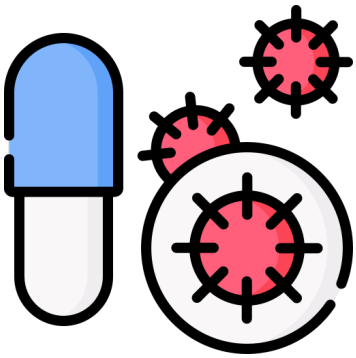
SWISS PHARMA SCIENCE DAY 2023

SAPhS
Swiss Academy of Pharmaceutical Sciences

# Saturday 23 September 2023
# Von Roll Campus University of Bern

## «ANTIBIOTICS»



# 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 9 October 2008, at the University of Bern. For congress reports 2008-2021 including all lecture and poster abstracts see www.saphw.ch**

**The 16th SPhSD offers again a platform to present, in a poster session, the latest research results of Master and PhD students, as well as Post-Docs of the Swiss Academic Institutions for Pharmaceutical Sciences, i.e .ETH Zürich, University of Geneva, University of Basel, University of Bern, and University of Applied Sciences FHNW-School of Life Sciences Muttenz. Three poster abstracts will be selected by the scientific committee for a short lecture.**

**The poster session is embedded in a series of invited lectures given by distinguished scientists. For this year we have selected the topical theme of antibiotics, and the speakers will address various aspects ranging from drug discovery to clinical use and supply issues.**

**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:**

**Rudolf Brenneisen, PhD, Prof., SAPhS**
info@saphw.ch

**Klaus Eyer, PhD, Prof., ETHZ, SAPhS**
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**Prof. Matthias Hamburger, PhD, Prof., SAPhS**
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# Program

| | |
|---|---|
| **09:00 – 10:00** | **Registration, Welcome Coffee** |
| **10:00 – 10:15** | **Welcome Addresses** |
| | • Ursula von Mandach, PhD, Prof.<br>Co-President SAPhS |
| | • Verena Schröder, PhD, Prof.<br>Co-President SAPhS |
| **10:15 – 11:30** | **Morning Session** |
| | Chair: Klaus Eyer, PhD, Prof. |
| **10:15 – 10:45** | **Lecture 1:** |
| | Annette Kuhn, MD, Prof.<br>Woman Hospital, University Hospital Inselspital Bern |
| | «Antibiotics in Clinical Practice - Urogynecology» |
| **10:45 – 11:15** | **Lecture 2:** |
| | Laurenz Kellenberger PhD, CSO<br>Basilea Pharmaceutica International Ltd, Allschwil |
| | «Developing New Antibiotics – Challenges and Opportunities» |
| **11:15 – 11:30 h** | **Discussion of Lectures 1 and 2** |
| **11:45 – 14:00** | **Lunch Break, Poster Session and Job Fair** |

# Program (cont.)

**14:00 – 16:15** **Afternoon Session**

Chair: Matthias Hamburger, PhD, Prof.

**14:00 – 14:45** **Short Oral Presentations – Selected Abstracts**

**14:00 – 14:15** Stephanie Vogt, University of Basel

«Structure-guided design of derivatives of the complement inhibitor compstatin with improved species specificity profiles»

**14:15 – 14:30** Viorica Patrulea, University of Geneva

«Chitosan-based chemical platforms for launching antimicrobial peptides against ESKAPE pathogens»

**14:30 – 14:45** Daniel Batora, University of Bern

«Combined targeted metabolomics and enzyme activity profiles reveal novel disease mechanisms of the symptomatology in hypercalcemia patients»

**14:45 – 15:15** **Lecture 3:**

Malte Kohns, MD
University Children's Hospital (UKBB), Basel

«Optimal Use of Antibiotics in Children»

**15:15 – 15:45** **Lecture 4:**

Isabelle Frey-Wagner, PhD, PD
University of Zurich, Institute for Medical Microbiology

«Antibiotics and Microbiome»

# Program (cont.)

| | |
|---|---|
| **15:45 – 16:15** | **Lecture 5:**<br><br>**Monika Schäublin**<br>**Federal Office for National Economic Supply (FONES, BWL)**<br><br>**«Supply of Antibiotics»** |
| **16:15 – 16:30** | **Discussion of Lectures 3 - 5** |
| **16:30 – 16:45** | **Coffee break** |
| **16:45 – 17:15** | **Award Ceremony**<br><br>**SAPhS Fellow 2023**<br><br>**Poster Prizes** |
| **17:15 – 17:30** | **Closing Remarks** |
| **17:30 – 18:30** | **Farewell Apéro** |

# Sponsors

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# Lectures

**L-1**

**Lecture 1: «Antibiotics in Clinical Practice - Urogynecology»**

**Annette Kuhn, MD, Prof.**

**Woman Hospital, University Hospital Inselspital Bern**

**Biosketch:**

Name: Annette Kuhn; Prof. Dr. med.
Geburtsort: Hannover
Geboren: am 5.3.1964
Adresse: Urogynäkologie, Frauenklinik, Effingerstr.102, 3010 Bern
Telefon: +41 31 632 18 38
Email: annette.kuhn@insel.ch
Zivilstand: verheiratet
Muttersprache: Deutsch

Schulen und Universitäten:

| | |
|---|---|
| 1983 – 1989 | Medizinische Hochschule Hannover, parallel dazu |
| 1985 – 1989 | Magisterstudium der Philosophie und Geschichte, Technische Universität Hannover |
| 1989 – 1990 | Praktisches Jahr (PJ) Universität Freiburg im Breisgau in den Fächern Innere Medizin, Chirurgie, Gynäkologie und Geburtshilfe |
| Mai 1990 | Abschlussexamen mit Summa cum Laude |
| 1986 – 1987 | Aufenthalt im Sudan zwecks Dissertation «Epidemiologie der Tuberkulose bei Kindern im Sudan» in Port Sudan, El Fasher, Darfur, Nordregion; Leitung: Prof. A. Windorfer, Hannover |

Assistenzärztin-Oberärztinstellen:

| | |
|---|---|
| 1990 – 1991 | Allgemeinchirurgie und Intensivmedizin Regionalspital Biel, Schweiz, Chefarzt Prof. H.R. Schultheiss |
| 1992 – 1993 | Urologie, Inselspital Bern, Chefarzt: Prof. E. Zingg |
| 1994 | Weltreise |
| 1995 – 1998 | Assistenzärztin, Gynäkologie und Geburtshilfe, Universitäts-Frauenklinik Bern, Direktor: Prof. H. Schneider |
| 1997 – 1998 | Fellowship bei Prof. S. Stanton, Urogynaecolgy, St. George's Hospital, London; combined Pelvic Floor Clinics Prof. Devinder Kumar |
| 1998 – 2000 | Oberärztin an der Universitäts-Frauenklinik Bern, Leitung Fachbereich Urogynäkologie und Physiotherapie |
| 2000 – 2002 | Research Fellow bei Mr. Ash Monga, Princess Anne Hospital, Southampton, Subspecialty training urogynaecology BSUG, MRCOG |
| Seit 9/2005 | Leitung Fachbereich Urogynäkologie und Ärztliche Leiterin der Physiotherapie |
| 6/2016 | Schwerpunkt operative Gynäkologie und Geburtshilfe FMH |
| 8/2016 | Schwerpunkt Urogynäkologie FMH |
| Seit 2/2019 | Chefarzt-Stellvertretung Gynäkologie und operative Gynäkologie. |

Mitgliedschaften:

Mitglied und Past President der Arbeitsgemeinschaft für Urogynäkologie; Vorstandsmitglied der Schweizerischen Gesellschaft für Blasenschwäche; Mitglied der Schweizerischen Gesellschaft für Gynäkologie und Geburtshilfe, der Internationalen Gesellschaft für Urogynäkologie (IUGA), der Britischen Gesellschaft für Urogynäkologie (BSUG), der internationalen Kontinenzgesellschaft (ICS).
Editor des International Journal for Urogynecology and Pelvic Floor Dysfunction.

**Lecture Abstract:**
Urinary tract infections (UTI) in women occur frequently and are mainly seen as infections of the bladder, sometimes of the upper urinary tract. Due to the short female urethra women are more prone to UTI.
Risk factors include sexual activity, barrier contraception, menopause, diabetes, abnormalities of the urinary tract system and incomplete voiding of the urinary bladder.
Historically, these frequent infections were treated with antibiotics; however, an increasing number of bacterial resistancies have lead to the search for alternatives. Commonly, the bacteria creating UTI are from the intestine.
The resistance development shows regional differences with alarming situations in southern Europe and some Eastern countries, therefore the use of alternatives is essential.
Nowadays we try to avoid antibiotic use in so called simple bladder infections in women and use plant derived substances, oral or parenteral vaccinations, local estrogens in postmenopausal women and we try to reduce the prophylactic use of antibiotics whenever possible.
The talk will go into details about the resistancy situation and highlight alternatives and indications.

**L-2**

**Lecture 2: «Developing New Antibiotics – Challenges and Opportunities»**

**Laurenz Kellenberger PhD, CSO**

**Basilea Pharmaceutica International Ltd, Allschwil**

**Biosketch:**
Laurenz Kellenberger is Chief Scientific Officer of Basilea Pharmaceutica International AG, a commercial stage biopharmaceutical R&D company, focused on the development of products in the therapeutic area of anti-infectives. He holds a Ph.D. in Organic Chemistry from the Swiss Federal Institute of Technology Zurich (ETH Zurich). After postdoctoral studies in the Department of Biochemistry at the University of Cambridge (UK) he joined F. Hoffmann-La Roche, where he held different positions in preclinical research and chemical technologies.
In 2000 he joined Basilea and held several leadership positions in research with responsibilities for key projects from lead finding and optimization through to preclinical development, including as Head of Chemistry.

**LectureAbstract:**
Antibiotics are essential in modern medicine but their widespread use led to the emergence of drug-resistant bacteria and antimicrobial resistance (AMR) is now recognized as a threat to society and public health. Yet, only few new antibiotics have been developed in recent years and no novel classes of antibiotics have reached the market. New, truly innovative antibiotics providing an option to combat future multi-drug resistant (MDR) pathogen outbreaks are required to address the public health need. However, the development of new antibiotics faces two main challenges: antibiotics are difficult to discover and antibiotics have limited commercial attractiveness. Therefore, revitalizing the antibiotic pipeline requires the joint actions by industry, academia, regulators, health authorities and government agencies. The increasing awareness of AMR and discussions around incentives and new economic models and investment into R&D of anti-infectives give hope for the future antibiotic pipeline.

**L-3**

**Lecture 3: «Optimal Use of Antibiotics in Children»**

**Malte Kohns, MD**

**University Children's Hospital (UKBB), Basel**

**Biosketch:**
Malte Kohns Vasconcelos is a Consultant in Infectious Diseases at the University of Basel Children's Hospital and Professor for Epidemiology and Head of the Department of Epidemiology at the University Medical Centre Hamburg-Eppendorf.
He is a member of the Joint Taskforce on Paediatric Antibiotic Dosing by the European Society for Paediatric Infectious Diseases (ESPID) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST). He is the coordinating investigator on various RCTs and observational studies with a focus on acute respiratory infections. His main research interests are the diagnosis and management of common infections in emergency care and equitable provision of care to migrant and refugee children.
He completed his undergraduate and doctoral medical degrees at Heinrich Heine University Düsseldorf in Germany and gained an MSc in Epidemiology from the London School of Hygiene and Tropical Medicine.

**Lecture Abstract:**
Antibiotics are among the most frequently used drugs in paediatric and adolescent medicine. In the context of increasing bacterial resistance to antibiotics, the considered and rational use of antibiotics has been increasingly identified as essential in the last decade in order to maintain the effectiveness of these drugs globally for as long as possible. Since children and adolescents receive a disproportionately high number of antibiotics compared to adults, especially in the outpatient setting, initiatives to promote rational antibiotic therapy in paediatrics are particularly desirable.
Data from Germany show that 70% of antibiotic prescriptions for children and adolescents younger than 15 years are for respiratory tract infections (25% acute tonsillitis, 17% bronchitis, 16% otitis media, 12% upper respiratory tract infections). Similar patterns were also observed in the United States of America (USA), where the next most common indications were skin infections (12% of total use) and urinary tract infections (2%). Together with the treatment of community-acquired pneumonia, it can thus be assumed that about 75-80% of all antibiotics prescribed in the outpatient setting are used for respiratory infections. Data from the USA suggest that antibiotics are prescribed unnecessarily for at least 30-40% of treated respiratory tract infections, leaving a considerable potential for optimisation.
The talk will discuss optimal use of antibiotics using the 5-dimensions approach: correct disease (indication), drug (choice of antibiotic), dose, delivery (formulation and route) and duration of therapy, with a focus on dosing and the ESPID-EUCAST Joint Taskforce's ongoing work on identifying paediatric minimal dosing necessary to secure applicability of EUCAST antibiotic susceptibility interpretation guidelines that were originally designed for adults.

**L-4**

**Lecture 4: «Antibiotics and Microbiome»**

**Isabelle Frey-Wagner, PhD, PD**

**University of Zurich, Institute for Medical Microbiology**

**Biosketch:**
Based on a background of food chemistry (LMU Munich) and human nutrition (ETHZ) I pursued a PhD in nutrition physiology at the Technical University of Munich (TUM) and continued as a Postdoc in experimental gastroenterology at the University Hospital Zurich (USZ). My early research focused on the comprehensive multi-omics analysis of a genetically modified mouse model lacking a peptide transporter for di-and tripeptides.
Research on inflammatory bowel disease involved application and development of animal models for intestinal inflammation and studying the impact of genetic background and the host gut microbiota on disease susceptibility and pathogenesis. Further studies addressed the interaction of the gut microbiota with alternative therapeutic approaches for inflammatory bowel disease and the impact of medication on inflammatory bowel disease susceptibility through alterations of the gut microbiota. In an SNF-exchange to the laboratory of Prof. Elaine Holmes, (Imperial College London), I completed my studies on host-microbiota interactions in intestinal inflammation with metabolome analyses.
Since moving to the Institute of Medical Microbiology of the UZH, I study the interaction between the gut microbiota and the intestinal pathogen Clostridioides difficile. Antibiotic treatment is the major risk factor for development of C. difficile infection, highlighting the role of colonization resistance against pathogens provided by gut microbiota commensals. Current studies address asymptomatic C. difficile colonization in populations at high risk for developing (recurrent) C. difficile infections and probiotics to support gut microbiota colonization resistance after disturbance through antimicrobial treatment. My approach is a comprehensive characterization of host – gut microbiota interactions through multi-omics analysis, detailed clinical characterization, and integrative data analysis in relevant patient cohorts to elucidate novel targets for support of gut microbiota mediated colonization resistance against pathogens.

**Lecture Abstract:**
Antimicrobial treatment is crucial for a wide variety of infectious diseases, yet it has profound impact on the gut microbiota. The last 25 years provided tremendous insights into interactions between the gut microbiota and its host. It has been shown that the gut microbiome is involved in essential functions of the host organism, e. g. immune maturation. Gut microbiota alterations are associated with numerous diseases, not only of the gastrointestinal tract like colon cancer, inflammatory bowel diseases, and irritable bowel disease, but also allergic- and auto-immune diseases, metabolic disease, various malignancies, cardiovascular and renal disease and via the gut-brain axis with psychiatric and neurodegenerative diseases. Depending on compound class and mechanism of action, antimicrobial drugs have more or less profound impact on the gut microbiome and the effect can be short- or long-lasting.
In particular, colonization resistance to the intestinal pathogen *Clostridioides difficile* is impaired by antimicrobial treatment, rendering patients treated with «high risk» antimicrobials, e. g. cephalosporins, quinolones and clindamycin prone to *C. difficile* infection (CDI). Antimicrobial treatment of CDI further impairs the gut microbiota colonization resistance, resulting in a high risk to enter a viscious cycle of recurrent infections that is associated with an overall high mortality. Currently, different approaches, e. g. fecal microbiota transfer, live biotherapeutic products and novel probiotics, are applied or under development to mitigate the impact of antimicrobial treatment on the gut microbiome. In addition, development of antimicrobial compounds with high specificity and

consequent implementation of antimicrobial stewardship programs and current treatment guidelines are crucial to minimize the side-effects of antimicrobial treatment on the gut microbiome.

**L-5**

**Lecture 5: «Supply of Antibiotics»**

**Monika Schäublin**

**Program Management Supply Security Therapeutic Products**
**Federal Department of Economic Affairs, Education and Research EAER**
**Federal Office for National Economic Supply FONES**

**Biosketch:**
Monika Schäublin-Müller graduated in pharmacy from the University of Bern in 1989. After working in a hospital pharmacy for a year, she worked in various functions in the pharmaceutical industry. From 2005 to 2016, she took over the development and management of the central cytostatics preparation at the cantonal hospital in Olten. Since 2016 she is working in the office of therapeutic products at the Federal Office for National Economic Supply.

**Lecture Abstract:**
The supply situation for medicinal products, including antibiotics, has been steadily deteriorating for several years. The number of notifications for essential medicines on the National Economic Supply's medicines platform has been rising constantly since the start of the obligation to notify shortages in 2015. Parallel to this, the requests to obtain from the compulsory stocks to support the market are also increasing. On 31.01.2023, the National Economic Supply newly classified the situation with regard to the supply of essential medicinal products as problematic, mainly due to the lack of supply with oral antibiotics and informed the Federal Council of this in its meeting on 01.02.2023.
The compulsory stocks of parenteral antibiotics have already been open since 2019, in 2020 the compulsory stocks were extended to all parenteral anti-infectives, and now in March 2023 they will be extended to the oral forms. The increasing number of market withdrawals makes it more difficult to replace affected medicines. Products with monopole character are increasingly affected. In 2022, of a total of 201 reported supply disruptions, 71 occurred with antibiotics containing 21 active substances (35% of all notified disruptions).
The demand for oral antibiotics can be met less and less by the marketing authorization holders. It has become very difficult to replace the missing products, since within one active principle (API) usually several suppliers and also many other related active principles are affected.
The reasons for the deterioration of the supply situation for antibiotics are manifold and have existed for a long time for the most part. Many active ingredients in this therapeutic group and in particular the affected APIs are relatively old and no longer protected by patents. The correspondingly low prices lead to numerous product range and supply chain adjustments and market withdrawals. In addition to the active ingredients, there is also an increasing lack of precursors, excipients and packaging. Moreover, Switzerland is a relatively small market for marketing authorization holders, which reduces its attractiveness for suppliers. The distortions in the market caused by Covid-19, the energy crisis and the war in Ukraine affect the global market and aggravated the situation further. For antibiotics it can be said that during the two Covid-19 years, infectious diseases declined worldwide due to the masking requirement. As a result, production capacities had to be reduced and some people had to be laid off. The loss of revenue also meant that there was no money to invest in expanding production. It takes time to ramp up this system again, and the production quantities still do not cover the demand adequately.

# Posters

## I. PHARMACEUTICAL BIOLOGY / PHYTOPHARMACOLOGY

**I-1** **M. Karpouchtsi:** Novel inhibitors targeting oncogenic ERK and AKT signaling in melanoma: From compound library screening to target identification
**I-2** **T. Balsiger:** Natural products reducing forgetting by inhibiting the human Musashi2 protein
**I-3** **L. Höing:** Biosynthesis of dihydroxytropolone in *Streptomyces sp.*

## II. PHARMACEUTICAL TECHNOLOGY

**II-1** **F. Abdi:** Colonic delivery of aqueous formulations using 3D printed capsules
**II-2** **N. Zoratto:** Bioinspired, low-cost device for minimally invasive blood sampling
**II-3** **O.B. Majchrzak:** Druggable targets on breast cancer tissues
**II-4** **A. Ramos Barros:** Development of nucleic acid-based vaccines against dengue fever using a Rational Design of Experiments (DoE) approach
**II-5** **L. Morici:** Avidin-based cartilage targeting delivery system for osteoarthritis therapy
**II-6** **I. Nikolić:** Navigating towards improved cytotoxicity assessment in nanomedicine development: shifting from colorimetric to fluorescence-based assays
**II-7** **M. Carone:** Temperature-triggered in situ forming lipid mesophase gel for local treatment of ulcerative colitis
**II-8** **S. Geisshüsler:** *In vivo* evaluation of cyclodextrin microneedles for particulate vaccine delivery
**II-9** **V. Patrulea:** Chitosan-based chemical platforms for launching antimicrobial peptides against ESKAPE pathogens
**II-10** **K.T. Sahni:** Trend analysis of analytical data in compounding
**II-11** **G. Bordon:** Liposomal aggregates sustain the release of rapamycin and protect cartilage from friction
**II-12** **C. Rodríguez-Nogales:** Chitosan microspheres for the intra-articular delivery of disease-modifying osteoarthritis drug nanocrystals

## III. PHARMACOEPIDEMIOLOGY

**III-1** **B. Polek:** The Round Table on Antibiotics, a multi-disciplinary Swiss initiative to foster the development and availability of antibiotics
**III-2** **K. Messner:** Attitudes of Swiss and German pharmacists regarding the dispensing of biopharmaceutical medicines pre- and post-COVID-19 pandemic
**III-3** **J. Weber:** Pharmacy students' perception of computer based simulation in the era of online learning expansion

## IV. CLINICAL PHARMACY / CLINICAL PHARMACOLOGY

**IV-1** **G. Castelletti:** NutriPro™: A product-specific e-tool for healthcare professionals in clinical nutrition
**IV-2** **V.V. Huwiler:** Compatibility of selected nanoparticulate IV iron medicinal products with all-in-one parenteral nutrition admixtures tested by ICP-MS
**IV-3** **C. Meyer-Massetti:** doMESTIC RedPIM - Study of Medication Safety in Home Care, Reducing Potentially Inappropriate Medications: A structured approach to interprofessional medication management for home care clients

**IV-4** **C. Meyer-Massetti:** Pharmaceutical care in asylum homes
**IV-5** **L.E. von Arx:** Optimizing paediatric care: Administering beta-lactams via extended infusion. A systematic review and meta-analysis
**IV-6** **U. Wernli:** Administration of intranasal midazolam for acute anxiety in palliative care - AIM CARE study protocol
**IV-7** **N. Schönenberger:** Consensus on indicators for medication-related readmissions: A Delphi study
**IV-8** **A. Bollinger:** Analgesic therapy failure in a COMT HPS/HPS diplotype carrier with fibromyalgia – A case report
**IV-9** **N. Fischer:** MOTIVATE – Motivation of pharmacists to participate in an organized cancer screening program
**IV-10** **D. Batora:** Combined targeted metabolomics and enzyme activity profiles reveal novel disease mechanisms of the symptomatology in hypercalcemia patients
**IV-11** **P. Meier:** Analysis of endocannabinoids, associated lipids and glucocorticoids in serum and CSF of control and multiple sclerosis patients: A retrospective study

## V. MOLECULAR PHARMACOLOGY / MOLECULAR MEDICINE

**V-1** **E. Nerger:** Investigation of the interplay between the membrane-palmitoylated protein 1 (MPP1) and the angiotensin II AT1 receptor (AGTR1)
**V-2** **S. Vogt:** Structure-guided design of derivatives of the complement inhibitor compstatin with improved species specificity profiles
**V-3** **J. Felsch:** Factor H-capturing on HMEC-1 cells with the cyclic peptide 5C6: Synthesis, cell surface modification and measurement of FH-capturing from human blood serum
**V-4** **M. Wittwer:** Analysis of SRSF1 functions in HEK cells by NGS and mutagenesis
**V-5** **N. Paloumpis:** CYP3A1 expression and activity in liver of SLCO2B1 +/+ and Slco2b1-/- rats – results from a study with erlotinib
**V-6** **E. Umnyakova:** Complement modulation on biosurfaces: click chemistry approach for natural regulators recruitment

## VII. PHARMACOLOGY / BIOPHARMACY

**VI-1** **S. Duwor:** Phylogenetic analysis of pyruvate-ferredoxin oxidoreductase; a redox enzyme involved in the pharmacological activation of metronidazole in anaerobic protozoa and bacteria
**VI-2** **J. Furrer:** *In vitro* antibacterial activity of arene ruthenium(II) compounds
**VI-3** **A.K. Mapanao:** Evaluation of folate radioconjugates: Implications of folate receptor isoform selectivity
**VI-4** **S.K. Lustenberger:** Towards refining cancer immunotherapy: PET tracers for investigating legumain targeting in the tumor microenvironment
**VI-5** **L. Warryn:** Repurposing drugs to develop treatments for Mycobacterium ulcerans disease
**VI-6** **A. Linder:** Measuring cytokine-secretion dynamics of single cells to deepen the understanding of systemic autoinflammatory diseases
**VI-7** **I. Grbo:** Human monocyte specific DNA inflammasome activation: Implication for liposome induced inflammatory response
**VI-8** **R.H. Wallimann:** Investigation of the spatial distribution of 175Lu-labeled small molecules using laser ablation ICP-MS
**VI-9** **M. Rysz:** Validation and implementation of a LC-MS/MS method to simultaneously quantify atorvastatin, erlotinib, and OSI-420 in experiments with rat liver microsomes
**VI-10** **L. Schlotheuber:** Investigating antibody-cytokine multifunctionality of human B cells using single-cell droplet microfluidics

## I. PHARMACEUTICAL BIOLOGY / PHYTOPHARMACOLOGY

### P-I-1

### Novel inhibitors targeting oncogenic ERK and AKT signaling in melanoma: From compound library screening to target identification

**M. Karpouchtsi[1], L. Dürr[1], M. Dobrzynski[2], S. Radetzki[3], T. Hell[1], M. Hamburger[1], J.P. von Kries[3], O. Pertz[2], R. Teufel[1], and E. Garo[1]**

[1] *Department of Pharmaceutical Sciences, University of Basel, 4056 Basel*
[2] *Institute of Cell Biology, University of Bern, 3001 Bern*
[3] *Leibniz-Forschungsinstitut für Molekulare Pharmakologie, 13125 Berlin, Germany*

**Introduction:** Malignant melanoma is the deadliest type of skin cancer with unmatched rates of mutations that frequently arise in the MAPK/ERK and PI3K/AKT signaling pathways. Although specific inhibitors of these pathways show spectacular initial results in the clinic, most patients relapse within just a few months [1]. Novel inhibitors targeting aberrant ERK/AKT signaling in melanoma are therefore urgently needed.
**Aim:** Discovery of novel natural products targeting oncogenic ERK/AKT signaling in melanoma.
**Method:** Our natural product lead discovery platform of plant extracts was combined with an innovative high-content screening (HCS) assay that quantifies downstream inhibitory activity at the ERK and AKT levels [2]. To further explore the coverage of chemical space for such inhibitors, this HCS was part of an EU-OPENSCREEN program. Transferring from 96- to 384-well format enabled the screening of large pure compound libraries by accessing high-throughput screening (HTS) pipelines.
**Results and Conclusion:** To this end, we screened our in-house library of 2,576 crude plant extracts as well as additional 25,696 pure natural and synthetic compounds through our scalable screening and discovery pipeline. A total of 46 active compounds with diverse natural scaffolds were confirmed as downstream inhibitors of ERK and/or AKT with $IC_{50}$ values in the low micromolar range. Our approach allows the exploration of the chemical space of natural product libraries consisting of crude extracts and pure compounds while targeting downstream activities of complex signaling pathways. The current challenge aims towards target identification of the most promising hits. Our strategy includes similarity searches and assessment of physical binding as well as enzymatic inhibition with heterologously produced pathway proteins. Ultimately, we envisage to develop these newly discovered inhibitors into lead compounds for future drug development.

**Keywords:** melanoma, natural products, MAPK/ERK and PI3K/AKT signaling, high-content screening, target identification

**References:**

[1] Lim S.Y. et al. Mechanisms and strategies to overcome resistance to molecularly targeted therapy for melanoma. Cancer 2017; 123: 2118-2129. doi: 10.1002/cncr.30435
[2] Dürr L., Hell T. et al. High-Content Screening Pipeline for Natural Products Targeting Oncogenic Signaling in Melanoma. J Nat Prod 2022; 85: 1006-1017. doi: 10.1021/acs.jnatprod.1c01154

**P-I-2**

## Natural products reducing forgetting by inhibiting the human Musashi2 protein

**T. Balsiger[1], A. Stetak[2,3], R. Hagmann[1], K. Huynh[2], P. Solis[4], M. Hamburger[1], A. Papassotiropoulos[2,3], R. Teufel[1], E. Garo[1]**

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[3] *University Psychiatric Clinics, University of Basel, 4056 Basel*
[4] *Centro de Investigaciones Farmacognosticas de la Flora Panamena (CIFLORPAN), Facultad de Farmacia, Universidad de Panama, Panama City, Panama*

**Introduction:** Memory maintenance and forgetting are fundamental processes in our lives. Pathological forgetting as in neurodegenerative diseases (e.g. Alzheimer`s disease) leads to serious cognitive impairment. Recently, Musashi2 (MSI2), an RNA-binding protein and translational regulator, has emerged as a crucial player in promoting forgetting [1]. As the global population ages, and no compound is available to treat forgetting, there is an evident need to discover compounds inhibiting MSI2.
**Aim:** Discovery of new lead compounds from plant natural products inhibiting MSI2.
**Methods:** Our in-house library of 2576 plant extracts underwent screening for human MSI2 inhibition by using a biochemical fluorescence polarization (FP) assay. A total of 61 hits were selected for HPLC-activity profiling, among which the MeOH extract of *Freziera candicans* was prioritized for scale-up isolation. Compounds responsible for the observed activity in the extract were subsequently isolated, and their structures were fully elucidated using mass spectrometry, NMR and ECD spectroscopy. Finally, the activity of all isolated compounds was assessed *in vitro* and the most active ones were further subjected to *in vivo* testing in a chemotaxis experiment using *Caenorhabditis elegans* [2].
**Results:** Our workflow enabled the isolation of 11 active natural products from *Freziera candicans*. They all inhibit MSI2 in the sub-nanomolar range *in vitro*. Interestingly, the most active compound was identified as ellagic acid, a polyphenol common in many foods such as nuts and berries. Notably, ellagic acid showed strong significant improvement of the short-term memory of *C. elegans in vivo*.
**Conclusions:** Further experiments are planned, including extended investigations into long-term memory studies in *C. elegans* regarding ellagic acid. Additionally, the specific binding of all isolated compounds to MSI2 will be verified by both thermal shift and cell proliferation assays.

**Keywords:** Memory & forgetting, natural products, Musashi2 inhibitors, ellagic acid, *C. elegans*

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**P-I-3**

## Biosynthesis of dihydroxytropolone in *Streptomyces sp.*

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**Introduction:** Tropolones are a group of natural products with potent metal-chelating properties that exhibit antibacterial, antiviral and antitumoral activity [1]. These compounds are hydroxylated derivatives of tropone that consists of a seven-membered, non-benzenoid, aromatic carbon-ring with an additional keto-group. In bacteria the precursor for these compounds surprisingly originates from primary metabolism, i.e. the CoA-dependent catabolism of phenylacetic acid (paa). However, depending on the producing strain, different sets of enzymes are used to modify this precursor. For the gram-positive *Streptomyces sp.*, the gene cluster encoding the dihydroxytropolone biosynthetic machinery was identified by gene-knockout studies [2].
**Aims:** In this study we investigated dihydroxytropolone formation in *Streptomyces sp.* by *in vitro* reconstitution of the biosynthetic pathway and elucidated the role of involved enzymes.
**Methods:** Heterologously produced enzymes were used to gain insight into the individual biosynthetic steps and reaction mechanisms of the partaking enzymes. Conducted assays were analyzed via LC-MS, accumulating products were compared to chemically synthesized standards. Structure of a key enzyme was analyzed by X-ray crystallography.
**Results:** Accordingly, the CoA-ester bond from the precursor molecule originating from phenylacetic acid catabolism gets cleaved of. In an unanticipated series of reactions comprising hydroxylation, decarboxylation and ring oxidation tropolone gets formed. This compound undergoes two consecutive ring-hydroxylations and is finally transformed to dihydroxytropolone. However, not all enzymes in the gene cluster contribute to the formation of the final product. Future investigations will focus on elucidating their overall role in the context of dihydroxytropolone formation. Additionally, a crystal structure of one of the core enzymes could be obtained, which gave hints about the underlying reaction mechanism.
**Conclusions:** The biosynthesis pathway for dihydroxytropolone could be reconstituted successfully *in vitro*. Taken together, the discovered enzyme functionalities substantially differ from the previously proposed roles that were based on gene knock out studies. Currently, co-crystallization studies are carried out, to get some final insights in possible reaction mechanisms of partaking enzymes.

**Keywords:** Tropolone, secondary metabolites, antibiotics, *Streptomyces sp.*

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## II. PHARMACEUTICAL TECHNOLOGY

### P-II-1

### Colonic delivery of aqueous formulations using 3D printed capsules

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**Introduction:** The human gut microbiota significantly impacts human health, and its imbalance can contribute to various diseases, influencing treatment outcomes. Fecal microbiota transplantation (FMT) has shown promise in treating *C. difficile* infections and is being explored for other conditions. However, its standardization is hindered by invasive administration routes and its effectiveness by high dosing requirements. Oral dosage forms can overcome these obstacles, however delivering live beneficial bacteria to the colon via the oral route is challenging due to harsh gastrointestinal conditions. Therefore, there is a need for new delivery systems to efficiently deliver live bacteria in sufficient amounts.
**Aims:** The objective of this work is to develop and characterize 3D-printed capsules that can encapsulate an aqueous suspension of live bacteria. These capsules are designed to protect the bacteria from the harsh conditions that are encountered during gastrointestinal transit and selectively release their content at the distal part of the intestine.
**Methods:** The water-insoluble lid and body were 3D-printed by digital light processing (DLP) using methacrylated poly(Ɛ-caprolactone) and its random copolymers with poly(D,L-lactic acid) and poly(glycolic acid). The locking cap was 3D-printed by fused deposition modeling (FDM) using a water-soluble poly(vinyl alcohol). The locking caps were dip-coated with an enteric polymer, Eudragit S100. The mechanical properties (tensile strength, elongation at break and compression deformation), degradation, and swelling of the capsules in simulated intestinal fluid (SIF) at pH 6.8 were evaluated. Their resistance to proton diffusion was assessed in simulated gastric fluid (SGF) at pH 1.2 by monitoring the pH changes of the inner solution. The release profiles of the capsules loaded with an aqueous solution of Evans blue were determined in SGF pH 1.2, SIF pH 6.8 and SIF pH 7.3. The release was further visualized by surface dissolution equipped with an UV-Vis camera. Finally, the performance of the capsules was evaluated *in vivo* in a beagle dog by monitoring the release of barium sulfate aqueous suspension with X-ray imaging.
**Results:** Utilizing FDM and DLP 3D printing, we achieved precise fabrication of a soft capsule body and lid, and a locking cap with an enteric coating of 40 µm. The capsules were able to resist compression forces that are expected in the GI tract and restricted proton diffusion. *In vitro* dissolution tests showed that the capsules remained intact for 4.5 h and achieved complete release of Evans blue after 5-6.5 h. X-ray images of an *in vivo* study on a beagle dog showed that the capsules did not leak for 2-2.5 h post administration and after 2.5-4 h they started to deform and release their content. These data suggest that the capsules can release their aqueous content in the distal part of the small intestine or the colon.
**Conclusions:** In this study, we report a simple design of 3D-printed capsules for the oral delivery of aqueous suspensions to the distal part of the intestine or the colon. These capsules protect their content from gastric fluids and withstand mechanical stress. They open in the late intestine, thus showing promise for the oral administration of bacterial suspensions.

**Keywords** Capsules, 3D printing, colonic delivery, aqueous suspension.

This work was financially supported by the SNSF (grant 315230_197644/1).

**P-II-2**

## Bioinspired, low-cost device for minimally invasive blood sampling

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**Introduction:** Blood sampling is the most prevalent route for disease diagnosis and monitoring [1]. However, traditional venipuncture is painful, invasive and costly, posing challenges in low and middle-income countries (LMICs) with limited resources [2]. Furthermore, venipuncture causes distress, particularly in children, leading to potential procedure avoidance. Although microsampling methods, such as finger sticks, offer a less invasive option, they suffer from low accuracy and high variability due to limited blood volumes [3]. Additionally, the current microsampling devices are too expensive for LMICs. Thus, alternative sampling approaches that allow easier and more reliable blood testing at a low cost are needed.
**Aim:** With the aim of improving children's acceptance and making blood sampling more accessible in LMICs, we developed a bioinspired device for liquid, capillary blood collection.
**Methods:** The device's designs were created in SolidWorks and fabricated using food-grade polydimethylsiloxane (PDMS) *via* mold-casting. Thereafter, their adhesive properties were measured *ex-vivo* on freshly extracted porcine skin with a texture analyzer. *In-vitro* fluid extraction experiments were performed with an *in-house* designed setup by using anticoagulated, fresh porcine whole blood. Customized stainless steel microneedle blades (MNs) were embedded in 3D-printed basins, mounted in suction cups and tested *ex-vivo* on porcine ear skin to determine their penetration depth. For the anticoagulant coating, polypropylene spheres were spray-coated with a 1% w/v $K_2$-EDTA solution and loaded into the devices. Finally, the assembled prototypes were tested *in-vivo* on shaved piglets and the collected blood was measured by weighing the devices before and after application.
**Results:** The design's operation principle was inspired by the anatomy of sanguivorous leeches. Similar to the anterior suction disk of the leeches, the device utilizes negative pressure to assist blood withdrawal and storage. However, in contrast to the leech jaws, the device uses hidden MNs to feature minimal invasiveness and good skin penetration.
Device's optimization and *in-vitro* blood extraction: The device's design was optimized to enable its one-hand application and reach a negative pressure of ~ –50 kPa, which was reported to increase the blood flow rate. *In-vitro* fluid extraction experiments confirmed the ability of our prototype to sample about 647 ± 250 µL of whole blood in 10 min.
MN array development: *Ex-vivo* experiments showed that a circular MN array, with a MN thickness of 75 µm and a tip angle of 13°, resulted in an increased skin penetration (1.70 ± 0.20 mm) and, therefore, was selected for the final version of the device.
Device assembling and *in-vivo* testing: The assembled version of the device consisted of a suction cup equipped with a metal MNs patch array, a storage compartment containing anticoagulant-coated spheres, a 3D printed adapter to facilitate its application, and a medical-grade adhesive to form an air-tight seal with the skin. The pilot *in-vivo* study, performed on shaved piglets, showed the ability of the best-performing microsampling device to extract about 195 µL of whole blood with minimal invasiveness.
**Conclusion:** In this project, we developed a minimally invasive and low-cost device able to sample about 195 µL of capillary blood *in-vivo*. The device geometry, MNs array, and anticoagulant coating were optimized to suit the requirements of LMICs. Being minimally invasive and cheap, this device would be an impactful contribution to medicine.

**Keywords:** leech-inspired, minimally-invasive device, blood micro-sampling.

**Acknowledgment:** Funding from the BRCCH is acknowledged.

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**P-II-3**

## Druggable targets on breast cancer tissues

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**Introduction:** Cancer cells express a range of surface receptors, some of which could serve as a means to access the intracellular compartment via receptor-mediated endocytosis. For instance, CD44, a cell surface glycoprotein expressed by various solid tumours, displays notable affinity for glycosaminoglycan polymers such as hyaluronic acid (HA). Creating a ligand that targets CD44 using the structure of HA as a reference and linking the new ligand to a platform nanocarrier offers a compelling approach for developing targeted drug delivery.
**Aims:** To investigate identifiable receptor sites present on cancer cells with a primary emphasis on breast cancer tissues. To establish a panel of ligands to functionalise platform polymers. To advance our understanding of receptor-ligand interactions enhancing the cellular uptake of nanocarriers therefore having implications for targeted therapies in breast cancer.
**Methods:** In this study, CD44 served as the model receptor, with hyaluronic acid as the reference compound that has been previously characterized in the scientific literature for their substantial affinity to this specific receptor of interest. We screened the Swiss Similarity library for compounds exhibiting similarity in terms of molecular descriptors or electronic cloud shape to HA. Molecular docking of HA-similars into CD44's binding pocket enabled the identification of promising candidates based on their docking scores. Selected ligands were then conjugated to poly(amidoamine). Characterization of the synthesized nanoconjugates was accomplished using NMR, AF4-DLS, NTA, and EM. Lastly, cytocompatibility was monitored using the MCF-7 breast cancer cell line.
**Results:** The reference HA docking into CD44 resulted in a docking score of -5.2. Looking for values below the reference, *in silico* simulation indicated 2'-deoxyguanosine-5'-mono-phosphate and D-mannuronic acid as the best HA-binding mimics, reaching the docking score of -6.3 and -5.8, respectively. However, following structural analysis, with docking scores of -5.7 and -5.4, 2'-deoxyadenosine-5'-monophosphate and alginic acid were applied instead. Subsequent conjugation yielded relatively heterogeneous populations (PDI = 0.4) of particles exhibiting sizes between 8-300 nm. The confirmation of successful synthesis resulting in the desired products was achieved by correlating NMR peak intensities (either their appearance or disappearance) with the structural alterations occurring during conjugation. EM images clearly show evolution of the morphological changes produced upon the conjugation influencing the shape of nanocarrier from round platform polymer to elongated particles of nanoconjugates.
**Conclusions:** Molecular dynamics *in silico* simulations led to a successful identification of ligands to be grafted onto platform polymers to facilitate cellular uptake of the nanocarriers.

**Keywords:** Molecular dynamics, *in silico* simulations, breast cancer, nanocarriers, drug delivery systems

**P-II-4**

## Development of nucleic acid-based vaccines against dengue fever using a Rational Design of Experiments (DoE) approach

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**Introduction:** Dengue fever is the most dominant arthropod-borne viral disease, majorly spread in tropical and subtropical regions, menacing almost half of the world's population [1]. There is a crucial need for a safe and cost-effective tetravalent dengue vaccine protecting all individuals against the four dengue serotypes regardless of their age and serostatus [2].
**Aims:** This project aims at developing an easily produced, stable at fridge temperature and intramuscularly delivered vaccine. It is a collaboration between Chula VRC, developing dengue virus (DENV) nucleic acid vaccines and ISPSO, formulating tetravalent nucleic acid lipid-based delivery systems using a rational DoE approach.
**Methods:** A full factorial 23 screening design was established using Statgraphics 19X-64 software investigating the impact of lipid composition on Z-Average, polydispersity index (PDI) and Zeta-Potential of a well described blank lipid nanoparticle (LNP) formulation [3] made of a cationic ionizable lipid (D-Lin-MC3-DMA) or a cationic lipid (DOTAP chloride), a phospholipid (DPPC or DOPC), a pegylated lipid (DMG-PEG2000 or DSPE-PEG2000-amine) and cholesterol (50:10:1.5:38.5 molar ratio), manufactured in triplicates by ethanol injection method (EIM). Samples were characterized by dynamic light scattering (DLS) before and after replacement of ethanol by 1xDPBS pH 7.4 by size exclusion chromatography (SEC). In a second step, the aqueous phase used during EIM was modified and 4 different CIL molar ratios were tested (25; 40; 50; 100) to possibly decrease the Z-Average of a formulation with D-Lin-MC3-DMA, DPPC, DSPE-PEG2000-amine and cholesterol, displaying a higher Z-Average than desired in the previous step. Samples were also manufactured in triplicates and characterized by DLS as described previously. In the third step, in a preliminary round of experiments (N=1), 2 previously selected LNP formulations (CIL1a and CL2) were formulated with a model phosphorylated Enhanced Green Fluorescent Protein (pN1-EGFP) DNA gifted from Prof. Prompetchara from the Chula VRC, at 3 different Nitrogen to Phosphate (N/P) ratios: 1/1; 1,5/1 and 2/1. The formulations were manufactured by Microfluidics (MF) and characterized by DLS. pN1-EGFP DNA encapsulation efficiency (EE) was determined using a Picogreen® assay. Cytotoxicity of samples were determined using a WST-1 assay using RAW 264.7 cells.
**Results:** Cationic (ionizable) lipid was found to be the only statistically significant factor on Z-Average, with a p-value of 0.029. LNPs with D-Lin-MC3-DMA showed a bigger Z-Average than those with DOTAP chloride. No factor had a significant impact on PDI nor Zeta-Potential. A formulation with DOTAP chloride, DOPC, DSPE-PEG2000-amine and cholesterol (CL2), meeting the desired criteria, was selected. The lipid molar ratio of a formulation with D-Lin-MC3-DMA, DPPC, DSPE-PEG2000-amine and cholesterol (CIL1), with a Z-Average initially higher than desired (248.4±31.6 nm) was modified to 25:10:1.5:38.5 (CIL1a) and showed a desired value (167.6 ± 31.6 nm), and thus was selected for future studies. In the third and last step, 5 out of 6 formulations met the desired Z-Average value (< 200 nm) and the desired PDI (<0.2). Due to the encapsulation of a negatively charged payload, Zeta-Potential values were expected to be lower than the blank LNP ones, which was confirmed. All formulations showed a pN1-EGFP DNA EE above 80%. The mitochondrial activity of the RAW 264.7 cells after 24 h exposure was above 80%, demonstrating the lack of cytotoxicity of the tested formulations.
**Conclusion:** The impact of lipid composition on Z-Average, PDI and Zeta-Potential of LNP formulations was investigated, showing bigger Z-Average for D-Lin-MC3-DMA LNPs. Lipid molar

ratio change [1] and aqueous buffer change proved to be an LNP Z-Average optimization tool. The manufacturing process was optimized and adapted from EIM to MF. Preliminary formulations with a model pN1-EGFP DNA showing acceptable Z-Average, PDI and Zeta-Potential very high EE and absence of cytotoxicity.

**Keywords:** dengue fever, nucleic acid vaccine, LNP, DoE

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**P-II-5**

## Avidin-based cartilage targeting delivery system for osteoarthritis therapy

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**Introduction:** Osteoarthritis (OA) is the most common degenerative joint disease worldwide. Disease evolution in knees and hips is associated with cartilage degradation. Treatment options are only symptomatic, and no disease-modifying therapy able to stabilize or revert OA progression has passed clinical trials due to systemic toxicity and lack of cartilage targeting. In this context, our research aims to design an avidin-biotin-based drug delivery system containing kartogenin (KGN) as a disease-modifying OA drug (DMOAD) for intra-articular (IA) administration. The drug should penetrate the cartilage's full depth to reach the chondrocytes and stimulate chondrogenesis. Cartilage has a negative fixed charge density that can be used to overcome the cartilage barrier by making drugs positively charged. We selected avidin, a positively charged protein, as delivery system to target chondrocytes in the deep zone of the cartilage, the nanosize allowing penetration through the cartilage's porosity.
**Aims:** Design a positively charged cartilage-targeting avidin drug delivery system containing KGN as DMOAD for IA administration.
**Methods:** The KGN was biotinylated in 2 steps and purified by preparative HPLC. The biotin-$PEG_2$-KGN was characterized by Electrospray ionization mass spectrometry (ESI-MS), Matrix-Assisted Laser Desorption Ionization - Time of Flight (MALDI-TOF), and Nuclear Magnetic Resonance (NMR). The HABA (4´-hydroxyazobenzene-2-carboxylic acid) assay was used to estimate the molar ratio of biotinylated conjugates to avidin, and the nanosized and Zeta potential was measured by Dynamic light scattering (Nano ZS). An *in vitro* drug release study over 7 days was realized in the presence of 1U and 100 U of porcine esterase.
**Results:** Biotin-$PEG_2$-KGN was synthesized and purified with a global yield of 27 %, and successfully characterized by ESI-MS, $^1$H-NMR, and MALDI-TOF. The HABA assay proved a preserved biotin-avidin affinity after KGN coupling. Four molar ratios of biotin-$PEG_2$-KGN were necessary to displace the HABA and generate the avidin conjugate. The size and zeta potential measured by DLS were 8.4 ± 3.6 nm and 18.3 ± 5.1 mV. After 24 h, 40 - 45 % of KGN was released from the avidin nanocarrier in the presence of 1 U and 100 U of porcine esterase. The enzymatic kinetic was faster with 100 U, and reached a plateau after 1 week. The *ex vivo* assay on bovine explant finally showed an increase of the cartilage uptake over 80% with the avidin-based nanocarrier.

**Keywords:** Cartilage targeting, delivery system, DMOAD, IA, OA

**Reference:**
Maudens P et al. Recent advances in intra-articular drug delivery systems for osteoarthritis therapy. Drug Discovery Today 2018; 23(10):1761-75.

**P-II-6**

## Navigating towards improved cytotoxicity assessment in nanomedicine development: Shifting from colorimetric to fluorescence-based assays

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**Introduction**: In the pharmaceutical R&D and regulatory sector understanding challenges in characterizing nanomedicine is crucial, as it can pursue different levels of complexity both in the development stage and in the quality control process. After physicochemical considerations, some specific obstacles have been encountered in biological safety assessment of nanomedicines, while anticipation of their immunogenic potential represents an additional challenge. Interactions between the test reagents and the nanomaterial have been identified as one of the most important hurdles that influence marketing authorization of nanomedicines. Relevant European scientific bodies have been collaborating, aiming to provide reliable protocols that would overcome at least some of the issues, which, in terms of cytotoxicity, have brought 2 colorimetric cytotoxicity assays employing LLC-PK1 (porcine kidney epithelial cells) and Hep-G2 (human hepatocarcinoma cells) cell lines [1]. However, the latest recommendations underline the demand for enhancing the testing procedures, overcoming the colorimetric approach, while proposing immune system cell lines as targets.
**Aims:** To adjust the available assays and establish fluorescent-based protocol as a counterpart to the colorimetric cytotoxicity evaluation procedures, applying immune system cell line.
**Methods:** In this study 2 inherently different types of pharmaceutical nanosystems were selected: nanoemulsion (NE) and solid lipid nanoparticles (LNP) and subjected to a set of orthogonal toxicity assays. Adjusted WST-1 (assessing mitochondrial activity as an indicator of cell proliferation) and LDH (lactate dehydrogenase release evaluation as an indicator of cell membrane damage) assays have been performed as the colorimetric tests, while propidium-iodide (PI)-based assay was developed as a fluorescent counterpart (directly distinguishing live *vs* dead cells), using RAW 246.7 cell line (murine macrophages). Starting concentration of the tested nanoformulations was 50 % *v/v*, subsequently diluted by 2-fold, to create a total of 8 concentrations. Incubation time was 4 h.
**Results:** Although similar toxicity trends were observed regardless the assay used, it was evident that the LDH assay required specific consideration. Since the supernatant is the subject of the analysis (not the cells directly), containing not only the enzyme of interest, but also the nanoformulations, in the wells corresponding to the 3 highest concentrations of the NE/LNP pronounced scattering effects were observed. Such an event could be easily overlooked, potentially affecting the conclusions. However, it was overcome by careful design of control and blank wells (each test concentration was coupled with its own blank well containing no cells, but the same concentration of the NE/LNP in the culture medium). In contrast, absorbance measurements in WST-1 assay were performed in the absence of the NE/LNP, avoiding any interactions or scattering effects. Finally, developed PI-based assay proved to be the most relevant. Based on the penetration of PI into the dead cell only, attaching to their DNA, the concentration of the dead *vs* live cells could be directly estimated. What is more, the measurements can be performed in the nanoformulation-free environment, surpassing the potential interactions. Notably, percentage of cell viability obtained in the PI-based assay followed the same trend as in the WST-1 assay.
**Conclusion**: This work provides revised protocols for specific cytotoxicity assays based on different biological bases, addressing limitations observed in the *in vitro* safety assessment of nanomedicines.
**Keywords:** nanoparticles, *in vitro* cytotoxicity, nanomedicines, *in vitro* safety assessment
**Reference:**
[1] Halamoda-Kenzaoui B. et al. Wiley Interdiscip Rev Nanomed Nanobiotechnol 2019; 11: e1531.

**P-II-7**

## Temperature-triggered in situ forming lipid mesophase gel for local treatment of ulcerative colitis

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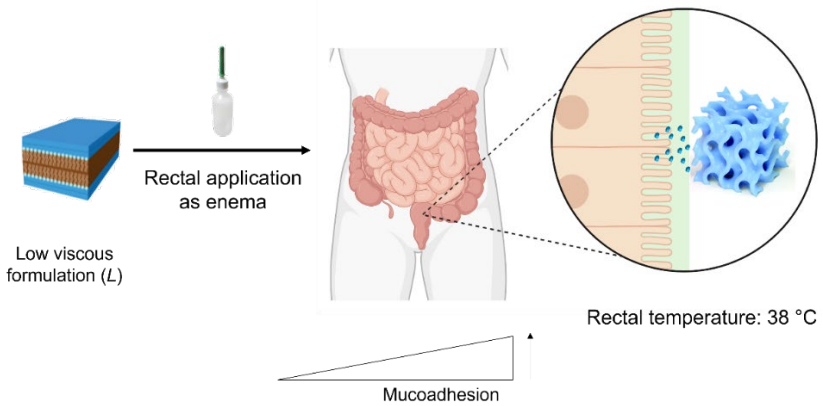
**Introduction**: Ulcerative colitis (UC) is a chronic inflammatory disorder affecting the colonic mucosa. There is no cure for UC and its chronic relapsing/remitting nature strongly affects patients' quality of life. Current treatments struggle to achieve desired remission rates, prompting the exploration of novel therapeutic approaches that enhance drug delivery to the inflamed region while minimizing systemic effects.
**Aim**: Leveraging the potential of biocompatible and biodegradable lipid mesophases, we designed a temperature-triggered in situ-forming lipid gel (TIF-Gel) as a platform for localized drug delivery in UC treatment.
**Methods**: We screened lipid mesophase compositions responsive to the colonic environment using Small Angle X Ray and rheology techniques. The chosen TIF-Gel formulation underwent *in vitro* and *ex vivo* drug release analysis via vertical Franz cells. Mucoadhesion and further validation, including pharmacokinetics, occurred via investigations in murine models of dextran sodium sulphate-induced colitis and T-cell transfer colitis.
**Results**: This versatile gel effectively accommodates and gradually releases drugs with varying polarities, such as tacrolimus and tofacitinib, over time. Notably, the gel's robust adherence to the colonic wall for a minimum of 6 h prevents leakage and improves drug bioavailability. In 2 established models of inflammatory bowel disease, the TIF-Gel demonstrates enhanced efficacy in reducing inflammation compared to conventional drug delivery methods.
**Conclusions**: TIF-Gel offers advantages over existing systems, being cost-effective, easy to manufacture, improved colonic retention time and capable of delivering high drug concentrations while minimizing systemic absorption.
**Keywords**: ulcerative colitis, lipid mesophase, local delivery, mucosa adherence




**Reference:** Carone, M., Spalinger, M.R., Gaultney, R.A. et al. Temperature-triggered in situ forming lipid mesophase gel for local treatment of ulcerative colitis. Nat Commun 2023; 14: 3489

**P-II-8**

## *In vivo* evaluation of cyclodextrin microneedles for particulate vaccine delivery

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**Introduction:** Microneedles have emerged as a promising and innovative approach for vaccine delivery, offering the advantages of painless application, improved stability, and the potential for self-administration. A key highlight is their ability to induce efficient immune activation through skin application. This becomes particularly significant for particulate vaccines, as the dermis houses dendritic cells crucial for the initiation of cellular immune responses. Dissolving microneedles can be fabricated using various matrix materials, including polymers and sugars. The utilization of cyclodextrins is widespread as excipients in pharmaceutical formulations, but largely unexplored as a matrix for microneedles.
**Aims:** In this study, we evaluate cyclodextrins as a matrix for microneedle fabrication in delivering particulate vaccines through skin. Initial physicochemical assessment was conducted *ex vivo*, and we further seek to assess the safety and immune stimulation in mice using the MHC class-I-binding peptide antigen SIINFEKL incorporated in nanoparticles.
**Methods:** The antigenic nanosuspension was mixed with cyclodextrins and a series of centrifugation and drying steps led to the formation of the microneedles by solvent casting. To facilitate detachment post-application, a layer of hydroxypropylmethylcellulose was interposed between the needles and the base plate. The histological impact of microneedle application to skin was assessed in mice subjected to a single patch application. The patch was kept for 3 min on the skin. Intravital imaging System (IVIS) was utilized to identify the deposition of labeled particles and subsequent distribution to organs. The immunological CD8 T-cell response stimulated by patch application was evaluated in C57BL/6 mice adoptively transferred T-cell receptor transgenic OT-I cells after microneedle-assisted intradermal model vaccine delivery.
**Results:** Cyclodextrins were found to be an effective matrix for microneedle fabrication in particulate vaccine delivery, maintaining particle compatibility and structural integrity. IVIS revealed successful particle deposition in mice after treatment. Histological examination displayed transient cellular reactions at the application site compared to non-involved skin. The immunization showed improved antigen-specific CD8 T-cell proliferation and activation towards effector functions, as evidenced by MHCI-SIINFEKL specific pentamer, CD44, and CD62L staining. Importantly, the immune responses were non inferior to intradermal administration of antigen with the poly I:C adjuvant, despite the substantially lower antigen content in microneedles.
**Conclusions:** This study sheds light on the potential of cyclodextrin-based microneedles for particulate vaccine delivery. Their successful fabrication, structural integrity, penetration efficiency, and immunological response all point to their viability as a promising candidate for further investigation. Future studies could explore the potential to incorporate inclusion complexes for the delivery of hydrophobic extracellular adjuvants.

**Keywords**: microneedles, vaccine delivery, nanoparticles, cyclodextrins

**P-II-9**

## Chitosan-based chemical platforms for launching antimicrobial peptides against ESKAPE pathogens

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**Introduction:** The burden of bacterial wound infections has considerably increased due to antibiotic resistance to most of the currently available antimicrobial drugs. The most oppor-tunistic and multidrug-resistant pathogens, which can colonize the wound, are part of the ESKAPE bacterial collection (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumonia*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa,* and *Enterobacter* sp.) [1]. Antimicrobial peptides (AMPs) have been recognized as promising alternatives to conventional antibiotics, that could fight antimicrobial resistance through different mechanisms of action [2]. Despite the high number of investigated AMPs, very few reached the clinics. This is mainly due to their low bioavailability, fast degradation, and high cytotoxicity. As such, AMP-chitosan conjugates and different delivery systems have been developed to overcome the side effects of AMPs.
**Aims:** To evaluate the activity and safety performances of chitosan-based platforms for coupling AMPs with different lengths and ramification degrees, including linear and dendrimeric AMPs. Additionally, to test different delivery strategies of the AMP-chitosan conjugates for topical applications, such as bandages, gels, and nanoparticles [3].
**Methods:** The chemistry for coupling 4 cationic *N,N,N*-trimethyl, *O*-carboxymethyl, and 2 *N*-aryl (pyridyl and aminocinnamyl) chitosan derivatives to AMPs of different generations (first, second, and third) was performed *via* thioether-haloacetyl reaction, following *in vitro* antimicrobial activity, hemolysis, and cytotoxicity assays. AMP-trimethyl chitosan conjugates were selected for further *in vivo* studies on Gram-negative *P. aeruginosa*-infected mice. AMP-chitosan was incorporated into hyaluronic acid (HA) hydrogel, which upon lyophilization turned into a foam/bandage-like formulation. Nanoparticles were obtained by coacervation with ultra-low molecular weight HA. Mice with bioluminescent *P. aeruginosa*-infected excisional wounds were treated with AMP-chitosan and chitosan ban-dages, sulfadiazine cream, or no treatment, followed by bioluminescence imaging for 7 days.
**Results:** The new chitosan-AMP conjugates showed high selectivity by killing the ESKAPE pathogens, including *P. aeruginosa,* and very low toxicity toward mammalian cells, as well as extremely low hemolysis to red blood cells. Electron microscopy revealed that the 4 chitosan derivatives coupled to AMP destroyed both the inner and outer membranes of *P. aeruginosa*. Moreover, chitosan-AMP conjugates showed synergetic effects at extremely low concentrations. AMP conjugates showed an *in vivo* antibacterial activity similar to the best antibiotic treatment.
**Conclusions:** We have successfully designed and coupled a library of at least 4 chitosan derivatives to several AMPs of different lengths and ramifications. The covalent coupling of AMPs to chitosan overcomes the drawbacks of AMPs alone by significantly reducing the cytotoxicity and hemolysis and increasing the bioactivity toward ESKAPE. The chitosan-AMP conjugates can be used as potent antimicrobial therapeutic agents, to eradicate pathogens such as those present in acute and chronic infected wounds.

**Keywords:** antimicrobial agents, infected wounds, ESKAPE pathogens

**References:**

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**P-II-10**

## Trend analysis of analytical data in compounding

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**Introduction**: Trend analysis is a monitoring tool used in the pharmaceutical Product Quality System to justify the safe and effective release of medicinal products, to identify potential process and analytical improvements and to reduce the risk of non-compliance with Good Manufacturing Practice (GMP) requirements. However, common practice and regulations in compounding rarely do enforce trending of analytical data. Even though within specification limits, it is often out of statistical control.
**Aims**: Perform trend analysis on existing analytical data of non-sterile compounded drugs manufactured between 2021 and May 2023 through semi-industrial and manual processes by KlusLab, a Swissmedic GMP-certified laboratory based in Zurich, Switzerland.
**Methods**: In 5 case studies, namely 3 oral suspensions, an oral solution, and a nasal spray solution, we monitored the proportion of unreleased batches due to Out-of-Specification (OOS) nonconformities. We identified Out-of-Expectation (OOE) data points using the Shapiro-Wilk test of normality. Non-normally distributed results were presented using appropriate charts. Excluding OOS and OOE results, we evaluated three analytical parameters (content, pH, and osmolality) using Shewhart individuals control charts and applying Western Electric decision rules. We interpreted their ability to consistently produce an output within specified limits using Critical Process Capability ($C_{pk}$) indices.
**Results**: Across the 5 case studies, we found 6% of OOS nonconformities (n=96). The Shapiro-Wilk test identified one OOE in 20% of the samples (n=15). The non-normal distribution of most pH values reflected a change of accuracy in pH measurements moving from 2 digits to 3. Although within specifications, 42% of the assessed control charts (n=12) featured a special cause variation violating Western Electric decision rules. For the nasal spray solution, obtained $C_{pk}$ indices for content and osmolality were high ($C_{pk}$=1.94 and 4.62, respectively).
**Conclusions**: Ongoing, systematic, and appropriate trend analysis of analytical data in compounding is highly desirable. The potential impact of human factors at this scale of manufacturing and quality control should be further investigated.

**Keywords**: quality control, drug compounding, quality improvement

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**P-II-11**

## Liposomal aggregates sustain the release of rapamycin and protect cartilage from friction

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**Introduction:** Liposomes have been recognized for their potential as biolubricants in the treatment of damaged cartilage in osteoarthritis (OA). However, their small size often results in limited retention within joints and on cartilage surfaces. Rapamycin (RAPA) is a small molecule drug that has been recently described as a promising agent for cartilage protection and attenuation of synovial inflammation. However, its systemic adverse effects, hinder its long-term systemic use.
**Aims:** Our aim is to develop a system composed of liposomal aggregates for intraarticular administration that would slow the rate of RAPA release and due to large size, prolong the retention in the synovial joints. Additionally, the system should exhibit improved lubrication properties.
**Methods:** Negatively charged liposomes were formed via thin-film hydration method and aggregated with $Zn^{2+}$. The aggregates were characterized with dynamic light scattering and laser diffraction, while the morphology was visualized with cryoTEM. RAPA concentration in release studies was measured with high-performance liquid chromatography. Antifibrotic effect of RAPA was evaluated with qPCR on human OA synovial fibroblasts that were stimulated with TGFb (10 ng/mL). Nanotribological measurements were performed with colloid probe lateral force microscopy on silica surface. On the other hand, macrotribological testing was evaluated with UMT-2 on cartilage explants from porcine knees, obtained from a slaughterhouse in Münchenbuchsee (Switzerland).
**Results:** The liposomal aggregates formed were approximately 100 µm in diameter, surpassing previously established thresholds for effective joint retention. Aggregates were irreversible and showed a significantly slower drug release compared to free liposomes over 7 days. RAPA encapsulation (>90%) had significant impact on aggregate morphology. Additionally, 1 ug/mL RAPA had significant anti-fibrotic activity on synovial OA fibroblasts. In tribological tests, the zinc-aggregated liposomes demonstrated friction reduction at both nano- and macrolevels. Furthermore, RAPA within this delivery system was found to mitigate fibrotic activity in human OA synovial fibroblasts [1].
**Conclusions:** Zinc-aggregated liposomes are irreversible and efficiently reduce the rate of RAPA release from the formulation, compared with free liposomes. Additionally, the system offers superior protection of the cartilage against friction, warranting further studies.

**Keywords:** rapamycin,lLiposomal aggregates, sustained release, liposomal morphology, osteoarthritis, cartilage lubrication

**Reference:**

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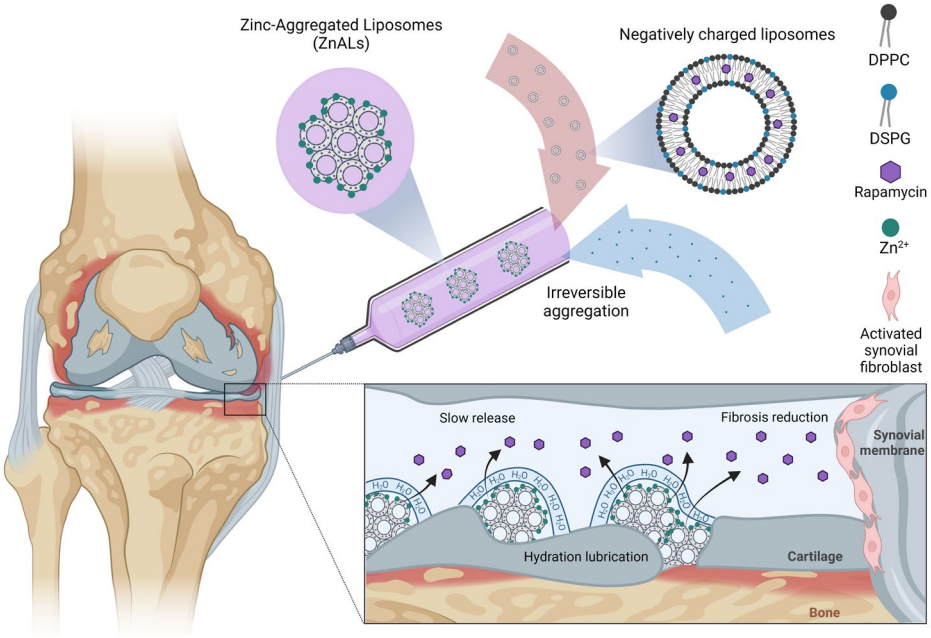


**Figure 1:** Schematic representation of zinc liposomal aggregate formation. The aggregates effectively control release of RAPA, which dampens fibrotic markers and exhibits a protective ability in synovial cartilage through a hydration lubrication mechanism [1]

**P-II-12**

## Chitosan microspheres for the intra-articular delivery of disease-modifying osteoarthritis drug nanocrystals

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**Introduction:** Osteoarthritis (OA) remains as the most common chronic joint disease and yet, the lack of efficient treatments is evident. This is mainly related to the local and degenerative nature of this disease. Kartogenin (KGN) was recently reported as a disease-modifying OA drug (DMOAD) promoting cartilage repair. However, its therapeutic effect is impeded by its very low solubility [1]. For that reason we have designed a KGN delivery system for intra-articular OA administration. This approach combines 2 formulation techniques: nanosize reduction of a drug by wet milling and subsequent spray drying of chitosan (CH) to form microspheres (MPs) [2]. This microparticle size is expected to delay KGN clearance from the joint space, and the positive zeta potential is expected to improve retention on the negatively charged cartilage surface.
**Aims:** To design positively charged KGN CH MPs for intra-articular OA administration.
**Methods:** KGN was first synthesized and recrystallized. Then, the drug was wet-milled, and the NCs were directly incorporated in the spray-drying feed solution containing CH crosslinked with glutaraldehyde. Particle size and morphology were evaluated by laser diffraction and scanning electron microscopy. KGN was quantified by UHPLC. WST-1 *in vitro* proliferation tests were performed on human fibroblast-like synoviocytes.
**Results:** Laser diffraction measurements confirmed an efficient size reduction of KGN using 2 different stabilizers (i.e., TPGS and PVP) with Dv50 and Dv90 values around 0.2 and 2 µm, respectively. After spray-drying optimization, we obtained resuspendable CH MPs with an efficacy of encapsulation around the 70 %. Dv50 and zeta potential values were around 10 µm and 30 mV, respectively. Scanning electron micrographs revealed that blank MPs exhibited a smooth surface whereas some nanocrystals were visualized entrapped onto the microsphere surface layer. The microspheres showed suitable stability and a controlled release profile in horse synovial fluid and were non-toxic in human synoviocytes *in vitro*. Their cartilage retention skills were also explored using an *ex vivo* cartilage device.
**Conclusion:** We have presented a technological combinatory approach (wet milling + spray drying) to develop an intra-articular formulation consisting in CH MPs loaded with the DMOAD KGN NCs. Further experiments *in vitro* and *in vivo* will determine if chitosan microspheres are able to improve retention on the cartilage surface and release KGN locally.

**Keywords:** osteoarthritis, microspheres, nanocrystals, spray-drying, chitosan, kartogenin

**References:**
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## III. PHARMACOEPIDEMIOLOGY

### P-III-1

### The Round Table on Antibiotics, a multi-disciplinary Swiss initiative to foster the development and availability of antibiotics

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**Introduction:** Causing 5 million deaths per year worldwide, antimicrobial resistance (AMR) is a major and steadily increasing public health threat which compromises the effectiveness of healthcare systems to control and limit bacterial infections, increases the risks of negative outcomes of medical interventions, and puts a heavy burden on the health care system. The recent and ongoing antibiotics shortages have revealed the vulnerability of supply chains and brought to light the necessity for action. The available treatments and current R&D pipelines are not sufficient to tackle AMR, and incentives are needed to support investments in new antimicrobials and lift hurdles to bringing new antibiotics and related products to the market. Additionally, stewardship of existing treatments must be stepped up to maintain their effectiveness and curb the development of additional AMR.

**Aims:** The Round Table on Antibiotics (RTA) is a unique multi-disciplinary, non-profit Swiss association which endeavors to support the development of antimicrobial technologies and ensure that patients with severe infectious diseases have access to treatment. Created in 2019, the association gathers stakeholders from the fields of healthcare, academia, politics, and industry and is active at the Swiss and international levels.

**Methods:** The RTA promotes public awareness on AMR and contributes to policy initiatives and projects. The association focuses its work on the following areas:

- Establishment of a financial incentive model in Switzerland that, in line with international efforts, fosters the development of new antimicrobial technologies and incentivizes their marketing in Switzerland
- Definition of measures to ensure the supply of antibiotics in Switzerland and worldwide.

At the heart of the RTA's activities is the development of a pull incentive for antimicrobials, with the objective of advancing innovation for the development of antibiotic treatments in a credible, sustainable, and timely manner. The project will be rolled out in several steps, starting with an assessment of existing pull models, based on lessons learned in other countries, and of the existing legal framework. A specific model will be developed and refined for Switzerland, to be implemented first as a pilot before it is fully integrated in the Swiss healthcare system. The project is conducted by the RTA and supported by public authorities and relevant stakeholders, both in Switzerland and abroad.

**Results:** The first phase of the project, the assessment, has started end of 2022. The association evaluated models proposed or piloted in other countries and conducted interviews with key actors in Switzerland, including the federal administration, the cantons, industry, and insurers, to better identify the specific needs for the Swiss market.

**Conclusions:** In line with public authorities advocating to intensify action against AMR, bold measures are required to combat pathogenic bacteria. A pull incentive would incentivize investments in the research and development of antibiotics and antimicrobial technologies and foster their availability. The RTA takes leadership in this mission.

**Keywords:** Antimicrobial resistance, pull incentive, innovation, multi-stakeholder, availability, access

**P-III-2**

## Attitudes of Swiss and German pharmacists regarding the dispensing of biopharmaceutical medicines pre- and post-COVID-19 pandemic

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**Introduction:** Using biosimilars instead of the original biologic drugs was supposed to help lower healthcare costs. In reality, biosimilars did not reach a market uptake as expected. One reason for the low acceptance among healthcare professionals might be that they do not feel confident handling them. This low confidence may be caused by knowledge gaps about biosimilars and their regulatory approval process.
**Aims:** To investigate pharmacists' attitudes and information needs regarding biologicals and biosimilars in 2020 and 2022.
**Methods:** In February 2020 (before) and August 2022 (after the COVID-19 pandemic), we invited Swiss and German pharmacists to participate in a 17–item online survey evaluating knowledge, frequency of dispensing, attitudes on substitution and information sources of biologicals/biosimilars. We calculated descriptive statistics and used Chi-Square test to compare categorical variables.
**Results:** A total of 764 individuals took part in the survey (390 in 2020; 374 in 2022) with comparable demographics. Overall, the similarities and differences in the attitudes of German (DE) and Swiss (CH) participants remained unchanged between both years. The familiarity with the term biosimilar was found to be equal among pharmacists (DE: 70% *vs* CH: 75%). Most of them felt sufficiently informed to dispense them (DE: 43% *vs* CH: 45%). In 2020, 37% of all participants were confident in handling patient queries regarding therapy with a biological. This confidence level changed in 2022, with significantly more Swiss and fewer German participants stating confidence in handling patients' queries (27% *vs* 44%; $p<0.01$). In both years and countries, the least confidence was observed regarding the substitution with a biosimilar (DE: 15% *vs* CH: 30%). Most pharmacists indicated that the pandemic had neither influenced their interest in biologicals/biosimilars (DE: 60.0% *vs* CH: 55.5%; ns) nor their readiness to assume more responsibility (DE: 45.3% *vs* CH: 52.5%; ns). More than 80% of German and Swiss pharmacists expressed the desire for additional training on this topic.
**Conclusion:** Overall, the similarities and differences between both countries regarding attitudes towards biologicals and biosimilars remained unchanged pre- and post-COVID-19 pandemic. There is still low confidence among community pharmacists in handling biosimilars, especially regarding the substitution of biopharmaceutical medicines. More training on this topic is desired.

**Keywords:** Biological, biosimilars, survey, community pharmacy, attitudes, covid-19 pandemic

## P-III-3

### Pharmacy students' perception of computer based simulation in the era of online learning expansion

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**Introduction:** Worldwide, pharmacy educators face the task of integrating theoretical knowledge and practical skills into the curriculum to prepare students for their future careers. Computer-based simulation bridges theory and practice and equips students for their future responsibilities as pharmacists. In recent years, digital simulation has experienced rapid expansion as an emerging approach within virtual learning. The digital platform «Pharmacy Simulator» offers computer-based interactions with virtual patients and facilitates the development of clinical and communication skills within a community pharmacy setting. Nevertheless, the COVID-19 pandemic brought forth a situation where students faced the challenge of learning entirely in a virtual format. In Western Australia, this exclusive digital instruction continued for 10 weeks.
**Aims:** We explored how pharmacy students perceived «Pharmacy Simulator» within the context of the surge in online learning.
**Methods:** Master of Pharmacy students at The University of Western Australia engaged in 2 scenarios on «Pharmacy Simulator» in 2019 (Anaphylaxis and Salbutamol) and in 2021 (Anaphylaxis and Vaccination). To evaluate the participants' perception of «Pharmacy Simulator», we conducted (i) qualitative semi-structured interviews in 2019 and (ii) a survey comprising 25 items derived from the earlier interviews in 2021. The verbatim transcription of the interviews was converted into electronic format and analyzed inductively using the Framework Method. Survey responses were examined using descriptive statistics, and insights from open-ended questions were analyzed inductively. We adopted a data triangulation approach to detect the potential impact of the rise of online learning.
**Results:** A total of 20 interviews and 31 surveys were analyzed. In 2019, participants rated «Pharmacy Simulator» as a user-friendly, engaging, and enjoyable learning tool that seamlessly complemented theory and community pharmacy practice. They reported the feedback at the end of the session to be most valuable. In 2021, participants agreed with seven usability attributes related to «Pharmacy Simulator», such as its usefulness for knowledge acquisition and engaging nature (median rating: 4 on a 5-point Likert scale). Additionally, participants expressed overall confidence in counseling skills across the 3 topics.
**Conclusions:** Master's students found «Pharmacy Simulator» useful for acquiring pharmacy practice skills, perceiving it as aiding theory-to-practice transition. Computer-based simulation is a valuable and accepted learning tool in university education, regardless of online learning challenges.

**Keywords:** Computer simulation, online learning, pharmacy students, pharmacy education

## IV. CLINICAL PHARMACY / CLINICAL PHARMACOLOGY

### P-IV-1

### NutriPro™: A product-specific e-tool for healthcare professionals in clinical nutrition

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**Introduction:** Malnutrition is a growing problem around the world [1]. About 20% to 70% of Swiss hospitalized patients suffer from or are at risk of malnutrition. Several robust studies have shown that individualized nutritional therapy can significantly improve patient outcomes, reducing severe complications and mortality with a number needed to treat (NNT) of 20 and 37, respectively [2, 3]. There are around 600 nutritional products (NPs) on the Swiss market to cover energy and protein needs, which can be used in the treatment of malnourished patients. They come from 11 manufacturers and are covered by health insurance. The comparability and correct use of NPs and their efficacy is hampered by the wide range of NPs, their diverse composition and the different ways in which information is presented. The selection and the correct use of NPs is complex, time-consuming and could be facilitated by digital, reliable, up-to-date, and easily accessible product information.
**Aims:** The goal is to develop and launch a free digital platform (App NutriPro™) that will make the process of choosing the right NP easier and faster. Enable users to select appropriate products based on their patient's personalized nutritional needs, preferences, and medical conditions. Provide a centralized overview of information for each product, enabling users to easily compare products and make informed decisions. Ultimately, to improve the quality of care, and outcomes as well to reduce healthcare costs for patients requiring nutrition therapy in Switzerland.
**Methods:** An open access and industry independent digital platform and app (NutriPro™) was designed for health care professionals (HCP) to select appropriate NP for patients' individual needs. A total of 92 Swiss HCP answered a questionnaire to define the selection criteria and to structure the app. Fact sheets for each NP were defined based on official, authority-approved NP data. A software company supported the coding and structuring of the app.
**Results:** The questionnaire data showed the need for such a tool for quick access to key information. The majority (54%, n=49) of the responders reported to be nutrition experts (>7 years of experience). The most important parameters to characterize the NP are energy content (81% consensus, n=73), macronutrients (79% consensus, n=71) with focus on protein content (98% consensus, n=89), and patient's condition (56% consensus, n=50). Some parameters were also highlighted by individual professions: For instance, osmolarity was relevant to pharmacists (61% consensus, n=11). These results were used to program and structure the application.
**Conclusions:** NutriPro™ is a novel e-tool to support NP selection based on standardized official data; it can be embedded in other app-based nutritional therapy support tools (e.g. clinicalnutrition. science) to improve quality of care and outcomes. Efficiency and suitability tests with HCP users will be conducted to evaluate how the app performs.

**Keywords**: digital platform and app, energy and protein, FSMP, Hospital malnutrition, open access, questionnaire, selection criteria, individualized nutritional therapy

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**P-IV-2**

## Compatibility of selected nanoparticulate IV iron medicinal products with all-in-one parenteral nutrition admixtures tested by ICP-MS

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**Introduction:** Free, polyvalent iron (Fe) shows redox reactivity, toxic radical formation, and incompatibilities. Fe deficiency is a prevalent condition often requiring IV Fe infusion. When parenteral nutrition (PN) is also needed, as in neonates or IBD patients, combined treatment is limited due to lack of specific stability and compatibility data. Selected IV Fe nanoparticles show promise to overcome this issue.
**Aims**: The aim of this project was to investigate stability and compatibility of different Fe nanoparticles admixed to all-in-one (AiO) PN admixtures at therapeutic daily Fe doses of 200 mg. Combined administration would facilitate the patient care management and reduce IV line and workload.
**Methods:** Nanoparticle IV Fe (Ferinject® (Fe(III) carboxymaltose), Venofer® (Fe(III) sucrose)) were added in two different commonly used commercial multi-chamber (MC) AiO PN admixtures (SmofKabiven®, Omegaflex special®). The nanocolloidal solutions were added to the ready-to-use PN admixture at Fe concentration of 0.1 and 0.4 mg/mL, corresponding to 200 mg Fe per PN bag. Fe concentration and pH were measured at 0, 4, 24, and 48 h after admixing. Visual sedimentation was checked at 24 h. Free and nanoparticulate Fe was determined at 4 and 24 h in 100 kDA dialysis tubes (SpectraPor®). We quantified Fe by inductively coupled plasma mass spectrometry (ICP-MS).
**Results:** The results showed Ferinject® was stable in the admixture for 20 h; only 2.3% of the total Fe was found in the dialysate. No sedimentation was observed. Diluting Ferinject® in glucose instead of saline solution made the colloidal solution unstable; 26% of the added Fe was released into the dialysate. Fe recovery was >90%. The validation experiments are conducted in a setting mimicking practical use.
**Conclusion:** Ferinject® allows stable IV-Fe admixes to the tested PN admixtures. This provides guidance for IV-Fe PN treatment. Future experiments should assess lipid emulsion stability.

**Keywords**: Parenteral nutrition, iron deficiency, iron admixing, nanoparticles

**P-IV-3**

## doMESTIC RedPIM - Study of Medication Safety in Home Care, Reducing Potentially Inappropriate Medications: A structured approach to interprofessional medication management for home care clients

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**Introduction:** Recent Swiss publications indicate that medication-related problems (MRPs) are especially frequent among home care clients, who are predominantly elderly, multimorbid and polymedicated. Interfaces of care are common, necessitating timely, complete and accurate communication of medication-related information.
**Aims:** In this study, we aimed to pilot-test a standardized approach to interprofessional medication management of home care clients, focusing on deprescribing.
**Method:** Home care clients of Spitex Bern, ≥64 years and taking ≥4 prescribed medications, were assessed for their medication-related risk and subsequent need for a medication review, using the 10-item doMESTIC RISK tool. For qualifying patients, pharmacists among 14 pharmacies performed a structured medication review, addressing resulting questions/ suggestions to their primary care provider (PCP) using a standardized form. Answers and the ultimate therapeutic decision by PCPs were communicated on the same form.
**Results:** With informed consent, nurses initiated 106 risk analysis; 75 (71%) could be completed by pharmacists. 26 patients scored <5, not necessitating a medication review. The 49 patients qualifying for a medication review were on average 84.0±7.7 years (65-103) and took 11.2±4.5 prescribed medications regularly (2–24), with an additional 2.8±3.5 as-needed (0–14) and 0-5 over-the counter medications. Pharmacists identified 120 potential MRPs (2.4/patient) with 64 potential interventions. Of those, 46 prioritized interventions concerning 20 patients were communicated to PCPs. The most commonly suggested interventions were dose reduction (27%) and therapy stop (23%), most often based on (potential) contraindications and potentially inappropriate medications. While only 45% of pharmacy requests (9/20 patients) were answered by PCPs, acceptance rate for the remaining suggestions was 57% (26/46 interventions), predominantly generic substitution and dose reduction (7 medications). Three medications were deprescribed.
**Conclusions:** In a structured medication management program, pharmacists identified various aspects for potential therapy improvement of medication in collaboration with home care nurses and PCPs. However, there is a lack of medical information accessible to all members of the healthcare team, limiting the pertinence of suggested interventions. Communication needs improvement and reimbursement should be discussed.

**Keywords:** polypharmacy, deprescribing, medication safety, clinical pharmacy

This project was funded by the KHM's Fonds interprofessionalité.

**P-IV-4**

## Pharmaceutical care in asylum homes

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**Introduction:** Pharmaceutical care for asylum seekers and refugees is a global challenge with many different obstacles and difficulties. It's significance is increasing in light of the current migrant crisis. Especially for the treatment of minor ailments with over the counter (OTC) medicines in the scope of primary care, there are few studies and consequently little knowledge on how to establish such care. The canton of Lucerne in Switzerland has set up a structure in its asylum centers (ACs) with a nurse-led primary care service and a pharmacist responsible for all processes related to OTC medications.

**Aims:** The aims of this project were

- to find out what role pharmacists in the asylum system play in providing asylum seekers with OTC medications based on the current literature and a process analysis in Lucerne;
- to develop suggestions a) at a meso level for pharmacists and b) at a micro level for the healthcare professionals and staff dispensing and administering medications in ACs.

**Methods:** The scoping literature review for OTC drug dispensing in ACs in the scope of primary care and preferably involving a pharmacist was conducted in PubMed, Embase and CINAHL databases. A process analysis was conducted locally, complemented with a data analysis of all drugs dispensed/ administered in one among 16 ACs in Lucerne from July 2021 until June 2022 and a staff survey.

**Results:** Four documents were identified in the scoping review, specifically addressing barriers of care, pediatric pharmaceutical care, treatment of minor ailments and a concept of the Swiss Federal Office of Public Health.

In the canton of Lucerne, the responsible pharmacist has the legally mandated responsibility of all medication use processes in the ACs. Nurses and medical practice assistants offer medical consultation hours and together with laymen, who administer medications outside of the consultation hours, they used medicinal products 844 times for 170 asylum seekers (range 1-52 drugs/person).

Medication administration was adequate (compliant with the quality management system) in 96.9%. The most commonly used medication classes grouped by the World Health Organization's Anatomical Therapeutic Chemical Code (ATC) are antiinflammatory and antirheumatic products, with non-steroidals (M01A) in 15.4% (130/844) of the cases. The most commonly presented symptom for all asylum seekers was headache (97/844, 11.5%), whereas for asylum seekers under 18 years of age cough was most common (45/210, 21.4%).

85.7% of the staff participated in the survey, with the majority agreeing with the process (10/12, 83.3%), having no concerns about their responsibility (8/12, 58.3%) and feeling secure in administering and dispensing medications (11/12, 91.7%).

**Conclusions:** There is opportunity for pharmacists to play a significant role and contribute valuably to the asylum system in order to establish compliance with regulatory requirements and in daily practice through designing and monitoring medication processes including treatment of minor ailments and handling OTC medications.

**Keywords:** pharmaceutical care, asylum homes, medication safety, OTC drugs

**P-IV-5**

## Optimizing paediatric care: Administering beta-lactams via extended infusion. A systematic review and meta-analysis

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**Introduction:** Optimizing antibiotic therapy is imperative with rising bacterial resistance and high infection mortality. Continuous infusion (COI) of the time-dependent antibiotics beta-lactams might improve efficacy and safety compared to their intermittent administration (IA). This is because COI avoids high peak concentrations and maximises the fraction of the time, during which the concentration is above the minimal Inhibitory concentration (MIC). In case COI is not manageable due to drug stability or convenience issues, prolonged infusion (PI) may also be an approach to optimize the mentioned parameters.
**Aims:** The aim of this study was to evaluate efficacy and safety of extended (COI or PI) in paediatric patients to build a basis for a potential clinical implementation of this mode of administration.
**Methods:** Adhering to Cochrane standards, we conducted a systematic review with meta-analysis investigating the efficacy and safety of COI (24 h/d) and prolonged infusion (PI, > 1h/dose) compared to IA (≤ 1 h/dose) of beta-lactams in paediatrics. Primary outcomes included mortality, clinical success, and microbiological eradication.
**Results:** For the efficacy outcome mortality, five studies could be included. The investigated drugs were meropenem, piperacillin/tazobactam, cefepime or combinations of these. The mortality with COI/PI of beta-lactams compared to intermittent administration was 2.8% (13/458) compared to 5.6% (32/567), respectively. The pooled relative risk estimate was 0.48 (confidence Interval 0.26 – 0.89, P = 0.02). Visual inspection of the forest plot suggested considerable heterogeneity between studies. For the further efficacy outcomes clinical success and microbiological eradication, no significant differences between the administration modes were found. No study reported additional safety issues, e.g. adverse drug reactions when using COI/PI *vs.* IA. The certainty of evidence was graded as very low for all primary outcomes.
**Conclusions:** Our findings suggest that administration of beta-lactams in a continuous or at least prolonged manner leads to a reduction of mortality for paediatric patients. However, more RCTs are required to further validate our findings. We suggest conducting an RCT to investigate the comparative benefit of COI combined with therapeutic drug monitoring (TDM) over IA of beta-lactams, specifically in critically ill paediatric patients, as they are likely to profit the most from COI.

**Keywords**: paediatrics, beta-lactam, antibiotic, continuous infusion

**P-IV-6**

## Administration of intranasal midazolam for acute anxiety in palliative care - AIM CARE study protocol

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**Introduction:** Midazolam (MDZ) is used off-label to manage anxiety, a common and highly distressing condition in palliative care (PC) [1,2]. Its intranasal application offers a minimally invasive route of administration with a fast onset and a good safety profile [3]. Doses administered for anxiety in PC are 0.45-1 mg, thus much lower compared to other indications, i.e., sedation or seizures (5-10 mg) [4,5]. Evidence on the effectiveness and safety of low dose intranasal MDZ to treat acute anxiety in PC, as well as pharmacokinetic (PK) and pharmacodynamic (PD) data, remains limited, hence, its use in clinical practice is based primarily on clinical experience [2].
**Aims:** To describe effects and safety of different doses of intranasal MDZ to treat acute anxiety in PC patients.
**Methods:** *AIM CARE* will be a double-blind, randomized, placebo-controlled parallel-group multicenter pilot study with three study arms and a nested PK analysis (i.e., predefined subgroup of participants). At least 30 patients (i.e., 10 per study arm) will be included. Each participant will receive one spray per nostril (placebo: 0 mg; A: 0.45 mg, B: 0.9 mg MDZ). Nasal irritation and a burning sensation of the nasal cavity are reported for intranasal MDZ. To safeguard blinding the placebo formulation will be formulated with the same pH as the active study drug formulations. All PC patients hospitalized at the three study sites which are prescribed intranasal MDZ in their as-needed regimen and meeting inclusion criteria are considered eligible. Patients will be asked for consent at the time of prescription by the attending physician. When the decision for administration of intranasal MDZ to relieve anxiety is made, patients who have provided consent and have been randomized to one of the arms will be included. All participants with venous access (venous catheter, PICC line, midline catheter or port-a-cath) will additionally be asked for consent to participate in the nested PK analysis.
**Results:** Baseline patient data (i.e., age, sex, co-medication, diagnoses, laboratory parameters) will be collected. Outcomes will be assessed at baseline and 30 min after MDZ administration. Primary outcome is a patient-reported anxiety level on a visual analogue scale (VAS 0-100 mm). Secondary outcomes are oxygen saturation, sedation (Richmond Agitation Sedation Scale Palliative Version RASS-PAL), saliva cortisol levels, PK parameters in predefined subgroup ($C_{max}$, $t_{max}$, $t_{1/2}$, $AUC_{0-T}$, $AUC_{0-\infty}$), time until first additional dose is requested, cumulative number of doses, and time points of additional doses during 24 h after the first application. The study duration will be 12 months. The pilot study aims to include patients starting January, 2024. Results are expected to be available in 2025.
**Discussion:** This pilot trial was designed to test whether the low intranasal MDZ doses used in clinical PC practice provide measurable effects in addition to placebo and the data obtained will serve as a basis for the design of subsequent clinical studies.

**Keywords:** anxiety, intranasal midazolam, off-label use, palliative care, pharmacokinetics

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**P-IV-7**

## Consensus on indicators for medication-related readmissions: A Delphi study

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**Introduction**: Effective patient prioritization of clinical pharmacy services at hospital discharge is important for optimizing the use of limited resources and reducing the risk of medication-related readmissions.
**Aims**: We conducted a Delphi Study to develop a comprehensive set of indicators for 30-day medication-related readmissions to guide patient prioritization for clinical pharmacy services at hospital discharge.
**Methods**: An expert panel of clinical pharmacists, physicians, and nursing experts from Switzerland was invited to participate in our two-round Delphi study. The indicators for the first round were based on a self-conducted scoping literature review (n = 20) and additional indicators deemed potentially relevant but not covered in the literature (n = 11). The experts rated the relevance of the proposed 31 indicators on a scale of 1 to 9. An indicator was defined as relevant if the median rating was 7 or higher. Consensus was defined using the RAND/UCLA method. In the second round, experts re-rated indicators without consensus and assessed expert-generated indicators. Additionally, specifications for indicators requiring more details, such as cut-off values or clinical situations, were requested. The main outcome measures were the relevance, consensus on, and completeness of the proposed indicators for 30-day medication-related readmissions.
**Results**: In the first round, 38 experts participated, and 25 indicators were included and 6 were excluded. All indicators reached consensus and 5 new indicators were suggested. In the second round, 34 experts participated. Of the 5 newly proposed indicators, 4 were included and 1 was excluded. All new items reached consensus. The expert panel prioritized the following indicators: (1) insufficient communication between different healthcare providers, (2) polypharmacy (7 or more medications), (3) low rate of medication adherence (forgetting to administer or administer the prescribed medications wrongly at least twice per week), (4) complex medication regimen that involves taking at least 3 doses per day, using at least 2 different dosage forms, and administering them through at least 2 different routes each day, and (5) multimorbidity (3 or more chronic conditions).
**Conclusions**: The developed set of indicators for medication-related readmissions could guide the prioritization of clinical pharmacy services at hospital discharge, leading to more efficient use of resources and potentially improved patient outcomes. Validation and subsequent prioritization of the identified indicators is planned.

**Keywords**: Clinical pharmacy services, medication safety, medication-related readmission, risk factors

**P-IV-8**

## Analgesic therapy failure in a *COMT* HPS/HPS diplotype carrier with fibromyalgia – A case report

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**Introduction:** Individuals' genetic variations can influence the response to analgesics, but may also affect pain sensitivity. The catechol-O-methyltransferase *(COMT)* has a major physiological function in the pathway of pain modulation, as it regulates catecholamine concentrations. Altered COMT activities result in altered levels of catecholamine, which then may influence pain perception. Variations in *COMT* single nucleotide polymorphisms (SNP) rs4680, rs6269, rs4633, and rs4818 are assigned to 3 major haplotypes, which relate to an individual's responsiveness to pain: low pain sensitive (LPS), average pain sensitive (APS) and high pain sensitive (HPS). The reliability of these haplotypes predicting a clinical outcome for pain control has not yet been well investigated.
**Aims:** We report the case of a 40-years-old female patient with fibromyalgia. Despite first-line indicated pharmacotherapy with 120 mg duloxetine and 150 mg pregabalin, she still suffered from severe chronic pain and insufficient pain relief. For this reason, 80 mg oxycodone, and additionally up to 2 g paracetamol and 1.6 g ibuprofen were administered daily. We aimed to investigate the genetic association of the patient's susceptibility to analgesic therapy failure (TF) and pain sensitivity.
**Methods:** PGx panel testing of 100 polymorphisms in 30 different genes, including *CYP2D6* and *COMT* rs4680, was conducted by a commercial provider. Additional genotyping of *COMT* rs6269, rs4633 and rs4818 was performed applying polymerase chain reaction (PCR), restriction fragment length polymorphism (RFLP) assay and sanger sequencing, using the patient's genomic DNA isolated from a whole blood sample.
**Results:** The patient was identified as rs6269 g.25690A>G [A/A], rs4633 g.25973 C>T [C/C] rs4818 g.26945 C>G [C/C], rs4680 c.472 G>A [G/G] predicting a *COMT* HPS/HPS diplotype. Additionally, the patient was identified as CYP2D6 intermediate metabolizer (IM) with a reduced enzyme activity. CYP2D6 is involved in the metabolism of numerous substances (e.g. tricyclic antidepressants, opioids). It is mainly responsible for the bioactivation of oxycodone to the active metabolite oxymorphone. Reduced enzyme activity of CYP2D6 may result in a lower plasma concentration of oxymorphone and therefore contribute to TF on pain relief. In contrast, no genetic variation could be associated with the ineffectiveness of the first-line therapy with duloxetine and pregabalin. The same applies for paracetamol and ibuprofen.
**Conclusion:** The patient was identified as *COMT* HPS/HPS diplotype carrier, implicating alterations in *COMT* activity and a higher pain sensitivity in general. Moreover, the identified drug-gene-interaction (DGI) between CYP2D6 and oxycodone further explains the observed lower response to the drug. It was recommended to switch to another opioid, whose metabolism is not influenced by CYP2D6 (e.g. morphine). Also, it was possible to provide preemptive recommendations, as tricyclic antidepressants (e.g. amitriptyline) should only be used at low-dose in CYP2D6 IM patients. Beside the DGI between oxycodone and CYP2D6, it was not possible to explain TF of duloxetine, pregabalin, paracetamol and ibuprofen by the genetic profile of the patient. Here, we assume that the observed broad TF on pain relief is attributable to the patient's *COMT* haplotype and the associated high pain sensitivity. However, this hypothesis needs to be validated by further investigations in a larger patient sample.
**Keywords:** therapy failure, COMT, high pain sensitivity, CYP2D6, intermediate metabolizer, oxycodone

**P-IV-9**

## MOTIVATE – Motivation of pharmacists to participate in an organized cancer screening program

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**Introduction:** Colorectal Cancer (CRC) is the second most common cause of cancer-related deaths in Switzerland. Screening can lower mortality through colorectal cancer by 50%. Programmatic screening can lower health and social disparities in screening uptake. In October 2022, an organized CRC screening program was implemented in the Canton of Lucerne. This program also includes pharmacists, tasked to recruit clients for the program, helps them with the program inclusion and support share decision making for FIT (fecal immunochemical test) *vs.* colonoscopy.
**Aims:** The aim of this master's thesis was to explore pharmacists' views on their role in a CRC screening program and identify participation facilitators and barriers.
**Methods:** We performed a scoping literature review in PubMed and Embase databases, exploring factors facilitating and barriers hampering pharmacists' participation in a CRC screening program. We also conducted 5 semi-structured interviews among pharmacists participating in the program, as well as a follow-up survey based on different implementation models, sent to all community pharmacists working in the Canton of Lucerne.
**Results:** In the scoping review, we could include 4 publications. Two papers were about a CRC screening program in Spain, 1 about a program in Connecticut (USA), and the fourth study was conducted in New Zealand about pharmacists' opinions to participate in a CRC screening program. A lack for resources (time, personnel) was a major barrier. The pharmacists participating in the interviews experienced their primary role in program inclusions upon request, not in actively advertising the program. The most common barriers mentioned were difficulties with logging into the software MC-SIS and staff shortages in the pharmacy. They would welcome and feel prepared for a more demanding role pertaining to counselling the use of FIT *vs.* colonoscopy.
In the online survey with responses from 34 pharmacists (response rate: 40%), 60% considered the software MC-SIS as helpful for doing a program inclusions once the client was identified. However, different pharmacists mentioned the same software as a reason for non-participation or dropping out of the program due to the difficulty of identifying clients. Acceptance of administrative effort expanded from 60% to 80%. While the readiness among participating pharmacists to commit long-term to the program has increased since the beginning (89% *vs.* 77%), overall motivation has decreased: 48% were fully or slightly motivated at follow-up *vs.* 72% at the start of the program. The public's lack of awareness about CRC risks resulting in a low number of clients seeking counselling and program inclusion in the pharmacy was considered as the main barrier to successful participation.
**Conclusions:** This study adds significantly to the very limited data on pharmacists' perspectives in participating in CRC screening programs. Pharmacists highly value the program and express a desire for more meaningful involvement. Addressing the specific concerns mentioned, such as improving software accessibility and considering limited resources, would further enhance the program's effectiveness and the pharmacist's engagement in preventive care.

**Keywords:** pharmaceutical care, community pharmacy, colorectal cancer screening, prevention

**P-IV-10**

## Combined targeted metabolomics and enzyme activity profiles reveal novel disease mechanisms of the symptomatology in hypercalcemia patients

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**Introduction:** The application of state-of-the-art bioanalytics and omics methods is critical for the discovery of novel predictors of disease parameters. However, the translational impact of such biomarkers is limited by the generalizability of the findings. Preanalytics, the sample size and heterogeneity are inherent constrains in such datasets that increase the stochasticity in the generated matrices and thereby the likelihood of false discovery.
**Aims:** The characterization of blood lipid and amino acid, and enzyme-activity fingerprint (EAF) profile of hypercalcemia patients in a Random Matrix Theory (RMT)-based analytical framework to uncover robust disease mechanisms associated with symptoms of unknown causes.
**Methods:** We developed a methodological framework based on RMT to separate and filter out the random component from the signal in large covariance matrices. In our clinical study, we collected plasma and the resected parathyroid adenomas from 90 hypercalcemia patients who underwent parathyroidectomy. We employed targeted metabolomics to quantify inflammatory lipids and amino acids in plasma and the surgically resected adenomas. Furthermore, we generated EAFs using an activity-based proteomics approach on the resected adenomas.
**Results:** Our results unveil strong alterations in the level of specific inflammatory lipids and amino acids that may contribute to the development of the major symptoms associated with the disease. We found several significant correlations between the severity of the symptoms and the measured analytes. By applying the recently developed RMT approach, we could test the robustness of our empirical results by separating and filtering the random component from the signal.
**Conclusions:** In summary, our clinical study reveals novel correlates with the key symptoms of hypercalcemia whose mechanistical origins largely remained unknown. Furthermore, we introduce novel model- and data-associated methods by RMT and EAFs.

**Keywords:** Random Matrix Theory, bioanalytics, metabolomics, hypercalcemia

**P-IV-11**

## Analysis of endocannabinoids, associated lipids and glucocorticoids in serum and CSF of control and multiple sclerosis patients: A retrospective study

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**Introduction:** Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS) characterized by neuroinflammation and demyelination causing neurodegeneration. The endocannabinoid system (ECS) was identified as interesting target to reduce the disease burden in rodent models and symptoms like muscle spasms and pain in MS patients. As an essential lipid signalling network in mammals, the ECS comprises the 2 main signalling lipid endocannabinoids (eCBs) 2-arachidonylglycerol (2-AG) and anandamide (AEA), the enzymes involved in their synthesis and degradation, the receptors targeted by the eCBs, as well as peptide eCBs. So far, the potential impact of MS on the endogenous eCB levels remains poorly understood. Only a few studies analysing eCB levels mainly in cerebrospinal fluid (CSF) and serum of MS patients have been published, with low employed patient numbers and opposing observed effects. Therefore, we performed a retrospective study and quantified lipid and peptide eCBs, eCB associated lipids and glucocorticoids in serum and CSF of MS and non-neuroinflammatory control patients.
**Aims:** First, we aimed to identify potential changes of the quantified analytes in serum and CSF of MS patients. Since several of the analytes are associated with each other, we secondly aimed to characterize potential changes in correlation patterns of the analytes in MS patients. Our third aim was to use available patient information e.g. age, gender and MS-type to investigate a potential impact of these factors on the analyte levels in serum and CSF in general and in the context of MS.
**Methods:** In a retrospective study we employed a liquid chromatography tandem mass spectrometry (LC-MS/MS) analysis to quantify eCBs, associated lipids and glucocorticoids in CSF and serum samples of MS (n=74) and non-neuroinflammatory control (Ctrl, n=80) patients of the Department of Neurology of the Inselspital Bern, using already available samples stored at the Liquid Biobank in Bern.
**Results:** Comparing MS and Ctrl patients, we observed a significant increase of stearoyl ethanolamide and prostaglandin E2 (PGE2) in the serum and 2-oleoylglycerol and cortisol in the CSF of MS patients. Further, changes of analyte correlation patterns could be identified, including a disturbance of the positive correlations between cortisol and AEA in MS patients. Additionally, 2-AG was significant negatively correlated with prostaglandin D2 (PGD2) in MS, but not Ctrl patients. Age and gender were identified as potential influencing factors for some of the quantified analytes including lipid eCBs. The positive correlation of 2-AG, AEA and arachidonic acid with age observed in the CSF of Ctrl patients was lost or reduced in MS patients. A comparison of the analyte levels of MS patients with relapsing-remitting MS (RRMS, n=58) and an age and gender matched sub-cohort of the Ctrl patients, revealed a significant increase of 2-AG and AEA in the CSF of young RRMS patients (<39 years), but not in older patients with RRMS (≥ 39 years).
**Conclusions:** We confirmed earlier published reports indicating an increase of PGE2 and cortisol in MS patients, which is probably caused by inflammation. The loss of the correlation between cortisol and AEA in MS patients suggests a disturbance of the interplay between the hypothalamic-pituitary-adrenal axis regulating the release of cortisol and the ECS. The negative correlation of 2-AG with PGD2 in MS patients might indicate a role of the endogenous eCBs in modulating inflammatory processes of MS. Interestingly, we observed an increase of the lipid eCBs with age mainly in the CSF of Ctrl patients. This might be associated with inflammaging, a new term describing a chronic, sterile, low-grade inflammation, which develops during aging and might be contributing to the pathogenesis of age-related diseases. Using age and gender matched sub-cohorts, we found that lipid eCB levels are already increased in CSF of young RRMS patients and

remain at those elevated levels also in older RRMS patients. Further, the identified potential influence of age and gender on eCB levels especially in CSF, might partially explain the opposing effects of MS on eCB levels described in earlier reports, emphasizing the importance of controlling factors like age and gender in future studies of eCBs.

**Keywords:** multiple sclerosis, endocannabinoid system, serum, cerebrospinal fluid, endocannabinoids, cortisol, prostaglandins

## V. MOLECULAR PHARMACOLOGY / MOLECULAR MEDICINE

### P-V-1

### Investigation of the interplay between the membrane-palmitoylated protein 1 (MPP1) and the angiotensin II AT1 receptor (AGTR1)

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**Introduction:** Scaffold proteins of the MAGUK (Membrane-Associated Guanylate Kinase) protein family are important regulators of signaling stimulated by G-protein-coupled receptors (GPCRs) and other membrane-spanning receptors. Functions of MAGUK family proteins in the neuronal system are well-established whereas a role of these scaffold proteins in signaling stimulated by cardiovascular GPCRs is barely understood. One of the most important GPCRs and drug targets for cardiovascular diseases is the angiotensin II type 1 receptor (AGTR1). Based on the function of MAGUK proteins as signaling organizers, we searched for a potential interplay between MAGUK proteins and AGTR1.
**Aims:** This study aimed to investigate the potential role of MAGUK family proteins in the heart and heart failure pathogenesis. Based on the finding of the consistent up-regulation of the MAGUK family protein, MPP1, in three different heart failure models, the interplay between MPP1 and the major cardiovascular drug target, AGTR1, was investigated *in vivo* and in cells.
**Methods:** The study applied transcriptome profiling data of 3 different murine heart failure models and searched for alterations of MAGUK family proteins. In the first model, heart failure was induced by chronic pressure overload. In the second model, heart failure was induced by long-term atherosclerosis in $Apoe^{-/-}$ mice. In the third model, heart failure was induced by cardiac lipid overload triggered by transgenic expression of the Raf kinase inhibitor protein (RKIP). *In vivo* effects were investigated in MPP1-transgenic mice with myocardium-specific MPP1 expression. The interplay between MPP1 and AGTR1 was also investigated in human embryonic kidney (HEK) cells with AGTR1-eYFP and fluorescence spectroscopy.
**Results:** MPP1 was found to be consistently up-regulated in 3 different heart failure models. Up-regulation of MPP1 was a sufficient cause of heart failure because transgenic Tg-MPP1 mice with 2-fold increased cardiac MPP1 levels developed symptoms of heart failure at an age of 8 months, as determined by echocardiography. In addition, radioligand binding detected increased cardiac protein levels of the AGTR1 protein in Tg-MPP mice compared to non-transgenic FVB control mice. The increased AGTR1 protein contents of Tg-MPP1 hearts were a direct effect of MPP1 because MPP1 also led to increased AGTR1-eYFP levels in non-cardiomyocyte HEK cells. Cellular AGTR1-eYFP levels of MPP1-co-transfected cells were 1.61 ± 0.21-fold higher than those of control cells transfected only with AGTR1-eYFP ($n = 8$; $p<0.0001$). MPP1 did not seem to «protect» the C-terminal domain of AGTR1, because MPP1 also enhanced the internalization-deficient AGTR1(1-319)-eYFP mutant. MPP1 could mediate its effect (at least partially) by an internal PDZ domain-binding motif of AGTR1. A mutated AGTR1-(1-319)-(213-220del)-eYFP with deletion of a putative PDZ domain binding motif was not enhanced by MPP1.
**Conclusions:** Taken together our studies found a previously unrecognized AGTR1-enhancing effect of MPP1. Findings have *in vivo* relevance for the pathophysiology of heart failure.

**Keywords:** AGTR1, MAGUK protein, MPP1, heart failure, eYFP

**P-V-2**

## Structure-guided design of derivatives of the complement inhibitor compstatin with improved species specificity profiles

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**Introduction:** Since its discovery in 1996 at the University of Pennsylvania [1], the [compstatin family of peptide-based complement C3 inhibitors has been continuously optimized and found broad applications in biomedical research and as complement therapeutic. Pegcetacoplan, a PEGylated compstatin derivative, has meanwhile been approved by the FDA for PNH and GA (Empaveli/Syfovre, Apellis) and next-generation analogs with enhanced PK/PD properties are in clinical development (AMY-101, Amyndas). While facilitating clinical development, compstatin's narrow species specificity for human/primate C3 prevents its evaluation in many preclinical disease models, thereby restricting translational studies [2, 3].

**Aims:** We therefore aim to identify and develop compstatin derivatives with complement-inhibiting activity in mouse and rat models, and to gain more insight into the pharmacokinetic properties of the compstatin family.

**Methods:** By taking advantage of recent structural insight from the clinical candidate compstatin Cp40 and combining it with experimental and homology models of mouse/rat C3b, we describe molecular determinants of compstatin's species specificity and use *in silico* methods to predict derivatives with activity for rodent C3b. These rational design efforts are supplemented by directed evolution approaches based on phage display library screening against C3b from different species. Promising candidates are produced using solid-phase peptide synthesis and tested for binding affinity for mouse/rat C3b (using surface plasmon resonance and biolayer interferometry) and complement-inhibitory activity (e.g., using ELISA).

**Results and Conclusion:** Our structural analysis revealed that the narrow species specificity of compstatin is determined by a reduced number of high-quality drug-target contacts in the binding pocket rather than by steric hindrance. Some key interactions between compstatin and human C3b were shown to be absent in the other species, and efficacy optimization achieved in Cp40 even accentuates the specificity profile. By selectively substituting amino acids in sequence of the first-generation compstatin analog Cp01, as guided by our structural models, and performing phage display screening, we are currently selecting lead peptides that show notable binding to rodent C3b. To account for missing drug-target contacts, we explore extended binding sites and chemical modifications to regain affinity. In addition to providing novel C3 inhibitors for translational studies, the in-depth structure-activity relationship analysis also increases our understanding of specificity, selectivity, and activity determinants of the compstatin family that may benefit the next generation of clinical C3 inhibitors.

**Keywords:** complement system, peptides, compstatin, pharmacokinetic, protein-protein inhibitor. complement component 3, innate immunsystem

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**P-V-3**

## Factor H-capturing on HMEC-1 cells with the cyclic peptide 5C6: Synthesis, cell surface modification and measurement of FH-capturing from human blood serum

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**Introduction:** As a central part of innate immunity, the complement system acts as first-line defense against pathogens and maintains homeostasis by clearing apoptotic cells. However, complement activation can also lead to undesirable attack of non-self surfaces, for instance in transplantation scenarios. Hence, the protection of graft cells against complement-mediated damage presents an urgent medical need. Owing to its ability to recognize host cells and prevent complement amplification, the natural regulator factor H (FH) is well-suited to serve as an intervention strategy. However, its direct therapeutic use on non-self surfaces is expensive and technically challenging. Mimicking evasion strategies of pathogenic organisms, surface coatings with the FH-binding peptide 5C6 provide an elegant alternative by recruiting the physiological regulator in its active conformation. While previous studies focused on biomaterial applications with direct peptide coupling, the transition to cell-based assays puts higher demands on coating strategies.
**Aims:** Herein, we describe the surface modification of endothelial cells (HMEC-1) with 5C6 using click chemistry-based metabolic labeling and its impact on FH-capturing.
**Methods:** Modified carbohydrates were added during the culture of HMEC-1 to introduce azide groups on cell surface glycans, and the efficient modification was confirmed using clickable dyes without impairing cell viability. Subsequently, a clickable 5C6-derivative was prepared by solid-phase peptide synthesis and could be covalently attached to the cell surface in an oriented manner.
**Results:** When exposed to purified FH or serum, 5C6-coated cells efficiently recruited FH to their surface as determined by flow cytometry and fluorescence microscopy; little to no FH-binding was observed on unmodified cells or cells coated with a scrambled 5C6 analog.
**Conclusions:** Our newly established model provides an elegant strategy to coat endothelial cells with FH-binders, with the opportunity to assess parameters such as coating densities in a controlled manner. Additionally, this work may also guide future efforts for the *ex vivo* coating of transplants cells or other non-self surfaces with 5C6 in preclinical disease models.

**Keywords:** Complement system, factor H, metabolic engineering, peptides

**Reference:**

[1] Bechtler C et al. Complement-regulatory biomaterial coatings: Activity and selectivity profile of the factor H-binding peptide 5C6. Acta Biomater 2023; 155: 123-138

**P-V-4**

## Analysis of SRSF1 functions in HEK cells by NGS and mutagenesis

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**Introduction:** The serine and arginine rich splicing factor 1 (SRSF1) was found to be overexpressed in different types of cancer. Disturbance of the physiological functions of SRSF1 led to pathological ontogenetic events. In addition to its role as a splicing factor, SRSF1 is involved in multiple other functions such as RNA polymerase II-mediated transcription, mRNA translation regulation, control of the nonsense-mediated decay of mRNA, miRNA processing, and the nuclear export of the mature mRNA. The protein sequence of SRSF1 presents different sites for post-translational modifications. It is well established that the phosphorylation of SRSF1 in the arginine/serine (RS)-rich domain is important for SRSF1 function control. However, it is unclear how SRSF1 changes the RNA transcriptome, and how the activity of SRSF1 is regulated by the RS-domain.
**Aims:** We want to deepen the knowledge of the diverse functions of SRSF1 in human embryonic kidney (HEK) cells as a cellular model.
**Methods:** The *in vitro* model used HEK 293A cells. To investigate the impact of SRSF1 up-regulation on the cell transcriptome, NGS was performed of SRSF1-overexpressing HEK cells and of control cells. The specific role of RS-domain phosphorylation was investigated with 2 different mutants of SRSF1. The SRSF1-SxxxA mutant and the SRSF1-SxxxD mutant have RS-domains in which all serines were exchanged with alanine or aspartic acid, respectively. The SxxxA mutant mimics the non-phosphorylated RS-domain whereas the SxxxD mutant mimics the charge of a fully phosphorylated RS-domain. For fluorescence microscopy, the SRSF1 variants were tagged with cerulean. To measure the influence on proliferation, cell counting was used. SDS-PAGE followed by western blotting was used to determine the molecular weight or protein amounts.
**Results:** SDS-PAGE followed by western blotting showed a significantly increased apparent molecular weight of wildtype SRSF1 compared to the mutants, SxxxA and SxxxD. Studies by fluorescence microscopy found that phosphorylated SRSF1-Cerulean was predominantly localized in the nucleus whereas the SRSF1-SxxxA-Cerulean was mainly localized in the cytosol. The cell proliferation experiments showed that increased levels of the phosphorylation-defective SxxxA mutant inhibited cell proliferation. Overexpression of SRSF1 wildtype in HEK cells showed a pro-proliferative trend after 4 days. Surprisingly, after 2 weeks of SRSF1 expression, an antiproliferative effect was detected. The overrepresentation analysis of NGS data found that SRSF1 triggered the significant up-regulation of transcripts in the Reactome pathways «RNA Metabolism» and «Nonsense Mediated Decay». In contrast, the «Gene Transcription» pathway was decreased.
**Conclusions:** We found that wild-type SRSF1 is highly phosphorylated and localized in HEK cell nuclei. The anti-proliferative effects of SRSF1-SxxxA seem to be associated with cytoplasmatic localization. NGS data speak for a decrease of «Gene Transcription» in favour of «RNA Metabolism» and «Nonsense Mediated Decay». Future studies need to elucidate mechanisms which control the switch between pro- and antiproliferative effects triggered by SRSF1.

**Keywords:** SRSF1, next generation sequencing, HEK cells, cerulean, arginine/serine (RS)-rich domain, phosphorylation, proliferation

**P-V-5**

## CYP3A1 expression and activity in liver of *SLCO2B1* $^{+/+}$ and Slco2b1$^{-/-}$ rats –results from a study with erlotinib

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**Introduction:** The organic anion transporting polypeptide (OATP) 2B1 (gene name SLCO2B1) is an uptake transporter that fa
cilitates cellular accumulation of its substrates, suggesting that its function could be a determinant of their pharmacokinetics. Despite the fact that OATP2B1 transports a variety of clinically used drugs, our understanding of its *in vivo* role is still limited. Recent findings from our laboratory show that genetic modification of *Slco2b1* in rats affects the expression of rCYP3A1 one of the orthologues of CYP3A4 in rats. For the human CYP3A4 we know it is the most abundant isoform of the CYP3A subfamily and responsible for the metabolism of about 50% of currently available drugs. Erlotinib is a substrate of OATP2B1, and the formation of its major metabolite OSI-420 is catalysed by CYP3A4 in humans and by CYP3A1 in rats.
**Aim:** In this study, we want to test whether humanization of OATP2B1 in rats affects the expression and activity of the rCYP3A1 protein using erlotinib as a substrate in *ex vivo* experiments.
**Methods:** Livers from non-treated *rSlco2b1* $^{-/-}$ and *hSLCO2B1* $^{+/+}$ rats were used for the preparation of mRNA, the membrane protein fraction, and liver microsomes. Amount of rCYP3A1 protein and mRNA was quantified by Western Blot analysis and real-time PCR, respectively. CYP3A activity in liver microsomes was assessed using erlotinib. A newly developed and validated LC-MS/MS method was applied to quantify erlotinib and its major metabolite OSI-420 in those samples**.** The bioanalytical method was also applied to the measurement of OSI-420 formation in CYP3A1 and CYP3A2 bactosomes.
**Results:** Detection of *Cyp3a1* mRNA in livers by real-time PCR showed no difference comparing untreated *rSlco2b1* $^{-/-}$ and *hSLCO2B1* $^{+/+}$ rats, while Western blot analysis applied to the enriched membrane protein fraction of the livers revealed significantly higher amounts of rCYP3A1 in the animals expressing the human transporter. However, measuring the formation of OSI-420 revealed significantly higher activity in the liver microsomes of the knock-out animals. This was also observed, when analysing the data for the OSI-420/erlotinib-ratio.
**Conclusions:** Our data indicate that there is an impact of the humanization of OATP2B1 in rats on CYP3A proteins. However, the increased rCYP3A1 protein levels were linked to a lower activity level measured by OSI-420/erlotinib ratio in treatment naive animals. Further phenotyping studies are warranted to shed more light on the impact of OATP2B1 on the expression and activity of rCYP3A1.

**Keywords:** erlotinib, OATP2B1, rCYP3A1, tissue, metabolism

**P-V-6**

## Complement modulation on biosurfaces: click chemistry approach for natural regulators recruitment

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**Introduction:** As essential part of innate immunity, the complement system recognizes non-self biomaterials and generates pro-inflammatory effectors such as anaphylatoxins, opsonins and membrane-attack complexes to eliminate potential threats. These undesirable defense reactions are enabled by the absence of complement regulators on such surfaces. One option to mitigate adverse complement activation is the recruitment of the abundant natural regulator factor H (FH) to the biomaterial or transplant surface using FH-binding peptides. Previously, in our group a cyclic peptide, termed 5C6, was described as a potent tool that is able not only to effectively recruit FH via complement control protein (CCP) domains 5-18 [1] but also decrease the deposition of complement activation products - C3b/iC3b - on tested surfaces [2].
**Aims:** To use click chemistry approach for decorating biosurfaces (agarose, HMEC-1 cell surface) with 5C6 and thus, modulate complement activation diminishing undesired and uncontrolled complement-mediated effects.
**Methods:** We used standard alkyne-azide click chemistry pair to form covalent bonds between 5C6 peptides and the surface. 5C6 peptides were synthesized with the addition of alkyne or strain alkyne (BCN) group to the N-terminus for the binding to active azido group of the target surface. As such surface, we used commercially available azido agarose matrix for affinity chromatography. After click reaction with alkyne-5C6 peptide we accessed FH binding using Western blotting. We also used metabolic glycoengineering to modify HMEC-1 cell surfaces introducing active azido group into sialic acid by growing cells in presence of Ac4ManNAz. We also assessed cell viability using XTT assay to exclude negative effect of azido group containing sugar. Incorporation of azido group was assessed using fluorophore modified with strain alkyne group - DBCO-AF647, thus allowing us to conduct flow cytometry and microscopy experiments. Flow cytometry method was also used to assess the ability of «clicked» BCN-5C6 to recruit FH on the surfaces of HMEC-1 cells and the deposition of complement protein fragments C3b/iC3b.
**Results: «**Clicked» 5C6 peptide to the azido-agarose matrix was able to bind effectively and selectively FH from normal human serum. This 1-step affinity chromatography method can be used for purification of FH from different sources. Azido sugar was shown to incorporate on the surface of HMEC-1 cells and this modification was not affecting cells viability. The FH-recruiting and complement-modulating capacities of 5C6 coatings on the cell surface were confirmed by flow cytometry data. 5C6, but not a scrambled derivative, was able to recruit FH and the active 5C6 coating also prevented C3b/iC3b deposition on HMEC-1 cells when exposed to serum.
**Conclusions:** Our results show that using click chemistry for biosurfaces coating with FH-binding peptide may be beneficial for biomaterials protection. This approach potentially allows to modify any biomaterial surfaces, including lipid nanoparticles, liposomes, filter materials etc. that are known to trigger complement activation.

**Keywords:** complement, complement regulators, factor H, factor H- binding peptides, click chemistry

**References:**
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## VI. PHARMACOLOGY / BIOPHARMACY

### P-VI-1

### Phylogenetic analysis of pyruvate-ferredoxin oxidoreductase; a redox enzyme involved in the pharmacological activation of metronidazole in anaerobic protozoa and bacteria

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**Introduction:** The distribution of typical bacterial redox enzymes such as pyruvate-ferredoxin oxidoreductase (PFOR) in protozoa remains interestingly puzzling. Previous studies have demonstrated diverse cellular localizations of PFOR in amitochondriate anaerobic protozoa such as *Trichomonas vaginalis* [1]. PFOR is of particular pharmaco-logical importance because it catalyzes the reductive bio-activation of metronidazole to cytotoxic radical metabolites. Metronidazole was developed primarily as an antiprotozoal agent against infections caused by *T. vaginalis* [2]. However, its antimicrobial spectrum was subsequently expanded to cover anaerobic bacterial infections. It has been shown that mutations in the genes encoding PFOR result in inherent resistance of *T. vaginalis* and anaerobic bacteria to metronidazole [3].
**Aims:** To analyze the phylogenetic distribution of PFOR in selected protozoa and bacteria using proteins encoded by housekeeping genes as controls. Using comparative bioinforma-tics to test the hypothesis that PFOR was most likely acquired through horizontal gene transfer from bacteria, proteome-wide analysis and gene expression analysis to identify other genes that were putatively acquired through horizontal gene transfer from bacteria to protozoa.
**Methods:** Sequence similarity queries were performed using the proteins of interest against the NCBI non-redundant protein sequence database with BLASTP version 2.12.0+ from the NCBI website. Multiple sequence alignments were performed with MEGA version X software using the Muscle algorithm. These were then exported in Mega format to construct phylo-genetic trees using the neighbor-joining algorithm and the Poisson substitution model. Complete proteomes of representative protozoan and bacterial species were downloaded in fasta format from the ensemblgenomes database. HMM profile libraries were used to screen the proteomes with hmmscan of the HMMer package. Whole proteome BLAST searches were performed between protozoan species of interest against closely related protozoa. The results were compared to the proteome BLAST against the intestinal bacteria *Desulfovibrio vulgaris*. Gene enrichment analysis was performed between the exclusively present proteins in the protozoa and *D. vulgaris*. Only results with p-values <0.05 were considered for analysis.
**Results and conclusions:** A plausible explanation for the restricted occurrence of PFOR in protozoa is based on the hypothesis that bacteria serve as potential sources of genes that enhance optimal adaptation of protozoa in hostile environments. The expanded cladograms of *Entamoeba* and *Cryptosporidium* with their closely related genera substantiated this hypothesis. The exclusively expressed proteins obtained from *E. histolytica* and the putative bacterial gene donor, *D. vulgaris*, showed an over-representation of eleven genes involved in small molecule metabolism, generation of precursor metabolites, and carbohydrate metabolism. If these results can be reproduced in other PFOR-possessing protozoa, it would provide a more validated evidence to support the horizontal transfer of *pfor* from bacteria. Subsequent syntenic analyses of the significantly enriched genes would be required to provide further information regarding the positional relatedness of these genes at the chromosomal level. Since metronidazole is an established and well tolerated drug for treating infections caused by PFOR-possessing pathogens, it can be considered as a potential drug candidate for the treatment of infections caused by *Cryptosporidium, Spironucleus* and *Blastocystis*.

**Keywords:** Pyruvate-ferredoxin oxidoreductase, metronidazole, reductive bio-activation, antimicrobial spectrum, comparative bioinformatics, horizontal gene transfer, phylogeny

**References:**

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**P-VI-2**

## *In vitro* antibacterial activity of arene ruthenium(II) compounds

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**Introduction:** To face the problem of bacterial resistance to antibiotics, the development of new classes of active compounds against which bacteria are less prone to develop resistances is crucial. Metal complexes reached clinical trials for the treatment of various disease and some show also interesting antibacterial activity.
**Aims:** Di- and trithiolato-bridged dinuclear ruthenium(II)-arene complexes have been investigated for more than a decade. The antibacterial activity of a series of 22 arene ruthenium(II) compounds bearing diverse types of ligands was assessed *in vitro* against *Escherichia coli*, *Streptococcus pneumoniae* and *Staphylococcus aureus*.
**Methods:** The MIC of the compounds were measured, fluorescence microscopy assays and inductively coupled plasma mass spectrometry (ICP-MS) experiments were performed.
**Results:** None of the compounds efficiently inhibited the growth of *E. coli*, but MIC values ranging from 1.3 to 2.6 µM (*S. pneumoniae)* and ranging from 2.5 to 5 µM (*S. aureus)* were measured. The compounds had a bactericidal effect significantly faster than that of penicillin. Fluorescence microscopy showed that the compounds enter the bacteria and do not accumulate in the cell wall of gram-positive bacteria. ICP-MS experiment confirmed the cellular internalization of the compounds [1].
**Conclusions:** This first antibacterial activity screening demonstrated that these arene ruthenium(II) compounds exhibit promising activity against *S. aureus* and *S. pneumoniae* and deserve to be considered for further studies. Overall, complexes with larger benzo-fused lactam substituents appear to be the most promising in this series.

**Keywords:** Ruthenium complexes, *Escherichia coli*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, MIC, fluorescence, uptake, ICP-MS, benzo-fused lactams.

**Reference:**
[1] Bugnon Q et al. Microbiol. Spectr., submitted.

**P-VI-3**

## Evaluation of folate radioconjugates: Implications of folate receptor isoform selectivity

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**Introduction:** The current applications of radiopharmaceuticals to treat prostate and neuroendocrine neoplasms have further raised interest to target other tumor-associated receptors and expand the applications of targeted radionuclide therapy. The folate receptor alpha (FRα) is a promising target as it is overexpressed in various epithelial malignancies. On the other hand, the beta isoform of this receptor (FRβ) is found in hematological tissues. It is, therefore, essential that FR-targeted radioconjugates selectively bind to the FRα to enable an optimum therapeutic efficacy while avoiding adverse hematologic effects.
**Aim:** The goal of this study was to evaluate 6*R*- and 6*S*-5-methyltetrahydrofolate-based radioconjugates in terms of their selective binding to FRα-expressing tissues. Potential undesired effects to the renal and hematologic tissues were investigated given the known expression of the FRα and FRβ in these tissues, respectively.
**Methods:** 6*R*-RedFol-1 and 6*S*-RedFol-1 were radiolabeled with lutetium-177, a clinically used $\beta^-$-emitter [1]. The selectivity of the radioconjugates to FRα was assessed *in vitro* and *in vivo* using Chinese hamster ovary cells transfected with FRα (RT16) or FRβ (D4). Tissue distribution studies were performed after injection of the radioconjugates in non-tumor bearing mice fed with standard or folate-free diet. Long-term effects of the application were evaluated through whole blood cell measurements and plasma chemistry analysis.
**Results:** [$^{177}$Lu]Lu-6*S*-RedFol-1 showed selective cell uptake in FRα-positive RT16 cells, while negligible uptake was seen with FRβ-positive D4 cells. In contrast, [$^{177}$Lu]Lu-6*R*-RedFol-1 was taken-up equally by both cell lines. Similar results were observed *in vivo*, demonstrated by a 20 times higher uptake of [$^{177}$Lu]Lu-6*S*-RedFol-1 in RT16 xenograft than in D4 xenograft at 24 h post-injection. The activity measured in most organs was higher after the injection of [$^{177}$Lu]Lu-6*R*-RedFol-1, which could have been influenced by its higher accumulation in the blood. However, evidently higher renal accumulation of the 6*S*-diastereoisomer was measured in mice under folate-free diet. Signs of nephrotoxicity and fewer erythrocytes were observed in mice that received [$^{177}$Lu]Lu-6*S*-RedFol-1. These effects were not seen in mice on standard diet. On the other hand, mice injected with [$^{177}$Lu]Lu-6*R*-RedFol-1 had low leukocyte counts, regardless of the rodent diet, which could be due to the higher blood accumulation and binding of this radioconjugate to FRβ present in hematologic tissues.
**Conclusions:** The use of [$^{177}$Lu]Lu-6*S*-RedFol-1 would be advantageous to selectively target FRα-expressing malignancies and avoid accumulation in FRβ-expressing blood cells. The consequent long-term effects were more favorable after the application of the 6*S*-diastereoisomer, provided that the mice were on standard diet. Dietary folate regulation would, therefore, be necessary to take full advantage of the use of [$^{177}$Lu]Lu-6*S*-RedFol-1 and prevent potential adverse effects. In addition, the renal accumulation of this folate radioconjugate should be addressed to enable effective and safe applications in a therapeutic setting.

**Keywords:** Folate receptor, 5-methyltetrahydrofolate, radionuclide therapy, lutetium-177

**Conflict of interest:** Patent applications on folate conjugates with albumin-binding entities have been filed by Merck & Cie, Schaffhausen, Switzerland. R. Schibli and C. Müller are listed as co-inventors. This research was also supported by the Swiss National Science Foundation.

**Reference:**
[1] Guzik P et al. Eur J Nucl Med Mol Imaging 2021; 48: 972.

**P-VI-4**

## Towards refining cancer immunotherapy: PET tracers for investigating legumain targeting in the tumor microenvironment

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**Introduction**: Anti-cancer treatment has undergone a paradigm shift with the advent of cancer immunotherapy. Despite promising achievements, these therapies are restricted to a limited range of cancer types and patients. The tumor microenvironment is a potential source of promising therapeutic targets, in addition to the well-established immune checkpoints. The cysteine endopeptidase legumain is overexpressed in tumor-associated macrophages and promotes cancer metastasis.
**Aims**: Our goal is to develop PET tracers to support research and development towards legumain targeting anti-cancer therapies and to noninvasively assess the immune state and metastatic potential of cancer lesions.
**Methods**: The affinity of the 3 legumain inhibitors RC-01, RC-02 and RO-01 towards legumain was assessed using proteolytic assays. The carbon-11 labeled compound was obtained by reacting the respective precursor with [$^{11}$C]-methyl-iodide. The binding specificity was evaluated by autoradiography on CT-26 mouse tumor tissue slices. Target expression in CT-26 tumor tissue (syngraft in immunocompetent mice), CT-26 cells, MDA-MB-468 tumor tissue (xenograft in immunocompromised mice) and MDA-MB-468 cells was quantified using RT-qPCR and western blot. Legumain fluorescence microscopy was performed using CT-26 tumors to compare with autoradiography and assess co-localization with tumor-associated macrophages. PET scans were conducted with CT-26 tumor-bearing mice to determine the *in vivo* tracer distribution. The results obtained from the scans were validated by analyzing the dissected tissues. Radiometabolites were evaluated using column-switch RP-HPLC.
**Results**: RT-qPCR and western blot unveiled elevated legumain expression in tumors compared to muscle tissue and cells. RC-01, RC-02 and RO-01 demonstrated nanomolar binding affinities (Ki) to mouse and human legumain. $^{11}$C-labeled compounds were synthesized with a radio-chemical purity of > 99 % and high molar activity, typically > 50 GBq/μmol. Autoradiography showed heterogeneous tracer accumulation in the tumor slices. However, the accumulation was not blocked by excess unlabeled compound. Fluorescence microscopy confirmed heterogeneous distribution of legumain within the CT-26 tumor tissue. In PET, [$^{11}$C]RC-01, [$^{11}$C]RC-02 and [$^{11}$C]RO-01 accumulated in the tumor periphery. Biodistribution analysis after dissection indicated no significant difference between baseline and blocking conditions in tumors. With each of the 3 tracers, the tumor uptake was significantly higher than in muscle and with [$^{11}$C]RO-01, blocking had an effect in kidney and spleen which display high legumain expression. [$^{11}$C]RC-01 and [$^{11}$C]RC-02 were rapidly metabolized. In contrast, [$^{11}$C]RO-01 was stable at 45 min post-injection, with plasma predominantly containing parent tracer.
**Conclusions**: We have successfully developed a stable, high-affinity legumain PET tracer. A blocking effect with RO-01 in kidney and spleen suggests high specificity. We are currently further investigating the tracer in an MDA-MB-468 mouse xenograft model.

**Keywords**: Immunotherapy, PET, legumain, cancer, microenvironment, carbon-11, preclinical

**P-VI-5**

## Repurposing drugs to develop treatments for *Mycobacterium ulcerans* disease

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[2] *Department of Chemistry and Applied Biosciences, ETH Zürich, 8093 Zürich*
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**Introduction:** *Mycobacterium ulcerans* disease – or Buruli ulcer (BU) – is a neglected tropical disease (NTD) affecting skin and soft tissue. BU is endemic in parts of Central and West Africa, and southeastern Australia. The current WHO recommended treatment involves a daily regimen of rifampicin and clarithromycin for 8 weeks. BU treatment is, however, still less than optimal for several reasons, including the current lack of effective replacements for rifampicin in the event of resistance development. Thus, development of new drug regimens is still a key aspect of effective BU control. Being an NTD, *de novo* drug discovery and development for BU is prohibitively expensive. Consequently, repurposing of drugs and drug candidates for other diseases is the most cost-effective way of developing new drugs for BU treatment. Accordingly, we assessed drugs and treatment modalities for other diseases to determine their potential for repurposing for BU treatment.
**Aims:** To identify drug candidates and other treatment modalities that could be repurposed for BU treatment.
**Methods:** Test compounds were assessed for activity against *M. ulcerans* using resazurin assays. The bactericidal activity of selected compounds were then assessed in time-kill assays.
**Results:** We recently showed *M. ulcerans* to be hypersensitive to the imidazopyridine carboxamide compound Q203 currently being developed as an antituberculosis drug. We therefore further explored this target space, focusing on 3 scaffolds with reported activity against cyt-$bcc_1$:$aa_3$ – the target of Q203. We performed SAR studies on 118 compounds representing these 3 scaffolds – arylvinylpiperazines, pyrrolopyridine diones, and quinazoline amines – and could determine modifications that enhance activity against *M. ulcerans*. All 3 scaffolds showed activity against *M. ulcerans* ranging from the micromolar to the low nanomolar. In addition, we found that an Acid-Oxidizing Solution (AOS)
being developed for the clinical management of chronic wounds was also highly active against large inocula of *M. ulcerans*, and AOS-pretreated bacteria were hypersensitive to sublethal concentrations of antibiotics.
**Conclusions:** We explored the repurposing potential of test compounds active against a valid target for antimycobacterial drug development, and identified scaffolds and derivatives that could potentially lead to improved BU treatment regimens. We also identified an AOS that could potentially contribute to the clinical management of BU.

**Keywords:** *Mycobacterium ulcerans*, Buruli ulcer, Q203, Acid-Oxidizing Solution

**P-VI-6**

## Measuring cytokine-secretion dynamics of single cells to deepen the understanding of systemic autoinflammatory diseases

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**Introduction:** Disruptions in the regulation of the immune response induce various disorders and clinical manifestations that can be potentially life-threatening. Manifesting by inflammatory flares, systemic autoinflammatory diseases (SAIDs) are a striking example of immune response dysregulation. SAIDs are rare heterogeneous conditions characterized by periodic serous and synovial membrane inflammation that spontaneously resolves. Due to their genetic nature, diagnostic currently relies mainly on genetic testing. However, disease-causing mutations cannot be identified for nearly half of the patients with clinical manifestations of the disease, SAIDs are most frequently of unknown pathophysiology. Therefore, dynamic and highly sensitive studies are needed to understand better the underlying mechanisms of SAIDs and evaluate the consequences of the immune response disruption.
**Aims:** To address this, we aim to directly measure the dysregulation and activation of the immune cells in response to stimulation on the single-cell level with our platform for functional single-cell measurements.
**Methods and Results:** We successfully integrated novel bioassays to quantify cytokines secretions dynamically on the single-cell level. Our methods can identify for each individual cell the secreted cytokines quantities, secretion rates, dynamics, co-secretion and different cellular subpopulation according to the secretion pattern.
**Conclusions:** These developed assays are currently employed in a proof-of-concept study of healthy donors and SAIDs patients of various genetic backgrounds with known or unknown mutations which enables us to measure the immune response with unprecedented resolution and precision. We are hoping that the cytokine profiling of SAIDs patients will deepen the understanding of the pathophysiology of the disease, identify the different disease pathways and could potentially help to define new objective diagnostic criteria based on the measured dysregulation.

**Keywords:** immunology, single-cell, immune dysregulation, cytokine, microfluidic

**P-VI-7**

## Human monocyte specific DNA inflammasome activation: Implication for liposome induced inflammatory response

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**Introduction**: Liposomes are highly promising vehicles for delivering genes and drugs, owing to their biocompatibility and modular properties. For several decades, researchers have dedicated significant effort to studying and optimizing liposomal formulations for various medical applications, such as cancer treatment and pain relief. Recently, lipid nanoparticles (LPN) have been widely used for manufacturing mRNA Covid-19 vaccines. Despite the advantages of using liposomes for drug delivery, it is crucial to consider their toxicity, as they present a real challenge for clinical translation. It is important to understand their toxicities to immune cells, as well as the regulation of inflammatory responses, to improve therapeutic benefits and avoid immune toxicity. In this study we confirm that liposomes activate inflammasome activation specifically in human monocytes. Inflammasomes are caspase-1 activating complexes containing an adaptor protein (ASC) and caspase-1. They process IL-1 cytokine members IL-1β and IL-18 which are associated with acute and chronic inflammation and play an essential role in the host response to infection.
**Aims**: The primary objective of this study is to validate previous findings of a liposome-specific inflammasome activation in human monocytes. These findings seek to deepen our understanding of the inflammasome activation in human myeloid cells, specifically human monocytes and human macrophages. As a recently published paper suggests a new pathway for the liposome activation in human monocytes, we aim to enhance the comprehension of inflammasome activation in myeloid cells.
**Methods**: In order to understand whether liposomes activate inflammasomes, we primed human and mouse primary monocytes and macrophages with Pam3CSK4 and activated with liposomes and nigericin. Inflammasome activation leads to capase-1 cleavage, which precedes to cell death (pyroptosis) and release of active-IL-1β. Pathway inhibitors were used to understand the mechanism. The release of IL-1β was measured by ELISA. Western blot was performed to check caspase-1 and IL-1β cleavage and other inflammasome components, such as NLRP3.
**Results**: As known from literature, liposomes did not activate inflammasome in murine myeloid cells such as macrophages and monocytes. In line with this we did not find inflammasome activation by liposomes in murine myeloid cells. Surprisingly, liposomes activated inflammasomes in human monocytes but not in human macrophages. Upon activation with liposomes human monocytes produced IL-1β and showed pyroptosis. We identified that liposome mediated IL-1β production and pyroptosis depends on NLRP3 inflammasome. Inhibiting NLRP3 abolished liposome induced IL-1β production. We further identified that liposome mediated NLRP3 inflammasome activation depends on potassium (K+) efflux.
**Conclusion**: We identified that liposomes are potent inflammasome activators specifically in human monocytes. In human macrophages, liposomes did not induce any inflammasome activation. As liposomes are commonly utilized for drug delivery in humans, the results of these studies hold significant translational relevance. It suggests that modulating liposome-mediated immune activation could be a viable strategy to reduce immune-mediated toxicity or can be used as an adjuvant to induce innate immunity in vaccinations.

**Keywords**: Human myeloid cells, human monocytes, liposomes, inflammation

**P-VI-8**

## Investigation of the spatial distribution of $^{175}$Lu-labeled small molecules using laser ablation ICP-MS

**R.H. Wallimann[1,2], R. Kneuer[1], M. Jivkov[1], V. Dubost[1], D. Beyer[2], C. Müller[2,3], R. Schibli[2,3]**

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**Introduction**: It was previously shown by our group, that inductively coupled plasma mass spectrometry (ICP-MS) serves as valid alternative to conventional radioactive assays for the preclinical characterization of future radiopharmaceuticals [1]. The established ICP-MS methods allowed quantitative investigation of the *in vivo* biodistribution of metal conjugates, but not their spatial distribution within specific tissue. Exact localization of metal-labeled receptor targeting agents in tissue would be possible when a laser ablation (LA) system is coupled with an ICP-MS [2].
**Aims**: The aim of this project was to evaluate if LA-ICP-MS can be used for *in vitro* and *ex vivo* imaging of tissue sections to evaluate target-specific binding, tumor penetration and off-target tissue distribution (e.g. in the kidneys) of $^{175}$Lu-labeled tumor-targeting agents similar to *in vitro* and *ex vivo* autoradiography of analogous radiopharmaceuticals.
**Methods**: Folic acid receptor (FR)-targeting 6*S*-RedFol-1 and 6*R*-RedFol-1 [3] were stoichiometrically labeled with the stable isotope lutetium-175. [$^{175}$Lu]Lu-6*R*-RedFol-1 and [$^{175}$Lu]Lu-6*S*-RedFol-1 were used to evaluate their *in vitro* binding on FR-positive KB tumor sections using LA-ICP-MS. To test organ distribution after injection of these FR-targeting metal conjugates, KB tumors and kidneys of mice were collected, cut into sections, and analyzed.
**Results**: The incubation of KB tumor and kidney sections with [$^{175}$Lu]Lu-6*S*-RedFol-1 and [$^{175}$Lu]Lu-6*R*-RedFol-1 allowed investigating the distribution of FR expression due to binding of the $^{175}$Lu-labeled small molecules *in vitro*. Sub-organ distribution of the $^{175}$Lu-labeled FR-targeting agents after injection in mice was also feasible using LA-ICP-MS for FR-targeting agents, but only in KB tumors and kidneys which accumulated the metal conjugates to a high extent.
**Conclusions**: Our study demonstrated that LA-ICP-MS has sufficient sensitivity to evaluate binding and spatial distribution of $^{175}$Lu-labeled small molecules by *in vitro* and *ex vivo* experiments in tissues with high target expression levels similar as it is commonly done with radioconjugates in *in vitro* and *ex vivo* autoradiography studies. Hence, it provides additional information to the already described ICP-MS technologies and allows detailed preclinical characterization of metal conjugates in conventional research facilities.

**Keywords**: laser ablation inductively coupled plasma mass spectrometry, nuclear theranostics

**References**:
[1] Wallimann R et al. Mol Pharm 2023; 20(4): 2150-2158
[2] Costa IM et al. Nucl Med Biol 2021; 98: 18-29
[3] Guzik P et al. Eur J Nucl Med Mol Imaging 2021; 48: 972-983

**P-VI-9**

## Validation and implementation of a LC-MS/MS method to simultaneously quantify atorvastatin, erlotinib, and OSI-420 in experiments with rat liver microsomes

**M. Rysz[1], J. Kinzi[1], A. Schäfer[1], K. In-Albon[1], S. Zürcher[1], S. Schmidlin[1], I. Seibert[1], O. Schwardt[2], D. Ricklin[2], H. Meyer zu Schwabedissen[1]**

[1] *Biopharmacy Lab, Department of Pharmaceutical Sciences, University of Basel, 4003 Basel*
[2] *Molecular Pharmacy, Department of Pharmaceutical Sciences, University of Basel, 4003 Basel*

**Introduction:** Erlotinib is a tyrosine kinase inhibitor (TKI) that is approved for the treatment of non-small-cell lung cancer (NSCLC). The pharmacokinetics of erlotinib involves drug transporters and drug metabolizing enzymes. Indeed, it is considered a substrate of OATP2B1 and of CYP3A4. The latter catalyzes the formation of the only pharmacologically active metabolite OSI-420 [1]. In rats the function of CYP3A4 is assumed to be taken over by either rCYP3A1 or rCYP3A2, but it is not known which of the isoforms is of higher relevance for the metabolism of erlotinib.
**Aims:** The aim of the study was to optimize and validate a LC-MS/MS method applicable to *ex vivo* experiments, to establish a CYP3A activity assay in liver microsomes using erlotinib as substrate, and to employ the method to quantify OSI-420 formation in rat and human liver microsomes.
**Methods:** For the validation of a LC-MS/MS-method previously established for the detection of erlotinib and OSI-420 in rat serum we followed the ICH M10 guidance criteria [2]. Livers collected from male and female Wistar rats were used for preparation of rat liver microsomes. *Ex vivo* formation of OSI-420 was determined exposing liver microsomes to erlotinib in presence or absence of the CYP3A-substrate atorvastatin. Western blot analysis was applied to determine the amount of rCYP3A1 and rGAPDH in rat liver microsomes.
**Results:** The LC-MS/MS method for atorvastatin, erlotinib, and OSI-420 in liver microsomes fulfilled the guidance criteria [2] for the selectivity, the linearity of the calibration curves, and the matrix effect and recovery, respectively. The method was then applied in microsomal studies. Assessment of time- and concentration-dependency of the OSI-420 formation rate in rat liver microsomes of male and female rats suggested that the reaction conditions of 25 µM erlotinib and a reaction time of 15 min should be optimal. Moreover, we saw a gender dependent reaction rate, with slower formation of OSI-420 in female liver microsomes, but presence of 2.5 µM atorvastatin inhibited the metabolism of erlotinib irrespective of the gender. A subsequently performed Western blot analysis revealed a lower amount of rCYP3A1 in liver microsomes of female compared to male rats
**Conclusions:** The validated LC-MS/MS method is applicable to the *ex vivo* assessment of the OSI-420 formation in rat liver microsomes, which revealed a lower formation rate in those isolated from female rat livers. Considering that we observed lower amounts of CYP3A1 in liver microsomes of female rats, suggests that this CYP3A-isoform is of major relevance for the formation of this biological active metabolite in rats.

**Keywords:** LC-MS/MS, method validation, erlotinib, CYP3A activity assay, liver microsomes

**References:**
[1] Ling J et al. Metabolism and excretion of erlotinib, a small molecule inhibitor of epidermal growth factor receptor tyrosine kinase, in healthy male volunteers. Drug Metab Dispos 2006; 34(3): 420-6
[2] ICH Guideline, Bioanalytical method validation and study sample analysis M10, ICH Harmonised Guideline: Geneva, Switzerland (2022)

**P-VI-10**

## Investigating antibody-cytokine multifunctionality of human B cells using single-cell droplet microfluidics

**L. Schlotheuber, D. Ferreira Garcia Rodrigues, K. Eyer**

*Laboratory for Functional Immune Repertoire Analysis, Institute of Pharmaceutical Sciences, Department of Chemistry and Applied Biosciences, ETH Zürich, 8093 Zürich*

**Introduction:** In recent years, B cells have been identified as key players in autoimmunity and tumour formation [1]. Indeed, B cells can infiltrate tumors and exert various functions. Firstly, B cells can undergo Germinal Center reactions to produce antibodies that target (tumour)-antigens Secondly, B cells are also capable of expressing and secreting other proteins such as IL-35 which regulate tumour immunity [2]. However, although it is clear that B cells exert various functions in multiple diseases, it is unclear if B cells are indeed polyfunctional at a single-cell level, how different sub-populations of B cells are formed and regulated and how antibody production and cytokine release cooperate.
**Aims**: This project aims to a) develop a platform for multiplexed, quantitative analysis of cytokine and antibody secretion from individual B cells and b) to apply them to study secretion patterns in health and diseases to uncover complex B cell signatures.
**Methods:** Previously, in our lab methods were developed to simultaneously detect and measure secretion from individual cells using droplet microfluidics which allows for a dynamic (over-time) and quantitative measurement [3]. For this purpose, B cells are isolated from patient or healthy donors, encapsulated in 50-100 pL droplets together with bioreagents and immobilized into reaction chambers for over-time analysis.
**Results**: We validated our assays using untouched B cells from healthy donors to measure secretion after toll-like receptor stimulation in single droplets allowing for read-outs from up to 50.000 cells.
**Conclusion**: We are able to determine unique co-secreting populations of Il-10/Il-6 and IgG, study secretion patterns of IL-35 and investigate the orchestration of sub-populations which are invisible to current phenotyping technologies. Moving now to applications, these tools will allow us to better define the functionality of B cells in the context of environmental and inflammatory stimuli as well as in patients suffering from autoimmunity and cancer.

**Keywords:** antibody secretion, single cell, droplet microfluidics, multifunctionality, B cells

**References:**
[1] Schumacher TN, Thommen DS. Tertiary lymphoid structures in cancer. Science 2022; Jan 7; 375 (6576): eabf9419.
[2] Mirlekar B, Wang Y, Li S, Zhou M, Entwistle S, De Buysscher T, et al. Balance between immunoregulatory B cells and plasma cells drives pancreatic tumor immunity. Cell Rep Med 2022; Sep 20; 3(9):100744.
[3] Bounab Y, Eyer K, Dixneuf S, Rybczynska M, Chauvel C, Mistretta M, et al. Dynamic single-cell phenotyping of immune cells using the microfluidic platform DropMap. Nat Protoc 2020 Sep;15(9): 2920–55.

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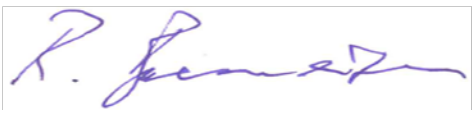

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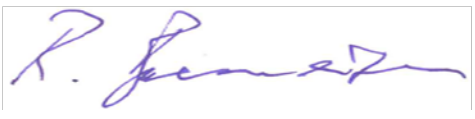

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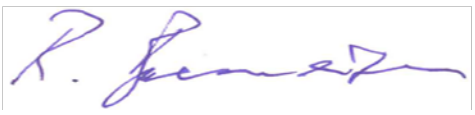

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**PharmaTalk**
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- fosters the young pharmaceutical scientific academics
- **fosters the communication between the pharmaceutical sciences in Switzerland and other scientific organisations,** as well as between pharmaceutical societies, their institutions and members
- **represents the Swiss pharmaceutical sciences on** a national and international level.

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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
- **fosters and supports the integration of pharmaceutical** competence in other sciences
- **develops recommendations and guidelines for the university education in pharmaceutical sciences**
- supports and coordinates the implementation of **the pharmaceutical knowledge in the pharmaceutical** practice
- **defines and introduces new fields of activities in pharmacy**
- **represents the pharmaceutical sciences in the public**
- **authors statements for media and advices authorities in** the preparation of laws and decrees.
- **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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## Tasks and Activities

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- **cooperates with important national professional societies and associations, such as GSIA, GSASA,** pharmaSuisse, asep and swissYPG
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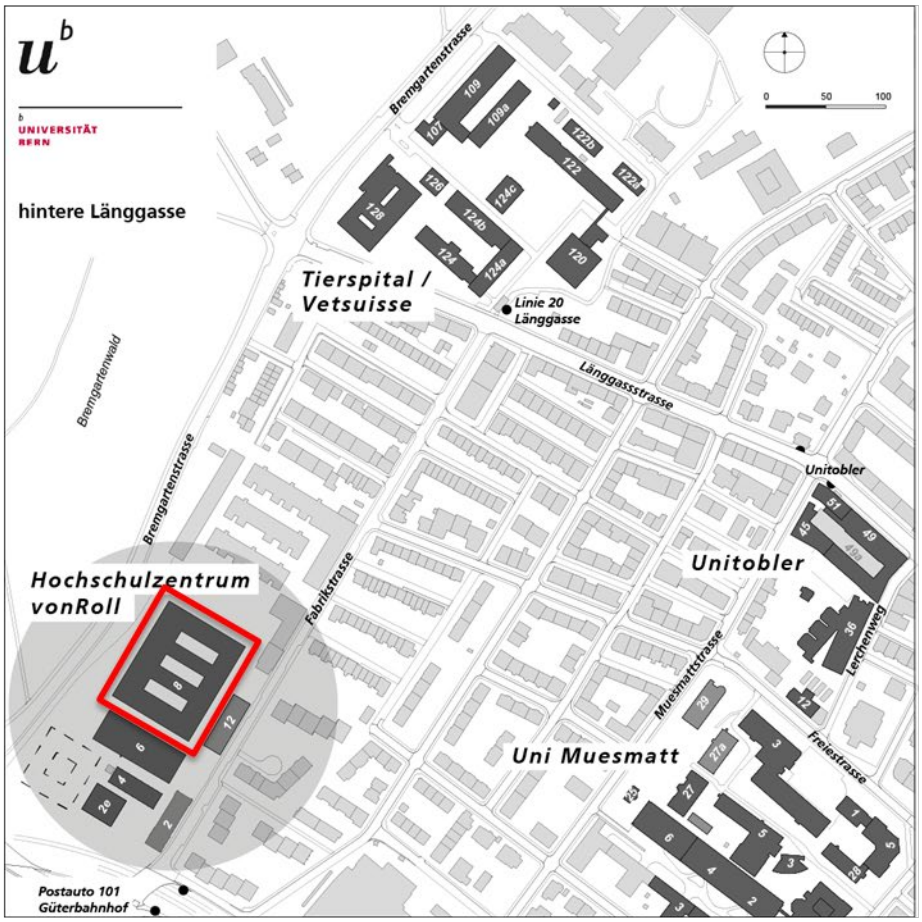


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