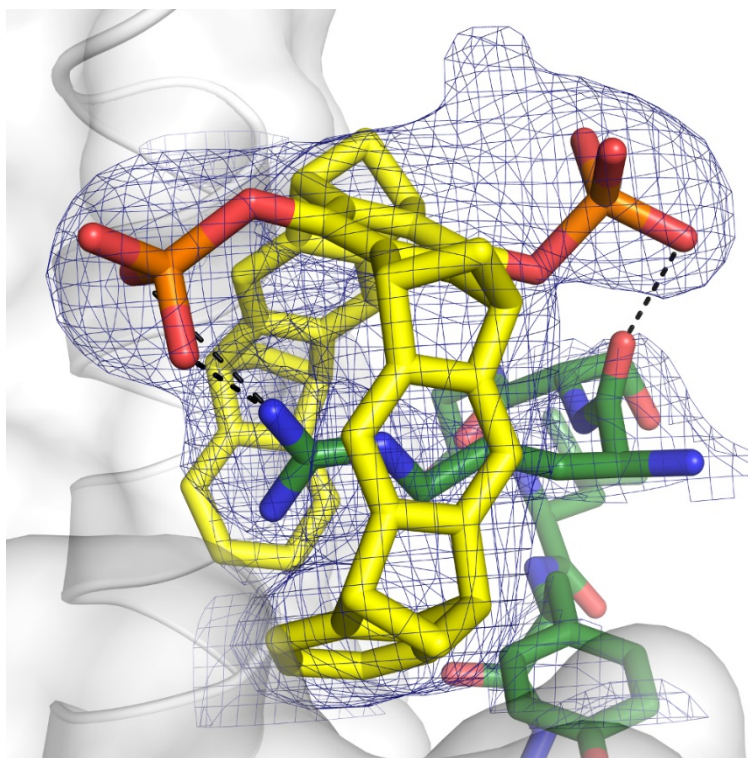


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Poster Abstracts

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Overview

(1) Ahlers et al.: External Stimuli Responsive Multi-Component Supramolecular Polymers with Tunable Properties	5
(2) Aschmann et al.: Polycationic supramolecular ligands for targeting Survivin	6
(3) Bäcker et al.: Dissection and Modulation of (patho)biological Survivin Functions by supramolecular Ligands	7
(4) Beuck et al.: NMR investigation of supramolecular ligand binding to proteins	8
(5) Bier et al.: Modulation of 14-3-3 protein-protein interactions (PPIs) by supramolecular chemistry.....	9
(6) Blümke et al.: Role of HTRA1 in the prion-like transmission of Tau aggregates in tauopathies.....	10
(7) Buten et al.: Immobilization of Carboxylic acids by Light-Induced Dipolar Addition to Nitrilimines and Microcontact Printing.....	11
(8) De Vink et al.: Controlling Protein-Protein Interactions by Cucurbit[8]uril Mediated Host-Guest Chemistry.....	12
(9) Gadre et al.: Synthesis of a modular system for major groove sequence-selective DNA recognition .	13
(10) Grad et al.: Molecular dynamics of highly flexible supramolecular ligands and proteins — challenges and solutions	14
(11) Gupta et al.: Therapeutic Potential of a Peptide based Carbene Complex	15
(12) Hayduk et al.: Novel luminophores with aggregation induced emission properties for protein recognition.....	16
(13) Heid et al.: Molecular Tweezers for Specific Protein Surface Recognition.....	17
(14) Homa et al.: Geometric factors and energetics of base stacking in absence of shape complementarity	18
(15) Jadhav et al.: Modulating supramolecular assembly in backbone expanded peptides	19
(16) Jaekel et al.: Rationally designed DNA-origami hosts for protein guests	20
(17) Killa et al.: Modulation of protein-protein-interactions	21
(18) Klenk et al.: Fighting Viruses with Viruses: A Supramolecular Multivalent Influenza Inhibitor based on the Bacteriophage Q β Capsid	22
(19) Klepel et al.: Dynamic Combinatory Approach towards synthetic Peptide-Receptors.....	23
(20) Klika Skopic et al.: Au(I)-mediated synthesis of hexathymidine-DNA-pyrazol(in)e chimeras, an efficient entry to DNA-encoded libraries inspired by drug structures	24
(21) Köcher et al.: Synthesis of Ahp-Cyclodepsipeptides as Serine Protease Inhibitors	25
(22) Kohlhaas et al.: Cage-like nanocapsules for molecular recognition and catalysis.....	26
(23) Kollenda et al.: Visualizing the fate of calcium phosphate nanoparticles inside living cells by a double fluorescent fusion protein.....	27
(24) Kornakov et al.: Analysis of lateral kinetochore transport by molecular motors	28
(25) Hatai et al.: Analyzing Amyloid Beta Aggregates with a Combinatorial Fluorescent Molecular Sensor	29

(26) Kracht et al.: Reconstitution of p97-mediated unfolding with pure components.....	30
(27) Kujawski et al.: Molecular Imprinting on Proteins by Tailor-made Polymers.....	31
(28) Lutz et al.: DNA-supported bimetallic photoredox catalysis.....	32
(29) Marek et al.: Why DNA Is a More Effective Scaffold than RNA in Nucleic Acid-Based Asymmetric Catalysis – Supramolecular Control of Cooperative Effects	33
(30) Miao et al.: Selective Functionalized PAMAM dendrimer' Surface Based on Dynamic Combinatorial Chemistry in The Presence of Biotemplates.....	34
(31) Mittal et al.: Inhibition of Huntingtin exon-1 aggregation by a molecular tweezer	35
(32) Octa-Smolín et al.: Rigidly tethered bis-phosphoric acids: Generation of tunable chiral fluorescent frameworks and unexpected selectivity for the detection of ferric ions[1]	36
(33) Ohl et al.: PolyLibScan: A computational framework for copolymer-protein interaction.....	37
(34) Pairault et al.: Conception of bifunctional hetero-[2]catenanes and -[2]rotaxanes based on phosphate/ammonium interactions	38
(35) Pfeifer et al.: Hierarchical assembly of DNA filaments with designer elastic properties	39
(36) Porfetye et al.: X-ray crystallography of supramolecular protein-ligand complexes	40
(37) Reuther et al.: Precision Macromolecules for the Multivalent Presentation of Supramolecular Amino Acid-Specific Binding Motifs	41
(38) Riebe et al.: Transfection Agents with Aggregation Induced Emission Properties.....	42
(39) Rojas Sanchez et al.: <i>Click chemistry</i> for the covalent surface modification of calcium phosphate nanoparticles	43
(40) Ruks et al.: Synthesis and Characterization of Surface-Functionalized Ultrasmall Gold Nanoparticles for Protein-Specific Targeting	44
(41) Schöneweiß et al.: The Collective Behavior of Spring-like Motifs Tethered to a DNA Origami Nanostructure	45
(42) Sebens et al.: Polycationic supramolecular peptide ligands targeting Survivin using Dynamic Combinatorial Libraries	46
(43) Sijbesma et al.: Controlling ER α Activity via 14-3-3 Protein-Protein Interactions	47
(44) Smolin et al.: Accelerated Autolysis of Trypsin by Tailor-made Copolymers.....	48
(45) Sokkar et al.: Multiscaling with Three Layers: QM/MM/CG Simulation.....	49
(46) Sokolova et al.: Comparison of calcium phosphate nanoparticle-mediated transfection in 2D and 3D cell culture models: Efficiency and cytotoxicity	50
(47) Sowa et al.: Supramolecular Photosensitizers for Biomedical Applications.....	51
(48) Sowislok et al.: Synthesis of Non-symmetric, Clickable Diphosphate Tweezers for Regioselective Protein Surface Recognition	52
(49) Tonali et al.: Monitoring conformational transitions <i>in vitro</i> of soluble A β 42 oligomers	53
(50) Vallet et al.: Molecular characterization and modulation of Survivin's cellular functions with supramolecular ligands.....	54
(51) Van den Boom et al.: The AAA-ATPase VCP/p97 extracts sterically trapped Ku70/80 rings from DNA in double strand break repair.....	55

(52) Van der Meer et al.: Specific targeting of proteins by surface-functionalized ultrasmall gold nanoparticles (2 nm) using click chemistry	56
(53) Van Dun et al.: Towards a supramolecular platform for protein modulation	57
(54) Walstein et al.: Cupin-domain mediated dimerization promotes centromere localization of CENP-C.....	58
(55) Wey et al.: Optical labelling of polymer nanoparticles by ultra-small gold nanoparticles	59
(56) Yilmaz et al.: Supramolecular ligands for 14-3-3 proteins	60
(57) Zakeri et al.: Label-Free and Site-Specific Probing of Molecular Recognition between Proteins and Multivalent Supramolecular Ligands by Ultraviolet Resonance Raman Spectroscopy	61

(1) External Stimuli Responsive Multi-Component Supramolecular Polymers with Tunable Properties

P. Ahlers¹, H. Frisch¹, K. Fischer², R. Holm¹, D. Spitzer¹, M. Barz^{1,3} and P. Besenius^{1,3}

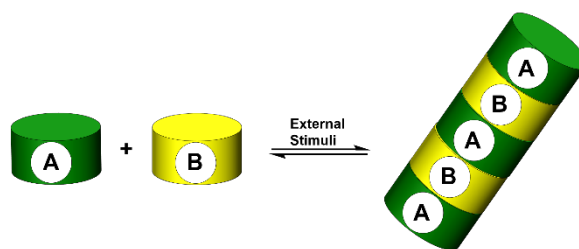
¹*Institute of Organic Chemistry, Johannes Gutenberg-University, 55128 Mainz, Germany*

²*Institute of Physical Chemistry, Johannes Gutenberg-University, 55128 Mainz, Germany*

³*Graduate School of Excellence Materials Science in Mainz (MAINZ), 55128 Mainz, Germany*
 paahlers@uni-mainz.de

Aqueous supramolecular polymers with stimuli responsive properties are promising candidates for biomedical applications. The challenge lies in installing functionality to a responsive and structurally well-defined material. Multicomponent supramolecular polymers are a particularly powerful tool to insert tunable and multiple functional groups into these dynamic materials. Here we report two different multicomponent systems. The first one is based on a cationic monomer with a GFKFKF encoded peptide sequence and an anionic component with a GFEFEF encoded peptide sequence. As already reported, such oppositely charged comonomers are able to self-assemble into supramolecular alternating copolymers.[1-3] Here we show the regulation of the pH-dependent switch from the copolymer to homopolymer state at acidic and basic pH values. Using light scattering we investigated the influence of the comonomer feed ratio on the degree of polymerization and self-assembly kinetics.

The second multicomponent system we report here is able to reversibly complex siRNA. Therefore we co-assemble an FHFHF encoded monomer equipped with tetraethylene glycol chains with a second monomer functionalized with an ethylene diamine dendritic building block to install positive charges at the periphery of the nanorod-like supramolecular polymers. In the polymeric state these are able to bind to siRNA. By lowering the pH below 6, the supramolecular nanorods disassemble because of the protonation of the histidine units and thus increased hydrophilicity. Releasing oligonucleotides via a pH-trigger is a promising strategy to release siRNA from intracellular compartments, like endosomes.



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(2) Polycationic supramolecular ligands for targeting Survivin

Dennis Aschmann, Carsten Schmuck*

*Institute of Organic Chemistry, University of Duisburg-Essen, Universitätsstraße 7,
D-45141, Essen (Germany), dennis.aschmann@uni-due.de*

Protein-protein interactions (PPIs) are involved in almost all biological processes, thus also in processes which lead to diseases.[1] Therefore the proteins involved offer potential targets to specifically modify PPIs and consequently to intervene in disease progression. One of these proteins is Survivin, which is associated with cancer.[2] Survivin is present in healthy cells only at low concentrations but is overexpressed in malignomas. It is a member of the apoptosis-inhibiting proteins (IAPs) and is involved in the formation of the INCEP complex at mitosis, hence providing a promising target for the development of new cancer therapies. As a result, there is interest in the development of ligands which are able to bind specifically and with a high affinity to such proteins. For this purpose, different amino acids are functionalized with the tailor-made artificial binding motif guanidiniocarbonyl pyrrole cation (GCP) alongside with different scaffolds to obtain a large library of ligands, which are investigated regarding their binding properties to different proteins.[3]

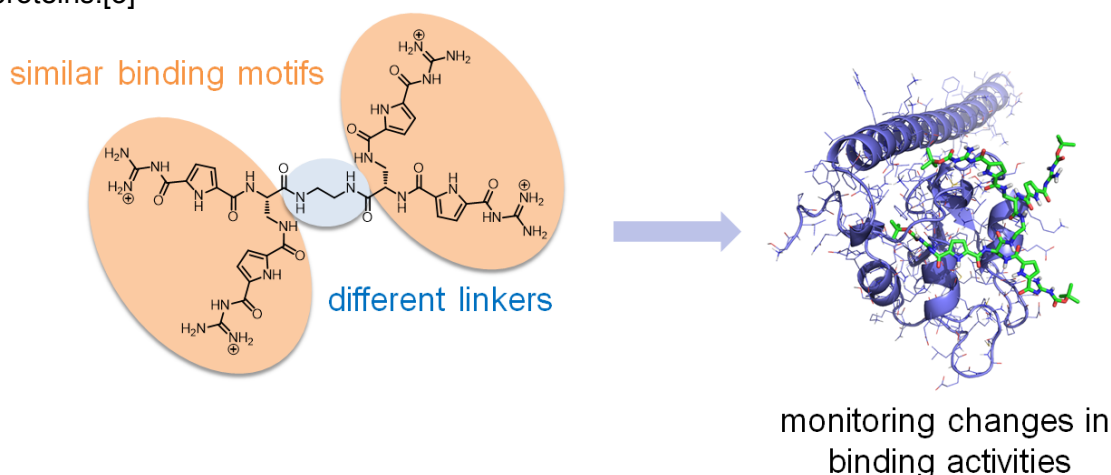


Fig.1: Schematic presentation of the development leading to ligands which should have high binding affinities to specific proteins.

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(3) Dissection and Modulation of (patho)biological Survivin Functions by supramolecular Ligands

Sandra Bäcker*, **Christian Heid****, **Cecilia Vallet***, **Stefanie Sichelschmidt***,
Christine Beuck***, **Peter Bayer*****, **Thomas Schrader****, **Shirley K. Knauer***

* *Department of Molecular Biology II, Centre for Medical Biotechnology (ZMB)*

***Department of Organic Chemistry*

*** *Department of Structural and Medicinal Biochemistry, Centre for Medical Biotechnology (ZMB)
University of Duisburg-Essen, 45117 Essen, Germany*

Survivin plays an important role in cancer. While it is mostly absent in normal resting adult tissues, it is up-regulated in almost all cancer types. Its overexpression is associated with a resistance of tumors against chemo- and radiotherapy, making Survivin an attractive target for novel therapeutic strategies³.

As a member of the IAP family, Survivin plays a role in the inhibition of cell death, but as part of the CPC it is also crucially involved in mitotic regulation. For both biological functions, an interaction with the nuclear export receptor Crm1 mediated by Survivin's NES is pivotal¹⁻³. Thus, interference with this interaction should lead to a loss of Survivin's functions and therefore to an inhibition of cancer cell proliferation.

Our project aims to characterize novel supramolecular binders targeting Survivin's NES by quantitative assessment of its interaction with Crm1 and a thorough analysis of the resulting biological effects.

Binding of a non- and a peptide-linked molecular tweezer molecule to Survivin could be demonstrated by ITC analyses and precisely linked at specific basic amino acids within or near Survivin's NES by NMR titration experiments. Biochemical pulldown assays show that both tweezers interfere with the Survivin/Crm1 interaction at effective concentrations of 10-50 µM. The establishment of cellular assays for Survivin/Crm1 co-localization and first evidence for cellular uptake of molecular tweezers enable further investigation of biological effects.

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(4) NMR investigation of supramolecular ligand binding to proteins

Christine Beuck, Andrea Sowislok, Christian Heid, Tatjana Ruks, Sandra Bäcker, Shirley Knauer, Matthias Epple, Thomas Schrader, Peter Bayer*

University of Duisburg-Essen, Structural & Medicinal Biochemistry, Universitätsstr. 1-5, 45141 Essen, Germany, peter.bayer@uni-due.de

Nuclear Magnetic Resonance (NMR) spectroscopy is ideally suited to monitor ligand binding to proteins with single-residue resolution. However, binding of large supramolecular ligands to proteins and protein-protein complexes poses additional challenges due to the size and complexity of the systems.

We present examples how NMR methodology has been extended to study supramolecular tweezers and nanoparticle binding to proteins.

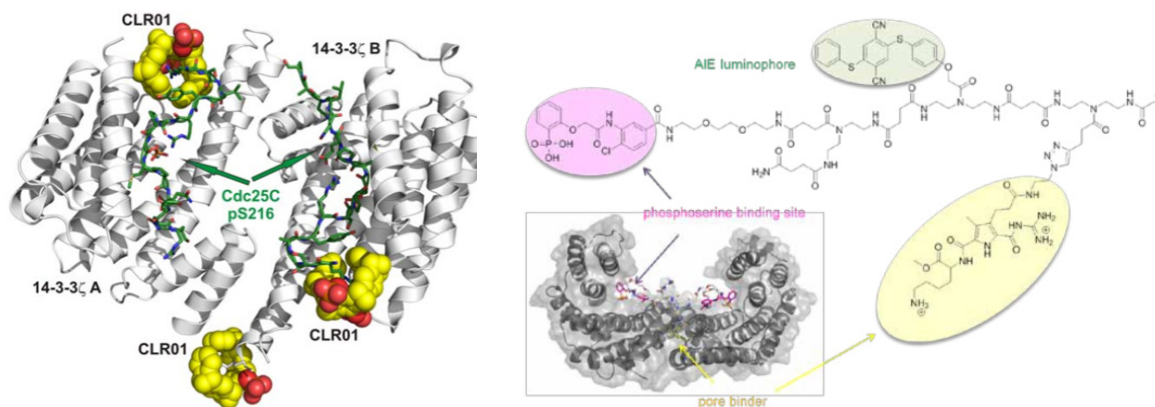
Side chain specific experiment for lysine and arginine residues directly observe the atoms encapsulated by the ligand and allow a precise ranking of multiple ligand binding sites on a given protein. TROSY spectra extend the size range suitable for NMR and allow to map ligand binding sites on larger or multimeric proteins. Diffusion and relaxation experiments are used to determine the size of peptide-fused nanoparticles and their complexes with a model protein.

(5) Modulation of 14-3-3 protein-protein interactions (PPIs) by supramolecular chemistry

David Bier^{1,2}, Xavier Guillory^{1,3} Christian Ottmann^{1,3}

¹Fakultät für Biologie, Universität Duisburg-Essen, Universitätsstr. 7, D-45117 Essen, Germany, ²Max-Planck-Institut für molekulare Physiologie, OttoHahn-Str. 11, 44227 Dortmund. ³Department of Biomedical Engineering, Chemical Biology, Technische Universiteit Eindhoven, 5600 MB EINDHOVEN

The interdisciplinary field of supramolecular chemistry focuses on the study of host-guest interactions. Mimicking the nature of the enzyme substrate binding, supramolecular ligands can be designed for the recognition of active sites, protein gaps and protein surfaces. The application of these ligands as modulators of PPIs in biological systems is very rare and has many advantages over the conventional small molecular or peptidic inhibitors. They exhibit a higher stability in the cellular environment and are less affected by regular degradation processes due to their artificial character. 14-3-3 proteins are particular suitable for study of supramolecular ligands and their influence on PPI modulation. These adapter proteins have more than 200 interaction partners and modulate their enzymatic activities or regulate transport processes between the cytosol and the nucleus. Most of 14-3-3 interaction partners comprise a specific recognition sequence, including a phosphorylated Serine or Threonine, and bind to 14-3-3 in a phosphorylation dependent manner. For example, 14-3-3 proteins recognize the c-terminal region of the tumor suppressor (p53) protein. Further proteins, such as Tau, α -Synuclein and dual specificity phosphatase CDC25C, exhibit specific binding motifs for 14-3-3 proteins. Here we present several supramolecular ligands which are specifically designed for modulation of 14-3-3 involved PPI. These ligands serve as molecular tweezers and stabilize PPI's or contain divalent GCP modifications with AIE properties.



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(6) Role of HTRA1 in the prion-like transmission of Tau aggregates in tauopathies

Anika Blümke¹ and Michael Ehrmann¹

¹*University Duisburg-Essen, Centre for Medical Biotechnology, Universitätsstraße 2, 45117 Essen*

Anika.Bluemke@uni-due.de, Michael.Ehrmann@uni-due.de

The abnormal aggregation of the microtubule-associated protein Tau into fibrillar deposits is a hallmark of neurodegenerative tauopathies, such as Alzheimer's disease (AD). Tau pathology spreads along distinct neural networks through the intercellular transfer of low-order Tau oligomers, or seeds (1,2). In a prion-like manner, Tau seeds are secreted into the extracellular space and subsequently endocytosed by neighboring cells. Upon internalization, seeds nucleate the fibrillization of endogenous Tau via direct protein-protein contact (2). The highly conserved serine protease HTRA1 degrades Tau fibrils via disintegration of core structures and subsequent proteolysis, implying its potential role in Tau spreading (3).

To address this model, a FRET-based flow cytometry assay was established that quantifies Tau seeding (2). The assay uses HEK293T cells overexpressing Tau tagged to CFP or YFP, respectively. Treatment of these Biosensor cells with Tau seeds resulted in intracellular aggregation and thus in an increased FRET signal in a dose-dependent manner. However, concomitant overexpression of HTRA1 counteracted Tau seeding and reduced the FRET signal. Further, a Tau spreading model was developed based on the indirect co-culture of HEK293T cells harboring Tau aggregates and Biosensor cells. Co-culture triggered the infection of Biosensor cells with Tau seeds, which was reduced in the presence of HTRA1. Additionally, the co-culture of HEK293T cells overexpressing HTRA1 and SHSY5Y cells revealed spreading of HTRA1, which might display a further mechanism of impairing Tau propagation.

Taken together, our data indicate an impact of HTRA1 on the intercellular transfer of Tau suggesting new opportunities for the treatment of tauopathies such as AD.

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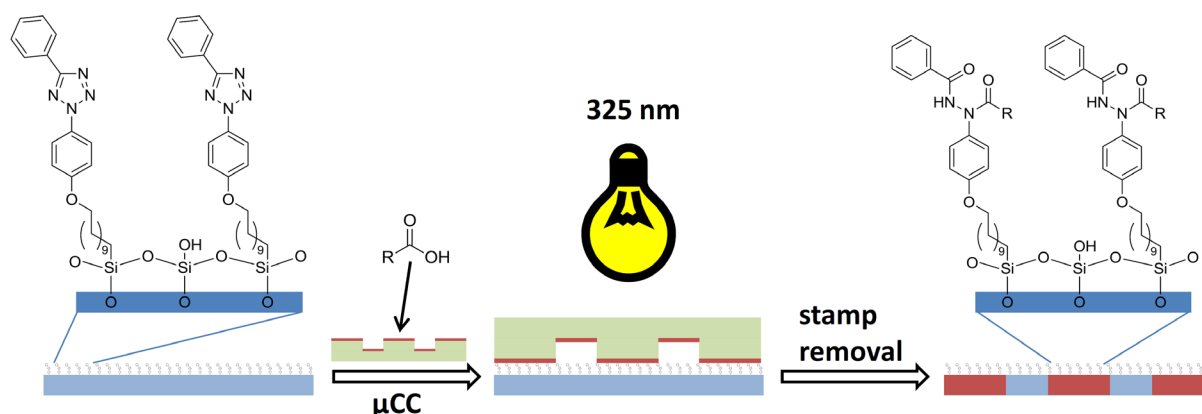
(7) Immobilization of Carboxylic acids by Light-Induced Dipolar Addition to Nitrilimines and Microcontact Printing

Christoph Buten, Bart Jan Ravoo

Organic Chemistry Institute, (Corrensstraße 40, Westfälische Wilhelms-Universität Münster, D-48149 Münster, Germany, christoph.buten@wwu.de)

Nitrilimines are in situ prepared, highly reactive 1,3-Dipoles, which undergo cycloadditions with a large number of dipolarophiles such as alkenes, alkynes,^[1] thiols and carboxylic acids.^[2] Nitrilimines are accessible from tetrazoles by photolytic elimination of Nitrogen.^[3] Advantages of this reaction over e.g. thiol-ene click chemistry or azide-alkyne cycloadditions are that no photoinitiators or catalysts are needed. Therefore this reaction found its way into the field of microcontact printing.

In this study, we focused on the addition of carboxylic acids to photolytically generated nitrilimines on surfaces, since many biological relevant molecules exhibit carboxylic acid functionalities in their structure and could thus be immobilized by this method. As model substrate, we immobilized biotin and carbohydrate derivatives via its carboxylic acid functionality and verified its retained bioactivity by their strong interaction with streptavidin and lectins. The surfaces were characterized by XPS, fluorescence microscopy and ToF-SIMS measurements.



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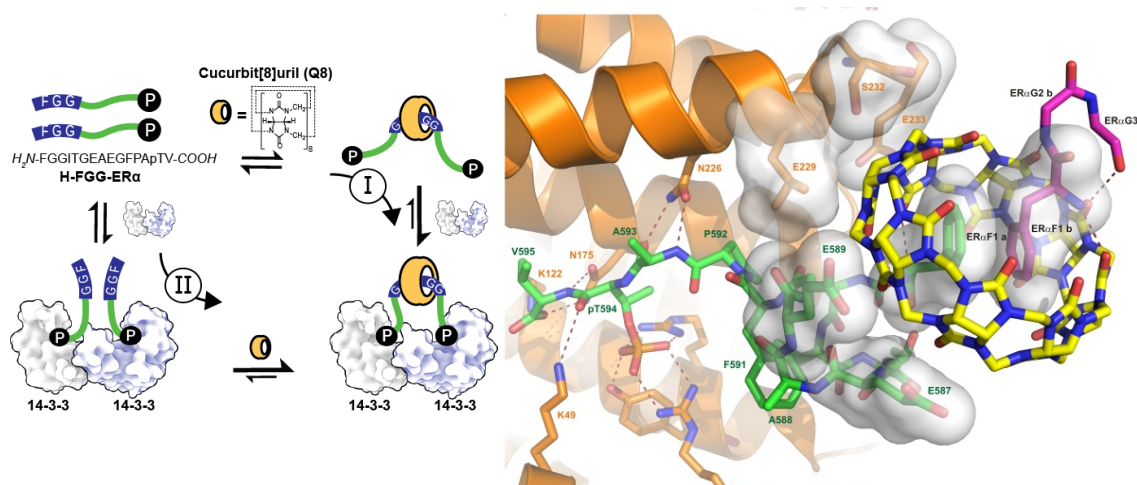
(8) Controlling Protein-Protein Interactions by Cucurbit[8]uril Mediated Host-Guest Chemistry

Pim J. de Vink, Jeroen M. Briels, Thomas Schrader, Lech-Gustav Milroy, Luc Brunsveld, and Christian Ottmann

P.J.d.vink@tue.nl, Laboratory of Chemical Biology and Institute of Complex Molecular Systems, Department of Biomedical Engineering, Eindhoven University of Technology, Den Dolech 2, 5612 AZ Eindhoven (The Netherlands)

Molecular recognition of amino acids through host-guest chemistry has great potential to control biomolecular assemblies¹. Supramolecular host molecules can be used as a tool to supplement, surrogate and extend the native interactions within a multicomponent complex. For examples, cucurbit[8]uril (Q8) recognizes phenylalanine-glycine-glycine (FGG) tripeptide motif on the N-terminus of peptides and proteins², thus allowing for bio-orthogonal control over protein dimerization, immobilization and enzyme activity. Here we describe the development of a (Q8)-based supramolecular system, with the 14-3-3 scaffold protein and two synthetic peptides derived from estrogen receptor α (ER α). A well-defined multi component complex is formed with Q8 (Figure 1)³.

Q8-induced dimerization of the ER α epitope increases its affinity towards 14-3-3. Also the affinity toward Q8 is enhanced in the presence of 14-3-3. The induced binary bivalence as was confirmed via various biophysical assays, fluorescence, scattering data, and AF4. In addition, the final structure is confirmed to atomistic resolution by protein X-ray crystallography which reveals the structural basis for the supramolecular chemically-induced switch between the mono- and bivalent modes of interaction thus shaping the way for future synthetic supramolecular signalling systems.



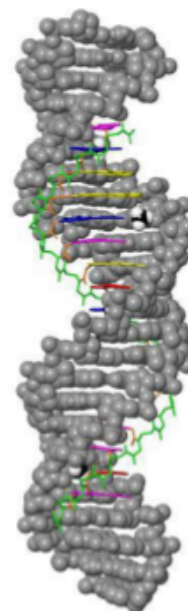
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(9) Synthesis of a modular system for major groove sequence-selective DNA recognition

Shubhankar Gadre, Max Peters, Álvaro S. Fariñas and Thomas Schrader*
University of Duisburg-Essen, Universitätsstr. 7, 45117 Essen, Germany

Nucleic Acid Recognition is a fundamental biological process. It is the basis of Central Dogma of Molecular Biology which allows for the flow of genetic information across all living organisms. Nature generally uses four different avenues for DNA recognition: intercalation into base pairs,¹ unspecific binding to the sugar phosphate backbone and minor² as well as major groove insertion.³ For the purpose of addressing a specific gene, a ligand must be directed towards the minor or major groove, because here the base sequence becomes freely accessible - and readable.



Numerous efforts have been previously made towards achieving the goal of DNA recognition. However, they suffer from limitations like invasion of Duplex DNAs⁴ due to extraordinary thermodynamic stability of the triplex, limited recognition up to only 7-10 base pairs^{5,6}, or being exclusive only to homopurines⁷. There exists therefore, necessity of creating a modular system which can bind sequentially to any given number of base pairs of a gene, specifically in the major groove of DNA.

We therefore, envisage the construction of synthetic sequence-selective Heterocyclic DNA ligands which operate by general base-pair recognition inside the major groove, thus providing a tool for Gene-specific manipulation of DNA. We intend to synthesize 4 hydrogen bonding ligands which would form a triplex with the each natural base pair (AT-, TA-, CG- and GC-) in a perpendicular orientation, fitting snugly into the major groove side of base pairs respectively. These new ligands are intended to be covalently fused to a template strand, which directs the whole recognition module inside the major groove.

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(10) Molecular dynamics of highly flexible supramolecular ligands and proteins — challenges and solutions

Jean-Noël Grad, Daniel Hoffmann

*Bioinformatics and Computational Biophysics, Center for Medical Biotechnology,
University of Duisburg-Essen, Universitätsstr. 7, D-45117 Essen, Germany*

Locating supramolecular ligands on proteins through molecular dynamics (MD) simulations can be challenging, as the ligand size, flexibility and ability to interact on a large surface force us to abandon the notion of the well-defined binding pose. Trajectory analysis is reduced to characterizing protein–ligand interfaces, which may not justify the computational cost of MD. Our research shows the same information can be extracted from an inexpensive FFT correlation using electrically charged fragments of the ligand[1]. This method estimates ligand probability distributions around proteins in the same way a long simulation would, allowing us to assess MD convergence or derive optimal MD starting conditions. We discuss applications in 14-3-3/C-Raf stabilization by dendrimers, heparin binding to sonic hedgehog, and present a novel statistical approach to evaluate salt bridge stability in survivin.

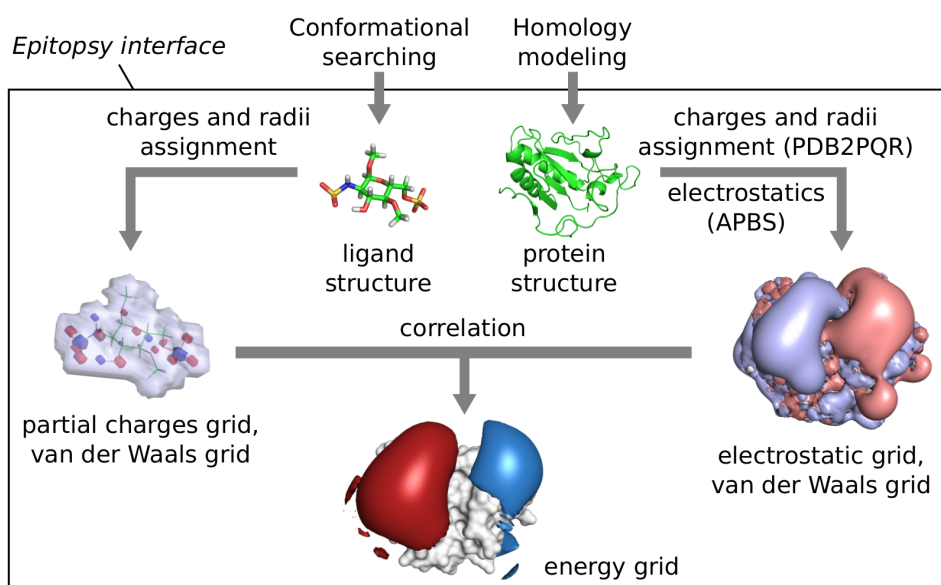


Figure 1: Computation of energy grids within our open-source Python package Epitopsy (<https://github.com/BioinformaticsBiophysicsUDE/Epitopsy>).

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(11) Therapeutic Potential of a Peptide based Carbene Complex

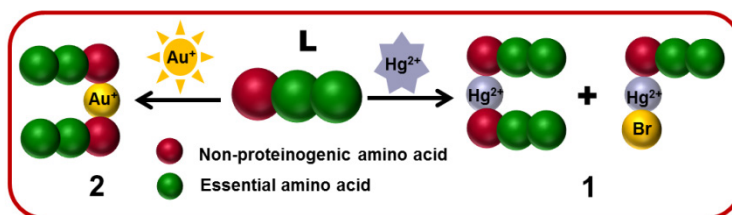
Astha Gupta^a, Sandeep Verma^{b*}

^aDepartment of Chemical Engineering, and ^bDepartment of Chemistry

Indian Institute of Technology Kanpur, Kanpur 208016

Uttar Pradesh, INDIA. E-mail: gasthaq@iitk.ac.in

We present the strategic design of a novel tripeptide that has the capacity to generate a carbene on its side chain. This tripeptide was used for the synthesis of an organometallic carbene complex by reaction with appropriate gold and mercury precursors. These complexes showed the characteristic features of carbene complexes i.e. disappearance of peak for the proton where carbene is generated in ¹H NMR and deshielding of the carbenoid carbon peak in the ¹³C NMR spectra. Their structures were elucidated by Density Functional Theory (DFT) calculations. The gold complex showed anti-microbial potential against the ESKAPE panel of pathogens. Additionally, it was also cytotoxic to MCF-7 tumor cell line. It showed maximum uptake into nucleus and mitochondria in the cells, which implicates its interaction with DNA and mitochondrial proteins for its activity. To summarise, this peptide based gold complex provides an insight into peptide based organometallic complexes for biomedical applications.



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(12) Novel luminophores with aggregation induced emission properties for protein recognition

Matthias Hayduk, Jens Voskuhl

University of Duisburg-Essen (e-mail: jens.voskuhl@uni-due.de)

Since the discovery of the fluorescence phenomenon called aggregation induced emission (AIE)^[1], it has become a versatile tool in different disciplines in modern bio-chemistry^[2]. The main advantage of AIE luminophores is their ability to light up when their motion is restricted. Only few examples are known from literature using this fluorophore class for the binding to proteins, so that the influence of the binding event on the protein structure and the protein activity in this context is largely unknown. This fluorescence “on” behaviour enables the direct read-out of binding processes or morphological changes such as gelation, crystallisation, binding or polymerisation, which gives the AIE important applications for bio-chemistry in future. Therefore our aim is the development of novel luminophores with AIE properties as ligands for the recognition of protein surfaces and binding pockets.

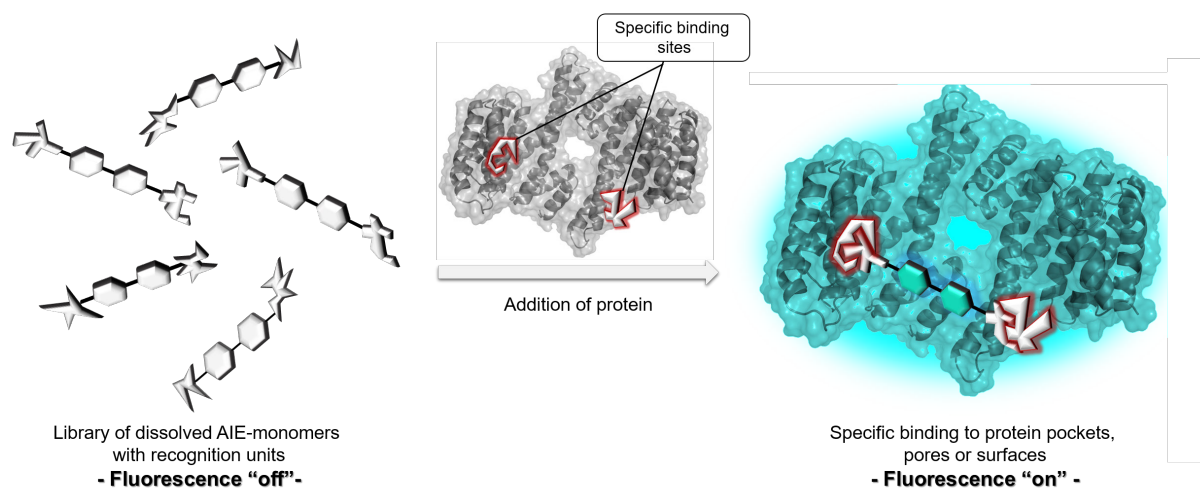


Fig. 1: Schematic presentation of the fluorescence “on” behaviour upon protein binding.

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(13) Molecular Tweezers for Specific Protein Surface Recognition

C. Heid, Essen/D, T. Schrader*, Essen/D

Prof. Dr. Thomas Schrader, Universität Duisburg-Essen, Universitätsstr. 7, 45117 Essen/D

Molecular tweezers are excellent binders for lysine and arginine by non-covalent interactions.¹ Their unique binding mode counteracts pathologic protein aggregation with potential applications in the treatment of Alzheimer's disease² and HIV infection.³ However, molecular recognition of lysines and arginines on protein surfaces is not selective. We now developed a new method for direct esterification of monoaryl phosphates. This method allows the convenient introduction of one or two additional linker arms for subsequent click reactions with modified peptides and fluorescence labels. These peptides act as additional recognition sites and direct the tweezers to a selected lysine residue on the protein surface. Herein we present the synthesis of these new molecular tweezers, including binding experiments.

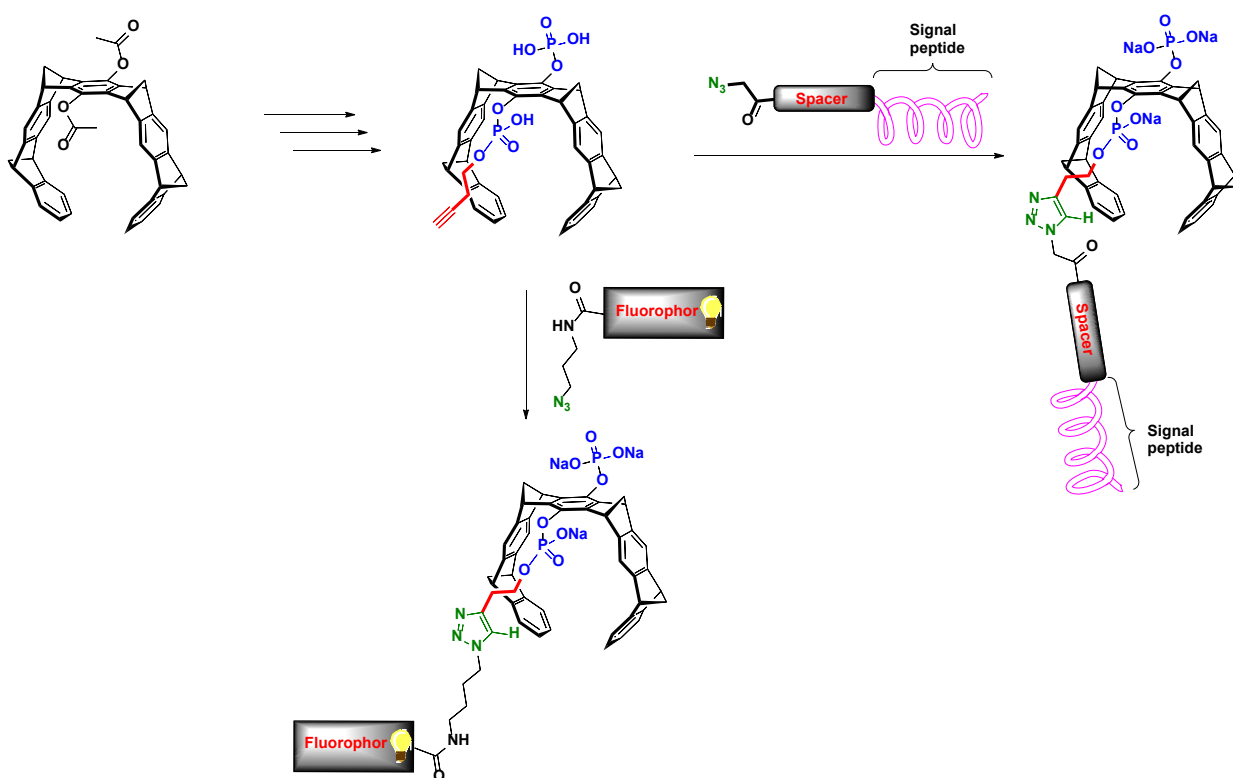


Figure 1: Synthesis of new molecular diphosphate tweezers with additional recognition units and fluorescence label.

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(14) Geometric factors and energetics of base stacking in absence of shape complementarity

Georg Homa, Wolfgang Pfeifer, Christian Denkhaus, Purya Menzel and Barbara Sacca*

**Centre for Medical Biotechnology (ZMB) and Centre for Nano Integration Duisburg-Essen (CENIDE), University of Duisburg-Essen, Universitätsstr. 2, 45117 Essen, Germany, barbara.sacca@uni-due.de*

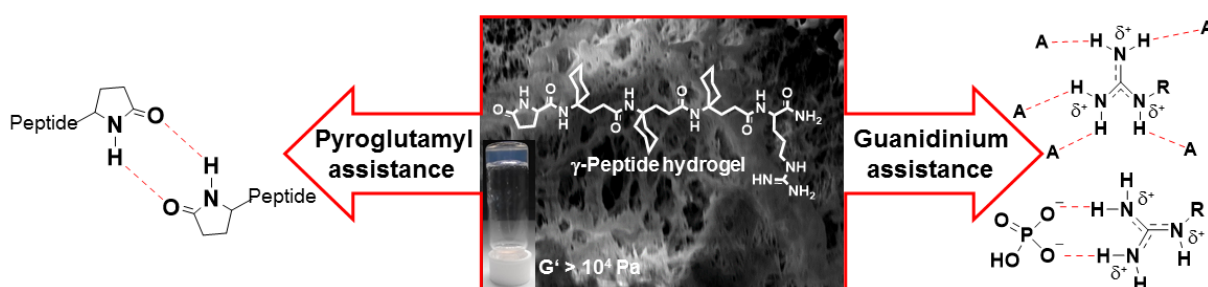
The self-assembly of multicomponent systems is often achieved through the step-wise association of distinct units into large architectures of higher hierarchical order. The process is driven by a subtle balance of intermolecular recognition forces and geometric factors, which eventually lead to the thermodynamically most stable product. Recent progresses in the DNA origami technology have shown that the large repertoire of tunable interactions offered by the DNA molecule make such structures ideal building blocks of hierarchical assemblies. In particular, besides canonical base hybridization, inter-unit association can be guided by base stacking between edges of complementary shape. In this work, we aim at a deeper understanding of the relationship between the geometry of blunt ends and the energetics of their stacking interactions in absence of any shape-induced process. At this purpose, we realized two rectangular DNA origami structures of identical size but opposite global twist and used them as component units of large two-dimensional lattices. Our preliminary results demonstrate that the efficiency of superlattice formation as well as the resulting ultrastructure are strongly affected by the structural properties of the interacting tiles, such as the crossover pattern at the edges, the twist and relative curvature orientation. This results in self-recognition events that favor the formation of homo- rather than hetero-oligomers, suggesting that geometry-related factors, other than shape complementarity, might drive base stacking in a selective fashion. We are currently employing ensemble FRET spectroscopy to investigate the spatial details of such interactions and the energetics involved. This will help to rationalize the programmable self-assembly of hierarchical structures and enable to extend our capability to control matter distribution and manipulation to macroscopic scales.

(15) Modulating supramolecular assembly in backbone expanded peptides

S. V. Jadhav and N. Sewald

Department of Chemistry, Organic and Bioorganic Chemistry
Bielefeld University
Universitätsstrasse 25, 33615 Bielefeld (Germany)
E-mail: sandip.jadhav@uni-bielefeld.de

Gabapentin, an *anti*-epileptic drug, is known to form stable helical structures in short peptides.¹ Distinctly, we report on the newly synthesized γ -analogue of gabapentin, that is, γ -gabapentin (γ -Gpn), which manifests β -sheet character at molecular and nanofibrous hydrogels at the supramolecular level. We investigated the influence of proximally immobilized cationic amino acids (lysine and arginine) on the self-assembly of backbone-expanded tripeptide motif. Interestingly, arginine was found to be superior, both physically and mechanically, over lysine in driving hydrogelation. We have concluded that intrinsic and biochemically distinct properties of the guanidinium ion of arginine (compared to ammonium ion of lysine) have contributed towards this effect. Furthermore, similar to pyroglutamyl (pGlu) modified amyloid β peptides,² *N*-pGlu modification of our self-assembling tripeptide motif exerts a dramatic influence on aggregation and exhibits enhanced β -sheet character, accelerated self-assembly kinetics, improved optical transparency and provides higher mechanical stiffness to the peptide hydrogel.³



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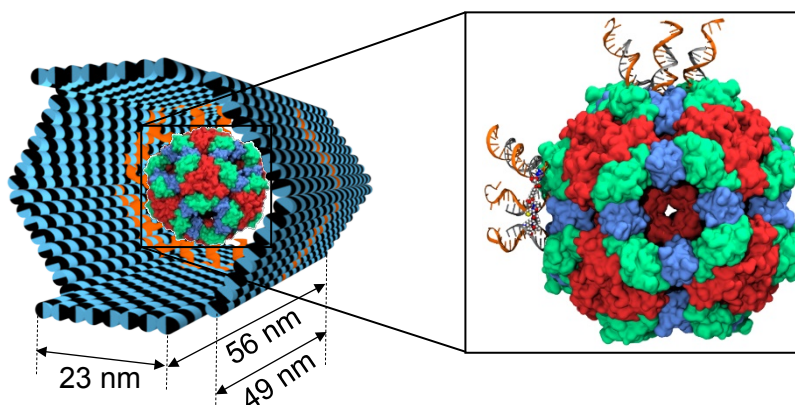
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(16) Rationally designed DNA-origami hosts for protein guests

Andreas Jaekel and Barbara Saccà*

**Centre for Medical Biotechnology (ZMB) and Centre for Nano Integration Duisburg-Essen (CENIDE), University of Duisburg-Essen, Universitätsstr. 2, 45117 Essen, Germany, barbara.sacca@uni-due.de*

Host-guest complexes rely on non-covalent interactions between complementary shapes: a concave host surface, displaying convergent ligands, and a convex guest surface, exposing divergent binding sites. Applying this basic principle, we have recently realized one of the largest DNA-protein complexes of semisynthetic origin held in place exclusively by spatially defined supramolecular interactions¹. Our approach is based on the decoration of the inner surface of a DNA origami hollow structure with multiple ligands converging to their corresponding binding sites on the protein surface with programmable symmetry and range-of-action. Our results demonstrate specific host-guest recognition in a 1:1 stoichiometry and selectivity for the guest whose size guarantees sufficient molecular diffusion, still preserving short intermolecular distances. In this work, we aim at the generalization of this construction principle using host/guest pairs of different sizes and symmetries and employing a large repertoire of currently available conjugation strategies. We will then investigate the effect of DNA caging on the stability and enzymatic activity of the internalized protein.



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(17) Modulation of protein-protein-interactions

Matthias Killa, Carsten Schmuck*

*Institute of Organic Chemistry, University of Duisburg-Essen, Universitätsstrasse 7,
D-45141, Essen (Germany), matthias.killa@uni-due.de*

The binding of small ligands to protein surfaces is usually based on aromatic and electrostatic or hydrophobic interactions.^[1] Therefore the developed guanidinocarbonyl pyrrol cation (GCP) group is ideal to bind carboxylates even in polar solvents.^[2] To address several binding sites on the surface at the same time with surface-binding-groups, a polar scaffold bridging these groups is necessary. The precision oligomers of our collaboration partner, the working group of Prof. Dr. Hartmann, are perfect for this usage. The length of the scaffolds can be adjusted for a rational design of ligands. The oligomers are also water-soluble, which is perfect for biological applications.^[3] The combination of the expertises of both working groups allows the design of precise ligands to address proteins. Our aim is to investigate the protein-protein-interactions for example the 14-3-3 Protein with the created Ligands.

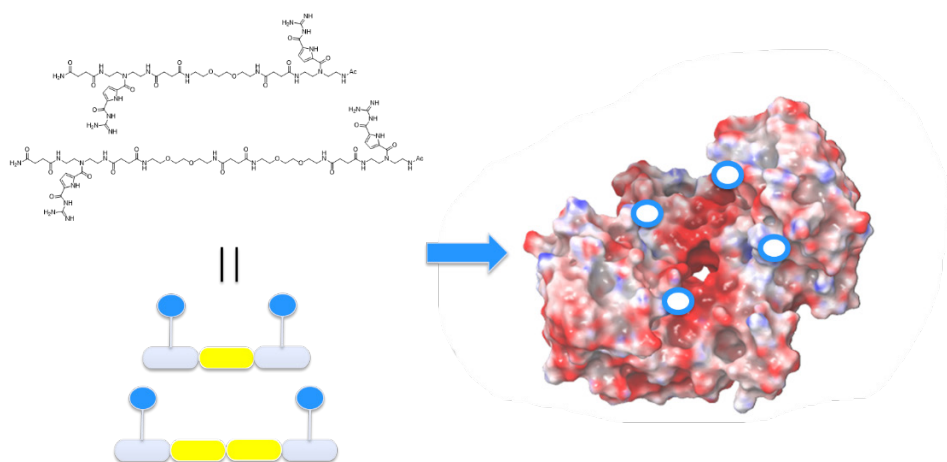


Fig. 1: A small GCP-oligomere and a bigger GCP-oligomere can address different binding sites on a protein (14-3-3 zeta homodimer).

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(18) Fighting Viruses with Viruses: A Supramolecular Multivalent Influenza Inhibitor based on the Bacteriophage Q β Capsid

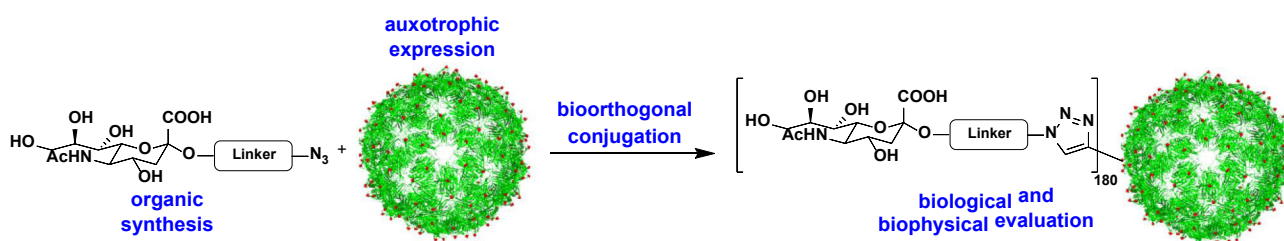
S. Klenk, D. Lauster, S. Liese, S. Nojoudi, S. Behren, K. Ludwig, S. Sanger, Th. Wolff, C. Bottcher, N. Budisa, A. Herrmann, C. P. R. Hackenberger

Leibniz-Forschungsinstitut fur Molekulare Pharmakologie (FMP),

Robert-Rossle-Str. 10, 13125 Berlin, klenk@fmp-berlin.de

Multivalent ligand–receptor binding events are crucial in nature and responsible for mediating biological interactions.[1] One particularly prominent example is the cellular uptake of influenza A viruses: Viral infection occurs by the recognition and binding of sialic acid terminated cell-surface glycans by the viral membrane protein hemagglutinin (HA).[2] Consequently, the inhibition of this binding event by a suitable HA inhibitor is regarded as a very promising strategy to develop new antiviral drugs.

In this presentation we describe the engineering of an HA inhibitor by displaying sialic acids on a multivalent proteinaceous platform. The use of bacteriophage Q β capsids as scaffold allowed us to create a monodisperse multivalent system, in which the valency, spatial arrangement and ligand identity can be tuned as desired.



Several sialic acid azides were synthesized and conjugated to Q β capsids bearing homopropargylglycine as an unnatural amino acid.[3] Bioorthogonal CuAAC reaction delivered fully functionalized and intact Q β particles, analyzed by mass spectrometry and cryogenic transmission electron microscopy. The obtained sialic acid decorated particles were tested in HA binding and infection inhibition assays revealing a highly potent virus inhibitor with impressive binding and inhibition parameters. The underlying binding modes were modeled and simulated by computational methods (e.g. molecular dynamics) which are consistent with the experimental data.

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(19) Dynamic Combinatory Approach towards synthetic Peptide-Receptors

Florian Klepel, Bart Jan Ravoo

*Organic Chemistry Institute, University of Münster, Corrensstraße 40, 48149 Münster, Germany,
florian.klepel@uni-muenster.de*

Rational design of artificial receptors for biomolecules remains a great challenge. Therefore, usually stepwise mutation of bulky antibodies and antibody mimetics, which are smaller protein scaffolds, is used to find new receptors.^[1] As an alternative approach, we aim to generate small novel receptor molecules by use of a dynamic combinatory library (DCL). Our method allows for simultaneous synthesis and screening of several compounds at once as well as screening for several targets (templates) in rapid succession.^[2]

We employ a library of short peptides with a CysXCys motive where the middle X can be any amino acid. After oxidation of the cystein-bound thiols cyclic disulfide bridged dimers are formed. Those cyclic dimers contain all possible combinations for their two amino acids X. Dynamic thiol disulfide exchange ensures an equilibrium of all those species. After addition of a template molecule the equilibrium will be shifted towards the peptide-templates-complex by thermodynamic stabilization, which can be observed via LC-MS.



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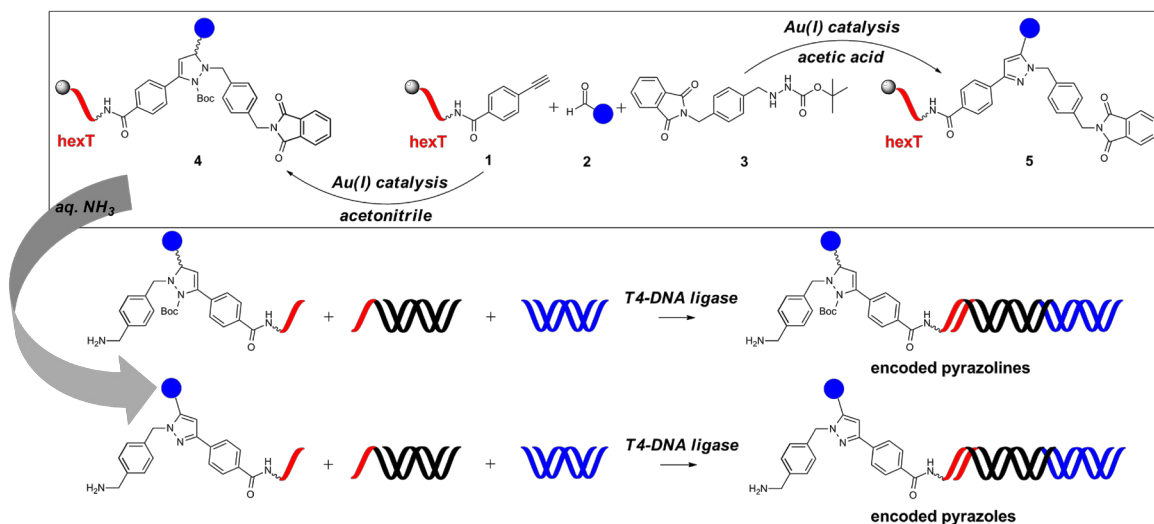
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(20) Au(I)-mediated synthesis of hexathymidine-DNA-pyrazol(in)e chimeras, an efficient entry to DNA-encoded libraries inspired by drug structures

M. Klika Škopić, K. Jung, A. Gohla, D. dos Santos, A. Brunschweiler*

TU Dortmund, Otto-Hahn Straße 6, 44227 Dortmund, Germany

The selection of large, pooled DNA-encoded small molecule libraries (DELs) is a validated technology for the target-based identification of bioactive compounds. DELs are synthesized by alternated organic synthesis and encoding steps in combinatorial manner.¹ Prerequisite for library synthesis are DNA-compatible preparative organic reactions. Au(I) catalysts enable access to drug-like heterocycles from simple educts, yet they are not available for library synthesis as they interact with purine nucleosides, eventually causing depurination. To circumvent depurination, we initiate library synthesis with a hexathymidine DNA sequence called “**hexT**” which allowed us to use a broader spectrum of catalysts in the very first step of DEL synthesis. Accordingly, we call this synthesis strategy “**TiDEC**” (oligoThymidine-initiated **DNA-Encoded Chemistry**).² Here, we demonstrate the synthesis of **hexT**-conjugates of highly substituted pyrazolines and pyrazoles from **hexT**-alkynes and readily accessible starting materials.³ The solid phase-bound **hexT**-alkyne **1** was reacted with aldehydes **2** and hydrazides **3** using a catalytic system consisting of a Au(I)-complex and a Ag(I)-salt in acetonitrile to give rise to **hexT**-pyrazolines **4**, whereas the same reaction performed in glacial acetic acid yielded **hexT**-pyrazoles **5**. The **hexT**-heterocycle conjugates were cleaved from the solid phase, and ligated to coding sequences to record the heterocycle synthesis.



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(21) Synthesis of Ahp-Cyclodepsipeptides as Serine Protease Inhibitors

Steffen Köcher, Juliana Rey, Jens Bongard, Michael Meltzer, Michael Ehrmann, and Markus Kaiser

Zentrum für Medizinische Biotechnologie, Universität Duisburg-Essen, Universitätsstr. 2, 45117 Essen, Germany; E-mail: steffen.koecher@uni-due.de, markus.kaiser@uni-due.de

S1 serine proteases are by far the largest and most diverse family of proteases encoded in the human genome and are involved in many important physiological processes like protein turnover, digestion or blood coagulation. Consequently, uncontrolled or undesired proteolysis can induce many diseases, for example stroke, viral infections or inflammation.

The natural product family of Ahp-cyclodepsipeptides are potent S1 serine protease inhibitors. All Ahp-cyclodepsipeptides feature a unique chemical scaffold structure including a denoting 3-amino-6-hydroxy-2-piperidone (Ahp) residue. Ahp-cyclodepsipeptides inhibit S1 serine proteases by simultaneous non-covalent binding to the S- and S'-subsites of the proteases.

In this work, we demonstrate that Ahp-cyclodepsipeptides represent a suitable scaffold structure for generating target-tailored inhibitors of serine proteases. For efficient synthetic access, we developed a practical mixed solid- and solution-phase synthesis that we validated through performing the first chemical synthesis of the two Ahp-cyclodepsipeptide natural products, Tasipeptin A (Fig. 1) and B. The synthetic route consists of i) anchoring of a Fmoc-(5-OH)-Nva-OAll building block via its side-chain hydroxyl group to a solid phase resin, ii) solid phase peptide synthesis to incorporate all amino acids, iii) on-bead cyclization to generate the cyclic structure and iv) oxidation with the Dess-Martin reagent to install the Ahp residue.

The suitability of the Ahp-cyclodepsipeptide scaffold for tailored inhibitor synthesis is showcased by the generation of the most potent human HTRA protease inhibitors to date.

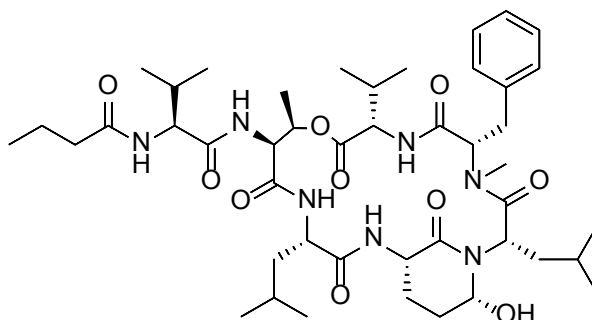


Fig. 1: Chemical structure of the Ahp-Cyclodepsipeptide Tasipeptin A

References:

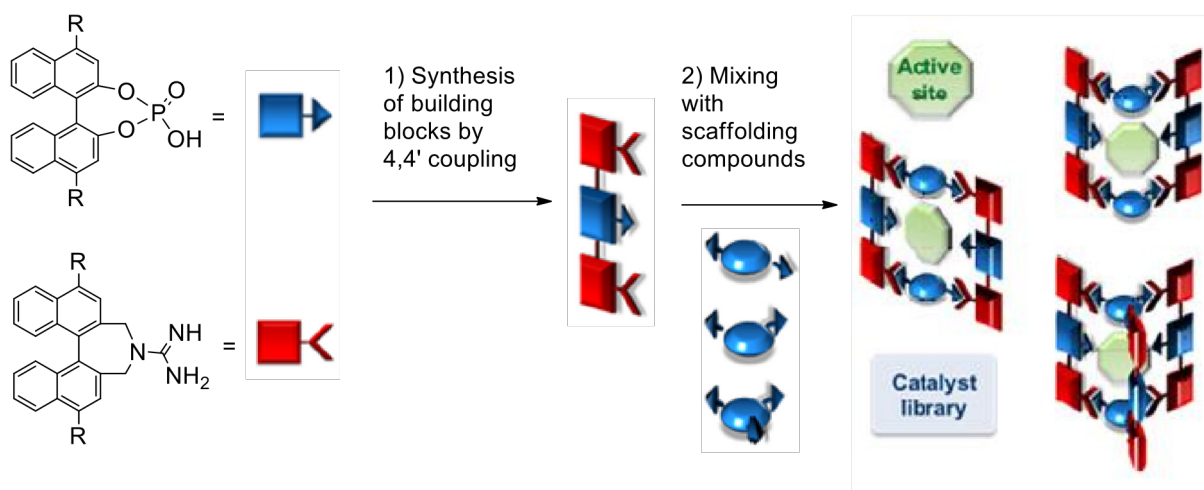
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(22) Cage-like nanocapsules for molecular recognition and catalysis

Martha Kohlhaas, Jochen Niemeyer

Naturally occurring catalysts such as enzymes are widely known for their excellent catalytic activities and ability to discriminate between different substrates. Their well-defined tertiary structure provides a suitable environment for host-guest chemistry and catalysis. It has been one of the central aims of supramolecular chemistry to mimic enzymatic behaviour for catalytic purposes, either by metal-based catalysis or organic molecule strategies.¹

This project focuses on the development of endohedrally functionalized supramolecular capsules with catalytically active groups. This simulates the active site of an enzyme by providing a closely confined reaction space, bringing the substrates in close proximity and thereby driving the reaction forward. Starting from different building blocks, the capsules obtained can vary in size and functionalization.



The formation of the hydrogen-bonded supramolecular capsules takes place by self-assembly of linear building blocks with suitable scaffolding compounds. The linear subunits are generated by 4,4'-coupling of binaphthyl-based phosphoric acids and guanidines, giving chiral building blocks. Upon mixing with suitable scaffolding compounds, the capsules form via self-assembly in a 2-to-2 or 3-to-2 fashion with an interior active site available for substrate binding and activation.

Using this approach, a catalyst library for different reaction types and sizes of substrate can be obtained, giving a promising approach for catalysis.

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(23) Visualizing the fate of calcium phosphate nanoparticles inside living cells by a double fluorescent fusion protein

Sebastian Kollenda and Matthias Epple

Inorganic Chemistry and Center for Nanointegration Duisburg-Essen (CeNIDE),

University of Duisburg-Essen, Universitätsstr. 7, 45141 Essen, Germany

Calcium phosphate naturally occurs in bone tissue and teeth and is generally considered to have a good biocompatibility and a high biodegradability in biological applications.^[1] Due to these characteristics of calcium phosphate, nanoparticles based on this have become a potent delivery system of a vast range of molecules for *in vitro* and *in vivo* experiments. Our aim is to create a tool to visualize the pathway and fate of nanoparticles inside the cell.

Calcium phosphate nanoparticles (CaP-NPs) are synthesized by a fast precipitation from aqueous solutions of calcium lactate and diammonium hydrogen phosphate. The nanoparticles are colloidally stabilized with poly(ethylene imine) and loaded with a tandem fusion protein consisting of DsRed-eGFP (red and green fluorescence).^[2] The nanoparticles are taken up by the cell together with the protein via endocytic pathways and then directed to lysosomes.^[3] At a physiological pH of 7.4 the fluorescence of both proteins (red and green) is detectable. Under the conditions of an acidic pH of about 4.5-5 inside the lysosomes, the green fluorescence will disappear^[4] due to the protonation of the chromophore.

As control, unloaded nanoparticles were synthesized and applied to the cells. An fluorescence assay is used to confirm the pH-dependent fluorescence decrease of eGFP alone and its fusion variant to DsRed. The particles were characterized by dynamic light scattering and scanning electron microscopy.

Acknowledgement

We thank the CRC 1093 and the Deutsche Forschungsgemeinschaft for generous support and funding this project.

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(24) Analysis of lateral kinetochore transport by molecular motors

N. V. Kornakov*, G. Hagemann**, F. Herzog**, S. Westermann*

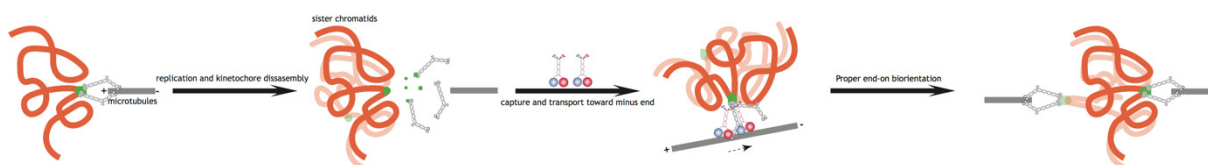
**Department of Molecular Genetics, University of Duisburg-Essen, Essen, Germany
 nikolay.kornakov@uni-due.de, stefan.westermann@uni-due.de*

***Gene Center, LMU, Munich, Germany*

During mitosis duplicated sister chromatids attach to plus-ends of spindle microtubules, allowing them to be pulled apart to the opposite sides of the cell. However, establishing correct microtubule-kinetochore connections for every pair of sister chromatids is a challenging problem. Initially, budding yeast kinetochores bind to the lateral microtubule surface and undergo fast transport towards the spindle pole, where their chance to encounter another microtubule's plus-end is significantly higher. However, it is unclear how kinetochores are transported by molecular motors and it is not known how lateral attachments can be converted into "end-on" connections. In budding yeast the molecular motor Kar3/Cik1, a member of the conserved family of Kinesin-14s, has been implicated in kinetochore transport.

I have created a conditional and acute Kar3/Cik1 depletion and complementation system, that allowed me define molecular requirements for motor function in cells. I have identified a short, conserved sequence in the Cik1 tail domain which is necessary and sufficient to perform Cik1-specific functions.

Recombinant expression and characterization of wild-type and mutant Kar3/Cik1 revealed that the conserved tail motif crosslinks to the Kar3 tail, and is required for interaction with the only known cargo, the plus-end binding protein Bim1. Future experiments will further elucidate how regulated, tail-dependent interactions facilitate kinetochore transport.



(25) Analyzing Amyloid Beta Aggregates with a Combinatorial Fluorescent Molecular Sensor

Joydev Hatai, Leila Motiei, and David Margulies

*Department of Organic Chemistry, Weizmann Institute of Science, Rehovot 7610001, Israel.
Joydev.hatai@weizmann.ac.il*

The self-assembly of amyloid beta ($A\beta$) peptides into insoluble aggregates is thought to play a major role in the progression of various neurodegenerative diseases, including Alzheimer's disease (AD). Although various studies have shown that subtle variations in the dynamics and compositions of $A\beta$ aggregates could have a significant impact on their physicochemical and pathological properties,¹ currently there is no effective means to straightforwardly characterize the $A\beta$ aggregation state. Fluorescent assays, which mainly rely on the 'turn-on' properties of a thioflavin T (ThT) molecule, can only detect the fibril formation, whereas other techniques that can determine the content of these assemblies require special expertise and are not high-throughput. To improve the ability to analyze $A\beta$ aggregates, we have developed a combinatorial fluorescent molecular sensor that generate a wide range of unique emission 'fingerprints' upon binding to distinct $A\beta$ aggregate species. The molecular sensor has been used to discriminate among aggregates generated from different alloforms (i.e., $A\beta_{40}$ and $A\beta_{42}$) or through distinct pathways, and it has also been used to track dynamic changes that occur in $A\beta$ aggregation states, which result from the formation of low molecular weight (LMW) oligomers, high molecular weight (HMW), oligomers, protofibrils, and fibrils (Figure 1).²

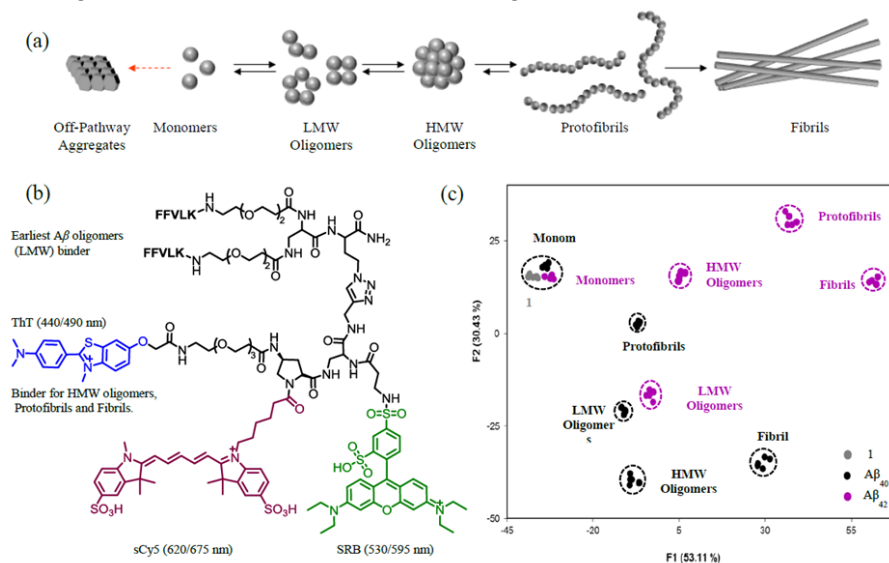


Figure 1. (a) Schematic representation of the $A\beta$ aggregation process. (b) Chemical structure of a combinatorial fluorescent molecular sensor **1**. (c) Linear discriminating analysis (LDA) showed the ability of sensor to discriminate among various aggregates.

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(26) Reconstitution of p97-mediated unfolding with pure components

Matthias Kracht, Johannes van den Boom, Hemmo Meyer

Molekularbiologie I, Fakultät für Biologie, Universität Duisburg-Essen Universitätsstr. 5, 45117 Essen, matthias.kracht@uni-due.de

The AAA+ ATPase p97 (also known as VCP, Cdc48 in yeast, Ter94 in flies) plays important roles in several cellular processes such as ER-associated protein degradation, chromatin-associated degradation, autophagy or membrane fusion. Its molecular function is to bind and unfold ubiquitinated substrate proteins to facilitate their degradation by the proteasome. p97 is a hexamer with each subunit containing an N-terminal domain (N-domain) for interaction with substrate adaptor proteins, as well as two ATPase domains (D1 and D2). The latter two form hexameric rings with the D1 domains stacked on top of the D2 domains.

The exact mechanism by which a substrate protein is processed by p97 is subject of intensive research. Recent advances have led, for the first time, to recapitulation of p97-mediated unfolding of a ubiquitinated model substrate with pure components^{1,2}. Our goal is to set up and further develop this assay in our laboratory in order to address and understand p97-mediated mechanisms by a combination of novel supramolecular chemistry and genetically encoded crosslink approaches. For this purpose, we expressed a fluorescent protein with an N-terminal diubiquitin moiety in *E. coli* and established an in vitro system for polyubiquitination, resulting in branched K48 linked chains. Upon incubation of the substrate with p97 and its cofactor Ufd1-Npl4, the unfolding activity of p97 will be determined by measuring the decrease of fluorescence. The effect of compounds that target distinct structural elements will be tested.

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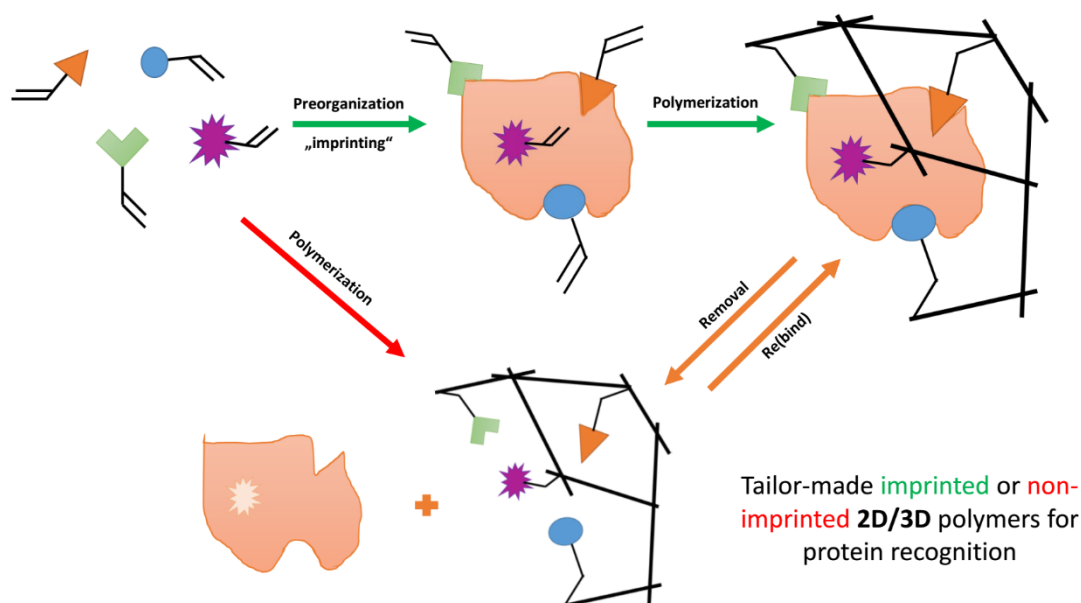
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(27) Molecular Imprinting on Proteins by Tailor-made Polymers

K. Kujawski¹, Prof. T. Schrader¹

¹Department of Organic Chemistry, University of Duisburg-Essen, Universitätsstr. 7, 45117 Essen, Germany

During the past two decades, there was an exponential increase of research containing molecular imprinted materials. It started from ions to small molecules over peptides and finally reached macromolecules and proteins, viruses, DNA and cells. The field of protein imprinting and recognition is just about to be further investigated and developed.^[1] We faced up to this challenging task and developed *tailor-made* molecular non-imprinted (NIP) and imprinted (MIP) polymers in two versions, hydrogels and nanoparticles. In contrast to literature, we use special designed and synthesized monomer library to create a specific polymer for a certain target. With the help of the amino acid complementary monomers, we want to enable a design of highly specific and selective polymers which can e.g. block protein or enzymatic functions, hinder protein-protein interactions or act like synthetic antibodies.^[2] The high affinity of our two main functional monomers could be demonstrated in imprinted biosensors for trypsin with a detection limit below picomolar (pM) concentrations.^[3]



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(28) DNA-supported bimetallic photoredox catalysis

F. Lutz and J. Niemeyer

*Institute of Organic Chemistry, University of Duisburg-Essen
(Universitätsstr. 7, 45141 Essen, fabian.lutz@uni-due.de)*

In the era of climate change and limited fossil resources, the search for higher efficiency or materials that are generated using renewable resources is particularly important. Over the last years, catalytically active bimetallic photoredox-systems have been developed to store solar energy in chemical bonds such as the creation of hydrogen from aqueous solutions or the formation of new C-C bonds.^[1,2] However, the rational design of effective photoredox-catalysts is still in its infancy, which has limited the success in generating highly active and stable systems. For this reason, novel approaches that allow for the fast generation of catalyst libraries are highly desirable, since these might allow the identification of promising new catalyst structures.

We herein present a concept for the generation of novel bimetallic photoredox-catalysts based on DNA-templation. We propose the synthesis of novel photoredox catalysts by tethering organometallic complexes (a photosensitizer and a reaction center) to complementary oligonucleotide strands. The coupling works via amide coupling as well as by strain-promoted copper-free click reaction. The resulting functionalized DNA-strands can undergo hybridization to generate the corresponding double-helical structures. This will bring the respective metal-complexes in close proximity, giving the desired bimetallic catalysts.

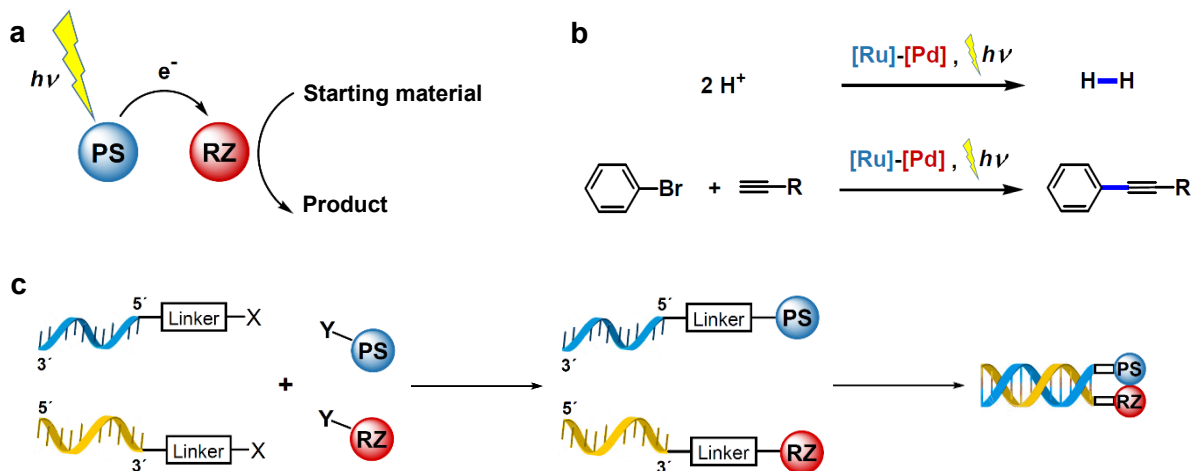


Image 1: **a)** Concept of photoredox-catalysis via photosensitizer and reaction center, **b)** Possible reactions via photoredox-catalysis, **c)** Generating a bimetallic catalyst-library by hybridization of differently functionalized oligonucleotides.

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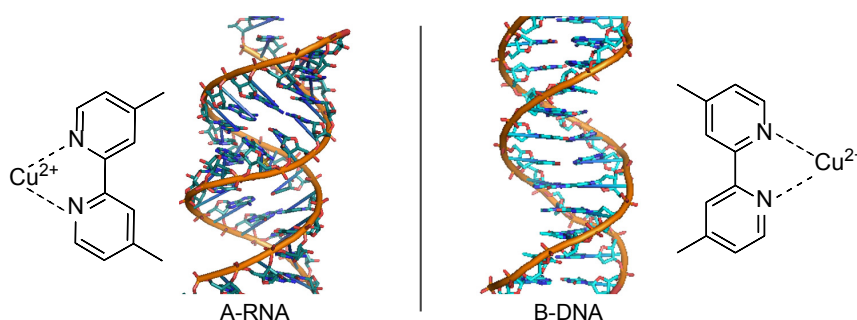
(29) Why DNA Is a More Effective Scaffold than RNA in Nucleic Acid-Based Asymmetric Catalysis – Supramolecular Control of Cooperative Effects

Jasmin J. Marek and Ulrich Hennecke

University of Münster, Organic Chemistry Institute, Corrensstr. 40, D-48149 Münster.

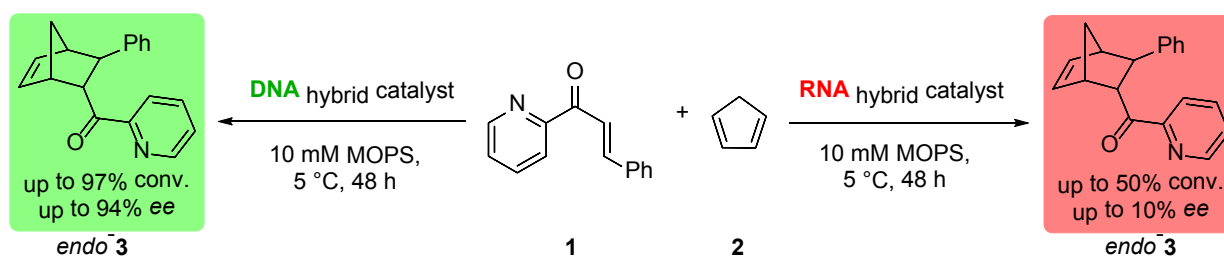
E-Mail: j_mare02@uni-muenster.de

Nucleic acids have, in addition to their unique helical structure, many interesting features that make them an attractive scaffold for the development of new hybrid catalysts. Consisting of a transition metal complex and achiral ligands together with the chiral double-stranded nucleic acid, such a hybrid catalyst can be applied as a source of chirality in asymmetric synthesis.



The use of DNA-based hybrid catalysts in asymmetric synthesis was first demonstrated by *B. Feringa* and *G. Roelfes* in 2005. In a copper(II)-catalyzed *Diels-Alder* reaction of azachalcone **1** and cyclopentadiene **2** the main product *endo*-**3** was generated with high enantioselectivity.^[1] While DNA-based hybrid catalysts have been intensively studied, RNA-based hybrid catalysts have not been reported.

In our work we set out to investigate the suitability of RNA as a scaffold for nucleic acid-based asymmetric catalysis. More specifically, mechanistic investigations were carried out to understand the influence of nucleic acid secondary structure on catalysis in general and enantioinduction in detail.^[2] To evaluate catalytic performance in a different structural context with reduced complexity, we also turned to nucleic acid hairpins, which have recently been shown to be a good model of *dsDNA* in DNA-based asymmetric catalysis.^[3]



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(30) Selective Fuctionalized PAMAM dendrimer' Surface Based on Dynamic Combinatorial Chemistry in The Presence of Biotemplates

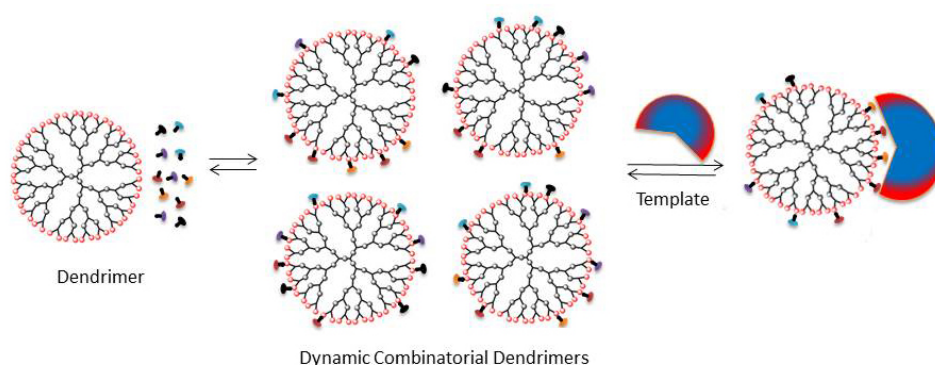
Xiaoming Miao, Piotr Nowak, Sijbren Otto

Xiaoming Miao, University of Groningen

x.miao@rug.nl

Molecular recognition plays a quite important role in biological systems such as receptor-ligand recognition, antigen-antibody recognition, and RNA-ribosome. With these accurate recognition processes, organisms can live and develop exquisite function, adaption and evolution, etc. Unlike the molecular recognition in synthetic systems, most of molecular recognition in biological systems involve macromolecular interactions. Currently, research is increasingly focusing on the interaction and recognition between biological functional macromolecule such as protein-protein interactions (PPI). Some new insights into processes central to life can be obtained through these studies, it also can contribute to find new lead compounds in the process of drug discovery.

Dynamic Combinatorial Chemistry (DCC) is an excellent method for achieving molecular recognition. DCC is a method of generating new molecules by reversible reaction of simple building blocks under thermodynamic control^[1]. Here, DCC was used for the surface functionalization of dendrimers aiming at the recognition of the surface of biomacromolecules, such as DNA^[2] and protein. Aldehyde groups were introduced on the surface of dendrimers which were reacted with amines to generate a dynamic combinatorial dendrimers through reversible imine bond formation in water solution. In the presence of biomacromolecules, surface functionalization was selective for those amines that have affinity with the biomacromolecules. The labile imine bonds was reduced to stable amine bonds, then resulting in dendrimers which had a surface complementary to the surface of biomacromolecules. Such dendrimers should then be able to interfere with protein-protein interactions in biological systems and may become useful tools for biochemical studies and may even have therapeutic potential.



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(31) Inhibition of Huntingtin exon-1 aggregation by a molecular tweezer

Sumit Mittal,¹ and Elsa Sánchez-García¹

¹*Fakultät für Biologie, T03 R01 D39, Universität Duisburg-Essen, 45117 Essen, Germany*

Huntington's disease (HD) is associated with the pathogenic expansion of the polyglutamine (polyQ) stretch of the huntingtin (htt) protein¹. The 17-residue N-terminal fragment of the htt exon-1 (N17) has been suggested to play a crucial role in modulating aggregation propensity and toxicity².

The molecular tweezer CLR01 selectively binds to lysine and, to a lesser extent, arginine residues. CLR01 has been reported to inhibit toxic aggregation in amyloidogenic proteins like amyloid polypeptide (hIAPP), α -synuclein and amyloid beta (A β) without toxic side effects³. Since the N17 region of htt contains three lysine residues, which could be important to the function of

the huntingtin protein, we studied the possible effect of the binding of CLR01 molecules on a htt protein with a pathogenic polyQ tract. For this purpose, we used classical and enhanced sampling molecular dynamics simulations to show that the binding of CLR01 induces structural rearrangements within the crucial N17 region of htt exon-1 monomer. QM/MM calculations allowed us to propose the preferred lysine for the tweezer. We also studied the interaction of another small molecule, CLR03, as a control system that does not form inclusion complexes with lysine and arginine residues. Our predictions were experimentally corroborated by circular dichroism spectroscopy and other biochemical techniques.

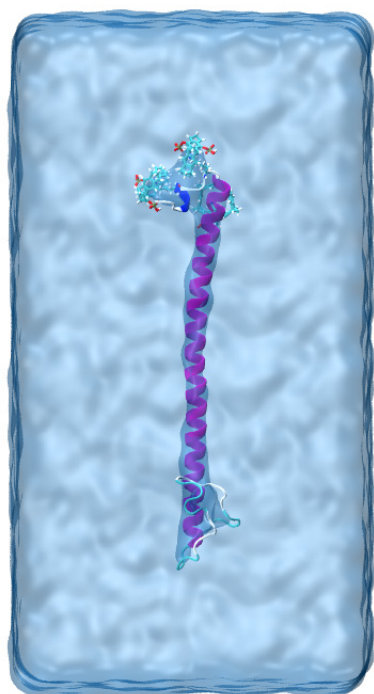


Figure. Htt exon-1 model with molecular tweezers in explicit solvent.

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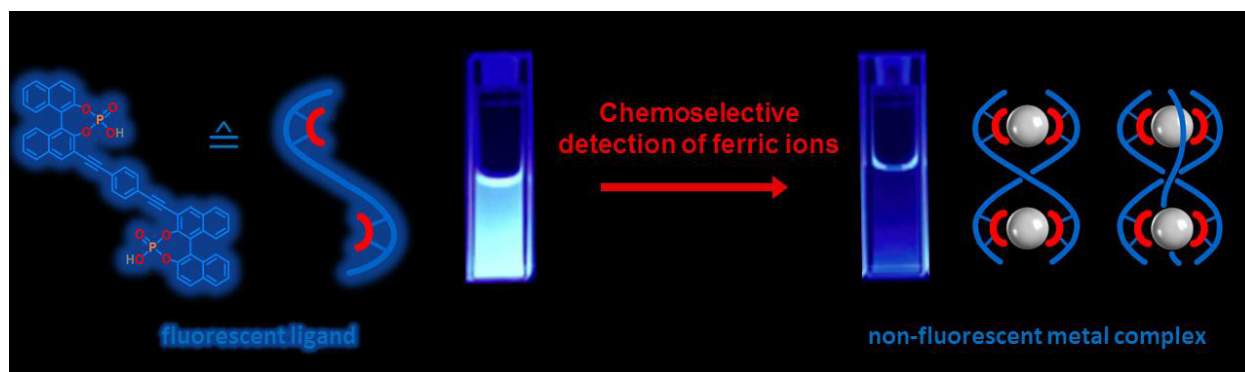
(32) Rigidly tethered bis-phosphoric acids: Generation of tunable chiral fluorescent frameworks and unexpected selectivity for the detection of ferric ions^[1]

Frescilia Octa-Smolín and Jochen Niemeyer

Institute of Organic Chemistry, University of Duisburg-Essen (Universitätsstr. 7, 45141 Essen, frescilia.octa-smolin@uni-due.de)

The double-helical structure of DNA has inspired chemists to design and synthesize artificial helical molecules for decades. Although numerous helical polymers have been reported since the 1950s,^[2] the formation of well-defined supramolecular double-helices has only been achieved more recently. Due to their close resemblance to DNA; such supramolecular double-helices have gained increased attention ever since.^[3]

We describe the straightforward synthesis of a series of bis-phosphoric acids, featuring two chiral 1,1'-binaphthyl-phosphoric acid units which are tethered by rigid, π -conjugated linkers. The nature of the linker has a profound influence on the properties of the bis-phosphoric acids, such as their self-association behavior and their interaction with metal ions. This led to the identification of one preferred bis-phosphoric acid, which shows selective fluorescence quenching through ferric ions, even in the presence of a variety of other metal ions. Due to the chiral nature of the bis-phosphoric acid, the interaction with ferric ions can also be followed by CD-spectroscopy, giving a complementary detection mode with the same probe.



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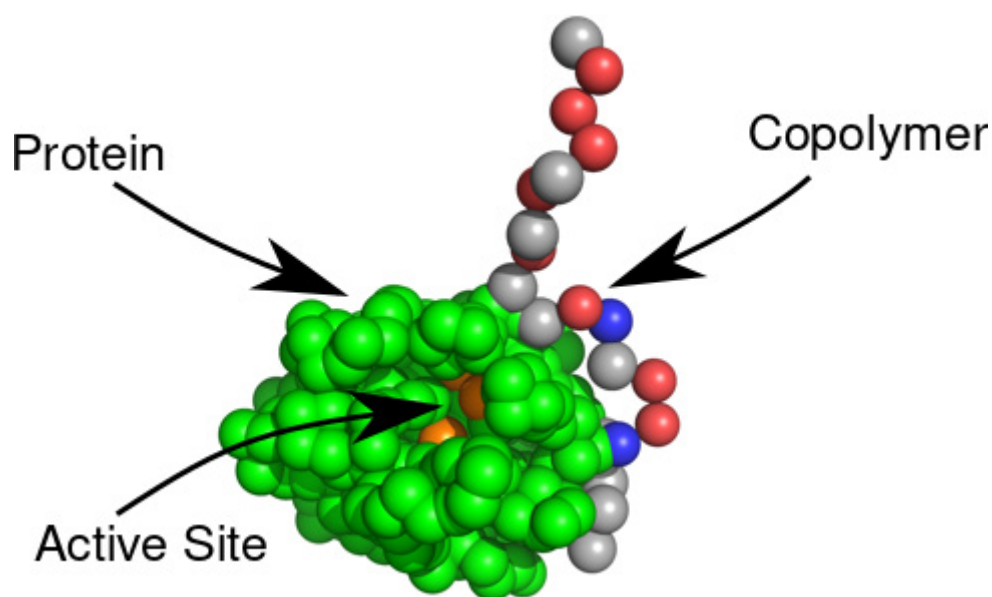
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(33) PolyLibScan: A computational framework for copolymer-protein interaction

Ludwig Ohl, Daniel Hoffmann

Project A7, Bioinformatics (Universitätsstr. 2, Ludwig.Ohl@uni-due.de)

While the interactions between copolymers, like glycosaminoglycan and heparan sulfates, and proteins play a vital role in biological organisms, many aspects of the interaction still remain unclear. These interactions occur throughout the extracellular matrix and are of significant importance in processes like intracellular signal transduction, cell migration and viral invasion of cells and angiogenesis. We are interested in the conformation of these copolymer-protein complexes and the needed properties that are necessary for strong binding and high specificity, to design and optimize new copolymers[1]. For this, we created the software package *PolyLibScan*, which uses a coarse grained model to simulate the interactions in molecular-dynamics (md) simulations. The model consists of united atoms that interact via the Coulomb, Lennard-Jones and an hydrophobic potential in an implicit solvent. *PolyLibScan* is able to quickly set up, perform and analyse thousands of md simulations that are necessary to ensure sufficient sampling of the sequence and conformational space. We validated the model with experimental inhibition data of 50 copolymers and six proteases[2]. In a next step, we try to design new polymers for the stabilization and destabilization of protein complexes and the inhibiting of proteins.



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(34) Conception of bifunctional hetero-[2]catenanes and -[2]rotaxanes based on phosphate/ammonium interactions

N. Pairault, J. Niemeyer

*Institute of Organic Chemistry, University of Duisburg-Essen
(Universitätsstrasse 7, 45117 Essen, Germany, noel.pairault@uni-due.de)*

The particular nature of mechanically interlocked molecules makes them suitable as artificial receptors or sophisticated chemical catalysts. For example catenanes (composed of interlocked macrocycles like the chain of a necklace) can afford a three dimensional central cavity for specific binding of guest molecules. Recently, a bifunctional chiral homo-[2]catenane based on 1,1'-binaphthyl-phosphoric acids has been synthesized in our lab.^[1] It has been used as receptor for dicationic molecules and as asymmetric organocatalyst for the stereoselective transfer hydrogenation of quinolines by Hantzsch-esters.^[2]

Here, we present the preliminary steps for the extension of this project towards the study of hetero-[2]catenanes and -[2]rotaxanes through the development of the bifunctional pseudo[2]rotaxane **1** (see Fig. 1). The stability of this architecture should be insured by the ion pairing of a chiral phosphate-macrocycle and a symmetrical secondary ammonium thread. Access to [2]rotaxanes **2** (by the *copper(I)-catalyzed alkyne-azide cycloaddition*) and [2]catenanes **3** (by *ring-closing metathesis*) could lead to the development of new synthetic receptors for zwitterionic species as amino-acids. It could also be used as new chiral bifunctional materials for asymmetric counteranion-directed catalysis.^[3]

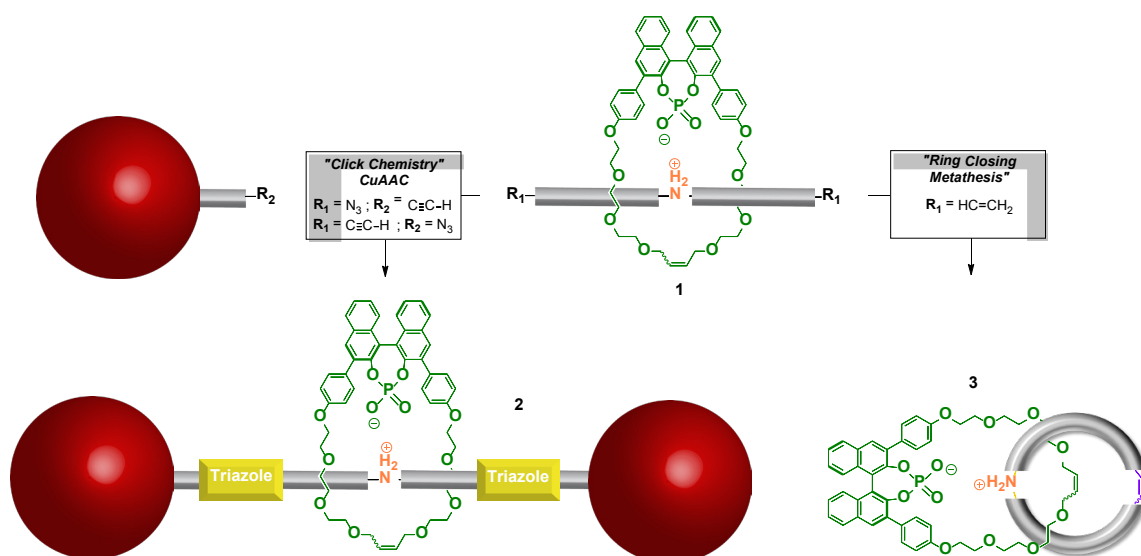


Figure 1: synthesis strategies for the conception of bifunctional [2]rotaxanes and [2]catenanes

References:

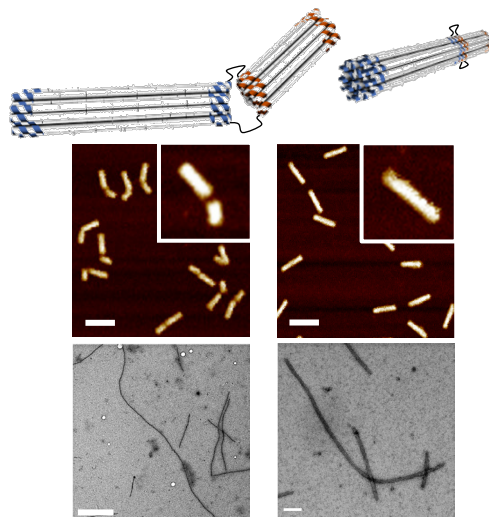
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(35) Hierarchical assembly of DNA filaments with designer elastic properties

Wolfgang Pfeifer, Pascal Lill, Christos Gatsogiannis and Barbara Sacca*

*Centre for Medical Biotechnology (ZMB) and Centre for Nano Integration Duisburg-Essen (CENIDE), University of Duisburg-Essen, Universitätstr. 2, 45117 Essen, Germany, barbara.sacca@uni-due.de

Many of the macromolecules of living organisms are filamentous. Relevant examples are microtubules and actin filaments, often organized into bundle suprastructures fundamental for cellular scaffolding and transport processes. The elastic features of such beams are encoded in their component units and in the way they are connected. In this sense, they may be viewed as hierarchical structures composed by the self-assembly of modular units into increasing levels of complexity according to specific recognition patterns. Using DNA origami design approaches, we here show the realization of a DNA module, whose fate can be controlled by selecting the type and force of inter-units associations, thus leading to a large variety of polymeric and suprapolymeric structures with distinct elastic properties. Our DNA building block is composed of two quasi-independent domains connected by two flexible hinges, thus defining four possible interfaces. Whereas the length and flexibility of the intra-domains region can be regulated by switchable DNA motifs, the inter-domain interfaces feature mutually and self-complementary shapes, which allow for their connection into filaments of programmable flexibility and periodical pattern. Thus, applying hierarchical strategies of DNA self-assembly on a reconfigurable module with complementary interfaces, artificial polymer-like materials with predictable pattern and elastic properties can be realized, which mimic the structural complexity and diversity of natural filaments.



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(36) X-ray crystallography of supramolecular protein-ligand complexes

Arthur T. Porfetye, David Bier, Patricia Stege, Ingrid R. Vetter

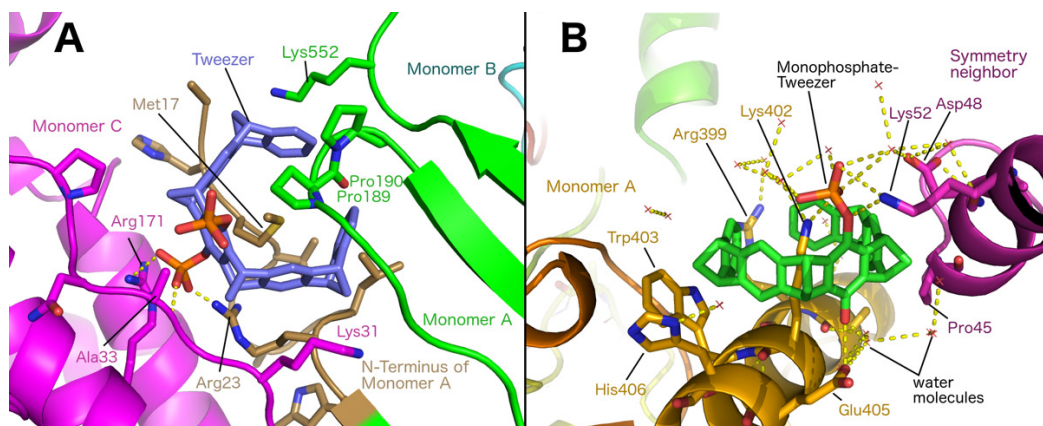
*Abteilung für mechanistische Zellbiologie, Max-Planck-Institut Dortmund,
Otto-Hahn-Str. 11, 44227 Dortmund, Germany
Arthur.Porfetye@mpi-dortmund.mpg.de*

Supramolecular ligands bind to the surface of a protein rather than to narrow pockets as conventional ligands do, thus opening a new approach to modulate protein activity by controlling accessibility and recognition of surface regions by interaction partners. As part of the CRC1093, we provide X-ray crystal structures of protein-ligand complexes to enable rational design and iterative improvement of supramolecular binders.

Molecular Tweezers have been shown to bind to surface-accessible residues (Lys, Arg) with low specificity [1] (Fig. 1), which can be increased using hybrids of tweezers coupled to peptides of the natural binding partner. Tweezer-peptide hybrids were designed to address the nuclear export sequence and histone H3 binding site of survivin, respectively.

Artificial ligands tailored to recognize specific amino acids (tweezers, guanidinocarbonyl pyrroles etc) can be combined to functionalized polymers to address extended surface patches.

DegS/HtrA serine proteases of the periplasmic space of *E. coli* are involved in stress response caused by accumulation of unfolded outer membrane peptides [2]. Cyclodepsi-peptides mimicking natural substrates were developed into potent antibiotically active inhibitors of DegS/HtrA proteases. The complex structures of the proteins with activating and inhibiting ligands is under structural investigation in our group, and enables structure-guided optimization of cyclodepsi-peptides into potent drug candidates.



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(37) Precision Macromolecules for the Multivalent Presentation of Supramolecular Amino Acid-Specific Binding Motifs

P. Reuther¹, M. Killa², K. Kujawski², T. Schrader², C. Schmuck², L. Hartmann¹

¹*Institute of Organic Chemistry and Macromolecular Chemistry, Heinrich-Heine-Universität Düsseldorf, Universitätsstr. 1, 40225 Düsseldorf, laura.hartmann@hhu.de;* ²*Institute of Organic Chemistry, Universität Duisburg-Essen, Universitätsstr. 7, 45117 Essen*

Inspired by Nature, synthetic biomimetic ligands can be designed to target various proteins. However, to effectively modulate protein function and intervene in physiological processes, an enhanced selectivity and affinity of the synthetic ligand is necessary. One concept to achieve such requirements is the multivalent presentation of the artificial binding motifs on a scaffold. Depending on the combination of ligand and scaffold, increased binding affinity and even selectivity can be obtained.

Recently, our research group introduced the solid-phase based synthesis of monodisperse, sequence-defined oligo(amidoamines), so-called precision macromolecules. Those precision macromolecules were previously employed as a platform for the multivalent presentation of biological ligands such as carbohydrates and peptides.^[1]

We here extend our concept and present a strategy for the synthesis of precision macromolecules equipped with artificial amino acid-specific binding motifs. Application of Fmoc-based solid phase synthesis allowed for the assembly of sequence-defined structures consisting of tailor-made building blocks. Obtained oligo(amidoamines) were subsequently sidechain-modified with guanidiniocarbonyl pyrrole (GCP)^[2] and xylylene bisphosphonate^[3] motifs. Initial binding studies of our GCP-containing structures were carried out by UV-titration with the model protein 14-3-3. First experiments indicate an influence of the valency and interligand distance on the resulting protein-ligand complex formation.

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(38) Transfection Agents with Aggregation Induced Emission Properties

Steffen Riebe, Jens Voskuhl*

*Institute of Organic Chemistry, University of Duisburg-Essen, Universitätsstrasse 7,
D-45117, Essen (Germany), steffen.riebe@uni-due.de*

In 2001 *Tang et al.* discovered a phenomenon called aggregation induced emission which describes the emission of a luminophore in the aggregated state but not when dissolved.^[1] This effect was used for different applications in the biomedical chemistry.^[2] In the past we investigated the formation of fluorescent micelles using hydrogen bonding^[3] as well as the recognition of lectins and carbohydrates using a novel class of AIE active compounds. Careful design of our luminophors enables the use as transfection agents with unique AIE properties. Suprastructures (micelles, vesicles, rods) formed by amphiphilic AIE luminophores in aqueous media can undergo efficient transfection (lipofection). These structures can bind negatively charged DNA or RNA on their positively charged surface and transport it into living cells.

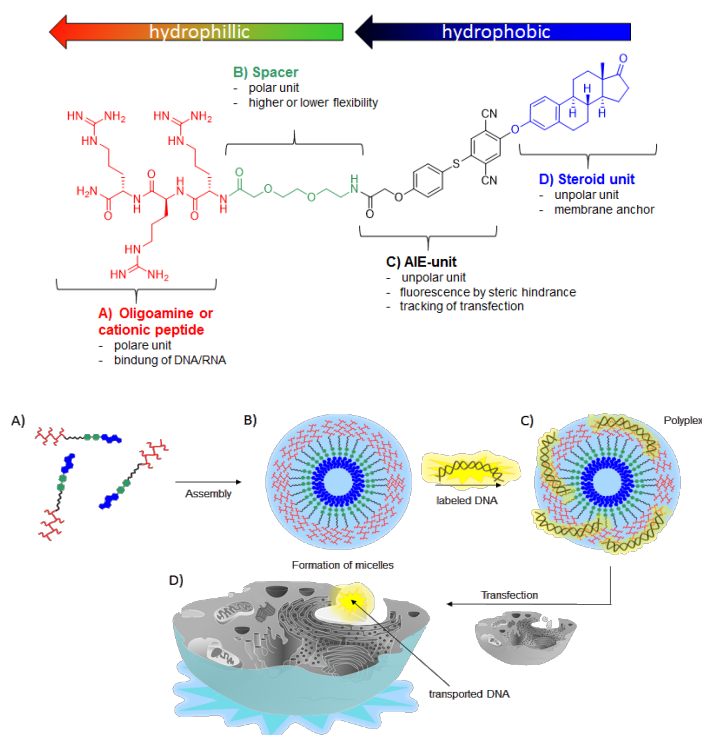


Fig.1: Structure of amphiphiles based on our AIE system and schematic presentation of the lipofection process of the novel AIE-active amphiphiles. A) Monomers, B) Formation of micelles, C) Binding of DNA and formation of a polyplex, D) Transfection.

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(39) Click chemistry for the covalent surface modification of calcium phosphate nanoparticles

L. Rojas Sánchez, M. Epple

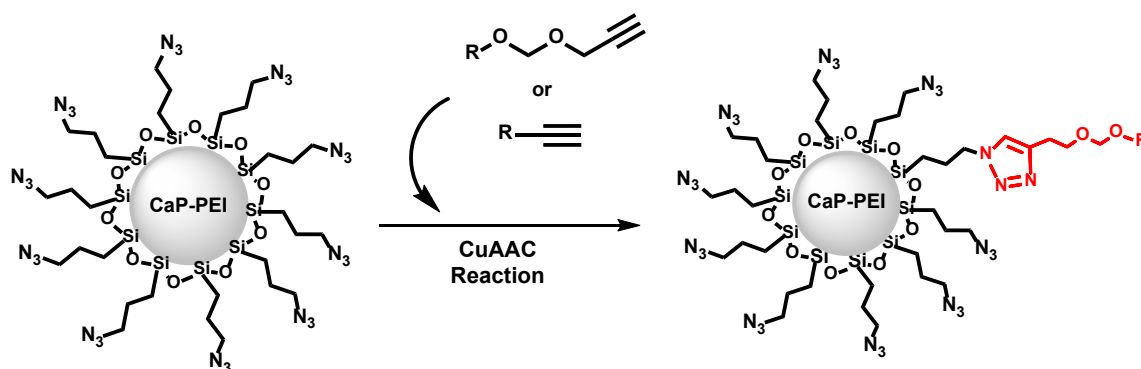
*Inorganic Chemistry and Center for Nanointegration Duisburg-Essen (CeNIDE),
University of Duisburg-Essen, Universitätsstr. 7, 45141 Essen, Germany
Email: matthias.epple@uni-due.de*

Our group has developed methodologies for the synthesis of calcium phosphate nanoparticles and their loading with cargo molecules as well as for the covalent surface attachment of proteins, antibodies and other biomolecules [1].

Seeking for a different and more specific chemical bond between the calcium phosphate nanoparticles surface and other (bio)molecules, the copper-catalyzed azide-alkyne cycloaddition (CuAAC) ("click reaction") [2] was established for calcium phosphate nanoparticles. With this reaction scheme, the selectivity in the anchoring point can be improved when a specific position of the alkyne group in the functionalizing molecule is used.

Calcium phosphate nanoparticles stabilized with polyethylene-imine (PEI) and a coating silica shell were synthesized as reported earlier [1]. Azide groups on the nanoparticles surface were attached by silanization on the silica shell. The reactivity of the surface azide group during click reaction was investigated using model alkyne-modified chromophores.

As demonstrated with different chromophores, this new methodology approach is suitable for the covalent functionalization of calcium phosphate nanoparticles. Below the silica shell, the calcium phosphate nanoparticles can carry their cargo like biomolecules or drugs. A selective surface functionalization by click chemistry can enhance their potential for imaging (by the attachment of dyes), for cellular targeting (by the attachment of antibodies, aptamers or peptides) and protein coupling.



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(40) Synthesis and Characterization of Surface-Functionalized Ultrasmall Gold Nanoparticles for Protein-Specific Targeting

Tatjana Ruks¹, Christine Beuck², Peter Bayer², Matthias Eppe¹

¹ *Inorganic Chemistry and Center for Nanointegration Duisburg-Essen (CeNIDE), University of Duisburg-Essen, Germany*

² *Faculty of Biology and Center for Medical Biotechnology (ZMB), University of Duisburg-Essen, Germany*

Ultrasmall gold nanoparticles with a diameter below 2 nm were prepared to target epitopes on the surface of proteins. These sub-protein sized nanoparticles are able to interact with single protein molecules or single epitopes on protein surfaces. Functionalized gold nanoparticles were prepared by reduction of HAuCl₄ with NaBH₄, together with in-situ functionalization with peptides that form a strong Au-S-bond via cysteine. In this case, the hexapeptide CGGpTPA was attached to address the WW domain of the protein hPin1. The attachment of the peptide to the gold nanoparticle was shown by NMR spectroscopy, i.e. 1D-¹H NMR spectroscopy and 2D-¹H,¹H-TOCSY NMR spectroscopy. ¹H-DOSY NMR spectroscopy, differential centrifugal sedimentation and transmission electron microscopic analysis were applied to determine the hydrodynamic radii of the functionalized gold nanoparticles. Quantification of particle surface loadings with protein specific peptide was investigated using the fluorophore-modified hexapeptide CGGpTPAAK-5,6-FAM-NH₂ by UV/Vis- and fluorescence spectroscopy. Specific protein binding of the functionalized nanoparticles was demonstrated by 2D-¹H,¹⁵N-HSQC NMR spectroscopy. ¹⁵N-isotope-labeled protein hPin1 was titrated with CGGpTPA-functionalized gold nanoparticles, specifically showing the interaction with the hPin1-WW domain.

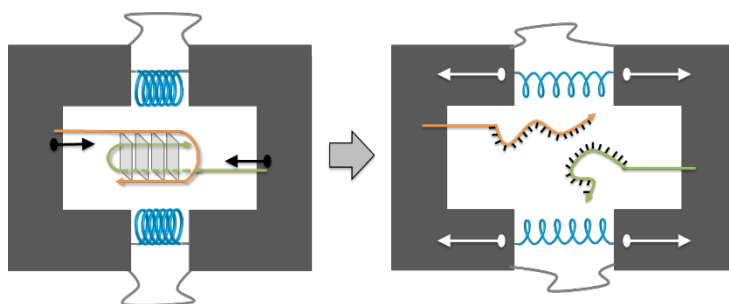
We gratefully acknowledge funding by the Deutsche Forschungsgemeinschaft (DFG) within SFB 1093: Supramolecular Chemistry on Proteins.

(41) The Collective Behavior of Spring-like Motifs Tethered to a DNA Origami Nanostructure

Elisa-C. Schöneweiß and Barbara Saccà*

*Centre for Medical Biotechnology (ZMB) and Centre for Nano Integration Duisburg-Essen (CENIDE), University of Duisburg-Essen, Universitätstr. 2, 45117 Essen, Germany,
barbara.sacca@uni-due.de

Dynamic DNA nanotechnology relies on the integration of small switchable motifs at suitable positions of DNA nanostructures, thus enabling to manipulate matter with nanometer spatial accuracy in a trigger-dependent fashion. Typical examples of such motifs are hairpins, whose elongation into duplexes can be used to perform long-range, translational movements. In this work, we used temperature-dependent FRET spectroscopy to extract the thermal stabilities of distinct sets of hairpins integrated into the central seam of a DNA origami structure. We then developed a hybrid spring model to describe the energy landscape of the tethered hairpins, combining the thermodynamic nearest-neighbor energy of duplex DNA with the entropic free energy of single-stranded DNA estimated using a worm-like chain approximation. We show that the organized scaffolding of multiple hairpins enhances the thermal stability of the device and that the coordinated action of the tethered motors can be used to mechanically unfold a G-quadruplex motif bound into the inner cavity of the origami structure, thus surpassing the operational capabilities of freely diffusing motors. Finally, we increased the complexity of device functionality through the insertion of two sets of parallel hairpins, resulting in four distinct states and in the reversible localization of desired molecules within the reconfigurable regions of the origami architecture.



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(42) Polycationic supramolecular peptide ligands targeting Survivin using Dynamic Combinatorial Libraries

Daniel Sebena, Carsten Schmuck*

*Institute of Organic Chemistry, University of Duisburg-Essen, Universitätsstrasse 7,
D-45141, Essen (Germany), daniel.sebena@uni-due.de*

As a member of the family of inhibitors of apoptosis (IAPs), Survivin is overexpressed in most human tumor cells. Therefore it is an interesting target for new therapies.^[1] Our aim is to design supramolecular ligands able to modulate protein-protein-interactions (PPIs) of Survivin with effector proteins, to gain insight and influence on their biological function. In this context the approach of Dynamic Combinatorial Libraries (DCLs) can be used as a powerful tool for development and evaluation of ligands.^[2] Based on previous results, which showed such an approach as feasible, polycationic peptide ligands are designed using the tailor-made artificial binding motif guanidiniocarbonyl pyrrole cation (GCP).^[3]

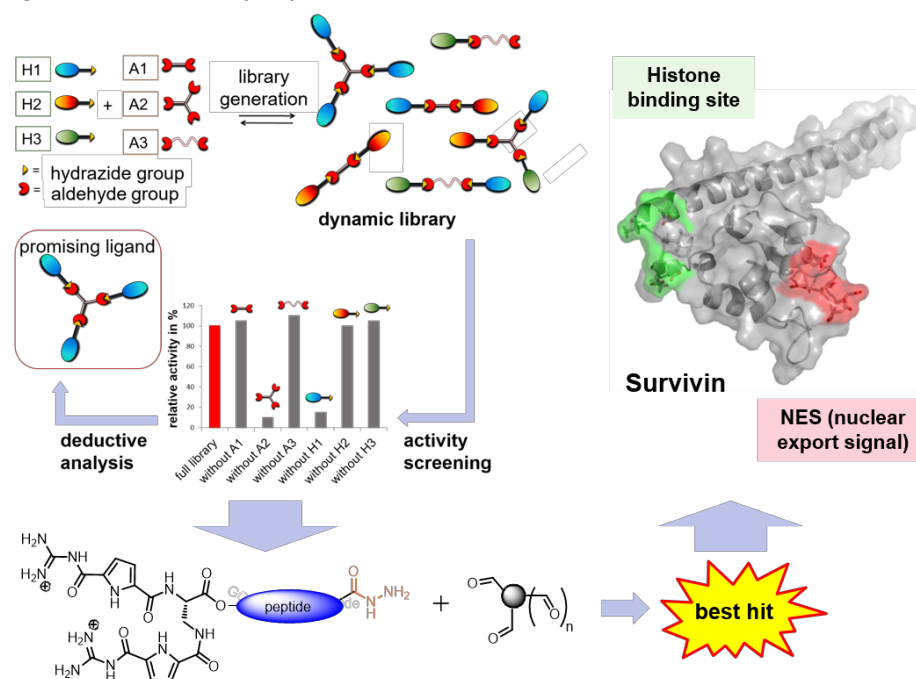


Fig.1: Schematic presentation of the development strategy of ligands able to bind to specific binding sites of effector proteins of Survivin, the nuclear export signal (NES) and the Histone binding site.

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(43) Controlling ER α Activity via 14-3-3 Protein-Protein Interactions

Eline Sijbesma¹*, K. K. Hallenbeck², L. Skora³, W. Jahnke³, M. R. Arkin², C. Ottmann¹, L. Brunsveld¹

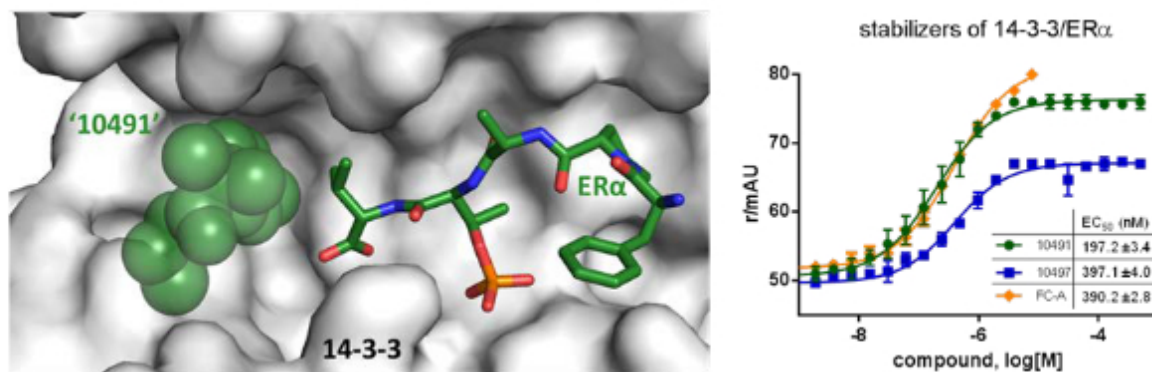
¹Laboratory of Chemical Biology, Eindhoven University of Technology, the Netherlands

²Small Molecule Discovery Center (SMDC) at University of California, San Francisco (UCSF), USA

³Chemical Biology and Therapeutics, Novartis Institutes for Biomedical Research, Basel, Switzerland

*E-mail: e.sijbesma@tue.nl

Protein-protein interactions (PPIs) are an important yet challenging target class in drug discovery.¹ PPIs were considered ‘undruggable’ mostly because of the challenges initially posed by the flat and expanded nature of the interfaces. In recent years a number of inhibitors have been developed that target unfavorable interactions, but despite the potentially enormous therapeutic benefit, the opposite strategy of PPI stabilization has not been systematically pursued.² We are interested in the interactions between Nuclear Receptors and 14-3-3, a hub protein that docks on to phosphorylated residues of its partner proteins and thereby influencing their activity, localization or dimerization behavior. These PPIs would greatly benefit from stabilization, as exemplified by the natural product Fusicoccin-A (FC-A) for the Estrogen Receptor alpha (ER α), an important breast cancer target.³



Inspired by nature and with FC-A as proof of concept, we aim to develop 14-3-3/ER α stabilizers that are selective and accessible via medicinal chemistry. This challenge is addressed by fragment-based drug discovery approaches including Disulfide Tethering and NMR screening, combined with X-Ray Crystallography. We here present a series of new small molecules that show binding to 14-3-3 in both cooperative and competitive modes with respect to an ER α phosphopeptide. These molecules are currently being optimized for improved cellular profiles and selective behavior.

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(44) Accelerated Autolysis of Trypsin by Tailor-made Copolymers**D. Smolin¹, T. Schrader¹**¹*Institute for Organic Chemistry, University of Duisburg-Essen, Essen, Germany,
Universitätsstr. 7, D-45141 Essen*thomas.schrader@uni-due.de

A major complication in pancreatitis, ischemia and cardiac surgery is the enzymatic self-digestion of the gastrointestinal walls. Most digestive enzymes are serine proteases and can hence be generally blocked by unspecific inhibitors such as aprotinin. However, stoichiometric amounts are required and other enzymes may be also affected (e.g. in blood clotting).

We developed selective serine protease inhibitors based on a polymeric backbone which carries amino acid-selective side chains. The corresponding binding monomers are subjected to free radical and controlled radical (ATRP) copolymerization and yield linear multivalent copolymers [1-3]. These affinity polymers recognize the surface of a given enzyme and in some cases, inhibit enzymatic activity in a highly substoichiometric manner.[4] Our studies show an efficient enzyme shut down either by steric blocking of the active site or accelerated self-digestion [5]. Trypsin is known for its physiologic self-digestion and our affinity polymers can accelerate the autolysis velocity drastically. In CD experiments, we see an accelerated destruction of the typical CD signature; gel filtration as well as SDS-PAGE reveal formation of smaller trypsin fragments after relatively short time.

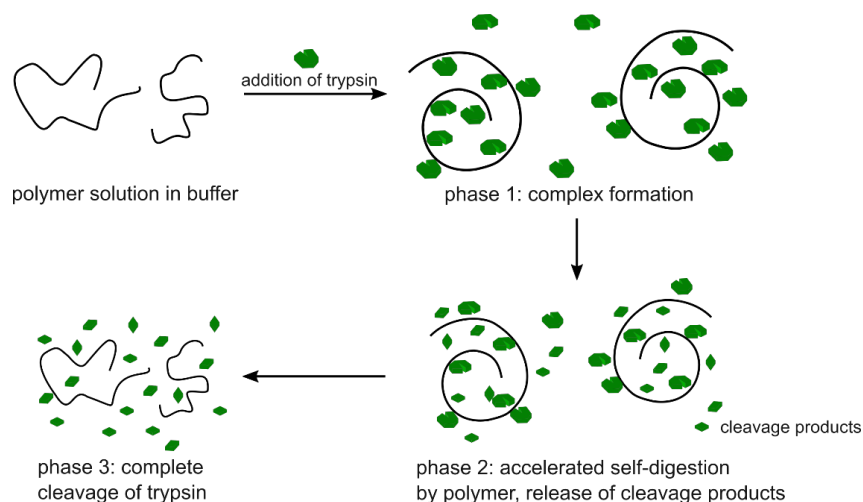


Figure 2: Supposed autolysis mechanism of trypsin by tailor-made affinity polymers.

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(45) Multiscaling with Three Layers: QM/MM/CG Simulation

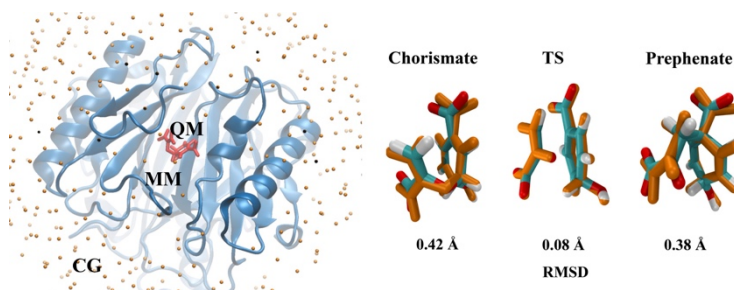
Pandian Sokkar¹, Eliot Boulanger², Walter Thiel², and Elsa Sanchez-Garcia¹

¹Universität Duisburg-Essen, 45141 Essen, Germany

²Max-Planck-Institut für Kohlenforschung, 45470 Mülheim an der Ruhr, Germany

elsa.sanchez-garcia@uni-due.de

We develop a hybrid quantum mechanics/molecular mechanics/coarse-grained (QM/MM/CG) multiresolution approach for solvated biomolecular systems. In this approach, the chemically important active-site region is treated at the QM level. The biomolecular environment is described by an atomistic MM force field, and the solvent is modeled with the CG Martini force field using standard or polarizable (pol-CG) water. The accuracy and efficiency of our implementation is tested for two enzymes, chorismate mutase (CM, Figure 1) and p-hydroxybenzoate hydroxylase (PHBH). In CM, the QM/MM/CG potential energy scans along the reaction coordinate yield reaction energies that are too large, both for the standard and polarizable Martini CG water models. The inclusion of a small layer of atomistic MM water around the QM region improves the energy profiles compared to the reference QM/MM calculations. In analogous QM/MM/CG calculations on PHBH, the use of the pol-CG description for the outer water does not affect the stabilization of the highly charged FADHOOH-pOHB transition state compared to the fully atomistic QM/MM calculations. Detailed performance analysis in a glycine-water model system indicates that computation times for QM energy and gradient evaluations at the density functional level are typically reduced by 40–70% for QM/MM/CG relative to fully atomistic QM/MM calculations. This method is particularly useful for systems which are very large for typical QM/MM calculations.



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(46) Comparison of calcium phosphate nanoparticle-mediated transfection in 2D and 3D cell culture models: Efficiency and cytotoxicity

V. Sokolova, L. Rojas and M. Eppe

Inorganic Chemistry and Center for Nanointegration Duisburg-Essen (CeNIDE), University of Duisburg-Essen, Essen, D-45117, Germany

The transfer of nucleic acids into living cells, i.e. transfection, is a major technique in current biochemistry and molecular biology. As nucleic acids alone are not able to penetrate the cell wall, efficient carriers are needed. Calcium phosphate is a well-suited delivery system due to its high biocompatibility and good biodegradability because it is the inorganic component of human bone and teeth [1-2]. By using appropriate synthetic methods, multi-shell nanoparticles, loaded with nucleic acids (e.g. plasmid DNA), were prepared and characterized. Here we report on the preparation of calcium phosphate nanoparticles and their further application in 2D and 3D cell culture models. 3D culture systems present more realistic spatial, biochemical and cellular conditions compared to 2D monolayer cell culture and serve as a bridge between *in vitro* and *in vivo* studies [3]. The uptake studies of functionalized calcium phosphate nanoparticles were carried out both in 2D and 3D cell culture models.

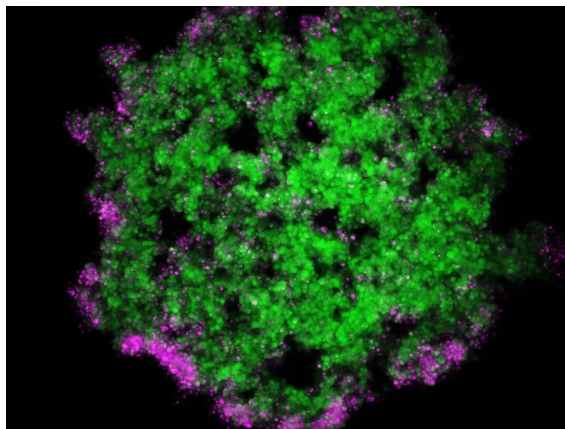


Figure: Uptake of calcium phosphate nanoparticles (violet dots) by a HeLa-EGFP spheroid (green cells) after 24 h of incubation.

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(47) Supramolecular Photosensitizers for Biomedical Applications

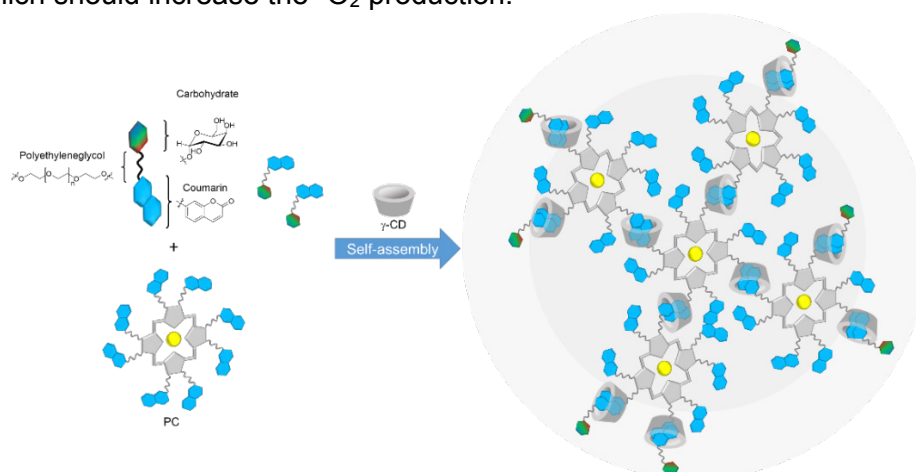
A. Sowa, N. Riek and J. Voskuhl

University of Duisburg-Essen, Universitätsstraße 7, 45141 Essen, Germany

Andrea.Sowa@uni-due.de

Photodynamic therapy is an important tool against cancer. Furthermore, light-induced activation reduces unwanted side-effects of drugs.^[1] Common photosensitizers are phthalocyanines (PCs) or porphyrins (PORs). They convert triplet oxygen ($^3\text{O}_2$) into cytotoxic singlet oxygen ($^1\text{O}_2$) when excited by long waved light. The most challenging part is to prevent π - π stacking of the PCs in water, leading to a significant decrease in fluorescence and $^1\text{O}_2$ production.^[2]

We have already shown that the generation of $^1\text{O}_2$ can be increased by up to 300 % by immobilization of unsymmetrical PCs on a supramolecular substrate.^[2] In this project, we present a novel photoresponsive, biocompatible coumarin derivative (**Scheme 1**). Coumarin derivatives form 2:1-complexes with γ -cyclodextrins (γ -CD) which can undergo a reversible, UV-light-induced [2+2]-cycloaddition.^[3] This allows the stabilization of supramolecular networks. Furthermore, multivalent coumarin decorated PCs can self-assemble in the presence of monovalent coumarin derivatives and γ -CDs as host molecules to form size-tunable, supramolecular nanoparticles (**Scheme 1**). The host-guest complex together with the polyethyleneglycol linker work as a spacer between the PCs. Therefore, a high local concentration of the PCs without aggregation is achieved which should increase the $^1\text{O}_2$ production.



Scheme 1: Structure of the novel coumarin derivative and self-assembly with PCs to supramolecular nanoparticles.

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(48) Synthesis of Non-symmetric, Clickable Diphosphate Tweezers for Regioselective Protein Surface Recognition

A. Sowislok, Essen/D, T. Schrader*, Essen/D

Prof. Dr. Thomas Schrader, Universität Duisburg-Essen, Universitätsstr. 7, 45117 Essen/D

Molecular diphosphate tweezers are able to bind to lysine and arginine residues on protein surfaces and are used as new enzyme inhibitors and blockers of pathological protein aggregation.^[1,2] In a first attempt to enhance selectivity, we replaced one phosphate group by a neutral linker unit for the introduction of additional recognition elements.^[3] Since the neutral linkers generally lowered tweezer affinities towards basic amino acids and peptides, we now pursue a new strategy which keeps both phosphate anions and allows introduction of one recognition unit by “click” chemistry. The introduction of the phosphate moiety containing the alkyne unit follows a classic phosphoramidite approach.

This poster presents synthetic methodology towards novel clickable asymmetric diphosphate tweezers and binding studies. These results will be used in the future to generate more potent tweezers species with higher specificity for their target proteins.

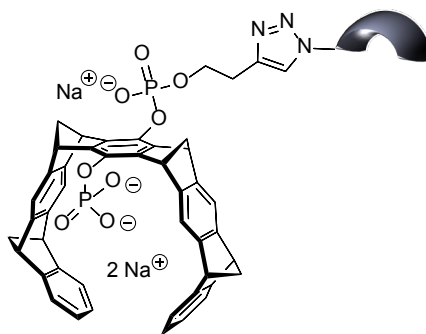


Figure 1. Molecular diphosphate tweezer for the binding of lysine and arginine with attached peptide ligand unit.

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(49) Monitoring conformational transitions *in vitro* of soluble A β 42 oligomers

N. M. Tonali, V. J. Dodero, G. M. Herrera, N. Sewald

Bielefeld University, Department of Chemistry D-33501 Bielefeld, nicolo-tonali@uni-bielefeld.de

Alzheimer's disease (AD) is a devastating and progressive neurodegenerative disease that leads to progressive cognitive decline, functional impairment and loss of independence. Numerous studies have shown that amyloid β -protein (A β) plays a significant etiologic role in AD. According to the amyloid cascade hypothesis, accumulation of synaptotoxic and neurotoxic A β 42 oligomers causes AD.¹ The nature of these soluble oligomers remains to be clarified, and spectroscopic detection of secondary structure conformations of soluble amyloid species using small molecular probes currently presents a challenge. Therefore, a better knowledge in the oligomerization process seems to be a hopeful and promising approach to further the understanding and clinical treatment of this disorder. The capillary electrophoresis (CE) method is able to monitor easily over time the very early steps of the A β 42 oligomerization process. This technique has the advantage of being able to follow three kinds of soluble species, (i) the monomer, (ii) different small metastable oligomers smaller than dodecamers, and (iii) transient species formed later and which correspond to species larger than dodecamers.² In literature it is described that triazole-containing dyes can be used to monitor amyloid conformational transitions *in vitro*. The novel ability of triazole-containing BODIPY dyes to distinguish between the unordered and ordered, β -sheet-rich conformations of soluble A β 42 oligomers was recently reported.³ We performed fluorescence spectroscopy by using one of these dyes as suitable *in vitro* probe for monitoring the oligomerization process of A β 42 and we compared its fluorophore properties with the known Thioflavin T dye. In addition, by combining circular dichroism (CD) and CE, we could follow the conformational transitions of the amyloid peptide during its oligomerization process, depending on the peptide preparation, the buffer medium and the pH. The results presented a good correlations between all the three techniques. Our approach revealed to be an efficient method to monitor the early stages of A β 42 peptide.

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(50) Molecular characterization and modulation of Survivin's cellular functions with supramolecular ligands

Cecilia Vallet*, Marcel Mertel, Dennis Aschmann**, Martin Ehlers**, Sandra Bäcker*, Jana Reich*, Christine Beuck***, Peter Bayer***, Carsten Schmuck**, Shirley K. Knauer***

** Department of Molecular Biology II, Centre for Medical Biotechnology (ZMB)*

*** Department of Supramolecular Chemistry*

**** Department of Structural and Medicinal Biochemistry, Centre for Medical Biotechnology (ZMB)
University of Duisburg-Essen, 45117 Essen, Germany*

Survivin was found to be upregulated in virtually all types of human cancers. It is associated with resistance against chemo- and radiotherapy, an increased tumor recurrence and an abbreviated patient survival, making it a promising target for cancer therapy. Survivin is involved in two key processes of carcinogenesis. As a member of the IAP family, it exhibits anti-apoptotic functions, but is also necessary for proper chromosome segregation during mitosis.

Our project aims to interfere with Survivin's (patho)biological role during cell death and proliferation using novel supramolecular ligands to target surface-accessible glutamate/aspartate residues either on Survivin's Histone H3 binding site or nuclear export signal (NES), which mediates interaction with the export receptor Crm1.

We were able to identify several promising candidate ligands affecting Survivin/Crm1 interaction and Survivin dimer formation in cell-based FRET- and proximity ligation (PLA) assays. With NMR titration experiments, we could map binding of one peptide ligand to acidic amino acid residues on Survivin's surface spanning across the Histone H3 binding site and reaching out to the vicinity of the NES and the dimerization interface. Currently, we are setting up additional cellular assays to investigate an effect on Survivin's anti-apoptotic and mitotic functions.

(51) The AAA-ATPase VCP/p97 extracts sterically trapped Ku70/80 rings from DNA in double strand break repair

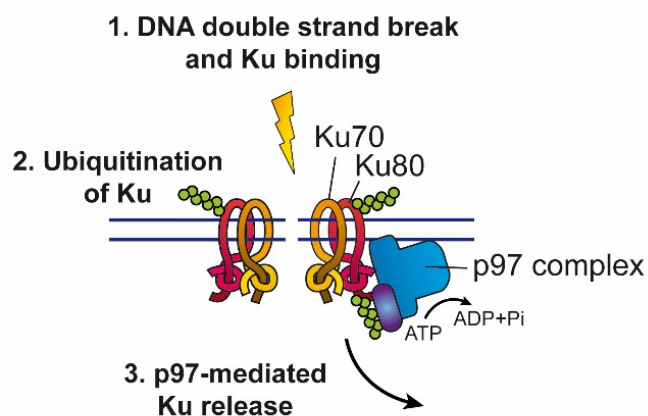
Johannes van den Boom, Markus Wolf, Lena Weimann, Nina Schulze, Fanghua Li, Farnusch Kaschani, Anne Riemer, Christian Zierhut, Markus Kaiser, George Iliakis, Hironori Funabiki, Hemmo Meyer

Molecular Biology I, Faculty of Biology, University of Duisburg-Essen, 45117 Essen, Germany

During DNA double strand break (DSB) repair, the ring-shaped Ku70/80 complex becomes trapped on DNA and needs to be actively extracted, but it has remained unclear how this is achieved and what are the consequences of failure to extract Ku70/80 at damage sites.

By reconstituting DSB repair on beads, we demonstrate that DNA-locked Ku rings are released by the AAA-ATPase, p97. To achieve this, p97 requires ATP hydrolysis, cooperates with the Ufd1-Npl4 ubiquitin adapter complex and specifically targets Ku80 that is modified by K48-linked ubiquitin chains. Consistent with a role of p97 in Ku release, chemical inhibition of p97 in U2OS cells, or siRNA-mediated depletion of p97 or its adapters impairs Ku80 removal after non-homologous end-joining of DSBs. Moreover, we find that p97 inhibition attenuates early steps in homologous recombination repair suggesting a broader role of p97-driven Ku release in repair signalling.

Thus, our data explain a key role of p97 in DSB repair and solve a central question regarding regulation of Ku in the process. Newest data on the mechanisms of Ku70/80 extraction and the implication of p97-driven Ku extraction for DNA repair pathway choice will be discussed.



(52) Specific targeting of proteins by surface-functionalized ultrasmall gold nanoparticles (2 nm) using click chemistry

S. van der Meer and M. Eppe

*Inorganic Chemistry and Center for Nanointegration Duisburg-Essen (CeNIDE),
University of Duisburg-Essen, Universitätsstr. 7, 45141 Essen, Germany*

Ultrasmall nanoparticles with a diameter of 2 nm or smaller were prepared in a one-pot synthesis by reducing tetrachloroauric acid in the presence of functional ligands.¹ These nanoparticles are autofluorescent and permit a label-free tracking in biological setups like cells.²

After a reduction step, the ultrasmall particles were functionalized with azido groups carrying ligands via ligand exchange reactions. By click chemistry, molecules with an alkyne function were covalently bound to the particles under mild reaction conditions.

These surface-functionalized ultrasmall particles permit a specific targeting of epitopes on the surface of a protein as they are smaller than most proteins. This is of special interest to influence the function or conformation of a protein, e.g. to inhibit its function. The protein-binding affinity is increased by the multiavidity (more than one ligand on each nanoparticle) or heteroavidity (different ligands on one nanoparticle) of nanoparticles. The heteroavidity can be realized by simultaneously clicking several molecules to the particle surface.

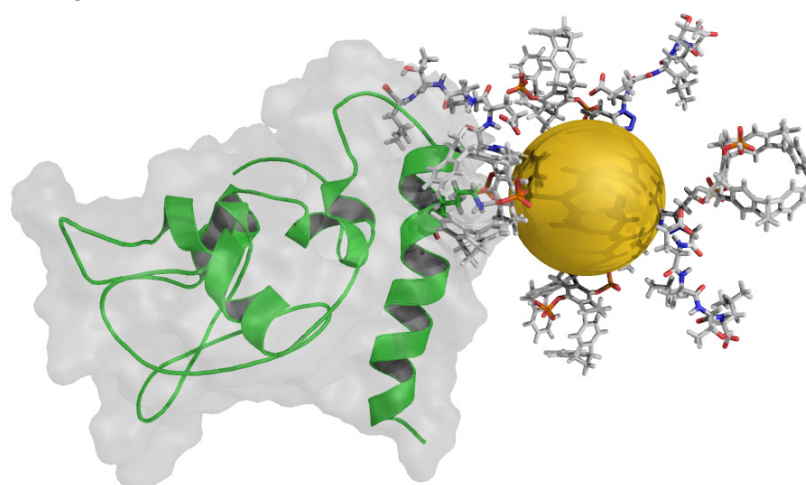


Figure: Model of an ultrasmall gold nanoparticle, functionalized with a molecular tweezer and a peptide to bind to a survivin monomer (collaboration within S. Knauer, Essen).

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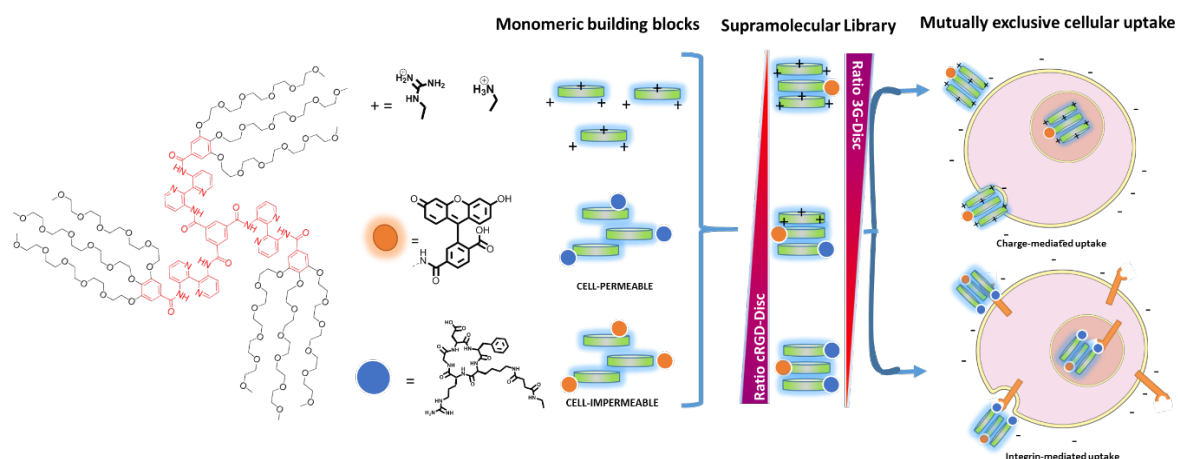
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(53) Towards a supramolecular platform for protein modulation**Sam van Dun,¹ Jurgen Schill,¹ Lech-Gustav Milroy,¹ Luc Brunsveld¹**¹ *Laboratory of Chemical Biology and Laboratory of Macromolecular and Organic Chemistry, Department of Biomedical Engineering, Eindhoven University of Technology, Netherlands.*s.v.dun@tue.nl

Proteins are crucial for life by taking part in nearly every process within the cell. Besides its structural functions, proteins are for instance involved in cellular transport, cell division, cell adhesion and many cell signaling processes. To enable the specificity and sensitivity required for all these processes in such a crowded environment, cells must have a very high control over both the temporal as well as the spatial orientation of proteins in order to organize subsets of proteins. This is facilitated by the compartmentalization of specific proteins in organelles, co-localization of proteins on the cellular membrane or via the use of protein scaffolds.

Inspired by the latter, self-assembling supramolecular Bipyridine-Discotic Amphiphiles (Discs) that self-assemble into columnar stacks have been explored extensively in order to create a dynamic and responsive platform that interacts with the cellular environment.

The Disc can interact with the cellular membrane via 1) the introduction of cationic groups or 2) the introduction of a cRGD peptide motif at the periphery of the Disc. Cationic Discs induce a fast, efficient, unspecific uptake whereas the peptide functionalized Discs are taken up slowly and show an uptake that is mediated by integrins. By making full use of the dynamic multicomponent nature of the columnar stacks, cationic and cRGD functionalized Discs were intermixed resulting into a mutually exclusive system where either one or the other uptake mechanism is dominating.



(54) Cupin-domain mediated dimerization promotes centromere localization of CENP-C

Kai Walstein, Dongqing Pan, Dorothee Vogt and Andrea Musacchio

Department of Mechanistic Cell Biology, Max Planck Institute of Molecular Physiology, Otto-Hahn-Straße 11, 44227 Dortmund, Germany, kai.walstein@mpi-dortmund.mpg.de

In metazoans, the centromere is defined by an enrichment of the histone H3 variant centromere protein A (CENP-A).¹ CENP-A is necessary to recruit subunits of the constitutive centromere associated network (CCAN), which forms the inner layer of the kinetochore. CENP-C directly binds CENP-A nucleosomes, mediated by two sequence-related motifs localized in the central and C-terminal region of CENP-C. The C-terminal Cupin domain of the *S. cerevisiae* CENP-C orthologue Mif2p has been shown to form a dimer.² However, the exact function of the Cupin domain in human CENP-C remains unclear. We investigated the role of the CENP-C Cupin domain in vitro and in HeLa cell experiments. Using analytical size exclusion chromatography (SEC), we compared the binding of an N-terminal and a C-terminal CENP-C fragment to CENP-A nucleosomes. We further used analytical ultracentrifugation (AUC) to investigate the oligomeric state of the C-terminal region of human CENP-C. Finally, we transfected HeLa cells with GFP-tagged CENP-C constructs and checked their centromere localization by immunofluorescence microscopy. The SEC results indicate that in vitro binding of both CENP-C constructs to CENP-A nucleosomes requires a functional CENP-C motif. Our AUC results confirm that the Cupin domain of human CENP-C forms a dimer. In HeLa cells, CENP-C constructs lacking the Cupin domain show a much weaker centromere localization compared to constructs containing the Cupin domain.

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(55) Optical labelling of polymer nanoparticles by ultra-small gold nanoparticles

K. Wey and M. Eppe

*Inorganic Chemistry and Center for Nanointegration Duisburg-Essen (CeNIDE),
University of Duisburg-Essen, Universitätsstr. 7, 45141 Essen, Germany
E-Mail: matthias.epple@uni-due.de*

Nanoparticles are an interesting tool for drug delivery into cells. Ultra-small gold nanoparticles (<2 nm) are autofluorescent, making them useful as a label-free material for detection inside cells. As fluorescent label, gold nanoparticles were encapsulated into the biodegradable polymer poly(D,L-lactide-co-glycolide) (PLGA).

Gold nanoparticles were prepared in a one-pot synthesis by reducing tetrachloroauric acid with sodium borohydride in water and then stabilised with 11-mercaptopundecanoic acid.^[1]

The encapsulation of the gold nanoparticles into PLGA-nanoparticles was accomplished by a water-in-oil-in-water ($W_1/O/W_2$) emulsion solvent evaporation technique,^[2] using the gold nanoparticles in the W_1 -phase, PLGA in dichloromethane as O-phase and polyvinyl alcohol (PVA) in water as W_2 -phase. To further enhance the cellular uptake, the particles were coated with polyethyleneimine (PEI), reversing their charge from negative to positive. Cell uptake studies were carried out with HeLa cells.

An average diameter of 1.8 nm was determined for the gold nanoparticles by differential centrifugal sedimentation (DCS). Fluorescence spectroscopy showed an emission maximum at a wavelength of 620 nm, making them suitable for intracellular detection by confocal laser scanning microscopy. The average PLGA particle diameter was 125 nm (by scanning electron microscopy) and after surface charge reversal, the zeta potential was +30 mV. Cell uptake studies proved that the polymer nanoparticles were taken by HeLa cells after 24 h.

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(56) Supramolecular ligands for 14-3-3 proteins

E. Yilmaz, Prof. Dr. M. Kaiser

Universität Duisburg-Essen, Universitätsstr.2, 45141 Essen, elvan.yilmaz@uni-due.de

14-3-3 Proteins are a highly conserved and abundant protein family found in all plants, vertebrates and higher eukaryotes. They are included in numerous cell biological processes like signal transduction, apoptosis or cell cycle regulation. Consequently, they are also involved in the development of diseases that are triggered for example by a malfunction of the respective protein. Therefore it is an attractive aim to generate inhibitors that are able to bind specifically to 14-3-3 proteins to prevent diseases. The idea is to synthesize bivalent inhibitors to increase the effect of inhibition. Virtual screening approaches have already identified phosphophenyl ethers as a novel class of 14-3-3 inhibitors. To prove the efficiency of bivalent inhibitors the phosphophenyl ethers are connected to each other with a linker. Due to their high polarity it is advisable to use PEG molecules as linkers, as they can increase the solubility of the inhibitor in aqueous media.

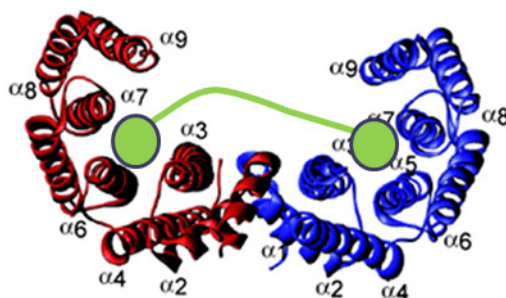


Fig.1: 14-3-3 protein with a bivalent inhibitor (green).

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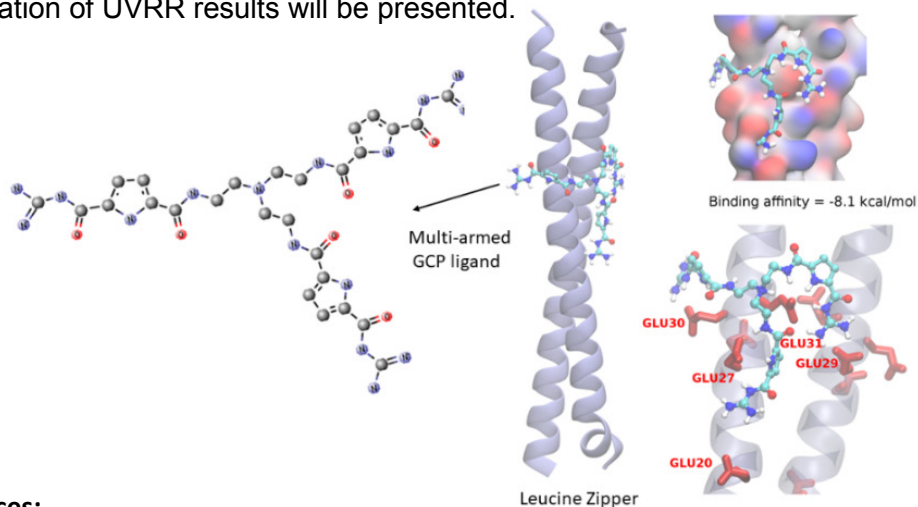
(57) Label-Free and Site-Specific Probing of Molecular Recognition between Proteins and Multivalent Supramolecular Ligands by Ultraviolet Resonance Raman Spectroscopy

B. Zakeri, A. G. Martinez, P. Sokkar, E. Sanchez-Garcia, C. Schmuck, S. Schlücker*

**Department of Chemistry, Physical Chemistry, University of Duisburg-Essen, Universitätsstr. 5, D-45117 Essen, Germany, Email: sebastian.schluecker@uni-due.de*

Supramolecular chemistry exploits non-covalent interactions between host and guest molecules. Artificial peptide ligands are versatile molecular model systems for investigating such interactions with peptides/proteins. A class of artificial carboxylate binders/receptors comprising a guanidinium carbonyl pyrrole (GCP) as a carboxylate binding site has been designed and synthesized by Schmuck and co-workers. Commonly used techniques for monitoring molecular recognition events require modifications of the system such as external labeling by fluorophores, which are often larger than the system of interest itself, or require the immobilization onto surfaces for surface plasmon resonance, which does not reflect the binding kinetics of the system in solution. Surprisingly, label-free vibrational spectroscopy (IR and Raman) has only rarely been employed for probing molecular recognition processes. In particular UV resonance Raman (UVRR) spectroscopy is ideally suited for site-specific and sensitive probing of binding sites comprising a UV chromophore. In proof-of-concept studies we demonstrated its application to the binding events between monovalent GCP ligands and small tetrapeptides [1, 2].

In this work, we use the site-specificity of UVRR to investigate the binding between a multi-armed GCP ligand to the alpha-helical protein Leucine Zipper. Making the transition from a tetrapeptide to a protein with more than 40 amino acids, i.e. increasing the size of the molecular system by one order of magnitude, was the major challenge of this dissertation project which has been dealt with ligand selectivity of laser wavelength. We will present the results of a UVRR binding study (“UVRR titration”) between a multivalent supramolecular ligand and Leucine zipper. A 90° scattering geometry with a rotating cell in combination with 266 nm excitation from a CW solid-state laser was employed to selectively enhance the vibrational Raman bands of the GCP subunit in the free and complexed form upon addition of Leucine Zipper. The qualitative and quantitative investigation of UVRR results will be presented.



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