



XVIII INTERNATIONAL MAGNESIUM SYMPOSIUM

New Frontiers in Magnesium Research:
Molecular Mechanism and
Clinical Implications

Research Institute of McGill University Health Centre
Montreal (Canada)
August 20-21, 2026



PROGRAM & ABSTRACTS

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IMS 2026 Organizer
Nathalie Letrillard

sdrm@sdrmsociety.org

SYMPOSIUM VENUE

Research Institute of McGill University Health
Centre - 1001, boul. Décarie
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International Society for the Development
of the Research on Magnesium
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Magnesium Research



SUMMARY

WELCOME LETTER

SCIENTIFIC PROGRAM

ACKNOWLEDGEMENTS

ABSTRACTS INVITED SPEAKERS

ABSTRACTS ORAL COMMUNICATIONS

ABSTRACTS POSTERS



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Welcome to the 18th International Magnesium Symposium. It is a pleasure to host this meeting at the Research Institute of the McGill University Health Centre in Montreal. This is the first time the symposium takes place in Canada and hopefully not the last. We look forward to welcoming you back to future meeting in our beautiful country. Over the past ten years there has been enormous progress in the field of magnesium research. This symposium highlights the latest discoveries in the field, presented by the world experts.

The 18th International Magnesium Symposium focuses on 'molecular mechanisms and clinical implications' and includes sessions on cellular homeostasis, TRP and cation channels, pathophysiology, immunomodulation, metabolism and therapeutic strategies. We are extremely honoured to welcome Prof Guy Rutter, Dept of Medicine, University of Montreal and Principal Scientist Research Institute of the University of Montreal Health Centre, who will open the symposium.

With participants from over 13 countries, including students, post doctoral fellows, early career researchers and senior investigators, the symposium offers an international platform for networking, discussion, brainstorming and connections and facilitates opportunities for new collaborations and friendships.

We are extremely fortunate to have received support from the Jain Foundation, Magtein, Targets in Toxicology (Research Training Group), Better You, CMER (Center for Magnesium Education & Research, VERLA-PHARM, Gesellschaft für Magnesium. Such commitment is truly appreciated and provides opportunities for trainee awards, special sessions and social events. My sincere thanks for the generous support.

I would like to thank Ms Nathalie Letrillard-Spinelli, the organising committee and staff of the RI-MUHC for making the symposium a reality, and to you the participants for joining us for an exciting and stimulating symposium of cutting edge magnesium research.

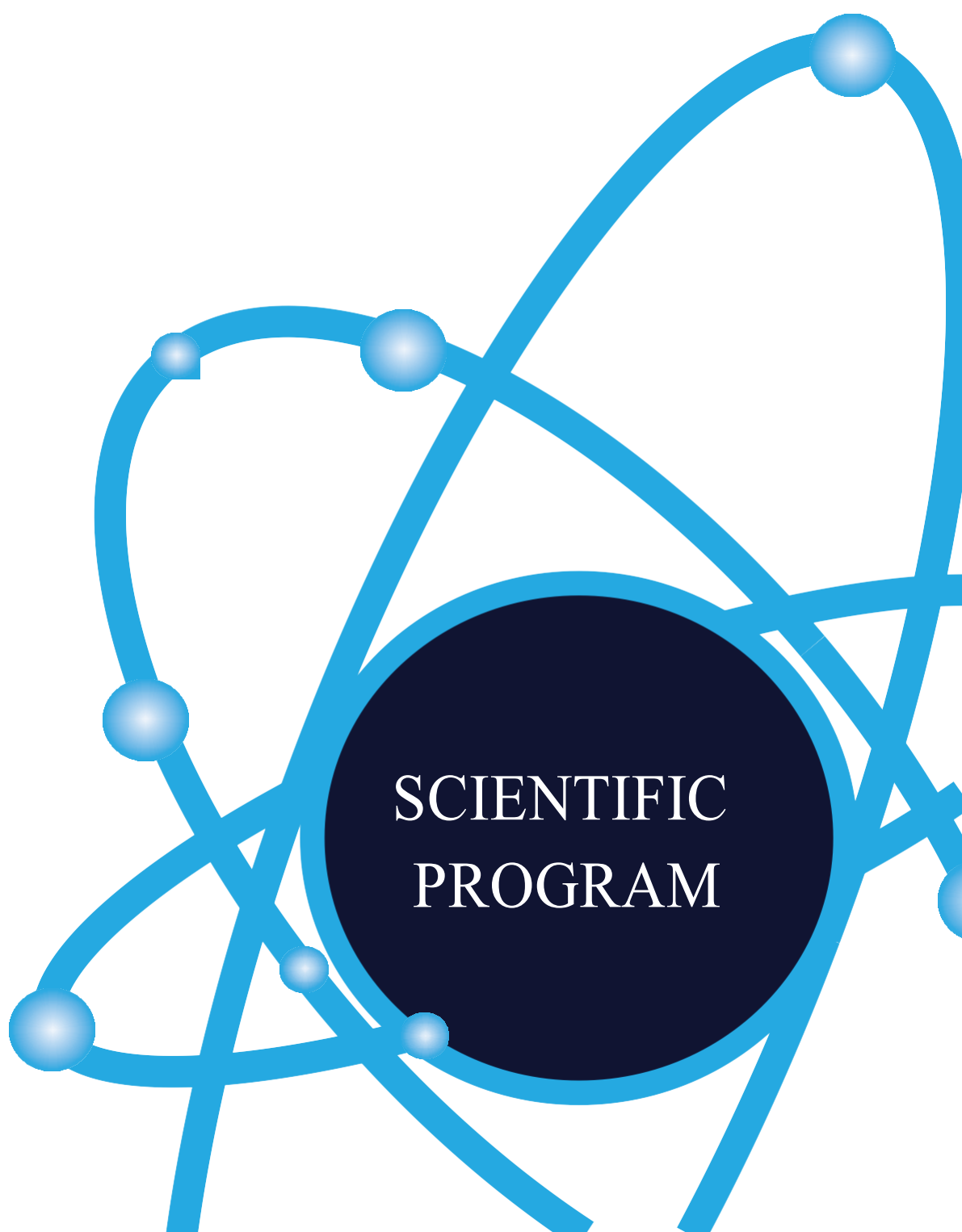
Beyond the science, please enjoy the beautiful city of Montreal – from spectacular parks to fine dining and many cultural activities.

Wishing you a stimulating, enjoyable and productive Symposium.

Rhian

Rhian M Touyz MBBCh, PhD, FRSE, FRCP, FRSC, FMedSci

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Francisco Rios, UK • Edmond Rock, FR
Rhian M. Touyz, CA • Federica I. Wolf, IT

SCIENTIFIC PROGRAM (EST TIME)
THURSDAY, AUGUST 20, 2026

08:00 - 08:30 Registration
08:30 - 08:45 Welcome Remarks
Rhian M Touyz
McGill University Health Centre Montréal, Québec, Canada
Federica Wolf
Università Cattolica del Sacro Cuore, Rome, Italy
08:45 - 09:10 OPENING LECTURE
Rhian M Touyz
McGill University Health Centre, Montréal, Québec, Canada
Divalent Metal Ions in the Control of Insulin Secretion
Guy Rutter
*PhD, Professor, Dept of Medicine, University of Montreal and Principal Scientist
Research Institute of the University of Montreal Health Centre, Canada*

SESSION I

MAGNESIUM HOMEOSTASIS - WASTING & TREATMENT

Chairpersons: **Federica Wolf**
Università Cattolica del Sacro Cuore, Rome, Italy
Chintan V. Shah
University of Florida – College of Medicine, FL, USA
09:10 - 09:35 SGLT2 Inhibition and Renal Magnesium Handling: Mechanisms and Clinical Implications
Adriana Girardi
Departamento de Cardiopneumologia, Faculdade de Medicina da Universidade de Sao Paulo (FMUSP), Sao Paulo, Brazil
09:35 - 10:00 SGLT2 Inhibitors for Hypomagnesemia: Case Series, Observational Studies, and a Clinical Trial
Chintan V. Shah
*Division of Nephrology, Hypertension & Renal Transplantation
University of Florida – College of Medicine, FL, USA*
10:00 - 10:25 Magnesium Reabsorption from the Proximal Tubule and the TAL
R. Todd Alexander
Departments of Pediatrics, University of Alberta, Canada
10:25 - 10:35 Coffee Break around Poster Session

SESSION II

MAGNESIUM HOMEOSTASIS - TRP - CHANNELS

Chairpersons: **Vladimir Chubанov**
Ludwig Maximilian University, Munich, Germany
Matthias Wolf
University of Michigan, Ann Arbor, MI, USA
10:35 - 11:00 New Insights into the Physiological Roles of TRPM6 and TRPM7
Vladimir Chubанov
Department of Pharmacology and Toxicology, Walther-Straub Institute, LMU Munich, Germany
11:00 - 11:25 The Magnesium Channel TRPM6 is Stimulated Synergistically by the Urinary Proteins Mucin-1 and Uromodulin
Matthias Wolf
Department of Pediatrics, Pediatric Nephrology, University of Michigan, Ann Arbor, MI, USA
11:25 - 11:50 The Role of Magnesium and TRPM Channels in Pancreatic Islets
Noushafarin Khajavi
Rudolf-Boehm-Institute for Pharmacology and Toxicology, Leipzig University, Germany
11:50 - 12:15 Structural Mechanisms of TRPM7 Activation and Inhibition
Alexander Sobolevsky
Columbia University, New York, USA
12:15 - 12:40 Uncovering the Function of TRPM7 and TRPM6 Kinase Domains
Alexey Ryazanov
*Department of Pharmacology Rutgers, Robert Wood Johnson
Medical School Piscataway, NJ, USA*
12:40 - 13:05 Modeling Calcium and Magnesium Balance: Regulation by Hormones
Anita T Layton
Department of Applied Mathematics, University of Waterloo, ON, Canada

13:05 - 14:00 Lunch around Poster Session
Chairpersons: **Rhian M Touyz**
McGill University Health Centre, Montréal, Québec, Canada
Federica Wolf
Università Cattolica del Sacro Cuore, Rome, Italy
14:00 - 14:25 Keynote Lecture - Sponsored by Magtein
"From Molecule to Mind: A 20-Year Journey in Magnesium Translational Research"
Guosong Liu, PhD
*Founder & CEO, Neurocentria, California, USA
Former professor at MIT and Tsinghua University*

SESSION III

MAGNESIUM HOMEOSTASIS - EVOLUTION & DEVELOPMENT

Chairpersons: **Michel L Tremblay**
*Department of Biochemistry and Goodman Cancer Institute,
McGill University, Montreal, Canada*
Eduardo A Groisman
Yale School of Medicine, Department of Microbial Pathogenesis, New Haven, CT, USA
14:25 - 14:50 Evolutionary Involvement of PTP4A-like Enzyme from TRANSLON to Infectious Agents
Michel L Tremblay
*Department of Biochemistry and Goodman Cancer Institute,
McGill University, Montreal, Canada*
14:50 - 15:15 Magnesium Control of Bacterial Physiology
Eduardo A Groisman
Yale School of Medicine, Department of Microbial Pathogenesis, New Haven, CT, USA
15:15 - 15:45 ORAL COMMUNICATIONS
15:15 - 15:30 Mean Serum Magnesium and Prevalence of CLMD in U.S. Adults >19 years
OC01 **Rebecca Costello**
CMER Center for Magnesium Education and Research, Pahoeh, Hawaii, USA
15:30 - 15:45 New Fluorescent Probes for Detection of (Sub)Cellular Magnesium with High Selectivity
OC02 **Daniela Buccella**
Department of Chemistry, Emory University, Atlanta, GA, USA
15:45 - 16:10 Coffee Break around Poster Session

SESSION IV

MAGNESIUM HOMEOSTASIS - CNNM-TRANSPORTERS

Chairpersons: **Kalle Gehring**
Department of Biochemistry, McGill University, Montreal, Canada
Maria Luz Martinez-Chantar
CIC bioGUNE. Liver Diseases Lab, Vizcaya, Spain
16:10 - 16:35 Regulation of Magnesium Transport by the PRL/CNNM Pathway
Kalle Gehring
Department of Biochemistry, McGill University, Montreal, Canada
16:35 - 17:00 Rewriting Liver Biology Through Magnesium Homeostasis
Maria Luz Martinez-Chantar
CIC bioGUNE. Liver Diseases Lab, Vizcaya, Spain
17:00 - 17:25 CNNM2 in Magnesium Handling and Balance
Onur Cil - Sponsored by the Jain Foundation
Department of Pediatrics, UCSF, San Francisco, California, USA
17:25 - 17:50 Open Resources to Understand and Target Membrane Transporters in Rare Neurological Diseases
David Sauer - Sponsored by the Jain Foundation
University of Oxford, Centre for Medicines Discovery, UK
17:50 - 18:05 ORAL COMMUNICATION
OC03 Proposed Novel Scale to Assess Mg Status with Serum Ca and Serum Mg Ratios
Andrea Rosanoff
CMER Center for Magnesium Education & Research, Pahoeh, Hawaii, USA
20:00 SOCIAL DINNER (Auberge Saint Gabriel)

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SCIENTIFIC PROGRAM (EST TIME)
FRIDAY, AUGUST 21, 2026

MEET THE SPONSORS

08:10 - 08:20 The Jain Foundation
08:20 - 08:30 Magtein

SESSION V

MAGNESIUM PATHOPHYSIOLOGY

Chairpersons: **Jeroen de Baaij**
Radboud University Medical Center, Nijmegen, the Netherlands
Francisco Rios
University of Portsmouth, Portsmouth, UK

08:30 - 08:55 Novel insights in renal Mg²⁺ transport
Jeroen de Baaij
Department of Medical BioSciences, Radboud University Medical Center, Nijmegen, the Netherlands

08:55 - 09:20 Mechanisms of Renal Magnesium Handling and Links to Hypokalemia
James McCormick
Division of Nephrology & Hypertension, Department of Medicine, Oregon Health & Science University (OHSU), Portland, OR, USA

09:20 - 09:45 The Mechanism whereby Mg treats Atrial Fibrillation and Heart Failure with Preserved Ejection Fraction
Samuel C Dudley
Lillelei Heart Institute, Minneapolis, MN, USA

09:45 - 10:10 The TRPM7-Magnesium Axis in Cardiovascular Inflammation and Fibrosis
Francisco Rios
School of Medicine, Pharmacy and Biomedical Sciences University of Portsmouth, UK

10:10 - 10:35 TRPM7-Mediated Pyroptosis in Ischemic Myocardial Injury
Lixia Yue
Department of Cell Biology, Pat and Jim Calhoun Cardiology Center, University of Connecticut Health Center, Farmington, CT, USA

10:35 - 11:00 Coffee Break around Poster Session

10:30 - 11:00 SDRM EXTRAORDINARY GENERAL ASSEMBLY (ROOM ES1.5077)

11:00 - 11:25 Renal Magnesium Conservation During Lactation
Evan Ray
Renal-Electrolyte Div., University of Pittsburgh, PA, USA

11:25 - 11:50 Altered Magnesium Metabolism in Primary Aldosteronism: Clinical Manifestations and Cardiovascular Effects
Marta Müller
Nephrology Department, University Hospital of Duesseldorf, Heinrich Heine University, Germany

11:50 - 12:20 ORAL COMMUNICATIONS

11:50 - 12:05 Aldosterone and Cardiac Fibrosis in TRPM7-Deficient Mice
OC04 **Liam Quigg**
Research Institute of McGill University Health Centre, McGill University, Montreal, Canada

12:05 - 12:20 TRPM7 and Inflammatory Macrophages are Required for Hypomagnesemia - Induced Heart Failure with Preserved Ejection Fraction
OC05 **Man Liu**
Cardiovascular Division, the Lillelei Heart Institute, Department of Medicine, University of Minnesota, Minneapolis, MN, USA

12:20 - 13:30 Lunch around Poster Session

SESSION VI

UNVEILING THE IMMUNOMODULATORY POWER OF MAGNESIUM: FROM CELLULAR MECHANISMS TO CLINICAL IMPACT

Chairpersons: **Stefano Iotti**
Department of Pharmacy and Biotechnology, University of Bologna, Italy
Federica Wolf
Università Cattolica del Sacro Cuore, Rome, Italy

13:30 - 13:55 TRPM7 and Magnesium in B Cell Biology
Bebhinn Treanor
*Department of Biological Sciences, University of Toronto Scarborough
Department of Cell and Systems Biology and Department of Immunology, University of Toronto, ON, Canada*

13:55 - 14:20 Hypomagnesemia in Lymphoma Patients Receiving CAR T Therapy Correlates with Immune Dysfunction and Decreased Survival
Thomas Witzig
Mayo Clinic, Department of Hematology, Hematology-Oncology, Rochester, MN, USA

14:20 - 14:50 ORAL COMMUNICATIONS

14:20 - 14:35 Local Sustained Magnesium Delivery for the Treatment of Murine Periodontitis Modulates Immune Response and Impact on the Microbiome
OC06 **Charles Sfeir**
Center for Craniofacial Regeneration, Department of Periodontics and Preventive Dentistry, School of Dental Medicine, University of Pittsburgh, PA, USA

14:35 - 14:50 Identification of TRPM7 and CNNM4 Complexes in Pancreatic Ductal Adenocarcinoma Cells
OC07 **Laure Noe**
UMR 1366 Inserm, University of Amiens, France

SESSION VII

MAGNESIUM ACROSS THE LIFESPAN: FROM CONCEPTION TO OLD AGE

Chairpersons: **Rafael Fissore**
Department of Veterinary and Animal Sciences, University of Massachusetts, Amherst, NJ, USA
Loren Runnels
Department of Pharmacology Rutgers, Robert Wood Johnson Medical School Piscataway, NJ, USA

14:50 - 15:15 How Cells Set Magnesium Levels During Development
Loren Runnels
Department of Pharmacology Rutgers, Robert Wood Johnson Medical School Piscataway, NJ, USA

15:15 - 15:40 Ca²⁺, Zn²⁺, and Mg²⁺: Ionic Control of Fertilization and Early Development
Rafael Fissore
Department of Veterinary and Animal Sciences, University of Massachusetts, Amherst, NJ, USA

15:40 - 16:05 From Petri Dish to Patient: Unraveling the Role of Magnesium in the Biology of Aging
Jeanette A Maier
Department of Biomedical and Clinical Sciences, University of Milan, Italy

16:05 - 16:30 Magnesium Involvement in Biomineralization: a Glimpse on the Aging Bone
Stefano Iotti
Department of Pharmacy and Biotechnology, University of Bologna, Italy

16:30 - 17:45 ORAL COMMUNICATIONS

16:30 - 16:45 TRPM7 in Neurodevelopment and Neuro-disorders
OC08 **Hong-Shuo Sun**
Departments of Surgery, Physiology, Pharmacology and Toxicology, Temerty Faculty of Medicine, Leslie Dan Faculty of Pharmacy, University of Toronto, ON, Canada

16:45 - 17:00 Transient Receptor Potential Melastatin 2 (TRPM2) as a Convergent Regulator of Neurodegeneration and Neuroinflammation
OC09 **Zhong-Ping Feng**
Department of Physiology, Temerty Faculty of Medicine, University of Toronto, ON, Canada

17:00 - 17:15 Magnesium Supplementation Improves Cognitive Frailty in Older Adults with Hypertension
OC10 **Pasquale Mone**
*Department of Medicine and Health Sciences "Vincenzo Tiberio", Campobasso, Italy
Casa di Cura Montevergine, GVM Care and Research, Mercogliano, Italy*

17:15 - 17:30 Chronic Magnesium Deficiency Affects Early Pregnancy
OC11 **Deanna J. Nelson**
North Carolina State University, Raleigh, NC, USA

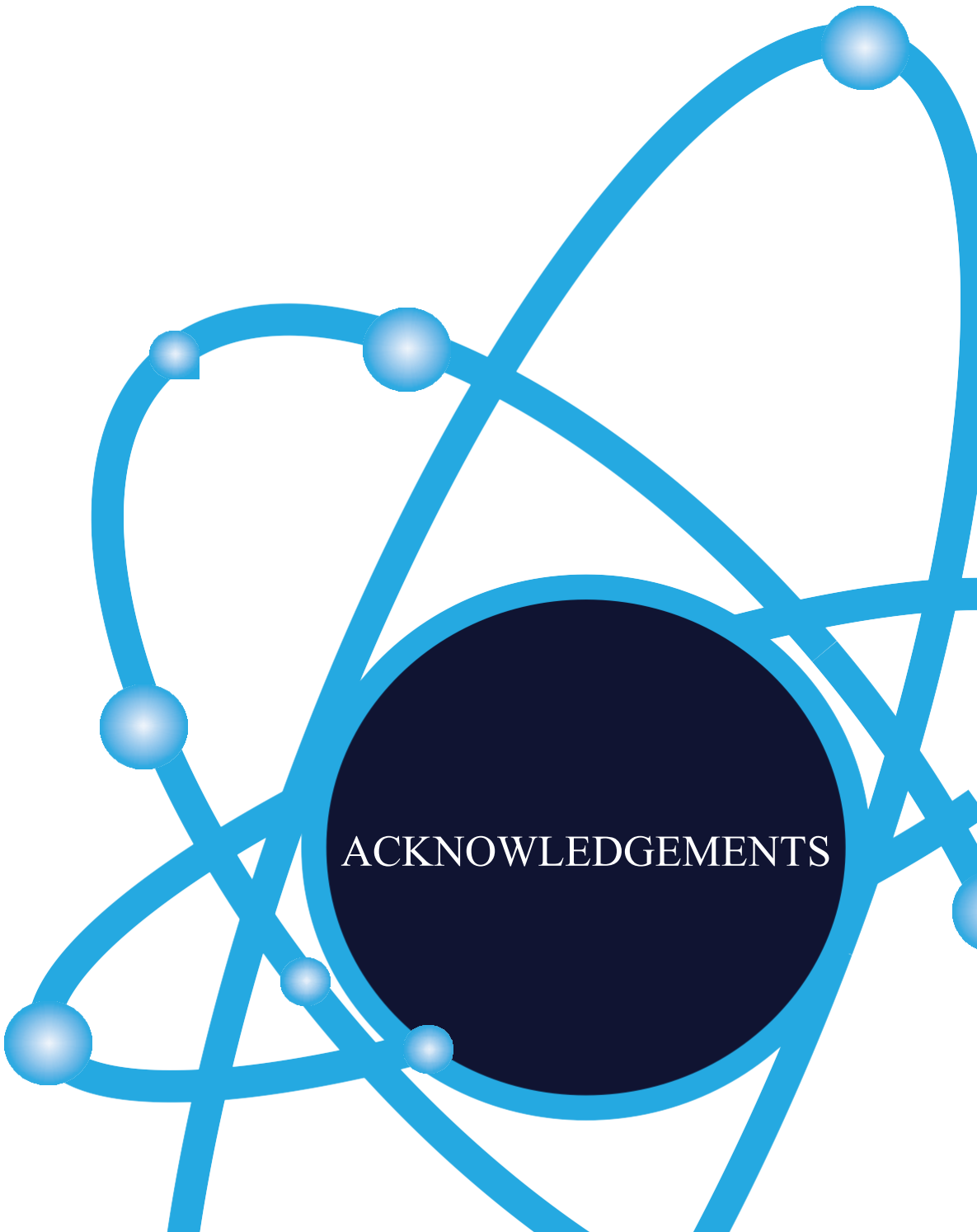
17:30 - 17:45 In Patients with Cardiovascular Disease Hypomagnesaemia Associated to High Serum Remnant Cholesterol Levels Determines an Increase in Atherosclerosis Risk Factors and Inflammation
OC12 **Ioan Axente Gutiu**
Carol Davila University of Medicine and Pharmacy-Bucharest, Romania

17:45 - 18:00 Coffee Break around Poster Session

18:00 - 18:30 Awards Nomination and Closing Ceremony

Chairpersons: **Rhian M Touyz**
McGill University Health Centre, Montréal, Québec, Canada
Federica Wolf
Università Cattolica del Sacro Cuore, Rome, Italy

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A stylized graphic of an atomic structure, featuring a central dark blue circle and several intersecting blue elliptical orbits with small blue spheres at various points.

ACKNOWLEDGEMENTS

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ABSTRACTS
Invited
Speakers

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Divalent Metal Ions in the Control of Insulin Secretion

Guy Rutter

PhD, Professor, Dept of Medicine, University of Montreal and Principal Scientist
*Research Institute of the University of Montreal Health Centre, **Canada***

Contact: guy.rutter@umontreal.ca



SGLT2 Inhibition and Renal Magnesium Handling: Mechanisms and Clinical Implications

Adriana Girardi

*Departamento de Cardiopneumologia, Faculdade de Medicina da Universidade de São Paulo (FMUSP), São Paulo, **Brazil***

Short biography:

Adriana Castello Costa Girardi, MD, PhD, is an Associate Professor at the Faculdade de Medicina da Universidade de São Paulo (FMUSP) and leads the Laboratory of Renal Physiology and Cardiometabolism at InCor–HCFMUSP. Her research focuses on renal tubular physiology, cardio-renal-metabolic pharmacology, and the molecular mechanisms underlying the effects of SGLT2 inhibitors, including magnesium handling, ion transporters, and signaling pathways relevant to cardiovascular and kidney diseases. She coordinates multiple nationally funded research projects and collaborates extensively with international research groups.

Contact: adriana.girardi@fm.usp.br



SGLT2 Inhibitors for Hypomagnesemia: Case Series, Observational Studies, and a Clinical Trial

Chintan V. Shah

*Division of Nephrology, Hypertension & Renal Transplantation
University of Florida – College of Medicine, FL, USA*

Description:

Sodium/glucose cotransporter 2 (SGLT2) inhibitors have emerged as a new class of drugs for treating hypomagnesemia, driven by their unique extraglycemic benefit. In this talk, I will discuss the current evidence from our most recent multicenter case series, two single-center observational studies, and interim results from a clinical trial examining the effects of SGLT2 inhibitors in patients with hypomagnesemia.

Bio sketch

I received my Bachelor of Medicine and Surgery (M.B.B.S.) from the Medical College of Baroda in India. Then, I completed an internal medicine residency at Cleveland Clinic/Fairview Hospital, followed by a nephrology fellowship at Wayne State University in 2015. I am a clinical associate professor and director of the Onco-Nephrology service at the University of Florida, Florida, U.S.A.

Contact: Chintan.Shah2@medicine.ufl.edu



**UNIVERSITY
OF ALBERTA**

Magnesium Reabsorption from the Proximal Tubule and the TAL

R. Todd Alexander

Departments of Pediatrics, University of Alberta, Canada

Biosketch:

Dr. Alexander is a Pediatric Nephrologist at the Stollery Children's Hospital, Professor and Chair of Pediatrics at the University of Alberta. He is the Canada Research Chair in epithelial transport physiology, processes that are abnormal in children with kidney disease. Integrating his fundamental research program examining paracellular divalent cation transport with his clinical practice, he seeks to advance care for children with disorders of renal tubular transport such as kidney stone formers and those with metabolic bone disease. This work is funded by the Canadian Institutes of Health Research (CIHR), the National Sciences and Engineering Research Council of Canada (NSERC), and the Women and Children's Health Research Institute (WCHRI).

E-mail: todd2@ualberta.ca



New Insights into the Physiological Roles of TRPM6 and TRPM7

Vladimir Chubanov

*Department of Pharmacology and Toxicology, Walther-Straub Institute, LMU Munich, **Germany***

Biographical sketch:

Vladimir Chubanov, PhD

Group Leader, Walther-Straub Institute of Pharmacology and Toxicology, LMU Munich, Germany.

Studies of my group are focused on TRPM6 and TRPM7, bifunctional proteins combining a channel segment with an α -type protein kinase. Mutations in the human TRPM6 and TRPM7 genes lead to systemic Mg^{2+} deficiency. However, the mechanisms behind how these channel-kinases regulate Mg^{2+} homeostasis and the are not fully understood. Therefore, our primary objective is to gain new insights into the physiological and pathophysiological roles of TRPM6 and TRPM7. We employ gene-modified mice along with a diverse array of biochemical, biophysical, and cell-biological techniques to achieve this goal.

Contact: vladimir.chubanov@lrz.uni-muenchen.de



The Magnesium Channel TRPM6 is Stimulated Synergistically by the Urinary Proteins Mucin-1 and Uromodulin

Matthias Wolf

Department of Pediatrics, Pediatric Nephrology, University of Michigan, Ann Arbor, MI, USA

Purpose: Single nucleotide polymorphisms (SNPs) in the Mucin 1 (*MUC1*) gene associated with serum magnesium levels. We have previously shown that Uromodulin (UMOD), another urinary protein, stimulates the magnesium channel TRPM6. UMOD and MUC1 share characteristics: 1) They are both membrane proteins which are secreted into human urine; 2) They create a protective layer on the surface of tubular cells by forming polymers; 3) Pathogenic variants in *UMOD* and *MUC1* cause autosomal dominant tubulo-interstitial kidney disease (ADTKD); 4) We have previously shown that UMOD and MUC1 stimulate the magnesium channel TRPM6 and the calcium channel TRPV5. Given these similarities, we investigated if UMOD and MUC1 physically interact and if both proteins stimulate TRPM6 synergistically.

Materials and methods: We analyzed if SNPs in *MUC1* are associated with serum magnesium levels in the Dallas Heart Study cohort. We applied whole-cell patch-clamp recording to determine TRPM6 current density and the half maximal effective concentration (EC₅₀) of UMOD and MUC1 to stimulate TRPM6. Immunofluorescent studies in human kidney biopsy tissue for co-localization of MUC1 and UMOD were performed. Physical interaction was evaluated by co-immunoprecipitation (Co-IP).

Results: 1. Patients with the *MUC1* rs4072037 SNP were characterized by a significantly lower serum magnesium level but not frank hypomagnesemia. 2. We found that 0.9 µg of wild-type (WT) UMOD-HA and 0.2 µg of MUC1 plasmid resulted in half maximal stimulation (EC₅₀) of TRPM6. While individual "subthreshold" doses of 0.6 µg of WT UMOD-HA and 0.2 µg of MUC1 plasmid did not enhance TRPM6, the combination of "subthreshold" UMOD plus MUC1 dosages stimulated TRPM6 indicating a synergistic effect. 3. Co-IP studies showed that WT UMOD and MUC1 physically interact. 4. UMOD and MUC1 co-localized in human kidney biopsy tissue. 5. We determined that the UMOD truncation plasmid R586XUMOD-HA stimulated TRPM6 but neither the L180X UMOD-HA nor C297X UMOD-HA constructs activated TRPM6 indicating that TRPM6 stimulation requires either UMOD's D8C and/or zona pellucida domain. 6. After determining the EC₅₀ for R586X UMOD-HA at 0.8 µg, neither the "subthreshold" dose for R586X UMOD-HA (0.6 µg) nor MUC1 (0.2 µg) alone enhanced TRPM6 while combined they stimulated the magnesium channel indicating that the glycosylphosphatidylinositol (GPI) anchor is not required for the UMOD-MUC1 interaction. 7. No synergistic action was found for C297X UMOD-HA and MUC1 regarding TRPM6 stimulation indicating that the UMOD zona pellucida domain is required for the synergistic action. 8. In Co-IP studies, we found physical interaction between MUC1 and the truncation mutant R586X UMOD-HA but not the truncation variant C297X UMOD-HA, suggesting that the missing zona pellucida domain is needed for UMOD to bind to MUC1.

Conclusion: We confirm that the *MUC1* SNP rs4072037 is associated with serum magnesium levels in the Dallas Heart Study cohort. Our findings outline that urinary proteins MUC1 and UMOD both synergistically stimulate the magnesium channel TRPM6. Both proteins co-localize in human kidney tissue and physically interact. The UMOD zona pellucida domain is required for physical interaction between UMOD and MUC1.

Biographical sketch: Matthias Wolf is the division director of Pediatric Nephrology at the University of Michigan. His research focuses on tubular electrolyte disturbances and drug development for rare kidney disorders. Regarding tubular electrolyte disturbances he is interested in proteins modifying the renal epithelial magnesium channel TRPM6. He studied the effects of urinary proteins such as Mucin-1, Uromodulin, and the hunger hormone Ghrelin on magnesium homeostasis. His research has been published in the Journal of the American Society, Kidney International, and the Journal of Biological Chemistry. His research has been supported by the NIH and the Department of Defense.

Contact: matwolf@med.umich.edu



The Role of Magnesium and TRPM Channels in Pancreatic Islets

Noushafarin Khajavi

Rudolf-Boehm-Institute for Pharmacology and Toxicology, Leipzig University, Germany

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Obesity and type 2 diabetes are characterized by progressive pancreatic islet dysfunction, highlighting the need to identify molecular mechanisms that preserve islet function and improve therapeutic responses. We recently investigated the role of transient receptor potential (TRP) channels in regulating pancreatic endocrine cell biology and metabolic homeostasis. We identified the Mg²⁺-permeable channel kinase TRPM7 as a key regulator of pancreatic islet plasticity. Using β -cell-specific TRPM7 KO and TRPM7-kinase deficient mouse models, we demonstrated that TRPM7 kinase is essential for maintaining β -cell identity, proliferation, and glucose-stimulated insulin secretion, particularly during metabolic stress. Mechanistically, TRPM7 regulates β -cell transcriptional networks, including PDX1 and MAFA, together with PI3K/AKT and ERK1/2 signaling. In α -cells, TRPM7 regulates glucagon production and cell mass through the mTORC–FOXA2 pathway, thereby contributing to whole-body glucose homeostasis.

More recently, we showed that the Ca²⁺-activated cation channel TRPM5 is required for the metabolic actions of the GLP-1/GIP/glucagon triagonist IUB447. Unlike classical incretin signaling, IUB447 activates a G α_q –PKC pathway that enhances insulin secretion through TRPM5 channel activity. Genetic deletion or pharmacological inhibition of TRPM5 abolished the insulinotropic and metabolic benefits of the triagonist in mice.

Together, our findings identify TRPM7 as a central regulator of pancreatic islet adaptation and establish TRPM5 as a critical effector of next-generation incretin therapies. These studies highlight TRPM channels as promising therapeutic targets for preserving islet function and improving metabolic control in type 2 diabetes.

Bio-sketch:

Noushafarin Khajavi is a Professor of Molecular Pharmacology at the Rudolf-Boehm-Institute for Pharmacology and Toxicology, Leipzig University. Her research focuses on the molecular mechanisms underlying metabolic diseases, with a particular emphasis on pancreatic islet biology and ion channel regulation. By integrating advanced imaging approaches with molecular and pharmacological techniques, she investigates how ion channels, especially TRP channels, regulate islet function, insulin secretion, and cellular communication. By bridging fundamental research with translational applications, she aims to identify novel therapeutic strategies for the treatment of diabetes and related metabolic disorders.

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Structural Mechanisms of TRPM7 Activation and Inhibition

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Purpose: The transient receptor potential channel TRPM7 is a master regulator of the organismal balance of divalent cations that plays an essential role in embryonic development, immune responses, cell mobility, proliferation, and differentiation. TRPM7 is implicated in neuronal and cardiovascular disorders, tumor progression and has emerged as a new drug target. While structures of TRPM7 have been determined previously, they represented the same closed conformation. To facilitate future structure-based drug design, we embarked on studies of the molecular mechanisms of TRPM7 gating and regulation.

Materials and methods: We used cryo-EM to solve structures of TRPM7 in different conformations, mutagenesis to probe ligand binding sites, aequorin-based bioluminescence assay to measure Ca^{2+} influx, patch-clamp and planar lipid bilayer techniques to measure TRPM7-mediated whole-cell and single-channel currents, respectively, and molecular dynamics (MD) simulations to assess ion channel conductance, conformational dynamics contribution of specific domains and interactions into channel gating.

Results: We used cryo-EM to solve structures of TRPM7 in the resting (apo) closed state. To study channel opening during constitutive activation, we determined structures of the gain-of-function mutant N1098Q. Upon channel opening, the S6 helices became two α -helical turns longer, while TRP helices became two α -helical turns shorter and rotated by $\sim 6^\circ$ in the plane of the membrane. These rearrangements caused a substantial dilation of the ion channel pore and slight movement of S5 away from the pore center, whereas the rest of the channel remained virtually unaffected. MD simulations of the N1098Q mutant suggested that the TRPM7 channel constitutive activity is controlled by N1097 and N1098 mediated hydrogen bonds. Structures of TRPM7 in complex with naltriben (NTB) revealed the mechanism of agonist-induced channel opening. NTB binding site is located at the intersubunit interface and formed by the MHR4/Pre-S1 region of one subunit and the loop connecting the MHR4 helices $\alpha 21$ and $\alpha 22$ of the neighboring subunit. NTB binding pulls the MHR4/Pre-S1 region of one subunit towards the MHR3 domain of the

neighboring subunit. During this motion, the entire NTD of each individual subunit undergoes a $\sim 21^\circ$ rigid-body rotation. Such dramatic movement of the NTDs causes a $\sim 21^\circ$ rotation of the TRP helices, leading to the transformation of the S6-TRP helix connection and pore opening. We also solved structures of TRPM7 in complex with two potent and structurally unrelated antagonists, VER155008 and NS8593. They share the same binding site contributed by the N-terminal part of S3, C-terminal part of S4, S4-S5 linker and TRP helix (vanilloid site) and act by stabilizing TRPM7 in the closed state.

Conclusion: Our study reveals the molecular basis of TRPM7 gating and inhibition and provides new mechanistic insights into the function of this ion channel, which is essential for the cellular uptake of divalent cations. Our structures as well as the identified agonist and antagonist binding sites provide templates for the design of new pharmacological modulators of TRPM7, which can be beneficial for patients with immune and cardiovascular disorders, tumors, and other pathologies.

Short biography:

Alexander Sobolevsky earned his PhD in biophysics in 1999 from the Moscow Institute of Physics and Technology, where he studied NMDA receptor channels under the guidance of Prof. Khodorov. He held his first postdoctoral position in the lab of Dr. Wollmuth at Stony Brook University, where he studied the functional architecture of ionotropic glutamate receptors (iGluRs) using the substituted cysteine accessibility method. He continued his postdoctoral training with Dr. Gouaux, first at Columbia University and then at OHSU, where he solved the first structure of iGluR. He became an Assistant Professor of biochemistry and molecular biophysics at Columbia University in 2010, focusing on the structure and function of iGluRs and TRP channels. In 2024, he was promoted to Professor.

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Uncovering the Function of TRPM7 and TRPM6 Kinase Domains

Alexey Ryazanov

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Short biography:

Dr. Alexey Ryazanov is a Professor of Pharmacology at Rutgers Robert Wood Johnson Medical School. Dr. Ryazanov identified phosphorylation of Elongation Factor 2 (eEF2) by eEF2 kinase as a mechanism of global protein synthesis regulation. This led to the discovery of alpha kinases, a family of atypical protein kinases which in addition to eEF2 kinase include channel-kinases TRPM6 and TRPM7 and an innate immunity receptor, alpha kinase-1 (ALPK1). Currently his laboratory is investigating various alpha kinases and their role in intracellular signal transduction.

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Modeling Calcium and Magnesium balance: Regulation by Hormones

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Biosketch:

Anita Layton is the distinguished University Professor and Professor of Applied Mathematics, Computer Science, Pharmacy and Biology at the University of Waterloo. Her research focuses on the development and application of mathematical models to gain insights into human and mammalian physiology and pathophysiology. In particular, she is interested in the effect of sex and circadian clock in kidney function, kidney disease, diabetes, and cardiovascular disease. She is the Editor of SIAM Review Book Section, a section editor of the SIAM journal on Life Sciences, an associate editor of SIAM Journal on Applied Dynamical Systems, Mathematical Medicine and Biology, Frontier in Physiology, Maple Transactions, and an AI/ Machine Learning Section Editor for Hypertension. She is a Fellow of the Royal Society of Canada, the American Physiological Society, the Canada Mathematical Society, and the Association of Women in Mathematics. She is also the 2021 winner of the Krieger–Nelson Prize of the Canadian Mathematical Society, a 2021 winner of the Top 100 Most Powerful Women in Canada by the Women's Executive Network, the 2023 winner of the Award of Merit by the Federation of Chinese Canadian Professionals, the 2023 winner of the John L. Synge Award by the Royal Society of Canada, the 2025 winner of the CAIMS Research Prize, and the 2026 winner of the Ernest H. Starling Distinguished Lecture Award, American Physiological Society Water & Electrolyte Homeostasis Section.

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Neurocentria
The Future in Mind

From Molecule to Mind: A 20-Year Journey in Magnesium Translational Research

[Guosong Liu](#)

Neurocentria, Inc., California, **USA**; formerly led neuroscience laboratories at MIT and Tsinghua University

Purpose: Cognitive ability depends on synapse density and plasticity. This lecture traces that journey. It began in 2004, when we found that synaptic plasticity can be enhanced by adjusting the voltage-dependent magnesium block of the NMDA receptor, with upregulation of NR2B-containing NMDA receptors (Neuron, 2004) — establishing magnesium as a critical lever on plasticity.

Materials and methods: The program integrated single-synapse electrophysiology, rodent behavioral and disease models, mechanistic studies of magnesium-L-threonate (MgT), and randomized, double-blind, placebo-controlled clinical trials.

Results: Among major magnesium compounds used for supplementation, MgT is the only one shown to effectively elevate brain magnesium, likely reflecting threonate's peripheral actions: enhancing gastrointestinal absorption and promoting entry into the brain (Neuron, 2010). Centrally, threonate — an endogenous CSF constituent — promotes entry of CSF magnesium into synaptic terminals, raising intracellular magnesium, the key regulator of synapse density and plasticity (Neuropharmacology, 2016; Zhou et al., 2015). In rodents, MgT increased functional presynaptic release sites, upregulated NR2B-NMDA receptors, enhanced long-term potentiation, and improved learning, working memory, and pattern completion, including in aged animals; in an Alzheimer's model it prevented and reversed synaptic loss and cognitive deficits even at end-stage pathology (J Neurosci, 2013). In older adults with cognitive impairment, MgT improved overall cognition versus placebo ($p = 0.003$; $d = 0.91$) and largely restored executive function (J Alzheimers Dis, 2016). Independent randomized controlled trials have since shown benefits for cognition in healthy adults (Zhang et al., 2022) and for sleep quality and daytime functioning (Hausenblas et al., 2024; Lopresti & Smith, 2026).

Conclusion: Brain-targeted elevation of magnesium is a mechanism-based strategy for supporting synaptic function and cognition across the lifespan. Recent work showing that intracellular magnesium reconfigures dendritic synaptic connectivity and restores a youthful configuration in aging animals (Zhou et al., Nat Commun, 2024) closes the loop to the single-synapse mechanism where the journey began.

Biographical sketch: Guosong Liu, PhD, is Founder and CEO of Neurocentria, Inc., and the inventor of magnesium-L-threonate (Magtein), a magnesium compound now used worldwide for brain health. He received his PhD from UCLA and completed postdoctoral training at Stanford, and subsequently led neuroscience laboratories at MIT and Tsinghua University. His research — published in journals including Nature, Neuron, and Nature Communications — established the magnesium ion as a central regulator of synapse density and plasticity, and pioneered the translation of brain-magnesium science from molecular mechanism to human clinical trials over more than two decades.

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Evolutionary Involvement of PTP4A-like Enzyme from TRANSLON to Infectious Agents

Michel L Tremblay

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A short biography

Professor Michel L. Tremblay, PhD, F.R.S.C., C.Q., is a Distinguished Professor in the Department of Biochemistry at McGill University and a member of the Goodman Cancer Institute. He holds the Jeanne and Jean-Louis Lévesque Chair in Cancer Research and is affiliated with the Departments of Oncology, Microbiology & Immunology, and Medicine. Trained at the Université de Sherbrooke, McMaster University, and the NIH (NICHD), he joined McGill in 1992 and served as Director of the McGill Cancer Centre/Goodman Cancer Centre from 2000 to 2012. His research focuses on the function and regulation of protein tyrosine phosphatases and their roles in cancer, diabetes, and neuroscience. He has authored over 250 publications, holds more than 30 patents, and has received nearly 25,000 citations (h-index 83). Among his several awards, he served as President of the Academy of Science of the Royal Society of Canada, received a Doctorate Honoris Causa from the Université de Bordeaux, and was elected a Knight of the National Order of Quebec.

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Magnesium control of protein homeostasis and metabolism in the intracellular pathogen *Salmonella enterica* serovar Typhimurium

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The bacterial pathogen *Salmonella enterica* serovar Typhimurium faces low cytoplasmic Mg^{2+} inside host macrophages. This specific signal slows bacterial growth, increases tolerance to clinical antibiotics, and activates the master virulence regulator PhoP. PhoP governs Mg^{2+} homeostasis by promoting expression of Mg^{2+} importers; of a protein that decreases concentrations of adenosine triphosphate (ATP), the Mg^{2+} chelator and energy currency of living cells; and of proteins that covalently modify the bacterial cell envelope, increasing resistance to antimicrobial peptides and favoring Mg^{2+} release for import into the cytoplasm. We determined that, surprisingly, *S. Typhimurium* responds to low cytoplasmic Mg^{2+} via PhoP-regulated gene products that supersede canonical control of protein homeostasis and metabolism.

The pathogen reduces protein synthesis by decreasing transcription of ribosomal RNA genes, which lowers the number of translating ribosomes, and by promoting transcription of the gene specifying protein chaperone DnaK, which binds to ribosomes and reduces their translation capacity. These activities are required for *S. Typhimurium* survival against low cytoplasmic Mg^{2+} .

And *S. Typhimurium* changes its metabolism by enabling synthesis of cyclic adenosine monophosphate (cAMP), the allosteric activator of cAMP receptor protein (CRP), the master regulator of carbon utilization. cAMP is made by adenylate cyclase, a Mg^{2+} -dependent enzyme that uses ATP as substrate. During infection, the low cAMP amounts generated cause *S. Typhimurium* to prefer gluconate and glycerol over glucose because transcription of gluconate and glycerol importers requires lower cAMP-CRP amounts than transcription of the glucose importer. These cAMP-CRP-directed metabolic changes thus provide substrates for PhoP-activated gene products that modify the bacterial cell envelope, thereby increasing resistance to antibacterial agents. In sum, low cytoplasmic Mg^{2+} governs pathogen growth in host tissues, and the production and activity of virulence determinants.

Bio-sketch:

Eduardo A. Groisman is originally from Argentina. He received an MS in Biochemistry from the University of Buenos Aires and a PhD in Molecular Genetics and Cell Biology from the University of Chicago. He carried out postdoctoral training at the Institut Pasteur in Paris, The Scripps Research Institute in La Jolla, California, and the University of California, San Diego. He was a faculty member of the Department of Molecular Microbiology at the Washington University School of Medicine between 1990 and 2010. From 2010 to the present, he is a faculty member of the Department of Microbial Pathogenesis and the Yale School of Medicine. He was an investigator of the Howard Hughes Medical Institute between 1997 and 2016. He was elected to Fellowship in the American Academy of Microbiology, the American Association for the Advancement of Science, and the American Academy of Arts and Sciences. Groisman has been investigating Mg²⁺ homeostasis in bacteria for over 30 years. His laboratory discovered the first sensors of extracytoplasmic Mg²⁺ and of cytoplasmic Mg²⁺, and established the central role that cytoplasmic Mg²⁺ plays in bacterial protein synthesis, metabolism, and pathogen virulence.

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Regulation of Magnesium Transport by the PRL/CNNM Pathway

Kalle Gehring

Department of Biochemistry, *McGill University, Montreal, Canada*

Prof. Gehring trained at the University of California at Berkeley (PhD, Microbiology) and at the Ecole Polytechnique in France where he used NMR spectroscopy to determine the first four-stranded intercalated DNA structure. At McGill University, his research group uses structural biology tools to work in two areas: 1) parkin, a ubiquitin ligase that protects against Parkinson's disease, and 2) the PRL/CNNM signalling pathway that regulates intracellular magnesium. His group published the first 3D structure of parkin and recently showed that a small molecule can activate parkin by acting as a molecular glue to bypass the need for parkin phosphorylation. In the area of PRL/CNNM signalling, Prof. Gehring's laboratory determined the first structure of a PRL/CBS domain complex in 2016 and the first CNNM-family transmembrane domain in 2020. His current work is focused on understanding how conformational changes in the CNNM cytosolic domains regulate ion transport and the role of cysteine phosphorylation as an upstream effector. Lab website: www.gehringlab.net

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Rewriting Liver Biology Through Magnesium Homeostasis

María Luz Martínez-Chantar

CIC bioGUNE. Liver Diseases Lab, Vizcaya, Spain

María Luz Martínez-Chantar is the head of the Liver Disease Laboratory at CIC bioGUNE (Spain). Internationally recognized in hepatology, her work has uncovered fundamental mechanisms linking **mitochondrial function, magnesium metabolism, and post-translational modifications (SUMOylation, NEDDylation)** to liver diseases such as MASLD/MASH and hepatocellular carcinoma. She has authored more than 230 publications in top-tier journals (*Cell Metabolism, Nature Communications, Gut, Hepatology*) and co-founded **Gibela Therapeutics GmbH** based on Basel (Switzerland), to advance RNA-based therapies. Dr. Martínez-Chantar is actually the panel manager for the **Spanish Research Agency, the French ANR, and the Italian AIRC**, and as a Scientific Advisory Board member for multiple national and international research centers. She has supervised over 20 PhD students and multiple postdocs, many of whom now lead independent groups. In recognition of her contributions, she was honored as an **Ikerbasque Woman in Science** in 2022. Her career uniquely bridges basic mechanistic insights, mitochondrial biology, metabolic regulation, and translational innovation in liver pathophysiology

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CNNM2 in Magnesium Handling and Balance

Onur Cil - Sponsored by the *Jain Foundation*

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Mg²⁺ is an abundant intracellular cation in humans and a cofactor of many intracellular enzymes, especially those involving ATP utilization. Mg²⁺ has key roles in muscle contraction, cardiac excitability, neural transmission, bone turnover, and vascular tone. Systemic Mg²⁺ balance is maintained through the coordinated function of three major organs: the intestine, which mediates absorption of ingested Mg²⁺; the kidney, which determines Mg²⁺ reabsorption and excretion; and the parathyroid gland, which integrates Mg²⁺ status into hormonal regulation. In the intestine and kidney Mg²⁺ is transported via both paracellular and transcellular pathways. Transcellular Mg²⁺ transport involves apical entry via TRPM6 and TRPM7, and basolateral extrusion mediated by CNNMs. CNNM family comprises of four membrane proteins (CNNM1-4) which have proposed key regulatory roles in Mg²⁺ balance. The CBS domains of CNNMs bind Mg-ATP, suggesting a dual role in Mg²⁺ transport and intracellular sensing. CNNM2 and CNNM4 are considered key players in cellular Mg²⁺ efflux. Although the exact function of CNNM2 as a Mg²⁺ transporter vs. sensor/regulator is subject to debate, genetic studies demonstrated that CNNM2 mutations cause hypomagnesemia, suggesting its essential role in Mg²⁺ handling. This presentation provides an overview of roles of CNNM2 in Mg²⁺ balance and its tissue specific roles in Mg²⁺ transport.

Biographical sketch: Dr. Onur Cil is an Associate Professor of Pediatrics at the University of California, San Francisco. He received MD-PhD degree from Hacettepe University (Ankara/Turkey) and completed pediatrics residency training in the same institution. He joined UCSF initially as a research fellow, where he completed a clinical fellowship in pediatric nephrology and established his lab as a physician-scientist faculty member. Cil Lab's research focus is drug discovery and repurposing for treatment of renal, gastrointestinal, cardiovascular, pulmonary and ocular diseases. Ultimate goal of the lab is advancing discoveries to clinical trials and establishing better and safer treatments. A major active focus of Cil Lab is identifying mechanisms of the efficacy of Mg²⁺ and leverage these to develop novel targeted treatments.



Open Resources to Understand and Target Membrane Transporters in Rare Neurological Diseases

David Sauer - Sponsored by the *Jain Foundation*
University of Oxford, Centre for Medicines Discovery, UK

Abstract: Mutations in membrane transporters are increasingly being recognized as the cause of several rare neurological diseases. However, these proteins are underdrugged due to difficulties understanding their native functions and pathophysiology, as well as a lack of suitable tools for therapeutic discovery. To address this, my group has worked within several public-private consortia to develop open platforms for studying and targeting transporters. Here, we present our work and experience on the causes of several transporter-associated rare diseases and the needed resources to enable their therapeutic targeting.

Short biography: David Sauer is a biophysicist focusing on the structure and function of membrane channels and transporters. As a principal investigator at the University of Oxford since 2021, he has been studying the structure and function of membrane proteins for 21 years. David completed his graduate degree studying potassium channel structure and ion selectivity with Youxing Jiang at the University of Texas Southwestern Medical Center. This was followed by postdoctoral training with Da-Neng Wang at New York University School of Medicine. There, he described the transport mechanism and chemical inhibition of SLC13/DASS membrane transporters, and the structural effects of mutations in the rare SLC13A5 Epilepsy.

Since joining Oxford's CMD, David has led a group studying membrane proteins' function, pathogenesis, and chemical targeting by small molecules. This has resulted in the first detailed study of proline import by the transporter SIT1, its complex with the SARS-CoV2 (COVID-19) receptor ACE2, and the effects of mutations in retinal disease. His group has also revealed the ping-pong reaction mechanism and the product-bound, inhibited state of ceramide synthase CerS6. Finally, in a collaborative study, David's group identified the substrate-binding and transport mechanisms of the immunoregulatory SPNS2 and the pathophysiology of variants associated with hearing loss.

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Novel Insights in Renal Mg²⁺ Transport

Jeroen de Baaij

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Bio-sketch:

Jeroen de Baaij is an Associate Professor in renal physiology at the Radboud University Medical Center in Nijmegen, The Netherlands. His research focusses on the identification and characterization of new genes involved in renal magnesium reabsorption. Using a wide range of molecular, cellular, and physiological techniques, he examines new genes or new regulatory pathways in magnesium (re)absorption in the kidney.

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Mechanisms of Renal Magnesium Handling and Links to Hypokalemia

James McCormick

Division of Nephrology & Hypertension, Department of Medicine, Oregon Health & Science University (OHSU), Portland, OR, USA

Dr. McCormick is a Professor in the Division of Nephrology and Hypertension at Oregon Health and Science University. He has made significant contributions to understanding of the role of the NaCl cotransporter (NCC) in hypertension and K⁺ handling. Key contributions include identifying kidney-specific isoforms of the NCC-activating protein kinase SPAK, determining the role of the K⁺ channel Kir4.1 in NCC regulation, and determining the mechanism by which mutations in the ubiquitin ligase Cullin 3 cause hypertension. This work has led to the concept of the “potassium switch” by which NCC activity is turned on or off to maintain K⁺ homeostasis under normal physiological conditions. More recent work has explored hypomagnesemia and its link to hypokalemia, and mechanisms of renal magnesium handling. In 2022, he received the Mid-career Achievement Award from the American Heart Association for his research contributions to the kidney in hypertension and cardiovascular disease.

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Mg²⁺-dependent TRPM7 kinase is the central mediator of diabetic atrial fibrillation and heart failure with preserved ejection fraction

Samuel C Dudley

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Purpose: Diabetic heart failure with preserved ejection fraction (HFpEF) and atrial fibrillation are inflammatory conditions that can be prevented with magnesium supplementation. We investigated how diabetic hypomagnesemia (HypoMg) can mediate the macrophage activation and cardiomyocyte mitochondrial dysfunction that are central pathogenic nodes.

Materials and methods: Wild type (WT) C57BL/6J, transgenic TRPM7^{K1646R} (no kinase function), Mφ-specific FABP4 knockout (MφFKO, depleted of inflammatory Mφs) mice were used. Diabetes was induced by high fat diet (HFD). Magnesium was manipulated by controlling Mg in the diet: 1) normal diet (2 g/kg Mg²⁺) or 2) low-Mg (15-30 mg/kg Mg²⁺) diet. The cardiomyocyte (CM) cell line RL-14 and Mφ cell line Raw264.7 were also used and treated with normal (0.81 mM Mg²⁺) or low-Mg medium (0.04 mM Mg²⁺) for 48 h. Atrial fibrillation and HFpEF were assessed by programmed electrical stimulation and echocardiography, respectively.

Results: Both diabetic and HypoMg mice showed HFpEF and increased risk of atrial fibrillation, and both pathologies could be prevented by Mg repletion, suggesting that HypoMg was a central mediator. In each case, diabetes or HypoMg was accompanied by increased cardiac macrophage infiltration and inflammatory activity and increased cardiomyocyte mitochondrial dysfunction and oxidative stress. Ultimately, the increased oxidative stress led to myofilament and sarcoplasmic reticulum Ca²⁺ release channel (RyR2) oxidation causing HFpEF and atrial fibrillation, respectively. Inhibition of the TRPM7 kinase without altering the Mg transport function prevented all the pathogenic changes seen with either diabetes or HypoMg. TRPM7 kinase inhibition prevented macrophage accumulation and inflammation as well as cardiomyocyte mitochondrial dysfunction and increased oxidative stress. TRPM7 kinase mediated phosphorylation of the electron transport chain through a Src family member kinase to cause the mitochondrial dysfunction. Reductions in the intracellular Mg level explained the upregulation of TRPM7 kinase, linking Mg regulation to pathogenic macrophage activation and cardiomyocyte dysfunction.

Conclusion: HypoMg mediates diabetic HFpEF and atrial fibrillation. HypoMg has its effect by changing intracellular Mg levels that are inversely related to TRPM7 levels. Ultimately, TRPM7 kinase is a central node mediating increased macrophage activation and cardiomyocyte mitochondrial dysfunction leading to diabetic HFpEF and atrial fibrillation.

Biography

Dr. Dudley is a physician scientist and Professor of Medicine at the Lillehei Heart Institute (LHI) of the University of Minnesota. He was a Chief of Cardiology in three Universities over 22 years and the former Director of the LHI. He is a Fellow of the American College of Cardiology and American Heart Association, Editorial Board member for the Journal of the American College of Cardiology, and a member of the Association of University Cardiologists and the American Society for Clinical Investigation. He is the founder of Diastol, a company commercializing treatments for heart failure with preserved ejection fraction. His research program focuses on inflammation and its effects on arrhythmia and diastolic heart failure. He has published more than 180 articles and chapters, has an H index of 57, and has submitted more than 30 patent applications on new diagnostics and therapeutics in these areas.

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The TRPM7–Magnesium axis in cardiovascular inflammation and fibrosis

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TRPM7 is a unique Mg^{2+} -permeable channel coupled to a serine/threonine kinase and a major regulator of cellular Mg^{2+} homeostasis. Our studies investigated the role of the TRPM7– Mg^{2+} axis in cardiovascular inflammation and fibrosis. TRPM7 deficiency and hypomagnesemia were associated with vascular dysfunction, hypertension, cardiac inflammation and fibrosis, with increased susceptibility to cardiovascular and renal injury induced by aldosterone. Mechanistically, TRPM7 deficiency promoted pro-fibrotic macrophage phenotype and cardiac fibroblast activation. In fibroblasts, impaired TRPM7 function reduced intracellular Mg^{2+} and increased TGF- β /Smad3, calpain and mineralocorticoid receptor (MR) signalling, leading to increased inflammatory and profibrotic responses. Comparison of TRPM7-deficient and kinase-dead fibroblasts further identified the contributions of channel vs kinase dependent mechanisms. Aldosterone reduced TRPM7 expression and amplified these responses. Together, our findings identify the TRPM7– Mg^{2+} axis as a protective regulator of cardiovascular inflammation and fibrosis and an important modulator of aldosterone/MR-dependent cardiovascular injury.

Biography and research interests: Dr Francisco J. Rios is a Lecturer in Pharmacology at the University of Portsmouth, UK. He trained in cardiovascular immunology and vascular biology in Brazil, Canada and the UK. His research is focused on understanding the interaction between immune and vascular cells in cardiovascular homeostasis and disease. In his recent work, he identified TRPM7 as an important regulator of cardiovascular inflammation and fibrosis, particularly in response to aldosterone and mineralocorticoid receptor activation.

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TRPM7-Mediated Pyroptosis in Ischemic Myocardial Injury

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Ischemic heart disease is one of the leading causes of death worldwide. Timely reperfusion is essential for myocardium salvage but triggers paradoxical cardiomyocyte death and contributes to up to 50% of the final infarct size, known as lethal ischemia/reperfusion (I/R) injury. The transient receptor potential melastatin 7 (TRPM7) is a divalent cation-permeable, nonselective channel kinase that can sense oxidative stress and release Zn^{2+} from unique intracellular TRPM7 vesicles. However, the pathophysiological role of intracellular TRPM7 remains poorly understood.

We analyzed TRPM7 expression in human hearts from patients with ischemic heart failure and in mouse hearts subjected to ischemia/reperfusion (I/R) injury. Global (*gTrpm7*^{-/-}), cardiomyocyte-specific (*cmTrpm7*^{-/-}), and fibroblast-specific (*fibTrpm7*^{-/-}) *Trpm7* knockout mice were used to determine the role of TRPM7 in I/R injury. Mechanistic investigations were conducted in neonatal and adult mouse cardiomyocytes, as well as human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs), using patch-clamp, Zn^{2+} imaging, and molecular biology techniques. An inducible TRPM7 channel-dead knock-in (TRPM7-E1047K) mouse model was generated. The TRPM7-E1047K channel-dead knock-in mice, together with kinase-inactive TRPM7 knock-in mice, were used to elucidate the functional domains of TRPM7 and identify potential therapeutic targets.

We found that TRPM7 was significantly upregulated in the myocardium of both patients with ischemic heart failure and mice subjected to I/R injury. Global TRPM7 deficiency markedly reduced infarct size and improved cardiac function after I/R injury. Using *cmTrpm7*^{-/-} and *fibTrpm7*^{-/-} mice, we demonstrated that TRPM7 deficiency in cardiomyocytes, but not in fibroblasts, protects against I/R injury by inhibiting pyroptosis. Furthermore, using mouse cardiomyocytes and hiPSC-CMs, we revealed that Zn^{2+} release from intracellular TRPM7 vesicles during I/R injury triggers cardiomyocyte death by activating gasdermin-D (GSDMD), leading to N-terminal fragment release and membrane pore formation. The critical role of intracellular TRPM7 was further supported by the finding that inhibition of plasma membrane TRPM7 failed to protect mice against I/R injury. To determine whether the channel or kinase activity of TRPM7 mediates

pyroptosis during I/R injury, we generated an inducible channel-dead TRPM7-E1047K knock-in mouse model. By comparing these mice with kinase-inactive TRPM7 knock-in mice, we demonstrated that the channel, but not the kinase, function of TRPM7 mediates I/R injury.

Taken together, our findings demonstrate that TRPM7-mediated intracellular Zn^{2+} release contributes to myocardial I/R injury by triggering cardiomyocyte pyroptosis. Given the marked upregulation of TRPM7 in patients with ischemic heart failure, our findings suggest that targeting TRPM7 may represent a promising therapeutic strategy for ischemic heart disease.

Dr. Lixia Yue is a Professor of Cell Biology at the University of Connecticut School of Medicine (UConn Health). Before joining UConn Health, Dr. Yue earned her Ph.D. from McGill University and completed postdoctoral training at Harvard Medical School. Her research focuses on elucidating the pathophysiological roles of TRP channels, particularly TRPM7, in the cardiovascular system and identifying potential therapeutic targets. Dr. Yue's laboratory has demonstrated that TRPM7 contributes to cardiac fibrosis, abdominal aortic aneurysm (AAA), and ischemic injury. Her research program is supported by grants from the American Heart Association and the National Institutes of Health. At the symposium, Dr. Yue will discuss TRPM7-mediated pyroptosis in ischemic myocardial injury.

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Renal Magnesium Conservation During Lactation

Evan Ray

Renal-Electrolyte Div., University of Pittsburgh, PA, USA

Biosketch:

Dr. Evan Ray, MD PhD is an Assistant Professor of Medicine at the University of Pittsburgh, in the United States. He pursued his graduate studies at the University of Pennsylvania, where his PhD dissertation explored regulation of gating in voltage-sensitive potassium channels. His clinical training included residency in Internal Medicine at the University of Pennsylvania and a fellowship in Nephrology at the University of Pittsburgh, followed by a basic sciences fellowship studying sodium homeostasis.

His work on clinical magnesium depletion includes studies showing that SGLT2 inhibitors can enhance Mg reabsorption in the nephron, increasing plasma Mg levels in patients with severe hypomagnesemia, and a publication showing that subcutaneous administration of Mg can more effectively treat persistent hypomagnesemia than intravenous Mg infusion.

Current laboratory studies include a focus upon regulation of epithelial Mg transport, including exploration into the mechanisms by which the mucin, MUC1, influences this process.

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Altered Magnesium Metabolism in Primary Aldosteronism: Clinical Manifestations and Cardiovascular Effects

Marta Müller

*Nephrology Department, University Hospital of Duesseldorf, Heinrich Heine University, **Germany***

Biography: Dr. Marta Müller is a clinician-scientist in the Department of Nephrology at the University Clinics of Düsseldorf, where she has been based since 2019. Her work integrates clinical nephrology with translational cardiovascular research, with a particular emphasis on endocrine hypertension and renal disease. During a dedicated research fellowship, Dr. Müller investigated the role of inflammation and early cardiovascular damage in primary aldosteronism. This work established the foundation for her ongoing research aimed at elucidating the molecular and pathophysiological mechanisms underlying the disproportionately high cardiovascular risk in patients with primary aldosteronism. In addition, her research portfolio includes clinical and translational studies in renal transplant recipients and patients with resistant hypertension. Her overarching objective is to identify mechanistic pathways and risk modifiers that may inform improved cardiovascular and renal risk stratification and therapeutic strategies in high-risk nephrology populations.

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TRPM7 and Magnesium in B Cell Biology

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Ion channels play a critical role in a myriad of biological functions. These proteins act as critical gatekeepers, regulating the entry of ions such as calcium and magnesium into cells. Despite their importance in human health, there remains a significant gap in our understanding of the role of ion channels in immune cell biology. We have previously shown that the ion channel TRPM7 is required during the early stages of B cell development in the bone marrow as deletion of this ion channel results in a complete loss of mature peripheral B cells, and a developmental block at the pro-B to pre-B transition. To understand the role of the Mg²⁺ transport function of TRPM7 in our observations, C57BL/6 mice were fed a Mg²⁺ deficient or control diet for eight weeks, which resulted in a 55% decrease in serum Mg²⁺. Interestingly, we found that female mice were particularly susceptible to Mg²⁺ deficiency compared to male mice. We also found that Mg²⁺ deficiency led to a significant defect in both developing B cells in the bone marrow as well as mature peripheral B cell subsets. To investigate the impact of more clinically relevant Mg²⁺ deficiencies prevalent within the human population, C57BL/6 mice were fed Mg²⁺ deficient diets corresponding to 25% and 50% deficient for eight weeks. In contrast to our previous findings in the context of a severe magnesium deficient diet, developing B cells in the bone marrow were not impacted by 25% and 50% Mg²⁺ deficient diets. However, in both magnesium deficient groups, we found alterations in the peripheral immune compartment, specifically, a reduction in the proportion of mature CD4 and T follicular helper cells, as well as immature transitional B cells in the spleen, most notably the anergic T3 population. Following immunization with a model antigen, we found that magnesium deficient mice in both groups exhibited reduced germinal center B cells, plasma cells, and memory B cells. Thus, our data identifies magnesium as a critical ion in B cell biology, and reveals that even modest magnesium deficiency, which is reflective of a large proportion of the human population, impacts B cell development and differentiation. Ultimately, our studies will help elucidate the role of magnesium in immune cell development, signaling, and regulation of the immune response, which is critical for understanding the potentially serious consequences of ion deficiencies in human health and disease.

Dr Bebhinn Treanor is a Professor and Canada Research Chair in Spatially-resolved Biochemistry in the Department of Biological Sciences at University of Toronto Scarborough. She completed her PhD at Imperial College London under the supervision of Dr. Daniel M. Davis, where she visualized the spatial confinement of phosphorylated NK cell inhibitory receptors to 'hotspots', providing a new framework for understanding how NK cells integrate activating and inhibitory signals. She then went on to complete her postdoctoral work in the laboratory of Dr. Facundo Batista at the London Research Institute of Cancer Research UK, where she identified that the cortical actin cytoskeleton plays a critical role in

controlling B cell receptor signaling. Her laboratory at the University of Toronto interrogates B cell biology at the level of single molecules within individual cells, and her group identified two novel regulators of B cell development and activation; the glycan-binding protein galectin-9, and the channel-kinase, TRPM7. Dr Treanor also co-leads ExPOSE (Exposomics of Persistent Organic Synthetic Envirottoxins), which takes a One Health approach to investigate the impact of organic pollutants on plant, animal, and human health. In 2014, Dr Treanor was awarded the CIHR Bhagirath Singh Early Career Award in Infection and Immunity, conferred by the Canadian Institutes of Health Research; in 2016 and 2021, a Tier 2 Canada Research Chair in Spatially-resolved Biochemistry; and in 2019 the Canadian Society for Immunology New Investigator Award.

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Hypomagnesemia in Lymphoma Patients Receiving CAR T Therapy Correlates with Immune Dysfunction and Decreased Survival

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Magnesium (Mg) is an essential element involved in cellular metabolism and immune function, and Mg deficiency has been associated with impaired T-cell and myeloid cell activity. We investigated the prognostic significance of serum Mg across the treatment continuum of large B-cell lymphoma (LBCL), including newly diagnosed diffuse large B-cell lymphoma (DLBCL), autologous hematopoietic stem cell transplantation (AH SCT), and chimeric antigen receptor (CAR) T-cell therapy.¹⁻⁵

Methods: Serum Mg levels and clinical outcomes were evaluated across three independent cohorts of patients with LBCL. In newly diagnosed DLBCL (n=408), Mg levels were evaluated using cutpoints of <1.7 mg/dL and <2.0 mg/dL. Among patients undergoing AH SCT (n=581), pre-transplant Mg levels were assessed for associations with event-free survival (EFS) and overall survival (OS). In patients receiving axicabtagene ciloleucel (axicel), the prognostic significance of pre-lymphodepletion hypomagnesemia was evaluated in the ZUMA-1 trial and independently validated in patients treated at Mayo Clinic.

Serum cytokine profiling and single-cell RNA sequencing (scRNA-seq) were used to investigate potential biological mechanisms associated with hypomagnesemia in the CAR-T setting.

Results: Across treatment settings, lower serum Mg was consistently associated with adverse clinical outcomes. In newly diagnosed DLBCL, 23% of patients had Mg <2.0 mg/dL, which was associated with higher disease stage, greater extranodal involvement, higher International Prognostic Index scores, and inferior EFS and OS. Among patients undergoing AH SCT, 14.1% had pre-transplant hypomagnesemia, which was associated with inferior EFS (HR 1.63, 95% CI 1.09–2.43; p=0.017) and OS (HR 1.90, 95% CI 1.22–2.96; p=0.005). Similarly, hypomagnesemia before lymphodepletion predicted inferior progression-free and overall survival following axi-cel therapy in ZUMA-1 and was validated in an independent Mayo Clinic cohort. In CAR-T recipients, hypomagnesemia was also associated with increased inflammatory markers and cytokines, including ferritin, IL-6, IL-1Ra, IL-8, and MIP-1α. scRNA-seq demonstrated altered monocyte–T-cell interactions and an immunosuppressive transcriptional profile associated with low Mg.

Conclusions: Low serum Mg is consistently associated with adverse disease characteristics and inferior survival across multiple stages of LBCL treatment, from initial diagnosis through AH SCT and CAR-T therapy. The association of hypomagnesemia with systemic inflammation and altered immune-cell interactions provides potential biological support for its prognostic significance. These findings identify serum Mg as an inexpensive, readily available, and potentially actionable biomarker in LBCL and provide a rationale for prospective studies evaluating whether Mg optimization can improve clinical and immunologic outcomes.

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How Cells Set Magnesium Levels During Development

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Abstract body:

Purpose: Magnesium homeostasis is essential for development, yet how cells establish intracellular Mg^{2+} as developmental state changes remains unclear. Human genetic evidence involving TRPM6, TRPM7, and CNNM2 links disrupted Mg^{2+} handling to hypomagnesemia and neurodevelopmental disease. In mouse preimplantation embryos, TRPM7-dependent Mg^{2+} influx is required for blastocyst formation; in *Xenopus*, our work showed that TRPM7 and TRPM6 control distinct Mg^{2+} -dependent cell-intercalation movements during gastrulation and neural tube closure. We therefore asked whether developmental transitions reconfigure the molecular machinery that sets Mg^{2+} .

Materials and methods: Using mouse embryonic stem cells (mESCs) and directed differentiation to neuroectoderm, we mapped endogenous TRPM7-, CNNM2-, and CNNM3-centered assemblies by immunoprecipitation and data-independent acquisition mass spectrometry. CRISPR/Cas9 knockouts, whole-cell patch clamp, ICP-MS ionomics, and RNA sequencing connected complex composition with channel activity, cation balance, and transcriptional state.

Results: In pluripotent mESCs, TRPM7 associated with CNNM2/3/4 and ARL15; CNNM2- and CNNM3-centered immunopurifications defined overlapping TRPM7 assemblies that also recovered PRL phosphatases. Neuroectodermal differentiation shifted CNNM usage toward CNNM4 and enriched the TRPM7 interactome for neural, chromatin/transcriptional, polarity, adhesion, and trafficking proteins. Loss of CNNM2 or CNNM3 reduced native TRPM7 current. TRPM7 deficiency depleted intracellular Mg^{2+} , Ca^{2+} , Zn^{2+} , and Mn^{2+} , whereas CNNM2 loss increased all four cations and resembled Mg^{2+} supplementation, supporting a TRPM7-independent Mg^{2+} -lowering role for CNNM2. Transcriptomics separated an acute, reversible Mg-responsive program from a reproducible TRPM7-core developmental signature.

Conclusion: Cells therefore appear to set magnesium through a balance of TRPM7-mediated cation entry and CNNM-dependent regulation within assemblies rewired by developmental state. This framework links Mg^{2+} homeostasis to broader multi-cation balance, developmental gene regulation, and the pleiotropic phenotypes associated with TRPM7/CNNM dysfunction.

Biographical sketch: Loren W. Runnels, PhD, is Professor of Pharmacology at Rutgers Robert Wood Johnson Medical School. His laboratory studies TRPM7, TRPM6, CNNM proteins, and associated magnesium-regulatory complexes in development, kidney physiology, and disease, using cell biology, electrophysiology, proteomics, and multi-omics approaches.

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Ca²⁺, Zn²⁺, and Mg²⁺: Ionic Control of Fertilization and Early Development

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Short biography:

Dr. Rafael Fissore earned his **Doctor of Veterinary Medicine (DVM)** from the **University of Buenos Aires, Argentina**. He completed a **clinical residency at the University of California, Davis**, followed by a **PhD at the University of Massachusetts Amherst**. He then pursued **postdoctoral training in the Department of Obstetrics and Gynecology at Harvard Medical School in Boston, Massachusetts**.

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UNIVERSITÀ DEGLI STUDI DI MILANO

From Petri Dish to Patient: Unraveling the Role of Magnesium in the Biology of Aging

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Aging is characterized by a progressive decline in physiological resilience and an increased risk of chronic diseases, including cardiovascular disease, metabolic disorders, neurodegeneration, and frailty. Increasing evidence identifies magnesium as a determinant of healthy aging. However, despite its fundamental biological importance, aging is frequently associated with suboptimal magnesium status due to dietary insufficiency, altered absorption, and increased renal losses.

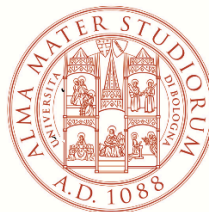
Experimental and clinical studies suggest that insufficient magnesium accelerates age-associated dysfunction by promoting chronic low-grade inflammation, mitochondrial dysfunction, genomic instability, and cellular senescence. Conversely, adequate magnesium status has been associated with improved metabolic health, preservation of musculoskeletal function, cognitive performance, and cardiovascular integrity. Furthermore, epidemiological studies consistently link higher magnesium intake and circulating magnesium levels with reduced mortality and lower incidence of age-related diseases. These findings support the concept that magnesium is not merely a nutritional factor but a potential modifier of the aging process itself.

Understanding the role of magnesium across the lifespan may provide new opportunities to improve healthspan and reduce the burden of age-associated diseases.

Biographical sketch:

MD, Professor of General Pathology at the University of Milan. She received advanced research training in the United States, where she investigated endothelial pathophysiology with a particular focus on aging and cellular senescence. Over the past 25 years, her research has focused on the cellular and molecular mechanisms underlying dysfunction associated with impaired magnesium homeostasis, using a variety of in vitro models, including human endothelial cells, human mesenchymal stem cells, and murine myoblasts. More recently, she has explored the effects of different magnesium salts on neurodevelopment using induced pluripotent stem cell (iPSC)-derived brain organoids.

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ALMA MATER STUDIORUM
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Magnesium Involvement in Biomineralization: a Glimpse on the Aging Bone

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Bone matrix is a multiscale composite material mainly composed of collagen, crystalline apatite mineral, water, and a small amount of non-collagenous proteins. The ultrastructural composition of the bone matrix, are modified during ageing.. Microdamage and micropetrosis (lacunar mineralization) may influence the mechanosensitivity of osteocytes, leading to a poor mechanical property of the bone matrix. The lacuno-canalicular space of apoptotic osteocytes eventually becomes mineralised in vivo. This condition is known as micropetrosis and is a fundamental characteristic of ageing bone (1). Increased prevalence of such hypermineralised osteocyte lacunae is viewed as a structural marker of impaired bone function – both mechanical and biological. Within the lacuno-canalicular space, mineralised apoptotic debris typically occurs as micrometre-sized, spherical nodules of magnesium-rich, carbonated apatite. It is likely that the lacunar mineralization process progresses from osteocyte apoptosis to full lacunar mineralization during ageing. Indeed, it has been found that the proportion of micropetrosis to the total lacunar number was less than 2% in young healthy individuals and up to 8% in the older healthy individuals. The elemental composition of the spherites filling the lacunar spaces showed differences in composition between the spherites of different sizes. Namely, the smaller spherites contain a higher magnesium concentration than the surrounding bone matrix. Whitlockite is the mineral phase of apatite containing a higher content of magnesium and magnesium whitlockite crystals have been found in micropetrosis (2). We performed elemental analysis by EDX–ESEM of mineral depositions of young and senescent bone marrow-derived mesenchymal stem cells (BMSCs). EDX–ESEM is a powerful, non-destructive analytical technique for mapping the morphology and elemental composition of samples. Interestingly, the deposits of senescent cells exhibited higher concentrations of magnesium respect to young cells. Furthermore, the deposits of senescent cells showed a calcium/phosphate stoichiometry compatible with the presence of whitlockite, the mineral phase reported in patients with micropetrosis.

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Biographical Sketch

Prof. Stefano Iotti, currently works at Department of Pharmacy and Biotechnology of the University of Bologna coordinating the research group of Molecular Imaging, Biosensors and Cell Biology. He has co-authored more than 120 publications which garnered > 4000 citations (H-index=34) and more than 500 impact points. He is also co-inventor of 6 patents. He has contributed to the development of in vivo NMR spectroscopy in basic research and in diagnostic applications. His scientific activity ranged from organic and physical chemistry to biochemical thermodynamics. He

contributed to the development of a novel approach to simplify the treatment of the thermodynamics of complex systems. At present the research activity is devoted to the study of magnesium homeostasis in cell culture combining synchrotron X-ray fluorescence and the use of a novel class of fluorescent chemo-sensors (DCHQs).

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XVIII INTERNATIONAL MAGNESIUM SYMPOSIUM
"New Frontiers in Magnesium Research: Molecular Mechanisms and Clinical Implications"
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ABSTRACTS

Oral Communications

OC01

Mean Serum Magnesium and Prevalence of CLMD in U.S. Adults >19 years.

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Purpose: A recent scoping review employing the Magnesium Depletion Score (MDS) documented the high prevalence of magnesium deficiency in the US population over multiple NHANES survey cycles.

We used cross-sectional data from nonpregnant and nonlactating civilian participants in the 2011–2018 NHANES data cycles to estimate the prevalence of chronic latent magnesium deficiency (CLMD) in the adult population. Current literature suggests the risk of CLMD increases with serum magnesium levels <2.06 mg/dL; <0.85 mmol/L.

Materials and Methods: Presented are analyses categorized U.S. adults (≥19 y) by sex, age, and metabolic health status (total population, metabolically healthy, hypertension, diabetes, and chronic kidney disease [CKD]). Metabolically healthy adults were defined as participants who had optimal levels of all metabolic syndrome risk factor variables and were not taking any medications related to these conditions. Linear regression models were used to compare subgroups, and sensitivity analyses were conducted to assess robustness of primary findings. The final analytic sample included 5474 adults aged 19+ years.

Results: The serum magnesium reference interval based on metabolically healthy participants was 1.7–2.3 mg/dL (0.7–0.95 mmol/L).

g/dL (0.7–0.95 mmol/L).

Women (n=2973)

Serum Magnesium (mg/dL)

	2.5 th Percentile	Mean	97.5 Percentile	% CLMD (<2.06 mg/dL)
All Women	1.53	1.96	2.23	69.8
Metabolically Healthy	1.70	1.98	2.21	69.8
Diabetes	1.29	1.86	2.24	80.9
Hypertension	1.46	1.94	2.23	70.2
CKD	1.33	1.91	2.28	72.4

Men (n=2501)

Serum Magnesium (mg/dL)

	2.5 th Percentile	Mean	97.5 Percentile	% CLMD (<2.06 mg/dL)
All Men	1.58	1.98	2.27	65.8
Metabolically Healthy	1.72	2.01	2.26	65.8
Diabetes	1.39	1.91	2.28	75.9
Hypertension	1.52	1.97	2.27	66.9
CKD	1.38	1.94	2.27	69.6

Conclusion: In this first estimate of a population-based prevalence of CLMD in U.S. adults, two-thirds of the population would be classified as having CLMD. This contemporary NHANES data highlight that a significant percentage of "healthy" adults are at risk for developing a chronic disease.

Biographical sketch:

Rebecca Costello, Ph.D., FACN, is a Senior Research Fellow with CMER Center for Magnesium Education and Research as well as an independent consultant. At CMER, she helped file an FDA Qualified Health Claim petition for magnesium and hypertension, helped to develop and pilot an electronic magnesium intake questionnaire (MagQuest) to assess the risk of magnesium deficiency, and has authored a number of publications and book chapters. She retired from the NIH Office of Dietary Supplements in September 2011 after 13 years of federal service where she served in various capacities as a Program Officer and as Director of Grants and Extramural Activities. She continued with ODS as a consultant until 2025. Dr. Costello also has an adjunct appointment in the Department of Military and Emergency Medicine at the Uniformed Services University in Bethesda, MD. She holds a Master's degree in Biology from American University and a Ph.D. in Clinical Nutrition from the University of Maryland. She is a Fellow of the American Society of Nutrition.

OC02

New Fluorescent Probes for Detection of (Sub)Cellular Magnesium with High Selectivity

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Analysis of magnesium(II) ions with high spatial and temporal resolution in cells and tissues remains an important challenge in the field. Fluorescent metal ion indicators offer the possibility of tracking metal cations in biological samples by a variety of techniques, aiding in the study of their cell biology. Nevertheless, limited selectivity against other biologically relevant divalent metal ions and pH is a common shortcoming of existing fluorescent indicators for magnesium(II) that has hindered the study of transport and accumulation of this cation in both physiological and pathological processes. Addressing this challenge, we report the development and application of new fluorescent indicators, the MagZet and MagP families, that enable detection of free magnesium(II) in live cells with high selectivity against calcium(II), low pH dependence, and controllable (sub)cellular localization.

Purpose: To enable highly selective detection of magnesium(II) in cells and subcellular compartments by fluorescence-based techniques.

Materials and methods: A new series of magnesium(II) indicators based on a quinoline dicarboxylate and quinoline phosphinate metal-recognition motifs have been synthesized. The carboxylate and phosphinate groups were masked as acetoxymethyl esters to enable passive cellular loading and activation by esterases in live cells. The photophysical properties as well as the metal binding, pH-dependent response, cellular uptake and localization of the new indicators were characterized by a combination of UV-Vis spectrophotometry, fluorescence spectroscopy, and fluorescence microscopy. Indicators were functionalized with chlorohexyl groups and conjugated *in situ* to HaloTag, a genetically encoded self-labeling protein, to generate chemigenetic hybrids.

Results: We developed a new family of small molecule fluorescent indicators, the MagZet and MagP family, for fluorescence-based detection of magnesium(II) in cells. All indicators display at least tenfold selectivity for magnesium(II) over calcium(II), with mM dissociation constant for the latter, which enables selective detection of free magnesium(II) at typical physiological levels. All compounds display a shift in the fluorescence emission spectrum that is amenable for ratiometric sensing of the metal, including by fluorescence microscopy and flow cytometry techniques. MagP displays reduced response to protons, thus enabling pH-independent detection of magnesium(II) in various environments. Chemigenetic versions of the indicators, conjugated to HaloTag, can be readily targeted to various cellular compartments of interest, enabling tracking of magnesium(II) with high sub-cellular resolution even in low resolution techniques such as flow cytometry. Changes in fluorescence ratio show changes in cellular free magnesium(II) that can be used to examine metal ion transport across the cell membrane.

Conclusion: New molecular indicators enable highly selective, ratiometric detection of magnesium in cells and sub-cellular compartments by a variety of fluorescence-based techniques not accessible by commercial indicators.

Biographical sketch: Daniela Buccella is a Professor in the Department of Chemistry at Emory University in Atlanta, USA. She received a BS in Chemistry from Simón Bolívar University in Caracas, Venezuela, and started research as an undergraduate in the Venezuelan Institute for Scientific Research. She moved to New York to pursue a PhD in Chemistry at Columbia University working with Prof. Ged Parkin in the area of inorganic synthesis and catalysis. Following an NIH postdoctoral fellowship at the Massachusetts Institute of Technology, where she worked with Prof. Stephen Lippard, she returned to New York City in the fall of 2011 to start her independent career at New York University, studying problems at the interface of inorganic chemistry and biology. At NYU, she was promoted to the rank of Associate Professor and Professor. In the Fall of 2024, Prof. Buccella joined the faculty at Emory University. Work in her research group focuses on the development of new molecular probes and imaging techniques for the study of cellular metal homeostasis, with a particular focus on divalent cations in the context of health and disease.

OC03

Proposed Novel Scale to Assess Mg Status with Serum Ca and Serum Mg Ratios

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Introduction: Given global trends towards lower dietary Mg intakes, a convenient, precise, reliable, standardized Mg assessment tool diagnosing need for therapeutic Mg is needed. Reliable markers of magnesium (Mg) status remain elusive. At least four serum Mg reference ranges in current use bring inconsistent diagnoses of hypomagnesemia. Perhaps Ratios between serum Mg and serum calcium (Ca) present more precise measures of physiological Mg status.

Serum Mg and Ca measures are non-invasive, widely available, their ratio easily calculated. Current Mg research studies report this ratio in various expressions but without any evaluative scale, making comparisons cumbersome.

Methods: We here introduce a novel Scale to assess Mg adequacy using the ratio between serum Ca and Mg in its four physiologically identical expressions: molar or weight calculations of either Mg:Ca or Ca:Mg. We tested this Scale, developed in private practice of B. Von Ehrlich, M.D., on published Mg research studies that measured and reported a version of the ratio.

Results: Scale proved useful on individual patients and a variety of research subject groups in assessment of physiological Mg deficit. For proper use, the Scale needs both Ca and Mg measures in identical units: mg/dl or mg% (weight ratio), mmol/L or mEq/L (molar ratio). Total Serum Ca measure should NOT be "corrected" for albumin. Further study needed to determine if Scale is appropriate for pregnancy, lactation, pediatrics, chronic kidney disease, whole blood, plasma or ionized measures of serum Ca and Mg.

Conclusions: We found this novel Scale's ability to assess individuals' Mg status promising in both case studies and existing published research; serum ratio between Mg and Ca assessed with this Scale showed higher diagnostic value for Mg status than serum Mg alone. Future study is needed to determine if this Scale's categories of Mg adequacy correspond to clinical assessments of Mg status.

Biographical sketch: Dr. von Ehrlich is a physician in private medical practice in Kempten, Germany and Andrea Rosanoff is Director of CMER Center for Magnesium Education & Research in Pahoa, Hawaii, USA.

OC04

Aldosterone and Cardiac Fibrosis in TRPM7-Deficient Mice

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Purpose: Transient Receptor Potential Melastatin 7 (TRPM7) is a ubiquitously expressed ion channel bound to a kinase domain that regulates cell homeostasis by influencing intracellular Mg^{2+} levels and/or regulating signalling cascades through its kinase activity and target proteins. We previously demonstrated that TRPM7 downregulation is associated with aldosterone-induced cardiovascular fibrosis. Here, we investigated whether activation of the mineralocorticoid receptor (MR) drives the fibrotic phenotype observed in wild-type and TRPM7-deficient mice.

Methods: Hearts and cultured cardiac fibroblasts (CF) from wild-type (WT) and TRPM7-deficient (M7+/Δ) were studied. Cells were exposed to aldosterone (aldo) and the MR antagonist, eplerenone ($10^{-5}M$). Cardiac collagen deposition was evaluated by picrosirius red staining. Fibroblasts pro-fibrotic and inflammatory signalling pathways were evaluated by examining; fibronectin, collagen-1, α-SMA, galectin-3, TGFβ, p-SMAD3, ENaC, SGK-1, ERK1/2 and p-Stat3 expression by immunoblotting.

Results: Hearts from M7+/Δ untreated control mice (n=20) exhibited collagen deposition (3.3% vs WT: 1.6%). CF M7+/Δ showed reduced influx of Mg^{2+} (106% vs WT 115%) and Ca^{+2} (132% vs WT 155%) induced by aldo ($10^{-7} M$). Untreated CF M7+/Δ exhibited upregulation of fibrotic markers: fibronectin (0.99 ± 0.18 vs WT 0.42 ± 0.12), α-SMA (1.51 ± 0.13 vs WT 0.55 ± 0.99) and galectin-3 (0.95 ± 0.3 vs WT 0.35 ± 0.02) which was associated with increased expression of TGFβ1 (2.14 ± 0.38 vs WT 0.25 ± 0.19) and phospho-SMAD3 (1.21 ± 0.06 vs WT 0.72 ± 0.05). Influx of Mg^{2+} and Ca^{2+} , expression of TGFβ1, and phospho-SMAD3 was normalized by Mg^{2+} treatment, indicating the role of TRPM7 channel. CF from M7+/Δ exhibited upregulation of MR activation markers (ENaC and SGK1). Treatment with eplerenone tended to reduce the expression of fibronectin and galectin-3 with no changes in α-SMA.

Conclusions and perspectives. TRPM7-deficiency is associated with cardiovascular fibrosis and activation of fibroblasts through some mechanisms that involve aldosterone/MR. Our findings suggest cross talk between aldosterone/MR and TRPM7 signaling

OC05

TRPM7 and Inflammatory Macrophages are Required for Hypomagnesemia-Induced Heart Failure with Preserved Ejection Fraction

Man Liu, Hong Liu, Eunji Kim, Gyeong-Jin Kang, Mitchell Neumann, Feng Feng, Madeline Johnson, Ruthvika Murikinati, Samuel C. Dudley, Jr.

Cardiovascular Division, the Lillehei Heart Institute, Department of Medicine, University of Minnesota, Minneapolis, MN, USA

Purpose: Diabetic cardiac diastolic dysfunction (DD) and heart failure with preserved ejection fraction (HFpEF) are mediated by hypomagnesemia (HypoMg) and transient receptor potential cation channel subfamily M 7 (TRPM7), a $Mg^{2+}/Ca^{2+}/Zn^{2+}$ channel with kinase function. Here, we used a HypoMg model of HFpEF to investigate the roles of TRPM7 and crosstalk between macrophages (M ϕ s) and cardiomyocytes (CMs) in DD.

Materials and methods: Wild type (WT) C57BL/6J, transgenic TRPM7^{K1646R} (no kinase function), and M ϕ -specific FABP4 knockout (M ϕ FKO, depleted of inflammatory M ϕ s) mice on normal (2 g/kg Mg^{2+}) or low-Mg (15-30 mg/kg Mg^{2+}) diet for 6 weeks were compared. The cardiomyocyte (CM) cell line RL-14 and M ϕ cell line Raw264.7 were treated with normal (0.81 mM Mg^{2+}) or low-Mg medium (0.04 mM Mg^{2+}) for 48 h.

Results: WT-HypoMg mice with DD had significant cardiac inflammation with elevated expression of inflammatory markers and cell adhesion molecules (MCP-1, VCAM-1/ICAM-1, and IL-1 β /IL-18), augmented pro-inflammatory M ϕ s infiltration, and decreased pro-resolving M ϕ s in the ventricles. M ϕ FKO mice were resistant to HypoMg-induced DD and showed decreased inflammatory signaling in ventricles. Inhibition of TRPM7 kinase function in TRPM7^{K1646R} mice reduced cardiac pro-inflammatory M ϕ s and normalized the changes of inflammatory markers in HypoMg mice with improved DD. In Raw264.7 M ϕ s, HypoMg elevated expression of TRPM7 and MCP-1 receptor CCR2, mitochondrial ROS production, and IL-1 β secretion. In RL-14 CMs, HypoMg increased expression of TRPM7, MCP-1, VCAM-1, and IL-1 receptor but not IL-1 β secretion. In both cell lines, TRPM7 kinase inhibition prevented the HypoMg-induced inflammatory changes.

Conclusion: Through TRPM7, HypoMg simultaneously induced inflammatory M ϕ activation, facilitated CMs signaling for M ϕ migration to the heart, and primed CMs to respond to M ϕ s secreted IL-1 β . These results demonstrate how M ϕ s and CMs interact to cause HFpEF and can explain how M ϕ depletion, IL-1 β antagonism, and TRPM7 inhibition can treat diabetes-associated HFpEF.

Biographical sketch:

BIOGRAPHICAL SKETCH

NAME: Liu, Man

eRA COMMONS USER NAME: MANLIU

POSITION TITLE: Assistant Professor of Medicine

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date MM/YYYY	FIELD OF STUDY
Tai University, Tianjin, China	B.S.	07/1997	Physics/Biophysics
Tai University, Tianjin, China	M.S.	07/2000	Physics
ut für Biophysik, Johann Wolfgang Goethe- rsität, Germany	Ph.D.	11/2003	Physics
chholm University, Stockholm, Sweden	Postdoctoral	12/2004	Physics
University of New York at Stony Brook, Stony k, NY	Postdoctoral	12/2007	Physiology and Physiology
University of Illinois at Chicago	Postdoctoral Associate	03/2010	Physiology and Physiology

A. Personal Statement

My research focuses on four projects. Hypomagnesemia (HypoMg) is often observed in diabetes mellitus (DM), cardiac diastolic dysfunction (DD), heart failure with preserved ejection fraction (HFpEF), and atrial fibrillation (AF), and Mg²⁺ supplementation has shown beneficial effects on treating both AF and HFpEF. My research has found that a Mg²⁺ transporter TRPM7 with a kinase domain shows important regulations on DD/HFpEF. The first project is TRPM7 kinase regulation on cardiac DD and HFpEF in DM- and HypoMg-induced mouse models. The second project is TRPM7 kinase regulation on DM- and HypoMg-associated AF. I am also working on the mechanism of how SGLT2 inhibitor dapagliflozin improves cardiac DD and HFpEF. The fourth project is mitochondrial dysfunction in cardiac diastolic dysfunction on diabetic mouse and rabbit models. Mitochondrial targeted antioxidants have been tested in the diabetic mouse model to reverse cardiac diastolic dysfunction and future tests on larger animals are planned. In the past, I have studied projects on the unfolded protein response and arrhythmias, and on NADH/NAD⁺ balance and cardiac Na⁺ channel functions in electrical remodeling and arrhythmias.

Complete List of Published Work in My Bibliography:

<https://www.ncbi.nlm.nih.gov/myncbi/man.liu.4/bibliography/public/>

OC06

Local Sustained Magnesium Delivery for the Treatment of Murine Periodontitis Modulates Immune Response and Impact on the Microbiome

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⁵UB Microbiome Center, University at Buffalo, State University of New York, Buffalo, NY, United States.

Purpose: Periodontitis (loss of bone around teeth) is associated with disrupted host–microbe homeostasis, resulting in immune-mediated progressive tissue destruction. Macrophages are key players in this dysregulated and destructive host response as effector cells of the innate immune system. Magnesium (Mg) was shown to have anti-inflammatory and immunomodulatory properties by promoting M2 macrophage polarization. In this study, we evaluate the feasibility of a novel controlled Mg delivery strategy to target macrophages and modulate the immune response for the prevention and treatment of periodontitis in a murine model.

Materials and methods: Mg-loaded controlled-release biodegradable poly(lactic-co-glycolic acid) (PLGA) microparticles were administered locally following the initiation of ligature-induced periodontitis in mice. Alveolar bone loss was assessed using micro-computed tomography (μ CT). Flow cytometry was performed to evaluate macrophage polarization. Microbiome composition was analyzed via 16S rRNA sequencing. Single-cell RNA sequencing was used to characterize the gene expression profiles of immune cells.

Results: Our data demonstrate that local sustained Mg delivery inhibited inflammatory bone loss and promoted M2 macrophage polarization in the surrounding tissues. Intriguingly, 16S rRNA sequencing revealed persistent microbial dysbiosis despite improved disease outcomes, suggesting an uncoupling of host-microbiome interactions. Single-cell RNA sequencing further showed that local Mg delivery reversed disease-associated inflammatory pathways by downregulating the STAT3 signaling pathway in macrophages and T cells.

Conclusion: Our findings suggest that locally sustained Mg delivery promotes M2-like anti-inflammatory macrophage polarization and mitigates alveolar bone loss, even in the presence of a dysbiotic microbiome, supporting its potential as a feasible immunomodulatory therapy for periodontitis.

OC07

Identification of TRPM7 and CNNM4 Complexes in Pancreatic Ductal Adenocarcinoma Cells

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² CRIL Laboratory, UMR 8188, University of Lens, FR

* Both authors contributed equally to this work

Purpose:

Pancreatic ductal adenocarcinoma (PDAC) is the most common form of pancreatic cancer. We have previously shown an overexpression of CNNM4 and TRPM7 in PDAC. These proteins are involved in cellular Mg²⁺

regulation by interacting with each other via small ARL15 or PRL proteins to form the PACT complex (PRL, ARL15, CNNM4, and TRPM7). Although it is known that magnesium regulates the migration of pancreatic cancer cells, the PACT complex has never been studied in this cancer. In this study, we aim to identify and characterize the PACT complex in PDAC.

Materials and methods:

The expression of the different components of the PACT complex was studied by transcriptomic analysis of TCGA databases, as well as by RT-qPCR and Western Blot in cancer (MiaPaCa2 and PANC-1) and non-cancer (hTERT-HPNE) pancreatic cell lines. Interactions within the proteins were then evaluated by coimmunoprecipitation, and their role in cell migration was addressed using Boyden chamber assays after silencing by siRNA.

Results:

Analyses of TCGA databases showed an overexpression of CNNM4, PRL1 and 2, and ARL15 in cancer tissues.

The expression of these actors was confirmed in cell lines, and an interaction between TRPM7, CNNM4 and ARL15 was shown PANC-1 cells but not in the hTERT-HPNE non-cancer cells. Furthermore, we showed that TRPM7 or CNNM4 silencing inhibited PANC-1 cell migration, with no effect on hTERT-HPNE cells.

Conclusion:

Our results show that most of the PACT complex components are overexpressed in PDAC tissues. Interestingly, an interaction between CNNM4 and TRPM7 is observed only in cancer cells. Moreover, these proteins regulate cancer cell migration, but are not involved in the migration of non-cancer cells. It is therefore necessary to further characterize this complex by studying the Mg²⁺ fluxes and the underlying oncogenic signaling pathways to propose the PACT complex as a potential target in PDAC therapy.

OC08

TRPM7 in Neurodevelopment and Neuro-disorders

Hong-Shuo Sun^{1,2,3,4}

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Purpose: This study investigates the dual role of the magnesium-sensitive Transient Receptor Potential Melastatin 7 (TRPM7) channel in neuronal development and ischemic brain injury. As a key non-glutamate mechanism in stroke, TRPM7's activation during hypoxic-ischemic conditions contributes to calcium overload and neuronal death. We aimed to characterize its impact on axonal maturation and to evaluate the neuroprotective potential of its selective pharmacological inhibition.

Materials and methods: In vitro studies utilized primary hippocampal neurons from E16 CD1 mice. TRPM7 function was modulated via virally mediated shRNA knockdown or pharmacological inhibition with the selective blocker waixenicin A. Neurite outgrowth, axonal specification, and calcium dynamics were assessed using immunocytochemistry, patch-clamp electrophysiology, and Fura-2 ratiometric imaging. In vivo neuroprotection was evaluated in neonatal (P7) and adult rodent models of hypoxic-ischemic encephalopathy (HIE) and global cerebral ischemia, using histological (TTC, Nissl), immunohistochemical, proteomic (LC-MS/MS), and neurobehavioral analyses.

Results: TRPM7 is highly expressed in neuronal growth cones and acts as a negative regulator of axonal outgrowth and polarization. Its inhibition, either genetically or with waixenicin A, enhanced neurite elongation, accelerated neuronal maturation, and reduced calcium influx. In vivo, TRPM7 knockdown in hippocampal CA1 neurons reduced ischemic cell death and preserved synaptic plasticity and memory function. In neonatal HIE, waixenicin A administered up to 1 hour post-injury significantly reduced infarct volume, attenuated apoptotic signaling (caspase-3/9, Bcl-2/Bax), improved short- and long-term neurobehavioral outcomes, and restored downstream CaMKII/calcineurin/p38/cofilin pathway dysregulation.

Conclusion: TRPM7 is a critical magnesium-sensitive regulator of neuronal development and a potent mediator of ischemic and hypoxic neuronal injury. Targeted inhibition of TRPM7 promotes axonal growth in vitro and confers robust, time-extended neuroprotection in vivo. These findings nominate TRPM7 as a promising therapeutic target for stroke and neonatal hypoxic-ischemic brain injury.

Biographical sketch:

Professor Hong-Shuo Sun is currently a tenured Full Professor and PhD Supervisor in Departments of Surgery, and Physiology and Pharmacology, Faculty of Medicine, University of Toronto, Canada. Professor Sun is also a co-chair of Division of Anatomy in Faculty of Medicine, and a course director in Leslie Dan Faculty of Pharmacy, University of Toronto. He is also a member for Collaborative Program in Neuroscience, Heart and Stroke Richard Lewar Centre of Excellence, Cardiovascular Sciences Collaborative Program, and Banting & Best Diabetes Centre, in Faculty of Medicine, University of Toronto. He also serves in the Award Committee in the Canadian Society of Pharmacology and Therapeutics. Professor Sun is currently Editorial Board member of *Acta Pharmacologica Sinica* and *Advanced Neurology*. Hong graduated in Zhongshan Medical College, Sun Yat-Sen University, and completed his training as a cardiologist at the First University Hospital of Zhongshan Medical College, Guangzhou, China. He obtained his MSc degree in Cardiovascular Pharmacology, Faculty of Pharmacy, University of Alberta, Canada; and his PhD degree in Neurosciences in University of Calgary, Canada. His postdoctoral training was in University Health Network, Toronto, Canada. He has received many grants from NSERC, HSFC, CIHR and CFI, etc. and published more than 100 papers. His research focus is on studying the role of ion channels in neuroprotection and drug development for stroke and hypoxia.

OC09

Transient Receptor Potential Melastatin 2 (TRPM2) as a Convergent Regulator of Neurodegeneration and Neuroinflammation

Zhong-Ping Feng

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Purpose:

Transient receptor potential melastatin 2 (TRPM2) is an oxidative stress-activated, calcium-permeable channel broadly expressed in neurons, glial cells, and peripheral tissues. Although TRPM2 has been implicated in multiple pathological conditions, its integrated role in neurodegeneration, neuroinflammation, and systemic tissue responses remains incompletely understood. We examined whether pharmacological inhibition or genetic deletion of TRPM2 modulates disease progression across Parkinson's disease (PD), hypoxic-ischemic (HI) brain injury, and peripheral tissue pathology.

Materials and methods:

Unilateral 6-hydroxydopamine (6-OHDA) mouse models of Parkinson's disease, and neonatal hypoxic-ischemic (HI) brain injury models were used. TRPM2 function was modulated using post-lesion pharmacological inhibition with AG490 or by partial and complete *Trpm2* gene deletion. Motor behavior was assessed using cylinder, rotarod, pole, and apomorphine-induced rotation tests. Dopaminergic neuron survival, TRPM2 expression, and intracellular signaling pathways (Akt/GSK-3 β /caspase-3) were examined by immunohistochemistry, immunoblotting, and RT-qPCR. Neuroinflammatory responses were quantified through microglial and astrocytic activation, including advanced morphometric, fractal, and cluster analyses to define glial phenotypes.

Results:

Across PD and HI models, TRPM2 inhibition or deletion significantly attenuated motor impairment and preserved neuronal integrity. Suppression of TRPM2 prevented activation of pro-apoptotic signaling while restoring Akt/GSK-3 β -mediated survival pathways. TRPM2 blockade also reversed disease-associated microglial and astrocytic morphological remodeling, shifting microglia from an amoeboid, pro-inflammatory state toward a surveillant, homeostatic phenotype. Genetic deletion of *Trpm2* produced a graded protective effect, with partial deletion conferring substantial benefit and complete deletion providing near-complete protection. Peripheral analyses revealed that TRPM2 modulation influenced systemic tissue responses, including bone-associated pathological changes.

Conclusion:

TRPM2 functions as a central integrator of oxidative stress, calcium dysregulation, neuronal death, neuroinflammation, and systemic tissue pathology. Targeting TRPM2 confers robust, sex-independent neuroprotection while normalizing glial and peripheral responses across distinct disease models. These findings establish TRPM2 as a unifying, disease-modifying therapeutic target for Parkinson's disease, hypoxic-ischemic injury, and related multisystem disorders.

Biographical sketch

Zhong-Ping Feng is a Full Professor in the Department of Physiology, Faculty of Medicine, and the Director of Collaborative Specialization Program In Neuroscience (CPIN) at the University of Toronto, Canada. She also serves as Associate Director of the Max Planck-University of Toronto Centre (MPUTC) for Neural Science & Technology. Professor Feng received her PhD degree in Neuroscience from the University of Calgary, an MSc in Pharmacology from the University of Alberta, and a medical degree from Zhongshan Medical College in China, completing her internship and residency at Peking Union Hospital. She obtained postdoctoral training at the University of Calgary while worked as a Scientist at the NeuroMed Drug Company based in Vancouver. Since establishing her research laboratory at the University of Toronto in 2003, Professor Feng has led a research program investigating the biophysical and pharmacological properties of ion channels, and calcium-dependent regulatory mechanisms of neurodevelopment and neural plasticity, with the goal of identifying potential drug targets for neurodevelopmental and neurological disorders. Her work has been supported by numerous research grants and personal awards, including funding from CIHR, NSERC, and NIH IGNIGHT, etc. She has published over 180 peer-reviewed research articles and reviews.

OC10

Magnesium Supplementation Improves Cognitive Frailty in Older Adults with Hypertension

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²*Casa di Cura Montevergine, GVM Care and Research, Mercogliano, Italy.*

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⁴*University of Naples "Federico II", Naples, Italy.*

⁵*City University of New York, Manhattan, USA.*

Introduction and Objection: Hypertension is a common condition among older adults and is linked to an increased risk of adverse outcomes, including frailty, which often involves cognitive decline. Cognitive frailty (CF) is a relatively new concept characterized by mild cognitive impairment (MCI) and physical frailty. Magnesium supplementation has been shown to be effective in managing blood pressure and supporting cognitive health. Our study aimed to evaluate the effects of magnesium supplementation on cognitive function and frailty levels in a population of hypertensive older adults with CF.

Materials and Methods: We conducted a prospective observational study with a one-year follow-up, enrolling consecutive older adults with CF and hypertension. The inclusion criteria were: age over 65 years and confirmed diagnoses of CF and hypertension. CF was diagnosed using the Clinical Dementia Rating Scale (with an MCI cut-off of 0.5) and the Fried Criteria, which defines frailty as the presence of at least three of five components: low physical activity, unintentional weight loss, exhaustion, weakness, and slowness. Participants were divided into two groups: those receiving magnesium treatment and those not receiving treatment.

Results: A total of 125 patients were screened. Of these, 40 did not meet the inclusion criteria, and 15 declined to provide clinical information, resulting in 70 enrolled participants. Patients were divided into two treatment groups: magnesium-treated (35 patients) and untreated (35 patients). Treatment with magnesium was associated with significant improvements in frailty levels ($p < 0.0001$) and cognitive function ($p = 0.0004$).

Conclusions: These findings suggest that magnesium treatment may provide anti-frailty and potentially anti-aging benefits for older adults with hypertension and CF. Further large-scale, randomized studies are necessary to confirm these results and to explore the underlying mechanisms linking magnesium to improved outcomes in frailty.

OC11

Chronic Magnesium Deficiency Affects Early Pregnancy

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¹ North Carolina State University, Raleigh, NC USA

² Precision Medical Writing, Knightdale, NC USA

Calcium (Ca) and magnesium (Mg) play vital roles in many physiological processes and work together to support each other's absorption and utilization. Maintaining a balance between these minerals appears to be necessary for each of them to carry out their individual roles, particularly under physiologically stressful conditions. Pregnancy constitutes such a condition and is characterized by calcium mobilization both early in pregnancy and during later trimesters. The fact that magnesium is mobilized together with calcium is often overlooked, an omission that may preclude consideration of the effects of chronic latent magnesium deficiency (CLMD) early in pregnancy. During pregnancy, a mother experiences increased metabolic demands to meet the needs of the fetus. A mismatch between the metabolic demands and nutrient intake at this time can result in a host of developmental abnormalities to the fetus and health risks to the mother. Several studies have reported strong correlations between deficiency of the essential mineral, magnesium (Mg), and pregnancy complications, including intrauterine growth restriction, preeclampsia, gestational diabetes, and preterm delivery. We evaluated recently published data to identify a range of serum Mg concentrations that may reflect CLMD (0.7–0.85 mmol/L). We then evaluated independent studies that reported on the relationship between Mg levels and pregnancy outcomes to assess whether this cutoff may help identify patients at risk for adverse events and inform therapeutic strategies. Our analysis showed that CLMD coupled with a molar ratio of serum calcium to serum Mg >3 may indicate increased risk to mother or fetus for conditions such as early gestational hypertension, abnormal embryonic or placental development, and adverse effects on fetal organ development. Given the high social and economic burdens of pregnancy complications, nutritional supplementation that includes Mg at all stages of pregnancy may be a safe and cost-effective way to mitigate the risk of adverse outcomes for mother and child.

Purpose: Several studies have reported strong correlations between deficiency of the essential mineral, magnesium (Mg), and many pregnancy complications, including intrauterine growth restriction, preeclampsia, gestational diabetes, and preterm delivery. However, an evaluation of how maternal levels of Ca and Mg during the first trimester of pregnancy affect health outcomes of both mother and fetus was not readily available. The goal of our analysis was to determine whether a cutoff concentration of serum Mg, which may reflect chronic latent Mg deficiency (CLMD), could potentially inform on adverse health risks to mother and fetus early in pregnancy (first trimester) and, in turn, direct future prospective studies to characterize the impact of early nutritional intervention on neonatal health outcomes.

Materials and methods: We searched scientific and clinical databases (e.g., PubMed, Medline Plus, Cochrane, clinicaltrials.gov), as well as private collections, to identify and analyze >2,000 publications for data related to maternal and fetal requirements for Ca and Mg during pregnancy. Searches included terms such as *pregnancy*, *calcium*, *magnesium*, *fetus*, *maternal*, *serum*, and related search terms. Editorials, letters, conference abstracts, and comments were omitted from consideration. The publications were then screened for relevance to the first trimester of pregnancy, resulting in 99 publications of interest.

Results: Our analysis led to these findings:

- Both calcium and magnesium are mobilized early in pregnancy.
- Serum magnesium concentrations of < 0.85 mmol appeared to be associated with chronic latent deficiency.
- If ratios of the serum concentrations of these two minerals were considered: (a) both clinical guidelines and published data indicated that the risk of adverse effects on mother and/or fetus is minimal when both serum Ca and serum Mg are at the upper end of the respective reference ranges; (b) recent reports raised minor concerns when serum Ca is at the lower end of the reference range; but (c) the published literature was rife with descriptions of adverse consequences of low serum Mg to mother and/or fetus, suggesting consideration of chronic latent magnesium deficiency early in pregnancy is warranted.
- Examples of increased risks potentially associated with low maternal serum magnesium and an unbalanced calcium-to-magnesium ratio early in pregnancy included: (a) adverse effects on glycosylation pathways; (b) adverse effects on embryonic and placental development; (c) adverse effects on both the folate cycle and one-carbon methylation cycles; and (d) adverse effects on maternal nutrient support that affected both mother and child.
- Thus, even early in pregnancy, a serum Mg concentration in the lowest quartile of the reference range (i.e., quartile 0.7–0.85 mmol/L) coupled with a high Ca/Mg molar ratio (i.e., a value in the range >3) may serve as biomarkers of increased risk of complications during pregnancy.

Conclusion: Taken together, a growing body of data suggests that both prior to and early in pregnancy, maternal counseling about potential risks should be considered if a patient presents with serum Mg <0.85 mmol/L (< 2.1 mg/dL) and serum Ca in the reference range (2.2–2.7 mmol/L), coupled with a serum Ca/Mg molar ratio >3 . Straightforward actions, such as counseling to improve a mother's diet and adding necessary supplements before, during, and after pregnancy, have proven valuable and cost-effective in the past and will continue to do so. Based on the information available in the scientific literature, we conclude that nutritional supplementation of both Ca and Mg at all stages of pregnancy may be a safe and cost-effective way to reduce the risk of pregnancy complications and adverse outcomes for mother and Child.

Biographical sketch: Dr. Nelson holds a PhD in Chemistry from Indiana University Bloomington and completed postdoctoral fellowships at the University of Leicester (England) and Argonne National Laboratories (USA). Her areas of expertise include drug and biologic product development, the biology of iron, calcium, and magnesium, as well as the biological impact of strontium, zinc, and chromium. She has directed research at major pharmaceutical companies and at her own company, BioLink Life Sciences, Inc. Recent publications describe her investigations into the physiology of calcium and magnesium, as well as novel methods for the quantification of these two minerals, both in the laboratory and in the clinic. She is adjunct professor at North Carolina State University and serves on local and national boards and review panels.

OC12

In Patients With Cardiovascular Disease Hypomagnesaemia Associated To High Serum Remnant Cholesterol Levels Determines An Increase In Atherosclerosis Risk Factors And Inflammation

Ioan Axente Gutiu SR¹⁾, Anton Iulian Gutiu²⁾, Gabriel Constantinescu²⁾, Flavian Stefan Radulescu¹⁾.

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Background:

In this work, we aimed to study the role of HMg in patients with CVD and high serum RC levels. For that, we analysed atherosclerosis risk factors (dyslipidemia, arterial hypertension, smoking, etc.) and the level of non-specific inflammation implicated in atherogenesis (serum CRP levels, fibrinogenemia (F), leukocytes, etc.).

Methods:

We selected 458 patients with CVD and increased serum RC (≥ 30): mean age 59.5 years, 112 (32%) men. In 60 patients from this group, we detected HMg (serum Mg $\leq 1.7\%$): mean age 63.7 years, 17 (28%) were men; 398 patients had no HMg (mean age 56.5 years, 110 (27%) were men)

Results:

Significant statistical differences between traditional atherosclerosis risk factors in patients with HMg versus no HMg were found for age (63.7 ± 14.35 versus 58.4 ± 10.6 mg%, $P < 0.001$), glycemia (135.2 ± 59.1 versus 109.5 ± 42.1 mg% $P < 0.001$) and weight (85.41 ± 23.21 vs 77.6 ± 17.6 mg%, $P < 0.02$). Regarding inflammation, comparing patient groups, we found serum F (447.1 ± 120.4 vs 410.9 ± 120.5 mg%, $P < 0.023$), CRP (9.2 ± 5.6 vs 6.4 ± 7.5 , $P < 0.01$), BSR (22.2 ± 12.2 vs 17.1 ± 11.1 mm at 1h, $P < 0.01$). Other risk factors don't differ significantly.

Conclusions:

The association of HMg and high RC serum levels may be found in 13.1% of our CVD patients. In these patients, we found a high serum levels of some atherosclerosis risk factors, such as age, glycemia, and the patient's weight. In addition, we found an obvious increase in non-specific inflammation for Fibrinogen, CRP, and BSR. In this preliminary study, we underscore the importance of HMg (with all consequences) in high-RC-level CVD patients, with potential for intervention using magnesium supplements.

ABSTRACTS

Posters

P1

Fusion-Protein Strategy for Structural Studies of the Bacterial Magnesium Transporter CorB

Sina Abedini¹, Ashkan Allahyar Shahsavan¹, Kalle Gehring¹

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CNNM (CBS-pair domain divalent cation transport mediators) proteins are an evolutionarily conserved family of four membrane proteins involved in magnesium transport and homeostasis. Mutations in CNNMs disrupt magnesium homeostasis, leading to diseases such as hypomagnesemia and cancer. All CNNM proteins have a conserved transmembrane domain (TMD) for ion transport. Currently, the structure of the TMD is available in only the inward-facing conformation, providing a single snapshot of the transport cycle. To fully understand the transport mechanism, assuming CNNMs operate via a rocker-switch mechanism, multiple conformations are required. We hypothesize that an outward-facing conformation exists and aim to determine the structure by cryo-Electron Microscopy (EM) using the CNNM prokaryotic ortholog, *TtCorB*. High-resolution structure determination of small proteins, such as CorB, remains difficult due to the challenges of particle alignment caused by size, flexible domains, and the absence of distinct structural features. To address this challenge, we employ a synthetic antibody (Fab) in complex with a nanobody (NB) as fiducial marks to add mass, stabilize the target protein, and assist orientation determination. An engineered protein named BRIL is fused into *TtCorB*, providing an epitope for a NB-stabilized, anti-BRIL Fab; the resulting CorB-BRIL:Fab:NB complex increases mass and asymmetry to facilitate high-resolution structure determination. Additionally, BRIL-fused proteins are incorporated into membrane-mimetic nanodiscs to preserve a native-like environment. We have designed and purified multiple CorB-BRIL constructs which form stable complexes with purified Fab and NB. The construct exhibiting better grid performance was selected for nanodisc reconstitution. Construct screening for better expression and stability is ongoing to optimize cryo-EM samples, with crystallization trials proceeding in parallel. Once the structure and transport mechanism of *TtCorB* are elucidated, they can serve as a basis for fully understanding the structure and function of human CNNMs, paving the way for designing small-molecule drugs with potential applications in disease treatment.

Purpose: The goal of this project is to establish a cryo-EM fusion protein strategy to enable fiducial-assisted, high-resolution structure determination of the bacterial CNNM orthologue *TtCorB*. This approach is intended to overcome the small size and limited structural features of *TtCorB*, thereby facilitating structure determination and providing a foundation for understanding the conformational mechanism of CNNM-mediated Mg²⁺ transport.

Materials and methods: BRIL insertion sites in *TtCorB* were first evaluated in silico using AlphaFold3 to assess whether the engineered BRIL domain adopted an exposed and structurally compatible position for downstream complex formation. Selected *TtCorB*-BRIL constructs were generated in a pET-29a(+) vector with a C-terminal His₆ tag using NEBuilder HiFi DNA Assembly and verified by whole-plasmid sequencing. *TtCorB*-BRIL proteins were expressed in *Escherichia coli* C41(DE3) cells, isolated from membrane fractions, solubilized in UDM detergent, and purified by Ni-NTA affinity chromatography followed by size-exclusion chromatography. The anti-BRIL BAG2 Fab, stabilizing nanobody, and MSP1D1 scaffold protein were expressed separately in *Escherichia coli* and purified using affinity and size-exclusion chromatography. Complex formation was assessed by incubating purified *TtCorB*-BRIL with BAG2 Fab and nanobody,

followed by size-exclusion chromatography and SDS-PAGE analysis. Selected *TtCorB*-BRIL constructs were reconstituted into MSP1D1 nanodiscs using soybean polar lipid extract and detergent removal with Bio-Beads. Nanodisc incorporation and sample quality were evaluated by size-exclusion chromatography, SDS-PAGE, and dynamic light scattering.

Results: The results show that *TtCorB* can tolerate BRIL insertion at multiple positions, that a BRIL-containing construct can be incorporated into membrane-mimetic nanodiscs, and the construct can recruit the BAG2 Fab and nanobody to form a stable ternary complex, and be visualized as a larger and more asymmetric particle by cryo-EM.

Conclusion: Overall, this work establishes a feasible strategy for structural investigation of *TtCorB* by combining BRIL insertion, fiducial recruitment, and nanodisc reconstitution. While further optimization will likely be required to improve rigidity and homogeneity, the present findings lay the groundwork for future high-resolution structural studies aimed at understanding the ion transport mechanism of CNNM proteins, defining their roles in disease, and supporting the design of possible drugs targeting this protein family.

Biographical sketch:

Sina Abedini is a thesis-based M.Sc. candidate in Biochemistry at McGill University in the Department of Biochemistry, working in Dr. Kalle Gehring's laboratory. He completed his B.Sc. in Biotechnology at the University of Tehran, where he ranked 2nd in his class. His graduate research focuses on the structural biology of magnesium transport proteins, specifically the prokaryotic CNNM orthologs CorB/CorC, with the goal of establishing engineered protein constructs suitable for high-resolution cryo-EM studies. His work combines membrane protein expression and purification, protein engineering, and biochemical and biophysical techniques to better understand the molecular basis of Mg^{2+} transport and its relevance to human CNNM-related diseases. Sina received the Graduate Excellence Award in Biochemistry and won Best Poster Presentation at the 7th Annual Centre de Recherche en Biologie Structurale (CRBS) Symposium. He has also served as a teaching assistant for Structural Biochemistry at the University of Tehran and for the Biophysical Methods in Biochemistry course offered at McGill University.

Magnesium in Otology – a Scoping Review

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Purpose: Magnesium (Mg) has been shown to exert neuroprotective, vasodilatory, and antioxidative effects, which may be beneficial in disorders of the inner ear. Experimental studies suggest that magnesium can improve cochlear blood flow, stabilize synaptic transmission, and protect sensory hair cells from oxidative damage. This scoping review aims to systematically assess the available clinical evidence for the role of magnesium in otological disorders, including tinnitus, sudden sensorineural hearing loss, vestibular disorders, age-related hearing loss, noise-induced hearing loss, and ototoxicity.

Materials and methods: A structured literature search was conducted using the Medline database. The following Medical Subject Headings (MeSH) were applied: *magnesium, tinnitus, sudden hearing loss, vestibular disorders, ototoxicity, and otoprotection*. Eligible studies were screened for relevance, study design, and clinical applicability. Based on the identified publications, a scoping review was performed to summarize and categorize the evidence according to clinical indication and level of evidence.

Results: Fifteen methodologically robust studies were identified, including eight controlled clinical trials comprising a total of 1,045 participants. The strongest evidence supports oral magnesium supplementation (>200 mg/day) for the prevention of age-related hearing loss (presbycusis). Moderate evidence also suggests a protective effect against noise-induced hearing loss, supporting magnesium as an evidence-based adjunct to established preventive measures such as hearing protection and noise exposure reduction. In cases of acute sensorineural hearing loss and tinnitus, magnesium may provide additional benefit when used alongside standard therapies, including corticosteroids and carbogen inhalation. Limited phase II trials and case series report positive effects of intravenous magnesium sulfate (1–2 g) in acute vestibular disorders, as well as oral magnesium (approximately 400 mg/day) for prophylaxis. Evidence for the prevention of cisplatin-induced ototoxicity is currently limited to isolated case reports.

Conclusion: Despite extensive experimental data supporting its otoprotective properties, clinical evidence for magnesium use in otology remains limited. Convincing data exist primarily for the prevention of presbycusis, whereas other therapeutic applications should currently be regarded as experimental or individualized. Further high-quality randomized controlled trials are needed to clarify magnesium's role in clinical otology.

Biographical sketch: Prof. Dr. med. Jens Büntzel is head of Otorhinolaryngology (ENT) and Head-and-Neck Surgery at Südharz Klinikum Nordhausen gGmbH, with clinical and research foci in head and neck oncology, palliative/supportive care, and integrative oncology. He also contributes to postgraduate teaching and clinical program development in these areas. Prof. Büntzel studied medicine at the University of Leipzig, completed his habilitation in ENT at Friedrich Schiller University Jena, and was appointed extraordinary professor there. His additional qualifications include board-level training in palliative medicine, nutritional medicine, sports medicine, and tumor therapy.

Prof. Büntzel is also an active member of national and international scientific societies related to otolaryngology, oncology, complementary medicine, and nutritional and mineral research, reflecting his interdisciplinary clinical and research interests. He has authored or co-authored approximately 392 scientific publications covering clinical and translational research in ENT, oncology care, supportive care, and integrative approaches

P3

Content Validation of the MagQuest Instrument to Support the Clinical Assessment of Magnesium Deficiency Risk

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Purpose: To assess the content validity of MagQuest, a computerized, self-administered screening instrument designed to identify risk factors of inadequate magnesium status. MagQuest includes items on dietary intake, medical diagnoses and medication use and is intended to identify subclinical deficiencies that may contribute to the pathogenesis of conditions such as hypertension and type 2 diabetes.

Materials and methods: Ten experts with demonstrated expertise in magnesium's role in human nutrition and clinical outcomes participated in a two-round Delphi process to evaluate MagQuest according to Lynn's (1986) content validation method. Experts rated each MagQuest item (or item set) for relevance to the instrument's intended construct using a 4-point Likert scale. Quantitative consensus was evaluated using the item-level Content Validity Index (I-CVI) and the scale-level Content Validity Index (S-CVI/Ave) for the overall instrument. Experts also provided qualitative feedback on item clarity and relevance and assessed the comprehensiveness of the instrument. Items were revised or added iteratively based on this feedback.

Results: Eighteen MagQuest items/item sets were evaluated in the first Delphi round. Fourteen achieved consensus (I-CVI $\geq .80$), and 14 new items were added based on expert feedback. The revised 28-item instrument was evaluated in the second round, in which 21 items achieved acceptable content validity (I-CVI $\geq .88$), with an overall S-CVI/Ave of .75. The seven items that failed to reach consensus (I-CVI $< .78$) were all newly proposed medications added after the first round.

Conclusion: MagQuest demonstrated acceptable content validity following removal of newly proposed medication items that did not meet consensus thresholds. Further evaluation of medication effects on magnesium homeostasis is warranted, and with additional validation, MagQuest may serve as a clinically useful screening tool for early identification of individuals at risk for suboptimal magnesium status.

Biographical sketch: Valerie Ciccone is a doctoral student at the University of Maryland studying magnesium's role in human health in Dr. Margaret Slavin's laboratory. Valerie earned a BA in Government from Georgetown University and worked in event and operations management before enrolling in graduate school to pursue a career in the field of nutrition. Following completion of her PhD, she intends to pursue a registered dietitian credential with the goal of conducting translational research that informs and enhances clinical practice.

P4

Regulation of CNNM Magnesium Transporters by PRL Phosphatase in Response to Environmental Magnesium Fluctuations

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Abstract body:

Magnesium is a critical divalent cation for cellular function, serving as a cofactor for over 300 enzymatic reactions. However, the pathways that control magnesium transport and homeostasis are poorly understood. The CNNM family of transmembrane proteins have been identified as key players in magnesium homeostasis, with CNNM2 and -4 serving as magnesium efflux pumps. Additionally PRLs, a family of 3 cytosolic pseudo-phosphatases, have been shown to regulate CNNM Mg²⁺ efflux by binding to the cytosolic domains of CNNMs and blocking their activity. PRLs have been proteins of interest in cancer research for many years, following the identification of their association with metastasis. More recently, it was shown that their interactions with CNNMs were necessary and sufficient to promote metastasis in mouse models, while their phosphatase activity was dispensable.

Purpose: The aim of this study is to characterize the regulatory and signalling pathways that modulate PRL-CNNM interactions and how they respond to environmental magnesium.

Materials and methods: The use of phos-tag gels has allowed us to monitor the formation of a long lasting phospho-cysteine intermediate which prevents PRLs from binding to CNNMs, while FRET based confocal microscopy has allowed us to observe PRL-CNNM interactions *in situ*

Results: The combination of these techniques has shown environmental acidification and PRL farnesylation to be a critical component of the PRL-CNNM response to magnesium. Additionally, inhibition of P13K shows a reduction in magnesium response.

Conclusion: The use of PRL phosphorylation as a marker for magnesium based signalling response provides a promising approach for further characterizing the regulation of magnesium transport by CNNMs.

Biographical sketch: Emma Lee is a third year PhD candidate in Biochemistry at McGill University. She is in the lab of Kalle Gehring, working on the PRL-CNNM regulatory axis in relation to magnesium homeostasis.

P5

Interaction of Viral Proteins with CNNM3 Enhances Magnesium Transport and Viral replication

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Purpose: Viruses have evolved diverse mechanisms to manipulate host cellular processes for their benefit. Research from our lab suggests that intracellular magnesium (Mg^{2+}) homeostasis is dynamically regulated during viral infection and contributes to efficient viral replication. Interactome data further suggest that multiple viral proteins target the PRL/CNNM magnesium regulatory complexes. Using adenovirus as a model system, we investigated how viral proteins modulate PRL/CNNM-dependent Mg^{2+} homeostasis, with a focus on CNNM3.

Materials and methods: Interactions between viral proteins and CNNM3 were identified through interactome studies and validated by co-immunoprecipitation. The functional consequences of Adenovirus type 5 protein E4orf4 was assessed by examining CNNM3 phosphorylation and intracellular Mg^{2+} levels. To determine the role of CNNM3 in regulating Mg^{2+} homeostasis during infection, CRISPR/Cas9-generated CNNM3 knockout cells were analyzed for Mg^{2+} levels, RNA translation, and viral replication.

Results: Expression of E4orf4 induced a PP2A-dependent dephosphorylation of several sites on CNNM3, revealing a mechanism by which adenovirus modulates CNNM3 activity. Furthermore, adenoviral infection increased total and soluble Mg^{2+} , an effect partially dependent on the presence of E4orf4 in the virus. Consistently, CNNM3 knockout cells exhibited elevated Mg^{2+} , increased RNA translation, and enhanced adenovirus replication compared with controls, indicating that CNNM3 plays a role in Mg^{2+} availability during infection. Interestingly, CNNM-interacting viral proteins identified in HIV, EBV, and SARS-CoV-2 were also associated with increased intracellular Mg^{2+} , suggesting that modulation of Mg^{2+} homeostasis is a conserved viral strategy.

Conclusion: These findings suggest that Mg^{2+} homeostasis is actively targeted during viral infection through modulation of the CNNM3 regulatory pathway. Specifically, adenovirus exploits the E4orf4–PP2A axis to modulate CNNM3 phosphorylation and increase Mg^{2+} availability, thereby promoting favorable conditions for viral replication. These findings suggest a conserved viral strategy for manipulating Mg^{2+} homeostasis, providing new insights into viral pathogenesis.

Biographical sketch: Cristina Fernandez is a graduate student in the laboratory of Dr. Jose Teodoro at the Rosalind and Morris Goodman Cancer Institute (McGill University, Montreal). Her research focuses on intracellular magnesium homeostasis during viral infection, with particular emphasis on the PRL/CNNM magnesium regulatory network. She uses molecular virology and cell biology approaches to investigate how viruses modulate host magnesium regulation to support replication.

P6

A Conserved Translational Mechanism Couples Magnesium Homeostasis to PTP4A2 Expression

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Purpose: PTP4A2 functions as a Mg²⁺ biosensor that regulates TRPM7, a major Mg²⁺ transporter in mammalian cells. We recently identified a novel mechanism by which intracellular Mg²⁺ controls PTP4A2 expression at the translational level. This regulation is mediated by a highly conserved 5' untranslated region (UTR) containing an upstream open reading frame (uORF), suggesting the existence of an evolutionarily conserved Mg²⁺-sensing mechanism. We hypothesized that the uORF functions as a Mg²⁺-responsive translational element that controls access of ribosomes to the PTP4A2 coding sequence.

Materials and methods: To investigate Mg²⁺-dependent translational regulation, we developed bioluminescent reporter assays in which the PTP4A2 coding sequence was replaced by firefly luciferase while preserving the native 5'-UTR. To directly assess uORF translation, the uORF, including its endogenous AUG and Kozak sequence, was fused in-frame to a firefly luciferase reporter lacking its initiation codon. Site-directed mutagenesis was used to evaluate the contribution of specific nucleotides and conserved amino acid residues to Mg²⁺ responsiveness.

Results: The PTP4A2 uORF conferred robust Mg²⁺-dependent translational regulation. Synonymous codon substitutions had minimal effects on Mg²⁺ responsiveness, indicating that nucleotide sequence alone is not the primary determinant of regulation. In contrast, extensive alteration of the encoded amino acid sequence abolished Mg²⁺ responsiveness, demonstrating that the peptide sequence encoded by the uORF is critical for function. Furthermore, mutation of specific conserved residues significantly impaired Mg²⁺-dependent regulation. This mechanism was independent of eIF2α phosphorylation, distinguishing it from canonical stress-responsive uORF-mediated translational control pathways.

Conclusion: Our findings identify a previously unrecognized Mg²⁺-sensing translational mechanism in vertebrates in which the amino acid sequence encoded by a conserved uORF governs PTP4A2 expression. This regulatory pathway links intracellular Mg²⁺ availability to PTP4A2 expression and, consequently, to TRPM7-mediated Mg²⁺ transport.

P7

Low ionized magnesium is associated with macrovascular events and atrial fibrillation in type 2 diabetes mellitus

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Purpose: Cardiovascular diseases (CVDs) are common amongst individuals with type 2 diabetes mellitus (T2DM). Micro- and macrovascular complications are the primary cause of morbidity and mortality and the CVD risk in T2DM is hypothesized to partly occur through magnesium homeostasis. Hypomagnesemia is common in T2DM and associated with increased risk of micro- and macrovascular events. However, total magnesium measurements may not be representative of the bodies' storage of magnesium. Ionized magnesium is available for the body, and not complexed to proteins or anions, making it a more accurate indicator of the magnesium storage.

In this study, the association of ionized magnesium with the incidence of cardiovascular events was investigated in individuals with T2DM.

Materials and methods: 4,202 samples from people with T2DM (mean age 65 ± 11 years, 44% female) from the Hoorn Cohort were analyzed for ionized magnesium at baseline (2008, 2009, 2012, 2013, and 2014). Participants were followed up until 2020 for major cardiovascular events, macrovascular events, microvascular events and atrial fibrillation. The analyses were carried out using Cox regression models, adjusted for demographics, CVD and T2DM risk factors and medication.

Results: The mean baseline concentration of ionized magnesium was 0.48 ± 0.06 mmol/L. Over the mean follow-up duration of 7.4 years, 3847 events of any cardiovascular event were identified. A low serum ionized magnesium concentration ($iMg^{2+} < 0.45$ mmol/L) was associated with macrovascular events (AMI, CHD, HF, CVA and PAD)(HR= 1.24[1.04-1.47]; $p=0.018$), but not with micro- and major cardiovascular events and all-cause mortality. Furthermore, low ionized magnesium was associated with PAD, diabetic foot and atrial fibrillation.

Conclusion: Low ionized magnesium is associated with macrovascular outcomes, PAD, diabetic foot and atrial fibrillation in individuals with T2DM. Moreover, ionized magnesium appears to have a specific range that is linked to a lower HR, indicating an optimal range.

P8

Effectiveness of Magne B6 Forte®/MAGNEVIE B6® on fatigue and its impact on Physical and Mental Health and Quality of Life in Adults with Magnesium Deficiency: A Real-World Observational Study in Poland and France (MAGNEFY)

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Purpose: Magnesium deficiency is frequently linked to fatigue, stress, anxiety, sleep disorders, and reduced quality of life. Despite widespread clinical use of Magne B6 Forte®/MAGNEVIE B6® (magnesium + vitamin B6 fixed-dose combination), real-world evidence across multiple symptom domains remains scarce. This study evaluated its real-world effectiveness on mental and physical fatigue, stress, anxiety, depression, sleep quality, and quality of life in magnesium-deficient adults under routine self-care conditions.

Materials and methods: Prospective cohort study (n=340) in Poland (PL) and France (FR) enrolling adults ≥18 years initiating Magne B6 Forte®/MAGNEVIE B6® with self-reported fatigue, MDQ-10 >5, and FAS ≥22. Recruited via pharmacists (November 2025–March 2026). Assessments at baseline, daily (14 days), weekly (Weeks 1–3), and monthly (Months 1–2). Primary endpoint: FAS fatigue change from baseline. Secondary endpoints: DASS-21, SF-12, PROMIS SD-SF-8b, and symptom ratings.

Results: At baseline, fatigue, stress, anxiety, and mental overload were most impactful symptoms (scores 4–6/6). **Fatigue (FAS):** Moderate baseline fatigue (PL: 32.7±5.8; FR: 31.3±5.6). Clinically meaningful reductions (>4 points) from Week 1, sustained through Month 2 (p<.001). **DASS-21:** Significant transition from moderate-to-severe to normal ranges at Month 1.(PL: depression 8.5→4.3; anxiety 7.4→3.2; stress 11.1→6.0). FR showed comparable reductions exceeding clinical thresholds. **SF-12:** Quality of life improved significantly from Month 1 through Month 2. PL: PCS increased from 47.2±10.1 to 57.6±8.9; MCS from 51.1±10.8 to 64.2±10.6. FR: PCS from 52.9±9.1 to 59.1±8.0; MCS from 48.8±9.0 to 60.5±9.7. All changes exceeded clinical threshold, with consistent cross-country patterns.

Conclusion: In this real-world study, Magne B6 Forte®/MAGNEVIE B6® demonstrated rapid, clinically meaningful, and sustained improvements across fatigue, stress, anxiety, depression, sleep, and quality of life in magnesium-deficient adults. Consistent findings across Poland and France, supported by multiple validated PRO measures, reinforce its real-world effectiveness and support its use across key symptoms

P9

Mapping PRL/PTP4A Phosphatase Signaling Landscape via Magnesium-Dependent Phosphoproteomics

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Introduction. Phosphatases of regenerating liver (PRLs, also known as PTP4A) are cysteine-based phosphatases that regulate magnesium homeostasis through CNNM Mg^{2+} transporters and the TRPM7 ion channel. PRLs exhibit unusual enzyme kinetics that lead to the accumulation of a stable phosphocysteine intermediate. Magnesium availability dynamically dictates this phosphorylation state, which likely impacts CNNM binding and regulation *in vivo*.

Objective: We leverage Mg^{2+} fluctuations to modulate PRL activity and to systematically identify signaling pathways that exhibit reciprocal changes in response to Mg^{2+} via global phosphoproteomics.

Materials and methods: HEK293T cells were cultured across three distinct experimental conditions: normal Mg^{2+} (baseline), 24-hour Mg^{2+} deprivation, and 24-hour Mg^{2+} deprivation followed by a 1-hour Mg^{2+} re-addition. Proteins were extracted, reduced, alkylated and trypsinized. Phosphopeptides were enriched using TiO_2 and analyzed via LC-MS/MS alongside total proteome to monitor relative protein abundances. Phosphopeptide fold changes were subsequently normalized using total protein abundance.

Results: Western blot analysis of PRL2 confirmed the accumulation of dephosphorylated PRL2 under Mg^{2+} deprivation and rapid re-phosphorylation upon Mg^{2+} re-addition. Our phosphoproteomics analysis detected 11955, 19531, and 21655 phosphosites under normal Mg^{2+} , deprivation and re-addition conditions, respectively. As a positive control, phosphorylation of proteins involved in the mTORC1 pathway decreased upon Mg^{2+} deprivation and increased upon re-addition. Notably, we detect phosphorylation on PRL1/2 catalytic cysteine for the first time with high probability score, showing an 8-fold increase upon Mg^{2+} re-addition. Characterization of other phosphosite changes upon Mg re-addition identified 226 sites that increase by at least 2-fold, marking them as potential candidates for PRL-regulated pathways.

Conclusion: Our workflow effectively captures the highly sensitive Mg^{2+} -dependent kinetic behaviour of PRLs. The isolation of distinct responsive hits offers a targeted candidate pool for downstream signaling. Future experiments will focus on validating the effects of these potential hits.

Biographical sketch: Luba Mahbub is a PhD Candidate in the Department of Biochemistry at McGill University, working under the supervision of Prof. Kalle Gehring. She holds a Bachelor and Master of Pharmacy from the University of Dhaka. Her current research focuses on the molecular regulation of magnesium homeostasis, with a specific emphasis on the signaling landscape of magnesium-sensitive PRL/PTP4A phosphatases and their interaction with CNNM transporters. To explore these pathways, she integrates diverse methodologies ranging from X-ray crystallography and NMR spectroscopy to proteomics and bioinformatics. Her work has led to co-authored publications in journals such as eLife and the Journal of Biological Chemistry, exploring how atypical GTPases like ARL15 and dynamic PRL phosphatases interact with cellular magnesium transporters.

P10

Deciphering the Molecular Mechanism of Mg^{2+} Transport by Human CNNM4 Using AI-Assisted Structural Modeling and Molecular Dynamics

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Magnesium is an essential cofactor involved in hundreds of enzymatic reactions, yet the molecular mechanisms governing its transmembrane transport remain poorly understood. Members of the Cyclin M (CNNM) family are key regulators of cellular Mg^{2+} homeostasis; however, the lack of high-resolution structural information for their transmembrane region has hindered mechanistic understanding. Here, we investigated the structural basis of Mg^{2+} recognition and transport through the DUF21 transmembrane domain of the human CNNM4 transporter using an integrative computational approach combining structural biology, AI-assisted structural modeling, and molecular dynamics simulations.

Purpose: To elucidate the molecular mechanism of Mg^{2+} transport through the DUF21 transmembrane domain of human CNNM4 by defining the ion translocation pathway and identifying the key residues governing Mg^{2+} recognition, coordination, and permeation.

Materials and methods: Four different structural models of the Metal Transporter CNNM4 protein including the DUF21 transmembrane domain plus the following alpha helical domain (AHD), or the AHD and the subsequent Bateman module, were analyzed. These structural templates were subjected to MD analysis in the presence of Magnesium Chloride, or in a mixed solution containing both $MgCl_2$ and Sodium Chloride. All salt concentrations were adjusted to a physiological concentration of 150 μM . To accurately mimic the native biological environment of CNNM4, the systems were embedded into a phospholipid bilayer. The lipid bilayers were generated using the Membrane Builder module available in CHARMM-GUI, employing a standard, representative mammalian lipid composition. Subsequently, the protein-lipid structures were assembled using the Multicomponent Assembler module of CHARMM-GUI, which solvated the models with TIP3P water molecules. The topology and coordinate files for all systems were obtained using the GROMACS 2025 suite. For each system, energy minimization was performed to remove unfavorable steric interactions using the steepest descent algorithm for 1000 steps. A starting position restraint of 1000 $\text{kJ}\cdot\text{mol}^{-1}\cdot\text{nm}^{-2}$ (equivalent to 20 $\text{kcal}\cdot\text{mol}^{-1}\cdot\text{\AA}^{-2}$) was imposed on the protein heavy atoms, which was then slowly reduced and completely removed across five consecutive minimization cycles. System equilibration was carried out in two stages. First, during the NVT ensemble, the system temperature was gradually increased from 0 to 310 K over 2.0 ns using a v-rescale thermostat. Initial position restraints of 25 $\text{kJ}\cdot\text{mol}^{-1}\cdot\text{nm}^{-2}$ (equivalent to 0.5 $\text{kcal}\cdot\text{mol}^{-1}\cdot\text{\AA}^{-2}$) were imposed on the protein atoms and progressively decreased to ensure gradual system relaxation. Second, in the NPT ensemble, the systems were simulated for 2.0 ns using the Berendsen barostat, maintaining a constant pressure of 1.0 atm and a temperature of 310 K. All hydrogen bonds were constrained using the LINCS algorithm. The production runs were executed for a trajectory of 20 ns per system using the GROMACS 2025 suite.

Results: The simulations reveal the structural organization of the CNNM4 transmembrane region (DUF21) and identify residues involved in Mg^{2+} recognition and transport. Mg^{2+} translocation occurs through a central pore formed at the interface between the DUF21 domains of the two protomers, highlighting the functional relevance of dimerization. The analyses define the intermolecular interaction surfaces stabilizing the transporter during ion permeation, characterize the conformational rearrangements associated with the transport cycle, and predict the maximum number of Mg^{2+} ions simultaneously accommodated within the permeation pathway. Dynamic coupling between the DUF21 transmembrane region and the cytosolic Bateman domain further supports a coordinated transport mechanism.

Conclusion: This work provides an atomistic framework describing Mg^{2+} transport by human CNNM4. The identification of the molecular determinants governing ion recognition, pore architecture, dimer stabilization and conformational transitions advances our understanding of CNNM-mediated magnesium homeostasis and provides a structural basis for future functional studies and the rational design of therapeutic modulators targeting CNNM transporters.

Biographical sketch: Luis Alfonso Martínez-Cruz is Associate Principal Investigator at the Liver Diseases Laboratory of CIC bioGUNE. He has worked as structural biologist in well-recognized institutions, in Spain, Germany and USA, including the Max Planck Institute for Medical research in Heidelberg, and University of California at Berkeley. He is also Associated Professor at the School of Medicine of Deusto, in Bilbao, Spain. As Principal Investigator, his interest has focused on the Structural and biophysical characterization of proteins with biomedical interest, with special attention on the enzymes of the Transsulfuration pathway, cystathionine beta-synthase (CBS) and Cystathionine gamma-lyase (CGL) from a wide variety of organisms from prokaryotes to humans. Among his major achievements is the elucidation of the long-sought crystal structure of the human cystathionine beta-synthase (CBS) enzyme both, in its basal and in its activated conformation. His lab is also involved in determining the structure of Magnesium transporters and their interactome: his lab unraveled the structural basis underlying the oncogenic interaction existing between magnesium transporters of the CNNM family and phosphatases of the regenerating liver (PRLs). These studies contributed to unravel the conformational changes induced by ATP and Mg^{2+} ions on the CNNMs and helped understand the pathogenic effect of several mutations found in patients.

P11

Magnesium in Oncology – Update 2026

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Purpose: Magnesium is an essential electrolyte with critical roles in neuromuscular transmission, cardiovascular stability, DNA repair, and cellular metabolism. In clinical oncology, disturbances in magnesium homeostasis, most notably hypomagnesemia, are frequently encountered and may significantly influence treatment tolerance, toxicity, and overall patient outcomes. This comprehensive narrative review aims to update and synthesize current clinical evidence on the relevance of magnesium in cancer care, with emphasis on pathophysiology, treatment-related disturbances, and clinical management.

Materials and methods: A comprehensive narrative review of the literature published up to 2026 was conducted using major medical databases, including PubMed, Scopus, and Web of Science. Clinical trials, observational studies, meta-analyses, and relevant clinical guidelines addressing magnesium balance in cancer patients were included. Particular focus was given to magnesium disturbances associated with chemotherapy, targeted therapies, immunotherapy, and supportive oncologic care.

Results: Magnesium deficiency is commonly observed in patients receiving platinum-based chemotherapy, epidermal growth factor receptor inhibitors, antiangiogenic agents, and certain immunotherapies. Clinically significant hypomagnesemia has been associated with neuromuscular symptoms, fatigue, cardiac arrhythmias, nephrotoxicity, and increased risk of treatment delays or dose modifications. Emerging evidence suggests that chronic magnesium depletion may adversely affect treatment tolerance and quality of life. Clinical studies indicate that timely oral or intravenous magnesium supplementation can effectively correct deficiencies and mitigate therapy-related toxicities, although standardized dosing strategies remain inconsistent across practice settings.

Conclusion: Magnesium imbalance is a prevalent and clinically meaningful issue in contemporary oncology practice. Routine monitoring and individualized management of magnesium levels should be considered integral components of supportive cancer care. Further prospective and interventional studies are needed to establish standardized protocols and to clarify the impact of magnesium optimization on long-term oncologic outcomes.

Biographical sketch:

Head of the department of radiotherapy and radiation oncology, and clinical director of the Franziskus Hospital Bielefeld, Germany, teaching hospital of the Hannover Medical School (MHH).

He is president of the German Magnesium Society and chairman of the German Working Group "Trace Elements and Electrolytes in Radiation Oncology" and associate editor of "Trace Elements and Electrolytes"- Official Organ of the "Society of Magnesium Research", Germany, and German Working Group "Trace Elements and Electrolytes in Radiation Oncology" AKTE, Germany.

He authored more than 250 publications in peer reviewed scientific journals and has been invited as speaker at national and international meetings.

P12

Magnesium deficiency in hypertensives with cirrhosis of liver

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Severe chronic alcohol consumption is known to cause hypomagnesemia and is often associated with liver diseases and/or primary hypertension (1-4).

In this context, we report 15 hypertensive (HCL) and 15 non-hypertensive alcoholics with cirrhosis of liver (NHCL). None of the patients was renal insufficient or diabetic. No diuretics, proton pump inhibitors (PPI) or minerals were taken before 4 weeks baseline. Clinical data concerning age, sex, Body Mass Index (BMI) or blood pressure values were similar in both groups. 30 patients served as controls. The study was performed in accordance with the declaration of Helsinki. Diagnosis of liver cirrhosis was done by liver biopsy. Duration and amount of alcohol abuse was not significantly different in groups. In each patient serum magnesium, erythrocyte magnesium and ionized blood magnesium were measured. Ionized magnesium was determined by a Prime Plus apparatus by NOVA (Andover, USA). ANOVA was used for statistics.

Hypertensive patients with liver cirrhosis showed a significantly decreased serum magnesium ($p < 0.05$). Intracellular (erythrocyte) magnesium, determined by atomic absorption spectroscopy was 1.76 ± 0.12 mmol/l in controls versus 1.38 ± 0.22 in NHCL and 1.25 ± 0.15 mmol/l in HCL ($p < 0.01$). Ionized blood magnesium was 0.62 ± 0.07 mmol/l in controls (C) and 0.52 ± 0.06 mmol/l in all patients with cirrhosis of liver (CL) ($p < 0.05$).

The negative magnesium status in serum, intracellular and in ionized form in blood in hypertensives with alcohol abuse and liver cirrhosis is of importance for cardiovascular outcome, morbidity and mortality and the development of HCC (4). Even in non-hypertensive liver cirrhosis patients a slighter magnesium deficiency intracellular and ionized is observed (5).

In conclusion, a magnesium supplementation is beneficial in hypertensives with and without alcohol induced cirrhosis of liver to avoid further damage.

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P13

A novel CNNM2 case study and the advent of Jain Foundation supported field-building for CNNM2-associated disease

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A 12 month old boy presented with focal seizures, hypotonia, and global developmental delay. Initial genetic testing revealed an invdupdel rearrangement in the 8p region spanning 26 genes and a heterozygous VUS (p.N327S) in CNNM2. He was treated with Keppra, then high doses of Lacosamide, Clobazam, and Epidiolex; combined with a ketogenic diet and relocation to a warmer climate, seizures were well-controlled for over a year. Upon reclassification of the CNNM2 mutation to Likely Pathogenic at 3 years of age, magnesium testing and urine excretion indicated borderline hypomagnesemia (1.3-1.8 mg/dL, reference range 1.7-2.4mg/dL) and urinary magnesium wasting (0.39 mg magnesium/mg creatinine) consistent with CNNM2-associated disease. Further testing revealed a history of normal-to-elevated calcium (9.7-10.8 mg/dL, reference ranges variable) and normal PTH (21.5-22.7 pg/mL, reference range 14.5-75.2 pg/mL). At 4 years of age, the patient displayed autism-like behaviors, continuing global delays, and no spoken words despite daily speech and occupational therapy. During a slow rollback of anti-epileptic measures, no seizures recurred.

The Jain Foundation operates on a fundamentally different model than traditional rare disease funders. All funding decisions are made by a full-time, in-house scientific advisory board – eliminating the conflicts of interest endemic to conventional peer review – and the Foundation actively manages its funded projects. In the dysferlin field, this approach produced two decades of compounding infrastructure: a global genetically-confirmed patient registry, shared research tools and reagents, physician and patient education programs, and the first multicenter international natural history study for dysferlinopathy. The Foundation now brings this same model to CNNM2-related disorders, committing substantial private funding in 2026 toward disease mechanism research, relevant tissue identification, a collaborative international research community, and freely available reagents and tools for investigators worldwide. This investment is expected to grow in the years ahead.

Biographical sketch:

Plavi Jain Mittal, Ph.D. is a molecular biologist and rare-disease strategist with a Ph.D. in Biology from Brandeis University and postdoctoral training at Brigham and Women's Hospital, Harvard Medical School. As founder and President/CEO of the Jain Foundation, she and her team spent two decades building the dysferlin field — from early science to coordinated global research and trial-ready infrastructure. She has since advised more than a dozen rare disease organizations across stages of development. She now leads Project CNNM2, applying that experience to building the field, supporting families, and advancing therapeutic options for patients with CNNM2-related disorders.

P14

Oral magnesium Supplementation to Bisphosphonates in Post-menopausal Osteoporosis : a randomised clinical trial

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Objectives. Bisphosphonates are recommended to improve bone mineral density (BMD) and fracture risk in post-menopausal osteoporosis. Magnesium (Mg) has a beneficial effect on BMD but no trial has so far studied its additive effect to bisphosphonates treatment. Our objective is to explore if Mg supplementation could have an additive beneficial effect with bisphosphonates on serum carboxy-terminal collagen crosslinks (CTX) concentration as a surrogate of bone status.

Methods. A pilot randomized controlled trial (NCT05328154) included 44 women with post-menopausal osteoporosis at University Hospital, Clermont-Ferrand, France. Patients were randomized, after zoledronate infusion to 200 mg/day oral Mg carbonate (n=22, "BMg") for 3 months, or standard care (n=22, "BMg0"). The primary endpoint was the comparison of variation in CTX at one year in both groups. Other bone markers and quality of life were also assessed. All statistical tests were two-tailed with type-I error set at $\alpha=0.05$.

Results. CTX substantially decreased in both groups, but without significant difference between groups. A subgroup analysis in those 30% with both baseline high CTX and low serum Mg levels showed they had the largest decrease in CTX levels ($\geq 89\%$). DKK1 was the only marker that decreased more in BMg group, suggesting the osteogenic effect of Mg. No other significant differences were observed.

Conclusions. This innovative pilot randomized trial may suggest that in clinical practice, the subgroup of post-osteoporotic women with high CTX values and low serum Mg concentrations might benefit from Mg supplementation in addition to zoledronate. A larger randomized trial targeting this subgroup is warranted.

P15

Sodium-Glucose Cotransporter-2 Inhibition Enhances Magnesium Reabsorption in the Thick Ascending Limb of Type 2 Diabetic Patients

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Purpose: The incidence of type 2 diabetes mellitus (T2D) is increasing worldwide, and kidney disease is a common comorbidity that improves with glucose-lowering interventions. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have been effective in reducing hyperglycemia in patients with T2D and have also been associated with higher serum Mg^{2+} concentrations, suggesting a potential therapeutic role in treating hypomagnesemia. Several different hypotheses have been proposed to explain how SGLT2i elevate serum Mg^{2+} concentrations, but the underlying mechanism remains elusive. We aim to investigate whether alterations in tubular ion transport in the thick ascending limb (TAL) and distal convoluted tubule (DCT) could explain this phenomenon.

Materials and methods: We performed single cell (sc)-RNA seq on kidney biopsies obtained from six healthy controls, six participants with T2D, and ten participants with T2D treated with SGLT2i. In parallel, qPCR was conducted on kidney tissue from db/db mice and db/db mice treated with 5mg/mL empagliflozin in the drinking water for 8 weeks starting at 28 weeks old.

Results: NKCC2, ROMK, and CLDN16 gene expressions are significantly elevated after SGLT2i treatment in both humans and mice. CLDN 19 gene expression is significantly elevated after SGLT2i treatment in humans but remains unchanged in mice. In the distal convoluted tubule (DCT) of human patients, TRPM6, TRPM7, NCC, and WNK4 expression are all significantly upregulated in after treatment with SGLT2i. The expression level of these magnesiotropic genes in the DCT remained unchanged in mice.

Conclusion: This data supports the hypothesis that SGLT2i augment the lumen-positive potential in the TAL driving Mg^{2+} reabsorption through the paracellular space in both human and mice. In addition, magnesiotropic genes in the DCT that stimulate TRPM6/TRPM7 channel may further increases Mg^{2+} reabsorption in human kidneys.

Biographical sketch: Matthias Wolf is the division director of Pediatric Nephrology at the University of Michigan. His research focuses on tubular electrolyte disturbances and drug development for rare kidney disorders. Regarding tubular electrolyte disturbances he is interested in proteins modifying the renal epithelial magnesium channel TRPM6. He studied the effects of urinary proteins such as Mucin-1, Uromodulin, and the hunger hormone Ghrelin on magnesium homeostasis. His research has been published in the Journal of the American Society, Kidney International, and the Journal of Biological Chemistry. His research has been supported by the NIH and the Department of Defense.

P16

Structural and functional studies of CNNM magnesium transporters

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Purpose: The CNNM family of magnesium transporters is essential for maintaining intracellular Mg²⁺ homeostasis and is regulated by auxiliary proteins including phosphatases of regenerating liver (PRLs) and ARL15. Dysregulation of CNNM-PRL complexes has been implicated in cancer progression and metastasis. CNNMs are proposed to function through a rocker-switch transport mechanism involving transitions between inward- and outward-facing conformations; however, direct structural evidence for these conformational states remains limited. This study aims to establish a cryo-electron microscopy (cryo-EM) platform to characterize the structural basis of CNNM conformational dynamics.

Materials and methods: A bacterial CNNM homolog (*Thermus thermophilus* CorB, TtCorB) containing a BRIL insertion was expressed and purified for cryo-EM analysis. To increase the effective molecular weight and provide fiducial features for particle alignment, the transporter was assembled into a complex with an anti-BRIL Fab and a Fab-specific nanobody. Vitriified samples were screened by cryo-EM to evaluate particle distribution, integrity, and suitability for high-resolution structural studies.

Results: Cryo-EM screening demonstrated well-dispersed particles with minimal aggregation and yielded high-quality 2D class averages of the TtCorB-Fab-nanobody complex. These results validate the BRIL-assisted fiducial strategy for structural studies of this relatively small membrane protein complex and establish a robust foundation for high-resolution data collection. Optimization of sample preparation and imaging conditions is ongoing to improve particle quality and resolve distinct conformational states.

Conclusion: This work establishes an effective cryo-EM workflow for structural investigation of CNNM transporters. High-resolution structural characterization of TtCorB will provide insight into the conformational changes underlying Mg²⁺ transport and contribute to a mechanistic framework for understanding the function and regulation of the CNNM family.

Biographical sketch:

Ashkan Shahsavan is a PhD candidate in the Department of Biochemistry at McGill University. His research focuses on the structural biology of membrane proteins involved in magnesium homeostasis, with an emphasis on the CNNM family of magnesium transporters. Using cryo-electron microscopy and complementary biochemical approaches, he investigates the conformational dynamics and regulatory mechanisms that govern magnesium transport. He has co-authored peer-reviewed publications in structural biology and was awarded a MITACS Globalink Research Award to conduct a research exchange in the laboratory of Professor Loren Runnels at Rutgers University.

P17

THE EFFECT OF GLYCEMIC CONTROL ON CORTISOL LEVELS AND CA/MG RATIOS IN TYPE II DIABETICS IN GENERAL HOSPITAL, YAOUNDE-CAMEROON

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Background and aims : The human body secretes diabetogenic hormones, such as cortisol, a situation that is further aggravated in the presence of diabetes. The combination of these factors can lead to poor metabolic control and early complications. Several large cohort studies have shown that type 2 diabetes is associated with increased serum calcium levels and magnesium deficiency. The major drug therapy for type II DM comprises of insulin secretagogues, biguanides, insulin sensitizers, alpha glucosidase inhibitors, incretin mimetics, amylin antagonists and sodium-glucose co-transporter-2 (SGLT2) inhibitors. This study aimed to investigate the effects of diabetic status and glycemic control on serum cortisol ~~these hormones~~, as well as on serum calcium and magnesium levels in T2D subjects on such pharmacological therapy, to better understand the complications linked to this complex disease.

Methods : An analytical case–control study was conducted. The patient group consisted of individuals with type 2 diabetes followed at the Yaoundé General Hospital (YGH), while the control group included apparently healthy individuals. Clinical and therapeutic histories of all participants were recorded. Glycemic control in diabetic patients was assessed through the measurement of glycated hemoglobin (HbA1c). Subsequently, blood glucose levels, as well as serum cortisol, magnesium, and calcium levels, were determined using spectrophotometric and immunoenzymatic method methods. The results from the biological analyses were summarized and statistically analyzed using the R software version 1.1. Qualitative variables were presented as frequencies and compared using the Chi-square test, while quantitative variables were presented as means and compared using the Student's t-test. Linear regression analysis was performed to determine the correlation between serum cortisol and both glycemia and HbA1c. A significance threshold of $p < 0.05$ was set for all analyses.

RESULTS : A total of 63 patients with type 2 diabetes attending YGH were included in the study. The median age was 60 years and the mean duration of diabetes was 6.47 ± 5.34 years. Overall, 25.4% of participants had good glycemic control (GGC) while 74.6% had poor glycemic control (PGC). Hypertension was the most frequent comorbidity, affecting 50% of the GGC group and 42% of the PGC group, whereas no cases were observed in the normal control (NC) group. Patients in the GGC group showed a significant reduction in HbA1c levels, reaching $6.3\% \pm 0.59\%$ ($p < 0.001$). In contrast, HbA1c levels remained elevated in the PGC group ($10.03\% \pm 2.27\%$). Patients with type 2 diabetes exhibited significantly higher serum cortisol levels compared with controls ($p < 0.01$). An increase in cortisol levels was positively associated with higher fasting plasma glucose (FPG) in both diabetic groups. Mean serum calcium concentrations were 10.12 ± 1.04 mg/dL in the PGC group, 10.30 ± 1.01 mg/dL in the GGC group, and 8.30 ± 0.85 mg/dL in the non-diabetic group. Despite the apparent variation across groups, no statistically significant

difference was observed. Mean serum magnesium concentrations were 2.38 ± 0.34 mg/dL, 2.27 ± 0.33 mg/dL, and 2.43 ± 0.29 mg/dL in the PGC, GGC, and non-diabetic groups, respectively. Additionally, no significant difference in the Ca/Mg ratio was observed between the GGC and PGC groups (4.53 ± 0.79 vs 4.26 ± 0.75). However, the Ca/Mg ratio was significantly higher in the overall diabetic population compared with the normal control group (4.13 ± 0.81 vs 3.42 ± 0.54 ; $p < 0.001$), indicating mild magnesium depletion according to the Ehrlich-Rosanoff scale.

CONCLUSION : Serum cortisol levels were associated with hyperglycemia and HbA1c in patients with inadequately controlled type 2 diabetes. In addition, the Ca/Mg ratio was significantly elevated in patients with type 2 diabetes compared with individuals with normal glycemic status. These findings suggest that morning serum cortisol and Ca/Mg ratio may represent useful metabolic indicators in the evaluation of glycemic control among patients with type 2 diabetes. Larger studies are required to confirm these associations.

Keywords

Cortisol; type 2 diabetes; glycemic control; HbA1c; General hospital; Yaoundé-Cameroon

P18

Magnesium-Activated UBXN1 Phase Separation Attenuates Pulmonary Arterial Hypertension

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Purpose: Magnesium supplementation represents a promising therapeutic strategy for pulmonary arterial hypertension (PAH), yet the underlying molecular mechanism has remained elusive. This study aims to investigate whether and how magnesium exerts its protective effects through liquid-liquid phase separation (LLPS) of UBXN1.

Materials and methods: Proteomic analysis was performed on pulmonary artery tissues from a monocrotaline-induced PAH model, combined with sucrose gradient fractionation of pulmonary artery smooth muscle cells (PASMCs). Smooth muscle-specific UBXN1 knockdown was used to assess magnesium's therapeutic benefits. Live-cell imaging and in vitro reconstitution assays were conducted to evaluate Mg²⁺-induced UBXN1 phase separation.

Results: Immunoprecipitation-mass spectrometry (IP-MS) identified interaction partners. Cell-permeable interfering and crosslinking peptides, along with VAPG-modified nanoparticles for in vivo delivery, were used for functional modulation.

Magnesium supplementation significantly upregulated UBXN1 and promoted its assembly into higher-order condensates. Smooth muscle-specific UBXN1 knockdown abolished magnesium's therapeutic benefits. Mg²⁺ acted as a direct inducer of UBXN1 phase separation. UBXN1 condensates recruited USP14 to enhance UBXN1 stability, HSP90AA1 to facilitate condensation, and sequestered key glycolytic enzymes to suppress pathological PASMC proliferation. An interfering peptide abrogated magnesium's benefits, whereas a phase separation-promoting peptide mimicked its therapeutic effects. Targeted modulation via nanoparticle delivery established UBXN1 phase separation as a viable therapeutic strategy for PAH.

Conclusion: Magnesium-induced UBXN1 condensates integrate protein quality control with metabolic reprogramming to attenuate vascular pathology, offering a novel framework for targeted biomolecular condensation therapy in cardiovascular diseases.

Biographical sketch: Jia-Yu Liu is affiliated with the Department of Physiology and Pathophysiology at Fujian Medical University, School of Basic Medical Sciences, and the Key Laboratory of Fujian Province Universities on Ion Channel and Signal Transduction in Cardiovascular Diseases. The research focuses on molecular mechanisms of cardiovascular diseases, particularly protein phase separation and ion signaling in pulmonary arterial hypertension.

P19

A magnesium chloride ointment for the stabilization of mast cells as a new strategy for seborrheic or atopic dermatitis and psoriasis

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A previous research showed that a 10% magnesium chloride ointment (Casida®) was effective for the treatment of seborrheic or atopic dermatitis. As this ointment is available over the counter, it was easy for eleven patients to test the effectiveness of such a local treatment. Results showed that local skin reactions have been largely reduced after 5/6 days. Thus, further research should investigate the specific cellular activity of magnesium chloride on tissue mast cells in order to confirm local treatments. A recent in vitro research showed that both magnesium chloride and zinc chloride reduced the number of degranulating rat mast cells in a dose-dependent manner confirming the in vivo clinical observations.

Purpose: We need to clarify the process to stabilize tissue mast cells when using a magnesium chloride ointment for seborrheic or atopic dermatitis and psoriasis.

Materials and methods: Use of a 10% magnesium chloride ointment (Casida®) to evaluate in eleven patients for the local treatment of seborrheic or atopic dermatitis and psoriasis. Such a cosmetic is available over the counter and was easy to test for all patients.

Results: Eleven patients showed a clear improvement of their dermatological reactions (seborrheic or atopic dermatitis and psoriasis) in an open-label study.

Conclusion: A 10% magnesium chloride ointment stabilizes skin diseases such as seborrheic or atopic dermatitis and psoriasis whose target cells appear to be tissue mast cells since histamine has been detected locally.

Biographical sketch: Bernard J.L. Sudan has been in charge of a Laboratory of Pharmacology and Toxicology in Basel, Switzerland for more than three decades and has jointly conducted his private research to elucidate the etiology of his familial seborrheic dermatitis, an allergy to the hapten nicotine.

P20

A qualitative exploration of users' perceived benefits of magnesium

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Purpose:

Magnesium deficiency is a widespread, underrecognized public health issue, affecting up to 31% of the global population, and its management is commonly poorly understood by users. To shape future research and enhance behavioural evidence regarding user lived experience, this study sought to understand magnesium users' perception of symptoms, product use and benefit.

Materials and methods:

A qualitative design employing semi-structured online in-depth interviews in France and Poland from December 2024 - February 2025. 46 adults (aged 18-65 years) using an over-the-counter magnesium product in the past 3 months, with current magnesium deficiency (as defined by the validated Magnesium Deficiency Questionnaire) were recruited via a multi-modal approach. Participants were stratified by attitude towards magnesium use into Advocates (22), Opportunists (12), and Sceptics (12). Interviews lasted 45 minutes with responses thematically analysed using MaxQDA software.

Results:

Fatigue (physical and emotional) (14 mentions), stress (13), muscle cramps (10), eyelid twitching (7), sleeping issues (6) and irritability (5), most often led participants to initiate magnesium. These were also most likely to impact daily lives. Participants observed and expected to see benefits within 1-3 weeks. Physical symptoms were usually described as relieved more quickly, and occasionally, completely than emotional ones. Opportunists and Sceptics tended to describe higher expectations and were consequently less satisfied compared to Advocates. Usage was primarily driven by emotional well-being associated symptoms in France versus physical symptoms in Poland.

Conclusion:

This study confirms and builds on existing literature, that user knowledge surrounding magnesium is limited, and seemingly influenced by pre-conceived beliefs and external sources of recommendations. This may lead to non-optimal use of magnesium, subsequently impacting experienced outcomes. As such, users of magnesium may benefit from additional support to enhance understanding around magnesium intake. Prevalence of physical and mental fatigue as an indicator of magnesium deficiency suggests further research into this area would be beneficial to users.

P21

Hypomagnesemia, Oral Magnesium Therapy, and Mortality in U.S. Veterans with Heart Failure

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Introduction and Objective

Magnesium is an essential mineral that affects multiple organ systems. Although magnesium deficiency is uncommon, patients with heart failure (HF) are susceptible to hypomagnesemia. Less is known about the effect of hypomagnesemia on death, and even less is known whether oral magnesium therapy may improve survival, the examination of which was the objective of our study.

Materials and Methods

We conducted two separate analyses of Veterans with HF (2001-2023). First, we identified 616,751 patients with ambulatory serum magnesium levels ≤ 2.6 mg/dL, of whom 39,596 (6.4%) had values <1.6 mg/dL. Next, from a cohort of 54,696 Veterans with HF and serum magnesium <1.7 mg/dL, including 10,695 who received new prescriptions for oral magnesium therapy, we assembled a propensity score-matched cohort of 21,098 patients (oral magnesium therapy, $n=10,549$). Cox regression and restricted cubic spline models were used to assess the associations of serum magnesium levels and oral magnesium therapy with one-year mortality.

Results

Mortality occurred in 15.4% and 12.1% of patients with serum magnesium <1.6 and 1.6–2.6 mg/dL, respectively (multivariable-adjusted HR for serum magnesium <1.6 mg/dL, 1.26; 95% CI, 1.22–1.29). In the matched cohort, mortality occurred in 14.2% and 12.8% of the patients not receiving and receiving oral magnesium therapy, respectively (HR associated with magnesium therapy, 0.89; 95% CI: 0.83–0.96). Restricted cubic spline analysis revealed the lowest mortality risk between 1.6 and 2.6 mg/dL, with higher risk outside that range. A restricted cubic spline analysis incorporating oral magnesium therapy demonstrated lower mortality HR at serum magnesium levels <1.6 mg/dL but higher at >2.1 mg/dL.

Conclusions

Among Veterans with HF, serum magnesium <1.6 mg/dL was associated with higher mortality and identified patients most likely to benefit from oral magnesium therapy. These findings suggest that 1.6 mg/dL may represent a clinically relevant therapeutic threshold for magnesium repletion.

Biographical sketch:

Dr. Yin received her Ph.D. in Pharmacology from the School of Medicine at Temple University. She then spent several years in industry as a consultant specializing in data analysis and visualization, serving clients across diverse sectors. In 2020, she joined GWU as a biomedical informatics researcher. Her background in biomedical science, combined with her applied experience in data management and analytics, has prepared her to address medical informatics challenges in real-world settings. Working closely with clinical experts, her research focuses on leveraging large datasets from electronic health records to conduct retrospective and predictive studies. She applies machine learning and statistical methods to summarize, compare, and predict clinical outcomes across different patient cohorts.



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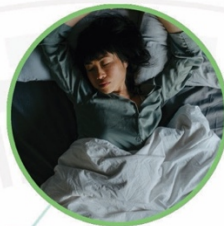
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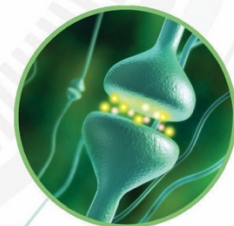
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