LE&RN Online Symposium:
Clinical Progress With Lymfactin©: Could Gene Therapy Cure Lymphedema?

Presented by Pekka Simula, CEO, Herantis Pharma Plc
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Lymphatic Education & Research Network
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Herantis Pharma Plc (HRTIS:FH)

- Herantis is a public drug development company advancing two highly-differentiated clinical assets for unique market opportunities
  - Lymfactin® gene therapy for secondary lymphedema
  - CDNF therapy for Parkinson’s Disease, with potential in treating other neurodegenerative diseases
- Both programs originate from scientific discoveries made by world-leading researchers at the University of Helsinki
- Clinical success will be based on company’s deep development expertise

We develop regenerative medicine based on cutting edge science, for patients in need.
Lymphedema: Significant and growing unmet need

“The psychosocial impact of lymphedema has been described to be as distressing as the initial diagnosis of Breast Cancer.”
– Shih et al., J Clin Oncol 2009
Secondary lymphedema
Disease, Market and Awareness

- **Lymphedema (LE)** is a chronic, progressive swelling of tissues caused by the dysfunction of the lymphatic vasculature
  - Lymphatic system is unable to return interstitial fluid to bloodstream
  - Estimated **140 million people** worldwide have LE; there is no cure
  - Estimated treatment cost **$10,000 per year** in the USA

- **Secondary lymphedema** is caused by e.g. disease, trauma, or surgery
  - **Disabling and disfiguring disease**, which severely affects quality of life

- **Herantis collaborates with international LE advocacy LE&RN** (Lymphatic Education & Research Network)

- **Lymphedema awareness is increasing:**
  - Hollywood superstar, lymphedema advocate **Kathy Bates is a strong and visible LE spokesperson**
Lymfactin® gene therapy:
Scientific background
What creates our lymphatic vessels?

• The formation of lymphatic vessels is called **lymphangiogenesis**

• Lymphangiogenesis is promoted by a protein called **VEGF-C**: A natural growth factor, which we all have

• Thus the damages of the lymphatic system could be repaired by increasing the VEGF-C levels. Unfortunately, just injecting the VEGF-C protein would not maintain high enough VEGF-C levels for a long enough time in the damaged area
Lymfactin® gene therapy aims to cure the underlying cause of secondary lymphedema

- Lymfactin® is a gene transfer vector carrying the human VEGF-C gene
- Lymfactin® instructs the patient’s own cells to produce VEGF-C in the damaged area where Lymfactin® is administered
- Single-dose treatment with local and transient VEGF-C expression for about two weeks
Clear dose response in lymph vessel sprouting following Lymfactin® administration in mice ear skin

Model:
- Mice were injected with $2 \times 10^6$ to $2 \times 10^9$ viral particles of Lymfactin® into the ear skin.
- The same concentration of a control vector coding for LacZ gene was injected into the contralateral side.
- LYVE1 staining 14 days after virus administration reflecting sprouting of lymphatic vessels.

Unpublished data
Perinodally administered Lymfactin® efficiently improves lymphatic vessel regeneration and lymph node function in a porcine model

Native lymphangiogram taken 2 months after the lymph node transfer:

<table>
<thead>
<tr>
<th></th>
<th>Intranodal AdVEGF-C</th>
<th>Intranodal AdLacZ</th>
<th>Perinodal AdVEGF-C</th>
<th>Perinodal AdLacZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no of lymphatic vessels</td>
<td>12.5±4.8</td>
<td>5.9±1.5</td>
<td>13.7±4.0</td>
<td>5.8±5.5</td>
</tr>
<tr>
<td>Lymphatic vessels connected</td>
<td>9.1±6.7</td>
<td>1.0±1.7</td>
<td>9.9±4.9</td>
<td>2.8±3.4</td>
</tr>
<tr>
<td>Size of lymph node (cm³)</td>
<td>29.9±7.4</td>
<td>12.0±5.9</td>
<td>27.7±12.4</td>
<td>11.5±4.7</td>
</tr>
</tbody>
</table>

Model
- Porcine lymphedema model mimicking lymph node transfer in human lymphedema patients.
- Lymphatic vasculature was destroyed by excising all afferent lymphatic vessels and all efferent lymphatic vessels from 5 cm and 3 cm radius, respectively, surrounding the lymph node.
- Virus carrying either VEGF-C or LacZ gene was injected subcapsularly into the exposed lymph nodes.

Reference:
Strong science: from VEGF-C discovery to adenoviral VEGF-C gene therapy

**Vol 15, Issue 2, 15 Jan 1996; Joukov et al**
A novel vascular endothelial growth factor, VEGF-C, is a ligand for the Flt4 (VEGFR-3) and KDR /VEGF-2) receptor tyrosine kinases

**Vol 276, Issue 5317, 30 May 1997; Jeltsch et al**
Hyperplasia of lymphatic vessels in VEGF-C transgenic mice

**Vol 5, Issue 1, Jan 2004; Karkkainen et al**
Vascular endothelial growth factor C is required for sprouting of the first lymphatic vessels from embryonic veins

**Vol 18, Issue 14, Nov 2004; Saaristo et al**
Adenoviral VEGF-C and VEGF-C 156S restore drainage of lymphatic fluid across the incision wound
Academy professor Kari Alitalo is the inventor of Lymfactin®

• Director of Translational Cancer Biology Research program, University of Helsinki
  — National Center of Excellence

• Internationally leading expert in endothelial growth factors in cancer
  — More than 500 peer-reviewed scientific publications in biomedicine, cancer research, and cell and molecular biology
  — Receiver of numerous international science prizes including InBev-Baillet Latour International Health Prize, Louis Jeantet Prize for Medicine, Anders Jahre Prize, Dr. A.H.Heineken Prize
  — Foreign associated member of the National Academy of Sciences of the USA

• VEGF-C growth factor was discovered by Prof. Alitalo, member of Herantis’ advisory board
Development of Lymfactin® into a therapeutic available for LE patients
So what good will that science do in practice?

Lymfactin® is currently in formal clinical development. If it works as well in humans as it does in the disease models:

1. Functional lymphatic vessels formed
2. Lymph flow normalized
3. Swelling reduced
4. LE cured?
Drug development is slow and regulated

The development of a new drug to market usually takes **10-15 years**; most drug candidates never reach clinical stage.

- **1%?**
- **10%?**
- **60%**
- **50%**
- **30%**
- **Lymfactin® has reached Clinical Phase 2**
- **Clinical Phase 3**
- **Clinical Phase 2**
- **Clinical Phase 1**
- **Preclinical development**
- **Selecting and optimizing the right molecule**

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Lymfactin® in clinical development

• Development of new drugs is very slow: Patient safety is always the #1 priority, and therefore years of preclinical studies are required before clinical studies
  — This is already completed for Lymfactin®

• As the next step, clinical safety is assessed in a Phase 1 clinical study
  — This is already completed for Lymfactin®, in real LE patients

• Efficacy is assessed in Phase 2 clinical studies, usually in a well-defined patient population
  — We have today launched Phase 2 study AdeLE in patients with breast cancer associated LE
  — The patients are undergoing lymph node transfer surgery as LE treatment; in this study, a single dose of Lymfactin® is administered as adjunct to surgery
Lymfactin® interim Phase 1 results

• Positive interim Phase 1 data on Lymfactin® were announced by Herantis in April 2018, in patients with breast cancer associated secondary lymphedema (BCAL) in combination with lymph node transfer

• Based on data from 15 patients with BCAL: Lymfactin® is safe and well tolerate

• Promising quality-of-life changes observed; however those are uncontrolled data
Phase 2 study AdeLE launched in 1H/2018

- **AdeLE**: Adenoviral gene therapy for the treatment of LE
- Randomized, **placebo-controlled**, double-blinded Phase 2 clinical study in patients with BCAL
  - Total of 40 patients will be randomized 20+20
  - Patients will be recruited at 5 - 6 clinical sites in Finland and Sweden
  - Lymph node transplantation + Lymfactin® vs. Lymph node transplantation + placebo
- Single dose Lymfactin® is administered ex vivo in the transplant
- Efficacy will be assessed by several endpoints
  - QoL, volumetric measurements, lymphoscintigraphy, MRI, and LymphScanner™
- The study is expected to be fully recruited by end of 2019
- Unblinding and efficacy read-out will be available after 12-month follow-up

6/19/18
Key Opinion Leader (KOL) reflections on Lymfactin® as a novel LE therapy

• KOLs are enthusiastic about Lymfactin® being a novel pharmacologic treatment adjunct to surgery with potential to achieve durable efficacy
• Delivering VEGF-C with an adenovirus to durably treat underlying pathology is highly attractive
• BCAL as the most prevalent cancer-related secondary lymphedema is considered a relevant starting primary indication for Lymfactin®
• Quality of Life measures are considered very important in clinical development
Lymfactin® as standalone therapy, and in other lymphedemas?

• In addition to the ongoing Phase 2 study in BCAL, Herantis is considering another Phase 2: Lymfactin® as standalone therapy in any secondary LE
  – Possible design of the clinical study: Lymfactin® administration in patients with secondary LE, after removal of scar tissue
  – Scientific rationale: Based on published scientific data Lymfactin® triggers the growth of new lymphatic vessels across incision wounds
Summary on Lymfactin®
Lymflectin® aims at curing secondary lymphedema

• Lymflectin® is the world’s first and only clinical stage gene therapy that repairs damages of the lymphatic system
• Currently in Phase 2 clinical study AdeLE in Breast Cancer Associated LE (BCAL) in Europe; initial safety has already been established in a Phase 1 clinical study
• Lymflectin® is based on the internationally leading scientific research by professor Alitalo, foreign member of the US National Academy of Sciences
• More information:
  – Introductory video on Lymflectin®: https://youtu.be/pJ-m9k3G38Q
Thank you

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