



Transplantation av dopaminerga celler vid Parkinson's sjukdom - en utopi?

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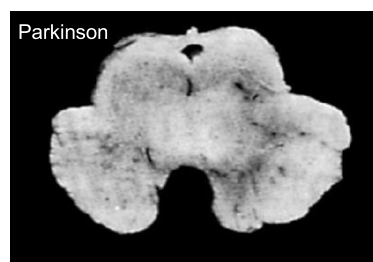
Vårdföreningen Movement Disorders
16 maj 2023

Varför?

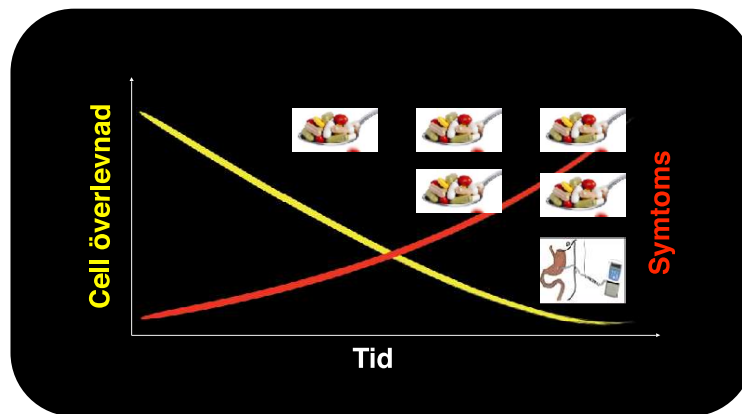


Parkinson's sjukdom

Fortskridande förlust av dopaminerga celler



Fortskridande förlust av dopaminerga celler



Hur då?



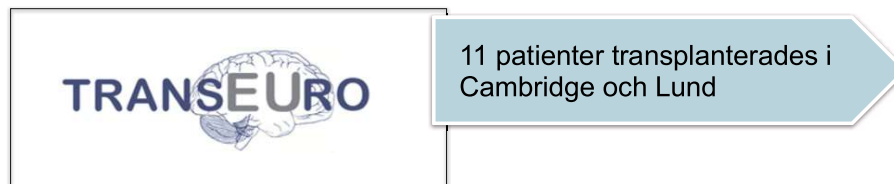
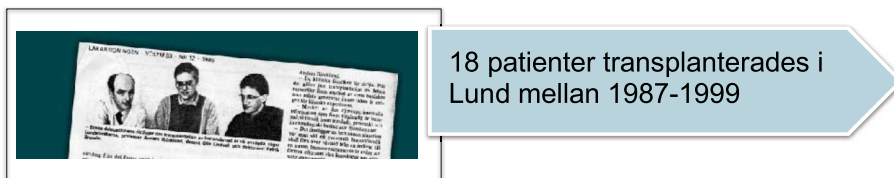
Cell terapi vid Parkinsons sjukdom är baserad på tre hypoteser:



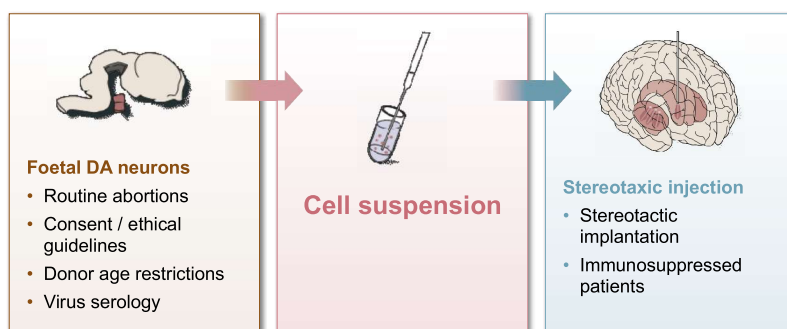
DA, dopaminergic; PD, Parkinson's disease.



Metoden utvecklades i Lund



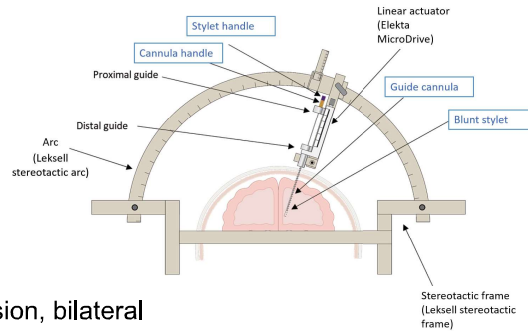
Transplantation av fetala dopaminerga nervceller



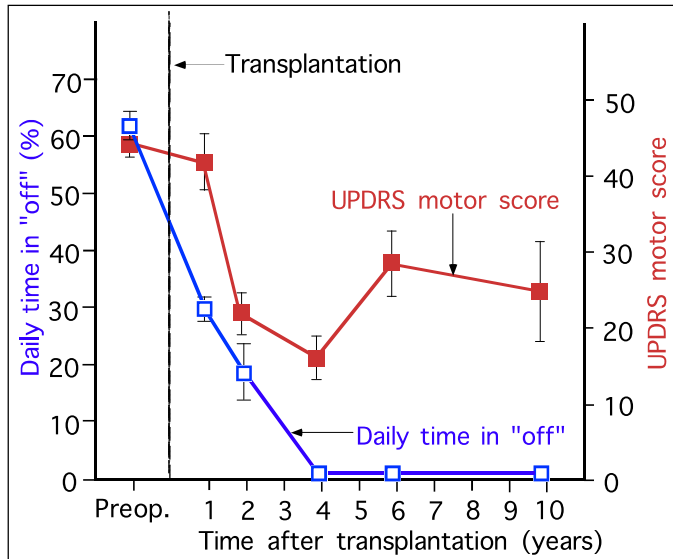
DA, dopaminergic



Surgical procedure at one surgical site

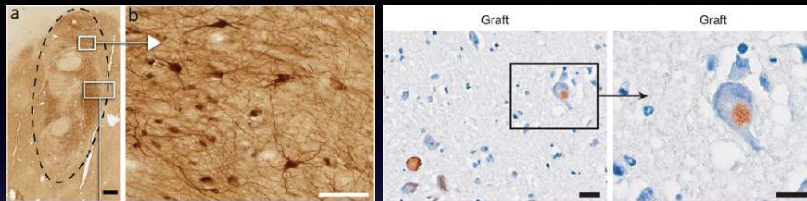


- one session, bilateral
- 5 tracts per putamen/deposits



Piccini et al. Nature Neuroscience 1999

Transplantatet överlever

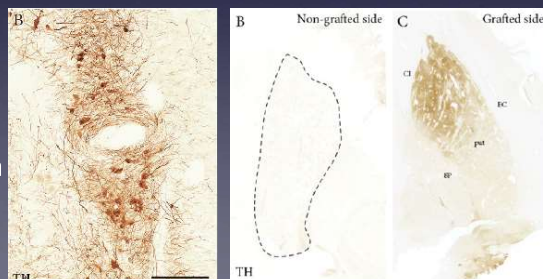


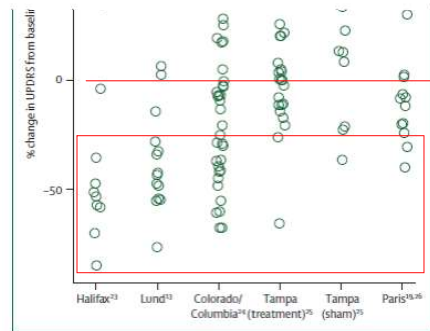
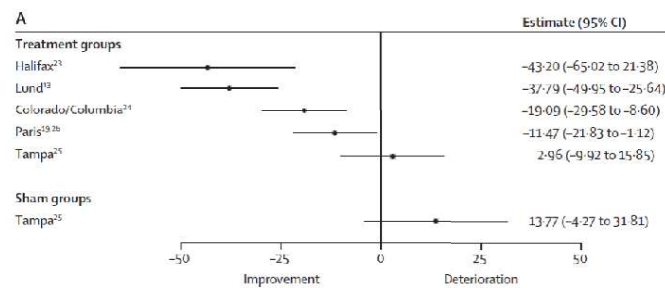
Li et al, Nature Medicine 2008

Graft överlevnad (12, 16 år)

Reinnervation av
putamen
24 år post transplantation

Li et al, PNAS, 2016





Systematisk metaanalys
1/3 av alla transplanterade
Patienter har mycket bra effekt

Figure 1: Change in UPDRS score for patients enrolled in ventral mesencephalic transplant trials

Barker et al. Lancet Neurology 2013

Varför kan man inte använda fetala celler från aborterade foster?

- ⚠ Stora skillnader mellan celler
- ⚠ Brist på material
- ⚠ Etiska övervägande som är olika i olika länder
- ⚠ Logistiska och praktiska problem



Verkligheten av en klinisk studie

Table 1 | The timetable of transplants and the reasons why planned surgeries were cancelled

	2015	2016	2017	2018*	Total
Theater slots	30	62	31	5	128
Completed procedures	7	9	4	1	21
Cancelled (due to)	23	53	27	4	107
Tissue supply	15	44	24	4	87
Tissue viability	1				1
Scheduling issues	2	6	3		11
Instruments	3				3
GMP airflow	2				2
Localization queries		2			2
Oncology case		1			1

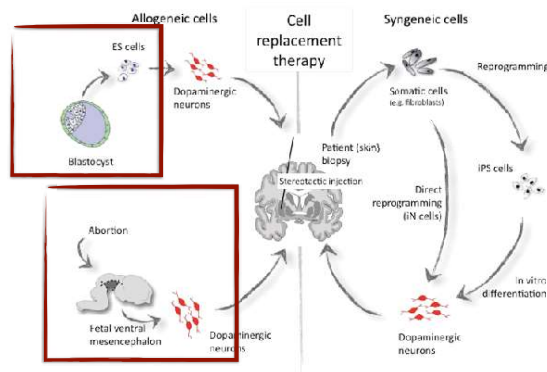
Twenty-one transplant surgeries were completed across the two sites. This included ten bilateral grafts that were done sequentially (that is, at two different surgical operations), and one patient elected not to have a second transplant after their unilateral surgery. *Final procedure March 2018

Barker et al., Nature Medicine 2019

En annan cell källa behövs

Cell sources for DA neurons

Preclinical work by Malin Parmars and Agnete Kirkebys group



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Brundin, Barker and Parmar, 2010

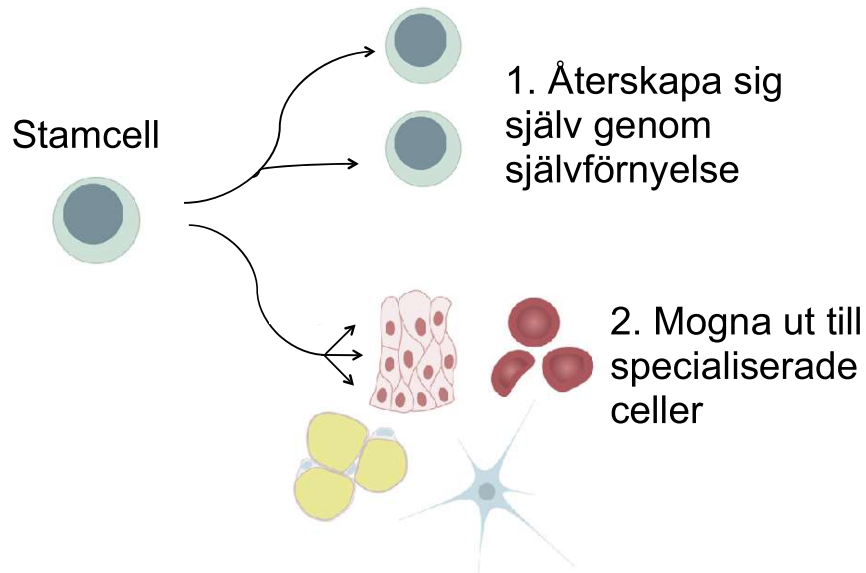
Nya celler från stamceller

- Kan framställas i stora mängder
- Standardiserad
- "Bankable"
- Skall vara minst lika bra som fetala celler

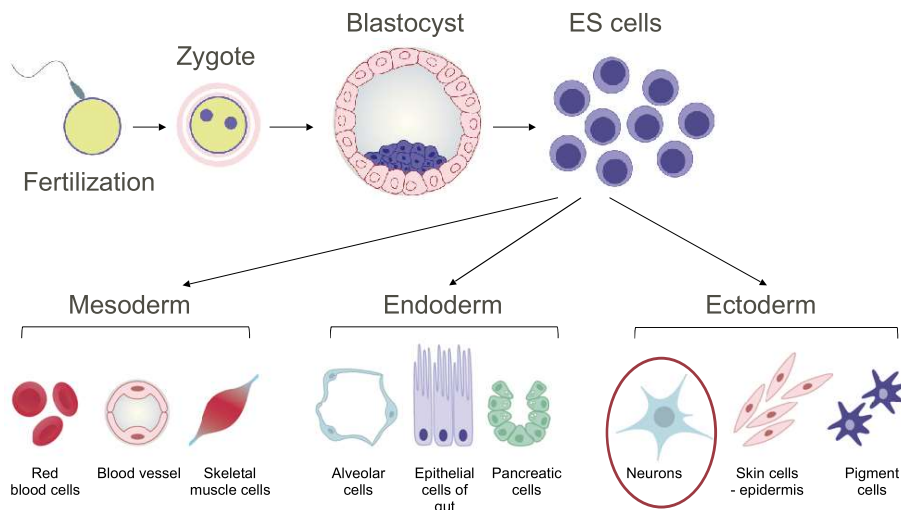
Human embryonic stem cells



Vad är en stamcell?



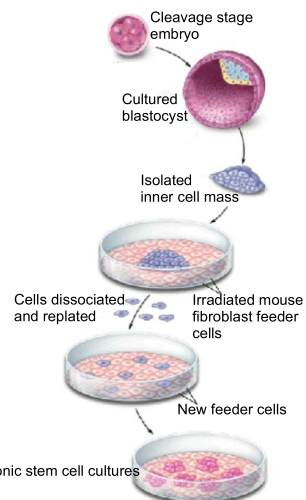
Embryonala stamceller är "pluripotenta" och kan bli alla (>200) av kroppens celltyper



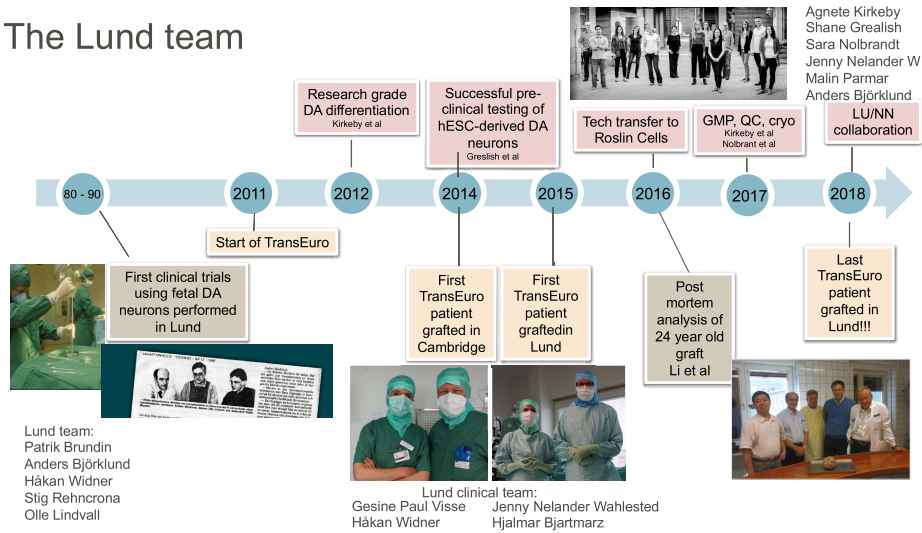
Embryonic stem cells are isolated from preimplantation blastocysts



Recept har utvecklats Vid Lunds Universitet



The Lund team



STEM-PD study



Invented drug product name	STEM-PD
Active substance	Allogeneic embryonic stem cell-derived ventral midbrain dopaminergic progenitor cells
Pharmaco-therapeutic group	Cell therapy (ATMP)
Indication	Parkinson's Disease
Dosage form	Cell suspension
Dosing regimen	Dose-escalation dose 1 and dose 2
Route of administration	Bilateral intraputamenal delivery
Device	Rehnroona/Legradi instrument, a non-CE marked class III neurosurgical medical device.



Objectives

Primary objective

To assess the **safety, tolerability** and **feasibility** of intraputamenal transplantation of the STEM-PD product in patients with moderate PD

Secondary objectives: To evaluate

- the **course and efficacy on clinical features** following transplantation
- the **survival of DA cells** using **PET imaging**
- the **safety and clinical efficacy between doses** of the STEM-PD product, including a **dose response effect**



Outcome measures

Primary outcome measures

- The number and nature of Adverse events (AEs) and serious adverse events (SAEs) in the first 12 months following transplantation
- Absence of space occupying masses on cranial MRI in the first 12 months following transplantation



Secondary outcome measures

- Changes in clinical effects at **36 months** following transplantation compared to baseline
- Changes in motor features (OFF)
- Change in anti-Parkinson medication
- Changes in F-DOPA uptake and DAT binding at 36 months on PET imaging compared to pre-transplant
- The number and nature of SAEs and AEs in the 12 to 36 months period following transplantation

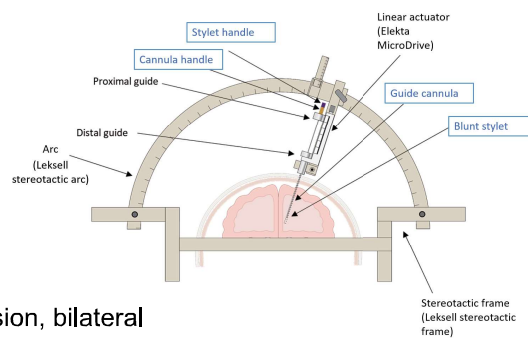
Studiepopulation

N=8



- Patienter med måttlig Parkinson's sjukdom Hoehn-Yahr stadium 2-3 i OFF
- Sjukdomsduration >10 år
- 50-75 år
- Välkända hos oss från TransEuro studien

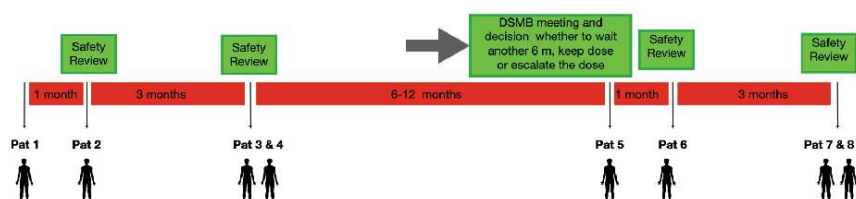
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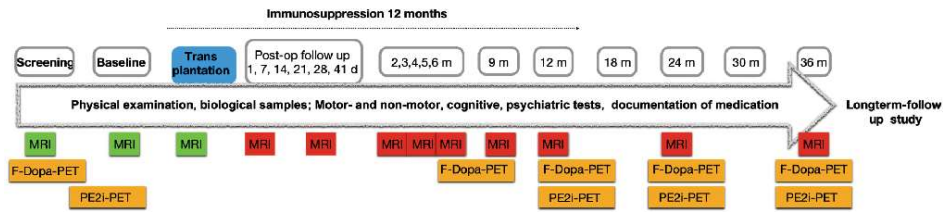


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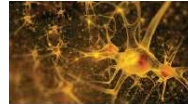
Staggered transplantation





Dose escalation

70,800 cells/ul
2.5 ul/deposit



Dose 1: 3.54 mill cells/hemisphere
20 deposits/hemisphere
to produce 100K mature DA neurons



Dose 2: 7.08 mill cells/hemisphere
40 deposits/hemisphere
to produce 200K mature DA neurons



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STEM-PD in LUND:

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