Приложение 7 к Протоколу заочного голосования Организационного комитета Международной олимпиады Ассоциации «Глобальные университеты» для абитуриентов магистратуры и аспирантуры от 20.06.2023 № 1-з

**Структура научного профиля (портфолио) потенциальных научных руководителей участников трека аспирантуры Международной олимпиады Ассоциации «Глобальные университеты» для абитуриентов магистратуры и аспирантуры.**

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| University |  |
| Level of English proficiency | fluent |
| Educational program and field of the educational program for which the applicant will be accepted | *31.06.01 Clinical medicine (educational program)**Nephrology (field of the educational program)**ZA Urology and Nephrology* |
| List of research projects of the potential supervisor (participation/leadership) | 1. Pathophysiology of Diabetic Kidney Disease
2. Vasopressin in Chronic Kidney Disease
3. Metabolic Effects of Vasopressin in Diabetes Mellitus
4. Renal Mechanisms of Potassium Homeostasis
5. Endoplasmic Reticulum Stress in Kidney Disorders
6. Vasopressin Renal Acid-Base Handling
7. Molecular Mechanisms of Kidney Aging
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| List of the topics offered for the prospective scientific research | List of 7-10 scientific topics, which are offered by the research supervisor for consideration of foreign applicants(During the course of the Interview the topic may be modified according to specific area of scientific interest of the applicant):1. Pathophysiology of Diabetic Kidney Disease
2. Vasopressin in Chronic Kidney Disease
3. Metabolic Effects of Vasopressin in Diabetes Mellitus
4. Renal Mechanisms of Potassium Homeostasis
5. Endoplasmic Reticulum Stress in Kidney Disorders
6. Vasopressin Renal Acid-Base Handling
7. Molecular Mechanisms of Kidney Aging
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|  Research supervisor:Kerim Mutig,Dr. med. / priv. Doz. (Humboldt University Berlin, Charité Medical University Berlin) | *Clinical Medicine**ZA Urology and Nephrology* |
| Supervisor’s research interests:*Kidney physiology, pathophysiology of diabetic kidney disease, role of vasopressin in chronic kidney disorders.* |
| Supervisor’s main publications*21 publications during the last 5 years.*1. *Calcineurin inhibitors stimulate Kir4.1/Kir5.1 of the distal convoluted tubule to increase NaCl cotransporter.*

*JCI Insight. 2023 Apr 10;8(7):e165987.**Abstract**We examine whether calcineurin or protein phosphatase 2B (PP2B) regulates the basolateral inwardly rectifying potassium channel Kir4.1/Kir5.1 in the distal convoluted tubule (DCT). Application of tacrolimus (FK506) or cyclosporine A (CsA) increased whole-cell Kir4.1/Kir5.1-mediated K+ currents and hyperpolarized the DCT membrane. Moreover, FK506-induced stimulation of Kir4.1/Kir5.1 was absent in kidney tubule-specific 12 kDa FK506-binding protein-knockout mice (Ks-FKBP-12-KO). In contrast, CsA stimulated Kir4.1/Kir5.1 of the DCT in Ks-FKBP-12-KO mice, suggesting that FK506-induced stimulation of Kir4.1/Kir5.1 was due to inhibiting PP2B. Single-channel patch-clamp experiments demonstrated that FK506 or CsA stimulated the basolateral Kir4.1/Kir5.1 activity of the DCT, defined by NPo (a product of channel number and open probability). However, this effect was absent in the DCT treated with Src family protein tyrosine kinase (SFK) inhibitor or hydroxyl peroxide. Fluorescence imaging demonstrated that CsA treatment increased membrane staining intensity of Kir4.1 in the DCT of Kcnj10fl/fl mice. Moreover, CsA treatment had no obvious effect on phosphorylated NaCl cotransporter (pNCC) expression in Ks-Kir4.1-KO mice. Immunoblotting showed acute FK506 treatment increased pNCC expression in Kcnj10fl/fl mice, but this effect was attenuated in Ks-Kir4.1-KO mice. In vivo measurement of thiazide-induced renal Na+ excretion demonstrated that FK506 enhanced thiazide-induced natriuresis. This effect was absent in Ks-FKBP-12-KO mice and blunted in Ks-Kir4.1-KO mice. We conclude that inhibition of PP2B stimulates Kir4.1/Kir5.1 of the DCT and NCC and that PP2B inhibition-induced stimulation of NCC is partially achieved by stimulation of the basolateral Kir4.1/Kir5.1.*1. *Furosemide rescues hypercalciuria in familial hypomagnesaemia with hypercalciuria and nephrocalcinosis model.*

*Acta Physiol (Oxf). 2023 Mar;237(3):e13927.**Abstract**Aim: Perturbed calcium homeostasis limits life expectancy in familial hypomagnesaemia with hypercalciuria and nephrocalcinosis (FHHNC). This rare disease occurs by loss-of-function mutations in CLDN16 or CLDN19 genes, causing impaired paracellular reabsorption of divalent cations along the cortical thick ascending limb (cTAL). Only partial compensation takes place in the ensuing late distal convoluted tubule, connecting tubule, and collecting duct, where the luminal transient receptor potential channel V5 (TRPV5), as well as basolateral plasma membrane calcium ATPase (PMCA) and sodium-potassium exchanger (NCX1) mediate transcellular Ca2+ reabsorption. The loop diuretic furosemide induces compensatory activation in these distal segments. Normally, furosemide enhances urinary calcium excretion via inhibition of the aforementioned cTAL. As Ca2+ reabsorption in the cTAL is already severely impaired in FHHNC patients, furosemide may alleviate hypercalciuria in this disease by activation of the distal transcellular Ca2+ transport proteins.**Methods: Cldn16-deficient mice (Cldn16-/- ) served as a FHHNC model. Wild-type (WT) and Cldn16-/- mice were treated with furosemide (7 days of 40 mg/kg bw) or vehicle. We assessed renal electrolyte handling (metabolic cages) and key divalent transport proteins.**Results: Cldn16-/- mice show higher Ca2+ excretion than WT and compensatory stimulation of Cldn2, TRPV5, and NCX1 at baseline. Furosemide reduced hypercalciuria in Cldn16-/- mice and enhanced TRPV5 and PMCA levels in Cldn16-/- but not in WT mice.**Conclusions: Furosemide significantly reduces hypercalciuria, likely via upregulation of luminal and basolateral Ca2+ transport systems in the distal nephron and collecting duct in this model for FHHNC.*1. *Unrecognized role of claudin-10b in basolateral membrane infoldings of the thick ascending limb.*

*Ann N Y Acad Sci. 2022 Nov;1517(1):266-278.**Abstract**Claudin-10b is an important component of the tight junction in the thick ascending limb (TAL) of Henle's loop and allows paracellular sodium transport. In immunofluorescence stainings, claudin-10b-positive cells exhibited extensive extra staining of basolateral, column-like structures. The precise localization and function have so far remained elusive. In isolated cortical TAL segments from C57BL/6J mice, kidney-specific claudin-10 knockout mice (cKO), and respective litter mates (WT), we investigated the localization and protein expression and function by fluorescence microscopy and electrophysiological measurements. Ultrastructural analysis of TAL in kidney sections was performed by electron microscopy. Claudin-10b colocalized with the basolateral Na+ -K+ ATPase and the Cl- channel subunit barttin, but the lack of claudin-10b did not influence the localization or abundance of these proteins. However, the accessibility of the basolateral infolded extracellular space to ouabain or fluorescein was increased by basolateral Ca2+ removal and in the absence of claudin-10b. Ultrastructural analysis by electron microscopy revealed a widening of basolateral membrane infoldings in cKO in comparison to WT. We hypothesize that claudin-10b shapes neighboring membrane invaginations by trans interaction to stabilize and facilitate high-flux salt transport in a water-tight epithelium.*1. *Claudin-10a Deficiency Shifts Proximal Tubular Cl- Permeability to Cation Selectivity via Claudin-2 Redistribution.*

*J Am Soc Nephrol. 2022 Apr;33(4):699-717.**Abstract**Background: The tight junction proteins claudin-2 and claudin-10a form paracellular cation and anion channels, respectively, and are expressed in the proximal tubule. However, the physiologic role of claudin-10a in the kidney has been unclear.**Methods: To investigate the physiologic role of claudin-10a, we generated claudin-10a-deficient mice, confirmed successful knockout by Southern blot, Western blot, and immunofluorescence staining, and analyzed urine and serum of knockout and wild-type animals. We also used electrophysiologic studies to investigate the functionality of isolated proximal tubules, and studied compensatory regulation by pharmacologic intervention, RNA sequencing analysis, Western blot, immunofluorescence staining, and respirometry.**Results: Mice deficient in claudin-10a were fertile and without overt phenotypes. On knockout, claudin-10a was replaced by claudin-2 in all proximal tubule segments. Electrophysiology showed conversion from paracellular anion preference to cation preference and a loss of paracellular Cl- over HCO3- preference. As a result, there was tubular retention of calcium and magnesium, higher urine pH, and mild hypermagnesemia. A comparison with other urine and serum parameters under control conditions and sequential pharmacologic transport inhibition, and unchanged fractional lithium excretion, suggested compensative measures in proximal and distal tubular segments. Changes in proximal tubular oxygen handling and differential expression of genes regulating fatty acid metabolism indicated proximal tubular adaptation. Western blot and immunofluorescence revealed alterations in distal tubular transport.**Conclusions: Claudin-10a is the major paracellular anion channel in the proximal tubule and its deletion causes calcium and magnesium hyper-reabsorption by claudin-2 redistribution. Transcellular transport in proximal and distal segments and proximal tubular metabolic adaptation compensate for loss of paracellular anion permeability.*1. *Angiotensin II receptor blockade alleviates calcineurin inhibitor nephrotoxicity by restoring cyclooxygenase 2 expression in kidney cortex.*

*Hu J, Xu Y, Bachmann S, Mutig K.**Abstract**Aim: The use of calcineurin inhibitors such as cyclosporine A (CsA) for immunosuppression after solid organ transplantation is commonly limited by renal side effects. CsA-induced deterioration of glomerular filtration rate and sodium retention may be related to juxtaglomerular dysregulation as a result of suppressed cyclooxygenase 2 (COX-2) and stimulated renin biosynthesis. We tested whether CsA-induced COX-2 suppression is caused by hyperactive renin-angiotensin system (RAS) and whether RAS inhibition may alleviate the related side effects.**Methods: Rats received CsA, the RAS inhibitor candesartan, or the COX-2 inhibitor celecoxib acutely (3 days) or chronically (3 weeks). Molecular pathways mediating effects of CsA and RAS on COX-2 were studied in cultured macula densa cells.**Results: Pharmacological or siRNA-mediated calcineurin inhibition in cultured cells enhanced COX-2 expression via p38 mitogen-activated protein kinase and NF-kB signalling, whereas angiotensin II abolished these effects. Acute and chronic CsA administration to rats led to RAS activation along with reduced cortical COX-2 expression, creatinine clearance and fractional sodium excretion. Evaluation of major distal salt transporters, NKCC2 and NCC, showed increased levels of their activating phosphorylation upon CsA. Concomitant candesartan treatment blunted these effects acutely and completely normalized the COX-2 expression and renal functional parameters at long term. Celecoxib prevented the candesartan-induced improvements of creatinine clearance and sodium excretion.**Conclusion: Suppression of juxtaglomerular COX-2 upon CsA results from RAS activation, which overrides the cell-autonomous, COX-2-stimulatory effects of calcineurin inhibition. Angiotensin II antagonism alleviates CsA nephrotoxicity via the COX-2-dependent normalization of creatinine clearance and sodium excretion.* |
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