HERANTIS PHARMA

PIPELINE PROGRAMME: LYMFACTIN® GENE THERAPY

Introduction:

Lymphedema is a progressive, chronic swelling disease caused by failure of the lymphatic vascular network to adequately drain interstitial fluid causing serious problems in everyday life. Predominantly it affects an arm or a leg, but may also affect face and neck, trunk or genitals. While primary lymphedema is a relatively rare genetic disorder, secondary lymphedema is common, affecting over 200 million people worldwide, and is caused by physical damage, infection, cancer or surgical removal of parts of the lymphatic network during cancer therapy. The disease is particularly common in breast cancer patients. Approximately 30% of breast cancer patients undergo surgical mastectomy, which frequently involves axillary lymph node removal; and up to 30% of these patients go on to develop breast cancer-related lymphedema (BCRL).

Herantis has developed Lymfactin®, a unique gene therapy for the treatment of breast cancer-related lymphedema (BCRL). The Lymfactin® gene therapy induces temporary local expression of human vascular endothelial growth factor C (VEGF-C), an endogenous protein that is naturally expressed in lymph nodes and is responsible for driving the growth and assembly of the network of lymphatic vessels. By stimulating the expression of VEGF-C, the lymphatic vasculature may be regenerated, thereby restoring the normal flow of interstitial fluid to the blood stream and reducing swelling.

The Science:

Secondary lymphedema can be caused by local injury to the lymphatic system, or as a consequence of surgery or radiotherapy. Where the normal flow of lymph is disrupted, local accumulation of interstitial fluid (ISF) occurs. This results in a chronic, progressive swelling that is often painful, deformative and debilitating, due to loss of mobility, and that can lead to severe infections. Over 150,000 cancer-related cases of secondary lymphedema are diagnosed annually across the USA and Europe.

Breast cancer treatment (e.g. mastectomy) frequently includes the surgical removal of axillary lymph nodes, which can lead to BCRL. Up to 30% of patients undergoing axillary node dissection present with disabling BCRL symptoms. Currently, there is no cure for this disease and no pharmaceutical treatment options for controlling symptoms. Complete decongestive therapy (CDT), comprising compression bandaging and exercise regimes, is the current gold standard in lymphedema treatment. In recent years, new surgical procedures have been developed that may offer some benefit to lymphedema patients. Vascularised Lymph Node Transfer (VLNT) is most commonly performed by a microvascular transfer of a functional lymph node tissue flap from the inguinal wall with re-implantation into the axillary region of the affected limb. Clinical results are somewhat variable, and success depends upon the spontaneous incorporation of the transplanted nodes into the lymphatic network.

Vascular endothelial growth factors (VEGF) are a sub-family of proteins that trigger vasculogenesis and angiogenesis, i.e. the development of blood and lymphatic vessels. VEGF receptors (VEGFR1-3) are transmembrane tyrosine kinases that are broadly expressed in most vascular endothelial cells. VEGF-C is essential for the formation of normal lymphatic vasculature and binds with high specificity to VEGFR3, see Figure 1.

Lymfactin® is a VEGF-C gene therapy with the potential to cure secondary lymphedema by driving regrowth and repair of lymphatic vasculature. Lymfactin® is a replication deficient adenoviral vector that transfers the gene into the cells for the synthesis of human VEGF-C.

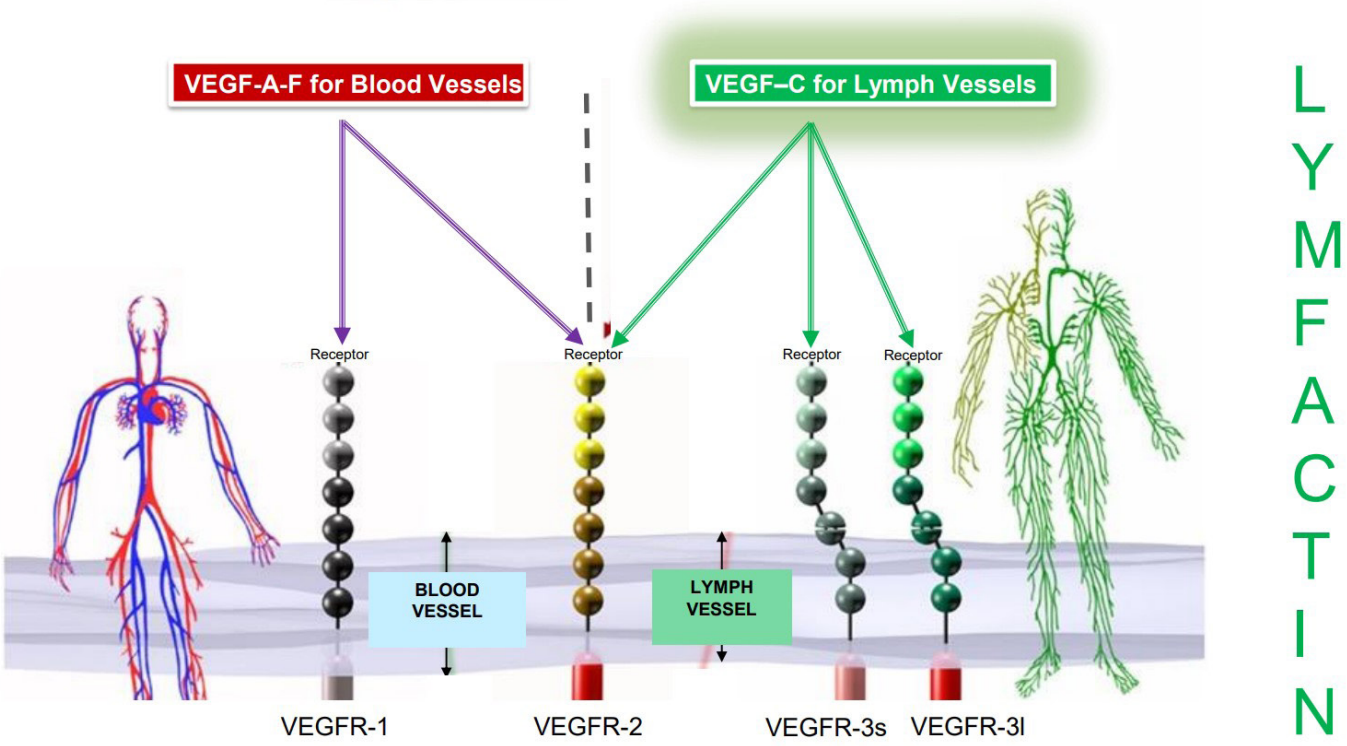


Fig 1: Vascular Endothelial Growth Factor sub-family – receptor and ligand binding

A single dose of locally administered Lymfactin® can drive VEGF-C expression for a period of around 2 weeks, which is sufficient to induce lymphangiogenesis and sprouting of new lymphatic capillaries, the first step in restoring the damaged lymphatic system to normal function. Adenovirus is able to transduce most human cell types and is a highly efficient vector for transgene delivery and expression. The adenovirus particle activates an innate immune response and is usually cleared from the body within a period of 2 weeks. The adenoviral vectors have excellent safety profiles and many thousands of patients have been successfully treated with adenoviral vector based drug candidates in clinical trials worldwide.

The Molecule:

Prof Kari Alitalo, director of Translational Cancer Biology at the University of Helsinki and member of Herantis' advisory board, discovered with his research group the therapeutic potential of VEGF-C for lymphedema. Their work demonstrated that continuous expression of VEGF-C in tissues surrounding a site of injury can stimulate the regrowth of lymphatic capillaries. Remarkably, continuous expression of VEGF-C for a period of just two weeks is sufficient to trigger clinically relevant lymphangiogenesis in preclinical models.

Lymfactin® comprises a serotype 5 adenovirus (Ad5). This has been established as the optimal expression vector for VEGF-C given its infection efficiency and high level of transgene expression. Expression of the VEGF-C transgene is usually evident within 24 hours of administration.

The Data:

Herantis has studied the efficacy of Lymfactin® in preclinical animal models. In a mouse ear-skin model, the growth of lymphatic vessels was accelerated in a dose-dependent fashion after a period of 14 days, following a single injection of Lymfactin®, see Figure 2.

Having established a proof of concept for stimulation of lymphangiogenesis, Herantis initiated further studies to determine the optimal injection site for the viral vector. In a porcine lymphedema model, Herantis investigated the relative efficiency of intranodal versus perinodal injection for Lymfactin®. Following the surgical removal of local lymphatic vessels, a single dose of an adenoviral vector, encoding either the VEGF-C or LacZ (negative control) transgene, was administered. A perinodal injection of VEGF-C produced the largest increase in lymphatic vessels and connections. See Figure 3.

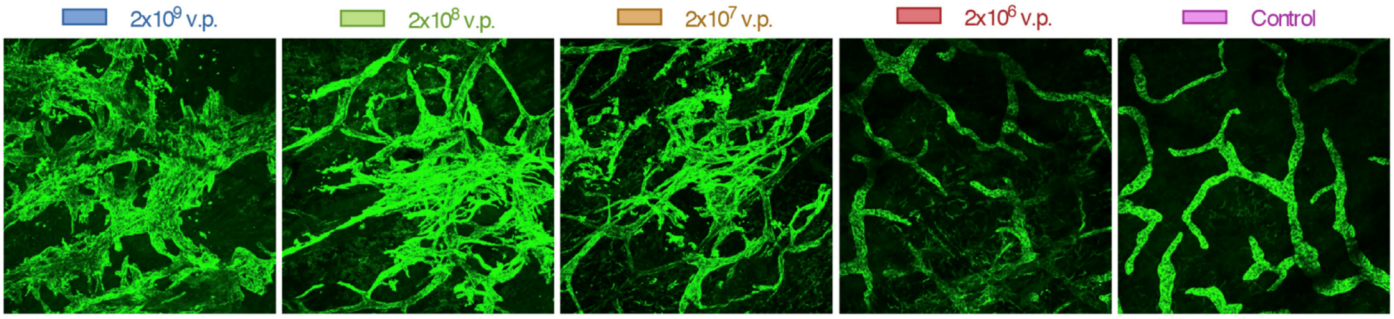
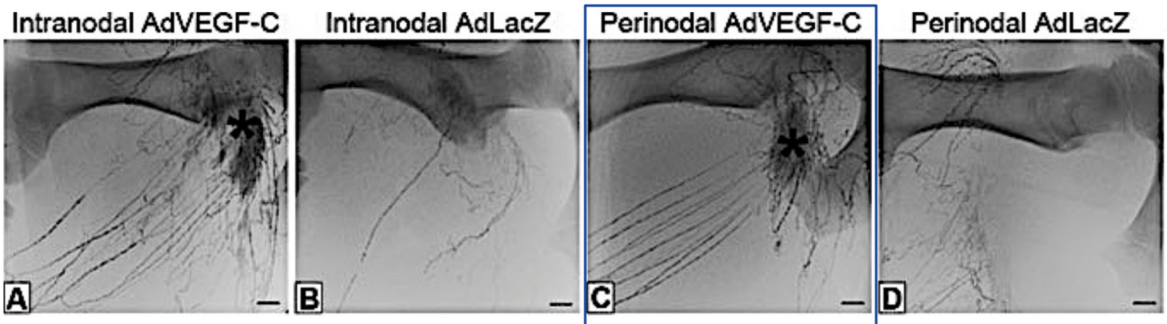


Fig 2: Dose-dependent growth of lymph vessels in mouse ear-skin model. LYVE-1 staining images taken 14 days after administration of $2x10^6$, $2x10^7$, $2x10^8$ and $2x10^9$ Lymfactin® viral particles.



Total no of lymphatic vessels	12.5±4.8	5.9±1.5	**13.7±4.0**	5.8±5.5
Lymphatic vessels connected	9.1±6.7	1.0±1.7	**9.9±4.9**	2.8±3.4
Size of lymph node (cm^3)	29.9±7.4	12.0±5.9	**27.7±12.4**	11.5±4.7

Fig 3: Extent of lymphangiogenesis after intranodal and perinodal injection of Lymfactin® and LacZ negative control in a porcine model of lymphedema. Lymphangiograms taken 2 months after administration showed perionodal administration significantly improved lymphatic vessel regeneration and lymph node function. Source: Honkonen et al, Ann. Surg. 257(5): 961-7, 2013

In ongoing clinical investigations, Herantis is pursuing BCRL as a primary indication for Lymfactin®, since this is the most prevalent cancer-related secondary lymphedema and represents the greatest unmet need. In the Phase I clinical study, the safety and tolerability of Lymfactin® adenoviral vector was successfully demonstrated in combination with surgical vascularised lymph node transfer (VLNT) in 15 BCRL patients (NCT02994771). Patients were placed into two dose cohorts (low: n = 3, $1x10^{10}$; high: n = 12, $1x10^{11}$ viral particles). Lymfactin® was administered as a single dose via perinodal injections into the transplanted tissue during the VLNT surgery. Herantis announced the results from the initial 12-month study read out in April 2019, which concluded that Lymfactin® continued to be safe and well-tolerated, with neither Lymfactin-related severe adverse events nor dose-limiting toxicities. The positive safety outcome was recently confirmed in the 24-month long term follow-up phase, announced late in 2020.

Although this study was not placebo controlled, and therefore is not considered an efficacy study, clinically meaningful improvement in lymphatic flow was observed in 3 out of 11 patients at the 12-month timepoint and in 4 out of 11 patients at the 24-month timepoint (high dose cohort), as measured by quantitative lymphoscintigraphy. Furthermore, 6 out of 12 patients at the 12-month timepoint and 4 out of 7 patients at the 24-month timepoint (high dose cohort) showed a considerable decrease in the affected arm volume. At 24 months, the majority of patients reported sustained quality of life improvements according to the Lymphedema Quality of Life Inventory (LyQLI) questionnaire.

Armed with the highly encouraging results, Herantis launched a Phase II, double-blind, placebo-controlled, randomized study in a larger cohort of 39 BCRL patients to assess efficacy and safety (AdeLE, NCT03658967). All patients are currently in the 12-month blinded follow-up phase, and headline results from this study are expected in Q1 2021.

The Administration:

Herantis is developing Lymfactin® as an adjunct therapy to lymph node transfer surgery in breast cancer-related lymphedema. Over 9,200 VLNT surgeries are performed per year in the USA, and this is increasing by approximately 15% each year. In this procedure, a tissue "flap" containing healthy lymph nodes is harvested from the patient's lower abdominal wall or groin. The adenoviral vector is then injected ex vivo into the tissue flap at various points surrounding the lymph nodes. Finally, the tissue flap is transplanted into the axillary region of the patient's affected upper limb. The expression of VEGF-C typically begins within the first 24 hours after transplantation.

The regenerative activity of Lymfactin® adjuvant therapy has the potential to revolutionise the treatment of BCRL. However, Herantis is already exploring additional applications for Lymfactin® as a stand-alone therapy in other secondary lymphedemas.

The Disease:

Lymphedema is a painful and debilitating swelling condition that usually manifests in the limbs. The disease is caused by failure of the lymphatic vasculature to drain interstitial fluid back to the blood stream. Over 200 million people worldwide suffer from lymphedema, but unfortunately, this is a life-long disease with very few therapeutic options. Symptoms may be relieved by wearing compression garments or through exercise, however there are no therapeutic options to treat the cause of the disease.

Every year around 150,000 cases of cancer-related lymphedema are diagnosed in the USA and EU. BCRL arises in up to 30% of patients undergoing surgical resection of breast cancer with axillary lymph node removal with around 29,000 new diagnoses per year in the USA and top 5 EU countries. However, the actual prevalence of BCRL is likely to be underestimated, as the disease can often be subclinical, mild or latent, and patients do not always seek treatment. Additionally, diagnosis is not highly specific and poorly defined. Despite some recent advances in diagnostic methods, an estimated 40-50% of subclinical and clinical lymphedema cases are missed due to poor specificity or inconsistent measurement criteria in the diagnostic method. In many patients, BCRL seriously reduces quality of life. In addition to infections, physical pain, loss of mobility and function, BCRL can have serious negative impacts on psychological and emotional well-being, including social disconnection, decreased self-confidence, anxiety, frustration and depression. Patients are often ashamed of their deformed appearance and resist seeking treatment. Indeed, for some patients the psychosocial impact of lymphedema can be as distressing as the initial diagnosis of breast cancer.

The Competition:

As stated, there are currently no approved pharmaceutical products for lymphedema or BCRL. Complete decongestive therapy (CDT) is considered to be the gold standard treatment regime for early-stage lymphedema. CDT focusses on reducing swelling through frequent manual lymphatic drainage, compression bandaging, and exercise. VLNT surgery is a relatively new treatment option for BCRL patients that involves the removal and relocation of inguinal nodes from the groin to the axillary region of the affected limb. In many cases, the surgery reduces limb volume, pain and the need for compression therapy, though results may be variable. Liposuction and lymphaticovenous anastomosis are also used to treat lymphedema.

The competitive pipeline for secondary lymphedema is very limited and Lymfactin® is currently the only drug candidate in clinical development for cancer-related lymphedema. With the increasing popularity and uptake of lymph node transfer surgery, Herantis will develop and launch Lymfactin® as an adjuvant therapy. With further evidence of clinical efficacy, Herantis may also pursue Lymfactin® as a standalone therapy for other secondary lymphedema forms.

The Market:

Lymfactin® is a single dose gene therapy product and will be the first disease-modifying, and potentially curative therapeutic to reach this market. Herantis has performed in-depth market research into the lymphedema market, and specifically the BCRL segment. Across the USA and top five European markets, 29,000 new patients are diagnosed with BCRL each year, however, it is likely that this number is substantially underestimated. In a 2-year follow-up study of breast cancer survivors, the direct medical costs for patients diagnosed with BCRL were calculated to be up to $23,167 higher (on average) compared to those without BCRL.

Our market research indicates that nearly 10,000 BCRL patients undergo VLNT surgery per year and this number that is expected to increase by 15% year-or-year. KOLs are strongly enthusiastic about Lymfactin® as a novel biologic adjuvant to VLNT surgery. Herantis could therefore reasonably expect to capture up to 40% of all VLNT surgeries in the USA, and 30% of surgeries in the EU. We therefore project at Lymfactin® peak sales could reach $600M in the USA and top five European markets.

The IP:

Herantis has a granted US patent (US8852936B2) protecting the use of VEGF-C gene therapy with autologous lymph node transfer for treatment of lymphedema. The patent was filed on 21 Sep 2012 and is expected to expire in 2032.

References

Hartiala et al. Journal of Plastic, Reconstructive & Aesthetic Surgery, 2020, 73, 1612-1621.

Honkonen et al. Ann. Surg. 2013; 257(5), 961-967.