BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Morava-Kozicz, Eva, M.D., Ph,D.

eRA COMMONS USER NAME (credential, e.g., agency login): emoravakozicz

POSITION TITLE: Professor of Medical Genetics, Senior Associate Consultant

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Pécs, Pécs ,Hungary	MD	09/1990	Medicine
University of Pécs, Pécs ,Hungary	Residency	11/1994	Pediatrics
Tulane University Medical School, LA	Fellowship	07/1998	Neonatology
University of Pécs, Pécs ,Hungary	Fellowship	10/1999	Clinical Genetics
University of Pécs, Pécs, Hungary	PhD	04/2000	Clinical Molecular Genetics
Radboud University, the Netherlands	Fellowship	06/2005	Biochemical Genetics

A. Personal Statement

As a clinical geneticist and metabolic specialist, I have a strong background and experience in pediatrics with specific focus on clinical biochemical genetics. My research focus and main expertise is inborn errors of metabolism, particularly congenital disorders of glycosylation (CDG). With many years of basic and translational research, diagnostic, and patient care of metabolic conditions, I was involved in several natural history studies in inborn errors. Following our previous retrospective studies[1] started to collect standard clinical data in glycosylation defects. I am the PD/PI with 12 study sites of the U54 FCDGC consortium studying CDG. As an international trainee, who has worked on 2 continents, I have a history of leading successful collaborations with American and European research groups on translational research projects, as demonstrated by prestigious multicenter publications. I am highly motivated to perform translational research, and my goal is to bring together clinicians, geneticists, basic scientists, and students involved in the field of biochemical genetics, which is essential to bring the current proposal to success. I have been collaborating with Drs. Sloan's, Flanagan Steet's and Kozicz's lab for many years on various projects involving perturbed glycosylation in various human diseases and their *in vivo* and *in vitro* model systems. Our team has also collaborated to generate the large body of preliminary data of the proposed studies.

I have focused on glycosylation since the beginning of my scientific carrier as a metabolic pediatrician in the Netherlands and investigated perturbed glycosylation in various human diseases and their *in vivo* and *in vitro* model systems. I established a disease severity scoring system for CDG, which has been used in practice in Europe and the US for 15 years[1]. In addition to defining a new genetic disorder group with abnormal glycosylation (metabolic cutis laxa; ARCL-2A); discovered several new inborn errors (MEGDEL syndrome, SRD5A3-CDG, SLC35A1-CDG, PGM1-CDG, ATP6V1A-CDG, ATP6V1E1-CDG, MAN2B2-CDG, STT3A-CDG)[e.g.,2] and described the first organ transplantations in CDG (MPI-CDG and DOLK1-CDG). Recently we reported on glycoproteomics and proteomics studies in PMM2-CDG patients and identified sorbitol as a marker for treatment response in PMM2-CDG[4]. Our team identified a new role of glycosylation of intermediate filament in dilatated cardiomyopathy development in PGM1-CDG. Our results provide a link between altered glycosylation and cardiac function. We also showed that we can correct cardiac pathology using an AVV vector expressing the wild type PGM1 cDNA laying the foundation for a novel therapy in PGM1-CDG[5].

1. Achouitar S, Mohamed M, ….Elson J, **Morava E**. Nijmegen paediatric CDG rating scale: a novel tool to assess disease progression. J Inherit Metab Dis. 2011 Aug;34(4):923-7. doi: 10.1007/s10545-011-9325-5. PMID: 21541726
2. Wilson MP, …, **Morava E**, Lefeber DJ. Active site variants in STT3A cause a dominant type I congenital disorder of glycosylation with neuromusculoskeletal findings. Am J Hum Genet. 2021 Oct 8:S0002-9297(21)00348-7. doi: 10.1016/j.ajhg.2021.09.012. **Lefeber and Morava shared last authors**.
3. Liver transplantation recovers hepatic N-glycosylation with persistent IgG glycosylation abnormalities: Three-year follow-up in a patient with phosphomannomutase-2-congenital disorder of glycosylation. Tahata S, Weckwerth J, Ligezka A, He M, Lee HE, Heimbach J, Ibrahim SH, Kozicz T, Furuya K, **Morava**

E. Mol Genet Metab. 2023 Mar 17;138(4):107559. doi: 10.1016/j.ymgme.2023.107559.PMID: 36965289

4. Ligezka AN, Radenkovic S, ….Pandey A, Perlstein EO, Kozicz T, **Morava E.,** Sorbitol is a severity biomarker for PMM2-CDG with therapeutic implications. Ann Neurol. 2021 Dec 90; 887-900. doi: 10.1002/ana.26245.
5. Balakrishnan B, Altassan R, Budhraja R, Liou W, Lupo A, Bryant S, Mankouski A, Radenkovic S, Preston GJ, Pandey A, Boudina S, Kozicz T, **Morava-Kozicz E**, Lai K. AAV-based gene therapy prevents and halts the progression of dilated cardiomyopathy in a mouse model of phosphoglucomutase 1 deficiency (PGM1-CDG). Transl Res. 2023 Jul;257:1-14. doi: 10.1016/j.trsl.2023.01.004. PMID: 3670992.

A. 1. Current and recently completed projects include:

A.1.a. Ongoing Research Support

1RO1HL167866-01A1 NIH/NHLB Lai/Boudina/Morava (PIs) 12/01/2023-11-30-2027
The objective of these studies is to delineate metabolic and biochemical changes underpinning the cardiac disease in inherited deficiency of Phosphoglucomutase-1 (PGM1) and to discover novel therapeutic avenues to reverse its related cardiac pathology.
Role: PI

1R44DK131708-01A1 Morava (PI) 10/01/2022-09/30/2024
This is a a Prospective, Multi-Center study of Oral Epalrestat Therapy in Pediatric Subjects with Phosphomannomutase Deficiency (PMM2- CDG).
Role: PI

Project Number: MNP #21.38 Morava (PI) and Kyriakie Sarafoglou (PI) 05/01/2022-04/30/2024
Major Goals of this proposal are (1) understand better why individuals with CDG are so vulnerable to endocrine abnormalities and (2) to identify predictive biomarkers for abnormal endocrine phenotypes for early diagnosis and treatment of endocrinopathies, and prevention of their associated co-morbidities.

1U54NS115198-01 Morava (PI) 09/15/2019-09/14/2024
NINDS&NICHD&NCATS
Frontiers in Congenital Disorders of Glycosylation Consortium
The overreaching goals of this grant are to address critical needs for clinical trial readiness, improve diagnostics and through these improve quality of life and life expectancy of patients affected by CDG.
Role PI

U01TR 02471-1 Lanza (PI) 08/01/2018-06/30/2023
Improving diagnostic success within the Undiagnosed Disease Network
Mayo Clinic Undiagnosed Disease Network Metabolomics Core
Role: Co-Investigator

GLY-101 Morava (PI) 09/15/2023-06/30/2024
A Phase 2, Randomized, Open-Label, 24-Week Study to Assess the Pharmacodynamics, Safety, Tolerability, and Pharmacokinetics of Multiple Doses of GLM101 Administered Intravenously to Adult Participants with PMM2-CDG
Role PI

GLY-000 Patterson (PI) 08/23/2018-08/22/2024
Glycomine, Inc.
Clinical and Basic Investigations into Phosphomannomutase deficiency (PMM2-CDG)
GOAL(S): Collecting natural history data on individuals with PMM2-CDG.

AVTX-803 Morava (PI) 12/23/2022-01/01/2024
A Phase 3, Open-Label, Extension Study to Assess the Long-term Safety and Efficacy of AVTX-803 in Subjects with Leukocyte Adhesion Deficiency Type II (LAD II)
Role PI

A. 1. b. Completed research support

PAU:93621005 Morava-Kozicz PIs 04/05/2021-04/04/2022
Ventures Innovation Program Award
The objective of this innovation award is to develop reliable biomarkers predicting disease severity and progression as well as treatment response for congenital disorders of glycosylation (CDGs). This proposal focuses on polyols such as sorbitol and mannitol that have been identified to predict disease severity and progression in PMM2-CDG, which is the most common CDG type.
Role: Co-PI

92541496-97 Kozicz/Morava (PIs) 2/1/2018 – 1/31/2021
Center for Individualized Medicine, Mayo Clinic, Rochester, MN, USA

Individual differences in mitochondrial function mediate the impact of stress and physical and mental health
This project concerns bridging basic and clinical research to gain a deeper understanding of how individual differences in mitochondrial structure and function mediate the impact of stress on mental health.
Role: PI

FWO clinical, research financing subsidy Morava (PI) 10/2017-2022
(Federal European grant)
Galactose therapy in PGM1 deficiency
The goal of this study is to evaluate the mechanism of action of galactose in PGM1 deficiency *in vitro* and *in vivo*
Role: PI

PAU 91516; Morava (PI) 01/15/2019 -01/14/2020
Mayo Clinic, Ventures Innovation Program;
Discovery of the Therapeutic Properties of Nucleotide Sugar Therapy Supplemented in Specific Ratios as a Novel Treatment of Congenial Disorders of Glycosylation
The objective of this research program is to discover novel and improved therapeutic options for the treatment of Congenital Disorders of Glycosylation.
Role; PI

E-RARE grant (European Union Grant) Matthijs (PI) 07/2016-12/2019
Developing novel treatments in disorders associated with abnormal glycosylation.
The goal of this study is to evaluate different therapeutic options in CDG in vitro and in vivo.
Role: Co-Investigator

Hayward trustee subsidy Morava (PI) 06/2017-12/2019
PGM1 deficiency with focus on treatment
The goal of this study is to understand the regulationof pathways by galactose in PGM1 deficiency.
Role: PI

B. Positions, Scientific Appointments, and Honors

Positions

2018-Present	Professor of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai
2018-Present	Visiting Professor of Pediatrics, KU Leuven University, Leuven, Belgium
2018-2024	Professor of Medical Genetics, Senior Consultant, Department of Clinical Genomics, Mayo Clinic, Rochester, MN
2016-2018	Professor of Pediatrics, KU Leuven University, Head of pediatric metabolic unit, Leuven, Belgium
2015-2018	Adjunct Professor of Pediatrics, University of Leuven, Head of Pediatric Metabolic Unit, Leuven, Belgium
2013-Present	Professor of Pediatrics, Tulane University School of Medicine, New Orleans, LA
2012-2018	Professor, Hayward Genetics Center, Tulane University School of Medicine, New Orleans, LA
2002- 2012	Associate Professor, Department of Pediatrics, Radboud University Medical Center, Nijmegen, The Netherlands
1998-2002	Adjunct Professor, Department of Pediatrics, Department of Medical Genetics, University of Pécs, Medical School, Pécs, Hungary
1996-1998	Clinical Fellow, Department of Pediatrics and Human Genetics, Tulane University School of Medicine, New Orleans, LA
1994-1996	Adjunct Professor, Department of Pediatrics, Department of Medical Genetics, University of Pécs Medical School, Pécs, Hungary
1990-1994	Pediatric Resident, Department of Pediatrics, , University of Pécs Medical School, Pécs, Hungary

Honors and Awards

2023	Teaching Excellence Award Mayo Clinic Alix School of Medicine Class of 2023
2021	Mayo Clinic Experience Top Provider Award REF:0011021374 for 2021
2013	CDG Hope and Dream award at the World Congenital Disorders of Glycosylation World Conference, Barcelona, Spain
2012	ESN team prize: best scientific team in metabolic medicine (Netherlands)
2012	Lecturer of the year: Master of Molecular Sciences course, Radboud University,
2010	Best metabolic pediatrician tutor prize - Radboud University, Nijmegen
2010	ESN prize: best lecture of the Dutch Metabolic Society

2009 Best Paper of the Year in Metabolic Medicine - ESN, Amsterdam, Holland, Netherlands 2010 ESN prize: best lecture of the Dutch Metabolic Society
2007 Habilitation in Human Genetics - University of Pécs Medical School
2001 ESHG Conference Young Scientist Travel Award
2000 Bolyai Janos Award and Stipendium (Research Fellowship for 3 years by the Hungarian Academy of Sciences)

Other Experience and Professional Memberships

2023 Editor of Molecular Genetics and Metabolism
2023 Co-chair of the Rare Disorder Clinical Research Network Steering Committee
2022 Co-chair of the Mayo Clinic Rochester site for NORD
2021 Co-chair of the RDCRN Diversity and Inclusion Committee
2020 Board member for the Minnesota Board of Newborn Screening
2017 Co-coordinator of MetabERN (European Reference Networks)
2017 Sub-coordinator of the glycosylation subnetwork in MetabERN
2017 Board member for the Metakids Foundation
2016 Editor in Chief for the Journal of Inherited Metabolic Diseases
2016 Council member for the international Society for the Study of Inborn Errors of Metabolism
2015 Advisory Board member for the CDG-CARE foundation
2012 Editorial board member of the Journal of Inherited Metabolic Diseases
2011 Board member for the Tjalling Roorda Foundation
2011 Communicating Editor for the Journal of Inherited Metabolic Diseases

C. Contribution to Science

1. **Mitochondrial disease.** Mitochondrial disorders are inborn errors with a highly variable multisystem phenotype, and a lot of overlap with other multisystem disorders. There has been a long search for reliable diagnostic criteria. I established a modified scoring system, (Morava et al., 2006, Neurology), which has been used for more than 10 years to diagnose mitochondrial disease. Recently I also defined the diagnostic flow chart for mitochondrial diagnostics and my updated flow chart, adapted for the next generation sequencing era published in *Genetics in Medicine.* Under my lead my group discovered a new genetic syndrome (MEGDEL syndrome), which is a mitochondrial disease, affecting several metabolic pathways. This disorder has a novel pathomechanism, through affecting phospholipid synthesis and membrane integrity and mitochondrial associated membrane structures. The description of MEGDEL syndrome and depicting its metabolic background led to the definition of the new metabolic disorder group, "phospholipid disorders" and brought a novel concept for 3-methyl glutaconyl acidurias, and understanding mitochondrial disease pathomechanism
   a. Witters P, Saada A, Honzik T, Tesarova M, Kleinle S, Horvath R, Goldstein A, **Morava E.** Revisiting mitochondrial diagnostic criteria in the new era of genomics. Genet Med. 2018 Apr;20(4):444-451..
   b. Wortmann SB, de Brouwer APM, Wevers RA**, Morava E.** MEGDEL Syndrome. 2014. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, Bird TD, Dolan CR, Fong CT, Smith RJH, Stephens K, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015.
   c. Wortmann SB *et al*.. Mutations in the phospholipid remodelling gene SERAC1 impair mitochondrial function and intracellular cholesterol trafficking and cause dystonia and deafness. Nat Genet. 2012;44(7):797-802. **Morava, Wevers and Brouwer: equal last author contributions.**
   d. Gardeitchik T *et al.* **.** Bi-allelic Mutations in the Mitochondrial Ribosomal Protein MRPS2 Cause Sensorineural Hearing Loss, Hypoglycemia, and Multiple OXPHOS Complex Deficiencies. Am J Hum Genet. 2018 Apr 5;102(4):685-695. PMCID: PMC5985281. **Morava last author.**
2. **Congenital disorders of glycosylation-new disorders.** Congenital disorders of glycosylation (CDG) form a novel, quickly growing group of inborn errors. Currently more than 10 types are known, and the list of types is continuously growing. There has been a large number of patients followed by CDG type x; already known with the biochemical diagnosis CDG, but without understanding the underlying genetic background. With my lead my group discovered several inborn errors of protein glycosylation and defined the phenotype in several rare CDG types. Initially using linkage and homozygosity mapping, recently, by next generation sequencing I had a crucial role in the definition of ATP6V0A2-CDG, SRD5A3-CDG, SLC35A1-CDG, ATP6V1A-CDG, ATP6V1E1-CDG, TRAPPC9-CDG and PGM1-CDG. I was also involved in the discovery of DPM2-CDG, DPM1-CDG, COG7-CDG, MAN1B1- CDG, ATP6VAP1-CDG, CCDC115-CDG, TMEM199-CDG, and STTA3-CDG. The discoveries of the new disorders had a major impact on patient care and

counseling and understanding much better glycosylation and its regulation.

a. **Morava E** *et al.* A novel cerebello-ocular syndrome with abnormal glycosylation due to abnormalities in dolichol metabolism. Brain. 2010;133(11):3210-20.
b. Mohamed M, *et a*l. Intellectual disability and bleeding diathesis due to deficient CMP--sialic acid transport. Neurology. 2013;81(7):681-7. **Morava last author.**
c. Tegtmeyer LC *et al*. Multiple phenotypes in phosphoglucomutase 1 deficiency. N Engl J Med. 2014;370(6):533-42. **Morava, Lefeber and Marquardt: equal last author contributions.**
d. Verheijen J, *et al.* Defining a new immune deficiency syndrome: MAN2B2-CDG. J Allergy Clin Immunol. 2020 Mar;145(3):1008-1011. **Morava last author.**

3. Congenital disorders of glycosylation: developing therapies. Until 2014, there were no reliable treatment options in CDG, only MPI-CDG type was treatable, by dietary mannose therapy. Under my lead my group discovered novel therapies and performed the first organ transplantations in previously not treatable types of congenital disorders of glycosylation. Based on the mannose therapy, increasing substrate availability we have been searching for novel options in dietary treatment. The first real breakthrough was done in phosphoglucomutase therapy with the use of the monosaccharide D-galactose added to the diet, improving endocrine, coagulation and liver function. Galactose treatment in PGM1-CDG led to treatment trials and successful dietary treatment in other types of CDGs as well. I also had a leading role in the first liver transplantation in MPI-CDG, with full metabolic recovery of the patient, the first heart transplantation in DOLK-CDG and an increasing number of transplantations in other milder forms of CDG.

a. Janssen MC, de Kleine RH, van den Berg AP, Heijdra Y, van Scherpenzeel M, Lefeber DJ, **Morava E.** Successful liver transplantation and long-term follow-up in a patient with MPI-CDG. Pediatrics. 2014;134(1):e279-83.
b. Wong SY *et al*. Oral D-galactose supplementation in PGM1-CDG. Genet Med. 2017;19:1226-1235. **Morava last author.**
c. Radenkovic S, et al.The Metabolic Map into the Pathomechanism and Treatment of PGM1-CDG. Am J Hum Genet. 2019 May 2;104(5):835-846. **Morava E, Ghesquière B. equal last authors.**
d. Witters P, *et al.* Clinical and biochemical improvement with galactose supplementation in SLC35A2-CDG. Genet Med. 2020 Jun 22 1102-1107. PMID: 32103184. **Morava last author.**

4. Discovering the new syndrome group metabolic cutis laxa previously defined as ARCL type 2A Cutis laxa syndrome is a growing group of connective tissue disorders, occurring due to congenital structural anomalies of the elastic fibers. Some patients however show a progressive improvement in their features (reverse aging), pointing towards a different pathomechanism. I described the first time the glycosylation abnormalities in autosomal recessive cutis laxa type 2A patients and defined the characteristic phenotype. This led to the multicenter project studying a large patient group and solving the underlying gene defect. Upon understanding the pathomechanism, based on abnormal Golgi trafficking and elastic fiber maturation, we discovered the abnormalities in glycosylation, leading to the clinically recognizable secondary COG syndrome. Consecutively I defined a new cutis laxa syndrome, also associated with COG, which was also genetically defined recently. Since my initial description of the new disease, metabolic cutis laxa, several new inborn errors have been found with different metabolic abnormalities, and the list of disorders is ongoing.

a. **Morava E,,** Wopereis S, Coucke P, Gillessen-Kaesbach G, Voit T, Smeitink J, Wevers R, Grünewald S. Defective protein glycosylation in patients with cutis laxa syndrome. Eur J Hum Genet. 2005;13(4):414-21.
b. Kornak U, Reynders E, Dimopoulou A, van Reeuwijk J, Fischer B, Rajab A, Budde B, Nürnberg P, Foulquier F; ARCL Debré-type Study Group, Lefeber D, Urban Z, Gruenewald S, Annaert W, Brunner HG, van Bokhoven H, Wevers R, **Morava E**, Matthijs G, Van Maldergem L, Mundlos S.. Impaired glycosylation and cutis laxa caused by mutations in the vesicular H+-ATPase subunit ATP6V0A2. Nat Genet. 2008;40(1):32-4.
c. Hucthagowder V, **Morava E** *et al*. Urban Z. Loss-of-function mutations in ATP6V0A2 impair vesicular trafficking, tropoelastin secretion and cell survival. Hum Mol Genet. 2009;18(12):2149-65. PMCID: PMC2685755

List of published work:
https://www.ncbi.nlm.nih.gov/pubmed/?term=Morava+E