

CHIMIA

CHIMIA 2017, Volume 71

ISSN 0009-4293

www.chimia.ch

Supplementa to Issue 7-8/2017



SCS

Swiss Chemical
Society

SCS Fall Meeting 2017
Oral Presentation Abstracts

Session of Medicinal Chemistry & Chemical Biology

August 21-22, 2017

University of Bern, Areal vonRoll

<http://scg.ch/fallmeeting/2017>

Swiss Chemical Society
Haus der Akademien
Postfach
3001 Bern
Switzerland
info@scg.ch
www.scg.ch

Annual report of the DMCCB and elections

Y. Auberson^{1,2}

¹Swiss Chemical Society, ²Novartis Pharma AG

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

L. C. Gobbi¹, M. Honer¹, H. Knust¹, M. Koerner¹, D. Muri¹, R. F. Dannals², D. F. Wong², E. Borroni¹

¹Pharma Research and Early Development, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, CH-4070 Basel, Switzerland, ²The 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 ¹H to ³H exchange reaction with Crabtree's catalyst. [³H]RO6931643 was prepared in one step by methylation of an anilinic precursor with [³H]MeONs. [¹¹C]RO6924963 and [¹¹C]RO6931643 were obtained by methylation of the corresponding precursors with [¹¹C]MeI. The ¹⁸F-fluorination of RO6958948 was accomplished by nucleophilic aromatic substitution of a nitro precursor. The tritiated ligands were 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 ¹¹C- and ¹⁸F-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%. ¹¹C-Labelled tracers were isolated with high SA > 200 GBq/mmol. [¹⁸F]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: [¹¹C]RO6924963, [¹¹C]RO6931643 and [¹⁸F]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).

[1] M. Ariza *et al.*, *J. Med. Chem.* **2015**, *58*, 4365-4382.

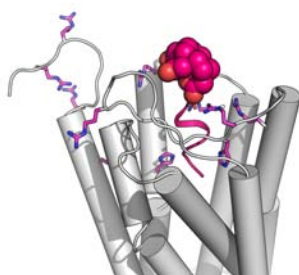
[2] A. Walji *et al.*, *J. Med. Chem.* **2016**, *59*, 4778-4789.

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

A. Ritler^{1,4}, X. Deupi², H. Wennemers³, R. Schibli^{4,1}, M. Béhé^{4*}

¹Department of Chemistry and Applied Biosciences (D-CHAB), Institute of Pharmaceutical Sciences (IPW), ETH Zurich, ²Laboratory of Biomolecular Research, and Condensed Matter Theory Group, Paul Scherrer Institute (Switzerland), ³Department of Chemistry and Applied Biosciences (D-CHAB), Laboratory of Organic Chemistry (LOC), ETH Zurich, ⁴Research Department Biology and Chemistry, Center for Radiopharmaceutical Sciences (CRS), Paul Scherrer Institute (Switzerland)

Radiolabelled minigastrin derivatives are used to target the cholecystinin 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-Glu¹⁻⁶, Nle¹¹]gastrin-13). The minigastrin derivatives were conjugated to 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), which allowed radiolabelling with ¹⁷⁷Lutetium. The radiolabelled ligands were examined for their *in vitro* properties (IC₅₀, 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 IC₅₀ 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-Glu)₃ sequence, (β^3 -Glu)₄ sequence, (D-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.

[1] Laverman, et al., *European Journal of Nuclear Medicine and Molecular Imaging* **2011**, 38 (8), 1410-1416.

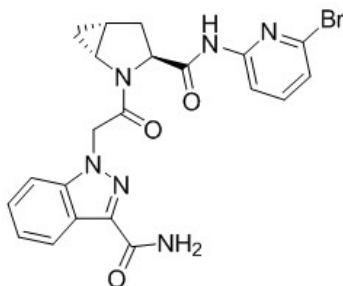
Discovery of Highly Potent, Selective and Orally Bioavailable Complement Alternative Pathway Inhibitors for Treatment of PNH

S. Flohr¹, J. Maibaum¹, E. L. Lorthiois¹, F. Cumin¹, A. Vulpetti¹, A. Schubart¹, A. Risitano², N. Ostermann¹, K. Anderson¹, J. Eder^{1*}

¹Novartis, ²University 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 Rüdissler, 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.

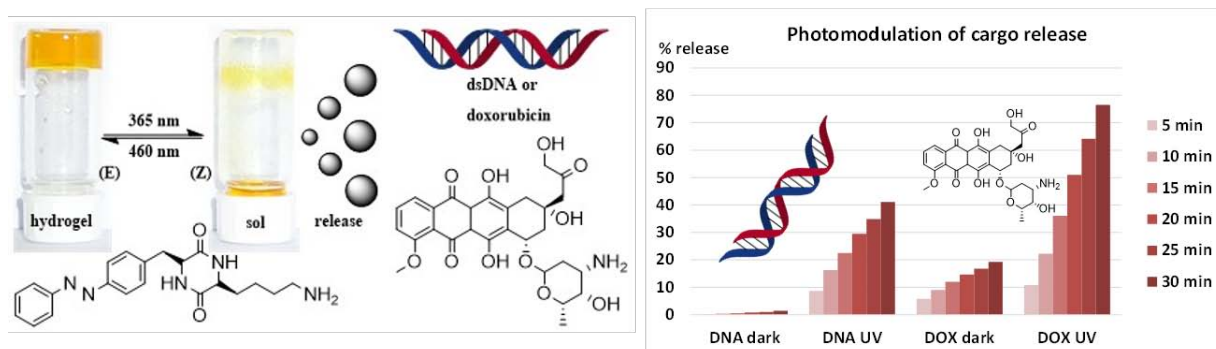
[2] Edwige Lorthiois, Karen Anderson, Anna Vulpetti, Olivier Rogel, Frederic Cumin, Nils Ostermann, Stefan Steinbacher, Aengus Mac Sweeney, Omar Delgado, Sha-Mei Liao, Stefan Randl, Simon Rüdissler, Solene Dussauge, Kamal Fettis, Laurence Kieffer, Andrea de Ekernez, Louis Yang, Constanze Hartweg, Upendra A Argikar, Laura R. LaBonte, Ronald Newton, Viral Kansara, Stefanie Flohr, Ulrich Hommel, Bruce Jaffee, and Jürgen Maibaum, *J. Med.Chem.*, **2017**, in press.

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

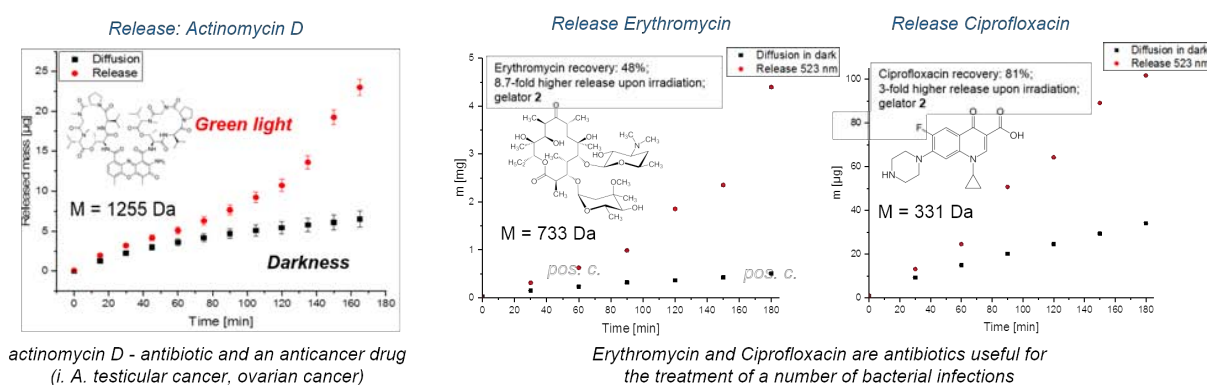
Z. Pianowski¹, J. Karcher¹, K. Schneider¹

¹IOC 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]



[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 10 014 034.6 (pending)*

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

F. Benfatti¹

¹Syngenta 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]

[1] R. J. Lind, D. T. Greenhow, J. Blythe, J. Goodchild, E. Hirst, S. J. Dunbar, F. G. P. Earley, *Proc. Brighton Crop Protection Conf: Pest and Diseases* **2002**, *1*, 145 - 152.

[2] A. Buchholz, A. C. O'Sullivan, S. Trapp, In *ACS Symposium Series: Discovery and Synthesis of Crop Protection Products*; **2015**, *1204*, 93-161

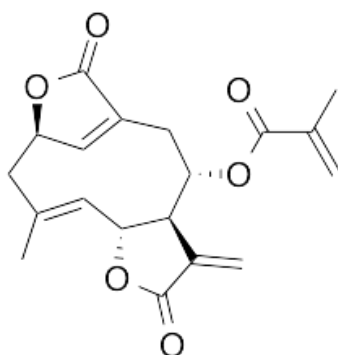
Divergent Synthesis and Identification of the Cellular Targets of Deoxyelephantopins

R. Lagoutte¹, C. Serba¹, D. Abegg¹, D. G. Hoch¹, A. Goujon¹, S. Soleimanpour^{1*}

¹University 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 pathway⁴ 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

- [1] M. Su, X. Wu, H. Y. Chung, Y. Li, W. Ye, *Nat. Prod. Commun.* **2009**, *4*, 1025-1030.
[2] C.-C. Huang, C.-P. Lo, C.-Y. Chiu, L.-F. Shyur, *British J. Pharmacol.* **2010**, *159*, 856-871.
[3] W.-L. Lee, T.-N. Wen, J.-Y. Shiau, L.-F. Shyur, *J. Proteome Res.* **2010**, *9*, 237-253.
[4] H. Ichikawa, M. S. Nair, Y. Takada, D. B. A. Sheeja, M. A. S. Kumar, O. V. Oommen, B.B. Aggarwal, *Clin. Cancer Res.* **2006**, *12*, 5910-5918.
[5] G. Zou, Z. Gao, J. Wang, Y. Zhang, H. Ding, J. Huang, L. Chen, Y. Guo, H. Jiang, X. Shen, *Biochem. Pharmacol.* **2008**, *75*, 1381-1392.
[6] R. Lagoutte, C. Serba, D. Abegg, D. G. Hoch, A. Adibekian, N. Winssinger, *Nat. Commun.* **2016**, *7*, 12470.

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

G. Rüedi¹, C. Zummbrunn¹, D. Ritz¹, T. Bruyère¹, H. H. Locher¹

¹Idorsia Pharmaceuticals Ltd, Heggenheimermattweg 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 reagentM. Heitz¹, T. Darbre¹, J. L. Reymond^{1*}¹University 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.

[1] Sayda M. Elbashir, Jens Harborth, Winfried Lendeckel, Abdullah Yalcin, Klaus Weber, Thomas Tuschl, *Nature*, **2001**, 411, 494-498.

[2] Albert Kwok, Gabriella Eggimann, Jean-Louis Reymond, Tamis Darbre, Florian Hollfelder, *ACS Nano*, **2013**, 7, 4668-4682.

[3] Albert Kwok, Gabriella Eggimann, Marc Heitz, Jean-Louis Reymond, Florian Hollfelder, Tamis Darbre, *ChemBioChem*, **2016**, 17, 2223-2229.

[4] Marc Heitz, Albert Kwok, Gabriella Eggimann, Florian Hollfelder, Tamis Darbre, Jean-Louis Reymond, *Chimia*, **2017**, 71, 220-225.

Model Peptide Studies of Ag⁺ Binding Sites from the Silver Resistance Protein SilEV. Chabert¹, K. M. Fromm^{1*}¹University 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

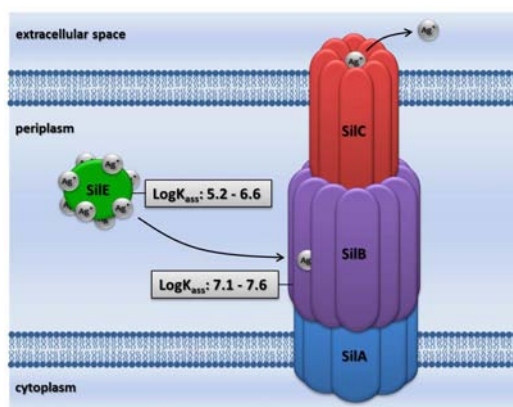


Figure 1: Schematic representation of the potential silver ion transfer between SilE and SilB proteins, based on the silver affinity gradient between the two partners.^{1,2}

[1] Model Peptide Studies of Ag⁺ Binding Sites from the Silver Resistance Protein SilE", V. Chabert *et al.*, *Chem Commun.*, **2017**, accepted.

[2] Structural and Functional Investigation of the Ag⁺/Cu⁺ Binding Domains of the Periplasmic Adaptor Protein SilB from *Cupriavidus metallidurans* CH34", P. Urbina *et al.*, *Biochemistry*, **2016**, 55, 2883-2897.

Design of Potent and Drug-like Non-phenolic Inhibitors for Catechol O-Methyltransferase

R. M. Rodríguez Sarmiento¹, C. Lerner¹, R. Jakob-Roetne¹, B. Buettelmann¹, A. Ehler¹, M. G. Rudolph¹

¹Pharmaceutical 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

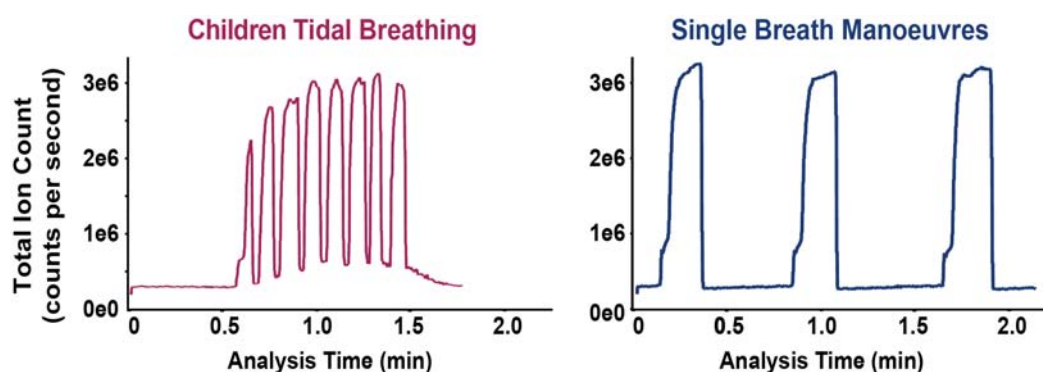
Feasibility of breath exhalomics studies with infants and young children for early detection of cystic fibrosis inflammation and infection

T. Bruderer^{1,2}, A. Baghdasaryan¹, J. Wyler², M. Kohler³, R. Zenobi^{2*}, A. Möller^{1*}

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

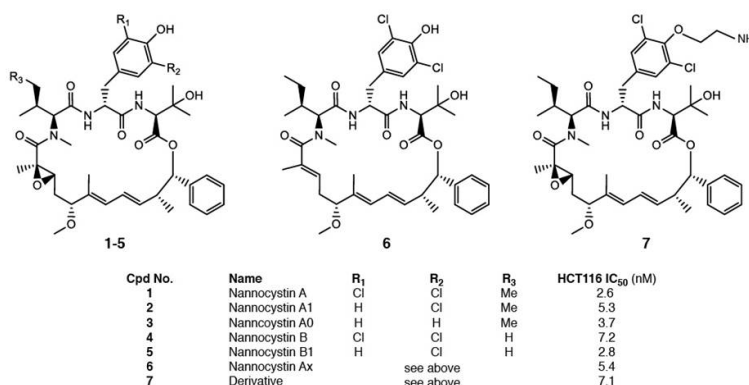
P. Krastel¹, E. Schmitt¹, D. Hoepfner¹, M. Schierle², S. Roggo¹

¹Novartis Institutes for Biomedical Research, Basel, Switzerland, ²Novartis 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 through the target identification of this compound class.



[1] E. Schmitt, D. Hoepfner, P. Krastel (2016), Natural products as probes in pharmaceutical research. *Journal of Industrial Microbiology & Biotechnology* 43, 1691-1699.

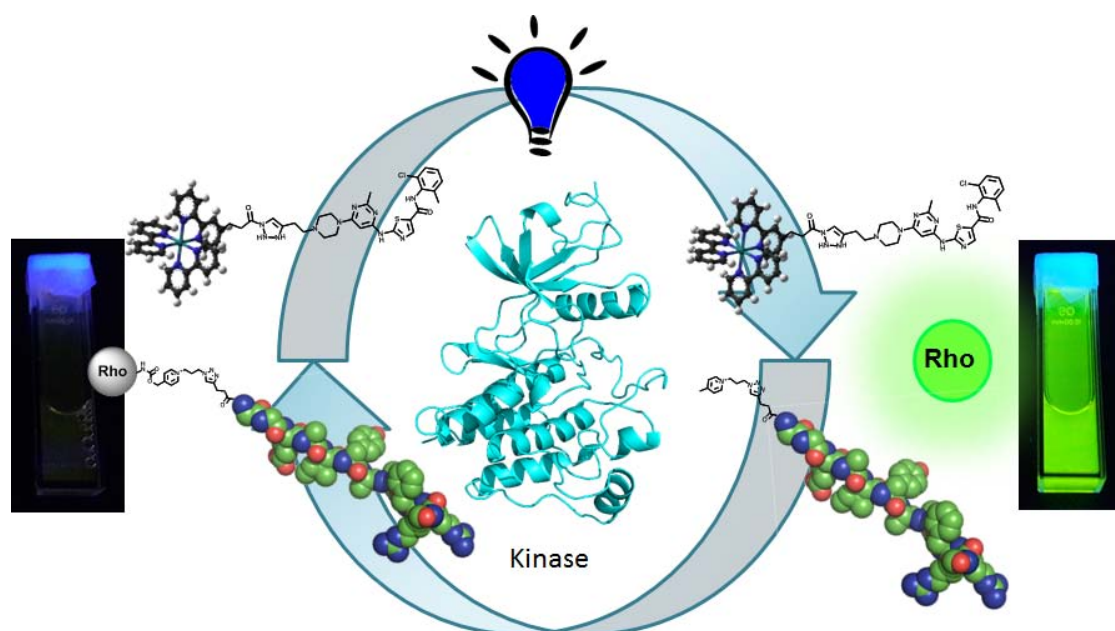
[2] P. Krastel, S. Roggo, M. Schierle, N. Ross, F. Perruccio, P. Aspesi, T. Aust, K. Buntin, D. Estoppey, B. Liechty, F. Mapa, K. Memmert, H. Miller, X. Pan, R. Riedl, C. Thibaut, J. Thomas, T. Wagner, E. Weber, X. Xie, E. Schmitt, D. Hoepfner (2015), Nannocystin A: an elongation factor 1 inhibitor from myxobacteria with differential anticancer properties. *Angewandte Chemie International Edition* 54, 10149-10154.

Kinase Templated Abiotic Reaction

J. Saarbach¹, E. Lindberg¹, S. Folliet¹, S. Georgeon², O. Hantschel^{2*}, S. Soleimanpour^{1*}

¹Faculty of Science, Department of Organic Chemistry, NCCR Chemical Biology, University of Geneva, 30 quai Ernest Ansermet, Geneva, Switzerland, ²Swiss 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 or Src kinase activity both in biochemical and fixed whole cell experiments.



[1] O. Hantschel, U. Rix, T. Buerckstuemmer, U. Schmidt, M. Kneidinger, K. L. Bennett, I. Kaupe, W. Ellmeier, P. Valent, G. Superti-Furga, *Blood* **2007**, *110*, 207b-207b.

[2] K. Gorska, I. Keklikoglou, U. Tschulena, N. Winssinger, *Chem Sci* **2011**, *2*, 1969-1975.

[3] K. K. Sadhu, T. Eierhoff, W. Römer, N. Winssinger, *J Am Chem Soc* **2012**, *134*, 20013-20016.

[4] D. Chang, E. Lindberg, N. Winssinger, *J Am Chem Soc* **2017**, *139*, 1444-1447.