From Molecular Receptors to Indicators

Topical Workshop: MOF-Based Chemical Sensors, Munich (12.03.2012)

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Content

What to expect during the talk?

1. Supramolecular chemistry: What is so interesting about it?
2. Molecular Recognition in Nature
3. From Artificial Receptors to Indicators
   Peptides, Proteins, nucleic acids
4. Summary

Content

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What I will NOT talk about

1. Synthesis of the compounds
2. Bioorganic and Medicinal chemistry projects
   inhibitors of cystein-proteases, anti-malaria compounds, anti-infectives, functionalized nanoparticles as enzyme inhibitors, SERS markers for imaging
3. Self-aggregating zwitterions: How to build nanostructures?
   vesicles, polymers, nanorods

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Supramolecular chemistry: What is so interesting about it?

Organic Chemistry

How to make molecules?

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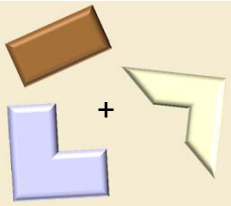
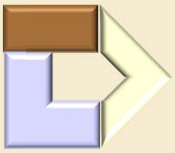
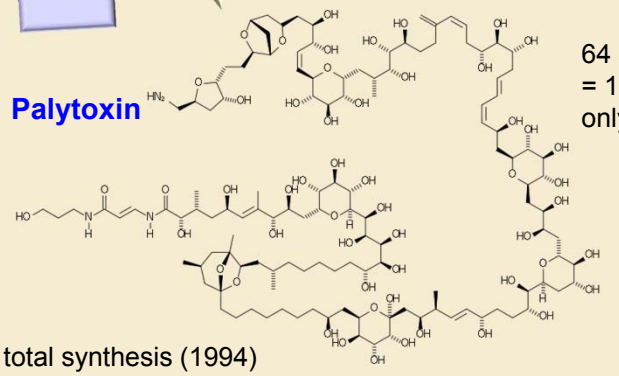


covalent synthesis



Yoshito Kishi

Palytoxin



64 stereocenters
= 1.8 •10^{19} stereoisomers
only 1 is naturally occuring

total synthesis (1994)

Palythoa toxica

Supramolecular Chemistry

„Chemistry beyond the molecule"

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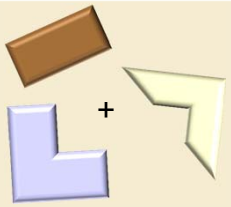
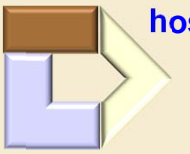


covalent synthesis



host

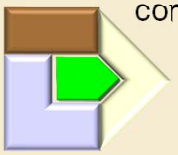
+

guest

non-covalent
interactions

reversible

complex



interacting molecules

J-M. Lehn

new properties & functions

Supramolecular Chemistry

How it all began….

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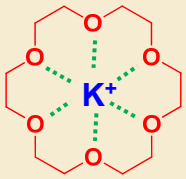
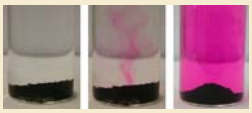
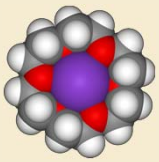
crown ethers





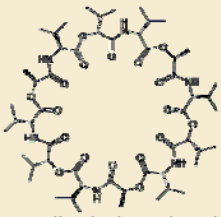
"purple benzene"

$KMnO_4$ dissolved in benzene

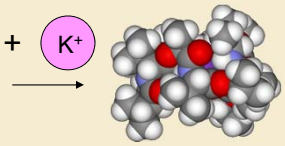


Nature uses the same principle: **ion transport across membranes**

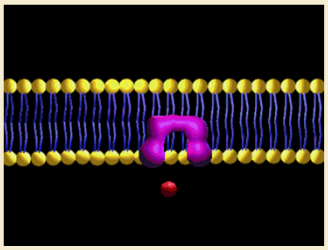
Valinomycin



cyclic dodecadepsipeptide



1:1-complex



Supramolecular Chemistry

Nobel Price in Chemistry 1987

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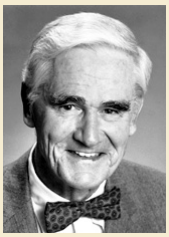
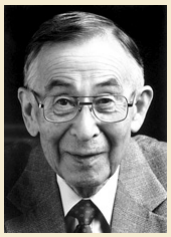


Donald J. Cram

Jean-Marie Lehn



Charles J. Pedersen

"for their development and use of molecules with structure-specific interactions of high selectivity"

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Molecular Recognition in Nature

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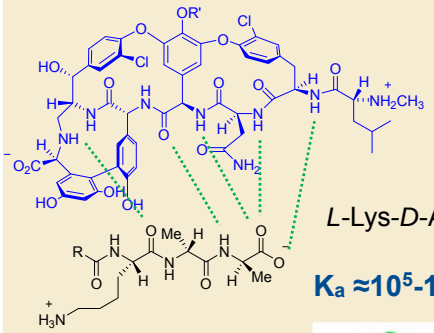
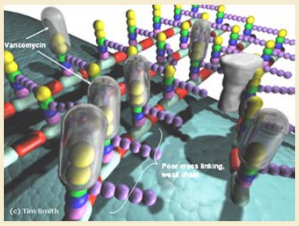
Peptide Recognition in Nature

Vancomycin, a glycopeptide antibiotic

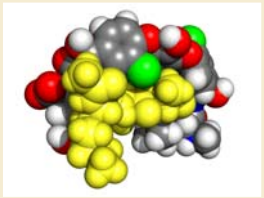


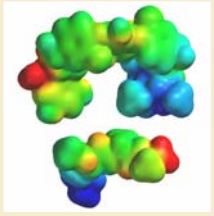
Inhibition of bacterial cell wall synthesis by reversible complexation of a specific peptide sequence.



L-Lys-*D*-Ala-*D*-Ala

$K_a \approx 10^5\text{-}10^6\ M^{-1}$





Vancomycin
drug of last hope

Peptide Recognition in Nature

Vancomycin resistance

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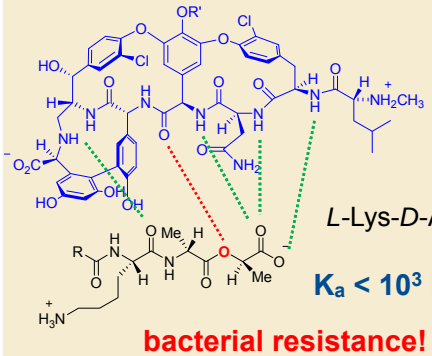
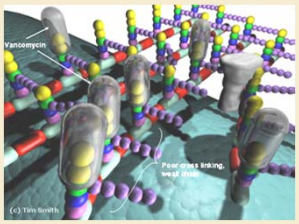


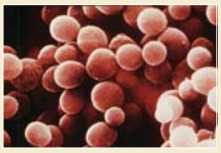
Inhibition of bacterial cell wall synthesis by reversible complexation of a specific peptide sequence.



L-Lys-*D*-Ala-*D*-Lac

$K_a < 10^3\ M^{-1}$

bacterial resistance!



replacement of *D*-Ala by *D*-Lac
⇨loss of one H-bond
⇨reduces affinity by a factor of 1000

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From Artificial Receptors to Indicators

Ionpair-based molecular recognition

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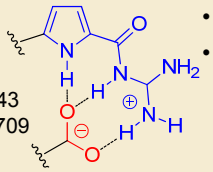
our favorite ionpair:

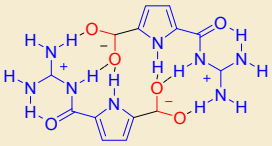


ChemCommun **1999**, 843
Chem. Eur. J. **2000**, *6*, 709

- H-bond enforced ionpair
- more stable than just Coulomb-interactions

K ca. 10^3 M^{-1} in aq. DMSO

host-guest-chemistry



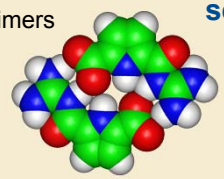
- zwitterion forms extremely stable dimers
  DMSO: $K_{ass} > 10^{10}$ M^{-1}, H_2O: $K_{ass} > 10^2$ M^{-1}

JACS **2003**, *125*, 452-459.

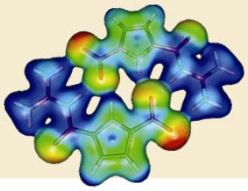
self-assembly

Review: *Chem. Soc. Rev.* **2010**, *39*, 3597

1:1-dimers



structure in the solid state



DFT-calculations
Prof. B. Engels (Würzburg)

JACS **2005**, *127*, 11115

Artificial Peptide Recognition

How to build a peptide receptor?

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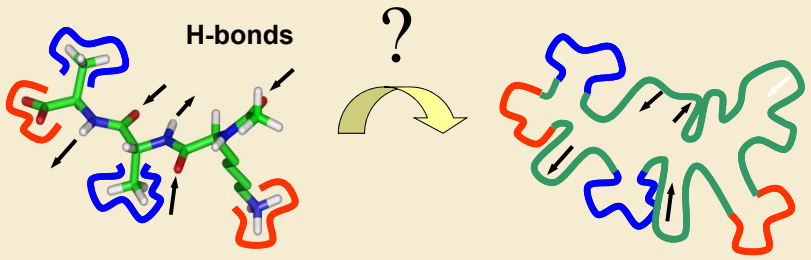
Chemical structure of peptides allows the use of different types of non-covalent interactions for binding.



hydrophobic contacts

ionpairs

artificial receptor

potential binding sites

De novo Design

A rational approach

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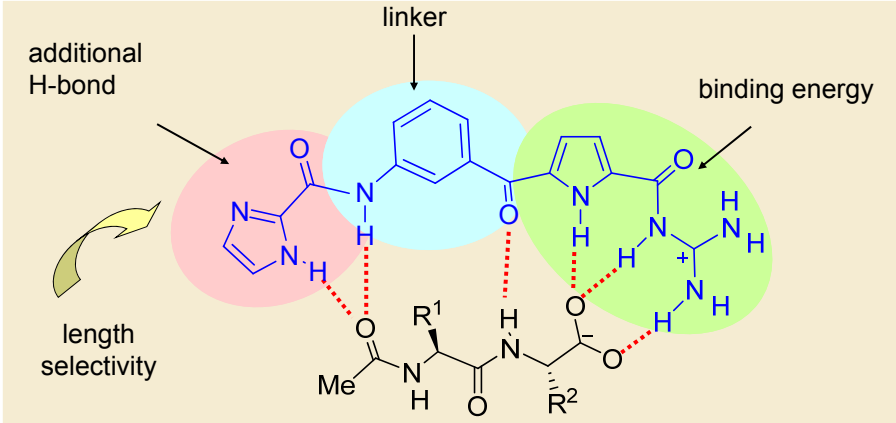

de-novo design
based on force field calculations

Artificial Peptide Receptors

Design based on modelling

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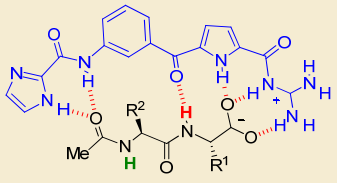
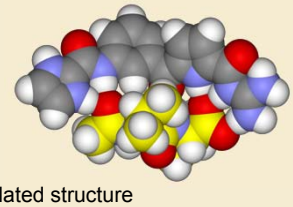
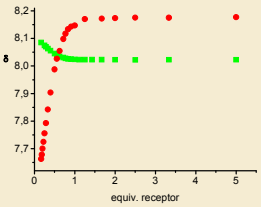


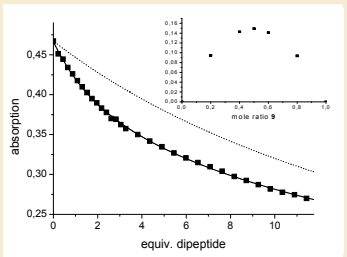


calculated structure

L. Geiger



nmr titrations
in 40 % water-DMSO



UV-titration in H_2O (buffer pH = 5.5)

Ac-Val-Val-OH	54.300
Ac-Val-Ala-OH	43.800
Ac-Ala-Ala-OH	30.600
Ac-Gly-Gly-OH	15.900
Ac-Ala-OH	7.400
Ac-Gly-OH	5.200

K in M^{-1} in water

dipeptide > amino acid
Val > Ala > Gly

JACS **2004**, *126*, 8898.

Artificial Peptide Receptors

Sequence dependent binding

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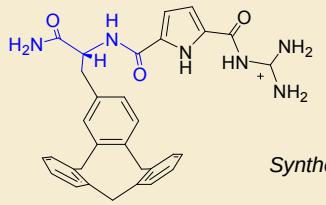
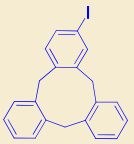


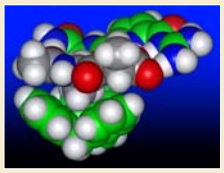


$(o\text{-Tol}_3P)_2PdCl_2$, DMF

75 %

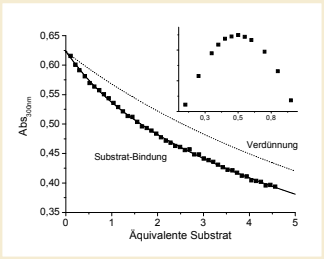
Synthesis **2002**, 655-663

W. Wienand



UV-titrations

D. Rupprecht



***D*-Ala-*D*-Ala: log K = 4.5**
Gly-*D*-Ala: log K = 3.6

in water

Chem. Eur. J. **2006**, *12*, 9186.

A Receptor for Citrate

A biological relevant tris-carboxylate

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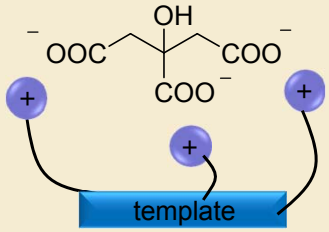
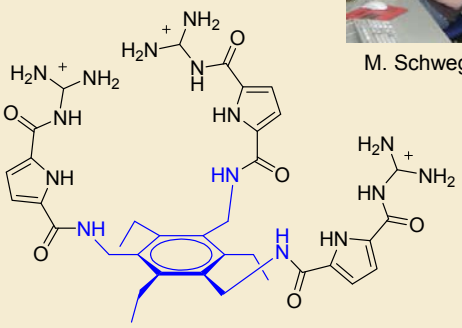
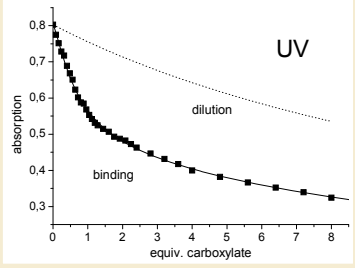


$K_b > 10^5\ M^{-1}$

M. Schwegmann





aqueous buffer, pH = 6.3

J. Am. Chem. Soc. **2005**, *127*, 3373.

From Receptors to Indicators

Indicator Displacement Assay

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„off“

fluorescence quenched

receptor

substrate

+

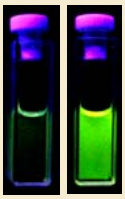
„on“

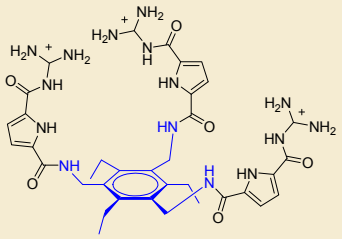
indicator

+

fluorescent

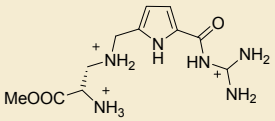
…for citrate

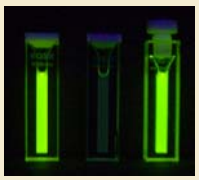




OBC **2006**, *4*, 836.

…for glutamate but not aspartate





JACS **2005**, *127*, 10486.

Recognition of Nucleic Acids

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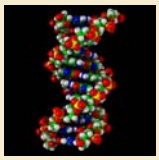
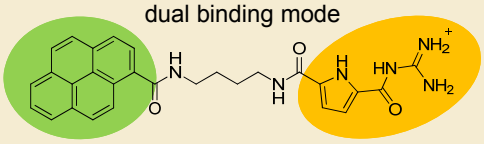
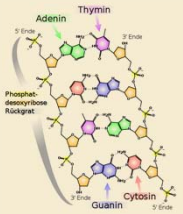


dual binding mode

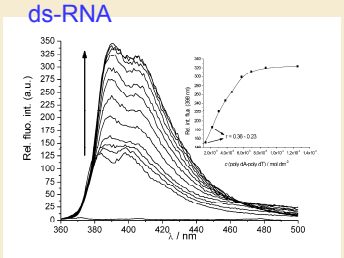


intercalator

ionpairing

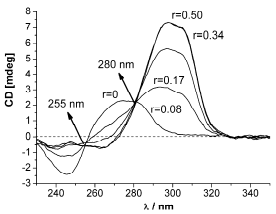


ds-RNA



strong **fluorescence increase**

ds-DNA



no fluorescence increase, but strong **induced CD** of the pyrrole

Recognition of Nucleic Acids

Sensing of secondary structure

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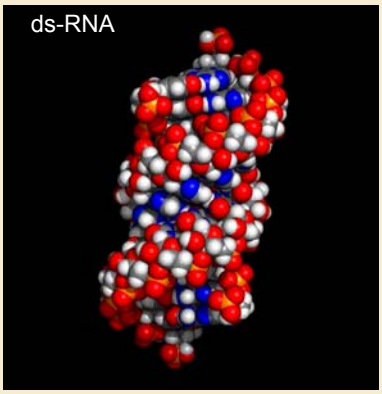
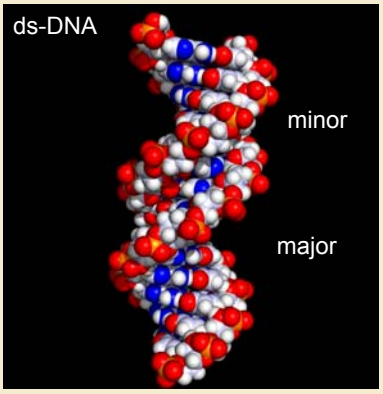


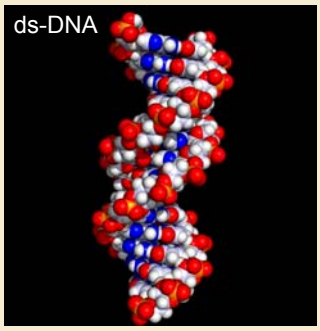


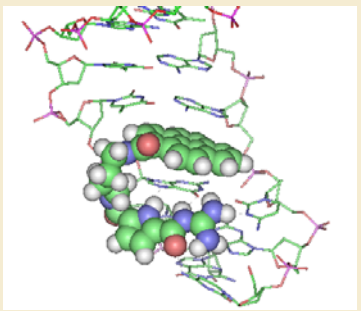
size and shape of the grooves determines binding mode

Recognition of Nucleic Acids

Sensing of secondary structure

UNIVERSITÄT DUISBURG ESSEN
Open-Minded





intercalation of the pyrene
= quenches fluorescence

alignment of pyrrole within minor groove
= strong **induced CD**

L. Hernandez

Recognition of Nucleic Acids

Sensing of secondary structure

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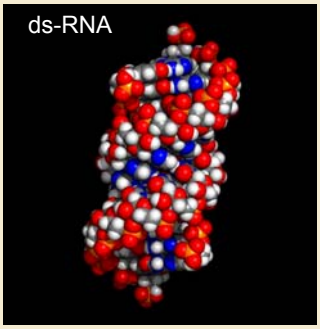

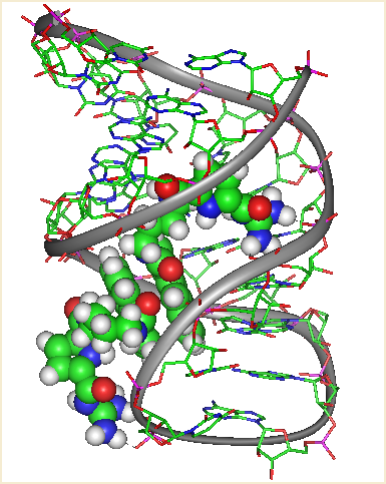

dimer formation within the major groove
= excimer formation
= strong **increase in fluorescence**

Bioorg. Med. Chem. Lett. **2008**, *18*, 2977
Chem. Eur. J. **2010**, *16*, 3036
OBC **2011**, *9*, 198.

Recognition of Nucleic Acids

Trivalent peptide ligands for DNA binding

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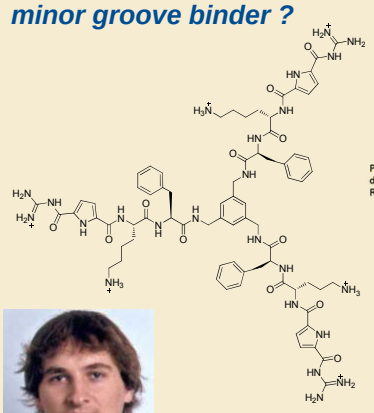
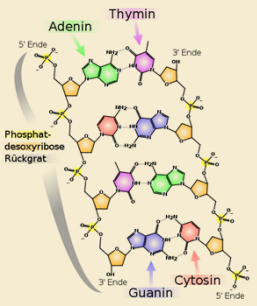
minor groove binder ?



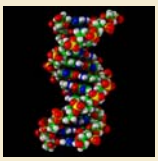
H. Kuchelmeister

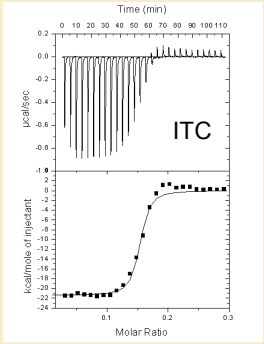
DNA is a polyanion



K	**$2.33 \cdot 10^7$ M^{-1}**
ΔH	-2142
ΔS	-38.1

ITC





New Transfection Vectors

Gene delivery by artificial DNA binders

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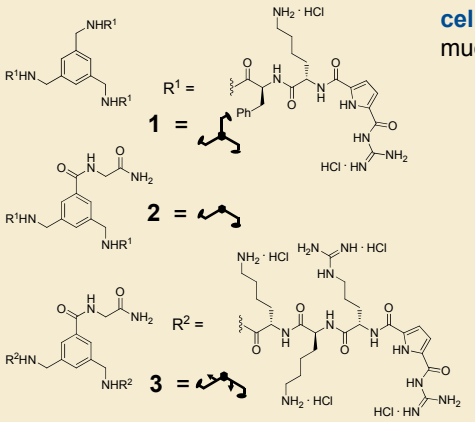
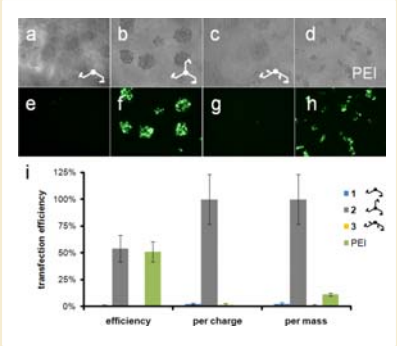


cell transfection (GFP plasmid)
much better than PEI („gold standard“)



Only the three-armed receptor leads to transfection!

together with Prof. Shirley Knauer (microbiology, Essen)

New Transfection Vectors

Gene delivery by artificial DNA binders

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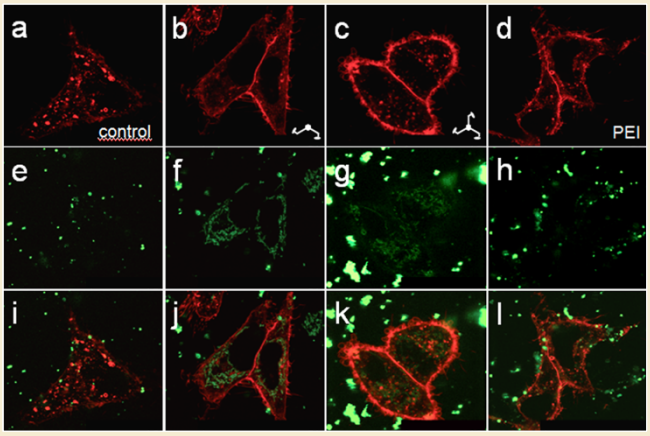
However all receptors facilitate DNA uptake!



Chemical Science **2012**, *3*, 996.

New Transfection Vectors

Gene delivery by artificial DNA binders

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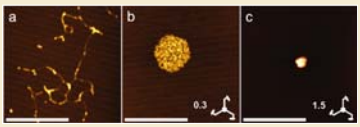
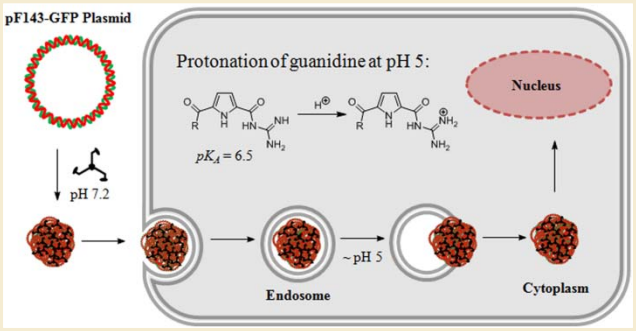


pure DNA with receptor

AFM and DLS study show DNA condensation
Chloroquine facilitates transfection (endocytosis)

Endosomal release seems to be critical!

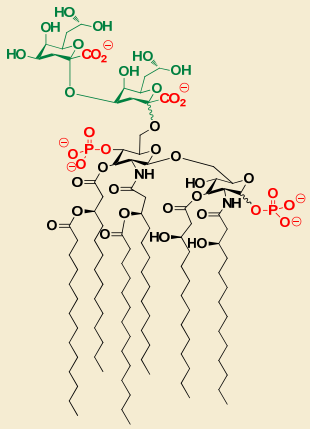


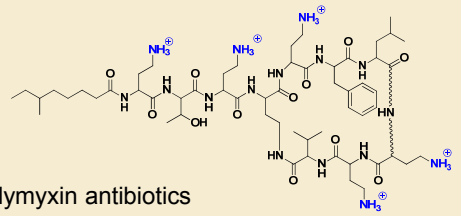
Chemical Science **2012**, *3*, 996.

Recognition of Bacterial Lipopolysaccharide

UNIVERSITÄT DUISBURG ESSEN
Open-Minded

lipopolysaccharide
= part of the bacterial cell wall





polymyxin antibiotics

Recognition of Bacterial Lipopolysaccharide

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Open-Minded

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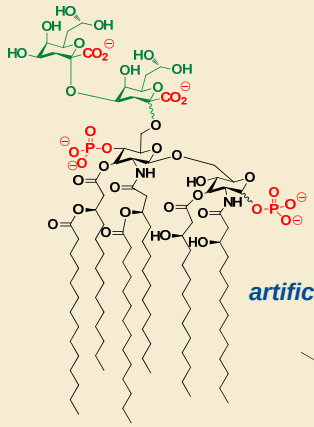
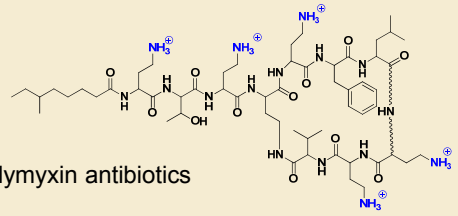
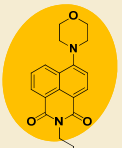


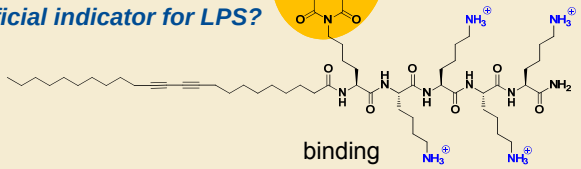


polymyxin antibiotics

artificial indicator for LPS?



sensing



binding

Functionalized Liposomes

Amphiphilic peptides as indicators

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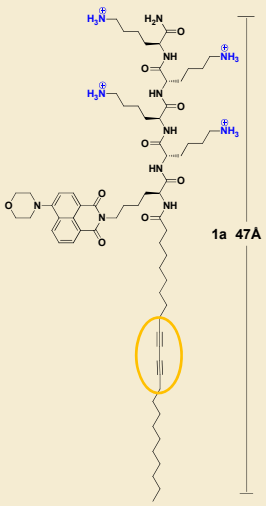

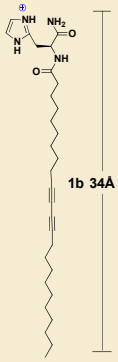

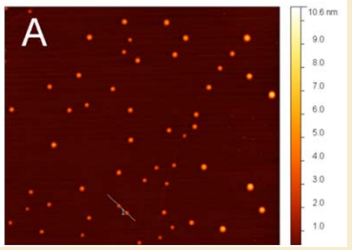

formation of vesicles in water (**1a**/**1b** = 1:9)

polymerization by UV irradition

J. Wu

Functionalized Liposomes

Amphiphilic peptides as indicators

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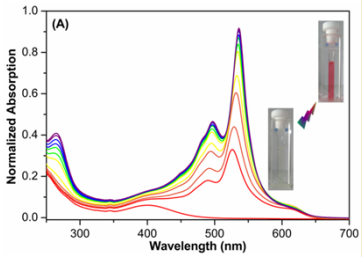
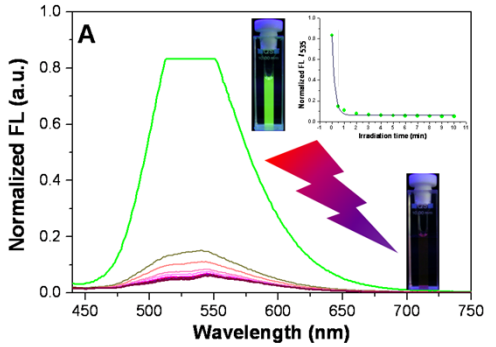


upon polymerization the optical properties change dramatically



Fluorescence is quenched!

Functionalized Liposomes

Amphiphilic peptides as indicators

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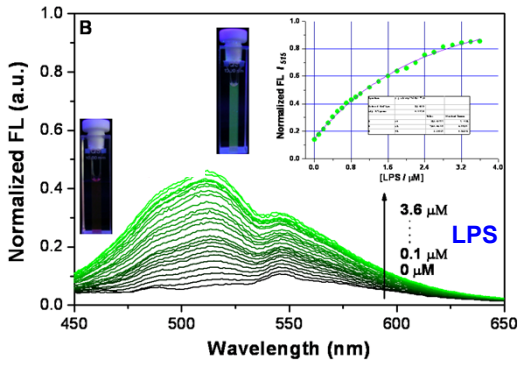
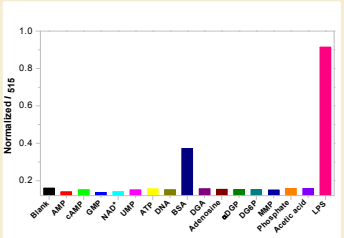


Upon LPS binding fluorescence is restored

switch on sensor



highly selective indicator for LPS

J. Am. Chem. Soc. **2011**, *133*, 9720–9723

Recognition of LPS
in E. coli bacteria

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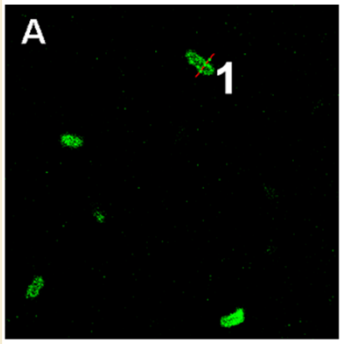

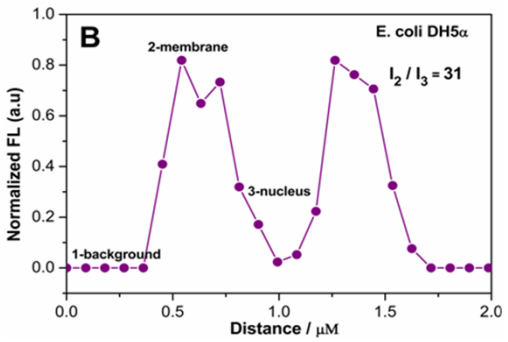

confocal laser scanning microscopy

J. Am. Chem. Soc. **2011**, *133*, 9720–9723

A Molecular Peptide Beacon
for DNA sensing

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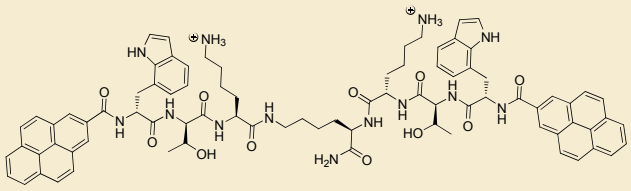
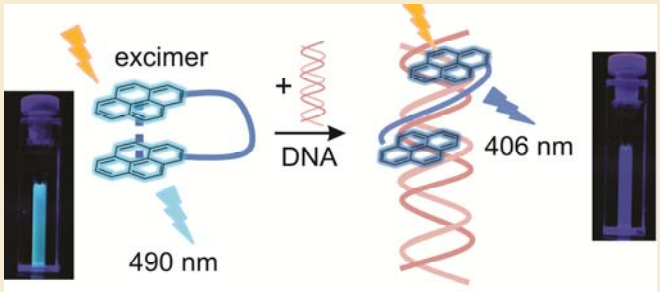
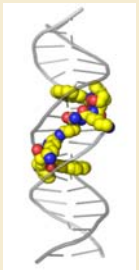


J. Wu





A Molecular Peptide Beacon

for DNA sensing

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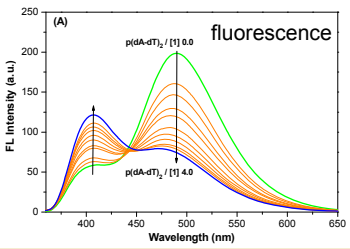

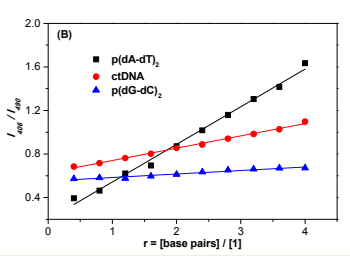

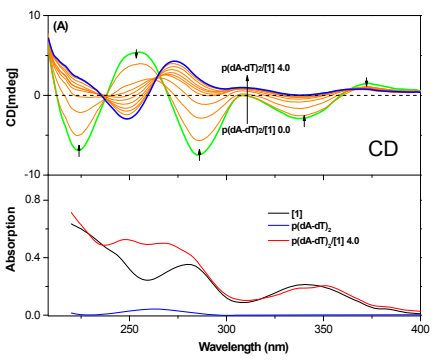

free beacon: excimer emission
bound beacon: monomer emisison
ratiometric sensing of nucleic acids

A Molecular Peptide Beacon

for DNA imaging in HELA cells

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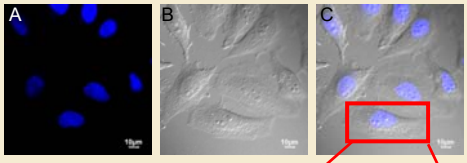
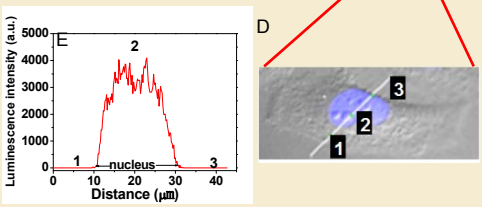
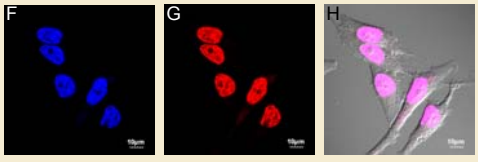
beacon



overlay



propydium iodide



overlay

JACS **2012**, *134*, 1958.

A Molecular Peptide Beacon

for DNA imaging in HELA cells

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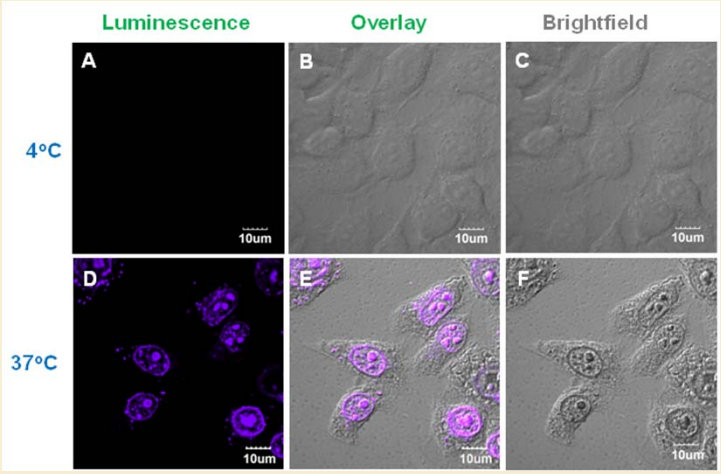

JACS **2012**, *134*, 1958.

Finally

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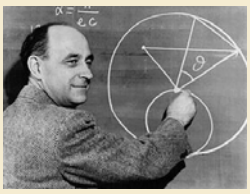
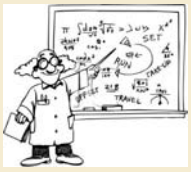


Enrico Fermi
Nobel price for Physics (1938)



„I am still confused, but on a higher level“

Acknowledgements

Many thanks to…

UNIVERSITÄT DUISBURG ESSEN

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…my group and my collaborators
and to the various funding agencies

Alexander von Humboldt foundation
Fonds der Chemischen Industrie
Deutsche Forschungsgemeinschaft:
SCHM 1501, SFB 630, SPP 1179
BaCaTec, COST D31, DAAD