LP-LDL®: Cholesterol & hypertension reduction

Next generation pre, pro, and synbiotics

Prevention  Management  Treatment

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Chief Executive Officer
Company Overview

- Founded in March 2012, LSE listing 2014
- Developing products and ingredients to modify the human microbiome to prevent and manage human disease

- Technology platforms
  - **OptiScreen®**: High throughput screening platform to allow the identification of probiotics with **specific health benefits**
    - Cholesterol/blood pressure reducing supplement: to reduce cardiovascular risk
  - **OptiBiotix®**: High throughput technology platform(s) which generates novel sugars which can **act as species, and genus specific prebiotics**

- Partnership model: scientific and commercial partners across all platforms
Current probiotics

- Traditional focus on general health benefit (dairy origins)
- Mechanism of action often not understood
- Growing trend towards products with a specific health benefit
  - As move from general to health benefit increased need to identify specific biomarkers and mechanism of action which evidence a health benefit
- Lack of scientific rationale in probiotic selection
  - Use of multistrain preparations common
  - Market view ‘more means better’ – more strains and greater numbers
- Synbiotics: lack of information on ability of the prebiotic to support probiotic activity and enhance survival (definition)
- Few good human studies evidencing health benefits of pro, pre, or synbiotic
  - Poor study design: Lack of appropriate controls, Statistical power
### Systematic approach to identifying probiotics with a health benefit

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<tr>
<th><strong>Biomarker</strong></th>
<th>Target biomarker identification: <strong>Cholesterol (TC, LDL, HDL)</strong></th>
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<td><strong>Mechanism</strong></td>
<td>Target mechanism which impacts on biomarker: <strong>Bile Salt Hydrolysis (BSH)</strong></td>
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| **Screening** | - High throughput screening for BSH activity and bile resistance (~4000 strains)  
- 353 *Lactobacillus* strains |
| **Selection** | - 45 lactobacilli selected for quantitative determination of BSH activity and bile tolerance  
- 24 strains with the highest BSH activities selected to quantify cholesterol assimilation capacity *in vitro*. 3 strains showed *in vitro* cholesterol reductions of 72-81% |
| **Pilot scale** | - Final selection (high manufacturability, gut survival): **Lactobacillus plantarum LP-LDL®**  
- Bacterial growth optimisation and pilot scale production |
| **Human study** | - Determination of the cholesterol lowering efficacy of *L. plantarum* LP-LDL®  
- **Human study** (49 subject, 12 week randomized, dbl-blind, placebo-controlled, parallel-group trial, tested at 0, 6, and 12 weeks) |
Human Study LP-LDL: Cholesterol in the active group compared to placebo

Data analysed at 0-6 weeks, 6-12 weeks and 0-12 weeks for all study participants and subgroups based on starting baseline total cholesterol, gender, and age

**Total Cholesterol (TC):**
- Consistent decrease in TC in active group compared to placebo
- A reduction in TC ($P=0.04$) from 0 to 6 weeks in the active group, which was not evident in the placebo group
- Reductions in TC of 4.2% in TC <5mmol/l and TC= 5-5.9 mmol/l and 36.7% ($P=0.045$) in the baseline TC≥6.0mmol/l group from 0 -12 weeks

**LDL Cholesterol (LDL):**
- Consistent reduction in LDL of 7.2% ($p=0.15$) in the active group when compared to the placebo
- A reduction in LDL ($P =0.01$) from 0 to 6 weeks in the active group, which was not evident in the placebo group
- Reduction in LDL of 13.9% ($p=0.03$) between 0 to 12 weeks in TC <5mmol/l group and 26.2% ($p=0.07$) in TC≥6.0mmol/l group
HDL Cholesterol (HDL):
- Consistent increase in HDL in active group compared to placebo (4.5%)
- Increase in HDL of 6.5% (p=0.06) in active group between 6 weeks and 12 weeks
- Increase in HDL of 14.7% (p=0.03) in 60+ group

Triglycerides (TAG):
- Reduction in TAG of 53.9% (p=0.002) between 0-12 weeks in the 60+ group not seen in the placebo

Systolic Blood Pressure (SBP):
- Significantly lower SBP of 6mmHg (5.1%, P=0.003) in the active group compared to placebo between 6-12 weeks - reduction consistent across testing periods

‘The ability to reduce both LDL and blood pressure has a multiplicative effect in reducing cardiovascular risk’ (European Society of Cardiology, August 2016)
**OptiScreen®**

A proprietary high throughput screening & optimisation technology platform designed to identify microbes with metabolic pathways with can interact with human physiological processes and bring health benefits

Probiotic with specific health benefit (e.g. cholesterol reduction)

**OptiBiotix®**

A proprietary technology which generates novel prebiotics & screens them for their ability to modulate target species within the human microbiome.

Prebiotic which selectively enhances the growth of specific strains, species, or genera of bacteria

**OptiBiotic®**

Combination of a targeted probiotic and prebiotic in which the prebiotic selectively enhances the *in vivo* growth of the probiotic and accentuates its functional properties and health benefits

Potential for designer prebiotics specific for a microbial genus, species, or strain associated with a health benefit and the ability to mix and match oligosaccharides to shape the human microbiome.
L. plantarum GOS enhances cholesterol reduction properties of LP-LDL

Faecal batch culture

~3X increase in cholesterol reduction

% cholesterol removal

0 5 10 15 20 25 30 35

Faeces Lp Faeces Lp PGOS PGOS+LP BGOS BGOS+LP Faeces Lp PGOS PGOS+LP BGOS BGOS+LP

0 8 24

0 5 10 15 20 25 30 35

OptBiotix

Faeces Lp Faeces Lp PGOS PGOS+LP BGOS BGOS+LP Faeces Lp PGOS PGOS+LP BGOS BGOS+LP

OptBiotix

Faeces Lp Faeces Lp PGOS PGOS+LP BGOS BGOS+LP Faeces Lp PGOS PGOS+LP BGOS BGOS+LP

OptBiotix
Conclusions

- A systematic approach to the identification of probiotics with **specific health benefits**
  - Scientific and mechanistic rational to probiotic strain selection
  - Reduces risk of poor outcomes in costly human studies

- **LP-LDL®** is safe and well tolerated with in vitro, faecal batch cultures, and human studies indicating a positive impact on lipid profiles and blood pressure
  - Publication submitted to Br Journal of Nutrition
  - Further studies in other countries: larger sample size, more regular testing, targeting a higher cholesterol population

- Potential to enhance growth, bile salt hydrolase activity, and cholesterol reduction of LP-LDL by combining with a targeted prebiotic (LP GOS)
  - Potential to improve efficacy of existing probiotic strains

- Next generation: A combination of a **targeted probiotic and prebiotic** which selectively enhances the *in vivo* growth of the probiotic and accentuates its functional properties and health benefits