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Ship-1 inhibitors for prophylactic treatment and/or prevention of infectious diseases

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Content

1. The Institution

The Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC) is a **leading international research center** devoted to the understanding of relevant human pathologies, particularly focused in cardiovascular diseases.

The CNIC is one of the main biomedical research centers in Spain, having awarded by the Spanish Ministry of Science and Innovation with the **"Severo Ochoa Centers of Excellence Program"**.

From research to health goes beyond our institutional slogan, reflecting our goal for translating basic research knowledge to new clinical and technological approaches.

2. The product / rationale

- Fighting infections represent a major issue in the clinics, with current therapies mostly focused in the administration of antimicrobial drugs (antivirals, antibiotics, fungicidals…).

- However, the massive use of these treatments is leading to a difficult-to-solve problem due to the appearance of multidrug resistances among the most common pathogens such as *Candida albicans* or *Staphylococcus aureus*.

- Therefore, we need alternative approaches to fight off these infections.

- The herein presented invention represents an unconventional therapeutic approach to combat a broad range of infectious diseases, by combining the induction of ***trained immunity*** and ***inhibitors of the SHIP-1 phosphatase***.

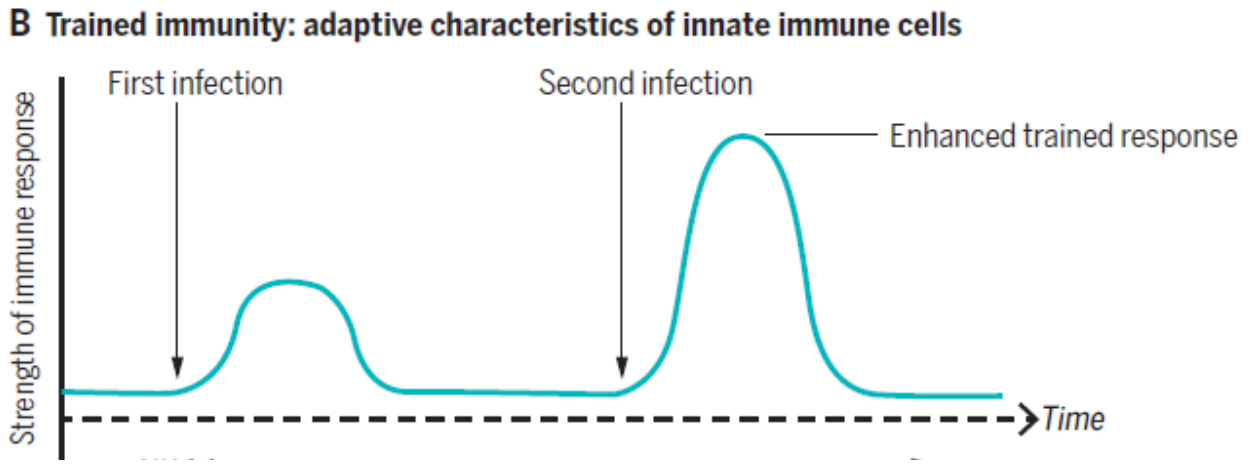
2. The product / rationale

- **Trained immunity (TI)** represents a new paradigm in immunology by which, innate immune cells, such as monocytes or macrophages, can develop long-lasting memory.

- Thus, the encounter of these cells with certain stimuli such as *ß-glucan from fungal cell walls* or the *tuberculosis vaccine, BCG,* allows them to develop enhanced responses when facing a second challenge.

Importantly, the second improved response can be triggered by different pathogens than the ones inducing the training process.

It means that ***TI represents a mechanism to fight a broad range of infections, no matters the inducer of that TI.***



Netea M., Science, 2016

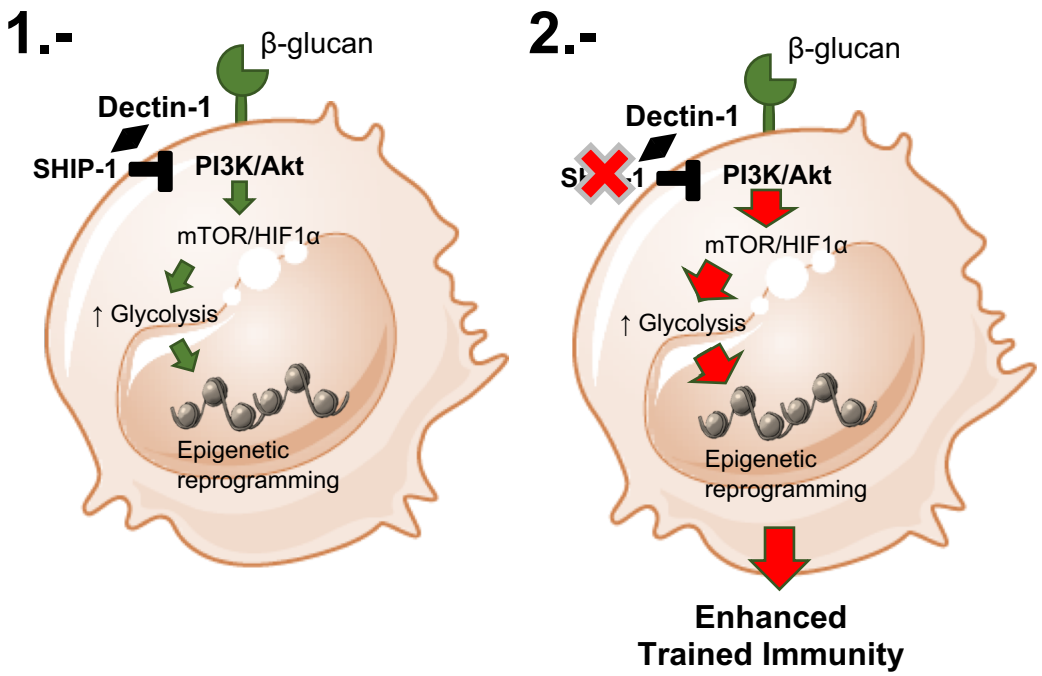
2. The product / rationale

- As indicated before, ß-glucan of fungal origin induces trained immunity. This compound is recognized by the receptor Dectin-1. This recognition triggers a cascade of events leading to a metabolic and epigenetic reprogramming of the cells that grounds the long-lasting effect of trained immunity.

- The earliest event after Dectin-1 engagement is the activation of PI3K/Akt kinases.

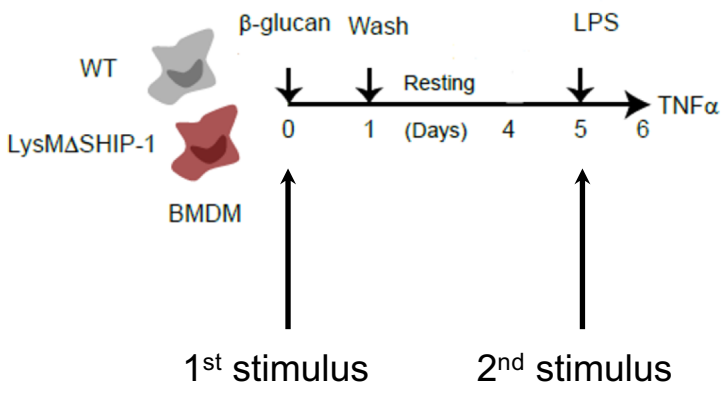
1.- In a former study we described that the phosphatase SHIP-1 binds the intracellular domain of Dectin-1, regulating its signaling *(Blanco-Menéndez, Del Fresno, et al, JI, 2015).*

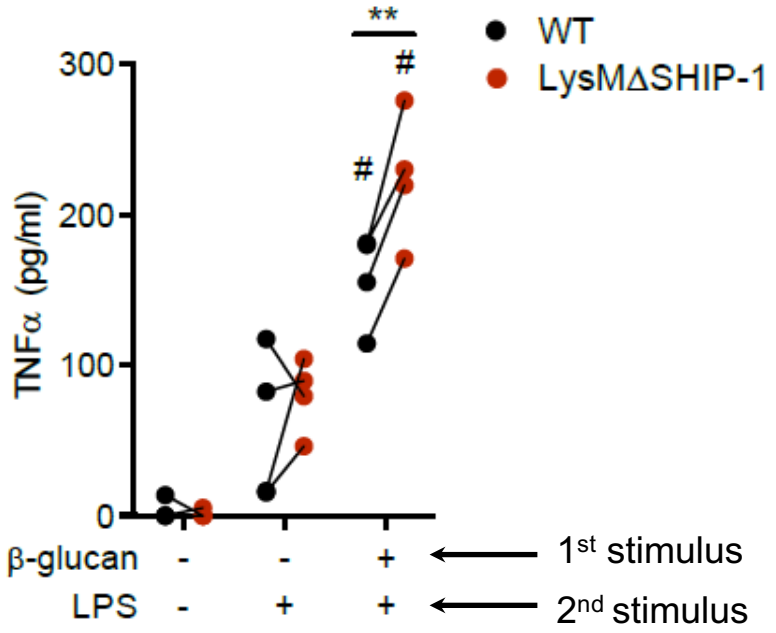
2.- Based on this, the current development aims to **improve antimicrobial protective responses triggered through trained immunity, by targeting SHIP-1.**



2. The product / proof of concept

- Mice with SHIP-1 specifically depleted in macrophages (LysMΔSHIP-1).
- *In vitro* experiments using Bone marrow-derived macrophages.



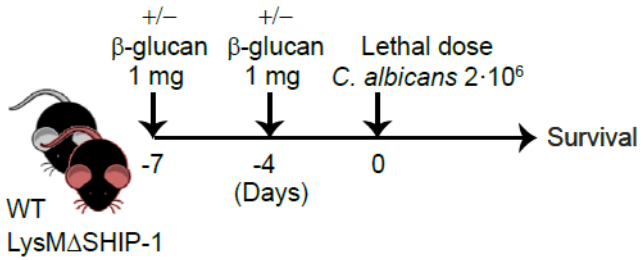


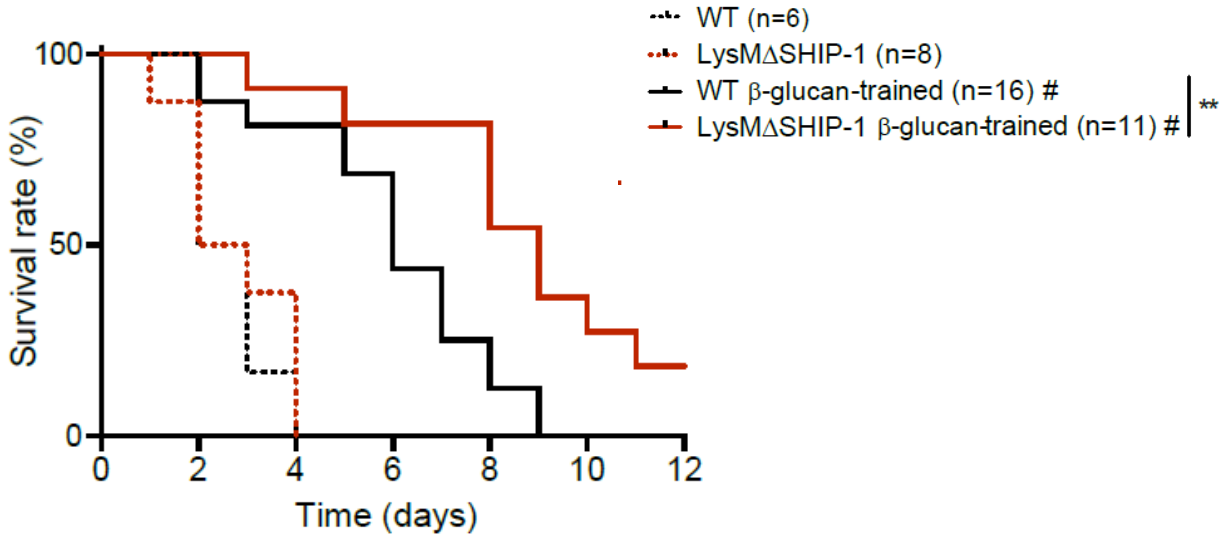
# indicates trained immunity (enhanced secondary response)

** denotes **boosted trained immunity in the absence of SHIP-1**

2. The product / proof of concept

- Mice with SHIP-1 specifically depleted in macrophages (LysMΔSHIP-1).
- *In vivo* experiments training with ß-glucan to protect against lethal candidiasis.



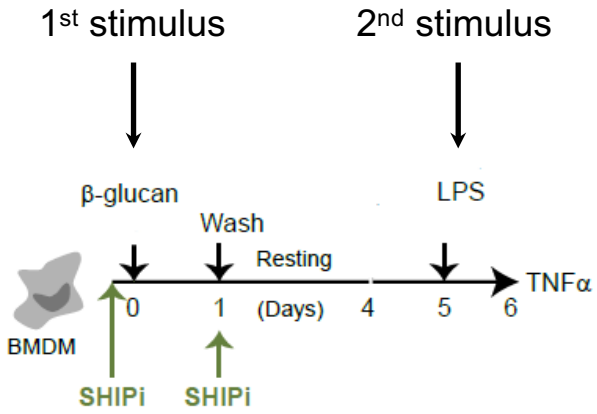


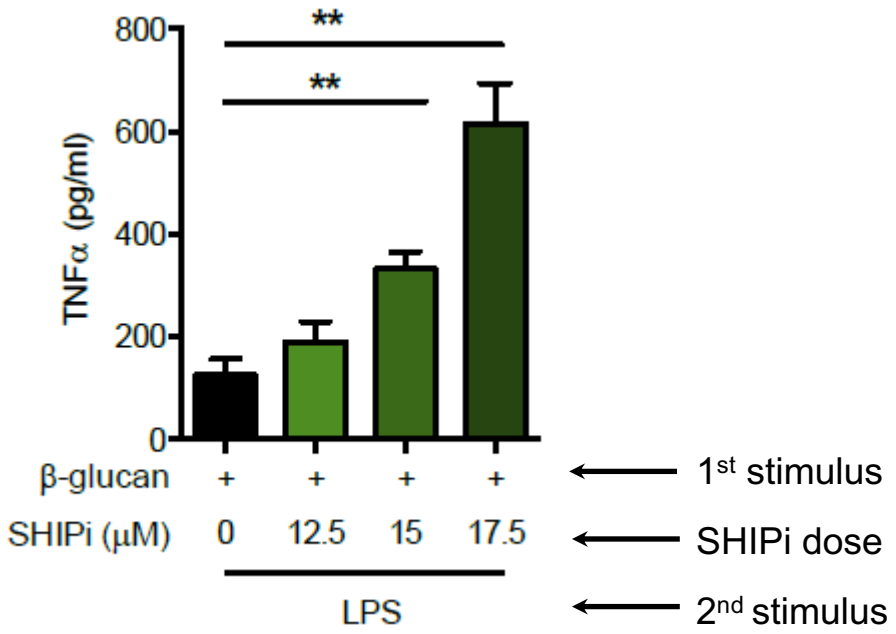
# indicates protection conferred by ß-glucan induced-trained immunity

** denotes **enhanced protection in the absence of SHIP-1 upon training**

2. The product

- Use of SHIP-1 inhibitor (SHIPi, small molecule) as a pharmacologic drug.
- *In vitro* experiments using Bone marrow-derived macrophages.

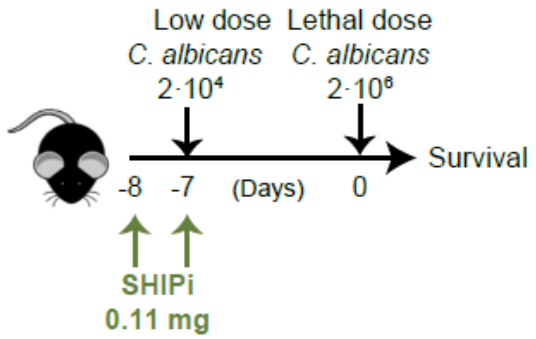


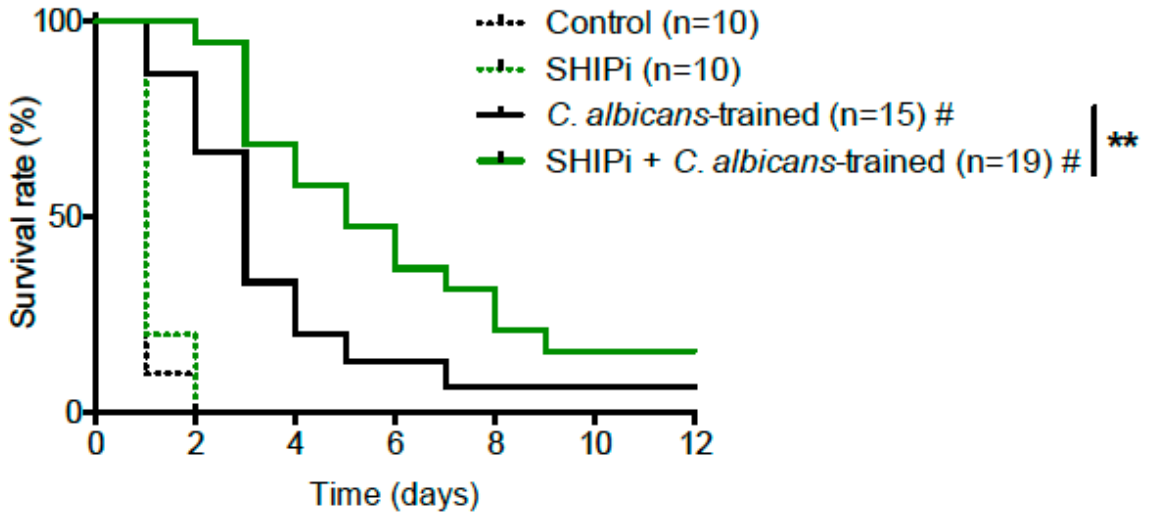


** indicates **enhanced trained immunity in the presence of SHIP-1 inhibitors** in a dose-dependent manner

2. The product

- Use of SHIP-1 inhibitor (SHIPi, small molecule) as a pharmacologic drug.
- *In vivo* experiments training with low *Candida* to protect against lethal candidiasis.



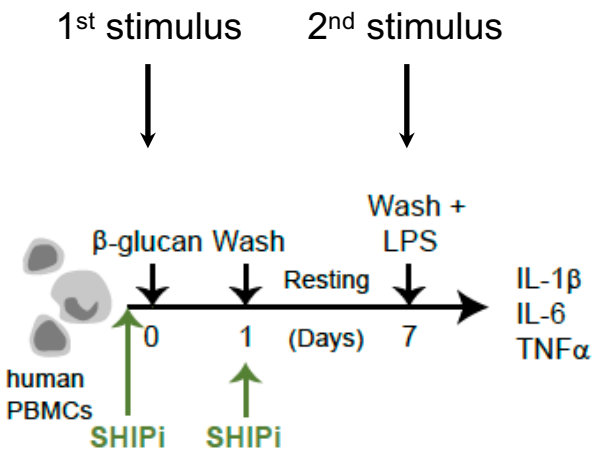


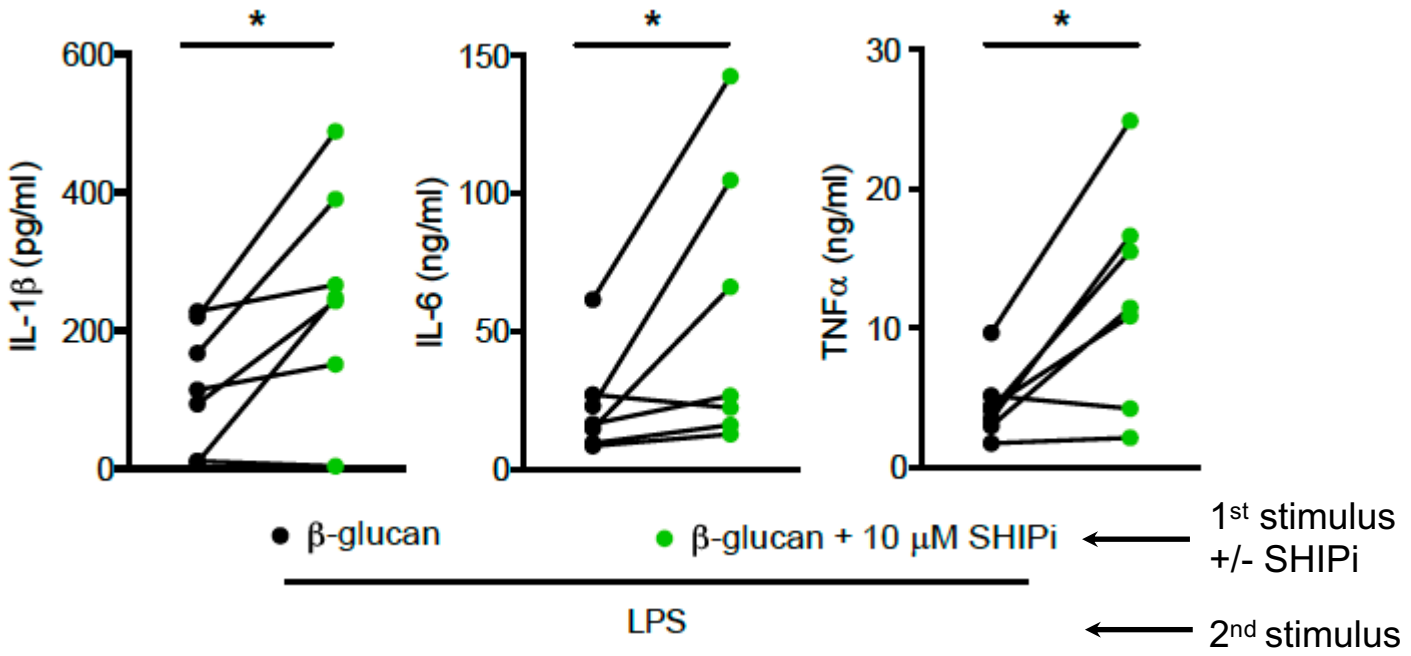
# indicates protection conferred by trained immunity

** denotes **enhanced protection in the presence of SHIP-1 inhibitors**

2. The product

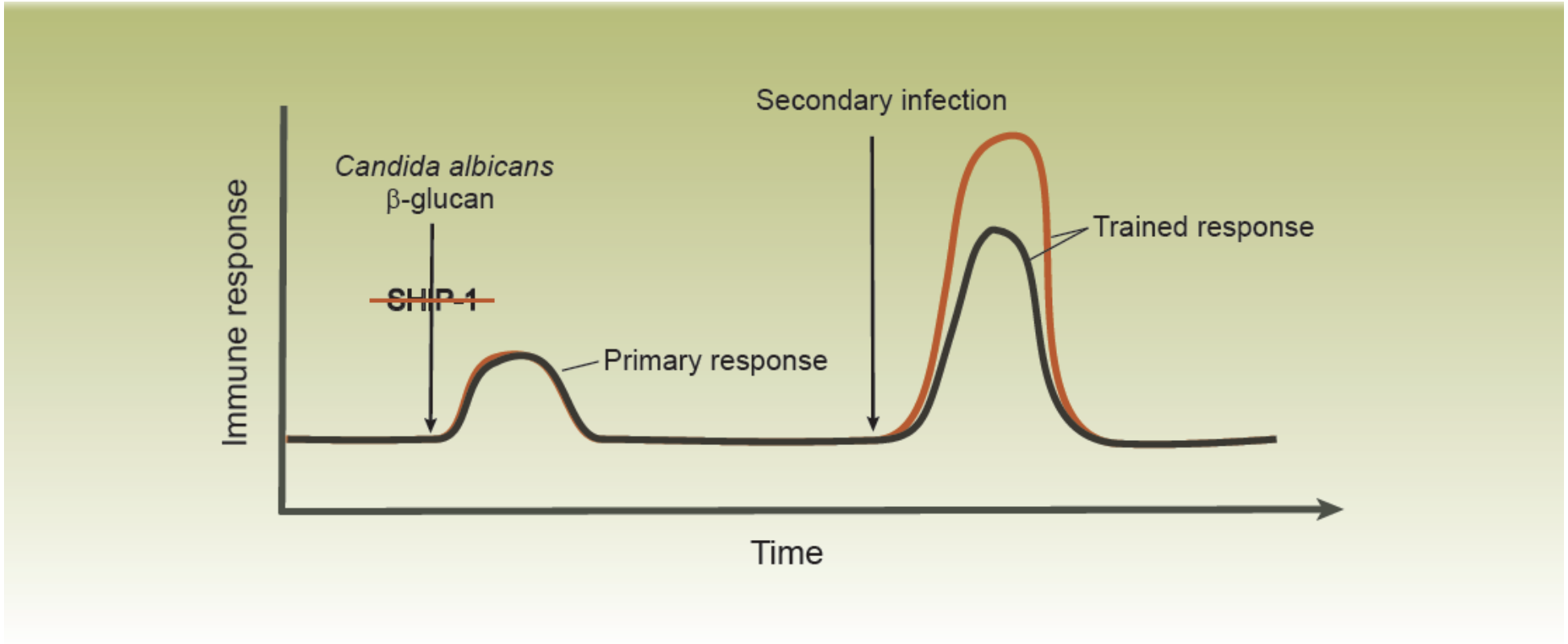
- Use of SHIP-1 inhibitor (SHIPi, small molecule) as a pharmacologic drug.
- *Ex vivo* experiments using human Peripheral Blood Mononuclear Cells (PBMCs).





* indicates **enhanced trained immunity in the presence of SHIP-1 inhibitors in human PBMCs**

2b. Innovative mechanisms of action



SHIP-1 INHIBITORS AS A PROPHYLACTIC TOOL TO ENHANCE ANTIMICROBIAL TRAINED IMMUNITY

2c. Differential features facing the market

- Current antimicrobial therapies are not fully effective against many relevant pathogens and the rise of multidrug resistance is a major concern in the clinical environment.

- The outbreaks of new pathogens generate an scenario of lack of specific antimicrobial treatments.

- In these conditions, non-specific approaches conferring protection against a unrelated pathogens are of great interest.

- Our proposed prophylactic approach aspires to combat a broad range of infectious diseases, by combining the induction of ***trained immunity*** and ***inhibitors of the SHIP-1 phosphatase***.

2d. Current status of development

- We plan to expand the knowledge generated from the data presented here (Saz-Leal, Del Fresno, *et al*., Cell Reports, 2018) to different heterologous infections, *with an special focus in virus responsible for viral outbreaks,* in the context of a **NIH R01 multicenter grant funded by the National Institute of Allergy and Infectious Diseases (NIAID).**

2e. IPR protection

- **International application:** PCT/EP2019/064871
- **Applicants:** CNIC, Syracuce University, the Research Foundation for the State University of New York
- **Title:** Enhanced Trained Immunity in myeloid cells by SHIP-1 inhibition

The PCT claims SHIP-1 inhibitor or a *molecule able to specifically target SHIP-1 gene and inhibit its translation* for use in the **non-specific prophylactic treatment or prevention of infectious diseases**, wherein the SHIP-1 inhibitor, or the molecule able to specifically target SHIP-1 gene an inhibit its translation, is administered before, after or simultaneously to a treatment with a pathogenic microorganism or any part thereof which causes a stimulus responsible for training the innate immune cells.

2f. Pitfalls and risks to be considered

We are open to study:

- Different formulations for the SHIP-1 inhibitors
- Alternative training stimulus to combine with SHIP-1 inhibitors

3. Partnering Opportunities

We are **interested in a cooperation with a pharma partner** in:

- Extend our knowledge on the effect of SHIP-1 inhibitors in additional pathological settings, even beyond infectious diseases (e.g. cancer).
- Translate the existing and/or future knowledge on the combination of trained immunity and SHIP-1 inhibitors to clinical trials.
- License the current PCT portfolio.