



Press Release, January 28, 2016

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Identifying Another Piece in the Parkinson's Disease Pathology Puzzle

International Consortium Identifies and Validates Cellular Role of Priority Parkinson's Disease Drug Target, LRRK2 Kinase

An international public-private consortium of researchers led by The Michael J. Fox Foundation for Parkinson's Research has had its work published in *eLife*. A team comprising investigators from the Max Planck Institute of Biochemistry, the University of Dundee, GlaxoSmithKline and MSD, known as Merck & Co., Inc., in the United States and Canada, has discovered that the LRRK2 kinase regulates cellular trafficking by deactivating Rab proteins. This finding illuminates a novel route for therapeutic development and may accelerate testing of LRRK2 inhibitors as a disease-modifying therapy for Parkinson's, the second most common neurodegenerative disease.

MARTINSRIED, GERMANY; DUNDEE, UNITED KINGDOM; NEW YORK (JANUARY 28) — An international public-private research consortium has identified and validated a cellular role of a primary Parkinson's disease drug target, the LRRK2 kinase. This important finding, published in the online, open-access *eLife* journal, illuminates a novel route for therapeutic development and intervention testing for Parkinson's, the second most common neurodegenerative disease after Alzheimer's.

A team of investigators from the Max Planck Institute of Biochemistry, the University of Dundee, The Michael J. Fox Foundation for Parkinson's Research (MJFF), GlaxoSmithKline (GSK) and MSD contributed unique tools and expertise toward rigorous systematic testing that determined the LRRK2 kinase regulates cellular trafficking by deactivating certain Rab proteins (3, 8, 10 and 12).

Mutations in the *LRRK2* gene are the greatest known genetic contributor to Parkinson's disease. Pharmaceutical companies are developing LRRK2 kinase inhibitors to correct the effects of those mutations and treat Parkinson's disease. This new breakthrough finding that links mutant LRRK2 to inappropriate deactivation of Rab function unlocks more than 20 years of accumulated knowledge



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of the roles of Rab proteins. This knowledge can now be integrated to significantly improve our understanding of LRRK2 dysfunction in the Parkinson's disease process.

“The pathological cascade leading to brain diseases such as Parkinson's likely includes many cellular players,” said Matthias Mann, PhD, Director of the Department of Proteomics and Signal Transduction at the Max Planck Institute of Biochemistry. “The identification of this LRRK2 substrate gives us a central piece in this puzzle and another potential place to intervene in the disease process.”

Marco Baptista, PhD, MJFF Senior Associate Director of Research Programs, said, “Identification of Rab proteins as a LRRK2 substrate presents a tool to measure the impact of these inhibitors not only on LRRK2 levels but also on LRRK2 function. This critical component will advance development of these therapies to slow or stop Parkinson's disease, patients' greatest unmet need.”

This MJFF-led consortium used a combination of tools in the discovery, including a knock-in mouse model of the most common *LRRK2* mutation strongly associated with Parkinson's (created by GSK), a second knock-in *LRRK2* mouse model generated by MJFF, LRRK2 kinase inhibitors from GSK and Merck, and state-of-the-art mass spectrometry. These tools — and the collaborative spirit that united the partners — were necessary to make this finding.

“This unique model of collaboration and our systematic approach across laboratories using advanced technologies and layers of confirmation provide a firm foundation from which to continue this line of investigation and further refine our understanding of the LRRK2 Rab relationship,” said Dario Alessi, PhD, Director of the Protein Phosphorylation and Ubiquitylation Unit at the University of Dundee.

With additional MJFF funding, this research group now is working to further characterize the Rab proteins modified by LRRK2 and to understand how an imbalance in cellular trafficking leads to the degeneration of neurons seen in Parkinson's disease.

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About the Max Planck Institute of Biochemistry

The Max Planck Institute of Biochemistry (MPIB) belongs to the Max Planck Society, an independent, non-profit research organization dedicated to top level basic research. As one of the largest Institutes of the Max Planck Society, 850 employees from 45 nations work here in the field of life sciences. In currently eight departments and about 25 research groups, the scientists contribute to the newest findings in the areas of biochemistry, cell biology, structural biology, biophysics and molecular science. The MPIB in Munich-Martinsried is part of the local life-science-campus where two Max Planck Institutes, a Helmholtz Center, the Gene-Center, several biomedical faculties of two Munich universities and several biotech-companies are located in close proximity. www.biochem.mpg.de





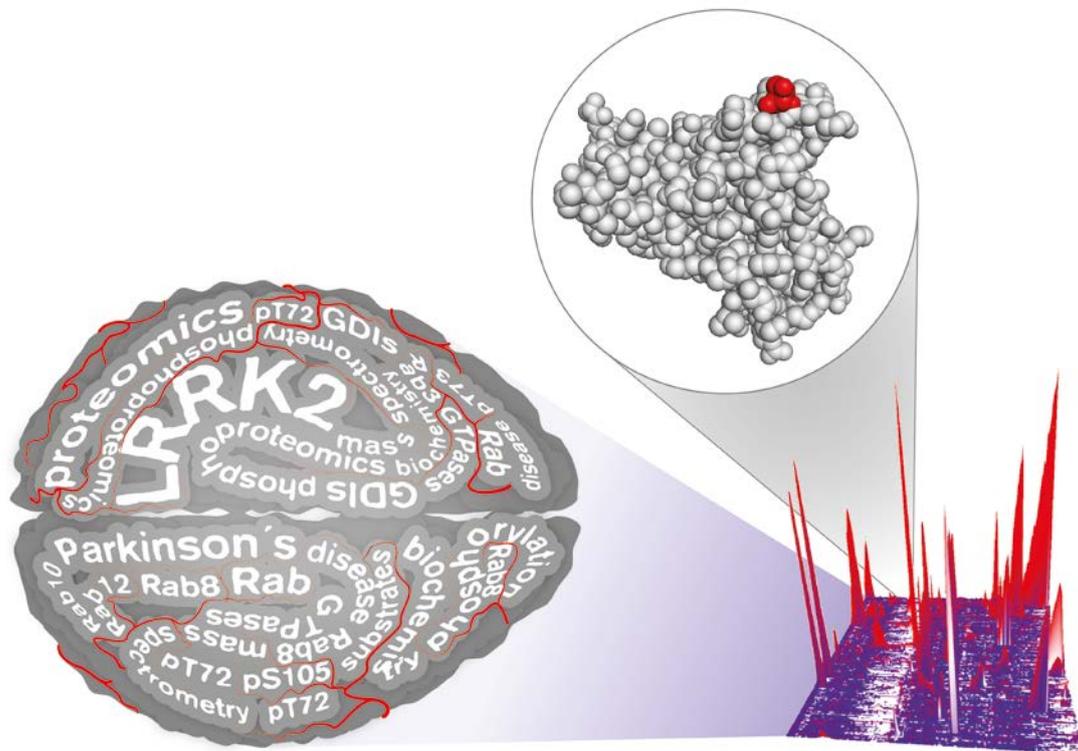
About the University of Dundee

The University of Dundee is the top ranked University in the UK for biological sciences, according to the 2014 Research Excellence Framework. Dundee is internationally recognised for the quality of its teaching and research and has a core mission to transform lives across society. More than 17,000 students are enrolled at Dundee, helping make the city Scotland's most student-friendly. The University is the central hub for a multi-million pound biotechnology sector in the east of Scotland, which now accounts for 16% of the local economy. www.dundee.ac.uk

About The Michael J. Fox Foundation for Parkinson's Research

As the world's largest nonprofit funder of Parkinson's research, The Michael J. Fox Foundation is dedicated to accelerating a cure for Parkinson's disease and improved therapies for those living with the condition today. The Foundation pursues its goals through an aggressively funded, highly targeted research program coupled with active global engagement of scientists, Parkinson's patients, business leaders, clinical trial participants, donors and volunteers. In addition to funding more than \$525 million in research to date, the Foundation has fundamentally altered the trajectory of progress toward a cure. Operating at the hub of worldwide Parkinson's research, the Foundation forges groundbreaking collaborations with industry leaders, academic scientists and government research funders; increases the flow of participants into Parkinson's disease clinical trials with its online tool, Fox Trial Finder; promotes Parkinson's awareness through high-profile advocacy, events and outreach; and coordinates the grassroots involvement of thousands of Team Fox members around the world. For more information, visit us on the [Web](#), [Facebook](#), [Twitter](#), and [LinkedIn](#).





Caption:

Parkinson's researchers used proteomics to identify Rab proteins as a physiological substrate of LRRK2, a Parkinson's drug target. This finding may accelerate current research and open a novel therapeutic avenue.

Original publication:

M. Steger, F. Tonelli, G. Ito, P. Davies, M. Trost, M. Vetter, S. Wachter, E. Lorentzen, G. Duddy, S. Wilson, M. A. S. Baptista, B. K. Fiske, M. J. Fell, J. A. Morrow, A. D. Reith, D. R. Alessi & M. Mann: Phosphoproteomics reveals that Parkinson's disease kinase LRRK2 regulates a subset of Rab GTPases, *eLife*, January 2016

DOI: <http://dx.doi.org/10.7554/eLife.12813>





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