Precision Biotics

Scientific Summary

Immune Health & The PB-VIR™ Probiotic Strain

SCIENTIFIC SUMMARY

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Key Points

- The immune system is a complex network of communication, pathways and mechanisms designed to protect health.[1,2]
- The gut microbiota plays a key role in the development and regulation of the immune system.[3-5]
- Gut dysbiosis is associated with an impaired immune response and increased risk of infection.[3]
- Specific probiotics have been shown to have strain-specific clinical benefits in people with respiratory infections.[3,6]
- Preclinical research has found that *Bifidobacterium longum* **PB-VIR**™ may significantly increase survival rates and significantly reduce viral loads, proinflammatory cytokines, and lung injury in influenza infection.[7]
- The **PB-VIR**™ strain has been carefully selected for its safety and efficacy by PrecisionBiotics, who have over 20 years' experience of scientific research and expertise in this field.

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Immunity

The immune system is an intricate network of communications and pathways working in synchrony to protect the host. Pivotal to the functioning of the immune system is its ability to differentiate self from not-self, enabling it to respond to invading pathogens, allergens and toxins, and to mobilise an appropriate and tailored response[1].

There are two parts of the immune system, differentiated by the speed and specificity of their response, which interact with each other[8].

The Innate Immune System[2,8,9]

The innate immune system involves elements of the immune system that provide an immediate host defence (within 4 hours). This is a non-specific response that has no memory, so it is unable to effectively resolve an infection alone. The innate response consists of **cellular, chemical** and **acute inflammatory** responses.

Cellular Response

Phagocytes (i.e neutrophils, dendritic cells, blood monocytes and tissue macrophages) recognise, engulf, kill and digest pathogens, breaking them down to their basic proteins. The phagocytes then present these digested proteins as antigens to the cells of the adaptive immune system.

Natural killer cells also work to destroy the pathogen, by releasing toxins.

The release of proinflammatory cytokines initiates the inflammatory response.

Chemical Response

The complement system initiates a cascade of chemicals which trigger further inflammation, coats pathogens to help phagocytes to recognise and digest them, triggers a pathogen membrane attack pathway, and supports the spleen to remove pathogens. This mainly occurs in response to pathogenic bacteria; in viral infections, interferons act in a similar way.

Proinflammatory cytokines, such as interleukins (IL), tumour necrosis factor alpha (TNFα) and interferon gamma (IFNγ), are released. These are involved in activating other immune cells, promoting antibody production, and mediating the acute inflammatory response.

Inflammatory Response

The site of the infection becomes inflamed to localise and contain the infection.

Whilst inflammation is required for an effective immune response, this must be regulated, as hyperinflammation (in response to ongoing infection) can be damaging.

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The Adaptive Immune System[2,8,9]

The adaptive immune system is activated within 4-96 hours of infection. Specific phagocytes (the dendritic cells) present their antigens to naïve T helper (TH) cells, which then differentiate into either TH1 cells to promote cytotoxic T cells and **cell-mediated immunity,** or TH2 cells to promote B cells and **humoral immunity.**

Cell Mediated Immunity

Designed to fight intracellular infections, including viruses, some bacteria and fungi, and protozoa.

When presented with antigens, TH1 cells activate the phagocytes, which optimises their ability to destroy ingested pathogens. This activation involves the secretion of IFNγ.

TH1 cells also activate cytotoxic T cells, which use several mechanisms to destroy pathogens. Some of these remain even after the infection is cleared, as dormant 'memory' T cells.

Humoral Immunity

Designed to fight extracellular infections including most bacteria, fungi protozoans and parasitic worms, through the production of antibodies.

TH2 cells activate B cells and release cytokines, such as IL-2, IL-4 and IL-5, which promote B cell development.

B cells mature into plasma cells to produce antibodies. Some of these remain even after the infection is cleared, as dormant 'memory' B cells.

The Gut Microbiome and the Immune System

Around 70-80% of immune cells are located in the gut, highlighting the interaction between the gut microbiota, the gut epithelium, and the immune system[3].

From infancy, the gut microbiota plays a key role in the development and regulation of the innate and adaptive immune systems, by producing metabolites such as short chain fatty acids, which support the differentiation and activation of T helper cells and other immune cells. This in turn also helps to regulate systemic inflammatory responses[3-5].

The gut microbiota also forms part of the barrier mechanisms of the local immune system, which can inhibit pathogens by[3,9]:

- Competing for substrates and adhesion sites
- Helping to maintain the integrity of the gut epithelial lining
- Producing metabolites to support the production of antimicrobial substances

As such, gut dysbiosis can impair the immune response to pathogens outside the gut, increasing the risk of and severity of extra-gastrointestinal infections caused by bacteria or viruses. The link between the gut (including its microbiota) and the lung, for example, has been termed the gut-lung axis[3].

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Probiotics in Immune Health

Research has demonstrated that the use of specific probiotics can reduce the incidence and improve the clinical outcomes of respiratory infections[3,6]. These effects are strain-specific[10].

The Immunological Effects of the *Bifidobacterium longum* PB-VIR™ Strain[7]

Preclinical research comparing intranasal administration of *Bifidobacterium longum* **PB-VIR**™ (at 1 x 10^9 colony forming units, CFU) to a control (saline) demonstrated significant benefits in a murine model of lethal influenza infection including[7]:

- Significantly improved survival rates (p=0.02)

	PB-VIR™	Control
% of subjects that survived	60%	0%

- Significantly reduced viral loads (p<0.01)
- Significantly lower levels of interferons (IFNα, IFNβ) (p<0.05) that stimulate proinflammatory cytokines (IL-6, IFNɣ), and which are associated with lung damage due to hyperinflammation in respiratory viral infection
- Significantly lower levels of albumin (p<0.001), a marker of lung injury

Overview of Research Methods[7]

In the pre-clinical trial with **PB-VIR**™, mice with viral influenza were randomly allocated to receive intranasal administration of either *Bifidobacterium longum* **PB-VIR**™ at 1 x 10^9 CFU, another *Bifidobacterium longum* strain (**35624**®) at 1 x 10^9 CFU, an isolated cell wall of the **35624**® strain, or a control (saline). Outcome measures included survival, viral load, cytokine and chemokine levels, and markers of lung injury. The trial was conducted in line with the ethical guidelines for the care, welfare and treatment of animals.

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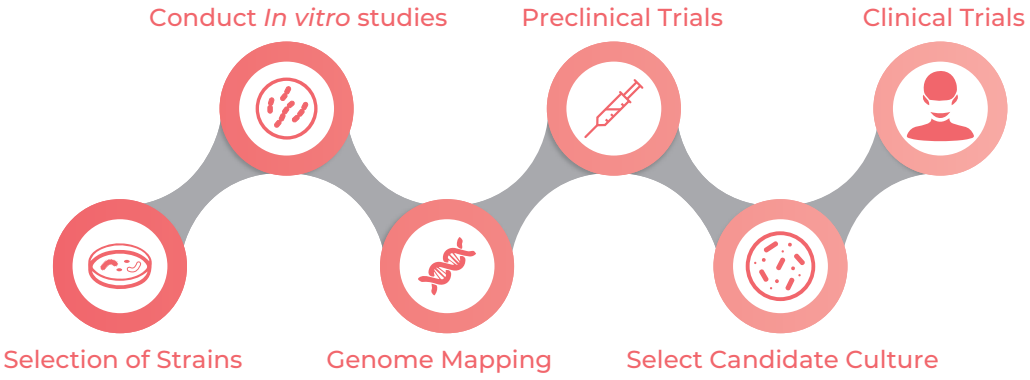
The Precision Approach to Probiotic Development

For over twenty years, PrecisionBiotics has discovered and developed unique probiotic strains in partnership with scientists and clinical experts from a world-leading centre of research into the microbiome and gut-brain axis - the APC Microbiome Institute, University College Cork, Ireland. This follows a robust process to develop targeted probiotics:



The result is safe, effective, evidence-based probiotic supplements with targeted strains selected for their specific action in the specific condition.

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