HERANTIS PHARMA

Toward clinical breakthroughs based on leading science

Vator Unicorn Summit, Stockholm 27 Nov 2019

Pekka Simula, CEO

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Breaking the boundaries of standard therapeutic approaches

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Herantis' target indications

Parkinson's disease (PD)

PD is an incurable brain disease whose first symptoms include tremors, muscle stiffness

→ Symptoms grow worse with disease progression

→ Known drugs only treat motor symptoms, only for a while

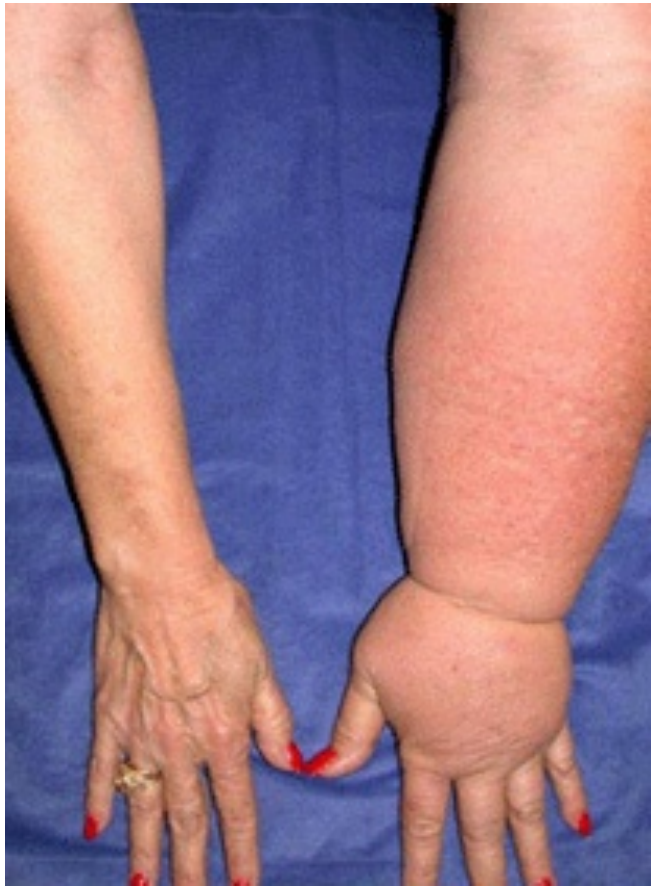
Lymphedema (LE) is chronic, progressive swelling due to accumulation of lymph

→ Common consequence of cancer therapies

→ Disabling, disfiguring and painful disease

→ No efficacious therapies

Secondary lymphedema



Parkinson's facts:

- Second most common neurodegenerative disease: **7-10 million patients**
- Estimated annual financial burden of PD is **$50 billion**
- Progression-stopping therapy would save the society over **$400,000 per patient** in the USA*

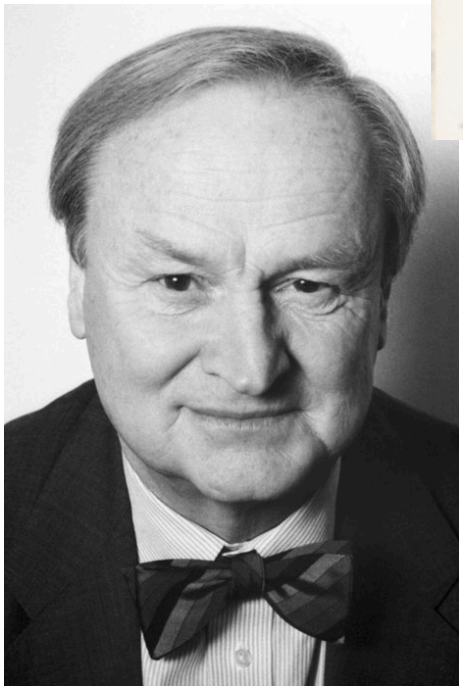
*University of Pennsylvania's National Parkinson Foundation

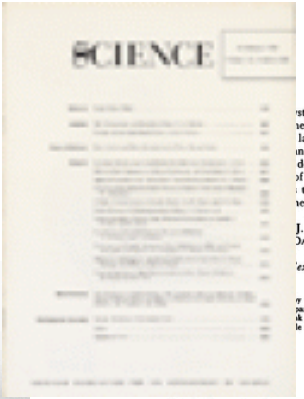
Lymphedema facts:

- 140 million LE patients
- 2 million breast cancer diagnosis annually
  - → 30% of patients who undergo mastectomy will develop Breast Cancer Associated Lymphedema (BCAL)
- In USA, **annual cost** of lifelong symptomatic BCAL treatment $10,000 - $20,000

Parkinson's is treated with levodopa… since 1960's!

- Professor Arvid Carlsson
  - → Lund University: Role of dopamine in the brain (Science 1958)
  - → First preclinical studies with levodopa
  - → Nobel price 2000 on signal transduction in the nervous system

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On the Presence of
3-Hydroxytyramine in Brain

The compound 3-hydroxytyramine has attracted interest as a probable intermediate in the biosynthesis of noradrenaline and adrenaline and also as a possible neurohumoral agent. It has been shown to occur in the urine (*1*), in the adrenals (*2*, *3*), and in the heart (*2*) of sheep and in the splenic nerve of the ox (*4*). The study of this compound has been hampered by lack of sensitive and specific assay methods. Apart from bioassay techniques, only the fluorimetric ethylenediamine condensation method of Weil-Malherbe and Bone (*5*) appears to be sufficiently sensitive for biological purposes. However, with this method the fluorescence spectra obtained from 3-hydroxytyramine and adrenaline are almost identical (*6*). In the fluorimetric method of Euler and Floding (*7*), the fluorescence obtained from 3-hydroxytyramine is very weak and amounts to only a few percent of that obtained from noradrenaline or adrenaline.

Recently we observed, however, that if the *p*H of samples prepared essentially according to this method was adjusted to about 5 by means of acetic acid, a fairly strong fluorescence developed. Furthermore, the activation and fluorescence peaks (345 and 410 mμ, respectively, as read in an Aminco-Bowman spectrophotofluorimeter) were at much shorter wavelengths than those obtained from noradrenaline and adrenaline, so that these compounds did not interfere, even if they were present in comparably large amounts.

Using this technique in combination with ion-exchange chromatography (Dowex 50), we have started to investigate the 3-hydroxytyramine content of various tissues. We have thus found that 3-hydroxytyramine is present in rabbit brain in an amount of about 0.4 μg/g, which is roughly equal to the amount of noradrenaline in this tissue. This may indicate that the function of 3-hydroxytyramine is not merely that of a precursor. The following criteria argue for the identity of the apparent 3-hydroxytyramine in brain with authentic 3-hydroxytyramine: (i) identical activation and fluorescence peaks, (ii) similar behavior on an ion-exchange column, and (iii) identical R_f values on paper chromatography.

Like noradrenaline (*8*), 3-hydroxytyramine is made to disappear almost completely from brain by intravenous injection of reserpine (5 mg/kg). On the other hand, the injection of the precursor 3,4-dihydroxyphenylalanine (150 mg of the DL form per kilogram, intravenously) caused a very marked increase in the 3-hydroxytyramine content of the brain (to about 2 μg/g in less than 1 hour). This was accompanied by central excitation (*9*). Both these phenomena were markedly enhanced by pretreatment with iproniazid (Marsilid). Simultaneous changes in the noradrenaline level of the brain were much less pronounced if present at all (*10*).

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References and Notes

1. P. Holtz, K. Credner, G. Kroneberg, *Arch. exptl. Pathol. Pharmakol. Naunyn-Schmiedeberg's* **204**, 228 (1947); U. S. von Euler, U. Hamberg, S. Hellner, *Biochem. J.* **49**, 655 (1951).
2. M. Goodall, *Acta Physiol. Scand. Suppl.* **24**, 42 (1951).
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5. H. Weil-Malherbe and A. Bone, *Biochem. J.* **51**, 311 (1952).
6. J. Kägi, M. Burger, K. Giger, *Arch. exptl. Pathol. Pharmakol. Naunyn-Schmiedeberg's* **230**, 470 (1957).
7. U. S. von Euler and I. Floding, *Acta Physiol. Scand. Suppl.* **33**, 45 (1955).
8. A. Carlsson *et al.*, in S. Garattini and V. Ghetti, *Psychotropic Drugs* (Amsterdam, 1957).
9. A. Carlsson, M. Lindqvist, T. Magnusson, *Nature* **180**, 1200 (1957).
10. A detailed discussion of these results is in preparation.

4 November 1957

Upper Atmosphere Densities from Minitrack Observations on Sputnik I

The analysis of Minitrack (*1*) data on the first U.S.S.R. satellite, 1957 Alpha 2 (*2*) provides information on the density of the atmosphere (*3*) above the perigee altitude of 232 km. We find that the observed rate of change of period for Alpha 2 may be explained by a model atmosphere which is in agreement with recently obtained data on air density and temperature at altitudes (*4*, *5*) up to ~200 km and constitutes a reasonable extrapolation of these measurements to higher altitudes. With allowance for the estimated probable errors in the density at 200 km and for the uncertainty in the orbit elements and ballistic drag parameter of Alpha 2, the data still yield a relatively unambiguous determination of density up to 400 km.

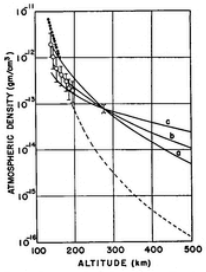
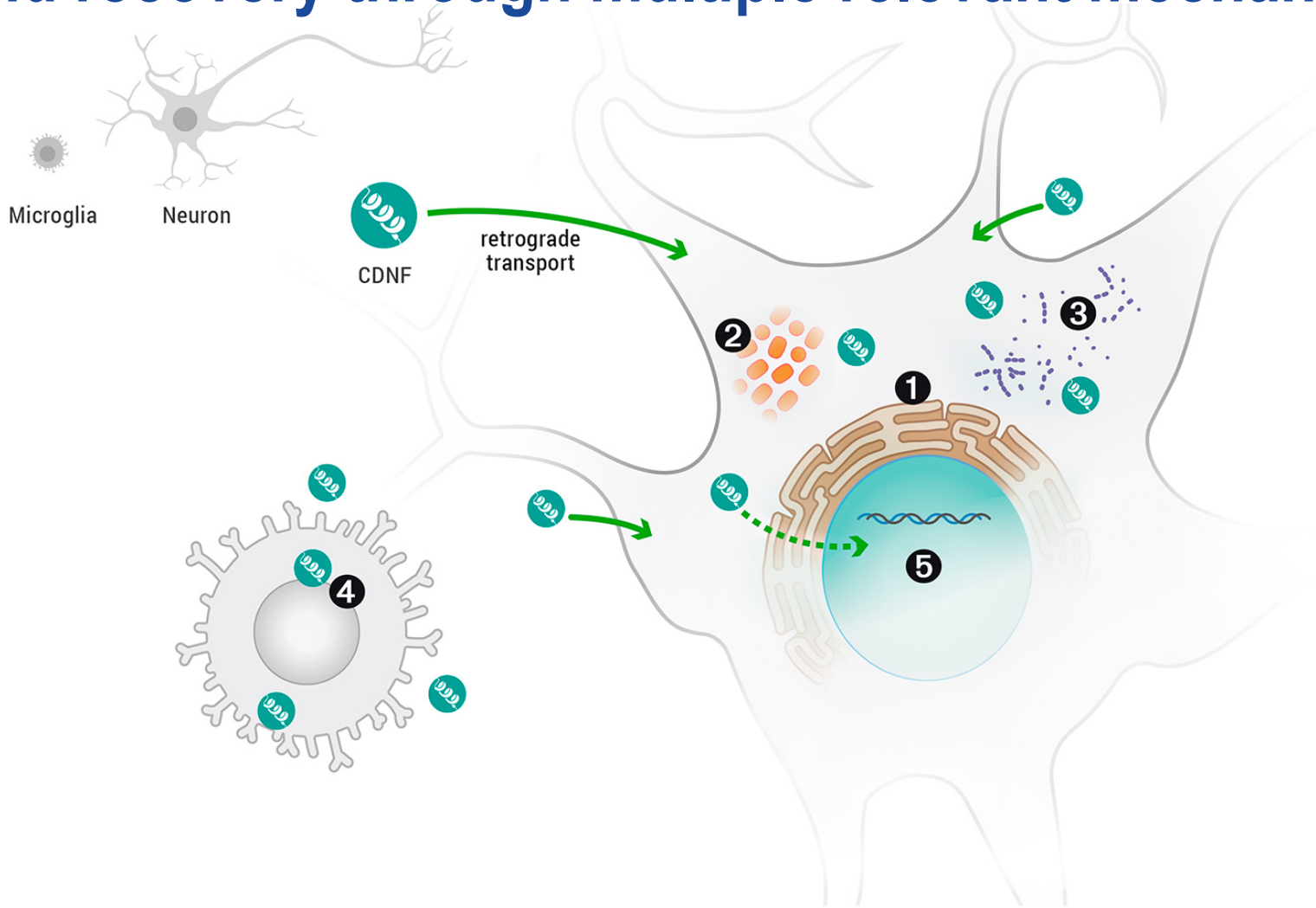


Fig. 1. Curves *a*, *b*, and *c* represent density distributions adjusted for simultaneous agreement with the rocket measurements and the α2 data. The dashed curve is the ARDC model atmosphere.

The determination of the density from the rate of change of the orbital period depends on the values of the ballistic drag parameter and the orbit constants of Alpha 2. The present calculations are based on a ballistic drag parameter of 89 ± 11 kg/m², derived from U.S.S.R. announcements of mass and area (*6*). The relevant orbit elements were deduced from Minitrack observations between 14 and 25 October, and their average values for that interval are as follows: perigee altitude = 232 ± 5 km; eccentricity = 0.047 ± 0.004; latitude of perigee = 39° ± 6°; equatorial inclination = 64.5° ± 0.3°; rate of change of period = 0.045 ± 0.003 min/day.

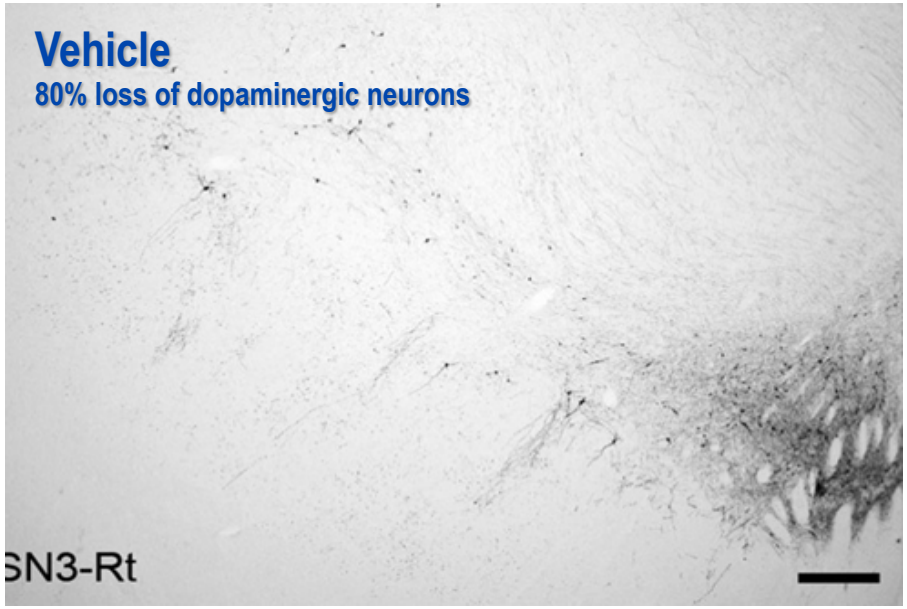
Our results are shown in Fig. 1. The solid lines represent three model atmospheres (*a*, *b*, and *c*) which agree with the rate of change of period of Alpha 2 and also fall within the limits of probable error in the rocket measurements of density up to 185 km. The data of Horowitz and LaGow (*4*) are indicated by circles, and the data of Byram, Chubb, and Friedman (*5*) by a dotted line. The dashed curve is the atmosphere proposed by Mizner and Ripley (*7*). The spread in the solid curves above 275 km indi-

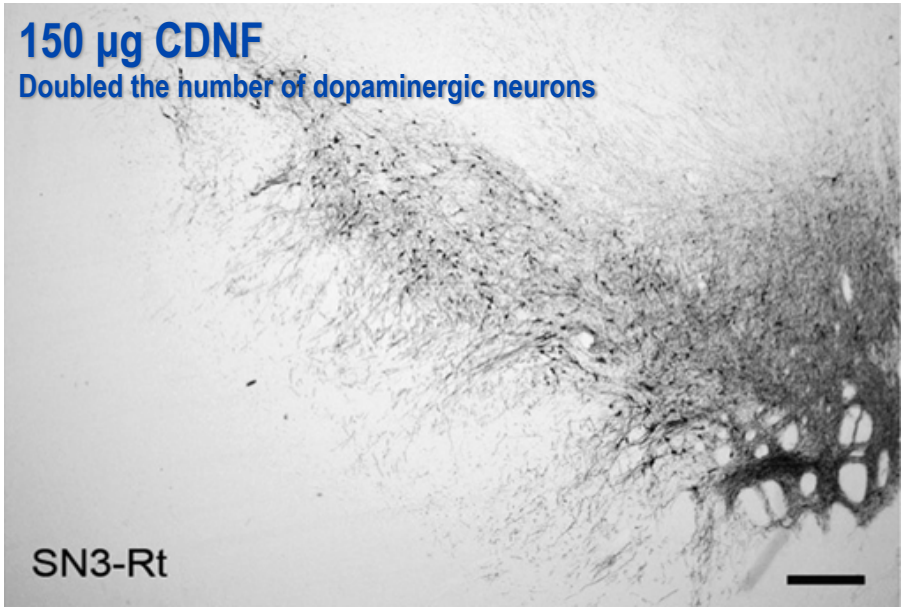
PD: Our drug candidate CDNF promotes neuronal survival and recovery through multiple relevant mechanisms



1. CDNF promotes neuronal survival and functionality by reducing endoplasmic reticulum (ER) stress
2. CDNF promotes neuronal survival by activating Protein Kinase B (Akt)
3. CDNF inhibits α-synuclein oligomerization and toxicity
4. CDNF suppresses production and secretion of proinflammatory cytokines by glial cells
5. CDNF supports maintenance of neuronal functions by enhancing transcription of genes involved in e.g. dopamine synthesis and metabolism

CDNF doubled the number of neurons in a PD model*





- Disease model: MPTP lesion model in aged Rhesus monkey
- Three monthly CDNF doses **doubled the number of DA neurons**
- Significant improvement in gross motor function, fine motor function, and **for the first time in the world**, non-motor symptoms

* Research collaboration with University of Pittsburgh funded by Michael J. Fox Foundation

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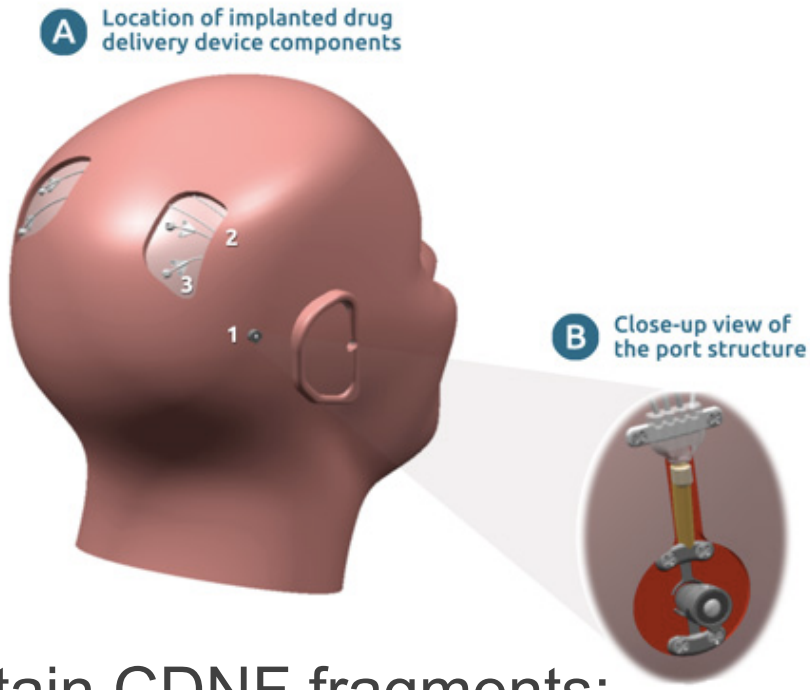
CDNF may change how patients live with PD

Currently in Phase 1-2 clinical study funded by EU: "**Leading science, greatest potential** to advance clinical practice"

- Study fully recruited: 17 patients randomized in CDNF vs. placebo groups
- Topline results expected in Q1/2020
- First-in-human study in advanced PD patients → Primary endpoint is safety

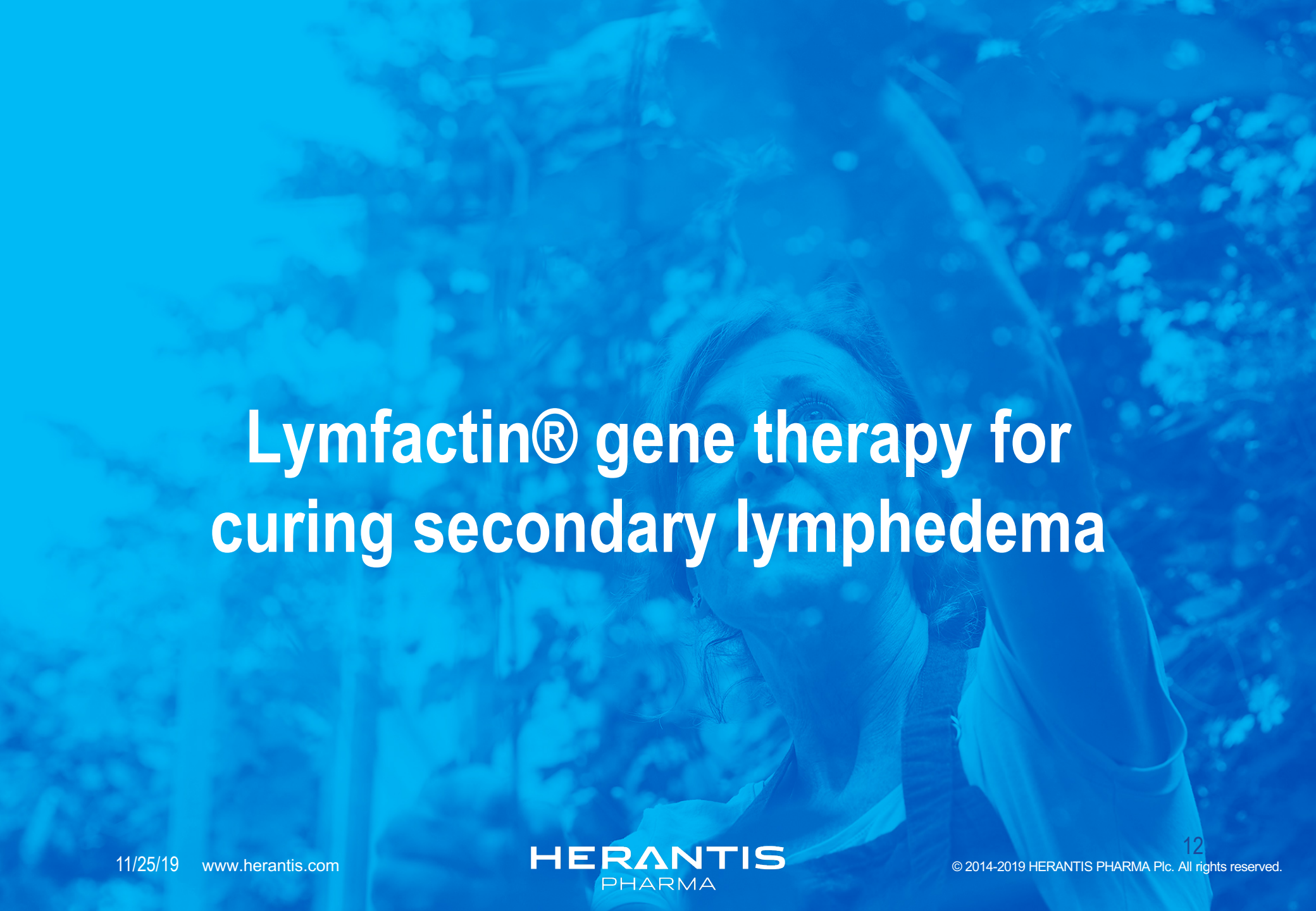
Next generation: xCDNF



- Common challenge in brain diseases is drug delivery in the brains → CDNF is dosed directly in brains using medical device

- Next step: we have shown that certain CDNF fragments:
  1. Retain its biological activity (comparable efficacy in PD models)
  2. Penetrate the BBB → **much simpler administration**
  3. Have potential in several indications beyond PD: E.g. Alzheimer's, ALS, stroke

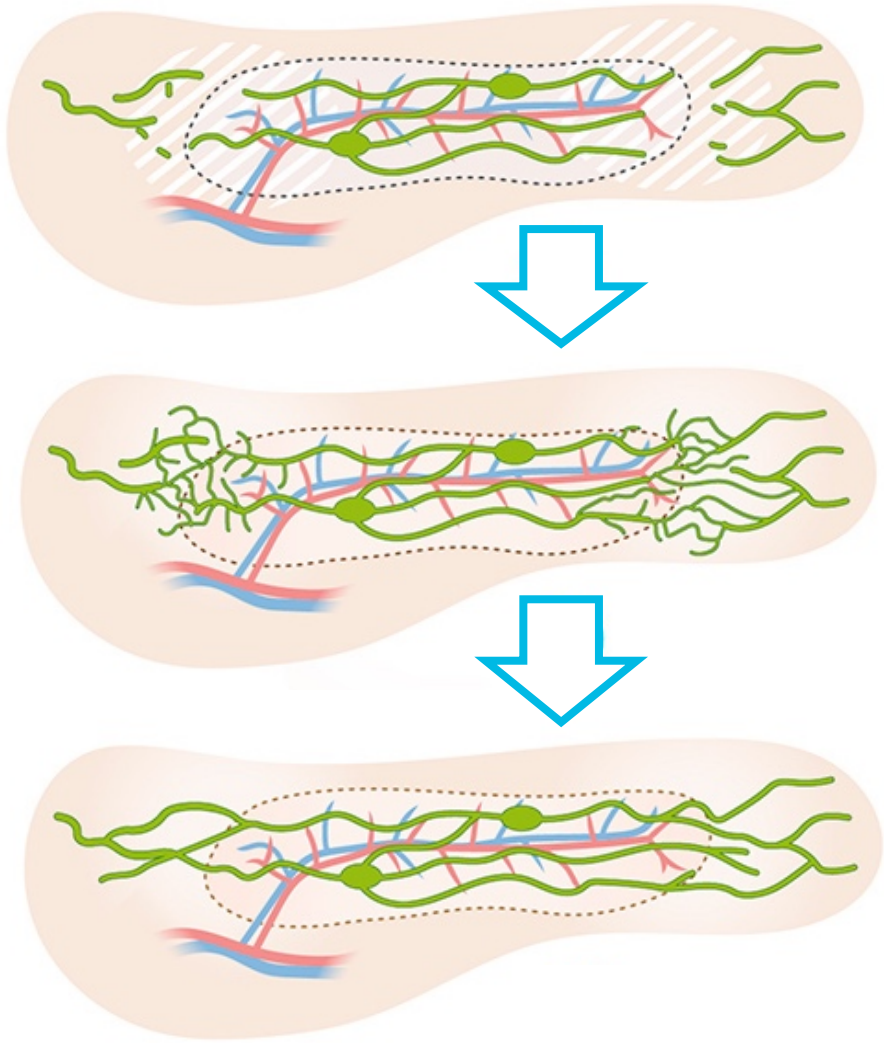
➢ **Based on current data xCDNF could be administered as easily as insulin**



Lymfactin® gene therapy for curing secondary lymphedema

Lymfactin®: VEGF-C gene therapy to reconstitute the lymphatic system

1. A single Lymfactin® injection results in local **VEGF-C expression** for about 2 weeks
2. VEGF-C is the natural human protein that promotes the **growth of lymphatic capillaries**
3. Lymphatic capillaries mature into functional lymphatic vessels, reconstituting the lymphatic system



Lymfactin® development

- Actively recruiting patients with breast cancer associated LE (BCAL)
  - → Adjunct to lymph node transplantation surgery, which attempts to relieve symptoms
  - → Study centers: 5 university hospitals in Sweden and Finland
- Safety established in Phase 1 study with same approach
  - → Promising improvements observed in signs and symptoms of LE (uncontrolled data)

- **Target: 40 patients randomized in Lymfactin® vs. placebo groups**
- **Topline results expected by end of 2020 (12-month follow-up)**
- **Primary endpoints: Efficacy in signs and symptoms of LE**

Lymphedema: Market and awareness

- 140 million LE patients worldwide
- €600M market for Lymfactin® as an adjunct therapy in BCAL*
  - → Significant potential in other lymphedemas
- Lymphedema awareness increases
  - → Herantis is a partner of LE&RN, international patient advocacy group
  - → Hollywood superstar Kathy Bates is an active LE&RN spokesperson

Summary and Public Offering in Sweden

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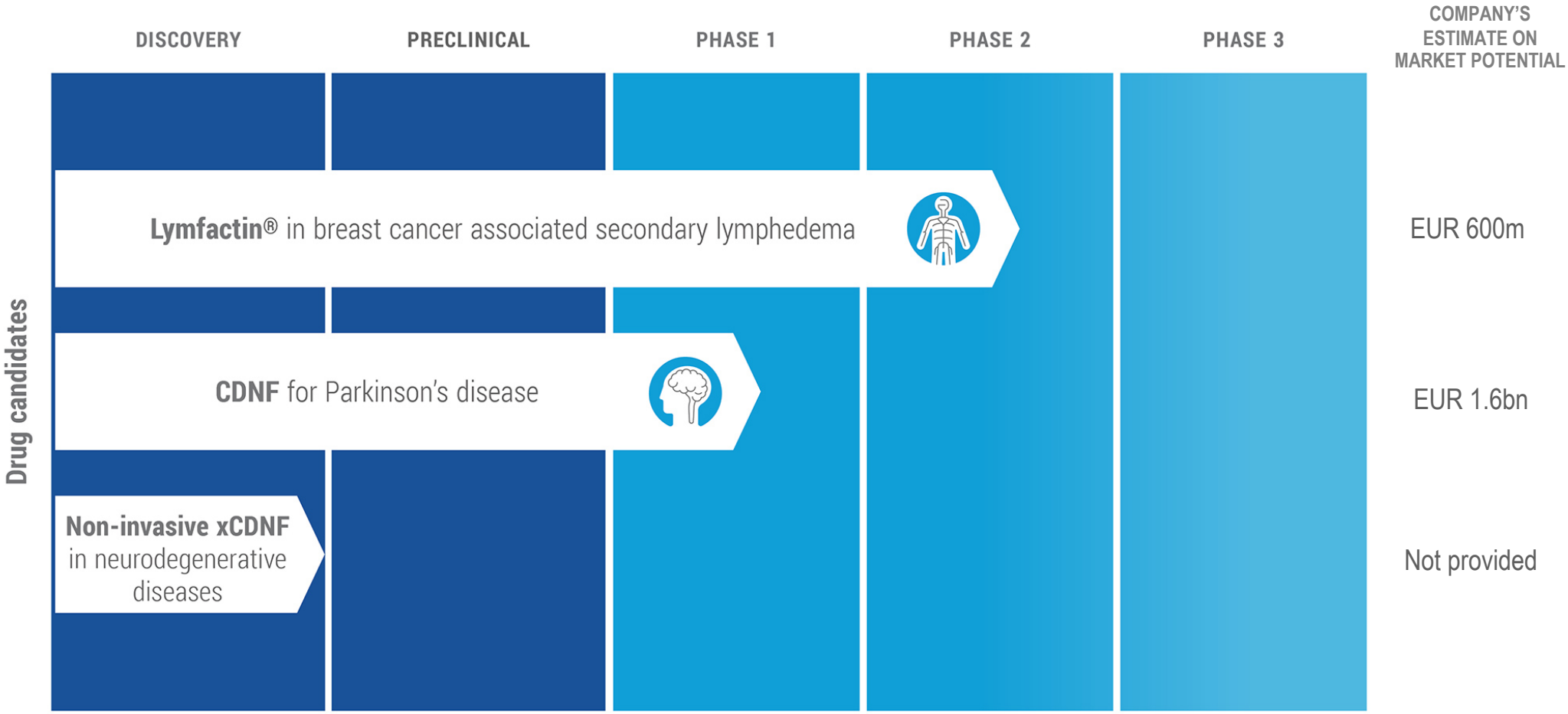
Based on leading science, CDNF and Lymfactin® are in placebo-controlled studies targeting unmet clinical needs



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Selected financials as reported 1H/2019

	H1/2019	H1/2018
Cash end of period	5.6 MEUR	4.0 MEUR
Cash flow from operations	-2.7 MEUR	-1.8 MEUR
Personnel	9	9

- Market cap approximately 450 MSEK (Nov 18th, 2019)
- Last funding round in 3/2019

  → Cornerstone investor: Swedbank Robur's healthcare fund Medica
- Company is **fully funded to reach unblinding** in both randomized trials

  → Full subscription in Swedish IPO would be expected to fund the company through Q1/2021

Public company in Finland since 2014: Now dual-listing in Sweden

HRTIS Nasdaq First North listed

- Herantis announced on 11 Nov 2019:
  - →Public offering in Sweden and Denmark, and private placement: max 618,018 shares to be issued at **71 SEK** (~€6.65) per share
  - →Target: Herantis' shares listed in Nasdaq First North Sweden in Dec
- Reason for dual-listing:
  - →Increase liquidity of our shares, prepare for next stage in development
- Details on the Swedish IPO:
  - →Subscriptions can be made through Nordnet and Avanza
  - →See herantis.com/information-memorandum/ for details

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Thank you

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