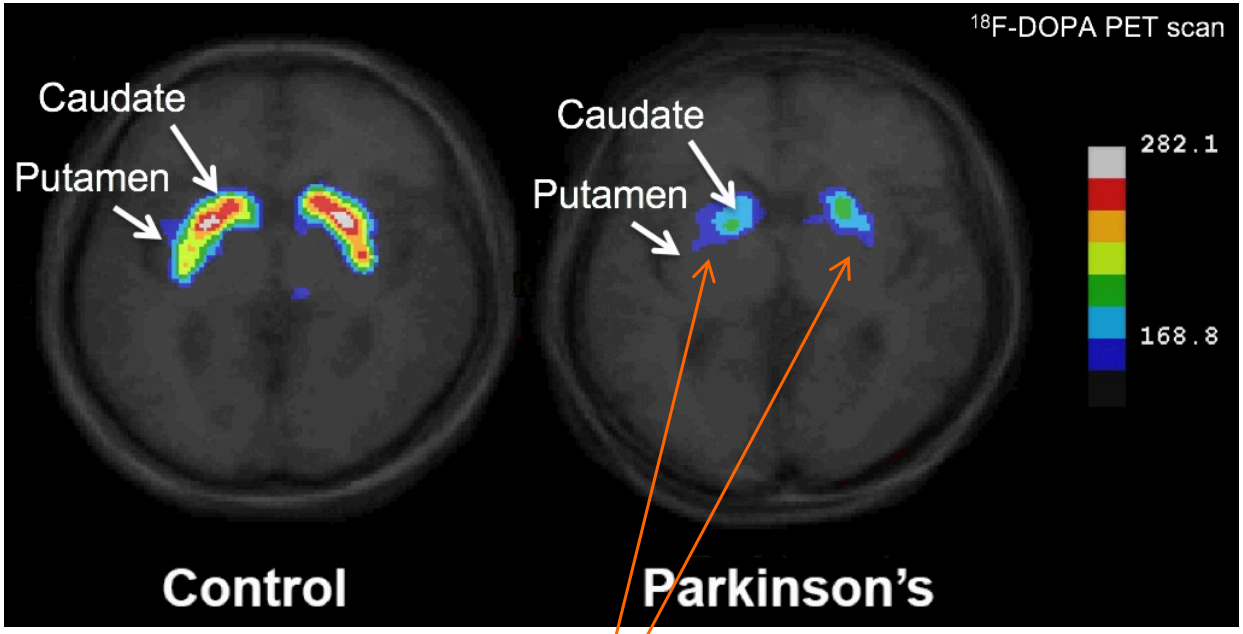
WPC 2019 meeting review

Tilo Kunath, 16th November 2019


Lindsey Isaacs
The Cure Parkinson's Trust

Cell replacement therapy for Parkinson's disease

- Motor symptoms caused by loss of **dopaminergic neurons**
- The loss is very localised to the **caudate** and **putamen**



Therapy: Transplant ***new*** dopaminergic neurons into putamen

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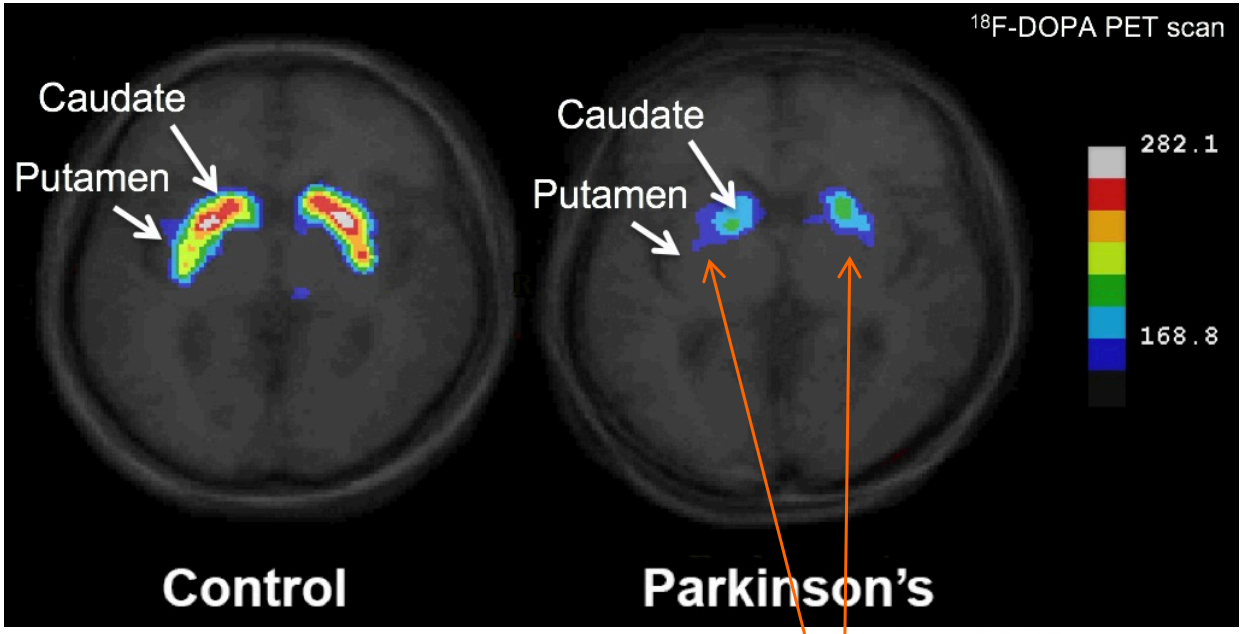
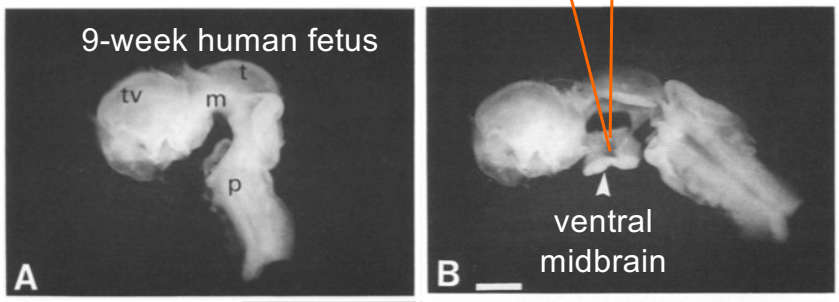
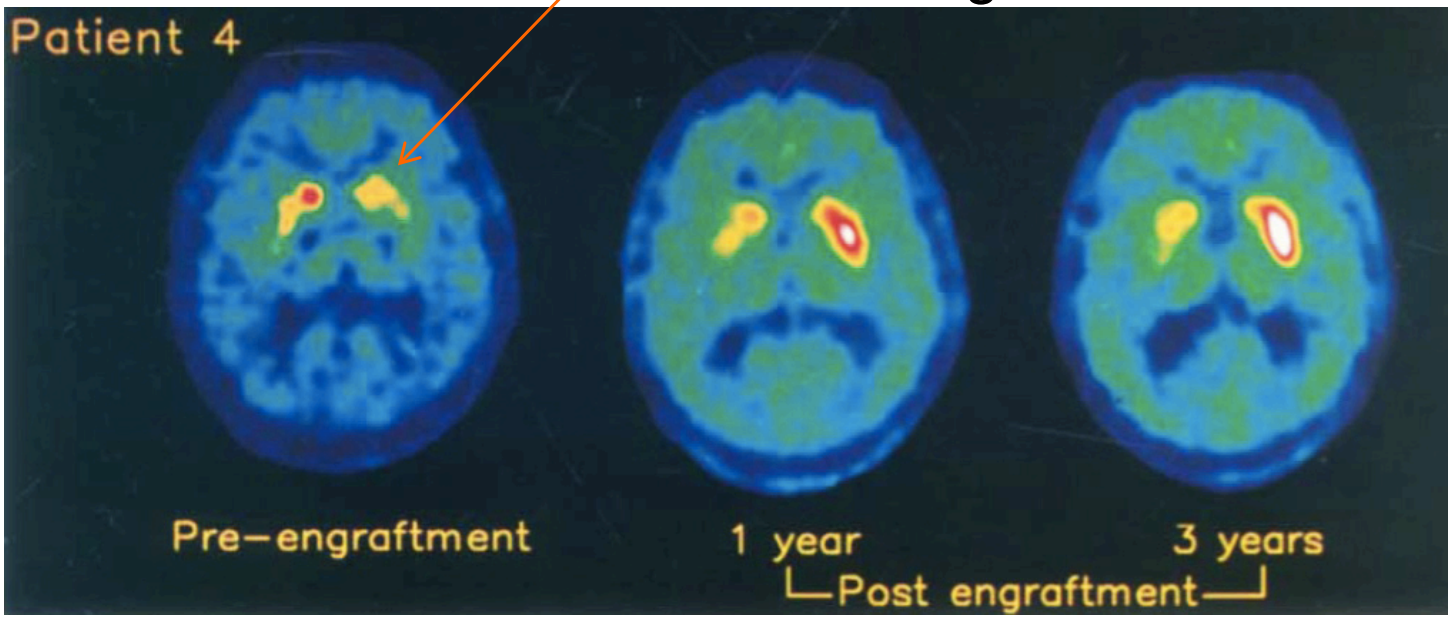




(Brundin *et al*, 1986, *Exp Brain Res*)

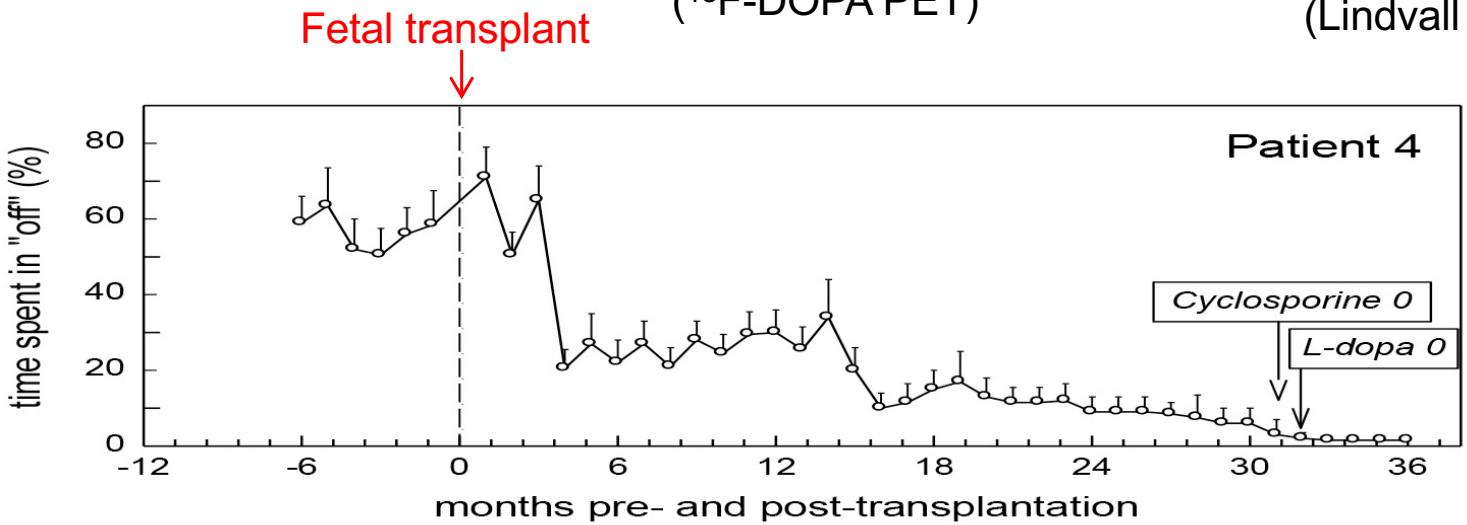
Clinical trials with fetal ventral midbrain tissue

unilateral fetal graft



(^{18}F-DOPA PET)

(Lindvall *et al*, 1994)



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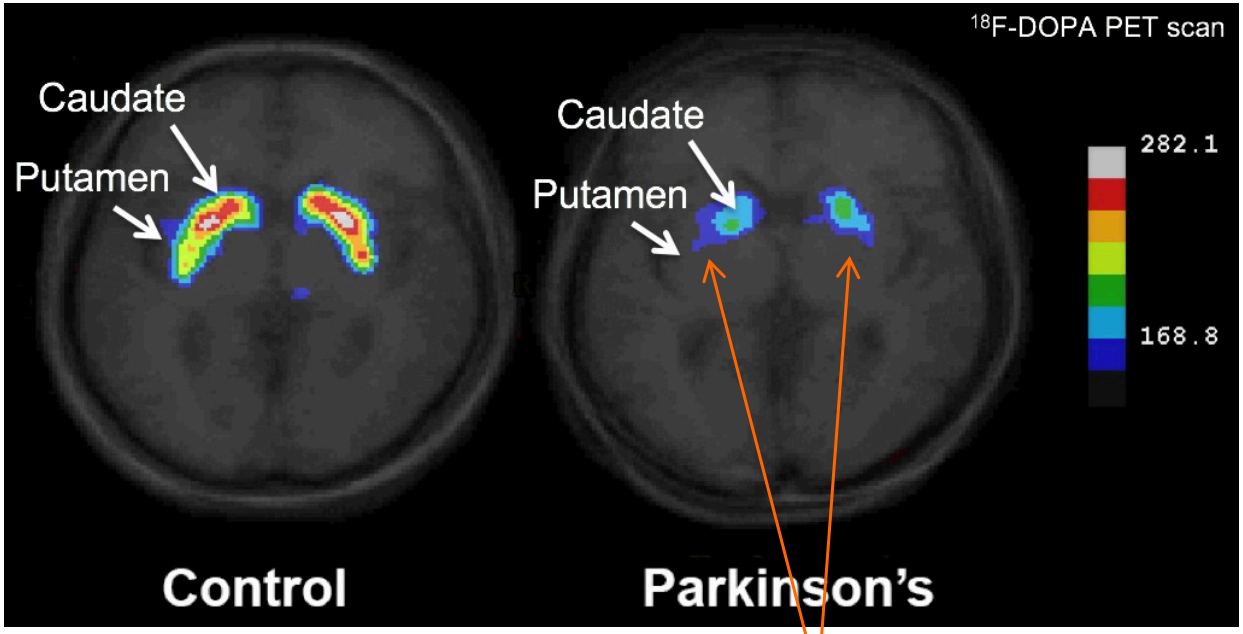
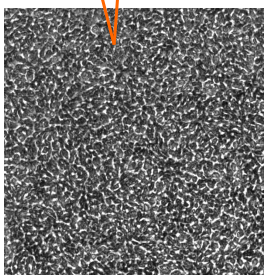


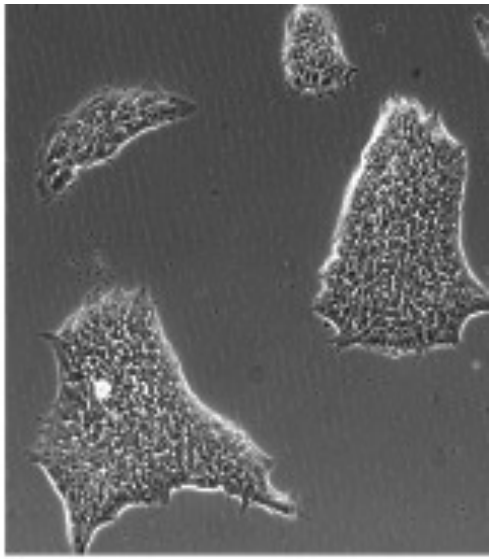
Human stem cell-derived dopaminergic cells



(2018 onwards…)

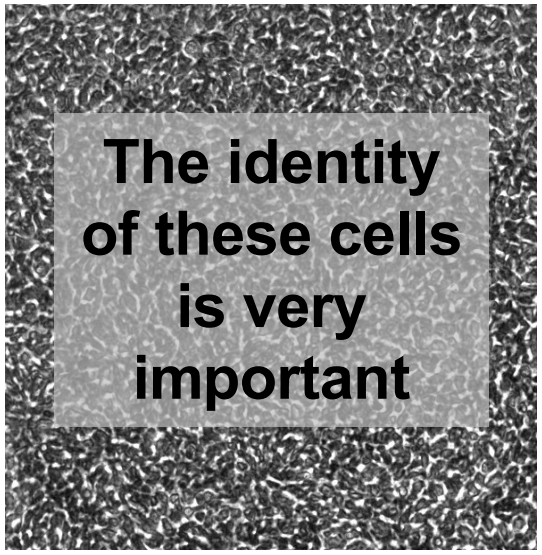
hESCs and iPSCs provide an *unlimited* source of cells for cell replacement therapy

Dopaminergic differentiation



iPSCs/ESCs

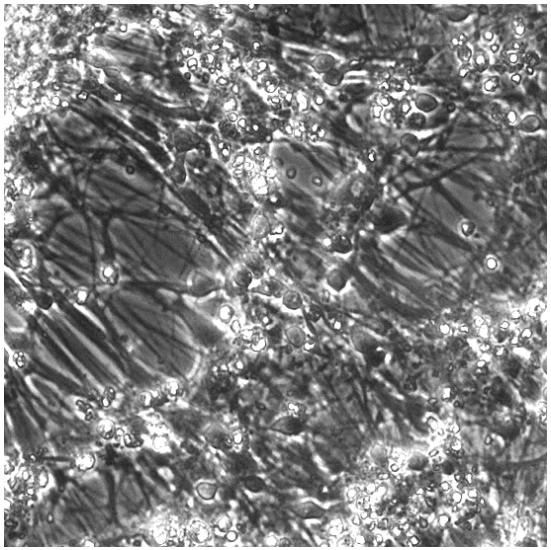
~16 days



Dopaminergic precursors

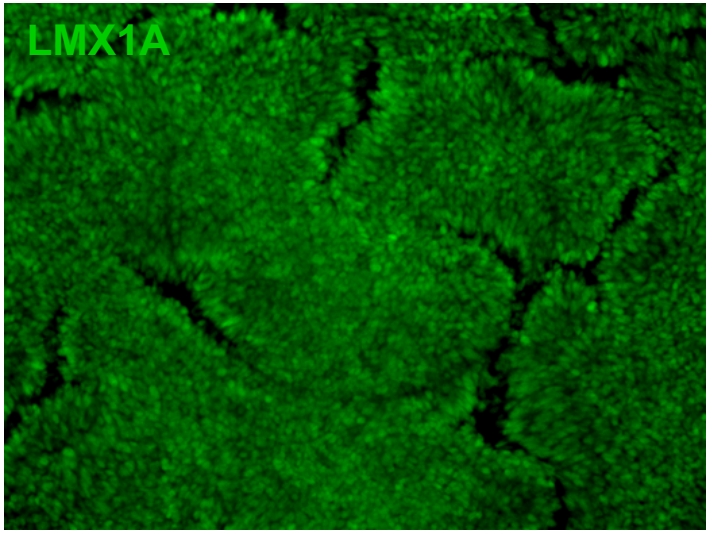
(transplant)

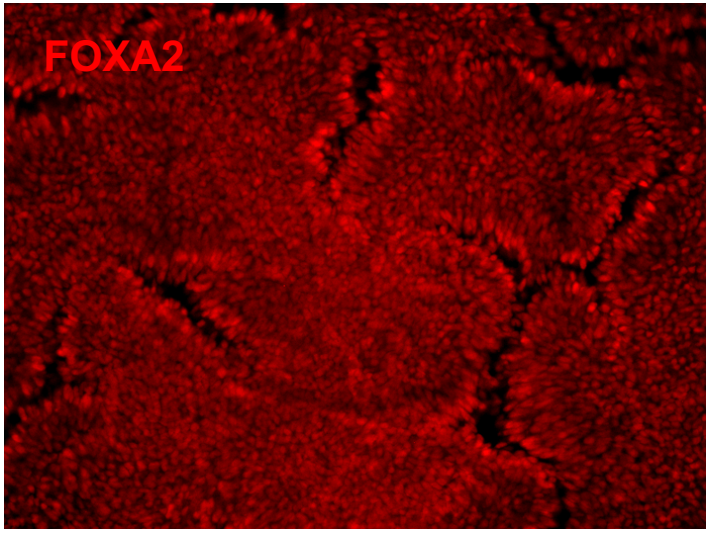
>30 days



Dopaminergic neurons

Agnete Kirkeby





Cell Stem Cell

Clinical Progress

Predictive Markers Guide Differentiation to Improve Graft Outcome in Clinical Translation of hESC-Based Therapy for Parkinson's Disease

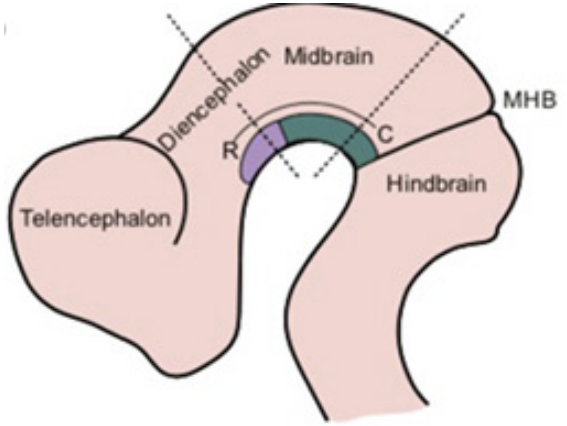
Agnete Kirkeby,[1,2,3,*] Sara Nolbrant,[1,3] Katarina Tiklova,[4] Andreas Heuer,[1,3] Nigel Kee,[4] Tiago Cardoso,[1,3] Daniella Rylander Ottosson,[1,3] Mariah J. Lelos,[5] Pedro Rifes,[2,3] Stephen B. Dunnett,[5] Shane Grealish,[1,3] Thomas Perlmann,[4] and Malin Parmar[1,3,6,*]

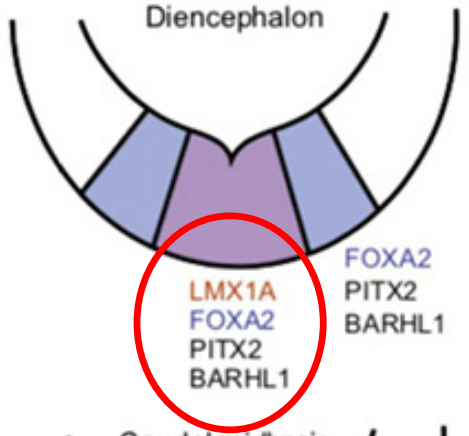
PITX2+ve cells are **bad** for transplantation, they designate presence subthalamic nucleus (STN) neurons – diencephalon

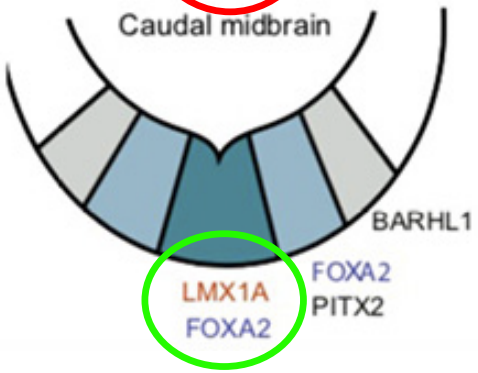
LMX1A+ve and **FOXA2+ve** are **good** for transplantation, they mark midbrain dopaminergic neurons

5th World Parkinson Congress
Kyoto, Japan

Agnete Kirkeby







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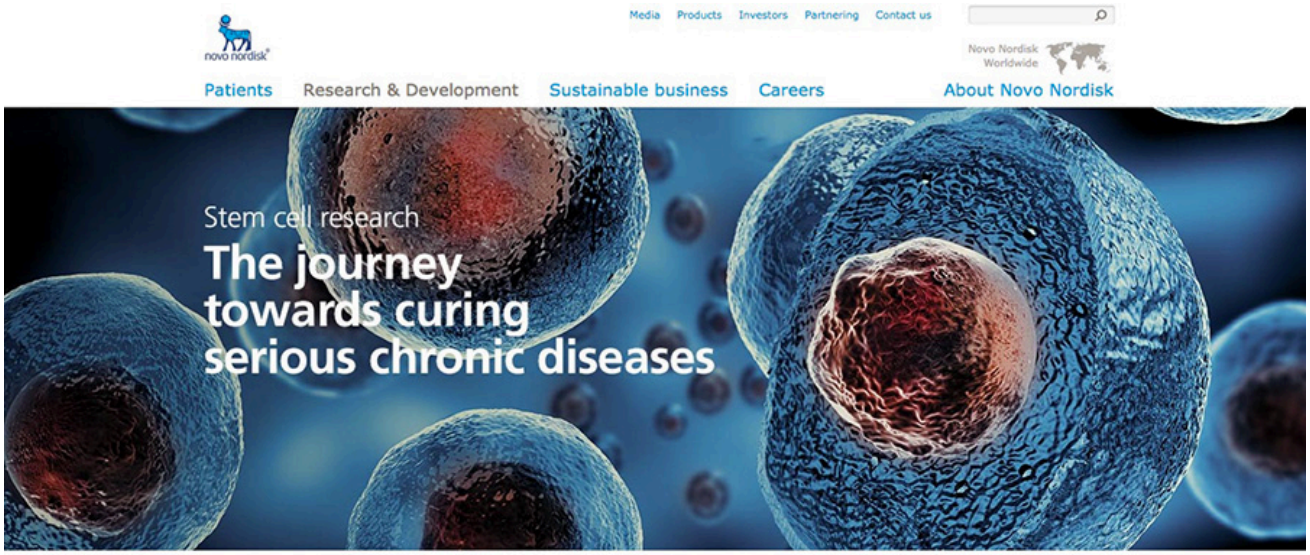
Agnete Kirkeby + Novo Nordisk



Partnering to pursue stem cell-based therapies

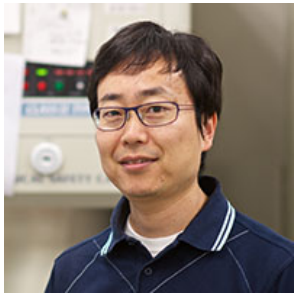
The development of GMP stem cell lines in collaboration with UCSF has enabled Novo Nordisk to expand our focus on serious chronic diseases beyond diabetes. Some of the challenges to overcome in stem cell-based research are the development of differentiation protocols for specific cell types as well as cell encapsulation technologies for transplantation purposes. In Novo Nordisk, we collaborate with scientific leaders around the world to overcome these barriers to stem cell-based treatment across a range of disease areas:

Parkinson's disease
Stem cell-based treatment in collaboration with Biolamina and Lund University

Chronic heart failure
Stem cell-based treatment in collaboration with Biolamina and DUKE National University Singapore Medical School

Dry age-related macular degeneration (AMD)
Stem cell-based treatment in collaboration with Biolamina and DUKE National University Singapore Medical School

Type 1 diabetes
Encapsulation device in collaboration with Cornell University



Asuka Morizane (CiRA)

Jun Takahashi, Kyoto, CiRA

iPSC-derived dopaminergic neurons rescue monkey model of Parkinson's

LETTER

doi:10.1038/nature23664

Human iPS cell–derived dopaminergic neurons function in a primate Parkinson's disease model

Tetsuhiro Kikuchi[1], Asuka Morizane[1], Daisuke Doi[1], Hiroaki Magotani[1], Hirotaka Onoe[2], Takuya Hayashi[2], Hiroshi Mizuma[2], Sayuki Takara[2], Ryosuke Takahashi[3], Haruhisa Inoue[4], Satoshi Morita[5], Michio Yamamoto[5], Keisuke Okita[6], Masato Nakagawa[6], Malin Parmar[7] & Jun Takahashi[1,8]

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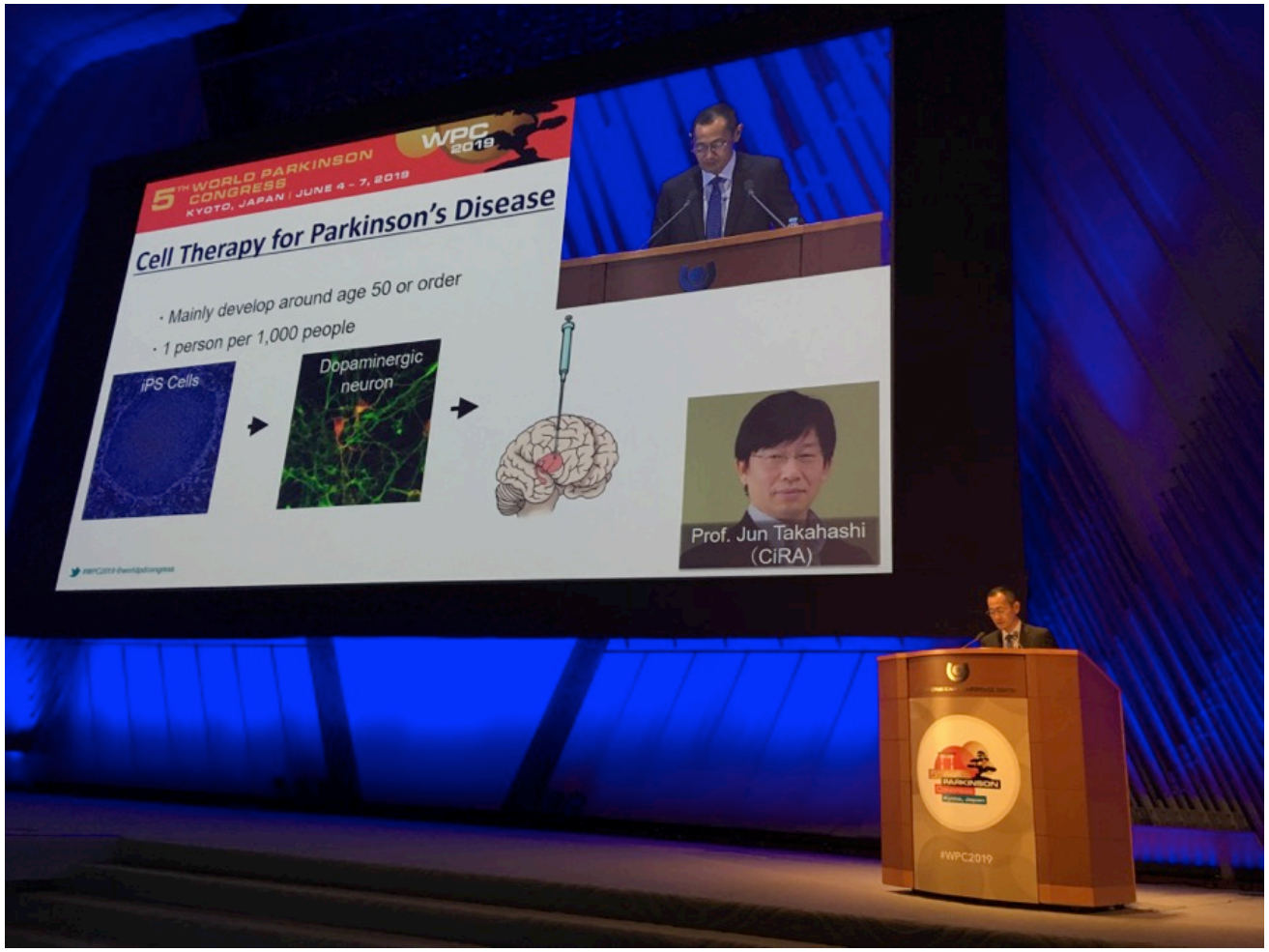
- **Dopaminergic cells are not *frozen* – freshly differentiated cells are transplanted**

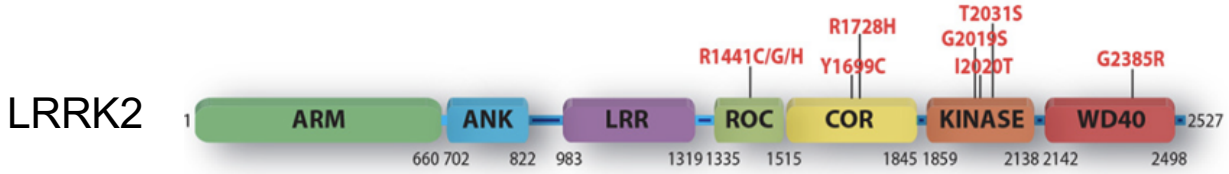
Shinya Yamanaka (CiRA)



Shinya Yamanaka “A total of 7 patients are in the trial. One patient has had a unilateral transplant (in October 2018). This patient will have the opposite side transplanted, and then the other 6 patients will be transplanted”

Matt Farrer (UBC, Vancouver)

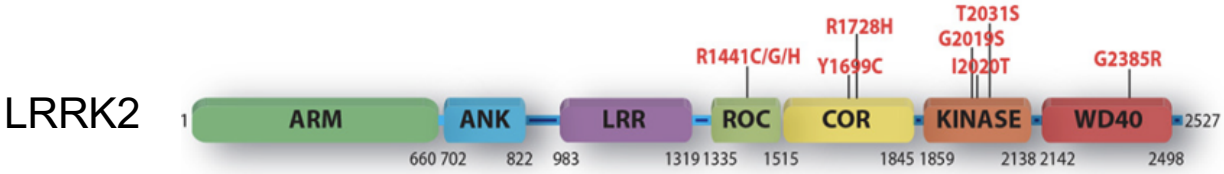
LRRK2 and origin of mutations



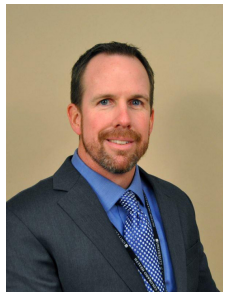
- LRRK2 **G2019S** originated about 3,000 years ago in northern tip of African, and also spread to Norway through “trading” in the area
- Age-of-onset for “G2019S” PD is **much later** in Norway, than in north Africa or Israel
- LRRK2 **G2385R** (low risk variant) arose in Asia about 4,800 years ago (*Does not increase kinase activity*)
- Some mutations in LRRK2 are actually protective against PD

Matt Farrer (UBC, Vancouver)

LRRK2 and inflammation



- LRRK2 mutations are associated inflammatory bowel disease, Crohn's disease, pediatric autoimmune disease, **chronic inflammatory diseases**
- **Hyperactive LRRK2** provides increased protection against **reovirus**.
- In Tunisia, **G2019S is increasing** in frequency in the population, and is thought to be due to **increased protection** against unknown pathogens**.**



David Beckham (UC Denver)

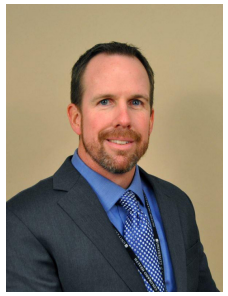
α-synuclein and inflammation

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Virology

Alpha-Synuclein Expression Restricts RNA Viral Infections in the Brain

Erica L. Beatman,[a] Aaron Massey,[a] Katherine D. Shives,[a,c] Kristina S. Burrack,[c]* Mastooreh Chamanian,[a] Thomas E. Morrison,[c] J. David Beckham[a,b,c]

Department of Medicine, Division of Infectious Diseases,[a] Department of Neurology,[b] and Department of Immunology & Microbiology,[c] University of Colorado School of Medicine, Aurora, Colorado, USA



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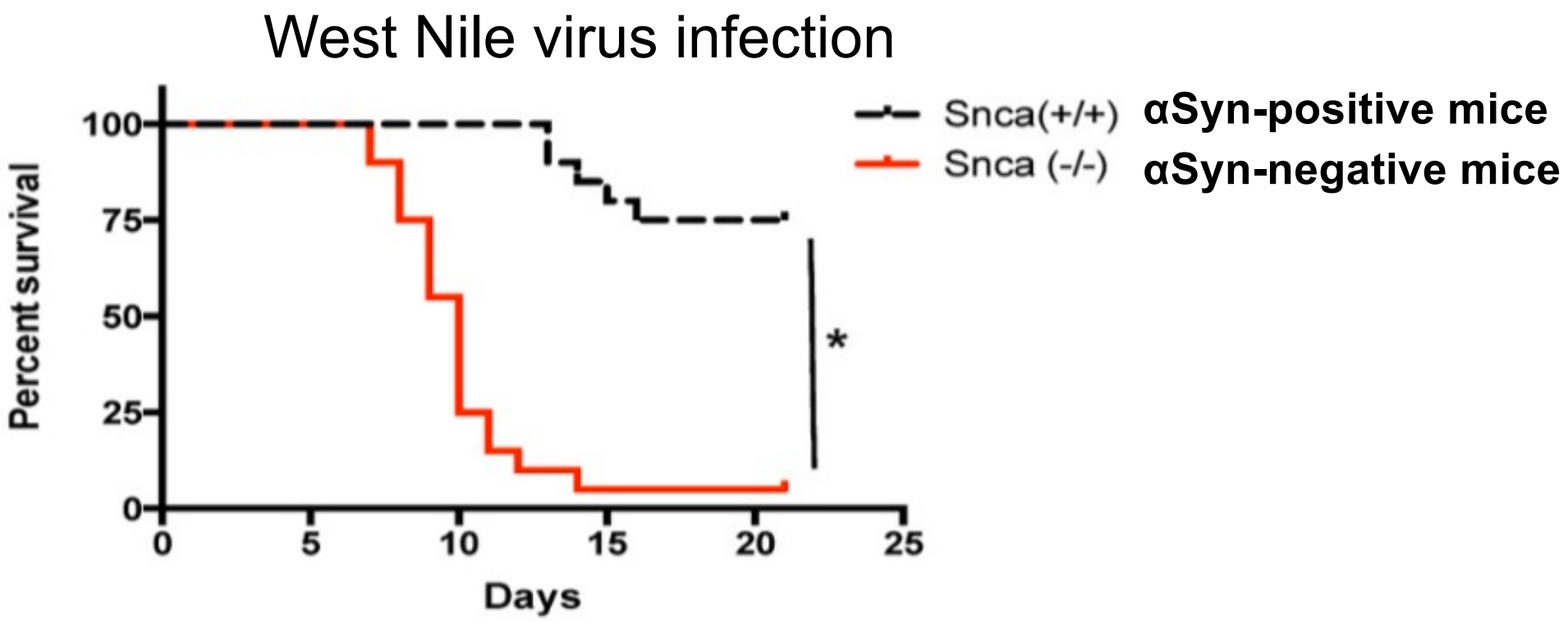
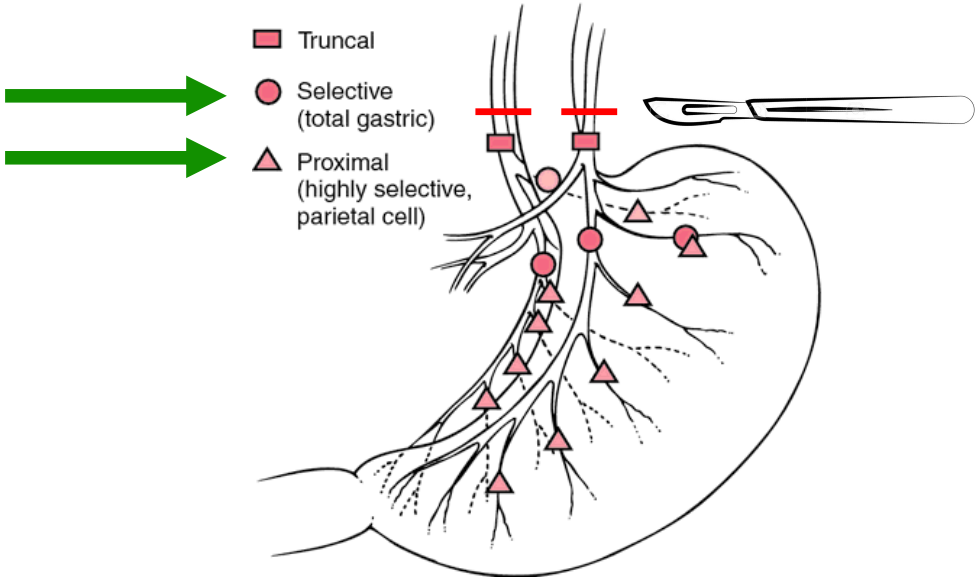
α-synuclein protects mice from West Nile virus



Per Borghammer (Aarhus University)

α-Synuclein 'spreading' in PD

- Vagotomy - vagus nerve has been cut - treatment for peptic ulcer
- 47% decreased risk of PD if you had complete vagotomy (Danish study)
- 40% decreased risk of PD in Swedish study
- Selective vagotomy did **NOT** decrease risk for PD



Per Borghammer (Aarhus University)

α-Synuclein 'spreading' in PD

- REM sleep behaviour disorder (RBD) patients – "early Parkinson's"
- Recruited 20 RBD patients, 18 PD patients, and 16 healthy controls

In-vivo staging of pathology in REM sleep behaviour disorder: a multimodality imaging case-control study

Karoline Knudsen, Tatyana D Fedorova*, Allan K Hansen, Michael Sommerauer, Marit Otto, Kristina B Svendsen, Adjmal Nahimi, Morten G Stokholm, Nicola Pavese, Christoph P Beier, David J Brooks, Per Borghammer*

Lancet Neurol 2018; 17: 618–28

Per Borghammer (Aarhus University)

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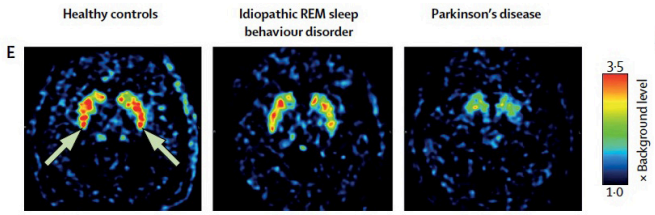
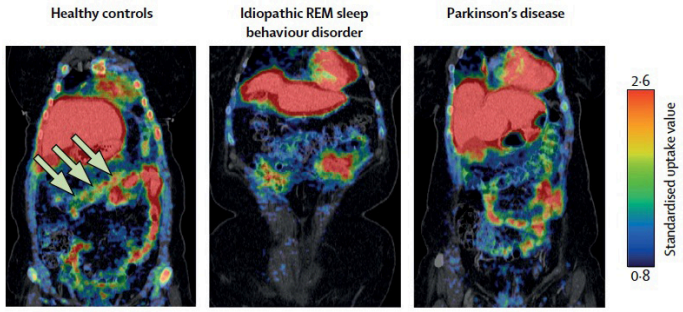
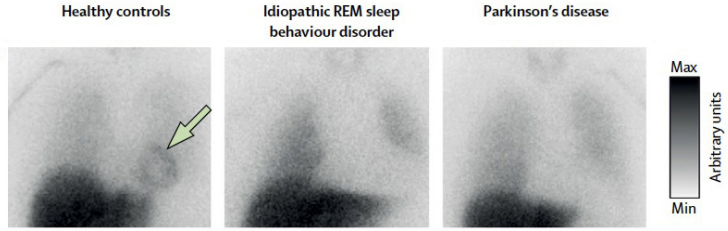
^{18}F-DOPA PET
(dopamine in striatum)



^{11}C-donepezil (DON) PET
(colon nerve function)



^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy
(cardiac nerve function)



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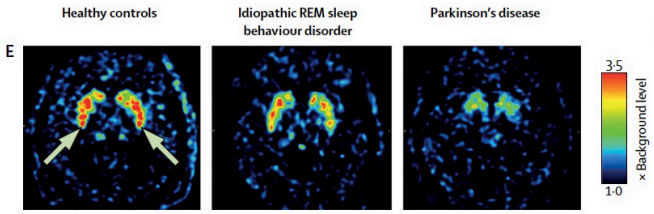

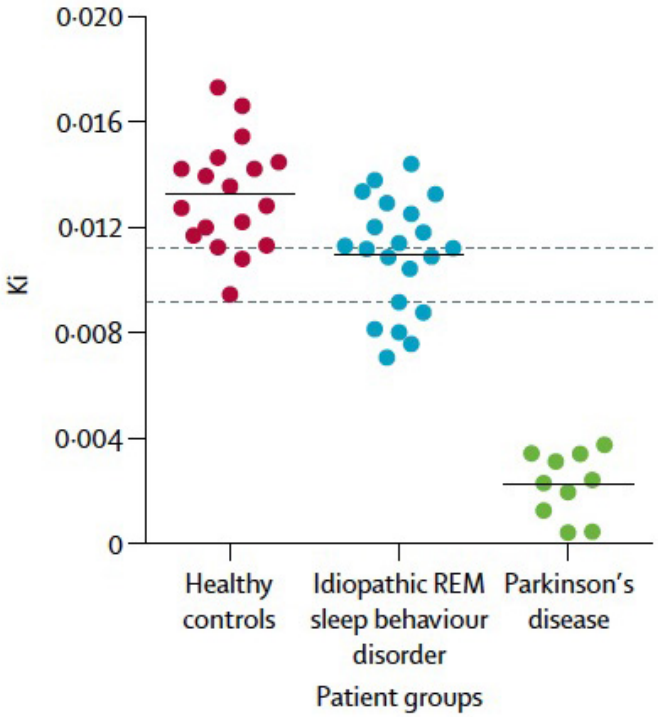

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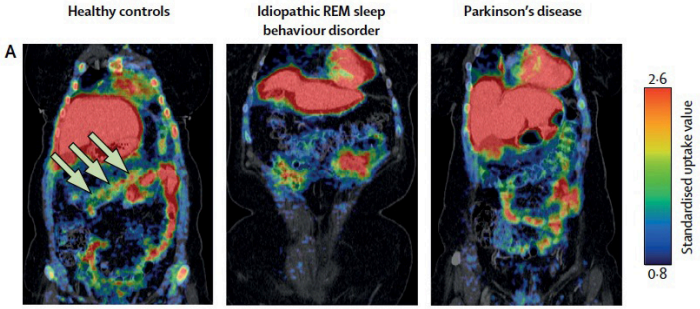

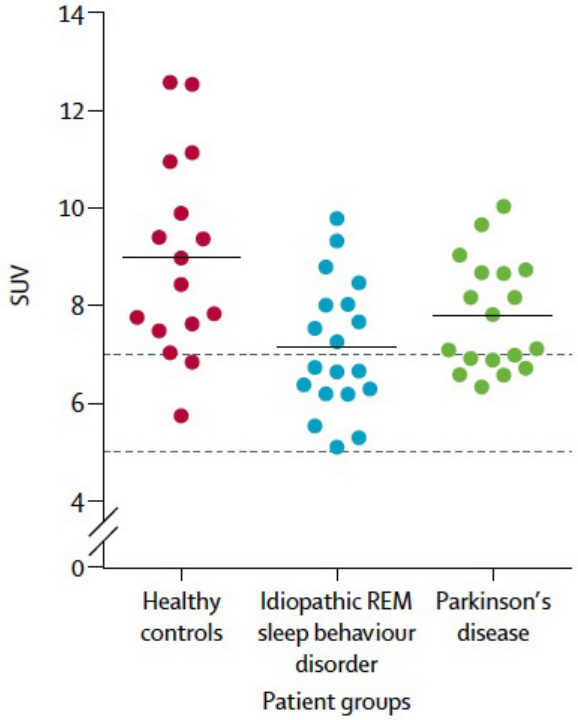

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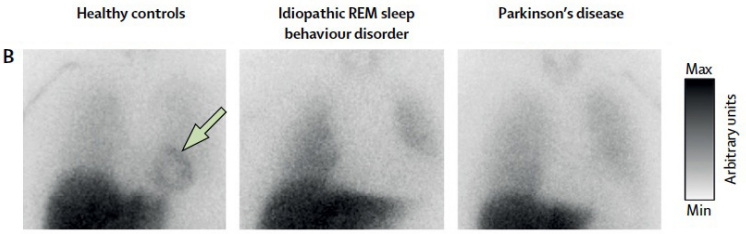

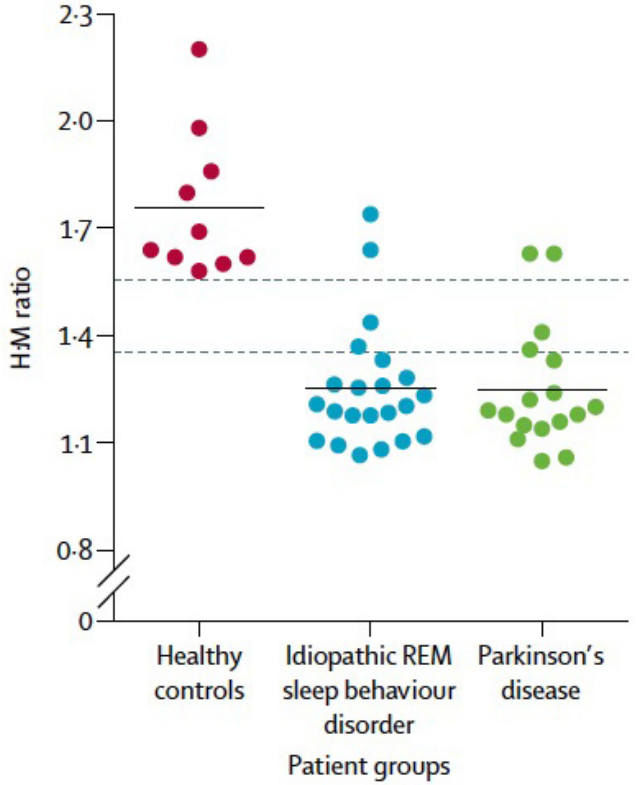

Per Borghammer (Aarhus University)

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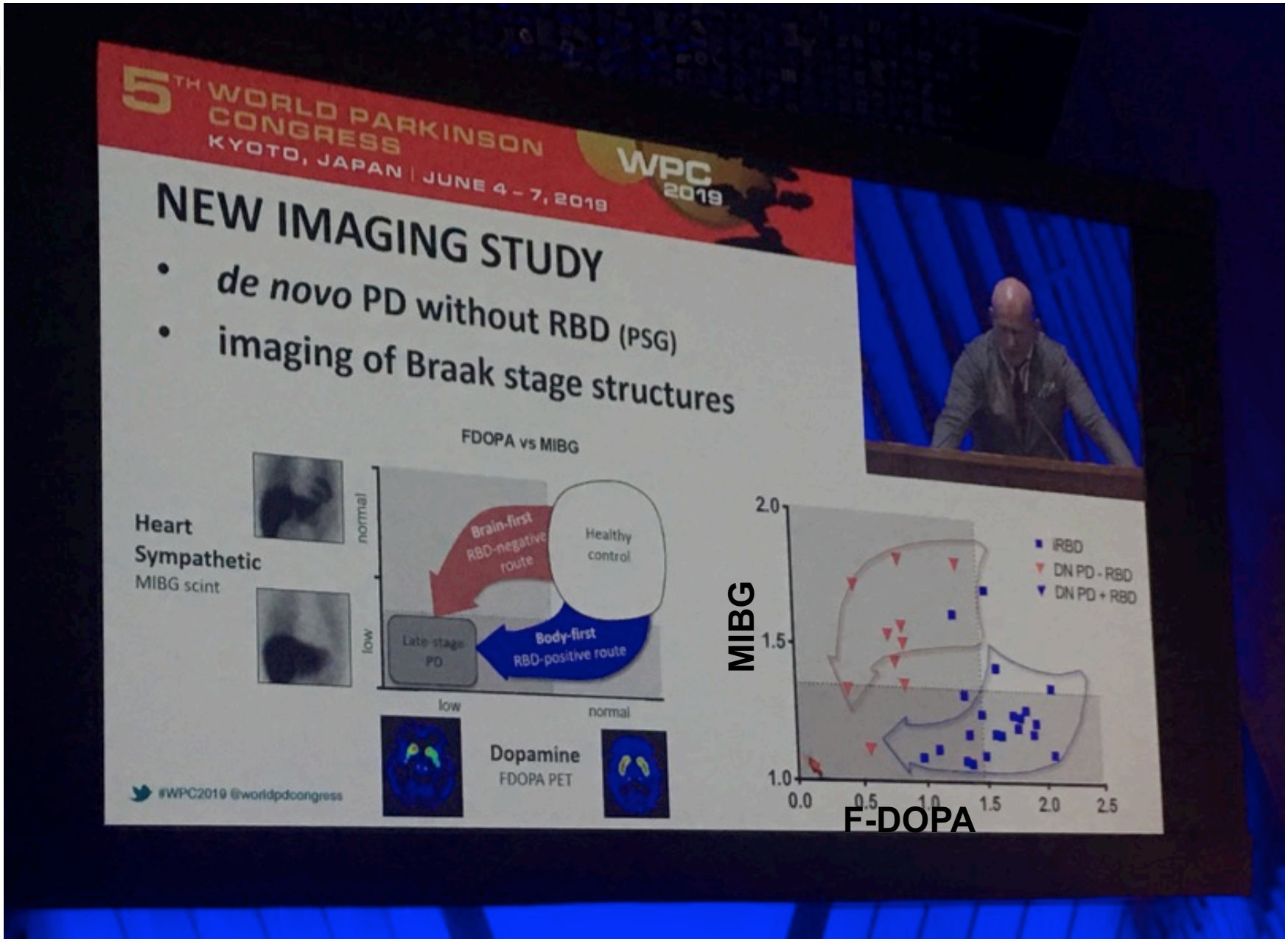
α-Synuclein 'spreading' in PD

- MIBG (cardiac) in RBD patients is **as low as PD**
- Most RBD patients had normal ^{18}F-DOPA
- If RBD present, then at high risk of **"Body-first" PD**.
- PD with RBD have high gut phospho-aSyn (Lewy bodies)
- PD without RBD have less gut phospho-aSyn (Lewy bodies) – **"Brain-first" PD**

Per Borghammer (Aarhus University)



Per Borghammer (Aarhus University)

Take-home messages

- Parkinson's is **highly complex** and **heterogeneous**
- **Non-motor** symptoms are very **significant** and occur **early**
- **BOTH** motor and non-motor symptoms should be:

  (i) **appreciated**, (ii) **measured** and (iii) **treated** accordingly.

7th – 10th June 2022