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2023–2025

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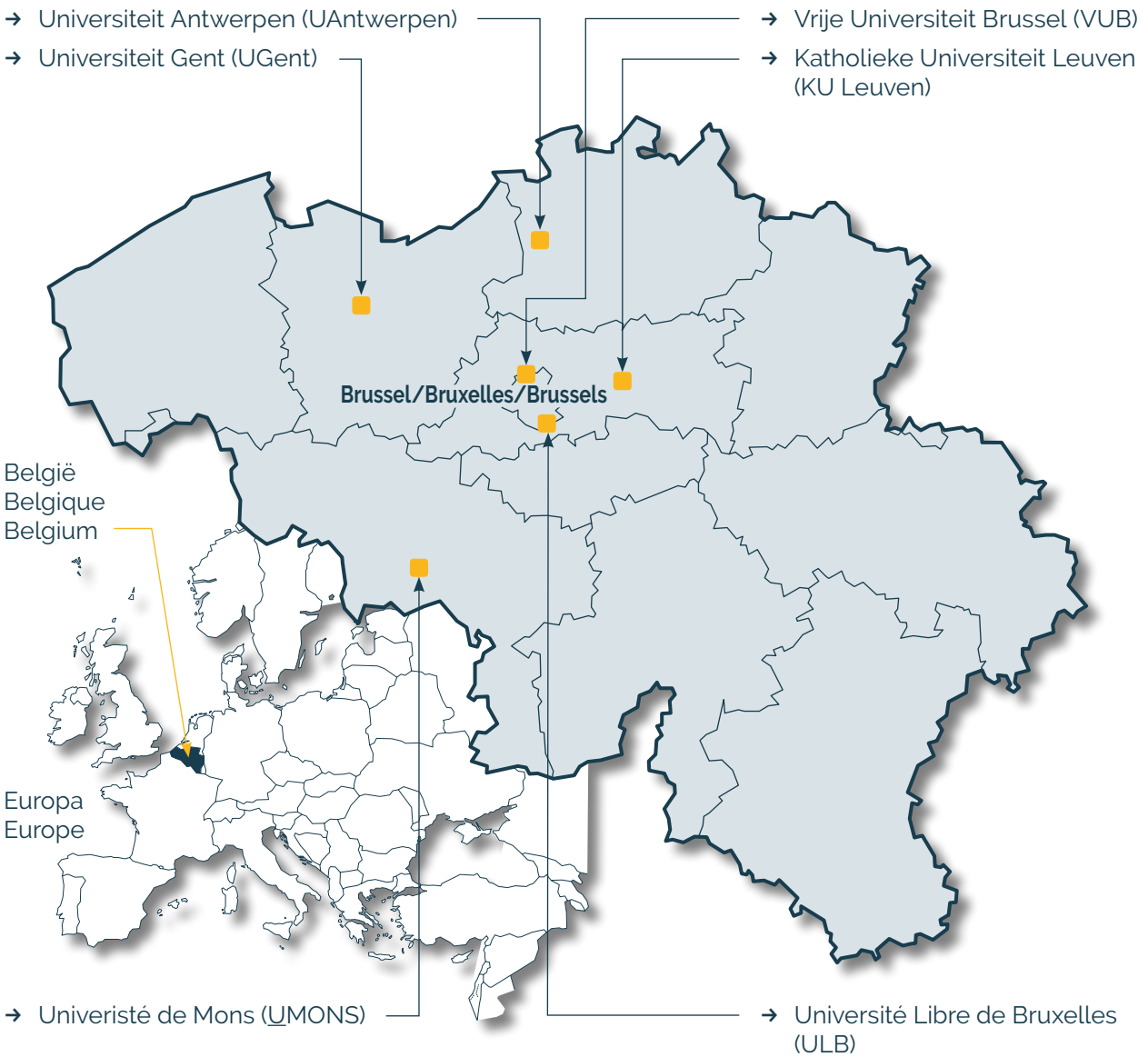

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Prof. dr. Geert Van Loo (UGent)
Prof. Kiavash Movahedi (VUB)
OTULIN in neuroinflammation and Alzheimer pathology

Prof. dr. Sarah Weckhuysen (UAntwerpen)
Prof. dr. Bjorn Menten (UGent)
Detection of somatic mutations and disease-defining methylation patterns in brain tissue and cerebrospinal fluid of patients with non-acquired focal epilepsy

Prof. dr. Renzo Manusco (UAntwerpen)
Prof. dr. Joris De Wit (KU Leuven)
Dissecting the molecular basis of microglia-synapse communication in AD

Prof. dr. Ann Massie (VUB)
Prof. dr. Lutgarde Arckens (KU Leuven)
The xCT-/- killifish to validate the potential of system xc- as therapeutic target in Parkinson's disease

Prof. dr. Karelle Leroy (ULB)
Prof. dr. Laurence Ris (UMONS)
Prof. dr. Kristel Sleegers (UAntwerpen)
Involvement of diabetes and antidiabetic treatment on tau pathology propagation

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Publications in 2023 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- SRINIVASAN, S*., KANCHEVA, D*., DE REN, S*., SAITO, T*., JANS, M., BOONE, F., VANDENDRIESSCHE, C., PAESMANS, I., MAURIN, H., VANDENBROUCKE, R.E., HOSTE, E., VOET, S., SCHEYLTJENS, I., PAVIE, B., LIPPENS, S., SCHWABENLAND, M., PRINZ, M., SAIDO, T., BOTTELBERGS, A+., MOVAHEDI, K+., LAMKANFI, M.+ AND VAN LOO, G+.
  Inflammasome signaling is dispensable for β-amyloidinduced neuropathology in preclinical models of Alzheimer's disease.
  Frontiers Immunol., in press. (IF : 7.3).

Publication 2024 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- ***Inflammasome signaling is dispensable for β-amyloidinduced neuropathology in preclinical models of Alzheimer's disease.***
  Frontiers Immunol: Jan 29:15:1323409. doi: 10.3389/fimmu.2024.1323409 .
  eCollection 2024. IF:7.3

Abstract

Background: Alzheimer's disease (AD) is the most common neurodegenerative disorder affecting memory and cognition. The disease is accompanied by an abnormal deposition of ß-amyloid plaques in the brain that contributes to neurodegeneration and is known to induce glial inflammation. Studies in the *APP/PS1* mouse model of ß-amyloid-induced neuropathology have suggested a role for inflammasome activation in ß-amyloid-induced neuroinflammation and neuropathology.

Methods: Here, we evaluated the *in vivo* role of microglia-selective and full body inflammasome signalling in several mouse models of ß-amyloid-induced AD neuropathology.

Results: Microglia-specific deletion of the inflammasome regulator A20 and inflammasome effector protease caspase-1 in the App^{NL-G-F} and *APP/PS1* models failed to identify a prominent role for microglial inflammasome signalling in ß-amyloid-induced neuropathology. Moreover, global inflammasome inactivation through respectively full body deletion of caspases 1 and 11 in App^{NL-G-F} mice and Nlrp3 deletion in *APP/PS1* mice also failed to modulate amyloid pathology and disease progression. In agreement, single-cell RNA sequencing did not reveal an important role for Nlrp3 signalling in driving microglial activation and the transition into disease-associated states, both during homeostasis and upon amyloid pathology.

Conclusion: Collectively, these results question a generalizable role for inflammasome activation in preclinical amyloid-only models of neuroinflammation.

Keywords: Alzheimer's disease; inflammasome; microglia; neuroinflammation; ß-amyloid.

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Elisabeth" (GSKE), the Charcot Foundation, and the "Concerted Research Actions" (GOA) of Ghent University (BOF23/GOA/001). Research in the Lamkanfi lab is supported by Ghent University (BOF23/GOA/001), and by research grants from the FWO (GOI5722N, G017121N, G014221N) and European Research Council (ERC-2022-PoC 101101075). Research in the Saito lab was supported by grants-in-aid for Scientific Research (20H03564) from MEXT, AMED (JP21gm1210010s0102 and JP21dk0207050h001), JST (Moonshot R&D; Grant Number JPMJMS2024), Grant-in-aid for Research in Nagoya City University (Grant Number 2021101), the Hori Sciences & Arts Foundation, and Toyoaki Scholarship Foundation. AB and KM were supported by VLAIO (HBC.2017.0948). GvL and AB were supported by VLAIO (HBC.2020.3240). MS was supported by the Berta-Ottenstein-Programme for Clinician Scientists, Faculty of Medicine, University of Freiburg, and the IMM-PACT-Programme for Clinician Scientists, Department of Medicine II, Medical Center, University of Freiburg and Faculty of Medicine, University of Freiburg, funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation, 413517907).

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- No publication in 2023

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Publications in 2023 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- No publication in 2023

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- N. DIRKX, WOUT J. WEURING , E. DE VRIENDT, N. SMAL, J. VAN DE VONDERVOORT, RUBEN VAN 'T SLOT, M. KOETSIER, N. ZONNEKEIN,TIM DE POOTER, S. WECKHUYSEN AND B. P. C. KOELEMAN·
  Increased prime edit rates in KCNQ2and SCN1A via single nicking all-in-one plasmids
  BMC Biol, 2023 Jul 13;21(1):156. Doi: 10.1186/s12915-023-01646-7.

Abstract

Background Prime editing (PE) is the most recent gene editing technology able to introduce targeted alterations to the genome, including single base pair changes, small insertions, and deletions. Several improvements to the PE machinery have been made in the past few years, and these have been tested in a range of model systems includ- ing immortalized cell lines, stem cells, and animal models. While double nicking RNA (dncRNA) PE systems PE3 and PE5 currently show the highest editing rates, they come with reduced accuracy as undesired indels or SNVs arise at edited loci. Here, we aimed to improve single ncRNA (sncRNA) systems PE2 and PE4max by generating novel all-in- one (pAIO) plasmids driven by an EF-1 promoter, which is especially suitable for human-induced pluripotent stem cell (hiPSC) models.

Results pAIO-EF1-PE2 and pAIO-EF1-PE4max were used to edit the voltage gated potassium channel gene KCNQ2 and voltage gated sodium channel gene SCN1A. Two clinically relevant mutations were corrected using pAIO-EF1-PE2 including the homozygous truncating SCN1A R612* variant in HEK293T cells and the heterozygous gain-of-function KCNQ2 R201C variant in patient-derived hiPSC. We show that sncRNA PE yielded detectable editing rates in hiPSC ranging between 6.4% and 9.8%, which was further increased to 41% after a GFP-based fluorescence-activated cell sorting (FACS) cell sorting step. Furthermore, we show that selecting the high GFP expressing popula- tion improved editing efficiencies up to 3.2-fold compared to the low GFP expressing population, demonstrating that not only delivery but also the number of copies of the PE enzyme and/or pegRNA per cell are important for efficient editing. Edit rates were not improved when an additional silent protospacer-adjacent motif (PAM)-removing alteration was introduced in hiPSC at the target locus. Finally, there were no genome-wide off-target effects using pAIO-EF1-PE2 and no off-target editing activity near the edit locus highlighting the accuracy of snc prime editors.

Conclusion Taken together, our study shows an improved efficacy of EF-1 driven sncRNA pAIO-PE plasmids in hiPSC reaching high editing rates, especially after FACS sorting. Optimizing these sncRNA PE systems is of high value when considering future therapeutic in vivo use, where accuracy will be extremely important.

Keywords Prime editing, EIEE, CRISPR, SCN1A, KCNQ2, Developmental and epileptic encephalopathy, EF-1alfa, Human-induced pluripotent stem cells, Gene editing, Monogenic diseases

Funding

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- KATRINE M. JOHANNESEN | ZEYNEP TÜMER | SARAH WECKHUYSEN | TAHSIN STEFAN BARAKAT | ALLAN BAYAT
Solving the unsolved genetic epilepsies: Current and future perspectives
Epilepsia: 2023 Dec;64(12):3143-3154. – doi: 10.1111/epi.17780. Epub 2023 Oct 17.

Abstract
Many patients with epilepsy undergo exome or genome sequencing as part of a diagnostic workup; however, many remain genetically unsolved. There are various factors that account for negative results in exome/genome sequencing for patients with epilepsy: (1) the underlying cause is not genetic; (2) there is a complex polygenic explanation; (3) the illness is monogenic but the causative gene remains to be linked to a human disorder; (4) family segregation with reduced penetrance; (5) somatic mosaicism or the complexity of, for example, a structural rearrangement; or (6) limited knowledge or diagnostic tools that hinder the proper classification of a variant, resulting in its designation as a variant of unknown significance. The objective of this review is to outline some of the diagnostic options that lie beyond the exome/genome, and that might become clinically relevant within the foreseeable future. These options include: (1) re-analysis of older exome/genome data as knowledge increases or symptoms change; (2) looking for somatic mosaicism or long-read sequencing to detect low-complexity repeat variants or specific structural variants missed by traditional exome/genome sequencing; (3) exploration of the non-coding genome including disruption of topologically associated domains, long range non-coding RNA, or other regulatory elements; and finally (4) transcriptomics, DNA methylation signatures, and metabolomics as complementary diagnostic methods that may be used in the assessment of variants of unknown significance. Some of these tools are currently not integrated into standard diagnostic workup. However, it is reasonable to expect that they will become increasingly available and improve current diagnostic capabilities, thereby enabling precision diagnosis in patients who are currently undiagnosed.
Keywords: DNA methylation; epilepsy; epilepsy genetics; metabolomics; non-coding regions; re-analysis; somatic mosaicism; transcriptomics.

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- ALLAN BAYAT, STEFANO IAVARONE, FRANCESCO MICELI, ANNE V. JAKOBSEN, KATRINE M., JOHANNESEN, MARINA NIKANOROVA , RAFAL PLOSKI , KRYSTYNA SZYMANSKA , ROBERT FLAMINI, EDWARD C. COOPER, SARAH WECKHUYSEN, MAURIZIO TAGLIALATELA, RIKKE S. MØLLER
Phenotypic and functional assessment of two novel KCNQ2 gain-of-function variants Y141N and G239S and effects of amitriptyline treatment
Neurotherapeitcs: doi: 10.1016/j.neurot.2023.10.006. Epub 2023 Dec 19.

Abstract
While loss-of-function (LoF) variants in KCNQ2 are associated with a spectrum of neonatal-onset epilepsies, gain- of-function (GoF) variants cause a more complex phenotype that precludes neonatal-onset epilepsy. In the present work, the clinical features of three patients

carrying a de novo KCNQ2 Y141N (n 1⁄4 1) or G239S variant (n 1⁄4 2) respectively, are described. All three patients had a mild global developmental delay, with prominent language deficits, and strong activation of interictal epileptic activity during sleep. Epileptic seizures were not reported. The absence of neonatal seizures suggested a GoF effect and prompted functional testing of the variants. In vitro whole- cell patch-clamp electrophysiological experiments in Chinese Hamster Ovary cells transiently-transfected with the cDNAs encoding Kv7.2 subunits carrying the Y141N or G239S variants in homomeric or heteromeric configu- rations with Kv7.2 subunits, revealed that currents from channels incorporating mutant subunits displayed increased current densities and hyperpolarizing shifts of about 10 mV in activation gating; both these functional features are consistent with an *in vitro* GoF phenotype. The antidepressant drug amitriptyline induced a reversible and concentration-dependent inhibition of current carried by Kv7.2 Y141N and G239S mutant channels. Based on *in vitro* results, amitriptyline was prescribed in one patient (G239S), prompting a significant improvement in motor, verbal, social, sensory and adaptive behavior skillsduring the two-year-treatment period. Thus, our results suggest that KCNQ2 GoF variants Y141N and G239S cause a mild DD with prominent language deficits in the absence of neonatal seizures and that treatment with the Kv7 channel blocker amitriptyline might represent a potential targeted treatment for patients with KCNQ2 GoF variants.
Keywords:
Voltage-gated potassium channel Developmental encephalopathy Genotype-phenotype Amitriptyline
Gain of function

Acknowledgements: The authors would like to thank the patients and their families for their participation in our research. AB is funded by a BRIDGE – Translational Excellence Programme grant funded by the Novo Nordisk Foundation, grant agreement number: NNF20SA0064340. FM received funding from the Italian Ministry for University and Research (MIUR) (PRIN2017YH3SXK). ECC received funding from the Jack Pribaz Foundation and Miles Family Fund. SW received funding from FWO (1861419 N, G041821 N and G056122 N), GSKE, KCNQ2-Cure, Jack Pribaz Foundation, KCNQ2e.v., European Joint Programme on Rare Disease JTC 2020 (TreatKCNQ). MT received funding from the Italian Ministry for University and Research (MIUR) (PRIN 2017ALCR7C; National Recovery and Resilience Plan (NRRP), Mission 4 Component 2 Investment 1.3 – PE12 Neurosci- ence “A multiscale integrated approach to the study of the nervous sys- tem in healt and disease” (MNESYS)”); the Italian Ministry of Health (Project RF-2019-12370491); the European Commission H2020 (UNI- COM – 875299); European Joint Programme on Rare Disease JTC 2020 (TreatKCNQ).

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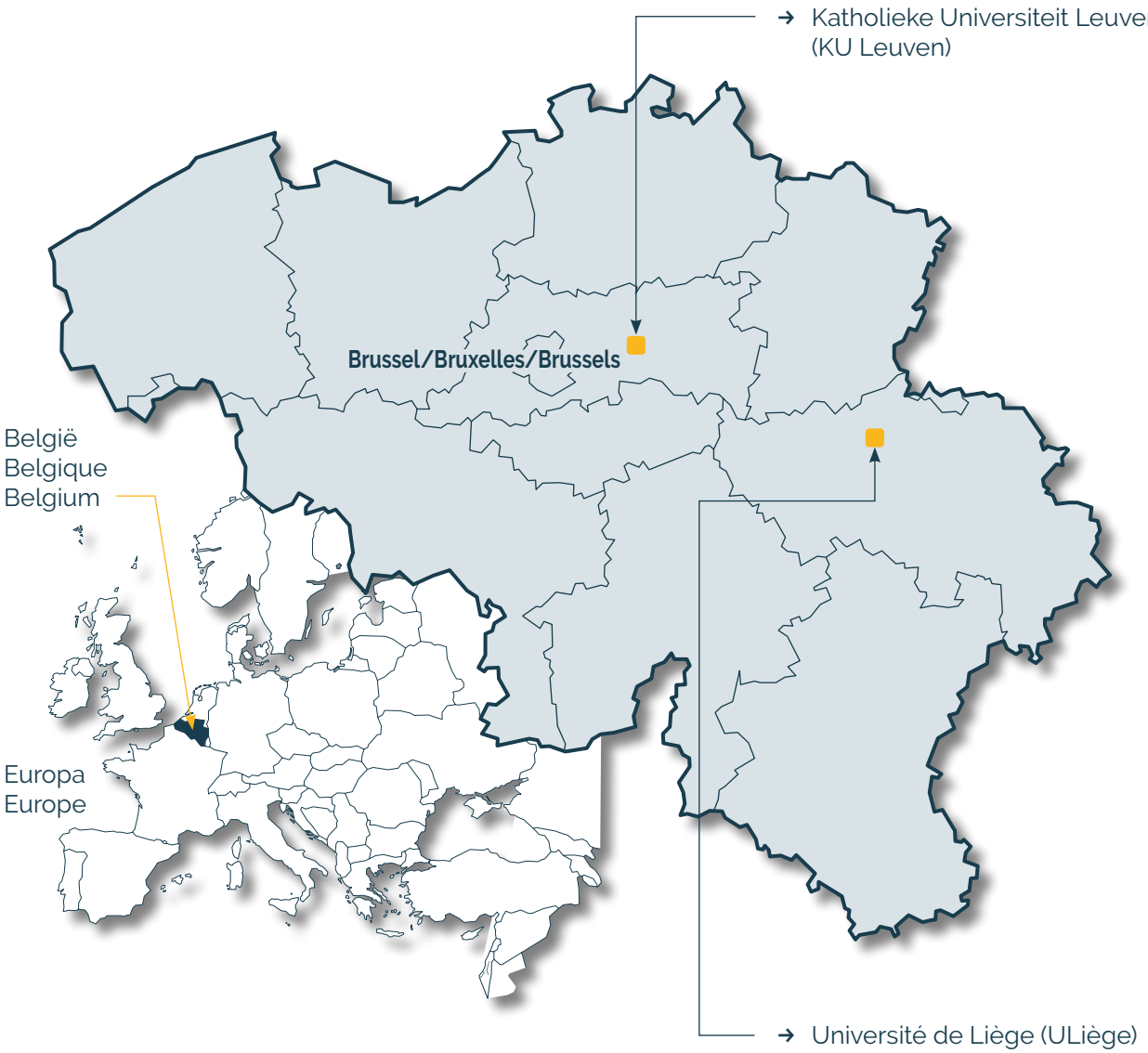

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A vicious Aβ oligomers-dependent neuron-microglia cycle fuels Alzheimer's Disease

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Deciphering the mechanisms underlying neurogenesis defects in mitochondrial diseases

Prof. dr. Veerle Baekelandt
The role of LRRK2 in the peripheral immune system and gut-to-brain spreading of alpha-synuclein pathology in Parkinson's disease

Prof. dr. Thomas Voets
Unraveling the etiology of TRPM3-dependent neurodevelopmental disorders

ULiège

Prof. dr. Pierre Maquet
Quantitative MRI at 7 Tesla addresses ten questions about brain small vessel diseases

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Publications in 2023 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- BALUSU, S., HORRÉ, K., THRUPP, N., CRAESSAERTS, K., SNELLINX, A., SERNEELS, L., T'SYEN, D., CHRYSIDOU, I., ARRANZ, A. M., SIERKSMA, A., SIMRÉN, J., KARIKARI, T. K., ZETTERBERG, H., CHEN, W.-T., THAL, D. R., SALTA, E., FIERS, M., & DE STROOPER, B. (2023).
MEG3 activates necroptosis in human neuron xenografts modeling Alzheimer's disease.
Science (New York, N.Y.), 381(6663), 1176–1182. https://doi.org/10.1126/science.abp9556 –

Abstract
Neuronal cell loss is a defining feature of Alzheimer's disease (AD), but the underlying mechanisms remain unclear. We xenografted human or mouse neurons into the brain of a mouse model of AD. Only human neurons displayed tangles, Gallyas silver staining, granulovacuolar neurodegeneration (GVD), phosphorylated tau blood biomarkers, and considerable neuronal cell loss. The long noncoding RNA *MEG3* was strongly up-regulated in human neurons. This neuron-specific long noncoding RNA is also up-regulated in AD patients. *MEG3* expression alone was sufficient to induce necroptosis in human neurons *in vitro*. Down-regulation of *MEG3* and inhibition of necroptosis using pharmacological or genetic manipulation of receptor-interacting protein kinase 1 (RIPK1), RIPK3, or mixed lineage kinase domain-like protein (MLKL) rescued neuronal cell loss in xenografted human neurons. This model suggests potential therapeutic approaches for AD and reveals a human-specific vulnerability to AD.

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S.B. is a Fonds voor Wetenschappelijk Onderzoek-Vlaanderen (FWO) senior postdoctoral scholar (12P5922N). A.M.A. receives funding from MCIN/AEI/10.13039/501100011033 (RTI2018-101850-A-I00 and PID2021-125443OB-100 grants), also by FEDER Una manera de hacer Europa and RYC2020-029494-I by FSE invierte en tu futuro, the Alzheimer's Association (grant AARG-21-850389), and the Basque Government (PIBA-2020-1-0030). E.S. receives funding from Alzheimer Nederland, the Ministry of Economic Affairs by means of the PPP allowance made available by the Top Sector Life Sciences & Health (Health Holland), and EU JPND/ZonMw. J.S. is supported by research grants from Stiftelsen för Gamla tjänarinnor, Demensfonden and Stohnes stiftelse. T.K.K. is funded by the Swedish Research Council (Vetenskäpradet, 2021-03244), the Alzheimer's Association (AARF-21-850325), the BrightFocus Foundation (A2020812F), the International Society for Neurochemistry's Career Development Grant, the Swedish Alzheimer Foundation (Alzheimerfonden, AF-930627), the Swedish Brain Foundation (Hjärnfonden, FO2020-0240), the Swedish Dementia Foundation (Demensförbundet), the Swedish Parkinson Foundation (Parkinsonfonden), Gamla Tjänarinnor Foundation, the Aina (Ann) Wallströms and Mary-Ann Sjöbloms Foundation, the Agneta Prytz-Folkes and Gösta Folkes Foundation (2020-00124), the Gun and Bertil Stohnes Foundation, and the Anna Lisa and Brother Bjornsson's Foundation. H.Z. is a Wallenberg Scholar supported by grants from the Swedish Research Council (2018-02532); the European Research Council (681712); Swedish State Support for Clinical Research (ALFGBG-720931); the Alzheimer Drug Discovery Foundation (ADDF), USA (201809-2016862); the AD Strategic Fund and the Alzheimer's Association (ADSF-21-831376-C, ADSF-21-831381-C, and ADSF-21-831377-C); the Olav Thon Foundation; the Erling-Persson Family Foundation; Stiftelsen för Gamla Tjänarinnor, Hjärnfonden, Sweden (FO2019-0228); the European Union's Horizon 2020 research and innovation program under the Marie Sklodowska-Curie grant 860197 (MIRIADE); European Union Joint Program for Neurodegenerative Disorders (JPND2021-00694); and the UK Dementia Research Institute at UCL. D.R.T. receives funding from FWO (G0F8516N

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Neurodegeneration cell per cell.
Neuron, 111(6), 767–786.
https://doi.org/10.1016/j.neuron.2023.01.016 –

Abstract
The clinical definition of neurodegenerative diseases is based on symptoms that reflect terminal damage of specific brain regions. This is misleading as it tells little about the initial disease processes. Circuitry failures that underlie the clinical symptomatology are themselves preceded by clinically mostly silent, slowly progressing multicellular processes that trigger or are triggered by the accumulation of abnormally folded proteins such as A, Tau, TDP-43, and -synuclein, among others. Methodological advances in single-cell omics, combined with complex genetics and novel ways to model complex cellular interactions using induced pluripotent stem (iPS) cells, make it possible to analyze the early cellular phase of neurodegenerative disorders. This will revolutionize the way we study those diseases and will translate into novel diagnostics and cell-specific therapeutic targets, stopping these disorders in their early track before they cause difficult-to-reverse damage to the brain.
Keywords: Alzheimer's disease; Parkinson's disease; neurodegeneration; single-cell sequencing.

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Early alterations in the MCH system link aberrant neuronal activity and sleep disturbances in a mouse model of Alzheimer's disease.
Nature Neuroscience, 26(6), 1021–1031. https://doi.org/10.1038/s41593-023-01325-4 –

- **Abstract**

Early Alzheimer's disease (AD) is associated with hippocampal hyperactivity and decreased sleep quality. Here we show that homeostatic mechanisms transiently counteract the increased excitatory drive to CA1 neurons in App^{NL-G-F} mice, but that this mechanism fails in older mice. Spatial transcriptomics analysis identifies Pmch as part of the adaptive response in App^{NL-G-F} mice. Pmch encodes melanin-concentrating hormone (MCH), which is produced in sleep-active lateral hypothalamic neurons that project to CA1 and modulate memory. We show that MCH downregulates synaptic transmission, modulates firing rate homeostasis in hippocampal neurons and reverses the increased excitatory drive to CA1 neurons in App^{NL-G-F} mice. App^{NL-G-F} mice spend less time in rapid eye movement (REM) sleep. App^{NL-G-F} mice and individuals with AD show progressive changes in morphology of CA1-projecting MCH axons. Our findings identify the MCH system as vulnerable in early AD and suggest that impaired MCH-system function contributes to aberrant excitatory drive and sleep defects, which can compromise hippocampus-dependent functions.

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The γ-secretase substrate proteome and its role in cell signaling regulation.
Molecular Cell, 83(22), 4106-4122.e10.
https://doi.org/10.1016/j.molcel.2023.10.029 –

- **Abstract**

Protein phosphorylation is an important cellular regulatory mechanism as many enzymes and receptors are activated/deactivated by phosphorylation and dephosphorylation events, by means of kinases and phosphatases. In particular, the protein kinases are responsible for cellular transduction signaling and their hyperactivity, malfunction or overexpression can be found in several diseases, mostly tumors. Therefore, it is evident that the use of kinase inhibitors can be valuable for the treatment of cancer. In this review, we discuss the mechanism of action of phosphorylation, with particular attention to the importance of phosphorylation under physiological and pathological conditions. We also discuss the possibility of using kinase

inhibitors in the treatment of tumors.
Keywords: protein phosphorylation, kinase, phosphatase, phospho-signaling networks, cancer, drug target

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- RUÉ, L., JASPERS, T., DEGORS, I. M. S., NOPPEN, S., SCHOLS, D., DE STROOPER, B., & DEWILDE, M. (2023).
Novel Human/NonHuman Primate Cross-Reactive Anti-Transferrin Receptor Nanobodies for Brain Delivery of Biologics.
Pharmaceutics, 15(6). https://doi.org/10.3390/pharmaceutics15061748 –

Abstract
The blood-brain barrier (BBB), while being the gatekeeper of the central nervous system (CNS), is a bottleneck for the treatment of neurological diseases. Unfortunately, most of the biologicals do not reach their brain targets in sufficient quantities. The antibody targeting of receptor-mediated transcytosis (RMT) receptors is an exploited mechanism that increases brain permeability. We previously discovered an anti-human transferrin receptor (TfR) nanobody that could efficiently deliver a therapeutic moiety across the BBB. Despite the high homology between human and cynomolgus TfR, the nanobody was unable to bind the non-human primate receptor. Here we report the discovery of two nanobodies that were able to bind human and cynomolgus TfR, making these nanobodies more clinically relevant. Whereas nanobody BBB00515 bound cynomolgus TfR with 18 times more affinity than it did human TfR, nanobody BBB00533 bound human and cynomolgus TfR with similar affinities. When fused with an anti-beta-site amyloid precursor protein cleaving enzyme (BACE1) antibody (1A11AM), each of the nanobodies was able to increase its brain permeability after peripheral injection. A 40% reduction of brain A_{1-40} levels could be observed in mice injected with anti-TfR/BACE1 bispecific antibodies when compared to vehicle-injected mice. In summary, we found two nanobodies that could bind both human and cynomolgus TfR with the potential to be used

clinically to increase the brain permeability of therapeutic biologicals.
Keywords: nanobody, VHH, transferrin receptor, blood-brain barrier, receptor-mediated transcytosis

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Selective inhibitors of the PSEN1-gammasecretase complex.
The Journal of Biological Chemistry, 299(6), 104794. https://doi.org/10.1016/j.jbc.2023.104794 –

Abstract
Clinical development of -secretases, a family of intramembrane cleaving proteases, as therapeutic targets for a variety of disorders including cancer and Alzheimer's disease was aborted because of serious mechanism-based side effects in the phase III trials of unselective inhibitors. Selective inhibition of specific -secretase complexes, containing either PSEN1 or PSEN2 as the catalytic subunit and APH1A or APH1B as supporting subunits, does provide a feasible therapeutic window in preclinical models of these disorders. We explore here the pharmacophoric features required for PSEN1 *versus* PSEN2 selective inhibition. We synthesized a series of brain penetrant 2-azabicyclo[2,2,2]octane sulfonamides and identified a compound with low nanomolar potency and high selectivity (>250-fold) toward the PSEN1–APH1B subcomplex *versus* PSEN2 subcomplexes. We used modeling and site-directed mutagenesis to identify critical amino acids along the entry part of this inhibitor into the catalytic site of PSEN1. Specific targeting one of the different -secretase complexes might provide safer drugs in the future.
Keywords: -secretase,inhibitors, selectivity, therapy, medicinal chemistry

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LRRC37B is a human modifier of voltage-gated sodium channels and axon excitability in cortical neurons.
Cell (2023) 186, 5766-5783. IF: 38 –

Summary
The enhanced cognitive abilities characterizing the human species result from specialized features of neurons and circuits. Here, we report that the hominid-specific gene *LRRC37B* encodes a receptor expressed in human cortical pyramidal neurons (CPNs) and selectively localized to the axon initial segment (AIS), the subcellular compartment triggering action potentials. Ectopic expression of *LRRC37B* in mouse CPNs *in vivo* leads to reduced intrinsic excitability, a distinctive feature of some classes of human CPNs. Molecularly, LRRC37B binds to the secreted ligand FGF13A and to the voltage-gated sodium channel (Nav) -subunit SCN1B. LRRC37B concentrates inhibitory effects of FGF13A on Nav channel function, thereby reducing excitability, specifically at the AIS level. Electrophysiological recordings in adult human cortical slices reveal lower neuronal excitability in human CPNs expressing LRRC37B. *LRRC37B* thus acts as a species-specific modifier of human neuron excitability, linking human genome and cell evolution, with important implications for human brain function and diseases.
Keywords: human brain evolution, gene duplicates, neuronal excitability, LRRC37, FGF13, voltage-gated channels, axon initial segment, cerebral cortex, SCN1B

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Mitochondria Metabolism Sets the Species-Specific Tempo of Neuronal Development.
Science (2023) 379, eabn4705 DOI: 10.1126/science.abn4705. IF: 41 –

Abstract
Neuronal development in the human cerebral cortex is considerably prolonged compared with that of other mammals. We explored whether mitochondria influence the species-specific timing of cortical neuron maturation. By comparing human and mouse cortical neuronal maturation at high temporal and cell resolution, we found a slower mitochondria development in human cortical neurons compared with that in the mouse, together with lower mitochondria metabolic activity, particularly that of oxidative phosphorylation. Stimulation of mitochondria metabolism in human neurons resulted in accelerated development *in vitro* and in vivo, leading to maturation of cells weeks ahead of time, whereas its inhibition in mouse neurons led to decreased rates of maturation. Mitochondria are thus important regulators of the pace of neuronal development underlying human-specific brain neoteny.

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- VANDERHAEGHEN P, FRANCK POLLEUX.
Developmental mechanisms underlying the evolution of human cortical circuits
Nat. Rev. Neurosci. (2023) 24, 213-232 IF: 39 –

Abstract
The brain of modern humans has evolved remarkable computational abilities that enable higher cognitive functions. These capacities are tightly linked to an increase in the size and connectivity of the cerebral cortex, which is thought to have resulted from evolutionary changes in the mechanisms of cortical development. Convergent progress in evolutionary genomics, developmental biology and neuroscience has recently enabled the identification of genomic changes that act as human-specific modifiers of cortical development. These modifiers influence most aspects of corticogenesis, from the timing and complexity of cortical neurogenesis to synaptogenesis and the assembly of cortical circuits. Mutations of human-specific genetic modifiers of corticogenesis have started to be linked to neurodevelopmental disorders,

providing evidence for their physiological relevance and suggesting potential relationships between the evolution of the human brain and its sensitivity to specific diseases.

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CROCCP2 acts as a human-specific modifier of cilia dynamics and mTOR signalling to promote expansion of cortical progenitors
Neuron (2023) 4;111(1):65-80. IF: 18

Abstract
The primary cilium is a central signaling component during embryonic development. Here we focus on CROCCP2, a hominid-specific gene duplicate from ciliary rootlet coiled coil (CROCC), also known as rootletin, that encodes the major component of the ciliary rootlet. We find that CROCCP2 is highly expressed in the human fetal brain and not in other primate species. CROCCP2 gain of function in the mouse embryonic cortex and human cortical cells and organoids results in decreased ciliogenesis and increased cortical progenitor amplification, particularly basal progenitors. CROCCP2 decreases ciliary dynamics by inhibition of the IFT20 ciliary trafficking protein, which then impacts neurogenesis through increased mTOR signaling. Loss of function of CROCCP2 in human cortical cells and organoids leads to increased ciliogenesis, decreased mTOR signaling, and impaired basal progenitor amplification. These data identify CROCCP2 as a human-specific modifier of cortical neurogenesis that acts through modulation of ciliary dynamics and mTOR signaling.
Keywords: CROCC; CROCCP2; cerebral cortex; cilia; evolution; human brain development; mTOR; neurogenesis; rootlet; rootletin.

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  Mutant LRRK2 exacerbates immune response and neurodegeneration in a chronic model of experimental colitis.
  Acta Neuropathologica, 146(2):245-261. (IF 15.9, cit 4)

Abstract
The link between the gut and the brain in Parkinson's disease (PD) pathogenesis is currently a subject of intense research. Indeed, gastrointestinal dysfunction is known as an early symptom in PD and inflammatory bowel disease (IBD) has recently been recognised as a risk factor for PD. The leucine-rich repeat kinase 2 (LRRK2) is a PD- and IBD-related protein with highest expression in immune cells. In this study, we provide evidence for a central role of LRRK2 in gut inflammation and PD. The presence of the gain-of-function G2019S mutation significantly increases the disease phenotype and inflammatory response in a mouse model of experimental colitis based on chronic dextran sulphate sodium (DSS) administration. Bone marrow transplantation of wild-type cells into G2019S knock-in mice fully rescued this exacerbated response, proving the key role of mutant LRRK2 in immune cells in this experimental colitis model. Furthermore, partial pharmacological inhibition of LRRK2 kinase activity also reduced the colitis phenotype and inflammation. Moreover, chronic experimental colitis also induced neuroinflammation and infiltration of peripheral immune cells into the brain of G2019S knock-in mice. Finally, combination of experimental colitis with overexpression of -synuclein in the substantia nigra aggravated motor deficits and dopaminergic neurodegeneration in G2019S knock-in mice. Taken together, our results link LRRK2 with the immune response in colitis and provide evidence that gut inflammation can impact brain homeostasis and contribute to neurodegeneration in PD.
Keywords: Alpha-synuclein; Inflammation; Inflammatory bowel disease; LRRK2; Parkinson's disease.

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TRPM3 as a novel target to alleviate acute oxaliplatin-induced peripheral neuropathic pain.
Pain, 164(9), 2060-2069. https://doi.org/10.1097/j. pain.0000000000002906 –

Abstract
Chemotherapy-induced peripheral neuropathic pain (CIPNP) is an adverse effect observed in up to 80% of patients of cancer on treatment with cytostatic drugs including paclitaxel and oxaliplatin. Chemotherapy-induced peripheral neuropathic pain can be so severe that it limits dose and choice of chemotherapy and has significant negative consequences on the quality of life of survivors. Current treatment options for CIPNP are limited and unsatisfactory. TRPM3 is a calcium-permeable ion channel functionally expressed in peripheral sensory neurons involved in the detection of thermal stimuli. Here, we focus on the possible involvement of TRPM3 in acute oxaliplatin-induced mechanical allodynia and cold hypersensitivity. In vitro calcium microfluorimetry and whole-cell patch-clamp experiments showed that TRPM3 is functionally upregulated in both heterologous and homologous expression systems after acute (24 hours) oxaliplatin treatment, whereas the direct application of oxaliplatin was without effect. In vivo behavioral studies using an acute oxaliplatin model for CIPNP showed the development of cold and mechano hypersensitivity in control mice, which was lacking in TRPM3 deficient mice. In addition, the levels of protein ERK, a marker for neuronal activity, were significantly reduced in dorsal root ganglion neurons derived from TRPM3 deficient mice compared with control after oxaliplatin administration. Moreover, intraperitoneal injection of a TRPM3 antagonist, isosakuranetin, effectively reduced the oxaliplatin-induced pain behavior in response to cold and mechanical stimulation in mice with an acute form of oxaliplatin-induced peripheral neuropathy. In summary, TRPM3 represents a potential new target for the treatment of neuropathic pain in patients undergoing chemotherapy.

- BECKER, L. L., HORN, D., BOSCHANN, F., VAN HOEYMISSEN, E., VOETS, T., VRIENS, J., PRAGER, C., & KAINDL, A. M. (2023).
Primidone improves symptoms in TRPM3-linked developmental and epileptic encephalopathy with spike-andwave activation in sleep.
Epilepsia, 64(5), e61-e68. https://doi.org/10.1111/epi.17586 –

Abstract
Developmental and epileptic encephalopathy with continuous spike-and-wave activation in sleep (CSWS) or DEE-SWAS is an age-dependent disease, often accompanied by a decline in cognitive abilities. Early successful treatment of CSWS is associated with a better cognitive outcome. We retrospectively analyzed the clinical, electrophysiological, radiological, and genetic data of children with DEE-SWAS associated with melastatin-related transient receptor type 3 gene (TRPM3) missense variants. We report two unrelated children with pharmacoresistant DEE-SWAS and developmental delay/regression and different heterozygous de novo missense variants in the TRPM3 gene (NM_001366145.2; c.3397 T > C/p.Ser1133Pro, c.2004G > A/p.Val1002Met). The variant p.Val1002Met (previously known as p.Val990Met or p.Val837Met) and p.Ser1133Pro were recently shown to result in a gain-of-function effect. Based on this finding, previous drug resistance, and the experimentally demonstrated inhibitory effect of primidone on TRPM3, we initiated an individualized therapy with this drug. In both children,

developmental regression was stopped, psychomotor development improved, and CSWS was no longer detectable. To our knowledge, this is the first report of a treatment with primidone in TRPM3-associated CSWS. Our results highlight the importance of early genetic diagnosis in patients with epilepsy and the possibility of precision medicine, which should be considered in the future in individuals with a TRPM3-linked DEE-SWAS.

- BURGLEN, L., VAN HOEYMISSEN, E., QEBIBO, L., BARTH, M., BELNAP, N., BOSCHANN, F., DEPIENNE, C., DE CLERCQ, K., DOUGLAS, A. G. L., FITZGERALD, M. P., FOULDS, N., GAREL, C., HELBIG, I., HELD, K., HORN, D., JANSSEN, A., KAINDL, A. M., NARAYANAN, V., PRAGER, C., VOETS, T.*, VRIENS, J.* (2023).
Gain-of-function variants in the ion channel gene TRPM3 underlie a spectrum of neurodevelopmental disorders.
Elife, 12. https://doi.org/10.7554/eLife.81032 –

Abstract
TRPM3 is a temperature- and neurosteroid-sensitive plasma membrane cation channel expressed in a variety of neuronal and non-neuronal cells. Recently, rare de novo variants in *TRPM3* were identified in individuals with developmental and epileptic encephalopathy, but the link between TRPM3 activity and neuronal disease remains poorly understood. We previously reported that two disease-associated variants in TRPM3 lead to a gain of channel function. Here, we report a further 10 patients carrying one of seven additional heterozygous *TRPM3* missense variants. These patients present with a broad spectrum of neurodevelopmental symptoms, including global developmental delay, intellectual disability, epilepsy, musculo-skeletal anomalies, and altered pain perception. We describe a cerebellar phenotype with ataxia or severe hypotonia, nystagmus, and cerebellar atrophy in more than half of the patients. All disease-associated variants exhibited a robust gain-of-function phenotype, characterized by increased basal activity leading to cellular calcium overload and by enhanced responses to the neurosteroid ligand pregnenolone sulfate when co-expressed with wild-type TRPM3 in mammalian cells. The antiseizure medication primidone, a known TRPM3 antagonist, reduced the increased basal activity of all mutant channels. These findings establish gain-of-function of TRPM3 as the cause of a spectrum of autosomal dominant neurodevelopmental disorders with frequent cerebellar involvement in humans and provide support for the evaluation of TRPM3 antagonists as a potential therapy.
Keywords: TRPM3; cell biology; cerebellar atrophy; epilepsy; gain-of-function; human; intellectual disability; neurodevelopment; neuroscience.

Funding
Queen Elisabeth Medical Foundation for Neurosciences: Thomas Voets

- DANILUK, J., & VOETS, T. (2023).
pH-dependent modulation of TRPV1 by modality-selective antagonists.
Br J Pharmacol, 180(21), 2750-2761.
https://doi.org/10.1111/bph.16173 –

Abstract
Background and purpose: Antagonists of TRPV1 that inhibit all activation modes cause hyperthermia, hampering their medical use as novel analgesics. TRPV1 antagonists that do not (fully) inhibit responses to low pH do not cause hyperthermia, but it remains incompletely understood how such antagonists affect channel gating. We tested the hypothesis that

pH-sparing antagonists act in a modality-selective manner on TRPV1, differentially affecting channel activation by protons and capsaicin.
Experimental approach: Using whole-cell patch-clamp and calcium imaging to measure channel activity in cells expressing wild type human TRPV1 or the pH-insensitive mutant F660A. Responses to protons and capsaicin were measured at different pH values in the presence of antagonists that reportedly partially spare (A-1165442) or potentiate (AMG7905) acid-evoked channel activation.
Key results: At pH 5.5, A-1165442 was equipotent at blocking acid- and capsaicin-evoked responses of wild type TRPV1. Its potency to inhibit acid-evoked responses was attenuated at pH ≤ 5.0. AMG7905, at a concentration (1 μM) that fully inhibits capsaicin-evoked responses, potentiated proton-evoked (pH 5.5) responses of wild type TRPV1. In the F660A mutant, the inhibitory efficacy of A-1165442 and AMG7905 towards capsaicin-evoked responses was reduced at lower pH values and AMG7905 acted as a partial agonist.
Conclusion and implications: Our findings show that A-1165442 and AMG7905 interact in a pH-dependent manner with TRPV1, but this pH dependence is not strictly modality-selective. Reduced TRPV1 antagonism at acidic pH may limit analgesic efficacy in injured tissue and needs to be considered in models explaining the effects of antagonists on core body temperature.
Keywords: TRPV1; hyperthermia; modality-selective antagonists; pain.

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- LUYTS, N., DANILUK, J., FREITAS, A. C. N., BAZELI, B., JANSSENS, A., MULIER, M., EVERAERTS, W., & VOETS, T. (2023).
Inhibition of TRPM8 by the urinary tract analgesic drug phenazopyridine.
Eur J Pharmacol, 942, 175512. https://doi.org/10.1016/ ejphar.2023.175512

Abstract
Background: and purpose: Phenazopyridine (PAP) is an over-the-counter drug widely used to provide symptomatic relief of bladder pain in conditions such as cystitis or bladder pain syndrome (BPS). Whereas the analgesic effect of PAP has been attributed to a local effect on the mucosa of the lower urinary tract (LUT), the molecular targets of PAP remain unknown. We investigated the effect of PAP on pain-related Transient Receptor Potential (TRP) channels expressed in sensory neurons that innervate the bladder wall.
Experimental approach: The effects of PAP on the relevant TRP channels (TRPV1, TRPA1, TRPM8, TRPM3) expressed in HEK293 or CHO cells was investigated using Fura-2-based calcium measurements and whole-cell patch-clamp recordings. Activity of PAP on TRPM8 was further analysed using Fura-2-based calcium imaging on sensory neurons isolated from lumbosacral dorsal root ganglia (DRG) of mice.
Key results: PAP rapidly and reversibly inhibits responses of TRPM8 expressed in HEK293 cells to cold and menthol, with IC_{50} values between 2 and 10 μM. It acts by shifting the voltage dependence of channel activation towards positive potentials, opposite to the effect of menthol. PAP also inhibits TRPM8-mediated, menthol-evoked calcium responses in lumbosacral DRG neurons. At a concentration of 10 μM, PAP did not significantly affect TRPA1, TRPV1, or TRPM3.
Conclusion and implications: PAP inhibits TRPM8 in a concentration range consistent with PAP levels in the urine of treated patients. Since TRPM8 is expressed in bladder afferent neurons

and upregulated in patients with painful bladder disorders, TRPM8 inhibition may underlie the analgesic activity of PAP.
Keywords: Analgesia; Molecular target; Phenazopyridine; TRPM8; Urinary tract.

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Research projects of young researchers 2023–2025 funded by the Q.E.M.F.

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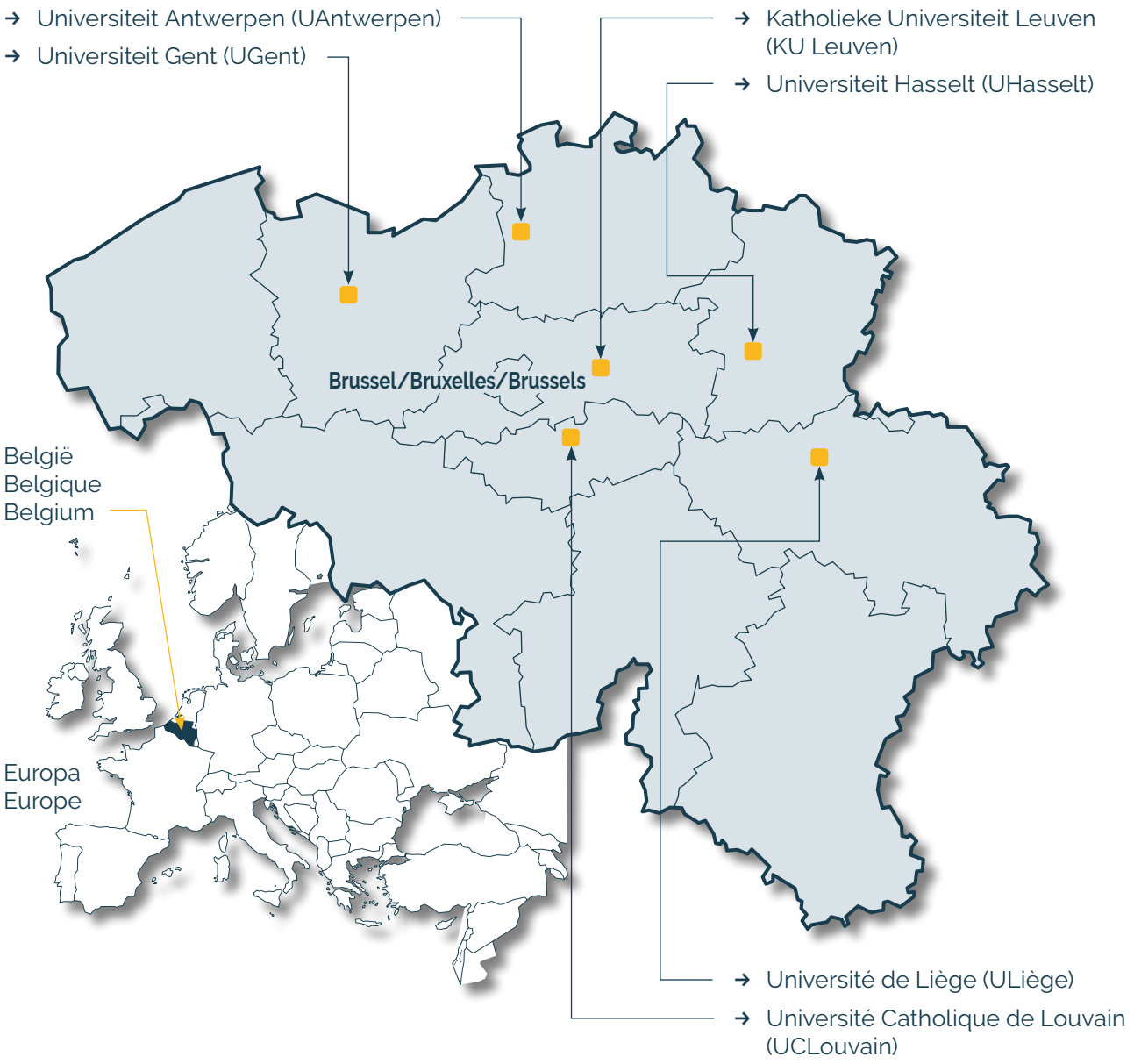
Universités ayant des programmes de recherche subventionnés par la F.M.R.E.

Universities having research programs supported by the Q.E.M.F.



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Projets de recherche de jeunes chercheurs 2023-2025 subventionnés par la F.M.R.E.

Research projects of young researchers 2023-2025 funded by the Q.E.M.F.

UGent

Sielke Caestecker (PhD student) & promotor prof. Robrecht Raedt

The role of the locus coeruleus noradrenergic system in seizures and epilepsy

Dr. Delfien Syx

Zebrafish as a model to study pain in Ehlers-Danlos syndromes

UAntwerpen

Dr. Marijne Vandebergh

World-wide systematic characterization of TMEM106B and ATXN2 genetic status Towards implementation of genetic testing of modifiers in clinical practice

Dr. Barbara M.P. Willekens

Unravelling the role of antigen-specific T cells in NMOSD and MOGAD

KU Leuven

Dr. Wouter Peelaerts

Peripheral infections as a trigger of multiple system atrophy

Dr. Sarah van Veen

The impact of ATP13A4-mediated polyamine transport in astrocytes on synaptogenesis and neurodevelopmental disorders

UCLouvain

Prof. Giulia Liberati

STIM-WAVES: Identifying pain biomarkers with invasive and non-invasive brain stimulation targeting ongoing neural oscillations

(UHasselt)

Prof. dr. Jeroen Bogie

Getting a grip on slippery protein modifications in multiple sclerosis

Prof. dr. Bieke Broux

High salt diet causes blood-brain barrier disturbances in multiple sclerosis: involvement of the renin-angiotensin-aldosterone system

ULiège

Dr. Sophie Laguesse

Unveiling the alcohol-dependent alterations in mRNA local translation and its consequences on adolescent prefrontal cortex maturation and function

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- LARS EMIL LARSEN, SIELKE CAESTECKER, LATOYA STEVENS, PIETER VAN MIERLO, EVELIEN CARRETTE, PAUL BOON, KRISTL VONCK, ROBRECHT RAEDT
  Hippocampal seizures differentially modulate locus coeruleus activity and result in consistent time-locked release of noradrenaline in rat hippocampus
  Neurobiol Dis, 2023 Dec:189:106355., doi: 10.1016/j.nbd.2023.106355. Epub 2023 Nov 15.

Abstract
The locus coeruleus (LC) is a small brainstem nucleus and is the sole source of noradrenaline in the neocortex, hippocampus and cerebellum. Noradrenaline is a powerful neuromodulator involved in the regulation of excitability and plasticity of large-scale brain networks. In this study, we performed a detailed assessment of the activity of locus coeruleus neurons and changes in noradrenergic transmission during acute hippocampal seizures evoked with perforant path stimulation, using state-of-the-art methodology. Action potentials of LC neurons, of which some were identified by means of optogenetics, were recorded in anesthetized rats using a multichannel high-density electrophysiology probe. The seizure-induced change in firing rate differed between LC neurons: 55% of neurons decreased in firing rate during seizures, while 28% increased their firing rate. Topographic analysis of multi-unit activity over the electrophysiology probe showed a topographic clustering of neurons that were inhibited or excited during seizures. Changes in hippocampal noradrenaline transmission during seizures were assessed using a fluorescent biosensor for noradrenaline, $GRAB_{NE2m}$, in combination with fiber photometry, in both anesthetized and awake rats. Although our neuronal recordings indicated both inhibition and excitation of LC neurons during seizures, a consistent release of noradrenaline was observed. Concentrations of noradrenaline increased at seizure onset and decreased during or shortly after the seizure. In conclusion, this study showed consistent but heterogeneous modulation of LC neurons and a consistent time-locked release of hippocampal noradrenaline during acute hippocampal seizures.
Keywords: Epilepsy; Locus coeruleus; Noradrenaline; Optogenetics; Photometry; Seizure.

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- WOUTER PEELAERTS, GABRIELA MERCADO, SONIA GEORGE, MARIE VILLUMSEN, ALYSA KASEN, MIGUEL AGUILETA, CHRISTIAN LINSTOW, ALEXANDRA B SUTTER, EMILY KUHN, LUCAS STETZIK, RACHEL SHERIDAN, LIZA BERGKVIST, LINDSAY MEYERDIRK, ALLISON LINDQVIST, MARTHA L ESCOBAR GAVIS, CHRIS VAN DEN HAUTE ,SCOTT J HULTGREN, VEERLE BAEKELANDT, J ANDREW POSPISILIK, TOMASZ BRUDEK, SUSANA AZNAR, JENNIFER A STEINER, MICHAEL X HENDERSON, LENA BRUNDIN, MAGDALENA I IVANOVA, TOM J HANNAN, PATRIK BRUNDIN
  Urinary tract infections trigger synucleinopathy via the innate immune response.
  Acta Neuropathol. 2023
  May;145(5):541-559., doi: 10.1007/s00401-023-02562-4. Epub 2023 Mar 30.
  PMID: 36991261, PMCID: PMC10119259, DOI: 10.1007/s00401-023-02562-4

Abstract
Symptoms in the urogenital organs are common in multiple system atrophy (MSA), also in the years preceding the MSA diagnosis. It is unknown how MSA is triggered and these observations in prodromal MSA led us to hypothesize that synucleinopathy could be triggered by infection of the genitourinary tract causing -synuclein (Syn) to aggregate in peripheral nerves innervating these organs. As a first proof that peripheral infections could act as a trigger in MSA, this study focused on lower urinary tract infections (UTIs), given the relevance and high frequency of UTIs in prodromal MSA, although other types of infection might also be important triggers of MSA. We performed an epidemiological nested-case control study in the Danish population showing that UTIs are associated with future diagnosis of MSA several years after infection and that it impacts risk in both men and women. Bacterial infection of the urinary bladder triggers synucleinopathy in mice and we propose a novel role of Syn in the innate immune system response to bacteria. Urinary tract infection with uropathogenic E. coli results in the de novo aggregation of Syn during neutrophil infiltration. During the infection, Syn is released extracellularly from neutrophils as part of their extracellular traps. Injection of MSA aggregates into the urinary bladder leads to motor deficits and propagation of Syn pathology to the central nervous system in mice overexpressing oligodendroglial Syn. Repeated UTIs lead to progressive development of synucleinopathy with oligodendroglial involvement in vivo. Our results link bacterial infections with synucleinopathy and show that a host response to environmental triggers can result in Syn pathology that bears semblance to MSA.

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- VAN VEEN S., IRALA D., HAYS K., AUSLOOS E., VAN ASSELBERGHS J., VAN DEN HAUTE C., BAEKELANDT V., EGGERMONT J., HOLT M.G., EROGLU C., VANGHELUWE P.
  Connecting polyamine transport in astrocytes to neurodevelopmental disorders via TP13A4. Manuscript in preparation.

  Abstract
  During my FWO PhD fellowship, I proved that ATP13A2 works as a lysosomal polyamine exporter implicated in neurodegenerative disorders. Here, I will focus on a closely related isoform, ATP13A4, which is genetically associated with neurodevelopmental disorders. ATP13A4 is localized predominantly in astrocytes and according to my preliminary data may also function as a polyamine transporter. Polyamines are regulators of astrocyte functionality and neuronal modulation, but how polyamines are taken up by astrocytes remains unknown. I therefore hypothesize that ATP13A4 may mediate polyamine uptake in astrocytes, whereas ATP13A4 dysfunction may disturb polyamine homeostasis, ultimately leading to astrocyte and/or neuronal dysfunction underlying neurodevelopmental disorders. To test this hypothesis, I will use complementary biochemical and cellular assays to characterize the molecular properties of ATP13A4 wildtype and disease mutants. I will further assess the impact of Atp13a4 deficiency on astrocyte polyamine homeostasis, endosomal functionality and relevant astrocyte functions. To analyse the in vivo consequences of Atp13a4 deficiency, an astrocyte-specific Atp13a4 knock-out mouse strain will be generated to determine the impact of Atp13a4 on astrocyte/neuronal interplay and mouse behaviour. Understanding the physiological role of ATP13A4 in astrocytes and in the brain may validate ATP13A4 as a candidate therapeutic target for neurodevelopmental disorders.

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Publications in 2023 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- No publications in 2023

Publications in 2024 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- CHIARI LEU, ESTHER GLINEUR and GIULIA LIBERATI
  Cue-based modulation of pain stimulus expectation: do ongoing oscillations reflect changes in pain perception? A registered report
  R Soc Open Sci 2024 Jun 19;11(6):240626. doi: 10.1098/rsos.240626. eCollection 2024 Jun

Abstract
A promising stream of investigations is targeting ongoing neural oscillations and whether their modulation could be related to the perception of pain. Using an electroencephalography (EEG) frequency-tagging approach, sustained periodic thermonociceptive stimuli perceived as painful have been shown to modulate ongoing oscillations in the theta, alpha and beta bands at the frequency of stimulation. Nonetheless, it remains uncertain whether these modulations are indeed linked to pain perception. To test this relationship, we modulated pain perception using a cue-based expectation modulation paradigm and investigated whether ongoing oscillations in different frequency bands mirror the changes in stimulus perception. Forty healthy participants were instructed that a visual cue can precede either a high- or low-intensity stimulation. These cues were paired with three different levels of sustained periodic thermonociceptive stimuli (low, medium and high). Despite a strong effect of expectation on perceived stimulus intensity, this effect was not reflected in the modulation of the ongoing oscillations, suggesting a potential dissociation of pain perception and these oscillatory activities. Rather, it seems that the intensity of stimulation is the primary generator of the frequency-tagged EEG responses. Importantly, these results need to be confirmed by further investigations that could allow the detection of smaller effects than originally estimated.
Keywords: expectation; frequency-tagging; neural oscillations; nociception; pain.

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