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SWISS PHARMA SCIENCE DAY 2008
University of Bern
9 October 2008
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Swiss Academy of Pharmaceutical Sciences (SAPhS)

Swiss Journal for the Pharmaceutical Industry

Schweizerische Zeitschrift für die pharmazeutische Industrie

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10/08

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SWISS PHARMA SCIENCE DAY 2008 University of Bern, 9 October 2008

Swiss Society of Pharmaceutical Sciences (SSPhS)

Swiss Academy of Pharmaceutical Sciences (SAPhS)

Dear Readers,

On April 24, 2007 the General Assembly of the members of the Swiss Society of Pharmaceutical Sciences SSPhS (for the portrait see SWISS PHARMA 7–8/08 and 9/08) have decided to approve the suggested changes in the Bylaws as follows: The highest organ is still the General Assembly, which includes the Senate and the Senate Committee as an executive organ. The Senate represents the individual and collective members of the SSPhS. The Fellows of the Society represent the Scientific Advisory Board of the SSPhS and form together with the Senate Committee the Swiss Academy of Pharmaceutical Sciences (SAPhS).

In this context it is necessary to notice that the most important annual event of the SSPhS is the SWISS PHARMA SCIENCE DAY organised under the patronage of the SSPhS. It has been decided that the journal SWISS PHARMA each year dedicates a special issue to this event.

This annual event offers a platform to present, in the form of a poster session, the latest research results of Master and Ph. D. students, as well as post-docs of all three Swiss Academic Institutions for Pharmaceutical Sciences (ETH Zürich, School of Pharmaceutical Sciences of the Universities Lausanne and Geneva EPLG in Genève and the University of Basel). Master students of the Universities of Applied Sciences, i. e. FHNW (School of Life Sciences, Muttenz) and ZHAW (Life Sciences and Facility Management, Institute of Biotechnology, Wädenswil) are also invited to participate in this event.

In addition, joint Foreign-Swiss Institutions such as the Russian-Swiss Science and Education Center for Transfer of Biopharmaceutical Technologies at the Mendeleyev University of Chemical Technology of Russia, Moscow (see SWISS PHARMA 7–8/08 and 9/08), CISDEM, (Catedra Iberoamericana-Suiza de Desarollo de Medicamentos) at the University of Sevilla, Spain, and the Institut Franco-Suisse des Sciences et Procédés Pharmaceutiques at the Ecole des Mines Albi-Carmaux, in Albi, France may participate in these annual SWISS PHARMA SCIENCE DAYS in order to boost the collaboration with Swiss Partners.

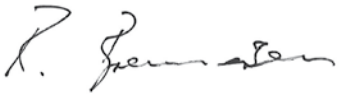
The poster session is embedded in a series of lectures given by invited distinguished scientists representing the broad field of pharmaceutical sciences, including Pharmaceutical Analytics, Biology, Chemistry, Engineering, Technology, as well as Pharmacology.

The 1st SWISS PHARMA SCIENCE DAY was held on October 9, 2008 at the Pathology Building of the University of Bern, attracting more than 120 participants. Lectures were given by excellent speakers, which were followed by animated discussions. The poster session of 69 accepted abstracts of high quality offered the opportunity for the students to discuss and network with experts and colleagues from all Swiss institutions. A jury had the not easy task to evaluate the posters and nominate the three award winners (see Conference Report in this issue SWISS PHARMA 10/08). The closing social event at the beautiful historic House of the University of Bern offered sufficient opportunity for relaxed discussions and for reflecting this stimulating scientific event. It was spontaneously decided to also use the same infrastructure for the 2nd SWISS PHARMA SCIENCE DAY, planned to take place in the first half of September 2009.

One of the primary goals of this annual event 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 in a public pharmacy. Thus a cooperation between the different institutions in academia and industry (see also Editorial SWISS PHARMA 7–8/08 and 9/08) and between the different fields of pharmaceutical sciences is being promoted.

Last but not least, the annual SWISS PHARMA SCIENCE DAY represents an ideal platform to meet young engineers and scientists, which may be recruited for a position in academia, hospital, industry, public health administration and/or public pharmacy.

The undersigned wish the greatest possible success for a sustainable development of the institution of the future SWISS PHARMA SCIENCE DAYS.



Prof. Dr. Hans Leuenberger
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SWISS PHARMA SCIENCE DAY 2008

Conference Report – A Short Flashback

Prof. Dr. Rudolf Brenneisen, University of Bern, President Scientific Advisory Board (SAPhS)
Prof. Dr. Hans Leuenberger, President (SSPhS)

Introduction

About 140 people, with more than 120 finally participating, registered for the 1st SWISS PHARMA SCIENCE DAY (SPSD 2008). This interest was quite surprising, as the date of this event could only be communicated a couple of months in advance and was interfering with the winter semester with fixed lecture and course schedules. According to the first feedbacks of a just started survey the 2nd SPSD will most probably take place during the first week of September 2009. This pre-semester timepoint should allow the attendance of even more students and faculty members.

The Langhans auditorium and foyer at the Pathology Institute of the University of Bern offered an ideal setting and infrastructure for the lecture and poster sessions as well as appetizing buffets delivered by the excellent catering service of the Inselspital Bern. Two lecture sessions (see "Program"), moderated by Prof. Rudolf Brenneisen and Prof. Hans Leuenberger, represented the multi-faceted Pharmaceutical Sciences. Beyond doubt, the seven distinguished speakers fascinated the audience with their scientific updates and reviews on pharmaceutical key disciplines, such as pharmaceutical technology, pharmacology, plant biochemistry, biopharmaceutics, and analytics (see "Lectures": abstracts).

A big compliment goes to the numerous poster presenters and their coauthors, who allowed spectacular insights in their project targets as well as daily, most challenging, complex and often frustrating lab research work. For that, the three poster awards (see below) were only a modest appreciation, however, should encourage our young scientific generation and successors to even more boost their research efforts and come back next year with new convincing and relevant data.

The SPSD 2008 officially ended by honoring two colleagues for their outstanding contributions to the pharmaceutical sciences and education (see "Fellows").

After a lot of science provided by outstanding speakers and poster authors the participants enjoyed the closing part of the SPSD 2008 in the beautiful House of the University of Bern, once owned by Prof. Theodor Kocher, Nobel Prize winner, University of Bern. The delicious Swiss wines facilitated easy socializing, networking, and the decision, to come back for sure to Bern for attending the 2nd SPSD 2009. After the obvious success and motivating numerous positive feedbacks it will be a real challenge for the next Organizing Committee to keep the set high scientific standard for the upcoming SPSDs. In this sense: see you hopefully all again next year – same site! And last but not least, many thanks to the sponsors (see box) – mainly professional organizations and foundations – whose support allowed to realize this quite ambitious event covering a broad palette of pharmaceutical sciences and research topics.

Prof. Isidoro Caraballo, President CISDEM, Catedra Iberoamericana - Suiza de Desarollo de Medicamentos, University of Sevilla, Spain, with charming colleagues.

Prof. Stefan Mühlebach, Head R&D, Vifor AG, Fribourg, in discussion with Prof. Georgios Imanidis, School of Life Sciences, University of Applied Sciences of Northwestern Switzerland.

Prof. Wolfgang Thormann, Institute of Clinical Pharmacology, University of Bern, meeting Dr. Stefan Fritz, President Apothekerverband Kt. Bern (AKB).

PD Dr. Stefanie Krämer, ETHZ, coworker of Prof. Wunderli-Allenspach, together with Prof. Robert Gurny, President EPGL University of Geneva, one of the promotors of the SPSD 2008.

House of the University of Bern.

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SSPhS

Lectures

Keynote Lecture

Dominik Hotz, MSc, Senior Manager Life Sciences Advisory, PricewaterHouseCoopers (PwC) AG, St. Jakobs-Str. 25, 4002 Basel. dominik.hotz@ch.pwc.com

Mr. Hotz has over 10 years' experience in the pharmaceutical and biotech industry. His past roles include director of finance for a Biotech company and various roles at Schering AG. Prior to that he worked as an analyst within private equity. He is now a member of the global pharmaceutical advisory team of PwC where he focuses on the strategic and operational issues. He holds a degree in Economics from the London School of Economics and Political Science.

"Pharma 2020: Virtual R&D – Which path will you take?"

The key note lecture explored PricewaterhouseCoopers' vision for the future of the pharmaceutical industry and in particular for pharmaceutical R&D.

The global pharmaceutical market will more than double in value to $1.3 trillion by 2020. The increase is driven by soaring worldwide demand for medicines and preventative treatments as the population grows, ages, becomes more obese and more prosperous. By 2020 the E7 countries – Brazil, China, India, Indonesia, Mexico, Russia and Turkey – could account for as much as one fifth of global pharmaceutical sales. Further, the chronic conditions in the developing world will increasingly resemble those of the developed world. But the current pharmaceutical industry business model is both economically unsustainable and operationally incapable of acting quickly enough to produce the types of innovative treatments demanded by global markets. In order to make the most of these future growth opportunities, the industry must fundamentally change the way it operates.

Despite unprecedented global demand for its products, the pharmaceutical industry is at a pivotal point in harnessing its ability to capitalise on these opportunities. Pharmaceutical companies are facing a dearth of new compounds in the pipeline, poor financial performance, rising sales and marketing expenditures, increased legal and regulatory constraints and challenges, and tarnished reputations. At the same time health care payers and providers everywhere have recognised that current health care expenditure levels are also unsustainable unless they deliver more demonstrable care and cost benefit over the long term.

Some of the major changes PwC anticipates for the industry are:

– Emphasis on outcomes to increase.
  The focus on outcomes and measurement of outcomes data will drive product development, pricing and reimbursement decisions and risk-sharing agreements between industry, health care payers and providers and regulators. Successful companies will prove that their products really work and add value. Companies will also be rewarded with a fair price for new therapies according to the level of improvement over existing medicines. Risk-sharing agreements will become more mainstream with drug manufacturers adjusting prices according to the results of outcomes analysis data that demonstrates drug efficacy.
– Compliance monitoring becomes win-win for patients, payers and providers.
  Solutions to monitor and ensure that patients are fully compliant with their medications could generate more than $30 billion of revenue a year in new sales, and would improve outcome and patient safety. One U.S. study found that 20% of Americans never fill their original prescriptions, or use other people's medicines, and 60% of patients cannot identify the drugs they are taking. This not only affects safety and outcomes, it creates risk and revenue loss for pharmaceutical companies. Pharmaceutical companies will revise their proposition, employ new technologies and develop personalised compliance monitoring techniques as a value-added service to patients, payers and providers. Improved patient compliance would also help clinical studies and outcomes.
– Focus will shift from treatment to prevention.
  Preventative health care represents a huge opportunity for both health care providers and the pharma industry. Currently only 3% of health care spending on OECD countries is used for prevention, yet the WHO says up to 80% of heart disease, stroke and diabetes and 40% of cancer could be prevented. Recognising the cost effectiveness of preventing diseases among healthy populations rather than treating sick populations, pharma will enter the realm of health management, with wellness programmes, compliance monitoring, vaccinations and other value-added services. There are currently 245 pure vaccines and 11 combination vaccines in clinical development, and the market is estimated to be worth as much as $42 billion by 2015.
– The blockbuster sales model will disappear.
  It will be replaced by a smaller, smarter and more effective sales force, led by key account managers who will negotiate tender based contracts on therapeutic benefit and outcomes. The imperative will be who can add the most value, not who can sell the most pills. Under this model, most pharmaceutical companies will sell integrated packages of medicines and services, and some services, such as patient monitoring and disease management, may be more valuable than the medicines themselves.
  By 2020 the Pharma R&D process may be shortened by two-thirds, success rates may dramatically increase, and clinical trial costs could be cut substantially. New computer based technologies will create a greater understanding of the biology of disease and the evolution of "Virtual Man" to enable researchers to predict the effects of new drug candidates before they enter human beings. Along with changes underway in the regulatory and socio-political environment, this will enable Pharma to overcome one of the most fundamental issues it needs to resolve over the next decade.
  Some of the major changes anticipated by PwC for pharmaceutical R&D are:
– New technologies will drive R&D.
  Transformational technological changes in the pharmaceutical industry will reshape the business strategies of pharmaceutical companies. The role of genetic-based diagnostics in the development of personalised medicines has already shortened the R&D cycle for those products. Further research into the human genome will open up a new world of opportunities in molecular science and new ways of looking at targets. These new technologies will be used to improve understanding of diseases and link genomic and clinical data. The development of molecular delivery platforms could speed the development of new products that leverage existing/approved platforms. The convergence of therapeutics and medical devices, which started in earnest with the drug releasing

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stent, will continue and they will become increasingly sophisticated, improving efficacy and reducing the risk profile of many existing therapeutic agents.
– In-silico technologies will play a pivotal part.
"Virtual man" could ultimately evolve from the deployment of existing technologies that are connected in a new way. Models of the heart, organ, cells systems and musculoskeletal architecture are already being developed by academics around the world. Such technologies can be used to simulate the physiological effects of interacting with specific drugs and identify which drugs have a bearing on the course of a disease. Some companies using virtual technology have reduced clinical trial times by 40% and reduced the number of patients required by two thirds. Virtually-modelled molecules will still have to be tested in real human beings. However as a complete picture is developed of human biology and reliable biomarkers for identifying and monitoring patients become widely available, pharma companies will be able to optimise their trial designs and minimise the number of patients on whom new medicines are tested. They will develop treatments which have value in the eyes of patients, healthcare payers and for the companies themselves.
– Greater collaboration is needed.
The necessary in-depth knowledge about the human body and the pathophysiology of disease will be generated through a collaborative research network of pharmaceutical companies, academia, independent research houses, IT providers, industry regulators, payers and providers. For the first time Pharma will have to consider sharing intellectual property (IP) with other research bodies and potentially new entrants such as IT providers.
– The current linear phase R&D process will give way to in-life testing and live licensing.
The current R&D model, involving phase I, II, III and IV clinical trials that typically end in submission for a drug licence and market approval, will be replaced by collaborative in-life testing and "live licences" being issued contingent on the performance of the drug over its lifecycle. The industry will conduct smaller, more focused clinical trials, continuously sharing results with regulators. If testing confirms that a medicine is safe and effective, a live licence will be issued permitting the company to market the drug on a restricted basis. Further in-life testing will extend the licence to cover a larger number of patients or a different patient population.

Albert Hofmann Memorial Lecture

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Franz X. Vollenweider received his MD degree at the University of Zurich. After completing his doctoral thesis in Experimental Medicine with Dr. Christian Schlatter's at the Institute of Toxicology of the ETH Zurich and University of Zurich in 1987, he went on to train in neurochemistry at the Brain Research Institute of the University of Zurich, and in neuroimaging at the PET Center of the PSI-ETHZ. In 1994 he became certified in the specialities of psychiatry and psychotherapy (FMH in Psychiatry). In 1995 Dr. Vollenweider became senior research psychiatrist at the Clinical Department of the University Hospital of Psychiatry (Burghölzli), where he has established a research program to investigate neuronal correlates of sensory gating deficits, neurotransmitter dynamics and associated cognitive functions in schizophrenia and affective disorders. He is currently the director of the Neuropsychopharmacology and Brain Imaging Research Unit at the University Hospital of Psychiatry and since 2000 appointed Professor of Psychiatry in the School of Medicine, University of Zurich. He is also Director of the recently established Heffter Research Center (HRC) for Consciousness Studies, the main objective of which is to inter-relate basic and clinical research into the neuronal basis of drug- and non-drug-induced altered states of consciousness (ASC) and to development translational models for application to psychiatric illnesses. Prof. Vollenweider's research has been continuously supported by the Swiss National Science Foundation, the Swiss Federal Office for Public Health Office (BAG), and the Heffter Research Institute, U.S.A. His laboratory has been supported by multiple NARSAD (National Association for Research on Schizophrenia and Affective Disorders) Awards for his study of the neurobiology of sensory information processing in schizophrenia (2000, 2004) and in-vivo psilocybin receptor pharmacology (2004). He has also received the Achievement Award of the Swiss Society of Psychiatry (1990), the Heffter Research Institute Award (1997), the Götz Prize (2000) of the University of Zurich, the British Association of Psychopharmacology Prize (2002) and the International Pharmaco-EEG Society Award 2008 for his research into the neurobiology of hallucinogens and the correlation with states of endogenous psychosis. His publications have appeared in peer reviewed scientific journals, including many addressing the mechanisms underlying the effects of psychostimulants, hallucinogens, and entactogens in humans.

"Structure and neurobiology of hallucinogen-induced mental states"
The fundamental idea that psychotic states seen in psychiatric disorders, such as schizophrenia, might be attributable, in part, to abnormalities in serotonergic systems began with the almost simultaneous discovery of the psychological effects of lysergic acid diethylamide (LSD) by Albert Hofmann (1943) and serotonin by Rapport (1948). Sixty years of studies have confirmed early speculations regarding the important relationship between serotonin and both drug-induced and disorder-based psychotic states. Now, modern biochemical, pharmacological, behavioral, neuroimaging, genetic, and molecular biological sciences are converging to understand how serotonergic systems interact with other monoaminergic and glutamatergic systems to modulate states of consciousness and contribute to psychotic disorders such as the group of schizophrenias. Specifically, pharmacological studies revealed that serotonergic hallucinogens such as LSD or psilocybin function as agonists at serotonin-2A receptors (Sanders-Bush et al 1988, Vollenweider et al. 1998). Moreover, brain imaging studies demonstrated that serotonergic hallucinogens can produce three different basic psychological syndromes that are differentially associated with prefrontal activations or deactivations and other changes in temporo-parietal, striatal, and thalamic regions (Vollenweider 2001). Together with the observation that serotonergic hallucinogens disrupt sensory gating in rats (Geyer 1998) and humans (Vollenweider et al. 2007) by acting on 5-HT2 receptors located in the cortico-striato-thalamic circuitry these finding suggest that disruption of cortico-subcortical processing leading to sensory overload of the cortex is a communality of drug-induced and naturally occurring psychoses. Finally, recent studies suggest that the prefrontal-limbic hyperactivity seen psilocybin states in humans is due to 5-HT2A receptor stimulation and a subsequently increased glutamatergic activity at metabotropic mGluRII receptors (González-Maeso, J. et al.2007).

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Pharmaceutical Technolgy Lecture

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Dr. Maxim Puchkov is CEO at CINCAP GmbH. He has graduated as chemical engineer and has finished his Ph. D. in the area of applying mathematical modeling and artificial intelligence to chemical processes design and automation. For more than 4 years he has worked at the Institute of Pharmaceutical Technology, University of Basel, in the field of pharmaceutical process understanding and optimization, PAT, and e-learning.

"Reasons and advantages of in silico approach in design of robust formulations"

Quality by Design (QbD) is the ultimate goal of the Process Analytical Technology (PAT) initiative, originally started by FDA. The contemporary paradigm is shifted from "testing-in" to "building-in" the quality, in order to achieve an optimal performance of the manufactured pharmaceutical products. However, the new paradigm is creating new challenges and needs to be fulfilled and has already triggered the processes of changing the entire research and development (R&D) structure for new pharmaceutical products. More and more of the "classical" laboratory work is shifted or subjected to a shift into a computer-aided development realm [1]. A clear need for new innovative modeling and simulation systems was also confirmed by a recent publication, which measured the return on investment on modeling and simulation tools in pharmaceutical development: "Based on in-depth interviews with research scientists in pharmaceutical development, Health Industry Insights (HII) concludes that there is a significant return on investment (ROI) to be realized from the use of modeling and simulation software tools. HII's ROI model is derived from conversations with researchers at major pharmaceutical companies and academia. The results of the model suggest a cumulative ROI on the order of $3 to $10 for every $1 invested in these tools [2]." Indeed, the successful formulations designed by using the in silico approach are only possible if the science-based, first-principle approach is used. This requirement sets up pre-requisites and primary requirements for successful formulation design: (1) It is required to have best possible knowledge of the physico-chemical and biopharmaceutical properties of the drug substance and of the excipients (e. g. drug/excipient compatibility, issue of polymorphism etc.); (2) Availability of a corresponding software to design the solid dosage form, taking into account percolation theory, physico-chemical and mechanical properties of the substances involved; (3) Availability of the corresponding hardware (supercomputer).
One of such solutions is F-CAD (Formulation Computer-Aided Design) software, which is based on 3-dimensional cellular automata and also takes into account percolation effects in complex formulations. Some of the selected features of F-CAD are the following:
Formulation design with F-CAD starts with final-product shape design.
F-CAD is "shape"-sensitive.
F-CAD can be used to find out differences in dissolution profiles for different shapes of tablets with identical composition.
Different particles size distributions of components will result into different dissolution profiles.
Effect of compact porosity is taken into account along with hydrophilicity/hydrophobicity, including solubility and swellability of the components.
Run-time visualization of tablet undergoing in-silico dissolution test.
The use of these features significantly reduces the time to come to the optimal formulation, "tailor-made" for designed product trade dress.
The use of the computer-aided formulation development could be advantageous in the following areas:
To interpret experimentally measured data by providing the underlying physical models.
To provoke experiments, that may confirm unexpected theoretical predictions.
To replace e. g. biological experiments in case that the accuracy of the in silico experiment is better than that of an experiment in a lab environment.
To establish intellectual property rights by providing results for systems that have not yet been performed experimentally.
In conclusion the idea of F-CAD is to shorten time to market following the concepts of aircraft industry being able to design fully in silico the prototype of Boeing 777 and Airbus 380, which were able to fly "right first time" [3].

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Plant Biochemistry and Biotechnology Lecture

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Rolf Müller studied Pharmaceutical Sciences in Bonn and received his Ph. D. with Professor Eckhard Leistner in 1994. He received a two years research fellowship from the Deutsche Forschungsgemeinschaft (DFG) to work in Prof. Heinz G. Floss's laboratory in Seattle, U.S.A. Starting in 1997, he studied myxobacteria at the German Research Centre for Biotechnology as a junior group leader and received his Habilitation at the Technical University Braunschweig in 2001. Prof. Müller has received several research prizes, among them the BioFuture prize of the Bundesministerium für Bildung und Forschung. In October 2003, he was appointed Professor of Pharmaceutical Biotechnology at the Saarland University. His current work focuses on the biosynthesis, regulation and heterologous production of secondary metabolites from myxobacteria and actinomycetes.

"Biotechnology of Myxobacteria – Promising resources for novel bioactive natural products"

Myxobacteria belong to the few established microbial sources for natural products exhibiting various bioactivities [1]. As they have been studied for almost 30 years by classical isolation and structural elucidation efforts, one may ask the question whether and how much chemical diversity is still to be found. We have initiated studies towards the isolation of novel myxobacterial isolates (now even including new families of myxobacteria) and combined the analysis of the resulting secondary metabolite spectra with bioin-

formatics-guided evaluation of UPLC-coupled high resolution mass spectrometry [2]. These studies reveal an astonishing variety of novel compounds to be present. In parallel, genetic information [3] is collected and molecular biological tools are developed to express and modify biosynthetic pathways from myxobacteria in heterologous hosts [4-6]. The genome information is also used to decipher regulatory mechanisms which can then be exploited to increase productivity [7]. In addition, analysis of biosynthetic genes/proteins has been shown to pave the way to elucidate the stereochemistry of bioactive secondary metabolites [8;9].

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Biopharmaceutics Lecture

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Gerrit Borchard is a licensed pharmacist and obtained his Ph. D. in pharmaceutical technology from the University of Frankfurt (Germany). After holding several academic posts, including a lecturer position at the Saarland University (Germany) and an Associate Professorship at the Leiden University (The Netherlands), he joined Enzon Pharmaceuticals, Inc. (USA) as Vice President Research. In 2005, he was appointed Full Professor of Pharmaceutics and Biopharmaceutics at the University of Geneva (Switzerland), and Scientific Director of the Centre Pharmapeptides in Archamps (France), an international center for biopharmaceutical research and training. In 2008, he was elected Vice President of the School of Pharmaceutical Sciences Geneva-Lausanne. His main areas of interest are macromolecular drug formulation and delivery, molecular biopharmaceutics and mucosal vaccination. He has served as Scientific Advisor for the International Controlled Release Society (CRS), as head of the academic section of the International Association of Pharmaceutical Technology (APV), and Scientific Secretary for the European Association for Pharmaceutical Biotechnology (EAPB). Prof. Borchard is editor of the European Journal of Pharmaceutics and Biopharmaceutics, and serves on the editorial boards of three other scientific journals.

"Exubera, biosimilars et al.: Development of biopharmaceuticals"
Biopharmaceuticals, drugs of usually high molecular weight and complexity, and based on amino acid or nucleic acid backbones, have increasingly become a mainstay of today's drug pipelines. About 200 biopharmaceuticals (198 of which are proteins) are on the market, with another 2000 in different phases of clinical trials. Biopharmaceuticals, especially recombinant proteins, require specific production, analytical and formulation technology, as they are fundamentally different from small molecules derived from chemical synthesis. Even small changes in the three-dimensional structure of these molecules, e. g. by process change or mishandling, can ultimately lead to a loss in activity or the development of immunogenicity. Therefore, generic molecules to biopharmaceuticals cannot exist, as the production process for the originator product must be different from the generic product. The EMEA, as first regulatory body, has therefore coined and put into legislation the term "Biosimilars" to define these follow-on biological drugs. Although the retraction of the first inhalable protein drug, Exubera, from the market represents a backdraw in the development of biopharmaceuticals applied by routes alternative to injection, other technologies are being implemented to enhance the pharmacokinetic and pharmacodynamic properties of protein drugs, and help in formulation development.

Hospital Pharmacy Lecture

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Friedrich Möll, born 1958 in Zurich, is a hospital pharmacist and head of the hospital pharmacy in Winterthur in Switzerland since 1998. He is responsible for the pharmacy service for the 500-bed cantonal hospital with a big oncology service and several geriatric and psychiatric institutions. Before he got his position in the hospital pharmacy, he held different positions in the pharmaceutical industry (head of the production at Spirig AG, assistant director for physical pharmacy & material science at Johnson & Johnson). As a hospital pharmacist, he is involved with the daily problems of handling and dispensing pharmaceuticals. For many years, he helds lessons for pharmacy students at the Swiss Federal Institute of Technology (ETH) in Zürich on the topic "correct application of drugs and delivery systems – mainly semisolid systems" and "compounding of preparations". In addition, he is involved in the education of Swiss hospital pharmacists. In this context, he organizes the biotech-forum twice a year.

"Evaluation of biopharmaceuticals by hospital pharmacists – What really matters is patient safety"
Biopharmaceuticals or Biologicals are very complex drugs with a size about 100 times bigger than conventional pharmaceuticals. Furthermore, the folding and glycosylation (type and length of any sugar or carbohydrate groups attached) make every biopharmaceutical unique in their way of production. They are produced in and isolated from living organism. Therefore, the meaningful sentence was created: *"The process is the product"*. The end product has to be purified from other biomolecules and finally formulated in a way, that the protein is stable enough to "survive" the supply chain to the patient. Therefore, another statement was made: *"The distribution is the product"*. Nowadays, relevant patents have expired and so called "biosimilars" enter the market. Consequently, hospital pharmacists are challenged to evaluate and select possible "Biosimilars" versus the "Reference-Biopharmaceutical". Since the manufacturing steps cannot be copied, minor or also major microheterogenities are possible, which have to be judged for patient safety – the most important goal. A Biosimilar is finally not a generic. For the evaluation, many questions are discussed: e. g. what is the difference of the formulation to the reference molecule? What about the cold chain during transportation and storage? Shelf-life and storage conditions? What happens in case of incorrect handling? Which serious adverse events and frequency are reported? Contraindications or warnings? Safety issues, i. e. immunogenicity and tolerability data

compared to the reference molecule? What are the post-marketing risk-minimisation programmes (short- and long-term)? Pharmacovigilance: how is it organized? Antibody testing: where? The clear identification of Biosimilars is still a problem due to the small differences in the molecules which are not covered by different names. The EMEA states: "In order to support pharmacovigilance monitoring, the specific medicinal product given to the patient should be clearly identified". A basic requirement for the traceability and substitution as "Aut Simile" is a clear identification with an unique name. With the INN-system, a distinct identification of small chemical molecules is possible, but this is not the case for Biosimilars. This is the reason why a substitution (automatic interchange) of Biosimilars is not allowed in France, only with restrictions in Spain and Germany and only after discussion with the prescriber in UK. Until enough safety data for Biosimilars will be available, we would recommend: First Application: Yes – Substitution: No.

Analytics Lecture

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Renato Zenobi is Professor of Analytical Chemistry at the Organic Chemistry Laboratory of the ETHZ. He is also one of the founders and directors of the center of excellence in analytical chemistry at the ETHZ. Renato Zenobi was born in Zurich in 1961. He received a M.S. degree from the ETHZ in 1986, and a Ph. D. at Stanford University in the USA in 1990, followed by two postdoctoral appointments at the University of Pittsburgh (1990–1991) and at the University of Michigan (1991). Renato Zenobi returned to Switzerland in 1992 as a Werner Fellow at the EPFL, Lausanne, where he established his own research group. He became assistant professor at the ETHZ in 1995, was promoted to associate professor in 1997, and to full professor in 2000. He was chairman of the Organic Chemistry Laboratory in 2002–2003. He was a visiting professor at the Barnett Institute (Boston) in 2004. Zenobi's research areas include laser-based analytical chemistry, electrospray and laser-assisted mass spectrometry, laser-surface interactions, and near-field optical microscopy and spectroscopy. He has made important contributions to the understanding of the ion formation mechanism in matrix-assisted laser desorption/ionization (MALDI) mass spectrometry and to the development of analytical tools for the nanoscale. Renato Zenobi has received several awards for his scientific work, aincluding the Thomas Hirschfeld Award (1989), an Andrew Mellon Fellowship (1990), the Ruzicka Prize (1993), the Heinrich Emanuel Merck-Prize (1998), the Theophilus Redwood Lectureship (2005), the Michael Widmer Award (2006), and a honorary Professorship at East China Institute of Technology (2007).

"Real-time, online mass spectrometry with modern atmospheric pressure ionization sources"

Extractive Electrospray Ionization (EESI) mass spectrometry is a novel, powerful analytical method for fingerprinting of a large variety of biological samples. It has been shown to be extremely useful for rapid, non-invasive, and real-time chemical analysis of compounds in breath, for metabolomics, for doping analysis, and for detecting compounds linked to the ripening of fruit. EESI has also been extended to the rapid analysis of volatile and semivolatile compounds sampled from various surfaces of biological matter, including human skin and food, by desorption of neutral molecules with a neutral gas beam. EESI is very simple to implement, and can be performed on any commercial mass spectrometer equipped for atmospheric pressure ionization.

In EESI, a neutral sample, in the form of a gas or aerosol flow is directed into a plume of charged droplets, generated by ESI of a pure solvent. Alternatively, analytes can be liberated form a hanging droplet or from a surface using desorption by a nitrogen jet. Neutral molecules are charged by protonation or cationizatioin from charged species in the electrospray, and are then sampled in a standard fashion by an atmospheric pressure interface. In our laboratory EESI-MS is performed on a slightly modified commercial ESI source coupled to a quadrupole/time-of-flight (TOF) hybrid mass spectrometer in positive ion mode.

Conference Program

- **Addresses of Welcome:**
  Prof. Dr. phil. nat. Hans Leuenberger, President SSPhS
  Prof. Dr. med. Felix Frey, Vice-Rector Research, University of Bern
- **Keynote Lecture:**
  Dominik Hotz, PricewaterhouseCoopers AG, Basel
  "Pharma 2020: Virtual R&D – Which path will you take?"
- **Albert Hofmann Memorial Lecture:**
  Prof. Dr. med. Franz Vollenweider, University Hospital of Psychiatry, Neuropsychopharmacology and Brain Imaging, Heffter Research Center, Zürich
  "Structure and neurobiology of hallucinogen-induced mental states"
- **Pharmaceutical Technology Lecture:**
  Dr. Maxim Puchov, Center for Innovation in Computer-Aided Pharmaceutics (CINCAP), Pfeffingen
  "Reasons and advantages of in silico approach in design of robust formulations"
- **Plant Biochemistry and Biotechnology Lecture:**
  Prof. Dr. phil. nat. Rolf Müller, Department of Pharmaceutical Biotechnology, Saarland University, Saarbrücken
  "Biotechnology of Myxobacteria – Promising resources for novel bioactive natural products"
- **Poster Session**
- **Biopharmaceutics Lecture:**
  Prof. Dr. phil. nat. Gerrit Borchard, School of Pharmaceutical Sciences Geneva-Lausanne (EPGL), Genève
  "Exubera, biosimilars et al.: Development of biopharmaceuticals"
- **Hospital Pharmacy Lecture:**
  Dr. phil. nat. Friedrich Möll, Cantonal Hospital of Winterthur, Winterthur
  "Evaluation of biopharmaceuticals by hospital pharmacists – What really matters is patient safety"
- **Analytics Lecture:**

  Prof. Dr. phil. nat. Renato Zenobi, Laboratory of Organic Chemistry, ETH Zürich
  "Real-time online mass spectrometry with modern atmospheric pressure ionization sources"
- **Award Ceremony:**
  Nomination of SSPhS Fellows
  Poster awards

EESI-MS has a surprisingly large range of applications relating to metabolic profiling of the samples (or human subjects). Latest results in several different areas of application were presented:

(1) Noninvasive medical diagnosis via analysis of exhaled breath. We have demonstrated the direct detection of metabolites of valproic acid in the breath of a volunteer under treatment with this antiepileptic. In the breath of another volunteer these signals were initially completely absent, but appeared within less than 1 h, peaked at 23 h, and were eliminated with a rate constant of 8.35 h.

(2) On-site doping tests via analysis of exhaled breath. Salbutamol and ephedrine, two stimulants on the "prohibited list" of the World Anti-Doping Agency were successfully detected in breath after administration of small doses. Quantitative analysis of compounds in breath was also illustrated, with limonene and nicotine as examples.

(3) Detection of spoiled food using neutral desorption EESI. In this case, metabolites released by bacteria growing on the infested food, e.g. spinach leaves, the surface of spoiled fish or meat, are deteced. Detection of spoilage of meat is even possible if the sample is still frozen (–20°C). ND-EESI was successfully used to differentiate between samples of meat and fish that were fresh or had been exposed to room temperature / air for 1 or 2 days. Biogenic amines such as histamine, tryptamine, cadaverine, or spermine, known metabolites from bacteria, were detected with excellent sensitivity (10 fg cm^{-2} for histamine), even if the samples were interrogated in the frozen state. In a related approach, metabolites and contaminants on human skin can be detected within sec, in an on-line and high-throughput fashion. Typical molecular markers are identified using both MS/MS data and comparison with reference compounds.

Finally, an outlook on doing EESI-MS with field-portable instrumentation was presented.

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SSPhS Fellows

Heidi Wunderli-Allenspach, Prof., Ph. D., Rector at the Swiss Federal Institute of Technology Zurich (ETHZ)

Heidi Wunderli-Allenspach has been Full Professor in Biopharmacy since October 1995. She is Rector at ETH Zurich since September 1, 2007. Heidi Wunderli-Allenspach was born in 1947 near St. Gallen, Switzerland. She took her masters degree in Biology from the ETH Zurich in 1970, and then worked as a research assistant at the Institute for Brain Research at the University of Zurich before she followed the Postgraduate Course in Experimental Medicine and Biology at the University of Zurich. She subsequently did her Ph. D. thesis at the Department of Microbiology at the Biozentrum in Basel. From 1976 to 1978 she was a research associate at the Department of Surgery, Duke University Medical Center, Durham N.C., U.S.A. Between 1978 and 1981 she worked as a postdoctoral fellow at the Swiss Institute for Experimental Cancer Research in Lausanne, and from 1981 to 1984 at the Institute for Immunology and Virology of the University of Zurich. In 1985 she came back to the ETHZ, where she joined the Department of Pharmacy, between 1986 and 1992 as an assistant professor and from 1992 to 1995 as an associate professor in Biopharmacy. Her research was focused on physicochemical and cell biological aspects of drug absorption, distribution and elimination in the body. Relevant in vitro models for the blood-brain-barrier as well as for epithelial barriers were established in order to study the transport of drugs through and the interaction of drugs and excipients with membranes and cells under standardized conditions. As a professor Heidi Wunderli-Allenspach assumed various charges in the university management. Among others she was Head of the Department of Pharmacy and later of the Department of Chemistry and Applied Biosciences. Education issues were always at her heart. She was a member of the Swiss Maturitätskommission and Deputy for the Curriculum of Pharmaceutical Sciences (1998–2007). During this time the curriculum was redesigned and the Bachelor/Master system was introduced. Since September 1, 2007, Heidi Wunderli-Allenspach is Rector at ETHZ and Deputy of the President. She is responsible for all aspects of education from the BSc/MSc level to Ph. D. and continuing education. As a representative of ETHZ she is a member of the foundation for student housing, for childcare, and of various institutions for the promotion of natural sciences in education (e.g. Technorama, NaTech). Furthermore she is a member of the board of the Zurich University Institute for Education and Didactics. At the Ecole Polytechnique de Paris she is a member of the supervisory board.

Laudatio, held by Prof. Hans Leuenberger, President of the SSPhS:

"Prof. Dr. Heidi Wunderli-Allenspach, Rector and Deputy President of the ETH Zurich, has been nominated as Fellow of the Swiss Society of Pharmaceutical Sciences (SSPhS) and Member of the Swiss Academy of Pharmaceutical Sciences (SAPhS) for her continuous and fruitful support of the Pharmaceutical Sciences as former Head of the Department of Pharmacy and later of the Department of Chemistry and Applied Biosciences at the ETHZ. She contributed substantially to redesign successfully the Pharmacy Curriculum in Switzerland during the introduction of the bachelor/ master program".

As Prof. Wunderli-Allenspach was unable to attend the First Swiss Pharma Science Day, Dr. Stefanie Krämer, coworker of Prof.

Wunderli-Allenspach, excused her absence and read the following message: "Unfortunately Heidi Wunderli-Allenspach cannot be present today. Therefore she asked me to bring to you her greetings and wish you a successful scientific meeting. Heidi Wunderli feels very much honoured for being nominated as a Fellow of the Swiss Society of Pharmaceutical Sciences. It is a pleasure for her to see the successful development of research and education in Pharmaceutical Sciences in Switzerland over the last 10 years and she sees it as a privilege having been part of the community during this interesting time".

Theo W. Guentert, Prof., Ph. D., F. Hoffmann-La Roche Ltd., Basel

Theodor W. Guentert is Senior Vice President in Nonclinical Safety at F. Hoffmann-La Roche Ltd. in Basel. Prior to this he held the positions of Head of Nonclinical Drug Development and Head of Nonclinical Drug Safety in the Research Department and Associate Clinical Pharmacology Area Head in the Clinical Research Department in the same company and hence has a broad experience in drug development. He is a pharmacist by training, certified Clinical Pharmacologist, and received his Ph. D. in Pharmaceutical Chemistry from the University in Basel. His special interests are PK/PD modeling and simulations to optimize drug development programme. Theodor W. Guentert was appointed Associate Professor of Pharmacy at the University of Basel in 1992 and today teaches regularly in Biopharmaceutics and in Drug Metabolism at the Universities of Basel and Leiden, The Netherlands, and at international training courses in PK/PD.

Laudatio:
"Prof. Dr. Theodor W. Guentert, Senior Vice President at F. Hoffmann-La Roche Ltd., Basel, has been nominated as Fellow of the Swiss Society of Pharmaceutical Sciences (SSPhS) and Member of the Swiss Academy of Pharmaceutical Sciences (SAPhS) for his substantial contribution to the area of PK/PD, i. e. Pharmacokinetics / Pharmacodynamics, modeling and simulations to optimize drug development programs. He was involved in the development of the important multi-media based teaching software RIDO, Right Dose First Time, being sponsored by the European Course of Pharmaceutical Medicine ECPM".

Prof. Guentert was also unable to attend the Conference and accept personnally the Fellowship.

Poster Awards

Sixty-nine poster abstracts were accepted, with more than half (!) submitted by members of the University of Geneva, followed by the ETHZ, the University of Basel, and Bern. Therefore, in contrast to the "Röstigraben" apparently no wall is existing between the francophone and the german part of Switzerland. We hope, that this appreciated domination of our dear colleagues from Genève will exemplary motivate and stimulate the students of the other Swiss Universities for the SPSD 2009. The facilities would allow the presentation of at least the double number of posters! Regarding the high scientific quality of the 69 presented posters, it was a pity, that only 3 could be nominated for the 1st, 2nd, and 3rd prize. The members of the poster reviewer board were: Prof. Gerrit Borchard (University of Geneva), Prof. Roger Schibli (ETH Zurich), Prof. em. Ueli Honegger (University of Bern), Prof. em. Hans Leuenberger (SSPhS), and Prof. Rudolf Brenneisen (University of Bern). The evaluation criteria for the jury were: Research project and study objectives innovative? Methods appropriate? Results significant and conclusions relevant? Overall scientific value? Graphical quality of presentation?

Prof. Rudolf Brenneisen, Head of the Organizing Committee, announces the poster award recipients.

Consequently, the following 3 presenting authors were awarded:

First Prize of the SSPhS:

Ralitza Boubeva
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R. Boubeva, L. Moretti, A. Cristiani, O. Vadas, R. Perozzo, and L. Scapozza: "Conformational Prevalence of c-Src Tyrosine Kinase Domain Dictated by a Single Amino Acid". (Poster no. 23).
In 2000, Ralitza Boubeva got her Maturity Degree at the Lycée Français "Alphonse de Lamartine", Sofia, Bulgaria. In 2005, she graduated in Pharmaceutical Sciences at the University of Lausanne. In 2006, she started her Ph. D. thesis work in Pharmaceutical Sciences under the supervision of Prof. Leonardo Scapozza, University of Geneva. The topic of her research is the biochemical and biophysical analysis of the tyrosine kinase domain of oncogenic fusion proteins for the development of selective inhibitors. Steps of her professional training are: Stage at the Pharmacy of the University Hospital (CHUV) Lausanne; International Pharmaceutical Students' Federation Exchange, Department of Pharmaceutical Biology, University of Ljubljana, Slovenia ("Selection of papain-binding phage-displayed peptides from combinatorial peptide library"); Diploma thesis in Pharmaceutical Chemistry ("New Real-Time Method Genotyping CYP 2B6 G516T and A785G & Allele Frequency Determination in Swiss Population"; supervised by Prof. Leonardo Scapozza and Dr. Pierre-Alain Menoud) at MCL Medical Laboratories, Fribourg; Member of "Pharmaciens Sans Frontières Switzerland"; Pharmacist at the Pharmacy "24 Heures", Lausanne; Assistant-Doctorand for practicals in organic chemistry, University of Geneva.

Second Prize of the Foundation of the Association of Bernese Pharmacists:

Sascha Kopp
Swiss Federal Institute of Technology Zurich (ETHZ), Institute of Pharmaceutical Sciences, HCl H 490, Wolfgang-Pauli-Str. 10, 8093 Zürich.
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S. Kopp, H. Möhler, and K.-H. Altmann: "Total Synthesis of Valerenic Acid and SAR Studies with Related Valerian Terpenoids" (Poster no. 2).
In 1996, Sascha Kopp got his Maturity Degree type C in Pfäffikon. In 2003, he got the Master in Chemistry at the ETHZ. Before, he was working in the group of Prof. Ulrich Suter at the Dep. of Materials (D-MATL), ETHZ, in the field of modified polyhydroxy butaric acids as biodegradable polymers, and in the group of Prof. Donald Hilvert at the Dep. of Chemistry, ETHZ, in the field of directed molecular evolution of proteins. He conducted his Diploma thesis in the group of Prof. Dieter Seebach at the Dep. of Chemistry, ETHZ, on "The synthesis of β2-Asp/β2-Asn and β2-Glu/β2-Gln". After graduation he joined the group of Prof. Karl-Heinz Altmann at the Department of Chemistry and Applied Biosciences (D-CHAB), ETHZ, and helds there a Ph. D. position. His research interests focus on the synthesis of valerenic acid and analogues to establish a structure/activity relationship to the GABA-A receptor and on the change of behaviour due to modulation of the GABA-A receptor activity. So far, he co-authored 2 publications in a peer-reviewed journal.

Third Prize of the Swiss Society for Radiopharmacy and Radiopharmaceutical Chemistry :

Charles Thürlemann, Ph. D.
University Hospital Inselspital, Clinic of Hematology, Research Lab (Prof. Bernhard Lämmle), 3010 Bern (up to Oct. 2008); Güterstr. 48, 3008 Bern (private address).
charles.thuerlemann@bluewin.ch

C. Thürlemann, E.J. Frenkel. R. Dinger, C. Caliezi, and A. Haeberli: "Development of a Biosensor-System for Self-Testing the Intensity of Anticoagulation by Anticoagulated Patients in Capillary Whole Blood". (Poster no. 13).
In 1994, Charles Thürlemann got his Maturity Degree type A at the Klosterschule Disentis. In 1999, he got the Federal Diploma in Pharmaceutical Sciences at the University of Basel. In 2005, he was promoted as Ph. D. in Pharmaceutical Sciences at the University of Basel with a dissertation entitled "Entwicklung eines Biosensor-Systems für ein Patienten-Selbstmanagement der Behandlung mit Vitamin K-Antagonisten". This Ph. D. work was conducted at the Dep. of Clinical Research, University of Bern (group Prof. André Haeberli) in collaboration with Asulab, Marin. From 2005–2006 he continued to work in the thrombose research group of Prof. Haeberli, followed by a stay at the research lab of the Clinic of Hematology, University Hospital Inselspital Bern (group Prof. Lämmle). Currently he works in a public pharmacy. In 2003, he got the prize "Best Clinical Work" of the Dep. of Clinical Research, University of Bern.

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Poster Session – Abstracts

P-1

GDNF and NGF Co-Delivery from Nerve Conduits for Peripheral Axonal Regeneration

Srinivas Madduri*[1], Michaël Papaloïzos[2], and Bruno Gander[1]
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The purpose of the study is to develop nerve conduits (NC) for controlled co-delivery of nerve growth factor (NGF) and glial cell line derived neurotrophic factor (GDNF), in order to exploit the beneficial effects of these two factors on axonal regeneration.
Collagen NCs were produced by spinning mandrel technology. NTFs were loaded on the NCs, which were subsequently coated with layers of poly(lactide-co-glyoclide). *In vitro* release of GDNF and NGF was quantified by ELISA, and the bioactivity of released NTFs was tested using DRG explants isolated from E9-chicken embryos (9 days old).
The *in vitro* release of GDNF and NGF from the NC was sustained over 30 days. The main parameter influencing the NTFs release was the dehydro-thermal (DHT) treatment of the NC. During the initial 2–3 days of release, the DHT-treated NCs released the NTFs at significantly lower rates, but this difference vanished after 3 days. Incubation of DRG explants with release medium from NGF- and GDNF-loaded NCs resulted in axonal outgrowth. The results demonstrate combined release of biologically active GDNF and NGF from collagen nerve conduits over 30 days.
Collagen nerve conduits were successfully developed with integrated delivery system for combined release of GDNF and NGF. Our results prove the feasibility of developing nerve conduits for co-delivery of NTFs. Future studies will assess the potential benefit of combined GDNF+NGF over single factor delivery in a nerve gap model in the rat.

P-2

Total Synthesis of Valerenic Acid and SAR Studies with Related Valerian Terpenoids

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Swiss Federal Institute of Technology (ETH) Zurich, Institute of Pharmaceutical Sciences, 8092 Zurich

Valeriana officinalis L. (valerian) is one of the oldest medicinal herbs used in Europe, but the molecular basis of its pharmacological effects even today are largely elusive. It is generally accepted that no single constituent of *Valeriana officinalis* is uniquely responsible for the effects of *Valeriana* preparations, which are assumed to be the result of the synergistic action of a multitude of compounds.
Valerenic Acid (VA) is one of the major constituents of *Valeriana officinalis* rhizome, which is routinely used as an analytical marker for the standardization of Valerian extracts, but until recently, has not been implicated in the pharmacology of *Valeriana* preparations. VA, which was first isolated by Stoll and Seebeck in 1957 [1], is a sesquiterpene carboxylic acid with a novel carbonskeleton [2] that has been designated as the valerenan type [3]. VA has recently been shown to act as a positive allosteric modulator on the $GABA_A$ receptor complex [4] and to function as a partial agonist on the $5\text{-}HT_{5a}$ receptor [5].
Up to now no stereoselective synthesis of VA has been reported in literature and very few syntheses of other 2,4,5,6,7,7a-hexahydro-1*H*-indenes with the particular valerenic acid substitution pattern have been described. Intrigued by the recent findings on the biological effects of VA on CNS-based receptors we have embarked on the total synthesis of VA and the preparation of analogs for SAR studies. In this paper we report the first enantioselective total synthesis of VA from readily available Pulegone in 17 steps. In addition, we have prepared a number of analogs for SAR studies on the GABA-A receptor.

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P-3

HPLC Method for the Determination of Gemcitabine in Plasma after Intravenous or Subcutaneous Administration

C. Lanz*[a], M. Früh[b], T. Cerny[b], W. Thormann[a], and B. H. Lauterburg[a]
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The deoxycytidine analogue chemotherapeutic agent 2`,2`-difluorodeoxycytidine (gemcitabine, dFdC) is a prodrug that is converted to the active metabolite gemcitabine triphosphate (dFdCTP). dFdCTP is incorporated into DNA, blocking DNA polymerase. On the other hand, gemcitabine is rapidly inactivated in the plasma by cytidine deaminase to the deaminated 2`,2`-difluorodeoxyuridine (dFdU). With the standard intravenous (i.v.) administration of the drug (1 g/m^2 over 30 min) up to 50% of the dose is lost because of the saturation of the activation process. Optimisation can be achieved with lower infusion rates. The goal of this project was to investigate an alternative strategy consisting of the repeated subcutaneous (s.c.) application of dFdC at low doses with a prolonged release of the drug into the bloodstream. To proof the concept, bioavailability and pharmacokinetic studies comparing i.v. and s.c. application were needed. Therefore, an assay that is sensitive enough for the determination of dFdC and dFdU in plasma after low dose treatment had to be developed.
dFdC could be quantitated sensitively in rat plasma after i.v. and s.c. administration of low doses. The doses given per kg of body weight corresponded to those intended for s.c. injection to humans (about 6% of the dose given in the standard i.v. treatment), showing the suitability of the assay for the determination of the mother compound. Three hours after the treatment s.c. and i.v.

drug levels became comparable. Peak plasma concentrations of dFdC after i.v. administration of 925–941 mg/m^2 were between 11400 and 18900 ng/ml (n=3). The LOQ was estimated to be 25 ng/ml for dFdC. dFdU levels further increased after the end of the infusion in most cases. Because of the lack of the analytical standard, dFdU was identified via inspection of the chromatograms of patient samples and analyzing UV spectra. The assay is believed to be suitable for the quantitation of dFdC and dFdU in samples after s.c. administration of the drug at low doses. Further work should address the determination of the active, intracellular metabolites of dFdC.

Reference:
Lanz C. et al. J. Sep. Sci. 2007; 30: 1811-20.

P-4

OP-088: A Promising Water-Soluble Cyclosporine A Prodrug

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Cyclosporine A (CsA) is a cyclic undecapeptide produced by Tolypacladium inflatum. This substance presents interesting immunosuppressive activities, and is thus routinely used after organ transplantation. However, its nephrotoxic and hypertensive side effects limit the systemic use.
In ophthalmology, topical application of CsA has been determined to be efficient in order to manage several ocular diseases, in which the immune system plays an important role, such as the eye dry syndrome or the prevention of corneal graft rejection. Nevertheless, the high lipophilicity of CsA makes its topical delivery to the eye a real challenge.
A novel water-soluble CsA prodrug, OP-088, appears to be a promising candidate, as its rapid degradation, under physiological conditions, leads to a constant and clinically significant CsA concentration. Our efforts focus on the investigation and elucidation of this phenomenon, trying to understand the real mechanism involved in this biotransformation; the final aim being to produce a stable pharmaceutical formulation containing OP-088.

P-5

Magnetic Biodegradable Microparticles for the Local Treatment of Arthritis: Synoviocyte Interaction, Intra-Articular Retention and Tissue Reaction

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Intra-articular corticosteroid injections, commonly used to treat arthritis, are not exempt of undesirable effects such as rapid clearance from the joint or crystal-induced arthritis. Biodegradable microparticles, gradually releasing dexamethasone, would circumvent these drawbacks. Furthermore, to maintain local drug release over longer periods, superpara-magnetic iron oxide nanoparticles were encapsulated into the microparticles, allowing their retention with an external magnet.
Microparticles were internalized by synovial fibroblasts through a phagocytic process. *In vivo* imaging in mice demonstrated that the presence of a magnet near the knee improves the microparticle retention in the joint over 3 weeks. Intra-articular injection of microparticle suspensions elicited only minor inflammatory response.
Magnetically retainable biodegradable microparticles represent an innovative approach, still clinically unexploited, in the field of drug delivery systems to the joint. By tailoring the polymer matrix, different release rates could be achieved, thus offering the possibility of using this type of system for the delivery to joints of other drugs.

P-6

In Vitro-Stability of Avastin and Lucentis in Combination with Anti-Inflammatory Drugs for Ophthalmological Applications

Marieke Veurink*, Cinzia Stella, Cyrus Tabatabay, Constantin J. Pournaras, and Robert Gurny
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Currently there is an increasing interest in monoclonal antibodies and their fragments for the treatment of age-related macular degeneration (AMD). On the market are Avastin®, a monoclonal antibody against vascular endothelial growth factor (VEGF) for the treatment of cancer, which is used off-label for this application, and Lucentis®, which is approved worldwide and is a fragment of the same antibody.
Both drugs show improvement in visual acuity in clinical studies, but a disadvantage is that they have to be injected intravitreally every month, for up to one year. For this reason, there is interest into finding solutions to prolong the interval between two injections, such as the combination of Avastin and Lucentis with anti-inflammatory drugs, which are also known to possess beneficial properties for the treatment of AMD.
In this study, we have compared the stability of Avastin and Lucentis in vitro, alone and in combination with anti-inflammatory drugs, such as triamcinolone and dexamethasone. Our results show that the combination with anti-inflammatory drugs does not decrease the stability of Avastin nor Lucentis based ophthalmic formulations.

P-7

High-Throughput log P Determination by Ultra Performance Liquid Chromatography: a Convenient Tool for Medicinal Chemists

Yveline Henchoz*[1,2], Davy Guillarme[2], Sophie Martel[1], Serge Rudaz[2], Jean-Luc Veuthey[2], and Pierre-Alain Carrupt[1]
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Precise knowledge of the physicochemical properties of new chemical entities is of prime importance. Among these properties, lipophilicity is a key parameter involved in pharmacokinetic processes such as absorption, distribution, metabolism and excretion (ADME). The advantages of reversed phase liquid chromatography techniques for lipophilicity indices measurements are recognized. Recently, liquid chromatography has evolved with the development of short columns packed with small particles (sub 2 µm) used in very high-pressure conditions (> 400 bar), enabling significant analysis time reduction without compromising chromatographic

performance. In this work, this new strategy was investigated for lipophilicity determination and offered a significant increase in the throughput (by a factor 12). Moreover, due to the high stability of the tested columns over a large pH range (2 < pH < 11), log P_{oct} of basic compounds could be determined. Finally, the hyphenation of UPLC with MS detection was investigated to further increase the throughput (up to an additional factor 10).

P-8

A Comprehensive Metabolite Profiling of *Isatis tinctoria* Leaf Extracts

Tobias Mohn*, Inken Plitzko, and Matthias Hamburger
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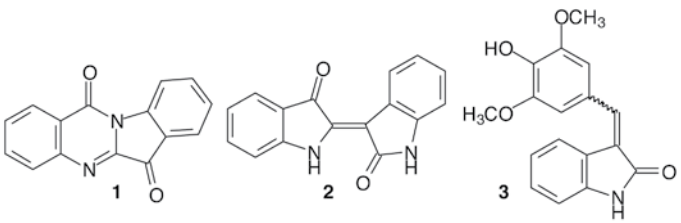
Woad (*Isatis tinctoria* L., Brassicaceae) is an ancient indigo dye and anti-inflammatory medicinal plant, which has been used and cultivated in Europe since antiquity. The anti-inflammatory potential of lipophilic leaf extracts was confirmed in a broad-based pharmacological profiling, in various animal models, and in a clinical pilot study [1]. Tryptanthrin **(1),** indirubin **(2),** indolin-2-one **(3),** and γ-linolenic acid were identified as active principles inhibiting COX-2, 5-LOX, the expression of the inducible nitric oxide synthase, human neutrophil elastase, and the release of histamine from mast cells. To further characterize the pharmacologically active extracts, we carried out a comprehensive metabolite profiling with the aid of online spectroscopic measurements (HPLC coupled to PDA, ELSD, APCI- and ESI-MS, and HRESI-MS). Off-line semi-preparative HPLC-NMR analysis was used for structure elucidation of some constituents. So far, more than 70 compounds belonging to various structural classes such as alkaloids, flavonoids, fatty acids, porphyrins, lignans, carotenoids, glucosinolates and cyclohexenones have been unambiguously identified, and tentative structures proposed for additional compounds.



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P-9

Optimizing Iontophoretic Delivery Kinetics of Diclofenac In Vitro

Alexandre Romand, Jennyfer Cázares-Delgadillo, Yogeshwar G. Bachhav*, and Yogeshvar N. Kalia
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Diclofenac is a potent, nonsteroidal anti-inflammatory drug (NSAID) indicated for relief of pain and inflammation in musculoskeletal and joint disorders including osteoarthritis and rheumatoid arthritis. Due to its limited cutaneous bioavailability, topical diclofenac is only indicated for the relief of local symptomatic pain and inflammation. Increasing diclofenac delivery efficiency could widen the range of indications for topical therapy – of particular benefit for elderly patients receiving chronic NSAID treatment. Our results showed that iontophoretic delivery of diclofenac from a commercial gel was superior to passive diffusion. Permeation was further increased by iontophoresing diclofenac sodium solutions. The results showed that the highest cumulative iontophoretic delivery and flux achieved were 142.7 ± 73.9 μg cm^{-2} and 52.1 ± 30.4 μg cm^{-2} h^{-1}, respectively – almost ~100-fold higher than the corresponding values seen after passive diffusion from the commercial gel (1.77 ± 0.79 μg cm^{-2} and 0.53 ± 0.20 μg cm^{-2} h^{-1}, respectively). Thus, it may be possible to expand the potential indications for topically delivered diclofenac using reasonably-sized iontophoretic patch systems.

P-10

Toward a Better Description of Hydrophobicity in Protein Binding Sites: Validation of the Molecular Lipophilicity Potential (MLP filter) within a GOLD Docking Strategy

Juan Bravo*, Antoine Daina, Sébastien Rey, Frédéric Ooms, and Pierre-Alain Carrupt
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GOLD is a genetic algorithm based software for docking small molecules into macro-molecules, using a fitness function relying mainly on hydrogen-bonding and steric interactions.
GOLD defines "Hydrophobic fitting points" solely based on steric considerations to guide the placement of ligand hydrophobic atoms into the binding site. Hence, we used an in-house molecular interaction field based on n octanol/water partition coefficients – the Molecular Lipophilicity Potential (MLP) – to evaluate this characterization of hydrophobicity by GOLD.
It appeared that a significant number of points considered as hydrophobic by GOLD were actually polar. An MLP-based filter retaining only real hydrophobic points was thus developed and applied during GOLD processes.
We describe here the assessment of our tool on a high-quality test set – the ASTEX Diverse Set, comprising 85 ligand-protein complexes. Results showed that the MLP-filter provides a more realistic description of hydrophobicity and thus increases the quality of the docking with GOLD.

P-11

Pharmacogenetic-based Population Pharmacokinetic Analysis of Efavirenz in HIV-1 Infected Individuals

M. Arab-Alameddine*[1,5], T. Buclin[1], M. Rotger[2], R. Lubomirov[2], J. Di Iulio[2], M. Cavassini[3], A. Fayet[1], L.A. Décosterd[1], C.B. Eap[4], J. Biollaz[1], A. Telenti[2], C. Csajka[1,5], and the Swiss HIV Cohort Study
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Besides *CYP2B6,* other polymorphic enzymes contribute to efavirenz interindividual variability. This study aimed to quantify the impact of multiple alleles on EFV disposition.
Plasma samples from 169 HIV patients characterized for *CYP2B6, CYP2A6* and *CYP3A4/5* allelic diversity were used to build up a population pharmacokinetic model using NONMEM, seeking for a general approach to combine genetic and demographic covariates.

CYP2B6 genetic variation explained 31% out of the 65% total interindividual variability in efavirenz clearance, which was further influenced by *CYP2A6, CYP3A4* and body weight (while pharmacogenetics fully accounted for ethnicity). Square root numbers of functional alleles best described the influence of each gene, without interaction.
Concluding, functional genetic variation in both principal and accessory metabolic pathways demonstrates a joint impact on efavirenz disposition. A common rule seems to govern their effects, which may allow transforming pharmacogenetic test results into clearance predictions.

P-12

Smoked Cannabis and Doping Control: Are we Looking for the Wrong Target Analyte?

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Since 2004, Cannabis is prohibited by the World Anti-Doping Agency (WADA) for all sports at competition. In the years since then, about half of all positive doping cases in Switzerland have been related to Cannabis consumption. Mostly the athletes plausibly claim to have consumed Cannabis several days or even weeks before competition and only for recreational purposes not related to competition. In doping analysis, the target analyte is 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH), the reporting threshold 15 ng/mL. However, the wide detection window of this long-term THC metabolite does not allow a conclusion concerning the time of consumption or the impact on the physical performance. Therefore, the evaluation of other target analytes with shorter elimination half-life is needed and the aim of the present pharmacokinetic study.
In a 1-session clinical trial, 12 healthy, male volunteers with Cannabis experience (≤ once/ month) smoked a Cannabis cigarette standardized to 70 mg THC/cigarette (Bedrobinol® 7%) following a paced-puffing procedure. Plasma and urine was collected up to 8 h and 11 days, respectively. THC, 11-hydroxy-THC (THC-OH), and THC-COOH concentrations were determined by SPE followed by GC/MS-SIM. The LOQ for all analytes was 0.1 ng/mL. Visual Analog Scales (VAS) were used for monitoring psychological and somatic effects.
Eight puffs delivered a mean THC dose of 45 mg. Mean plasma levels of THC, THC-OH and THC-COOH were measured in the range of 0.1–20.9, 0.1–1.8, and 1.8–7.5 ng/mL, respectively. Peak concentrations were observed at 5, 10, and 90 min. Mean urine levels were measured in the range of 0.1–0.7, 0.10–6.2, and 0.1–13.4 ng/mL, respectively. The detection windows were 2–8, 2–96, and 2–120 h. No or only mild effects were observed.
Instead of THC-COOH, the pharmacologically active THC and THC-OH should be the target analytes for doping urine analysis. This would allow the detection of recent Cannabis consumption probably influencing performance during competition. However, retesting of positive athletes B samples is necessary before implementation in doping analysis.

P-13

Development of a Biosensor-System for Self-Testing the Intensity of Anticoagulation by Anticoagulated Patients in Capillary Whole Blood

C. Thürlemann*[1], E.J. Frenkel[2], R. Dinger[2], C. Caliezi[1], and A. Haeberli[1]
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Coagulation disorders often require therapy with oral anticoagulation drugs during months, years or even for life in order to prevent hemorrhagic problems. To achieve a most effective therapy, avoiding bleeding (overdose) or thrombosis (insufficient medication), steady control of the intensity of anticoagulation is necessary. Therefore an easy to use Biosensor-System for monitoring the intensity of anticoagulation is developed. Its use is foreseen for a portable piece of equipment.
The measuring system consists of a single use electrochemical sensor in the shape of a strip and a handy, battery-operated measuring unit recording the electrical signal and calculating the intensity ratio, expressed as 'International Normalized Ratio' (INR). The principle of measurement is as follows: Blood is added to a specific reagent mixture immobilized in dry form on the strip (including a thromboplastin and a substrate sensitive to the enzyme thrombin). The thromboplastin activates the coagulation system, resulting in thrombin formation. Thrombin cleaves the tripeptidic substrate, giving rise to an amperometric signal. The algorithm integrated in the instrument transforms this signal – in consideration of the temperature – to the corresponding INR-value. Taking into account the type of samples used, measurements are possible with capillary whole blood, venous whole blood and plasma samples.
In order to validate the Biosensor-System, measurements with capillary whole blood of orally anticoagulated patients have been performed. A good correlation between the Biosensor-System and the reference method in the clinical laboratory ($r = 0.92$) was obtained. The Biosensor-System is primarily meant for Home-Care. During a field test, patients using already the CoaguChek S®-system from Roche Diagnostics and answering to general criteria for patient self-monitoring were asked to perform parallel measurements with both systems. Patient data, used in the analysis were taken from 33 patients who executed 5 to 18 comparative measurements according to the guidelines; the mean number is 10.3. With a total of 308 comparative measurements the mean value with our biosensor system was INR 2.65 ± 0.72, the mean value of the parallel CoaguChek S measurements was INR 2.71 ± 0.71. The mean relative deviation (MRD %) of both methods was 0.27%. The 'bias' of the deviations was INR 0.063 ± 0.64. Taking into account only the mean INR-value of the individual patient series ($n = 33$), a mean Asulab biosensor -INR of 2.64 ± 0.37 and a mean CoaguChek-INR of 2.72 ± 0.48 is obtained.
In clinical tests, using samples of patients on oral anti-coagulation therapy, the validity of measurements, both performed on plasma samples and on samples of capillary whole blood, is demonstrated. In addition, in a field test at home by patients on oral anti-coagulation therapy, a good correlation was shown between the Biosensor-System and an already commercialized reference system.

P-14

Methods for the characterization of protein-aluminum vaccines

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Different analytical approaches are presented to characterize the stability of therapeutic protein vaccines consisting of protein solutions that use an aluminum suspension as adjuvant. The characterization of protein-adjuvant vaccines is typically performed prior to mixing on the protein and the adjuvant; characterization of the mixture is an analytical challenge.
In this work a protein vaccine model, bovine serum albumin (BSA), was mixed with aluminum hydroxide (Alhydrogel®) and its physical properties were evaluated.
The characterization of the BSA-adjuvant complexes was performed with UV-Vis spectroscopy, steady-state fluorescence, time-correlated single photon counting fluorescence lifetime, 90° light scatter, steady-state anisotropy, attenuated total reflection Fourier-transform infrared spectroscopy, gravitational sedimentation analysis and LUMiSizer® Dispersion Analyzer.
Our results suggested that conformation of adsorbed BSA on aluminum hydroxide differed from the free BSA in solution. The data presented in this work show the advantage of using complementary analytical methods for the optimization of stable and active protein vaccines.

P-15

Site-Specific and Stoichiometric Functionalization of Tumour-Targeting Antibodies Using Transglutaminase

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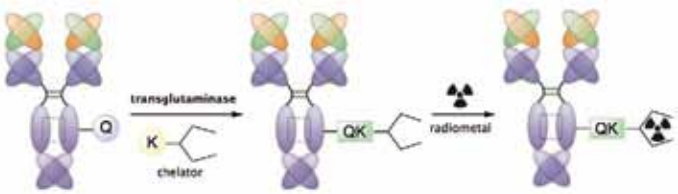
Modification of monoclonal antibodies (mAbs) with chelating agents is a challenging step in the design of radioimmunoconjugates. To overcome drawbacks associated with conventional chemical conjugation methods (lack of control over stoichiometry and site of functionalization) [1], we have developed an enzyme-aided approach to produce immunoconjugates of uniform and reproducible composition with well-defined ligand-to-protein ratios (see Scheme).
Using the enzymatic activity and specificity of bacterial transglutaminase, we coupled derivatives of different metal chelators (deferoxamine (DF), 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) and 4-(1,4,8,11-tetraazacyclotetradec-1-yl)-methyl benzoic acid (CPTA)) to glutamine (Q) residues of the tumour-targeting mAbs rituximab and chCE7agl. The immunoconjugates were produced under physiological conditions in a single step. LC/MS analyses revealed the presence of single protein species with exactly two (rituximab) and four (chCE7agl) metal chelators per antibody molecule at the Fc region. The immunoconjugates were stably labelled with a variety of radiometals (DF with ^{67}Ga and ^{89}Zr, DOTA with ^{177}Lu and CPTA with ^{67}Cu) and evaluated *in vitro*. The tested compounds retained their high binding affinity to the corresponding antigen-expressing tumour cells.
The first comparative *in vivo* biodistribution studies of enzymatically versus conventionally chemically modified mAb were performed with ^{67}Ga-DF-chCE7agl in nude mice bearing human ovarian carcinoma metastases. The immunoconjugates reached maximal tumour accumulation 48 h post injection with 44% ID/g for ^{67}Ga-$[DF]_{enz}$-chCE7agl and 21% ID/g for ^{67}Ga-$[DF]_{chem}$-chCE7agl. Whereas tumour-to-blood ratios were equal for both conjugates, the enzymatically modified mAb showed a 3-fold lower uptake into the liver, which is often the dose-limiting organ in radioimmunotherapy.
The novel enzymatic antibody functionalization strategy allows for the design of radioimmunoconjugates with more favourable biological and pharmaceutical characteristics than chemically modified mAbs.



[1] Chapman et al. Nat. Biotech. 1999; 17: 780-783

P-16

BMP-2-Induced Ectopic Bone Formation: Influence of Formulation pH

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Carefully designed drug delivery systems are required to preserve protein biological activity and prevent rapid local clearance from the application site. Using one of the promising growth factors for the treatment of bone defects, recombinant human bone morphogenetic protein (rhBMP-2), we investigated in rodents the influence of two different pH of an injectable chitosan-based hydrogel on ectopic bone formation.
Our results show increased bone formation when rhBMP-2 was incorporated in pH 5 chitosan hydrogel, as compared to pH 6.8 formulation. In contrast, no bone formation was observed after storing BMP-2 chitosan formulation at neutral pH for a few hours. The pH of the delivery system affects in vivo protein activity, possibly through a decreased stability.

P-17

TLR-2 Agonist Functionalized Biopolymer for Mucosal Vaccination

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Mucosal DNA vaccination using chitosan nanoparticles as a delivery system was demon-strated to be effective, e. g., after endotracheal application in mice. One concept to enhance mucosal immune stimulation using biopolymers is the functionalization with immunogenically active compounds, which may enhance both mucosal and systemic immunity after local application. Auspicious candidates were screened and Toll-like receptor (TLR) agonists attracted much attention. Among various TLR agonists, the synthetic lipopeptide

Pam3Cys-peptide was demonstrated to exhibit adjuvant capacity through targeting TLR-2 expressed on the surface of dendritic cells. Moreover, it was previously shown that a conjugate of a Pam3Cys moiety and a PEG polymer retains its immunostimulatory properties while being water-soluble. In our study, we report the covalent coupling of Pam3Cys to a chitosan derivative biopolymer.
N,N,N-Trimethyl-chitosan (TMC) with a suggested optimum degree of quaternization (50–60%) for mucosal vaccination and O-carboxymethylated-TMC (CM-TMC) were synthesized as previously described. Synthesis of NH-2-PEG-Pam3Cys (ω-amido-[Nα-palmitoyl-oxy-S-[2,3-bis(palmitoyl-oxy)-(2R)-propyl]-[R]–cysteinyl]-α-aminopoly (ethylene glycol) was performed according to the reaction sequence published by Metzger et al. [1]. NH2-PEG-Pam3Cys was coupled to CM-TMC by activation of the carboxylic moiety with O-(benzotriazol-1-yl)-N,N,N´,N´-tetra-methyluronium hexa-fluorophosphate (HBTU) and N-(3-dimethylamino-propyl)-N´-ethyl-carbodiimide hydrochloride (EDC). The conjugate was isolated by precipitation and exhaustively washed with ethanol in order to remove unreacted NH2-PEG-Pam3Cys. Finally, the polymer was washed twice with diethyl ether and dried in vacuo. The successful synthesis of the TLR-2 ligand NH2-PEG-Pam3Cys was confirmed by 1H-NMR, 13C-NMR, and MS. Moreover, modification of chitosan polymer to CM-TMC and subsequently functionalization with NH2-PEG-Pam-3Cys was verified by 1H and 13C-NMR spectroscopy. Hereby, the degree of functionalization was firstly determined by comparison of the integrals of the carboxylic peak before and after the reaction. Additionally, the integral of the polyethylene unit was compared to the integral of trimethylation, and a degree of functionalization of around 4% was calculated. This was expected in view of applying a ratio of free PEG amine to COOH (20% carboxymethylation for CM-TMC) of 1:4.
In conclusion, a water-soluble TLR-2 ligand was synthesized and successfully coupled to a chitosan derivative. This new polymer is under investigation as DNA vaccine carrier material for mucosal vaccination.

[1] Metzger J. W. et al. Int. J. Peptide Protein Res. 1991; 38: 545-554.

P-18

Urokinase-Sensitive Photosensitizer Prodrugs (uPA-PPPs): Design, Synthesis and In Vitro Evaluation

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Protease-sensitive macromolecular prodrugs have attracted interest for bio-responsive drug delivery to sites with up-regulated proteolytic activities such as cancerous or inflammatory lesions. In the current study we have developed a novel protease-sensitive macromolecular photosensitizer prodrug for target-selective eradication of prostate cancer cells, over-expressing urokinase plasminogen activator (uPA). In those prodrugs, multiple photosensitizer units are tethered to a polymeric backbone via short, uPA-cleavable peptide linkers. Photoactivity of the intact prodrug is efficiently impaired due to energy transfer between neighbouring photosensitizer units and can be restored by enzymatic cleavage of the peptide linker and release of the photosensitizer-peptidyl-fragment. The targeting strategy of those prodrugs is triple and involves passive accumulation of the macromolecular carrier at the tumor site via the enhanced permeation and retention effect (EPR), site-selective uPA-mediated release of the photosensitizer, and in situ generation of cytotoxic reactive oxygen species generation after localised irradiation. Here, we report the design, synthesis and in vitro evaluation of uPA-PPPs.

P-19

Structure-Activity Relationships of C12-C13-Oxazoline Derivatives of Epothilone A

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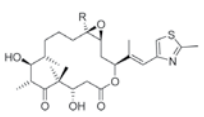
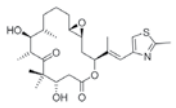
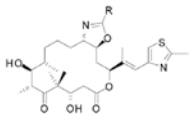
The inhibition of cancer cell growth by epothilones (Epo's) (1), natural products isolated from the myxobacterial strain Sorangium celluosum, is based on the stabilization of cellular microtubules, i. e. they exhibit a "taxol-like" mechanism of action. The widespread interest in the chemistry and biology of these macrolide-based microtubule-stabilizing agents, expedited by their potent in vitro and in vivo antiproliferative activity, has resulted in an advanced understanding of the structure-activity relationships for epothilones. The advances in the synthesis and semi-synthesis of epothilones lead to numerous active analogues of which at least seven have entered clinical evaluation as potential anticancer drugs and one of them has recently obtained FDA approval for the treatment of breast cancer [1].
One such epothilone analogue, trans-epothilone A (2), was shown to exhibit antiproliferative activity in a similar concentration-range as the natural epothilone A (1a) itself [2]. As a further extension of our previous work on trans-epoxide and trans-cyclopropane-based analogs of Epo A we now present the synthesis and biological evaluation of a series of epothilone derivatives that are characterized by the presence of a 2-substituted transfused C12-C13-oxazoline ring (3). Some of these derivatives show antiproliferative activities and tubulin-polymerizing potencies that are comparable with those of the parent compound Epo A. A clear structure-activity relation-ship can be delineated for these analogs with respect to the nature of the 2-substituent on the oxazoline ring. Possible interaction modes of these new epothilone derivatives with tubulin have been investigated by molecular-modeling.



(1a) R=H Epothilone A
(1b) R=Me Epothilone B



(2) trans-Epothilone A



(3) R = aryl, alkyl

[1] K.-H. Altmann, B. Pfeiffer et al. Chem. Med. Chem. 2007; 2: 396-423.
[2] K.-H. Altmann et al. Helv. Chim. Acta. 2002; 85: 4086-4110.

P-20

Party with a Mobile High-Tech Lab: 1001 Pills Tested on the Dance Floor

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For more than 10 years the mobile lab unit of the Office of the Cantonal Pharmacist (Health & Social Welfare Department, Canton of Berne, Switzerland) is testing so called "Party Drugs" on the dance

floor. In cooperation with "Streetwork Zurich" the team has tested since 2001 more than 1001 samples at about 70 events.
The mobile lab consists of three custom made subunits mounted in steel framed racks on wheels, one for weighing and documentation, one for sample preparation and one with the equipment for chemical analysis (HPLC-DAD).
The lab is operated by two experienced technicians. Before analysis the interested customer is asked by the lab crew to fill out a questionnaire concerning information about the sample; thereafter every sample is digitally documented and characterized by physical appearance (form, weight, dimensions etc.).
Due to the very sensitive analytical methods, only a representative part of the sample is used for further analysis. Sample preparation is quick and effective; principally it consists of ultrasonic extraction with an appropriate solvent and filtration.
Qualitative and quantitative chemical analysis is performed simultaneously on a high-tech instrument (high performance liquid chromatograph with diode-array detection, HPLC-DAD). Analytical results are available within about 20 min. Routinely, about 50 active substances can be reliably characterized. In cases of unknown or dangerous compounds, hazardous combinations or high doses, the potential consumers and – if necessary – a greater public is warned with appropriate means.
The lab is the focal point for counselling activities and facilitates the contact with festive people. During the analysis of the sample, which is free of costs and anonymous for the interested customers, they attend a structured counselling session with social workers. The implicit scientific background of the lab reinforces the credibility of the information provided concerning potentially risky substances and/or behaviour.
On the long run, attending about 10 parties per year gives an insight into the situation on the illegal market regarding new drugs and changes in consumption trends.
The intention of this contribution is to present technical aspects of equipment, sample handling and chemical analysis methods developed at our lab, the interdisciplinary cooperation of the lab staff with social workers as well as a survey of the results of the 1001 analyzed samples.

P-21

Analysis of the Pharmaceutical Quality of Methadone Preparations

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In the Canton of Berne, over the last years an average of about 2500 individuals is participating in a methadone substitution program. Most of the patients receive their daily dose of methadone in form of oral solutions witch are predominantly produced in public pharmacies. Methadone therefore belongs to the group of narcotics with the highest per capita consumption, especially amongst the not industrially manufactured preparations.
As the competent supervisory authority the Office of the Cantonal Pharmacist inspects the sites (i. e. pharmacies, doctor's practices and specialized treatment institutions) that produce and/or dispense methadone in substitution programs in the Canton of Berne. Most of the analyzed samples were collected during inspections. A smaller part came from other cantons whereas Swissmedic coordinated the sampling.
It was the aim of the present study to check in form of a continuous monitoring for compliance with the legal requirements concerning quality, labeling and dispensing in order to prevent incidents potentially hazardous to health. In the laboratory the samples were checked for the content of methadone and the liquid preparations additionally for the presence/content of preserving agents with HPLC-DAD.
Results from the analytical series of the years 2004–2006 are presented. Even though there exists for many years a monograph in the Formularium Helveticum ("Methadoni solutio 1% FH") with definite requirements concerning compounding and labeling, an uncontrolled growth of a huge variety of compositions concerning the concentration of methadone as well as type and concentration of preserving agents was observed.
Because of quality deficiencies (low content, missing or insufficient preservation) 15% of the solutions were objected. Labeling not according to the requirements of the Swiss Pharmacopoeia and inappropriate containers especially with samples from doctor's practices were additional reasons for objections. Insufficient attention to further legal requirements (Ph. Helv. 10, Chapter 20.1), inappropriate devices for measuring the prescribed dose (syringes, droppers) and problematic packaging are concurrently causative for the observed quality deficiencies.
For the treatment with methadone oral solutions the Office of the Cantonal Pharmacist of the Canton of Berne recommends the formulation according to the Monograph "Methadon-hydrochlorid-Lösung 10 mg/mL" (Ph. Helv. 10) implemented 2006. For the consumption out of sight dispensing in well suited, tightly closing single dose containers with childproof closure and labeling according to the Pharmacopoeia (Ph. Helv. 10, Chapter 17.1) is required. The testing series will be continued.

P-22

Inhibition of mTOR in Combination with Doxorubicin in an Experimental Model of Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is resistant to chemotherapy. We reported that sirolimus, an mTOR inhibitor, has antiangiogenic properties in HCC. Antiangiogenic therapies may enhance chemotherapy effects and inhibition of mTOR sensitized tumor cells to DNA-damaging agents by down-regulating p21 expression. We investigated sirolimus in combination with doxorubicin in an experimental model of hepatocellular carcinoma.
Single cubes of subcutaneously grown Morris Hepatoma (MH) cells were implanted into livers of syngeneic rats. Animals were assigned to sirolimus, liposomal pegylated doxorubicin, both in combination or no treatment. Tumoral growth was followed by MR imaging. Antiangiogenic effect was assessed by CD31 immunostaining and capillary tube formation assay. Cell proliferation was monitored by thymidine incorporation. Expression of p21 and phosphorylated MAPKAP kinase-2 was quantified by immuno-blotting. p21 half-life was determined by blocking the nascent translation with cycloheximide, followed by immunoblotting.
Animals treated with combination developed in comparison to animals receiving drugs in monotherapy smaller tumors with a marked decrease in tumor microvessel density. Inhibition of mTOR further impaired capillary tube formation in presence of doxorubicin. Doxorubicin reduced endothelial cell and Morris Hepatoma cell proliferation and inhibition of mTOR accentuated this effect in the endothelial cells only. No apoptosis was observed. Doxorubicin stimulated the expression of p21 and the phosphorylation of MAPKAP kinase-2 in endothelial cells. Addition of mTOR inhibitor down-regulated p21, but did not decrease the phosphorylation of MAPKAP kinase-

2 in endothelial cells. In presence of cycloheximide, the half-life of p21 was shortened in endothelial cells by the combination of mTOR inhibitor with doxorubicin compared to no treatment or monotherapy. In Morris Hepatoma, the half-life of p21 was not affected by the drugs.
In experimental HCC, sirolimus has additive antitumoral effects when combined with doxorubicin and this is associated with a strong antiangiogenic effect. These findings offer a mechanistic rationale for combining mTOR inhibitors to chemotherapy in HCC treatment.

P-23

Conformational Prevalence of c-Src Tyrosine Kinase Domain Dictated by a Single Amino Acid

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The crystal structures of c-Src kinase domain in an active and in an inactive conformation have been resolved but the molecular mechanism allowing the structural switch remains unknown. To bind imatinib, a tyrosine kinase inhibitor binding to the inactive conformation of Abl (IC_{50} = 25 nM), c-Src undergoes a thermodynamic penalty resulting in IC_{50} value of 221 µM [1].
In this work, we aimed at the identification of key amino acid residues that are dictating the transition from the active to the inactive protein conformation and the conformational prevalence in time and thus, to better understand the molecular basis of conformational plasticity of tyrosine kinases.
We first performed a comparative structural analysis using molecular modelling and depicted a pool of residues at the hydrophobic interface (H1-H2) of the N- and C-lobes that appears to be important for the protein conformation and motion.
We performed site-directed mutagenesis studies that showed that mutating a single residue at the hydrophobic interface influences drastically the conformational balance of c-Src rendering the mutated protein much more sensitive to imatinib (IC_{50} = 37 nM).
Concluding, this study reveals that one amino acid of the hydrophobic H1-H2 interface is crucial for the conformational prevalence and transition of c-Src.

[1] Seeliger M. et al. Structure 2007; 15: 299-311

P-24

From Hit to Target: Toward a New Therapeutic Strategy Against Human African Trypanosomiasis

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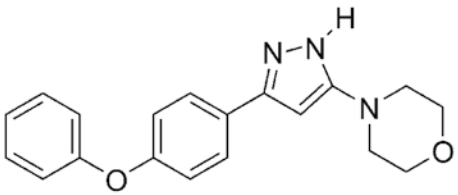
Recently, we discovered 4-[5-(4-phenoxyphenyl)-2*H*-pyrazol-3-yl]morpholine (compound **1)** to exhibit specific antitrypanosomal activity with an IC_{50} of 1 µM on *Trypanosoma brucei rhodesiense (T. b. rhodesiense),* the causative agent of the acute form of Human African Trypanosomiasis (HAT). The purpose of this study was to identify the corresponding target within the parasite cell using a chemical proteomics approach.
Three derivatives of compound **1**, each containing an additional amine group, were synthesized and immobilized via the amine group on epoxy-activated agarose to perform affinity chromatography. Total cell lysate of *T. b. rhodesiense* was incubated with the matrix and bound proteins were separated by SDS-PAGE. Proteins were detected by silver staining and identified by trypsin digestion which was followed by LC/ESI/MS/MS-QTOF mass spectrometry and database searches using the ProteinLynx Global Server (all species) and Mascot (other eukaryotes) search programs. Adenosine kinase of *T. b. rhodesiense* (TbrAK) was identified as the intracellular target of compound **1**. TbrAK is a key enzyme of the parasite purine salvage pathway, which is vital for parasite survival. The TbrAK gene was cloned and recombinant protein was purified to homogeneity for subsequent chemical validation. CD spectroscopy and ITC measurements unambiguously demonstrated that compound **1** interacted specifically and tightly with TbrAK with a binding affinity in the nanomolar range (K_D of 75 ± 20 nM and 497 ± 34 nM for the high and low affinity binding site, respectively). To reveal the mechanism of action at molecular level *in-vitro* activity measurements were performed. Their results clearly showed that compound **1** was a strong activator of TbrAK activity. The subsequent enzyme kinetic analysis provided strong evidence that the observed hyperactivation of TbrAK conferred by compound **1** is due to the abolishment of the intrinsic substrate-inhibition.
Taken together, these results suggest that hyperactivation of TbrAK may represent a novel therapeutic strategy for the development of trypanocidals.



compound **1**

P-25

Evaluation of AZT for Suicide Gene Therapy

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Herpes simplex virus Thymidine Kinase (HSV1-TK) together with Gancyclovir (GCV) is a well investigated as a failsafe for allogeneic haematopoietic stem cell transplantation (allo HCT). Patients who received donor T lymphocytes transduced previously with a retroviral vector coding for HSV1-TK, were successfully treated with GCV in case of Graft versus Host Disease (GvHD). Despite the demonstration of the efficacy of HSV1-TK/GCV suicide strategy, this system is limited by the viral origin of the suicide gene, which can lead to immune mediated elimination of the engineered lymphocytes.
The aim of our project is the development of a new suicide gene/prodrug system with reduced immunogenicity in order to improve the treatment. To achieve this aim we chose AZT as prodrug and focused on engineering human TK (hTK1) and thymidylate kinase (TMK), with an enhanced ability to phosphorylate AZT and a reduced specificity for thymidine (dT).
Target-based assay using recombinant mutated hTK1 revealed that the substrate specificity of the hTK is shifted towards AZT. To enhance the effect, the modified hTK was fused with a modified TMK. Measurements of the cell viability of 143B osteosarcoma cells lacking the hTK1 and transiently transfected with the engineered hTK1-TMK fusion protein (fp) revealed a 100-fold higher sensitivity towards AZT treatment compared to cells carrying the wild type hTK1. Jurkat cells expressing wild type hTK1 were stably transduced with the fusion protein (lentiviral transduction). In contrast to the transiently transfected cells, transduced jurakat cells were not sig-

nificantly sensitive to AZT treatment, despite the expression of the fusion protein (WB), and high accumulation of AZT-TP.
The results indicate that AZT toxicity is coupled more with NTP depletion than with the direct toxic effect of AZT-TP, thus the system might be more useful in HIV therapy than in GvHD therapy.

P-26

The Non-Globular Domain in *P. falciparum* Enoyl-ACP Reductase (PfFABI) and its Role in Substrate Specificity and Turnover

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The analysis of complete genomes has shown that Intrinsically Unstructured Proteins (IUPs) are common among organisms. Thanks to their structural flexibility, non-globular domains are involved in several cellular activities enabled by protein-protein, protein-DNA and protein-RNA interactions.
Genes of *Plasmodium falciparum* are known to be characterized by long insertions called Low Complexity Regions (LCRs), which often give rise to regions lacking a well-defined 3D structure [1]. These regions were recently shown to be important for protein functions in this parasite [2].
This work aims at elucidating the role played at a molecular recognition level by the non-globular domain present in *P. falciparum* enoyl-ACP reductase (PfFabI), an enzyme involved in the type-II Fatty Acid Synthesis (FAS-II) pathway. For this purpose, a mature form deletion mutant lacking the PfFabI 43-residues long LCR was created, and kinetic parameters were compared to those of the mature, wild-type PfFabI, using crotonoyl-CoA and enoyl-ACPs as substrates. Structural and stability studies were also performed in presence and absence of the cofactor NADH.
The results of this study show that the non-globular domain of PfFbaI is not important in maintaining the overall structure of the enzyme, but directly influences the affinity of PfFabI for its artificial and natural substrates and the catalytic efficiency of the enzyme. Moreover, the deletion mutant showed to be more susceptible to NADH stabilization.

[1] Brocchieri L. Genome Res. 2001; 11: 195-197.
[2] Jean L. et al. Mol. Biochem. Parasit. 2005; 144: 187-197.

P-27

Transgenic Selection of Embryonic Stem Cell Derived Cardiac Cells Using Herpes Simplex Virus 1 Thymidine Kinase

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Embryonic stem (ES) cell derived cardiac cells have the potential to become a powerful tool within drug screening assays or cell replacement therapies. An enriched and homogenous population of cardiac cells is necessary in order to further characterize and exploit this powerful tool.
We present an enrichment strategy combining a TetR-Krab repressor system with a herpes simplex kinase 1 thymidine kinase (HSV1-TK) ganciclovir based selection. We created two plasmids, i. e. one coding for a Repressor under transcriptional control of the cardiac tissue specific Nkx-2.5 promoter/enhancer and the second plasmid coding for the ubiquitous promoter EF1-α promoting expression of a non-spliceable version of the HSV1-TK gene. Our selection system is supposed to mediate HSV1-TK expression and apoptosis upon ganciclovir treatment in all cells during embryoid body (EB) development except in cardiac cells, where HSV1-TK translation is expected to be blocked by the repressor.
Double retroviral transduction of mouse ES cells shows no alterations in respect to the cells' morphology, doubling time or beating capacity as EBs compared to control. Following ganciclovir treatment, enrichment of beating foci were observed and positive cardiac staining shows increased beating areas within double transduced EBs in comparison to untransduced EBs.

P-28

Targeting the Imatinib-Resistant T315I Mutant of Abl: Design, Synthesis and Experimental Validation of Potent Inhibitors

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Chronic myelogenous leukemia (CML), characterized by unregulated proliferation of myeloid cells in the bone marrow, accounts for 15 to 20% of all adult leukemia cases in the Western population. The molecular cause for the disease is a characteristic translocation between chromosome 9 and 22 which results in the so called Philadelphia chromosome (Ph) and in the formation of the chimeric BCR-ABL1 gene. In CML the protein product of this hybrid gene is a constitutively active protein kinase. BCR-ABL kinase drives the pathogenesis of CML through the phosphorylation and activation of a broad range of downstream substrates playing a critical role in cellular signal transduction and transformation. ABL tyrosin kinase therefore represents an interesting therapeutic target and many potent inhibitors have been developed and brought to the clinic in recent years, including Imatinib, Nilotinib and Dasatinib.
However, the T315I mutant form of BCR-ABL, which is frequently found in CML patients, mediates complete resistance to Imatinib and many of the next generation Abl kinase inhibitors like Dasatinib and Nilotinib. Therefore, there is an eminent need for the development of drugs which are active against the T315I mutant of ABL.
Here we present the design and testing of compounds with a novel scaffold, compared to known BCR-ABL inhibitors, which are able to inhibit the T315I mutant of ABL in the nM range and in some cases even potently inhibit ABL wt.

P-29

Designing PET Tracers for HSV1-TK-Based Gene Therapy Using Molecular Dynamics

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Therapeutically efficient nucleoside analogues against Herpes Simplex Virus 1 are selectively activated via its Thymidine Kinase (HSV1-TK). Further metabolized to triphosphates, they inhibit viral

replication by blocking the viral DNA-polymerase. Being trapped inside the cell due to their negative charges, they are suitable Positron Emission Tomography (PET) tracers to monitor HSV1-TK activity *in situ*. Here, we apply classical (MD) and Steered Molecular Dynamics (SMD) to the design of PET tracers for HSV1-TK-based gene therapy.
First, we assessed the stability of 3 crystal structures of HSV1-TK with the substrates thymidine, DHBT, and NMeDHBT by MD. We present the protocol setup as well as the method validation combining AMBER 9.0 [1] and NAMD 2.6 [2], including a 50 ps minimization-equilibration and a 5 ns trajectory simulation.
Second, we predicted the relative binding affinities of the substrates by SMD and compared them to experimentally obtained values. For each substrate, the force needed to extract it from the binding site correlated well with experimentally measured binding affinities. SMD enables to overcome a limitation of docking, i. e. the ranking does not always reflect binding energy.
Our approach will allow us to estimate and ameliorate the binding of docked substrate analogues by adding affinity improving substitutions guiding the search for new target-specific PET tracers.

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P-30

Assessing the Design of PET Tracers for HSV1-TK-Based Gene Therapy Using Structural Biology

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Nucleosides such as thymidine analogues display antiviral activities against herpes virus. They are selectively transformed *in vivo* into monophosphate derivatives by the herpes simplex virus type 1 Thymidine Kinase (HSV1-TK) [1,2]. Once converted into the triphosphate form, they stop the viral replication by inhibiting the viral-DNA polymerase [3]. Due to their negative charge, the phosphorylated metabolites remain trapped, and accumulate in the cell. Radiolabeling of these antiviral agents with a positron-emitting isotope such as ^{11}C or ^{18}F allows noninvasive imaging of viral-kinase-enzyme activity by means of positron emission tomography (PET) [4-7]. PET Monitoring of the expression of a therapeutic gene, with the (HSV1-TK) gene being used as a reporter gene, has emerged as a promising approach in gene therapy.
Previous biochemical and structural studies have shown that pyrimidine derivatives with a sidechain attached to the C-6 of the pyrimidine ring (alkylated side-chain) display good binding affinities for HSV1-TK and no cytotoxic effects [8,9], and that they could be used as new non-toxic PET-tracer molecules.
With the aim to continuously improve the design of a PET-tracer harbouring better pharmacokinetics, we have elucidated the structure of HSV1-TK at 2.0 Å complexed with a C-6 alkylated pyrimidine derivative, namely N-Methyl-DHBT (N-Methyl-6-(1,3-dihydroxy-isobutyl)thymine). The structure reveals that the introduced N-methyl group stabilizes the molecule due to its increased bulkiness. Moreover, the structure displayed a new feature of the binding of the pyrimidine derivatives: a water molecule mediates interactions between the side chain of N-Methyl-DHBT and residues E225 and Y101 of HSV1-TK. These new insights will help us to further optimize a PET-tracer molecule.

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P-31

Distinct Effects of Cholesterol on Basal and Verapamil-Induced P-Glycoprotein ATPase Activities**

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Cholesterol promotes basal and verapamil-induced ATPase activity of P-glycoprotein (P-gp) [1]. We investigated whether these effects are related to each other and to the impact of the sterol on bilayer fluidity and verapamil membrane affinity.
P-gp was reconstituted in egg-phosphatidylcholine (PhC) liposomes with or without cholesterol, 1,2-dipalmitoyl-phosphatidylcholine (DPPC), α-tocopherol (α-Toc) or 2,2,5,7,8- pentamethyl-6-chromanol (PMC). Basal and verapamil-induced ATPase activities were studied with an enzymatic assay [2]. Membrane fluidity was characterized with diphenylhexatriene anisotropy measurements and membrane affinity by equilibrium dialysis [3].
DPPC (70% mol/mol) decreased the fluidity of PhC bilayers to the same level as 20% cholesterol. PMC (20%) and α-Toc (20%) decreased the fluidity to lesser extents. α-Toc and PMC, but not DPPC increased the verapamil membrane affinity. While 20% cholesterol strikingly enhanced the basal ATPase activity, none of the other constituents had a similar effect. In contrast, verapamil stimulation of P-gp ATPase activity was not only enabled by cholesterol but also by α-Toc and DPPC while PMC had no effect.
In conclusion, cholesterol exerts distinct effects on basal and verapamil-induced ATPase activity. The influence on basal ATPase activity is sterol-specific while its effect on verapamil-induced ATPase activity is unspecific and not related to its influence on membrane fluidity and on verapamil membrane affinity.

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P-32

Quenching-Induced Deactivation of Photosensitizers by Nanoencapsulation to Improve Phototherapy of Cancer

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Photodynamic therapy (PDT) has emerged as a promising alternative to current therapeutic methods offering the possibility of more effective eradication of cancers such as ovarian cancer. Hypericin (Hy), a natural photosensitizer (PS), has been used as a promising drug for PDT of the ovarian cancer. However, PS still suffer from several drawbacks such as difficult pharmaceutical formulation and lack of selectivity. Our strategy was to exploit the advantages of both nanoparticles (NPs) and quenching-induced deactivation of PS to produce "activatable" drug delivery systems. Biodegradable NPs should not only overcome most of the problems related to the formulation of Hy but also increase the preferential accumulation of Hy in tumors due to the enhanced permeability and retention effect. Moreover, the PS quenching upon encapsulation is used as a beneficial process to silence the PS activity until its target. We have prepared Hy-loaded biodegradable NPs with similar characteristics except drug loading. Efficient fluorescence and activity quenching were obtained by increasing the drug loading rate of Hy-loaded NPs. *In vitro* assays confirmed the reversibility of the quenching-induced deactivation of Hy. Indeed, upon cell internalization, the Hy fluorescence and activity were recovered.

P-33

Characterization of Biopharmaceutical Protein Formulations by Ultraviolet Resonance Raman Spectroscopy

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Therapeutic proteins represent an important part of the pharmaceutical industry. Different spectroscopic techniques such as fluorescence, Circular Dichroism and Fourier Transform Infrared are used to perform studies on protein conformation and structure. A new technology is Ultraviolet Resonance Raman (UVRR). This method requires intense laser sources which are still unavailable on commercial scale but available in some national facilities such as the Rutherfold Appelton Laboratory (UK), where experiments presented here were performed.
The goal of this study was to evaluate the ability of UVRR to detect conformation and other structural changes of proteins. Aqueous and solid samples were analyzed. Data will be presented on three different pharmaceutical samples: i) a liquid formulation of salmon Calcitonin (sCT), not aggregated and fibrillated, ii) a peptide coupled to a starch carrier designed to circulate longer in the bloodstream, and iii) a formulation of Transforming Growth Factor β3 adsorbed onto Tricalcium Phosphate (TCP) granules for orthopaedic applications.

P-34

Toll-Like Receptor Expression and Activation in Human Epithelial Cell Lines

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Pathogen pattern-recognition receptors (PRRs) play a major role in the activation of the innate and, successively, acquired immune system. A family of PRRs, the so-called Toll-like receptors (TLRs) has been in the focus of recent research, and ligands of TLRs are being examined as immune stimulators. In order to established cell-based assays to screen mucosally applied vaccine delivery systems, we first have examined the expression and activation of TLR-7 in several human cell lines.
Firstly, with regard to *tlr7* expression, Caco-2 (non-pulmonary) and HBE (pulmonary) cells were selected using Real Time quantitative PCR (RT-PCR) for further screening. In parallel, A549 cells were used as another representative cell line (alveolar epithelium) expressing extreme low *tlr7* levels.
Secondly, upon TLR7 ligand administration (imiquimod, Cl097), we could effectively activate specifically TLR-7 and its downstream target Il-8 not only at the RNA, but also at the protein level. Each selected cell line responds differently but in general, imiquimod was the best ligand to use as a reference in our experiments. This stimulation may be applied to any TLR using specific ligands. Lastly, a model for the hyper-reactive lung by priming A549 cells with TNF-α was established. Upon stimulation, cells present a strong but transient up-regulation of *tlr7* and *il-8* mRNA. We could prolong the peak of expression of the receptor by 6h, while the pro-inflammatory cytokine remained highly expressed.
In summary, we established cell-based assays for an efficient screening of our TLR7-based vaccine delivery systems, not only in pulmonary cells (HBE, A549) but also intestinal cells (Caco-2) and under inflammatory conditions (TNF-α primed-A549 cells).

P-35

Preparation and In Vitro Evaluation of a Novel Nanoparticulate Delivery System for Bladder Cancer Immunotherapy

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Vaccination is the most efficient and cost-effective way to prevent and control diseases. However, there is a rising need to develop a new generation of safer preventive and therapeutic vaccines that can be effectively administered by simple, economical, and practical immunization procedures. Immunotherapy of bladder cancer, involving intravesical application of bacille Calmette-Guérin (BCG) vaccine as immune modulator, is fraught with a high number of patients discontinuing therapy due to side effects. Studies are under way to more specifically evoke an immune response, using specific Toll-like receptor (TLR) ligands.
In this work, N-trimethyl chitosan nanoparticles, cross-linked with TPA, were loaded with bovine serum albumin (BSA) as a model vaccine and imiquimod as a TLR7-agonist. Nanoparticles showed a size of 418 ± 24 nm post lyophilization, a positive zetapotential of 10.0 ± 2.1 nm, and a good loading capacity for both albumin and imiquimod (11.5 ± 0.2% and 0.8 ± 0.1%, respectively).

In vitro release profiles of the nanoparticles showed a slow, sustained release of imiquimod at pH 7.4, which was significantly more pronounced at pH 5. Albumin release did not change with pH.
The prepared nanoparticles appear to represent a versatile technology platform as mucosal cancer vaccine carrier system, and is currently submitted to cell-based assays evaluating the potential immune modulator and vaccine delivery system.

P-36

Quantitative Analysis of a Therapeutic Protein in Human Plasma by LC-MS/MS Using Accelerated Digestion

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Protein quantitation is most often performed using immunoassays. Despite the great sensitivity of this approach (i. e. nano to picomolar concentrations), antibodies are required and the presence of endogenous analytes can severely affect the selectivity of the assay.
Mass spectrometry, either with electrospray or MALDI ionization, has great potential because it can differentiate between the various peptide analogs based on their collision-induced dissociation spectra or the protein isoforms based on their molecular weight or product ion spectra. Using liquid chromatography coupled to tandem mass spectrometric detection (LC-MS/MS), similar approaches to low molecular weight compounds can be applied to quantify proteins in plasma [1], including mAbs [2,3]. All the approaches for the absolute quantitative analysis of proteins included the following steps: 1) selective sample preparation, 2) digestion of the protein, 3) quantitation of a specific peptide of the protein (i. e. a signature peptide) by LC-MS/MS in the selected reaction monitoring (SRM) mode.
Generally, the reduction/alkylation step is performed in 1–2 hours and the tryptic digestion is performed overnight. The aim of the present study is to investigate the potential to accelerate the trypsin digestion by using microwave irradiation. Indeed microwave-assisted digestion has been described to enhance and accelerate tryptic digestion [4,5].
For that purpose a therapeutic human monoclonal antibody was selected as a model analyte. An analytical strategy was implemented to quantify the disappearance of the intact protein and appearance of the peptides. Microwave digestion was compared to classical overnight digestion at 37 or 60 °C. Different times were tested (e. g. 2, 5, 10, 15, 30 and 60 minutes) as well as an overnight digestion.
The validated quantitation method for this mAb using the stable isotopically labelled mAb as internal standard is described in [3]. In this method overnight digestion was used, our goal was to speed up the digestion process.

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P-37

New Phenylethanoid Glycosides from *Jacaranda caucana* (Bignoniaceae)

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As a part of our ongoing investigations on Bignoniaceae from Panama, several species were submitted to a rapid DPPH TLC test for radical scavenging activity. *Jacaranda caucana* Pittier, a tree which grows from Costa Rica to Colombia, was selected due to its interesting activity, and the lack of phytochemical studies on the polar extract. Nevertheless, several quinones and tri-terpenes have been already isolated and characterised from the chloroform-soluble fraction of a total methanol extract.
The methanol extract has been partitioned between ethyl acetate, butanol and water. The EtOAc fraction was chromatographed on a reversed-phase MPLC column. This separation afforded directly two new phenylethanoid glycosides, along with protocatechuic acid, acteoside, and jionoside D. Further purifications by semi-preparative HPLC allowed the isolation of isoacteoside and martynoside. The structures were determined by means of spectrometric methods, including 1D and 2D NMR experiments and MS analysis.

P-38

Synthesis of Novel Cationic NSAID Derivatives to Facilitate Electrically-Assisted Transdermal Delivery

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NSAIDs (Nonsteroidal Anti-Inflammatory Drugs) are commonly used for the treatment of inflammation and pain. However, their oral administration is associated with severe gastrointestinal side effects. Improved transdermal delivery would increase their local bioavailability and expand the range of indications for targeted, topical therapy. The aim of this study was to synthesise novel cationic ester NSAID derivatives optimised for transdermal administration by *anodal* iontophoresis. Our hypothesis is that the cationic prodrugs will electromigrate into the skin under the influence of the applied iontophoretic current. When they reach the viable epidermis and dermis they will be subject to hydrolysis by endogenous esterases and hence release the active molecule.
NSAID candidates, diclofenac (DCF) and indomethacin (INDO) were coupled to a charged aminoalcohol (choline) via an ester bridge. Two esterification pathways were tested using different coupling agents: dicyclohexylcarbodiimide (DCC) and carbonyldiimidazole (CDI). Successful synthesis of the cationic INDO-Ester, using CDI, at high yield (90%) was achieved. In contrast, there was a very poor yield of the DCF-Ester with both DCC and CDI, due to the formation of a lactam side-product. Moreover, the main challenge encountered during the synthesis, using DCC, was the removal of the reaction by-product dicyclohexylurea (DCU). Future studies will focus on the characterisation and iontophoretic delivery of other indomethacin ester derivatives synthesised using CDI.

P-39

Qualitative and Quantitative Analysis of *Indigo naturalis* Samples by HPLC-UV and qNMR

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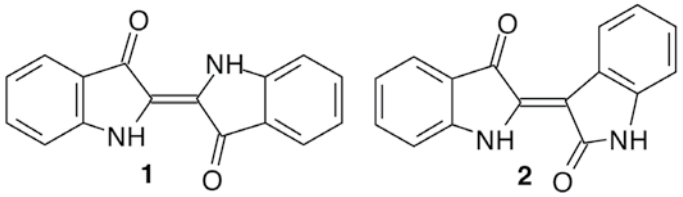
Indigo naturalis (Quingdai) is used in the Traditional Chinese Medicine (TCM) to treat chronic diseases such as psoriasis, and various cancers. The drug is obtained from indigoferous plants such as *Baphicacanthus cusia* (Acanthaceae), *Isatis indigotica* (Brassicaceae) or *Polygonum tinctorium* (Polygonaceae) via a fermentative extraction process. *Indigo naturalis* contains indigo **(1)** and indirubin **(2).** Indirubin is a kinase inhibitor, mainly of CDK5/GSK2 [1]. A proposal for a European Pharmacopeia monograph for *Indigo naturalis* has been published recently, whereby **1** (minimum content 2.0%) and **2** (minimum content 0.13%) should be determined by HPLC [2]. The remaining 97% were undefined. We determined the indigo content of eight different *Indigo naturalis* samples via quantitative ^{1}H-NMR. A comparison with the results of the proposed Pharmacopoeia method clearly revealed, that the HPLC assay consistently gave much lower indigo concentrations due to poor solubility of indigo. NMR spectra showed that one *Indigo naturalis* sample contained significant amounts of sucrose as formulating agent. All *Indigo naturalis* samples contained large amount of inorganic material (mainly Ca^{2+} and CO_3^{2-}).



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P-40

Profiling of a *Piper Nigrum* Extract by LC-TOF-MS and Semi-Preparative Off-Line NMR

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HPLC based activity profiling is an effective approach to find new lead structures from natural products, but a subsequent isolation of the active compounds for adequate structure elucidation by NMR spectroscopy is often expensive and time consuming [1]. HPLC and LC/MS analysis are therefore an useful tool to quickly identify constituents of a plant extract.
The aim of this study was to examine the applicability of an off-line semi-preparative HPLC – NMR analysis combined with TOF-MS spectrometry as a method for fast structure elucidation of natural compounds out of an extract. For this purpose 5 mg of an ethylacetate extract of *Piper nigrum* L. fruit was injected onto a semi-preparative HPLC column. Collection of peaks was performed manually and was monitored at 285 and 254 nm. Next to piperine, which is the main constituent of black pepper, the structure of several other compounds of the collected fractions could be elucidated by 1H-, COSY-, and HSQC-NMR experiments (Bruker Avance III 500MHz, 1 mm TXI probehead) and TOF-MS-analysis (Bruker microTOF system). Furthermore, the limit of detection for a qualitative off-line semi-preparative HPLC-NMR analysis was tested with a dilution series of piperine. 1H-NMR experiments of injected amounts from 500 to 0.5 µg revealed that the minimal amount of a constituent to be isolated and identified with this method is 5 µg.
With the presented results we discuss the applicability of an off-line semi-preparative HPLC-NMR- combined with TOF-MS analysis as a fast and low cost structure elucidation method as part of HPLC-based activity profiling.

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P-41

Immunophotodynamic Therapy for Cancer and Other Angiogenesis Related Diseases

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One avenue towards the development of more selective, better anti-cancer drugs consists in the targeted delivery of bioactive molecules (drugs, cytokines, procoagulant factors, photo-sensitizers, radionuclides, etc.) to the tumour environment by means of binding molecules (e. g. human antibodies) specific for tumour-associated markers. The targeted delivery of pharmaceutical agents to new blood vessels appears to be particularly attractive, due to their accessibility for agents coming from the bloodstream, and because new blood vessels are different from the mature ones at a molecular, anatomical and pathophysiological level. Furthermore, angiogenesis, i. e. the proliferation of new blood vessels from pre-existing ones, is an underlying process not only in cancer, but also in many human diseases, including blinding ocular disorders and chronic inflammatory conditions.
Over the years, our lab has developed a number of antibodies capable of selectively targeting markers of angiogenesis like ED-B. Notably, L19, a human antibody isolated from phage display library, which displays high affinity and specificity for ED-B and excellent tumour targeting performance is now under clinical and pre-clinical evaluation. Moreover, novel binding molecules based on protein frameworks are actually under advanced development in our team as antibody substitutes for vascular tumour therapy.
Photodynamic therapy is a non-invasive, oxygen-dependent treatment modality exploiting a light-activated photochemical reaction using a suitable chemical compound, called photo-sensitizer. One of the major drawbacks of current photosensitizers is the low selectivity. However, using high-affinity antibodies for the selective delivery of the photosensitizer has proven to be an optimal strategy to enhance its effects in the target tissue. In addition, the tumour neo-vasculature appears to be an attractive target since the selective delivery of photosensitizers may occlude the tumour blood vessels, causing the cancer cells death.
The aim of this project involves the conjugations of novel photosensitizers to SIP(L19), followed by an evaluation of the conjugates and an extensive testing *in vitro*. The agents will then be tested in rodent models of cancer and, if successful, will open novel therapeutic opportunities.

P-42

Controlled Release of Tetracycline from Biodegradable and Biocompatible Tricalciumphosphate Bone Substitute Material

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A novel delivery system for use in the prevention of bone infections was developed and characterized *in vitro* and *in vivo*. Therefore, β-tricalcium phosphate (TCP) granules were coated with different biodegradable poly(lactide) and poly(lactide-co-glycolide) (PL(G)A) polymers to incorporate the antibiotic drug tetracycline. The release of tetracycline from TCP composites was dependent on the biodegradability of the used polymer and on physico-chemical interactions of tetracycline with the biomaterial. Three characteristic release profiles were obtained: slow-release lasting up to 67 days, intermediate release with 60% of the total dose released up to day 20 and fast release with a high initial burst and 90% of tetracycline released within 4 days. The biological activity of tetracycline after incorporation into PL(G)A films was confirmed using a tetracycline-repressible promoter system in genetically-engineered Chinese Hamster Ovary (CHO) cells and *in vitro* cytotoxicity testing showed no reduction in osteoblast cell viability. After implantation of tetracycline-loaded TCP compo-sites into cancellous bone defects in sheep, a good biocompatibility and osteoinduction was observed in the histological analysis. These experimental results indicate the potential of coated TCP composites to be used as controlled delivery system with good *in vitro* and *in vivo* biocompatibility.

P-43

Antibody-Based Vascular Targeting for the Treatment of Rheumatoid Arthritis

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The antibody-based targeted delivery of bioactive agents (e. g. cytokines or radionuclides) to sites of angiogenesis is an attractive therapeutic strategy for cancer treatment, but is largely unexplored for chronic inflammatory diseases.
Splice isoforms of abundant ECM components seem to be particulary suited for antibody-mediated targeting applications, including extradomain A and B of fibronectin and large isoforms of tenascin C. A strong expression of EDA and to a lesser extent EDB, as well as of tenascin C, had previously been found in the synovium of patients with rheumatoid arthritis.
The anti-inflammatory cytokine interleukin 10 (IL10) has been investigated for the treatment of patients with chronic inflammation (e. g. rheumatoid arthritis) but clinical development was discontinued due to insufficient efficacy. However, in a placebo controlled phase I/II study ACR20 responses were 63% for the rhuIL10 groups, compared to 10% for placebo. We hypothesized that a targeted delivery of IL10 to arthritic joints would be therapeutically more efficacious than the administration of untargeted IL10.
In this work, previous studies, which suggested a strong expression of EDA in rheumatic lesions, could be confirmed by a comparative immunohistochemical analysis. Furthermore, *in vivo* targeting experiments showed an efficient and selective accumulation of the antibody F8, specific to EDA, in the inflamed extremities of CIA mice.
It was possible to successfully clone and express the F8-IL10 fusion protein in a non-covalent homodimeric format, which was confirmed by SDS-PAGE and gel filtration. Furthermore, cytokine activity of the fusion proteins was demonstrated *in vitro* using a MC/9 cell proliferation assay. F8IL10 had a clear therapeutic effect on arthritic score and paw swelling in the CIA mouse model.

P-44

Critical Points of HPMC K100 LV and HPMC K4M in Hydrophilic Matrices

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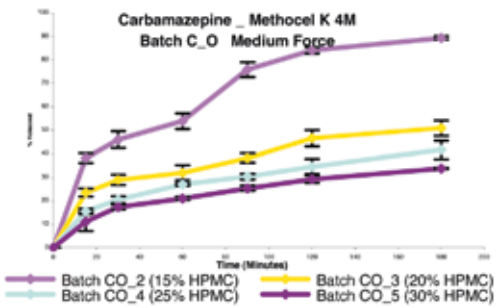
The purpose of this work was to estimate with a better accuracy the critical ranges attributed to the excipient percolation thresholds and the role of the viscosity within the system. The application of the Percolation theory to study the hydration and drug release from hydrophilic matrices has allowed formulation scientists to explain changes in release kinetics of swellable matrix type controlled delivery systems (1-3). These formulations included Carbamazepine, and two different hydrophilic matrix forming polymers. Fillers and lubricant mixture have also been included.
Preparation of matrix tablets: Initially, all materials, with the exception of magnesium stearate and Colloidal Silicon Dioxide, were blended for 10 min in a Turbula mixer. Magnesium stearate and Colloidal Silicon Dioxide were added and blended for an additional period of 5 min. The mixtures (600 mg, 12 mm diameter) were prepared by direct compression, using a standard eccentric tablet machine (Bonals A-300). The polymer concentrations were 15, 20, 25, 30% w/w for the 30 assayed lots.
Drug dissoluton study: Drug Dissolution Matrix tablets were subjected to a modified dissolution assay. More drastic conditions have been used in comparison to the standard assay, as an attempt to appreciate in a faster way the critical points of the system: 900 ml of distilled water at 37±0.5 °C, USP II paddle method, rotational speed 150 rpm. Samples were withdrawn at 0.25, 0.5, 1, 1.5, 2, and 3 h. The percent of Carbamazepine released was measured via UV spectrophotometry (Hitachi U-2000) at a wavelength of 284 nm. The assay was performed in three replicates.
Evaluation of the release mechanism: Release data analyses were performed using Higuchi (1963), Korsmeyer et al. (1983) and Peppas and Sahlin (1989) equations and SYSTAT program. Linear (Higuchi) and non-linear least squares fitting methods were used to determine the optimum values for the parameters included in each equation (1, 4).

Figure 1
Dissolution Profiles for Batch containing Carbamazepine and HPMC K4M – Medium Force. Porosity between 15 and 20%



Critical ranges found for HPMC K100LV:
- Minimum force: 11.9–15.7% v/v
- Medium force: 13.5–17.9% v/v
- Maximum force: close to 15.1% v/v

Critical ranges found for HPMC K4M:
- Minimum force: 11.8–15.8% v/v.
- Medium force: 13.6–17.9% v/v
- Maximum force: below 15.2% v/v

In conclusion, as percolation theory predicts, the studied properties show a critical behaviour as a function of the volumetric fraction of the components, which can be attributed to the polymer percolation threshold. Above this point, a sample spanning gel layer will exert a stronger control of the release rate. Although different viscosities, porosities and compression forces have been employed, the obtained release profiles are compatible with a common critical point around 13%–15% v/v of excipient, indicating the robustness of this parameter.

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New Technology Transfer Structures for the Iberoamerican and Swiss Pharmaceutical Industry

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Different structures have been created from the University of Seville in the last two years, aiming to promote the contact between Academia and Pharmaceutical Companies:
- **CISDEM** (Iberoamerican-Swiss Center for Development of Dosage Forms): this is a Center of the University of Seville, devoted to promote contact between the agents involved in the development of dosage forms (including Academia and Pharmaceutical Industry), especially in the Iberoamerican and Swiss regions.
- **Cronofarma S.L.L.:** this is a Technology-Based Innovative Enterprise (EIBT) created as a Spin-off Company, devoted to design, preparation and characterization of Dosage Forms making outsourcing for pharmaceutical and related companies. Cronofarma is conceived as a tool allowing a fast application of the new research findings and concepts to the Pharmaceutical Market.
- **Technology Transfer Network:** is a network composed by several Iberoamerican and Swiss research groups. The aim of the network is to promote technology transfer bringing to the pharmaceutical companies information about the skill, findings and specialties of the Research Groups.

The whole objective of the creation of these entities is to enhance the Technology Transfer in the field of Pharmaceutical Technology in different ways, including training and development of contracts for direct application of the recent know-how in a concrete subject.

Objectives of CISDEM and its Technology Transfer Network:
– Organization and Development of a Network for *Technology Transfer in Pharmaceutical Technology,* in the context of International Cooperation.
– Organization of *Specialized Laboratories* to develop Scientific Studies.
– Coordination of the *student's education through Special Courses,* using the Network Facilities, following the European Standards and Technical guidelines.
– *Advanced Training of Specialists* from the Industry.
– *Publication of the main Scientific Findings* of the Iberoamerican and Swiss Research Organizations, to improve their commercial appeal to the International Market.

Current Members of the Technology Transfer Network of CISDEM:
Univ. Nacional de Córdoba (Argentina), Univ. Federal do Ceará (Brasil), Univ.e Estadual de Maringá (Brasil), Centro de Química Farmacéutica. C. Habana (Cuba), Instituto de Farmacia y Alimentos, Univ. de la Habana (Cuba), Univ. Central de Las Villas (Cuba), Centro de Ingeniería e Investigaciones Químicas (Cuba), Univ. de Antioquia (Colombia), Univ. de Cuenca (Ecuador), Facultad de Química y Farmacia. Univ. de El Salvador (El Salvador), Univ. de Navarra (España), Univ. de Santiago de Compostela (España), Univ. de Sevilla (España), Univ. de Salamanca (España), Univ. San Carlos de Guatemala (Guatemala), Univ. Autónoma de Puebla (México), UAM (México), UNAM (México), Univ. de Coimbra (Portugal), Schweizerische Gesellschaft für Pharmazeutische Wissenschaften (SGPhW) (Schweiz), Universität Basel (Schweiz), Univ. de Los Andes (Venezuela).

P-46

Effects of 1,3-Dihydro-3-[(4-hydroxy-3,5-dimethoxyphe nyl)methylene]-2 H-indol-2-one (Indolinone) from *Isatis tinctoria* on Mast Cell Degranulation

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Isatis tinctoria L. (woad, Brassicacea) is an ancient European dye and medicinal plant. Several anti-inflammatory constituents have been identified by *in vivo* and *in vitro* studies, namely tryptanthrin, α-linoleic acid, indirubin, and indolinone.
In a recent study we showed that indolinone *in vitro* inhibits compound 48/80 derived degranulation in rat peritoneal mast cells. To elucidate the underlying signalling processes, we studied the effects of indolinone on degranulation in murine bone marrow derived mast cells (BMMC).
Pretreatment with indolinone blocked the phosphorylation of Protein Kinase B (PKB), Mitogen-activated Protein Kinase (MAPK), and MEK upon stimulation with adenosine or stem cell factor (SCF), whereas activation of PKC remained intact. Fluorescence microscopy revealed that indolinone was equally distributed in the cytoplasm and its incorporation was terminated shortly after administration. Inhibition of phosphatidylinositol (3,4,5)-trisphos-phate production due to stimulation with adenosine after pretreatment with indolinone was equivalent to repression observed with wortmannin. Also degranulation was blocked in BMMC, suggesting that indolinone inhibits the PIP_3/Akt pathway.

P-47

An Analytical Method to Control the Quality of *Bryophyllum pinnatum* Preparations

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Preparations of *Bryophyllum pinnatum* (Crassulaceae) are used for 30 years in the anthroposophic medicine to treat preterm labour. Identified constituents belong to the class of flavonoids, cinnamic acid derivatives, and bufadienolids. However, the active principles of the juice are not yet known. Nevertheless, quality control and HPLC-profiling is required by regulatory authorities, as well as stability studies. Depending on factors like plant origin and harvesting time, the composition of *B. pinnatum* preparations may vary qualitatively and quantitatively from batch to batch.
Consequently, a HPLC gradient method was developed and validated enabling the chromatographic profiling of *B. pinnatum* juice preparations. The identification of constituents was performed tentatively by diode array UV spectra or by standards, whereas their concentration was estimated relatively vs. internal standards (hesperidin, bufalin) and based on peak areas.
The HPLC profiling method showed to be suited for quality control purposes as well as stability tests. It is planned, that the described procedure will be used routinely in form of a standard operating procedure (SOP) by the manufacturer of *B. pinnatum* preparations (Weleda AG Arlesheim).

P-48

Detection and Enantioselective Separation of Hydroxylated Ketamine Metabolites in Equine Biofluids

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Ketamine (R,S-2-(2-chlorophenyl)-2-methylamino)cyclohexanone) is an intravenous dissociative anesthetic and analgesic used in clinical practice of man and animals. Ketamine undergoes extensive hepatic first-pass metabolism, with the major pathway involving N-demethylation to norketamine. Other metabolites include hydroxylated derivatives of ketamine and norketamine and 5,6-dehydronorketamine. Ketamine and its metabolites are chiral compounds. Ketamine is used extensively in horses. In analogy to the findings in human medicine, administration of S-ketamine instead of racemic ketamine could be of great clinical interest. This prompted us to assess the use of racemic ketamine vs. S-ketamine for anesthesia and pain therapy in horses, work that required the development of a stereoselective assay for the monitoring of plasma levels of ketamine and norketamine enantiomers.
A capillary zone electrophoresis (CZE) assay featuring multiple isomer sulfated β-cyclo-dextrin as chiral selector was developed for the simultaneous analysis of the enantiomers of ketamine and its metabolites in liquid/liquid extracts of biofluids [1,2]. Efforts leading to the identification of the hydroxylated norketamine metabolites in equine blood, urine and micro-somal preparations of the liver are presented in this work.
Hydroxynorketamine metabolites were identified via HPLC fractionation of extracts of hydrolyzed urine and using LC-ESI-MS/MS with 1 mmu mass discrimination on the LTQ Orbitrap MS. The CZE assay revealed unequal amounts of the enantiomers of the hydroxy-lated norketamine metabolites in the investigated samples. The data suggest that the metabolism of ketamine is highly stereoselective.

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P-49

Solubility of Curcumin - Gelucire® 44/14 Solid Dispersion Obtained by Spray Drying

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Curcumin, a naturally occurring highly lipophilic molecule, has a wide range of pharmacological activities. However, the main problem in the development of a pharmaceutical formulation is the limited solubility of curcumine in water, restricting its bioavailability. Among the strategies to improve the solubility of drugs, one such that holds much promise is the solid dispersion employing lipophilic materials and other polymers, such as PEG, PVP, MEG, and Gelucire. These processes are usually carried out by solvent evaporation or melting, however the spray drying method has shown to be a suitable alternative to obtain these formulations, especially because of its wide use and its low cost.
In this work a pre-formulation study with physical mixtures of curcumin with three different excipients, PEG 6000, PVP, and Gelucire®44/14 was performed to identify the most suitable excipient for this purpose. The results showed that the most effective solubility enhancer excipient was Gelucire®44/14. An increase of about 4,500 times in solubility of the drug was reached with the drug/excipient ratio of 1/10. Then solid dispersion were prepared by spray drying, employing Gelucire®44/14 and Aerosil® as drying excipient. The use of the drying excipient was due to the high adhesiveness shown by the particles of solid dispersion using the lipophilic polymer Gelucire®44/14 alone. The study followed a Box-Behnken design, where the factors studied were the drug/excipient ratios, Aerosil® content and the drying air outlet temperature, while the dependent variable was the solubility of the drug. The solubility study showed that the solid dispersions increased up to 2,956 times the aqueous solubility of the drug, which was lower than the highest solubility increase provided by the physical mixtures of the curcumin with Gelucire®44/14. The study showed that the Aerosil® addition decreased the water solubility of the drug, and the statistical analysis confirmed this hypothesis, showing that the Aerosil® content was the only significant factor studied. Although the solubilities of the solid dispersions were lower than the physical mixtures, this is a good strategy to obtain solid dispersion of curcumin and Gelucire®44/14, which may increase its bioavailability.

P-50

Ultrafast Quantitation of Saquinavir in Human Plasma Using Maldi-SRM

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Matrix-assisted laser desorption/ionization combined with time-of-flight mass spectrometer (MALDI-TOF), mostly used for the analysis of biomolecules (i.e. peptides and proteins), showed its applicability for the quantitation of low molecular weight compounds. More recently, the hyphenation of MALDI with triple quadrupole mass spectrometer allowed to perform selected reaction monitoring (MALDI-SRM) experiments. The latter has emerged as a new approach, which leads to ultra-high analysis speed, a sample analyzed in a few seconds. The SRM mode has also the advantage to eliminate the interfering background noise due to matrix ions. We show herein its applicability for the high-throughput quantitation in human plasma of saquinavir, an anti-retroviral drug, in the range of concentrations corresponding to those monitored in clinical trials (5 to 10000 ng/ml) using a pentadeuterated saquinavir internal standard. The assay was found precise and accurate within the requirement of bioanalytical work. Its potential with a non-deuterated internal standard is also demonstrated. A cross-validation using real samples was successfully performed between the MALDI-SRM and the LC-SRM approach.

P-51

Large Scale Comparative Proteomic Study of Accessible Vascular Proteins in Mouse Liver Metastases and Normal Liver

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The aim of our study is the identification of tumor associated antigens (TAA) localized at newly formed blood vessels or in the surrounding stroma as a tool for the development of novel antibody-based therapy with special focus on the metastatic process.
Three murine cancer cell lines metastasizing to the liver (M5076, Colon38 and SL4) were injected into C57BL/6 mice and tested for their metastatic potential. Tumor-bearing and healthy mice were subjected to terminal perfusion with a reactive ester derivative of biotin (Sulfo-NHS-LC-Biotin) in order to chemically modify proteins accessible from the bloodstream. Biotin labeled proteins were purified on streptavidin resin, trypsinized on resin and subsequently analysed by RP-nano-HPLC and MALDI-TOF/TOF procedures. Peptides were identified by Mascot and Protein Pilot search engines and relatively quantified using the newly developed DeepQuanTR software.
Three different syngenic mouse models were set up in order to study the complex hepatic metastasis process. Namely, M5O76 (mouse reticulum sarcoma), Colon38 (mouse colon carcinoma) and its highly metastatic variant SL4. Mice were then subjected to the *in vivo* biotinylation technique and biotinylated organs were excised for further analysis. Successful biotinylation of vascular structures was assessed by histochemical analysis. Results show a strong staining of blood vessels with some degree of diffusion into the surrounding stroma of both normal and metastatic tissue. Organs were homogenized and processed as described above. A total of 36 samples was analyzed by mass spectrometry resulting in the identification of 9481 different peptides which could be clustered to 1902 proteins. More than 500 proteins were exclusively identified in tumor samples but neither in healthy livers nor in negative controls. The choice of candidate marker proteins, the expression of suitable domains and the selection of monoclonal antibodies by phage display technology is ongoing.
In this study we show successful chemical modification of membrane proteins of selected mouse models which closely mimic the metastatic spread of colorectal cancer. Our proteomic results allow for the first time the creation of comprehensive tissue specific protein lists which promise to identify novel TAA easily reachable by antibody derivatives for the therapy and diagnosis of metastatic colorectal carcinoma.

P-52

Chemical Constituents from *Amomum tsao-ko*

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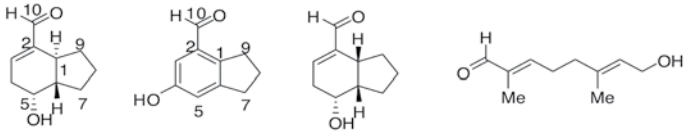
Amonum tsao-ko Crevost et Lemaire, a member of the family Zingiberaceae, has been used for centuries as food, spice and perfume in China, Japan, and Korea. Its fruits also have found applications in traditional Chinese medicine (TCM) for the treatment of stomach illness, digestive disorders and throat infections. In previous phytochemical investigations of the species, bicyclic nonane aldehydes, tsaokoin, isotsaokoin [1], trans-2,3,3a,7a-tetrahydro-1H-indene-4-carbaldehyde, cis-2,3,3a,7a-tetrahydro-1H-4-carbaldehyde, 4-indanecarbaldehyde, and 5-indanecarbaldehyde [2] had been reported.



1 **2** **3** **4**

In our systematical search for bioactive principles from traditional Chinese medicines, two new monoterpenes, rel-(1S,5R,6S)-5-hydroxybicyclo[4.3.0]non-2-ene-2-carboxaldehyde **(1)** and 6-hydroxy-4-indancarboxaldehyde **(2)** were isolated from the fruits of *Amomum tsao-ko,* together with eleven known compounds. The structures of **1** and **2** were determined on the basis of extensive spectroscopic analysis, including 1D and 2D NMR. Evaluation of cyto-toxity of all of the isolated compounds against some human cancer cell lines is ongoing.

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P-53

Profiling of two Chinese Medicinal Plants, *Sophora flavescens* and *Ligusticum chuangxiong* by Off-Line LC-NMR and LC-MS

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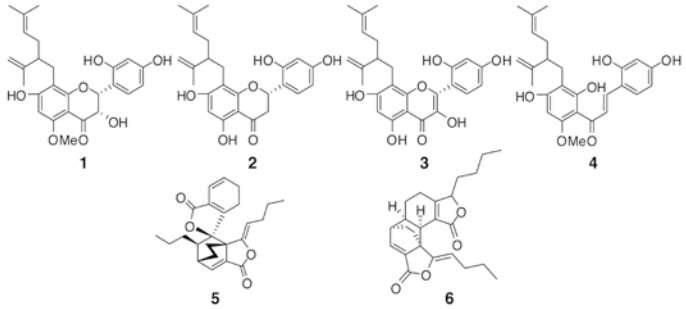
For the identification of new natural product-based lead compounds, we combine initial screening of extract libraries in a range of functional assays with HPLC-based micro-fractionation for activity profiling and chemical profiling by LC-MS and off-line NMR [1]. A 1-mm microprobe with z-gradient was used to measure one- and

two-dimensional NMR spectra [2], and fractions were obtained by peak-based fractionation of a single injection of 40 mg of extract on a semi-preparative (10 x 250 mm i. d.) HPLC column. The protocol was applied to two plants used in Traditional Chinese Medicine (TCM), *Sophora flavescens* and *Ligusticum chuanxiong,* to identify 32 compounds including **1-4** and **5-6,** respectively, as structures with promising activity in a CNS-related target.



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P-54

Design and Study of Theophylline Fast Disintegrating Multiple Unit Pellets Systems (MUPS)

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The purpose of this study was to formulate fast disintegrating multiple unit pellets tablets containing theophylline. Theophylline pellets were prepared by direct pelletization and compressed into MUPS. A 2^3 central composite design was used to optimize tablet formulation and tableting condition. Effects of compression force, amount of Ac-Di-Sol, and amount of fine pellets were investigated in order to achieve fast disintegrating tablets with high pellet loading, appropriate hardness and short disintegration time.
Results from experimental design showed that compression force and amount of fine pellets affected tablet hardness whereas amount of Ac-Di-Sol and compression force affected disintegration time. Increasing compression force gave harder MUPS but longer disintegration time. Disintegration time was also reduced by the addition of Ac-Di-Sol. Amount of fine pellets, as high as 20%, had no influence on disintegration time and was not the most potential effect on tablet hardness.
Concluding from the present results, MUPS tablets with as much as 60% pellet loading can be prepared by the combination of 40% loading of 430 µm pellets and 20% loading of 250 µm pellets. In this study, appropriate process conditions for fast disintegrating tablet formulations, that gave the shortest disintegration time and desirable tablet hardness with tablet friability less than 1%, was at 7 kN compression force and 1.5% Ac-Di-Sol.

P-55

Novel Hexyl Substituted Polylactide Micelles as Drug Carriers of Poorly Soluble Drugs

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Polymeric micelles are of great interest as nanoscopic carrier systems for diagnostics and therapies. Amongst others, amphiphilic polyethylenglycol-polylactide (PEG-PLA) copolymers, with their biocompatible hydrophilic PEG- and biocompatible and -degradable hydrophobic PLA parts, are well studied for various drug delivery applications. Nevertheless the incorporation of poorly water soluble drugs into the PLA core is limited. Therefore the hydrophobicity of PLA was increased by introduction of hexyl groups along the polymer backbone, leading to novel "hexPLA" polymers. These hexPLAs are synthesized by controlled ring-opening polymerization from either mono-hexyl or di-hexyl substituted lactide monomers [1].
In aqueous solutions the PEG-hexPLA copolymers form stable spherical nano-sized micelles, they are non-toxic and haemocompatible. The increased hydrophobicity of the hexPLA leads to a more efficient incorporation of hydrophobic drugs in comparison to standard PEG-PLA micelles [2,3]. The water solubility of some drugs can be increased by more than 200 times, and thus the PEG-hexPLA drug delivery system can be envisioned to replace other less optimal, but actually applied surfactants in current pharmaceutical formulations. Currently we are investigating the PEG-hexPLA delivery system for potential cancerous, dermatologic and ophthalmic applications.

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P-56

Magnetic Hyperthermia of Solid Tumors Through Injectable In Situ Forming Implants

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Localized mild hyperthermia sensitizes tumoral tissues to radio- or chemotherapy, and can even destroy these tissues. We developed formulations of precipitating polymers that, once injected intratumorally, form an implant entrapping *in situ* superparamagnetic particles. The implant can be heated by applying an external alternating magnetic field, delivering heat to the surrounding tumoral tissues.
We have shown the feasibility of this technique in mice bearing subcutaneous necrotizing human colocarcinoma. Entrapment of microparticles was highly efficient and biostable over a few months. At a frequency of 141 kHz, magnetic field strength ranging from 9 to 12 mT induced average temperatures ranging from 40.0 °C (non damaging heat dose: AUC = 131 °C·min) to 47.8 °C (heat dose: AUC = 282 °C·min, resulting in over 70% tumor necrosis. Survival study revealed a tumor growth delay of 27 and 37 days using magnetic field strengths of 10.5 mT and 12 mT, respectively. At 12 mT, 5

of 11 mice (45%) survived one year without any tumor recurrence, demonstrating the potential of implant-mediated hyperthermia.

P-57

Novel Degradable and Drug-Eluting Small Vascular Grafts by Electrospinning of Drug Loaded PCL-Nanofibers

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In some cardiovascular diseases partial replacement of vascular vessels is necessary. For this purpose synthetic polymeric vascular prosthesis have been developed and are currently used in surgery. However, these commercially available devices are made of biostable polytetrafluoro-ethylene, and are only suitable for replacement of blood vessels having a diameter above 6 mm, since smaller grafts have shown a high occlusion and failure rate due to thrombosis and intimal hyperplasia [1]. In order to avoid these drawbacks, we prepared biodegradable poly-ε-capro-lactone (PCL)-based small prostheses containing anti-inflammatory or anti-proliferative drugs which are assumed to favour the natural blood vessel reconstruction. PCL was chosen as it is a well known biodegradable and biocompatible polymer providing both good mechanical properties and suitable release profiles. Electrospinning of PCL/drug solutions was used for the preparation of non-woven nano- and microfibers based grafts. Morphological aspects, mechanical properties, and drug release results are discussed in relation to the pharmaceutical application.

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P-58

Hexylsubstituted Poly(lactides) for Ophthalmic Applications

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Hexylsubstituted poly(lactides) (hexPLA) are new polymers with improved characteristics for ophthalmic applications. The hexyl substituents increase enormously the polymer hydrophobicity compared to standard PLA, improving hydrophobic drug incorporation for the preparation of ophthalmic formulations. The presence of hexyl groups along the polymeric backbone has a strong impact on the glass transition temperature (Tg < -30 °C), which is much lower compared to standard PLA (Tg = +41 °C), therefore these polymers are viscous and injectable at room temperature.

Typical ophthalmic formulations such as eye drops are useful only for the treatment of the anterior segment of the eye, because of the difficulty to penetrate the cornea to reach the posterior segment. Consequently, many diseases affecting posterior segment of the eye need intraocular injections, causing pain and possible side effects like haemorrhages and retina detachment. An ideal ophthalmic drug delivery systems for the anterior segment of the eye should prolong the precorneal residence time and improve cornea penetration after topical instillation. Formulations for the posterior segment should allow controlled release for extended time after intraocular injections.

The delivery systems based on hexPLA, like semi-solid carriers, polymeric micelles and microemulsions, could overcome these problems tied to ocular treatment. Concerning the anterior segment treatment, the polymeric micellar solutions based on hexPLA could prolong drug precorneal residence time, minimizing lachrymation and reflex blinking, because of their transparency, easy instillation and no irritation. The prolongation of precorneal residence time and the small size of the micelles around 40 nm could increase drug cornea penetration after instillation compared to standard eye drops formulations. Concerning the posterior segment treatment, semisolid carriers based on hexPLA could increase the residence time of the drug in the ocular tissues giving a long time drug release, reducing the number of intraocular injections needed to maintain therapeutic levels of the drug during the therapy.

We will present our strategy to synthesize the hexylsubstituted poly(lactides) as well as the preparation of polymeric micelles and semi-solid carriers and the preparation of ophthalmic formulations.

P-59

Green Tea Polyphenols as Potential Treatment of Duchenne Muscular Dystrophy

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Duchenne Muscular Dystrophy (DMD) is a frequent inherited muscular disorder. DMD patients show muscular weakness, that progresses towards paralysis and leads to death at age 20–30. DMD patients present with muscular weakness that progresses towards paralysis. They usually die in the third decade because of respiratory or cardiac failure. DMD is caused by mutations in the gene encoding dystrophin, a cytoskeletal protein that normally contributes to the stabilization of the muscle fibre membrane during muscle activity. In DMD, dystrophin is absent, leading to numerous cell dysfunctions that culminate in muscle cell necrosis. Subsequently, an inflammatory response develops in the necrotic muscle tissue, resulting in increased oxidative stress, responsible for secondary tissue damage. In the *mdx* dystrophic mouse, both inflammatory response and oxidative stress has been identified as aggravating factors for the course of the disease.

We investigated the ability of Green Tea Extract (GTE) and its major component, (-)-epigallo-catechin gallate (EGCG), in improving *mdx*^{5Cv} mouse muscle function and histology. Three-week old *mdx*^{5Cv} mice were fed for either 1 or 5 weeks or 15 months on control chow or on chow containing GTE or EGCG. Normal C57Bl/6 mice were used as control. Muscle histology showed that GTE and EGCG reduced muscle necrosis after 1 week; fibrosis occurring late in the disease was strongly attenuated in 15-months old mice. Electrically evoked properties of the triceps surae muscles were recorded. Phasic and tetanic forces of treated *mdx*^{5Cv} mice were increased up to 94%, close to values of normal mice. In addition, muscles from treated *mdx*^{5Cv} mice exhibited a 30 to 50% increase in resistance in a fatigue assay. These results suggest that administration of GTE or EGCG to *mdx*^{5Cv} mice caused a delay in muscle necrosis, and stimulated muscle adaptation towards a slower, more resistant phenotype. *In vitro* studies showed potent anti TNF-α and TGF-β activities. Investigations regarding the mechanisms of action indicate an inhibition of the calcium-insensitive isoform of phospholipase A_2, which is a regulator of

store operated calcium channels, known to be overactive in DMD and the *mdx* mouse model.
In view of these encouraging results, we are looking for partners willing to perform clinical studies in DMD patients.

P-60

Influence of Roll Pressure During Roll Compaction on the Granule- and Tablet Properties Produced with Paracetamol/ Microcrystalline Cellulose-Mixture

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Roll compaction is a widely used dry granulation method. It can be especially suitable for moisture or heat sensitive drugs, because this technique requires no liquid binder and drying step. In roll compaction process the powder is fed between two counter-rotating rolls and compacted to dense ribbons. The produced ribbons are subsequently broken into granules. In most cases roll compaction is performed prior to tabletting.
There are several process factors affecting the properties of produced granules by roll compaction and the resulting tablets. For example, roll pressure, roll speed, roll gap, and the speed of powder feeding can be the critical parameters. The aim of this study is to investigate the influence of roll pressure during roll compaction on the properties of granules and tablets prepared with a paracetamol/microcrystalline cellulose (1:1) mixture. Paracetamol is well known as a poorly compactable drug. Due to this characteristic the production of paracetamol tablets is almost exclusively by wet granulation. For this reason, paracetamol was chosen as a model drug for roll compaction and the effect of roll pressure on the granule properties and the tensile strength of tablets was investigated.
The mean particle size of granules was increased with increasing roll pressure accompanied with decreasing the tensile strength of produced tablets. This result was in agreement with previous studies. It could be explained by the relationship between the density, the particle size of granules and the tensile strength of tablets. With increasing roll pressure the mean particle size of granules was increasing while the tensile strength of the final tablets was decreasing. This is suggested due to the decreasing bonding area with increasing particle size of granules. The roll pressure showed considerable influence on the properties of resulting granules and tablets. It is necessary to optimize process variables to obtain the desirable product, therefore further investigations on the interactions with other process variables are in progress in our laboratory.

P-61

Structural Analysis of β-Catenin Conformations and an Early SAR Study of BCL9-β-Cateinin Inhibitors

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The Wnt signaling pathway regulates cell growth and differentiation and implicates β-catenin. The deregulation of this protein is tightly associated with several cancers, including colon cancer. β-catenin can interact with BCL9 and enhance transcription in colorectal cancer cells. The interaction of β-catenin and BCL9 has been described in crystallization studies [1]. The aim of the present study was to assess the "drugability" of the BCL9 binding pocket of β-catenin. To achieve this aim, different crystal structures of β-catenin have been compared and docking studies of small molecular inhibitors have been performed.
The structural comparison, combined with the results of the docking studies, revealed that local conformational rearrangements occur and drastically influence the drugability of the N-terminus of β-catenin where BCL9 binds.

[1] J. Sampietro et al. Mol. Cell 2006; 24: 293-300.

P-62

Does Your Drug Permeate Lipid Membranes? It is a Matter of Entropy

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The ability to predict and interpret membrane permeation coefficients is of critical importance, particularly because passive transport is crucial for the effective delivery of many pharmaceutical agents to their targets. We present a liposomal luminescence assay for the quantitative measurement of the kinetic and thermodynamic parameters of permeation across lipid bilayers of drug-like compounds which is based on the energy transfer of the permeant to intraliposomal terbium(III). The assay allows the direct measure of the permeation kinetics over a wide range of pH [1]. The permeation kinetics of the model compound 2-hydroxynicotinic acid (OHNA) were investigated at various temperatures between 5 and 50 °C, membrane bilayers were composed of egg phospha-tidylcholine. Interestingly, the permeation process of the neutral and the anionic species of OHNA revealed the same enthalpy of activation while they differed in the entropy of activation.
The results indicate that lipid bilayer permeation of an acidic compound can be completely controlled by the anion at physiological pH, in contrast to the expectations of the pH-partition hypothesis. The reasons for these differences are discussed, and we suggest that the pH-permeation hypothesis requires re-evaluation.

[1] A.V. Thomae, H. Wunderli-Allenspach, S.D. Kramer. Biophys. J. 2005; 89: 1802-1811.

P-63

In Vitro and In Vivo Investigations of Reactive Metabolites of Fipexide

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In drug metabolism, electrophilic metabolites are intensively studied due their potential to lead to idiosyncratic drug reactions. In the present work, the in-vitro and the in-vivo metabolism of fipexide, a nootropic drug withdrawn from the French market in 1991 due to toxic effects, was revisited using modern mass spectrometric techniques.
In vitro metabolism of this drug has been reinvestigated via microsomal and hepatocytal incubations. Interestingly, the hydrolysis of fipexide leads to formation of two potentially toxic species, 3,4-methylenedioxybenzylpiperazine (MDBP) and 4-chlorophenoxyacetic acid (4-CPA). The formation of reactive metabolites was monitored by the formation of glutathione adducts. A strategy

has also been developed to monitor the covalent binding of reactive metabolites to proteins. To complete the understanding of the fate of fipexide reactive metabolites with *in vitro* studies, a 5-days multiple dose study was performed on rats. Multiple scan types approaches using the capabilities liquid chromatography to a hybrid quadrupole-linear ion trap instrument (QTRAP) coupled to LC have been performed in order to follow the different metabolites in urine or plasma.

P-64

Structure Activity Studies for Hypermodified Epothilone Analogs with Potent In Vitro Antitumor Activity

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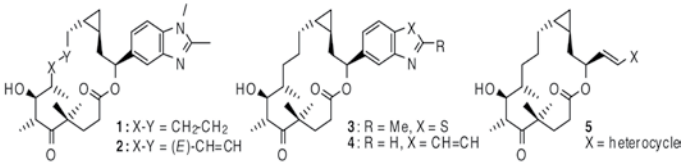
Epothilones are microtubule-stabilizing agents with potent *in vitro* and *in vivo* antitumor activity. Although the SAR of this highly promising compound class has been extensively investigated, specific aspects still remain unaddressed [1]. In a synthetic endeavor to deviate more and more strongly from the original natural product leads we discovered that the hypermodified *trans* cyclopropyl epothilone analogs **1** and **2** inhibit human cancer cell growth *in vitro* with low- to sub-nM IC_{50} values. Most remarkably, their activity is significantly more pronounced for the multidrug resistant KB-8511 cell line than for the corresponding drug-sensitive KB-31 line. With this potentially highly active macrocycle in hand the aim is to further probe the effects of side chain modifications for this new chemotype. With an efficient synthesis for structures of type **1-4** available [2], a convergent new synthetic strategy for the generation of macrolide scaffold **5** was developed. The omission of the naturally occurring methyl group at C16 has been shown not to be connected with major activity losses for natural epothilones and is thus expected to produce highly active analogs in combination with the newly designed macrolide structure and various hetero-cycles as the aromatic side chain.



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P-65

Dietary Fatty Acids – Are They a Risk Factor for Alzheimer's Disease?

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The cleavage of the transmembrane amyloid precursor protein (APP) at the beta-cleavage site gives rise to amyloid beta (Aβ), a signature peptide found in neuronal plaques of Alzheimer's disease patients. Enhancing cleavage of APP at its alpha-cleavage site may reduce the load of the neurotoxic Aβ. As the alpha-cleavage position is located in close vicinity of the membrane surface [1], dietary fatty acids may influence alpha cleavage via their effects on the membrane properties. With liposomes as model membranes we found an influence of the lipid bilayer thickness on the hydrolysis at the alpha-cleavage site by trypsin [2].

To study the effect of dietary fatty acids on APP processing, we supplement neuronal SH-SY5Y cells with various fatty acids and quantify the soluble APP cleavage products sAPPα and sAPPβ in the culture medium with ELISA.
Preliminary results with the control docosahexaenoic acid and a so far untested fatty acid indicate that alpha cleavage depends on fatty acid supplementation in the culture medium.

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P-66

Elucidating Structure-Based Rules for Lipid Bilayer Permeation and P-Glycoprotein Transport

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Pressure keeps mounting for development and improvement of methods to predict ADME properties of drug candidates early in discovery process. Lipid bilayers and efflux transporters such as P-glycoprotein (P-gp, MDR1) represent the major *in vivo* barriers for drugs. They are involved in all pharmakokinetic processes. The existing models to predict barrier passage of a compound and especially its recognition by efflux transporters are not satisfactory.
To study lipid bilayer permeation and P-gp efflux transport, P-gp is purified in high quality and incorporated into liposomes. The goal is to combine these proteoliposomes with a lanthanide-based liposomal permeation assay, developed in our group [1]. It is based on the interaction of lanthanides with aromatic ligands, resulting in a characteristic luminescence signal.
In this work, permeation profiles of the tetracycline group have been measured with liposomes; tetracycline represents a well characterized P-gp substrate.
In a next step, the lanthanide permeation assay will be adapted to its use with proteoliposomes to measure lipid bilayer permeation and P-gp transport in parallel.

[1] A.V. Thomae et al. Biophys. J. 2005; 89: 1802-1811.

P-67

Investigations on Cellulose I and II Powders as Multifunctional Excipients for Direct Compaction

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Cellulose is a commonly applied in direct compaction, and exists in 4 different polymorphic forms: cellulose I-IV. However, only cellulose I is used commercially. The aim of the present study was to compare cellulose I and II as multifunctional pharmaceutical excipients through the investigation of powder properties, such as compressibility and compactibility behaviors, as well as disintegration dissolution profiles of the prepared tablets. Tablets of pure *cellulose I* and *cellulose II* were manufactured using the compaction simulator Presster, each tablet had 300 mg of mass and 10 mm of diameter, simulating Korsch PH 336 at speed of 19.0 RPM. The compression behavior analysis has been done with the

application of Heckel and modified Heckel plot equations. Compactibility of both excipients was assessed using Leuenberger eq. different ratios of binary mixtures consisting of cellulose I and the model drug ibuprofen, and cellulose II and ibuprofen as well, at different ratios were prepared to perform disintegration and dissolution testing. All Tablets were manufactured using the compaction simulator and tooling mentioned above, and the gap was adjusted to achieve a constant porosity of 12% for all tablets.The values of the yield stress (σ) and the constant C for Heckel and modified Heckel eq. respectively showed that, both materials behave as plastic material upon. The values, constant A and the critical density (ρ_{rc}) in Heckel and modified Heckel eq. showed that cellulose I can form more mechanically rigid compact at lower compaction pressures. Tensile strength profiles showed that both materials exhibited good bonding properties at various compaction pressures, however, cellulose I powder exhibited higher tensile strength at higher compaction pressures. The ability of cellulose II tablets to disintegrate was excellent and robust at all drug/excipient ratios, compared to cellulose I, which had a higher disintegration time and was more dependent on drug loading ratio. Dissolution profiles showed enhanced drug release for the formulation containing cellulose II as an excipient. Cellulose II powders exhibited good compression and compaction behavior compared to cellulose I, additionally, tablets prepared from cellulose II showed extraordinary disintegration behavior, and subsequently enhanced drug release profiles, which makes it a potential multifunctional excipient for direct compaction.

P-68

Co-Cristals and Salts of Paroxetine Hydrochloride

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The aim of this master thesis was to search for co-crystals of paroxetine HCl and salts of paroxetine from the point of view of the nineties. During this decade the patent of paroxetine HCl anhydrate expired and the pharmaceutical company Apotex developed a generic product which contains paroxetine HCl anhydrate. Therefore, the original manufacturer Beecham (now Glaxo SmithKline) sued Apotex for infringement. They argued that the formulation is contaminated with the more stable paroxetine HCl hemihydrate form. Apotex could have avoided this conflict if they had searched for other solid state forms of paroxetine.
A co-crystal and a salt screening study was carried out. In each screening 24 co-crystal formers and 4 different solvents were used. Through each screening 5 leads were identified. In a second step the obtained leads were confirmed or rejected by performing appropriate scale-up experiments. In addition, it was investigated whether the crystals were real co-crystals or salts. The results of the scale-up of the co-crystals showed that the two leads paroxetine HCl-fumaric acid and paroxetine HCl-oxalic acid can be reproduced. However, further investigations revealed that the two successful leads were not co-crystals but instead rather salts. This observation could only be made because the corresponding salts were found during the scale-up of the salts. Scale-up experiments from the salt screening study led to confirmation of all obtained leads (paroxetine fumarate, paroxetine cinnamate, paroxetine oxalate, paroxetine D-tartrate and paroxetine maleate). Finally, the physico-chemical characteristics of the fumarate, cinnamate, D-tartrate und maleate salts were investigated. The physico-chemical characterization showed that all of these salts would probably be as suitable as paroxetine HCl hemihydrate for the development of a drug.
In conclusion, because of the patent situation in the nineties a generic manufacturer would be forced to evaluate another salt form (for instance the maleate) of paroxetine in order to avoid any patent disputes.

P-69

$Na_v1.4$ Deregulation in Dystrophic Skeletal Muscle Leads to Na^+ Overload and Enhanced Cell Death

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Duchenne Muscular dystrophy (DMD) is a hereditary degenerative disease manifested by the absence of dystrophin – a structural, cytoskeletal protein – leading to muscle degeneration and early death through respiratory and cardiac muscle failure. Whereas the rise of cytosolic Ca^{2+} concentrations in muscles of *mdx* mouse, an animal model of DMD, has been extensively documented, little is known about the mechanisms causing alterations in Na^+ concentrations. Here we show that the skeletal muscle isoform of the voltage-gated sodium channel, $Na_v1.4$, which represents over 90% of voltage-gated sodium channels in muscle, plays an important role in development of abnormally high Na^+ concentrations found in muscle from *mdx* mice. The absence of dystrophin modifies the expression level and gating properties of $Na_v1.4$ leading to an increased Na^+ concentration under the sarcolemma. Moreover, the distribution of $Na_v1.4$ is altered in *mdx* muscle while maintaining the colocalization with one of the dystrophin associated proteins – syntrophin α-1, thus suggesting that syntrophin is an important linker between dystrophin and $Na_v1.4$. Additionally, we show that these modifications of $Na_v1.4$ gating properties and increased Na^+ concentrations are strongly correlated with increased cell death in *mdx* fibers and that both cell death and Na^+ overload can be reversed by 3 nM tetrodotoxin, a specific $Na_v1.4$ blocker.

Ref.:
C. Hirn, G. Shapovalov, O. Petermann, E. Roulet, U.T. Ruegg. J. Gen. Physiol. 2008; 132: 199-208.

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