FAIR-PARK II

Conservative iron chelation as a disease-modifying strategy in Parkinson's disease:

a multicentric, parallel-group, placebo-controlled, randomized clinical trial of deferiprone

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement N° 633190

Context

The problem: Parkinson's disease (PD) is a common, chronic, fast-progressing disease, PD affects millions of people - about 1% of the over-60s. It is estimated that the prevalence will at least double by 2030. **None of the currently available drugs can slow down the dramatic progression of the motor handicap (e.g. falls) and non-motor handicap (dementia), which generally lead to institutionalization and death. Today, most patients with PD irremediably progress to a severe state of dependence.** In Europe, the cost of PD was estimated to be at least €14 billion. The huge and increasing socio-economic impact of PD and the immense emotional burden placed on patients and their caregivers represent a great challenge to society.

The symptoms are related to the degeneration of a brain region named substantia nigra which produces dopamine. **Excess iron** is primarily detected in the substantia nigra. Our European project aims to demonstrate that reducing the excess iron with a particular iron chelator, taken orally, could improve the symptoms and decrease the rate of disease progression. This would be the **first non-dopaminergic treatment for neuroprotection**, which could also be of help for other neurodegenerative diseases.

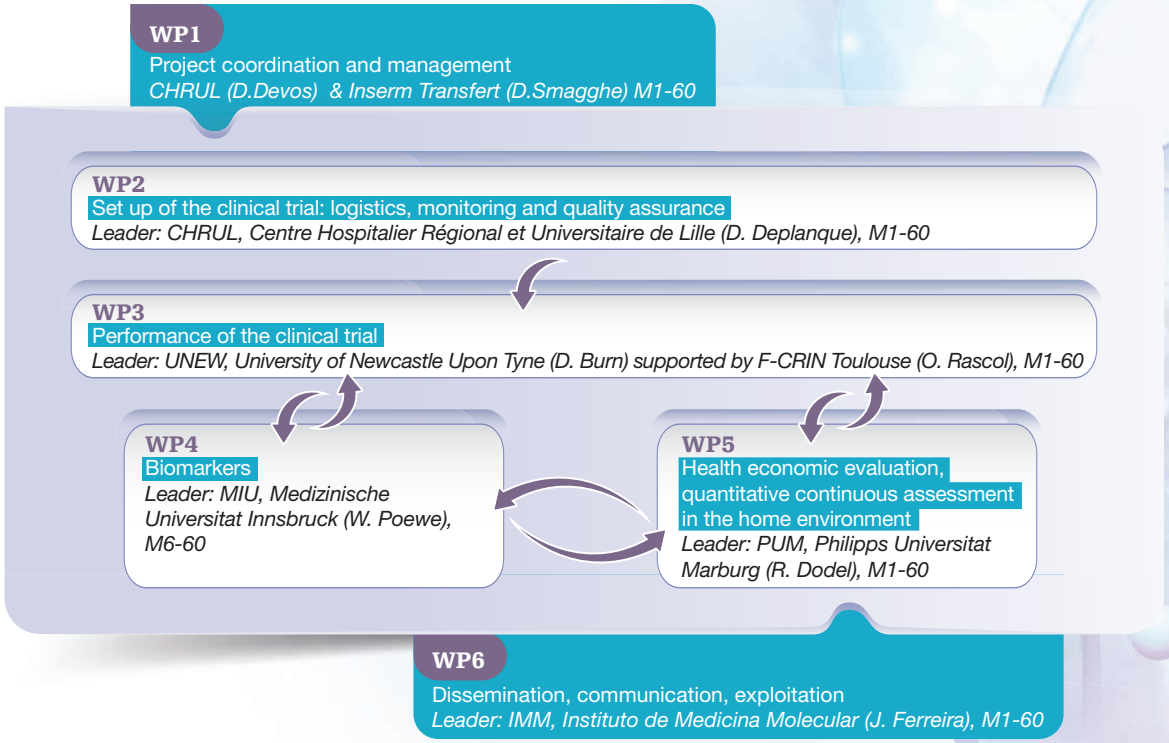
For many years, the excess oxidative stress related to mitochondriopathy has been considered as one of the main mechanisms involved in cell death. Oxidative stress is exacerbated by free iron. Chelation of this free iron has powerful antioxidant properties known to dramatically increase cell survival.

However, we reasoned that to develop this therapeutic approach in humans, chelation strategies that target local and regional iron overload in the brain will necessarily need to avoid systemic iron depletion via the redistribution of iron to endogenous acceptors (i.e. in order to prevent harmful systemic metal loss): this is the new concept of "conservative iron chelation" **(*Cabantchik et al. 2013*).**

We recently demonstrated (for the first time) the feasibility, efficacy and acceptability of the conservative iron chelation approach in pilot translational studies in PD with a prototype drug: deferiprone (DFP). This was demonstrated in the FAIR-PARK-I project led by the Centre Hospitalier Régional Universitaire de Lille, and funded by French Ministry of Health with the support of the University of Lille *(Devos et al., 2014)*.
Interestingly, these clinical results were recently supported by another independent pilot study **(*Dexter et al., 2015*)**. In this context, the CHRUL with the support of NS-PARK/F-CRIN network embarks on a larger Phase II b placebo control confirmatory study.

At present, no neuroprotective drugs are available. If our academic proof-of-concept FAIR-PARK-II study demonstrates a disease modifying effect, this new therapeutic strategy could be offered to the population of patients with PD as a whole. This would represent a considerable advance for patients and would have a huge socio-economic impact.

FAIR-PARK II strategy



The trial's overall objective can be summarized as follows: to demonstrate for the first time in a large phase III, multicentre, parallel-group, placebo-controlled, randomized clinical trial (RCT) **that conservative iron chelation, with the prototype drug, DFP, will slow down the progression of handicap in PD patients** and will not be associated with clinically significant adverse haematological events or other systemic effects. A putative slow-down in the progression of handicap will be monitored in a multicentre, placebo-controlled RCT with 338 patients with *de novo* PD (169 patients per arm). They will be assigned to receive either DFP (15 mg/kg bis in die (BID)) or placebo. Based on the two pilot studies, the optimal dose of 30 mg/kg/day will be used. A 9-month treatment period (period 1) will be followed by a 1-month post-treatment monitoring period (period 2), in order to assess the disease-modifying effect in the absence of a symptomatic effect (i.e. an effect of Inhibition of Catechol-O-Methyl Transferase (ICOMT) activity on dopamine metabolism) of DFP (versus placebo).

The project will run for 60 months and we shall address:

- the risk/benefit balance of this new disease-modifying treatment strategy for PD.
- surrogate and theranostic biomarkers of efficacy and safety.
- health economics and societal impacts.

For the risk/benefit balance, the primary efficacy criterion will be the total score on the Movement Disorders Society- Unified Parkinson's Disease Rating Scale (MDS-UPDRS), which encompasses motor handicaps and non-motor handicaps (i.e. cognition and behaviour) and activities of daily living.

The secondary criteria will include the separate analysis of the MDS-UPDRS subscale scores, quality of life, personal autonomy, safety criteria, and biomarkers of efficacy and safety.

The surrogate and theranostic biomarkers will include:

- Magnetic resonance imaging (MRI), i.e. indirect measurements of iron with an R2* sequence.
- Transcranial ultrasound (i.e. indirect measurements of iron via the hyperechogenicity of substantia nigra).
- Dopamine transporter SPECT imaging (123I-FP-CIT, DATscan®).
- Biochemical biomarkers (in blood and cerebrospinal fluid (CSF)).
- Pharmacogenetic markers (i.e. ceruloplasmin genotypes for the disease-modifying effect of iron chelation and catechol-O-methyltransferase (COMT) genotypes for the symptomatic action of DFP; ***Grolez et al.***, *2015*).

Expected outcomes

- We expect to observe a significantly lower mean total MDS-UPDRS score at weeks 36 and 40 in the DFP group (relative to the placebo group). **This will enable us to demonstrate the efficiency of iron chelation as the first non-dopaminergic disease-modifying strategy in PD. This will be the first in class treatment to slow down the disease progression.**

- **We do not expect to observe anaemia** (or other iron metabolism disorders); anaemia was not a problem in the two independent pilot studies of smaller numbers of patients. **We expect to see a good safety profile**, with a low drop-out rate due to adverse events in all European centres and a low rate of neutropenia/agranulocytosis (with no harmful consequences), thanks to close monitoring with weekly blood counts. This will enable us to demonstrate the safety of the new therapeutic concept of conservative iron chelation in PD.

- **We aim to demonstrate a positive impact on the quality of life.**

- We intend to demonstrate the theranostic value of the clinical, radiological, biological and genetic biomarkers for the response to DFP (i.e., markers which predict answer to the treatment by DFP) - notably the ferric iron overload measured by ultrasound and MRI, the level of degeneration measured by DaT imaging), and the ceruloplasmin genotype for the disease modifier effect and the blood and CSF levels of ferritin.

- We expect to demonstrate the surrogate value of clinical, radiological, biological and/or genetic biomarkers (i.e., markers which predict progression of the disease: prognosis) for monitoring PD progression by analysing the large population of *de novo* patients. Results will be obtained at end of the fourth year of the project and publications will be made at the end of the fifth year.

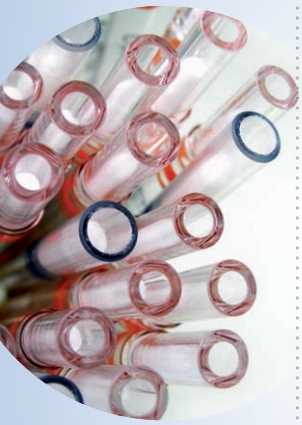
- We intend to demonstrate that DFP has a favourable impact on health economics.

- **We also expect to see a concomitant, positive impact** on the activities of daily living by performing the continuous assessment of the PD-relevant domains with an unobtrusive, quantitative, continuous measurement tool (SENSE-PARK, FP7).

- **In collaboration with NS-PARK/F-CRIN network, we expect to set up an efficient European clinical trial network in PD, in order to promote forthcoming European studies.**

- If the data demonstrate the anticipated effects, we expect to widely disseminate the findings of this new therapeutic concept, in order to promote and support the clinical development of DFP and other selected iron chelators for PD and, where suitable, other neurodegenerative diseases.

17 national, european and international studies will be linked with the project. The study results should prompt academic and industrial research on iron chelation as a disease-modifying treatment in neurodegenerative diseases.



FAIR-PARK II consortium

FAIR-PARK II has established a consortium of excellence that involves experienced neurologists, pharmacologists, methodologists, radiologists, biologists, haematologists, and scientists in the fields of Parkinson's disease, clinical trials, iron metabolism and iron chelators.

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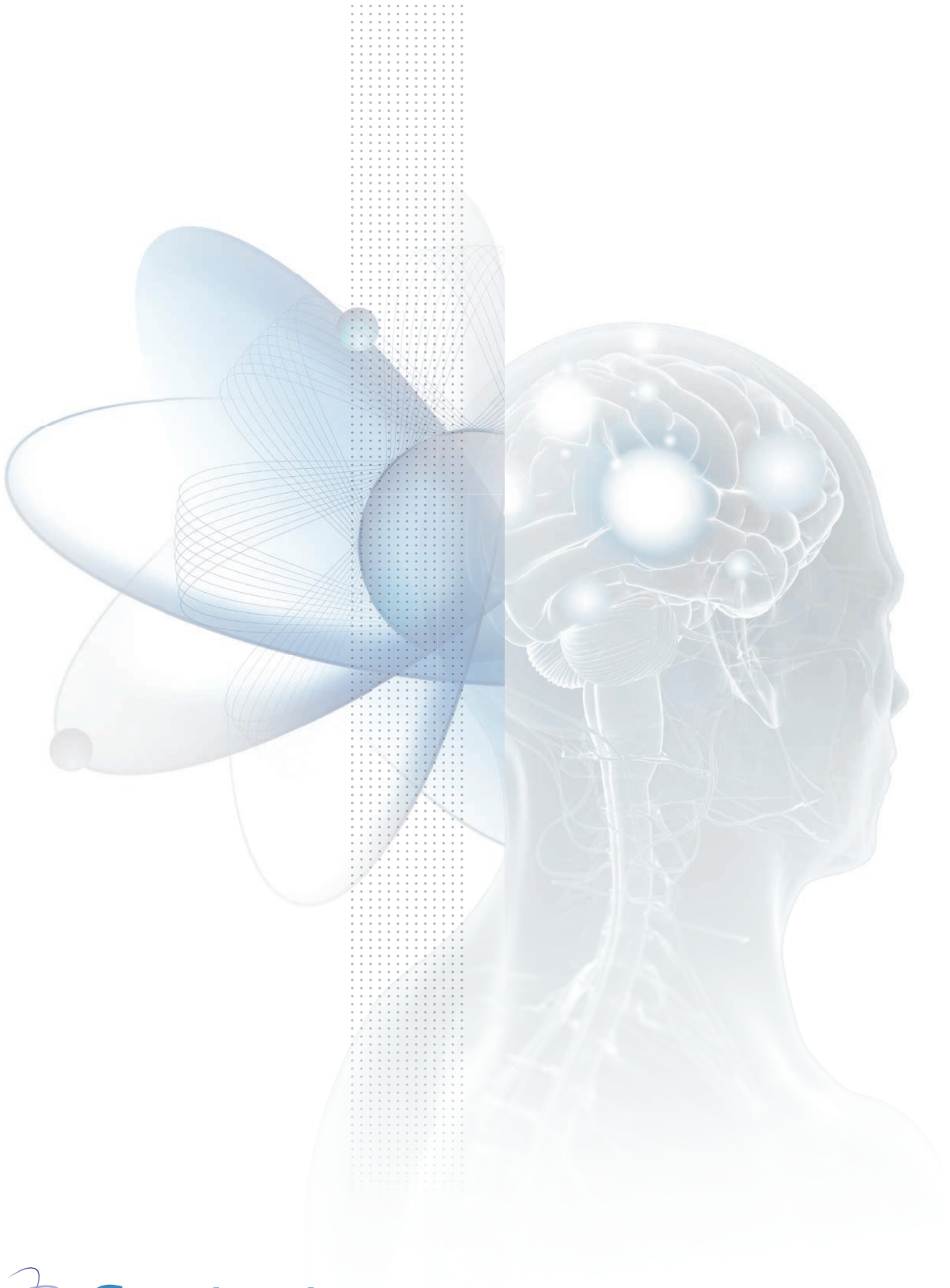

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