => development of a series of diagnostic kits)

3. **To continue and implement the protection of the asset (patent).**

4. **To perform a Market Research and Budget Impact study** comparing GOAT with the gold standard, PSA, and other available technologies and its impact in the healthcare system.

5. **Delineate a Business Plan** to be presented to the investors.
2. The Product: d) Current status of development

GOAT in prostate cancer

4 different and relevant groups of patients: healthy individuals, patients with suspect of PCa but negative biopsy and PCa patients, which were divided into non-significant and significant PCa patients.

GOAT behaves as a better diagnostic tool than PSA.

RESULTS (first approach: n>300 patients confirmed initial results)
2. The Product: d) Current status of development

GOAT in prostate cancer

GOAT, but not PSA, levels can discriminate between PCa patients and controls with high sensitivity, in the so-called grey zone of PSA (3-10ng/ml).

- GOAT levels positively correlates with Gleason Score

Potential utility as Prognostic value
2. The Product: d) Current status of development

1) GOAT outperforms the capacity of the actual gold-standar (PSA) to predict the presence of PCa, specially in the case of those patients in the so-called grey-zone.

2) that GOAT levels also may also be used as a prognostic tool of PCa agresiveness.

Therefore, **GOAT levels could represent a novel PCa biomarker that can complement, or even substitute, PSA for PCa detection.**
2. The Product: d) **Current status of development**

**Eladio Crego Gil**
Consultant at EFT Consulting
Santiago de Compostela, Galicia, España
Servicios financieros
Actual: EFT Consulting, Mtrap Inc, Nasasbiotech
Anterior: UNINVEST, Unirisco Galicia, Hijos de
Educación: ESADE

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**Proyectos de desarrollo tecnológico en salud (DTS)**

Instituto de Salud Carlos III - Acuse de recibo

**DATOS GENERALES**

Regulatory strategy roadmap for the diagnostic kit for GOAT Project
Roadmap report

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**FIPSE**
FUNDACIÓN PARA LA INNOVACIÓN Y LA PROSPECTIVA EN SALUD EN ESPAÑA

**GOAT Project**
Project code 18-026-01

**GENESIS Biomed**
2. The Product: e) IPR protection

Level of development and protection of the asset

"GHRELINA-O-ACIL TRANSFERASASA (GOAT) Y SUS USOS"

- Spanish Patent (P201531731) was requested on December 27th, 2015

- Patent extension to PCT was carried out on November 28th, 2016, patent number: PCT/ES2016/070844.
2. The Product: f) Pitfalls & Risks to be considered

Risk Plan

<table>
<thead>
<tr>
<th>POSITIVE</th>
<th>NEGATIVE</th>
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<td>HIGH IMPORTANCE</td>
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<tr>
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<td>- Appearance of a good novel biomarker</td>
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<tr>
<td></td>
<td>- KOLs negative opinion of the asset</td>
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<tr>
<td>MEDIUM IMPORTANCE</td>
<td>MEDIUM IMPORTANCE</td>
</tr>
<tr>
<td>- Early licensing of the asset</td>
<td>- Industry not interested in GOAT after valorization</td>
</tr>
<tr>
<td></td>
<td>- Negative Market Research or Budget Impact study</td>
</tr>
<tr>
<td>LOW IMPORTANCE</td>
<td>LOW IMPORTANCE</td>
</tr>
<tr>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Contingency Plan (two main risks)**

- **Negative Market Research or Budget Impact study:**
  - To implement methodological improvements
  - To explore putative combinations with other markers in order to increase the power of the asset.

- **KOLs negative opinion of GOAT.**
  - To prepare scientific papers and documents comparing PSA with GOAT in order to convince scientific society of GOAT abilities and possible impact.
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3. Partnering Opportunities
3. Partnering Opportunities

“COLLABORATION is the best way to became the translational research into reality.”

Licensing strategy
We are looking for an early license to a company that can finance the clinical development

Co-development
We are looking for an collaboration agreement with the industry which allows:
- Analysis of combination of GOAT with other biomarkers
- Development of a new ELISA kit

We offer you the opportunity to participate in the development, manufacturing and exploitation of a strategic opportunity in prostate cancer biomarker area.

Commercialization
We are looking for a company that would also carry out the market launch
GOAT (Ghrelina-O-aciltransferasa), nuevo biomarcador en orina para el diagnóstico de cáncer de próstata

Madrid, 28th November, 2018