

1,2,3,5-tetrasubstituted pyrroles: new molecules with potent antiinflammatory activity in acute lung injury



Barcelona, 14 de marzo de 2012

Content

1. The Research Group

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

Content

1. The Research Group

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

Programa Cooperación Farma-Biotech

Jornada 1-2012: Áreas Terapéuticas de Inflamación, Infección y Respiratorio

Research Group



Biomedical Research Network in Respiratory Diseases

Group number 29 CIBERES began its research activity last 2007 in studies about acute lung injury induced by sepsis and/or mechanical ventilation.

❖ From beginning, this group has published more than 50 international research articles and it has participated in more than eleven research projects.

❖ This group has obtained industry contracts and different clinical trials as well as invention patent applications.

Programa Cooperación Farma-Biotech

Jornada 1-2012: Áreas Terapéuticas de Inflamación, Infección y Respiratorio

Research Group



Dr. Jesús Villar Hernández

*MD, PhD, FCCM

*Head of Group number 29. CIBERES



Dr. José Manuel Padrón Carrillo

*PhD

*University of La Laguna



Dra. Nuria Esther Cabrera Benítez

*PhD

*Group number 29. CIBERES



Dña. Ángela María Ramos Nuez

*MLT

*Group number 29. CIBERES

Programa Cooperación Farma-Biotech

Jornada 1-2012: Áreas Terapéuticas de Inflamación, Infección y Respiratorio

Scientific Advisory Board

Arthur S. Slutsky, MD	<i>Keenan Research Center at the Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, Canada.</i>
Carla Ríos-Luci, PhD	<i>BioLab, Instituto Universitario de Bio-Orgánica "Antonio González" (IUBO-AG), Universidad de La Laguna, La Laguna, Spain.</i>
Eduardo Pérez-Roth, PhD	<i>BioLab, Instituto Universitario de Bio-Orgánica "Antonio González" (IUBO-AG), Universidad de La Laguna, La Laguna, Spain.</i>
Carlos Rodríguez-Gallego, PhD	<i>Department of Immunology, Hospital Universitario Dr. Negrin, Las Palmas de Gran Canaria, Spain.</i>
Ithaisa Sologuren, PhD	<i>Department of Immunology, Hospital Universitario Dr. Negrin, Las Palmas de Gran Canaria, Spain.</i>

Programa Cooperación Farma-Biotech

Jornada 1-2012: Áreas Terapéuticas de Inflamación, Infección y Respiratorio

1. The Research Group

2. The Product

a) Target indications

b) Innovative mechanisms of action

c) Differential features facing the market

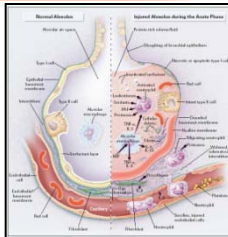
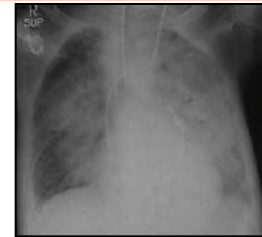
d) Current status of development

e) IPR protection

f) Pitfalls & Risks to be considered

3. Partnering Opportunities

Target indications: Acute Lung injury induced by sepsis



❖ Acute lung injury (ALI) is relatively common and is associated with high morbidity and mortality. Data (ALIVE) Study demonstrated that about 7% of all ICU patients develop ALI, and that sepsis is the most common predisposing factor.

❖ Sepsis is characterized by a systemic inflammatory state in response to circulating microbes or microbial toxins (LPS or bacterial DNA).

❖ The ultimate cause of death in septic patients is usually development of MOSF, which frequently starts as lung dysfunction.

Target indications: Acute Lung injury induced by sepsis

Overall 3034 infectious patients at ICU admission (crude incidence: 21.1%). From them: sepsis (28%) , severe sepsis (24%) and septic shock (30%).

In Spain,

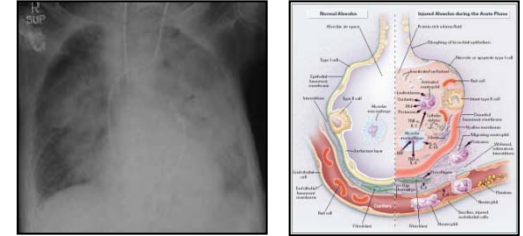
- *More frequently identified microorganisms : Streptococcus sp., Staphylococcus sp., Escherichia coli and Candida sp.
- *Most frequent organic dysfunctions : renal (39.7%) and respiratory (35.7%).
- *Mortality: 33%.
- *Mean length of stay : 28.9 days.
- *Annual overall costs : 70 million Euros.

Target indications: Acute Lung injury induced by sepsis

Conclusions

Severe sepsis is a frequent process,
with a high mortality and a
significant impact on health care
resource utilization.

Target indications: Acute Lung injury induced by sepsis



Actually, **septic patient** treatment which develops, between another, acute lung injury, includes antibiotic treatment, supplementary oxygen, endo-tracheal intubation and mechanical ventilation.



The use of **exclusive pharmacological treatment** for patients with acute lung injury induced by sepsis is still poorly known.

Programa Cooperación Farma-Biotech

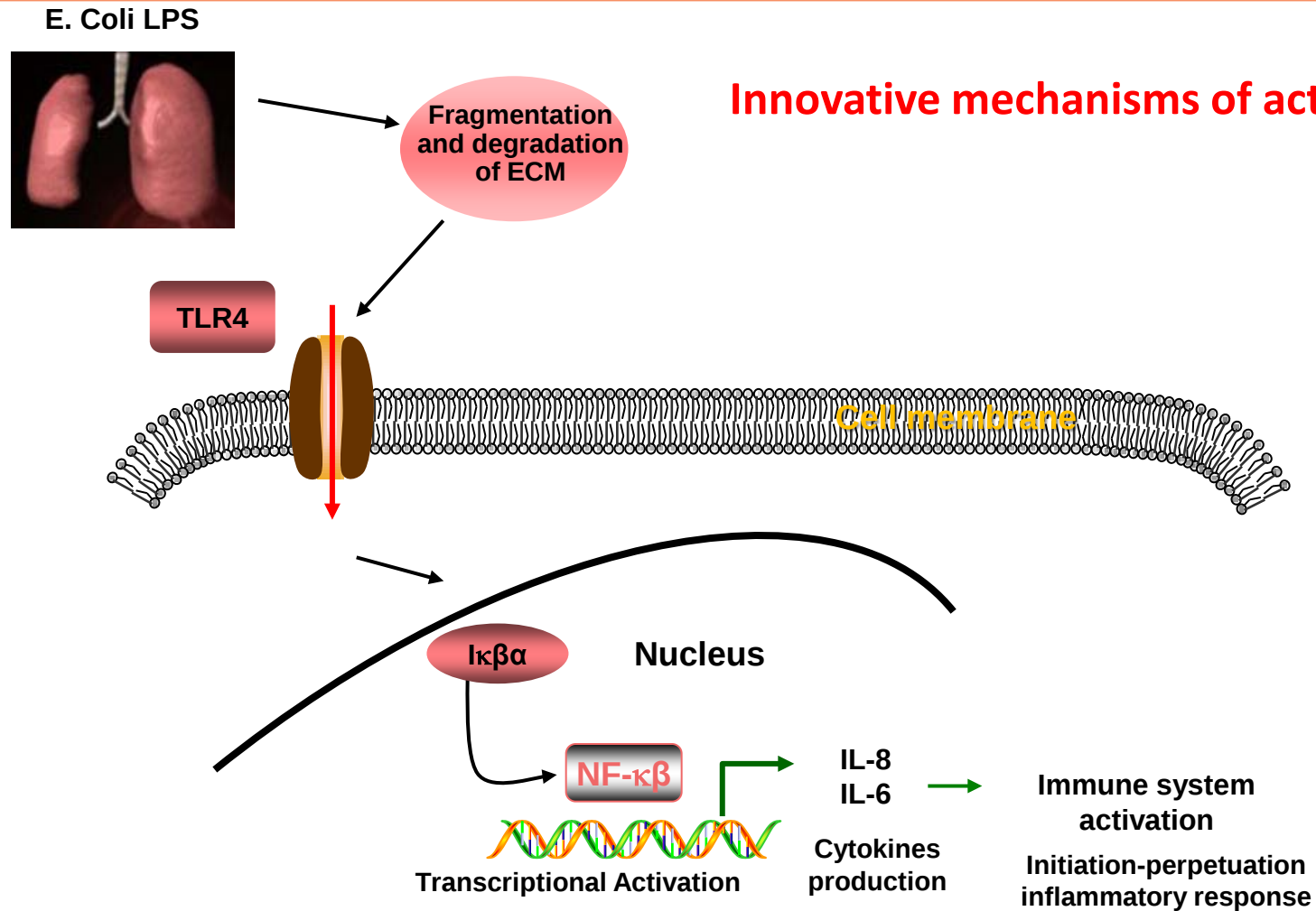
Jornada 1-2012: Áreas Terapéuticas de Inflamación, Infección y Respiratorio

1. The Research Group

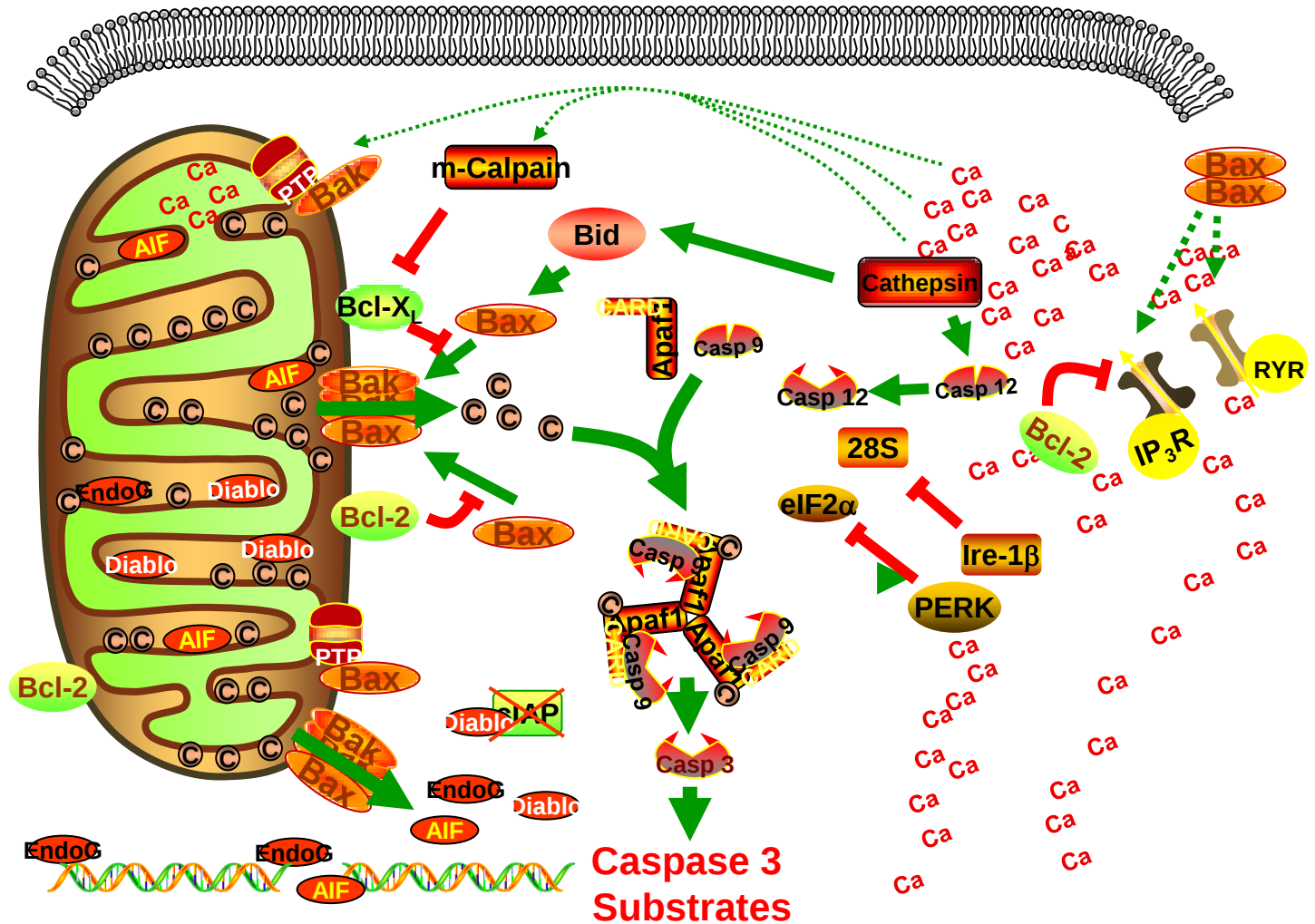
2. The Product

- 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



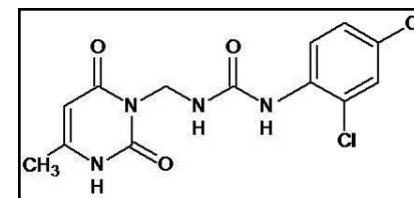
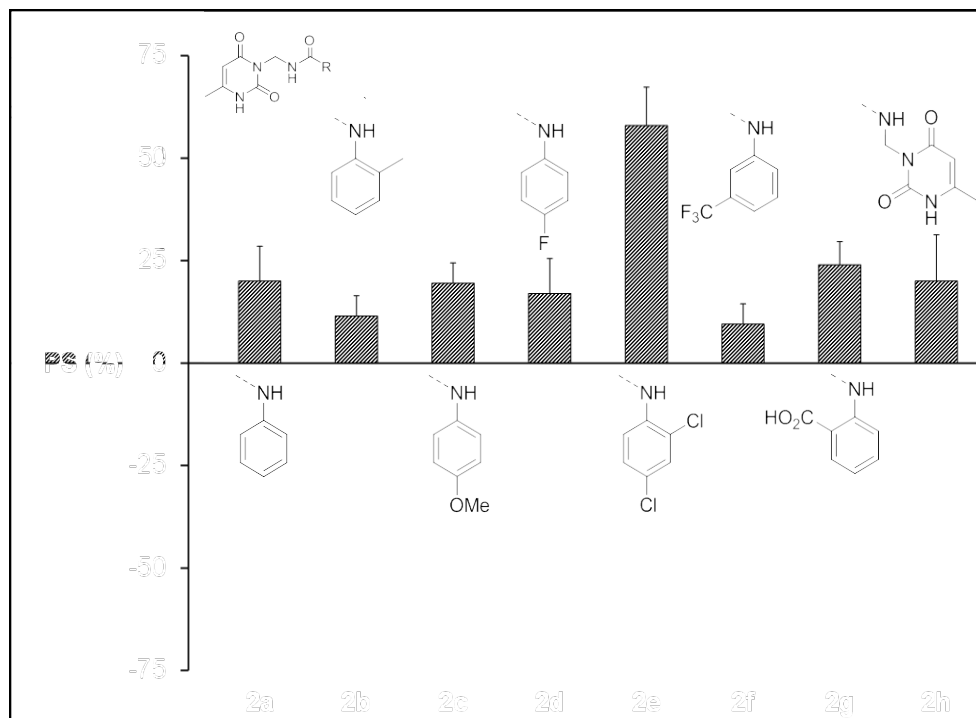
Innovative
mechanisms
of action



Programa Cooperación Farma-Biotech

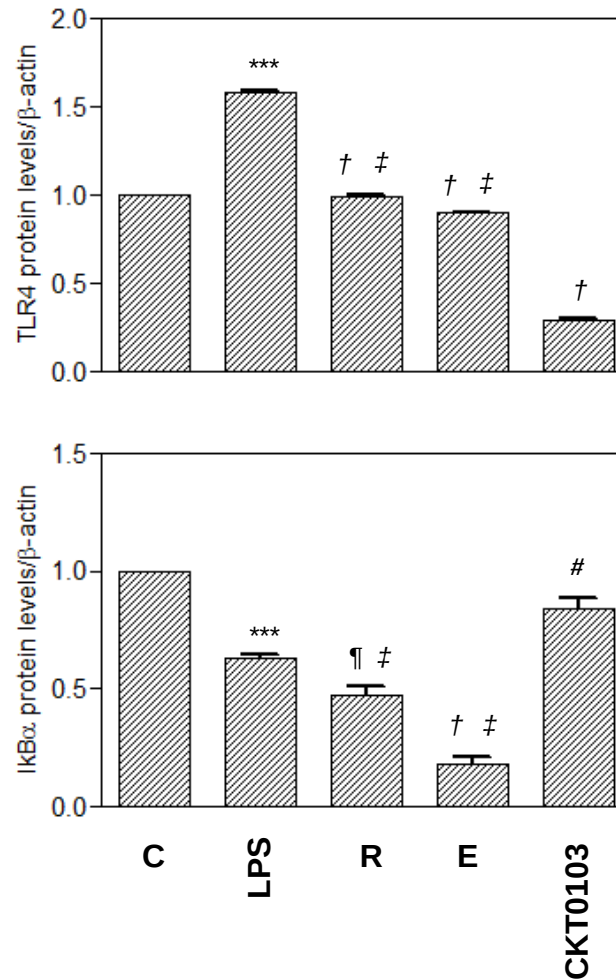
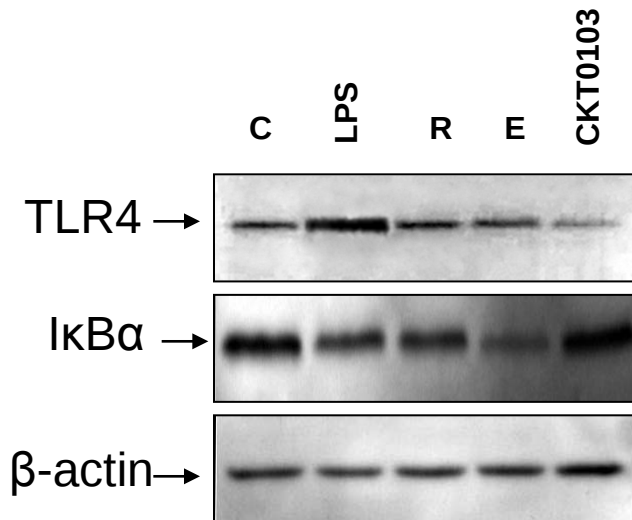
Jornada 1-2012: Áreas Terapéuticas de Inflamación, Infección y Respiratorio

Pyrimidinic aryl-ureas compounds



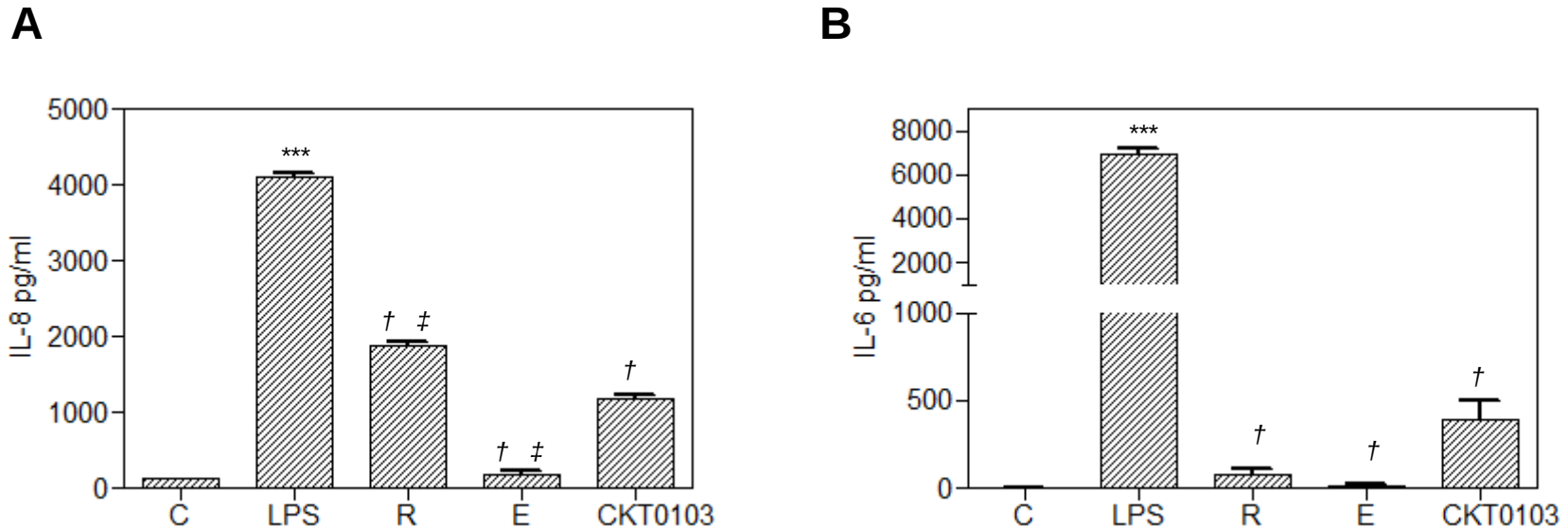
CKT0103

Pyrimidinic aryl-ureas compounds



***p<0.001 vs. C; ¶ p<0.05 vs. LPS; † p<0.001 vs. LPS; # p<0.01 vs. LPS + CKT0103; ‡ p<0.001 vs. LPS + CKT0103.

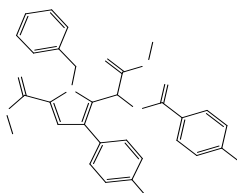
Pyrimidinic aryl-ureas compounds



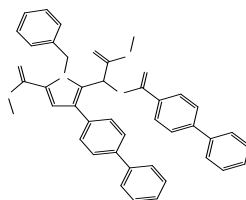
***p<0.001 vs. C;
† p<0.001 vs. LPS;
‡ p<0.001 vs. LPS + CKT0103.

1,2,3,5-tetrasubstituted pyrrols compounds

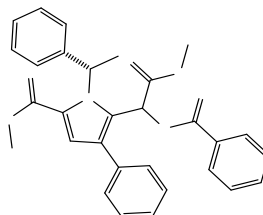
DTA0118



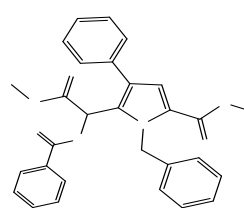
DTA0119



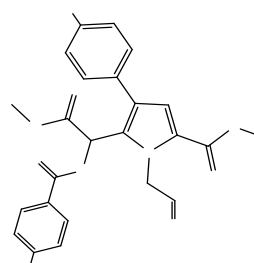
DTA0124



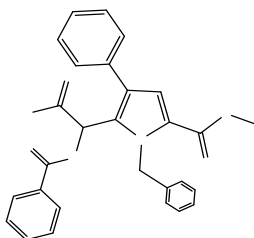
DTA0140



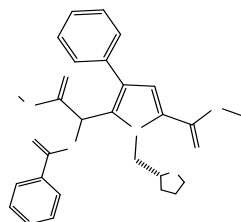
DTA0141



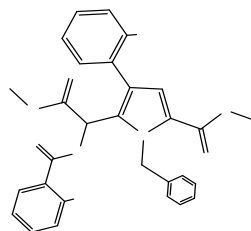
DTA0142



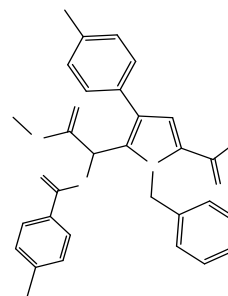
DTA0143



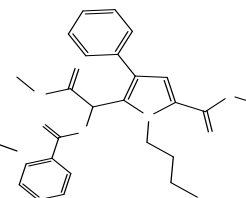
DTA0144



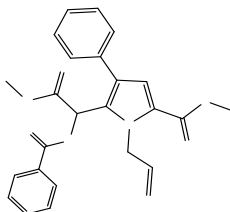
DTA0145



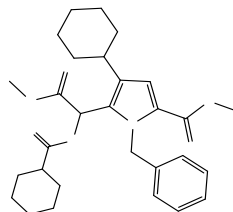
DTA0146



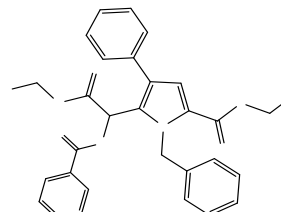
DTA0147



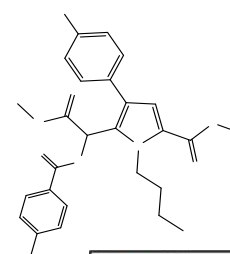
DTA0148



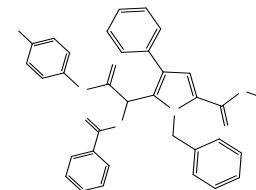
DTA0149



DTA0150



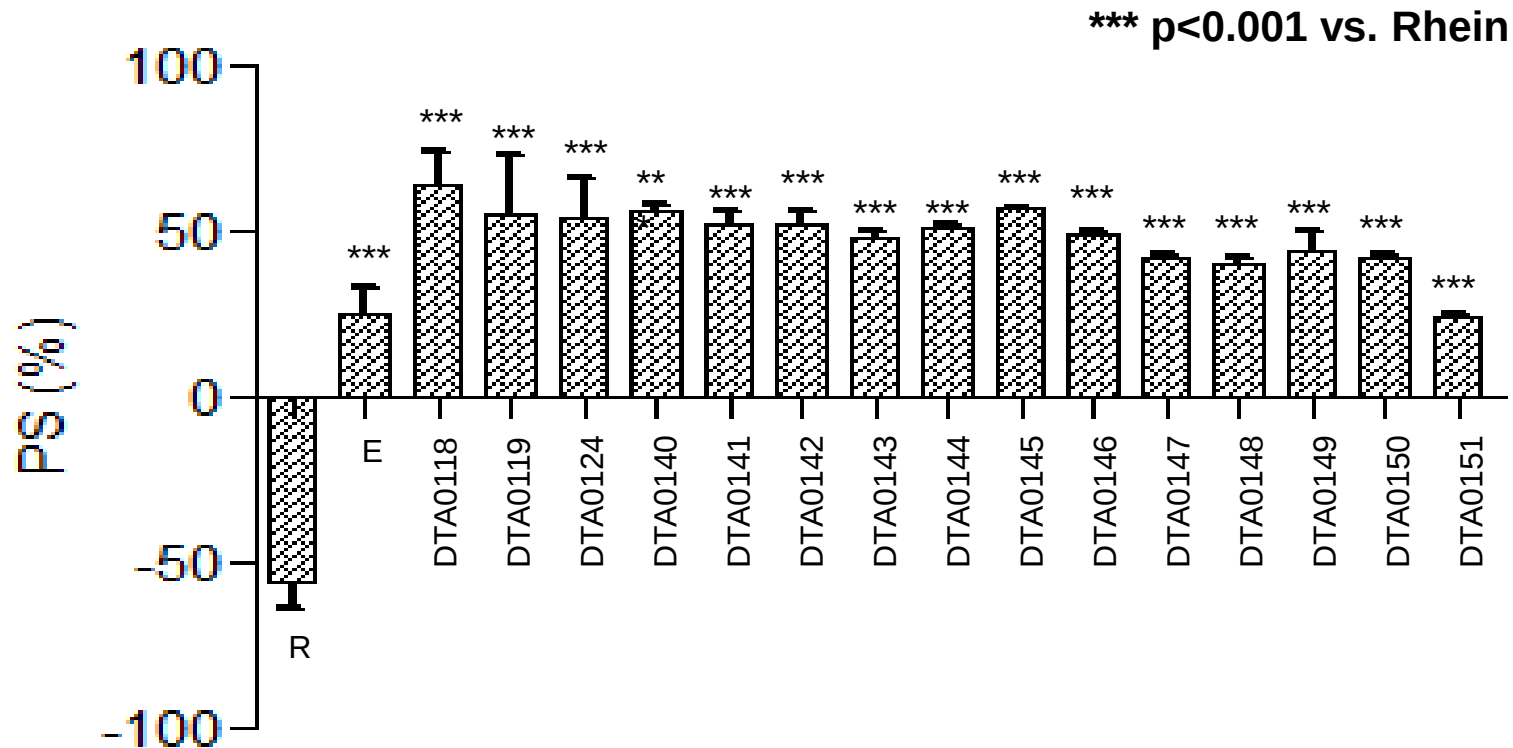
DTA0151



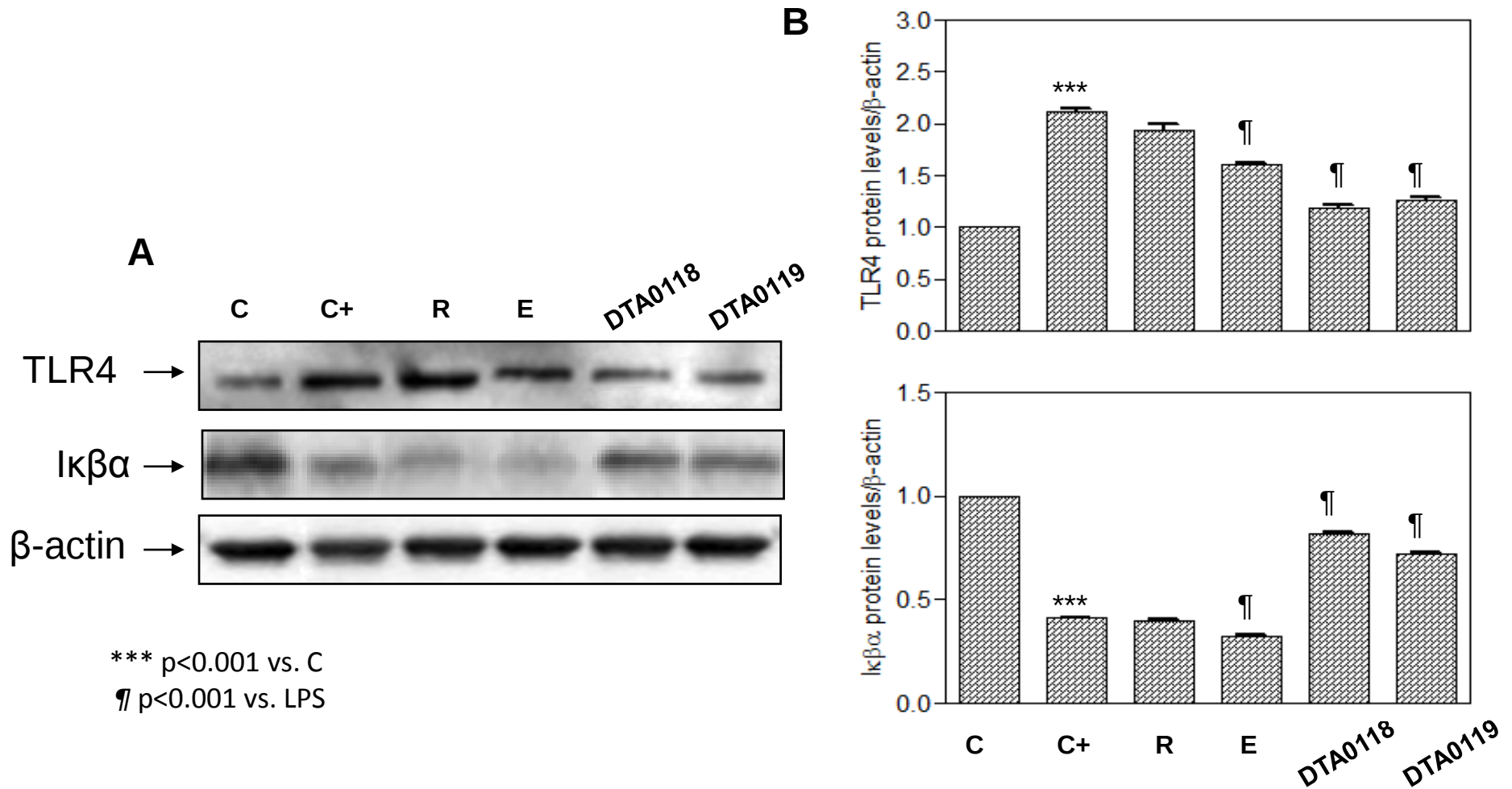
Programa Cooperación Farma-Biotech

Jornada 1-2012: Áreas Terapéuticas de Inflamación, Infección y Respiratorio

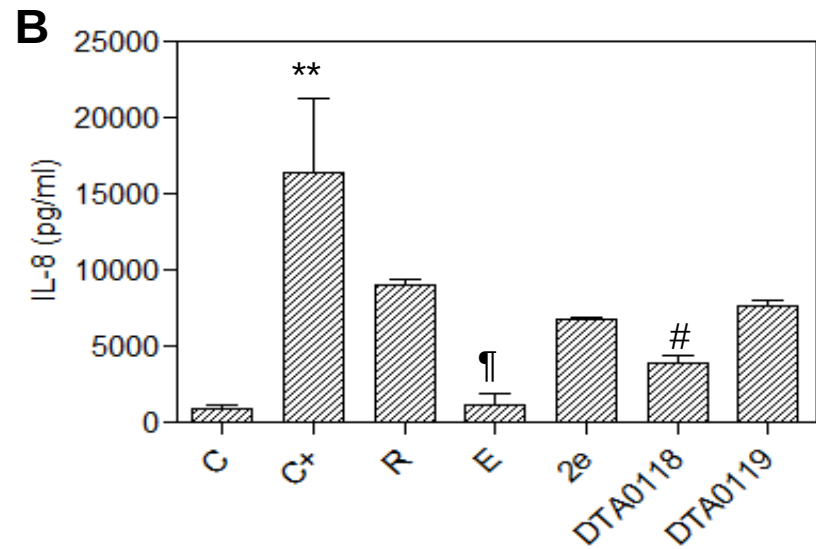
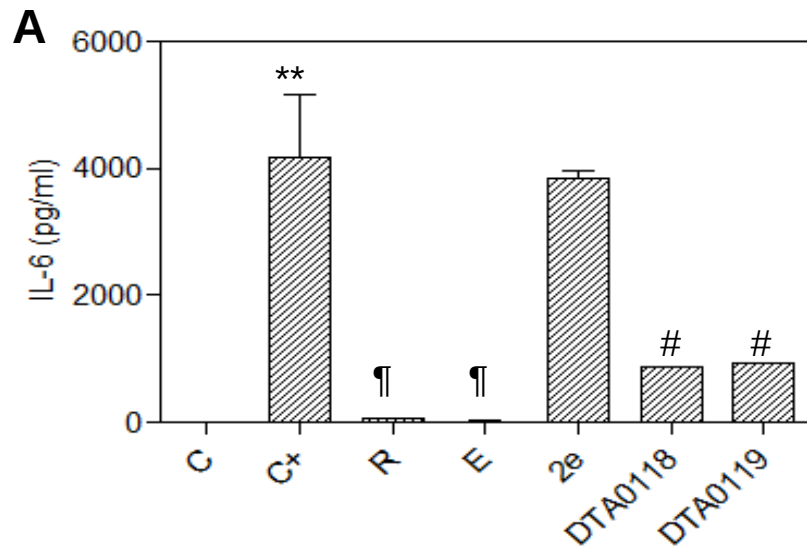
1,2,3,5-tetrasubstituted pyrrols compounds



1,2,3,5-tetrasubstituted pyrrols compounds



1,2,3,5-tetrasubstituted pyrrols compounds

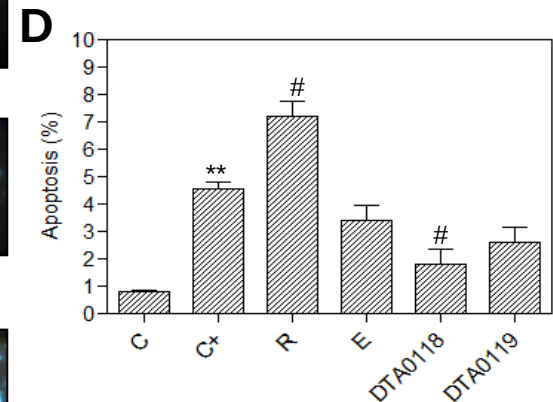
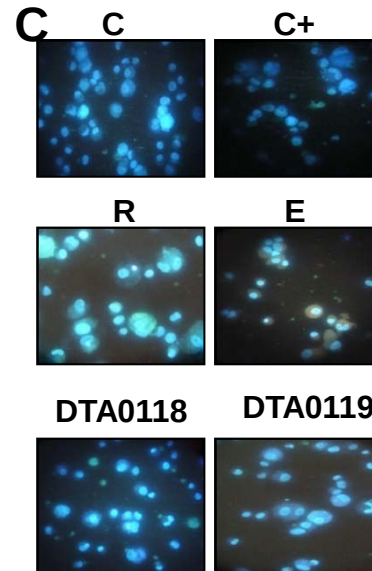
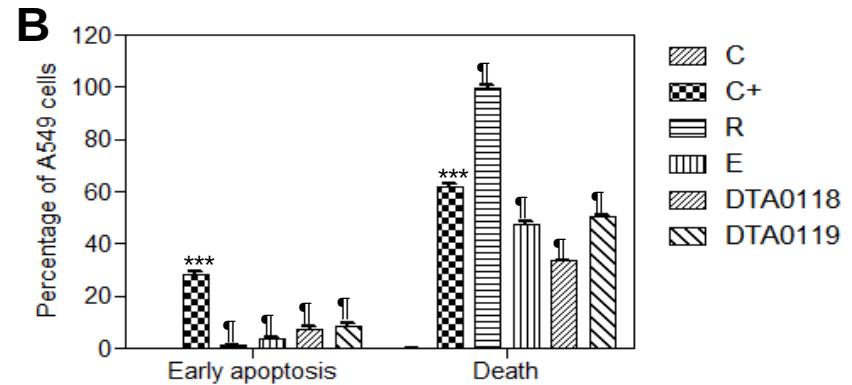
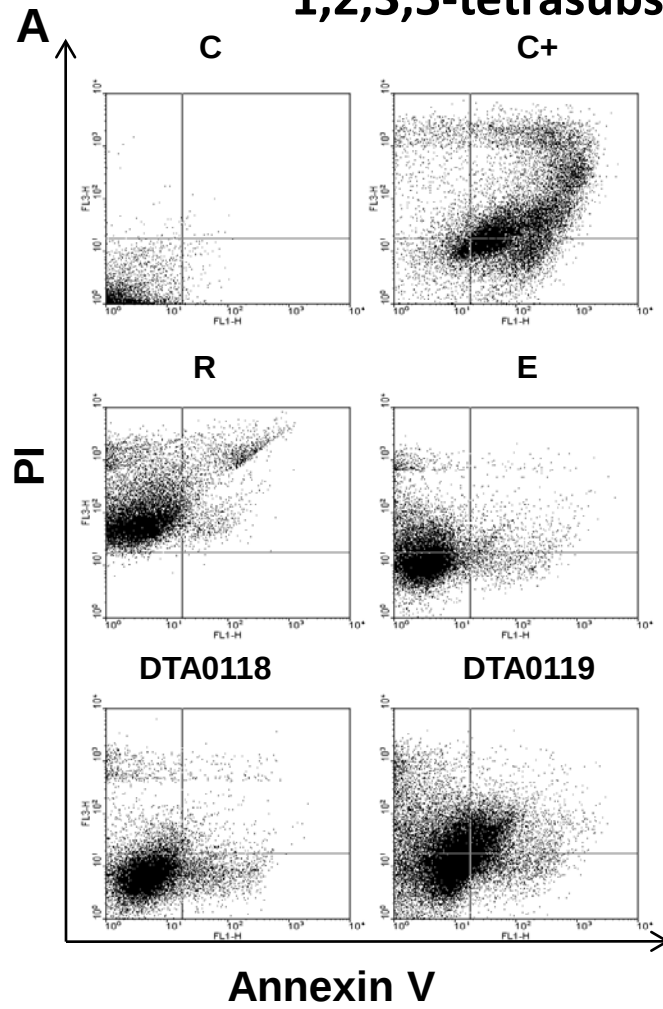


** $p < 0.01$ vs. C

$p < 0.05$ vs. LPS

¶ $p < 0.01$ vs. LPS

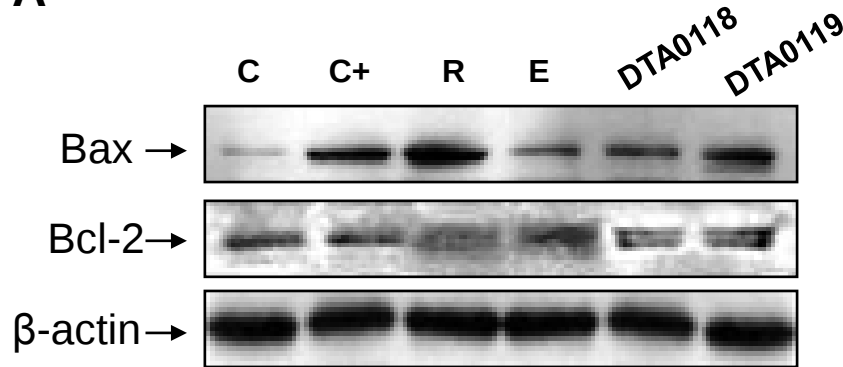
1,2,3,5-tetrasubstituted pyrrols compounds



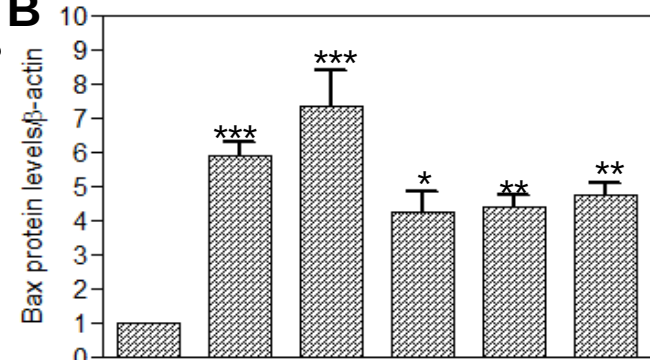
** p<0.01 vs. C
 *** p<0.001 vs. C
 # p<0.05 vs. LPS
 ¶ p<0.001 vs. LPS

1,2,3,5-tetrasubstituted pyrrols compounds

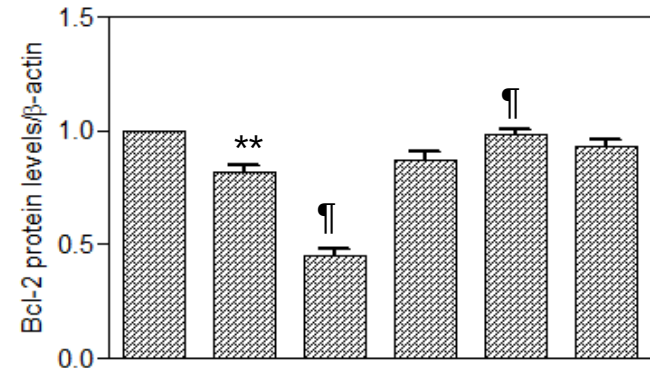
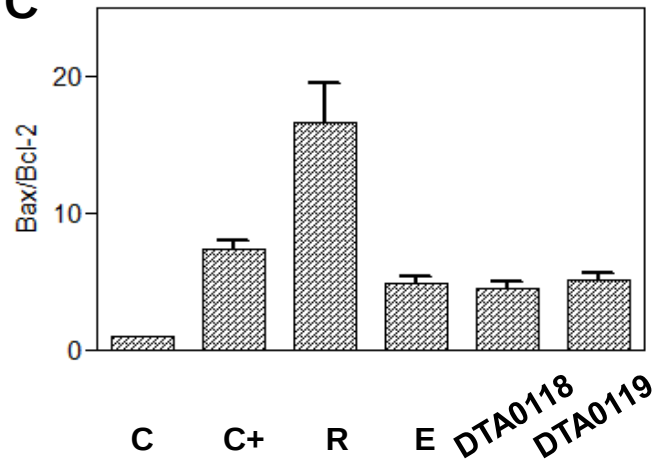
A



B

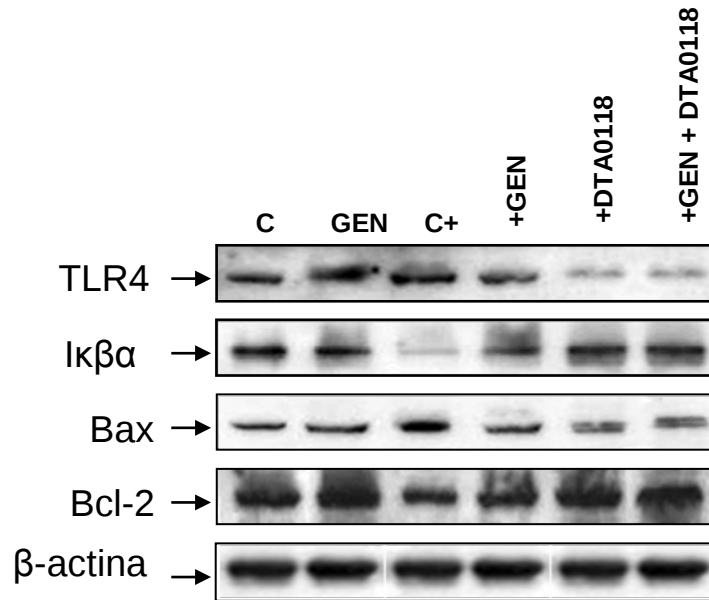


C



C C+ R E DTA0118 DTA0119
 * $p < 0.05$ vs. C; ** $p < 0.01$ vs. C;
 *** $p < 0.001$ vs. C; ¶ $p < 0.01$ vs. LPS

1,2,3,5-tetrasubstituted pyrrols compounds does not act through Tirosin kinase Inhibition

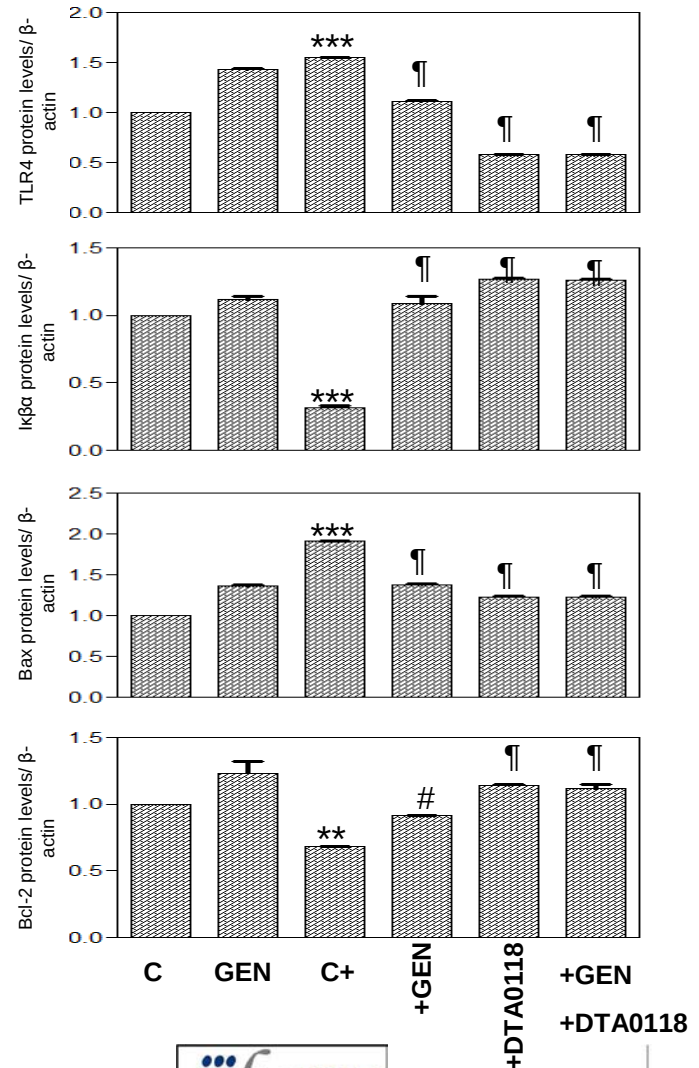


** $p < 0.01$ vs. C

*** $p < 0.001$ vs. C

$p < 0.05$ vs. LPS

¶ $p < 0.001$ vs. LPS



Programa Cooperación Farma-Biotech

Jornada 1-2012: Áreas Terapéuticas de Inflamación, Infección y Respiratorio

1. The Research Group

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

Programa Cooperación Farma-Biotech

Jornada 1-2012: Áreas Terapéuticas de Inflamación, Infección y Respiratorio

Differential features facing the market



Xigris (recombinant C-reactive protein), launched in 2001. Limitations in actual practice due to secondary effects, in its fourth year sold \$ 200 million, then decline in 2009 sales to be 161 million.



CytoFab TM (agreement with Protherics in 2006), polyclonal antibody fragment. Currently entering Phase IIB with 300 patients; scheduled launch by 2015.



TAK-242: TLR4 antagonist; discontinued in phase III.



E5564: inactive LPS analogue; currently in phase III.



SUNITINIB: Sutent[®]. Tyrosin kinase Inhibitor. Cancer treatment.

Programa Cooperación Farma-Biotech

Jornada 1-2012: Áreas Terapéuticas de Inflamación, Infección y Respiratorio

Differential features facing the market

Specific action mechanism:
TLR4-IK β inhibition

TLR4 receptors highly
expressed in lung epithelial
cells

Different administration
route (treatment)

Anti-inflammatory and Anti-
apoptotic activity

Non-cytotoxic activity

High efficacy

Programa Cooperación Farma-Biotech

Jornada 1-2012: Áreas Terapéuticas de Inflamación, Infección y Respiratorio

1. The Research Group

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

Programa Cooperación Farma-Biotech

Jornada 1-2012: Áreas Terapéuticas de Inflamación, Infección y Respiratorio

Current status of development

	Discovery	Preclinic	Phase I	Phase II	Phase III	Market	Partner
pyrimidinic aryl-ureas							
1,2,3,5-tetrasubstituted pyrrols							

Actually, our research group are carrying out toxicity assays and in vivo studies about the prevention of pyrimidinic aryl-ureas and 1,2,3,5-tetrasubstituted pyrrols compounds in a model de acute lung injury induced by sepsis.

Programa Cooperación Farma-Biotech

Jornada 1-2012: Áreas Terapéuticas de Inflamación, Infección y Respiratorio

1. The Research Group

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

IRP PROTECTION

***Pyrimidinic aryl-ureas compounds:** Spanish invention patent application (P201031978) y PCT Extension (PCT/ES2011/070822).

***1,2,3,5-tetrasubstituted pyrrols compounds:** Spanish invention patent application (P201131785).

Programa Cooperación Farma-Biotech

Jornada 1-2012: Áreas Terapéuticas de Inflamación, Infección y Respiratorio

1. The Research Group

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

Pitfalls & Risks to be considered

Pitfalls & Risks to be considered

- *Toxicity and side effects.
- *No enough therapeutic effectiveness.
- *To find the best *in vivo* administration route.
- *To find minimum *in vivo* effective dose.
- *Needs 1-2 years to reach clinical trials.

Programa Cooperación Farma-Biotech

Jornada 1-2012: Áreas Terapéuticas de Inflamación, Infección y Respiratorio

1. The Research Group

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

Programa Cooperación Farma-Biotech

Jornada 1-2012: Áreas Terapéuticas de Inflamación, Infección y Respiratorio

Partnering Opportunities

**Co-
Development**

**Venture
capital
Investment
(Start-up)**

Group number 29 CIBERES is looking for an experienced partner that help us to move the program forward in a faster and more efficient way

**Another
agreement
options as license,
financial support**

.....

Programa Cooperación Farma-Biotech

Jornada 1-2012: Áreas Terapéuticas de Inflamación, Infección y Respiratorio

Thank you !



Contact Information

Jesús Villar, MD, PhD, FCCM

CIBER de Enfermedades Respiratorias,
Instituto de Salud Carlos III
Multidisciplinary Organ Dysfunction Evaluation Research Network,
Research Unit, Hospital Universitario Dr. Negrin
Barranco de la Ballena, s/n - 4th floor, south wing
35010 Las Palmas de Gran Canaria
Canary Islands, Spain
Phone: (+34) 928-449413
Fax: (+34) 928-449813
Cellular: (+34) 606 860027
e-mail: jesus.villar54@gmail.com

Nuria Esther Cabrera Benítez, PhD

Ciber de Enfermedades Respiratorias
Unidad de Investigación
Hospital Universitario de G. C. Dr. Negrín
Bco. de la Ballena s/n
CP: 35.010 Las Palmas de Gran Canaria
TLF: (+34) 928 44 92 78
FAX: (+34) 928 44 91 91
E-mail: nuriaecb@gmail.com