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Neuroprotection by lysosomal transport mechanisms in Parkinson's disease

I would like to express my sincere gratitude to the Queen Elisabeth Foundation for supporting our research. It has been a true honor to interact with the Foundation, which offered important exposure to my team and provided important support to conduct pioneering research that is now being published in high impact factor journals. We obtained ground-breaking discoveries in cell transport biology, disease mechanisms in neurodegeneration, which culminated in drug discovery programs. We identified the transporters ATP13A2 and ATP10B as important mediators of lysosomal functionality and membrane integrity by preventing toxic substrate accumulation in the lysosome. Both transporters are implicated in Parkinson's disease. As such, our work opened possibilities for drug discovery in Parkinson's disease, which occurs in collaboration with CD3 and pharmaceutical companies.

1. Aims of the Project

Parkinson's disease (PD) is one of the most common neurodegenerative disorders. The neurons in PD patients accumulate protein aggregates and impaired mitochondria, which contributes to cell death. Lysosomes provide protection by efficiently removing damaged proteins and mitochondria, and are disturbed in PD. Genetic evidence points to two lysosomal transport systems that are impaired in PD, which are the subject of this project: ATP13A2/PARK9 and ATP10B, a novel, candidate PD gene. Both ATP10B and ATP13A2 belong to the P-type ATPase family of active transporters.

The overall aim of the study is to unravel and compare the transport function and cellular implications of ATP13A2 and ATP10B in endo-/lysosomes, establish their role in PD onset and assess their value as therapeutic targets.

2. Progress report ATP13A2

At the end of the program we managed to reach all major project goals. In short, we established ATP13A2 as a lysosomal polyamine exporter and ATP10B as a lysosomal glucosylceramide exporter. These two transport systems are critical for lysosomal and mitochondrial functionality. Our study offers novel insights into lysosomal biology, reveals new disease pathways in neurodegeneration and validates ATP13A2 and ATP10B as two interesting drug targets.

2.1. ATP13A2 results

(a) Results obtained from this part of the study were reported in a research article accepted in Nature.

Sarah van Veen*, Shaun Martin*, Chris Van den Haute, Veronick Benoy, Joseph Lyons, Roeland Vanhoutte, Jan Pascal Kahler, Jean-Paul Decuypere, Géraldine Gelders, Eric Lambie, Jeffrey Zielich, Johannes V. Swinnen, Wim Annaert, Patrizia Agostinis, Bart Ghesquière, Steven Verhelst, Veerle Baekelandt, Jan Eggermont, Peter Vangheluwe (*equal contribution). ATP13A2 deficiency disrupts lysosomal polyamine export. **Nature**, accepted Dec 2nd 2019, anticipated e-publication Jan 29th 2020. (IF 43.07).

Summary of our research findings:

ATP13A2 (PARK9) is a late endo-lysosomal transporter of unknown function that is genetically implicated in a spectrum of neurodegenerative disorders, including Kufor-Rakeb syndrome, a parkinsonism with dementia and early-onset Parkinson's disease (PD). ATP13A2 offers protection against genetic and

environmental risk factors of PD, whereas loss of ATP13A2 compromises lysosomal function. The lysosomal transport function of ATP13A2 remained unclear, but here, we establish ATP13A2 as a lysosomal polyamine exporter with highest affinity for spermine. Polyamines stimulate the activity of purified ATP13A2, while disease mutants are functionally impaired to a degree that correlates with the disease phenotype. ATP13A2 promotes cellular polyamine uptake via endocytosis and transports polyamines into the cytosol, which highlights a role for endo-lysosomes in cellular polyamine uptake. At high concentrations, polyamines induce cell toxicity, which is exacerbated by ATP13A2 loss due to lysosomal dysfunction, lysosomal rupture and cathepsin B activation. This phenotype is recapitulated in neurons and nematodes with loss of ATP13A2 or its orthologues. Thus, defective lysosomal polyamine export is a new mechanism for lysosome-dependent cell death that may be implicated in neurodegeneration. Our findings further shed light on the molecular identity of the elusive mammalian polyamine transport system.

(b) In a follow-up study, we report the mitochondrial phenotype of ATP13A2 loss of function models. We found that impaired lysosomal polyamine export following ATP13A2 loss of function reduces the cells anti-oxidative capacity and sensitizes cells to mitochondrial-derived oxidative stress. This highlights that polyamines are important ROS scavengers in cells.
Stephanie Vrijsen*, Laura Besora-Casals*, Sarah van Veen, Jeffrey Zielich, Chris Van den Haute, Christian Fischer, Patrizia Agostinis, Veerle Baekelandt, Jan Eggermont, Eric Lambie#, Shaun Martin#, Peter Vangheluwe#. (equal * first and # last contribution). ATP13A2-mediated endo-lysosomal polyamine export provides a mitochondrial antioxidant response. Under review in **PNAS** (IF 9.58).

Summary of our research findings:
Loss-of function mutations in ATP13A2 are implicated in neurodegenerative disorders, including Parkinson's disease (PD). We recently discovered that the late endo-/lysosomal ATP13A2 exports endocytosed polyamines into the cytosol, whereas ATP13A2 dysfunction causes lysosomal accumulation of polyamines and rupture. Here, we reveal how ATP13A2 provides protection against mitochondrial toxins such as rotenone, an environmental PD risk factor. Rotenone promoted mitochondrial-generated superoxide (mitoROS), which was exacerbated by ATP13A2 deficiency in SH-SY5Y neuroblastoma cells and patient derived fibroblasts, disturbing mitochondrial functionality and inducing toxicity. Moreover, following ATP13A2 knockdown rotenone induced an ATF4-CHOP dependent stress response that was blocked with MitoTempo, a mitochondrial antioxidant. The impact of ATP13A2 on mitoROS can be explained by the anti-oxidant properties of the polyamine spermine. Indeed, the polyamine transport activity of ATP13A2 is required for lowering the mitoROS levels. Supplementation of exogenous spermine quenched rotenone-induced mitoROS production, which requires ATP13A2. Moreover, pharmacological inhibition of the intracellular polyamine synthesis increased mitoROS accumulation when ATP13A2 is deficient. These results support a model of endocytic spermine uptake that is subsequently transported in the cytosol via ATP13A2 to quench mitoROS. Importantly, our cellular observations were recapitulated *in vivo*, in a *Caenorhabditis elegans* strain deficient in the ATP13A2-orthologue *catp-6*. These animals exhibited elevated mitoROS, induction of an ATF4-dependent stress marker and mitochondrial dysfunction in basal conditions, which was reversed with MitoTempo. Moreover, this strain was hypersensitive to rotenone toxicity and rescued by catp-6 expression. Our study reveals a novel, conserved and protective antioxidant response that depends on ATP13A2-mediated lysosomal spermine export.

2.2. ATP13A2 impact

(a) ATP13A2 belongs to the enigmatic polyamine transport system in mammalian cells, which remained unknown for several decades, despite intensive research. This is highly relevant since polyamines are vital and abundant molecules that are important for cell survival and proliferation, and determine longevity of organisms.

(b) ATP13A2 is implicated in Parkinson's disease, and loss of ATP13A2 causes lysosomal dysfunction, which causes cell death, and reduces the anti-oxidant capacity in cells, contributing to oxidative stress. This represents a new disease mechanism in neurodegeneration that will be highly influential in the field of Parkinson's research.

(c) ATP13A2 is a member of four isoforms belonging to the P5-type ATPases. Based on sequence comparison these related isoforms ATP13A2-5 are most likely polyamine transporters that together may represent the mammalian transport system. Several of these isoforms are implicated in a broad range of major human diseases, ranging from cancer, neurodegeneration, neurodevelopmental and cardiovascular diseases. Our findings are therefore relevant to study impaired polyamine homeostasis and P5-type ATPases in multiple diseases.

2.3. ATP13A2 perspectives for drug discovery

We identified a drugable activation mechanism of ATP13A2, which may be targeted by small molecules as a possible treatment of PD. ATP13A2 activation may improve lysosomal function and decrease oxidative stress, i.e. targeting two major defects in PD.
Two patents were filed based on these discoveries, and a project with the Center for Drug Design and Discovery (CD3) for high throughput screening of ATP13A2 activator molecules is initiated started, which will be funded by the Michael J. Fox Foundation.

3. Progress report ATP10B

3.1. Results

(a) The results obtained from this part of the study were summarized in a research article currently in revision in Acta Neuropathologica.
Shaun Martin*, Stefanie Smolders*, Chris Van den Haute, Bavo Heeman, Sarah van Veen, David Crosiers, Igor Beletchi, Aline Verstraeten, Helena Gossye, Géraldine Gelders, Philippe Pals, Norin Hamouda, Sebastiaan Engelborghs, Jean-Jacques Martin, Jan Eggermont, Peter Paul De Deyn, Patrick Cras, Veerle Baekelandt, Peter Vangheluwe#, Christine Van Broeckhoven# (shared * first and # last co-authors). Mutated ATP10B increases Parkinson's disease risk by compromising lysosomal glucosylceramide export. Under review in **Acta Neuropathologica (IF 18,17)**.

Several PD-associated mutations were identified in the ATP10B gene, a P-type ATPase with unknown function (Prof. C. Van Broeckhoven, joint patent WO2016166373A1). We established that the *ATP10B* gene encodes a late endo-lysosomal lipid flippase that translocates the lipids glucosylceramide (GluCer) and phosphatidylcholine (PC) towards the cytosolic membrane leaflet. The PD associated ATP10B mutants are catalytically inactive and fail to provide cellular protection against the environmental PD risk factors rotenone and manganese. In isolated cortical neurons, loss of ATP10B leads to general lysosomal dysfunction and cell death. Impaired lysosomal functionality and integrity is well known to be implicated in PD pathology and linked to multiple causal PD genes and genetic risk factors. Our results indicate that loss of function mutations in ATP10B increase risk for PD by disturbed lysosomal export of GluCer and PC. Both ATP10B and glucocerebrosidase, encoded by the PD risk gene GBA1, reduce lysosomal GluCer levels, emerging lysosomal GluCer accumulation as a potential PD driver.

3.2. ATP10B impact

(a) We discovered that GluCer transporters are implicated in PD. We found that ATP10B transports GluCer from the lysosomal compartment in cells, which is a novel insight, opening a novel and highly relevant research area about the translocation and redistribution of GluCer in mammalian cells, and how this may be implicated in PD.

(b) GBA1 mutations are the most common PD risk factor affecting 10% of the PD population. GBA1 encodes for GCase that degrades GluCer in lysosomes. Since loss of either GBA1 or ATP10B leads to an increased lysosomal GluCer content, lysosomal GluCer accumulation emerges as a critical regulator of neuronal health and survival, which is an important message for the PD field.

(c) Based on similarities between both studies lysosomal substrate accumulation is emerging as a likely driver for PD, which is a key finding and novel insight in PD.

3.3. ATP10B perspectives for drug discovery

Our study shows that ATP10B modulators may be of therapeutic interest to improve lysosomal dysfunction and prevent accumulation of glucosylceramide in lysosomes, which is of interest for GBA1-associated PD (10% of the PD population). With our established biochemical and cellular assays, we're preparing for a high throughput screening to identify ATP10B modulators, which occurs in collaboration with the Center for Drug Design and Discovery (CD3). A patent on ATP10B in neurodegeneration was filed.

4. Publications and Events (2017-2019)

4.1. Events and media coverage

- On November 23rd 2017, Princess Astrid visited the Laboratory of Cellular Transport Systems of Prof. Dr. Peter Vangheluwe and the Laboratory of Ion Channel Research of Prof. Dr. Thomas Voets in the Department of Cellular and Molecular Medicine, KU Leuven. This event has been covered by the press to inform the broad public about our research activities:
  http://www.robtv.be/nieuws/leuven/prinses-astrid-bezoekt-laboratoria-ku-leuven;
  http://www.nieuwsblad.be/cnt/dmf20171123_03203478;
  https://www.hln.be/regio/leuven/prinses-astrid-bezoekt-gasthuisberg~aeaaf126/;
  https://nieuws.kuleuven.be/nl/2017/prinses-astrid-bezoekt-leuvense-labos;
  https://www.facebook.com/ROBtv.be/videos/10154952286531825/;
  https://www.monarchie.be/nl/agenda/vib-center-for-brain-disease-research;
  http://www.fmre-gske.be/pages/nl/bezoekKULeuven3.html

- **Ernest Solvay prize**, Queen Elisabeth Foundation (€ 25,000) - Prof. Dr. Peter Vangheluwe (KU Leuven) - Neuroprotection by lysosomal transport mechanisms in Parkinson's disease
  - Award ceremony at the Palace, 26/04/2018
  - https://gbiomed.kuleuven.be/english/research/50000618/spotlight/ernest-solvay-prijs-voor-prof-peter-vangheluwe-voor-zijn-onderzoek-neuroprotection-by-lysosomal-transport-mechanisms-in-parkinsons-disease-1
  - Video interview and coverage of the research topic (by Reinout Goddyn)
  - https://vimeo.com/266308386

- Press release highlighting our findings reported in the Nature paper, currently scheduled January 29th 2020, subject to change.

4.2. Patents

– A novel gene in neurodegenerative disease; inventors: Christine Van Broeckhoven, Jessie Theuns, Aline Verstraeten, Bavo Heeman, Peter Vangheluwe, Filing date: April 18th 2016; ZL990060
– Screening Methods and Pharmaceutically active compounds for neurodegenerative diseases; inventors: Peter Vangheluwe, Veerle Baekelandt, Patrizia Agostinis, Chris Van den Haute, Sarah van Veen, Shaun Martin, Jan Eggermont. Filing date: July 3rd 2017; ZL916077
– Screeningsmethode ATP13A2; inventors: Peter Vangheluwe. Filing data: December 18th 2019; ZL919090

4.3. Publications in 2017-2019 (*** directly related to the project and with GSKE acknowledgement)

2019

- *** van Veen, S.*, Martin, S.* Van den Haute, C., Benoy, V., Lyons, J., Vanhoutte, R., Kahler, J.P., Decuypere, J.-P., Gelders, G., Lambie, E., Zielich, J., Swinnen, J.V., Annaert, W., Agostinis, P., Ghesquière, B., Verhelst, S., Baekelandt, V., Eggermont, J., Vangheluwe, P. (*equal contribution) ATP13A2 deficiency disrupts lysosomal polyamine export. *NATURE,* accepted Dec 2, 2019 (Impact factor: 43.07)
- Chen, J., Sitsel, A., Benoy, V., Sepúlveda, M.R., Vangheluwe, P. (2019). Primary Active Ca2+ Transport Systems in Health and Disease. *Cold Spring Harb Perspect Biol*. doi: 10.1101/cshperspect.a035113 (Impact factor: 9.11)
- Herrmann, A-K., Wuellner, V., Moos, S., Graf, J., Chen, J., Kieseier, B., Kurschus, F.C., Albrecht, P., Vangheluwe, P., Methner, A. (2019). Dimethyl fumarate alters intracellular Ca2+ handling in immune cells by redox-mediated pleiotropic effects. *FREE RADICAL BIOLOGY AND MEDICINE*, *141*, 338-347. doi: 10.1016/j.freeradbiomed.2019.07.005 (Impact factor: 5.66)
- Chen, J., Smaardijk, S., Mattelaer, C-A., Pamula, F., Vandecaetsbeek, I., Vanoevelen, J., Wuytack, F., Lescrinier, E., Eggermont, J., Vangheluwe, P. (2019). An N-terminal Ca2+-binding motif regulates the secretory pathway Ca2+/Mn2+-transport ATPase SPCA1. *JOURNAL OF BIOLOGICAL CHEMISTRY*, *294* (19), 7878-7891. doi: 10.1074/jbc.RA118.006250 (Impact factor: 4.11) Open Access
- Gorski, P.A., Jang, S.P., Jeong, D., Lee, A., Lee, P., Oh, J.G., Chepurko, V., Yang, D.K., Kwak, T.H., Eom, S.H., Park, Z-Y., Yoo, Y.J., Kim, D.H., Kook, H., Sunagawa, Y., Morimoto, T., Hasegawa, K., Sadoshima, J., Vangheluwe, P., Hajjar, R.J., Park, W.J., Kho, C. (2019). Role of SIRT1 in Modulating Acetylation of the Sarco-Endoplasmic Reticulum Ca2+-ATPase in Heart Failure. *Circ Res*, *124* (9), e63-e80. doi: 10.1161/CIRCRESAHA.118.313865 (Impact factor: 15.86)
- *** Wauters, F., Cornelissen, T., Imberechts, D., Martin, S., Koentjoro, B., Sue, C., Vangheluwe, P., Vandenberghe, W. (2019). LRRK2 mutations impair depolarization-induced mitophagy through inhibition of mitochondrial accumulation of RAB10. *AUTOPHAGY*. doi: 10.1080/15548627.2019.1603548 (citations: 2) (Impact factor: 11.06)
- Sitsel, A., De Raeymaecker, J., Drachmann, N.D., Derua, R., Smaardijk, S., Andersen, J.L., Vandecaetsbeek, I., Chen, J., De Maeyer, M., Waelkens, E., Olesen, C., Vangheluwe, P.*, Nissen, P.* (*equal contribution) (2019). Structures of the heart specific SERCA2a Ca2+-ATPase. *EMBO JOURNAL*, *38* (5), Art.No. ARTN e100020. doi: 10.15252/embj.2018100020 (citations: 4) (Impact factor: 11.23) Open Access

2018

- Bittremieux, M., La Rovere, R.M., Schuermans, M., Luyten, T., Mikoshiba, K., Vangheluwe, P., Parys, J.B., Bultynck, G. (2018). Extracellular and ER-stored Ca2+ contribute to BIRD-2-induced cell death in diffuse large B-cell lymphoma cells. *CELL DEATH DISCOVERY*, *4*, Art.No. ARTN 101. doi: 10.1038/s41420-018-0118-6 (citations: 3) Open Access
- Pessina, F., Gamberucci, A., Chen, J., Liu, B., Vangheluwe, P., Gorelli, B., Lorenzini, S., Spiga, O., Trezza, A., Sgaragli, G., Saponara, S. (2018). Negative chronotropism, positive inotropism and lusitropism of 3,5-di-t-butyl-4-hydroxyanisole (DTBHA) on rat heart preparations occur through reduction of RyR2 Ca2+ leak. *BIOCHEMICAL PHARMACOLOGY*, *155*, 434-443. doi: 10.1016/j.bcp.2018.07.026 (citations: 1) (Impact factor: 4.83)
- Smaardijk, S., Chen, J., Kerselaers, S., Voets, T., Eggermont, J., Vangheluwe, P. (2018). Store-independent coupling between the Secretory Pathway Ca2+ transport ATPase SPCA1 and Orai1 in Golgi stress and Hailey-Hailey disease. *BIOCHIMICA ET BIOPHYSICA ACTA-MOLECULAR CELL RESEARCH*, *1865* (6), 855-862. doi: 10.1016/j.bbamcr.2018.03.007 (citations: 6) (Impact factor: 4.74) Open Access
- *** Sorensen, D.M.*, Holemans, T.*, van Veen, S., Martin, S., Arslan, T., Haagendahl, I.W., Holen, H.W., Hamouda, N.N., Eggermont, J., Palmgren, M., Vangheluwe, P. (*equal contribution) (2018). Parkinson disease related ATP13A2 evolved early in animal evolution. *PLOS ONE*, *13* (3), Art.No. ARTN e0193228. doi: 10.1371/journal.pone.0193228 (citations: 2) (Impact factor: 2.78) Open Access
- Mikkelsen, S.A., Vangheluwe, P., Andersen, J.P. (2018). A Darier disease mutation relieves kinetic constraints imposed by the tail of sarco(endo)plasmic reticulum Ca-ATPase 2b. *Journal of Biological Chemistry*, *293* (11), Art.No. jbc.RA117.000941, 3880-3889. (citations: 2) (Impact factor: 4.11) Open Access

2017

- Martin, S., Dudek-Peric, A.M., Garg, A., Roose, H., Demirsoy, S., Van Eygen, S., Mertens, F., Vangheluwe, P., Vankelecom, H., Agostinis, P. (2017). An autophagy-driven pathway of ATP secretion supports the aggressive phenotype of BRAF(V600E) inhibitor-resistant metastatic melanoma cells. *Autophagy*, *13* (9), Art.No. 10.1080/15548627.2017.1332550, 1512-1527. (citations: 13) (Impact factor: 11.06) Open Access
- Demirsoy, S., Martin, S., Motamedi, S., van Veen, S., Holemans, T., Van den Haute, C., Jordanova, A., Baekelandt, V., Vangheluwe, P., Agostinis, P. (2017). ATP13A2/PARK9 regulates endo-/lysosomal cargo sorting and proteostasis through a novel PI(3, 5)P2-mediated scaffolding function. *Human Molecular Genetics*, *26* (9), Art.No. 10.1093/hmg/ddx070, 1656-1669. (citations: 10) (Impact factor: 4.54)

- Chen, J., De Raeymaecker, J., Hovgaard, J.B., Smaardijk, S., Vandecaetsbeek, I., Wuytack, F., Møller, J.V., Eggermont, J., De Maeyer, M., Christensen, S.B., Vangheluwe, P. (2017). Structure/activity Relationship of Thapsigargin Inhibition on the Purified Golgi/secretory Pathway Ca2+/Mn2+ Transport ATPase (SPCA1a). *Journal of Biological Chemistry*, *292* (17), Art. No. jbc.M117.778431, 6938-6951. (citations: 8) (Impact factor: 4.11) Open Access
- Smaardijk, S., Chen, J., Wuytack, F., Vangheluwe, P. (2017). SPCA2 couples Ca influx via Orai1 to Cauptake into the Golgi/secretory pathway. *Tissue & Cell*, *49* (2), Art.No. S0040-8166(16)30097-0, 141-149. doi: 10.1016/j.tice.2016.09.004 (citations: 10) (Impact factor: 1.55) Open Access
- Bittremieux, M., Gerasimenko, J.V., Schuermans, M., Luyten, T., Stapleton, E., Alzayady, K.J., De Smedt, H., Yule, D.I., Mikoshiba, K., Vangheluwe, P., Gerasimenko, O.V., Parys, J., Bultynck, G. (2017). DPB162-AE, an inhibitor of store-operated Ca2+ entry, can deplete the endoplasmic reticulum Ca2+ store. *Cell Calcium*, *62*, 60-70. doi: 10.1016/j.ceca.2017.01.015 (citations: 8) (Impact factor: 3.93)
- Estrada-Cuzcano, A., Martin, S., Chamova, T., Synofzik, M., Timmann, D., Holemans, T., Andreeva, A., Reichbauer, J., De Rycke, R., Chang, D-I., van Veen, S., Samuel, J., Schöls, L., Pöppel, T., Sorensen, D.M., Asselbergh, B., Klein, C., Zuchner, S., Jordanova, A., Vangheluwe, P.*, Tournev, I.*, Schüle, R.* (*equal contribution) (2017). Loss-of-function mutations in the ATP13A2/PARK9 gene cause complicated hereditary spastic paraplegia (SPG78). *Brain*, *140* (2), 287-305. (citations: 39) (Impact factor: 11.81)
- Tharkeshwar, A.K., Trekker, J., Vermeire, W., Pauwels, J., Sannerud, R., Priestman, D.A., Te Vruchte, D., Vints, K., Baatsen, P., Decuypere, J-P., Lu, H.Q., Martin, S., Vangheluwe, P., Swinnen, J., Lagae, L., Impens, F., Platt, F.M., Gevaert, K., Annaert, W. (2017). A novel approach to analyze lysosomal dysfunctions through subcellular proteomics and lipidomics: the case of NPC1 deficiency. *Scientific Reports*, *7*, Art.No. 10.1038/srep41408. (citations: 24) (Impact factor: 4.01)

4.4. Publications in revision (*** directly related to the project and with GSKE acknowledgement)

- *** Stephanie Vrijsen*, Laura Besora-Casals*, Sarah van Veen, Jeffrey Zielich, Chris Van den Haute, Christian Fischer, Patrizia Agostinis, Veerle Baekelandt, Jan Eggermont, Eric Lambie#, Shaun Martin#, Peter Vangheluwe#. (equal * first and # last contribution). ATP13A2-mediated endo-lysosomal polyamine export provides a mitochondrial antioxidant response. Under review in **PNAS**.
- *** Shaun Martin*, Stefanie Smolders*, Chris Van den Haute, Bavo Heeman, Sarah van Veen, David Crosiers, Igor Beletchi, Aline Verstraeten, Helena Gossye, Géraldine Gelders, Philippe Pals, Norin Hamouda, Sebastiaan Engelborghs, Jean-Jacques Martin, Jan Eggermont, Peter Paul De Deyn, Patrick Cras, Veerle Baekelandt, Peter Vangheluwe#, Christine Van Broeckhoven# (shared * first and # last co-authors). Mutated ATP10B increases Parkinson's disease risk by compromising lysosomal glucosylceramide export. Under review in **Acta Neuropathologica**.