SAPhS
Swiss Academy
of Pharmaceutical
Sciences
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11th Swiss Pharma Science Day 2018

Wednesday, August 22, 2018

University of Bern, Langhans Auditorium, Pathology Building and House of the University of Bern

Intention

The SWISS PHARMA SCIENCE DAY (SPhSD) is an annual event of the Swiss Academy of Pharmaceutical Sciences (SAPhS, www.saphw.ch). The 1st SPhSD was held on October 9, 2008, at the University of Bern. For congress reports 2008-2017 including all lecture and poster abstracts see www.saphw.ch. The SPhSD offers a platform to present, in form of a poster session, the latest research results of Master and PhD students, as well as Post-Docs of all the three Swiss Academic Institutions for Pharmaceutical Sciences, i.e. ETH Zurich, School of Pharmaceutical Sciences of the Universities of Geneva and Lausanne (EPGL) in Geneva and the University of Basel. Master students of the Universities of Applied Sciences, i.e. FHNW (School of Life Sciences, Muttenz) and ZHAW (Life Sciences and Facility Management, Institute of Biotechnology, Wädenswil) are also invited to participate in this event.

The poster session is embedded in a series of lectures given by invited distinguished scientists representing the broad field of pharmaceutical sciences, such as Pharmaceutical Biology, Biotechnology, Technology, Chemistry, Analytics, Engineering, Pharmacology, or Molecular Biology.

One of the primary goals of the SPhSD is to further stimulate professional and social contacts between the students still undergoing training and Alumni, having already a position in industry, hospital, public health administration or public pharmacy. Thus, cooperation and networking between the different institutions in academia and industry and the different fields of pharmaceutical sciences is being promoted.

Last but not least, the SPhSD represents an ideal platform to meet young engineers and scientists, who may be recruited for a position in the academia, hospital, industry, public health administration or public pharmacy.

Organizing Committee:

Prof. Dr. Rudolf Brenneisen, SAPhS, Secretary General, Bern

saphw@saphw.ch

Prof. Dr. Gerrit Borchard, SAPhS, President

School of Pharmaceutical Sciences EPGL, University of Geneva

gerrit.borchard@unige.ch

Program

«Cancer»

9:00-9:30 h	**Registration, Coffee**
9:30-10:00 h	**Addresses of Welcome** **Prof. Dr. Gerrit Borchard** **University of Geneva, President SAPhS** **Prof. Dr. Rudolf Brenneisen** **Secretary General SAPhS** **Dr. med. h.c. Uwe E. Jocham** **CEO Inselspital / Spitalgruppe Bern**
	Plenary Lectures **Chair: Prof. Dr. Roger Schibli, ETH Zurich**
10:00-10:45 h	**Keynote Lecture 1: Public Health** **Dr. sc.nat. Michael Röthlisberger** **Nationale Strategie gegen Krebs, Oncosuisse:** **«The Swiss National Strategy Against Cancer»**
10:45-11:30 h	**Lecture 2: Nanomedicines** **Dr. Scott McNeil** **NCL-NCI Frederick MD, U.S.A.:** **«Preclinical Evaluation Strategies for Nanomedicines and Other Non-Biological Complex Drugs»**

Program (cont.)

11:30-12:15 h	Lecture 3: Medicinal Chemistry Prof. Dr. Daniel Rauh Technical University Dortmund, Germany «Lessons to be Learned: The Molecular Basis of Kinase-Targeted Therapies and Drug Resistance in Non-Small Cell Lung Cancer»
12:15-13:30 h	Lunch
13:30-15:00 h	Poster Session
	Plenary Lectures (cont.) Chair: Prof. Dr. Norbert Lange, University of Geneva
15:00-15:45 h	Lecture 4: Clinical Pharmacology Prof. Dr. pharm. et med. Stephan Krähenbühl University Hospital & University of Basel: «Development of Oral LFA-1 Inhibitors»
15:45-16:30 h	Lecture 5: Clinical Outpatient Pharmacy Dr. Marie-Paule Schneider Policlinique Médicale Universitaire and EPGL University of Geneva: «Nonadherence to Oral Targeted Anticancer Drugs: What's the Problem and How to Address It ?»

Program (cont.)

16:30-17:00 h	Coffee
17:00-17:30 h	Award Ceremonies
17:30-17:45 h	Closing Remarks Prof. Dr. Rudolf Brenneisen, Secretary Gen. SAPhS
18:00-19:00 h	Apéro at the House of the University of Bern

Sponsors

Swiss Industry Science Fund (SISF)
Platin Sponsor (to be confirmed)

AKB-Stiftung zur Förderung des Pharmazeutischen Nachwuchses
Gold Sponsor
Sponsoring 1st poster prize and lecture of Prof. S. Krähenbühl

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Sponsoring 3rd Poster Prize

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Lectures

L-1

Dr. sc.nat. Michael Röthlisberger, Nationale Strategie gegen Krebs, Oncosuisse

CV:

Geburtsdatum	4. Dezember 1978
Staatsangehörigkeit	CH
Kinder	Tian (12.2013) & Luk (3.2016)
Adresse	Bachmattstrasse 23 8048 Zürich
Telefon	078 827 25 55
E-Mail:	mroethli@gmail.com

Berufliche Tätigkeit

Seit 2017	Co-Leiter Gesamtprojekt «Nationale Strategie gegen Krebs» Oncosuisse / Krebsliga Schweiz im Auftrag von Bund & Kantonen www.nsk-krebsstrategie.ch
2016-2017	Forschung, Innovation & Entwicklung, Krebsliga Schweiz www.krebsliga.ch
2015-2016	Leiter Ressort Forschung, Schweizerische Akademie der Medizinischen Wissenschaften SAMW www.samw.ch
2013-2015	Ressort Forschung, Schweizerische Akademie der Medizinischen Wissenschaften SAMW
2011 - 2013	Projektleiter Dialog Wissenschaft-Gesellschaft, Stiftung Science et Cité (Kompetenzzentrum für Dialog der Akademien der Wissenschaften Schweiz)

Ausbildung

Diplom & Doktorat 2001 - 2009	Diplomstudium & Doktorat in der Molekularbiologie / Krebs Grundlagenforschung, Gruppe Konrad Basler, Universität Zürich, „A targeted Knock-Out of the Drosophila TNF-Receptor Grindelwald“ & «*A protease that regulates Drosophila BMP signaling and a microarray based screen for Targets of Drosophila BMP signaling*»
SNF-Programm: 2005 - 2009	NCCR Frontiers in Genetics Doctoral School,
Publikation:	«*The Drosophila TNF receptor Grindelwald couples loss of cell polarity and neoplastic growth*», Nature 522, 482–486 (25 June 2015)

Lecture Abstract:

«The Swiss National Strategy Against Cancer»

In order to coordinate projects and players in the cancer field on a national level, the Swiss governement together with the cantonal Health Directors mandated Oncocuisse to design and run the Swiss National Cancer Plan (Nationale Strategie gegen Krebs NSK) in 2014. Oncosuisse is a consortium of seven leading swiss cancer institutions.
The ongoing projects are divided into the areas prevention/early detection, care/aftercare and research/data, respectively. In total there are 28 activities, involving more than 50 partner-institutions. Apart from these well defined projects, the NSK has the task to prepare organisatorial structures and networks that will guarantee the continuation of national coordination in cancer projects after the strategy will be finished in 2020. In this lecture you will be given an overview regarding structure, projects and (future) challenges.

Dr. Scott McNeil, Nanotechnology Characterization Laboratory, Cancer Research Technology Program, Leidos Biomedical Research, Inc., Frederick National Lab, Frederick, MD 21702, U.S.A.

CV:

Dr. McNeil serves as the Director of the Nanotechnology Characterization Laboratory (NCL) for Leidos Biomedical Research at the Frederick National Laboratory for Cancer Research, where he coordinates preclinical characterization of nanotech cancer therapeutics and diagnostics. At the NCL, Dr. McNeil leads a team of scientists responsible for testing candidate nanotech drugs and diagnostics, evaluating safety and efficacy, and assisting with product development -- from discovery-level, through scale-up and into clinical trials. NCL has assisted in characterization and evaluation of nearly 400 nanotechnology products, several of which are now in human clinical trials.

Dr. McNeil is a member of several working groups on nanomedicine, environmental health and safety, and other nanotechnology issues. He is an invited speaker to numerous nanotechnology-related conferences and has several patents pending related to nanotechnology and biotechnology. He is also a Vice President of Leidos Biomedical Research.

Prior to establishing the NCL, he served as a Senior Scientist in the Nanotech Initiatives Division at SAIC-Frederick where he transitioned basic nanotechnology research to government and commercial markets. He advises industry, State and US Governments on the development of nanotechnology and is a member of several governmental and industrial working groups related to nanotechnology policy, standardization and commercialization. Dr. McNeil's professional career includes tenure as an Army Officer, with tours as Chief of Biochemistry at Tripler Army Medical Center, and as a Combat Arms officer during the Gulf War. He received his bachelor's degree in chemistry from Portland State University and his doctorate in cell biology from Oregon Health Sciences University.

Lecture Abstract:

«Pre-Clinical Evaluation Strategies for Nanomedicines and Other Non-Biological Complex Drugs»

Preclinical characterization enables drug developers to identify features of the formulation that are necessary for its intended therapeutic function and safety profile in the clinic. These critical quality attributes (CQA) define the biological safety and efficacy of the drug product. However, non-biological complex drugs (NBCDs) are intricate formulations, composed of multiple components, with inherent overall polydispersity. This complexity highlights the challenges in identifying the critical quality attributes of NBCDs, as well as defining bioequivalence during generic nanomedicine development. The Nanotechnology Characterization Lab (NCL) leverages over 14 years of direct preclinical experience with a diverse range of nano-based platforms and therapeutic products to develop methods aimed at addressing the regulatory questions and commercialization of nanomedicine products. This presentation will discuss NCL's experience with the current issues facing nanomedicine and generic nanomedicine development, strategies in the preclinical characterization of NBCDs, and the advancing collection of assays being developed to meet the evolving needs of drug developers.

Keywords: nanotechnology, bioequivalence, regulatory, CQA, NBCDs

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Prof. Dr. Daniel Rauh, Department of Chemistry and Chemical Biology, TU Dortmund University, Dortmund, Germany

CV:

Daniel Rauh, Univ.-Prof. Dr. rer. nat.

Technische Universität Dortmund
Fakultät für Chemie und Chemische Biologie
Otto-Hahn-Strasse 4a
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Phone: + 231 - 755 - 7056
daniel.rauh@tu-dortmund.de

Date of Birth:	August 3rd, 1972
Place of Birth:	Frankfurt am Main, Germany
Nationality:	German
Marital status:	Married, two children

Education

1993	Abitur, Peter-Petersen-Schule, Hamburg
1993 – 1994	Military Service, Bundesmarine, Flensburg

University career

1994 – 1998	Pharmacy at the Ernst-Moritz-Arndt University Greifswald, Germany State Examination in Pharmacy
12/1998 – 06/1999	Diploma thesis *Design and synthesis of new serine-protease inhibitors based on natural products* under the supervision of PD Dr. Gregor Radau in the group of Prof. Dr. Hans-Hartwig Otto, Institute for Medicinal Chemistry, Ernst-Moritz-Arndt University, Greifswald, Germany
06/1999	Dipl.-Pharm.
02/2000	Approbation pharmacist, (Apotheker)

Ph.D. thesis

01/2000 – 12/2002	Ph.D. thesis *Trypsin Mutants for Structure-Based Drug Design: Expression, Refolding and Crystallization* under the supervision of Prof. Milton Stubbs in the group of Prof. Dr. Gerhard Klebe, Institute for Pharmaceutical Chemistry, Phillips-University Marburg, Germany
09/2002	Research fellow with Jennifer Harris, Ph.D., Genomics Institute of the Novartis Research Foundation (GNF), San Diego, USA. *Profiling serine-protease specificity with fluorogenic peptide substrates*
03/2003	Dr. rer. nat., March 4th 2003, *summa cum laude*

Postdoctoral projects

01/2003 – 03/2004	Postdoctoral Fellow with Prof. Dr. Milton T. Stubbs, Institute of Biotechnology, Department of Physical Biotechnology, Martin-Luther-Universität Halle-Wittenberg, Germany.
04/2004 – 04/2006	Postdoctoral Fellow with Prof. Kevan M. Shokat, Howard Hughes Medical Institute, Department of Cellular and Molecular Pharmacology, University of California San Francisco, USA.

Independent research

04/2006 – 10/2010	Independent Group Leader at the Chemical Genomics Centre of the Max Planck Society, Dortmund, Germany
11/2010 – 07/2013	W2 Professor for Chemical Biology and Biochemistry at the TU Dortmund University, Germany
since 08/2013	W3 Professor, Chair for Medicinal Chemistry and Chemical Biology at the TU Dortmund University, Germany

Awards

2010	Innovation-Prize for Medicinal and Pharmaceutical Chemistry of the German Chemical Society (Innovationspreis in Medizinisch und Pharmazeutischer Chemie der GDCh)
2013	Novartis Early Career Award in Organic Chemistry
2015	Prize of the Berlin-Bradenburgischen Akademie der Wissenschaften gestiftet von der Monika Kutzner Stiftung zur Förderung der Krebsforschung
2017	Prize of the Mercator Research Center Ruhr

Activities

since 08/2012	Associate Editor for ACS Chemical Biology
May 2014	Co-founder, Integrated Research Center for Active Pharmaceutical Ingredients at the TU Dortmund University
since 12/2015	Chairman of the selection committee of the Klaus-Grohe Prize of the German Chemical Society (GDCh)
since 01/2017	Coordinator of the “Drug Discovery Hub Dortmund at the ZIW” (DDHD)

Lecture Abstract:

«Lessons to be Learned: The Molecular Basis of Kinase-Targeted Therapies and Drug Resistance in Non-Small Cell Lung Cancer»

The treatment of genetically defined cancer is currently experiencing a revolution. Over the last decade, the knowledge gained about the biochemical features of biomarkers and their predictive abilities has led to the development of targeted small-molecule inhibitors that present an alternative to harsh chemotherapy. The use of these new therapies has improved the quality of life and increased the survival of patients. The occurrence of inevitable drug resistance requires the constant development of precision medicine. The detailed understanding of the target biology and the search for innovative chemical approaches has encouraged investigations in this field [1]. Against this background, research in our lab is dedicated to medicinal chemistry, compound screening technologies and chemical biology approaches. It is our goal to develop, synthesize and facilitate desperately needed tools to study target protein function in cells and organisms to push research to exciting new frontiers. In our research, we employ organic synthesis [2], biochemical and cellular compound screening [3], structural biology, structure-based design as well as target identification [4] for the development of inhibitors and functional probes to perturb proteins of interest [5]. A strong focus in the lab is on personalized medicine for the treatment of cancer [6]. Here, we closely collaborate with clinical oncologists to better understand the mechanisms of resistance and to develop compounds to overcome acquired drug resistance in non-small-cell lung cancer [7] and gastrointestinal stromal tumors [8]. We are motivated that our techniques and investigations will lead to a better understanding of the molecular and cellular causes of fatal diseases and stimulate the development of new drugs. We are also interested in developing means to bridge the gap between basic university-based research and practical application. We recently established the «Zentrum für integrierte Wirkstoffforschung (ZIW)» as well as the «Drug Discovery Hub Dortmund (DDHD)». Some of the our endeavors will be outlined during the talk.

Keywords: protein kinases, academic drug development, inhibitors, covalent, drug-target residence time

References:

[1] Lategahn J et al. Angew Chem Int Ed Engl 2018, in press.
[2] Engel J et al. Angew Chem Int Ed Engl 2016; 55: 10909-12.
[3] a) Mayer-Wrangowski SC et al. Angew Chem Int Ed Engl 2015; 54: 4379-82.
b) Schneider R et al. J Am Chem Soc 2013; 135: 6838-41.
c) Simard JR et al. Nat Chem Biol 2009; 5: 394-6.
[4] Bührmann M et al. Angew Chem Int Ed Engl 2017; 56: 13232-36.
[5] a) Fang Z et al. ACS Chem Biol 2015; 10: 279-88.
b) Fang Z et al. ACS Chem Biol 2013; 8: 58-70.
[6] Weisner J et al. Angew Chem Int Ed Engl 2015; 54: 10313-16.
[7] a) Engel J. J Med Chem 2017; 60: 7725-7744.
b) Sos ML et al. Cancer Res 2010; 70: 868-74.
[8] a) Kaitsiotou H. J Med Chem 2017; 60: 8801-15.
b) Richters A et al. J Med Chem 2013; 56: 5757-72.

Prof. Dr. pharm. et med. Stephan Krähenbühl, University Hospital & University of Basel

CV:

Stephan Krähenbühl, born November 29, 1953
Business address: Clinical Pharmacology & Toxicology, University Hospital, CH-4031 Basel, Switzerland
Tel: +41 61 265 47 35, Fax: +41 61 265 45 60, e-mail: Kraehenbuehl@uhbs.ch

Education and employment:

- 1972 - 1978: School of Pharmacy, University of Berne, Diploma 1978
- October 1978 - October 1981: Ph.D. thesis in Pharmaceutical Sciences
- 1979 - 1985: School of Medicine, University of Berne, Diploma 1985
- 1985: M.D. at the Institute of Clinical Pharmacology of the University of Berne
- January 1986 - December 1986: Internship, Internal Medicine, Bezirksspital Langnau
- January 1987 - February 1989: Fellow, Institute of Clinical Pharmacology, University of Berne
- March 1989 - March 1991: Fellow und Senior Fellow, Department for Clinical Pharmacology, Case Western Reserve University, Cleveland, Ohio 44106
- April 1991 - March 1993: Resident, Department of Internal Medicine, Inselspital, Berne
- April 1993 - March 1997: Senior Physician, Division of Clinical Pharmacology & Toxicology, Department of Internal Medicine, University Hospital Zürich
- April 1997 – December 1999: Senior Physician, Department of Internal Medicine, General Internal Medicine, Inselspital Berne and 1st Senior Physician, Clinical Pharmacology & Toxicology, University of Berne
- January 2000 – today: Head of the Division of Clinical Pharmacology & Toxicology and attending chief physician at the Clinics of Internal Medicine at the University Hospital of Basel. Double professorship in the medical faculty and in the faculty of natural sciences
- January 2002 – today: Head of the human medical experts committee of Swissmedic

Professional Training and Experiences:

- April 1978: Swiss Federal Diploma in Pharmacy (University of Berne)
- November 1985: Swiss Medical Diploma (University of Berne)
- April 1993: Specialist for Internal Medicine (FMH)
- May 1994: Specialist for Clinical Pharmacology (FMH)
- October 1997: FAMH Title in Clinical Chemistry
- April 1997-December 1999: Training in Hepatology (there is no title in Hepatology)

Scientific Training and Awards:

- November 1981: PhD in Pharmaceutical Sciences (University of Berne), Thesis: "Entwicklung eines neuen Enzymassays für die N-Acetylglutamat-Synthetase: Bestimmung der Enzymaktivität in Geweben von Ratte und Mensch sowie Untersuchung der kinetischen Eigenschaften von menschlichem, aufgereinigtem Enzym."
- December 1985: MD (University of Berne), Thesis: "Defective bile acid transport in an animal model of defective debrisoquine hydroxylation."
- May 1988: Young Investigator Award of the American Gastroenterology Association (AGA) for: „Effect of secretin on bile formation in rats with cirrhosis of the liver: Structure-function relationship.„
- November 1993: Venia Legendi in the fields of Internal Medicine and Clinical Pharmacology (University of Zürich):"Alterations in mitochondrial function and morphology in chronic liver disease: pathogenesis and potential for therapeutic intervention."
- October 1996: Special award of the Swiss Society of Gastroenterology and Hepatology (SGGH) for: „Reduced antioxidative capacity in liver mitochondria from bile duct ligated rats„
- October 1996: Special award of the Swiss Society of Gastroenterology and Hepatology (SGGH) for a poster presentation: „Der Benzoesäuremetabolismus ist ein Mass für die mitochondriale Funktion in cholestatischen Ratten„
- November 1997: Research award of the Swiss Society for Research in Surgery for: „Benzoic acid metabolism reflects hepatic mitochondrial function in rats with long-term extrahepatic cholestasis.“
- June 1998: Research award of the Swiss Society of Surgery for: „Rapid normalization of hepatic glycogen metabolism in rats with long-term bile duct ligation after biliodigestive anastomosis“
- September 1999: Professor for Clinical Pharmacology and Internal Medicine, University of Berne
- Since January 2000: Professor for Clinical Pharmacology/Toxicology and Internal Medicine, University of Basel
- June 2005: Research award of the Swiss Society of Cardiology for: „Kinetics and dynamics of furosemide in

healthy volunteers after oral or sublingual administration“

GCP experience/clinical studies:
Theoretical knowledge in GCP by training in Clinical Pharmacology & Toxicology (requirement for obtaining title). Extensive practical experience by many self-conducted clinical studies.

Teaching:
- Lectures and courses in clinical pharmacology & toxicology for medical students and pharmacy students since 1993
- Approximately 50 dissertations and 8 habilitations since 1993

Publications:
More than 300 original publications listed in PubMed. Areas of special interest are drug-drug interactions, dose adjustment in organ failure, toxicological mechanisms, and energy metabolism.

Lecture Abstract:

«Development of Oral LFA-1 Inhibitors»

The leucocyte function-associated antigen-1 (LFA-1) is an integrin expressed on leucocytes that plays a crucial role in T cell adhesion, migration and immunological synapse (IS) formation. LFA-1 is a heterodimeric glycoprotein containing an α_L and a β_2 chain. The principle ligand of LFA-1 is ICAM-1 (expressed mainly on endothelia but also on other cells) and the binding site of ICAM-1 is on the α_L chain. Normally, LFA-1 is in the inactive or bent state, hiding the ICAM-1 binding site. Activators such as chemokines cause a conformational change, which opens the α_L-chain allowing contact between the active site of LFA-1 and ICAM-1. Considering its role in cell adhesion and migration, LFA-1 is an interesting drug target. The aim of the current project was to develop a small molecular weight allosteric inhibitor of the activation of the binding site on the α_L chain of LFA-1. Based on the available information about the 3-dimensional structure of LFA-1, we obtained a lead compound of a LFA-1 antagonist using molecular modeling. For testing the IC_{50} for LFA-1 inhibition, we had to develop an in vitro assay based on the interaction of LFA-1 on lymphocytes and ICAM-1 attached to the wall of reagent tubes. More than 200 compounds were synthetized and investigated, eventually resulting in a compound inhibiting LFA-1 activation in the low nanomolar range. The pharmacokinetics in mice showed 100% bioavailability and a half-life in the range of 5 hours. Acute toxicity in mice was negligible at concentrations up to 10 micromolar and the substance was not degraded by human liver microsomes. The selectivity in inhibition of LFA-1 was excellent and, compared to monoclonal antibodies and low molecular weight inhibitors of the β_2-chain, lymphocytes exposed to the developed α_L-chain inhibitor showed no activation. Proof of concept was obtained in a rabbit model of uveitis, which could be prevented by application of the newly developed inhibitor. After finishing a state of the art toxicology program, phase I studies are planned in healthy humans before proof-of-concept studies can be performed in patients with uveitis.

Dr. Marie-Paule Schneider, Policlinique Médicale Universitaire and EPGL University of Geneva

CV:

CURRICULUM VITAE

Marie Paule Schneider Voirol, 19.11.1968, married, 3 children, Swiss nationality

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ORCID ID http://orcid.org/0000-0002-7557-9278

RESEARCH & CLINICAL PHARMACY EXPERIENCE

2018 -	Titular professor of medication adherence and interprofessionnality (0.5 FTE) at the School of pharmaceutical sciences, University of Geneva, University of Lausanne (EPGL), Switzerland
2018 -	Director of pharma24 (0.4 FTE), Community academic pharmacy, Geneva
2012-2018	Senior research associate (0.5 FTE) at the School of pharmaceutical sciences, University of Geneva, University of Lausanne (EPGL), Switzerland.
2006-2018	Deputy head (0.4 FTE) of the Centre of community pharmacy & head of its research unit, Dept of ambulatory care & community medicine (PMU), University of Lausanne.
2003-2006	Senior researcher, PMU, University of Lausanne.
2000-2003	Scientific advisor (0.5 FTE) at Aprex Ltd, San Francisco, USA
1995-2000	Doctoral position (0.7 FTE), School of Pharmacy, University of Lausanne & pharmacist (0.3 FTE), PMU, University of Lausanne
1998-2000	Member of the research ethics committee of the University Hospital (CHUV)

RESEARCH INTERESTS

My research focuses on medication adherence in chronic diseases and aims at better understanding this behaviour, its determinants and consequences for the patients and the healthcare system through validated measure methodology. I am collecting routine-based research data thanks to a unique medication adherence clinic, which I set up scientifically in 2003 (PMU - University of Lausanne). I am also managing the research quality project of the PMU. I am a regular reviewer for *International Journal of Clinical Pharmacy (medication adherence)* and several other clinical pharmacy and HIV journals.

GRANTS AS PRIMARY APPLICANT

- Grant from *le Fonds qualité et recherche de SANTÉSUISSE, CURAFUTURA ET PHARMASUISSE* : 'Medication adherence in diabetes and renal failure' (CHF 110'000 ; March 2018) ;
- Grant from the Swiss Cancer Research Foundation - Health Services Research 'Optimizing targeted anti-cancer therapies: from better medication adherence to individualized treatments' (HSR-4077-11-2016) (CHF 248'200; April 2017);
- Grants from the Swiss National Foundation (CHF 10'000 as deficit warranty), from the Faculty of Science (CHF 4'900) and the administrative commission (CHF 5'000) of the University of Geneva for the organization of 2014 ESPACOMP annual meeting in Lausanne;
- Grant from the *Bureau qualité stratégie* CHUV, Lausanne (2010) (CHF 50'000) for developing a research quality project;
- Grants from the Swiss HIV Cohort Study (2006) (CHF 50'000); (2015) (CHF 9'500).

SCIENTIFIC OUTPUT

Author of 39 publications of peer-reviewed journals, 6 book chapters, 21 publications for didactic purposes, over 30 invited presentations, co-supervisor of 7 PhD theses, and supervisor of 8 master theses.

NETWORK PARTICIPATION I am an executive and board member of the European Society for Patient Adherence, Compliance and Persistence (ESPACOMP); I am leading the 14-hr ESPACOMP education course in medication adherence. I was the guest editor with Prof. Parisa Aslani (University of Sydney) for a series of papers on adherence in the journal Pharmacy Practice (2008 and 2009) and a special issue on medication adherence in International Journal of Clinical Pharmacy (2013).

EDUCATION

2011-2012	**Certificate of Advanced studies (CAS) in clinical research,** University of Lausanne.
2011-	Member of the **Motivational Interviewing Network of Trainers Incorporated** (TNT).
2010	**Basic education for clinical investigators** (Swissmedic), Lausanne, CHUV, 06-08.09.2010
1995-2000	**PhD. Thesis,** Pharmacy, Dept of ambulatory care & community medicine, Lausanne. Title: 'Managing patient non-adherence to drug therapy: the use of new electronic technologies' (Supervisor: Prof. Michel Burnier, Faculty of medicine, UniL). *PhD degree in **Pharmaceutical Sciences,*** University of Lausanne 10.09.2003
1993-1994	**Postgraduate education in hospital pharmacy**, Pharmacy, CHUV, Lausanne. ***French speaking Swiss Universities Certificate in Hospital Pharmacy,*** University of Lausanne 07.12.1994
1988-1993	**Pharmacy student**, University of Lausanne ***Swiss Federal Degree in Pharmacy,*** University of Lausanne 28.10.1993

TEACHING AND MENTORSHIP

SUPERVISION OF DOCTORAL AND MASTER'S THESES

PhDs (joint direction with Prof. O. Bugnon):

- One on-going theses: Jennifer CELIO.
- Susan KAMAL. *Adherence to Antiretrovirals among HIV-infected Adults in Lausanne*, University of Geneva - 2018
- Mélanie LELUBRE. *Implementation Study of Professional Pharmacy Services in Community Pharmacies.* Université Libre de Bruxelles and University of Geneva – 2018.
- Aurélie ROTZINGER GERTSCH. *Adhésion médicamenteuse lors de l'infection au VIH : cinq études tirées de la pratique quotidienne d'une consultation d'adhésion.* University of Geneva – 2015.
- Julien MARQUIS. *Implementation of a medication adherence enhancing program for cardiovascular patients in community pharmacies*. University of Geneva – 2014 – Thesis Nr 4732.
- Isabelle KRUMMENACHER. *Evaluation of an interdisciplinary intervention programme for therapeutic adherence among HIV-positive patients*. University of Geneva – 2010 – Thesis Nr 4176.
- Hugo FIGUEIREDO. *The dispensing pharmacist's contribution to the correct use of medicines: examples of two interdisciplinary programmes on the prescription of antibiotics and patient adherence to antihypertensives*. University of Geneva – 2010.

Master theses:

- Carla MOYANO. Evaluation d'applications mobiles smartphone de soutien de l'adhésion thérapeutique – 2017 (1st prize OFAC Pharmacy Awards)
- Mickaël RYCHEN, Accuracy of measures of medication adherence to antiretroviral therapy. University of Geneva – 2016.
- Sabrina MAEDER. Dialyse chronique et adhésion thérapeutique *évaluation des perceptions des patients en dialyse chronique au CHUV face à leurs médicaments.* University of Geneva – 2015.
- Asemaneh SEHHAT. *Impact des troubles neurocognitifs sur l'adhésion thérapeutique chez les patients infectés par le VIH*. University of Geneva – 2015.
- Margaux RODUIT. *Etude observationnelle des prescriptions de médicaments allongeant l'intervalle QT à la Pharmacie de la PMU.* University of Geneva – 2014.
- Odile MICHEL. *Evaluation de l'adhésion thérapeutique aux traitements antirétroviraux durant la grossesse et le post-partum.* University of Geneva – 2012.
- Valérie PAYOT. *Evaluation des difficultés de déglutition des formes orales solides chez les patients à l'officine.* University of Geneva – 2010.
- Ming Yan LAU. *Analyse comparative des sujets séropositifs bénéficiant d'une consultation d'adhésion thérapeutique versus les sujets bénéficiant d'un suivi pharmaceutique standard.* University of Geneva – 2009.

TEACHING AT THE SCHOOL OF PHARMACY (EPGL), UNIVERSITY OF GENEVA

- Master level: 31 periods/year (e.g. medication adherence, motivational interviewing) & scientific supervision for the EPGL annual objective structured clinical examinations (OSCE-June).
- PhD level: quality in patient-oriented research (1ECTS)

Lecture Abstract:

«Nonadherence to Oral Targeted Anticancer Drugs: What's the Problem and How to Address It?»

In comparison to chemotherapy infusions, the increasing number of oral targeted treatments for cancer reinforces the patient's active, autonomous and responsible role in acute and long-term treatment management. Patient adherence is a complex behaviour, which revolves around three distinct and complementary components: medication initiation, medication implementation (taking the right drug, at the right dosage, with the right timing) and medication persistence (no premature treatment discontinuation).

According to the World Health Organization, the epidemic of nonadherence to treatment affects 40 to 50% of the chronic population, with drastic consequences on clinical and economic outcomes. In cancer, medication nonadherence is a determinant among others responsible for loss of response and treatment resistance. Early in the patient treatment journey, side effects to oral targeted anticancer drugs are the main determinants responsible for non-implementation, with patients adjusting their treatment, sometimes unilaterally, by postponing or skipping doses. In long-term treatments (e.g. breast cancer, leukaemia or gastrointestinal cancers), probability of treatment discontinuation increases with pill burden and with the declining threat of the disease.

This lecture will highlight important facts about medication adherence to oral targeted treatments published in the scientific literature. It will then reflect on the transfer of knowledge to the healthcare system, in particular the continuity of care between oncology centres, pharmacology units and community pharmacy. The Lausanne Interprofessional Medication Adherence Program (IMAP) will be presented as well as our on-going, randomized clinical trial in health service research, integrating pharmacokinetic-pharmacodynamic knowledge and patient medication adherence, to allow the best patient experience with oral targeted treatments.

Posters

P-1

Selective HDAC6 Inhibitor Activity in a Multiple Myeloma 3D Co-Culture Model

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Introduction: Multiple myeloma (MM) is a hematological cancer that despite not having a strong incidence, displays a high rate of relapse and resistance to conventional therapies. It is therefore very important to find new therapeutic strategies to overcome both situations. Currently, most of the MM treatments involve the use of proteasome inhibitors, such as bortezomib. Resistance to those is mostly mediated by histone deacetylase (HDAC) 6 through the aggresome pathway. Pan-HDAC inhibitors, e.g. vorinostat and panobinostat, are already being used in combination with other drugs to treat MM. Despite being very effective and allowing to overcome resistance to bortezomib, these drugs display high toxicity and consequently numerous side effects. These side effects may be due to the lack of specificity of pan-HDAC inhibitors since they inhibit not only HDAC6 but also all classes of HDACs leading to a strong imbalance affecting multiple pathways. Therefore, selective HDAC6 inhibitors should be as effective as non-selective inhibitors and at the same time have a lower global toxicity. Ricolinostat, the first selective HDAC6 inhibitor in clinical trials, exhibited an improved safety profile when compared to panobinostat, and at the same time was able to overcome resistance to bortezomib. Hence, the use of selective HDAC6 inhibitors in combination with proteasome inhibitors or other classes of drugs may be a very promising strategy.
Aims: To evaluate the cytotoxic activity of selective HDAC6 inhibitors, alone or in combination, in a MM 3D co-culture model.
Methods: MM tumors are very complex entities. To mimic the tumor heterogeneity and the microenvironment, a 3D co-culture model of MM is being used to screen HDAC6 inhibitors alone or in combination with other classes of compounds. The screen involved both viability assays using CellTiter-Glo 3D and HDAC6 inhibition using a UHPLC-MS-based method.
Results: These assays led to the identification of good HDAC6 inhibitors that were less toxic when compared to panobinostat. The compounds were also tested for HDAC1 inhibition to confirm their selectivity for HDAC6 in a complex relevant *in vitro* model. PB 8-140 and PB 10-8, two HDAC6 inhibitors, displayed low toxicity towards MM cells with an HDAC6 inhibitory activity similar to tubastatin A, the positive control.
Conclusions: Therefore, these are good candidates for combination studies with other classes of compounds, e.g. proteasome inhibitors, with the main goal of contributing to control MM.

Keywords: multiple myeloma, 3D co-culture model, HDAC inhibitors, HDAC6

P-2

In Vitro Investigation of CYP3A4/5 and CYP2D6 Mediated Inhibition Potentials of Standardized Mistletoe (*Viscum album*) Preparations on Main Tamoxifen Metabolite: (E/Z)-Endoxifen

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Introduction: *Viscum album* L. extract (VAE) is often used by breast cancer patients as complementary treatment to chemotherapy [1]. Tamoxifen is one of the most widely used drugs for the treatment of estrogen receptor-positive breast cancer and is therefore often taken together with VAE. Tamoxifen is a prodrug, and formation of the main active metabolite (E/Z)-endoxifen is catalyzed by CYP2D6 and CYP3A4/5. So far, little is known about the effect of VAE on cytochrome (CYP) isoenzymes responsible for the metabolization of tamoxifen and, thus, possible herb-drug interactions (HDIs).
Aims: The aim was to investigate *in vitro* the potential inhibition of CYP3A4/5 and CYP2D6 in the presence of commercial mistletoe preparations, Iscador® P 10 mg, Qu 5 mg and M 5 mg.
Methods: Reliable UPLC-MS/MS methods were developed for the following specific CYP substrates: tamoxifen (3A4/5 and 2D6), dextromethorphan (2D6), testosterone (3A4/5) and corresponding metabolites: endoxifen, dextrorphan, 6β-hydroxytestosterone in order to support CYP inhibition assays. Pooled human liver microsomes (50-donor mixed gender) and specific inhibitors (ketoconazole for 3A4/5 and quinidine for 2D6) were selected to determine each specific substrate *in vitro* inhibition profile.
Results: For all investigated mistletoe preparations (VAEP, VAEQ, and VAEM), no statistically significant inhibition of CYP3A4/5 and CYP2D6 was detected *in vitro* at physiologically relevant concentrations.
Conclusions: The *in vitro* results support the safety of the use of marketed mistletoe extracts to treat cancer related fatigue in breast cancer patients receiving tamoxifen.

Keywords: herb-drug interactions, mistletoe, *Viscum album*, Iscador®, CYP inhibition assay, breast cancer

Reference:
[1] Balneaves LG et al. Patient Educ Couns 1999; 38:143-153.

P-3

LST-3TM12 is Regulated by the Farnesoid X Receptor in Human Hepatocytes

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Introduction: We have recently reported, that LST-3TM12 is a functional transporter and a member of the OATP1B (*SLCO1B*) –family, which transports estradiol 17β-glucuronide and dehydroepiandrosterone sulfate [1]. A particularity of LST-3TM12 is, that *SLCO1B3* (OATP1B3) encodes for its initial 333 base pairs, while the rest of the mRNA originates from the gene locus *SLCO1B7,* whereby suggesting that transcription of LST-3TM12 is controlled by the promoter of OATP1B3. One nuclear receptor shown to modulate OATP1B3 transcription and expression is the bile acid sensor farnesoid X receptor (FXR, *NR1H4*) [2].
Aims: It was aim of this study to elucidate whether *LST-3TM12* transcription depends on transcriptional activation of *SLCO1B3.* Moreover, the involvement of LST-3TM12 in the FXR network was intended to be explored.
Methods: The 5'-untranslated region of LST-3TM12 was unraveled by 5'-RACE (rapid amplification of cDNA ends). *SLCO1B3*-siRNA experiments were conducted to investigate the transcriptional association of *SLCO1B3* and *LST-3TM12*. After FXR induction, transcription of *LST-3TM12* and *SLCO1B7* was determined by quantitative real-time PCR. Interaction of LST-3TM12 with bile acids was assessed in transport experiments.
Results: *SLCO1B3* and *LST-3TM12* have the same 5'-UTR suggesting that transcription of both mRNAs is governed by the OATP1B3 promoter. Silencing of *SLCO1B3* by a siRNA directed to one of its initial exons not only lowered the amount of *SLCO1B3* mRNA, but also that of *LST-3TM12* in siRNA-transfected cells. Testing the impact of FXR on *LST-3TM12* transcription revealed that *LST-3TM12* mRNA transcription was augmented to a similar extend as that of *SLCO1B3*. Finally, the observed interaction of primary and secondary bile acids with LST-3TM12 transport suggested that this transporter takes part in bile acid homeostasis, which is further supported by our findings showing direct transport of taurocholic acid by LST-3TM12.
Conclusions: Taken together our data further support the notion that LST-3TM12 is a splice variant of OATP1B3, and is regulated by FXR. Furthermore, LST-3TM12 transports taurocholate. Considering the previous finding that LST-3TM12 is localized in the endoplasmic reticulum, we hypothesize that LST-3TM12 facilitates access of bile acids to enzymes exerting their metabolic function in the lumen of the ER, such as the UDP-glucuronosyltransferases.

Keywords: FXR, SLCO1B7, SLCO1B3, LST-3TM12, organic anion transporting polypeptides

References:

[1] Malagnino V et al. Biochem Pharmacol 2017; 148: 75-87.
[2] Jung D et al . Gastroenterology 2002; 122(7): 1954-1966.
[3] Makishima M et al. Science 1999; 284(5418): 1362-1365.

P-4

In Vitro and *In Vivo* Testing of MMP-9 Sensitive PDMS-PMOXA Nanoparticles for Application in Breast Cancer

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Introduction: Cytotoxic compounds used to treat cancer are often associated with adverse effects. The development of formulations activated by tumor-specific triggers would allow a reduction of systemic exposure while maintaining therapeutic concentrations in the tumor [1]. One enzyme with proteolytic activity reported to be involved in tumor progression and assumed to be enhanced in the tumor environment is the matrix-metalloproteinase 9 (MMP9) [2].
Aims: It was the aim of the herein reported study to develop surface modified PDMS-PMOXA nanoparticles able to release their cytotoxic payload upon digestion by MMP-9.
Methods: Expression and activity of MMP-9 were determined by quantitative real-time PCR, Western Blot analysis, zymography, and ELISA. Polymersomes were characterized applying dynamic light scattering and electron microscopy. The Resazurin Fluorometric Cell Viability Kit was used to assess cytotoxic activity of the formulation. The stably transfected mKate2-MCF7 cells were generated by transfection with mKate2-pcDNA3.1, the recombinant protein was detected by real-time PCR or confocal laser scanning microscopy in injected zebrafish embryos.
Results: Applicability of an MMP-9-triggered drug delivery system was verified testing the expression of MMP-9 in human breast cancer samples. The surface-modified polymersomes were synthesized and formulated resulting in paclitaxel-loaded particles of about 220.5 ± 6.9 nm in size with a surface potential of 0.04 ± 0.007 mV. After verifying expression and activity of MMP-9 in MCF7 cells, this cell line was used for further *in vitro* analysis. Treatment of MCF7 cells with the nanoparticles significantly reduced cell viability (0.86 ± 0.08 fold of control), this effect was abolished by addition of MMP-inhibitors (1.01 ± 0.14 fold of control), suggesting proteolytic activation. In the zebrafish xenograft model, the amount of cancer cells detected by qPCR significantly decreased after treatment with PDMS-PMOXA-SRL paclitaxel polymersomes.
Conclusions: Taken together, our data suggest that nanoparticles modified with an MMP-9 labile peptide and loaded with paclitaxel can be formulated and its payload possesses pharmacological activity upon enzymatic digestion in breast cancer.

Keywords: enzyme triggered release, breast cancer, PDMS-PMOXA polymersomes, MMP-9, paclitaxel, zebrafish in vivo testing

References:

[1] Kim CS et al. Nano today. 2013; 8(4): 439-47.
[2] Van den Steen PE et al. Critical reviews in biochemistry and molecular biology 2002; 37(6): 375-536.

SwissHPN-II Study: Intermediate Results After one Year Focused on Catheter and Related Complications

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Introduction: Incidence of home parenteral nutrition (HPN) in Switzerland is about 4/a per 1 million inhabitants [1]. Although necessary, no representative national registry exists up to now to compare and evaluate treatments with other countries and healthcare systems. This SwissHPN-II study in adults implements a first, smaller, prospective study from 2013/2014 (SwissHPN-I) [1] to get a robust national registry.
Aims: This study aims to characterize adult Swiss HPN patients, their underlying diseases, HPN indications and complications, and living conditions. This intermediate analysis focusses on PN catheters and related complications, including regimen after half of the study period.
Methods: Data from a questionnaire filled every 6 months by the patient and their treating physician of 50 patients (52% women) were analyzed.
Results: Hickmann (58%), Port-a-Cath (34%), and PICC (8%) are the used central venous catheters. Except one, all patients were provided with commercial multi-chamber all-in-one nutritional admixtures from home care services. Half of the patients manage HPN administration themselves or with help of family members. Most prevalent underlying diseases are cancer (30%), Crohn's disease (14%), and bariatric surgery (12%). Mechanical and infectious catheter complications were experienced by 38% and 36% of the patients, respectively. Catheter thrombosis occurred in 16% of the patients.
Conclusion: The increased patient's number (+50%) compared to SwissHPN-I gives a representative picture of the adult SwissHPN cohort. Oncologic patients account for only one third. Mechanical and infectious catheter-related complications affected almost every third, thrombosis every sixth studied patients. More comprehensive data will be presented after the study completion.

Keywords: Swiss home parenteral nutrition, quality of life, catheter type and related complications

Reference:
[1] Aeberhard C et al. Ann Nutr Metab 2015; 67: 210-217.

P-6

Consensus Paper on Safe Refeeding Protocol in Anorexia Nervosa Patients

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Introduction: Anorexia nervosa (AN) patients are at high risk for developing refeeding syndrome (RFS) when starting refeeding. The hormonal and physiological changes occurring in AN have a great influence on metabolic response in the early replenishment phase.
Aims: The aim of this study is to provide a consensus based on current literature regarding risk factors, clinical manifestations, preventive and therapeutic methods as well as appropriate monitoring of RFS in AN patients.
Methods: We searched EMBASE and MEDLINE following the systematic literature review of Friedli et al. [1], focussing on RFS in AN patients, excluding case reports and reviews. We extracted data based on a predefined case report form.
Results: Of 4477 potential abstracts, 28 articles a total of 2471 patients were included in the evaluation (one interventional trial). Based on the results, a protocol about management of RFS will be worked out as a consensus in a network of opinion leaders.
Conclusion: The opinion of several international experts in the field will be presented as a consensus supported protocol in terms of prevention, management and monitoring of RFS in AN.

Keywords: Anorexia nervosa, management, refeeding, refeeding syndrome

Reference:
[1] Friedli N et al. Nutrition. 2017; 35:151-60.

Ketogenic Diet and its Evidence Based Therapeutic Implementation in Endocrine Diseases: a Literature Review

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Introduction: Ketogenic diets (KD) have been in clinical use for treatment of therapy-resistant epilepsy in children since the 1920. Implementation of KD in other target populations is increasingly being discussed (i.e. oncology, endocrinology).
Aims: In this literature review, we assessed the efficacy of KD for the treatment of metabolic disorders such as type 2 diabetes mellitus (T2DM) and polycystic ovary syndrome (PCOS).
Methods: We searched MEDLINE and EMBASE focussing on efficacy of KD in T2DM and PCOS, excluding case reports.
Results: A total of 271 studies for T2DM and 81 for PCOS were identified, of which 16 (8 RCT, 8 interventional studies) and 12 studies (6 RCT, 6 interventional studies) were included in the analysis. Restriction of carbohydrates without energy restriction leads to significant weight loss in most studies. In case-control studies with T2DM, KD significantly reduced HbA_{1c}-levels compared to reference diet. Fasting blood glucose levels were significantly lowered by KD across almost all studies. Moreover, positive effects of KD on insulin resistance and lipid blood profile were observed in several but not all studies. Of the 28 included studies, diet-induced ketosis was biochemically confirmed in two studies only. Inconsistency among studies mainly relate to quantity and quality of dietary fats in KD and regimes of reference diets.
Conclusion: Although preliminary evidence supporting clinical benefits of KD in T2DM and PCOS exist, study results are highly heterogenic, what makes a general recommendation difficult. To evaluate efficacy, safety and usability of KD in T2DM and PCOS, further well-designed studies are needed.

Keywords: ketogenic diet, PCOS, type 2 diabetes mellitus

P-8

A Comparison of New Drugs Approved by the FDA, the EMA, and Swissmedic: an Assessment of the International Harmonization of Drugs

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Introduction: Since 1990, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) collaborates with national and regional agencies to harmonize the requirements for registration to ensure drug efficacy, safety, and high-quality. Despite the regulatory harmonization initiatives, differences between legislation and practices of regulatory agencies persist. This study compared the time lag and differences in indications of new drugs and therapeutic biologics approved by the Food and Drug Administration (FDA), the European Medicine Agency (EMA) and Swissmedic (SMC) from 2007 to 2016 [1, 2].
Methods: The list of all new drugs and therapeutic biologics approved by the FDA, EMA and SMC in the period of 2007 to 2016 was collected from the respective websites. The study includes the following regulatory information: approvals, approval date, and complete indication of the new drugs and biologics in the assessment period. The therapeutic classes were derived from the Anatomical Therapeutic Chemical (ATC) classification system. Descriptive statistical analyses were performed for all variables. t-test and x^2-test were used to assess differences.
Results: A total of 134 new drugs and therapeutic biologics were approved by the FDA, the EMA and SMC from 2007 to 2016. Antineoplastic and immunomodulating agents represented 41% (n = 55) of the new drugs and therapeutic biologics approved by the 3 agencies. Overall, 66.4% of the drugs were first approved by the FDA, 30.6% by the EMA, and 3.0% by SMC. The difference in approval dates between SMC and the EMA ($p < 0.0001$), SMC and the FDA ($p < 0.0001$), and the FDA and the EMA ($p = 0.017$) was statistically significant. The indications approved by the FDA, the EMA, and SMC for the same drugs were similar in content for 23.1% drugs and different in 76.9% of the drugs. Significant differences in indications existed between FDA and SMC, and FDA and EMA, but not between EMA and SMC.
Conclusion: The FDA approved first most new drugs and therapeutic biologics. Significant differences in indications occurred among the 3 agencies. Despite international drug regulation harmonization trends significant differences in the characteristics of new drugs and therapeutic biologics approved by regulatory agencies persist.

Keywords: US Food and Drug Administration, European Medicines Agency, Swissmedic, drug approval, drug labeling

References:

[1] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. http://www.ich.org/home.html (24.06.2018)
[2] Zeukeng MJ, Seoane-Vazquez E, Bonnabry P. Eur J Clin Pharmacol 2018; 74: 811–818.

P-9

A Pharmaceutical Chemistry R&D Project Performed with the Students of 2nd Year Bachelor in Pharmaceutical Sciences: Synthesis of Aminopyrazole Analogues for the Treatment of Leishmaniasis

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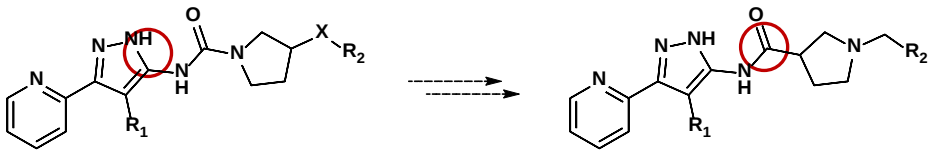
Introduction: Leishmaniasis is a neglected tropical disease, an illness that kills up to 30,000 people yearly. Existing drugs have serious drawbacks in terms of safety, resistance, stability, difficulty of administration, and cost. Thus, there is a need for new treatments. The aminopyrazole class of compounds originally from Pfizer has shown promising early profiles for the treatment of both visceral and cutaneous leishmaniasis [1,2,3].
Aim: In the frame of an Open Synthesis Network (OSN) between the University of Geneva and Drugs for Neglected Diseases initiative (DNDi), we aimed at synthetizing new aminopyrazole analogues for early stage discovery into new treatments for leishmaniasis.



DNDi lead chemotype **Targeted analogues**

Methods: In order to explore the aminopyrazole chemotypes, we set up a 5-steps synthesis starting from (R/S)-β-proline, 14 different aldehydes and 3 different aromatic cores to obtain 42 different products. The 2 key reactions are reductive amination, during which a first structural diversification occurs and the last coupling by amidation that led to the final expected compounds.
Results: The first 3 steps of synthesis led to the new compounds in high yield (14 intermediates). Despite difficulties occurring in the amidation coupling, a new valid protocol was found to obtain the expected compounds in a sufficient yield (32-36%). New condition to optimize this step are now being tested in our laboratory.
Conclusions: The open source nature of this project aims to deepen the learning of laboratory work in the context of R&D practical work. The collaborative spirit of the students has been necessary to develop a scientific rigor of work which includes the preparation and the follow-up plans of experiment. In this context, DNDi will test these analogues against leishmaniasis and the results added into a Master Data table, shared with all OSN participants.

Keywords: Leishmaniasis, DNDi, aminopyrayoles

References:
[1] Oehler RS et al. MRes Drug Discovery & Development, 2017
[2] Fernández-Llaneza D et al. MRes Drug Discovery & Development, 2017
[3] Mowbray CE et al. J Med Chem 2015; 58 (24): 9615-9624

P-10

In Vitro Characterisation of a Novel Calcification Inhibitor

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Introduction: Deposition of calcium and phosphate minerals in the vascular system results in the pathological state of vascular calcification (VC). To date, no approved treatment exists raising the need for novel therapies. The formation of nanoparticles composed of mineral and serum proteins and termed calciprotein particles (CPPs) promote this process. The transition from primary particles into their secondary and pathogenic form represents a possible target for the treatment of VC. Naturally occurring *myo*-inositol-hexaphosphate (IP6) acts on CPPs and is in clinical development for VC. From this, a novel bis-PEG2-IP4 molecule was derived with improved drug like properties.
Aims: Herein, we aim to investigate the drug-target interaction of bis-PEG2-IP4 with CPP and elucidate superiority regarding *in vitro* safety of the proposed molecule compared to IP6.
Methods: Using diffractive light scattering and transmission electron microscopy, the interaction of bis-PEG2-IP4 with CPP compared to IP6 with CPP could be studied. To elucidate the influence on inflammation, TNF-α release from compound and CPP treated human THP-1 macrophages was assessed. Furthermore, the compounds' impact on cell viability was investigated.
Results: Transmission electron microscopy and diffractive light scattering showed that bis-PEG2-IP4 stabilises CPP in their primary form, whereas IP6 does not. IP6 induced inflammation and reduced cell viability in CPP treated macrophages, whereas bis-PEG2-IP4 had no impact.
Conclusions: Bis-PEG2-IP4 was superior to IP6 in stabilising CPP and in *in vitro* safety studies. Therefore, the presented data supports the further development of this molecule as an inhibitor of vascular calcification.

Acknowledgements: We acknowledge funding by the Scholarship Fund of the Swiss Chemical Industry (SSCI) and Innosuisse.

Keywords: Vascular calcification, calciprotein particle, inositol hexaphosphate, PEG

P-11

Coupling Urine Metabolomics and CT-Scan to Unveil Early Lung Cancer Biomarkers in A/J Mice

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Introduction: With 1.72 million deaths in 2015, lung cancer is the most lethal cancer worldwide [1]. The global 5-year survival rate remains around 15% because of late diagnosis, occurring mainly at metastatic stages. Improvement of early diagnosis should dramatically change the outcome of this disease, as exemplified by the 20% decrease in lung cancer mortality following low dose CT-scan screening in the US [2]. However, this technique presents a high rate of false positive and is too expensive to be implemented in most countries. Therefore, finding early non-invasive lung cancer biomarkers is the topic of active research.
Aim: The aim of this work is to investigate the presence of potential urine lung cancer biomarkers in A/J mice and to correlate their apparition with visible tumors seen on CT-scan images.
Methods: The urine of A/J mice, not treated or having received 4-[methyl(nitroso)amino]-1-(3-pyridinyl)-1-butanone (NNK), was harvested once per week for 25 weeks after tumor induction. A/J mice were selected for their high propensity to spontaneously develop lung cancers over time, and carcinogenesis was boosted with NNK treatment, one of the most potent carcinogens from tobacco smoke. The urine content of healthy mice will be compared to the one of tumor-bearing mice using UHPLC-HRMS/MS profiling. Differences in metabolites will be assessed through unsupervised and supervised multivariate data analysis (PCA and OPLSDA) to identify putative biomarkers. The analysis of weekly harvested urine samples should then allow assessing the chronology of apparition of candidate biomarkers and evaluating their interest as early biomarkers. Finally, the relevance of these biomarkers will be established by comparing the correlation between their first occurrence and observations of lung tumors on CT-scan images that were taken once per month for the entire study.
Results: Compared to previously published urine lung cancer biomarker studies led in humans and mice, the present approach could provide critical information about the chronology of biomarker apparition and lead to the discovery of early biomarkers that could be useful for general screenings of the population. Further clinical studies would then be needed to validate their relevance and specificity in human cancers.
Conclusion: If successful, the discovery of specific and early lung cancer biomarkers in the urine will be an important step towards the reduction of lung cancer mortality.

Keywords: Lung cancer biomarker, urine metabolomics, CT-scan

References:
[1] Fitzmaurice C et al. JAMA Oncol 2017; 4: 524-548.
[2] Aberle DR et al. N Engl J Med 2011; 365: 395-409.

A Bufadienolide-Enriched Fraction of *Bryophyllum pinnatum* Inhibits Human Myometrial Contractility *In Vitro*

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Introduction: *Bryophyllum pinnatum* has been used in the treatment of premature labour, first in anthroposophic hospitals and, recently, in conventional settings often as an add-on medication [1, 2]. However, the compounds contributing to the tocolytic effect are still unknown.
Aims: To investigate the effects of a flavonoids-enriched fraction (FEF), the corresponding flavonoid aglycon mixture (A-Mix), a bufadienolide-enriched fraction (BEF) [3], and *B. pinnatum* juice (BPJ) on human myometrial contractility *in vitro*.
Methods: Myometrial biopsies were collected during elective Caesarean section. Strips of tissue were mounted in an organ bath system (myograph), and spontaneous contractions were recorded. Aliquots of a stock solution of FEF, A-Mix, BEF, *B. pinnatum* juice (BPJ) or a vehicle control (Krebs solution or DMSO), were repeatedly added (4 times) in 20-min intervals. The strength (i.e. AUC and amplitude) and the frequency of contractions were recorded for each 20-min period. After a washout period, vitality of strips was observed for additional 30 min. Cell viability assays were performed with the human myometrial hTERT cell line.
Results: Compared to initial values, the repeated addition of FEF, A-Mix, BEF or BPJ led to significantly lower contraction strength (AUC and amplitude) in a concentration-dependent manner (in all cases, $p<0.05$). BEF was the most active (e.g. 1 µg/mL BEF lowered AUC to 40.1 ± 11.8% of initial, whereas 150 µg/mL FEF, 6.2 µg/mL A-Mix, and 1% BPJ (i.e. 10 µg/mL) were required to obtain comparable inhibition). All test substances, except A-Mix, led to a progressive increase of contraction frequency. A-Mix, BEF and BPJ did not decrease viability of hTERT cells at concentrations up to 40 µg/ml, 15 µg/ml and, FEF only at the highest test concentration of 1000 µg/ml.
Conclusion: The data confirm previous observations showing that *in vitro* myometrial contractility can be inhibited by *B. pinnatum* leaf press juice and fractions without affecting viability. The fraction enriched in bufadienolides appears mainly responsible for the observed relaxant effect.

Keywords: *B. pinnatum*, bufadienolides, flavonoids, myometrium, *in vitro*

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Understanding HTA and Patient Engagement: Effect of Integrating Experiential and Knowledge Learning Modules

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Introduction: Patient Engagement (PE) is a relatively new societal movement especially for the medicines development life cycle including market access. Patient Engagement or Involvement is thought to lead to more meaningful outcome measures and may help to improve recruitment and retention in clinical trials [1]. During the market access phase, patients perspectives are increasingly thought to complement and/or transform the Health Technology Assessment (HTA) and value assessment process of new technologies [2]. HTAs are conducted and is a requirement during the market access reviews.
Aims: A new workshop format was developed with the goal to achieve a deeper understanding of the unique perspective of patients in the development or evaluation of new therapies and to increase the awareness of healthcare industry stakeholders for the importance and techniques of PE in preparing for HTA.
Method: A one-day pilot workshop, was held in November 2016 in Basel, Switzerland. Multidisciplinary participants (n=12) from the life sciences industry and 2 patient representatives attended. Interest in improving their understanding on knowledge component(s) was a criteria. Recruitment happened via networks of faculty members. HTA and PE content sessions were followed with experiential sessions using drawing exercises, which guided the participants through the experience of being diagnosed with a life threating condition and, subsequently, the possibility to participate in a clinical trial. The workshop concluded with the participants prioritizing their personal expectations for innovation and HTA, starting as patients and subsequently as citizens.
Results: Overall, participants rated the pilot workshop as excellent or good for knowledge and experiential sessions. Integration of both learning modalities was described as innovative, useful, and enjoyable. Participation in the clinical trial session triggered cognitive responses among participants working in the life sciences industry, which limited their experiential learning. In response, patient perspectives were useful to consider perspectives beyond those of industry employees, which prioritized advancement of science for societal good. Emotions describing the personal experiences included despair, shock, anger, guilt, hope, and the will to live. As citizens, they emphasized expectations such as finding solutions, remaining independent, enjoying life and «giving back».
Conclusion: Training on PE and HTA was linked successfully in one workshop by integrating knowledge and emotional-experiential learning modules. Session on participating in clinical trials would require modifications, in order to improve on the learning outcomes for participants, working in the life sciences. Innovative learning structures can allow researchers, marketers, or other stakeholders from the life-science industry to gain knowledge and better understand the patient perspectives.

Keywords: Patient Engagement, Health Technology Assessment, innovative, workshop

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Epithelial Tight Junctions Modulation by Short Peptide Inhibitors of Protein Kinase C

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Introduction: More and more new drug candidates suffer form poor solubility and bioavailability. Drug delivery by the nasal mucosa by opening intercellular tight junctions offers the advantages to avoid gastrointestinal metabolism and faster onset of drug activity due to the high level of perfusion present in the nasal epithelium.
Aims: Nasal administration of BCS class III drugs exploiting the paracellular pathway by reversibly and safely modulating tight junction (TJs). Several kinases [1] regulate the expression of the proteins present in the TJs. One of these is the protein kinase C zeta (PKC ζ). Its inhibition was shown to result in a reversible opening of TJs [2].
Methods: We have developed PKC ζ inhibitory myristoylated peptides [3] able to temporarily open TJs of primary human nasal and bronchial cells grown in inserts (Mucilair™). The enhanced diffusion of fluorescein, fluorescein dextran of molecular weights of up to 150 kDa and naloxone was studied. Potential toxicity of inhibitory peptides was assessed by measuring the ciliary beating frequency (CBF) and lactate dehydrogenase (LDH) release.
Results: Our PKC ζ inhibitors enhance considerably the cell monolayer permeability and permit molecules of different molecular weight (400 Da-150 kDa) to diffuse through nasal and bronchial cell monolayers. No acute toxicity on both cell types was observed. Structural modifications of the peptide (exchange of one amino acid, usage of D-amino acids) yielded different effects on permeability enhancement.
Conclusions: Peptidic inhibitors of PKC ζ enhance paracellular permeability of solutes across epithelial cell monolayers *in vitro*. They may serve as safe and efficient adjuvants to increase bioavailability of BCS class II drugs, which is currently under investigation in *in vitro* and *in vivo* studies.

Keywords: Tight junctions, permeability, peptide, PKC ζ, naloxone

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P-15

Effects of Molecularly Interacting Additives on Polymeric Hot Melt Extrusion

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Introduction: Amorphous solid dispersions represent a key approach to cope with formulation of poorly water-soluble drugs. Typical manufacturing methods are hot melt extrusion or spray drying. Polymeric excipients should be appropriate regarding processing, physical stabilization and regarding aqueous dispersion. However, the variety of suitable polymers is limited and the development of a new chemically engineered polymer would come with similar toxicological and regulatory hurdles as any development of a new chemical entity. Therefore, we are working on the concept of combining established pharmaceutical polymers with interacting additives for hot melt extrusion (HME).
Aim: The aim of this work, to study specific polymer-additive-combinations, was realized using fenofibrate as model drug. A particular emphasis was on technical feasibility, nature of molecular interaction, stability of amorphous state, and dissolution performance.
Methods: As amorphous solid dispersions, extrudates containing fenofibrate in a combination with malic acid and Eudragit E PO were studied. The extrusion process was performed on a 9-mm Three Tec extruder at 130 °C and a screw rotation speed of 80 rpm. The molecular interaction in these formulations was investigated by nuclear magnetic resonance spectroscopy (NMR) and Fourier-transform infrared spectroscopy (FTIR). For the assessment of the amorphous stability, x-ray powder diffraction (XRPD) polarized light microscopy and atomic force microscopy were used.
Results: During the manufacturing of the extrudates the addition of malic acid showed a positive effect on melt viscosity and later easier processing was facilitated in a subsequent milling step. These improved formulation characteristics resulted in adequate powder flow in comparison with the pure polymer Eudragit E and the formulation containing Eudragit E and fenofibrate. The improvements were indeed attributed to the molecular interaction between polymer and malic acid in the modified matrix. This interaction could be shown in peak shift of the carbons in the carboxyl group in the ^{13}C-NMR, which was confirmed by the reduction of the peak in the FTIR around 3430 cm^{-1} corresponding to the hydroxyl group of the malic acid. The interaction was further harnessed to improve the stability of the fenofibrate in the extruded formulation. The microscopic pictures of extrudates revealed crystalline drug only in the formulation of fenofibrate and Eudragit E after two weeks at ambient conditions. By contrast, the formulation containing malic acid with and without fenofibrate presented no indication of crystallization.
Conclusion: A molecularly modified matrix for hot melt extrusion was successfully obtained as a polymeric glass by adding the co-former to the polymer without indication of any phase separation. Furthermore, utilizing a drug highlighted the stabilizing and processing properties of the newly designed matrix. More research is needed with additional compounds to more broadly explore this novel approach and to harness its full potential.

Keywords: Hot melt extrusion, amorphous solid dispersion, designed polymeric matrix

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P-16

Characterization of Spatial Material Deposition/Distribution in Porous Functionalized Calcium Carbonate by a Combination of Mercury Intrusion Porosimetry and FIB-SEM Microscopy

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Introduction: Loading of substances into the porous structure of prefabricated carriers has advantages, such as protection of the active substance and predictable processing characteristics. Mercury intrusion porosimetry is the most common technique for characterization of porous material, although this method uses assumptions that can lead to errors in interpretation. A direct imaging technique could elucidate the pore structure and help to better interpret the results of mercury intrusion porosimetry.
Aim: The aim was to investigate the deposition of two model substances in a porous micro particle (functionalized calcium carbonate) using a combination of mercury intrusion porosimetry and FIB-SEM. These findings will help to understand the influence of physicochemical properties of a substance on the loading process.
Methods: Functionalized calcium carbonate was loaded with a phospholipid (DPPC) and a protein (BSA) as model substances in different loading ratios. We consolidated the loaded powders to remove inter-particle pores. We carried out mercury intrusion porosimetry and FIB-SEM as a direct method for analysing the changes in porosity and pore size distribution after loading. Physicochemical characterization of the substances was done to identify properties influencing the loading process.
Results: For DPPC in spite of mercury intrusion results showing complete pore filling in some samples, images of the cross sections of consolidates showed pore clogging. For BSA, mercury intrusion results showed altered pore size distribution towards bigger sizes. We confirmed this as external crystallization of BSA that renders the consolidation incomplete. Solubility of the substance in loading solvent and surface energy of the solutions were found to be important factors in deep pore filling.
Conclusions: We propose that for investigation of drug loading in porous drug carriers, a combination of FIB/SEM and mercury intrusion porosimetry for pore analysis is required. The ambiguities of mercury intrusion porosimetry could be clarified with direct visualization by FIB-SEM. Results indicate, that substance-dependent properties like surface energy of the solution and the solubility control the spatial deposition within FCC.

Keywords: Porous drug carrier, functionalized calcium carbonate, drug loading, FIB-SEM, Mercury intrusion porosimetry

Age-dependent Deposition Patterns and Quantitative Biokinetics of Inhaled 20-nm Gold Nanoparticles in Rat Lungs

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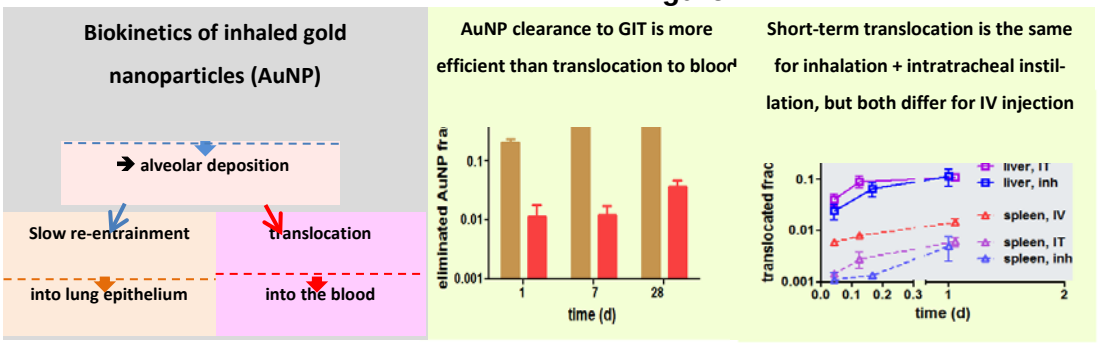
Introduction: The increasing industrial use of gold nanoparticles leads to an increase of an unintentional exposure by inhalation. The application of aerosolized gold nanoparticles as pulmonary drug delivery vehicle leads to an intentional exposure.
Aim: We studied the deposition patterns of inhaled 20-nm gold nanoparticles (AuNPs) in 7 to 90 days old rats and their biokinetics in 60 days old rats in order to understand an intentional and unintentional inhalation of AuNPs.
Methods: Wistar-Kyoto rats inhaled intratracheally 20-nm ^{195}Au-radiolabeled AuNPs by negative pressure ventilation over two hours. Immediately afterwards lungs were excised, inflated and micro-wave dried. AuNP deposition was analyzed by single-photon-emission computed-tomography, computed-tomography and autoradiography. Completely balanced, quantitative biodistributions in major organs and all body tissues and total excretion were analyzed from 1 hour to 28 days after inhalation.
Results: Intratracheal inhalation caused AuNP deposition predominately in the caudal lungs, independent of age. About 30% AuNP were deposited on airway epithelia and rapidly cleared by mucociliary clearance. About 80% of AuNP deposited in alveoli was relocated from the epithelium into the interstitium within 24 h and was inaccessible to broncho-alveolar lavage. During interstitial long-term retention re-entrainment within macrophages back onto the lung epithelium and to the larynx and gastro-intestinal-tract (GIT) dominated AuNP clearance (rate 0.03 d^{-1}). In contrast, AuNP-translocation across the air-blood-barrier was much smaller leading to persistent retention in secondary organs and tissues in the ranking order liver > soft issue > spleen > kidneys > skeleton > blood > uterus > heart > brain.

Figure 1



Conclusion: The age-independent, inhomogeneous AuNP deposition was probably caused by a ventilation which was mainly driven by the diaphragm (like breathing in rest). For drug delivery a more homogenous ventilation pattern should be used. Long-term AuNP clearance is dominated by macrophage-mediated transport from the interstitium to the larynx and GIT. Because the translocation across the rat air-blood-barrier appeared to be small, direct systemic side effects of pulmonary drug delivery by AuNP are expected to be small, too.

Keywords: Gold nanoparticles, aerosol inhalation, air-blood-barrier translocation, clearance, epithelial re-entrainment

Hyperforin Mediated PXR Activation is Influenced by the Uptake Transporter OATP2B1

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Introduction: St. John's wort (SJW) is an herbal remedy commonly used to treat moderate depressive symptoms. Beside its pharmacological effects, SJW is known for its drug-drug interaction potential, where enhanced expression of CYP3A4 modifies the clearance of concomitantly applied substrates. One constituent of SJW known for its alteration in CYP3A4 expression is hyperforin [1]. This phloroglucinol is a potent activator of the nuclear receptor Pregnane X Receptor (PXR), which functions as transcriptional regulator of a gene network summarizing multiple genes involved in drug metabolism and elimination. Little is known about the transmembrane transport of the lipophilic hyperforin. One membrane protein which is involved in cellular entry of drugs is the uptake transporter, organic anion transporting polypeptide (OATP) 2B1 [2].
Aims: It was aim of this study to test whether hyperforin interacts with OATP2B1, and whether interaction with the transporter influences hyperforin-mediated PXR activation.
Methods: Transport inhibition studies and competitive counterflow (CCF) experiments were conducted using the MDCKII-OATP2B1 cell line. CCF was performed as previously reported by Harper et al. [3]. CCF results were supplemented by cell based-reporter genes assays testing the influence of heterologously expressed OATP2B1 on hyperforin-mediated transactivation of CYP3A4 in HepG2 and HeLa cells. Caco-2 Transwell® experiments using the known OATP2B1-substrate atorvastatin were applied to test the influence of the phloroglucinol on transcellular fluxes. Hyperforin content was determined by HPLC.
Results: Transport inhibition and CCF experiments suggested that hyperforin is an inhibitor and substrate of OATP2B1. The latter was validated showing that presence of OATP2B1 significantly enhanced the hyperforin-induced PXR activation in cell based luciferase assays, whereby supporting the notion that this transporter may be a determinant of hyperforin-drug interactions as the transporter is known to be expressed in hepatocytes. The role of OATP2B1 inhibition in intestinal absorption was investigated in Transwell® experiments revealing a significant increase in the efflux-ratio of atorvastatin. Testing the influence of the 11 SJW formulations currently marketed in Switzerland on OATP2B1-mediated estrone 3-sulfate accumulation revealed significant inhibition for most of the tested formulations, but Rebalance™, Remotiv™, Hyperimed™ and Hyperiforce™. Importantly, assessing the content of hyperforin in all formulations suggested a direct correlation between amount and PXR activation as determined in subsequent luciferase assays.
Conclusions: Taken together, our results show that hyperforin is a substrate of OATP2B1, which is not only known to contribute to hepatocellular uptake, but also to intestinal absorption of its substrates. Our findings extend the complexity of drug-hyperforin interactions that have to be considered, when evaluating the interaction potential of the herbal remedy.

Keywords: Transmembrane transport, OATP2B1, St. John's wort, pregnane X receptor, hyperforin

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Development of a Sustained-Release Formulation of Buprenorphine for Pain Relief in Experimental Animals

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Introduction: Buprenorphine is a fast-acting semisynthetic opioid derivative, frequently used in veterinary medicine for post-surgical pain relief in mice and rats. Since no depot formulations are available on the market, and due to its short half-life, repeated injections are required to maintain analgesic effects in experimental rodents. As a consequence, the animals are exposed to increased levels of stress and might suffer under additional pain.
Aims: The goal of this project is to develop a sustained-release formulation of buprenorphine to prolong the analgesic effect up to three days after surgical intervention in rodents.
Methods: The proposed formulation is based on drug loaded microparticles composed of the biocompatible polymer PLGA (Poly (D,L-lactic-*co*-glycolide)). Microparticles were prepared by a single emulsion (o/w) method also known as solvent evaporation/solvent extraction technique. Morphology of microparticles, particle size distribution, and polymorphism were characterized by scanning electron microscopy, laser diffraction spectroscopy, and X-ray powder diffraction (XRPD), respectively. *In vitro* release was studied over three weeks in water at 37°C.
Results: Microspheres ranging in size from 3 – 100 µm were obtained through a solvent evaporation/ extraction method and subsequently characterized. The dry particles consist of a smooth surface and a porous inner structure. XRPD data shows an amorphous inclusion of the otherwise crystalline drug. *In vitro* dissolution was studied showing prolonged release of buprenorphine over 21 days.
Conclusions: We are presenting here a novel sustained-release formulation of buprenorphine based on loaded PLGA microparticles of defined sizes. This new developed formulation has a high encapsulation efficiency and allows the prolonged release of buprenorphine over several days. To achieve a targeted sustained-release over up to 3 days *in vivo* several different drug carriers will be produced and evaluated. Pharmacokinetic experiments in rodents will allow to establish a correlation between *in vitro/in vivo* drug release.

Keywords: Poly (D,L-lactic-*co*-glycolide), microparticles, sustained-release, buprenorphine

P-20

Cell-Type Specific Mixtures of Small Molecule-Based Compounds Overcome Sunitinib Resistance, Induce G1 Cell Cycle Arrest, Cell Senescence and Apoptosis

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Introduction: In the clinical management of primary and metastatic renal cell carcinoma (RCC), targeted agents have generally shown good efficacy with sunitinib being one of the most commonly used first-line therapies. Unfortunately, clinical success has been diminished by the development of resistance to sunitinib. Therefore, there is unmet need to clarify the alterations in various cellular processes underlying this phenomenon. Recently, various studies focused on identification of combinations of targeted agents using either simultaneous or sequenced administration in order to maximize their clinical benefits and overcome resistance of sunitinib.
Aim: Within this project, we investigated the impact of drug combination treatment on sunitinib-resistant RCC cell lines and on the modulation of the cell fate.
Methods: In this study, we established sunitinib-resistant cell lines (A498-SR, 786-O-SR and Caki-1-SR) using chronic sunitinib treatment. For each cell line, 3- or 4- synergistic drug combinations at low doses were optimized.
Results: Induced resistance to sunitinib, as well as optimized drug combination (ODC) activity in cell viability inhibition of 60%, 70% and 70% (in A498, 786-O and Caki-1 cells, respectively) was stable and maintained for several months. The cell cycle analysis after 24 h of drug incubation with the cells revealed that treatment with ODCs led to a G1 cell arrest followed by apoptosis induction. Consequently, after 72 h of incubation with ODC cell cycle progression was significantly affected (A498-SR and 786-O-SR) throughout several mitotic stages. Preliminary flow cytometry results revealed that ODCs might induce cell senescence, as measured via p21 overexpression in 786-O-SR cells by 30% default change compared to the sham control. Moreover, none of the sunitinib-resistant cell line when treated with ODCs underwent necrosis, which was the case for high doses of cisplatin (400 μM) and sunitinib (10 μM), used as positive controls.
Conclusion: Our results indicate that acquired sunitinib-resistance could differentiate the cell fate. Further analysis of genetic alterations between naïve and resistant cell lines will provide information about activation or blockade of certain cell signaling pathways related to cell fate.

Keywords: Small molecule compounds, optimized drug combinations, renal cell carcinoma, cell fate, sunitinib-resistant

P-21

An MRI-Guided HIFU-Triggered Wax-Coated Capsule for Supertargeted Drug Release

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Introduction: Compared to the systemic administration of drugs, controlled drug release reduces systemic toxicity while enhancing drug concentrations at the required site [1]. A variety of galenic formulations pursuing this goal exists, but methods to externally control the release of the active substance temporally and spatially as well as to monitor the process have not yet been developed and would be of great advantage [2].
Aims: To develop a thermoresponsive drug delivery system for personalized non-invasive therapy with magnetic resonance imaging (MRI)-guided high-intensity focused ultrasound (HIFU) as an externally controlled heat trigger and the possibility of monitoring the release of the active substance using MRI.
Methods: Mixtures composed of lanolin and cetyl alcohol in different ratios were characterized regarding their thermoresponsiveness. Capsules were loaded with lyophilized gadolinium-based contrast agent (GBCA), coated with a wax layer of lanolin/cetyl alcohol 1:1 and placed in a HIFU gel phantom. The release of GBCA was triggered by an MRI-guided HIFU pulse (200 W, 1195 kHz) and monitored using T1- and T2-weighted MRI before and after the HIFU pulse.
Results: The mixture of lanolin and cetyl alcohol in a ratio of 1:1 showed a suitable melting point of approximately 43°C. The T2-hypointensity of the wax-coated capsule allowed tracking of the drug delivery system. While T1-hyperintensity was lacking pre-exposition, a T1-hyperintense signal was observed in close proximity to the capsule after the application of a HIFU pulse (200 W, 1195 kHz), indicating that the HIFU pulse lead to melting of the wax coating and in consequence to the hydration and outflux of the GBCA. Visual examination of the capsule revealed that the HIFU pulse melted a localized distinct hole into the capsule.
Conclusions: We developed a thermoresponsive wax-coated capsule for supertargeted release of any active substance at a specific time point at the required site in the gastrointestinal tract. Also, we provide the proof-of-concept for the application of MRI-guided HIFU as an externally controlled heat trigger for drug release in a non-invasive manner. Furthermore, we introduced a method to visualize and monitor the capsule and its active principle release based on its specific T1- and T2-MRI signal pattern. We therefore provide a novel externally controllable and monitored drug delivery system which may open up new perspectives in the personalized treatment of gastrointestinal diseases.

Keywords: High intensity focused ultrasound, drug delivery system, magnetic resonance imaging, gastrointestinal tract, contrast agent

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P-22

Augmented Drug Combination Efficacy in 3D and 3D Co-Culture Models of Colorectal Carcinoma

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Introduction: Targeted drug combinations have the potential to improve treatment activity through synergistic interactions, simultaneously allowing reductions in drug dosing, and by reducing drug resistance through cell viability inhibition on multiple levels. However, few targeted drug combinations have been approved and clinical drug attrition rates are still high. Current clinical trials often lack scientific evidence on the fitness of the drugs in the combination. This might be due to the fact that preclinical testing is often performed in simple two-dimensional (2D) cell cultures. Currently, three-dimensional (3D) cancer cell models are gaining attention as pre-clinical alternatives.
Aims: We compared drug combination efficacy and drug interactions between culture systems with various complexity, i.e. 2D, 3D and 3D co-cultures, to bridge the gap between *in vitro* research and possible translation to *in vivo* models.
Methods: We established the 3D and 3D co-culture (3D-CC) systems for a panel of human colorectal carcinoma (CRC) cell lines of various origin and genetic background to mimic the diversity observed in CRC patients. The 3D cultures formed compact heterogeneous shapes that increased in size over time and presented a remodeled periphery. The 3D-CC were established with clinically relevant number of endothelial cells (EC) and fibroblasts (FB), two cell types interacting with CRC cells in the tumor microenvironment. The 3D-CC were characterized with more heterogeneous shapes, and intra-spheroid organization of the FB and EC was cell-type dependent. The 3D-CC developed a core of fibroblasts with pockets of endothelial cells in close proximity or had FB and EC distributed throughout the spheroid.
Results: Three CRC cell types (HCT116, DLD1 and SW620) were selected for treatment optimization with CRC clinically relevant drugs, including the chemotherapeutic 5-fluorouracil and small molecule-based drugs, i.e. regorafenib and erlotinib, targeting VEGFR2-3/Ret/Kit/PDGFR/Raf and EGFR, respectively. We used cell metabolic activity as a readout in cell proliferation assays and incubated the cell cultures incubated with the drugs for 72 h. Interestingly, when comparing dose-response curves between 2D and 3D cultures, we observed a cell-type dependent increase in drug sensitivity in 3D versus 2D cultures for erlotinib. In the next step, we investigated the differences in drug combination efficacy and drug interactions between the CRC cell types and the culture systems at two dose levels, i.e. clinically relevant maximum plasma concentrations (MPCs) and at low dose (LD), representing a dose inducing approx. 20% of activity, to more optimally study drug interactions. We identified cell-type and culture-system dependent differences between the drug combinations. A key observation was a reduction in treatment efficacy of the 3D-CC and/or 3D cultures versus 2D cultures for 2-drug combinations at LD. Consistently, the increase in drug concentration from LD to MPC correlated with a shift from synergy/additivity towards additivity/antagonism. Moreover, some drug combinations did not gain activity when treatment was performed with MPC compared to LD. Retreatment resulted in striking cell type-dependent improved treatment efficacy, highlighting the potential of personalized low dose drug combinations.
Conclusion: Taken together, in our *in vitro* 3D (co-)cultures we detected culture system-dependent differences in drug combination efficacy and interactions and optimizing low-dose combinations with a personalized approach can improve current treatment options.

Keywords: Colorectal cancer, 3D cultures, 3D co-cultures, endothelial cells, fibroblasts, drug combinations, drug interactions, retreatment

P-23

Inhibition of TLS DNA Polymerases to Combat Platinum-Based Anti-Cancer Drug Resistance

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Introduction: Cisplatin and oxaliplatin are platinum-based chemotherapeutic agents used for the treatment of a diverse range of cancer types, for example, testicular, ovarian, head, neck, bladder, cervical, and lung. After activation in the body, these drugs covalently bind to DNA to form DNA adducts. The most prevalent DNA adduct is an intrastrand cross-link between two adjacent guanines (Pt-GG). The formation of these adducts evoke cell death in cancerous cells. An adverse outcome of platinum-based drug therapy is the development of drug resistance. One strategy to combat this resistance is the inhibition of enzymes involved in the tolerance of these DNA adducts during DNA replication. Human DNA polymerases eta (hPol η) and zeta (hPol ζ) are two enzymes responsible for Translesion DNA synthesis (TLS) past cisplatin and oxaliplatin DNA adducts. TLS is a mechanism that involves DNA replication past DNA adducts, thus resulting in tolerance of DNA damage. The inhibition of hPol η and hPol ζ provides a novel strategy to combat resistance to platinum-based chemotherapy [1,2].
Aims: The aims of this work are twofold. First, to determine the mechanism of bypass by TLS DNA polymerases in replicating past cisplatin and oxaliplatin adducts. Second, to design and synthesize a series of small molecule TLS polymerases inhibitors and to evaluate their effectiveness with both biochemical and cytotoxicity assays.
Methods: Biochemical primer extensions assays are performed to investigate the mechanism of bypass by TLS polymerases. Rational design of small molecule by computational modeling and their chemical synthesis are employed to generate TLS polymerase inhibitors. The inhibitory effect of the small molecule inhibitors will be measured by various biochemical assays.
Results: We show that hPol η can bypass both cisplatin and oxaliplatin DNA adducts, albeit with low fidelity. In addition, hPol η is most efficient at inserting nucleotides directly opposite the 3' G and 5' G of the Pt-GG lesion, and least efficient at extension after the Pt-GG lesion. For the oxaliplatin-containing DNA, hPol η is more efficient at bypass than for the cisplatin-containing DNA. Finally, *in silico* modeling identifies a potential binding pocket for a small molecule hPol ζ inhibitor that would result in the disruption of an important protein-protein interaction.
Conclusions: This work provides novel insights into mechanisms of human TLS DNA polymerases to bypass platinum-based DNA adducts. In addition, the development of new inhibitors that target TLS polymerases will contribute to the development of more effective chemotherapeutic strategies aimed at combating drug resistance.

Keywords: Drug discovery, platinum-based drugs, drug resistance, TLS polymerases

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Development of an Oral Polymersome Formulation for Ammonia Detoxification

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Introduction: In hepatic encephalopathy (HE), a highly prevalent complication in patients with liver cirrhosis, systemic ammonia levels are chronically elevated due to a reduced hepatic ammonia clearance, which can lead to potentially life-threatening neuropsychiatric symptoms [1]. As systemic ammonia mainly originates from bacterial urease activity in the gut, sequestering gut ammonia is a promising strategy to reduce systemic ammonia levels [1]. Recently, we developed a transmembrane pH-gradient liposome formulation for peritoneal dialysis which selectively sequestered ammonia in the peritoneum and decreased systemic ammonia levels [2,3]. Due to its invasiveness, this treatment is reserved for acute hyperammonemic crises.
Aim: We aim to develop an oral ammonia-sequestering formulation based on transmembrane pH-gradient vesicles for use in chronic hyperammonemia. These vesicles should exhibit excellent stability in the harsh environment encountered in the gastro-intestinal (GI) tract (bile slats, variable osmolarity, digestive enzymes [4]).
Methods: Polymersomes made of diblock copolymers with a low or a high glass transition temperature (LGT and HGT, respectively) were prepared with an emulsification-based method in acidic buffer, yielding vesicles with an acidic core. Highly stable PEGylated liposomes composed the unsaturated lipid 1,2-distearoyl-*sn*-glycero-3-phosphocholine and a high cholesterol content (~45 mol%) were prepared by film rehydration in acidic buffer. The polymersomes and liposomes were exposed to ammonia-containing GI tract-simulating media with high bile salt concentrations at pH 6.8 and compared in terms of ammonia uptake capacity. The ammonia uptake capacity of HGT polymersomes was further assessed in severely hypo- and hyperosmolar bile salt-containing solutions and in intestinal enzyme-containing buffer (trypsin and alpha-chymotrypsin each at 1 mg/mL, lipase 3 mg/mL). Finally, the HGT polymersomes were incubated in a buffer containing the caecal content from healthy rats.
Results: While transmembrane pH-gradient liposomes and LGT polymersomes efficiently captured ammonia in phosphate buffer after 6 h (860.8 ± 2.4 µM and 260.2 ± 5.3, respectively), their capture capacity was reduced in a cholate- and deoxycholate-containing (each at 25 mM) solution (135.2 ± 26.8 µM and 7.4 ± 3.6, resp.). In contrast, HGT polymersomes sequestered ammonia in bile salt concentrations largely exceeding those found under physiological conditions (307.3 ± 52.4 µM, cholate, deoxycholate, and taurocholate, each at 30 mM), at extreme hypo- (283.5 ± 76.9 µM, 160 mOsmol/kg) and hyperosmolal conditions (331.5 ± 27.1 µM, 620 mOsmol/kg) after 24 h, and in pancreatin-containing simulated intestinal fluid (361.4 ± 41.6 µM) after 4 h. Upon incubation in buffered caecal fluid for 6 h, the HGT polymersomes showed a similar uptake capacity as in simple buffers.
Conclusion: We developed a transmembrane pH-gradient-based HGT polymersome formulation which strongly sequesters ammonia in simulated GI fluids. LGT polymersomes and liposomes, on the other hand, were not stable in bile salt-containing solutions. These findings underline that the HGT polymersome formulation warrants preclinical testing in bile duct-ligated rats, an animal model of hyperammonemia.

Keywords: Polymersomes, liposomes, gastrointestinal tract, hyperammonemia, liver cirrhosis

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P-25

Altered Expression and Function of Hepatic and Renal Drug Transporters in Polycystic Kidney Rats

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Introduction: Autosomal dominant polycystic kidney disease (ADPKD) is an inheritable genetic disease and leads to kidney failure in approximately 50% of affected individuals. In addition to renal cysts, patients with ADPKD often develop hepatic cysts, which may influence the disposition of endogenous (e.g., bile acids, coproporphyrin (CP)-I and CP-III) or exogenous compounds and could lead to altered efficacy or toxicity of medications. The polycystic kidney (PCK) rat is a model of polycystic kidney disease (PKD) and polycystic liver disease (PLD), and is used as a model for ADPKD.
Aim: To gain insight into hepatic and renal transporter expression and function in PCK rats, mRNA and protein levels were measured, and CP-I and CP-III, transporter probes of organic anion transporting polypeptides (Oatps) and multidrug resistance-associated protein 2 (Mrp2), were analyzed in serum, urine, and bile of PCK and wild-type (WT) Sprague Dawley rats.
Methods: Membrane proteins from the livers and kidneys of PCK and WT rats (16-20 weeks old; n = 3-4 per group) were extracted using a ProteoExtract® native membrane protein extraction kit. mRNA levels of Oatp1a1, Oatp1a4, Oatp2b1, Mrp2, Mrp3 organic solute transporter (Ost)α, Ostβ, and multidrug resistance protein 1 (Mdr1) were measured by qPCR in liver samples. Protein levels of Oatp1a1, Oatp1a4, Oatp2b1, Mrp2, Mrp3, and OSTβ in liver samples, and of Mrp2, Mrp4, and OSTβ in kidney samples, were detected by western blot. In addition, a LC-MS/MS assay was developed and validated to quantify CP-I and CP-III concentrations in PCK and WT rat serum, urine, and bile samples.
Results: The mRNA of Mrp3, Ostα, and Ostβ were significantly increased by 9-, 120-, and 34-fold, respectively, in livers from PCK compared to WT rats. Western blot analysis confirmed upregulation of OSTβ (2-fold), and downregulation of both Mrp2 (3.1-fold) and Oatp1a4 (2.9-fold) in PCK rat liver samples. In the kidney, Mrp2, Mrp4, and OSTβ protein levels in PCK rats were significantly increased by 3.3-, 2.6-, and 1.8-fold, respectively. Serum and urine CP-I and CP-III concentrations were elevated in PCK rats. Although biliary CP-I concentrations did not change significantly, biliary CP-III concentrations were decreased in the PCK compared to WT rats, consistent with altered hepatic and renal transporter expression in PCK compared to WT rats.
Conclusion: Differences in hepatic and renal transporter expression may contribute to altered drug disposition in PKD and PLD.

Keywords: Transporters, coproporphyrin, polycystic kidney

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Chemical Composition and Antibacterial Activities of Different Conifer-Derived Essential Oils

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Introduction: Essential oils (EOs) are mixtures of natural chemical substances and they are widely used in folk medicine. Due to the increased resistance of microorganisms against conventional antibiotics (e.g. β-lactams) the focus is set again on EOs as new antibacterial alternatives or as new lead compounds in drug discovery projects. Conifer-derived EOs (CEOs) are known to be able to inhibit the growth of gram-positive and gram-negative bacteria, but the exact mechanism of action of the compound(s) is still unknown.
Aims: The present work represents a detailed chemical characterization of several CEOs and their corresponding antibacterial activity applying standardized approaches.
Methods: EOs derived from the conifer species *Abies pectinata* (AP), *Abies sibirica* (AS), *Pinus sylvestris* (PS), *Picea mariana* (PiM) and *Pseudotsuga menziesii* (PM) were analyzed and characterized with regard to monoterpene and sesquiterpene profiles using gas chromatography (GC) hyphenated to mass spectrometry (MS). Characterized oils were subsequently screened *in vitro* for the antibacterial activity against *Staphylococcus aureus* ATCC 29213 and *Escherichia coli* ATCC 25922 to determine the minimum inhibitory concentration (MIC) by broth microdilution method.
Results: Monoterpene hydrocarbons were predominant in all CEOs whereas sesquiterpenes were only present in a low amount. Santene was used as marker to identify species of *Abies* and *Picea*. All CEOs showed antibacterial activity. AS (MIC values: 0.1-1.6 µg/mL (*S. aureus*) and 1.6-3.1 µg/mL (*E. coli*), respectively) showed the highest antibacterial activity followed by PS (MIC values: 1.6 µg/mL (*S. aureus*) and 6.3 µg/mL (*E. coli*), respectively). AS exhibited even stronger antibacterial activity against both bacteria strains than the antibiotic ampicillin (MIC values: 3.1 µg/mL (*S. aureus*) and 3.1 µg/mL (*E. coli*), respectively), whereas PS possessed stronger activity against *S. aureus* than ampicillin.
Conclusion: The presented chromatographic approach is suitable to identify and characterize CEOs obtained from different conifer species. Selected CEOs were able to inhibit the growth of gram-positive and gram-negative bacteria in a standardized assay format. Further investigation on the exact composition of these CEOs is needed to identify potential antibacterial compound(s) and elucidate their exact mode of action.

Keywords: Conifer-derived essential oil, standardization, GC-MS, antibacterial activity

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Altered Synaptic Transmission in *Sapap3-/-*Mice Driving Behavioral Hallmarks of Obsessive-Compulsive Disorder

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Introduction: Obsessive-compulsive disorder (OCD) is a potentially debilitating psychiatric condition, manifested by obsessive thoughts and anxiety, along with behavior arising from aberrant formation of habits. High failure rates of approved pharmacological OCD treatments are typical. The development of improved, mechanism-based therapy is hampered by a deficient understanding of the pathophysiology of OCD.
Aims: Identifying the circuit-pathology that drives compulsive behavior may help to overcome these limitations.
Methods: Here we revisit the behavioral phenotype of the *Sapap3*-/- line, a bon fide mouse model for OCD. We focus on the excitatory synapses of cortical projections in the dorsal striatum.
Results: In an operant lever-press task with sucrose as reward, WT mice exhibited goal-directed behavior whereas the *Sapap3*-/- mice showed habitual actions after a two-week training period. *Sapap3*-/- mice exhibited excessive grooming and decreased locomotor activity. We then characterized three distinct cortical projections to the striatum originating in the orbitofrontal (OFC), motor (M1/2) and cingulate (Cg1) cortex. Paired pulse facilitation, a measure to screen from alteration in presynaptic release probability, was comparable between *Sapap3*-/- and WT mice in all three projections. Synaptic currents from M1/2 onto D1- and D2-MSNs and from Cg1/M2 onto D2-MSNs had decreased AMPA vs. NMDA components in *Sapap3*-/- mice, while this was not the case for OFC afferents.
Conclusion: Restoring normal synaptic transmission in selected circuits not only allows establishing links of causally with pathological behavior but may inspire novel treatment strategies.

Keywords: OCD, *Sapap3*, synapse, mouse model

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Nutritional Assessment in Patients Affected by Cystic Fibrosis (NACYFI Study)

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Introduction: Cystic fibrosis (CF) patients are at nutritional risk. One of the main pathologic issues are viscous mucus blocking pancreatic ducts, leading to reduced production of pancreatic enzymes. Therefore, maldigestion and consequently malabsorption occur, particularly of fats and liposoluble vitamins, resulting in steatorrhoa, vitamin deficiencies, and subsequently malnutrition.
Aims: We aimed to determine the prevalence of malnutrition and investigate the nutritional status of an adult Swiss CF cohort.
Methods: We contrasted CF patients with healthy controls [1] regarding nutritional status and dietary habits in an observational cohort study. Assessment was based on nutritional risk screening (NRS-2002), dietary habits (7-day food record), body composition (bioelectric impedance analysis, anthropometrics), resting energy expenditure (REE; indirect calorimetry), and physical/mental function (SF-36v2®).
Results: Nineteen patients (13 men, median age 32 years) and 15 controls (8 men, median age 52 years) were included. Eight patients (42%) were at nutritional risk (NRS-2002≥3). According to ESPEN guidelines [2], 8 (42%) patients were malnourished. Energy intake per kg body weight was significantly higher in patients ($p=0.015$). No significant differences arose in REE ($p=.451$) and estimated energy requirements ($p=0.202$). Energy balance is +648 kcal in patients and +57 kcal in controls ($p=0.176$). Patients' body fat-free mass percentage ($p<0.001$) was significantly higher and BMI ($p=0.027$) and physical/mental health scores ($p<.001$) were significantly lower.
Conclusions: Malnutrition is highly prevalent in this CF cohort (47%). Energy intake and body weight are highly discrepant in patients. In clinical practice, energy requirements of CF patients are approximately twice the Harris-Benedict estimation [3] and adequate intake of pancreatic enzyme substitution is crucial.

Keywords: Cystic fibrosis, malnutrition, nutritional screening, nutritional assessment

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Adherence to and Preference for Vitamin D in Different Pharmaceutical Forms and Administration Frequencies – A Study Design

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Introduction: The importance of vitamin D supplementation, particularly during winter, is increasingly recognised in Europe. Most supplements in Switzerland are oily or alcoholic liquids intended for daily administration. Although intermittent, weekly and monthly, administration has demonstrated equal efficacy, patients' preference and adherence have rarely been studied.
Aim: To assess adherence to and preference for vitamin D in different pharmaceutical dosage forms and frequencies of administration in outpatients.
Methods: Experts, health professionals and patients, discussed during a focus group, which pharmaceutical form and which administration frequency of oral vitamin D supplementation would lead to the best adherence at different ages of life. Power calculation showed that 59 patients per group will be sufficient to detect a difference of 25% in timing adherence with a 80% power.
Results: Study design: Interventional, randomized, cross-over study with 8 general practitioners in Switzerland. Patients obtain vitamin D supplements either as tablets (5600 IU) and capsules (20'000 IU) or oily (5600 IU) and alcoholic drops (24'000 IU), for weekly and monthly administration over 3 months, respectively. Blood samples and questionnaires are obtained at inclusion, 3 and 6 months. Adherence is monitored electronically, for the solid forms with POEMS technology, and for the liquid forms with Time4Med smart cards. Patients ≥ 18 years old with vitamin D level < 50 nmol/L at baseline, taking at least one oral medication are recruited. Patients with hypercalcemia or nephrolithiasis are excluded. Primary outcome is adherence (taking and timing). Secondary outcomes are preferences and improvement of vitamin D levels.
Conclusion: This study will provide information on patients' preference and its influence on adherence to vitamin D supplementation, comparing liquid and solid forms under two types of intermittent administration.

Keywords: Vitamin D, intermittent oral supplementation, adherence

Oral Vitamin D Substitution – Pharmaceutical Form and Administration Frequency for Best Adherence

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Introduction: Vitamin D may be supplemented in deficient individuals at every age for therapeutic or prophylactic purposes using recommended daily dosages. Different pharmaceutical forms (liquid, solid, injection) and different strengths exist. Adherence to medication depends greatly on the frequency of administration. Recent studies have shown equivalent outcomes after daily or intermittent (weekly or monthly) administration.
Aims: To find consensus with experts on optimal form and frequency of oral vitamin D administration for best adherence in different stages of life.
Methods: A focus group was held to rate various items regarding vitamin D supplementation. The group consisted of 5 health care professionals (2 prescribing doctors, 2 dispensing pharmacists, 1 administrating home care nurse) and 5 patients. All group members had taken vitamin D supplementation during the previous winter, 6 in a lower than recommended dose. Participants first scored their preferred dosage form and interval on a 5-point Likert scale (from -2: strongly disagree to +2: strongly agree) and then voted (yes/no) after debating their personal vote. Consensus was defined as unanimous, strong (9/10 identical votes) or firm (7 or 8/10 identical votes). Importance of reimbursement and doctor's awareness were also answered with a 5-point Likert scale (from -2: not important to +2: very important) before and after debate.

Results: Scores of the preferred dosage form and interval in different stages of life are shown in table 1.

Table 1.

Age Group	Preferred Dosage Form	Consensus	Preferred Dosage Interval	Consensus
Adults	Tablets	Unanimous	Monthly	Strong
Infants	Oily drops	Strong	Weekly	Unanimous
Home residents	Tablets	Unanimous	Daily or weekly	Strong

For home residents, both daily and weekly administration seem to be advantageous. Reimbursement by health insurances was considered important (mean +0.4) while doctor's awareness of vitamin D supplementation was considered very important (mean +1.5).

Conclusion: Tablets for all adults and oily drops for infants are the favorite pharmaceutical form. Monthly for adults, weekly for infants and weekly or daily for home residents is the favorite administration frequency. These preliminary results will be used to design an adequately powered randomized trial addressing optimal vitamin D supplementation.

Keywords: Vitamin D, oral supplementation, adherence

Laboratory Values of Vitamin D and Vitamin B_{12} Do Not Correlate – A Combined Substitution Is Nevertheless Valuable

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Introduction: Vitamin D plays a major role in calcium homeostasis. Vitamin B_{12} is important for cell division, blood formation and the nervous system. Simultaneous deficiency of both vitamins is supposed to be common, particularly among older people and vegans. Substitution in Switzerland mostly consists of oral vitamin D daily or monthly, and i.m. vitamin B_{12} monthly. The oral daily application of the extrapolated weekly dose of vitamin B_{12} is equivalent to i.m. injections. The intermittent oral administration of both vitamins concomitantly, could facilitate their supplementation and ameliorate adherence.
Aims: To investigate the relationship between serum values of vitamin B_{12} and vitamin D and to draw lessons for a combined substitution.
Methods: We obtained de-identified laboratory reports from the laboratory Medics AG (Bern, Switzerland) of the year 2017. Measurements were performed with standard immunoassay (ECLIA) (COBAS, Roche).
Results: We analysed 49'323 laboratory reports (65.2% women) with simultaneous vitamin D and vitamin B_{12} values. Spearman' correlation was 0.09 (p=0.001), indicating the absence of relationship between both variables. The risk ratio for concomitant deficiencies of vitamin D (< 50 nmol/L) and vitamin B_{12} (< 140 pmol/L) was 1.22, indicating similar incidence in both groups. A total of 822 (1.7%) patients had simultaneous deficiencies.
Conclusion: The serum values of vitamin D and vitamin B_{12} do not correlate. However, for patients with simultaneous deficiencies or barely sufficient values, concomitant weekly or monthly administration of both vitamins could contribute to reduce polypharmacy and improve adherence.

Keywords: Vitamin D, vitamin B_{12}, oral substitution, adherence

Enhancing Bioavailability with Amorphous Solid Dispersions: The Effect of Embedded Surfactants on *In Vitro* and *In Vivo* Drug Delivery Characteristics

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Introduction: Recurrent drop-outs of poorly soluble drug candidates during drug development due to low bioavailability create a need for delivery systems that improve drug solubility. Amorphous solid dispersions (ASDs) are systems in which an active pharmaceutical ingredient (API) is embedded amorphously into a solid polymer matrix. Their use in oral drug delivery can increase bioavailability *in vivo* and clinically. Manufacturing by hot-melt extrusion has the advantage of being a solvent-free and continuous process. Mechanisms that lead to increased bioavailability *in vivo* are understood incompletely. Increased solubility of the amorphously delivered API is considered equally relevant as the formation of particles upon dissolution of the ASDs in aqueous medium [1]. Particles can be of various morphologies (e.g. polymeric micelles or drug-rich particles) and are generated by different mechanisms (e.g. hydrophobic interactions or glass-liquid phase separation). As the delivery system is formed upon dissolution *in situ*, compounding is the key strategy to optimize drug delivery. This reasons increased interest in the effect of additional excipients embedded into ASDs on their delivery characteristics [2, 3].
Aims: The present study aims to evaluate the influence of additional excipients, such as surfactants or water soluble polymers embedded into ASDs, on their *in vitro* and *in vivo* drug delivery characteristics.
Methods: ASDs were produced by hot-melt extrusion on a lab-scale co-rotating twin screw extruder with combined solid-liquid feeding. Efavirenz was used as a poorly soluble model API and HPMCP HP50 as main component polymer. The effect of admixing water soluble polymers (PEG 6'000, PEG, PEO 100'000, Soluplus® and Kollicoat® IR) and surfactants (polysorbate 80, Kolliphor® EL and TPGS, Surphore® SE D1615 and Transcutol®) into the melt, alone and in combinations, was screened by *in vitro* dissolution tests. Promising formulations were imaged in a dissolved state by cryogenic transmission electron microscopy (TEM), characterized for particle size by dynamic light scattering (DLS). Their absolute *in vivo* bioavailability and pharmacokinetics were determined in jugular vein cannulated rats using tandem mass spectrometry for plasma level quantification.
Results: The addition of water soluble polymers into ASD showed no improved *in vitro* dissolution of efavirenz. In contrast, addition of combinations of surfactants resulted in 100% drug release within 16 min compared to 30% drug release in the marketed efavirenz formulation (Stocrin®). Cryogenic TEM revealed that particles are formed with diameters of 100 to 500 nm as well as aggregates larger than 10 µm, which was confirmed by DLS. *In vivo* results showed that the administration of efavirenz as ASD without surfactants was poorly bioavailable. While the ASD without surfactants in a predissolved state resulted in higher bioavailability than the marketed formulation, embedding surfactants into the ASD showed an inferior increase in bioavailability.
Conclusions: It was possible to improve *in vitro* and *in vivo* delivery characteristics of ASDs by embedding surfactants. While *in vitro* results were promising, *in vivo* results showed constraints in the *in vivo* dissolution of ASDs. The limiting step in bioavailability seems to be the formation of particles from the ASD and not the drug release from the formed particles.

Keywords: Bioavailability, drug delivery, *in vivo*, amorphous solid dispersion (ASD), hot-melt extrusion

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Overcoming Current Restraints in Assessing Powder Flowability in Early Pharmaceutical Development Using Novel SSSpinTester Technology

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Introduction: Currently available methodologies for the assessment of powder flowability pose several disadvantages, including sample amount and pressure conditions, which significantly limit their use in early pharmaceutical development. Due to structural constraints, measurements with the Schulze ring shear cell are restricted to the pressure range above 1000 Pa [1], eventually leading to non-predictive results as the conditions faced in typical pharmaceutical processes are rather below 500 Pa. Furthermore, a sample of 30 g is required for the analysis, which is often far more than available for analysis in early phases of development. Novel SSSpinTester technology [2] now aims at solving these issues. By making use of centrifugal forces, measurements down to 10 Pa are possible for cohesive APIs and poorly-flowing pre-blends. The small cell with a volume of 0.38 cm^3 requires as little as 100-250 mg of a sample per run, depending on the bulk density of the substance.
Aims: The objective was to evaluate the new SSSpinTester method for assessing the powder flowability regarding its applicability in early pharmaceutical development. If necessary, the existing SSSpinTester method should be further optimized to better reflect the processes and thus obtain more predictive results.
Methods: The flowability of minimal amounts of sample was assessed using both the traditional Schulze ring shear cell as well as the novel SSSpinTester technology. In subsequent experiments, the influence of the cell geometry in the pre-existing SSSpinTester method was studied and the method optimized to exclude the influence of the wall friction.
Results: The flow function of a cohesive API and various corresponding formulations could be assessed using the SSSpinTester in the pressure range of 50-1000 Pa. However, in the SSSpinTester's standard setup, there was a high influence of the sample preparation, leading to increased variability of the obtained data. By designing a new cell geometry with a cylindrical cavity and a protruding edge, the reproducibility of the measurement could be significantly improved. Clear differences could be observed depending on the cell type used for the analysis while the cell wall material had only little influence on the measured results.
Conclusions: Experiments showed that the SSSpinTester is indeed able to generate flowability data in the process-relevant low-pressure range and thus relatively classify APIs and corresponding formulations in respect to the flowability. The optimized method with the new cell geometry thereby successfully helps to guide the formulation design of poorly-flowing APIs.

Keywords: Powder flowability, SSSpinTester, Schulze ring shear cell

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In Vivo Physiologically-Based Pharmacokinetic Modelling in Mice by Positron Emission Tomography (PET)

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Introduction: Pharmacokinetic analyses are generally based on plasma concentration-time curves and possibly information on renally excreted drug amounts determined from continuously collected urine. Both is challenging to obtain in preclinical pharmacokinetic studies on mice.
Aims: Our goal was to evaluate dynamic positron-emission tomography (PET) combined with physiologically-based pharmacokinetic modelling as a method to study pharmacokinetics in mice. We aimed at providing a method for the non-invasive assessment of drug-drug interactions resulting from hepatic transporter inhibition.
Methods: We re-purposed PET data which were generated with mice during the development of the N-[^{11}C]methylated PET tracer [^{11}C]MT107, a derivative of our recently published tracer [^{11}C]AM7 [1]. PET images showed high accumulation in gall bladder and intestines which was reduced after cyclosporine administration (50 mg/kg i.v., 1 min before tracer intravenous administration). We applied a multi-compartment model and the numerical solutions of the respective differential equations for non-linear regression analysis of the time-activity curves of blood, liver, gall bladder/intestines, kidneys and muscle tissue. Pharmacokinetic parameters were calculated from the fitted rate constants and known physiological parameters such as organ weights and organ blood flows.
Results: The modelling revealed good fits for all time-activity curves and allowed to calculate the biliary clearance, hepatic extraction ratio, renal clearance and tissue/blood distribution coefficient of [^{11}C]MT107. The sum of renal and biliary clearance calculated from the modelling was in agreement with the total clearance calculated from the blood radioactivity time-curves (47.1 ± 11.9 µL/min *vs* 56.1 ± 13.0 µL/min). The modelling revealed a significant reduction in biliary clearance from 35.2 ± 10.9 µL/min to 17.1 ± 5.6 µL/min when cyclosporine was administered (p = 0.025, n = 4).
Conclusions: Physiologically-based pharmacokinetic modelling with dynamic PET data allows to determine renal and biliary clearances in mice and to detect reductions in biliary clearance due to the inhibition of hepatic transporters. Small animal PET offers the possibility to study pharmacokinetics and drug-drug interaction potentials in mice during drug development. The method may reduce the number of animals in pharmacokinetic studies [2].

Keywords: PET, physiologically-based pharmacokinetic modelling, cyclosporine, biliary clearance, preclinical

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In Vivo Study for Gd-Micelles – an MRI Contrast Agent for Vascular Imaging

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Introduction: Efficient cardiovascular imaging procedures are needed to enable the accurate diagnosis of related diseases, such as stroke, thrombosis or heart failure. Magnetic Resonance Imaging (MRI) is a non-invasive technique providing a clear benefit compared to other imaging techniques by avoiding ionizing radiation for contrast creation. However, MRI suffers from poor inherent sensitivity and exogenous contrast agents (CAs) are frequently injected before imaging. Unfortunately there are no CAs currently on the market that allow clear imaging of central blood compartment (blood-pool agents, BPCA). These CAs should circulate in the vasculature without fast diffusion. Commercially available CAs diffuse rapidly into tissues and cardiovascular imaging becomes very challenging. Recently, a macromolecule designed as a building block for self-assembling Gd-micelles containing large amounts of Gd-DOTA-chelate was synthesized [1]. These Gd-micelles should persist a long time in the blood compartment opening the possibility for use as BPCA.
Aims: We have formulated the Gd-micelles and performed an *in vivo* study to evaluate their potential as BPCA.
Methods: Mice were injected in the tail vein and imaged on a 3T small animal MRI at 7 timepoints. Gd-DOTA was chosen as control CA. Blood samples were withdrawn from the tail vein at 4 timepoints and organs withdrawn after 3 hours of experiment. Gadolinium (Gd) was quantified in blood and organs by inductively coupled plasma mass spectrometry (ICP-MS). For more details about the formulation see [2].
Results: The MR image analysis showed persistence of Gd-micelles for more than 3 h and less than 30 min for Gd-DOTA in the blood compartment. The presence of Gd-micelles was observed in vessels and heart chambers with a hyperintense signal compared to the pre-injection image. The Gd quantification by ICP-MS indicated that up to 50% of the initial dose was still present in blood 3 h after injection, additionally no organ accumulation was observed. The detection of Gd in liver suggest a hepatic elimination route for Gd-micelles. On the other hand Gd-DOTA was completely eliminated by kidneys and up to 100% of the initial dose was quantified in bladder 3 h post injection.
Conclusions: Compared to marketed CAs, Gd-micelles seem to enable cardiovascular imaging due to their nano-micellar structure, size, and high Gd-loading [3]. As a consequence of these carefully engineered parameters, the Gd-micellar CA remains in the vascular compartment for prolonged periods of time. They show promise as blood pool CA for vascular- and cardio-MRI [4]. Further long term *in vivo* experiments are ongoing to confirm the results of this study and provide additional safety parameters. In the future, targeting ligands may be added to the surface of MRI Gd-micelles to enable molecular imaging.

Keywords: MRI, contrast agent, blood pool, cardiovascular, micelles

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Polymeric Micelles Based on ε-Poly-L-Lysine for siRNA Delivery

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Introduction: Gene therapy is considered a promising method for cancer treatment. Despite all optimism that therapeutics based on RNA interference has aroused, there are still some challenges to face for a successful delivery. Regarding non-viral vectors, polymeric micelles constitute a more recent class of nanosystems [1], which might overcome transfection problems of nucleotide-based therapeutics. Complexation of siRNA with biocompatible polycations in a micellar system requires the selection of cationic charge density and the appropriate size of the polymer for an optimum balance between safety and efficacy.
Aim: Synthesis and characterization of a novel polymeric platform for the complexation of siRNA.
Methods: ε-Poly-L-Lysine (PLL, 10 units 1.3 kDa) was selected based on computational simulation of binding mechanism to a siRNA against human STAT3 [2]. Preparation of amphiphilic co-polymers was performed by amide bond formation of boc protected PLL to polyethylene glycol methyl ether amine (PEG, 2 kDa). This was followed by a polymerization of lactide with PEG-PLL acting as macroinitiator. The primary amines were deprotected successively. Micelles were prepared by an evaporation technique and the mean size determined by dynamic light scattering (DLS) at an angle of 173° at 25°C using a Malvern Zetasizer, and by transmission electron microscopy. Fluorescence measurements were performed using Nile Red to determine the critical micellar concentration (CMC). *In vitro* cytotoxicity assays were performed by WST-1 on lung carcinoma cells (A549).
Results: The dispersity is monomodal and the size obtained by measuring intensity of scattered light was correlated in number by TEM with an average of 80 nm in diameter and zeta potential of approximately 35 mV. The micelles are stable in a diluted concentration with a critical micellar concentration of 50 mg/L. *In vitro* cytotoxic assays demonstrated that the novel triblock co-polymer is biocompatible and non-toxic on cells.
Conclusions: The amphiphilic triblock co-polymers were successfully synthesized, self-assembled into cationic polymeric micelles, characterized and the safety of the new biomaterial was demonstrated *in vitro*. Studies of complexation with siRNA are currently under investigation.

Keywords: Polymeric micelles, siRNA delivery

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Development of Recombinant Proteins Targeting CD80 for Imaging of Atherosclerosis and Chronic Inflammation

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Introduction: Cardiovascular diseases (CVD) account for 45% of all deaths in Europe (2017) and atherosclerosis is considered the major cause of cardiovascular diseases (CVD). The cardiovascular events associated with atherosclerosis are usually triggered by a ruptured atherosclerotic plaque. So far, the detection of «vulnerable plaques» defined as rupture-prone or event-prone plaques remains elusive, preventing a targeted surgical or pharmacological intervention. Molecular imaging using specifically targeted radiolabelled probes to track active *in vivo* atherosclerotic mechanisms noninvasively, may potentially provide a method to help detecting vulnerable plaques. The immunomodulatory molecule CD80 is upregulated in vulnerable plaques [1]. The fusion proteins abatacept and belatacept based on CTLA-4, an endogenous ligand of CD80/CD86, were previously developed by our group for the imaging of immune-relevant tissues [2]. However, they are not selective for CD80 and as IgG fusion proteins have unfavourable pharmacokinetic properties for imaging.
Aim: The aim of this project is to develop CTLA-4 based protein radiotracers with a reduced molecular weight (≤18 kDa) and improved binding affinity and selectivity for CD80 to overcome the previous limitations.
Methods: Monomers and dimers based on the sequence of endogenous sCTLA4, including point mutations to increase the affinity and selectivity towards CD80 [3] were generated and purified. Their affinity and binding properties towards CD80 and CD86 were characterized using Surface Plasmon Resonance (SPR). The proteins were labelled with ^{99m}Tc by complex formation with the included His tag. *In vitro* autoradiography was performed with CD80-positive and negative tissue slices.
Results: The generated proteins showed higher affinity towards hCD80 than hCD86 in the SPR measurements, this can be attributed to the lower k_{off} observed with hCD80. In the autoradiography experiments, the proteins bound to hCD80-positive Raji xenograft slices. This binding was blocked by an excess of belatacept. The hCD80-negative NCI-H69 xenograft slices did not show specific binding of the protein. Slices of vulnerable human plaques showed higher uptake than slices of stable plaques and healthy artery wall.
Conclusion: The optimized CD80-binding proteins present a promising mean for selectively imaging CD80 in inflammatory processes such as atherosclerosis. *In vivo* studies to verify their potential as radiotracers are currently performed.

Keywords: Atherosclerosis, imaging, PET/SPECT, immunogenicity, CD80

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Counselling for Emergency Hormonal Contraception in Swiss Community Pharmacies - A Simulated Patient Study

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Introduction: Since November 2002, the emergency hormonal contraception (EHC) has been dispensed as a pharmacist-only medicine in Switzerland. A counselling interview is required based on an official protocol containing 23 questions. The first 11 questions assess the need for EHC and are mandatory, the rest consists of counselling topics on contraception, sexually transmitted infections (STIs), and records pharmacists' actions.
Aims: We aimed to evaluate the pharmacists' counselling topics during an EHC consultation.
Methods: We conducted a simulated patient study with female 4th-grade pharmacy students who visited a pharmacy each in the German speaking part of Switzerland. In our scenario, the simulated patient requested the «morning-after pill» because the condom had allegedly torn during sexual intercourse the night before. The situation required the delivery of EHC. However, an imminent bus travel would impede the patient to swallow EHC on site because of a history of nausea with anterior intake of EHC. The mention of a new boyfriend since one week was designed as a trigger statement to elicit counselling on STIs. An assessment form was adapted from the Medication Related Consultation Framework (MRCF) and was developed as an online form (EvaSys). The form consisted of 38 items grouped into 6 sections with tick boxes to be completed immediately after the consultation with the pharmacist.
Results: A total of 69 pharmacies were visited between the 17th January 2018 and 17th February 2018. All but one practitioner used the official Swiss protocol. On average, 10.9 of the 11 clinical assessment items were asked. All practitioners identified the need for EHC and 65% supplied EHC for later ingestion. Counselling on EHC was given in 93% of cases, mostly on what to do if patients vomit shortly after use (79%). Pharmacists who did not supply EHC for later ingestion (35%) offered alternative solutions such as the use of an antiemetic drug or checking whether EHC is available at the final destination of the bus travel. STIs were addressed during the consultation in 56% of cases.
Conclusions: Community pharmacies highly complied with the official protocol when suppling EHC. Counselling is predominantly on EHC and concerns rarely STIs.

Keywords: Emergency hormonal contraception (EHC), simulated patient study

Targeting the Endocannabinoid System: Phyloactivity Screening of Medicinal Plants Against Fatty Acid Amide Hydrolase

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Introduction: Fatty acid amide hydrolase (FAAH) is a key enzyme involved in the termination of endocannabinoid signalling via the degradation of the endocannabinoid anandamide. Inhibition of FAAH by natural and synthetic molecules represents a pharmacological strategy to tackle conditions reflecting imbalanced endocannabinoid signalling such as anxiety, depression or metabolic disorders with important implications for human health and nutrition [1]. During the last decades of endocannabinoid research, several plant-derived compounds beyond *Cannabis* components have been reported to modulate the endocannabinoid system [2]. Interestingly, isoflavonoids, which are widely distributed in plants, have been shown to inhibit FAAH [3].
Aims: The main purposes of the present work were (1) to identify potentially new plant-derived FAAH inhibitors in a comprehensive screening. To that aim, 670 medicinal plant extracts (an almost complete representation of Dioscorides' *De Materia Medica*) were tested. (2) we wanted to challenge the hypothesis that a relation between plant phylogeny and biological activity exists and to understand the correlation between FAAH inhibition and cytotoxicity for the extracts screened. (3) Given that plants express FAAH, we tested the hypothesis that endogenous FAAH inhibitors change the *N*-acylethanolamines (NAEs) lipid profile in native tissue.
Methods: Inhibition of FAAH was assessed in *in vitro* preparations of intact and homogenated U937 cells and mouse brain membrane preparations. Cytotoxicity was evaluated in HeLa cells using the MTT colorimetric assay. Competitive activity-based protein profiling was performed on mouse brain membrane proteomes. NAEs in plant extracts were analysed via LC-MS/MS.
Results: At 10 µg/mL 1.7 % of the plant extracts showed significant FAAH inhibition and at 25 µg/mL 8% were cytotoxic. A weak negative correlation between the two variables was observed. Interestingly, we did not see a phylogenetically-biased distribution of FAAH inhibition in the plant extract library. Nevertheless, the plants that showed significant activity belong to the Fabaceae family. We identified isoflavonoids and prenylated derivatives thereof as the most potent FAAH inhibitors, some with IC50 values in the lower nM range.
Conclusions: Prenylated derivatives of flavonoids are a class of bioactive secondary metabolites produced in specific genera of the Fabaceae. Biochemical analyses on the most potent prenylated isoflavonoids showed that these natural products penetrate cells and have a reversible and substrate competitive mechanism of action with a discrete structure-activity relationship. Moreover, the phyloactivity screening hits allow for a comprehensive ethnomedical comparison with FAAH as a validated drug target.

Keywords: Medicinal plants, cytotoxicity, endocannabinoid system, fatty acid amide hydrolase, isoflavonoids

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- fosters the pharmaceutical education and post-graduate education, and coordinates the continuing education by combining education and research at a high scientific level
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- assists in the preparation of Swiss science politics and represents the interests of all pharmaceutical disciplines in the Swiss universities' politics

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