

Drug combination for the treatment of bacterial infections

Brief description

The fight against bacterial infections, especially those caused by multi-drug resistant strains, is one of the greatest threats to global health. Due to this health emergency, there is a growing need to find new therapies to treat respiratory diseases. In order to develop new therapeutic strategies, a combination of two compounds with antimicrobial activity has been tested: a last-resort antibiotic (polymyxin B, PMB) and an antimicrobial lipid found in the respiratory tract (sphingosine, Sph).

After combining both components in what would be considered suboptimal quantities, a synergistic effect is achieved. This promises to be effective in treating infectious respiratory diseases, especially pneumonia and acute bronchitis caused by Gram-negative bacteria. The drug combination and its use in treating bacterial infections have been protected by a patent ([ES3030207A1](#)).

How does it work?

The mechanism of action is based on the synergistic effect of both compounds, allowing for the use of suboptimal concentrations. The amount of PMB included in this combination is much lower than the amount used to treat respiratory diseases with PMB alone. Similarly, the amount of Sph used in this combination is also considered suboptimal compared to the amount that would be needed to observe an effect if it were used alone.

PMB is a last-resort antibiotic due to its adverse effects. Its mechanism of action is based on its ability to alter the permeability of the outer and inner membranes of Gram-negative bacteria, causing the leakage of intracellular material and bacterial death. **Sph** is an antimicrobial lipid present in the respiratory tract, capable of interacting with negatively charged phospholipids in bacterial membranes. It is a broad-spectrum antibacterial agent that can act directly on the bacterial cell membrane and lyse it, efficiently eliminating both Gram-positive and Gram-negative bacteria.

The combined treatment of PMB and Sph is effective at reducing both bacterial growth and metabolic activity. PMB, by promoting contact between the outer and inner membranes of Gram-negative bacteria and the exchange of phospholipids between the two membranes, likely facilitates the binding of Sph to certain bacterial membrane lipids, enhancing its antimicrobial effect. This combination is especially indicated for the treatment of respiratory infections such as acute bronchitis or pneumonia, preferably caused by Gram-negative bacteria, and even more so those caused by multi-drug resistant Gram-negative bacteria, such as those belonging to the genera *Klebsiella*, *Acinetobacter*, *Pseudomonas*, or *Haemophilus*. Furthermore, the composition can be administered simultaneously or sequentially via inhalation or intranasal routes.

In vivo, we have demonstrated the efficacy of PMB/Sph combination treatment in a murine model of respiratory infection. Co-instillation of the pathogen along with the PMB/Sph combination has shown a significant reduction in pulmonary bacterial load at 24 hours compared to untreated infected mice or infected mice treated with PMB or Sph separately. Additionally, its therapeutic effect has also been demonstrated in a murine model of mice with a pre-established respiratory infection, where treatment with the PMB/Sph combination significantly reduced the bacterial load.

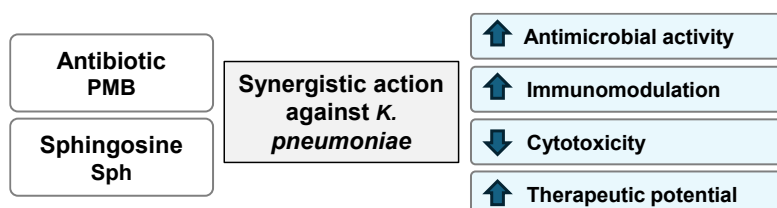


Figure 1. Advantages of the combination of PMB and Sph for the treatment of bacterial infections



What problem does it solve?

Bacterial infections, especially those caused by multi-drug resistant bacteria, constitute one of the main health problems worldwide, which is why there is a demand for new therapies that can combat infectious diseases. With the therapeutic combination we present, by using suboptimal levels of two drugs, a very promising synergistic effect is obtained for the treatment of infectious respiratory diseases.

What future products will it develop?

We provide a new combined therapy for the treatment of bacterial infections.

Competitive advantages compared to other research

- **Greater Efficacy:** The combination of PMB and Sph has a clear synergistic effect against Gram-negative bacteria, which significantly reduces the bacterial load in respiratory infections.
- **Reduction of Adverse Effects:** As it is a synergistic therapy, the amount of PMB needed is less than what would be used individually. This is crucial as PMB is a last-resort antibiotic with severe side effects.
- **Improved Immune Response:** Treatment with PMB and Sph promotes the recruitment of neutrophils, which increases the host's defense.
- **Proven Therapeutic Value:** The treatment has proven its efficacy even in pre-established infections.

Where has it been developed?

The work was developed by the UCM "Respira" Research Group, which has extensive experience in the areas of respiratory diseases, host-pathogen interaction, and the molecular and cellular biology of the alveolus.

The group's current work focuses on innate pulmonary immunity with two key objectives:

1. The identification of pulmonary anti-infectious factors and the synergies between them and antimicrobial drugs.
2. The study of immunomodulatory factors in alveolar fluid such as pulmonary collectins (SP-A and SP-D) and alveolar phospholipids, which activate the molecular and cellular mechanisms necessary to limit inflammation, repair damaged tissue, and restore homeostasis.

And furthermore...

We seek companies in the sector interested in continuing the development of this research and exploiting the patent.

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