

# Putting a stop to dyskinesia



Riccardo

## Project information

Lead researcher	Professor Riccardo Brambilla
Location	University of Cardiff
Cost	£251,496 over 3 years
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Type of project	Project grant
Project code	G-1001

## Project background

Levodopa is the main drug used to treat Parkinson's. It helps the brain to produce more of the chemical dopamine, which is very important for controlling voluntary movement.

People with Parkinson's don't have enough dopamine because most of the nerve cells in the brain that produce it have died. But although the drug can work well for a number of years, people taking levodopa long-term begin to develop the unwanted side-effect of uncontrollable movements, called dyskinesias.

- **Why does taking levodopa lead to dyskinesia?** Parkinson's is a progressive condition which means that, while current treatments help the symptoms, the dopamine-producing nerve cells continue to die. Levodopa helps the remaining ones to make more dopamine but it can only work if there are enough of the cells. As more nerve cells die, a larger dose of levodopa is needed to do the same job. But taking more levodopa makes nerve-cells overactive in other brain areas involved in movement, and this is what results in dyskinesia.
- **Is it possible to prevent levodopa from making nerve-cells overactive?** Nerve cells are controlled by complex chains of events involving different genes and proteins.

Genes tell the cells which proteins to make in order to do their various jobs. Recent research has discovered more about which genes and proteins are involved in the over-activity in nerve cells caused by taking levodopa long-term. One chain of events called the 'Ras-ERK pathway' could be very important for Parkinson's.

- **What is the Ras-ERK pathway?** It's a chain of events that affects how active the nerve cells are in the brain regions controlling movement. Prof Brambilla's research team has some early results showing that stopping the Ras-ERK pathway from working dampens down the over-activity. But the Ras-ERK pathway is also involved in cell survival and is active in other parts of the body. So it's vital that any new treatment that targets this pathway only stops it from working in the specific brain regions affected in Parkinson's.

### What the researchers are doing

Prof Brambilla and his research team are studying a molecule called Ras-GRF1 that's part of the Ras-ERK pathway. They aim to find out whether blocking Ras-GRF1 from working can reduce or stop the involuntary movements that develop with high doses of levodopa. Ras-GRF1 is a good target because it's not involved in cell survival and is only found in the brain. The team will measure nerve cell activity in mice that have an animal version of Parkinson's to find out what happens when Ras-GRF1 is either active or inactive. They'll also study how the mice behave to see whether blocking Ras-GRF1 gives them better movement control.

### How the research will help people with Parkinson's

When the project ends, Prof Brambilla's team should have learned whether blocking Ras-GRF1 can prevent dyskinesia in a mouse-model of Parkinson's. If so, they'll try to develop a drug that could be tested in people with Parkinson's. Having a drug like this would mean that people could control their symptoms with levodopa for longer, without developing the unwelcome side-effect of involuntary movements. This would greatly improve the quality of life for people with Parkinson's.

### For more information, please talk to the Research Team

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