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: 26
- Doctors (of Medicine): 2
- Scientists: 12 (thereof funded externally: 8)
- 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 German Cancer Aid, BMBF, the German Federal Ministry of Health (BMG) and the Wilhelm Sander-Foundation 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 for drugs and endogenous substances
PI: Prof. Dr. J. König, Prof. Dr. M.F. Fromm
Transport proteins in the plasma membrane of cells are important for the uptake, distribution and excretion of endogenous substances and drugs or drug metabolites. Using double-transfected cell models recombinantly overexpressing an uptake transporter together with an export protein we could demonstrate that the renal uptake transporter OCT2, localized in the basolateral membrane of proximal tubule cells together with the export protein MATE1, located in the luminal membrane mediate the polarized transport of the anticholinergic drug trospium. Transport proteins are also important for the renal handling of arginine metabolites. We could demonstrate that the uremic toxin asymmetric dimethylarginine (ADMA) as well as the cardioprotective biomarker L-homoarginine are substrates of the renal transport protein OATP4C1. Using a double-transfected cell model recombinantly overexpressing basolaterally localized OATP4C1 together with the apically localized export pump P-glycoprotein we could further demonstrate that both transporters mediate the vectorial transport of both arginine metabolites. Supported by the Wilhelm Sander-Foundation we further investigated a splice variant (Ct-OATP1B3 = cancer-type OATP1B3) of an uptake transporter, expressed in several tumor tissues and could demonstrate that the Ct-OATP1B3 protein is localized in intracellular vesicles mediating the sequestration and therefore inactivation of chemotherapeutic agents.

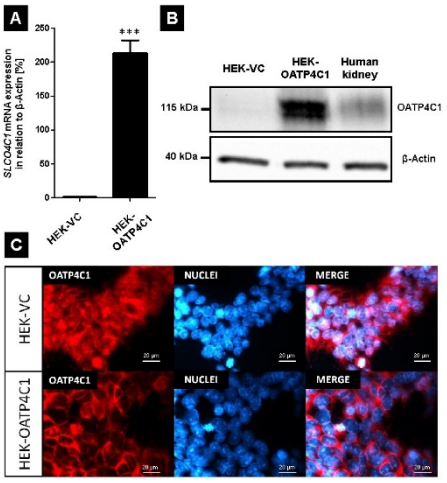

Fig. 1: Characterization of HEK293 cells, which were stably transfected with the renal transporter protein OATP4C1 (Reproduced with permission from Taghikhani E et al, PlosOne 2019)

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, γ-aminoisobutyrate, nitrate and the methylarginines ADMA and SDMA. The investigations are conducted in long standing cooperations with the Department of Medicine 4, the Universities of Dresden and Kiel. In the reporting period we established population-based reference values for the two new biomarkers trimethylamine-N-oxide (TMAO) and N^{ε}-acetyllysine. In 2020 the research was supported by FAU and the Medcial Faculty by a new gas chromatography / mass spectrometer.

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, pop-gen). 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), N^{ε}-acetyllysine and γ-aminoisobutyric acid. Recently, the methodological spectrum was broadened to targeted and untargeted metabolomics due to a new mass spectrometer (Q Exactive Focus with UHPLC) funded by the DFG. The available technologies can be used for cooperations within the Faculty and FAU as well as for external cooperations.

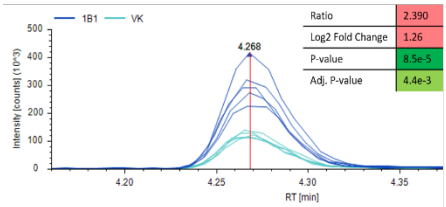

Fig. 2: Metabolomics of HEK-OATP1B1-and HEK-control cells. Intracellular concentration of a detected endogenous molecule is significantly higher in cells expressing the uptake transporter OATP1B1 (dark blue) in comparison to the control cells (bright blue)

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

Funding: German Cancer Aid
An innovative, three year clinical study was conducted in patients treated with new oral antitumor therapeutics in collaboration with the pharmacy of UK Erlangen (Prof. Dr. F. Dörje), the Comprehensive Cancer Center Erlangen-EMN (CCC), and collaborating private practices. This prospective, randomized trial showed that intensified clinical pharmacological/clinical pharmaceutical support improves patient safety, convenience and knowledge in patients newly treated with new oral antitumor therapeutics (AMBORA study).

Funding BMG
Clinical Pharmacology in Erlangen coordinates the establishment and evaluation of a ‘medication

safety stewardship' at a large tertiary hospital. The project objective is to optimize the medication process in a sustainable and efficient manner in order to improve medication safety.

Funding BMBF
The use case 'Polypharmacy, drug interactions and risks (POLAR)', which includes all four consortia of the Medical Informatics Initiative Germany, aims to assess using methods and processes of the Medical Informatics Initiative Germany health risks in patients with polypharmacy. Clinical Pharmacology in Erlangen coordinates the Pharmacology / Pharmacy work packages of POLAR.

The Chair participates in a continuing medical education program of the Center of Clinical Studies (CCS) in Good Clinical Practice for physicians, as required for clinical trials of medicines, and medicinal products.

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

Gessner A, König J, Fromm MF. Clinical aspects of transporter-mediated drug-drug interactions. Clin Pharmacol Ther, 2019, 105: 1386-1394

Schlichtig K, Dürr P, Dörje F, Fromm MF. New oral anti-cancer drugs and medication safety. Dtsch Arztebl Int, 2019, 116: 775-782

Gessner A, Mieth M, Auge D, Chafai A, Müller F, Fromm MF, Maas R. Establishment of reference values for the lysine acetylation marker N^{ε}-acetyllysine in small volume human plasma samples by a multi-target LC-MS/MS method. Amino Acids, 2019, 51: 1259-1271

Taghikhani E, Maas R, Taudte RV, Gessner A, Fromm MF, König J. Vectorial transport of the arginine derivatives asymmetric dimethylarginine (ADMA) and L-homoarginine by OATP4C1 and P-glycoprotein studied in double-transfected MDCK cells. Amino Acids, 2020, 52: 975-985

Gessner A, di Giuseppe R, Koch M, Fromm MF, Lieb W, Maas R. Trimethylamine-N-oxide (TMAO) determined by LC-MS/MS: distribution and correlates in the population-based PopGen cohort. Clin Chem Lab Med, 2020, 58: 733-740

Wiebe ST, Giessmann T, Hohl K, Schmidt-Gerets S, Hauel E, Jambrecina A, Bader K, Ishiguro N, Taub ME, Sharma A, Ebner T, Mikus G, Fromm MF, Müller F, Stopfer P Validation of a drug transporter probe cocktail using the prototypical inhibitors rifampin, probenecid, verapamil, and cimetidine. Clin Pharmacokinet, 2020, 59: 1627-1639

International cooperations
Prof. J. Backman, Prof. M. Niemi, University of Helsinki, Helsinki, Finland,

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

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

Prof. R.L. Woosley, The University of Arizona, Phoenix, USA,

Dr. J.A. Zerillo, Harvard Medical School, Boston, USA