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“Higher Education, Research and Entrepreneurship” are guiding principles of the School of Life Sciences FHNW. In our understanding well trained professionals, innovative ideas combined with solid scientific knowhow and a mindset to application are the basis for successful outcome of “applied” research. In this sense research is a cornerstone at the School of Life Sciences FHNW.

The present report provides an insight into our research. It covers three main areas “Molecular Technologies”, “Therapeutic Technologies” and “Environmental Technologies”. These are handled jointly by our institutes. The described projects range from comprehensive disease diagnosis, development of innovative healthcare products and procedures for sustainable manufacturing and environmental solutions. In fact, technology development is central in our research. It opens up ways to new Life Sciences products, to industrial process innovations and to novel environmental solutions. A good example is chemical sensing as described in two projects or bio-nanotechnology and material sciences used for biomedical and medtech product development. Sophisticated analytical technologies may even lead to novel healthcare products as illustrated by the bamboo project. Finally, the increasing importance of environmental problems/issues can be addressed using bio-technology and process technology, e.g. for wastewater treatment or for gaining materials from renewable resources.

Our researchers collaborate closely with industry – regionally, nationally and internationally. The success of the technology transfer is shown by many projects directly funded by industry or co-funded with the Commission for Technology and Innovation CTI. Successful funding through Swiss National Science Foundation and the European FP7 Program further shows the attention to interdisciplinary projects and inclusion of academic partner which is crucial for those agencies. Finally, we are happy that first spin-off companies evolve from our research.

Overall, the development of our research activities is very positive. I hope you enjoy reading this report.

Gerda Huber
Director, School of Life Sciences FHNW
**Molecular Technologies (MT)**
Technologies for the synthesis and analysis of active compounds and biological systems
Novel viscosity- and density-meters for process monitoring and biomedical sensing applications

The NoViDEMo project investigates application of nanomechanical resonators (cantilevers) for real-time viscosity and density measurements in biomedical research and industrial applications. Here real-time chemical polymer-reaction measurements were studied in order to monitor the degree of polymerization.

Olfa Glaied, Joachim Köser
School of Life Sciences, FHNW

Keywords: Microcantilever, micro-viscometer, sensing, polymer characterizations

Introduction
Development of a nanomechanical real-time viscosity- and density-meter is a challenge for small fluid volumes, as well as applications of such sensor in industry and biomedical research. Here micro-cantilevers are operated in a dynamic vibration mode to measure the properties of fluids in volumes down to 10µl (Fig. 1). This sensing principle is developed for two main applications:

(i) New in-line viscosity and density sensors for process-monitoring and quality control of test liquids. The general performance of the sensor, such as its resolution, dynamic range and liquid compatibility, will be evaluated according to industrial needs (Rheometer Testing Lab AG). Furthermore, a chemical polymer reaction measurement in real-time is studied to monitor the degree of polymerization. Here the polymerization characterization with the Microcantilever is described.

(ii) New sensing platform for analytical detection and activity tests. The sensor is studied for specific stimulus-respon- sive polymer-based detection of glucose.

Viscosity and density are important liquid characteristics and are highly sensitive to the composition and physical state of the fluid. However, real-time measurement of these properties is still challenging, especially for small sample volumes below 40µl. Current commercial micro-viscometers need sample volumes of at least 50µl and do not provide in-situ viscosity information (1). Several publications discuss the use of micro-fluidics for rheological measurements. These methods are based on differential-pressure measurements (2,3), or microscopic particle tracking in micro-channels (4). Unlike cantilever sensors these alternatives do not provide simultaneous information on the viscosity and density. Currently, no commercial instrument based on these techniques is available. The only technology for label- and functionalization-free sensing of molecular interactions is micro-calorimetry; the smallest volume in commercial instruments is 190µl and is used by Nano FTC.

No commercial cantilever based system for viscosity and density measurements is known; however, in recent years research in this direction has accelerated. A prototype cantilever based real-time viscosity- and density-meter was developed within an SNF project (NSX1003 granted to TB and Chr. Gerber, SNN). Here the development of a real-time sensor, simultaneously detecting the viscosity and density of fluids is planned. We used micro-cantilevers operated in a dynamic vibration mode and evaluated the response spectra of the excited cantilevers to extract viscosity and density values.

The application of this new sensor is important in various industrial scenarios. The small sample volumes required for measurements allows further miniaturization of test production or even the implementation of this technology on a so-called ‘analytical platform’. Within this contribution particular application is monitoring of the polymerization level of a chemical reaction, to stop the reaction at a desired polymer length.

Polymer characterization measurements were used in order to explore the potential and limitations of the sensor device.

Results
For applications in research, e.g. biology and chemistry, the sensor offers several advantages: it is a new sensing principle for analytical detection and activity tests. Currently, most molecular sensors rely on fluorescent or mass sensitive detection methods. Within this study, we explore a novel reaction monitoring method allowing the monitoring of the polymerization level of a chemical reaction, to stop the reaction at a desired polymer length.

Polymer characterization measurements were used in order to explore the potential and limitations of the sensor device.

In macromolecular chemistry, the characterization of a cationic polymer and especially the determination of its molar mass are problematic. The determination of molar mass and polydispersity of polymers are usually studied by size exclusion chromatography. However, for a cationic polymer this method is not trusted, because of the electrostatic attraction between the cationic charge and the separation column material. Alternatively, viscosimetry is used applying the Mark-Houwink model. To this end, the intrinsic viscosity of the polymer solution is determined. For our study, we developed protocols and synthesized test materials using the atom transfer radical polymerization (ATRP) of two different monomers (Fig. 3): The first cationic, (2-[methacryloyloxy]ethyl)-trimethylammoniumchloride (MeDMA), and the second neutral, 2-hydroxyethyl methacrylate (HEMA). These two monomers were chosen for several reasons: (i) the difference in the chemical structure based on the quaternary ammonium introducing a positive charge in one of the monomers, (ii) the same polymerization method (ATRP) of the two monomers, (iii) easy synthesis, (iv) the neutral polymer will provide a good “positive sample”, which can be analyzed with standard methods for comparison. We are now comparing the results between micro-viscometry and SEC analysis and the potential effect of the high measurement speed in our micro-viscometer.

Conclusion and outlook
The in-situ characterization of chemical polymerization reactions was investigated. These experiments are ongoing. The results obtained so far show that the new sensor can characterize the polymerization growth in real-time. The kinetics of the polymerization also shows two kinetic regimes, depending on the degree of polymerization. The obtained results suggest that the micro viscometer will be able to characterize the behaviour of stimuli responsive polymers and their application as (bio)sensors.

References:

Research Focus Area: Molecular Technologies (MT)
Project Team: Olfa Glaied, Joachim Köser (Institute for Chemistry and Bioscience, School of Life Sciences FHNW), Thomas Braun (Center for Colloid Stu- dies and Nanosystems, Biozentrum, Universität Basel), Jürgen Blind (Institut für Pathologie, Universitätsspital Basel), Nico Bruns, Kasper Bengtsg (Universität Basel)
Partners: Mike Touzin, Christof Stuber (Endress+Hauser Flettner AG)
Funding: Swiss Nanoscience Institute (SNI)
Economic efficiency and benefit to society
Sensitive and precise density and viscosity measurements are important for e.g. quality control of medical formulations to ensure their safety and efficacy. Furthermore the presented measurement method has the poten- tial to increase the workflow in chemical research laboratories. Finally, the presented sensor system may be used for medical diagnostics, e.g. early detection of neurodegenerative diseases.

Figure 1 Schematic and photograph of the improved experimental setup. To drive and detect the vibration of microcantilevers a modulated laser (980nm) was used and an optical lock-in detection system are used. The cantilevers (1) are mounted in a 2µl fluid cell: The fluid cell (2) is fabricated from PDMS and bonded onto a temperature controlled (15 – 40°C) glass slide mounted on an xy-stage (3). The samples are introduced through tubing connected to a valve equipped with two 2µl sample-hoops (4).

Figure 2 Polymerization of acrylamide. After recording a baseline in water (b) and acrylamide monomer (a) the reaction is initiated with ammonium persulfate (APS). The increase in viscosity indicates ongoing polymerization into polyacrylamide (PAam).

Figure 3 ATRP polymerization reactions: a) Polymerization of 2-hydroxyethyl methacrylate, a neutral monomer (HEMA); b) polymerization of the cationic monomer [2-(methacryloyloxy)ethyl]-trimethylammoniumchloride (MeDMA) monomer.

Figure 4 In macromolecular chemistry, the characterization of a cationic polymer and especially the determination of its molar mass are problematic. The determination of molar mass and polydispersity of polymers is usually studied by size exclusion chromatography. However, for a cationic polymer this method is not trusted, because of the electrostatic attraction between the cationic charge and the separation column material. Alternatively, viscosimetry is used applying the Mark-Houwink model. To this end, the intrinsic viscosity of the polymer solution is determined. For our study, we developed protocols and synthesized test materials using the atom transfer radical polymerization (ATRP) of two different monomers (Fig. 3): The first cationic, (2-[methacryloyloxy]ethyl)-trimethylammoniumchloride (MeDMA), and the second neutral, 2-hydroxyethyl methacrylate (HEMA). These two monomers were chosen for several reasons: (i) the difference in the chemical structure based on the quaternary ammonium introducing a positive charge in one of the monomers, (ii) the same polymerization method (ATRP) of the two monomers, (iii) easy synthesis, (iv) the neutral polymer will provide a good “positive sample”, which can be analyzed with standard methods for comparison. We are now comparing the results between micro-viscometry and SEC analysis and the potential effect of the high measurement speed in our micro-viscometer. These experiments are currently being completed.
Biomimetic membranes from supported block copolymers and Aquaporins for environmental sensing applications

Synthesis of chemically stable and mechanically robust biomimetic membranes was investigated as new materials for applications in environmental engineering. The membranes are based on amphiphilic block copolymers and embedded Aquaporins immobilized on nanoporous alumina substrates. These novel systems will provide highly selective water membranes that allow desalination and production of pure water.

Introduction
A decline in water supplies and the growing demand for fresh water is a motivation for desalination of seawater. The conventional membrane treatments processes for sea desalination are energy intensive and water recovery is often limited. Biomimetic membranes are designed to mimic the highly-selective water transport across cell membranes. One promising biomimetic membrane technology employs natural proteins called aquaporins to regulate water flow. Aquaporins are biological water channel proteins that provide a selective and rapid transport of water across cell membranes. It acts as water channels which selectivity allows water molecules to pass through while the transport of ions, proteins and hydroxyl ions is prevented. The result is that only water molecules, and nothing else, can pass through aquaporin water pores. The understanding of aquaporins and their role as water channels has opened up the possibility to use this technology in water purification and in an industrial context. However, the use of aquaporins in a biomimetic filter membrane requires a suitable support material to stabilize the biomimetic matrix against hydraulic pressure forces. In order to address this, new kinds of supported bio-artificial compounds suitable for making stable protein incorporation membranes are required.

The membrane formation and protein incorporation have been explored by the group of Prof. Meier from the University of Basel [1, 2]. They used an ABA amphiphilic block copolymer for the synthesis of a free-standing stable membrane, suitable to accommodate active membrane proteins in a hydrophobic environment. Taking the work of Meier’s group as a starting point [3], this project aims to environmental applications based on amphiphilic block copolymers and naturally occurring proteins, i.e. aquaporins. Aquaporins were incorporated into synthetic biomimetic polymer supported membranes and their potential in water purification desalination is currently being investigated.

Methods and Results
The project is a multidisciplinary approach to develop biomimetic membranes for applications in environmental engineering. The main idea is based on the use of biological water channel Aquaporins and artificial membranes for the fabrication of new hybrid materials for industrial application in desalination and water purification. These systems could provide highly selective water membranes that allow the production of pure water or salinity power. The incorporation of Alginate (Aquaporins) into block copolymer membranes will produce membranes requiring substantially less energy to achieve the same water flux and selectivity as existing water treatment membranes. The synthesis and the study of this membrane is based on three main steps: 1. The synthesis of amphiphilic block copolymer membranes and embedded aquaporins, immobilized on nanoporous alumina substrates. 2. The effective incorporation of Aquaporins in this membrane. 3. The study of membrane capacity and effectiveness in water filtering devices. The biomimetic membranes designed from supported type ABA amphiphilic block copolymers and aquaporins is detailed in figure 1.

The membrane is based on nanostructured alumina surfaces (Fig. 3-a) covered with a layer of amphiphilic triblock copolymer poly(2-methyl-2-oxazoline)-b-poly(dimethylsiloxane-b-poly(2-methyl-2-oxazoline) (PMOXA-PDMS-PMOXA) containing aquaporins. The first step was the functionalization of the nanoporous alumina with an active site, a “cross-linker group” and the functionalization of the active site with the block polymer and the alumina surface. The activation of the nanoporous alumina was obtained by grafting of methacrylate groups onto the surface, meaning that they were open on the surface and filled the alumina pores homogeneously. The incorporation of the vesicles on the surface was complete. To the best of our knowledge, this is the first time that incorporation of vesicles on a porous surface has allowed a uniform filling of the pores. The potential in water purification of the developed membranes is currently being investigated.

Conclusion and outlook
The development of nanostructured alumina surfaces covered with a layer of amphiphilic triblock copolymer embedded with aquaporins was investigated. The characterization and the activation of “nanoporous alumina” support membranes were studied. For the polymer synthesis, the poly(2-methyl-2-oxazoline- b-poly(dimethylsiloxane-b-poly(2-methyl-2-oxazoline) (PMOXA-PDMS-PMOXA) block copolymers were synthesized and self-assembled into polymer vesicles acting as containers for aquaporins. Vesicles were incorporated on the surface with a grafting approach. The polymer and the surface were end terminated with a methacrylate group allowing coupling reaction under UV light and controlled pressure. The uniformity and stability of the polymer layer on the solid surface is one of the crucial points that established the parameters.

On the other hand, the result of the incorporation of vesicles in the nanoporous alumina surface with size pores of 200 nm was very promising and unexpected. No vesicles are observed on the surface, meaning that they were open on the surface and filled the alumina pores homogeneously. The incorporation of the vesicle on the alumina surface to the pores was complete. To the best of our knowledge, this is the first time that incorporation of vesicles on a porous surface has allowed a uniform filling of the pores. The polymer was incorporated on the surface with a “grafting to” method on which vesicles were linked to the surface with a coupling reaction between the surface and the polymer under UV light. The study of the SEM pictures (Fig. 3-b) shows that the vesicles were open on the surface and filled the alumina pores homogeneously. The incorporation of polymer vesicles containing aquaporins on the nanoporous surface allowed a uniform filling of the pores.

References:

Research Focus Area:
Molecular Technologies (MT)

Project Team:
Olfa Glasé, Uwe Fieles, School of Life Sciences FHNW

Keywords: Biomimetic Membranes, Block Copolymers, Aquaporins, desalination, water purification.
Optimized fluoride nanoparticles for dental care

Fluoride is a widely accepted compound in dental care for the reduction of enamel eroding processes. Calcium fluoride particles have been synthesized which adhere to enamel surfaces and which can serve as constant release devices to maintain increased fluoride levels in the time intervals between applications of dental care products.

Joachim Köser
School of Life Sciences, FHNW

Keywords: dental care, fluoride particles, adhesion, release

Introduction

The use of fluoride-containing dental care products has a beneficial effect on the reduction of tooth enamel destroying processes such as caries and erosion. The mode of action of fluoride is twofold: while high concentrations of fluoride during dental care result in the incorporation of this fluoride as more acid resistant fluorapatite into the surface layer of the tooth enamel, constant low concentrations in the intervals between the applications positively influence the enamel de- and re-mineralization cycles [1].

On the enamel surface of teeth treated with soluble fluoride ions calcium fluoride (CaF₂) particles are formed which could serve as reservoirs for fluoride in the time intervals between the applications [2]. Little is known about the formation of these particles, nor about their adhesion to the tooth enamel and their dissolution over time, especially during cariogenic and erosive challenges. The aim of the project presented here is to gain more insights into the CaF₂ particle formation process and to optimize these particles with respect to enamel adhesion and fluoride release kinetics.

Results

The first step of the project was the investigation of the structural flexibility of CaF₂ particles and the possibilities to influence their crystallization. For pharmaceutical companies such knowledge is very valuable since the crystal structure of active ingredients can influence their dissolution behaviour and tissue interaction. Modelling results from the group of S. Goedcker at the University of Basel suggested that small CaF₂ assemblies can exist in different amorphous states, whereas for larger systems, crystal structures with (111) planes are favoured, which would result in octahedral particles. In this study we were able to generate in situ such octahedral CaF₂ particles, however additional different morphologies can be achieved by tuning the mixing ratio of soluble calcium and fluoride ions. Particles ranging from approximately 50 nm to several µm in diameter can be produced. Their shapes range from perfectly cubic to more octahedral and round. Figures 1a-1d show the appearance of some of these particles by scanning electron microscopy (SEM). The systematic investigation of the effect of the concentrations of calcium and fluoride ions during synthesis on the shape of the final particles are summarized in Fig. 1e. Generally, larger particles are formed at lower concentrations and in some instances intermediates between different shapes can be observed, as e.g. when at a fixed fluoride concentration of 4 mM and calcium varying between 10 mM and 120 mM the particles change from cubic to round.

The strength of adhesion of the synthesized CaF₂ particles to tooth enamel is another major criterion for their designated application as fluoride storage forms and is investigated together with our project partners from the group of E. Meyer at the University of Basel. They applied AFM (atomic force microscopy) based methods to determine the adhesion of individual CaF₂ particles to the enamel surface. Comparing different particles’ geometries, strong adhesion was observed for cubic particles with diameters in the range of 50-100 nm (see Fig 1a). In collaboration with the Department of Preventive, Restorative and Pediatric Dentistry University of Bern the interaction of these particles with tooth surfaces was analyzed by SKM. CaF₂ particles were applied in concentrations corresponding to the fluoride concentrations typically present in dental care products like toothpastes and mouthrinses. Particles adhere to intact as well as initially damaged tooth enamel which would allow their use for both prevention of enamel erosion and repair (Fig. 2). Fluoride ions have been demonstrated to support the re-mineralization of damaged tooth enamel in concentrations as low as 0.05 ppm and studies report lower caries incidence in individuals with salivary fluoride concentrations of 0.04 ppm as compared to 0.02 ppm individuals (see [1] and references therein). To compare the CaF₂ particles synthesized here, with slow release fluoride devices reported in the literature, it is important to analyse their dissolution behaviour under oral conditions [3]. Furthermore it is desirable to be able to tune the fluoride release kinetics. In the literature, increased fluoride dissolution has been reported when CaF₂ particles were produced in the presence of phosphate [4]. Following the line of these results we synthesized CaF₂ particles in the presence of increasing concentrations of phosphate and compared the dissolution of pure and phosphate incorporated CaF₂. Fig. 3 shows the release of fluoride from the different particles in artificial saliva. The different CaF₂ particles dissolved fast, leading to concentrations of soluble fluoride between 0.15 ppm and 0.4 ppm within 10 minutes. This is expected to be fast enough to achieve similar fluoride levels under the conditions of constant saliva production and flow in the mouth.

Conclusion and Outlook

This report describes factors which influence the morphology of CaF₂ particles and investigates their suitability as fluoride storage forms for dental care. The synthesized particles adhere to tooth enamel surfaces and can be fine-tuned to release varying levels of fluoride. Experiments are under way in order to quantify the benefit of these slow fluoride release reservoir particles on models of caries, dental erosion and re-mineralization.

Figure 1: Examples of fluoride particles obtained by mixing different concentrations of soluble calcium and fluoride ions (a-d) and scheme of particle shapes with respect to parent ion concentrations (e). Scalebars: 200 nm.

Figure 2: SEM images of CaF₂ particles adhering to tooth enamel surfaces. Scalebars: 1 µm (a, b), 0.5 µm (c).

Figure 3: Release of fluoride from CaF₂ particles synthesized in the presence of 0 mM (blue diamonds), 0.05 mM (green triangle) or 0.1 mM (red squares) phosphate.

References:


Remineralisation of carious lesions by self-assembled peptide supramolecular networks and Hydroxyapatite nanocrystals

A tooth model was developed using synthetic nanopenous hydroxyapatite microparticles and rapid prototyping, to investigate the regeneration process of artificially induced carious lesions. Upon application of the self-assembling peptide P11 a supposed supramolecular 3D network is formed in the lesion, inducing remineralization by hydroxyapatite nanocrystals along the peptide fibrous nanostructure.

Alain Wüthrich, Lucy Kind, Uwe Pieles
School of Life Sciences FHNW

Keywords: Self assembly; carious lesion, remineralization, peptide, hydroxyapatite, supramolecular network

Introduction

Enormous efforts are undertaken worldwide to prevent and treat caries, but none of the provisions have proved to be effective enough [1]. Therefore the majority of all treatments still rely on the classical restorative treatment exhibiting significant drawbacks and leading to further destruction of the teeth over time. In addition it has been reported that potentially harmful additives might leach out of the polymeric or ceramic/polymer composite fillers [2].

At present only a few approaches have been followed and reached the market to regenerate carious lesions via remineralisation, but with only very limited success [3]. In addition the therapeutic approaches are not suitable for regenerating carious lesions. In 2007 Kirkham et al. [4] proposed a new approach based on a short peptide P-11 (10 to 12 amino acids of a particular monomeric (pH>7 salvia) form through the enamel into the natural human tooth proved to be difficult, experiments are ongoing and various binders are currently under investigation.

In a recently acquired (SNSF) follow up project, new peptides exhibiting self-assembly properties are being synthesized and studied in order to follow the efficient diffusion of the peptide into the artificial carious lesions through the enamel has been followed, therefore the white spots have been treated with the peptide followed by an excision (drilling) of the carious area and subsequently analyzing the resulting powder by Maldi-TOF mass spectrometry to detect and verify the diffusion of the peptide. The mass analysis clearly gives evidence that the peptide (15981 D) has been diffused through the enamel into the lesion, which is one of the most critical steps of the whole process. Maldi-TOF Mass spectrometry turned out to be sensitive enough to detect the small peptide quantities and will be further investigated in course of the project.

Results

A predictive 3D tooth model based on a RP process to investigate the effect of the peptide P11 is currently under development. Both dense hydroxyapatite and nanoporous material were synthesized by a wet precipitation and spray drying and/or calcination process (batches +1kg/day) providing spherical particles (Fig. 2), which are suitable for the use with the rapid prototyping technology. The synthesized powders have been characterized by all means of analytical techniques.

Figure 2: First promising trials on the Z-Corp RP machine. The carious region was subsequently treated with peptide P11. The verification of the process is in progress.

Carious lesions have been artificially induced by treatment of a human tooth with an acidic demineralization solution and the success of the process was analyzed by all means of analytical techniques in particular with x-ray microcomputer tomography (Fig. 3). The lesions are clearly visible (darker squares on the outer surface) in the upper rendered 3D view.

Figure 3: The carious region was subsequently treated with the peptide P11 (2min) and then immersed in the remineralization solution (buffered saturated hydroxyapatite solution pH 7.4). The verification of the process is in progress. First results indicate a deposit of the peptide in the carious lesion. Because the identification of the protein diffusion, the network formation and detection of the remineralization inside the artificial human tooth proved to be difficult, experiments have been carried out to initiate the gelation of the protein on a planar silicon wafer surface followed by the initiation of the growth of hydroxyapatite crystals. SEM analysis revealed the formation of a 3D network and nucleation of the crystalization of HA. Another approach to prove the initial possibilities to Hydroxyapatite: A Possible Mechanism for Subsurface Demineralization of Teeth, J. Res. Natl. Inst. Stand. Technol. 2010;115 (4): 217-234

Conclusion and Outlook

Hydroxyapatite microparticles have been synthesized in the quality and amount suitable for the 3D RP process and methods to artificially induce carious lesions in human teeth have been successfully established.

Based on first promising results, indicating the deposition/network formation and growth of hydroxyapatite nanocrystals, the process will be further studied utilizing the artificial tooth model. Both fluorescently labeled and radiolabeled peptides will be synthesized and studied in order to follow the diffusion and self assembly process. In future we hope to gain better understanding of the whole remineralization process, allowing further improvement of this new therapy of early carious lesions. In a recently acquired (SNSF) follow up project, new peptides exhibiting self assembly properties assisting the nucleation of hydroxyapatite will be developed and their properties will be studied and compared to the peptide P11.

References:

School of Life Sciences

Figure 1: Proposed mechanism of the regeneration process. The formation of a 3D network and nucleation of the crystalization of HA. Another approach to prove the initial possibilities to Hydroxyapatite: A Possible Mechanism for Subsurface Demineralization of Teeth, J. Res. Natl. Inst. Stand. Technol. 2010;115 (4): 217-234

Research Focus Area: Molecular Technologies (MT)

Project Team:
Lucy Kind, Alain Wüthrich, Sabrina Sternerovic, Annalisa Frommherz, Chantal Ullmer, Uwe Pieles, Ralf Schumacher, Philipp Chravenieux, Stefanie Gschwind, School of Life Sciences FHNW

Partner:
Bert Müller (BMC Biomaterials Science Center), Michael Hug (Credent AG)

Funding:
Swiss National Science Foundation (SNSF), Swiss Nanoscience Institute (SNI), Fördervorstand Aargau, canton Aargau

Economic efficiency and benefit to society:
We report the development of an artificial tooth model for the investigation of a new approach to regenerate carious dental lesions: a self-assembling peptide is applied, forming a fibrous 3D network followed by remineralization along the 3D structure. The results will help to improve therapeutic carious treatments and to reduce health care costs significantly in the future.
**Introduction**

In Europe, bamboo is mainly known as an ornamental plant, as a source for applications in the wood and fibre industry and as an energy crop. However, a growing interest in an alternative use of bamboo can be observed. This fast-growing plant provides a rich natural source of promising phytochemicals such as flavonoids. These secondary plant metabolites exhibit many beneficial physiological effects such as anti-inflammatory, anti-oxidative, anti-viral and anti-ageing properties or prevention of cardiovascular diseases [1, 2].

Despite this, there is still a lack of information on the secondary metabolites responsible that are present in the many different bamboo species available. Phytochemical investigation of heterogeneous bamboo species were determined by high performance liquid chromatography mass spectrometry (HPLC-MS), with a focus on flavonoids. The 24 species, belonging to three different bamboo genera, *Phyllostachys*, *Fargesia* and *Sasa*, originate from a Swiss organic bamboo forest close to Waldkirch (SG). In addition, extraction of leaf material was optimized on a pilot scale by application of high-end analytical technologies for exact characterization of the plant material gains great synergy in combination with process technology. On the basis of the combination of those disciplines, appropriate selection of bamboo species and a tailored process for a pilot plant extraction unit was achieved.

**Results of analytical investigations**

One desired criterion for utilization of bamboo as a therapeutic crop is a naturally high content of total flavonoids. This property might be influenced by genus, species, age or geographic origin of the plant. Extraction yield (in % of dry weight leaves) and total flavonoid content served as read out for the evaluation and differentiation of bamboo species. Classical natural product extraction procedures such as maceration, digestion, Soxhlet, microwave and solvent extraction were assessed to find the most efficient and economical process. Tight feed-back loops between process engineering and analytical techniques were established and allowed a thorough evaluation of the process from the outset. However, it is not only the total flavonoid content that determines the assets of a species but also the individual flavonoid composition.

**Robust liquid chromatography (HPLC) tandem mass spectrometry (MS/MS) analysis allowed for flavonoid characterization and quantification. Based on retention time and MS/MS fragmentations, the flavonoids Orelutin, Luteolin, Vitexin, Vitexin, Rutin, Isovitexin and Tricin were identified and quantified as major components. Myricetin, Quercetin, catechin, trans-p-Coumaric acid, Caffeic acid and Gallic acid were also identified.**

The resulting average concentrations of the three different bamboo genera obtained by triplicate determination (in mg substance per kg leaf) are depicted in figure 1. Different bamboo species can be clearly distinguished by an altered flavonoid profile. In addition, different bamboo genera show characteristic patterns of individual flavonoids. Phylostachys bamboo genetically exhibits both higher total and higher individual flavonoid levels compared to *Fargesia* and *Sasa* (Fig. 1). Tricin is most prominent in the bamboo leaf material.

**Anti-oxidative activity was tested for all bamboo species by assessing the anti-oxidative capacity (ORAC) [3].** It was shown that all bamboo species exert potent antioxidative effects in vitro (Fig. 2). From the results mentioned above it is obvious that bamboo is an important source of antioxidative compounds and therefore represents an interesting raw material for further development of bamboo-derived food, beverage additives, supplements or cosmetic formulations. Principal component analysis, based on flavonoid levels for the 24 different bamboo species, clearly reveals similarities within a genus and differences in between the genera as illustrated in figure 2.

**Conclusion and Outlook**

A robust LC-MS/MS method was developed for quantification of individual flavonoids in bamboo leaf extracts that allows a detailed selection of the best suited species. All bamboo genera reveal high radical scavenging properties. Principal component analysis allows the straightforward differentiation between bamboo species. Further studies on other beneficial physiological effects of bamboo are currently under investigation in our labs. Based on the very high level of analytical information, basic engineering for a technical bamboo leaf extraction plant could be carried out. Supported by pilot plants in the chemical engineering test facility in Muttenz, the design of apparatus and of a complete environmentally-friendly extraction plant could be generated. Based on this information, the customer’s project has entered the realization phase.

**References:**


**Keywords:** Bamboo, flavonoids, in-vitro anti-oxidative properties, extraction, engineering, pilot plant

**Figure 1: Flavonoids determined by LC-MS/MS in Swiss bamboo**

**Figure 2: Principal Component Analysis of Swiss bamboo reveal similarities within genus**

**Table 1: Flavonoids in bamboo leaves as measured by HPLC-MS/MS**
Cyclodextrin-based polymers: efficient binders of pharmaceuticals in water

In a world facing water scarcity, the presence of pharmaceuticals in water represents serious environmental and human health issues. In the present project, we are working to develop new polymeric materials for the detection of pharmaceuticals in water.

Patrick Shahgaldian
School of Life Sciences FHNW

Keywords: Polymers, cyclodextrins, pharmaceuticals, water

Introduction

In the last decades, the presence of pharmaceuticals has been reported in the water cycle, including surface water, wastewater, groundwater and drinking water. We are working on the development of synthetic materials that can be used for the detection and removal of these pharmaceuticals from water.

The production of synthetic materials possessing specific molecular recognition properties is a continuous challenge, with a wide range of industrial applications including bio-medical, pharmaceutical and environmental, as well as separation techniques, to name but a few. In the 1980s molecular imprinting came to the fore as a versatile technique for the production of polymers with enhanced molecular recognition properties. It is based on the polymerization of functional monomers with crosslinkers in the presence of a template molecule (i.e. target). The functional monomers interact with the template to form a supramolecular complex before the cross-linking reaction. After polymerization, the template is removed to yield recognition sites complementary to the template structure. While a vast number of reports have been published on molecularly imprinted polymers (MIPs), their commercial use is still limited. The inherent constraint of MIPs is their relative high production costs, due partly to the cost of the starting building blocks but mainly to the difficulty of removing the template from the MIP at the completion of the synthesis.

We have developed a new approach to producing polymers (CDPs) that may be crucial for decreasing the production costs of the CDPs and thus facilitating their industrial application.

Results

We have developed two different approaches for the high-throughput production of a series of cyclodextrin-based polymers (CDPs). The first approach is based on the photo-catalyzed reaction of a cyclodextrin derivative with additional monomers and cross-linkers (cf. Fig. 2) [2]. The synthesis was carried out in a multowell plate using an acryloyl β-cyclodextrin and 1-hydroxycyclohexyl phenyl ketone as an initiator. A number of additional monomers (acrylates, vinyl ethers, styrene, acrylic acid, 2,5-dihydroxyterephthalic acid, 2,5-dihydroxybenzoic acid, 2,5-dihydroxyterephthalic acid, and 1,4-dihydroxy-2-naphthoic acid). It allowed the production of 91 different polyurethanes that were assayed for their ability to complex drugs [3]. In addition to the enhancement of the recognition properties of the CDPs produced, this method allows the direct use of native cyclodextrins, that may be crucial for decreasing the production costs of the CDPs and thus facilitating their industrial application.

The synthetic methods developed allowed the development of polymers specific for a series of pharmaceuticals of interest including diclofenac, sulfamethoxazole and levodopa (4).

Conclusion and Outlook

We have developed a new approach to producing polymers with specific molecular recognition properties for pharmaceuticals. It was demonstrated that this method allows the production of polymers with enhanced molecular recognition of a series of pharmaceuticals in water.

References

Recombinant Immunoglobulins for Autoimmune Medical Diagnostics

Autoimmune diseases are challenging for current medical diagnostics. These diseases arise through mechanisms of compromised immune self-tolerance, commonly through autoantibodies recognizing self-antigens. This report outlines the development of recombinant disease-state specific autoantibodies for application in one a autoimmune disease.

Ronald Tynes, Daniela Tobler, Irina Bauer, Dieter Eibl, Bernhard Mani, Thomas Jermann, Daniel Gygax
School of Life Sciences FHNW, IBT ZHAW Wädenswil, Bühlmann Laboratories

Keywords: diagnostics, recombinant proteins, antibodies, autoimmune disease

Introduction
Autoimmune diseases are associated with loss of immunological tolerance, which is the normal ability of an individual to ignore endogenous “self” pathogens, while still reacting to “non-self” pathogens. Loss of immune tolerance leads to the immune system’s mounting a detrimental and specific immune response against self-determinants, giving rise to a spectrum of disease states. Guillain-Barré syndrome is one acute autoimmune polyneuropathy, a disorder affecting the peripheral nervous system. The clinical relevance of the ganglioside autoantibodies (gangliosides are “self”) to contribute directly to the pathogenesis of these peripheral neuropathies is well established [1]. For applied diagnostics, the detection of anti-ganglioside autoantibodies in patients is vital; usually these are the IgM autoantibody isotype and are associated with multifocal motor neuropathy and lower motor neuropathy, clinically characterized later-stage by muscle weakness and atrophy. Polyclonal antibodies of IgG type may also be detected in certain patients. Gangliosides are acidic glycosphingolipid species found in the outer layer of plasma membranes and abundant in the myelin sheath of Schwann cells of peripheral nerves. Ganglioside M1 (GM1) is the most abundant ganglioside; it has important physiological properties and affects neuronal plasticity and repair. Gangliosides are long-chain aliphatic ceramides linked to 2 or more hydrophilic sugars and 1 to 4 sialic acid residues (N-acetylneuramic acid) (Fig. 1). The surface displayed similarity with host antigens to lead to the cross-activation to 2 or more hydrophilic sugars and 1 to 4 sialic acid residues (N-acetylneuramic acid) (Fig. 1). The surface displayed structural valency which confers greater avidity.

Molecular masses of approximately 1,000 and 200 kilodalton (kD) respectively, consistent with their native structure. To characterize antibody-antigen interactions Biacore was used, a surface plasmon resonance based biosensor that determines active concentrations and characterizes molecular interactions in terms of both affinity and binding kinetics. On plate binding (strong up-slope) and off-phase release (break down slope) are shown. The recombinant IgM and IgG show dissociation constants (KD), defined as an equilibrium constant measuring propensity of the antibody to separate (dissociate) from its GM1 target, as approximately 30 nM and 1 nM, respectively. The higher KD for the IgM recombinant antibody, despite it having the identical variable binding domain as the IgG, is consistent with its higher antigenic structure which confers greater avidity.

Specificity of the antibodies for ganglioside GM1 was measured by Enzyme-linked immunosorbent assay (ELISA) using microtiter plate positive and negative samples of six related gangliosides (GM1, GD1b, GD1a, GM2, GA). The recombinant antibodies were shown to specifically bind only GM1. In the anti-ganglioside antibody kit format, ganglioside GM1 was covalently coupled to microtiter plates, incubated with patient serum and subsequently detected using secondary antibody binding followed by an enzyme label reaction. Technical issues uncovered during this project included the not expected instability of anti-GM1 IgG and difficulties in IgM purification. One separate target we originally planned was also the anti-MAG autoantibody (myelin-associated glycoprotein), remaining work uncompleted.

Figure 1: Structure of the ganglioside autoantigen GM1 present on the surface of peripheral nerve cells

Figure 2: Scheme of human antibodies of the isotype IgG and IgM

The recombinant antibodies were produced by the technology of transient gene expression in mammalian suspension CHO cell culture. The production phase lasts from 2-10 days until the proteins are ready to harvest. Recently scientists in biotechnology have started to replace traditional stainless steel bioreactors with single-use systems in order to increase process efficiency, with the advantages of avoiding tedious cleaning and re-sterilization, controlled contamination risks as well as short set-up times and installation [3].

This project used the Millipore CellReady 2.4 Liter disposable bioreactor kits.

The recombinant antibodies were characterized in vitro using the biochemical methods of capillary electrophoresis, analytical size-exclusion HPLC and target binding analysis using Biacore (Fig. 3). On size-exclusion chromatography the recombinant IgM and IgG showed relative molecular masses of approximately 1,000 and 200 kilodalton (kD) respectively, consistent with their native structure. To characterize antibody-antigen interactions Biacore was used, a surface plasmon resonance based biosensor that determines active concentrations and characterizes molecular interactions in terms of both affinity and binding kinetics. On plate binding (strong up-slope) and off-phase release (break down slope) are shown. The recombinant IgM and IgG show dissociation constants (KD), defined as an equilibrium constant measuring propensity of the antibody to separate (dissociate) from its GM1 target, as approximately 30 nM and 1 nM, respectively. The higher KD for the IgM recombinant antibody, despite it having the identical variable binding domain as the IgG, is consistent with its higher antigenic structure which confers greater avidity.

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Conclusions and Outlook
Our investigations showed that specific recombinant antibodies of IgM and IgG isotypes can be generated with GM1 autoantigen specificity. Moreover, these enabling technologies should further extend the discovery, characterization and standardization of autoantibodies for other challenging autoimmune diseases. Diagnostics for autoimmune diseases represent a fast-growing area. These diagnostics help the clinical physician in the testing of parameters relevant to the diagnoses of these disease states, for comparative or progressive diagnosis or for determining the therapeutic effectiveness of treatment or relapse.

The commercial advantages of human-similar recombinant proteins over the use of patient derived sera are manifold; the material is homogeneous, well characterized, reproducible and potentially available in unlimited supply. It is also not associated with any legal, ethical or safety issues surrounding the use of human derived material. In the future such diagnostic reagents might serve as gold standard reference materials for international quality circles and regulatory authorities [4, 5].

References
Meso scale technology: an effective tool for the development of multiplex immunoassays

Immunoassays, and especially Enzyme-linked Immunosorbent Assays (ELISA), are bioanalytical tools of proven accuracy and robustness for a variety of applications. Meso scale technology confers valuable additional features in terms of dynamic range and multiplex promising a new age of immunodetection.

Michel-Angelo Sciotti1, Elena Fernàndez2, Peter Sagelsdorff2, Daniel Gygax1
1School of Life Sciences FHNW 'Harlan Switzerland'

Keywords: Electromulinescence, immunoassay, meso scale, preclinical studies, multiplex, dynamic range

Introduction

Multiplex assays enable the simultaneous detection of several biomarkers in a unique sample. In basic research, multiplexing technologies for instance micro-arrays, are already effectively implemented. The methods target thousands of different molecules and provide impressive screening capacity generating significant amounts of investigative data. The bioanalyst, as an application scientist, pursues more practical purposes. He is indeed demanding for procedures enabling simultaneous detection of multiple targets in a single sample, but he necessarily favors accuracy over multiplicity. He might consider multiplexing only in the case that 1) the same or better accuracy than the acknowledged single marker method is achieved and 2) the application confers an objective practical advantage in terms of time or costs. Despite constant industrial and research innovation efforts in this direction, the multiplex methods of proven utility may today still be considered as a rarity in the eyes of a bioanalyst.

The meso scale technology provided by Meso Scale Discovery allows the simultaneous analysis of multiple biomarkers. The MSD system combines in a very simple and elegant manner micro-array technology and ELISA. Each well of the microtiter plate is organized like a micro-array (chess-board). Discrete areas of the well are spotted with four to ten capture antibodies. There are two architectures to run an assay. Either the biomarker captured by the antibody will further be tied to a ruthenium-chelate labeled detection antibody (sandwich assay) or unoccupied biomarker binding sites on the capture antibody are saturated with the ruthenium-chelate biomarker conjugate (competitive assay; Fig. 1b). The ruthenium-chelate label used emits light at 620 nm which is non-overlapping with the signal of the standard curves of the rat inflammation panel 1 assay (testosterone, estradiol, progesterone and DHEA), as published by the manufacturer [2]. The graph illustrates the broad dynamic range from 0.001 to 300 ng/mL marker concentration.

Results

The focus of the CTI project is not on evaluating the meso scale technology, but rather seeks to assess the technical and practical feasibility of reconfigured multiplex assays. The tailored configuration allows the analysis of a set of biomarkers dedicated to support toxicological studies of drug candidates according the client’s demand.

In the course of the CTI project, three novel multiplex assays will be developed. As an example we reconfigured the commercial steroid hormone panel 4-plex, which allows the analysis of estradiol, progesterone, testosterone and DHEA by replacing DHEA with estriol. In a first step we have screened several anti-estriol antibodies and selected an antibody which showed an optimal binding performance. Because of the low molecular mass of the biomarkers, the architecture of the assay requires a competition mode (Fig. 1b). Consequently, a conjugate of estradiol coupled to ruthenium was synthesized. Thereafter, the assay was set up and optimized by varying the concentration of involved reagents (Fig. 2). We demonstrated that the assay delivers the necessary sensitivity. The assay is specific as confirmed by the absence of cross-reactivity with the three other markers of the multiplex. Simultaneously we already developed a nephrotoxicity 6-plex in the same manner.

Extending these technical issues concerned with development, optimization and validation of a set of multiplex tox assays, the project also treats aspects of regulatory nature. Particularly the whole process of validation has to be carried out in a GLP-regulated environment. Therefore we are in the process of establishing a laboratory which conforms to GLP regulations. Collaborators involved in the project will be trained in accordance to Harlan’s quality management system. This endeavor represents an exceptional achievement for the School of Life Sciences.
De-alcoholisation of beer using membrane technology

Non-alcoholic beer is becoming more and more a lifestyle soft drink, especially if the typical “beery” flavor can be maintained during the de-alcoholisation process. Here a compact membrane device is described which allows the production of 50 hl of alcohol-free beer – with a great taste.

Wolfgang Riedli
School of Life Sciences FHNW

Keywords: De-alcoholisation, beer, membrane technology, refractometer

Introduction

The demand for non-alcoholic beer has grown steadily in recent years, which means that even small- and medium-size breweries are faced with the question of how to serve this market. Once a brewery has decided to enter the non-alcoholic market, it must find appropriate technologies that meet its specific requirements in terms of robustness, staffing and adaptability within a given space. In many cases, classical thermal treatment to remove alcohol from water is applied [1]. However Nanofiltration membrane technology could be used for this application, due to its being non-thermal and kind to aroma and taste components. During this project, a compact unit for the de-alcoholisation of up to 50 hl/day should be developed with the focus on using the best available membrane and robust process conditions [2].

Results

Nanofiltration is described as a technology which is kind to aroma compounds during de-alcoholisation of beer since no thermal treatment is required, as opposed to distillation. The specific structure of the membrane impedes passage of molecules with a greater molecular weight than 100–300 g/mol, corresponding to the weight of most of the aroma compounds responsible for the typical beer taste. Hence, only lower molecular-weight compounds such as water and alcohol can pass through the membrane to the so-called permeate side. However, when removing alcohol from beer by means of membranes, not only alcohol passes through the membrane but also water and a few beer aroma compounds. In a batch mode operation this leads to an aroma concentrate anyway, reduced in both the alcohol and water content. In order to generate an alcohol free beer, the permeate side allows the generation of information about the actual alcohol concentration in beer. This is required for the definition of stop criteria for the de-alcoholisation process.

Of the four membranes with a selectivity >1, however, only two membranes (no.s 5 and 9) had a sufficiently high flux. Hence, for the on-going design of a compact de-alcoholisation skid mounted unit, only these two membranes were used. It needs to be mentioned that with each of the membranes tested, permeates were clear and colorless, which indicates that only a small quantity of beer components enters the permeate. However the familiar ethanol smell could be found in every permeate. Comprehensive GC analysis confirmed these impressions.

The absence of color in the permeate allowed for the use of an online refractometer to measure the alcohol concentration in the permeate. In general, refractometry allows for the determination of a compound in a binary solution, whereby the deflection angle of a light beam (=refraction) serves as the direct measure of the concentration of the target component. In beer, which is a multi-component mixture of several hundred substances, this technique fails because the refractive index cannot be associated with any particular compound. Once the concentration of a membrane with a well described separation characteristic and selectivity, the installation of a refractometer on the permeate side allows the generation of information about the actual alcohol concentration in beer. This is required for the definition of stop criteria for the de-alcoholisation process.

Since the removal of alcohol from beer is the main focus of the process, a selectivity-factor greater than 1 is required, otherwise ethanol would be concentrated in the beer. Since the refractometric index of beer and permeate differ so much, it can also be used as a control mechanism for the stability of the membrane. In the event of a membrane failure, beer enters the permeate side unhindered and will be detected immediately (Fig. 2. The refractometer features a programmable turn-off function that is triggered when the inspected solution reaches certain threshold values, which is directly linked to a regulation system, the membrane unit turns itself off automatically and reverts to a safe sleep mode. Using a screened membrane for the separation of alcohol and a refractometer for online measurement and controlling, the industrial partner could plan and erect a compact skid mounted unit (see Fig. 3) which enables particularly mid-scale breweries to use an innovative technology for the generation of a market-free beer. This unit was presented to the public at the international fair “brau beveja” 2011 in Nuremberg, Germany.

Conclusion and Outlook

The joint project between a commercial enterprise and the School of Life Sciences shows that knowledge of membrane technology can be combined with robust design and functionality to generate an interesting, compact system. This skid-mounted unit saves space, is easy to operate, and requires no special knowledge to use correctly. This makes this innovative technology for removal of alcohol from beer easily accessible, especially for small- and medium-size breweries [3].

References

[2] Riedli, W. nanoparticles in membrane technology can be combined with robust design and functionality to generate an interesting, compact system. This skid-mounted unit saves space, is easy to operate, and requires no special knowledge to use correctly. This makes this innovative technology for removal of alcohol from beer easily accessible, especially for small- and medium-size breweries [3].

Research Focus Area:
Molecular Technologies (MT)

Project Team:
Wolfgang Riedli, Daniel Mallet, Gitta Schlatterbeck (Institute for Chemistry and Bioanalytics, School of Life Sciences FHNW)

Partner:
Rudolf Graf (Anlagenbau AG)

Funding:
Anlagenbau AG

Economic efficiency and benefit to society:
Nanofiltration for the de-alcoholisation of beer maintains the typical beer aroma. Due to its operation at ambient conditions it reduces both the required thermal energy and product stress and represents a true commercial alternative for breweries.
**Therapeutic Technologies (TT)**
Technologies for the development and production of pharmaceutical, biomedical products and therapeutic systems
Synthesis and study of silica nanoparticles grafted with biocompatible polymers and loaded with Indocyanine green

Hybrid nanoparticles consisting of the combination of an inorganic silica core and a biodegradable polymeric shell are used for the stable encapsulation of highly light and highly water sensitive dyes indocyanine green, allowing applications in a body fluid environment. The dye is protected by encapsulating it in the biodegradable polymeric layer, consisting of polyacrylate coated onto the surface of the silica core.

Andrea Schönbächler, Olfa Glaied, Uwe Pieles
School of Life Sciences FHNW

Biocompatible nanoparticles; Indocyanine green (ICG); block copolymer PCL-b-PLLA; grafting from.

Introduction
Indocyanine green (ICG), first reported by Fox et al. [1], has recently received considerable attention due to its widespread use for the stable encapsulation of highly light and highly water sensitive dyes indocyanine green, allowing applications in a body fluid environment. The dye is protected by encapsulating it in the biodegradable polymeric layer, consisting of polyacrylate coated onto the surface of the silica core.

Andrea Schönbächler, Olfa Glaied, Uwe Pieles
School of Life Sciences FHNW

Biomimetic nanoparticles; Indocyanine green (ICG); block copolymer PCL-b-PLLA; grafting from.

Results

In order to determine the ICG loading content and entrapment efficiency, the amount of ICG encapsulated into the PCL shell was determined indirectly from the unincorporated ICG inside the body and to stabilize the dye and furthermore to decompose ICG, is quenched by the polymer, circumventing the physiochemical properties of the dye and enables their use for a variety of in vivo imaging applications and novel minimally invasive surgery methods (rinless tissue soldering).

Conclusion and Outlook

The approach to synthesizing ICG loaded NPs presented in this abstract demonstrates a new route to stabilizing ICG by embedding the dye in a hydrophobic biocompatible matrix. In order to increase the colloidal stability of an aqueous environment as required for in vivo applications, the surface of the particles was modified with PLLA. A maximum ICG loading content of 2.36 % of the overall mass was obtained by following this synthetic route. Moreover, the ICG in the NPs exhibits excellent stability against aqueous decomposition. During a period of 14 days no significant change in fluorescence intensity was observed. We therefore conclude that, although the ICG was extremely tightly packed in the NPs, there is no significant self-quenching of the dye. Most probably the singlet oxygen, produced by possible photosensitization of indocyanine green, is effectively absorbed by the polymer, thus inhibiting further decomposition of ICG.

The silica core has been chosen in first instance to obtain particles in a uniform and controllable size range. In a later stage of the project the synthesis of poly(ε-caprolactone) containing biocompatible embedded dye and other core matrix materials is foreseen.

References:

Research Focus Area: Therapeutic Technologies (TT)

Project Team:
Andrea Schönbächler, Olfa Glaied, Uwe Pieles (Institute of Chemistry and Bioanalytics, School of Life Sciences FHNW)

Partner:
M. Frasn (Department of Biomedical Photonics, University of Bern), M. Roenert (Department of Neurosurgery, Bern University Hospital), M. Weisser (Institute of Veterinary Pharmacology & Toxicology, University of Bern), J. Hoyley (Department of Pharmaceutical Sciences, University of Basel)

Funding:
Swiss National Science Foundation (SNSF) within the National Research Programme SNSF 64 “Opportunities and Risks of Nanomaterials”

Economic efficiency and benefit to society:
We report in the design and synthesis of highly stable silica core polymer shell NPs acting as a carrier system for the light and highly water sensitive dyes ICG. Encapsulation of ICG in the hydrophobic polymer shell circumvents the physicochemical properties of the dye and enables their use for a variety of in vivo imaging applications and novel minimally invasive surgery methods (rinless tissue soldering).

Figure 1: Anionic coordinated ICP of ICG from the amino activated silica surface and LLA from the GCLC of PCL-SiPCC-LLA-ICG

Figure 2: Influence of temperature on aqueous stability of Si@PCL-l-PLLA/ICG

Figure 3: Influence of temperature on aqueous stability of Si@PCL-l-PLLA/ICG: ICG (stored lyophilised) over a period of 14 days. Bars represent the standard deviations (n=3). Fluorescence intensity indicated as % remaining 14 days at a) RT and b) 37°C.
Active load control bedding system for an operating table in hospital environment

Suffering from decubitus ulcers, also known as bedsores, leads to long term treatment of the affected region and contributes significantly to health care expenditure. Acquiring a decubitus ulcer during a hospital stay is often related to time consuming surgical procedures. Therefore a new approach towards an active load controlled bedding system for operating rooms is being investigated.

David Hradetzky, Stephan Böhringer, Matthias Jeker,
School of Life Sciences FHNW

Keywords: Decubitus ulcer, prophylaxes, prevention, active bedding, operating table

Introduction
Decubitus ulcer, known as a bedsore or pressure ulcer, is often induced by an increased external local load or pressure on tissue. This results in squeezing the tissue towards underlying bones and decreasing or disabling peripheral circulation and perfusion. Typically tissue not protected by muscles or fatty tissue is affected. Therefore anatomically exposed bony regions of the human body such as the sacrum, ischium and calcaneus are subject to an increased risk of developing a decubitus ulcer. In addition to the applied mechanical load the duration of exposure of the load increases the risk of developing a decubitus ulcer [1]. Therefore bedridden persons with limited mobility opportunities are particularly affected. This risky situation is reflected in different scenarios, where prolonged periods of lying down without repositioning the body occur, for instance in home care or intensive care.

Besides the impact on the life of individuals, a decubitus ulcer is also a significant clinical and financial issue for health care providers. A decubitus ulcer may cause a longer hospital stay. The German Robert Koch Institute estimates a financial burden of around 2 billion Euros in 2002 in Germany for the health care system [2], while other experts estimate annual costs for UK from 1.4 to 2.1 billion GBP corresponding to 4% of the total National Health Service (NHS) expenditure [3].

Besides the home care or intensive care scenario as a risky situation, the operating room (OR) is getting more and more attention. This environment may increase the risk of a pressure ulcer, as patients are kept immobile for long periods of time. Due to anaesthesia procedures, patients are unable to shift their weight, feel pain or complain. Enhanced anaesthetic procedures enable surgeons to perform complex and delicate procedures, resulting in an increased risk of developing a decubitus ulcer [5].

Nowadays strategies to decrease this risk in an operating room environment are limited to reducing the load by optimising mat materials and pressure distribution surfaces. So far no active or controlled load regulating system is known. Within this project we investigated a novel approach for an active support system, capable of reducing local pressure on tissue by an active load controlled bedding system.

Results
The approach to a smart decubitus prophylaxis system integrates into an operating table focuses on detecting the load applied from patient to the OR-table and releasing overloaded regions by lowering the height within this region. Therefore an array-like structure of single elements containing load detection and a mechanism for changing height were developed and a demonstrator built.

Each single element contains a sensor (force sensing resistor), detecting the force applied to that area. It is located at the top of the element and is covered by a force distribution plate to ensure homogenous load distribution on the sensing element. The mechanics of each element is based on two rollers, driven by a worm gear, approaching or moving away from each other. The rollers create a height change of a surface with a tilted sub-structure, as shown in Figure 1 (top). The gearing is designed to be self-blocking, only during the height adjustment an external power source required. For the demonstrator the mechanics of each element, including the gearing, was generated by rapid prototyping. Multiple elements are arranged in an array structure (Fig. 1), a modular rack suitable to replace single modules of the commercial OR-table (Fig. 2).

The results of a closed loop active load control of a single element which ignore the history of the element are shown in Figure 3, where repetitive application indicated by blue arrows and removal (indicated by green arrows) of a load are shown. As soon as the load exceeds the threshold value the height changing element is lowered until the applied force drops below a second threshold value. By removing the load completely, the element will rise to its initial position.

Various approaches to control the height are currently under investigation. Based on up-to-date and providing data from the elements, including neighbouring elements, the OR-personnel will receive a recommendation to shift the height of single or multiple elements on a display if a recommended threshold value is exceeded. The decision to change patient positioning has to be verified and approved by OR-personnel. If the change is accepted, an electric motor will lower the affected element and/or raise the neighbouring ones by up to two centimetres until the applied load decreases to a predefined acceptance level.

Conclusion and Outlook
A demonstrator proving the feasibility of the linear stage concept was created and integrated into a commercial OR-table in our demo lab. Within this feasibility study, we set up an active load control module as a demonstrator for a decubitus prophylaxis during surgical procedures. As the current demonstrator is not manufactured in a final way, the mechanical properties do not meet the requirements yet. Nonetheless the basic concept was successfully verified.

The element foot print, will be addressed in more detail, requiring a complete active bedding system. Only single elements have been evaluated. New strategies of control are being developed this distribution module as a demonstrator for a decubitus prophylaxis during surgical procedures. As the current demonstrator is not manufactured in a final way, the mechanical properties do not meet the requirements yet. Nonetheless the basic concept was successfully verified. The element footprint, will be addressed in more detail, requiring a complete active bedding system. Only single elements have been evaluated. New strategies of control are being developed this distribution module as a demonstrator for a decubitus prophylaxis during surgical procedures. As the current demonstrator is not manufactured in a final way, the mechanical properties do not meet the requirements yet. Nonetheless the basic concept was successfully verified.

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Medical imaging: A robust and accurate segmentation of the knee bones from computer tomography data

Medical Imaging plays a central role in the cost-effective use of patient-specific tools in surgical technique. The production of cutting blocks – for knee-joint implant positioning – requires a precise segmentation of femur and tibia from preoperatively acquired image data. Due to low bone density and osteophytes, this segmentation is done manually by experts and requires several hours. Here a novel, robust and accurate segmentation method for a medical planning system is described.

Alex Ringenbach
School of Life Sciences FHNW

Keywords: CT Data, Knee Bones, Segmentation, Statistical Shape Model, Fast Marching

Introduction
For the accurate implant positioning of a knee-joint replacement, it is increasingly common to use custom-made cutting blocks (Fig. 1, left), which indicate the cutting plane to the surgeon. The advantage of this method over conventional surgical techniques is the simpler alignment of the implants, a shorter operation time as well as fewer instruments [1].

The specific geometric information for the cutting blocks has to be taken from preoperatively acquired image data, this is a key aspect of medical imaging and is called segmentation. Due to low bone density and osteophytes (Fig. 1, right) the automated segmentation of knee bones from computer tomography (CT) data can be a major challenge. Osteophytes are an overgrowth of bone tissue, especially in older people, they are filigree and can hardly be captured by prior knowledge based segmentation approaches.

As part of an industrial project, we have developed a hybrid segmentation method - essentially based on statistical shape models and the Fast Marching algorithm, which is stable and has good accuracy.

Method
Our approach to the knee joint segmentation consists essentially of two steps: first, a robust pre-segmentation is performed (a knowledge based approach with a statistical shape model) to identify and separate the bones. This is followed by a sensitive fine-segmentation (a locally data-driven approach with non-local control parameters) in a narrow band around the pre-segmented boundary to detect the local nuances and osteophytes on the bones as accurately as possible.

With the statistical shape model (Fig. 2) we capture the prior knowledge of the shape variability of knee bones. For that we used 30 CT data sets and computed (for femur, tibia und patella) the average models and their shape variations [2] [3].

In a first step the statistical shape model was registered with the image data (Fig. 3, left) by matching the average models with the image to get an initial position and then by adapting the first five shape variations iteratively [2].

Due to the limited statistical data and the presence of osteophytes, which are not captured by the statistical model, the automated pre-segmentation leads to a mean deviation error of 2.2 mm – compared to manual segmented data.

In a second step, the bones were approached from the outside in a narrow band with the front-propagation Fast Marching method [4] (Fig. 3, right). This algorithm describes a monotonically increasing propagation front, defined by the initial position and by the speed function $\phi(x)$, which represents the image data.

This view of Fast Marching – as an initial value problem – shows the similarity to the region growing algorithm and emphasizes the locally sensitive acting mechanism, which is needed for the detection of filigree structures. On the other hand, the Fast-Marching method (in the boundary value problem representation) solves the Eikonal equation of optics, which determines the minimal optical distance [5]. This explains that the Fast Marching method determines – by using an edge controlled speed function – an edge-weighted distance to all propagation points. And this is the advantage of the Fast Marching method – compared e.g. to the region growing approach – it provides an additional non-local parameter to control the local acting segmentation process, within the narrow band. So, also weak edges can be well captured. With this fine-segmentation step the mean deviation error is reduced to 0.3 mm – compared to manual segmented data.

Results
A hybrid segmentation method was developed for knee bones from CT data which is stable and has good accuracy. The model-based approach guarantees robust detection and separation of femur, tibia and patella for all CT images, and the local acting front propagation method Fast Marching improves accuracy for most CT images to a mean deviation error of 0.3 mm. The implementation of the algorithm in a planning tool for designing cutting blocks has reduced the processing time for the whole workflow from 90 or more minutes to less than 10 minutes. It has already been successfully used more than three thousand times.

Conclusion and Outlook
Advanced image segmentation methods are mainly based on global optimization, and therefore robust but not always accurate enough. With the Fast Marching algorithm a locally post segmentation is realizable without losing the benefits of the global approaches. In a next step the planning system will be expanded for MRI images.

References:

Research Focus Area:
Therapeutic Technologies (TT)
Project Team
Alex Ringenbach, Roman Ramsayer, Erik Schkommodau (Institute for Medical and Analytical Technologies, School of Life Sciences FHNW)
Partner
Tobias Schwäglik, Jan Stifler/Medivation AG
Funding
Föderalins Aargau, canton Aargau
Economic efficiency and benefit to society
The implementation of our algorithm in a planning tool for cutting blocks has reduced the manually processing time (over the whole workflow, for trained staff) from 90 or more minutes to less than 10 minutes.
Acceleration Measurement for objective symptom evaluation during Deep Brain Stimulation surgery

Deep Brain Stimulation (DBS) is a common neurosurgical procedure for relieving movement-related disorders such as Parkinson’s disease. However, an incomplete understanding of the mechanism of action and suboptimal exploitation of intraoperative data, target selection is not yet optimal. Our aim is to evaluate the feasibility of objectively assessing the clinical effect during intraoperative stimulation tests using acceleration measurements.

Ashesh Shah, Erik Schülermodau, Simone Hemm-Ode
School of Life Sciences FHNW

Keywords: Deep Brain Stimulation, Parkinson’s Disease, movement related disorders, acceleration measurements

Introduction

Deep brain stimulation (DBS), the electrical stimulation of structures deep within the brain through surgically implanted electrodes, is now an effective and widely-used method of treating movement related disorders (Parkinson and rigidity) such as Parkinson’s Disease (PD) [1]. During a typical surgical procedure, a thin probe is stereotactically inserted along a preoperatively calculated trajectory, which has been determined on the basis of magnetic resonance imaging (MRI) and computed tomography (CT).

As the action mechanism of DBS is not fully understood, optimal target definition is difficult and thus most groups use complementary intraoperative methods. In addition to the preoperatively obtained anatomical data, further information about the structures along the electrode trajectory is acquired. For example, by using microelectrode recording (MER), neuronal activity deep in the brain can be recorded [2] which is analysed regarding the discharge pattern. When MER is performed, recordings are made along up to five trajectories in the volume of interest. This is to identify the boundaries of the different structures, in general starting up 10mm in front of the target and going down in 0.5 to 2mm steps until the target is reached or even 1 to 5 mm beyond it. Most centres also perform intraoperative stimulation along the trajectories to evaluate the clinical effects on rigidity and tremor at increasing stimulation voltages, determining the thresholds for clinical effects (subjective threshold) and side effects at each anatomical measurement point. The final surgical target in which the chronic stimulation electrode is implanted afterwards is chosen by the neurosurgeon by mentally integrating the multitude of patient information collected before surgery. As DBS has many advantages over other surgical treatments of movement disorders, but there are a few uncertainties associated with it as well [3]. The targeting procedure is the part of the surgical protocol that can still be improved from an engineering point of view [4]. Existing data can be acquired more objectively than is done today, for example with the aid of quantitative movement analysis via sensors. As the data interpretation for target selection is based on all of the obtained measurements, it would be desirable to optimise data presentation and visualisation. These are the main aims of the current research project. The basic idea is to assess the patients’ symptoms objectively and help the doctors visualise them along the planned trajectory on the MRI/CT images. Clinical studies in Basel and Clermont-Ferrand (France), including 30 patients, have been approved by the local ethics committees. The objective assessment is achieved by measuring the acceleration of the wrist of the patient (for tremor analysis) and neurologist (for rigidity analysis) before, during and after the DBS surgery. An accelerometer, (device measuring acceleration) placed inside an in-house developed plastic case, is tied to the patient’s/neurologist’s wrist (Fig. 1) and connected to a laptop which uses a house developed application to record data and display it in graphical form. Data from the accelerometer is recorded without any stimulation (i.e. baseline), during the MER recording and the test stimulation.

Results

A protocol was established where accelerometer data is continuously recorded at every stimulation position on all the trajectories to evaluate the clinical effects on rigidity and tremor (Fig. 2). The data recorded during the surgery is post-operatively grouped according to the stimulation amplitude and statistical features (standard deviation, energy, entropy) are extracted from it (Fig. 2A). The values of those features before the subjective threshold were statistically compared to the ones at the subjective threshold. So far, in most cases results confirmed the presence of significant clinical changes. For tremor, a statistically significant change (p<0.01) was found for signal entropy, energy and standard deviation. For rigidity, a statistically significant change (p<0.01) was found for signal energy and entropy.

In a second step, the calculated features are then normalized to the baseline values and used to identify an accelerometer threshold (amplitude at which accelerometer data alone would have been different based on accelerometer data than on the subjective evaluation due to a higher difference between clinical and side effect thresholds).

Conclusion and Outlook

The initial results from this project have demonstrated the feasibility of performing objective assessments using mathematical features (signal energy, entropy and standard deviation) extracted from the acceleration signal of the patient’s or the neurologist’s wrist. New statistical features based on frequency analysis are being considered and continuous changes are being made to the software and hardware to improve data acquisition and visualization. The possibility to visualize the planned trajectory with the effects and side effects on the images is already implemented. Real-time analysis of the accelerometer data and its visualization along with other intra-operative data, have been planned for future updates of the software. The introduction of these technologies in the OR will probably result in greater objectivity of the surgeon’s decision on the final target and trajectory compared to the current method. The measurements will allow further individualisation of functional parameters and might increase electrode positioning quality as well as the safety of the target identification procedure. This has to be confirmed after the inclusion of all 30 patients. In addition to the practical aspects these measurements and their correlation with clinical evaluations and MER data might generate new information and knowledge useful for the development of the human connectome and its correlation to the functional connectivity of the human brain.

References:


School of Life Sciences

Figure 1 Accelerometer tied to the patient’s wrist for evaluation of tremor.

Figure 2 Accelerometer data and stimulation amplitude against time.

Figure 3 Comparison of different thresholds and of the final implant site based on accelerometer data and subjective clinical evaluations.

Research Focus Area:
Therapeutic Technologies (TT)

Project Team: Ashesh Shah, Gregor Ibhoend, Erik Schülermodau, Simone Hemm-Ode

Funding:
Swiss National Science Foundation (SNSF), Germaine de Stael foundation

Partner:
Le Centre Hospitalier Universitaire de Clermont-Ferrand (CHU de Clermont-Ferrand, France), Research Group on Image-Guided Clinical Neurosciences and Connectomics (IA 7922, IGCC, Université d’Auvergne, Clermont-Ferrand, France), University Hospital Basel.

Economic efficiency and benefit to society:
Objective assessment of symptoms during Deep Brain Stimulation surgery and better visualization of intra-operative data will allow doctors to more accurately define patient-specific targets for treatment of movement related disorders, hopefully resulting in better clinical results. Furthermore new knowledge about the mechanism of action of the stimulation may be created.
Supporting Strategic Planning with Interactive Visualization: A Case Study of Patient Flow Through a Large Hospital

Hospitals routinely collect large amounts of data that can be used to improve administrative processes, in addition to their primary clinical purpose. Strategic infrastructure planning, for instance, can be supported by the analysis of enriched data relating to patient flow through a hospital. Using our dedicated visual analysis software, analysts were able to identify several sub-systems of clinics that will play a central role on the future hospital campus.

Dominique Brodbeck, Markus Degen
School of Life Sciences FHNW

Keywords: clinical informatics, interactive visualization, visual data analysis, patient flow, hospital planning

Introduction
Hospital sites develop in an evolutionary manner over a long period. This usually leads to physical and organizational lay-outs of the facilities that are no longer optimal after a certain time. Strategic planning with time horizons of 25 years and more provides the opportunity to correct this degeneration and optimize the layout when the campus is enlarged, new facilities are built, or old ones replaced.

The optimal configuration of departments, their organizational units and technical facilities is not always evident. Questions such as “where should the emergency department be placed, and if we locate it in a new building, do we need an additional radiology facility?” should be answered based on evidence and insights rather than intuition, subjective opinions, or obsolete experience [1]. The idea therefore was to use past real data to identify existing clusters of organizational units that are related based on what they actually do, and not on where they are placed in the organization chart. With these insights, it should be possible to define future sub-systems of organizational units and medical functions which are optimized for efficiency. These new sub-systems can then be characterized again with the past data for further analysis and communication to stakeholders.

We present a case study where we collected, combined and enriched data from a large university hospital, and used interactive visualization to access, analyze, and interpret the data to support strategic infrastructure planning.

Results
In our project, information from several sources of the hospital’s IT-infrastructure was used and linked. We collected one full year of data from 40 clinics comprising 300 organizational units that treated 40,000 cases from 30,000 in-patients, with 320,000 transfers between the organizational units.

With all the data integrated and available, the next challenge was to render it usable for the planning experts. For the type of problems found in our case study, analysts often only have vague notions of what they are looking for (“I know it when I see it”). It is therefore crucial to make the data visible from various angles, and to provide highly interactive tools to identify interesting patterns and access details in context. We developed a visual analysis application to support analysts in making sense of the collected data. The application offers four principal views (Fig. 1):

- Organizational (Fig. 1, top left): Shows the organizational structure and how the actual medical activities shape the administrative space. A circular layout is used to arrange all the major clinics of the hospital. Circular layouts have proven effective to show genetic sequences and relationships between genomic positions [2]. We adapted this technique to show the flow of patients in relation to the organizational structure of the hospital.

- Systemic (Fig. 1, center): Reveals the operational structure as it emerges from patients flowing through the hospital. The movement of patients between clinics effectively creates a network of relationships, where clinics that move more patients between them are closer, or more similar, than clinics with fewer or no transfers. To make this network visible, we employ a multidimensional scaling algorithm [3].

- Topographical (Fig. 1, top right): Shows the actual physical situation as a structure that evolved through many individual decisions. The topographical view shows the patient transfers on a geographical representation of the current hospital campus.

- Chronological (Fig. 1, bottom): Adds the dynamic view on how events and quantities change over time. The in- and out-transfers for each day are shown as a mirrored stacked bar chart. The mirroring makes it easy to spot imbalances between in- and out-flows. The net flow for each day is cumulated and over-plotted as a black line. This essentially shows the number of patients that are present in a clinic on a particular day.

In order to rationalize and interpret the insights and hypotheses generated by the four principal views, it is necessary to drill-down to the level of individual cases. Cases can be filtered either by the organizational units that they have visited on their journey through the hospital, or by various categorical or numerical case attributes (e.g., destination after discharge, diagnosis, length of stay). In a separate view, we show all the filtered cases at the same time. In order to display several hundred case histories in parallel, their representation is condensed to a single line that is only one pixel high, but still preserves the essential information about the case history (Fig. 2).

Conclusion and Outlook
Our analysis with this application allowed us to gain an overview of the big picture of the hospital system. By making the flow of patients visible, we were able to contrast the hierarchical organizational structure with the actual implemented working relationships. This showed the difference between the operational structures that developed through medical consequences, and the theoretically defined organizational structure. Based on this difference, we were able to describe new sub-systems and identify an organizational form that corresponds to the current actual needs.

It was not really a surprise that the core functions of a hospital such as emergency department, operating rooms, and diagnostic functions appeared in the center of the system, but it was not expected to be so pronounced. A new insight was the role of the cardiology clinic as an important service center for diagnostics. This led to the decision to also assign it a central role on the campus. Also new was the interpretation of the role of the clinic for internal medicine as being primarily a receiving station for the emergency room, with the further distribution into the specialized clinics taking place only one or two days later.

In summary, our case study has shown that there is a wealth of interesting information in the data that is collected in large hospitals, beyond their immediate and intended use. We took a different view of electronic health records to support strategic infrastructure planning.

References:

Research Focus Area:
Therapeutic Technologies (TT)

Project Team:
Dominique Brodbeck, Markus Degen Institute for Medical and Analytical Technologies, School of Life Sciences FHNW, Andreas Walter (Bern University Hospital)

Partner
Bern University Hospital

Funding
Bern University Hospital

Economic efficiency and benefit to society
This project saves a great deal of money and improves well-being.
The Interplay of NiTi shape memory alloys and human Bone Marrow-Derived Mesenchymal Stromal Cells

NiTi shape memory alloys (SMA) have unique mechanical and physicochemical properties that are attractive for a wide variety of biomedical applications. With the ultimate goal of fabricating complex 3D NiTi implants for orthopedic and dental applications, we assessed the biocompatibility, proliferation and osteogenic differentiation of human bone marrow-derived mesenchymal stromal cells (hBMSC) cultured on additive manufactured (AM) NiTi disks.

Waldemar Hoffmann1, Theresa Bormann1, Falko Schlottig2, Matthias Mertmann1, Ralf Schumacher1, Uwe Pieles1, Erik Schkommodau1, Bert Müller2, David Wendt3, Ivan Martin4, Michael de Wild4
1School of Life Sciences FHNW, 2Thommen Medical AG, 3SAES Memry AG, 4University of Basel, 5University Hospital Basel

Keywords: differentiation, stem cells, additive manufacturing, implant development, NiTi shape memory alloy (SMA)

Introduction
Selective laser melting (SLM) is an additive manufacturing (AM) process, which enables the CAD-designed complex-shaped and highly porous 3D structures [1]. Using this AM technique, NiTi-SMA based constructs are produced [2-3]. NiTi-SMA exhibit unique mechanical and physicochemical properties that could benefit a wide variety of biomedical applications [4]. Ultimately, we aim to fabricate and validate complex-shaped 3D NiTi constructs as implants for orthopedic and dental applications. Therefore SLM-fabricated NiTi disks (Ø 14 mm) were used as substrates for human Bone Marrow-Derived Mesenchymal Stromal Cells cultures. Cell cultures were performed in order to assess biocompatibility of substrates used as well as the proliferation and differentiation capacity of hBMSC on those substrates. Besides NiTi, passivated NiTi-pNiTi, SLM-Ti (Ti), sand-blasted and acid etched SLM-Ti (Ti-SLA) and commercially produced and clinically used SLA-Ti (Ti ref) [5] were used as substrates and compared to TCP (tissue culture plastic [6]).

Results
The substrate morphology was assessed by scanning electron microscope (SEM) imaging and is depicted in figure 1, revealing the surface topography of all substrates tested. The native surfaces of NiTi and Ti, both produced by SLM, are solidified casts with incorporated spherical particles, being sintered powder residues. These attached particles give the native surface a characteristic morphology [7]. Ti-SLA and the clinically proven Ti ref are equivalent surfaces with a very rough surface both on the micro and nano scale. The difference between both titanium materials is the production process of the starting material, the former was produced generatively, whereas the latter was made conventionally. The pNiTi surface is free of spherical particles due to the etching process and exhibits micro scale structures (moon-like landscape). All substrates tested were found to be biocompatible according to ISO 10993-5 [8]. 80% of seeded hBMSC attached to the surfaces tested within 12 hours and thereafter proliferated exponentially, with similar growth rates as on TCP. NiTi-SLA cultured on metallic substrates exhibit growth rates of 0.133 ± 0.026 1/d comparable to the growth rate obtained on TCP (0.128 ± 0.020 1/d), with the maximal growth rate obtained on NiTi, whereas the minimal growth rate was obtained on Ti-SLA.

As illustrated in figure 2, cell morphologies of hBMSC cultured in culture medium (CM) or osteogenesis inducing medium (OM) for 21 days are similar within the groups, elaborating a dense extracellular matrix (ECM) layer beneath the cell layer with randomly oriented cells in CM versus a directed cell orientation in OM. In both media conditions cells cultured on SLM-based, untreated substrates (NiTi, Ti) are more sprout as compared to spindel-shaped cells on post treated substrates. hBMSC produced a dense layer of ECM on the metallic substrates and covered the ECM in multiple layers, as revealed by confocal fluorescence (data not shown).

In order to assess osteogenic differentiation capacity of hBMSC cultured on metallic substrates, cells were cultured either for 14 or 21 days in OM and both gene expression for BSP by quantitative real-time PCR and matrix mineralization by alizarin red staining were examined. Bone sialoprotein (BSP) is a component of mineralized tissues such as bone and calcified cartilage. It is a significant component of the bone extracellular matrix. Gene expression measurements of BSP revealed an up-regulation for cultures in OM as compared to CM on all substrates (Fig. 3). Nevertheless, in CM conditions hBMSC cultures on NiTi express the smallest amount of BSP, almost at the level of post expanded cells (dotted line). Additionally, alizarin red staining revealed high ECM mineralization during 21 days of culture in OM although the donor used does not exhibit a high intrinsic matrix mineralization capability (TCP versus metallic substrates). In CM the matrix mineralization occurs as well but to a lesser extent.

Conclusion and Outlook
The growth rates of hBMSC on metallic substrates are equivalent to growth rates on TCP indicating high biocompatibility and good hBMSC proliferation capacities. SEM and confocal fluorescence imaging identify hBMSC on top of a dense CM layer on all substrates tested.

Considering the up-regulation of BSP expression and the highly positive alizarin red staining in OM, the permissibility of all substrates tested to osteogenic differentiation is given. At the same time NiTi seems to facilitate maintenance of the progenitor fate in CM, suggesting a binary effect depending on the biological signals available. Summarizing these results, SLM-Ti is a promising material for the design of customized load-bearing implants. Currently, further studies are being carried out to analyze hBMSC performance in terms of proliferation and differentiation capacity of hBMSC cultured for 21 days.

References:

Research Area Focus: Therapeutic Technologies (TT)
Project Team: Therese Bormann, Waldemar Hoffmann, Uwe Pieles, Erik Schkommodau, Ralf Schumacher, Michael de Wild (Institute for Medical and Analytical Sciences Northwestern Switzerland, the University of Basel and the University Hospital Basel). Funding: Swiss National Science Foundation (SNSF) and Commission for Technological and Innovation (ITI) within the National Research Programme NFP 62 “Smart Materials”.

Economic efficiency and benefit to society: The interdisciplinary collaboration between the University of Applied Sciences Northwestern Switzerland, the University of Basel and the University Hospital Basel is developing additive manufactured shape memory scaffolds for the generation of biomedical engineered bone implants. These smart implants with shape memory properties and specific surface topography open new perspectives of biofunctionalization.

Figure 1: SEM images of metallic substrates. Upper panel depicts surface morphology of untreated samples. Lower panel depicts surfaces post associated treatments.

Figure 2: SEM images of hBMSC cultured on metallic substrates in culture medium (CM) and osteogenesis inducing medium (OM).

Figure 3: a) gene expression level normalized to GAPDH (dotted line) + post expansion expression level post 14 days of culture, B alizarin red staining of hBMSC cultured for 21 days.
Size Reduction of Liposomes with a novel Type of Stirred Bead Mill (Nanomill)

The potential of liposomes as carriers for drug delivery and drug targeting has frequently been reported but the production of liposomal formulations on an industrial scale remains a challenge. Consequently a novel nano-milling unit has been developed and investigated. The new nanomill fulfills the GMP standards of the pharmaceutical industry and remains entirely closed also when cleaned, sterilised and prepared for another batch.

Martin Studer, Berndt Joost
School of Life Sciences FHNW

Introduction

Over the last years the application of liposomes in the pharmaceutical, cosmetics and food industries has elicited novel breakthroughs and products [1]. e.g. the encapsulation of enzyme active enzymes in liposomes [2], skin care preparations for the treatment of dry skin [3] and different drug delivery systems [4]. Clinical applications in the field of drug delivery and passive targeting of solid tumors have demonstrated their potential for pharmaceutical applications. Therefore, the production of liposomal formulations on an industrial scale remains a challenge. Ideally, an industrial production scheme should be versatile, simple, robust and cost-effective. Up to now, the large scale production of liposomes with a definite size requires high pressures and high shear rates; this entails the disadvantage of generating mechanical and thermal stress at the same time.

This research project had two major targets: The development of a novel type of nanomill dedicated to the production of liposomes and the determination of the influence of the main operating parameters necessary to form liposomes. Therefore, multi-lamellar large vesicles were stressed in the milling chamber. The remaining volume in the milling chamber is filled with a suspension of the product to be ground, in which the large scale production of liposomes with a definite size requires high pressures and high shear rates; this entails the disadvantage of generating mechanical and thermal stress at the same time.

The results of the experiments were conducted in circular mode with yttrium accelerators which generate a reverse flow inside the process chamber divided by the stressed product mass. Consequently, the size of the liposomes can be controlled by the specific energy input. This energy input is affected by the grinding beads and the filling ratio of grinding beads [4].

The specific energy $E_{sp}$, understood as an integral parameter, describes the influence of different operating parameters. It can also be defined as the product of stress energy provided by the grinding beads ($SE_{GB}$) and the number of stress events ($SNr$) [4].

In order to obtain the optimal set of operating parameters in case of nano-milling of inorganic materials the optimum stress energy has to be determined first: The question is how much energy must be exchanged at each milling event inside the mill, fig. 3. The nano-milling of poorly water soluble drug substances. The novel nanomill was developed, built and presented at the ACHHEMA 2012.

The pro-liposome solution with a concentration of 10 mmol/l was produced by thin lipid film hydration. First –60 % phosphatidylcholine (PC) from egg yolk and 95 % cholesterol were dissolved in a mixture of chloroform and methanol in a 2:1 ratio. The solvent was removed by evaporation under vacuum at 50°C. A thin lipid film remained on the side of the round-bottomed flask, which was then hydrated with an adequate amount of phosphate buffered saline (PBS, pH 7.4) at 50°C. The particle size of the liposomes was analyzed by dynamic light scattering using a Zetasizer Nano ZS.

The newly stressed bead mill allows gentle stressing of the liposomes under controlled conditions. The size of liposomes produced correlates directly to the specific energy brought into the liposome suspension, which is the energy input into the milling chamber divided by the stressed product mass. Consequently, the size of the liposomes can be controlled by the specific energy input. This energy input is affected by the stirring speed, the geometry of the stirrer, the grinding beads and the filling ratio of grinding beads [4].

The new stirred bead mill allows gentle stressing of the liposomes under controlled conditions. The size of liposomes produced correlates directly to the specific energy brought into the liposome suspension, which is the energy input into the milling chamber divided by the stressed product mass. Consequently, the size of the liposomes can be controlled by the specific energy input. This energy input is affected by the stirring speed, the geometry of the stirrer, the grinding beads and the filling ratio of grinding beads [4].

The present study aims to test the hypothesis that different milling conditions yield liposomes with different sizes which can be used as drug delivery systems.

Figure 1: New reverse flow milling chamber

Figure 2: Prototype of nano-milling unit

Figure 3: Comparison of liposome size reduction result vs. reduced stress number $SNr$

References:

Project Team:
Martin Studer, Berndt Joost (Institute for Pharma Technology, School of Life Sciences FHNW)
Willy A. Bachofen AG Maschinenfabrik

Funding:
Co-financed by Commission for Technology and Innovation (CTI)

Economic efficiency and benefit to society:
The novel nanomill fulfills the high GMP standards of the pharmaceutical industry and is ready for SIP/CIP as this unit remains closed for filling, bead and product emptying, or cleaning. This new milling unit allows fast batch changes and short cycle times so that production can be more efficient and cost-effective.
Ultrasound-Based Process Analytical Tools for Homoge- 
\textit{nization of Nanoparticulate Pharmaceutical Dispersions}

Process analytics is an important part of designing quality into pharmaceutical products. This project evaluates ultra-
sonic-based process analytical tools (PAT) in a homogenization process of nanoparticulate systems that are intended 
for oral administration.

Martin Kuentz
School of Life Sciences FHNW

Keywords: Ultrasound, resonator technology, manufacturing, process analytics, pharmaceutical dispersions

Introduction
These days the pharmaceutical industry attempts to design 
quality into their products rather than relying only on final 
end-product testing. This concept of “Quality by Design” 
was coined by the Food and Drug Administration (FDA) and 
should be implemented in pharmaceutical product develop-
ment. A first step for pharmaceutical companies is to iden-
tify which material and process factors are critical to the 
relevant quality attributes. Such critical material/process 
variables should then be monitored. However this requires 
adequate process analytical technology (PAT). Much research 
has been dedicated to PAT and as a result of these efforts, 
several new PAT technology have been successfully ap-
plied in pharmacutes. The use of such techniques in deve-
lopment mainly targets better process understanding. On 
the other hand, PAT in production aims to reduce manufac-
turing failures and can help to cope with the variability of 
raw materials whilst still obtaining final product quality 
that is reproducible. While the majority of process analytical 
technology (PAT) focused on solid dosage forms or biophar-
aceuticals, there was only limited work dedicated to stu-
dying pharmaceutical dispersions. Spectroscopic tools such 
as dispersive Raman sensors were used, as well as different 
techniques for particle characterization, e.g. the focused 
beam reflectance measurement. These tools may be used for 
diluted suspensions or emulsions but process analytics in 
turbid or concentrated dispersions remains a challenge. It 
was Medendorp et al. [1] who pioneered using acoustic reso-
nance spectroscopy as a PAT tool in semisolids formulations.
We were interested in a similar technique called ultraso-
nic resonator technology (URT). One of our projects employed 
this ultrasound technique to monitor drug concentrations 
in self-emulsifying drug delivery systems [2].

For the current project, we focused on the mixing of pharma-
ceutical solids and liquids to manufacture dispersions under 
high shear in a vacuum. For the initial feasibility study we 
first selected pharmaceutical nanosuspensions. Another aim 
of this project was to evaluate combinations of process ana-
lyzers. Since ultrasound analysis is very sensitive to density 
changes, we aimed to combine ultrasound measurement with 
a flow-through Coriolis force sensor.

Results
A series of suspension vehicles were investigated using ul-
tasonic resonator technology (URT). For the initial feasibil-
ity study, the samples (170 µL) were removed from the process 
stream, which is called at-line sampling. Fig. 1 shows how 
samples were collected from different positions within the 
mixing and homogenization vessel (Mi-Molto, Krieger AG).

We measured the ultrasound velocity relative to a reference 
change. We aimed to combine ultrasound measurement with 
a flow-through Coriolis force sensor.

Conclusion and Outlook
The feasibility study indicated the usefulness of ultraso-
nic resonator technology as a PAT tool for pharmaceutical dispersions. First, at-line sampling was employed and 
in a second step, an on-line PAT version was developed. 
The technology can help in the development of pharmaceutical 
dispersions. The phase of process development in particular 
can profit from direct monitoring of the different ultrasound 
properties. However, the new technology also seems highly 
promising on the manufacturing level. A production environ-
ment often has to cope with the natural variability of raw 
materials. The ultrasound-based analytics can assess batch-
to-batch variability and process times can be optimized for 
the individual product. A shortening of process times may 
lead to substantial cost savings in production. Further re-
search will explore additional options to couple different 
sensors with the ultrasonic resonator technique.

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Based Process Analytical Tool for Homogenization of Nanoparticulate 

Research Focus Area: 
Therapeutic Technologies (TT)

Project Team: 
Martin Kuentz, Martin Cavegn, Andreas Niederquell (Institute for Pharma-
techology, School of Life Sciences FHNW)

Partner: 
Guy Aikermann (Krieger AG)

Funding: 
Co-funded by Commission for Technology and Innovation (CTI): 
Economic efficiency and benefit to society: 
A first benefit is given for the industrial partner who is active in the nu-
meric manufacturing industry. Moreover, the new manufacturing equip-
ment will provide better process understanding and fewer failures in 
the pharmaceutical production. This and the potential reduction of 
process times are benefits for the pharmaceutical industry.
Determination of Degradation and Saturation Solubility of an Unstable Phytopharmaceutical Compound

One important step in drug development is assuring the bioavailability of an active compound. For this reason, physicochemical properties such as stability and solubility, which are essential for absorption, have to be determined. This is essential for understanding and improving bioavailability and hence enhancing the success of drug development.

Introduction
Knowledge of stability and solubility of the drug in different vehicles is required for absorption studies with the in vitro Caco-2 cell culture model. Such studies are carried out using in the apical compartment aqueous solutions or biorelevant media simulating the contents of the intestine under fasted and fed conditions [1]. In the experimental design with the biorelevant media, liposomal dispersions that are well tolerated by the cells are used in the basal compartment in order to guarantee cell viability. Chemical stability of the compound in these different vehicles can be measured at concentrations below saturation. Direct measurement of solubility at equilibrium in a saturated solution is not possible, however, because of the fast degradation that takes place. The aim of this study was to investigate the degradation of the phytopharmaceutical compound Nobilin that is unstable in water and to develop a kinetic model for determining its saturation solubility in different vehicles.

Materials and Methods
Nobilin is a sesquiterpene lactone isolated from the flowers of Anthemis nobilis L. that was used as a model compound. Aqueous media (aq-TMaco), fasted state simulated intestinal fluid (FaSSIF-TMaco), fed state simulated intestinal fluid (FeSSIF-TMaco), and two liposomal formulations in aq-TMaco, with the same lipid concentrations as FaSSIF-TMaco and FeSSIF-TMaco, respectively, were used as vehicles in stability and solubility studies.

Stability
The degradation was observed for 5-7 hours and was described by first order kinetics.

\[ C(t) = C(0) e^{-kt} \]  
(1)

where, \( C(0) \) and \( C(t) \) is the concentration at time points 0 and \( t \) respectively and \( k \) is the degradation constant. The observed degradation products were analyzed by LC-MS.

Solubility
Nobilin was added in excess to the vehicle and the change in concentration of dissolved drug was monitored for 7-7.5 hours. The data were evaluated with a kinetic model by EASY FIT II fitting software. The least square-based regression analysis provided an estimate of solubility.

Results
Stability
The degradation constant decreased in FaSSIF-TMaco, FeSSIF-TMaco, and Liposomes, and FeSSIF-TMaco-Liposomes.

Solubility
The calculated logP of Nobilin is 2.572 (±0.601) [2] which suggests an encapsulation of the drug in colloidal lipid particles. This effect solubilizes Nobilin increasing its equilibrium solubility, and protects it from water addition, thus improving its stability. Furthermore, it seems that the structure of the particle plays an additional role. The liposomes increased stability and solubility of the compound more than the mixed micelles of the biorelevant media, even though their concentrations were the same. There are several examples in the literature which show that the addition of surfactant increases the stability and solubility of a drug. It was seen that penicillins were stabilized by cationic and nonionic micelles in acid solutions which prevent acid-catalyzed degradation. It was assumed that this stabilization was because of the lipophilic character of the compounds which led to incorporation into the micelles. This effect also increased solubility in the presence of nonionic micelles [2]. The mathematical model developed in this study allowed the calculation of the solubility of a compound while degradation and transfer in and out of lipid particles took place. Hence, this model can be a useful tool in drug development for estimating saturation solubility of an unstable drug. Interestingly, the model envisages that the dissolving drug first enters the water phase before transferring into the lipid particles. Assuming a direct transfer of drug from the solid state into the lipid particles did not provide a satisfactory description of the experimental data. It should be further noted that the transfer coefficient, \( h \), did not appear to be a factor for drug concentration in the water phase and the lipid particles, \( C_L \) and \( C_w \) respectively, was not known.

The understanding of Nobilin interaction with the vehicles is very important for future absorption studies with the Caco-2 cell model and the calculation of permeability coefficients. It also provides insights into the possible improvement of bioavailability under biorelevant fasted and fed conditions.

References

Research Focus Area: Therapeutic Technologies (TT)
Project Team: Georgios Imanidis, Ursula Thormann, and Sheela Verjee.
Partner: Alpinia Laudanum Institute of Phytopharmaceutical Sciences AG
Funding: Alpinia Laudanum Institute of Phytopharmaceutical Sciences AG

Figure 1: Chemical structure and chromatograms of Nobilin and its degradation products at time point 0 and 7 min in water (37 °C).

Figure 2: Temporal variations of Nobilin in different vehicles.

Figure 3: LogP of Nobilin in different vehicles.

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The understanding of Nobilin interaction with the vehicles is very important for future absorption studies with the Caco-2 cell model and the calculation of permeability coefficients. It also provides insights into the possible improvement of bioavailability under biorelevant fasted and fed conditions.
Environmental Technologies (ET)
Technologies and management for the sustainable use of resources and the preservation of the environment
Environmental Risk Assessment of UV-Filters

UV-absorbing chemicals (UV-filters) are increasingly used in sunscreens, personal care products (cosmetics) and in the protection of materials against harmful UV-irradiation. They enter the aquatic environment, where contamination occurs in waters influenced by wastewater. In previous projects, we have shown that some of these UV-filters have hormonal activities in fish.

Karl Fent, Nancy Blüthgen, Verena Christen, Sara Zucchi
School of Life Sciences FHWN

Keywords: Environmental Risk Assessment, UV-filters, Fish, Effects on hormone system

Introduction
Excess UV-radiation may lead to skin irritation and in the long-term, to skin cancer in humans. Materials are also negatively affected. To prevent exposure to increased UV-radiation, sunscreen lotions containing sun protection factors (SPF) are applied. Inorganic nanoparticles (titanium dioxide, zinc oxide) that scatter UV-radiation are employed in sunscreens and material protection. With increased sun protection factors and in particular with the inclusion of UV-filters in all sorts of cosmetics, the use of organic UV-filters is steadily increasing and for 14 days respectively, several genes belonging to different biological functions are altered after exposure to 312 µg/L BP-3. No histological changes were observed in the testes after BP-3 treatment. Thus low concentrations of BP-3 exhibit similar multiple hormonal activities at the transcription level in two different life stages of zebrafish. Forthcoming studies should show whether this translates to additional physiological effects.

The UV-filter EHMC is heavily used in sunscreens and cosmetics and potential adverse effects or modes of action have not been investigated. We evaluate potential effects in another fish species, the fathead minnow (Pimephales promelas) to establish, whether the effects at most UV-filters are universal. We show that BP-3 is partly transformed into BP-1 in adults. The altered gene expression profile of BP-3 indicates down-regulation of the female sex hormone vitellogenin (VTG) content, secondary sex characteristics, and gonad histology. Transcripts of the androgen receptor (ar) are significantly down-regulated in the liver of females at 37.5 µg/L and higher. Additionally, the 3ß-hydroxysteroid dehydrogenase (3β-HSD) activity of the androgen receptor (ar) are significantly down-regulated in the liver at these concentrations. The expression changes are tissue-specific in most cases, being most significant in the liver. Vitellogenin plasma concentrations increased significantly at 244.5 µg/L EHMC in males. EHMC also induces significant histological changes in testes and ovaries at 394 µg/L. The induction of VTG plasma concentration and the histological changes in gonads suggest an estrogenic and/or antiandrogenic activity of EHMC. On the other hand, the gene expression profile shows an antiestrogenic (e.g. down-regulation of esr1) activity of EHMC. Whole-genome transcriptome analysis revealed that over 1000 transcripts of genes involved in hormonal pathways and physiological functions are altered. In conclusion, our data demonstrate that EHMC displays low but multiple hormonal activities in fish.

Materials and Methods
Mature male and female fathead minnows (Pimephales promelas) were acclimated in 30°C for 7 days before the experiment. To ensure equilibrium, the fish were exposed to a control group of water. The water temperature was reduced to 15°C and the pH was adjusted to 7.6. Fish were exposed to 200 µg/L EHMC and 300 µg/L BP-3 for 24, 48, and 120 hours post fertilization. After exposure, the fish were euthanized by immersion in 2% aqueous solution of tricaine methanesulfonate (MS-222). Subsequently, blood samples were collected from the caudal vein and stored at −20°C. The brain, liver, and gonads were dissected and stored at −80°C. For histological analysis, the liver and gonads were fixed in 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4) for 24 h and then processed for paraffin embedding. Tissue sections (6-10 µm) were stained with hematoxylin and eosin. The expression levels of VTG was measured in liver and gonads using 2−ΔΔCT method. Results are given as the mean value ± standard deviation. RT-qPCR data are normalized using Gapdh and β-actin as housekeeping genes. The data were analyzed by one-way ANOVA using GraphPad Prism 7 for Windows (GraphPad Software, CA, USA).

Results
In zebrafish embryos and adult males exposed to concentrations between 30 and 3000 µg/L, for 3 days after hatching and for 14 days respectively, several genes belonging to the hormonal systems are altered [3]. They include steroid hormone receptors and genes coding for enzymes involved in the endogenous synthesis of steroid hormones (Fig. 1). In embryos, transcripts of vtg1, vtg3, esr1, esr2b, hsd17b3, cyp19b1 are upregulated at 312 µg/L BP-3, which points to a low estrogenic activity and interference with early thyroid development respectively. In adult males, BP-4 displays multiple effects on gene expression in different tissues. In the liver, vtg1, vtg3, esr1 and esr2b transcripts are down-regulated, while in the brain, vtg1, vtg3 and cyp19b1 transcripts are up-regulated. The transcript profile reveals that BP-4 interferes with the expression of genes involved in hormonal pathways and steroid hormone synthesis. The effects of BP-4 differ in life stages and adult tissues and point to estrogenic activity in eleuthero-embryos and the adult brain, and antiestrogenic activity in the liver. Furthermore, effects of BP-3 are evaluated in embryos and adult zebrafish that were exposed for 120 hours post fertilization and 14 days, respectively, to 2.4–312 µg/L and 8.2–438 µg/L BP-3 (Fig. 2) [4]. Chemical analysis of water and fish demonstrates that BP-3 is partly transformed into benzophenone-3 (BP-1) and both compounds are accumulated in adult fish. Biotransformation into BP-1 is absent in eleuthero-embryos. In the brain of adult males, esr1, ar and cyp19b1 are down-regulated at 84 µg/L BP-3. There is no induction of vitellogenin expression by BP-3, either at the transcriptional or protein level. An overall down-regulation of the hsd1b, hsd17b3, hsd11b2 and esr2 transcripts is evident in male adults. The expression of cyp19a, hhex and cyp19b is decreased in male adults, while expression of cyp19b is increased in adult females. The expression of 5α, 3α, 244.5 and 394.5 µg/L EHMC on the expression of genes involved in hormonal pathways in the liver, testis and brain of male and female fish. We compare the transcript profile with the plasma vitellogenin (VTG) content, secondary sex characteristics, and gonad histology. Transcripts of the androgen receptor (ar) are significantly down-regulated in the liver of females at 37.5 µg/L and higher. Additionally, the 3ß-hydroxysteroid dehydrogenase (3β-HSD) activity of the androgen receptor (ar) is significantly decreased in the liver at these concentrations. The expression changes are tissue-specific in most cases, being most significant in the liver. Vitellogenin plasma concentrations increased significantly at 244.5 µg/L EHMC in males. EHMC also induces significant histological changes in testes and ovaries at 394 µg/L. The induction of VTG plasma concentration and the histological changes in gonads suggest an estrogenic and/or antiandrogenic activity of EHMC. On the other hand, the gene expression profile shows an antiestrogenic (e.g. down-regulation of esr1) activity of EHMC. Whole-genome transcriptome analysis revealed that over 1000 transcripts of genes involved in hormonal pathways and physiological functions are altered. In conclusion, our data demonstrate that EHMC displays low but multiple hormonal activities in fish.

Conclusion and Outlook
Our data indicate that the UV-filters BP-4, BP-3 and EHMC alter the expression of genes involved in hormonal pathways, hormonal signalling and in the synthesis of steroid hormones. Alterations of gene transcription occur in adult fish and in embryos, which may ultimately influence the development of gonads and the brain. The transcriptional changes in adult fish may lead to an imbalance of sex hormones, alterations in the gonads, as in the case of EHMC, and possibly to alteration of fertility and reproduction. Our data on several UV-filters may help to identify how hormonal pathways in fish. However, these occur mostly at concentrations higher than those found in the environment. On the other hand, for other UV-filters we have previously shown that the effects of individual compounds are additive and may cumulatively lead to unwanted adverse effects of these cosmetic ingredients. Therefore, further research is needed to pin down the potential environmental risks of these frequently used chemicals.

References:

Research Focus Area:
Environmental Technologies (ETT)

Project Team:
Karl Fent, Verena Christen, Sara Zucchi, Nancy Blüthgen, Karin Girard, Franziska Dr. Christiansen, School of Life Sciences FHWN

Partner:
Axel Oehme (University of Basel)

Funding:
Swiss National Science Foundation (SNSF) and Federal Office for the Environment (FOEN)

Economic efficiency and benefit to society:
The results of this project allow the evaluation of potential environmental risks of UV filters and help in reducing potential human and environmental health risks associated with widespread use by alternative UV protection agents.
Sustainability, environmental fate and ecotoxic effects of organic photovoltaics

Organic photovoltaic solar cells are a promising new energy-delivering technology. Based on organic molecules, they are developed as an alternative to silicon-based solar cells because of their lightweight thin-layer structure, semi-transparent and mechanical flexibility. Within the SUNFLOWER project, the environmental fate, ecotoxicological risks and sustainability aspects of this cutting-edge technology are investigated.

Yannick-Serge Zimmermann, Nadja Häfeli, Corinna Baumgartner, Dirk Hengevoss, Markus Lenz, Philippe Corvini, Karl Fent, Christoph Hugi
School of Life Sciences FHNW

Keywords: Organic photovoltaics, life cycle assessment, sustainability, environmental fate, ecotoxicity

Introduction

With fossil fuels dwindling, great efforts are currently being made to develop novel ‘green’ technologies in order to cover the ever-increasing worldwide demand for energy [1]. Organic photovoltaic solar cells (OPVs), see Fig. 1, are promising as a renewable energy source because of the low energy requirement for production, low resource extraction and absence of greenhouse gas emissions during use. In contrast to established silicon-based solar cells, OPVs have the advantages of lightweight, semi-transparent and mechanical flexibility. In the SUNFLOWER project [2], funded by the European Commission, 16 academic and industrial partners are trying to develop new OPVs to improve their competitive efficiency and market price, as well as extend their lifetime to 20 years. Within the consortium, we focus on environmental aspects: in the context of possible large-scale production, the sustainability, environmental impact and ecotoxicological risks of OPVs are assessed and compared to the current best available technologies. Recommendations should be given to the industrial partners on how to make the production and disposal/recycling of such OPVs as eco-friendly as possible (see Fig. 2).

One target is to carry out a ‘cradle to grave’ Life Cycle Analysis (LCA) [3]. This means that from the extraction of raw materials, their transportation, production of the OPV cell and its operation, until disposal or recycling, energy and material fluxes are determined to identify process steps which could be optimized.

Another objective is the investigation of environmental fate aspects [1]. The probability of a release of OPV components into the environment during the use and end-of-life phase of OPVs is high. Furthermore, it should be investigated whether such leaching compounds are bioavailable and can therefore be taken up by organisms in which they potentially cause toxic effects, whether they adsorb to organic material/soil or remain in water phase, and whether they are biodegraded under environmental conditions or by microorganisms.

The third purpose is to look into the ecotoxicological effects of OPV compounds [4]. A release of large concentrations of harmful substances under use-phase conditions is not expected but can potentially occur in the end-of-life phase. Whether or not a potential hazard for the environment from the different OPV components that are used in OPVs (pure compounds as well as weathering products) exist, needs to be assessed by appropriate bioassays such as general toxicity and cellular stress responses.

Results

The initial LCA and eco-efficiency assessment shows unique opportunities for a scenario of coating windows using transparent OPV in the large market of building integrated photovoltaics (see Fig. 3). In the reference OPV produced by one of the project partners, the two electrodes consisting of transparent indium tin oxide (ITO) and silver are the main contributors to the environmental impact due to high energy consumption during production and uncertain environmental effects of ITO, which have not been investigated at all so far. Due to the high costs of scarce indium, replacement of ITO is an aim of the SUNFLOWER project. In addition to the replacement of ITO, emissions for OPV production could be reduced by using already existing renewable energies. Furthermore, the initial operational health and safety assessment revealed a lack of documentation for some materials, which should be further examined.

Concerning the fate and behaviour of OPV compounds in the environment, there is a general lack of information in literature about most of the main components. During use, when the OPV is in an intact state with almost impermeable barrier layers, the release of compounds into the environment is considered to be negligible. During the ageing process however, factors such as UV irradiation, water, oxygen, high surface temperatures and mechanical damage could lead to a release of OPV compounds. Initial results indeed confirm that metals may leach out of decomposed OPVs under harsh conditions such as cutting into pieces and agitating in artificial lake water. The extent, however, appears to be very low and metals are found only in trace concentrations in the tested leachate. Therefore, our preliminary data suggest that leaching of environmentally relevant concentrations of metals from OPVs might only occur under harsh conditions upon improper disposal in the end-of-life phase.

In toxicity tests, the potential effect of nanoparticles (e.g. ZnO) needs to be assessed. The biological activity of the pure chemicals/metals and leachates is analysed in fish cell systems (in vitro) and in early-life-stages of zebrafish (in vivo). Potential ecotoxicological activities are determined by biomarkers and targeted gene expression analysis. Different substance concentrations, from predicted environmental concentrations up to toxicological levels, will be tested. In a preliminary study, zebrafish embryos were exposed to nanoparticulate ZnO in media containing alginic acid as a natural dispersant. First results demonstrate an induction of the oxidative stress marker gene catalase at high concentrations, but not agnostic marker genes. In addition, the hatching rate was reduced. Overall, the preliminary results indicate a low ecotoxicological potential of nanoparticulate ZnO. Further, however, analyses are needed to assess the environmental safety of this and additional components of OPVs and leachates.

Conclusion and Outlook

So far, initial LCA shows that OPVs could have a considerable chance of success on the market with relatively low environmental impacts compared to other PV technologies. Assuming that the target of replacing ITO within the SUNFLOWER project will be achieved, the environmental impact of OPV will be further reduced. Concerning environmental fate aspects, until now there is no evidence for a worrying threat from OPVs since leaching concentrations are very low even under worst case scenarios. But since at present no policy/legislation and technologies regarding recycling of OPVs are in place, improper end-of-life disposal in particular might result in an adverse effect of OPVs in the environment, if applied on a large-scale. For ecotoxicity, in addition to single priority OPV components, tests using actual leachates i.e. containing a cocktail of metals and organics will be conducted using the developed set-ups. Here, biological activity will be analysed by applying an Effect Directed Analysis (EDA) based on the most promising bioassays.

In summary, our preliminary data indicate that OPVs can be considered to be a safe, eco-friendly and sustainable new technology.

References

[2] www.sunflower-project.eu

Research Focus Area: Environmental Technologies [IT]

Project Team

Christoph Singi, Philippe F.-X. Corvini, Karl Fent, Markus Lenz, Yannick-Serge Zimmermann, Nadja Häfeli, Dirk Hengevoss, Corinna Baumgartner (Institute for Ecopreneurship, School of Life Sciences FHNW)

Partners

Centro Suisse d’Electronique et de Microtechnique SA (Switzerland), BASF AG (Switzerland), DuPont Teijin Films O.K. Limited (United Kingdom), AMCOR Flexible Kreuzlingen AG (Switzerland), AGFA-Gevaert AG (Belgium), Flexim AG (Switzerland), Energie-Technologie-Technologie (Italy), CNR – ISEM Bolzano (Italy), University of Chalmers (Sweden), Fraunhofer Gesellschaft zur Förderung der angewandten Forschung e.V (Germany), Lappeenranta University of Technology (Finland), GenesInk Srl (France), Centro Interdisciplinare di Nanoscienze di Marsiglia (France)

Funding

European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement no 269406.

Economic efficiency to benefit to society

It is of high importance to gain insights into sustainability, environmental fate and ecotoxicological effects of the materials already used during OPV product development. In this manner, the production processes can be crucially influenced to that near future, large-scale manufacturing of OPVs can be achieved with less environmental impact.
Advanced Concentrate Treatment for Integrated Membrane Based Water Reuse Systems

High quality water reuse with dense membranes is applied progressively but produces reject streams with elevated concentrations of organics and salts. This project aims to develop sustainable zero liquid discharge technologies allowing the application of dual membrane systems in inland locations. The main focus is on the behaviour and removal of bulk and trace organics to limit fouling and safeguard the quality of the water produced.

Christian Kaner and Thomas Wintgens
School of Life Sciences

Keywords: Water reuse, water scarcity mitigation, RO concentrate treatment, zero liquid discharge, environmental impact

Introduction

In the context of water scarcity mitigation, high quality water reuse based on dense membrane treatment is expected to be progressively applied to provide the additional water resources required. Environmental concerns and the high costs associated with membrane concentrate management limit however the application of high quality water reuse, especially in inland locations. The project investigates integrated reverse osmosis and nanofiltration membrane concentrate treatment concepts, with minimized costs and environmental impact. The volume of the concentrate streams typically ranges from 15 to 25% of the feed stream. High salinity, a common feature of RO concentrate, is a danger to many plants and animals. All available methods have serious shortcomings either from an environmental or an economic perspective [1]. Applying the sustainable Water Discharge principle, the ACTIVATE project combines treatment methods for the removal of bulk and trace organics with a subsequent desalting system. The concentrate desalination will be based on a low energy consumption and low fouling concentration step, such as electrodialysis [2] or forward osmosis, thus increasing the salt concentration of the brine significantly in order to precipitate the salts, simple technologies such as wind aided intensified evaporation are used as a final stage for salt production. The system configuration, whether designed for reverse osmosis or nanofiltration concentrates, will differ due to different ion compositions. Instead of producing additional disposable waste, the salts should be recyclable. The focus of the research will be on the optimal removal of micropollutants and foultants affecting the desalting system - the concentrate desalination will be based on a low energy consumption and low fouling concentration step, such as electrodialysis or forward osmosis. The experiment design will be based on the removal of organics in concentrates from two advanced dual membrane water recycling plants in Sydney, Australia. The presence of organic micropollutants and bulk organics in relevant and typical concentrations was confirmed. The concentration of dissolved organic carbon was about 25 to 30 mg/L, mainly consisting of humic acids and building blocks.

The main critical pharmaceuticals such as carbamazepine, diclofenac, and sulfamethoxazole were detected in the brine in concentrations of around 0.1 to 1 µg/L, using liquid chromatography with mass spectroscopy detection after enrichment of the target compounds by solid phase extraction. The removal of organics can be achieved through a number of treatment technologies, e.g. ozonation, advanced oxidation processes, adsorption and biological treatment. Tests with granular activated carbon using rapid small-scale column tests with three different carbon types (two fresh carbons and one reactivated) revealed a rapid breakthrough of bulk organics after 2000 to 4000 bed volumes irrespective of the chosen carbon type. Organic compounds, however, were adsorbed to a significantly higher degree. Fresh mesoporous carbon was found to provide the best performance for the majority of micropollutants. Figure 2 illustrates the differences between typical compound classes based on key properties such as charge and hydrophobicity. Positively charged and neutral compounds were removed very stably, in particular by the fresh carbon. Negatively charged pharmaceuticals however started to break through after 5000 bed volumes. Besides compound charge, hydrophobicity seems to play a main role to allow complete removal as shown in Figure 2 (log Kow pH 7.5: diclofenac 0.74 compared to sulfamethoxazole - 1.51).

Oxidative methods to partially break down bulk organics allow extending of the carbon usage. They appear to be advantageous, particularly in combination with biological activated carbon. A broad range of advanced oxidation methods and biological GAC have been tested earlier by [3, 4].

Results from the study on brine concentration

Electrodialysis (ED) and forward osmosis (FO) have been investigated regarding desalination performance and susceptibility to fouling. Both processes proved to be applicable for brine concentration when pH is properly controlled and the water is softened to avoid scaling by calcite. The tests for preferential process conditions are ongoing. Fouling of ED and FO (cf. Fig. 3) was studied with model solutes containing humic acid, alginates and bovine serum albumin representing the key foulants: humic substances, polysaccharides and proteins. Tests with synthetic RO concentrate and model foulants were compared to tests with RO concentrate. It was found that in general, FO exhibited higher flux with supporting the idea of a “critical flux”. Two different membrane types were tested. The cellulose triacetate (CTA) membrane had a clean water flux around 12 LMH (draw solution 4M NaCl) whereas the novel polyamide (PA) membrane exhibited a clean water flux of 18 LMH (DS: 4M NaCl). When treating real RO concentrate for about 9 hours, the flux of PA membrane decreased by 30% whereas the CTA membrane lost only 1% in flux, indicating a significant influence of the membrane type and flux on FO fouling.

Conclusion and Outlook

Zero Liquid Discharge is gaining importance in the handling of municipal and industrial brine streams. Concentrates from water reclamation plants with dense membrane processes can be treated with a number of available and emerging treatment trains. The composition of reverse osmosis concentrates is complex and challenges the technologies for brine concentration such as forward osmosis or electrodialysis. Trace and bulk organics are present in elevated concentrations in reject streams from RO and NF up to 100 mg/L DOC. Organic compounds have to be removed prior to the concentration and desalting units to avoid severe fouling and performance loss of the desalting units. Combinations of oxidative and adsorptive processes appear to be most promising.

References:

Depolymerization of lignin by biocatalytic nano composites

Gregor Hommes, Christoph Gasser, Erik Ammann, Melanie Mucha and Philippe Corvini

Keywords: Lignin, enzymes, membrane technology, fine chemicals

Introduction

Needs for alternatives concerning the production of chemicals from renewable materials

Dwindling stocks of fossil fuels and growing concerns over excessive emissions from greenhouse gases have forced researchers to investigate renewable, abundant and comparatively clean alternatives to liquid fuels and chemicals produced from petroleum. The option of replacing oil by biomass as raw material for both fuel and chemical production is of great interest. In so-called biorefineries, almost all types of biomass feedstock can be converted to different classes of biofuels, biochemicals or value added products through jointly applied conversion technologies. The biorefinery principle is currently gaining particular relevance for untypeed or not sufficiently used resources such as bio waste or lignocellulosic material [1].

Lignin as a relevant source for value added chemicals

Lignocellulosic biomass consists of three basic components: cellulose, hemicellulose and lignin. Most of the biorefinery subsequent focus on using easily convertible fractions and hardly exploit lignin. For example, the lignocellulosics-to-ethanol process makes use of the cellulose and hemicelluloses, leaving lignin as waste. In addition, pulp and paper refineries also generate huge amounts of lignin as by-product. Lignin is, next to cellulose, the most abundant renewable resource. It is an amorphous and highly branched polymer of phenylpropanol units, accounting for up to 40% of the dry biomass weight. Presently, lignin is used as a low grade boiler fuel to provide heat and power needed for the process. However, the chemical structure of lignin suggests it to be a good source of value-added products: it could be broken down into smaller molecular units. Several studies were carried out to convert lignin to more value-added products. The challenge, however, is that lignin is very difficult to decompose, leaving high amounts of solid residue as compared to other components of lignocelluloses [2].

Aims of this study

The overall scientific goal of the present RD&D project is to develop and apply a new biocatalytic nanomaterial-based process for the value-adding depolymerization of organosolv lignin extracted from straw and giant grass (Fig. 1). The biocatalysts, i.e. modified enzymes (LME) such as laccases and lignin peroxidase [4] are immobilized on the nanostructures of either magnetic fumed silica or ultrafiltration (UF) membranes. These materials are applied to eco-efficient (in terms of activity, stability and recyclability) membrane filtration-based processes operated in continuous mode for the production of lignin oligomers and monolignols with concomitant fractionation of the reaction products. The industrial relevance of these lignin depolymerization products is also discussed. A further aim is to use immobilization of an LME (i.e. laccase) resulted in magnetic nanoparticles bearing an enzymatic activity of 0.79 ± 0.02 U mg⁻¹ (Fig. 3). In contrast, immobilization of the same enzyme on fumed silica nanoparticles yielded activities of 1.53 ± 0.02 U mg⁻¹ fumed silica nanoparticles [4].

Another possibility to characterize the molecular structure of lignin and biotransformation products of lignin is analysis by pyrolysis-gas chromatography/mass spectrometry. Pyrolysis is the thermochromical decomposition of organic substances in an oxygen-free atmosphere. Through cracking of the macromolecular structures, a heterogeneous gas is formed containing molecules of lower molecular weight. These compounds can be separated by chromatography according to their polarity and vapor pressure (Fig. 2, right). Some of the resulting phenolic fragments are displayed in Figure 2, which are typical for lignin and derive from guaiacylpropanol and syringylpropanol lignin units, for example p-cresol, catechol, 3-methoxy-pycocatohel, pyrocatechol, vinylniagluc, 2,6-dimethyldihydroquinone, vanillin and syringaldheyd (listed from left to right).

Magnetic Nano biocatalyst

In order to facilitate the recycling and recovery of the biocatalyst, a second goal was to develop a magnetic nanobiocatalyst based on a recently published protocol [4]. The immobilization of an LME (i.e. laccase) resulted in magnetic nanoparticles bearing an enzymatic activity of 0.79 ± 0.02 U mg⁻¹ (Fig. 3). In contrast, immobilization of the same enzyme on fumed silica nanoparticles yielded activities of 1.53 ± 0.02 U mg⁻¹ fumed silica nanoparticles [4].

Conclusion and Outlook

By developing and establishing thorough analytical methods for the characterization of lignin and lignin transformation products, essential tools for the evaluation of the tested conversion processes were obtained. Methods that allow identification of changes in the molecular weight distribution of lignin (i.e. SEC) are of particular interest for the identification of conversion processes which lead to lignin depolymerization. The enzyme immobilization technology has been transferred to INOFEA Gmbh, which enables the company to produce nanobiocatalysts at large scale.

Using magnetic nanobiocatalysts a separation technology can be developed to quickly and easily separate and recycle catalysts. Complex, multifunctional magnetic nanoparticle systems with designed active sites, i.e. LMEs, are promising candidates for the application in biocatalytic lignin conversion. The range of industrial applications which can be developed for such a system in the frame of DELICATE will depend on the possibility to further develop stable, robust magnetic nanoparticles withstanding the conditions encountered in the conversion process to effectively depolymerize lignin in an economical and scalable fashion.

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Figure 1 Schematic overview of the project.

Figure 2 Size exclusion chromatograph of organosolv lignin (3D absorption spectra from 240 to 400nm, left), organosolv lignin recorded after pyrolysis (200°C) and detected by GC/MS system, after thermal monomers fragments of lignin are formed and their molecular structures can be determined via MS fingerprints (right).

Figure 3 Immobilization of LME onto magnetic silica nanoparticles, from left to right migration of the magnetic nanoparticles forming a dark spot of where the magnet is located.
Comparing two Hybrid-Membrane-Processes to remove micropollutants from wastewater treatment plant effluent

Federal regulations for the removal of micropollutants from the effluent of wastewater treatment plants (WWTP) in Switzerland are expected to demand a upgrade of around 140 WWTP with an additional treatment step within the next 20 to 25 years. Within the project Aquarius the feasibility of two Hybrid Membrane Processes (HMP) is investigated and their performance is compared.

Jonas Löwenberg1, Armin Zenker2, Martin Baggenstos2, Gerhard Koch3, Thomas Wintgens2
1School of Life Sciences FHNW, 2WABAG Wassertechnik AG, 3Amt für Industrielle Betriebe Baselland (AIB)

Keywords: Tertiary wastewater treatment, powdered activated carbon, membrane filtration, Micropollutants

Introduction

The presence and accumulation of synthetic organic contaminants in natural and artificial water bodies is a known phenomenon in industrial countries and a rising concern to efforts of protecting drinking water resources as well as the environment from negative human influences. The use of synthetic substances in household products, pharmaceuticals and pesticides is steadily increasing and their negative effect on marine environments has been demonstrated [1], [2]. The discharge of micropollutants through the effluent of wastewater treatment plants (WWTP) has been identified as one main entrance path into the natural water bodies [2].

Serious efforts are underway in Switzerland to reduce the discharge of micropollutants into natural water bodies. Within the next 20 to 25 years around 100 of the currently operating WWTP are supposed to be upgraded with an additional treatment step to reduce the discharge of micropollutants, according to a proposed amendment of the Water Protection Ordinance (WPO) in 2009 [2], [3]. Not only in Switzerland but also in other industrialized countries within Europe efforts are taken to reduce the discharge of micropollutants [3].

Efforts to identify suitable and economically feasible process combinations have been a focus of environmental research in Switzerland as well as Germany over the last years. Powdered activated carbon (PAC) adsorption has been identified as one promising option [3].

Membrane filtration offers several advantages over other separation technologies such as sandfiltration or dissolved air flotation by completely retaining solids and PAC from the effluent, complete bacteria and partial virus removal and less space demand as well as a removal of many micropollutants. The addition of PAC was performed at a target concentration of 20 mg/L, while the membrane surface underneath appeared smooth and clean. The surface of the submerged membrane (Fig. 3, left) was covered by a layer of PAC particles as well as organic fouling. The different fouling layers on the membranes are an explanation for the difference in operational performance and are caused by the different process conditions.

In the period from the 8th of July until the 9th of August 2011 the removal of micropollutants from the wastewater treatment plant effluent was evaluated. The comparison of both HMPs concerning their capability to eliminate micropollutants from the WWTP effluent showed a removal in the range of 60-90% for most analyzed substances over the tertiary treatment step. Only Sulfamethoxazole was removed to a lower degree due to its hydrophilicity.

Conclusion and Outlook

The comparison of both HMPs showed general feasibility of both systems to eliminate micropollutants from the WWTP effluent at stable operating conditions of the membrane processes. Retention for all analyzed substances was in the range of 60-90%, except for Sulfamethoxazole which adsorbed to a lower degree due to its high hydrophilicity and the comparison of both systems to eliminate micropollutants from the WWTP effluent showed a removal in the range of 60-90% for most analyzed substances over the tertiary treatment step. Only Sulfamethoxazole was removed to a lower degree due to its hydrophilicity.

Further experiments are planned on a pilot scale to confirm the results of the small scale experiments. It is assumed that in upcoming pilot scale experiments the PAC dosage will be achieved at much more stable conditions. The influence of the contact time of PAC and the elimination rate of the chosen micropollutants will be studied. Furthermore, the influence of two different PAC types will be investigated and the membrane process will be further optimized regarding its recovery rate and energy demand.

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Research Focus Area: Environmental Technologies (ETI)

Project Team: Jonas Löwenberg, Armin Zenker, Thomas Wintgens (Institute for Entrepreneurship, School of Life Sciences FHNW)

Partner: WABAG-Wassertechnik AG, Amt für Industrielle Betriebe Basel Land (AIB), Bödeli AG

Funding: Federal Office for the Environment (FOEN)

Hybrid Membrane Processes are capable of improving the water quality of wastewater treatment plants to a high degree, by retention of bacteria and viruses as well as the removal of micropollutants to a high degree. This lowers the human impact on the environment.
Introduction
Emerging technologies can be accompanied by risks for the environment, human health and safety. The MINOTAURUS project develops new bio-remediation processes aimed at reducing the emission of organic pollutants and by that lowering the negative impact of these substances on the environment. The common principle of the new processes is the immobilization of biocatalysts; the negative impact of organic pollutants on the environment and humans will be reduced by these innovations. This paper presents a methodology to assess any additional or newly-occurring harmful effects of the innovative technologies. Since these effects are mainly related to risks caused by failures and the operation of the new processes, the possible harm is described and assessed in terms of risks.

For this risk assessment the general framework of the International Risk Governance Council was used [1]; the structure and the main steps are shown in Figure 1. The parts marked in red are the focus of the study presented in this paper. Risk is understood as “an uncertain consequence of an event or activity with respect to something that humans value” [1], [2]. Risk assessment aims to estimate the frequency of occurrence of adverse effects as a function of the consequences of these adverse effects. Sources of adverse effects are often referred to as hazards. The exposure and vulnerability assessment considers the various pathways along which subjects of protection (e.g. groundwater, soil) might come into contact with hazards.

The complete framework aims to generate not only knowledge, in the form of information about and characterization of risks, but also measures to control these risks which were estimated to be not (fully) acceptable. The concept of risk governance has to be understood as a cyclical process: in the case of remediation technologies, the technology itself can already be seen as a risk reduction option.

Results
The new technology addressed here consists of a membrane reactor containing nanoparticles with immobilized enzymes. The pre-treatment, the production process of the nanoparticles-enzyme-conjugation, the required transport, the membrane reactor operation and the disposal of wastes were all taken into account in the assessment [3]. The new technology is still under development and naturally not much statistical data is yet available. Frequencies and consequences can therefore only be estimated in a semi-quantitative or qualitative way.

According to the high uncertainty of the results of the risk estimations, it is not possible to rely strongly on the calculated values as exact numbers for the total risk of the technology nor for individual risks. The benefit of this study is rather a comparison of the risk connected to different events and hazards. It is possible to set out a prioritization of risk reduction measures, as well as a comparison of the shape of the risks in the corresponding decision diagram. The risk assessment at this stage of development of the technology is suitable for the identification of relevant events and hazards.

First results of the comparative risk assessment are shown in Figure 3 as a so-called loss exceedance frequency curve. This curve represents the frequency of events increasing the corresponding consequence given on the x-axis. It can be clearly observed that the shape of the loss exceedance curve changes significantly. For the situation that the technology is not applied, there are only risks with a very high frequency but with a relatively low consequence. The technology addresses micro pollutants which are continuously emitted from the WWTP at a low concentration leading to small effects especially to aquatic ecosystems. If the technology is applied, risks with extremely high frequency and consequence are significantly but new risks with low frequency but relatively high consequences are increased. Examples are the release of harmful chemicals by failure in the transport chain and membrane integrity failure.

Conclusion and Outlook
The results show that the risk assessment methodology helps to identify possible risks connected with a new technology systematically and at an early stage of development. Risk reduction options can hence already be taken into consideration before the first full scale installation.

During the future periods of the MINOTAURUS project it is planned that this methodology will be applied to further new biological remediation technologies.

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Risk characterization of innovative bio-processes for water purification

New technologies may come with new risks. This is also true for environmental technologies aimed at reducing the pollution coming from contaminated sites or wastewater release. The MINOTAURUS project (Microorganism and enzyme Immobilization: NOvel Techniques and Approaches for Upgraded Remediation of Underground- wastewater and Soil) project investigates such immobilization technologies and aspires to undertake a proper risk characterization at an early stage of technology development. To this end a risk characterization approach is being adopted.

Claudia Niewersch, Olga Steiger, Christoph Hugi, Luca Antonozzi, Gregor Hommes, Rita Hochstrat, Thomas Wintgens School of Life Sciences FHNW

Keywords: Risk assessment, risk characterization, International Risk Governance Council, immobilization-processes
EcoWater: Meso-level eco-efficiency indicators to assess technologies and their uptake in water use sectors

The EcoWater research project aims to develop meso-level eco-efficiency indicators for technology assessments using a system optimising approach which is tested in case studies on different water service systems. The case studies in urban water systems are a first step where the water value chain was mapped and environmental and economic impact indicators were proposed.

Olga Steiger, Christoph Hugi, Claudia Niewersch
School of Life Sciences FHNW

Keywords: Water resource management, eco-efficiency, meso-level, innovation and technology assessment

Introduction

Innovative techno-economic systems, able to decouple eco-economic growth from resource use and depletion, are essential for a resource-constrained world. Significant research effort is dedicated to measuring progress towards this goal, focusing on improving eco-efficiency - the development of more economically valuable goods and services, while using fewer resources and generating less waste and pollution. Although eco-efficiency metrics are widely applied at the micro- and macro-levels, the corresponding indicators are not well suited to analysing systemic changes on a meso-level. Meso-level assessments, which focus on the dynamic behaviour of product and service systems, i.e. whole value chains, can be used to analyse interdependencies and heterogeneity among actors, and can thus support policies aimed at sustainable systems.

EcoWater seeks to address the existing gap in eco-efficiency metrics by adopting a system approach for developing meso-level indicators and for assessing the system-wide impact of innovative technologies. The approach is tested through case studies on water service - water user systems. The reasons for this are manifold. Water is a crucial life and production factor and causes significant environmental impacts and costs for securing, distribution, collection, and treatment. Further reasons are the need for holistic approaches in assessing the performance of different water-related innovative technologies and the fact that so far the uptake of innovations in the water sector remains primarily regulatory-driven.

Results

By relating the whole water value chains, as well as the interactions of the relevant actors, EcoWater will try to understand how technological changes in water service systems interrelate and influence the economic and environmental profile of water use in different sectors.

One of the research objectives of EcoWater includes the selection of eco-efficiency indicators, suitable for measuring the system-wide eco-efficiency improvements from innovative technologies. Eco-efficiency generally refers to a relationship between socio-economic benefits and environmental impacts (mainly negative) of a certain activity. Often this relationship is expressed as the ratio of an economic benefit and an environmental impact parameter. This ratio allows the comparison of system options, surveying development over time or even benchmarking with similar systems [1]. Such calculations often form the basis for improving the ratio between economic benefits and environmental impacts.

The challenge in EcoWater is the identification of suitable eco-efficiency indicators for the meso-level. The water sector is especially interesting for such investigations due to the heterogeneous actors and the interdependent system dynamics. For the main system components, i.e. the supply, use, and wastewater treatment system, different actors are relevant. These include political actors of different levels, operators for the water supply and wastewater treatment systems and industries, as well as small and medium enterprises and households in the water use system. In an interdependent system, measures implemented in one component can result in positive or negative impacts in another component of the value chain. Furthermore, some measures might improve the eco-efficiency of the whole water system but are not implemented due to a prohibitive cost-benefit distribution. To overcome such sub-optimal system configuration and foster the uptake of eco-efficient improvement technologies a framework for assessing technology impacts on the eco-efficiency of the whole water system will be developed by the project partners.

This framework development runs in parallel with, and at the same time is tested by, case studies, the elaboration of which is another research objective of the EcoWater project. These sample case studies are performed in a range of systems and sectors to assess innovative technologies and practices and to improve the understanding of the socio-technical dynamics that influence technology uptake and implementation in the water system. Two case studies are being undertaken by project partners in the agricultural sectors in Portugal and Italy and four in the industrial sector: one in the textile industry in Italy, one in the automotive industry in Sweden, one in the dairy sector in Denmark and one in energy production in the Netherlands (Fig. 1). We work package leader for the case studies in urban water systems. One case study is being carried out in the Canton of Zurich (Waedenswil) and one in the city of Sofia, Bulgaria, in cooperation with the University of Architecture, Civil Engineering and Geodesy in Sofia.

For the Waedenswil urban case study we are closely cooperating and coordinating its activities with AWEL, the Office of Waste, Water, Energy and Air in Canton Zurich. So far, the whole water supply chain for the Waedenswil system has been mapped (Fig. 2) and the water system structured in three stages: water supply, water use and wastewater disposal. Within these three stages six nodes were selected for closer analysis and site visits were carried out to the Hirsacker and Appitral drinking water treatment plants, four sample SMEs and the Waedenswil Rietliau wastewater treatment plant. There, water-related processes were investigated and data collected on water and resource flows, environmental issues related to water, and on costs and financial flows. With this data a value chain mapping of the system was drawn up, including relevant actors and stakeholders and the product and services among them (Fig. 3). In addition to the water flows, energy and financial flows were also mapped. As a next step the relevant environmental impact indicators and the economic benefits and costs for each actor in the system will be identified. Energy consumption and water contamination by micro-pollutants will be among the most relevant environmental impact indicators for this case study [2]. These indicators, combined with the associated benefits and costs, will result in an indication of the eco-efficiency of the processes involved in the whole value chain, i.e. on a meso-level.

Conclusion and Outlook

For the case study in Waedenswil the detailed value chain mapping has been completed. A range of indicators will now be tested to calculate different eco-efficiency ratios of the current water service systems and innovative technologies able to improve the calculated baseline eco-efficiency will be identified. Finally, the potential improvement of eco-efficiency will be assessed and scenarios will be formulated in order to identify barriers for technology uptake and measures to encourage technology implementation will be proposed. The progress of the project can be followed at the EcoWater project website [3]. The outputs from the development of the case studies will be cross-compared and used as a basis for the formulation of policy recommendations that could foster technology implementation and uptake in the relevant water use sectors.

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Research Focus Area: Environmental Technologies (ET)
Project Team: Christoph Hugi, Claudia Niewersch, Olga Steiger (Institute for Ecoprevention, School of Life Sciences FHNW)
Partners: National Technical University of Athens (Greece), Centro Internazionale di Altii Studi Agronomici Mediterranei - Istituto Agronomico Mediterraneo di Bari (Italy), Stichting Deltares (Netherlands), Universidade do Porto (Portugal), Universidade de Évora - Faculdade de Engenharia (Portugal), University of Architecture, Civil Engineering and Geodesy (UACEG, Bulgaria), Open University (United Kingdom), DHI Group (Denmark), Tovarna Miljične Institutet AB (Sweden), MTA Study
Funding: European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement no: 221862
Economic efficiency and benefit to society: Urban water systems are crucial for society. They are analysed in order to account for the different economic values and environmental impacts associated with water use by different actors and to assess opportunities and barriers for the uptake of innovations to improve the eco-efficiency of the whole system.
New insights on the environmental fate and effects of the “essential toxin” Selenium

Selenium is of key importance to human health due to its essential character as a trace element. Due to the mere trace concentrations present in the environment, its analysis is challenging and many aspects of selenium environmental chemistry are still little understood. This study tends to shed light on the environmental fate of selenium, linking its speciation to mobility, bioavailability and potential effects on model organisms.

Markus Lenz, Philippe Corvini
School of Life Sciences FHNW

Keywords: Selenium speciation, trace element cycling, selenium deficiency

Introduction
Selenium is a natural trace element that has been referred to as the “essential toxin”, both being essential yet highly toxic to humans and animals. Human nutrition with selenium is a delicate balance, since levels that are considered sufficient (>40 µg / day) are only marginally lower than excess levels (>400 µg / day, recommendation by WHO). There are large geographical variations in selenium concentration, with selenium rich soils at times only separated by a few kilometres from selenium deficient soils. Causes for selenium contamination are usually assignable to anthropogenic activities (e.g. mining, combustion of fossil fuels or irrigation with naturally rich selenium rich water) [1, 2] (Fig. 1). In contrast, factors that favour selenium deficiency are far less well understood. Whereas selenium contamination is usually a local or regional problem, selenium deficiency concerns more widespread areas, for instance large parts of China, Siberia, Japan and Korea. Overall, an estimated 0.5 to 1 billion people suffer from a risk of Se deficiency, or as the “essential toxin”, both being essential yet highly toxic to humans and animals. Human nutrition with selenium may be affected by selenium deficiency worldwide [3]. Most countries within Europe suffer from a risk of Se deficiency, most prominently Finland and parts of the UK, where soil selenium contents are particularly low. However, it should be stressed that selenium concentrations in forage usually be assimilated by plants, interact with the soil matrix leading to immobilization or even leach from soil. Therefore it is crucial to determine speciation when evaluating the selenium status of a soil. If one considers the mere trace concentrations in which selenium occurs in soils (usually well below 1 mg per kg), the inherent analytical challenges become evident, in particular regarding selenium deficient soils. Consequently, the study of selenium in natural environments requires highly sensitive and species-specific methods that are time- and cost-effective. In the frame of the present study, such a method based on online preconcentration ion chromatography Inductively Coupled Plasma Mass Spectrometry (IC-ICP-MS) was developed [4]. The applicability of the new method was proven on leachates of pristine volcanic ash (IC-ICP-MS) for Selenium quantification and speciation at ultra-traces, which is necessary to understand the environmental chemistry of selenium in volcanic ash impacted soils and in particular in selenium deficient areas. Furthermore, the method can be straightforwardly expanded to quantify other anions of environmental concern, such as arsenic, uranium, chromium and others.

Results
A strong anion exchange column was online coupled to a Dionex 2100 IC system, equipped with an online eluent generator and self-regenerating suppressor, using a computer controlled automated switching valve. In this manner, samples of volumes between 40 µL and 8 mL can be preconcentrated, whereas the volume can be set using the chromatography software. Chromatographic separation of the analytes was achieved at 35°C using a flow of 0.5 mL min-1 and a multi-step gradient of OH-. Peaks of the selenium species predominated in most aqueous environments – the oxyanions selenite (Se(IV)) and selenate (Se(VI)) – were separated within 300 seconds after injection and a total analytical time of 420 seconds was needed to equilibrate the analytical column for the subsequent injections.

Response for all three Se isotopes studied was linear to the total amount of Se and Se(VI) injected (i.e. volume×concentration), while the capacity of the preconcentration column was reached at more than 0.57 mg C (concentration×volume) injected. The instrumental set-up made use of two specific components that allowed the achieving of the required ultra-trace sensitivity: the electrolytic suppressor of the IC and the Octopole Reaction System (ORS) of the ICP-MS. Firstly, the suppressor was used to remove both cations and hydroxide anions from the mobile phase, which resulted in less interference and a stable eluent composition, beneficial for ICP-MS analysis. Secondly, the use of the ORS allowed monitoring of the selenium isotopes with the highest natural abundance (i.e. 78Se) with 23.5% and 80Se 49.8%. These isotopes cannot be analysed by conventional ICP-MS, since they are prone to abundant Ar–Ar interference. Resulting Limits of Detection (LOD) and Limits of Quantification (LOQ) were in the low picogram range for all isotopes studied. The lowest LOD/LOQ were observed on 78Se (0.3 and 3.7 pg total injected for selenite, 3.0 and 8.3 pg total injected for selenate, respectively).

The applicability of the method was then demonstrated on pristine volcanic ash of the volcanos Chaitén (Chile), Santaiguito (Guatemala), Fuego (Guatemala), Eyaðafjalla jökull (Iceland), Etna (Italy), Sakurajima (Japan), and Volcan de Colima (Mexico). For aqueous speciation samples were leached under shaking at a solid to water ratio 1:25 w/w following the standardized methodology for leachates of volcanic ashes. Only two samples contained a single Se species (selenite), while all other samples showed mixtures of different selenium species (oxyanions plus an additional unknown species). We could confirm for volcanic ashes that total Se content is not necessarily correlated to its mobility (assessed here by extent of selenium leached). For instance the Japanese sample showed little selenium leached (1%), while containing the highest (1.1 mg Se kg-1) total Se concentration. Most other volcanic ashes studied were consistent in showing low leachability, since in only 2 out of 12 samples was more than 10% of the total Se found in the leachates.

Conclusion and Outlook
Due to the mere trace concentrations, environmental selenium speciation requires sophisticated, sensitive analytical techniques, commonly relying on a preconcentration step prior to ICP-MS analysis. Existing preconcentration methods are costly and labor intensive, yet more importantly time-consuming and often not species-specific, which may be a source of bias in redox sensitive selenium speciation. We described for the first time a novel, robust, work- and time-efficient analytical approach that overcomes all the latter disadvantages by automating the preconcentration step and coupling it online to IC-ICP-MS analysis. It does not require any sample preparation except filtration. With the method presented here it was possible to measure picogram amounts of the prevalent oxygenian (selenite, selenate) and further anionic species in an automated manner within 7 minutes. The volcanic ash leachates analysed showed a great variability in both selenium concentration and speciation, but were mostly characterized by low selenium leachability. The online coupling of IC-ICP-MS provides a tool for future routine analysis at ultra-traces, which are necessary to understand the environmental chemistry of selenium in volcanic ash impacted soils and in particular in selenium deficient areas. Furthermore, the method can be straightforwardly expanded to quantify other anions of environmental concern, such as arsenic, uranium, chromium and others.

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Figure 1 Schematic of the analytical set up developed.

Figure 2 Factors potentially leading to Se deficiency or excess farming symbols. Reprinted with permission from Winkl et al. © 2012 ACV.
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Hemm S, Richter J, Zsigmond P, Wardell K.
Laser Doppler for guidance during DDS - typical optical trajectories toward Vim and STN. XXth Congress of the German Society for Biomedical Engineering, Jena, 16.-19.09.2012

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School of Life Sciences

19.-22.03.2012

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Compatibility study of liquid-filled hard capsules with lipid formulations containing critical levels of co-solvents. AAPS annual meeting and congress, Chicago, 25.-29.10.2012

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Novel thermoplastic capsules for robust encapsulation of hydrophilic lipid-based formulations. 5th Swiss Pharma Science Day, Bern, 29.08.2012

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Novel thermoplastic capsules for robust encapsulation of hydrophilic lipid-based formulations. 5th Swiss Pharma Science Day, Bern, 29.08.2012

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Stillhart C, Kubenz M.

Is ultrasonic resonator technology an alternative to Raman spectroscopy for drug quantification in complex lipid-based formulations? EUpAT 5, Ghent, 09.-10.05.2012

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Raman spectroscopy as novel process analytical tool for drug quantification in self-emulsifying drug delivery systems. 8th World Meeting on Pharmaceutics and Pharmaceutical Technology, Istanbul, 19.-22.03.2012

School of Life Sciences

19.-22.03.2012

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Ringenbach A, Schwägli T.


Ryter N, Köser J, Hoffmann W, Pieles U, Jung C, Schlottig F, de Wild M.


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Schumacher R, Coigyn F, Beuth J, Schumacher R, Schkommodau E, Hemm S.


Shah A, Coste J, Gmündner D, Ulla M, Lemaire JJ, Schkommodau E, Hemm S.

Acceleration measurements during DBS surgery for tremor. Talk: 1st international symposium on deep brain connectomics, Clermont-Ferrand, 26.-29.09.2012

Shah A, Hemm S.

Miniaturized electrical impedance spectroscopy for intelligent implants. Talk. 20th Biannual Meeting and Match Meeting: Intelligent implants, Strasbourg, 20.05.2011
The School of Life Sciences FHNW has established itself as a competent address for qualified research. The cooperation with industrial and academic partners is strong and nowadays the School is part of many nationally and internationally funded projects. It is also active in promotion of spin-off companies. Within the last 2 years four new companies started.

The following table gives an overview:

<table>
<thead>
<tr>
<th>Spin-Off</th>
<th>Business Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>INOFEA GmbH</td>
<td>Design, development and production of innovative nanomaterials with remarkable recognition properties for industrial applications and products.</td>
</tr>
<tr>
<td>AlloCyte Pharmaceuticals AG</td>
<td>Drug discovery programs on therapeutically validated targets and translational clinic research to indications of high medical need.</td>
</tr>
<tr>
<td>MiniNaviDent AG</td>
<td>Innovative solutions in the area of dental implantology.</td>
</tr>
<tr>
<td>NeoMedz Sàrl</td>
<td>Designing and manufacturing of new tools and technologies for minimally invasive medical procedures.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Research Projects (2011-2012)</th>
<th>10'000–100'000 CHF</th>
<th>&gt; 100'000 CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>758</td>
<td>139</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Type of Funding (% of current projects)</th>
<th>Research Focus Areas (2011–2012) (% of external Funds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU</td>
<td>Environmental Technologies (ET) 37%</td>
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<tr>
<td>Swiss Federal Office</td>
<td>Molecular Technologies (MT) 37%</td>
</tr>
<tr>
<td>Third Parties (direct funding)</td>
<td>Therapeutic Technologies (TT) 26%</td>
</tr>
<tr>
<td>CTI</td>
<td></td>
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<td>SNSF</td>
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## Research Fields and Competences

<table>
<thead>
<tr>
<th>Institute</th>
<th>Fields of Research</th>
<th>Competences</th>
<th>Research Focus Area</th>
</tr>
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<tbody>
<tr>
<td>Institute for Chemistry and Bioanalytics (ICB)</td>
<td>Biochemistry, Bioanalytics, Diagnostics (Bio)-Nanotechnology, Instrumental Analysis, Organic Synthesis, Chemical Engineering</td>
<td>Biochemistry, Bioanalytics, Diagnostic (Bio)-Nanotechnology, Molecular Recognition, Organo- and Biocatalysis, Synthesis / Sustainable Development, Molecular Diagnostics and Preclinical Development of Pharmaceuticals, Instrumental Analytics, Organic and Organometallic Synthesis, Chemical Engineering</td>
<td>MT, TT</td>
</tr>
<tr>
<td>Institute for Ecopreneurship (IEC)</td>
<td>Resource Management, Cleaner Production, Ecotoxicology, Environmental, Biotechnology and Engineering</td>
<td>Environmental Engineering/Clean Technologies, Ecotoxicology, Environmental Biotechnology/Microbiology, Cleaner Production in Industry (CP), green Chemistry</td>
<td>MT, ET</td>
</tr>
<tr>
<td>Institute for Pharma Technology (IPT)</td>
<td>Dosage Forms, Drug Delivery, Procedures and Production Processes</td>
<td>Formulation research and dosage form design and preparation, Process development and process engineering, Quality by design and process analytical technologies, Intestinal and transdermal drug delivery and absorption, Pharmacokinetics and pharmacodynamics of natural products</td>
<td>MT, TT</td>
</tr>
</tbody>
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Research Seminars
Autumn 2011–Summer 2013

Michael Stumm, F. Hoffmann-La Roche AG, Basel
Histopathology and Clinical Development: a Phase II Case Study

Jürg Noser, Kantonales Laboratorium, Basel
Spurenanalytik in der Lebensmitteluntersuchung

Joachim Köser, School of Life Sciences FHNW, Muttenz
Fluoride particles for oral care

Fotos Hocha, School of Life Sciences FHNW, Muttenz
Design and study of catalysts for selective hydrogenations - an overview of ETH and future HLS projects

Jens Gobrecht, Paul Scherrer Institut PSI, Villigen
Micro- and Nanofabrikationstechnologien für Life Sciences und andere Anwendungen

Therese Bormann, School of Life Sciences FHNW, Muttenz
Memorymetalle / NiTi in der Medizinotechnik

Atanas Koulou, Novartis Pharma AG, Basel
Protein Aggregation in Biopharmaceuticals - Why do we need to measure it and how

Gerhard Gakos, Paul Scherrer Institut PSI, Villigen
Novartis Pharma AG, Basel
Drug Discovery in Autoimmunity

Serge Reichlin, Siemens Schweiz AG, Zürich
Aktuelle Trends im Schweizer Gesundheitswesen mit Fokus auf Spitälfinanzierung

Ron Tynes, School of Life Sciences FHNW, Muttenz
The "Gene-to-Protein" Recombinant Protein Production Platform

Martin Graf, F. Hoffmann-La Roche AG, Basel
Stem Cells as Research Tool

Berndt Grunert, School of Life Sciences FHNW, Muttenz
Zucker ist nicht nur süß – Einblicke in die Kohlenhydratchemie

Giampiero Beroggi, Switzztech AG, Dübendorf
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Andreas Gerber, Buss ChemTech AG, Pratteln
Challenges in the Modern Speciality Chemicals Industry

Roy Siegel, University of Bern, Bern
Effiziente Versuchsdatenauswertung mit der Software Origin

Markus Hübner, Additive GmbH, Friedrichsdorf
Based drug delivery systems using Raman spectroscopy

Rong Ji, Nanjing University, Nanjing
Stimulated bioremediation of soil by earthworms

Eric Kübler, School of Life Sciences FHNW, Muttenz
Molekulare Diagnostik

Yves Sainte Eugenia, Russ ChemTech AG, Pratteln
Hydrofluoric Acid and Downstream - Fluorochemicals from Fluosilicic Acid

Christof Bühler, Supercomputing Systems AG, Zürich
Towards User-independent Object Recognition & Classification for Cellular Systems

Rong Ji, Nanjing University, Nanjing
Application of isotope-labeling techniques in studies on degradation of organic substances

Nancy Blüthgen, School of Life Sciences FHNW, Muttenz
Effects of UV filters on aquatic organisms

Sven Kerzenmacher, Institut für Mikrosystemtechnik – IMTEK, Freiburg
Biobrennstoffe – Strom aus Blutzucker, Biomasse und Abwässern

Jörg Ringwald, TBF + Partner AG, Zürich
Studie zum Ausbau der ARA Basel

Mathias Häfeli, Universitätsspital Basel, Basel
Additive Manufacturing: Anwendungen in der Handchirurgie

Martin Stumpf, Russ ChemTech AG, Pratteln
Optimierung von stoffübergangslimitierten Gas/Flüssig-Reaktionen im Schlaufenreaktor

Jürgen Burger, University of Bern, Bern
Intelligente Implantate und Instrumente für Anwendungen in der Neurologie und Neurochirurgie

Thomas Lischm menu and Thomas Martin, Dottikon Exclusive Synthesis AG, Dottikon
Herausforderung der modernen Spezialitätchemie

Lenny Winkel, Eawag, Dübendorf
Global trace element cycling

Olfa Glaied, School of Life Sciences FHNW, Muttenz
Influence of the vehicle on stability and in vitro absorption of a phytopharmaceutical compound

Knut Hinkelmann, School of Life Sciences FHNW, Muttenz
Spurenanalytik in der Lebensmitteluntersuchung

Buss ChemTech AG, Pratteln
Older trends in the pharmaceutical industry - a fast and reliable way to characterize the rheological properties of semi-solid pharmaceutical formulations

Reinhild Oehrel, BASF Schweiz AG, Basel
Effiziente Versuchsdatenauswertung mit der Software Origin

Markus Höhner, Additive GmbH, Friedrichsdorf
School of Life Sciences FHNW, Muttenz
Efficient synthesis of biocompatible silica Nanomaterials

Zdravka Misic, School of Life Sciences FHNW, Muttenz
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Josef Trapl, M+W Group GmbH, Stuttgart
Case Study – Modern Fill & Finish Production Facility

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Case Study – Modern Fill & Finish Production Facility
Contact

University of Applied Sciences and Arts Northwestern Switzerland
School of Life Sciences
Gründenstrasse 40
CH - 4132 Muttenz
Tel +41 61 467 42 42
info.lifesciences@fhnw.ch

Director, School of Life Sciences
Prof. Dr. Gerda Huber, Tel +41 61 467 42 42
gerda.huber@fhnw.ch

Director of Studies
Prof. Dr. Frank Pude, Tel +41 61 467 42 84
frank.pude@fhnw.ch

Technology Transfer
Dr. Arnulf Bohnacker, Tel +41 61 467 46 55
arnulf.bohnacker@fhnw.ch

Institute for Ecopreneurship (IEC)
Prof. Dr. Philippe Corvini, Tel +41 61 467 43 44
philippe.corvini@fhnw.ch

Institute for Chemistry and Bioanalytics (ICB)
Prof. Dr. Gerhard Grundler, Tel +41 61 467 42 27
gerhard.grundler@fhnw.ch

Institute for Medical and Analytical Technologies (IMA)
Prof. Dr. Erik Schkommodau, Tel +41 61 467 42 46
erik.schkommodau@fhnw.ch

Institute for Pharma Technology (IPT)
Prof. Dr. Georgios Imanidis, Tel +41 61 467 46 80
georgios.imanidis@fhnw.ch

Bachelor of Science (B.Sc.)
– Life Science Technologies
  Prof. Gianni N. di Pietro, Tel +41 61 467 46 94
gianni.dipietro@fhnw.ch

– Molecular Life Sciences
  Prof. Dr. Daniel Gygax, Tel +41 61 467 45 62
daniel.gygax@fhnw.ch

Master of Science (M.Sc.)
– In Life Sciences
  Prof. Dr. Georg Lipps, Tel +41 61 467 43 01
  georg.lipps@fhnw.ch

Master of Advanced Studies
– MAS Environment Technology and Management
  Prof. Dr. Markus Wolf, Tel +41 61 467 43 51
  markus.wolf@fhnw.ch

– MAS Nano-Micro-Technology (cooperation)
  Prof. Dr. Uwe Pieles, Tel +41 61 467 44 53
  uwe.pieles@fhnw.ch