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The Moco riboswitch: the missing metabolite

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Riboswitches are highly structured RNA elements located in mRNA non-coding regions. They regulate the expression of specific genes depending on the cellular concentration of a particular metabolite. In fact, the riboswitch-metabolite interaction induces a structural rearrangement in the RNA causing an alteration in the expression of the proteins encoded by the relative mRNA. About 20 types of riboswitches have been confirmed so far, each one responding to a specific molecule [1]. Bioinformatical studies on several bacterial genomes have recognized the Moco RNA motif (or Moco riboswitch) as a promising riboswitch candidate [2]. If so, Moco itself would be involved in the regulation of its own biosynthetic pathway. The biosynthesis of Moco is well described [3], however, there is no decisive prove that its regulation is indeed based on a riboswitch [4], This lack in evidence is probably due to the instability, high oxygen sensitivity and scarce availability of Moco and its precursors. The goal of our research is to confirm that the Moco riboswitch is actually a riboswitch. In this context, we are exploring for the first time the direct interaction that the Moco RNA motif from *E. coli* might undergo not only with the molybdenum cofactor itself, but also with other metabolites along its biosynthetic pathway. Structural studies on the Moco RNA motif have been performed in order to find the conditions that ensure a stable and uniform three-dimensional structure of the RNA. Moreover, its interaction with each metabolite is detected by footprinting assays [5] e.g. in-line probing, terbium cleavage, hydroxyl radical partial digestion, enzymatic probes and by spectroscopic methods e.g. CD, DLS, UV and fluorescence.

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Nucleic Acid Templated Chemical Reaction in a Live Vertebrate

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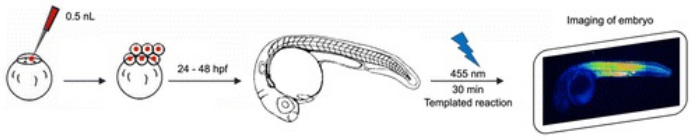
[1]University of Geneva

Nucleic acid templated reactions are enabled by the hybridization of probe-reagent conjugates resulting in high effective reagent concentration and fast chemical transformation. We have developed a reaction that harnesses cellular microRNA (miRNA) to yield the cleavage of a linker releasing fluorogenic rhodamine in a live vertebrate. The reaction is based on the catalytic photoreduction of an azide by a ruthenium complex. We showed that this system reports specific expression of miRNA in living tissues of a vertebrate.



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Exploring chemical space beyond GDB17

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The chemical space contains all possible molecules. We are interested in characterizing and studying this space to understand its properties and to aid in the process of drug discovery (such as finding new and unexplored chemotypes). In order to do that, we exhaustively sample parts of it. The GDB database family [1], which are a set of databases that contain all possible organic molecules with a given number of heavy atoms or less, has proven extremely successful and we have been able to describe and study most of the chemical space of drug-like molecules with 11 ($\sim10^7$) [2], 13 ($\sim10^9$) [3] and 17 ($\sim10^{11}$) [4] or less atoms. The huge size of both databases make the widely used chemoinformatics methods not feasible, so we are constantly developing new methods to work with such enormous databases [5]. Currently, we are working on the exploration of drug-like molecules that are bigger than 17 atoms [5]. As the size of such databases would easily exceed the available computational power (GDB-20 would be $\sim10^{18}$), we are sampling more specialized databases. Also, to be able to work with this large amount of molecules, we are currently developing machine learning technologies that will enable us to perform better searches on the databases.

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The polypharmacology browser for ligand based target prediction

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Target identification plays an important role in drug discovery. Its applications include the identification of biologically active molecules and promiscuous drugs, drug re-purposing, toxicity prediction, and understanding the molecular mechanism of action of bioactive compounds obtained from phenotypic screening.

Polypharmacology Browser (PPB) presented herein allows the target predictions for any given compound, by comparing the query to other small molecules with annotated targets information available in the ChEMBL database. Browser is unique in way that it performs the molecular comparison and target prediction simultaneously in ten different chemical spaces. We used PPB for the identification of off-targets of “CIS22a”, an inhibitor of the calcium channel TRPV6 recently developed in our group. “CIS22a” was found to be active against Dopamine receptor subtypes D2, D4, Alpha-1A adrenergic receptor (ADRA1A), and Serotonin receptor (5-HT1A).

PPB is freely accessible at www.gdb.unibe.ch.

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X-Ray crystallography of antimicrobial peptides as Lectin complexes

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We recently reported that the X-ray crystal structure of difficult to crystallize molecules such as peptide dendrimers and non-natural oligonucleotides can be readily obtained by co-crystallization of fucosylated derivatives with the microbial lectin LecB.[1, 2] Here we used this approach to study the structure of short antimicrobial peptides (AMPs) known to adopt a helical conformation by circular dichroism, but whose structures have never been obtained directly. We successfully obtained X-ray structures of five such AMPs, revealing unexpected aspects of their conformations and intermolecular associations.

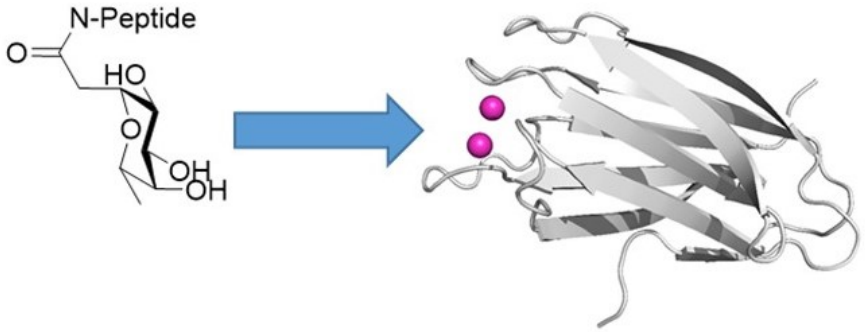

Figure 1: LecB-cFucoside co-crystallization principle

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A Search for Hydride Shift Mechanism in Enzymatic Synthesis of Tetrahydrobiopterin

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Sepiapterin reductase (SR) is a homodimeric enzyme responsible for the synthesis of tetrahydrobiopterin (BH_4), a multifunctional cofactor associated with neuropsychiatric diseases[1,2,3]. Based on biochemical and crystallographic data[4,5], it has been hypnotized that SR reduces the C1' carbonyl and then catalyses an isomerization reaction shifting the C2' carbonyl group to the C1' position. The final catalytic step includes NADPH-dependent reduction of the carbonyl group and generates *L-erythro*-BH_4. However, underlying mechanistic details of every step are not completely understood. In this computational study, we seek an answer for the following outstanding question: Is there a potential hydride shift mechanism in the isomerization step? Molecular dynamics and QM/MM molecular dynamics are in progress to provide precise information for enzymatic formation of BH_4. The underlying chemistry of this intriguing reaction may facilitate drug design for diseases such as Alzheimer's and Parkinson's disease.

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Interaction between steroid hormone receptors and the protein FKBP52: towards new molecular patterns

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In living cells, c*is* to *trans* (i.e., ω = 0° to ω = 180°) amide bond isomerization occurs at specific sites of proteins to allow backbone re-orientations that are essential for biological effects. Such isomerization reactions are reached at a very slow timescale, even in the case of x-Pro amide bonds, where the rotational energy barrier is strongly decreased. As molecular timers, peptidyl-prolyl isomerase (PPIase) enzymes are able to accelerate x-Pro isomerization to rapidly converge towards specific biological effects.

The 52 kDa immunophilin FKBP52, which contains an N-terminal PPIase FK1 domain, is known to participate in the expression and in the processing of steroid receptors (SRs). Although its PPIase activity is not essential for receptor regulation, the FKBP52 FK1 domain interacts directly with the ligand-binding domain of the unliganded SRs to stabilize the SR / Hsp70 / Hsp90 / p23 complex and / or to modify ligand affinity.

With respect to the identified interaction between the FK1 domain of FKBP52 and a β-turn of the human estrogen receptor α (ERα) located in its ligand-binding domain, we engaged in a "bioinspired" approach consisting of the synthesis of peptidic and peptidomimetic modulators derived from this interacting ERα β-turn and containing the sequence $K^{363}RVPGFVD^{370}$, where the turn motif is centered on the PG motif. In this study, we adopt the technique of NMR in order to design and test new peptidomimetics as inhibitors of the PPIase activity of the FKBP52 FK1 domain and, therefore, as competitive binders of FKBP52 protein partners.

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Critical Analysis of Rate Constants and Turnover Frequency in Nucleic Acid-Templated Reactions: Reaching Terminal Velocity

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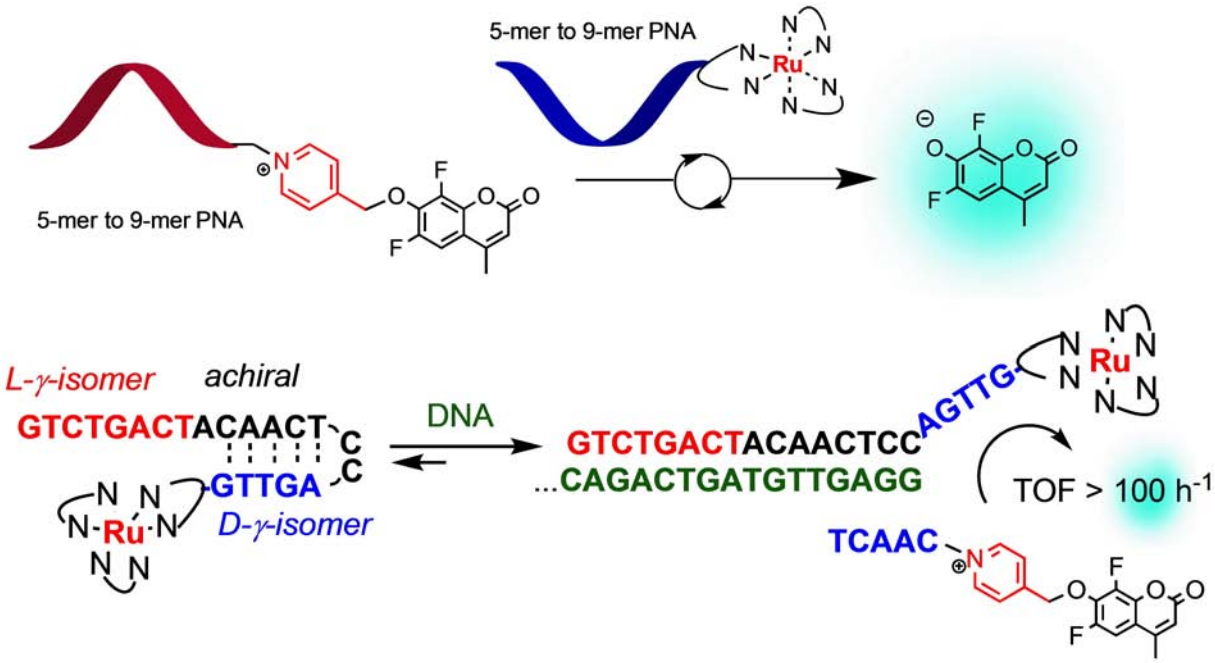
[1]University of Geneva

Templated chemical reactions have a long history dating back to prebiotic chemistry.[1] Based on the hybridization of probe to a template, reactions are promoted by the high effective concentrations. [2] [3] Nucleic acid templated chemical reactions have recently attracted significant attention for nucleic acid sensing and imaging. However, the rapid detection and high level of signal amplification are ongoing challenges for further application in biology. Herein, we have developed a new templated reaction with a pyridinium linker that is photocatalytically reduced with a ruthenium complex, which achieved the fastest rate reported to date for nucleic acid templated reactions. This reaction reaches the rate of notable enzymes. The catalytic efficiency of the systems (k_{cat} /K_M) is 10^5 $M^{-1}s^{-1}$. This fast templated reaction can be applied to the sequence specific detection of longer target sequences by embedding the template into a beacon architecture which is opened in the presence of the analyte.



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Bioactivity of polyoxometalate-chitosan nanocomposites

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Since the 1970s the discovery of new drug delivery systems was continuously improved.[1] The use of biodegradable and biocompatible polymers as encapsulating agents has been proposed as way to enhance the bioactivity and on the other hand to decrease the overall toxicity. Here we investigated the formation and the bioactivity of nanocomposites between polyoxometalates (POMs) and biopolymers (chitosan and carboxymethyl chitosan (CMC)). POMs are negatively charged early oxo-clusters of transition metals (e.g. W, Mo, and V) in their high oxidation states with promising anticancer and antiviral activity.[2] $K_6[P_2W_{18}O_{62}]$ (P_2W_{18}) and $(NH_4)_{17}Na[NaSb_9W_{21}O_{86}]$ (Sb_9W_{21}) were encapsulated either with chitosan or CMC forming nanoparticles in the size range of 100-200 nm. Nanoparticles were investigated with FT-IR, UV-Vis, DLS and electron microscopy (SEM and TEM). The bioactivity of the nancomposites was investigated on HeLa and MRC-5, cancer and fibroblasts cell lines, respectively. Two different behaviour patterns were observed: P_2W_{18} exhibits higher toxicity when it was applied alone compared to the nanocomposite. On the contrary, Sb_9W_{21} showed decreased cytotoxicity in its free form compared to the encapsulated material. This behaviour was maintained when the same compounds were applied on 3D *in vitro* cell model (spheroids). Furthermore, no difference in the bioactivity of the nanocomposites was detected when chitosan or CMC were used as encapsulating agents. The different behaviour types could pave the way to develop a strategy of selective and localized drug release.

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Functionalization of harmonic nanoparticles for targeted tumor imaging and multimodal cancer diagnosis

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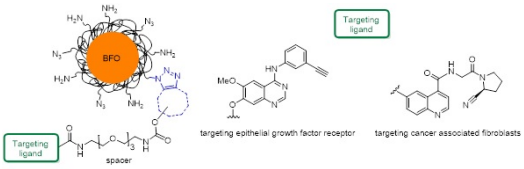
The recent and rapid progress in nanotechnologies has paved the way for the investigation of nanomaterials in clinical settings for early detection, diagnosis and targeted treatment of cancer, which represents a major health burden in developed countries.[1] The ability to produce inorganic nanoparticles of tunable size and composition, combined with their surface properties suitable for chemical functionalization have generated intense efforts to develop novel theranostic tools based on multifunctional nanomaterials.[2]

In this work, we present the synthesis of an Erlotinib analogue as targeting ligand for epithelial growth factor receptor (EGFR) which is an important prognosis biomarker for breast cancer. This compound was evaluated for its selective association to cancer cells and was further conjugated to poly(ethylene glycol) coated bismuth ferrite (BiFeO3, BFO) nanoparticles (NPs) through click reaction.[3] Development of a synthetic pathway for fibroblast activation protein α inhibitors suitable for post-conjugation to coated imaging harmonic NPs is currently investigated for targeting the tumor microenvironment.



Taking advantage of the second harmonic generation properties of the BFO NPs, the resulting nanomaterials were evaluated for their ability for cancer cells and tissue imaging by multiphoton microscopy.

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Diatoms functionalized with Vitamin B_{12} as micro-shuttle for targeting delivery of water poor soluble Ruthenium complex

Joachim Delasoie[1], Jérémie Rossier[1], Fabio Zobi*[1]

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Over the past few years, an ever-increasing awareness of our environment has prompted us to find new, greener manufacturing processes for our products, and our medicines are no exception to this rule. Porous silica-based materials and nanoparticles are particularly attractive for drug-delivery applications due to the excellent biocompatibility, biodegradability, thermal stability and chemical inertness of the materials. In our work, bio-inspired materials are employed as a drug vector to target different sites of interest. However, instead of the typical synthetic nanoporous silica nanoparticles, the greener and more accessible diatoms, which offer excellent manufacturing support for a large variety of poorly soluble drugs, are used.To date, several studies have already been carried out on the potential of this material in the field of targeting drug delivery. In particular, Walker et al. reported the specific binding and uptake of B_{12}-nanoparticles in Caco-2 cells from apical to basal chambers and showed that an increased density of vitamin B_{12} at the particle surface increased their uptake[1]. More recently, Losic et al. reported studies on diatoms functionalized with different compounds and used for the delivery of Indomethacin[2],[3] and Levoflaxin[4]. In the current study, we report the use of vitamin B_{12} for the surface functionalization of diatoms in order to achieve the specific targeting and delivery of a very cytotoxic ruthenium tris(bipyridyl) complex of poor water solubility. We showed that the release of the drug from B_{12} functionalized diatoms is achievable in different media which is very promising for further investigation. Currently in vitro experiments are ongoing to assess the efficiency of the concept.

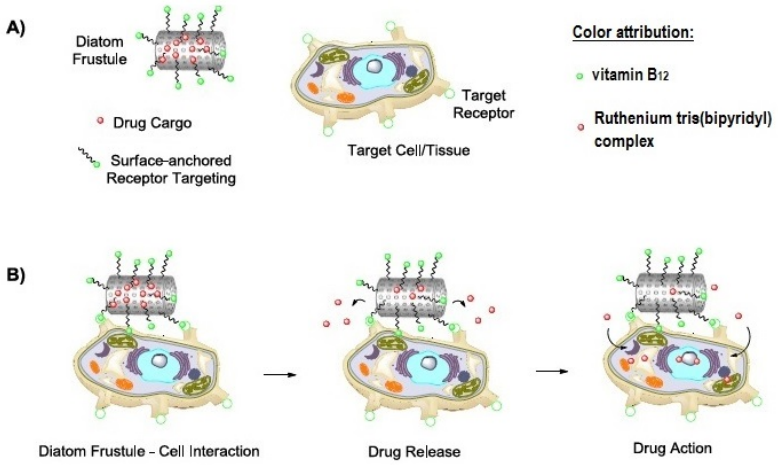

Figure 1: Conceptual representation of the diatom frustules as cell-targeting/drug delivery capsules. A) Definition of components in diatom frustule delivery system and target cell. B) From left to right: receptor-mediated frustule-cell interaction; drug delivery following drug penetration or action at target site (drug action)

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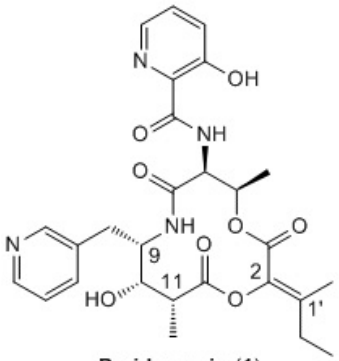
Dihydropyridomycins as New Antitubercular Agents: Synthesis and SAR Studies

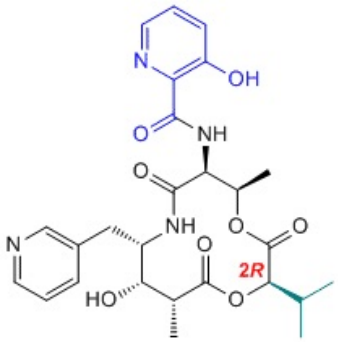
M. Dong[1], O. P. Horlacher[1], R. C. Hartkoorn[2], S. T. Cole[2], K. Altmann[1]*

[1]ETH Zürich, [2]EPFL

Pyridomycin (**1**) is a bacterial natural product that was first isolated in 1953 by Maeda and coworkers from the *Streptomyces* strain 6706.[1] The compound was shown to exhibit significant *in vitro* anti-tubercular activity (MIC = 0.3 µg/mL, H37Rv) and low cytotoxicity in mice.[1,2] The molecular target of **1** has recently been identified as the NADH-dependent enoyl-ACP reductase InhA, which is also the target of the clinically used anti-TB drug isoniazid.[2]



Pyridomycin (**1**)



2

So far, only one total synthesis of pyridomycin (**1**) has been reported in the literature in 1989 by Kinoshita *et al.*,[3] mainly due to the difficult establishment of the enol-ester double bond between C2 and C1'. To overcome this difficulty, (*S*)- and (*R*)-2,1'-dihydropyridomycins were synthesized. Biological results showed that the dihydropyridomycin analog **2** retained most of the antibacterial activity of **1**, while the corresponding 2*S* isomer was substantially less potent.[4]

Based on this initial finding, we have investigated variants of **2** with alternative alkyl substituents attached to C2 in an *R* configuration. Likewise, we have investigated dihydropyridomycin analogs where the hydroxypicolinic acid moiety was replaced by acyl residues incorporating different heteroaromatic structures. In addition, we have also prepared different analogs, one where a quinolinone group replaces the pyridine moiety in the C9 side chain and another with inversed stereocenters at C10 and C11. This contribution will discuss the synthesis of these new dihydropyridomycin derivatives and their InhA-inhibitory activity.

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Engineered protein superstructures for the encapsidation of nucleic acid therapeutics

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The potential of proteins for the fabrication of new functional nanostructures is yet to be fully exploited. This is due to the permissive complexity of self-assembly information encoded in peptide chains. However, it is this diverse range of physical and chemical functionality which holds much potential for new technologies in a variety of fields. One example is proteins which self-assemble into hollow structures that can encapsulate cargo. These appear in nature with various roles, such as reaction vessels for catalysis, storage containers and delivery vectors. Recently, the first examples of artificially engineered protein containers have appeared, presenting an exciting opportunity to develop synthetic assemblies that mimic the structure and function of their biological counterparts. The research presented concerns the development of a protein cage which can load nucleic acids into its core, as a potential solution to the intracellular delivery of therapeutic nucleic acids. A protein-based carrier has distinct advantages over other nanoparticles, due to biocompatibility, atomic level structural control and potential for site-specific modification. Here electrostatic interactions are used, exploiting the anionic nature of nucleic acids and directing them to the positively charged cavity of the protein cage. The first challenge is the design and expression of a hollow protein structure with a positively charged lumen. Secondly, the capacity for loading is studied, with a focus on complex stability and capacity of the capsule to protect its cargo from degradation. Finally, the ability of the device to enter cells and regulate protein expression is investigated, including modification of the capsid surface to control cellular uptake and trafficking. This research focuses on nanomedicine but in a broader sense aims to show that a simple, rational approach combining supramolecular chemistry and biotechnology can be used to create new function in protein materials.

Characterization of Ergothioneine Biosynthesis in a thermophilic fungus

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Ergothioneine (EGT) is a N-α-trimethylhistidine derivative that is synthesized by many bacterial and fungal organisms.[1] Animals and plants assimilate EGT from the environment or through the food chain. Detailed characterization of EGT biosynthesis in mycobacteria revealed a catalytic pathway comprising five enzymes (EgtA-E).[2,3,4] The central step in this pathway is oxidative sulfur transfer to the imidazole ring of N-α-trimethylhistidine. This reaction is catalyzed by the iron-dependent sulfoxide synthase EgtB. Eukaryotic EGT biosynthesis appears to differ by several key aspects from the prokaryotic model. In this presentation we discuss the substrate selectivity and product specificity of fungal EgtB.

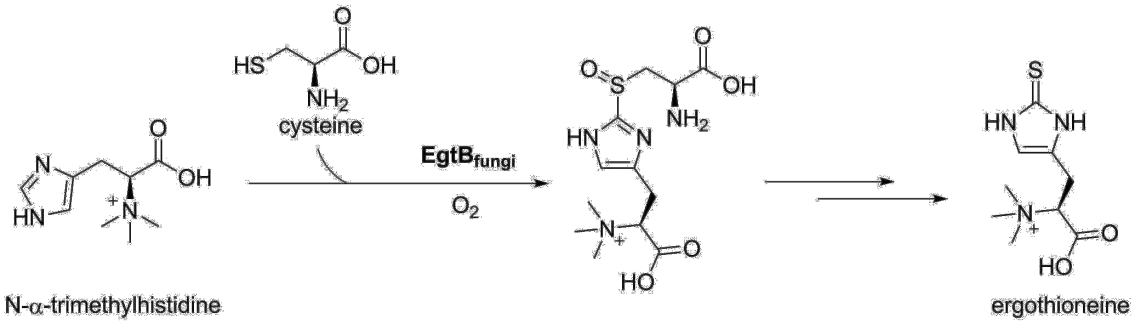

Fig. 1: The sulfoxidation step of EgtB$_{fungi}$ in the biosynthesis of EGT.

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Fluorescent Labeling of the Antimicrobial Peptide Dendrimer G3KL to Probe Its Entry into Pseudomonas aeruginosa

B. Gan[1], T. Darbre[1], J. L. Reymond[1]*

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We recently showed that peptide dendrimer **G3KL**, with amino acid sequence $(KL)_8(KKL)_4(KKL)_2KKL$, exerts strong antimicrobial activity against multidrug resistant clinical isolates of the Gram negative bacteria *A. Baumanii* and *P. aeruginosa*[1,2]. **G3KL** was further shown to have positive impact in burn wound-healing processes and pro-angiogenic effect[3]. Inspired by imaging studies with fluorescent analogs of the cyclic antimicrobial peptide polymyxin B,[4] we have modified **G3KL** at its C-terminus and obtained fluorescent analogs that retain the antimicrobial activity of **G3KL**, and used super resolution STED nanoscopy imaging to investigate how these fluorescent **G3KL** analogs penetrate *P. aeruginosa* cells.

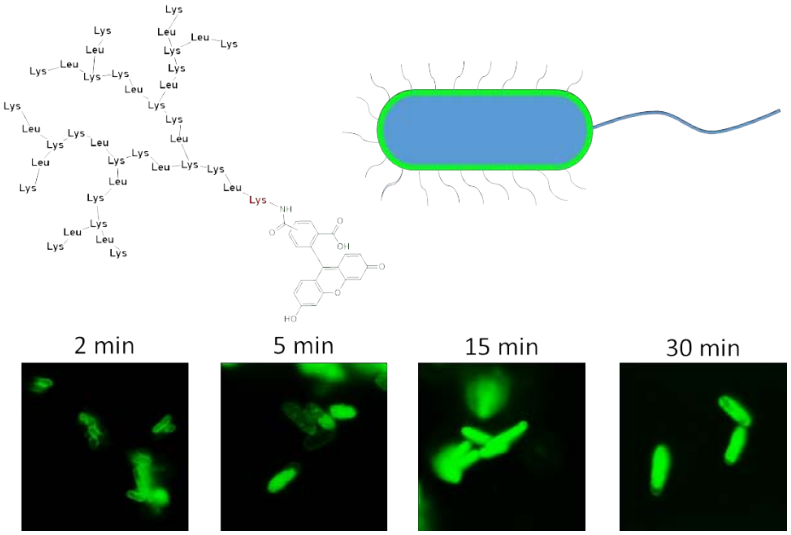

Figure 1: Structure of the fluorescein labeled peptide dendrimer **G3KL** and nanoscopy STED imaging of *Pseudomonas aeruginosa*.

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Targeting RNA structure in SMN2 reverses Spinal Muscular Atrophy molecular phenotypes

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Modification of *SMN2* exon 7 (E7) splicing to increase SMN protein production is a validated therapeutic strategy against Spinal Muscular Atrophy (SMA). Based on this, we have performed the first small molecule screening described for SMA, choosing a stem-loop RNA structure TSL2 that partially overlaps with the E7 5’ splicing site (5’ ss) of SMN2 as the biological target. TSL2-binding hit PK4C9 was found to also increase E7 splicing and rescued downstream molecular alterations in transfected HeLa cells, transgenic Drosophila, and SMA patient cells. High-resolution NMR combined with *in silico* modeling revealed that PK4C9 binding to TSL2 promotes a conformational shift towards a triloop conformation, which we also demonstrate that is associated with an enhanced E7 splicing efficiency. This work not only provides one of the few examples of small molecules with direct *SMN2*-spllicing modifier activity, but also opens new avenues for rational drug discovery in SMA and other splicing-mediated diseases where similar RNA structures are involved.

Characterizing the β1 adrenergic receptor and its intact noncovalent complexes with small molecules and a nanobody using native mass spectrometry

A. Gavriilidou[1], H. Hunziker[1], D. Mayer[2], Z. Vuckovic[2], D. Veprintsev[2]*, R. Zenobi[1]*

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G-protein-coupled receptors (GPCRs) are a prominent class of membrane proteins. GPCRs account for roughly 40 % of all medical targets, for diseases such as cardiac dysfunction, obesity and pain. They are dynamic entities that induce signal transduction pathways upon binding of extracellular ligands. Recently, native mass spectrometry (MS) has been applied to study intact membrane protein complexes. These complexes are released from detergent micelles formed in solution and are transmitted to the gas phase revealing the subunit stoichiometry. High collisional energies need to be applied in order to remove the detergent and therefore preserving drug binding is challenging. Despite the great advances of native MS in the field of membrane proteins, studying G proteins and drug binding to receptors has not yet been investigated.

In this study the turkey β1 adrenergic receptor (tβ1AR) has been investigated with native MS. β-adrenergic receptors activate or deactivate intracellular G proteins upon binding agonists or antagonists respectively. MS experiments were carried out under native-like conditions in 200 mM ammonium acetate, pH 8, supplemented with 1.9 mM n-decyl-β-D-maltopyranoside detergent, a concentration above its critical micelle concentration (CMC). Binding experiments of a G protein mimetic nanobody, NB80, against tβ1AR in the presence/absence of the agonist isoprenaline (Iso) and the antagonist S32212 hydrochloride (S3) were acquired on a Q-TOF ULTIMA, (Waters/Micromass, Manchester, U.K) in positive ion mode using a commercial nano ESI ion source.

The binding of NB80 to tβ1AR was characterized with native MS in the presence/absence of Iso and S3. In the absence of Iso, NB80 bound the receptor with a low affinity. This implied that the active and inactive states of the apo receptor are in equilibrium and therefore binding of the NB80 could occur. However, in the presence of Iso the equilibrium is strongly shifted towards the active state and the affinity of the NB80 to the receptor is greatly increased. The antagonist stabilizes the inactive state of the receptor. Therefore, the disruption of the tβ1AR-NB80 complex upon addition of S3 was observed, as expected. The efficiency of S3 to compete Iso was studied by titrating S3 to the tβ1AR-NB80-Iso complex, which showed that the affinity of Iso is substantially higher than that of S3. The results suggest that the high collision energy applied to the complex is needed to remove the detergent therefore maintaining the complexes intact and allowing the study of GPCRs with native MS.

Native MS can significantly improve our understanding of the GPCR mechanism, giving an insight into their function. This study shows the potential of native mass spectrometry in characterizing the binding of agonists, antagonists and G proteins to receptors. In this case, it was used to directly determine the degree of NB80 and ligand binding to tβ1AR.

Tamoxifen increases survival, improves motor function and reduces levels of BIN1 and DNM2 in a mouse model of X-linked centronuclear (myotubular) myopathy

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[1]University of Geneva, School of Pharmaceutical Sciences, [2]IGBMC - INSERM, CNRS, University of Strasbourg Dpt of Translational Medicine and Neurogenetics, Illkirch France

X-Linked centronuclear myopathy (XLCNM) is a rare and severe congenital myopathy characterised by generalised muscle weakness and abnormal nuclei positioning. Most affected boys die in their first year of life and survivors fail to achieve independent ambulation. It is caused by mutations in the
Mtm1 gene encoding myotubularin, a ubiquitously expressed phosphoinositide phosphatase. No cure exists and very few pharmacological avenues are being explored. Here, we treated Mtm1-null mice with tamoxifen (TAM), a drug that modulates estrogen actions and that we have shown earlier to be
efficacious in dystrophic (mdx5Cv) mice, a model of Duchenne muscular dystrophy (DMD).

We report that TAM is also effective in Mtm1-null mice, a model of XLCNM. Wild type and Mtm1-null mice were given normal chow or a TAM-supplemented chow starting at weaning. Non-treated Mtm1-null mice died at around 40 days. By contrast, about half of the Mtm1-null mice treated with clinically relevant doses of TAM survived beyond 365 days of age. Clinical scoring showed that the motor function of the affected mice was markedly improved. In vivo force recordings performed at D40 and D80 revealed that the force of treated Mtm1-null was significantly improved after only 3 weeks
of treatment. Histological and electron microscopy analyses show partial rescue of muscle structure and triads, consistent with improved calcium homeostasis in FDB fibres. Quantitative PCR and western blots demonstrate reduction of BIN1 and DNM2, which act downstream of MTM1.

In conclusion, we found that tamoxifen extends the lifespan of Mtm1-null mice up to 10-fold and rescues their motor skills. Collectively, these findings suggest that estrogen signalling is a key pathway that modifies disease severity in unrelated myopathies as diverse as DMD and XLCNM. Tamoxifen is
safe and readily available. We believe that it deserves clinical evaluation for XLCNM.

Total Synthesis, Target Evaluation and Structure-Activity Studies of Mycolactone and its Analogs

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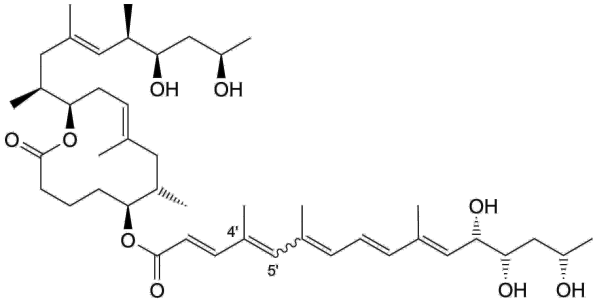
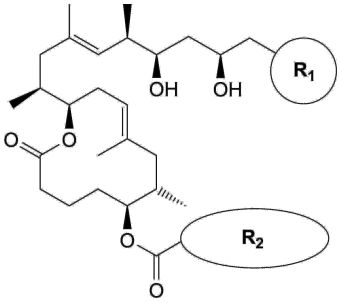
[1]Swiss Federal Institute of Technology (ETH) Zuerich, Department of Chemistry and Applied Biosciences, Institute of Pharmaceutical Sciences, Vladimir-Prelog-Weg 1-5/10, 8057 Zürich, Switzerland, [2]Swiss Tropical and Public Health Institute, Socinstrasse 57, 4002 Basel, Switzerland, [3]Department of Pharmaceutical/Medicinal Chemistry, Eberhard-Karls-University Tuebingen, Auf der Morgenstelle 8, 72076 Tuebingen, Germany

Mycolactones are a group of macrolides which exhibit cytotoxic, immunosuppressive and analgesic properties. As the exotoxins of the human pathogen *Mycobacterium ulcerans*, mycolactones are central to the pathogenesis of the neglected disease Buruli ulcer, a severe and chronic medical condition characterized by necrotic skin ulcers. Despite extensive research in several academic laboratories, the molecular mechanism of action of mycolactones is still heavily debated and it is not even clear whether the *cis*-Δ4',5' or the respective *trans*-derivative is the major contributor to bioactivity.



Mycolactone A/B



Mycolactone analogs

Driven by the desire to understand the action of mycolactones on a molecular level, we prepared a plethora of mycolactone analogs for SAR and target deconvolution studies. By using two distinct biotinylated mycolactone-derived probes in conjunction with real-time PCR, RNA interference and other techniques, we recently identified the mechanistic Target of Rapamycin (mTOR) signaling pathway as the key-driver of mycolactone-promoted apoptosis. [1] By interacting with the intracellular 12 kDa FK506-binding protein (FKBP12), mycolactone A/B inhibits the assembly of the mTORC2 multiprotein complex thereby blocking the phosphorylation of the downstream mediators Akt and FoxO3. The latter triggers the expression of the pro-apoptotic regulator Bim, which finally drives cells into apoptosis. Intriguingly, Bim knockout prevented the typical Buruli ulcer phenotype in *M. ulcerans*-infected mice thus confirming our results *in vivo*.

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Probing Cellular Uptake of Different Delivery Approaches for Porphyrinic Photosensitizers on HeLa cells

E. Girousi[1], N. Schnidrig[1], I. Gjuroski[1], S. Pfister[1], J. Furrer[1]*, M. Vermathen[1]*

[1]University of Bern

Porphyrinic photosensitizers are used in Photodynamic therapy (PDT) of cancer and other non-cancerous diseases. They are promising compounds because of their intrinsic phototoxicity, tumor accumulation and low dark toxicity. Porphyrin-polymer systems are used in order to prevent porphyrin aggregation and increase or maintain PDT efficacy. Previously, we have shown by 1H NMR spectroscopy that the photosensitizer serine-chlorin e6 (SerCE) is disaggregated upon insertion into either the polymer polyvinylpyrrolidone (PVP) or into polymer micelles consisting of Kolliphor P188 (KP188) [1, 2].

The aim of the current study was to probe and compare the impact of the carrier systems, i.e. PVP and KP188, on the cellular uptake of two different porphyrinic compounds, SerCE and chlorin e4(CE4), after treatment in the dark. Compared to SerCE, the serine-amide side chain is replaced by a methyl group in CE4 rendering the molecule more hydrophobic forming larger aggregates. Similar to SerCE, CE4 aggregates could be dissolved upon insertion into PVP or KP polymers. Uptake of both compounds into HeLa cells was tested using the ImageStream flow cytometer. The fluorescence data indicated that the cellular uptake was decreased in the presence of Kolliphor P188 compared to SerCE alone. Similarly, a slight decrease was observed when SerCE was combined with PVP. On the contrary, CE4 exhibited three times higher cellular uptake when combined with Kolliphor P188 and four times higher uptake when combined with PVP. The increased uptake of CE4 may be attributed to its hydrophobicity, allowing more efficient incorporation into Kolliphor P188 micelles and the PVP network. Even though successfully monomerized by the carrier systems, the more hydrophilic properties of SerCE most likely account for the lack of improved carrier-mediated cellular uptake. In conclusion, oligomer or higher aggregated species forming porphyrinic compounds exhibit different cell uptake behavior when combined with polymeric carriers.

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Enhancing the Properties of Chlorin e4 as Porphyrinic Photosensitizer by Polymer Encapsulation

I. Gjuroski[1], N. Schnidrig[1], E. Girousi[1], J. Furrer[1], M. Vermathen[1]

[1]University of Berne

Polymer nanoparticles are well suited delivery systems for porphyrin photosensitizers in photodynamic therapy (PDT). Photolon® is an approved polyvinylpyrrolidone (PVP) complex with chlorin e6 (Ce6) for medical application. Polymer carrier nanoparticles can promote porphyrin disaggregation, and enhance solubility and stability under physiological conditions, overcoming the drawbacks arising from porphyrin intrinsic propensity for aggregation, thus improving the efficiency of PDT.

Previously we have reported the polymer matrices- PVP [1] and the triblock copolymer Kolliphor P188 (KP) [2] as suitable systems for encapsulating various amino acid derivatives of chlorin e6 (xCe). Moreover, we have studied the xCe aggregate structures by NMR-spectroscopy showing that small modifications on the xCe side chains can have a large impact on the aggregation behavior. Accordingly, Ce4 forms highly aggregated species in aqueous solutions. [3]

This study was aimed at assessing the previously applied block copolymer micelles (BCMs) as well as PVP as suitable carriers for Ce4. UV-VIS-, NMR- and Fluorescence-spectroscopy as well as Imaging flow cytometry were applied as complementary techniques to characterize the polymer-Ce4 systems with a focus on the structural characterization, polymer disaggregation capability, Ce4 solubility and stability under physiological conditions. The results indicated high efficiency of KP-BCMs towards disaggregation and encapsulation of Ce4, improving Ce4 solubility and stability in the presence of serum proteins. Compared to the previously investigated xCe, the efficiency in disaggregation of KP-based BCMs is comparable good for both, highly and less aggregating chlorin species. However, binding properties and thus stability seemed to be improved for the more hydrophobic Ce4 as opposed to the more amphiphilic counterparts xCe. In addition, cellular uptake of both KP- and PVP-encapsulated Ce4 was enhanced (see contribution of E. Girousi).

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SAR of New Hetero-Monocyclic Analogs of (-)-Zampanolide

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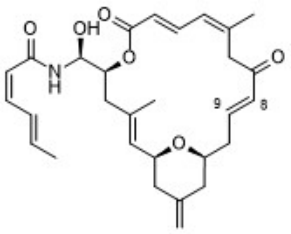
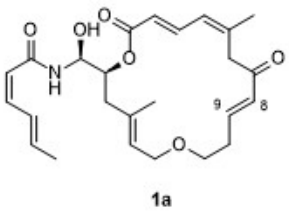
[1]ETH Zürich

The marine natural product zampanolide (**1**) acts as a potent microtubule inhibitor with binding at the taxane site on b-tubulin and it inhibits human cancer cell proliferation in vitro with single digit nM IC50 values. The structure of zampanolide (**1**) incorporates a highly unsaturated 20-membered macrolactone ring, an *N*-acyl hemiaminal-linked side chain, and a THP ring containing an exo-methylene group.[1]



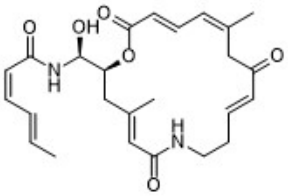
(-)-Zampanolide (1)



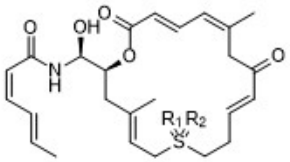
1a

Zampanolide binds to b-tubulin in a covalent fashion through 1,4-addition of His229 to the C8 – C9 double bond in the macrocycle. In contrast to the essential nature of the enone double bond, we have previously shown that the removal of the THP ring in zampanolide (**1**) is relatively well tolerated; thus, des-THP analog **1a** retains significant antiproliferative activity.[2] As part of a comprehensive project on the SAR of zampanolide-type structures, we have targeted various heteroatom-analogs of **1a** for synthesis (**2**-**8**), in order to evaluate if some the activity difference between **1** and **1a** could be recovered without a (re)increase in structural complexity.[3]

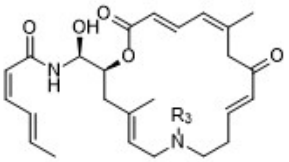
This contribution will discuss the synthetic chemistry of zampanolide analogs 2-8. In addition, the biological activity of selected compounds will be presented.



2



3: $R_1 = R_2 = X$
4: $R_1 = O$, $R_2 = X$
5: $R_1 = R_2 = O$



6: $R_3 = H$
7: $R_3 = Boc$
8: $R_3 = Ac$

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Studying the splicing of the wild type group II intron Sc. ai5g at non-physiological and near-physiological conditions

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[1]University of Zurich, [2]University of Zürich

The group II intron family represents a large class of non-coding RNA elements found in bacteria and lower eukaryotes. *In vitro,* group II introns are known to undergo Mg^{2+} dependent self-splicing during mRNA maturation. [1]. Under near physiological conditions the intron folding and splicing is assisted by a cofactor, namely the DEAD-box ATP dependent helicase Mss116 [2]. The aim of our research is to study these mechanisms in the wild type group II intron *Sc.* ai5γ from *Saccharomyces cerevisiae.* We are investigating the splicing during the mRNA maturation at non-physiological (high Mg^{2+}) or near-physiological (low Mg^{2+}) conditions and in the presence or the absence of the coenzyme Mss116. Intensive studies over the past decades have concentrated on an engendered intron model, whereas we are interested in the wild type molecule. *In vitro* splicing mechanism of the full-length intron will be followed by fluorescent native polyacrylamide gel electrophoresis (PAGE). We established a strategy for visualizing the splicing process by labelling the flanking exons with peptide nucleic acids (PNA) [3], both carrying fluorescence dyes. We are interested in the RNA splicing behavior at different salt concentration and in the presence of the cofactor. A comparison of the splicing between the wild type group II intron and the well-studied truncated model at non-physiological conditions will allow the investigation of two models at near natural or non-natural state and give insights of similarities and lead to a better understanding of the splicing processes

Financial support by SystemsX.ch, the Forschungskredit F16-083, the Swiss National Science Fondation and the University of Zurich is gratefully acknowledged.

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Histidine-rich metallothioneins – the next chapter for bacterial MTs

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[1]Department of Chemistry, University of Zurich

Metallothioneins (MTs) are ubiquitous metalloproteins characterized by a high amount of cysteine residues, a low molecular weight and the formation of unique metal clusters. As a consequence of their metal binding abilities and abundance of Cys residues, they are important partakers in various physiological processes (e.g. metal homeostasis, metal detoxification, oxidative stress). While all MTs share these properties, across the different kingdoms of life a high diversity in amino acid sequences, 3D structures and functionalities have evolved.Although bacterial MTs (bacMTs) have resided for a long time in the shadows of their mammalian counterparts, they have several unique features that break with many MT paradigms, i.e. the contribution of histidine residues to metal ion binding, a higher percentage of secondary structure elements, as well as the presence of aromatic amino acids.[1]

The presence of MTs in *Pseudomonas* species has become more apparent after sequencing of numerous bacterial strains in the last decade. These MT sequences reveal unusually high amounts of histidine residues and a high diversity in the primary structure. At the same time, they show a rather conserved Cys distribution pattern consisting of an N-terminal CxCxxCxC motif, a central YCC/SxxCA stretch, as well as a C-terminal Cxxxx(x)CxC part.

We are investigating, how differences found in the primary structure of these novel bacterial MTs influence function and 3D structure, including protein fold and the metal clusters.

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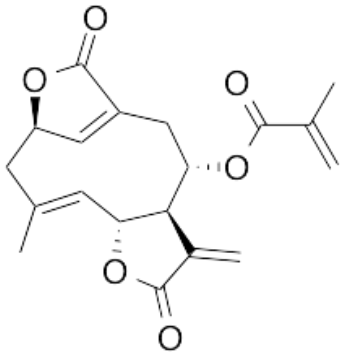
Divergent Synthesis and Identification of the Cellular Targets of Deoxyelephantopins

R. Lagoutte[1], C. Serba[2], D. Abegg[1], D. G. Hoch[1], A. Goujon[1], S. Soleimanpour[1]*

[1]University of Geneva, [2]University Of Geneva

The sesquiterpene lactone Deoxyelephantopin is the most active ingredient in extracts of *Elephantopus scaber*.[1] Biological investigations have demonstrated cytotoxicity against several human cancer cell lines, and cytotoxicity superior to that of Paclitaxel in breast cancer models.[2] Moreover, it suppresses proteasome activity,[3] inhibits the NF-κB pathway[4] and is a partial PPARγ agonist.[5]

A divergent synthesis of Deoxyelephantopin analogues and their biological evaluation will be presented, including the identified pharmacophores, novel potential drug targets and the binding mode with PPARγ.[6]



Deoxyelephantopin

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Fluorescent Bile Salt Derivatives for the Investigation of the Canalicular Lipid Transporter System

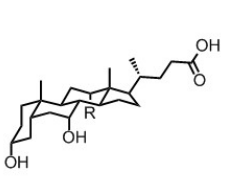
M. Leuenberger[1,3], S. Bernhard[2], B. Stieger[2], M. Lochner[1,3]*

[1]Department of Chemistry and Biochemistry, [2]Department of Clinical Pharmacology and Toxicology, [3]Institute of Biochemistry and Molecular Medicine

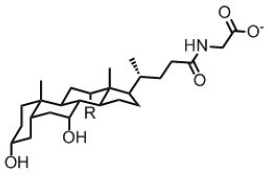
The liver is the biggest gland and a vital organ for animals and humans. Hepatocytes are complex cells responsible for the metabolism and filtration of xenobiotics and toxic compounds from the body. The correct function of these cells is crucial for a healthy organism. One of their major functions is the formation of the bile. The canalicular bile formation implicates the concomitant interplay of a series of ABC-transporters, i.e. BSEP (Bile salts export pump), MDR3 (or ABCB4) and ABCG5/G8. This process regulates the quantity of all ingredients and ensures the formation of a healthy bile. The disruption of the equilibrium between cholesterol, phospholipids and bile salts can lead to cholestatic liver injury. For instance, several drugs interact with this system, although the exact mechanism remains uncertain.

Here, we present the preparation of fluorescent bile salt derivatives in order to investigate the transport of the bile salts from the blood into the hepatocytes and then their secretion into the *canaliculi*. Three different fluorescent dyes were coupled to the side chains of cholic acid (CA) and Chenodeoxycholic acid (CDCA) to mimic known transport substrate Glycocholate (GC) and Glycochenodeoxycholate (GCDC). Nitrobenzofurazan (NBD), dansyl and a coumarin dye (Pacific Blue) were selected to investigate the impact of these different dyes on transport behaviour. Transport of the synthetic fluorescent bile salts was assessed in CHO cells expressing NTCP (Na+-taurocholate co-transporting polypeptide), organic anion-transporting polypeptides OATP1B1, OATP1B3 or OATP2B1, as well as in Sf9 cell vesicles expressing BSEP.

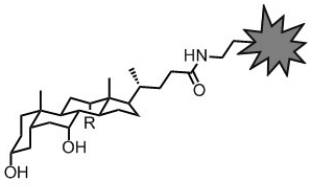
Our data show that the probes are transported with different selectivity with respect to the various transporters and that subtle structural changes can have a significant impact on transport behaviour. As such, our florescent bile salt probes might be promising tools for the selective examination of the individual transport pathways.



R = OH; **Cholic acid** (**CA**)
R = H; **Chenodeoxycholic acid** (**CDCA**)



R = OH; **Glycocholate** (**GC**)
R = H; **Glycochenodeoxycholate** (**GCDC**)



Fluorescent bile salts

Dynamic cooperative glycan assembly blocks binding of bacterial lectins to epithelial cells

T. Machida[1], A. Novoa[1], É. Gillon [2], S. Zheng[3], J. Claudinon[3], T. Eierhoff[3], A. Imberty[2], W. Römer[3], N. Winssinger[1]*

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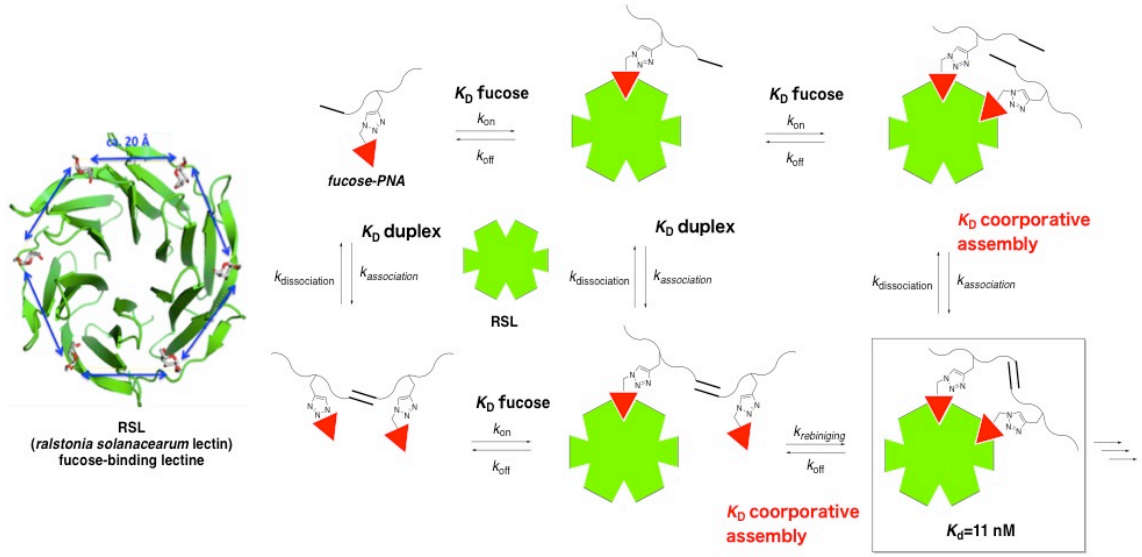
Pathogenic bacterial infection to the host frequently utilizes lectin which recognizes glycan on cell surface of host. Lectin usually has multiple glycan-binding pockets and the multivalent inhibitor which simultaneously blocks multiple pockets is potent anti-bacterial medication strategy.

RSL was successfully blocked by conjugate with fucose and short peptide nucleic acid (PNA) with palindromic sequence (K_D=11 nM) in which neither fucose nor PNA had comparable affinity (fucose: K_D=2200 nM. PNA: GGCC, self hybridization K_D=3800 nM). That suggested that host protein stabilize beneficial dimer formation. This conjugate had IC_{50} of 555 nM to inhibit the binding of fucose-binding lectin BambL to epithelial cells with efficiency of more than 700-hold compared to L-fucose.



1) T. Machida, A. Novoa, É. Gillon, S. Zheng, J. Claudinon, T. Eierhoff, A. Imberty, W. Römer, N. Winssinger, *Angew. Chem. Int. Ed*. **2017**, *in press.*

Boronic Acids Facilitate Oxime and Hydrazone Formation, Leading to a Fluorogenic Variant

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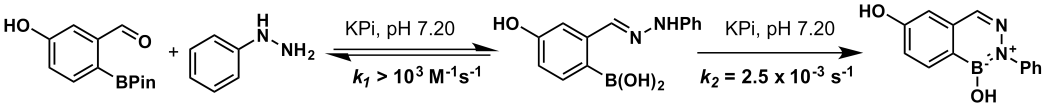
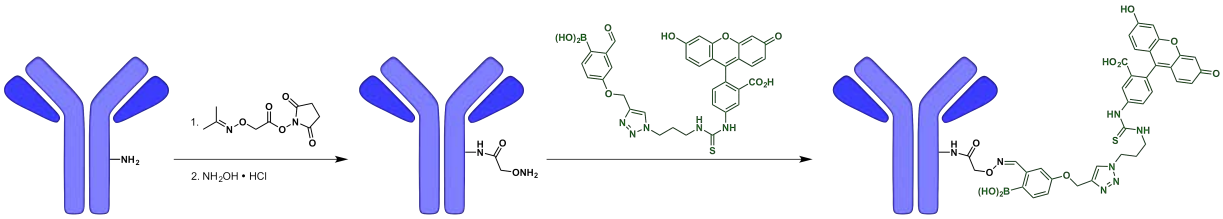
The reaction between α-effect amines (e.g. hydrazines, hydroxylamines) and carbonyls is a very well known method for bioconjugation. The main drawbacks of this reaction is the slow kinetics at neutral pH and the reversibility in aqueous systems. We have recently shown that the incorporation of a boronic acid, which acts as Lewis acid, in close proximity to the carbonyl (aldehyde in our case) greatly enhances the reaction rates under neutral aqueous conditions. We investigated the mechanism for this transformation by HPLC and NMR experiments.
Hydroxylamines and hydrazines show equal efficiency for oxime/hydrazone formations but the latter undergoes a second, much slower intramolecular reaction. The formed boron-containing heteroaromatic compounds (Borazaroisoquinolines, BIQ) were found to be very stable and no reversibility could be detected. Modification of the extended aromatic ring system led to the discovery of a new turn-on fluorophore.



With these results in hand we could create a guidebook for the different α-effect amine condensations. We furthermore used oxime formation for the labeling of an antibody as well as we are currently exploring the scope of these condensation reactions within biological systems.



[1] C. J. Stress, P. J. Schmidt, D. G. Gillingham, *Org. Biomol. Chem.* **2016**, *14*, 5529–5533.
[2] P. Schmidt, C. Stress, D. Gillingham, *Chem. Sci.* **2015**, *6*, 3329–3333.

Native mass spectrometry study of the displacement of proteins bound to DNA G-quadruplexes by small molecules

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G-quadruplexes (G4s) are nucleic acid structures made of stacked guanine quartets, four guanines interacting via hydrogen bonds. G4s are over-represented in key regions of the genome such as in promoters of oncogenes or in telomeres. When formed in gene promoters, it is proposed that the G4 would act as an obstacle for the replication of the gene by acting as a knot.

Many studies report the use of small molecules (called ligands, L) to stabilize G4s and affect these biological events. However, while G4:L interactions are often investigated, whether ligands are able or not to disrupt interactions between G4s and proteins (P) remain poorly studied.

We investigated G4:P interactions and ternary complexes like G4:P:L using native mass spectrometry (native MS). Thanks to advances in soft ionization methods, native MS has become an indispensable tool for the study of biomolecules and noncovalent biomolecule complexes. MS can provide unambiguous information about the stoichiometries of the complexes and their respective abundances. Quantification allows one to determine equilibrium constants.

We have developed a competition experiment in which some of the most potent G4 binders reported in the literature compete with a helicase, an enzyme that recognize G4s and unwind them. We found that these ligands, indeed, compete for the same G4 binding sites as the protein. Therefore, we confirm that they are potential anticancer drugs. Based on this principle, we have screened a chemical library for G4 ligands able to displace the bound protein.

DNA single strands and duplexes with two sequentially incorporated squaraine molecules

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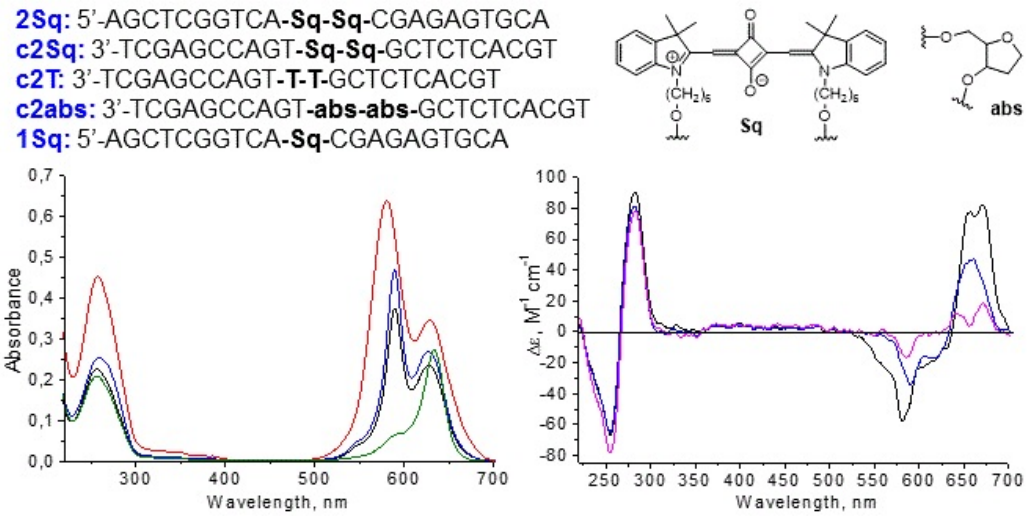
DNA´s remarkable self-recognition properties make it one of the most promising systems for studying interactions between synthetic molecules precisely incorporated into duplexes. Sequence-defined oligonucleotides modified with target molecules can be obtained by solid-phase synthesis using readily available reagents.

In this work, oligonucleotides **2Sq** and **c2Sq** with two squaraine molecules sequentially incorporated in the backbone were synthesized by phosphoramidite approach and their absorption, fluorescence, circular dichroism (CD) spectra and quantum yields (Q.Y.) were studied before and after hybridization. The same spectral properties were investigated for duplexes **2Sq*c2T** and **2Sq*c2abs** where deoxythymidine (**T**) or abasic site (**abs**), correspondingly, were placed opposite squaraine (**Sq**) molecules. Melting temperatures (Tm) of the duplexes were also studied.



Left: absorption spectra of the squaraine-modified oligonucleotides **2Sq** (black), **c2Sq** (blue) and **1Sq** (green) and duplex **2Sq*c2Sq** (red). Right: CD spectra of the duplexes **2Sq*c2Sq** (black), **2Sq*c2T** (magenta) and **2Sq*c2abs** (blue). Conditions: 1 µM of each strand, phosphate buffer 10 mM, NaCl 100 mM.

The incorporation of two **Sq** units into single DNA chain results in the appearance of a new absorption band at shorter wavelength (588 nm *vs*. 633 nm for **1Sq**). Additionally, the quenching of fluorescence is observed (3.1% *vs*. 29% for **1Sq**). These effects are attributed to the dimerization of squaraines by H-type. The hybridization of **2Sq** leads to more pronounced quenching of the fluorescence.

Oligonucleotides **2Sq** and **c2Sq** do not show noticeable CD signals in the spectral range 500-700 nm. However, the CD spectra of the duplexes exhibits the signals with amplitude A = +141 (**2Sq*c2Sq**), +81 (**2Sq*c2abs**) and +36 (**2Sq*c2T**).

Probing the CPEB3 structure by NMR

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[1]University of Zürich

This work is aimed at the investigation of the nuclear magnetic resonance (NMR) solution structure and folding mechanism of the cytoplasmic polyadenylation element binding protein 3 (CPEB3) ribozyme to better understand its catalytic activity. Ribozymes are RNA molecules that act as chemical catalysts in the cells. The discovery of ribozymes was a milestone in RNA research and disclosed the unique role of RNA in a multitude of cellular reactions. The CPEB3 ribozyme is until now the only confirmed ribozyme in mammals and its role remains still elusive.[1] As RNA function is directly linked to structure, structural studies are the basis to understand RNA function.

The CPEB3 secondary structure belongs to the Human Delta Virus (HDV)-like family of self-cleaving ribozymes.[2] Therefore it is suggested that the mechanism of self-cleavage reaction of the CPEB3 ribozyme is very similar to the one of the HDV ribozyme. The cleavage reaction of the HDV follows a Mg^{2+} facilitated acid-base mechanism that is based on a perturbed pK_a of the conserved cytosine C75 in the catalytic core. In analogy to C75 of the HDV, the CPEB3 ribozyme contains a conserved cytosine C57 that might also have an elevated p*K*a value, and could be therefore directly participating in the cleavage reaction. Therefore we started to determine the pK_a value of C57 in the absence and in the presence of Mg^{2+}. The first pH-titrations results of chimp CPEB3 construct with and without Mg^{2+} did not show a shift in pK_a. Another goal of this work is the elucidation of the NMR solution structure of the CPEB3 ribozyme. Using various truncated constructs and labeling schemes in multinuclear and multidimensional NMR spectroscopy, the vast majority of resonances could be unambiguously assigned. We are now introducing 5-fluoro-uridine-5'-triphosphate into the construct using in vitro transcription and apply ^{19}F NMR spectroscopy to support and facilitate the assignment, on the one hand, and on the other hand, to allow to directly follow the folding of the CPEB3 into its active state. These results will be the basis to understand the individual steps of the ribozyme work on a structural level and maybe help to enlighten the biological role of the CPEB3 ribozyme.

Financial support by the University of Zurich and the Swiss National Science Foundation are gratefully acknowledged.

[1] Joel Richter, Trends Biochem Sci, 2007, 32, 279.
[2] Kourosh Salehi-Ashtiani, Andrej Lupták, Alexander Litovchick, Jack Szostak, Science, 2009, 313, 1788-1792.

Catalytic mechanism of a novel type of copper-dependent formylglycine generating enzyme

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Copper is a versatile catalyst for the transfer of electrons from organic matter to molecular oxygen. Some copper-oxygen adducts can cleave very strong C-H bonds. Understanding the nature of these catalytic species is a major scientific objective and allows controlling their specific activities by proteins or synthetic ligands. Mononuclear copper enzymes are a particularly promising class of such catalysts. The formylglycine generating enzyme (FGE) as a novel type of copper-dependent oxidase participates in activation of pro- and eukaryotic sulfatases by converting specific Cys residue into formylglycine (fGly) [1].

The proposed catalytic cycle of FGE *T. curvata* involves the stereo selective C-H bond abstraction as the rate limiting step that was proved by significant KIE = 3.7 ± 0.1 [2]. Recent structural and kinetic evidences identify that Cu(I), bounded to two Cys in the active site of FGE, plays a role of redox cofactor [3].

In this presentation, we will discuss our recent efforts in deciphering the catalytic mechanism of this enzyme.

[1] Jens Fey, et al., *J Biol Chem*, **2001**, 276(50), 47021-8.
[2] Matthias Knop, et al., *Chembiochem*, **2015**, 16(15), 2147-50.
[3] Matthias Knop, et al., *Chembiochem*, **2017**, 18(2), 161-165.

Filling a Transient Subpocket of tRNA-guanine transglycosylase (TGT)

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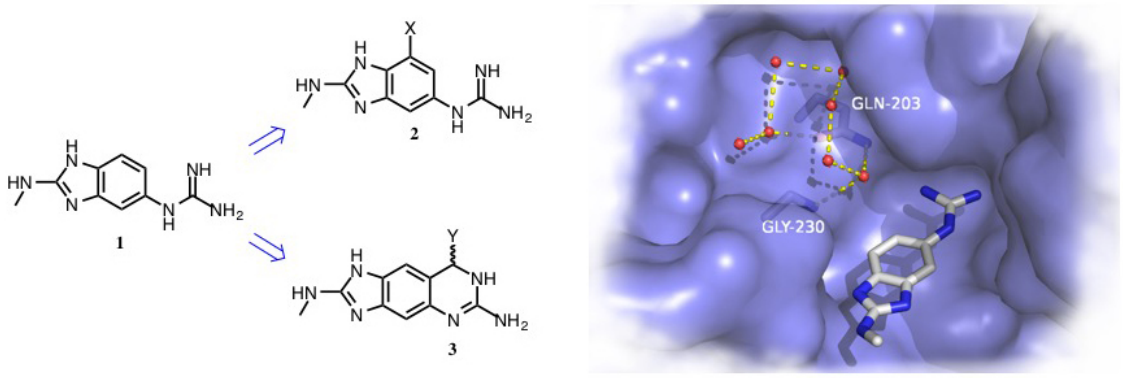
[1]ETH Zurich, [2]Philipps-University Marburg

The bacterial enzyme tRNA-guanine transglycosylase (TGT) plays an important role in the control of virulence of *Shigella flexneri* and is a potential target in the treatment of shigellosis.[1] The active site of bacterial TGT is highly conserved among species, and the enzyme is only active as homodimer, whereas in many eukaryotic species TGT is active as a heterodimer.[2] Remarkably, with some benzimidazole-type ligands, tethered to a guanidinium moiety, a small subpocket in the active site of *Z. mobilis* TGT is opened.

An X-ray co-crystal structure of *Z. mobilis* TGT and ligand **1** revealed that the opened subpocket is hydrophilic and filled with water molecules, one of which solvates the Gly230 and Gln203 residues close to the entrance of the transient subpocket.

To exploit the newly opened chemical space for drug development, a series of ligands with vectors targeting this sub-pocket have been prepared (ligand series **2** and **3**). This work presents the synthesis and initial results on the development of a new class of TGT inhibitors occupying the newly observed subpocket.



[1] (a) Simone R. Hörtner, Tina Ritschel, Bernhard Stengl, Christian Kramer, W. Bernd Schweizer, Björn Wagner, Manfred Kansy, Gerhard Klebe, François Diederich, *Angew. Chem. Int. Ed.* **2007**, 46, 8266-269. (b) Yi-Chen Chen, Allen F. Brooks, DeeAnne M. Goodenough-Lashua, Jeffrey D. Kittendorf, Hollis D. Showalter, George A. Garcia, *Nucleic Acid Res*. **2011**, 39, 2834-2844.
[2] Inna Biela, Naomi Tidten-Luksch, Florian Immekus, Serghei Glinca, Tran Xuan Phong Nguyen, Hans-Dieter Derber, Andreas Heine, Gerhard Klebe, *Klaus Reuter PLoS ONE* **2013**, 8, e64240

Design, Synthesis and Biological Characterization of Potent and Selective Molecular Probes for the CREBBP Bromodomain

V. Pascanu[1], A. Dolbois[1], A. Caflisch[1]*, C. Nevado[1]*

[1]University of Zurich

The ε-*N*-acetylation of lysine residues on histone tails is one of the most prevalent post-translational modifications. Bromodomains are protein modules (*ca.* 110 amino acids) that specifically recognize (read) these acetylated marks, mediating protein-protein interactions and their downstream biological function. Therefore, bromodomains are interesting targets for "reprogramming" the epigenome with the potential to access a previously unexplored therapeutic space.[1] Out of 61 different bromodomains identified in humans, BRD4(1) and the BET family have been the most investigated so far, leading to inhibitors already in phase II of clinical trials.[2] In sharp contrast, the biological relevance of other bromodomains, like the CREBBP/EP300, remains unclear.

Originating from an in-silico fragment–based approach, our group has successfully designed, synthesized and biologically characterized a series of acetylbenzene derivatives as potent and selective CREBBP ligands.[3] Based on the information obtained from the X-Ray structure of the parent compound in complex with CREBBP, compounds with improved potency and unprecedented selectivity against BRD4(1) have been identified. These compounds have been further optimized in terms of solubility, cell permeability and PK/PD properties. Furthermore our lead compound has been tagged with a fluorescent probe that facilitates its study in relevant *in vivo* models. This represents a valuable tool for understanding the biological consequences of CREBBP misregulation.

[1]Muller, S.; Filippakopoulos, P.; Knapp, S. *Expert Rev. Mol. Med.*, **2011**, 13, e29.
[2] Filippakopoulos, P.; Knapp, S. *Nat. Rev. Drug Discov.*, **2014**, 13, 337-356.
[3] a) Unzue, A.; Xu, M.; Dong, J.; Wiedmer, L.; Spiliotopoulos, D.; Caflisch, A.; Nevado, C. *J. Med. Chem.*, **2016**, 59, 1350-1356. b) Xu, M.; Unzue, A.; Dong, J.; Spiliotopoulos, D.; Nevado, C.; Caflisch, A. *J. Med. Chem.*, **2016**, 59, 1340-1349. c) Unzue, A.; Zhao, H.; Lolli, G.; Dong, J.; Zhu, J.; Zechner, M.; Dolbois, A.; Caflisch, A.; Nevado, C. *J. Med. Chem.*, **2016**, 59, 3087-3097.

Photocontrolled release of antibiotics and other bioactive molecules from supramolecular hydrogels with green light

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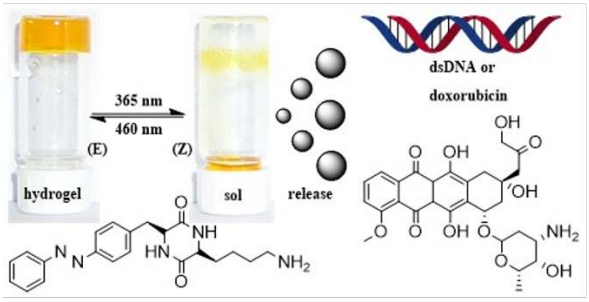
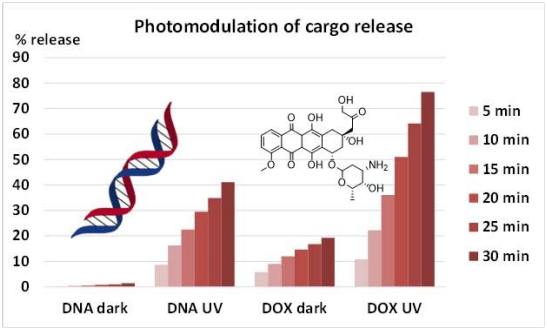
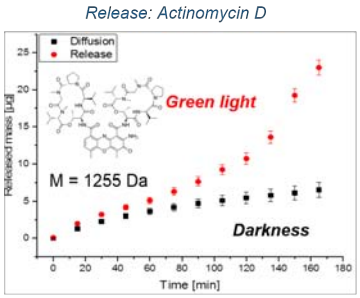
[1]IOC KIT Karlsruhe, Germany

Recently we have reported [1] photoresponsive supramolecular hydrogels based on an azobenzene-containing cyclic dipeptide (or 2,5-diketopiperazine; PAP-DKP-Lys), which is a low-MW hydrogelator. The gelation process can be triggered with temperature, pH, light, and ionic strength. The resulting gels exhibit excellent self-healing properties. In presence of DNA the compound forms hydrogels that release the oligonucleotides upon irradiation with 365 nm UV light. Hydrogels formed in presence of anticancer drug doxorubicin also release the cargo in a light-dependent manner.

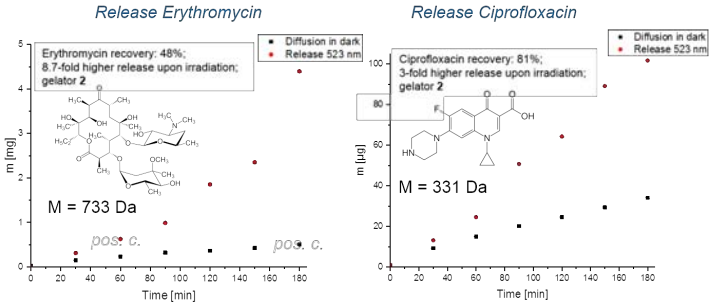




The current report regards modified supramolecular hydrogel matrix, which now became capable of efficiently releasing cargo molecules upon irradiation with green light (530 nm). In case of antibiotic molecules as guest, we achieved up to eight-fold release discrimination between samples irradiated with green light and those kept in darkness. [2]



actinomycin D - antibiotic and an anticancer drug (i. A. testicular cancer, ovarian cancer)



Erythromycin and Ciprofloxacin are antibiotics useful for the treatment of a number of bacterial infections

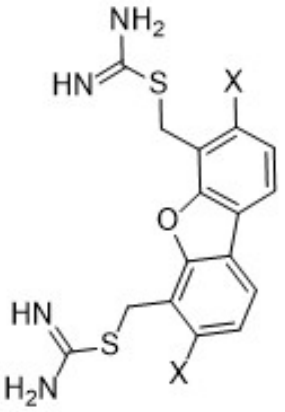
[1] Zbigniew Pianowski*, Johannes Karcher, Knut Schneider, *Chem. Commun.* **2016**, *52,* 3143-3146
[2] Johannes Karcher, Zbigniew Pianowski* *manuscript in preparation*
[3] Zbigniew Pianowski, Johannes Karcher, Knut Schneider, *German patent application 10* ***2015*** *014 834.6 (pending)*

Synthesis and characterization of DMT1 inhibitors

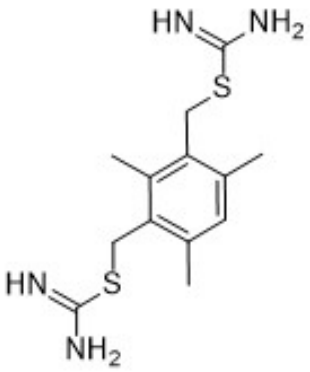
M. Poirier[1], J. Pujol-Gimenez[2], C. Manatschal[3], I. Ehrnstorfer[3], R. Dutzler[3], J. L. Reymond[1]*, M. A. Hediger[2]*

[1]Department of Chemistry and Biochemistry, [2]IBMM, [3]Department of Biochemistry

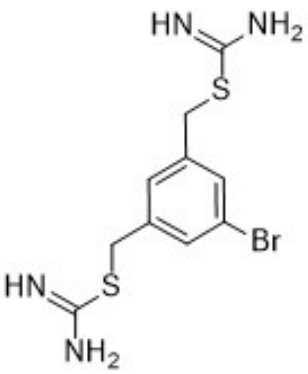
DMT1 is a proton coupled iron transporter which plays an essential role in iron homeostasis, and whose deregulation is linked to hemochromatosis. In the context of studying the structure and biological role of DMT1 in iron overload, we aim to obtain potent and selective small molecule inhibitor tool compounds. As a starting point we resynthesized the bis-cationic inhibitors **1, 2** and **3** previously reported by Cadieux *et al.*, [1], and confirmed their activity using both a radiolabeled iron uptake assay, although to a lower level than the reported values. We further confirmed their inhibitory activity using a fluorescence assay [2] as well as by electrophysiology in *Xenopus laevis* oocytes, and prepared heavy atom analogs such as the bromo-aromatic derivative **4** to assist structural studies. Inhibitory activity was further explored with purified prokaryotic DMT1 analogs [3] in proteoliposomes, and in ex-vivo intestinal iron uptake assay. These data show that these bis-cationic inhibitors represent a robust starting point to develop more potent analogs as DMT1 tool compounds.



1 (X = Br, IC_{50} = 1.52 µM *(lit.: 0.11 µM)*)
2 (X = H, IC_{50} = 1.83 µM *(lit.: 0.05 µM)*)



3 IC_{50} = 0.35 µM



4 IC_{50} = 4.66 µM

[1] Cadieux *et al, Bioorganic & Medicinal Chemistry Letters*, **2012,** *22*, 5108 – 5113.
[2] Montalbetti *et al. J Biomol. Screen.,* **2014**, *19,* 900 - 908**.**
[3] Ehrnstorfer *et al*., *Nat Struct Mol Biol*., **2014,** 21, 990 – 6. Ehrnstorfer *et al*., *Nature Communication,* **2017,** 8, 14033.

^{1}H HR-MAS NMR based metabolomics of cells lines responding to treatment with the diruthenium trithiolato complex $[(p\text{-}MeC_6H_4{}^{i}Pr)_2Ru_2(SC_6H_4\text{-}p\text{-}Bu^{t})_3]^+$ (DiRu-1)

H. Primasova[1], L. E. Paul[1], M. Vermathen[1], G. Diserens[2], P. Vermathen[2], J. Furrer[1]*

[1]Departement für Chemie und Biochemie, Universität Bern, Freiestrasse 3, CH-3012 Bern, Switzerland, [2]Departement Klinische Forschung und Radiologie, Universität Bern, Erlachstr. 9a, CH-3012 Bern, Switzerland

The diruthenium trithiolato complex $[(p\text{-}MeC_6H_4iPr)_2Ru_2(SC_6H_4\text{-}p\text{-}Bu^{t})_3]^+$ (DiRu-1) is highly toxic against human ovarian cancer cells A2780 and the corresponding ciscisplatin resistant variant A2780cisR in vitro with IC_{50} value of 0.03 µM [1]. In vivo experiments showed that the survival rate of mice could be significantly prolonged using DiRu-1 compared to cisplatin, and proved presence of ruthenium in cancer cells. In vitro measurements revealed inhibition of mitochondrial respiration and decrease in glutathione levels [2], and showed that DiRu-1 causes increased levels of reactive oxygen species (ROS) in cells and induces caspase-driven apoptosis in estrogen-responsive breast adenocarcinoma (MCF-7) cells as well as necrosis, mitotic catastrophe, necrosis and autopaghy [3].

In order to gain more insight into its modes of action, ^{1}H high resolution magic angle spinning (HR-MAS) NMR spectroscopy was employed to analyze the metabolic profile of ovarian cancer cells A2780, A2780cisR, and Human embryonic kidney cells HEK-293, used as a model for healthy cells treated with 0.03 µM and 0.015 µM of DiRu-1, respectively, for 24 h. The data have been analyzed using a classical principal component analysis (PCA) and partial least squares discriminant analysis (PLS-DA) to evaluate the effects of the treatment by DiRu-1 on the metabolic profile and to provide a hint on metabolites or groups of metabolites correlated with the cellular response, as shown previously for a ruthenium hexacationic metallaprism [4].

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Unpacking the Black Box: Facilitating Visual Inspection of Large Datasets by Means of Interactive Web-Based Visualizations

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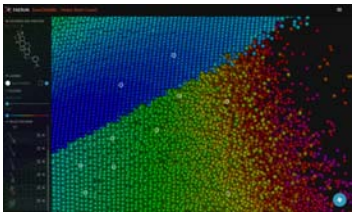
During the past decade, big data has become a major tool in scientific endeavours. While statistical methods and algorithms are well-suited for analysing and summarizing enormous amounts of data, the results do not allow for a visual inspection of the entire data. Current scientific software, including R packages and Python libraries, do not support interactive visualizations of large datasets. However, recent hardware developments, especially advancements in low energy graphical processing units (GPUs), allow for the rendering of millions of data points on a wide range of consumer hardware like laptops, tablets and mobile phones. Similar to the challenges and opportunities brought to virtually every scientific field by big data[1], both the visualization of and interaction with copious amounts of data is both demanding and holds great promise.



Building on the Java-based mapplets our group has published in the past[2], we work on furthering the concept of interactively exploring chemical data in spatial representations as a complement to searching the data, which is often the only way to access databases such as ChEMBL, SureChEMBL or even relatively small data sets such as Drugbank. Given recent developments in web technology and broadband infrastructure, we focus our work on web-based applications[3,4].

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Using “old methods” to solve new structures: crystallization of the human CPEB3 ribozyme

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Catalytically active RNA called ribozymes play substantial roles in a variety of biological functions including protein synthesis (ribosome), tRNA maturation (RNase P) and RNA splicing (group I and II introns). Ribozymes are much more widely distributed than previously thought and understanding their structure and function is the focus of many studies. One of the best studied ribozymes is the hepatitis delta virus (HDV) ribozyme originally identified in the human pathogen. So far, the HDV ribozyme is the fastest naturally occurring ribozyme known with a cleavage rate of more than 1 per second at 65°C (**1**). Its crystal structure was reveled in 1998 revealing the complex fold in a nested double pseudoknot with 5 paired regions that form two coaxial stacks, which are linked by single-stranded joining strands (**1**). In 2006, the genome-wide search identified the human cytoplasmic polyadenylation element-binding protein 3 (hCPEB3) ribozyme as the first HDV-like ribozyme (**2**). This small ribozyme (68 nucleotides) is located within the second intron of a single-copy gene and is highly conserved in all mammalians. Its exact function is yet unknown but it may be involved in the regulation of CPEB3 mRNA stability. However, CPEB3 proteins are known to be crucial for synaptic plasticity and memory (**3**). Most of our knowledge on the CPEB3 ribozyme folding and activity is based on comparative studies with the HDV ribozyme (**4**). Like all HDV-like ribozymes, CPEB3 ribozymes folds into a double-pseudoknot structure (**5**) and possesses an active-site cytosine (C57) located in the J4/2. However, the hCPEB3 ribozyme cleavage rate is much slower compared to HDV ribozyme. Even if, the primary nucleotide sequence of both ribozymes are very different (with exception of severals nucleotides including catalytic cytosine), their secondary structures and their role in separation of multimeric precursor claimed the new hypothesis that HDV ribozyme may have arise from ancestral hCPEB3 (**6**).

In order to better understand the complex folding that leads to cleavage activity of hCPEB3 ribozyme, we aim o solve the three-dimension structure by X-ray crystallography. However, many factors affect crystallizability of RNA sample including purity, homogeneity, ligand binding and structural dynamics. In order to stabilize the structure of hCPBE3 and to improve its crystallization, we follow different strategies which will be presented.

Financial support from the University of Zürich and the Swiss National Science Foundation is gratefully, acknowledged.

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Organometallic cobalamin anticancer derivatives for targeted prodrug delivery via transcobalamin-mediated uptake

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Cobalamin (Cbl, vitamin B12) is a water-soluble vitamin of primary importance to the metabolism of every cell in the human body. Once ingested, it is actively carried by proteins and ultimately internalized into the cells by a receptor-mediated endocytosis. Confined inside the cell, the cobalt center of Cbl undergoes a series of enzymatic reductions that triggers therelease of the β-axial ligand. Over the past few years, this feature has been explored in order to use vitamin B12 against cancer cells in the manner of a Trojan horse. Indeed, the ability of the cyanide ligand in CNCbl to bridge metal centers has been successfully used to attach metal complexes[1]. Based on recent advances in organometallic chemistry applied to Cbl[2,3], a new structural design was developed[4] and resumed herein. This approach offers the advantage of: 1. a better comparison between the cytotoxity of the complexes before their attachment to Cbl and after their release inside the cells; 2. a broader range of imaginable motifs; 3. an increased water solubility of the complexes.

Thus far, a series of fours vitamin derivatives of Pt (B12-1), Ru (B12-2 and B12-3) and Re (B12-4) were prepared and characterized (see Image). As a common structure, the attached complexes exhibit a bipyridine modified at the para position with a simple alkyne. The latter serves as a point of attachment between the cobalt of Cbl and the anticancer metal complexes. Chemical reduction using either cobaltocene or Zinc showed that the four complexes are released entirely from Cbl.

In term of serum stability, both ruthenium derivatives showed no evidence of human serum albumin binding after 24h. On the other hand, the free fraction of the Pt derivative was measured at 61% and 40% for the Re in the same period. B12-4 andB12-3 showed comparable/lower cytotoxicity to that of cisplatin, while B12-1 was less effective and B12-2 essentially non-cytotoxic. To measure the affinity of the derivatives with Cbl carrier proteins (TCII and IF), a fluorescent B12 (B12-CBC) [5] was prepared in order to perform competitive displacement assays which indicated that our derivatives are recognized by these transport proteins. Furthermore, fluorescence imaging show that the compound were internalized inside the cells and that they followed the natural cobalamin uptake.

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Enzymatic construction of metallo-DNA

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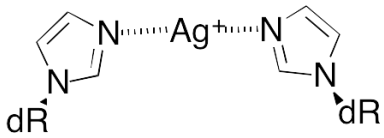
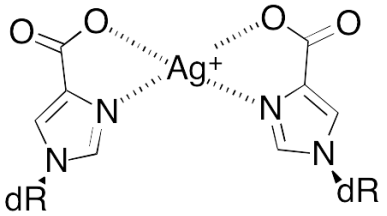
The expansion of the genetic alphabet using an artificial base pair is of high relevance in synthetic biology and could augment nucleic acid functionalities by increasing their components. Efforts in this context have produced several types of unnatural base analogs that are well tolerated by enzymes *in vivo* and *in vitro* during replication and transcription. Surprisingly, the enzymatic formation of artificial metal base pair has been vastly under-explored. These base pairs are interesting candidates for the expansion of the genetic alphabet since they are fully orthogonal to the natural Watson-Crick base pairs and marginally distort the duplex structure. Apart from the metal mediated incorporation of of **T-Hg-T** [1] or **C-Ag-T** [2] there are only a very few examples of fully orthogonal incorporations such as the **Sal-Cu-Sal** [3] or the **Pur^{DC}-Cu-3-Py** [4]. Herein, we investigated on the potential incorporation of imidazol (**dIm**) base analogs since they are known to have beneficial thermodynamic properties and only marginally distort the duplex structure.



dIm

dIm



dClm

dClm

A biochemical analysis allowed to show us that templated incorporation of **dImTP** occurs selectively and this analog has potential to act as an orthogonal nucleotide. However, the incorporation occurs also under metal free conditions and shows limitations regarding multiple inclusions of **dImTP** [5]. Thus, thermodynamic and minimal structural changes to the duplex are not the only factors to be considered when designing the enzymatic construction of orthogonal metal base pairs. A second generation imdiazol base analog bearing an additional carboxylic metal coordinating site (**dClm**) was synthesized to better understand the enzymatic incorporation of metal base pairs. Currently the acceptance of ligases and terminal transferases for metalllo base nucleotides is analyzed in order to study the formation of long stretches of DNA-metal chains or develop polyimidazol tags with a high affinity to metal cations [6].

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Kinase Templated Abiotic Reaction

J. Saarbach[1], E. Lindberg[1], S. Folliet[1], S. Georgeon[2], O. Hantschel[2]*, S. Soleimanpour[1]*

[1]Faculty of Science, Department of Organic Chemistry, NCCR Chemical Biology, University of Geneva, 30 quai Ernest Ansermet, Geneva, Switzerland, [2]Swiss Institute for Experimental Cancer Research (ISREC), NCCR Chemical Biology, School of Life Sciences, École Polytechnique Fédérale de Lausanne (EPFL), CH-1015 Lausanne, Switzerland

Protein kinases are essential regulators of cellular signalling and have been at the centre stage of drug discovery for the past decade. The successful development of kinase inhibitors demonstrated that kinases were drugable and triggered tremendous research effort in this area. However, inhibitors developed so far often target the conserved ATP binding site of the protein and thus are lacking selectivity[1], and the more selective ones are targeting an inactive form of the protein. These features limit their use as chemical probes to sense kinase activity. Herein we report a strategy based on two reacting probes[2] targeting both nucleotide and substrate binding sites[3]. The reaction used[4] allows to use fluorescence readout to selectively sense Abl of Src kinase activity both in biochemical and fixed whole cell experiments.

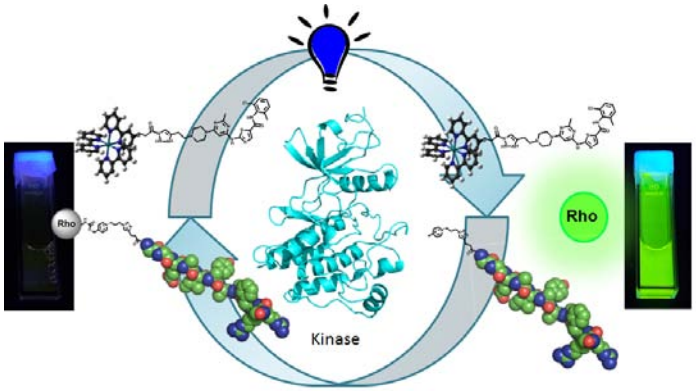

Fig1. Cartoon of fluorophore release through the reaction templated by Abl kinase (PDB: 2GQG)

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Can Polymeric Nanoparticles protect Porphyrinic Compounds from reacting with Proteins? – An NMR Spectroscopic Investigation

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In Photodynamic therapy (PDT), porphyrinic compounds can be used as photosensitizers (PSs), owing to favourable features such as low dark toxicity, high singlet oxygen quantum yield and absorption bands in the spectral region of red light. To overcome a major drawback of porphyrinic compounds, which is self-aggregation in aqueous media and as consequence a diminishing effect on these favourable features, polymeric nanoparticles have been used for encapsulating and thus monomerizing them. [1]

Previously, we tested systems consisting of serine chlorin e6 (SerCE), an amphiphilic PS, and either kolliphor 188 (KP), a micelle forming poloxamer, or polyvinylpyrrolidone (PVP) as carriers for their capability of protecting the PS from reacting with five abundant human proteins. [2] In addition, the interaction between the PS and phospholipid bilayers was probed, where an affinity towards the membrane could be observed. For these investigations ^{1}H - and DOSY-NMR measurements were performed. The results suggested that without being embedded in a carrier system, SerCE reacts immediately with all five proteins tested. Different results were obtained in the presence of the carrier systems KP and PVP. PVP was able to protect the PS from reacting with all the proteins. In the presence of KP micelles, a reaction between the PS and serum albumin occurred immediately and a delayed one with myoglobin. These results demonstrated the importance of the carrier as a protective system against proteins and potentially other molecules. The lack of stability observed for the SerCE-KP system against HSA and Mb led us to the hypothesis that increasing the affinity between the PS and the polymer may enhance the stability of poloxamer-based micellar carrier systems,

Therefore, our current investigation is focused on the more hydrophobic compounds chlorin e6 dimethyl- and trimethyl ester, chlorin e4 and chlorin e6 mono ethylene diamine monoamide. They are investigated with respect to incorporation into polymeric carrier systems, loading capacity, and stability against proteins. For these hydrophobic chlorin derivatives, the carrier is essential for overcoming the problem of insolubility in aqueous media. Moreover, a higher affinity towards cell membranes is expected for these compounds, owing to their more lipophilic nature. Preliminary results obtained with this class of compounds will be presented and compared to the previously investigated amphiphilic SerCE.

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Diaryl Borinic Acids Modulate Store-operated Calcium Entry (SOCE)

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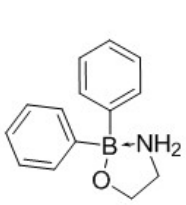
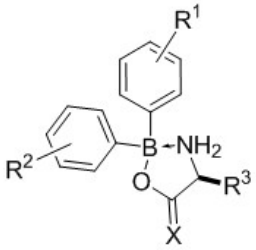
The intracellular Ca^{2+} concentration is carefully controlled, as changes in $[Ca^{2+}]_i$ mediates a plethora of cellular and ultimately physiological processes, such as cell differentiation, muscle contraction, neurotransmission, proliferation and immune cell mobility, among many others.

Intracellular Ca^{2+} is stored in the endoplasmic reticulum (ER) and released upon activation of ER-receptors (e.g. IP_3). Refilling of the ER Ca^{2+} stores requires an intricate interplay and assembly between Ca^{2+} sensing proteins (STIM1 and STIM2) located in the ER membrane and proteins (Orai1, 2 and 3) in the plasma membrane. The resulting STIM/Orai complexes form a Ca^{2+} channel that causes a measurable calcium-release activated calcium current (I_{CRAC}). Mutations in STIM or Orai that either cause enhanced or reduced store-operated calcium entry (SOCE) have been associated with muscular and immunodeficiency diseases, respectively.

Diphenyl borinate 2-APB (**1**) exhibits a dual function on SOCE, as it blocks at high concentration (e.g. 50 µM) but potentiates SOCE at lower concentrations (e.g. 5 µM). In this work, we present the synthesis of novel 2-APB analogues (**2**), some of their crystal structures and their concentration-dependent influence on SOCE. Specifically, we have investigated Orai-subtype selectivity (Orai1 vs. Orai3) and have also generated some fluorescent 2-APB congeners.



1: 2-APB



2: X = H_2 or O

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Olfaction of biologically relevant vapors

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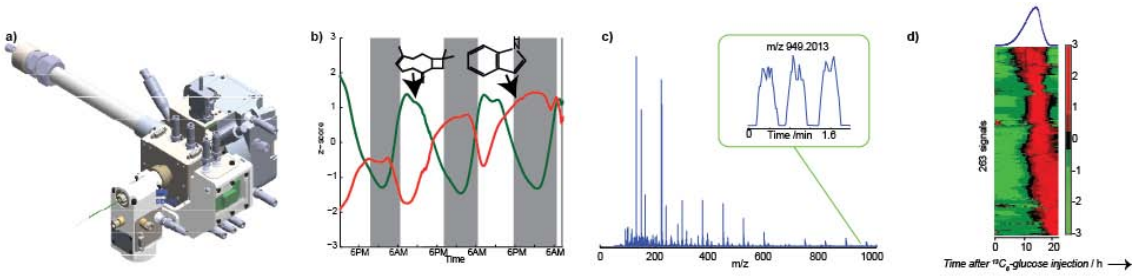
The analysis of trace gases is of paramount importance in a wide range of applications. We have developed analytical instrumentation to address these needs. A secondary electrospray ionization source has been constructed and tested to detect vapors in metabolomics applications.[1] *Ion source development:* Figure 1a shows the ion source developed in collaboration between ETH and an industrial partner. The geometry has been numerically optimized to analyze continuous gas flows as low as 0.5 L/min. *Plant emissions:* Figure 1 b shows two examples of real-time traces captured during monitoring of plant emissions during the course of three consecutive days.[2] *Breath analysis:* Figure 1c shows a breath mass spectrum, whereby new species as high as m/z 949.2 were detected for the first time.[3] *Yeast volatile metabolomics:* Figure 1d displays a heatmap showing 263 time-dependent signals detected in vivo during yeast growth. For reference, the ethanol signal is shown on the top. We conclude that commercial atmospheric pressure ionization mass spectrometers can be upgraded into sensitive real-time sniffers for a variety of applications.



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Combinatorial Discovery of Broad Spectrum Antimicrobial Peptide Dendrimers

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Multi-drug resistant bacteria (MDR) are major threat to public health and lead to untreatable infections. Notable pathogens include Gram-negatives such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii,* and Gram-positives such as Methicillin-resistant *Staphylococcus aureus* (MRSA). We have recently reported that peptide dendrimers with multiple cationic and hydrophobic groups can exert potent antibacterial effects by a membrane disruptive effect.[1] However, our most active antimicrobial peptide dendrimer (AMPD) **G3KL** was 37 residues in size and was therefore too large for practical application. Here we focused on discovering much smaller AMPDs using our previously reported combinatorial approach to peptide dendrimers.[2] We prepared a combinatorial library of potentially membrane active peptide dendrimers on a photolabile support[3, 4] and screened them for antimicrobial activity against *P. aeruginosa* using an agar-plate assay tailored for library screening.[5] Bead decoding, resynthesis and testing revealed several particularly potent antimicrobial peptide dendrimers (AMPDs). These AMPDs are much smaller than our previous best compound **G3KL** yet also act by a membrane disruptive mechanism similar to that of polymyxin. Most remarkably, our new AMPDs can be readily prepared in large scale with excellent isolated yields, and show activity against both Gram positive and Gram negative MRD strains including MRSA.

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Transporters for Thiol-Mediated Uptake

N. Chuard[1], P. Morelli[1], E. Bartolami[1], L. Zong[1], S. Lörcher[2], C. G. Palivan[2], W. Meier[2], S. Matile[1]*

[1]University of Geneva, [2]University of Basel

The delivery of functional substrates into living cells is one of the main challenges in chemistry and biochemistry. In order to address this, we have developed two type of transporters: Cell-penetrating poly(disulfide)s (CPDs) and strained cyclic disulfides.[1] The efficiency of uptake for both methods involves the underestimated thiol-mediated uptake coupled with counterion-mediated uptake for CPDs and ring tension release for strained cyclic disulfides. A large variety of compounds have been delivered by those transporters, from small molecules such as fluorophores[1,2] to giant substrates such as liposomes and polymersomes.[3] Different strategies are now being investigated to broaden the scope of substrates to be delivered such as the streptavidin/biotin technology, side-chain and terminator functionalization for CPDs, and new cyclic molecules for strained-promoted thiol-mediated uptake as presented in Figure 1.

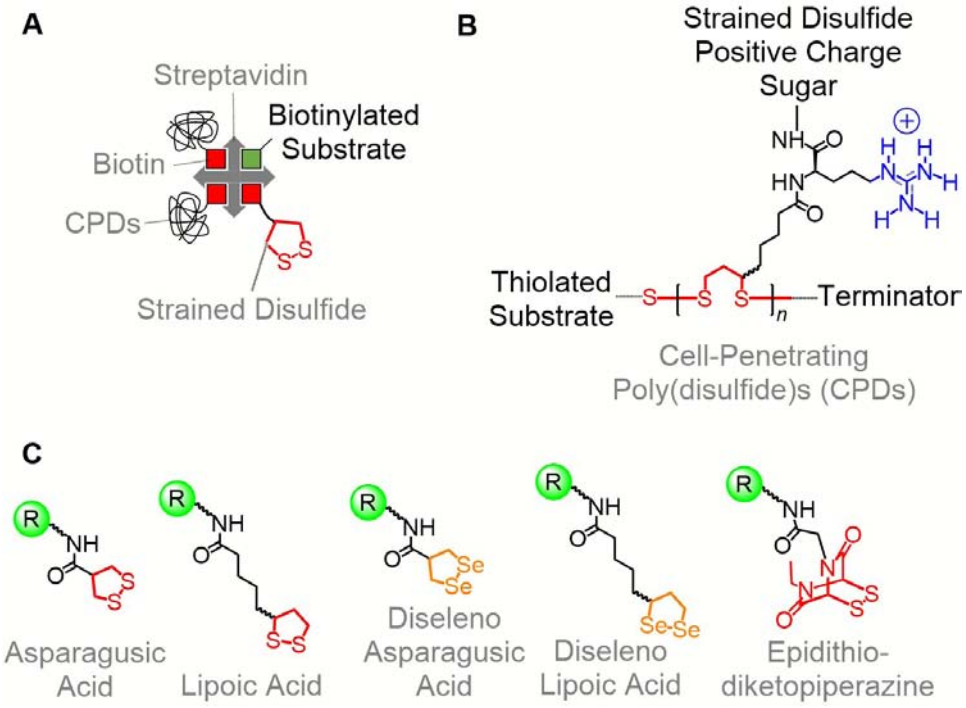

Figure 1. Transporters for thiol-mediated uptake. Streptavidin complexes are formed with a biotinylated substrate and multiple CPDs or strained disulfides (A). The substrate can be directly attached to CPDs (B). Library of compounds for strained cyclic thiol-mediated uptake (C).

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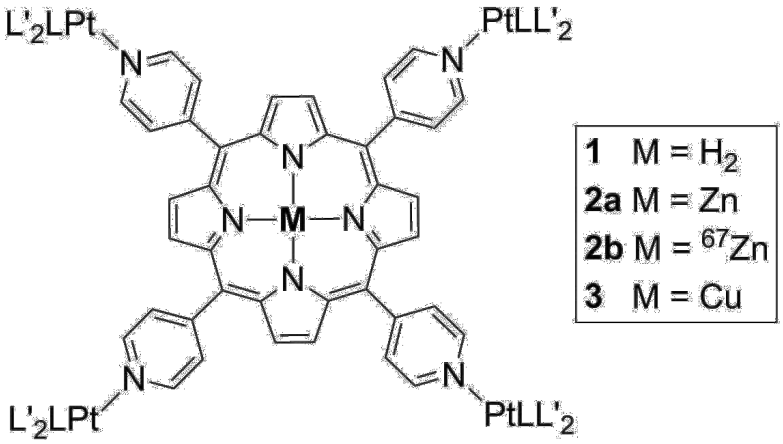
What is the Influence of the Central Metal Atom in Platinum-Porphyrin Conjugates on their Phototoxicity?

B. Spingler[1], M. Larocca[1], R. Rubbiani[1], A. Naik[1], G. Gasser[1,2]

[1]University of Zurich, [2]Chimie ParisTech, PSL Research University

Our group has reported recently about the very promising *in vitro* light-induced anticancer properties of novel tetraplatinated porphyrins **1**.[1] This family of platinum-porphyrin conjugates **1** had only minor dark toxicity, however upon visible light irradiation (420 or 575 nm), IC_{50} values down to 19 ± 4 nM could be observed. These values correspond to an excellent phototoxic index (PI = IC_{50} dark / IC_{50} light) of greater than 5000.



We have now started to study similar systems that contain a metal in the central position of the porphyrin (**2** and **3**). We will discuss the influence of the metal on the singlet oxygen yield, cellular dark and (photo)toxicity as well as cellular localisation. For the latter we employed the isotopically labelled ^{67}Zn complex **2b** in order to determine, by ICP-MS, the cellular distribution of ^{67}Zn and platinum, which in turn allowed us to study the stability of the platinum - pyridine nitrogen bond within the cells. We included the copper(II) **3**, since we previously discovered the first phototoxic copper(II) complex of a porphyrin.[2]

Acknowledgements

We thank for financial support by the University of Zurich and the Swiss National Science Foundation.

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Escape from ‘availability bias’ in compound design

A. Stracz[1], A. Tarcsay[1], G. Imre[1], I. Solt[1]

[1]ChemAxon

Small molecule design is an information demanding activity, since all relevant knowledge is to be accessible within a single space and requires synchronized application of computational models to assist decision making on synthesis candidates. Our study aims to evaluate a software platform coping with this complexity (Marvin Live[1]). The tool provides central management of innovative ideas and helps triage them based on predicted properties and available knowledge collected from a variety of sources. The calculated properties span phys-chem descriptors, combined metrics like MPO score[2], 3D overlay and modelling results conducted with KNIME. Use cases of rapid freedom to operate analysis by ultra-fast searching (MadFast Similarity Search[3]) of exemplified structures from patents (SureChEMBL[4], ~16M entries) and SAR by catalog via searching large set of synthesizable compounds (Enamine REAL DataBase[5], ~170M entries) real time will be shown to ensure that designers can seamlessly exploit the chemical space around their ideas. The presentation will walk through an example drug design cycle to obtain statistical results regarding performance as well as to demonstrate the suitability of the calculations.

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Para-Substituted-Phenazopyridines (PAP) Demonstrate Enhanced Potency in Early Neuronal Differentiation of ES Cells Compared to PAP.

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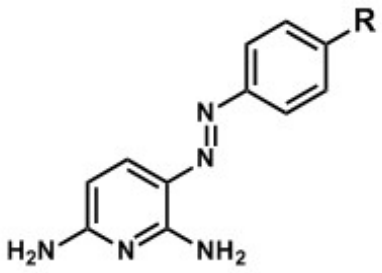
Embryonic stem (ES) cells are powerful tools to understand mechanisms of neuronal differentiation and to engineer neurons for in vitro studies and cell therapy. The team of Prof. Krause, University of Geneva, developed a screening approach to identify small organic molecules driving neuronal differentiation of ES cells[1]. Phenazopyridine (PAP) resulted as positive validated hits from the screening campaign. Phenazopyridine is a drug that is rapidly excreted into the urine and has a local analgesic effect. In a first SAR study, it was demonstrated that PAP and few analogues enhanced neuronal differentiation, increased cell survival, decreased the amount of non-neuronal and undifferentiated cells and synchronized the cellular differentiation state. In the present study aiming at expanding the SAR study and develop PAP derivatives with enhanced potency compared to PAP, we synthetized a series of 20 original analogues of PAP exploiting different approaches in the diazotation reaction[2].



para-substituted Phenazopyridine PAP

The para-substituted-PAPs showed up to 250 fold potency increase in early neuronal differentiation compared to PAP (EC50 = 7.7 mM). This work led to the discovery of more potent compounds that will further foster the development of differentiation protocols compatible with the generation of clinical grade neural precursors, which are able to differentiate into different neuronal subtypes, astrocytes and oligodendrocytes.

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Photoactivatable phosphine probes for the induction of intracellular reductive stress

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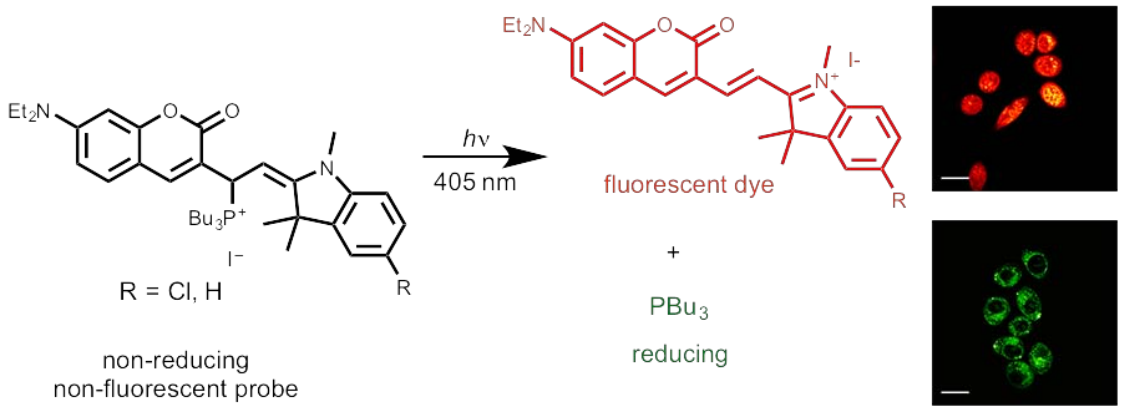
[1]Laboratorium für Organische Chemie, ETH Zürich, Vladimir-Prelog-Weg 1-5/10, 8093 Zürich

Reductive stress is a result of redox homeostasis imbalance towards more reducing species inside the cell.[1] This condition has been associated with numerous pathologies, such as cancer, inflammation, metabolic disorders and neurodegenerative diseases. Reductive stress can be induced by some pharmacological agents which contain free thiols, but, even though efficient, these reagents lack spatiotemporal resolution.[2,3]

Photoactivatable probes are an important class of molecules as they can be used to release bioactive compounds with spatiotemporal control.[4,5] We have developed a photoactivatable phosphine probe that is cell-permeable, and, upon photoactivation, releases a fluorescent reporter dye and a trialkylphosphine that induces intracellular reductive stress, followed by formation of protein aggregates which were identified with Thioflavin T.[6]



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Synthesis of novel probes based on GSK7975A to study SOCE

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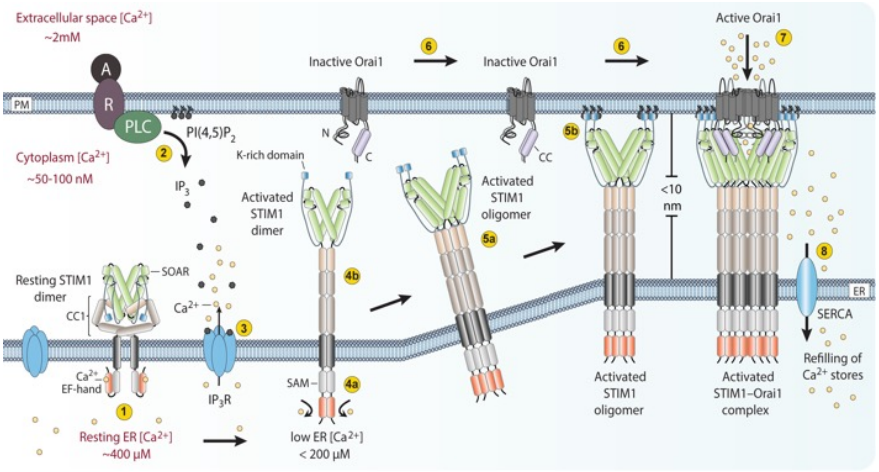
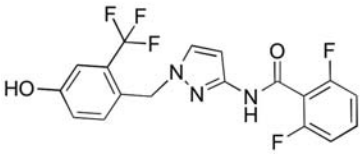
A wide array of physiological functions including cell differentiation, proliferation, muscle contraction, neurotransmission and fertilization are regulated by calcium cations. Ca^{2+} signaling pathways that induce endoplasmic reticulum store depletion trigger a refilling process known as store operated Ca^{2+} entry (SOCE). Enhanced SOCE has been associated with severe diseases such as several types of cancer (e.g. breast, prostate). Deficiency of SOCE has been related to immunodeficiency and autoimmune diseases.

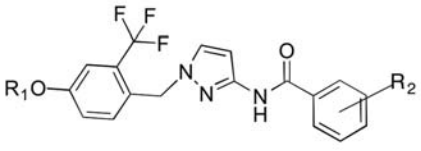


To provide a better understanding of the process of SOCE and the proteins involved (i.e. Orai, STIM), we synthesized novel probes based on the known SOCE-inhibitor GSK7975A. This class of inhibitors feature two functionalities: a photo-crosslinking moiety for covalent target modification as well as a handle for bioorthogonal chemical modifications. Herein, we present the synthesis of these novel probes and their preliminary biological assessment.

GSK7975A



Novel probes featuring additional functionalities



Peptidomimetic antibiotics targeting essential outer membrane proteins as a new weapon in the fight against resistance in Gram-negative bacteria

M. O. Urfer[1], J. A. Robinson[1]*

[1]University of Zürich

Infectious diseases and the emergence of new multi-drug resistant (MDR) bacteria are one of the major contributors to human morbidity, and it has become a pressing issue to find new antibiotic classes, which can kill bacteria via novel mechanisms of action. Although synthetic med-chem approaches have allowed the discovery of some antibiotics (sulphonamides, quinolones and oxazolidinone), most of them have been isolated from natural sources. The cationic antimicrobial peptides (CAMPs) are naturally occurring molecules acting in the innate immune systems of many organisms. We have shown that CAMPs provide an important source of inspiration for the discovery of new antibiotics with novel mechanisms of action.

The β-hairpin is a recurring structural motive found in naturally occurring CAMPs, which also often mediates protein-protein and protein-nucleic acid interactions. The design of protein epitope mimetics (PEMs) based on this structural motive is now recognized as a successful approach for antimicrobial discovery [1]. A new family of ß-hairpin antibiotics based on the antimicrobial peptide protegrin-I was synthesized, and several rounds of optimization gave L27-11 as a novel pseudomonas-specific antibiotic. A clinical lead compound called murepavadin (POL7080) active in the nanomolar range against Gram-negative *Pseudomonas* spp. is now in clinical development, but is largely inactive against other Gram-negative and Gram-positive bacteria. Studies on the mode of action of L27-11 showed that the peptidomimetic targets the essential β-barrel protein LptD, which functions in outer-membrane biogenesis [2]. Based on the same approach, another interesting peptidomimetic antibiotic was discovered, called JB-95, with potent antimicrobial activity against *Escherichia coli*. Studies on its mode of action showed that JB-95 could selectively destabilize the OM but not the inner membrane of *E. coli,* likely through interaction with selected β-barrel OM proteins, including BamA and LptD [3].

These discoveries have proven the importance of essential OM proteins in Gram-negative bacteria as targets to kill Gram-negative bacteria, and opened a door for the discovery of new clinical candidates. The vast possibilities in PEM design to find new specific antibacterial agents are still underexploited. The ability to target essential bacterial proteins, including for example the lipopolysaccharide transport (Lpt) machinery, can provide new weapons to fight antimicrobial resistance.

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Artificial lipid droplets as a model lipid system

V. Vezočnik[1], S. Sitar[2], K. Kogej[1], M. Tušek-Žnidarič[3], V. Hodnik[1], K. Sepčić[1], E. Žagar[2], P. Maček[1]*

[1]University of Ljubljana, [2]National Institute of Chemistry Slovenia, [3]National Institute of Biology Slovenia

After a century of being underappreciated, natural lipid droplets (LDs) have been finally recognised as important intracellular organelles. Due to the recent discovery of their involvement in various diseases, such as cancer, atherosclerosis or obesity, this area is the subject of intensive research that requires the use of fundamental knowledge. Since the natural systems are complex and unstable, we prepared model artificial LDs with controlled characteristics, using natural lipids.

Our research is aimed to improve preparation and characterization of artificial lipid droplets, nanoemulsions of LDs composed of trioleoylglycerol core covered by a monolayer of sphingomyelin (SM) and cholesterol (Chol). So far, it has been confirmed that those artificial lipid species share many physico-chemical characteristic in common with natural LDs. Furthermore, nanoemulsions covered by a SM/Chol monolayer have been very poorly characterized in contrast to respective SM/Chol vesicles. For that reason, a first detailed characterization of this lipid system has been made using several (bio)chemical and (bio)physical methods and techniques. In parallel, large unilamellar vesicles (LUVs) have been studied, too.

Additionally, a combined modified reverse-phase evaporation/ultrasonication method has been developed for the LDs preparation. Stable LDs and LUVs in controllable sizes in the range of 140 nm to 200 nm for the SM/Chol molar ratio of 1/1 and 4/1 (mol/mol) were prepared and characterized. These LDs and LUVs with defined composition and physical properties were used in studies of interactions of Chol-binding protein perfringolysin O (PFO) as compared to the Langmuir monolayer technique. We suggest that artificial LDs may serve as a useful model lipid system for studying protein-lipid interactions, complementary to the Langmuir monolayers.

Effects of CPP-conjugated ERα17p peptide derivatives on the activation of ERK1/2 in breast carcinoma cells

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The molecule ERα17p is an estrogenic peptide (sequence: H_2N-PLMIKRSKKNSLALSLT-OH) that exerts its action through conventional nuclear pathways, according to the following process: (*i*) interaction with the estrogen receptor ERα, (*ii*) dimerization / phosphorylation, (*iii*) recruitment of coactivators, and, *in fine*, (*iv*) interaction with estrogen-response elements (EREs). It acts also through membrane-initiated signalling events, including the membrane estrogen receptor and the heptatransmembrane G protein-coupled receptor GPR30. In steroid-deprived conditions, it activates ERK1/2, the redistribution of actin, transcription, and cell proliferation.

We have studied the effects of this peptide alone or conjugated to the cell-penetrating peptides (CPPs) Arg_9, RW9 and penetratin on ERK1/2 phosphorylation, on the redistribution of actin, and on cell proliferation in ERα-positive human MCF-7 breast carcinoma cells. We have also quantified the amount of internalized peptide by using MALDI-TOF.

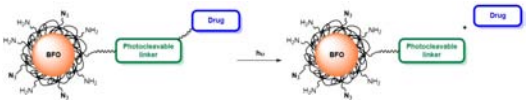
We show here that the penetratin-ERα17p conjugate enters cells much more efficiently than the other CPP conjugates. Moreover, this conjugate strongly modifies the distribution and the density of actin, and induces the loss of some of the morphological characteristics related to cell proliferation and invasiveness. Also, it is responsible for a decrease in cell proliferation at 48h and 72h.

Functionalization of second harmonic generation nanoparticles for theranostic applications

J. Vuilleumier[1], R. de Matos[1], S. Passemard[1], L. Bonacina[2], S. Gerber-Lemaire[1]*

[1]EPFL / Institute of chemical sciences & engineering, [2]University of Geneva, GAP-Biophotonics

Nowadays, cancer is the leading cause of death in developed countries. The emergence of new multimodal nanodevices for *in vivo* imaging offers the perspective of cancer detection at a very early stage.[1] The recent progress in nanotechnologies has generated high expectation that nanomaterials could provide unprecedented contrast agents in imaging set-ups and multifunctional platforms for drug delivery.[2] In this context, harmonic nanoparticles (HNPs), which are composed by non-centrosymmetric materials, can be easily imaged by their second harmonic generation signal in multiphoton imaging platforms.[3]



We recently disclosed efficient protocols for the biocompatible coating [4] and post-functionalization of bismuth ferrite ($BiFeO_3$, BFO) and $LiNbO_3$ HNPs as well as their favorable properties for targeted imaging of human cancer cells and tissue.[5] We report therein the conjugation of BFO HNPs to caged molecular cargos through a photocleavable linker based on coumarinyl and *o*-nitrobenzyl derivatives. Excitation of these functionalized HNPs in the visible or near IR region generated second harmonic UV emission [6] and subsequent selective release of the conjugated drug models.

These multifunctional HNPs offer the possibility for decoupled imaging modality and photo-activation process by tuning the wavelength of the excitation beam.

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Photophysical insight on the interaction between an RNA G-quadruplex and fluorescent platinum(II) complexes

Z. Wang[1], F. D. Steffen[1], A. Dominguez-Martin[1], Y. Zhong[2], Q. Cao[2], Z. Mao[2], R. K. Sigel[1]*, R. Börner[1]*

[1]Department of Chemistry, University of Zürich, [2]School of Chemistry and Chemical Engineering, Sun Yat-sen University

G-quadruplexes (G4s) are believed to play crucial roles in regulating gene expression.[1] In contrast to DNA G4s, which have been extensively investigated, there are much less studies on RNA G4s. In particular, studies on the interaction of RNA G4s with metal complexes are still missing to date. As various clinically relevant genes are known to harbor G4s forming sequences,[1] small molecules, especially metal complexes which can target to RNA G4s are potential regulators for gene expression.

Here we applied photophysical methods to understand the interaction between an RNA G4 and two fluorescent platinum(II) complexes. The investigated RNA sequence is a triple-mutant that forms one specific conformational state of the wildtype G4 forming BCL-2 (B-cell lymphoma 2) RNA, present in the mRNA of the BCL-2 onco-gene.[2] Fluorescence lifetime measurements show the binding affinities of both metal complexes to the G4 to be in the nM range. Further, we find 1:1 and 1:2 binding equilibria of this G4 RNA to the metal complex depending on the concentration ratio. Interestingly, the binding to the G4 RNA can also induce a conformational change of both complexes, which is indicated by a change of the fundamental fluorescence anisotropy. These findings, which enlight the particular interaction of the RNA G4 with the platinum(II) complexes, are beneficial for the design of metal complexes as particular RNA G4 binders.

Acknowledgment: This work was supported by the Swiss National Science Foundation (RKOS), the China Scholarship Council (to ZW, ZH, No. 201506190127), the Fundacion Ramon Areses (to ADM), and the UZH Forschungskredit (to ADM and RB).

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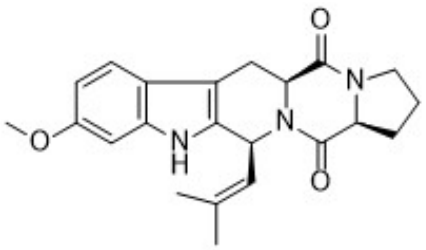
Synthesis and biological evaluation of Ko143 derivatives

M. Zechner[1], S. Jackson [2], C. A. Castro Jaramillo[3]

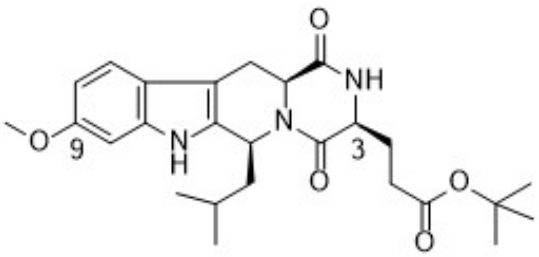
[1]Prof. Dr. Karl-Heinz Altmann , [2]Prof. Dr. Kaspar Locher , [3]Prof. Dr. Stefanie Krämer

Fumitremorgin C (FTC) is a natural product produced by the fungus *Aspergillus fumigatus* that was first isolated in 1977 by Clardy. The compound is a potent and partly selective inhibitor of the ABCG2 transporter, but it also exhibits profound neurotoxicity. Ko143 is a synthetic analog of FTC, which is not neurotoxic, but retains the ABCG2-inhibitory capacity of the naturalproduct.[1] Over the course of this project, several analogues of Ko143 with modifications at positions 3 and 9 of the tricyclic scaffold as well as a ring expanded analogue were synthesized. Moreover, a new and more efficient synthesis of Ko143 and fumitremorgin C was developed. This involves an improved route to the 6-methoxytryprophan building block, a stereoselective reduction of an imine-intermediate and a more efficient approach to amide bond formation.

The biological activity of the Ko143 analogs was evaluated in an ATPase assay in proteoliposomes incorporating recombinant ABCG2. Several analogs with potencies similar to or potentially better than that of Ko143 have been identified. More recently the compounds have also been assessed in a proliferation assay in PC-9 cells in combination with the EGFR kinase inhibitor gefitinib.



Fumitremorgin C



Ko143

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Annual report of the DMCCB and elections

Y. Auberson[1,2]

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The DMCCB focuses on the organization of scientific events, networking and communication.

This talk will briefly review the recent activities of the Division (12th Swiss Course on Medicinal Chemistry, Frontiers in Medicinal Chemistry), its interactions with the European Federation of Medicinal Chemistry, and its efforts to increase communication. It will also provide information about future events, and opportunities to participate in the activities of the DMCCB.

Members will be welcome to ask questions and make suggestions for future activities.

Discovery of Novel PET Tracers to Image Aggregated Tau in Alzheimer's Disease

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[1]Pharma Research and Early Development, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, CH-4070 Basel, Switzerland, [2]The Johns Hopkins University School of Medicine, Department of Radiology, Nuclear Medicine – PET Center, Baltimore, USA

Objectives: Aggregates of tau and beta amyloid (Ab) plaques constitute the histopathological hallmarks of Alzheimer's disease (AD) and are prominent targets for novel therapeutics and biomarkers for diagnostic in vivo imaging. In recent years much attention has been devoted to the discovery and development of new PET tracers to image tau aggregates in the living human brain [1,2]. The objective of this study was to identify such a novel radiotracer, in order to support the clinical development of novel therapies targeting aggregated forms of tau.

Methods: A medicinal chemistry PET tracer discovery program identified several candidate structures. Among these, the three novel tau ligands RO6924963, RO6931643 and RO6958948 were selected for radiolabelling alternatively with tritium and a PET nuclide. Tritiation of RO6924963 and RO6958948 was achieved by direct ^{1}H to ^{3}H exchange reaction with Crabtree's catalyst. [^{3}H]RO6931643 was prepared in one step by methylation of an anilinic precursor with [^{3}H]MeONs. [^{11}C]RO6924963 and [^{11}C]RO6931643 were obtained by methylation of the corresponding precursors with [^{11}C]MeI. The ^{18}F-fluorination of RO6958948 was accomplished by nucleophilic aromatic substitution of a nitro precursor. The tritiated ligands where evaluated by in vitro autoradiography on AD and healthy control brain sections. Additional co-localization experiments with selective antibodies for tau or Ab were performed. The ^{11}C- and ^{18}F-labelled tracers were evaluated in PET in tau-naïve baboons after *i.v.* administration.

Results: The tritiated ligands were obtained with SA > 900 GBq/mmol and radiochemical purities > 94%. ^{11}C-Labelled tracers were isolated with high SA > 200 GBq/mmol. [^{18}F]RO6958948 was obtained with SA > 660 GBq/mmol. In vitro autoradiography revealed a heterogeneous distribution pattern co-localized with the binding pattern of the tau antibody. Very low non-specific binding in healthy brain tissue excluded significant radioligand binding to any other CNS target. The time-activity curves for brain regions in baboons indicated good brain uptake and rapid washout for all three tracers.

Conclusions: [^{11}C]RO6924963, [^{11}C]RO6931643 and [^{18}F]RO6958948 are promising PET tracers for the visualization of tau aggregates in AD. On account of these results, these tracer candidates have been progressed into a clinical validation study in healthy controls and patients with AD (ClinicalTrials.gov Identifier: NCT02187627).

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Elucidating the structure-activity relationship of the pentaglutamic acid sequence of minigastrin with the cholecystokinin receptor subtype 2

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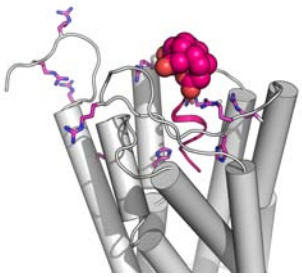
Radiolabelled minigastrin derivatives are used to target the cholecystokinine receptor subtype 2 (CCK2R) which is overexpressed on neuroendocrine tumors.[1] Binding behavior as well as undesired kidney uptake are influenced by the pentaglutamic acid sequence of minigastrin, but the interactions and structural influences on a molecular level are not fully understood. We replaced the pentaglutamic acid sequence in minigastrin with linkers differing in their structural features, their flexibility and the number of anionic charges in order to elucidate the structure-activity relationship of this sequence with the CCK2R. Specifically, a flexible aliphatic linker, a linker with only three D-Glu residues and a structured linker with four adjacent β^3-glutamic acid residues were evaluated and compared to the lead compound PP-F11N (DOTA-[D-Glu$^{1-6}$, Nle^{11}]gastrin-13). The minigastrin derivatives were conjugated to 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), which allowed radiolabelling with ^{177}Lutetium. The radiolabelled ligands were examined for their *in vitro* properties (IC_{50}, internalization and serum stability) and for their *in vivo* behavior in tumor bearing mice with a human medullary thyroid cancer cell line (MZ-CRC1). Structural features of the ligands were evaluated by molecular modelling and CD-spectroscopy.



The obtained IC_{50} values are in the low nanomolar range (15-35 nM), with the aliphatic elongated peptide as the only exception with almost one order of magnitude higher values (>100 nM). *In vitro* internalization into MZ-CRC1 cells and *in vivo* tumor uptake, as well as human blood plasma stability increased in the following order: no linker, aliphatic sequence, $(D\text{-}Glu)_3$ sequence, $(\beta^3\text{-}Glu)_4$ sequence, $(D\text{-}Glu)_6$ sequence. The tumor uptake was dependent on the amount of anionic charges and structural features present. We envision that correlating the observed biological properties with structural features will lead to a better understanding of the molecular structural binding behaviour of peptidic CCK2R ligands which enables an improved rational design of such ligands.

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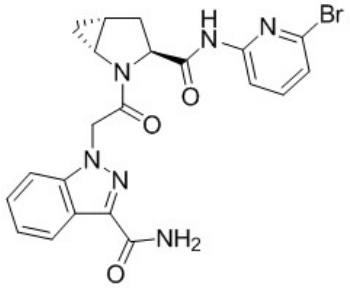
Discovery of Highly Potent, Selective and Orally Bioavailable Complement Alternative Pathway Inhibitors for Treatment of PNH

S. Flohr[1], J. Maibaum[1], E. L. Lorthiois[1], F. Cumin[1], A. Vulpetti[1], A. Schubart[1], A. Risitano[2], N. Ostermann[1], K. Anderson[1], J. Eder[1]*

[1]Novartis, [2]University of Naples

The complement system is one of the major defense mechanisms of the innate immune system composed of the classical pathway (CP), the lectin pathway (LP), and the alternative pathway (AP). There is strong scientific evidence for AP involvement in Paroxysmal Nocturnal Hemoglobinuria (PNH) and other immune disorders. The serine proteases Factor B (FB) and Factor D (FD) are part of the central amplification loop of the AP.

We report on the discovery and preclinical evaluation of highly potent and selective low-molecular weight FD inhibitors which were identified using structure guided optimization. Oral administration of these inhibitors blocked systemic and ocular lipopolysaccharide (LPS)-induced activation of the AP in mice. In vitro inhibition of FD is shown to prevent both hemolysis and erythrocyte C3 deposition on human PNH erythrocytes ex vivo differentiating it from the standard of care, eculizumab.



[1] Jürgen Maibaum, Sha-Mei Liao, Anna Vulpetti, Nils Ostermann, Stefan Randl, Simon Rüdisser, Edwige Lorthiois, Paul Erbel, Bernd Kinzel, Fabrice A Kolb, Samuel Barbieri, Julia Wagner, Corinne Durand, Kamal Fettis, Solene Dussauge, Nicola Hughes, Omar Delgado, Ulrich Hommel,Ty Gould, Aengus Mac Sweeney, Bernd Gerhartz, Frederic Cumin, Stefanie Flohr, Anna Schubart, Bruce Jaffee, Richard Harrison, Antonio Maria Risitano, Jörg Eder and Karen Anderson, *Nature Chemical Biology*, **2016**, 12, 1105–1110.

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Photocontrolled release of antibiotics and other bioactive molecules from supramolecular hydrogels with green light

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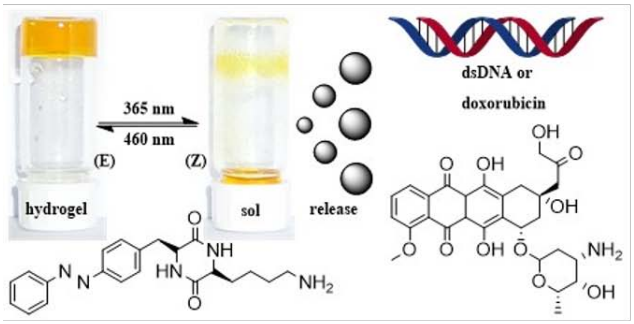
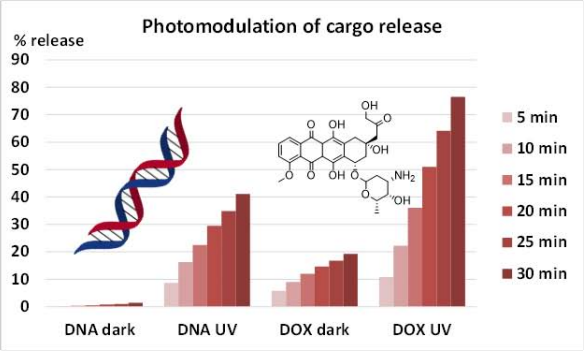
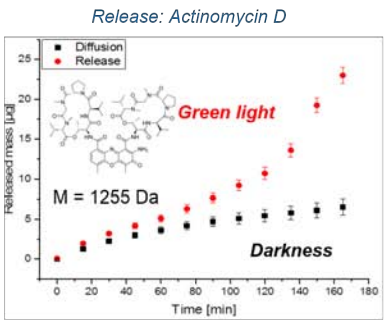
[1]IOC KIT Karlsruhe, Germany

Recently we have reported [1] photoresponsive supramolecular hydrogels based on an azobenzene-containing cyclic dipeptide (or 2,5-diketopiperazine; PAP-DKP-Lys), which is a low-MW hydrogelator. The gelation process can be triggered with temperature, pH, light, and ionic strength. The resulting gels exhibit excellent self-healing properties. In presence of DNA the compound forms hydrogels that release the oligonucleotides upon irradiation with 365 nm UV light. Hydrogels formed in presence of anticancer drug doxorubicin also release the cargo in a light-dependent manner.

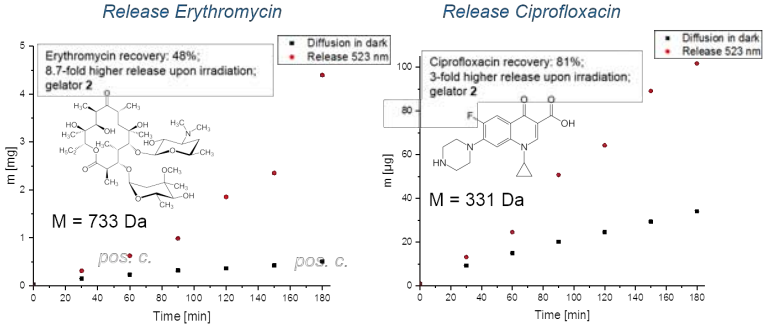




The current report regards modified supramolecular hydrogel matrix, which now became capable of efficiently releasing cargo molecules upon irradiation with green light (530 nm). In case of antibiotic molecules as guest, we achieved up to eight-fold release discrimination between samples irradiated with green light and those kept in darkness. [2]



actinomycin D - antibiotic and an anticancer drug (i. A. testicular cancer, ovarian cancer)



Erythromycin and Ciprofloxacin are antibiotics useful for the treatment of a number of bacterial infections

[1] Zbigniew Pianowski*, Johannes Karcher, Knut Schneider, *Chem. Commun.*, **2016**, *52*, 3143-3146
[2] Johannes Karcher, Zbigniew Pianowski* *manuscript in preparation*
[3] Zbigniew Pianowski, Johannes Karcher, Knut Schneider, *German patent application 10* ***2015*** *014 034.6 (pending)*

Chemical ecology at work: plant defense alkaloids as source of inspiration for crop protection

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[1]Syngenta Crop Protection AG

Plants produce alkaloids as defence against insects, a result of a dynamic and complex co-evolution over millions of years. These bioactive natural products may repel or intoxicate insects and as such constitute a source of inspiration for the design of synthetic active ingredients in insect control.

Herein, we present the discovery of pyridinylcyanotropanes,[1] inspired by the plant defence alkaloid Stemofoline. Furthermore, we describe how the physical chemical properties of pyridinylcyanotropanes and structurally-related analogues dictate their localization in plant tissue and ultimately their performance in crop protection.[2]

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Divergent Synthesis and Identification of the Cellular Targets of Deoxyelephantopins

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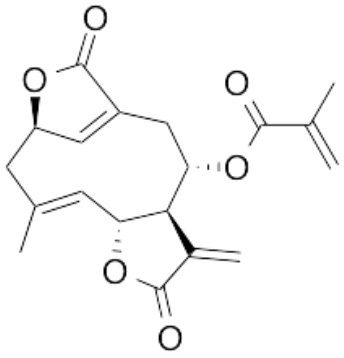
[1]University of Geneva, School of Chemistry and Biochemistry, NCCR Chemical Biology

The sesquiterpene lactone Deoxyelephantopin is the most active ingredient in extracts of *Elephantopus scaber*.[1] Biological investigations have demonstrated cytotoxicity against several human cancer cell lines, and cytotoxicity superior to that of Paclitaxel in breast cancer models.[2] Moreover, it suppresses proteasome activity,[3] inhibits the NF-κB pathway[4] and is a partial PPARγ agonist.[5]

A divergent synthesis of Deoxyelephantopin analogues and their biological evaluation will be presented, including the identified pharmacophores, novel potential drug targets and the binding mode with PPARγ.[6]



Deoxyelephantopin

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From Gram Positives to Gram Negatives: Discovery of Novel Aryloxazolidinone-Linked Bacterial Topoisomerase Inhibitors (NBTIs)

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[1]Idorsia Pharmaceuticals Ltd, Hegenheimermattweg 91, CH-4123 Allschwil

The emergence of infections caused by multidrug-resistant Gram-negative organisms is one of the biggest threats to global health today. While many bacterial infections are becoming increasingly untreatable large pharmaceutical companies have left the field. As a result, the approval of novel and more effective antibiotics has been dramatically declining over the last decades.

Bacterial topoisomerases, such as DNA Gyrase and Topoisomerase IV, are important antibacterial targets and several classes of inhibitors were discovered in the past, but only the fluoroquinolones (FQs) became clinically successful. Unfortunately, their utility has been significantly compromised due to emerging resistance. Over the last years compounds of a novel class of bacterial topoisomerase inhibitors (NBTIs) devoid of cross-resistance with FQs have advanced to clinical stage. However, despite promising properties the latter show no significant activity against the most problematic Gram-negative pathogens, particularly against *E. coli*, *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa*.

Presented herein are the discovery and characterization of novel aryloxazolidinone-linked bacterial topoisomerase inhibitors (NBTIs) representing a new chemical class with potent broad-spectrum antibacterial activity, including the most difficult-to-treat multidrug-resistant Gram-negative bacteria. Compounds with Gram-negative whole cell activity could be designed by improving target potency and increasing intracellular accumulation.

Peptide dendrimer as siRNA transfection reagent

M. Heitz[1], T. Darbre[1], J. L. Reymond[1]*

[1]University of Bern

RNA interference (RNAi) allows effective and specific silencing as described by Tuschl and co-workers in their proof-of-principle experiment demonstrating that synthetic double stranded small interfering RNA (siRNA) could achieve sequence-specific gene knockdown in a mammalian cell line by promoting the degradation of complementary mRNA via RNA induced silencing complex (RISC).[1] Potential therapeutic applications of RNAi are crucially dependent on the delivery of siRNA into the cytosol to avoid that this step becomes a bottleneck. Naked or chemically modified siRNA delivery is of limited application and therefore nanoparticles encapsulating siRNA molecules have been investigated as a more general method to bring siRNA into cells.

We have previously explored a collection of peptide dendrimers for the transfection of plasmid DNA and siRNA and found efficient reagents that obeyed distinct structure-activity relationships. Of crucial importance were the distribution of cationic charges across the three dendrimer generations for DNA, the two outer generation only for siRNA and in both cases the use of DOTMA/DOPE as helper lipids.[2,3,4]

We are now exploring peptide dendrimers as delivery agents for siRNA in the absence of the helper lipids. In this project, a library of 100 peptide dendrimers was prepared by solid phase peptide synthesis and their gene silencing ability investigated. The biological experiments included treatment of HeLa, CHO, HEK-293, PC-3, HT-1080, SH-SY5Y and CACO-2 cells by the new transfection agents and siRNA targeting GAPDH (siGAPDH) or scrambled (siNC) in the absence and presence of serum. The knockdown efficiency was measured by monitoring enzyme activity of GAPDH and quantification of GAPDH mRNA level. The parameters necessary for efficient gene silencing have been discovered and optimized to lead to some only amino acid and some lipid-containing dendrimers.

Additionally, we discovered that diastereomers and enantiomers of these lead compounds influence and ultimately allowed a higher transfection efficiency. In order to understand the underlying principle, these potent compounds were then coupled to fluorophores that maintain the overall knockdown efficiency and therefore allow studies on the internalization process and intracellular localization of siRNA and dendrimer by flow cytometry and confocal microscopy.

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Model Peptide Studies of Ag^+ Binding Sites from the Silver Resistance Protein SilE

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[1]University of Fribourg

The silver cation Ag^+ and its compounds have been known for their antibacterial properties. However, an increasing number of reports have highlighted the emergence of silver resistant bacterial strains isolated from burn care centers or silver contaminated media. The resistance is provided by the SilCFBA transporter, which contains eight proteins that act together to export silver ions. Among them, the SilE protein is the only one of which the role is still unknown, although it is mandatory to provide the resistance.

A model peptide study identifies and characterizes several Ag^+-binding sites of the bacterial silver resistance protein SilE, providing new insights on the Ag^+ coordination sphere and on the physiological role of the protein.[1]

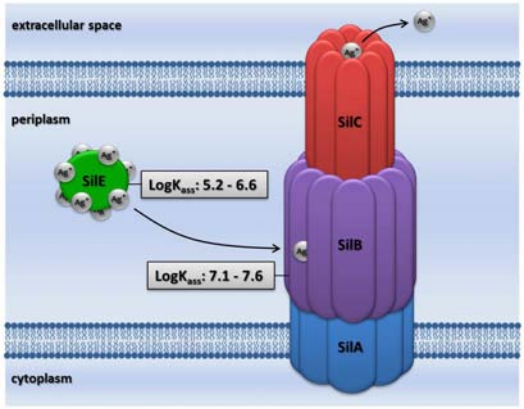

Figure 1: Schematic representation of the potential silver ion transfer between SilE and SilB proteins, based on the silver affinity gradient between the two partners.[1,2]

[1] Model Peptide Studies of Ag^+ Binding Sites from the Silver Resistance Protein SilE", V. Chabert *et al., Chem Commun.,* **2017**, accepted.
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Design of Potent and Drug-like Non-phenolic Inhibitors for Catechol O-Methyltransferase

R. M. Rodríguez Sarmiento[1], C. Lerner[1], R. Jakob-Roetne[1], B. Buettelmann[1], A. Ehler[1], M. G. Rudolph[1]

[1]Pharmaceutical Research and Early Development (pRED), Roche Innovation Center Basel, F.Hoffmann-La Roche

For the first time nonphenolic and small low nanomolar potent, SAM competitive COMT inhibitors are reported. Initial fragments with high ligand efficiency, were identified in a fragment screening approach designed to target specifically the *S*-adenosyl-L-methionine pocket of catechol *O*-methyl transferase. By use of a reliable enzymatic assay together with X-ray crystallography as guidance, a series of fragment modifications revealed an SAR and, after several expansions, potent lead compounds could be obtained.

[1] Christian Lerner, Roland Jakob-Roetne, Bernd Buettelmann, Andreas Ehler, Markus G. Rudolph and Rosa María Rodríguez Sarmiento*, *J. Med: Chem.* **2016,** 59, 10163-10175

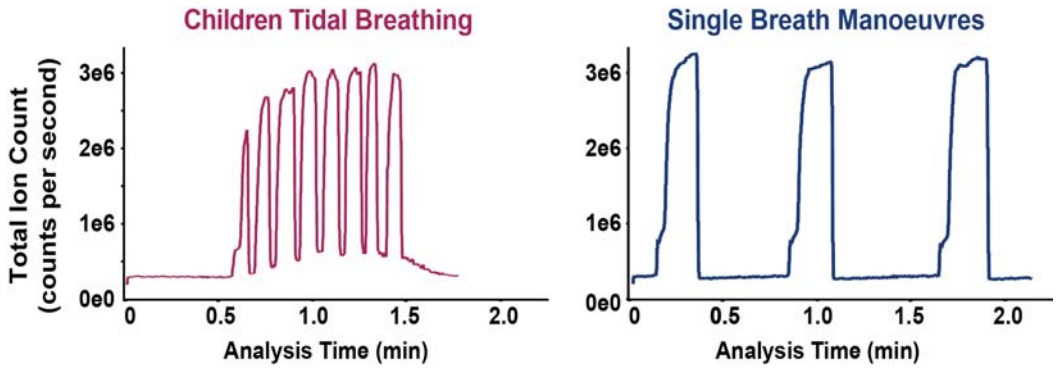
Feasibility of breath exhalomics studies with infants and young children for early detection of cystic fibrosis inflammation and infection

T. Bruderer[1,2], A. Baghdasaryan[1], J. Wyler[2], M. Kohler[3], R. Zenobi[2]*, A. Möller[1]*

[1]University Children's Hospital, Division Respiratory Medicine, Zürich, Switzerland, [2]Swiss Federal Institute of Technology in Zürich, Department of Chemistry and Applied Biosciences, Zürich, Switzerland, [3]University Hospital, Department of Pulmonology, Zürich, Switzerland

Objectives: Early and often subclinical pulmonary infection and pronounced neutrophilic inflammation are major contributors to CF-related morbidity. There is a causal relationship between high airway neutrophil elastase activity and the development of bronchiectasis. Early detection of disease and disease-associated complications is crucial for implementing timely therapeutic measures to reduce disease burden and improve prognosis. Secondary Electrospray Ionisation Mass Spectrometry (SESI-MS) is an extremely efficient method for ionizing compounds in exhaled breath allowing extending the number of compounds that can be detected in exhaled breath.

Methods: We developed a sampling device which can be used with non-cooperative children with tidal breathing and facemask. The device was optimized for real-time, sensitive analysis by introducing a temperature, humidity and flow controlled air supply. A feasibility study was done with 20 children (age range 3-12y), 9 with stable CF and 11 healthy controls. All children performed 6 measurements with tidal breathing and facemask (TBFM) and single breath with mouthpiece (SBMP).



Results: The success rate was 100% for TBFM but SBMP analysis was not feasible for 3 children of age 3y, 4y and 6y. The average *m/z* features per measurement in positive mode were 713 for SBMP and 702 (-2%, SD11%) for TBFM for molecules detected in the range of *m/z* = 50 - 320. Data analysis is on-going with a set of 28 breath biomarkers (amino acids, fatty acids and aldehydes) which we identified during previous exhalomics studies with adults. Non-targeted screening for statistical significantly different features (between groups) has started and will be followed by compound identification based on high-performance liquid chromatography (UHPLC-HRMS/MS) of exhaled breath condensates and pure reference standards. Our preliminary results reveal comparable number of features and intensities between TBFM and SBMP.

Conclusions: Breath exhalomics studies with SESI-MS are feasible in children from 3 years of age. Measurements by TBFM and SBMP resulted in similar number of features and intensities. Therefore, optimized SESI-MS can be applied in young non-cooperative children.

Natural products as probes in pharmaceutical research: Nannocystin A, an inhibitor of the elongation factor 1a

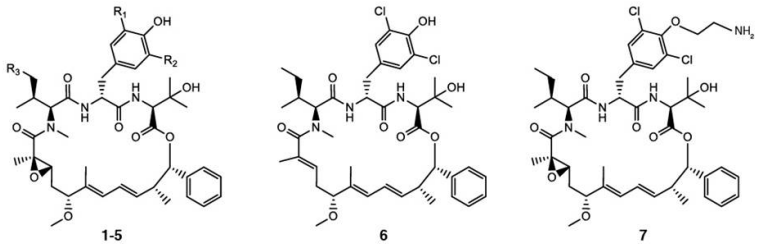
P. Krastel[1], E. Schmitt[1], D. Hoepfner[1], M. Schierle[2], S. Roggo[1]

[1]Novartis Institutes for Biomedical Research, Basel, Switzerland, [2]Novartis Institutes for Biomedical Research, Cambridge, US

From the start of the pharmaceutical research natural products played a key role in drug discovery and development. Over time many discoveries of fundamental new biology were triggered by the unique biological activity of natural products. Unprecedented chemical structures, novel chemotypes, often pave the way to investigate new biology and to explore new pathways and targets [1].

The cyclic lactone Nannocystin A, obtained from the cultivation of myxobacteria from the Nannocystis genus, displayed in biological assays antifungal and cytotoxic activities. Combined genetic and proteomic approaches identified the eukaryotic translation elongation factor 1a (EF-1a) as the target of this compound class [2].

The talk will focus on the discovery of this compound class and will guide trough the target identification of this compound class.



1-5 6 7

Cpd No.	Name	R_1	R_2	R_3	HCT116 IC_{50} (nM)
1	Nannocystin A	Cl	Cl	Me	2.6
2	Nannocystin A1	H	Cl	Me	5.3
3	Nanncoystin A0	H	H	Me	3.7
4	Nannocystin B	Cl	Cl	H	7.2
5	Nannocystin B1	H	Cl	H	2.8
6	Nannocystin Ax		see above		5.4
7	Derivative		see above		7.1

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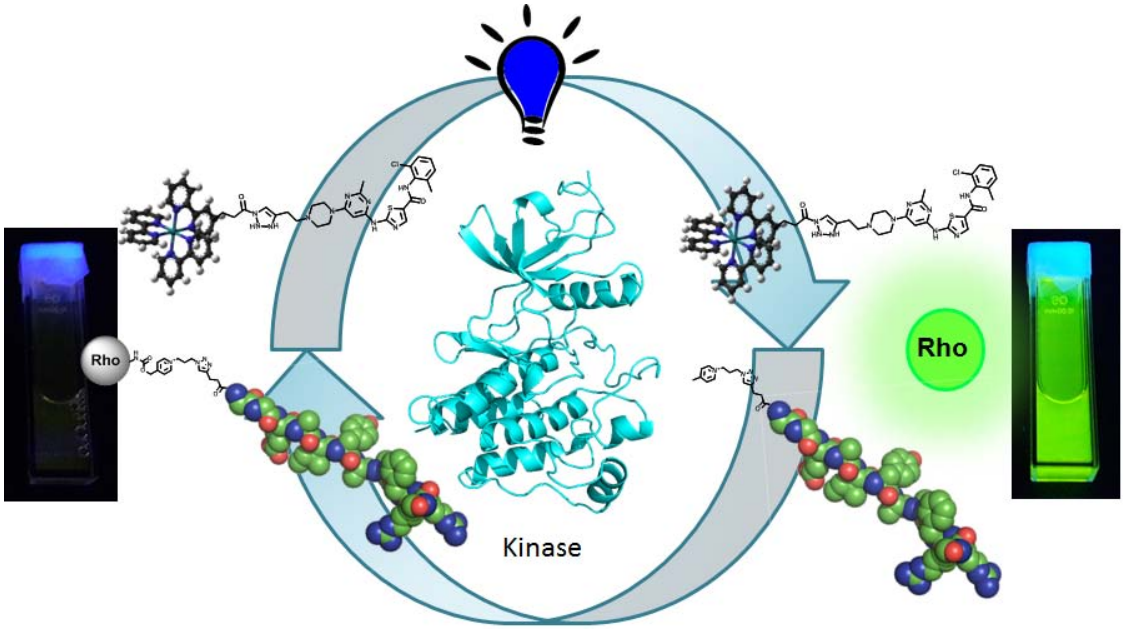
Kinase Templated Abiotic Reaction

J. Saarbach[1], E. Lindberg[1], S. Folliet[1], S. Georgeon[2], O. Hantschel[2]*, S. Soleimanpour[1]*

[1]Faculty of Science, Department of Organic Chemistry, NCCR Chemical Biology, University of Geneva, 30 quai Ernest Ansermet, Geneva, Switzerland, [2]Swiss Institute for Experimental Cancer Research (ISREC), NCCR Chemical Biology, School of Life Sciences, École Polytechnique Fédérale de Lausanne (EPFL), CH-1015 Lausanne, Switzerland

Protein kinases are essential regulators of cellular signalling and have been at the centre stage of drug discovery for the past decade. The successful development of kinase inhibitors demonstrated that kinases were drugable and triggered tremendous research effort in this area. However, inhibitors developed so far often target the conserved ATP binding site of the protein and thus are lacking selectivity[1], and the more selective ones are targeting an inactive form of the protein. These features limit their use as chemical probes to sense kinase activity. Herein we report a strategy[2] based on two reacting probes[3] targeting both nucleotide and substrate binding sites. The reaction[4] used allows to use fluorescence readout to selectively sense Abl of Src kinase activity both in biochemical and fixed whole cell experiments.



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