Institute of Experimental and Clinical Pharmacology and Toxicology

Chair of Clinical Pharmacology and Clinical Toxicology

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Research focus
- Molecular characterization of drug transporters and transporter-mediated drug-drug interactions
- Molecular and clinical characterization of new cardiovascular risk factors and risk markers
- Quantification of drugs and endogenous substances including metabolomics
- Medication safety

Structure of the Chair

Professorships: 2
Personnel: 25
- Doctors (of Medicine): 3
- Scientists: 7 (thereof funded externally: 3)
- Graduate students: 8

Special structural feature
The position of the executive director of the Institute rotates between the Chair of Pharmacology and Toxicology and the Chair of Clinical Pharmacology and Clinical Toxicology on a two-year basis.

Clinical focus areas
- Drug analysis
- Clinical trial unit
- Drug information service for physicians

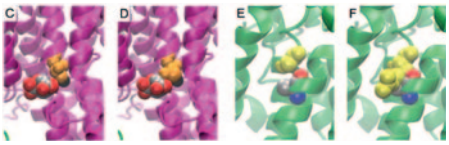
Research

The groups at the Chair of Clinical Pharmacology and Clinical Toxicology investigate mechanisms underlying interindividual differences in drug effects using molecular and cellular biology as well as clinical studies. The following topics, funded e.g. by the DFG, the German Cancer Aid and the German Federal Ministry of Health (BMG), are in the focus of our studies: Uptake and efflux transporters for drugs and endogenous compounds, mechanisms underlying drug-drug interactions, genetic determinants of drug effects (pharmacogenomics), cardiovascular pharmacology and risk factors, alterations of the L-arginine-NO-metabolism, and medication safety.

Molecular characterization of transporters and transporter mediated drug-drug interactions

PI: Prof. Dr. J. König, Prof. Dr. M.F. Fromm

Transport proteins located in distinct membrane domains are important for the uptake, distribution, and excretion of drugs and drug metabolites. Simultaneously administered drugs or food constituents can modify transporter-mediated uptake or elimination of victim drugs. This leads to altered plasma concentrations and drug effects of the victim drug and possibly an increased risk of adverse drug reactions. For example, we identified using *in vitro* models the importance of the export transporter MATE1, which is localized in the luminal membrane of renal proximal tubular cells, for the renal secretion of drugs (e.g. memantine, metformin) and endogenous biomarkers (trimethylamine-N-oxide). Moreover, we investigated the functional relevance of transporters for endogenous substances. For example, functional consequences of mutations in the SLC13A5 gene, which encodes for the uptake transporter NaCT (sodium-coupled citrate transporter), were investigated. This transporter plays an essential role in cellular energy metabolism and in brain development. Alterations in function of NaCT are associated with epileptic encephalopathy.

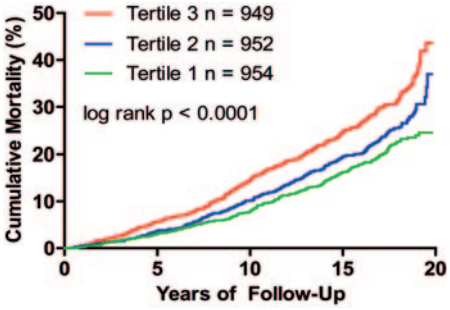


Influence of the T227M (C, D) and the G219R (E, F) mutations on structure of the NaCT transporter, which is important for cellular energy metabolism and in brain development (Reproduced with permission from Selch S et al, Sci Rep. 2018)

Molecular and clinical characterization of new cardiovascular risk factors and risk markers

PI: Prof. Dr. R. Maas

A major focus of the group is the experimental and clinical characterization of new cardiovascular risk markers and risk factors as potential targets for therapeutic intervention. Currently the group investigates transport and metabolism of homoarginine, β-aminoisobutyrate, nitrate and the methylarginines ADMA and SDMA. The investigations were conducted in long standing cooperations with the Department of Medicine 4, the Universities of Dresden and Kiel and the Framingham Heart Study (USA). In the reporting period we identified an independent association of the risk markers ADMA, SDMA, and homoarginine with the intake of several drugs. Furthermore, we could provide direct evidence that the protective risk marker homoarginine is a substrate of the cationic amino acid transporters CAT1, CAT2A, and CAT2B.



Kaplan–Meier plot for the relationship between tertile of plasma nitrate and survival (tertile 1=low, tertile 2=intermediate, and tertile 3=high plasma nitrate; reproduced with permission of Maas R et al, J Am Heart Assoc. 2017)

Analysis of drugs and endogenous substances including metabolomics

PI: Dr. A. Gessner, Dr. V. Taudte

The mass spectrometry unit uses samples from both, cell culture experiments and clinical and large epidemiological trials (GCKD study, popgen). Analytical methods (mostly LC/MS/MS) are developed, optimized, and validated in our laboratory. The spectrum of the analytes ranges from various drugs, such as pravastatin, etoposide, metformin, clopidogrel, and trimethoprim, to endogenous substances, such as derivatives of arginine, N^1-methylnicotinamide, trimethylamine-N-oxide (TMAO), and β-aminoisobutyric acid. In 2018, the methodological spectrum was broadened to targeted and untargeted metabolomics due to a new mass spectrometer (Q Exactive Focus with U-HPLC) funded by the DFG. The available technologies can be used for cooperations within the Faculty and FAU as well as for external cooperations.

Medication safety

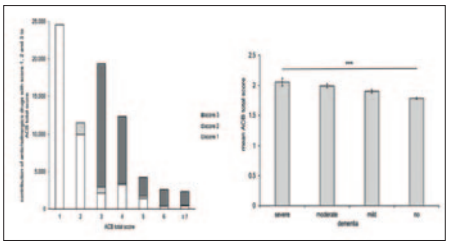
PI: Prof. Dr. R. Maas, Prof. Dr. M.F. Fromm

A project funded by the German Cancer Aid was conducted with a focus on dose adjustment in oncological patients with renal insufficiency (cooperation with Prof. Dr. F. Dörje, pharmacy of UK Erlangen). Moreover, an innovative, three year clinical study is conducted in patients treated with new oral antitumor therapeutics in collabo-

ration with the pharmacy of UK Erlangen, the Comprehensive Cancer Center Erlangen-EMN (CCC), and collaborating private practices, which is also funded by the German Cancer Aid. This prospective, randomized trial is currently testing the hypothesis whether clinical pharmacological/clinical pharmaceutical support improves patient safety, convenience and knowledge in patients newly treated with new oral antitumor therapeutics (AMBORA study).

In addition, problems of medication safety in elderly patients (e.g. anticholinergic burden and cognitive function in elderly patients) are in the focus of collaborative projects with the Geriatrie in Bayern-Database (GiB-DAT). Moreover, in a BMG-funded collaborative project, we evaluated the new nationwide medication plan in clinical praxis (MMP16).

The Chair coordinates the community of practice "Medication Safety" of the Medical Valley EMN e.V. In addition, the Chair participates in a continuing medical education program in Good Clinical Practice for physicians, as required for clinical trials of medicines, and medicinal products.



Distribution of the anticholinergic burden in 76,934 patients of the GiB-DAT Database (left) and association of anticholinergic burden and cognitive function in elderly patients (right); reproduced with permission from Pfistermeier B et al, PLoS One. 2017

Teaching

The Chair of Clinical Pharmacology and Clinical Toxicology coordinates the interdisciplinary lecture series and seminar clinical pharmacology/pharmacotherapy for medical students applying problem-based learning. In addition, we teach students of the degree programs Dentistry, Molecular Medicine, pharmacy, and Medical Process Management. In a cooperation project with the Technical University of Munich, we established two online teaching modules for drug therapy of common diseases. Students of pharmacy and medicine are welcome to work with us during their final year.

The Chair of Clinical Pharmacology and Clinical Toxicology offers supervision of Bachelor's and Master's theses as well as of MD and PhD theses.

Selected publications

von Loeffelholz C et al. The human longevity gene homolog INDY and interleukin-6 interact in hepatic lipid metabolism. Hepatology, 2017, 66: 616-630

Pfistermeister B, Tümena T, Gaßmann K-G, Maas R, Fromm MF. Anticholinergic burden and cognitive function in a large German cohort of hospitalized geriatric patients. PLOS ONE, 2017, 12: e0171353

Maas R, Xanthakis V, Göen T, Müller J, Schwedhelm E, Böger RH, Vasan RS. Plasma nitrate and incidence of cardiovascular disease and all-cause mortality in the community: The Framingham Offspring Study. J Am Heart Assoc. 2017 Nov 18;6(11). pii: e006224

Müller F, Sharma A, König J, Fromm MF. Biomarkers for in vivo assessment of transporter function. Pharmacol Rev, 2018, 70: 246-277

Selch S, Chafai A, Sticht H, Birkenfeld AL, Fromm MF, König J. Analysis of naturally occurring mutations in the human uptake transporter NaCT important for bone and brain development and energy metabolism. Sci Rep, 2018, 8: 11330

Maas R, Mieth M, Titze SI, Hübner S, Fromm MF, Kielstein JT, Schmidt M, Köttgen A, Kronenberg F, Krane V, Hausknecht B, Eckard KU, Schneider MP. Drugs linked to plasma homoarginine in CKD patients – A cross-sectional analysis of the German Chronic Kidney Disease Cohort (GCKD). Nephrol Dial Transplant, 2018 Nov 23. doi: 10.1093/ndt/gfy342

International cooperations

Prof. L. Gustafsson, Karolinska Institutet, Stockholm: Sweden

Prof. J. Backman, Prof. M. Niemi, University of Helsinki, Helsinki: Finland

Prof. R. Vasan, Framingham Heart Study, Framingham: USA

Prof. R. Masereeuw, Utrecht University, Utrecht: The Netherlands

Prof. A. Sparreboom, Ohio State University, Columbus, OH: USA