C4BP(β-): a therapeutic anti-inflammatory and immune-modulatory agent in autoimmunity

Madrid, 27 de noviembre de 2013

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1. The Institution:

Institut d'Investigació Biomèdica de Bellvitge (IDIBELL)

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

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Institut Català d'Oncologia

UNIVERSITAT DE BARCELONA

IDIBELL
Institut d'Investigació Biomèdica de Bellvitge

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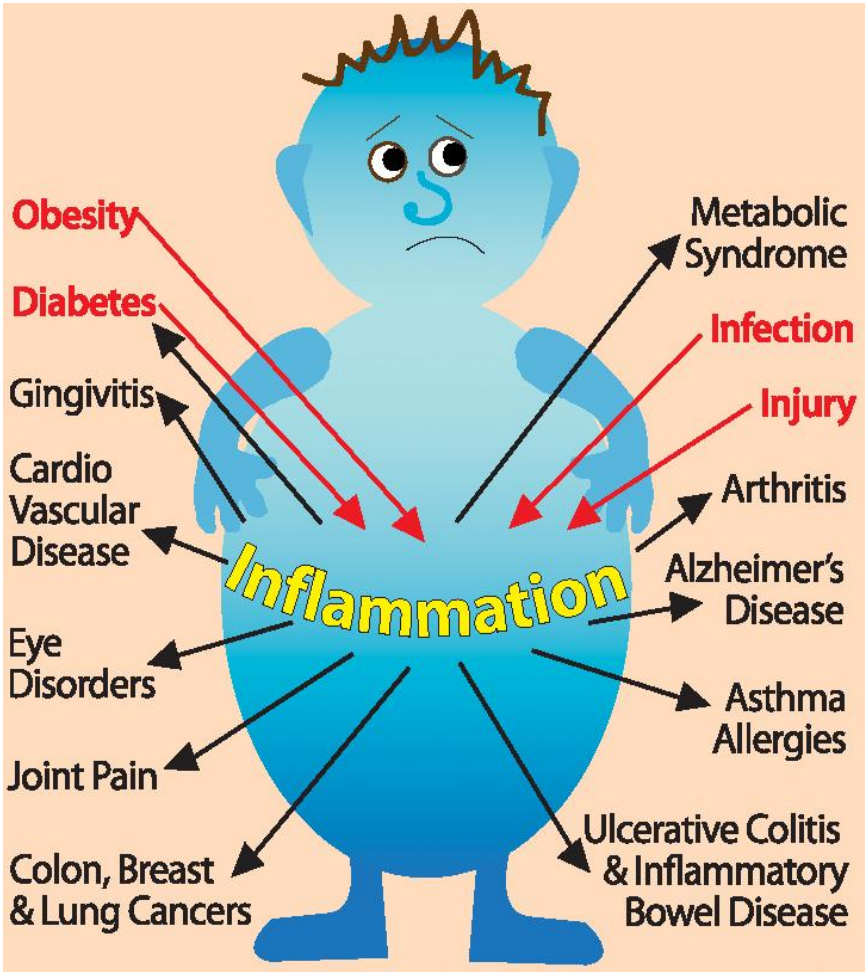
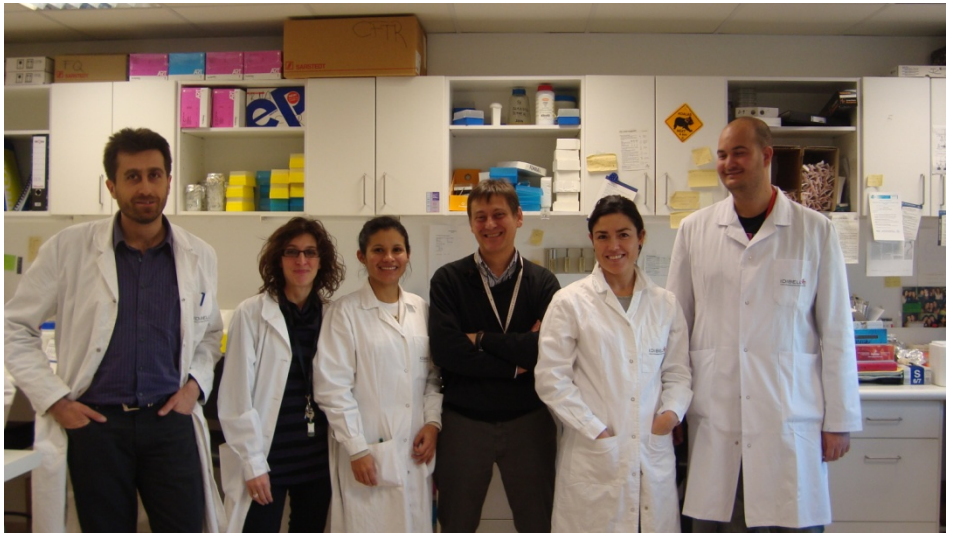
Bellvitge Hospital

IDI
INSTITUT DE DIAGNÒSTIC PER LA IMATGE

1. The Research Group:

"Immune-inflammatory processes and gene therapeutics"





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

- **Sonia Cárdenas-Brito**
- **Itziar Martínez-González**
- **Ana Luque**
- **Abduljalil Farwati**
- **Andreu García**
- **Josep M. Aran (coordinator; jaran@idibell.cat)**

1. The Research Group (II):

"Immune-inflammatory processes and gene therapeutics"

Projects and areas of interest

1) *RNAi and immunomodulation*

EUROPEN PATENT: "Oligoribonucleotide sequence homologous to a CDNA region which codes for the human CD40 receptor and duplex oligoribonucleotides, vectors, pharmaceutical compositions and uses associated thereto"
EUROPEAN PATENT No.: EP 1 614 751
INVENTORS: **Aran, J.M.**, Grinyó, J.M., Torras, J., Pluvinet, R., Herrero, I., Cruzado, J.M.

- Pluvinet, R., et al. (2004) RNAi-mediated silencing of CD40 prevents leukocyte adhesion on CD154-activated endothelial cells. ***Blood*****.** 104: 3642-3646.

- Ripoll, E., et al. (2013) Silencing CD40 slows the progression of experimental autoinmune nephritis. ***PLOS ONE*** 8: e65068.

2) *Mesenchymal stem cells and immunomodulation*

EUROPEN PATENT: "Engineered stem cells and their therapeutic use"
PCT/ES2012/070823 (23/11/12)
INVENTORS: **Aran, J.M.**, Cruz, M.J., Martínez-González, I, Roca, O., Masclans, J.R., Muñoz, J.

- Martínez-González, I., et al. (2013) Human mesenchymal stem cells overexpressing the IL-33 antagonist soluble IL-1 receptor-like-1 attenuate endotoxin-induced acute lung injury. ***Am. J. Respir. Cell Mol. Biol.*** 49: 552-562.

3) *Complement inhibition and immunomodulation*

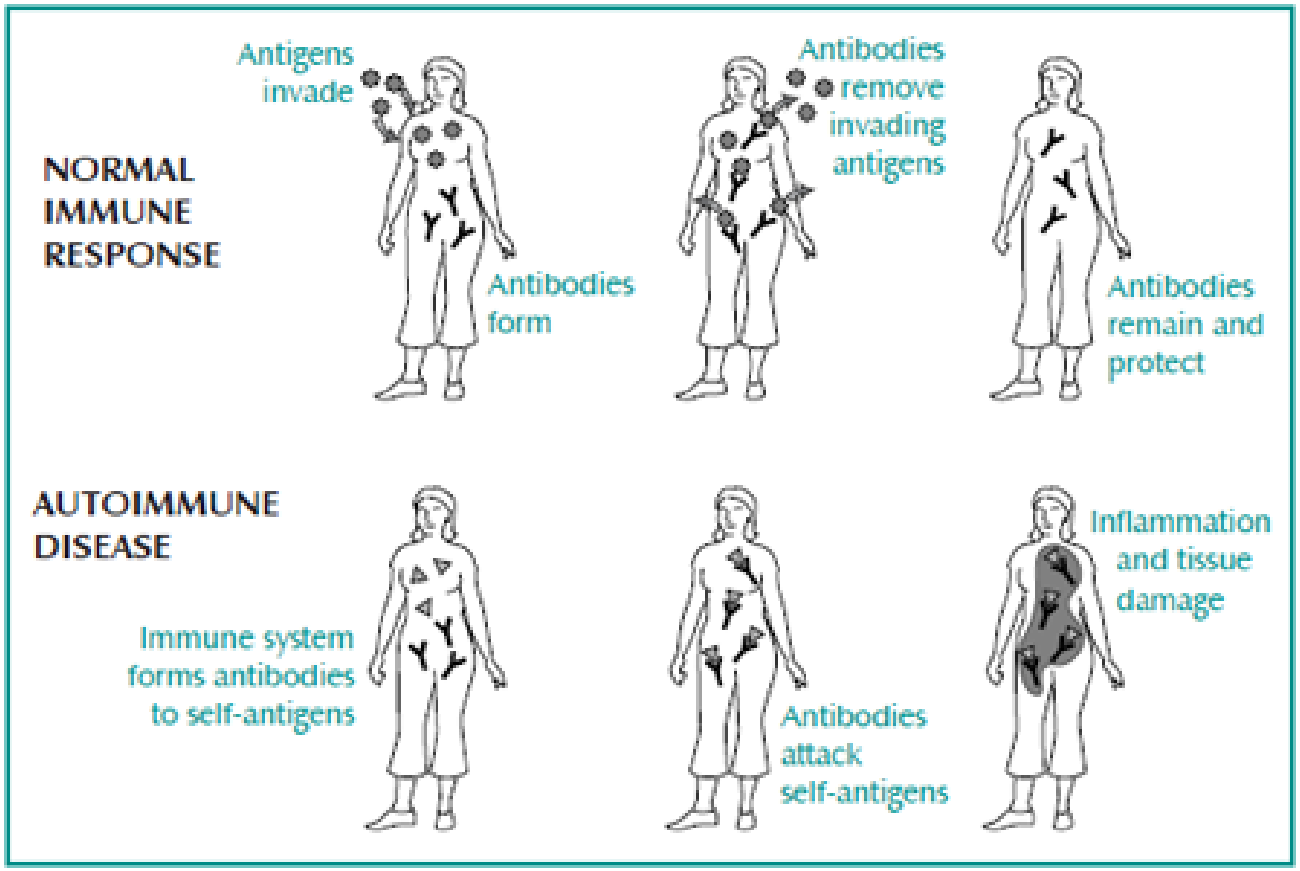
EUROPEN PATENT: "Compositions and Methods for immunomodulation"
PCT/ES2012/063932 (16/07/2012)
INVENTORS: **Aran, J.M.**, Olivar, R.

- Olivar, R., et al. (2013) The $\alpha 7\beta 0$ isoform of the complement regulator C4b-binding protein induces a semimature, anti-inflammatory state in dendritic cells. ***J. Immunol.*** 190: 2857-2872.

2. The Product: C4BP(β-)

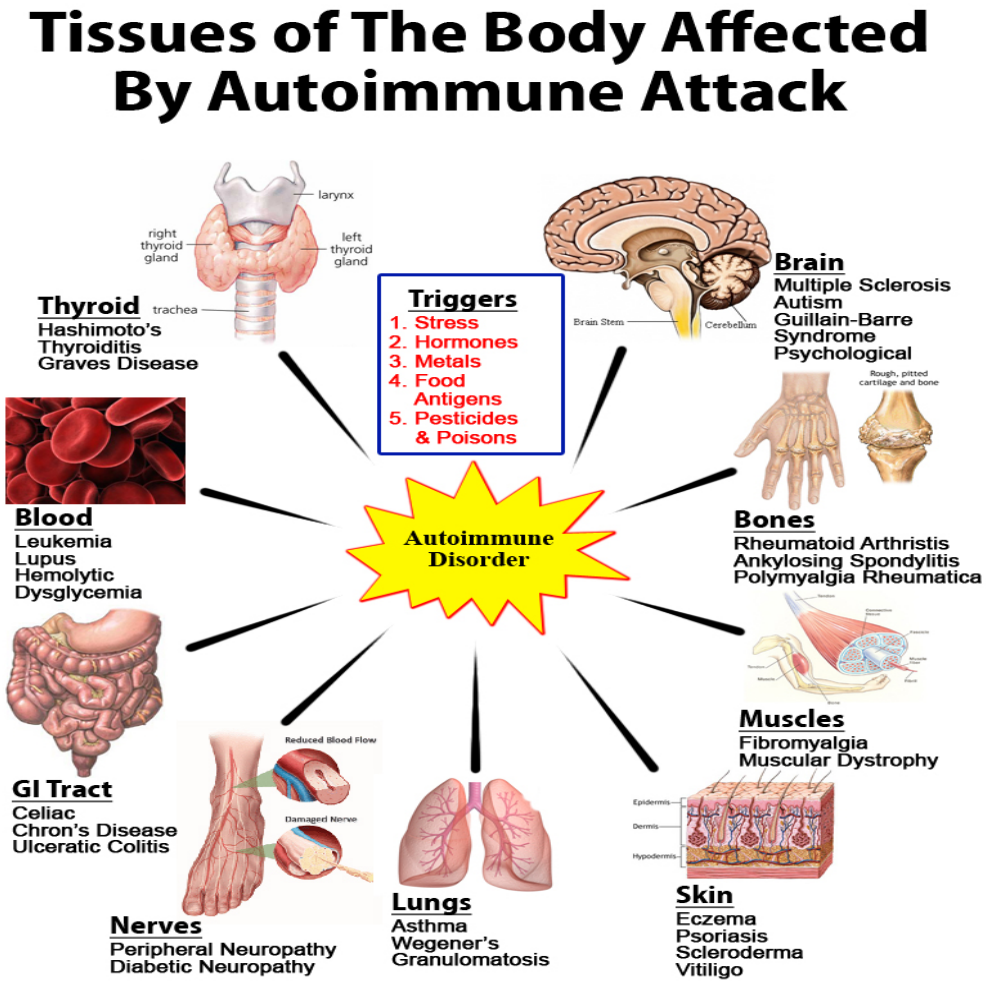
Innovative mechanisms of action

Autoimmune diseases



2. The Product: C4BP(β-)

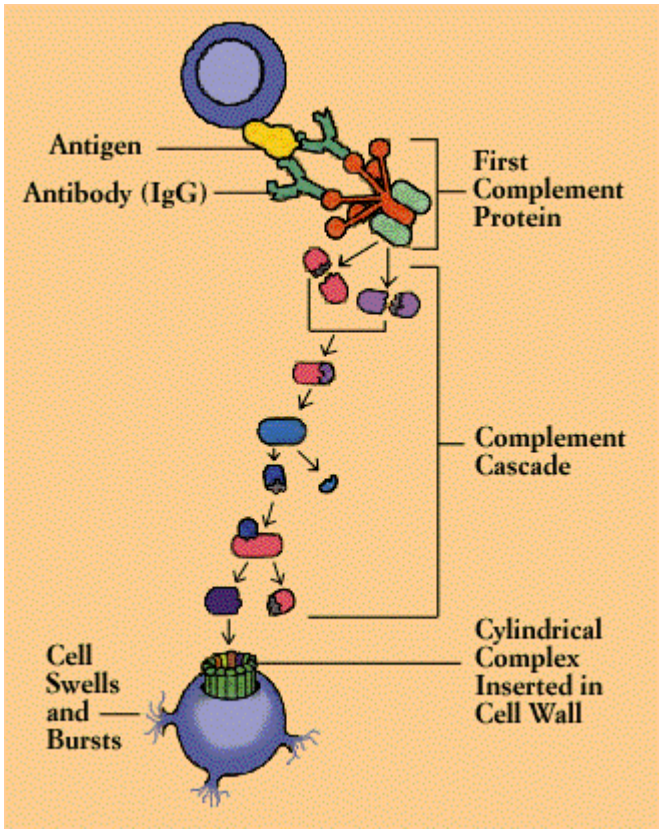
Innovative mechanisms of action

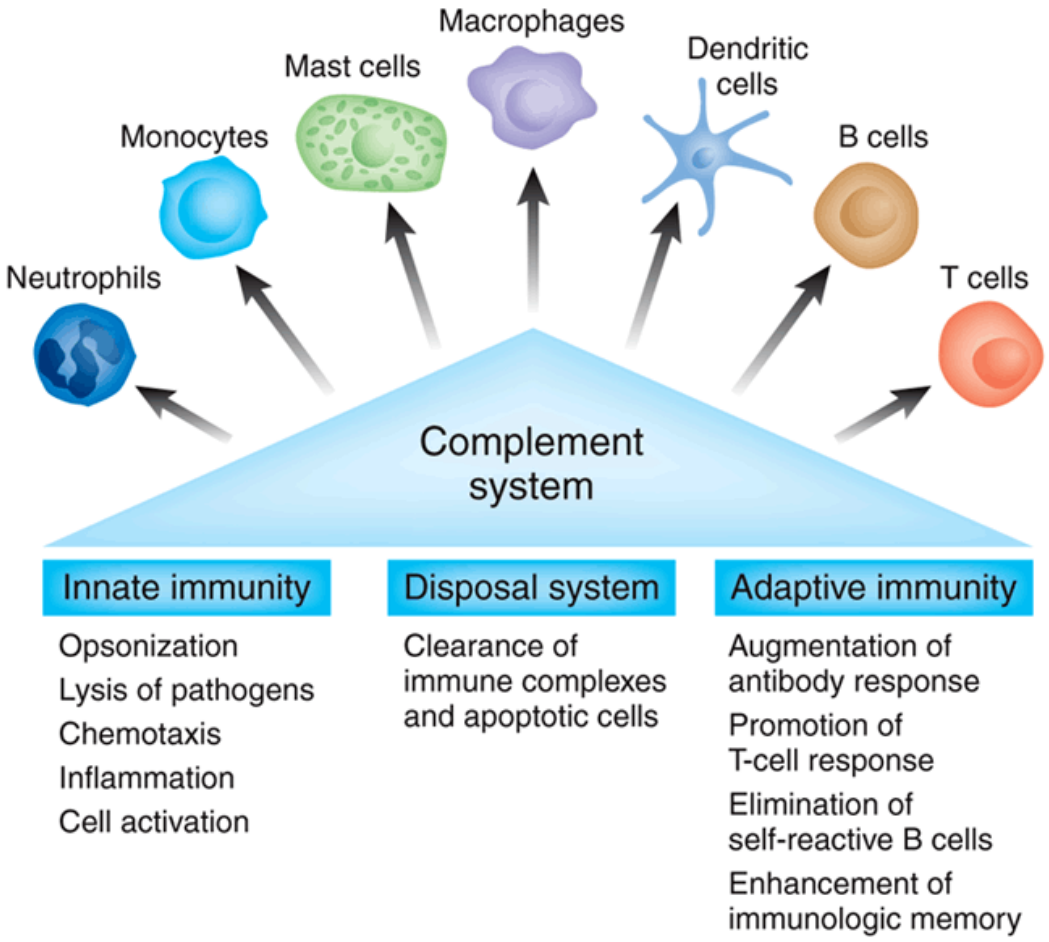


2. The Product: C4BP(β-)

Innovative mechanisms of action

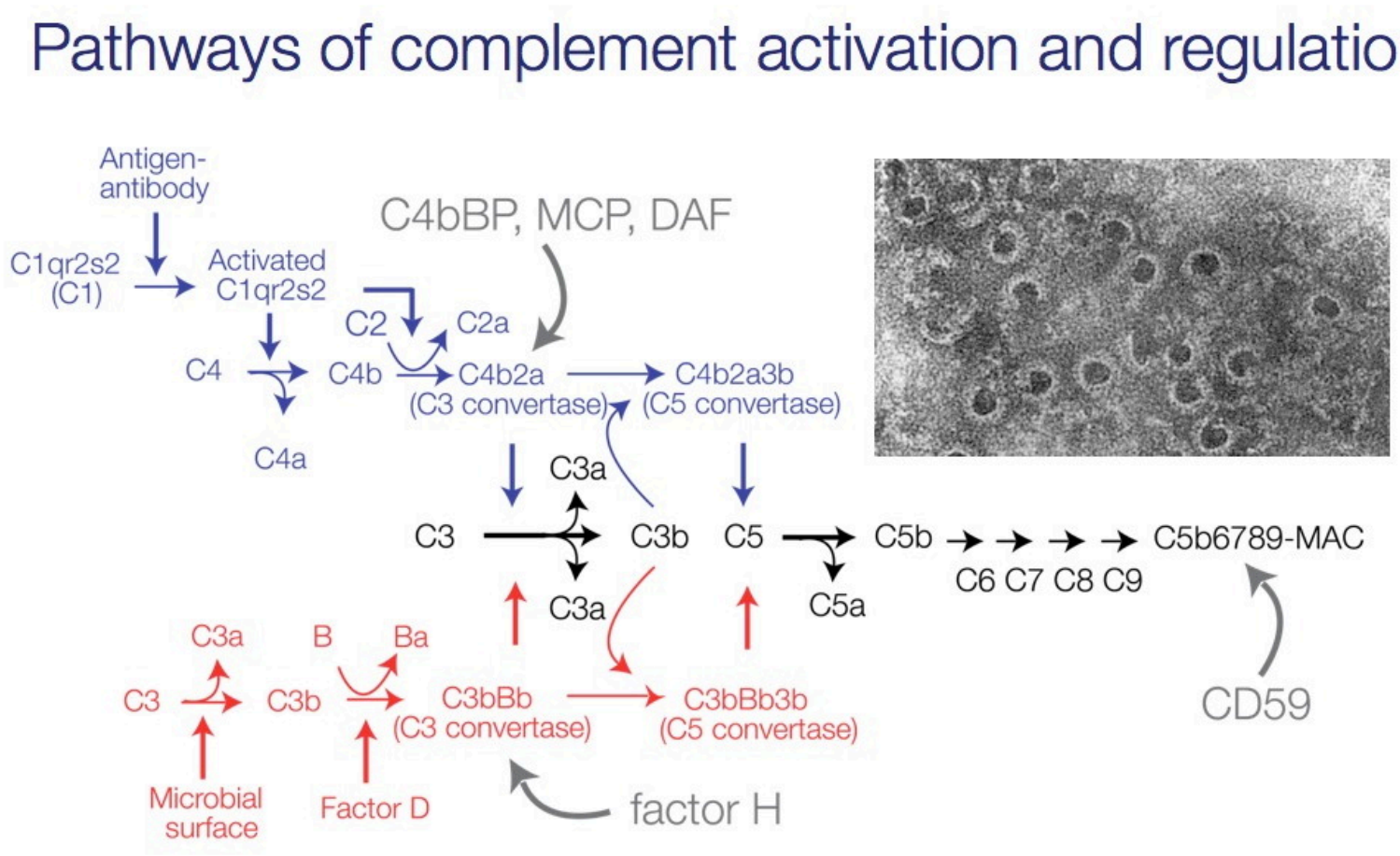
The complement system: bridging innate and adaptive immunity





2. The Product: C4BP(β-)

Innovative mechanisms of action

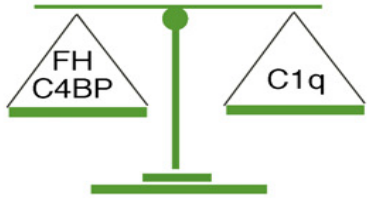


2. The Product: C4BP(β-)

Innovative mechanisms of action

SOLUBLE COMPLEMENT REGULATORS

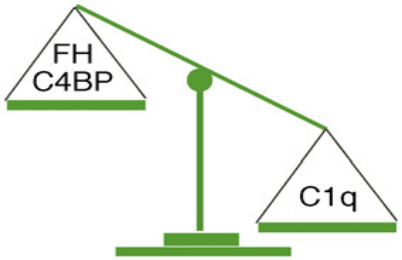
Correct balance of the complement system



Opsonizacion

Prevention of inflammation and injury

Inbalance beneficial to combat pathogens

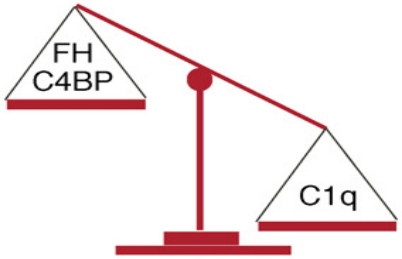


Activation of the complement system

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.

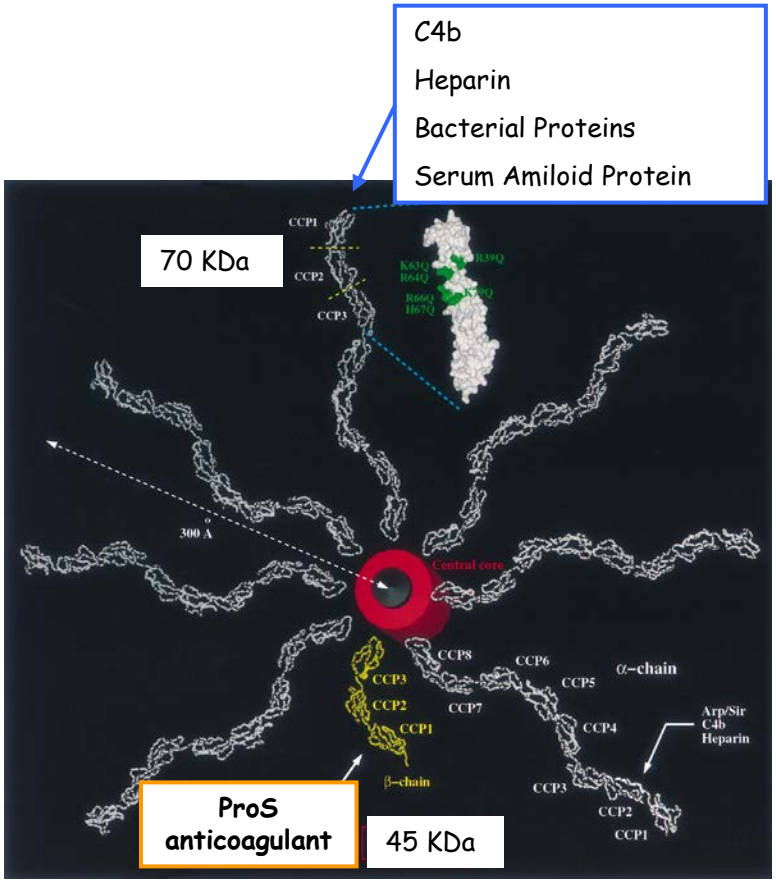
Present in the circulation (200 mg/l) in **three isoforms α7β1** (major), **α7β0** and **α6β1**.

Heterooligomer composed by:

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

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

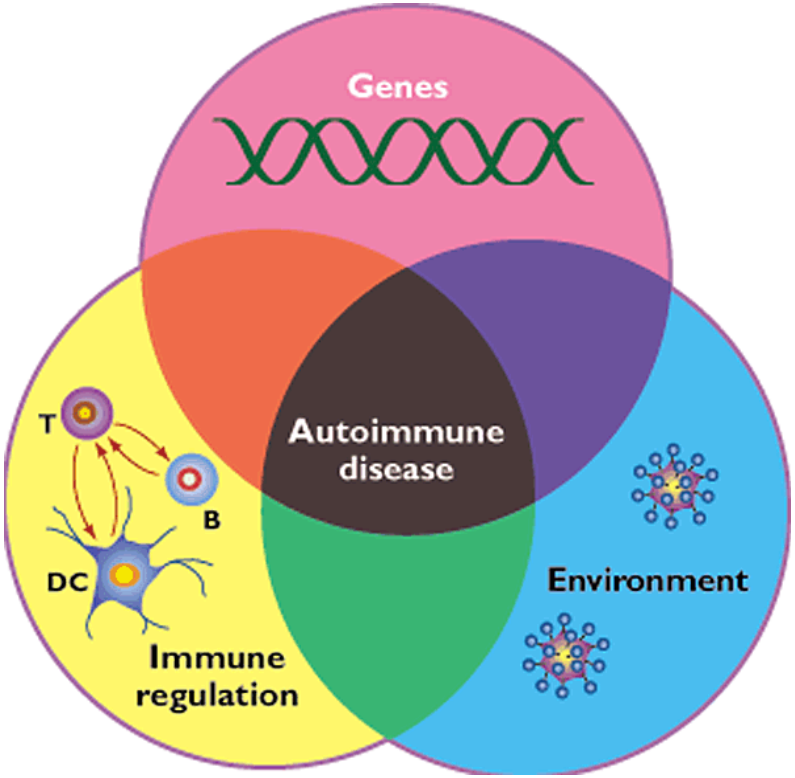
Efficient inhibition of the classical and alternative pathways of complement activation. Prevents the assembly of the C3 convertase (C4b2a) and accelerates the degradation of the complex.

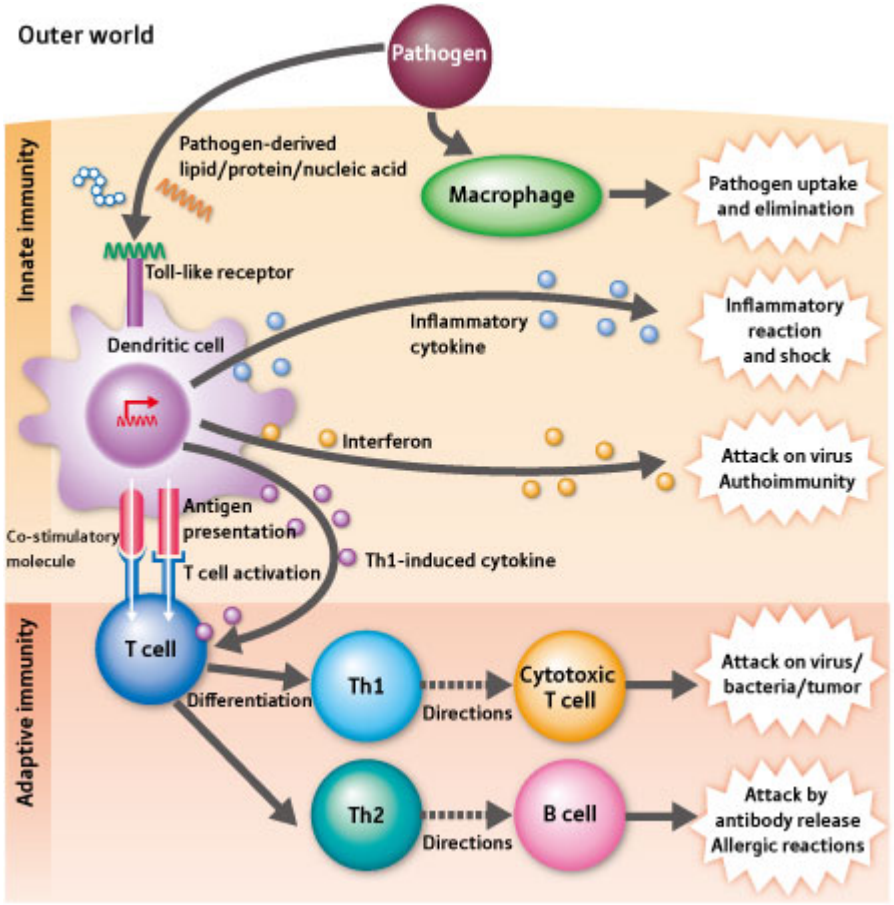


2. The Product: hASC-sST2

Innovative mechanisms of action

Dendritic cells: bridging innate and adaptive immunity



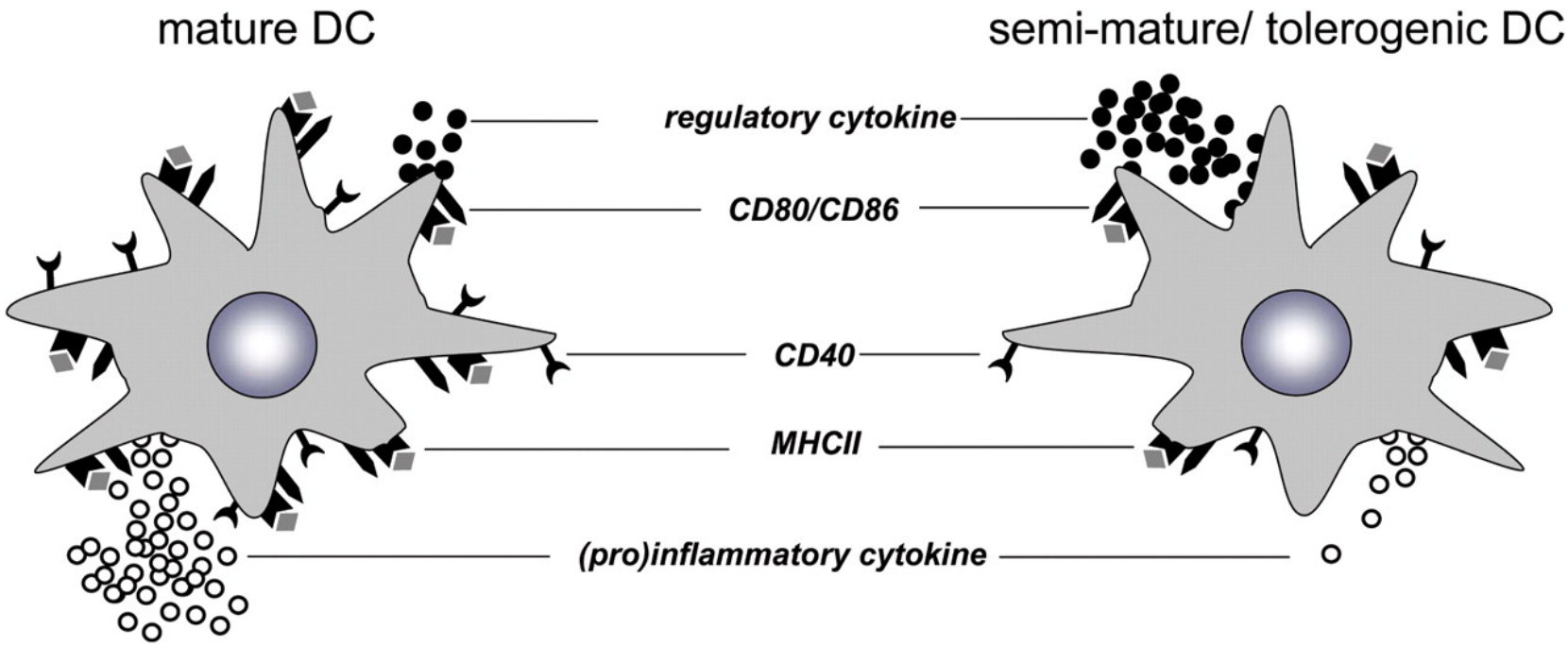


2. The Product: C4BP(β-)

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-)

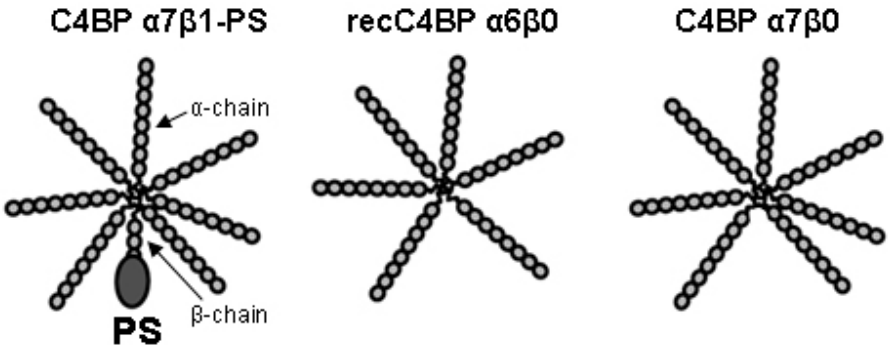
Current status of development

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

Olivar *et al*. (2013) *J. Immunol.* 190: 2857-72

2. The Product: C4BP(β-)

Current status of development

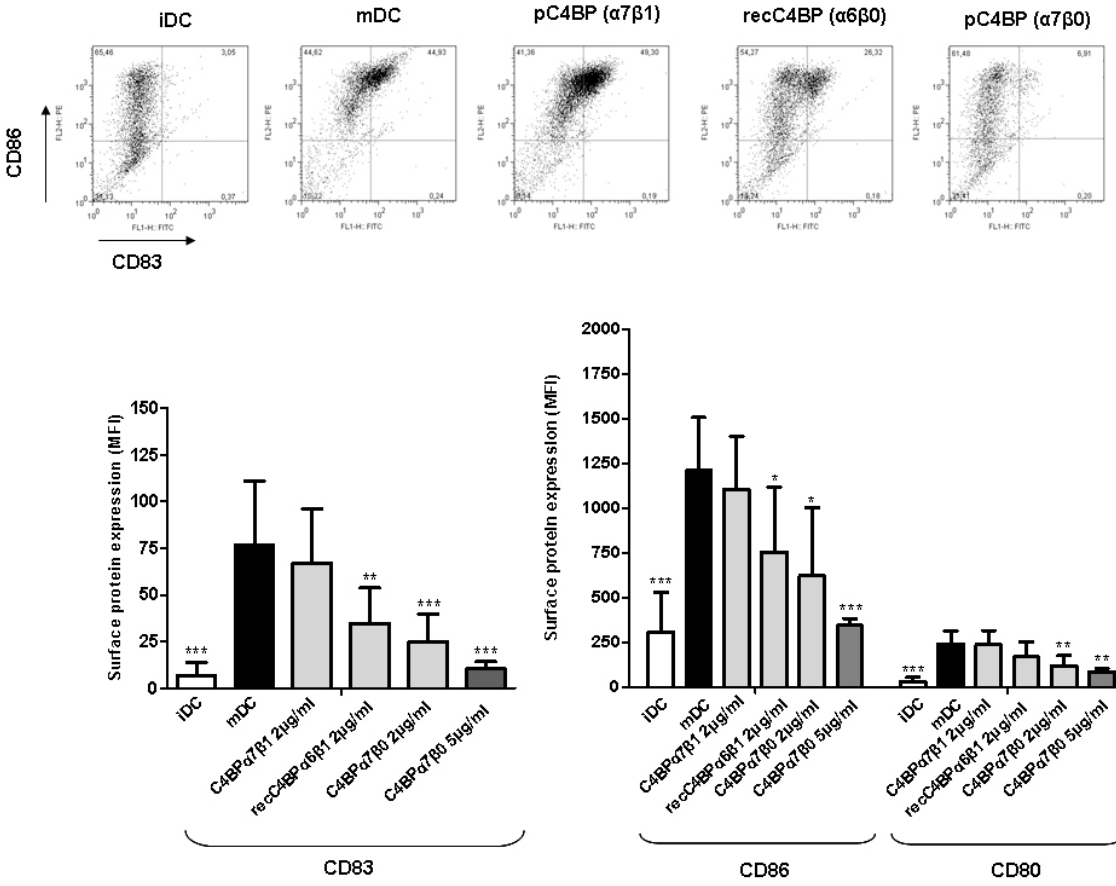


Schematic structure of the C4BP isoforms employed

2. The Product: C4BP(β-)

Current status of development

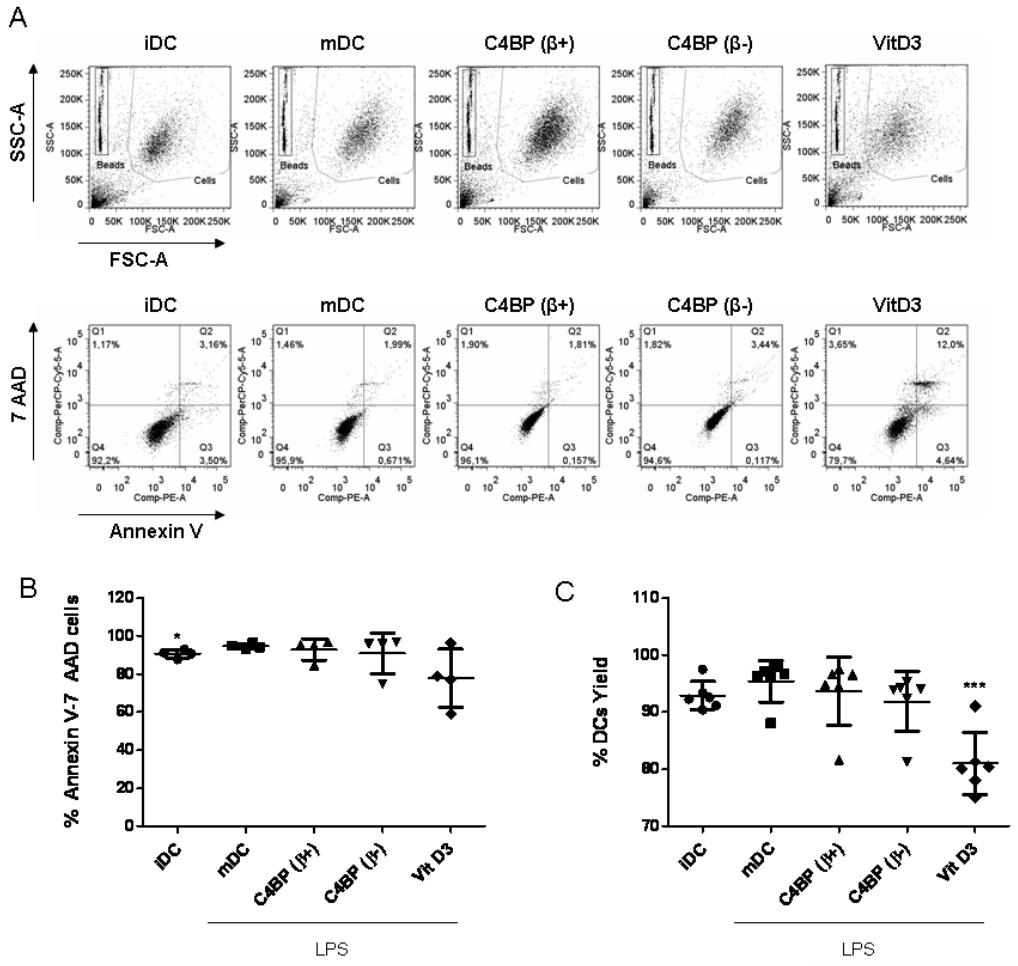
C4BP isoforms lacking β-chain down-regulate the activation phenotype of human DCs



2. The Product: C4BP(β-)

Current status of development

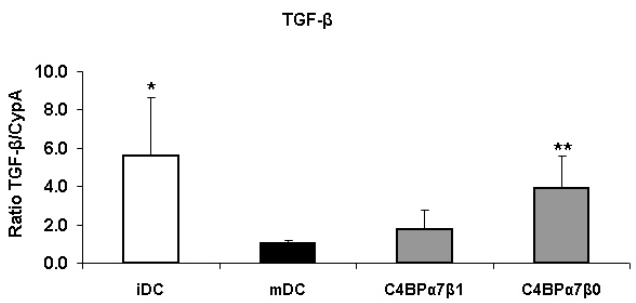
C4BP treatment does not affect the viability of human DCs

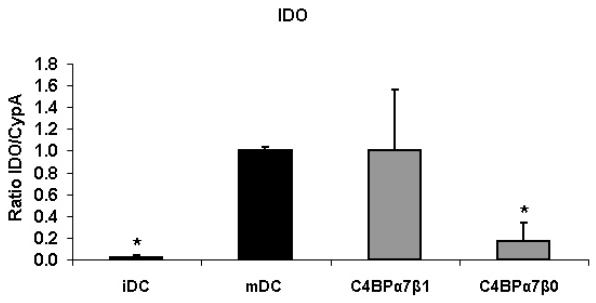


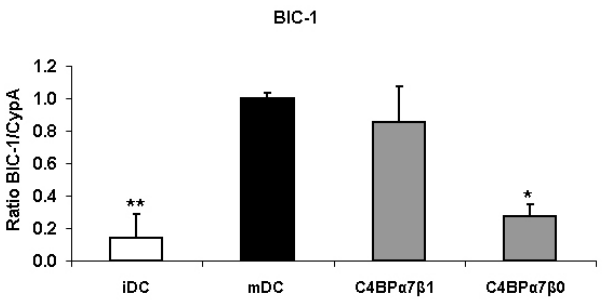
2. The Product: C4BP(β-)

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





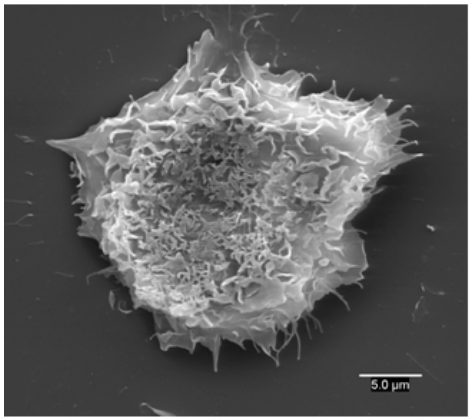


2. The Product: C4BP(β-)

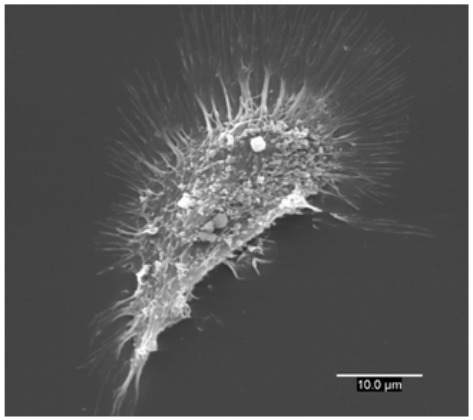
Current status of development

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

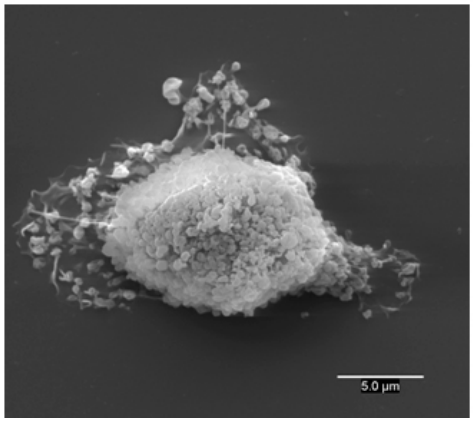
iDC



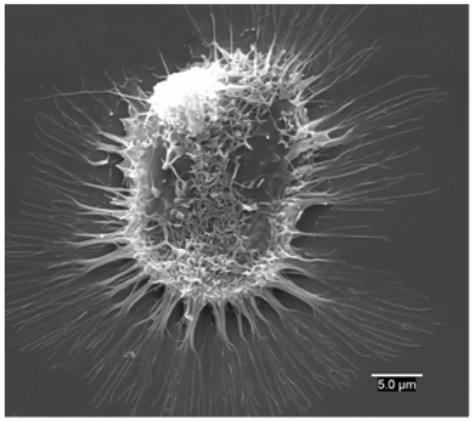
mDC



α7β0



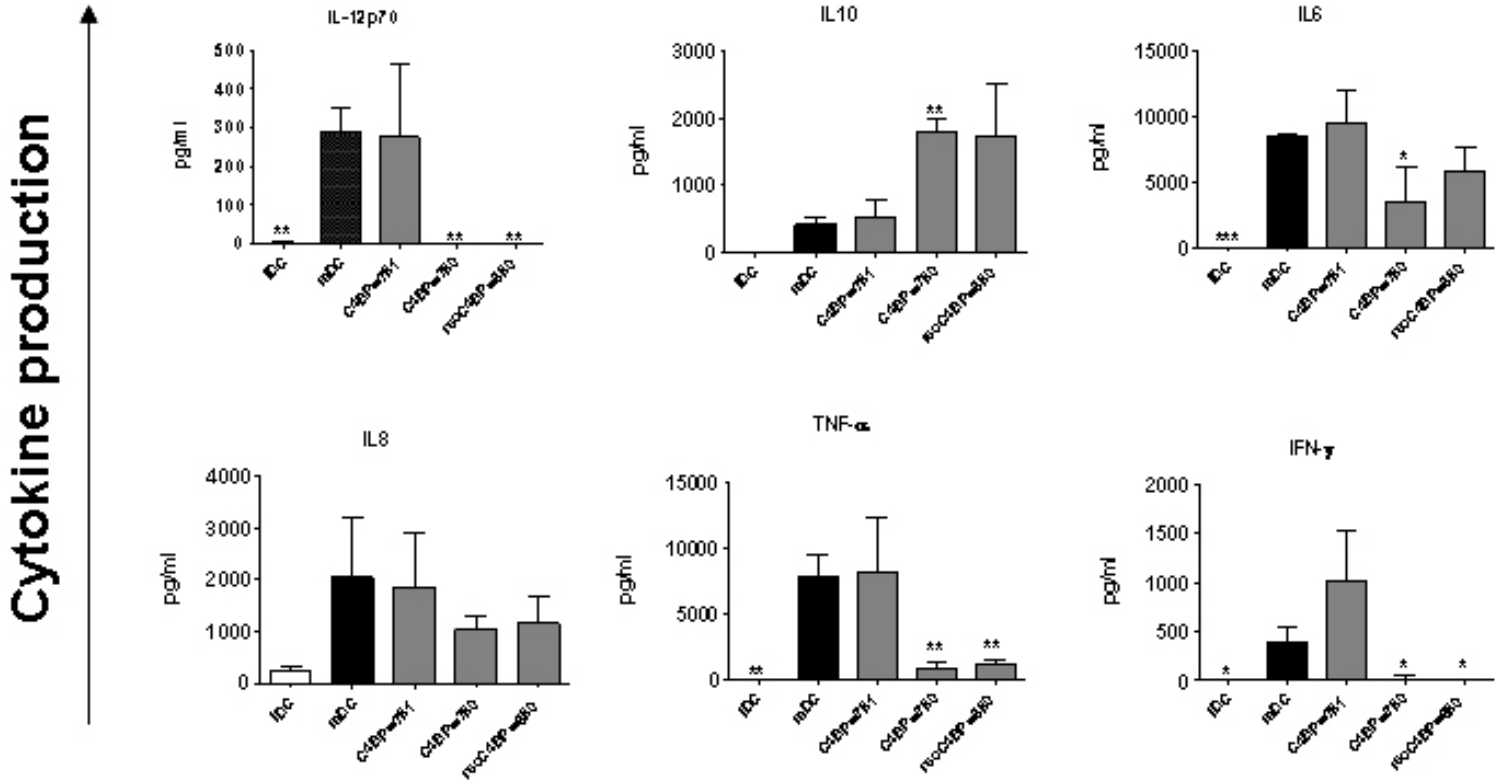
α7β1



2. The Product: C4BP(β-)

Current status of development

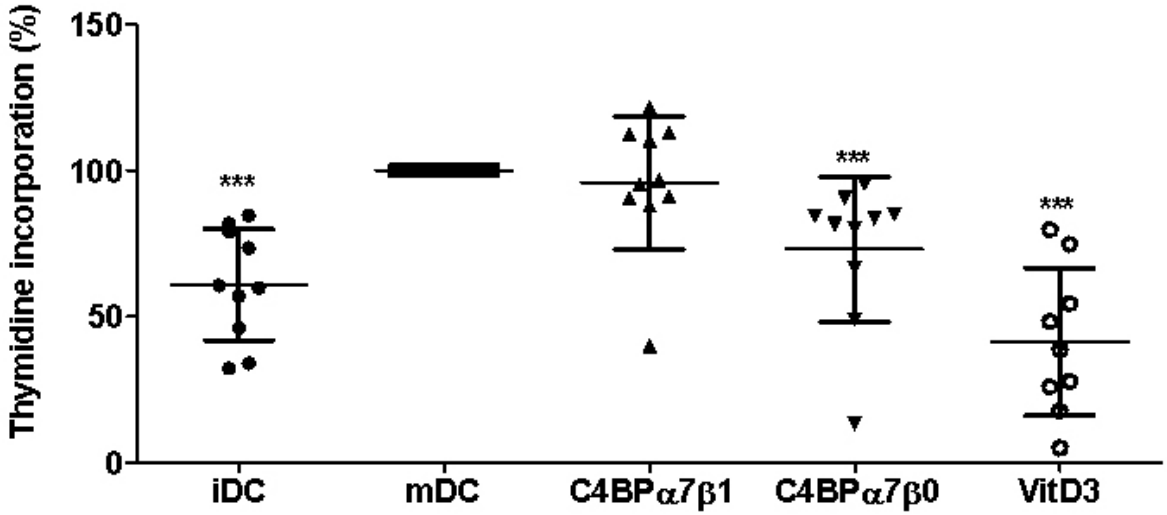
C4BP (β-) isoforms inhibit the release of inflammatory cytokines by LPS-matured human DCs



2. The Product: C4BP(β-)

Current status of development

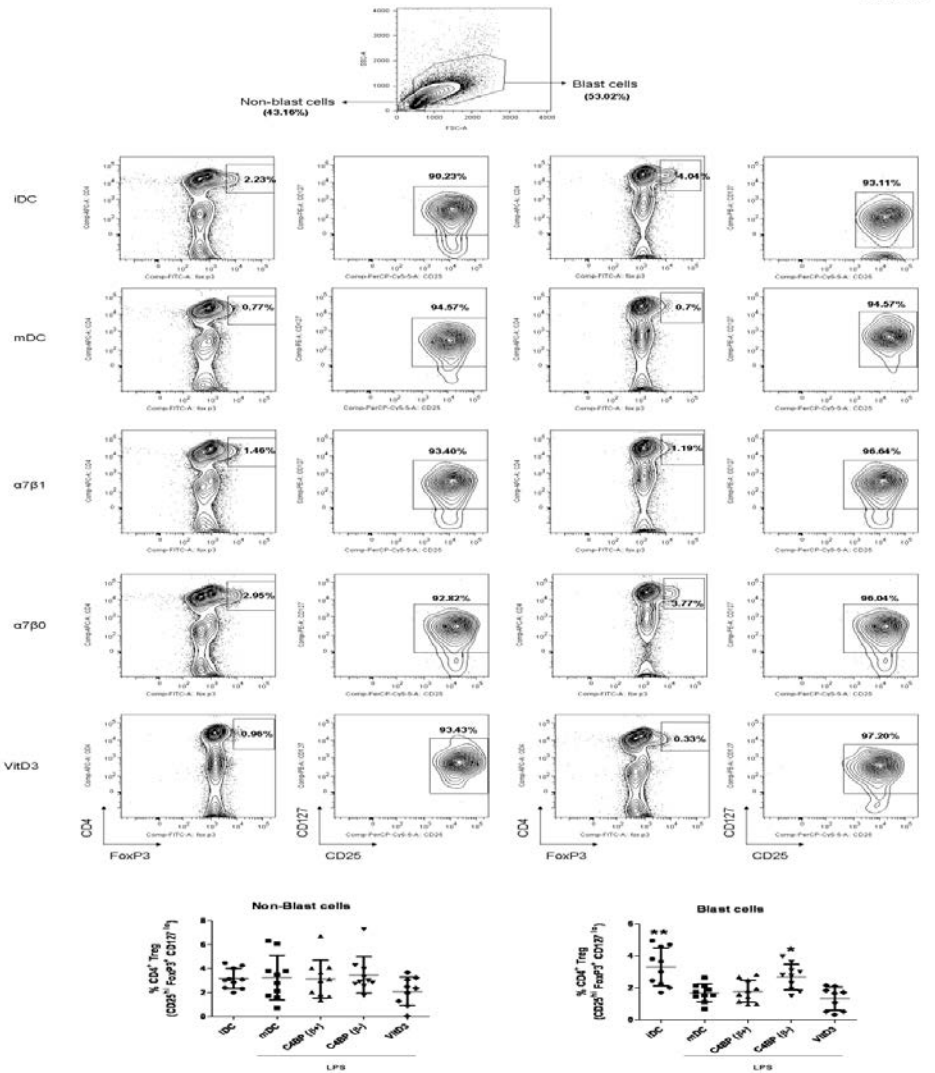
Human DCs exposed to C4BP(β-) isoform inhibits allogeneic T cell proliferation



2. The Product: C4BP(β-)

Current status of development

Human DCs exposed to C4BP(β-) isoform induce allogeneic Treg generation upon LPS stimulation



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:

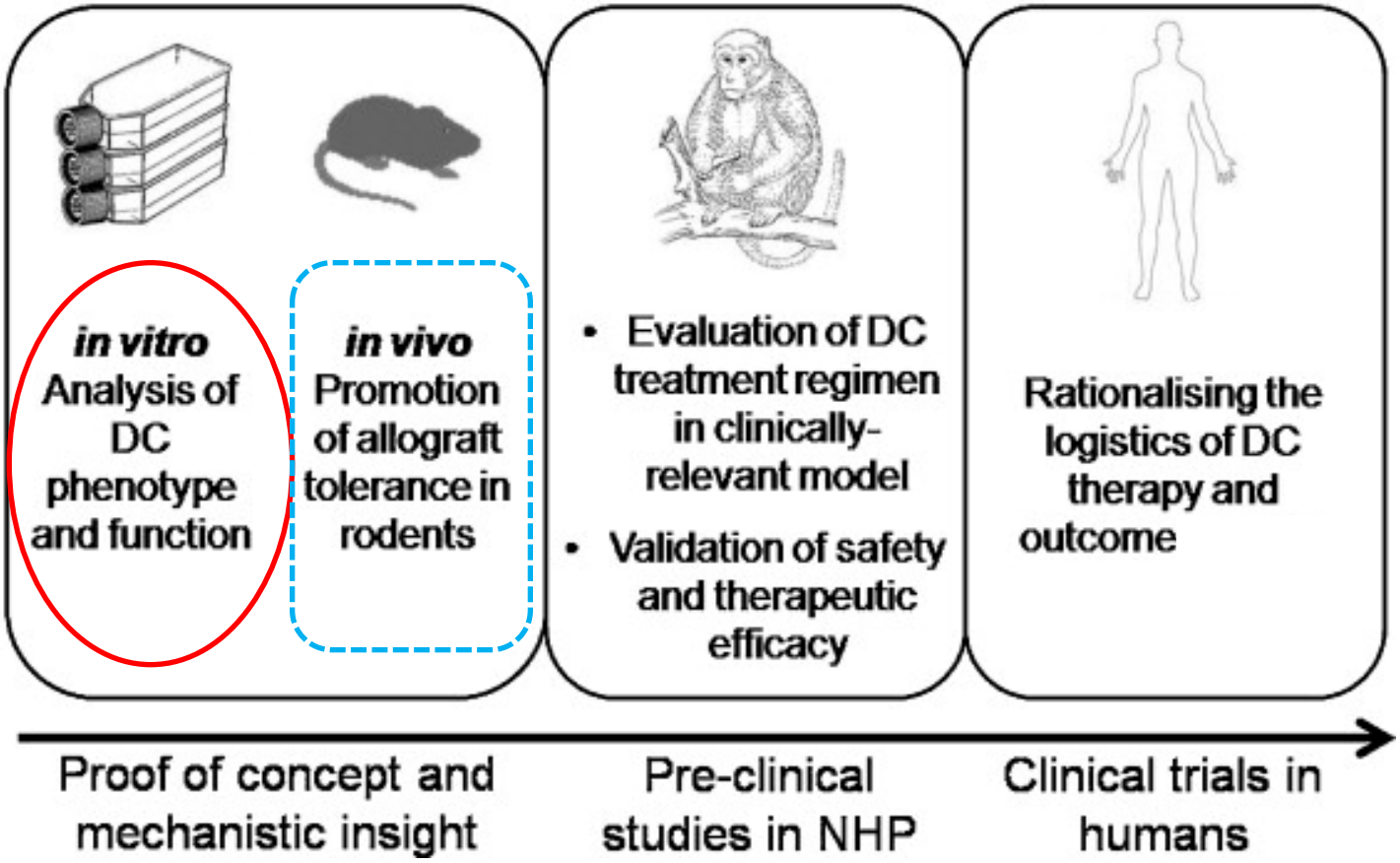
-Immune-inflammatory diseases (acute and chronic)

-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

2. The Product: C4BP(β-)

Current status of development



2. The Product: C4BP(β-)

Differential features facing the market

Ongoing clinical trials using DCs or targerting DCs for multiple disease indications.

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

-Novel anti-inflammatory and immune-modulatory physiological C4BP(β-)-based therapy (circulating levels of C4BP(β-) increase in acute phase patients in response to inflammation).

-Efficacy and specificity 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).

- Comparison with Vitamin D3 as immunomodulator:

- Vitamin D3 [1,25(OH)2D3] is a pleiotropic hormone. Has pleiotropic effects also in immune cells.

- Immunomodulatory effects in vivo require supraphysiological doses of 1,25(OH)2D3, which are associated with the undesired risk of hypercalcemia.

-Direct comparison of the immunomodulatory effects of C4BP(β-) and VitD3 in vitro, in moDCs (Olivar et al. (2013) *J. Immunol.* 190:2857-2872) has revealed inmunomodulatory activity of C4BP(β-) and absence of immunomodulatory activity of VitD3 regarding:

- Percentage of IFN-γ-producing T cells that responded to allostimulation.
- Treg generation.

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**
PCT APPLICATION: PCT/EP2012/063932 (16/07/12)
ENTITY: IDIBELL
LICENSED: Janus Developments, S.L.

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(*).

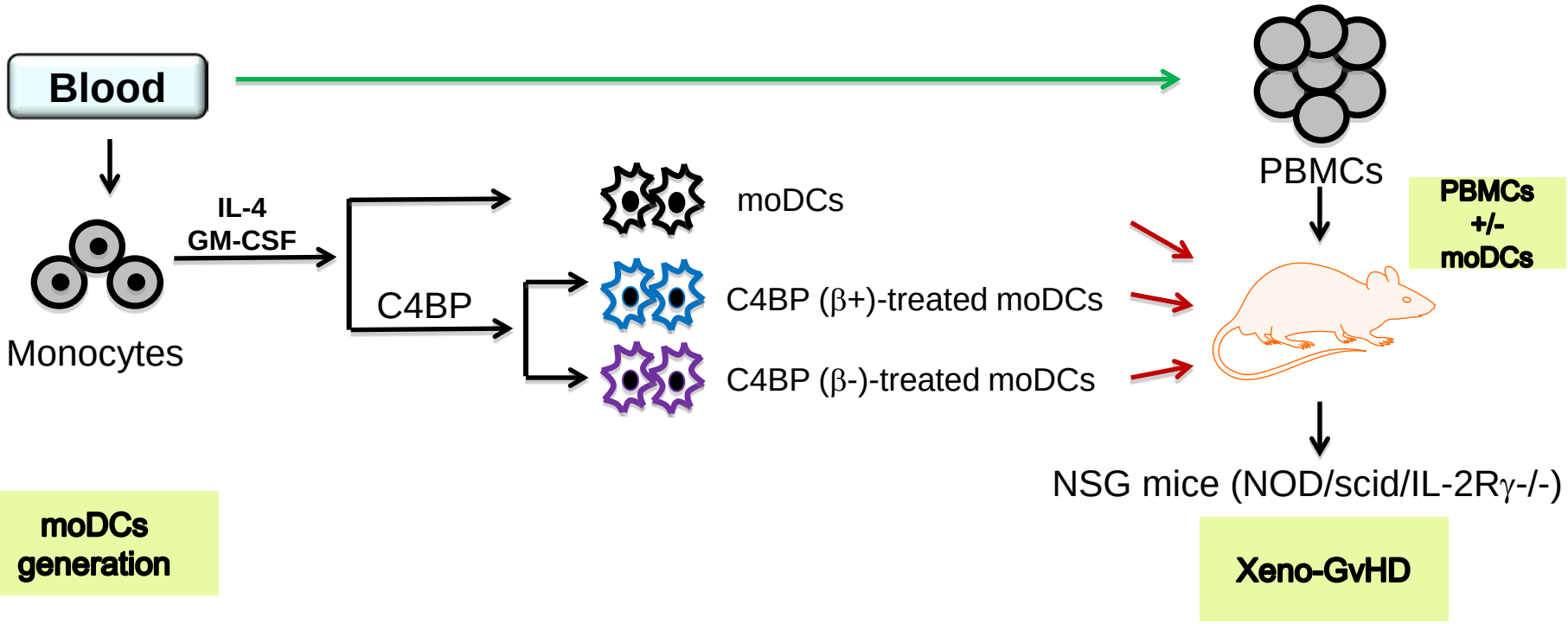
(*) A source of purified, GMP-compliant C4BP(β-) would be highly desirable for *in vivo* pre-clinical and clinical testing (agreement Janus-BioIngenium).

2. The Product: C4BP(β-)

Primary proof of principle (ongoing)

Strategy for pre-clinical assessment of adoptive cell therapy in xeno-GvHD:

Goal: Potential of C4BP(β-) to suppress alloimmunity *in vivo*



End points: Survival over time. Histopathology.

2. The Product: C4BP(β-)

Preclinical perspectives

-Therapeutic potential of C4BP (β^-) or their analogues in animal models of autoimmunity.

In collaboration with the Experimental Nephrology Lab., CSUB-IDIBELL (Dr. Grinyó) (Ripoll, E., et al. (2013) ***PLOS ONE*** 8: e65068)**:**

-Lupus nephritis

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.