C4BP(β-): a physiologic anti-inflammatory and immune-modulatory agent.

Barcelona, 14 de marzo de 2012

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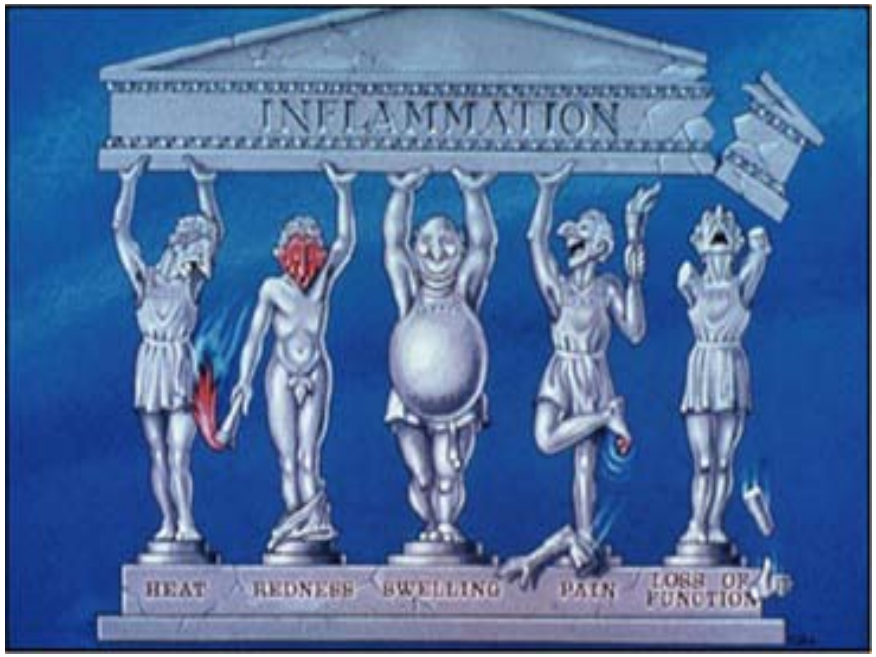
1. The Research Group (I):

"Immune-inflammatory processes and gene therapeutics"

INFLAMMATION = LOVE

Everybody talks about it, nobody understands it.

Levy-Sensei 2000



Experienced team with advanced academic degrees, performing translational research:
Molecular basis of the immune-inflammatory processes.

- **Rut Olivar**
- **Itziar Martínez-González**
- **Ana Luque**
- **Abduljalil Farwati**
- **David Ahumada**
- **Josep M. Aran (coordinator; jaran@idibell.cat)**

1. The Research Group (II):

"Immune-inflammatory processes and gene therapeutics"

Bellvitge Biomedical Research Institute (IDIBELL) is a research centre focused on cellular medicine, where the high level basic research focuses and works on relevant clinical matters and the economic development.

biopol'H

ICO Institut Català d'Oncologia

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IDIBELL
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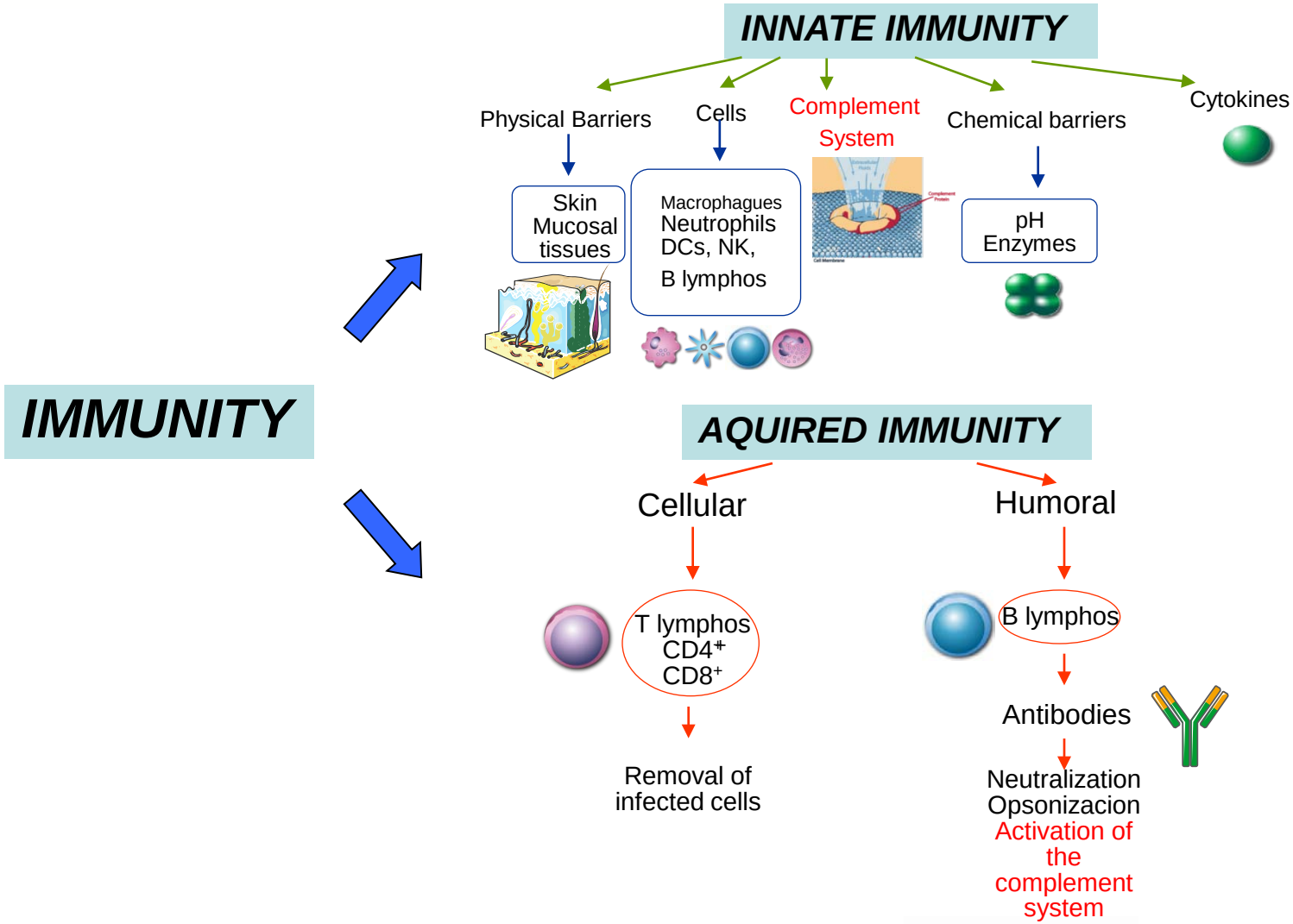
Bellvitge Hospital

IDI INSTITUT DE DIAGNÒSTIC PER LA IMATGE

2. The Product: C4BP(β-)

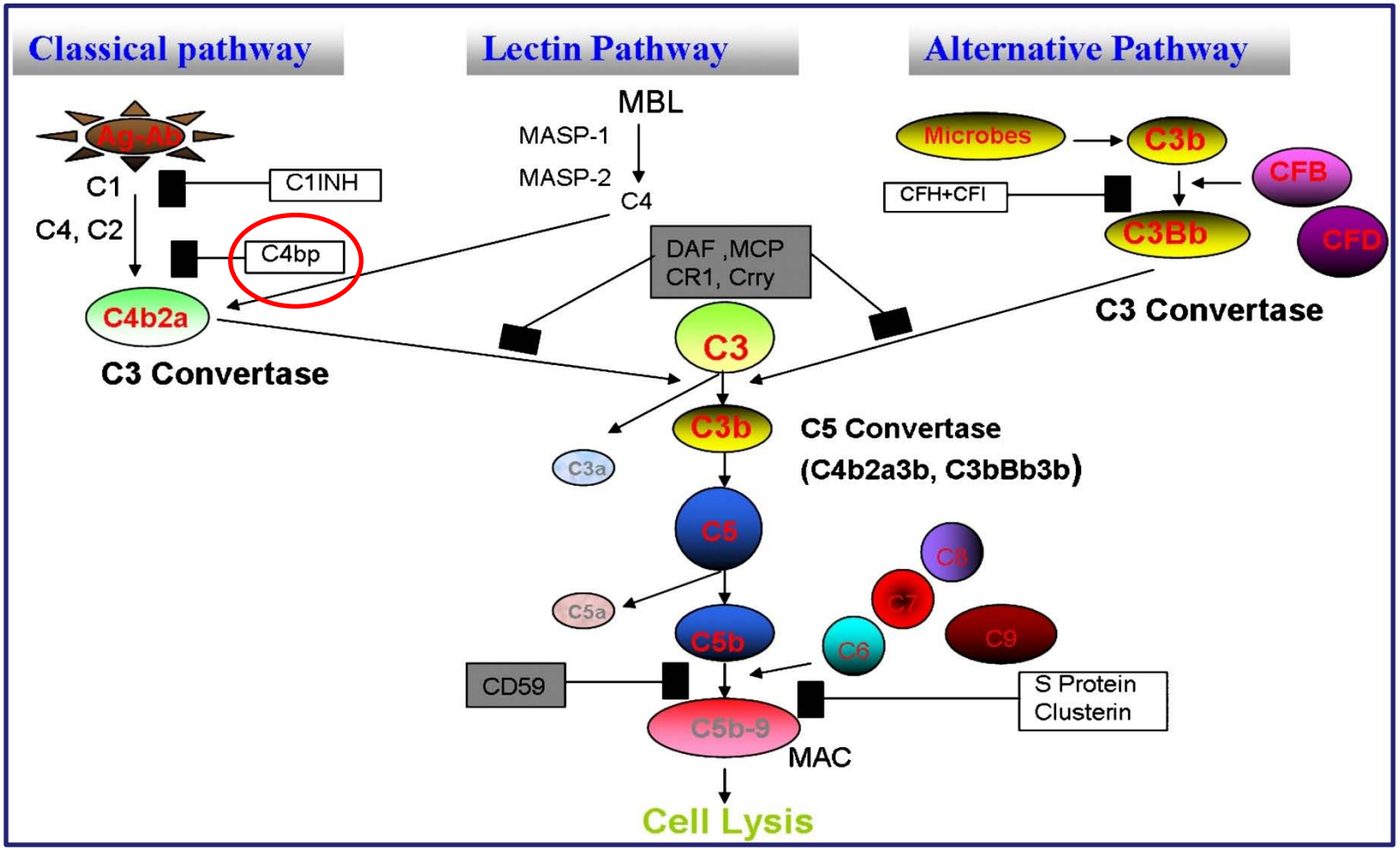
Innovative mechanisms of action



2. The Product: C4BP(β-)

Innovative mechanisms of action

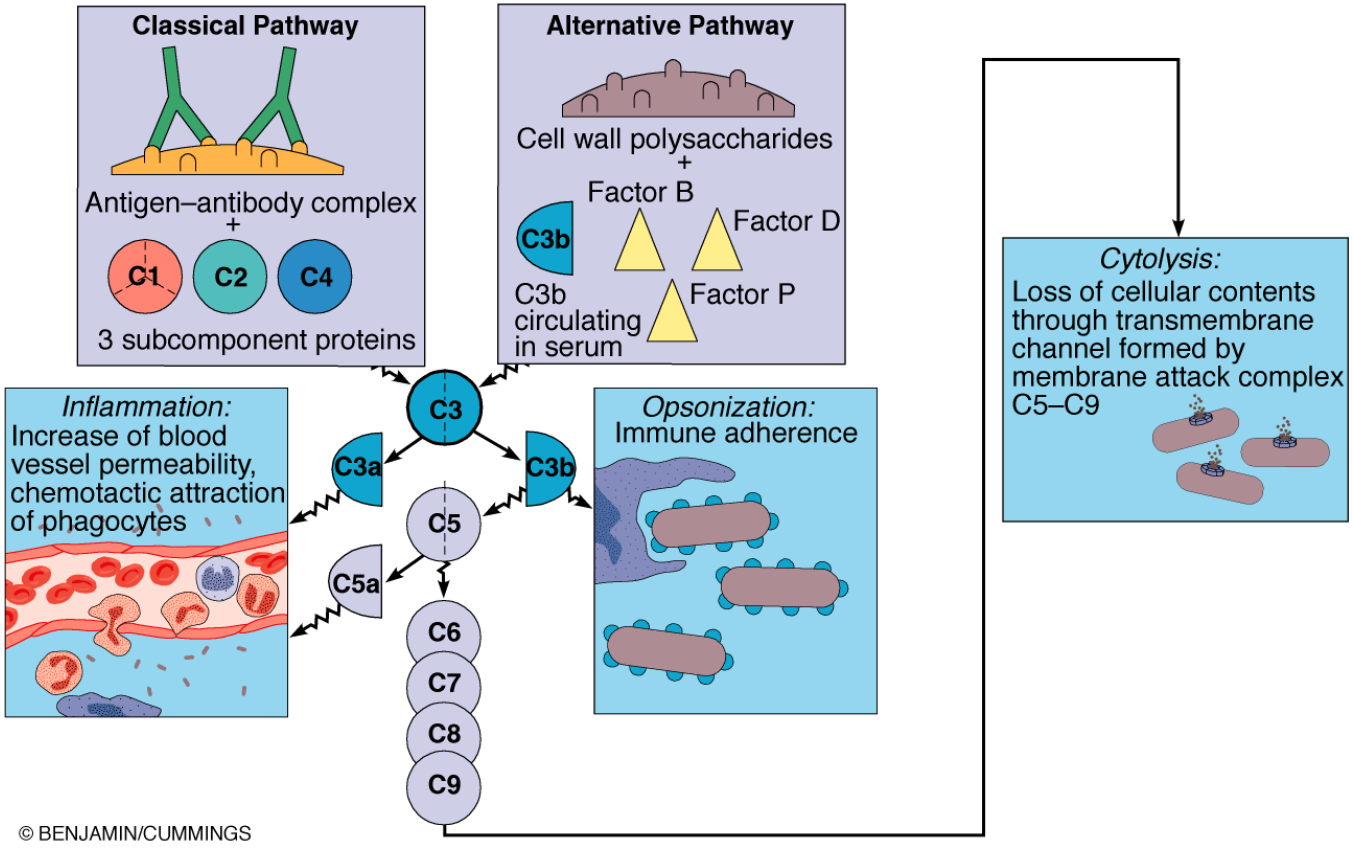
Complement system and complement regulatory proteins



2. The Product: C4BP(β-)

Innovative mechanisms of action

Classical and Alternative Complement Pathways cause Inflammation, Opsonization, and Cytolysis

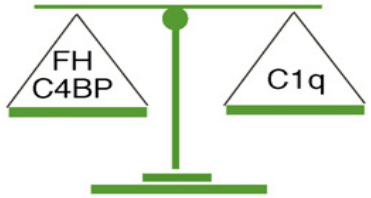


2. The Product: C4BP(β-)

Innovative mechanisms of action

SOLUBLE COMPLEMENT REGULATORS

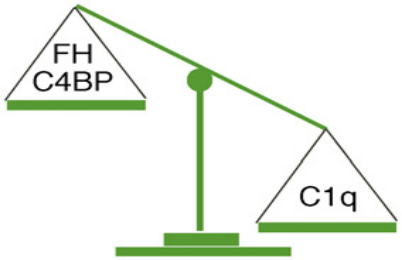
Correct balance of the complement system



Opsonizacion

Prevention of inflammation and injury

Inbalance beneficial to combat pathogens

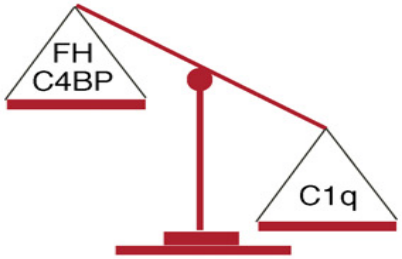


Activation of the complement system

lysis, inflammation and activation of the Immune system

Immunopathology

Excessive autoreactivity



Activation of the complement system

lysis, inflammation and risk of autoimmunity

2. The Product: C4BP(β-)

Innovative mechanisms of action

C4BP: C4b-*binding protein*

Plasma glycoprotein (570 kDa) synthesized mainly in the liver.

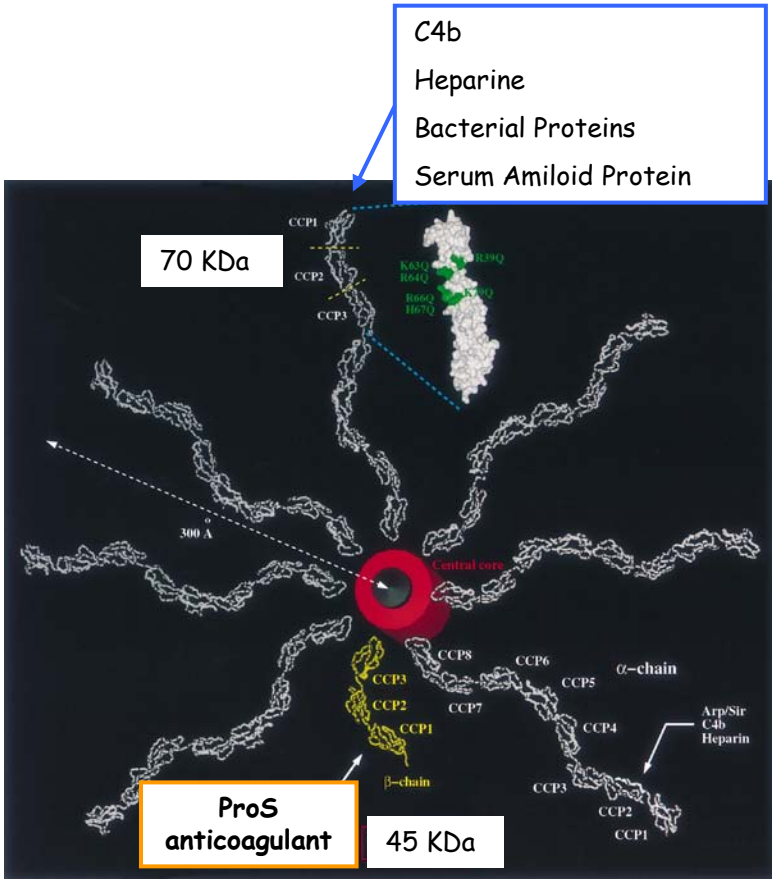
Present in the circulation (200 mg/l) in three isoforms α7β1 (major), α7β0 and α6β1.

Heterooligomer composed by:

- Alpha chain: 8 CCP domains
- Beta chain: 3 CCP domains

α7β0 (C4BP (b-)) is overexpressed by acute phase conditions and pro-inflammatory cytokines.

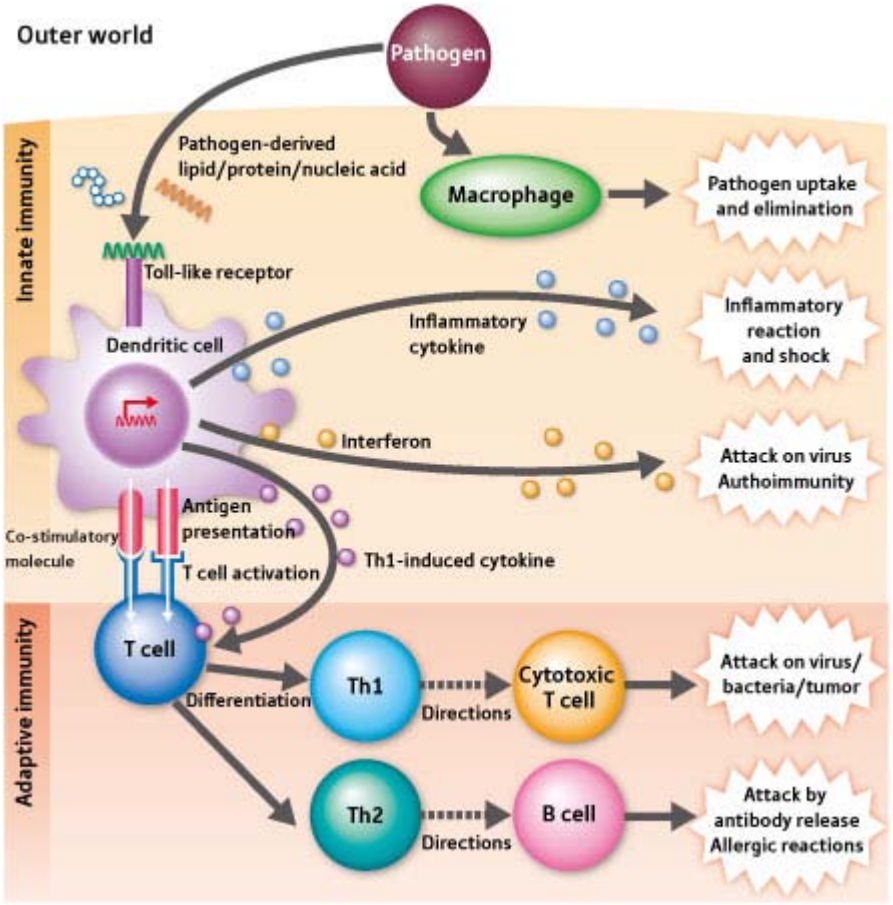
Efficient inhibition of the classical and alternative pathways of complement activation. Prevents the assembly of the C3 convertase (C4b2a) and accelerates the degradation of the complex.



2. The Product: hASC-sST2

Innovative mechanisms of action

Dendritic cells: bridging innate and adaptive immunity

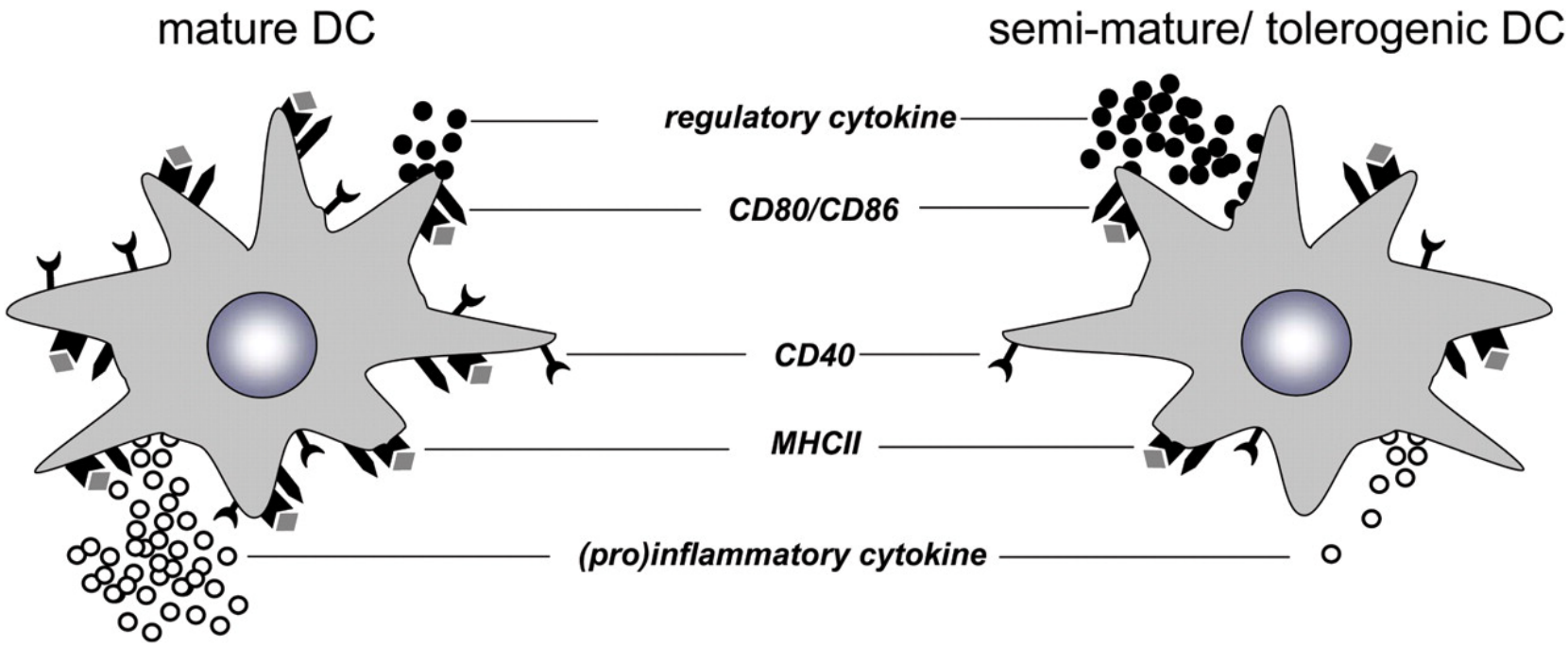


2. The Product: C4BP(β-)

Innovative mechanisms of action

TOLEROGENIC DENDRITIC CELLS

The modulation of DC function generating tolerogenic DCs could be used as a powerful therapeutic approach in certain pathologic conditions, such as autoimmune diseases and transplantation.



2. The Product: C4BP(β-)

Target indications

Diseases characterized by a un undesired activation of the immune system

Uses:

1. Conventional drug
2. Tolerogenic DC therapy

Indications:

-Immune-inflammatory diseases (acute and chronic)

-Autoimmune diseases (systemic lupus erythematosus (SLE), diabetes mellitus (type I), asthma, ulcerative cholitis, Grave's disease, arthritis, including rheumatoid arthritis and osteoarthritis, pernicious anemia, and multiple sclerosis, among numerous others)

- Transplantation

Tolerogenic dendritic cells: applications for solid organ transplantation.

KEY POINTS

- Dendritic cells constitute a promising therapeutic tool in clinical organ transplantation to minimize immunosuppressive treatments.
- In rodents, donor or recipient-derived tolerogenic dendritic cells (TolDC) promote lasting, donor-specific T-cell unresponsiveness and transplant survival.
- Administration of unpulsed, autologous dendritic cells is a well tolerated, clinically relevant approach for solid organ transplantation.
- Clinical grade human TolDC can be generated from blood monocytes.
- TolDC therapy is already underway in human autoimmune disease.

2. The Product: C4BP(β-)

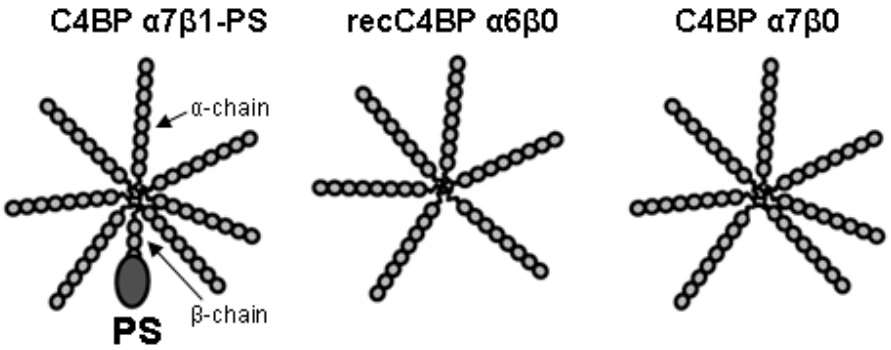
Current status of development

The minor complement inhibitor C4BP α7β0 isoform induces a semimature, tolerogenic state in dendritic cells

Olivar *et al*. (2012) Submitted

2. The Product: C4BP(β-)

Current status of development

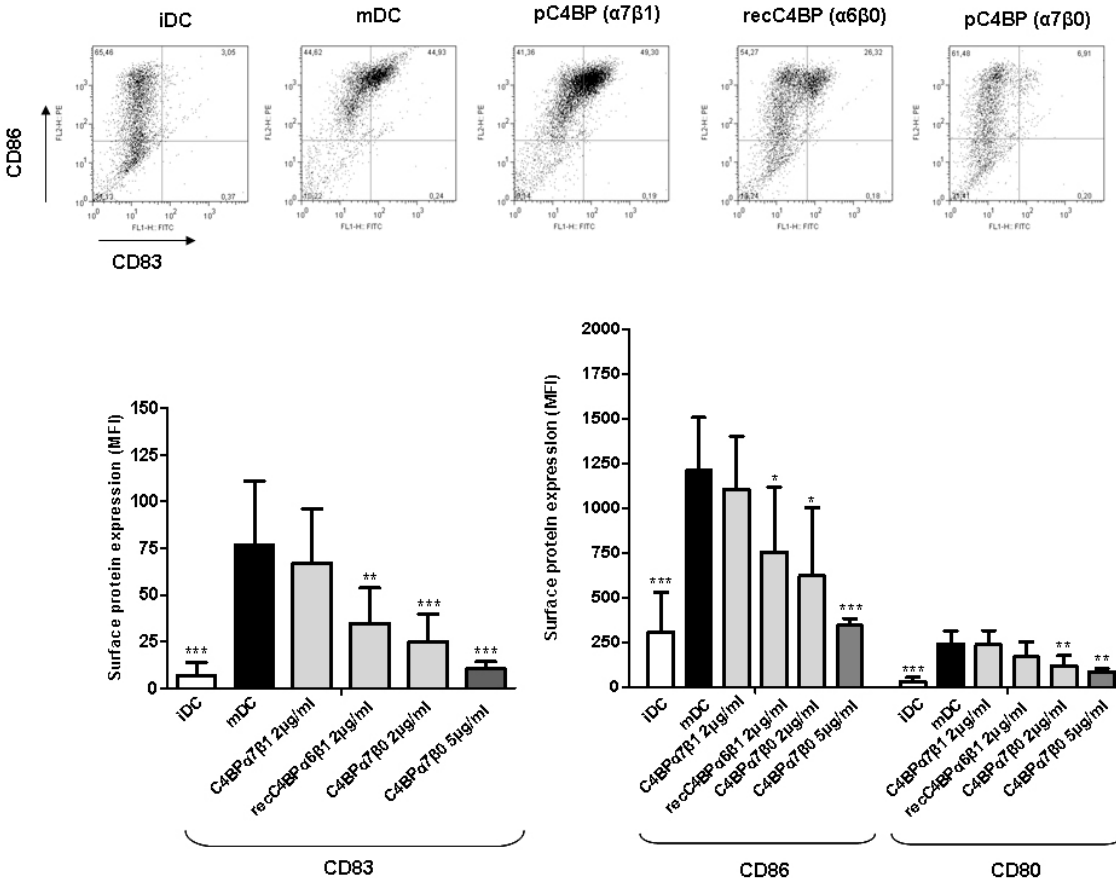


Schematic structure of the C4BP isoforms employed

2. The Product: C4BP(β-)

Current status of development

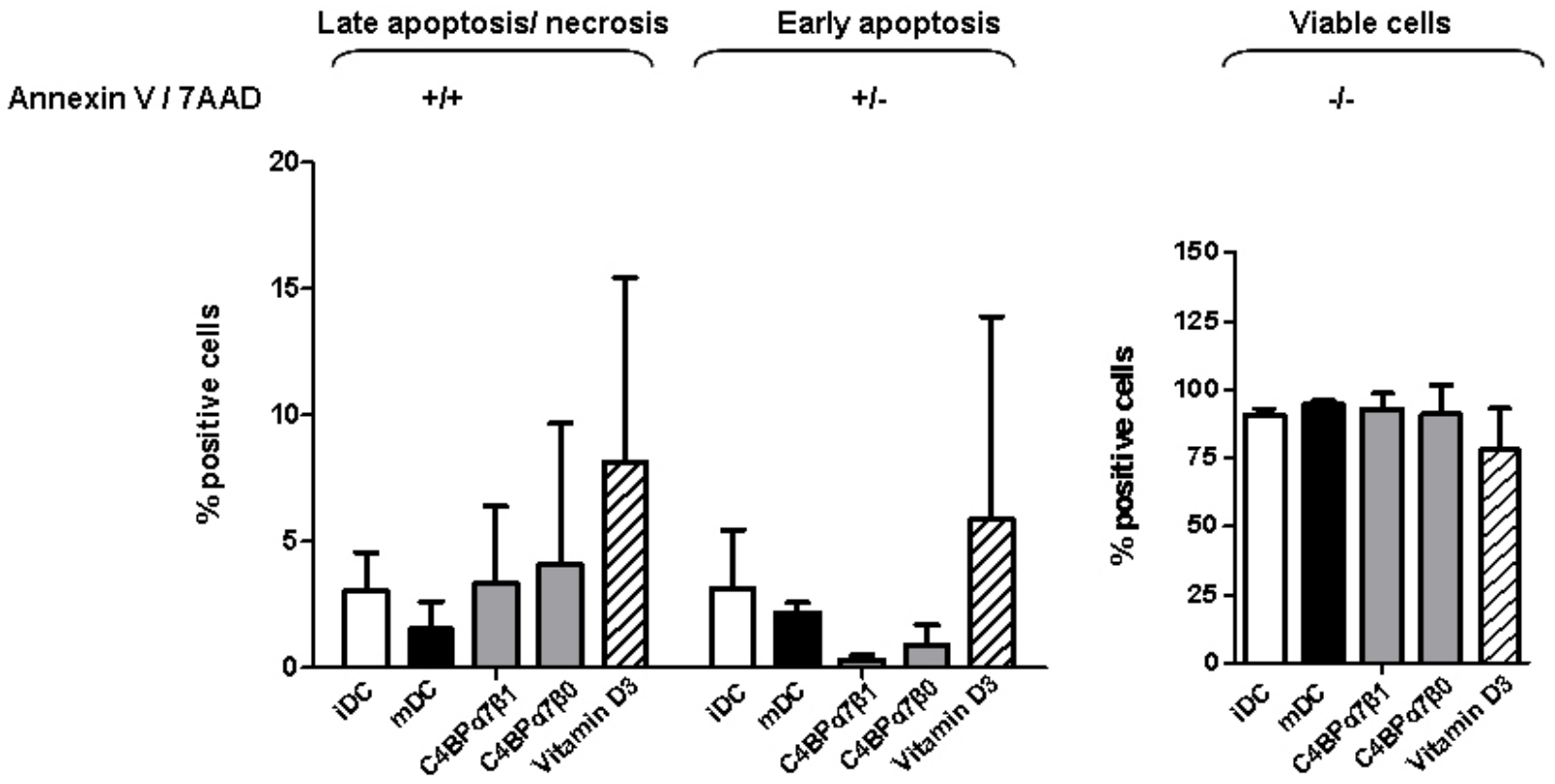
C4BP isoforms lacking β-chain down-regulate the activation phenotype of human DCs



2. The Product: C4BP(β-)

Current status of development

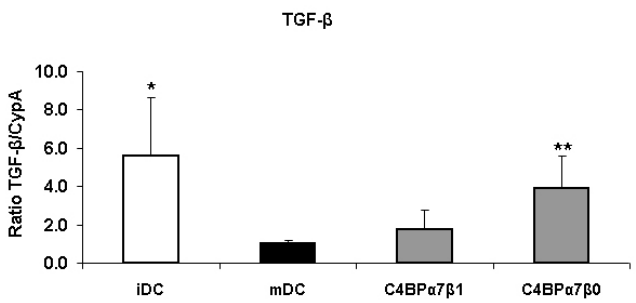
C4BP treatment does not affect the viability of human DCs

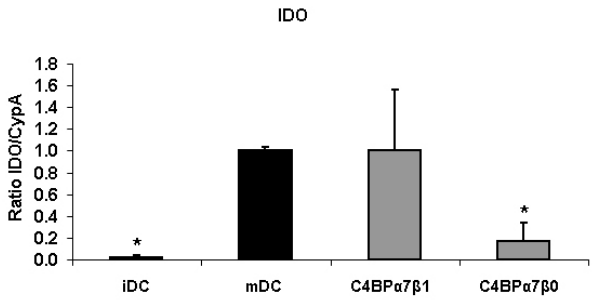


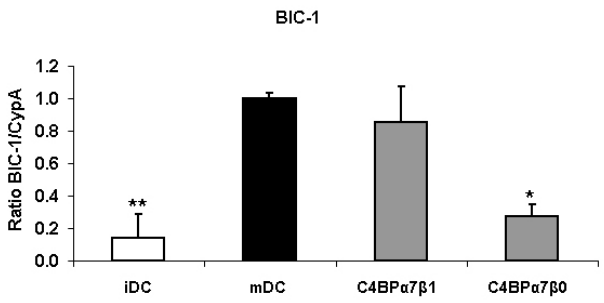
2. The Product: C4BP(β-)

Current status of development

Human DCs exposed to the C4BP(β-) isoform up-regulate TGF-β1 and down-regulate IDO and BIC-1 upon LPS induction



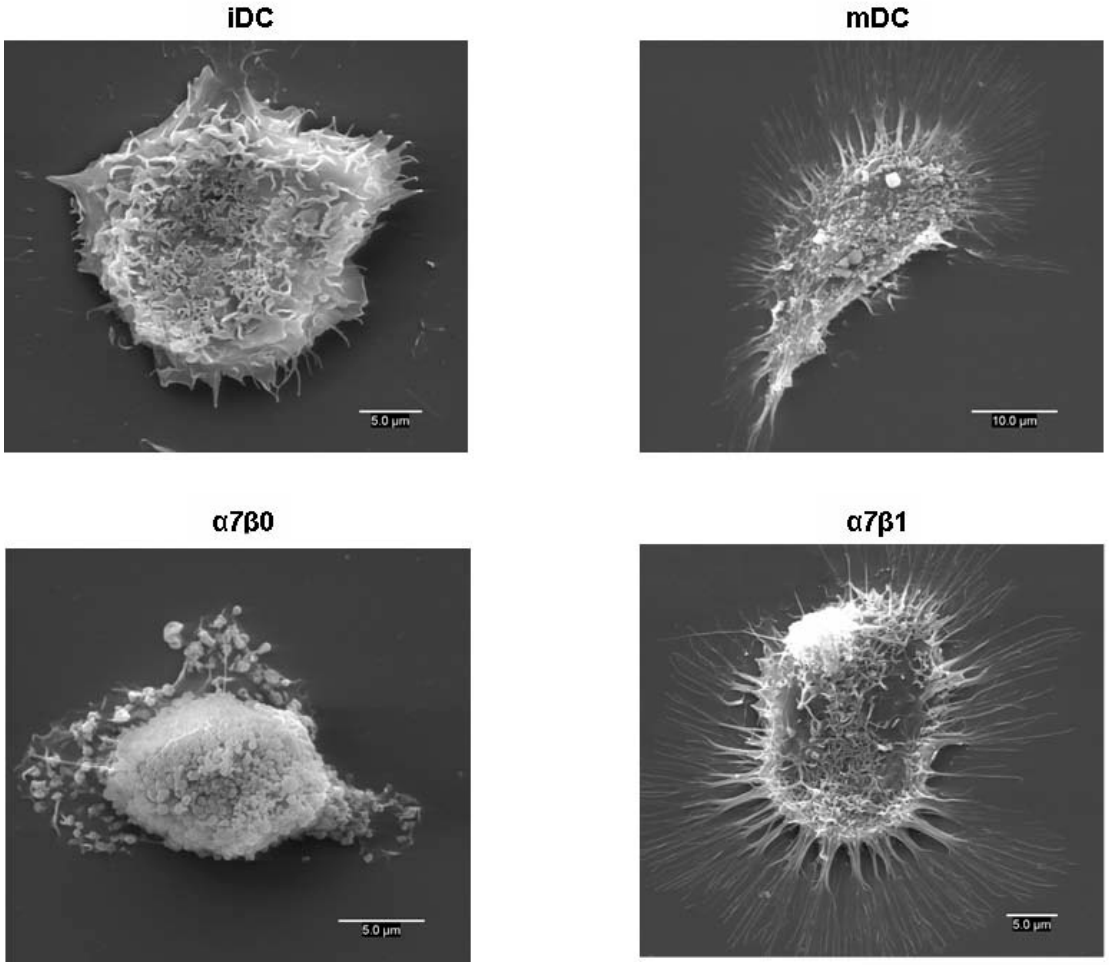




2. The Product: C4BP(β-)

Current status of development

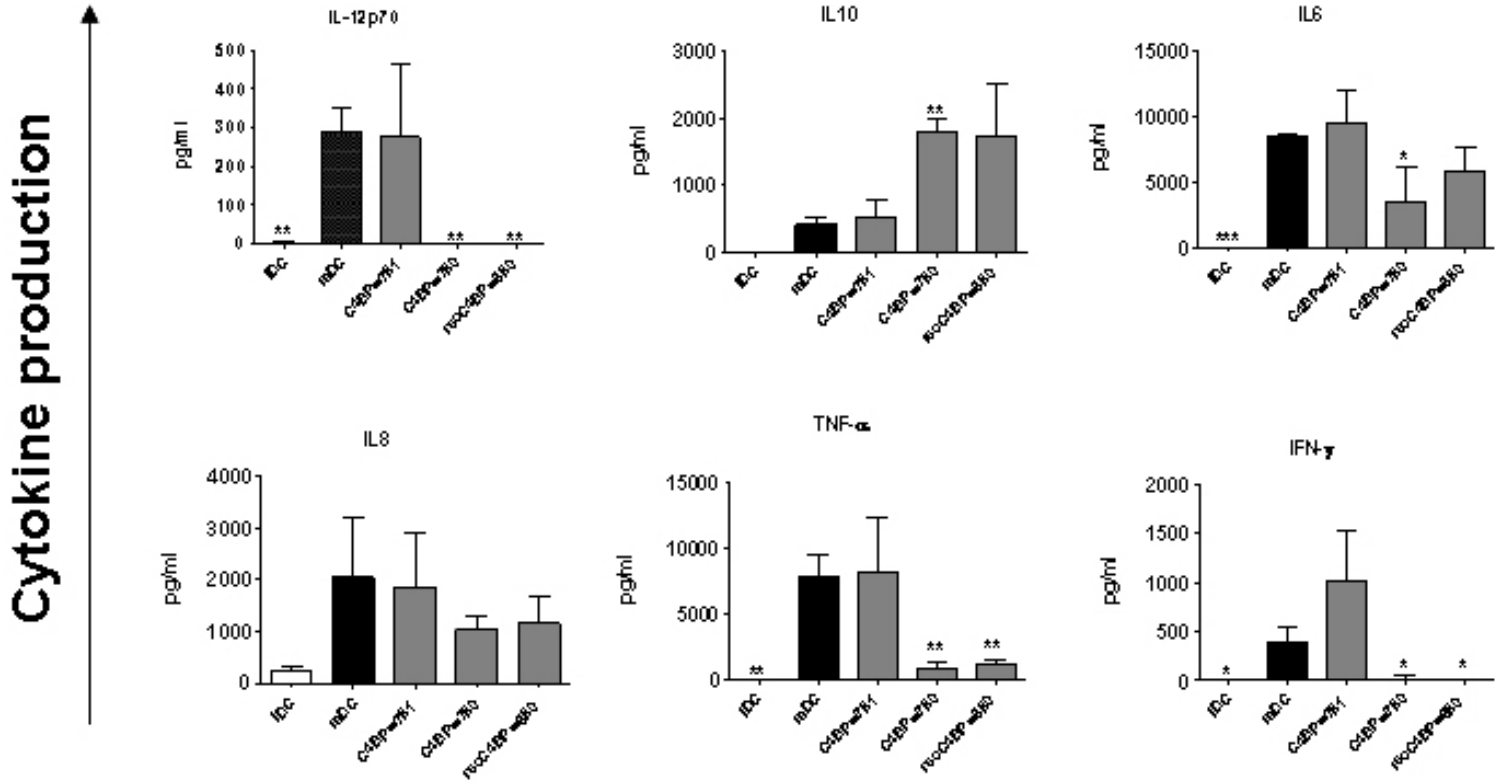
C4BP isoforms lacking b-chain modify the morphology of human DCs



2. The Product: C4BP(β-)

Current status of development

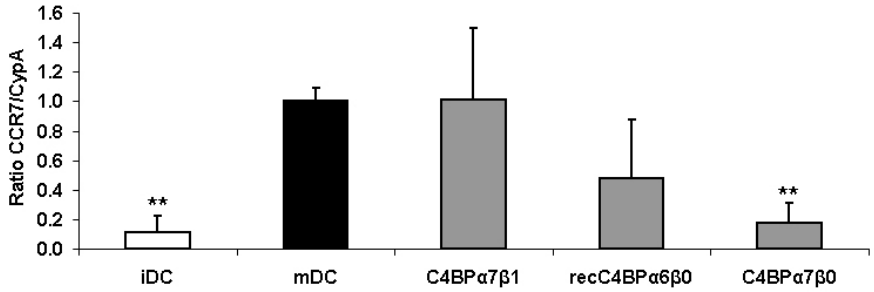
C4BP (β-) isoforms inhibit the release of inflammatory cytokines by LPS-matured human DCs

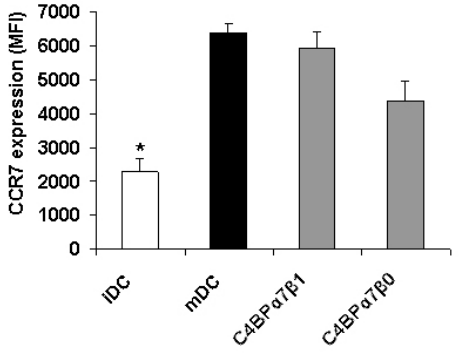


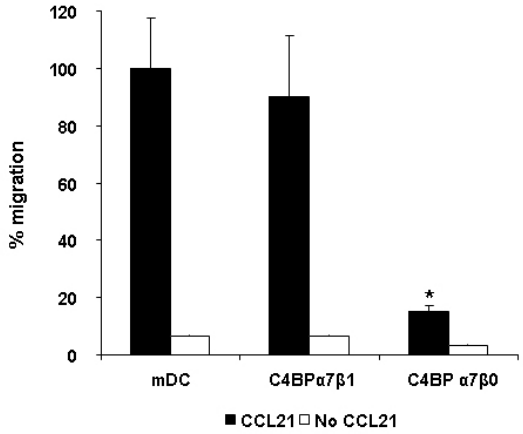
2. The Product: C4BP(β-)

Current status of development

C4BP(β-) isoforms down-regulate CCR7 expression and alter the chemotaxis of human DCs



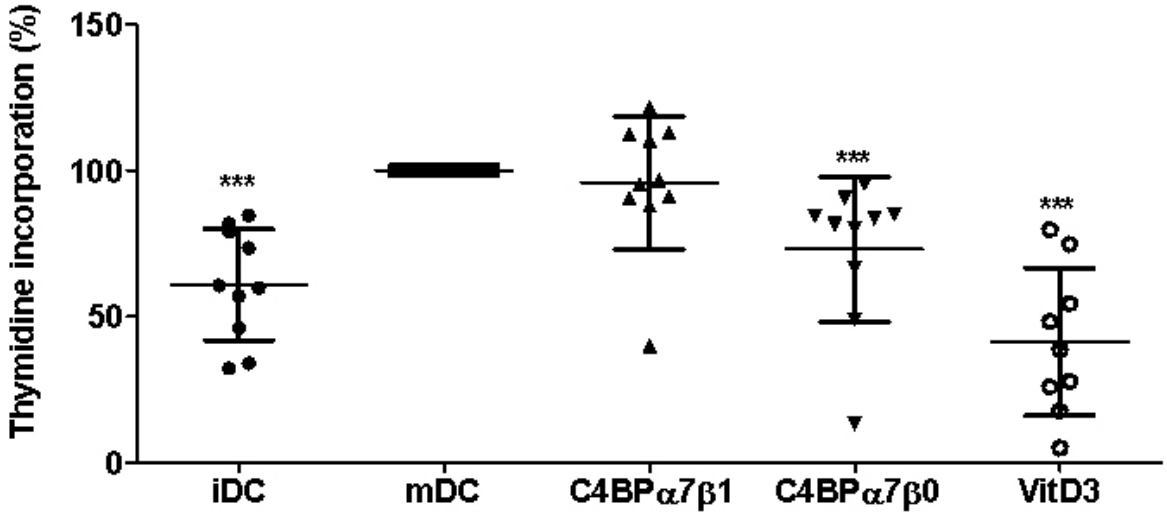




2. The Product: C4BP(β-)

Current status of development

Human DCs exposed to C4BP(b-) isoform inhibits allogeneic T cell proliferation

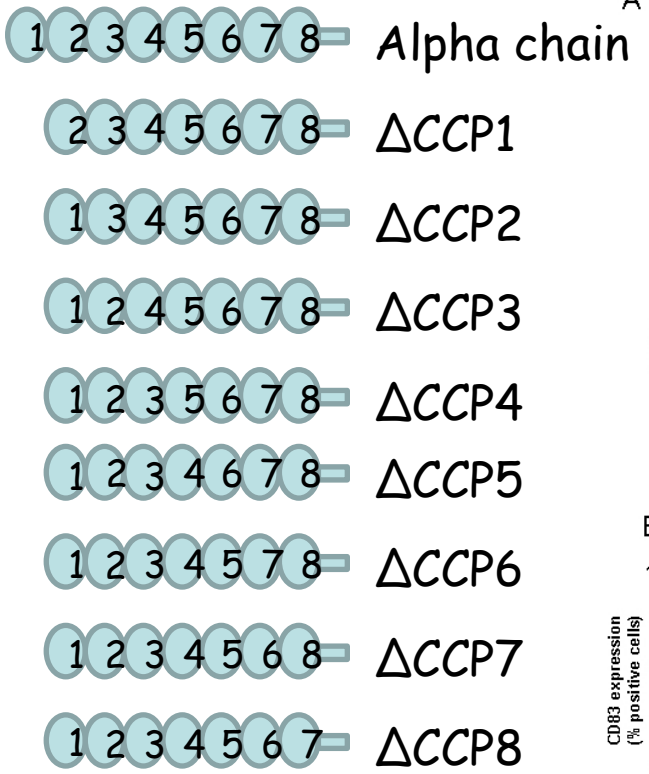


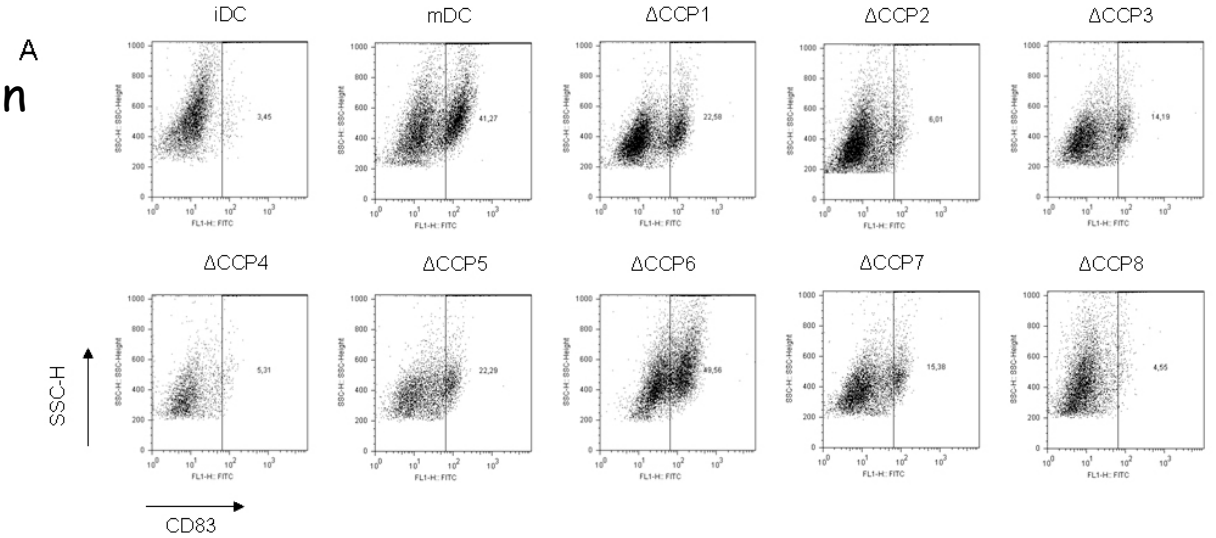
2. The Product: C4BP(β-)

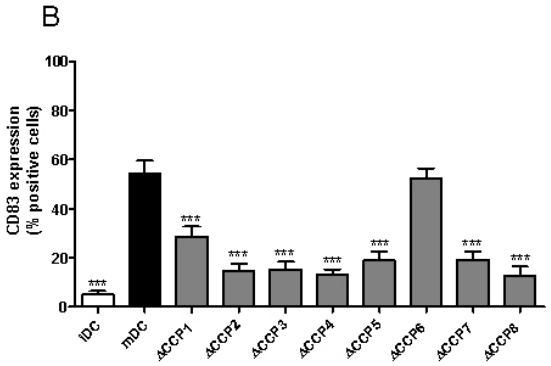
Current status of development

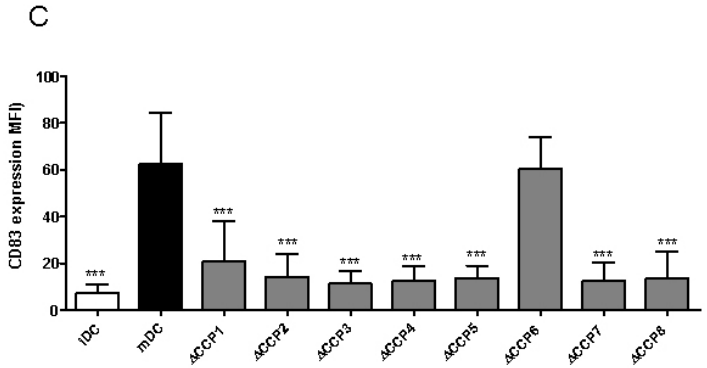
The CCP6 domain of C4BPA is necessary for the tolerogenic activity of C4BP over human DCs

Figure 10









GOBIERNO DE ESPAÑA · MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

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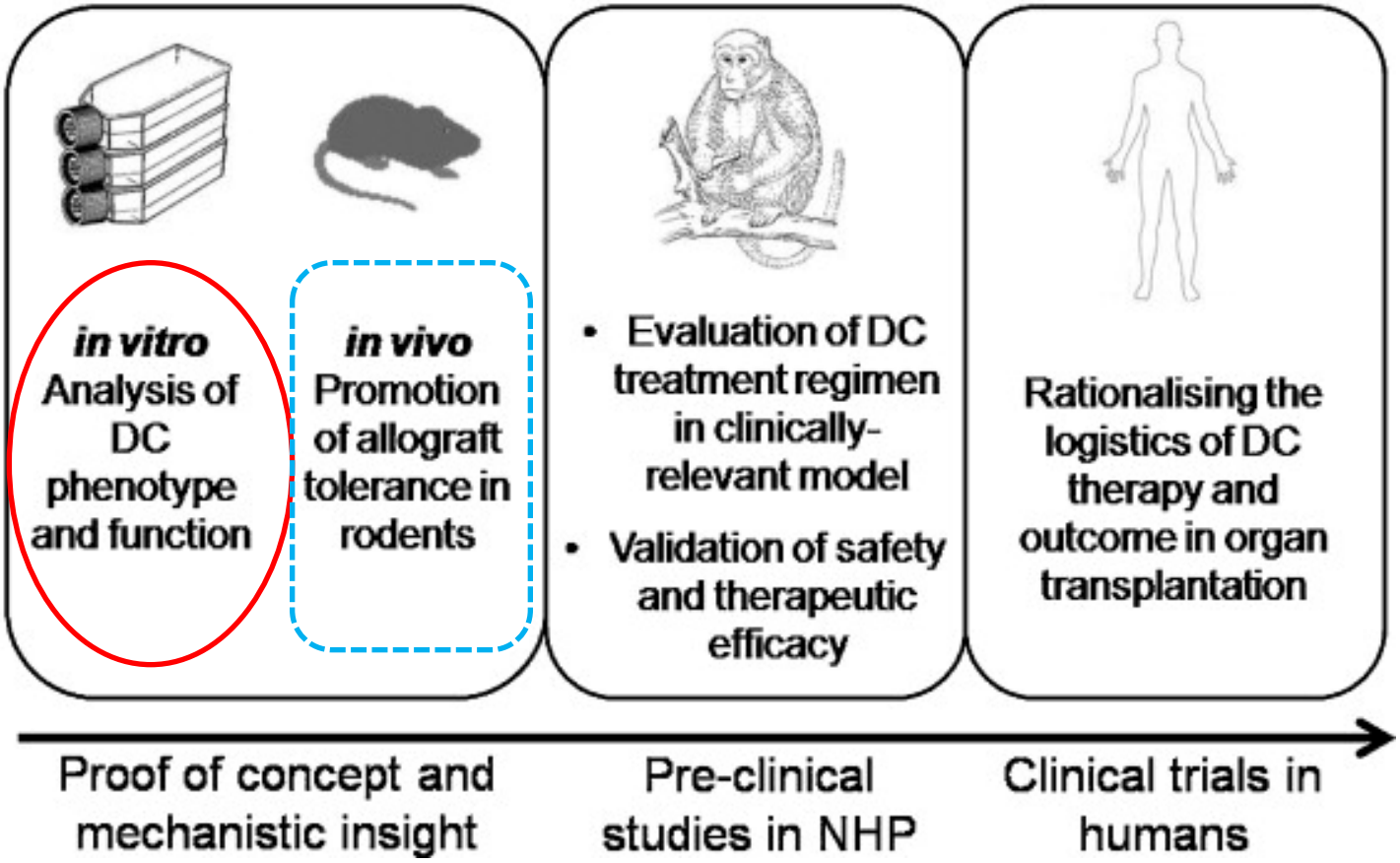
2. The Product: C4BP(β-)

Current status of development



2. The Product: C4BP(β-)

Differential features facing the market

Ongoing clinical trials using DCs for multiple disease indications.

· ***Differential and innovative aspects of C4BP(β-)***:

-Novel anti-inflammatory and immune-modulatory physiological C4BP(β-)-based therapy.

-Efficacy of C4BP(β-) without the side effects of the present immunosuppressive and anti-inflammatory drugs.

-Possibility to perform pharmacological therapy (direct C4BP(β-) administration), or cell therapy using ex vivo C4BP(β-)-conditioned DCs..

-Synergistic potential of use together with other conventional drugs (no cross-reactivity).

2. The Product: C4BP(β-)

IPR protection

PATENT: "***Compositions and methods for immunomodulation*** "

INVENTORS: (by order of signature): **Aran, J.M.**, Olivar, R.
REQUEST No.: **EP11382240**
PRIORITY COUNTRY: European Union
PRIORITY DATE: **15/07/11**
ENTITY: IDIBELL.

The invention relates to the field of immunology and, more in particular, to compositions based on the complement C4BP polypeptide which are capable of inhibiting maturation of dendritic cells and to the uses thereof for the treatment of diseases characterized by a un undesired activation of the immune system.

2. The Product: C4BP(β-)

Pitfalls and risks to be considered

-Thorough understanding of C4BP(β-) function and mechanism of action remain to be fully elucidated.

-Dosage regime, C4BP(β-) administration and safety for use in pre-clinical models and patients all need to be established.

-Regulatory hurdles ?

3. Partnering opportunities

Therapeutic opportunities (C4BP(β-))

-Main therapeutic areas: inflammatory diseases, autoimmune diseases, transplantation.

-Suboptimal alternative therapeutic agents/drugs.

-Social unmet need.

-Broad applicability.

-Innovative approach.

From the opportunity to the market (C4BP(β-): optimal cost/benefit)

- Market application: Biotechnology / Pharmaceuticals.

- Cooperation type:
  - -License agreement.
  - - Joint further development (adaptation to specific needs):
    - *Pre-clinical and clinical co-development*
    - *Know how in immunology*
    - *Regulatory compliance*
    - *Future scaling up*
  - - Testing new applications.
  - - Joint venture agreement.
  - - Financial resources.