XI Encuentro de Cooperación Farma-Biotech

New therapeutic agents in the treatment of inflammatory disorders characterized by high levels of TNF- α

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Universidad de Alcalá

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GOBIERNO DE ESPAÑA MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

MEDICAMENTOS INNOVADORES Plataforma Tecnológica Española

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1. The Institutions

Collaboration

- Group of Biological Chemistry (Universidad de Alcalá, RedinRen)
  - **Anti-inflammatory compounds**
  - **Calpain inhibitors**
  - **Protein tyrosine phosphatase 1B inhibitors**
  - **A-FABP inhibitors**
  - **Angiotensin II antagonists**
  - **Synthesis of heterocyclic compounds**
  - **PET radiotracers**
  - **Antileishmanial compounds**

- Group of Nephrology (IdiPAZ, RedinRen)
  - **Diseases involving renal and peritoneal disorders/inflammation**

- Laboratory of innate immunity and hypersensitivity (IdiPAZ)
  - **Involvement of the innate immune system in peritoneal inflammation and fibrosis**
  - **Innate and adaptive immune response to CMV in renal transplant**
  - **Cytotoxic immune response in severe cutaneous drug hypersensitivity reactions**

2. The Product

a) Target Indications

Indolinium and Benzimidazolium salts as new TNF-α inhibitors

Targets: Inflammatory disorders characterized by high levels of TNF-α

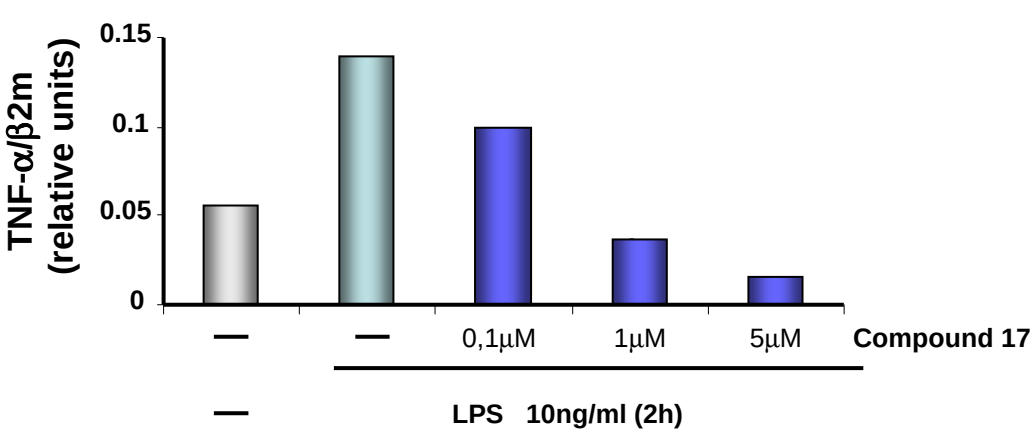
- Immune mediated inflammatory diseases (IMIDs)
- Metabolic disorders

2. The Product

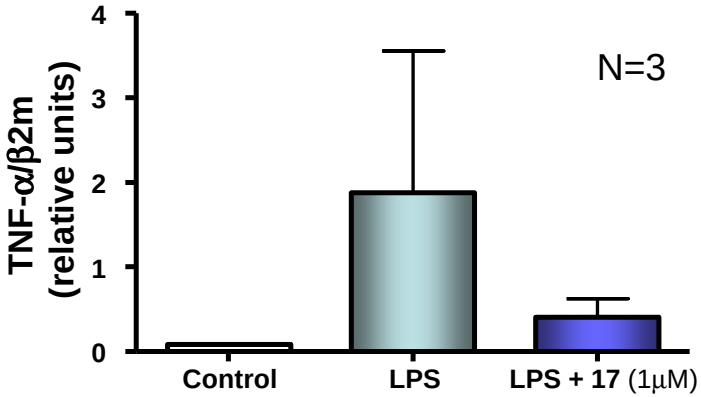
b) Mechanisms of action I

Compound 17 inhibits TNF-α production at the transcriptional level

Dose dependent inhibition of transcription in human PBMCs



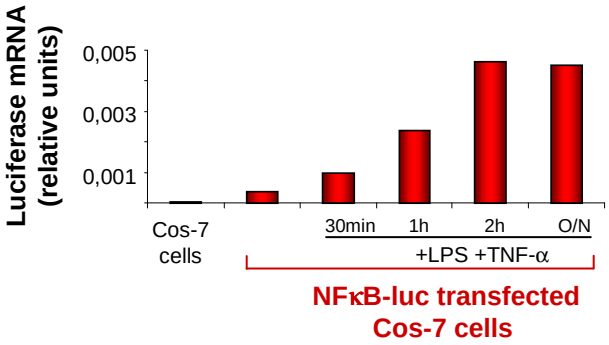
Transcription inhibition in human monocytes

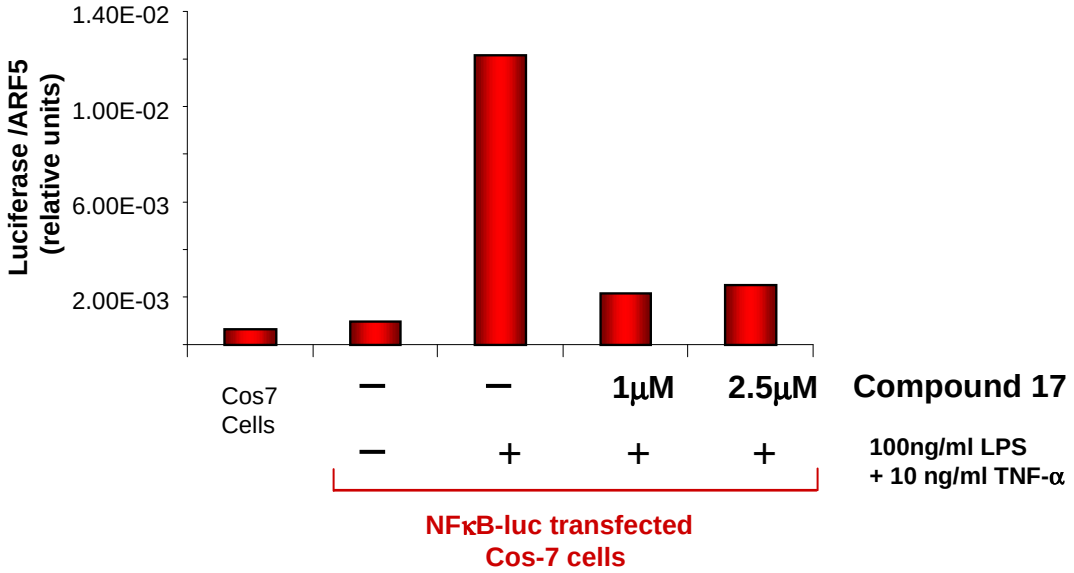


2. The Product

b) Mechanisms of action II

Compound 17 inhibits NFκB transcriptional activity





2. The Product

c) Differential features facing the market

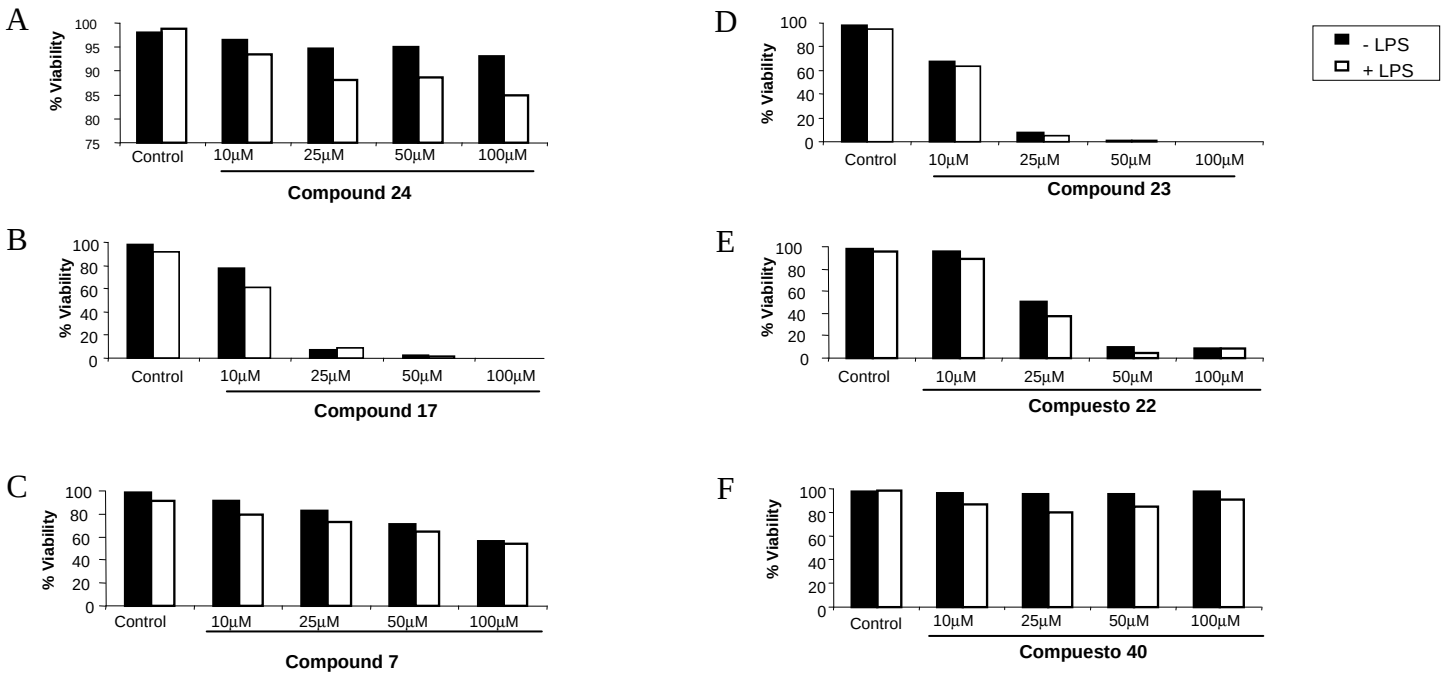
❖These new compounds, besides showing a marked efficacy in inhibiting production of proinflammatory cytokines or signaling -strategy that has proved to be the most effective in treating inflammation- allow at the same time their **oral administration**, unlike recent antiinflammatory protein-based biological therapies.

❖On the other hand, the majority of drugs currently available in the market for the treatment of inflammatory disorders, such as steroidal anti-inflammatory agents (hormones), nonsteroidal anti-inflammatory agents (NSAIDs) show numerous **side effects**, which make worth to explore the potential of new drugs

2. The Product

d) Current status of development I

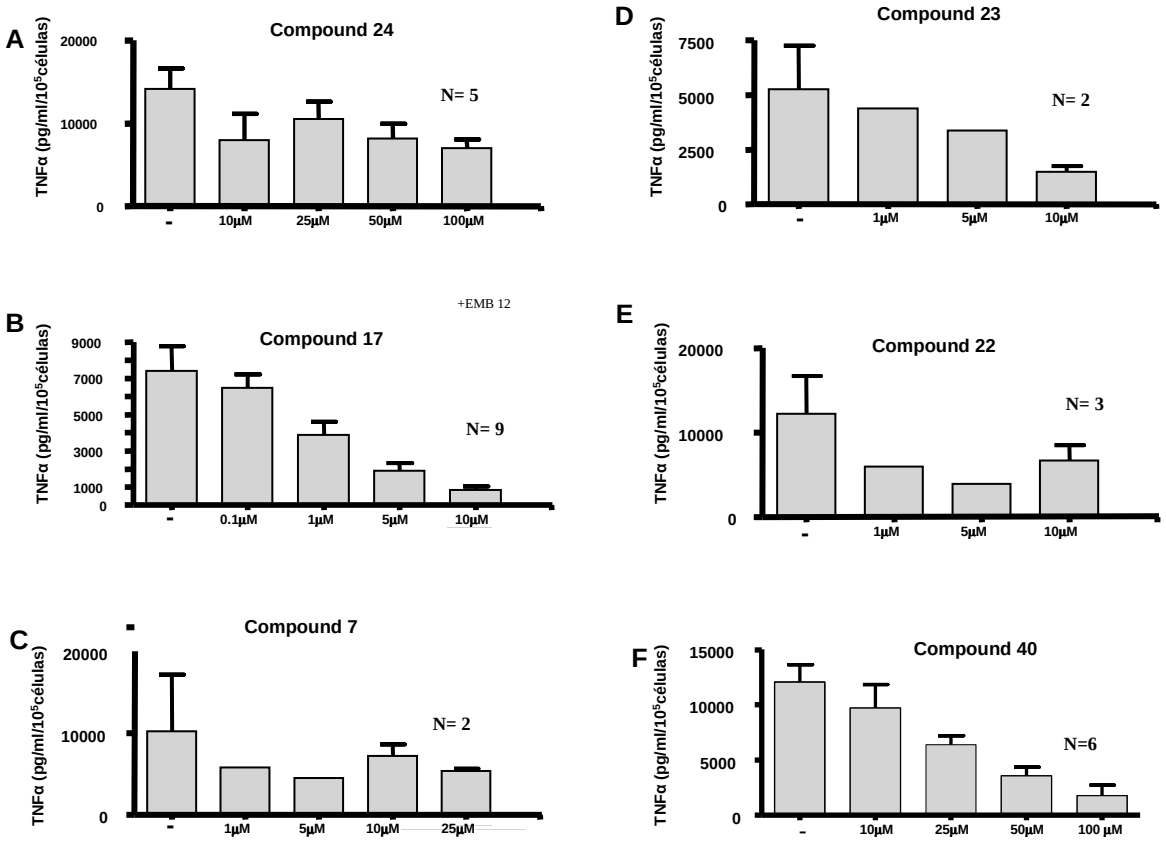
Viability of THP-1 human monocytic cell line preincubated with synthesized compounds



2. The Product

d) Current status of development II

TNF-α production of THP-1 cells stimulated with 100 ng/ml LPS

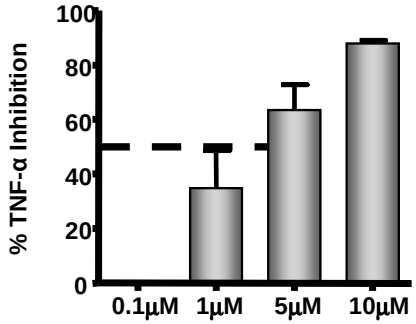


2. The Product

d) Current status of development III

Calculation of IC_{50} of compound 17 for TNF-α production in response to LPS

THP-1 human monocytic cell line

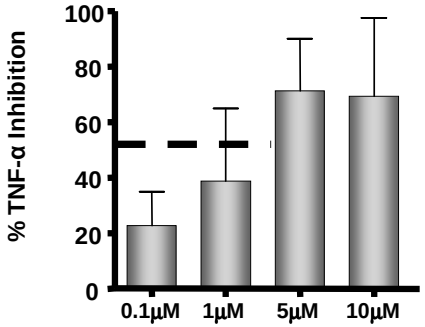


Compound 17

IC_{50} 4.49 µM

THP-1

Human PBMCs

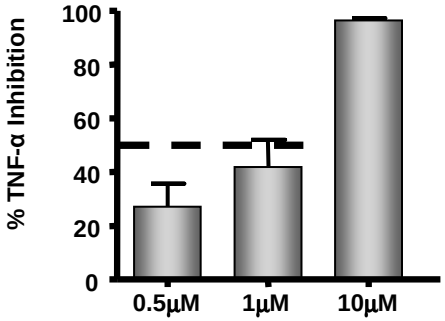


Compound 17

IC_{50} 3.91 µM

PBMCs

Human purified monocytes



Compound 17

IC_{50} 1.82 µM

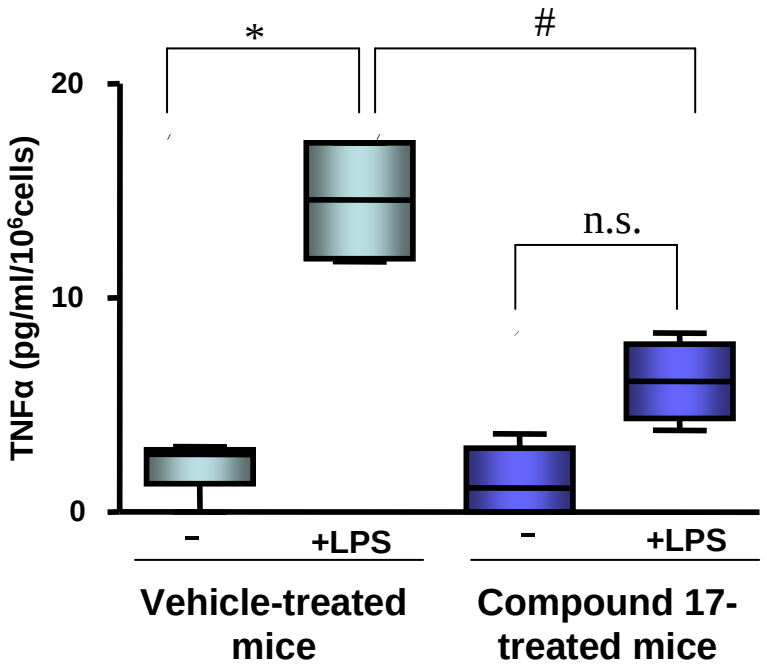
Monocytes

2. The Product

d) Current status of development iV

Splenocytes from mice treated with compound 17 do not respond to LPS

2mg/kg = 40µg /mice
200µl PBS (i.p.)
2x

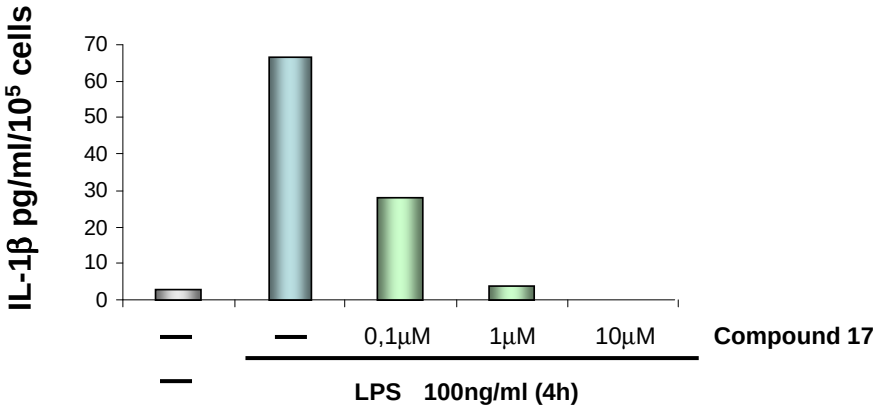


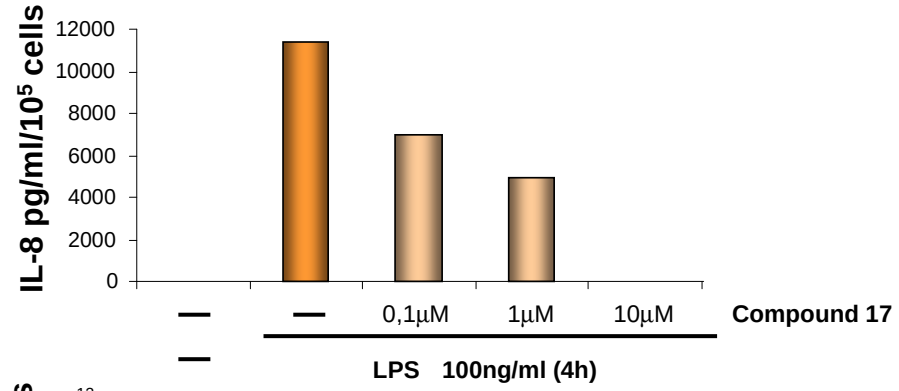
2.5µM = 1 µg daily
1ml PBS (30 days)
Showed no toxicity

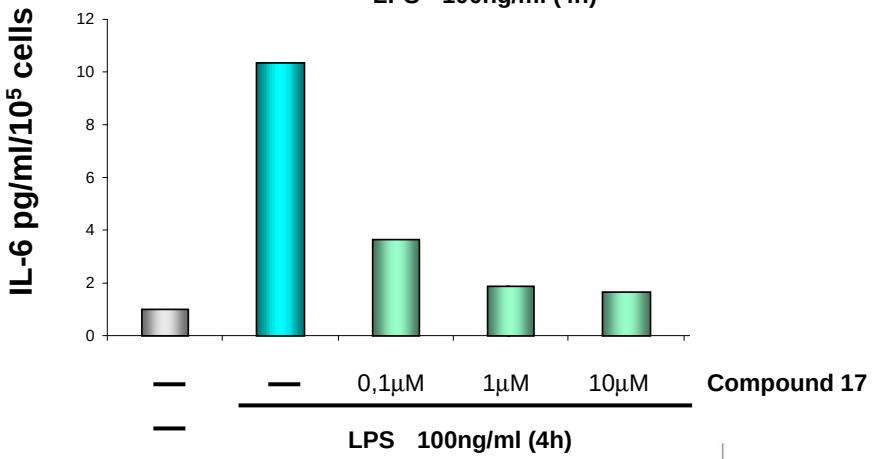
2. The Product

d) Current status of development V

Other cytokines modulated by compound 17 in response to LPS in THP-1





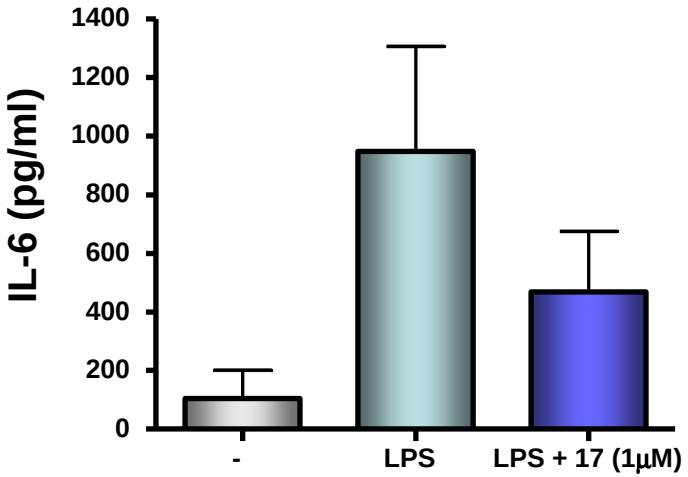


2. The Product

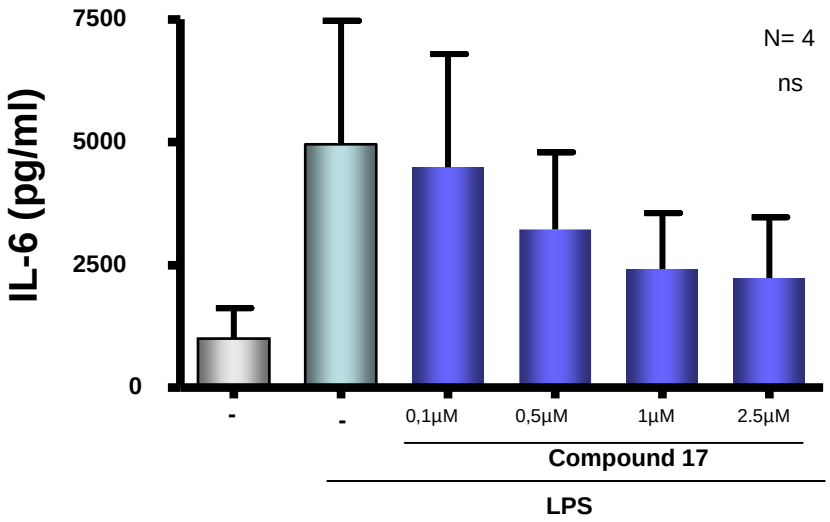
d) Current status of development VI

Compound 17 modulates the production of IL-6 in response to LPS in different human primary cell lineages

Purified human monocytes



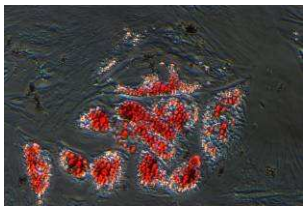
Human mesenchymal stem cells

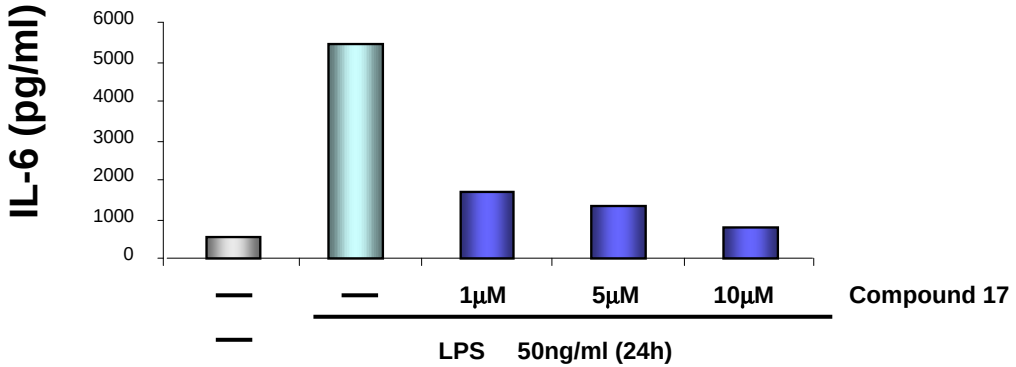


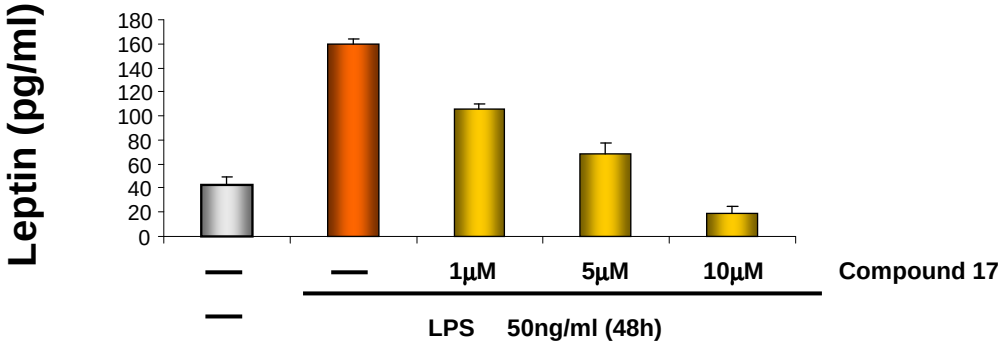
2. The Product

d) Current status of development VII

Compound 17 modulates the production of IL-6 and leptin in *in vitro*-differentiated human adipocytes



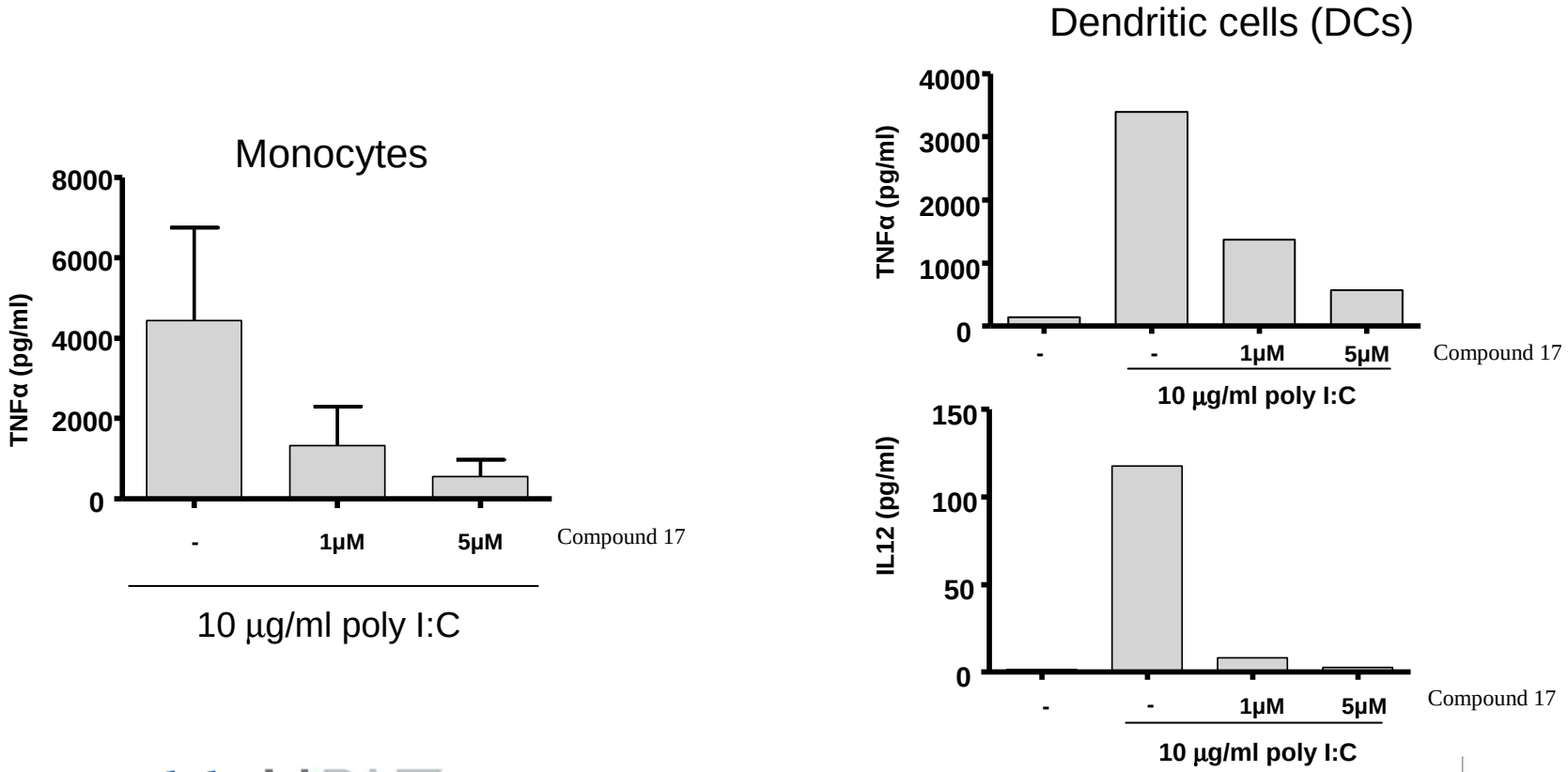




2. The Product

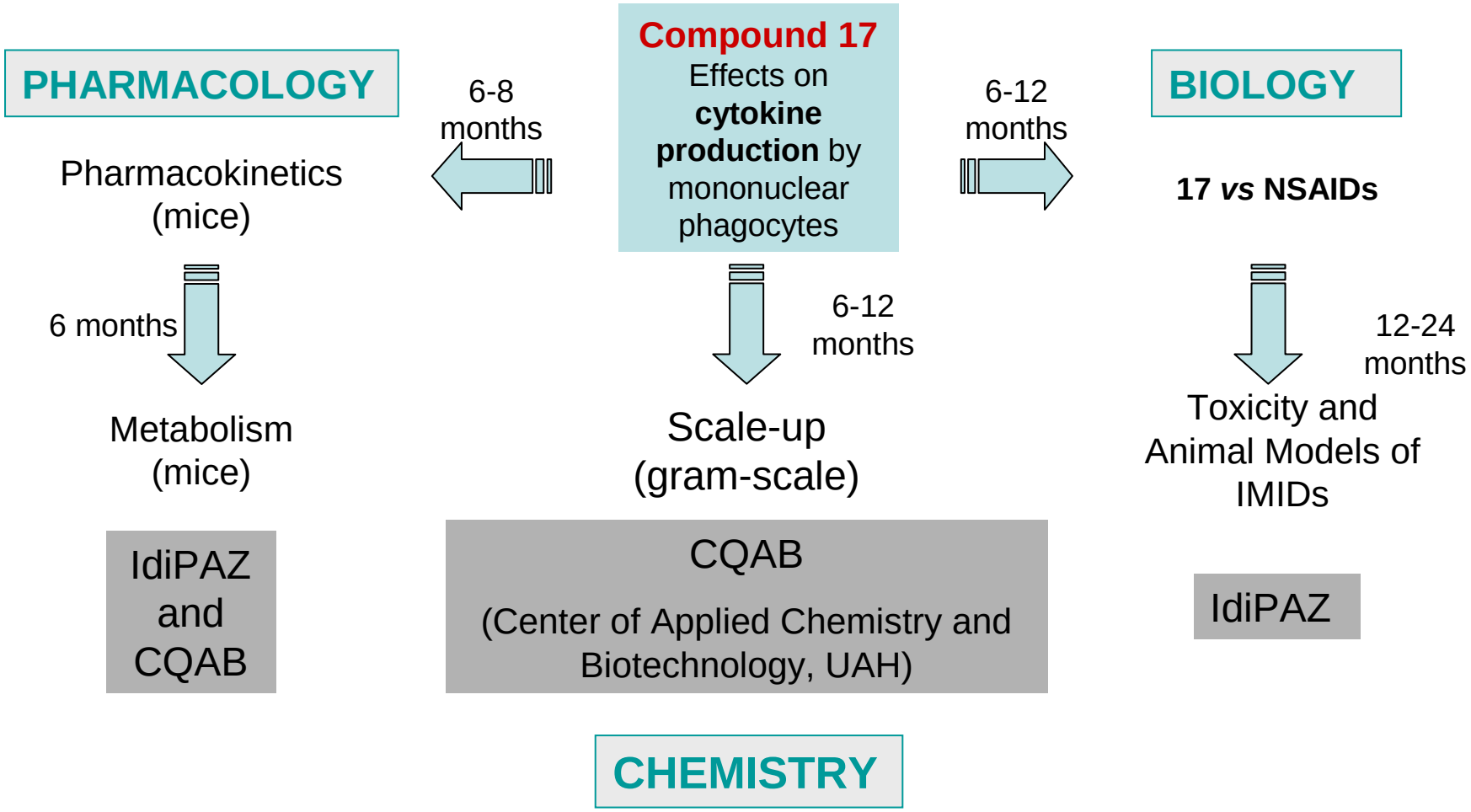
d) Current status of development VIII

Compound 17 modulates the inflammatory response to poly I:C in human monocytes and DCs



2. The Product

d) Current status of development: Further research



2. The Product

e) IPR protection

Spanish patent P201331143 filed in July 2013.

Shortly it will be internationally extended through PCT route.

2. The Product

e) Pitfalls and risks to be considered

- Not compared to other NSAIDs in the market
- Primary molecular target not defined
- Not enough in vivo assays for efficacy and safety

3. Partnering opportunities

We would like to find any party interested in partnering, licensing or investing in the technology:

- Investors to finance the subsequent phases of the research project, but specifically and as a first step, the gram-scale synthesis of the product (this step could be done in CQAB)
- Patent licensees
- Partners interested in getting involved in the subsequent phases of the research project, including animal tests