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
- Analysis of drugs and endogenous substances
- Medication safety

Structure of the Chair

Professorships: 2
Personnel: 25
- Doctors (of Medicine): 3
- Scientists: 7 (thereof funded externally: 2)
- Graduate students: 10

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

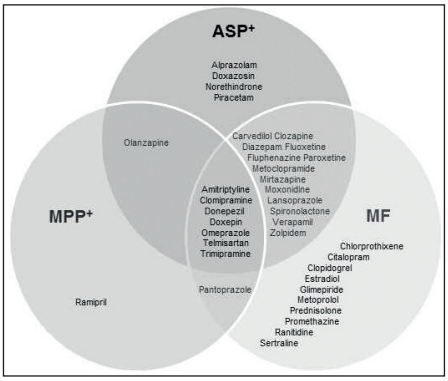
Research

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, the German Federal Ministry of Health (BMG), and the BMBF, are in the focus of our studies: Uptake and efflux transporters for drugs, 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 drug 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. We could identify functionally relevant amino acid residues in the hepatic uptake transporter OATP1B1. We could show that in vitro inhibition of the renal uptake transporter OCT2 depended on the used substrates. Furthermore, the molecular mechanism of renal secretion of the dopamine receptor agonist pramipexole could be identified and evidence was generated for the use of the endogenous metabolite N1-methylnicotinamide as potential biomarker for renal drug-drug interactions mediated by cation transporters.



Selective or overlapping inhibition of OCT2-mediated uptake of the oral antidiabetic drug metformin (MF) and of the prototypical OCT2 substrates ASP+ (4–4-dimethylaminostyryl-N-methylpyridinium) and MPP+ (1-methyl-4-phenylpyridinium) by frequently used drugs (reproduction with permission of PLOS ONE from Hacker et al., PLOS ONE 2015, DOI:10.1371/journal.pone.0136451)

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, ß-aminoisobutyrate, nitrate and the methylarginines ADMA and SDMA. The investigations were conducted in long standing cooperations with the Department of Medicine 4 – Nephrology and Hypertension, the Universities of Dresden and Kiel and the Framingham Heart Study (USA).

Analysis of drugs and endogenous substances

PI: Dr. M. Mieth

The drug analysis unit uses samples from both, cell culture experiments and clinical trials. 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 and β-aminoisobutyric acid.

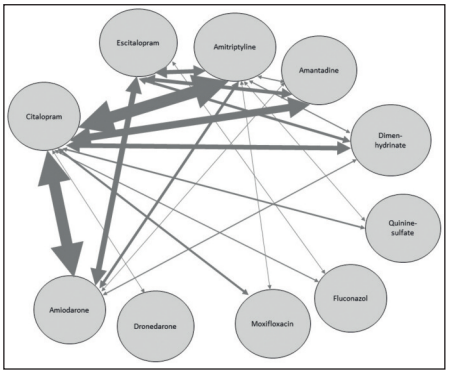
Medication safety

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

As a partner of the therapeutic systems project that is part of the BMBF funded cluster Medical Valley EMN, we developed a new software to improve medication safety in psychiatry. In a joint project with Prof. Dr. F. Dörje (Pharmacy of UK Erlangen), we conducted a project within the Comprehensive Cancer Center Erlangen-EMN on medication safety in oncology with a particular focus on drug-drug interactions by abiraterone and enzalutamide in patients with metastatic castration-resistant prostate cancer (in cooperation with the AURONTE unit of the UK Erlangen).

Funding: German Cancer Aid

In addition, problems of medication safety in elderly patients (e.g. QT-interval prolonging drugs) are in the focus of collaborative projects with the Geriatrie in Bayern-Database (GiB-DAT). Moreover, in a BMG-funded collaborative project, we evaluate the new nationwide medication plan in clinical praxis (MMP16). The Chair also coordinates the community of practice "Medication Safety" of the Medical Valley EMN e.V.



Simultaneous prescription of QT-interval prolonging drugs in a cohort of 130,434 patients treated in geriatric units. The thickness of the arrows is proportional to the number of patients who received the respective combination (co-

operation with Prof. K.-G. Gaßmann, Geriatrie-Zentrum Erlangen and GiB-DAT; reproduction with permission of PLOS ONE from Schächtele et al., PLOS ONE 2016: DOI:10.1371/journal.pone.0155649)

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 dental medicine, 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

Müller F, Pontones CA, Renner B, Mieth M, Hoier E, Auge D, Maas R, Zolk O, Fromm MF. N^1-methylnicotinamide as an endogenous probe for drug interactions by renal cation transporters: studies on the metformin-trimethoprim interaction. Eur J Clin Pharmacol, 2015, 71: 85-94

Knop J, Misaka S, Singer K, Hoier E, Müller F, Gläser H, König J, Fromm MF. Inhibitory effects of green tea and (-)-epigallocatechin gallate on transport by OATP1B1, OATP1B3, OCT1, OCT2, MATE1, MATE2-K and P-glycoprotein. PLOS ONE, 2015, 10: e0139370

Stratz C, Bömicke T, Younas I, Kittel A, Amann M, Valina CM, Nührenberg T, Trenk D, Neumann FJ, Hochholzer W. Comparison of immature platelet count to established predictors of platelet reactivity during thienopyridine therapy. J Am Coll Cardiol, 2016, 68: 286-93

Schächtele S, Tümena T, Gaßmann KG, Fromm MF, Maas R. Co-prescription of QT-interval prolonging drugs: an analysis in a large cohort of geriatric patients. PLOS ONE, 2016, 11: e0155649

Gruetz M, Sticht H, Glaeser H, Fromm MF, König J. Analysis of amino acid residues in the predicted transmembrane pore influencing transport kinetics of the hepatic drug transporter organic anion transporting polypeptide 1B1 (OATP1B1). BBA Biomembranes, 2016, 1858: 2894-2902

Schlesinger S, Sonntag SR, Lieb W, Maas R. Asymmetric and symmetric dimethylarginine as risk markers for total mortality and cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. PLOS ONE, 2016, 11: e0165811

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. S. Misaka, Fukushima Medical University, Fukushima: Japan

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