Autologous neural cell ecosystems (ANCE) transplantation as therapy for Parkinson’s disease: a promising approach

Cognition day – the 5th of October 2016 – University of Fribourg

Simon Borgognon

Laboratory of Prof. Eric Rouiller (UNIFR)
In collaboration with Dr. Jocelyne Bloch & Dr. Jean-François Brunet (CHUV)
Motor cortices & corticospinal tract (CST)

Dum & Strick (2002). *Physiology & Behavior*

[Link to Physiology & Behavior](http://www2.fiu.edu/~condon/pathway.htm)
Simplified motor circuits: direct and indirect pathways

Parkinson’s disease (PD): 2nd most common neurodegenerative disease

Dauer & Przedborski (2003). *Neuron*

Gowers (1886). *A manual of disease of nervous system*

Wolter & Baumann (2014). *Parkinson Disease and Other Movement Disorders*
Parkinson’s disease (PD): treatments

**Pharmacological treatments:**
Levodopa, dopa agonist, ...
→ dyskinesia,...

**Surgical approach:**
Deep brain stimulation (DBS)
→ symptomatic treatment

**Cell therapies:**
- Stem cells
- induced pluripotent stem cells (iPSCs)
→ Immune limitations, tumors, ...

Autologous neural cell ecosystems (ANCE) transplantation

Primate adult brain cell autotransplantation, a new tool for brain repair?

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3 Received 21 December 2004; revised 3 April 2005; accepted 7 April 2005

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Primate Adult Brain Cell Autotransplantation, a Pilot Study in Asymptomatic MPTP-Treated Monkeys

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Primate Adult Brain Cell Autotransplantation Produces Behavioral and Biological Recovery in 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine-Induced Parkinsonian St. Kitts Monkeys

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**Experimental design**

4 adult female macaque monkeys (*Macaca fascicularis*) → Parkinsonian (MPTP) lesion **AND** the cells transplantations

Bloch et al., 2014: efficiency of ANCE transplantation in parkinsonian monkeys

Present study: investigation of the ANCE impact assessing with brain imaging & with fine manual motor behavior

**Comparison between** PRE VS POST-LESION VS POST-TRANSPLANTATION **for each monkey**
Pre-lesion phase: quantitative evaluation of the motor performance

Modified-Brinkman board task
Reach and grasp drawer task
Parkinsonian lesion: the MPTP non-human primate model

2010

months

jan   feb   ...   jul   aug   sep   oct

2014
Cortical biopsies & cell cultures

~10mm$^3$ of cortical tissue from the dorsolateral prefrontal cortex (dLPFC)

Ecosystem formation \textit{in-vitro}
Post-lesion phase: quantitative evaluation of the motor deficits

Monkey-MY – 7 days post-lesion  Monkey-MI – 14 days post-lesion
Cells transplantation: Stereotaxic implantations

Coordinates in MRI scans → Transplantation

6 implantation sites within the Striatum

<table>
<thead>
<tr>
<th>Left hemisphere</th>
<th>Right Hemisphere</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caudate nucleus</td>
<td>Caudate nucleus</td>
</tr>
<tr>
<td>Putamen anterior</td>
<td>Putamen anterior</td>
</tr>
<tr>
<td>Putamen posterior</td>
<td>Putamen posterior</td>
</tr>
</tbody>
</table>

Biopsy

Cells transplantation

MRI acquisitions

2010

months

jan  feb  ...  jul  aug

2014

sep  oct  nov  dec
Post-transplantation phase: quantitative evaluation of the motor improvement

**In-vivo imaging: state of the dopaminergic system with \(^{18}\text{F}\)-Dopa PET scan**

Example in human

Piccini & Whone (2004). *The Lancet Neurology*

![PET scan images](image)

Patlak algorithm → influx rate constant (Ki)
**MPTP lesion and symptoms**

- **Pre-lesion** and **Post-lesion**


\[ ^{18} \text{F-Dopa influx constant (Ki)} \% \]

- **% of pre-lesion Ki**

- **Parkinsonian symptoms evaluated with the Schneider scale**

- **Total Schneider score**

- **Sessions (71 days) from cells transplantations**

- **Monkey-LY** → resistant to MPTP
- **Monkey-LL** → recovered to MPTP
- **Monkey-MY** → moderate PD symptoms
- **Monkey-MI** → severe PD symptoms
Fine manual dexterity in the Modified-Brinkman board task

**Monkey-LY**

<table>
<thead>
<tr>
<th></th>
<th># of pellets in 30 seconds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left hand</td>
<td>ns</td>
</tr>
<tr>
<td>Right hand</td>
<td>ns</td>
</tr>
</tbody>
</table>

**Monkey-LL**

<table>
<thead>
<tr>
<th></th>
<th># of pellets correctly retrieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left hand</td>
<td>***</td>
</tr>
<tr>
<td>Right hand</td>
<td>ns</td>
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</table>

**Monkey-MY**

<table>
<thead>
<tr>
<th></th>
<th># of pellets in 30 seconds</th>
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<tbody>
<tr>
<td>Left hand</td>
<td>**</td>
</tr>
<tr>
<td>Right hand</td>
<td>***</td>
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</table>

**Monkey-MI**

<table>
<thead>
<tr>
<th></th>
<th># of pellets in 30 seconds</th>
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</thead>
<tbody>
<tr>
<td>Right hand</td>
<td>***</td>
</tr>
</tbody>
</table>
Time to execute movement in the drawer task

### Monkey-LY
- *ns*  
- ***ns***

### Monkey-LL
- *ns ns*
- ns

### Monkey-MY
- ***ns***
- ***ns***

### Monkey-MI
- Trials duration [s]
- ***
- *x*
State of the dopaminergic system

PET influx constant (Ki) %

- Monkey-LY: +17.53%
- Monkey-LL: +12.21%
- Monkey-MY: +21.37%
- Monkey-MI: +10.82%

Images show pre-lesion, post-lesion, and post-transplantation states.
• All the four animals were differentially affected by the MPTP lesion (*inter-individual variability*)
  - No correlation between lesion level and behavioral functions
  - Complexity of the MPTP model (Elsworth et al, (2000). *Neuroscience*)

• Cell transplantation promoted *recovery* in voluntary motor tasks and *increase of striatal activity* 

• ANCE transplantation represents an *attractive approach* in order to treat brain dysfunction or brain lesion.

• This promising technique might add *new therapeutic strategies* leading to clinical applications.
Next step: fate of the implanted cells

- **Histological readout**: cells survival, migration, astrocytes activation, 5-HT in resistant and/or recovered monkeys?

![](image1.png)

Implanted cells in Monkey-MY, Caudate nucleus. Scale = 50um

- **Hypothesis**: release of neurotrophic factor (BDNF, GDNF,…) -> **Neuroprotection** effect? **Sprouting** of the remaining dopamine fibers (already suggested by PETscan)?

![](image2.png)

<table>
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<tr>
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<tr>
<td>Severe parkinsonian Monkey-MI (4 days post-lesion)</td>
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