LACTOBACILLUS RHAMNOSUS

ROSELL-11

The *Lactobacillus* genus currently consists of over 125 species and encompasses a wide variety of organisms. These organisms are strictly fermentative, aerotolerant or anaerobic and have complex nutritional requirements.

STRAIN PROPERTIES

1. IDENTIFICATION

Lactobacillus rhamnosus is a natural component of the intestinal, vaginal and oral microflora[1]. It is the most studied species in the probiotic world, and most of the health benefits of probiotics have been demonstrated with this species.
L. rhamnosus Rosell-11 is from dairy origin and has been selected for its prolific and probiotic qualities.

Strain Identification

Name: *Lactobacillus rhamnosus* Rosell-11
Origin: Dairy
Molecules produced: L(+) Lactic acid, Folate and Exopolysaccharides (*Lactobacillus rhamnosus* Rosell-11 can produce heteropolysaccharides when grown on basal minimum medium supplemented with glucose or lactose[2]).
Strain deposit: I-1720, CNCM *(Collection Nationale de Cultures de Microorganismes),* Institut Pasteur, France.
Cell morphology: Rods, non-sporulating, non-motile, gram-positive, homofermentative, facultative anaerobic; isolated or tend to form short to medium chains. Grows well in commercially available media for lactic acid bacteria (MRS, Mann Rogosa and Sharp) at 37°C (98°F) and forms small white colonies.

Phenotypic Identification

Carbohydrate fermentation pattern: API 50 CHL
Biochemical characterization: API Zym

Genotypic Identification

16S rDNA sequence confirms the species designation and the specific identity of our strain[3]. The complete genome of *Lactobacillus rhamnosus* Rosell-11 has been sequenced and annotated and deposited in GenBank under accession number AGKC00000000.1[4].

2. SAFETY

- In the QPS (Qualified Presumption of Safety) list published by the EFSA (European Food Safety Authority) (EFSA 2013).
- In the monograph for Live Microorganisms (probiotics) issued by Health Canada – Natural Health Products Directorate (NHPD) (NHPD 2014).

- In the Australian TGA (Therapeutic Goods Administration) list of “Substances that may be used in listed medicines in Australia” (TGA 2011).
- In the International Dairy Federation (IDF) and European Food and Feed Cultures Association (EFFCA) list of microorganisms (Bourdichon *et al.* 2012).
- Available Lallemand safety files in Common Technical Document format.

Antibiotic resistance

Screening for Minimal Inhibitory Concentration (MIC) has been completed with the recommended methods[5]. Microbiological breakpoints were based on the “Guidance on the assessment of bacterial susceptibility to antimicrobials of human and veterinary importance” by the EFSA Panel on Additives and Products or Substances used in Animal Feed (2012).
In addition, Lallemand Health Solutions has also customized a specific microarray for an optimal screening. This microarray is regularly updated, and more than 350 genes known to be associated with resistance to antibiotics are currently included.
Based on the current testing methods, *L. rhamnosus* Rosell-11 doesn’t possess any antibiotic resistance known to be transferable.

3. TECHNICAL FEATURES

Our team of fermentation specialists optimizes growth parameters, cryo-protection conditions and environmental controls to offer optimal probiotic survival.

- Rosell-11 is available as “non-dairy strain”.
- Rosell-11 is offered as standardized strain at 150 billion CFU/g.
- Rosell-11 is protected by Bio-Support™ technology and available with Probiocap® technology.
- Rosell-11 can be produced as an Active Pharmaceutical Ingredient (API).

STRAIN DOCUMENTATION

1. GASTROINTESTINAL SURVIVAL

Resistance to gastric acidity and bile

Probiotics should remain alive, after passing through the stomach and the upper gastrointestinal (GI) tract, until they reach their target site of action - the lower small intestine.

In acidic conditions, *L. rhamnosus* Rosell-11 shows a survival rate of 70% (pH 4) and 72% (pH 3) after 2 hours[3].

A dynamic model of the human upper GI tract, the *In Vitro* Digestive System (IViDiS) model, was used to examine the survival of probiotic strains. *L. rhamnosus* Rosell-11, delivered in a capsule form, remains stable under normal stomach and duodenal conditions[6].

Survival in faecal samples after transit

A trial done on healthy individuals who received a dietary supplement containing *L. rhamnosus* Rosell-11 demonstrates survival of the strain through the human intestinal tract[7].

2. STUDIES

GASTROINTESTINAL HEALTH

Adhesion capacity:

- *L. rhamnosus* Rosell-11 is able to adhere to intestinal epithelial cell lines (HT-29, T84) which may be important for competition with pathogens, stimulation of mucus production and the modulation of the host immune system (Fig.3)[8, 9].

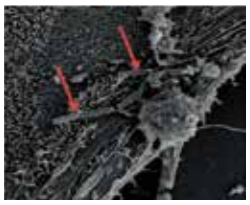

Figure 3: Adhesion of Rosell-11 to T84 epithelial cells. Courtesy of Kathene Johnson-Henry, Hospital for Sick Children, Toronto, Canada.

Barrier maintenance:

- *Lactobacillus rhamnosus* Rosell-11 can participate in the epithelial defense against pathogens by stimulating the production of mucin by epithelial cells (Fig. 4)[10]. *Lactobacillus rhamnosus* Rosell-11 is also able to produce exopolysaccharides *in vitro*[2, 11]. Exopolysaccharides contribute to biofilm formation, and reinforce the competition against pathogens for adhesion to the epithelium.
- *In vitro, L. rhamnosus* Rosell-11 stimulates the proliferation of intestinal epithelial cells (Fig. 5), reinforcing the physical barrier that separates pathogens in the gut from the body's circulatory system[8].

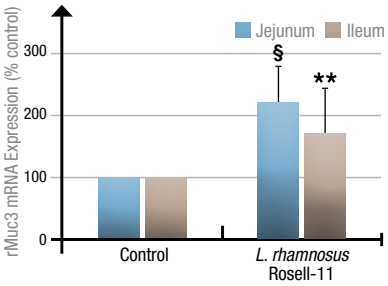

*Figure 4: Regional intestinal mucin mRNA expression in rats after oral ingestion of live probiotic microbes; **p≤0.01, §p≤0.0001.*

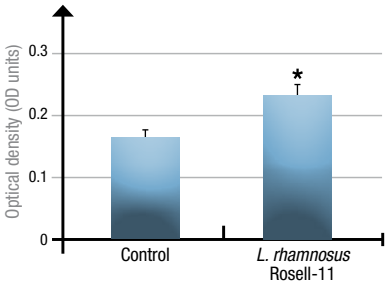

Figure 5: Activation and proliferation of the human intestinal epithelial cell line HT-29 after stimulation by L. rhamnosus Rosell-11.

Inhibition of intestinal pathogens growth and adhesion:

- *Lactobacillus rhamnosus* Rosell-11 has the ability to adhere to host epithelial cells and reduce the binding of both *E. coli* O157:H7 and E. coli O127:H6 that cause protracted diarrhea in infants and hemorrhagic colitis to host epithelial cells in a concentration-dependent manner *in vitro*[9].
- During an *in vitro* study, incubation of *Citrobacter rodentium* with *L. rhamnosus* Rosell-11 and its culture supernatant inhibited *Citrobacter rodentium* growth in a time-dependent manner[12]. *Citrobacter rodentium,* a close relative of *E. coli,* is used as a model to study the pathogenic mechanisms of enteropathogenic and enterohaemorrhagic *E. coli.*
- An *in vitro* study has shown that *L. rhamnosus* Rosell-11 attenuates *Campylobacter jejuni* virulence properties (a common bacterial causes of gastroenteritis)[13].
- In an *in vitro* screening, *L. rhamnosus* Rosell-11 has shown an antimicrobial activity against enteric pathogens such as *Escherichia coli, E. coli* ETEC, *Salmonella typhimurium, Staphylococcus aureus, Staphylococcus aureus SARM, Cronobacter sakazakii, Clostridium difficile, Enterococcus faecium VRE, Bacillus cereus, Listeria monocytogenes and Klebsiella pneumoniae*[3].

- In combination with *Lactobacillus helveticus* Rosell-52, the effect of *L. rhamnosus* Rosell-11 has also been evaluated in animal studies. The infectious models have focused on three pathogens: *Citrobacter rodentium* as a rodent model for enterohemorrhagic *E. coli* (EHEC) such as strain O157:H7[14]; *Helicobacter pylori* models of gastric ulceration[15, 16, 17] ; and *Candida albicans* infections following gastric ulceration or ulcerative colitis[18, 19]. Overall the various pathogen challenge models show that the probiotic blend acts to reduce the pathogen load and to modulate the pro-inflammatory responses.

In a review performed on a combination of *L. rhamnosus* Rosell-11 with *L. helveticus* Rosell-52 (Lacidofil®), it was shown that the probiotic blend could have a beneficial effect on antibiotic-associated diarrhea (AAD) and acute gastroenteritis, irritable bowel syndrome (IBS), *Helicobacter pylori* eradication and lactose intolerance[20].

ANTIBIOTIC-ASSOCIATED DIARRHEA (AAD): Several randomized trials conducted on the blend of *L. rhamnosus* Rosell-11 and *L. helveticus* Rosell-52 have demonstrated its efficacy to prevent antibiotic-associated diarrheas when used during antibiotherapy, especially in children who are more sensitive to ADD[21, 22]. In a study performed on 75 children, the probiotic combination given along with an antibiotic treatment resulted in less days with diarrhea when compared with antibiotic treatment alone (Fig.6)[21].

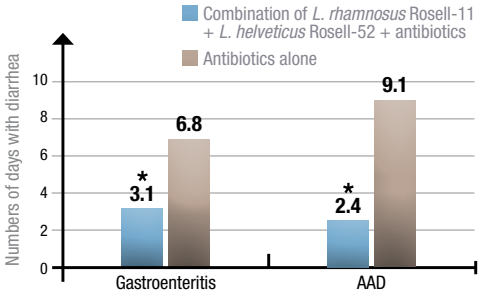

*Figure 6: Reduction of AAD and Gastroenteritis in children. *: p<0.01*

IRRITABLE BOWEL SYNDROME (IBS): An open study (50 patients) has shown that the administration of *L. rhamnosus* Rosell-11 and *L. helveticus* Rosell-52 improved clinical symptoms in IBS patients with longstanding symptoms (Fig 7)[23].

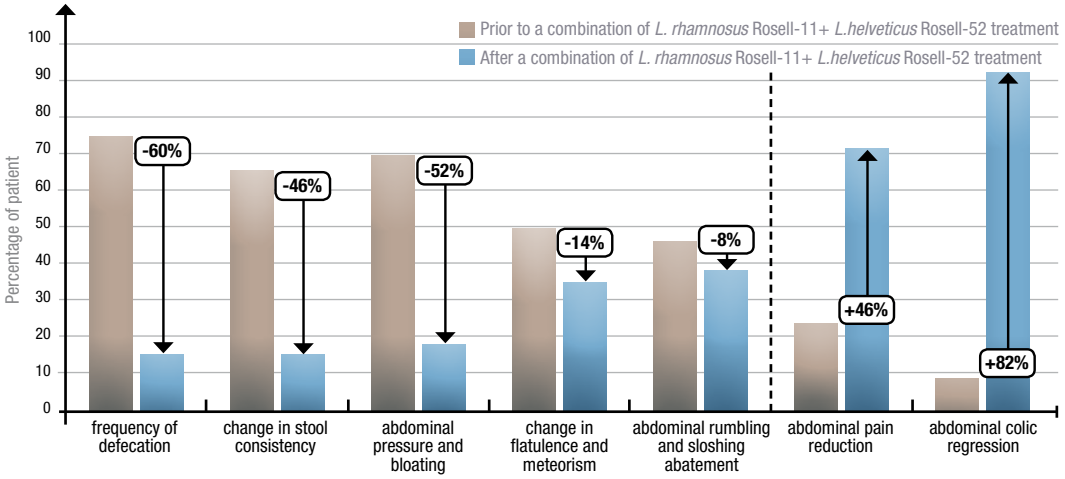

Figure 7: Reduction of complaints and symptoms associated with IBS

***HELICOBACTER PYLORI* ERADICATION:** Two clinical trials (397 patients in total) have demonstrated that the addition of *L. rhamnosus* Rosell-11 (one of the two strains of Lacidofil®) to usual eradication therapy improves eradication efficacy of *H. pylori* and reduces complications after antibiotic therapy[24, 25].

LACTOSE INTOLERANCE: Tested in patients suffering from lactose intolerance, the combination *L. rhamnosus* Rosell-11 and *L. helveticus* Rosell-52 has been shown to improve the quality of life of lactose intolerant patients by reducing abdominal pain, number of stools, and improving lactose adsorption[26].

IMMUNE HEALTH

Modulation of inflammatory response:

- *L. rhamnosus* Rosell-11 strongly downregulates the production of cytokines and chemokines associated with cells mediated immunity (TGF-ß, TNF-α) (Fig.8), and also IL-8 when it is produced by intestinal and gastric epithelial cells stimulated by pathogens or inflammation *in vitro.* Moreover, it prevents over expression of RANTES which is apparent in inflammatory states[8, 27].

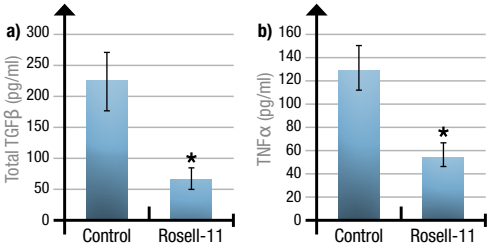

Figure 8: Downregulation of TGF-β a), TNF-α b), production by HT-29 stimulated by Rosell-11.

Cytokine levels:

- *L. rhamnosus* Rosell-11 treatment on intestinal mucosa significantly decreases Th-2 (IL-4, IL-5, IL-6, IL-10) and Th-1 (TNF-α, IFN-γ) cytokine levels in *Nippostrongylus brasiliensis* infected rats. This study suggests that *Lactobacillus rhamnosus* Rosell-11 treatment could exert a positive modulatory effect on the immune parameters of Th2- or Th1-oriented physiopathological conditions[28].

WOMEN'S HEALTH

Adhesion capacity: *L. rhamnosus* Rosell-11 is able to bind moderately to vaginal cell lines (HMVII)[3].

Protection against pathogen adhesion:

- *In vitro* studies have shown the ability of *L. rhamnosus* Rosell-11 to contribute to the formation of a biofilm which may protect the vaginal epithelium from pathogen adhesion[2, 10, 11].
- *L. rhamnosus* Rosell-11 has shown an *in vitro* antimicrobial activity against *Atopobium vaginæ* which is known to be a genital pathogen as it is associated with bacterial vaginosis[3].

Decreased incidence of vaginal dysbiosis:

- A study was carried out on 103 pregnant women supplemented with *L. rhamnosus* Rosell-11 and *L. helveticus* Rosell-52 before and after caesarean section, along with an antibiotic treatment. It was shown a decrease in gastrointestinal discomfort vs. antibiotic treatment, a reduced opportunistic microflora (esp. *Candida*) and a decreased colonization of amniotic fluid and gastro-intestinal tract of the newborns (fig.9)[29].

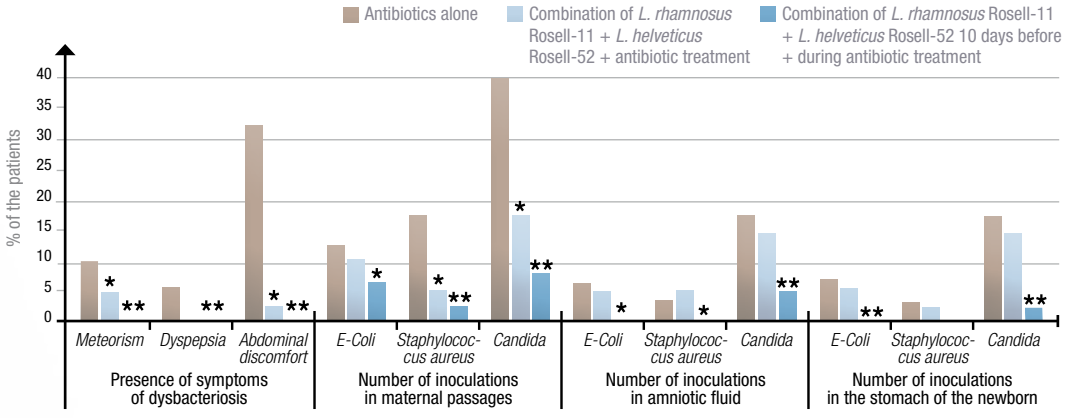

*Figure 9: Evaluation of dysbacteriosis symptoms and presence of E.coli, Staphylococcus aureus and Candida. *Significant difference with placebo group p<0, 05. **Significant difference with a combination of L. rhamnosus R11 + L. helveticus R52 group as a treatment and with placebo group. p<0,05.*

- A randomised controlled study performed on 96 women receiving prophylactic antibiotic therapy after caesarean section delivery has shown that 89.3% of patients receiving a supplementation of *L. rhamnosus* Rosell-11 (in combination with *L. helveticus* Rosell-52) with antibiotic therapy were considered eubiotic (i.e. having a balanced microbiome) following therapy, while none of the patients of the control group were eubiotic. Antibiotic-associated diarrhea did not develop in any of the patients receiving the probiotic blend, however it was recorded in 10% of patients from the control group ($p<0.05$)[30].

Prevention of bacterial vaginosis recurrence: Three clinical studies have been conducted with a probiotic blend containing *Lactobacillus rhamnosus* Rosell-11 and Yogurt Culture involving a total of 170 patients.

- Doucha and Citterbart performed a study on 50 patients with vaginal infections. It was concluded that the probiotic combination may have a beneficial impact on the treatment of bacterial vaginosis[31].
- Hatala and Pokorny involved successively 40 and 80 patients suffering from vaginal infections, and showed an improvement in the relapse in vaginal infections in women 2-4 months after treatment (with or without conventional treatment)[32, 33].

As a result of its ability to restore the vaginal flora to a healthy state, the addition of *Lactobacillus rhamnosus* Rosell-11 with Yogurt Culture to the conventional treatment might therefore be beneficial in reducing the recurrence rate of vaginal infections.

ATOPIC DERMATITIS

IMPROVEMENT OF ATOPIC DERMATITIS IN CHILDREN:

- A clinical trial, conducted on 58 children, has shown that a combination of *L. rhamnosus* Rosell-11 and *L. helveticus* Rosell-52 is able to significantly reduce clinical signs of atopic dermatitis in children (measured with SCORAD, SCORing Atopic Dermatitis - clinical tool), increasing their quality of life (fig.10)[34].
- **Immunomodulatory properties:** In the same study, a significant increase of the antibody IgG4 was observed after *L. rhamnosus* Rosell-11 and *L. helveticus* Rosell-52 treatment, signifying a better tolerance to cow milk. Moreover, it has been demonstrated a decreased activation of T-cells, indicating a reduced immune response[34].

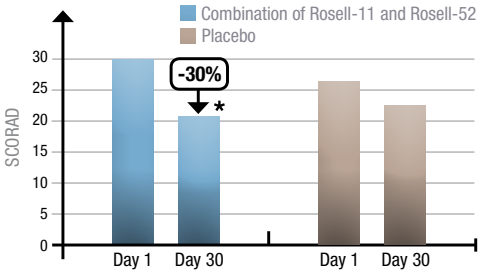

*Figure 10: Improvement of the SCORAD with a combination of Rosell-11 and Rosell-52 and the standard treatment (Trixera®). *: $p<0.01$.*

ORAL HEALTH

- **Antimicrobial activity:** *L. rhamnosus* Rosell-11 has shown an *in vitro* antimicrobial activity against *Streptococcus mutans,* an oral pathogen which is the main bacterial contributor to tooth decay[3].
- **Modulation of the inflammatory response:** *L. rhamnosus* Rosell-11 strongly downregulates the production of cytokines and interleukins associated with inflammation, which may be beneficial in case of gingivitis[8, 27].

Three clinical studies have evaluated the effect of a probiotic combination containing *L. rhamnosus* Rosell-11 on **dental plaque** and **gingivitis** as well as on the reduction of ***Streptococcus mutans:***

- In a study performed on 150 children (7-14 years), the probiotic blend was given following swish and swallow method. After 14 days of probiotic ingestion, a statistically significant reduction ($p<0.01$) in salivary ***S. mutans*** counts was recorded[35].
- A further study involved 90 school children aged between 13 and 15 years during a 2-month period. *L. rhamnosus* Rosell-11 in combination with additional probiotic strains was given as a mouth rinse and compared to chlorhexidine. After 14 days of intervention and also after 3 weeks of discontinuation of intervention, the probiotic mouthrinse as well as chlorhexidine were significantly effective for inhibition of **dental plaque** ; with a trend to an additional benefit of the probiotic combination[36].
- The probiotic blend containing *L. rhamnosus* Rosell-11 has also been studied in 90 schoolchildren aged 15-16 years to investigate its efficacy in reducing plaque and gingivitis. The probotic mouth rinse showed significant reduction in **plaque score** and **gingival index** after 14 days ($p<0.05$)[37].

PHYSICAL AND EMOTIONAL EQUILIBRIUM

Today, it appears that the microbiota plays a role in the bidirectional dialogue between the brain and the gut. Thus, probiotics capable to interact with the digestive microbiota can have an effect on psychological troubles such as stress and anxiety.

- Using post-infections models[17, 38] and psychological stress models[39, 40], studies demonstrate that *L. rhamnosus* Rosell-11 in combination with *L. helveticus* Rosell-52 reduced stress-induced responses, such as increased gut permeability, inflammatory and serum corticosterone levels. The impact of the probiotic blend seems to be mediated through the HPA (hypothalamic-pituitary-adrenal)-axis.
- The most recent findings performed on this probiotic combination implicate an important role for the adaptive immune system in aiding the normal development of the gut-brain-microbiota axis, by mediating signaling between the gut and the central nervous system[41].

ADDITIONAL AVAILABLE STUDIES

Liver alcoholic disease: The effects of *Lactobacillus rhamnosus* Rosell-11 (in combination with *Lactobacillus helveticus* Rosell-52) on the gut-liver axis have been studied in mouse models of alcoholic liver disease (ALD). Important factors in the pathogenesis of ALD such as toll-like receptor-4 (TLR-4) and IL-1β levels were decreased among the probiotics groups. Even if no differences were observed with regard to liver function, mean body weight of the alcohol group was significantly lower than that of the probiotics group ($p<0,05$)[42].

Autism: Nowadays, antifungal drug therapy may be considered as a promising therapeutic method for the treatment of autism. D-arabinitol (DA) is a metabolite of most pathogenic *Candida* species and its extraction in urine is elevated in autistic patients. The level of DA and the ratio of D-/L-arabinitol (DA/LA) in the urine of children with autism were investigated in a pilot study following a supplementation with *Lactobacillus rhamnosus* Rosell-11. The probiotic intake lead to a significant decrease in DA and DA/LA and to a significant improvement in ability of concentration and carrying out orders[43].

Quality of life in colorectal cancer patients: The probiotic combination *Lactobacillus rhamnosus* Rosell-11 and *Lactobacillus helveticus* Rosell-52 was given for 12 weeks to colorectal cancer survivors. The administration of probiotics showed significant and positive differences in changes of the proportion of patients with bowel symptoms, functional well-being scores and cancer-related quality of life scores compared to the placebo group[44].

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