



# Gel forming supramolecular polymer complex used as drug delivery matrix

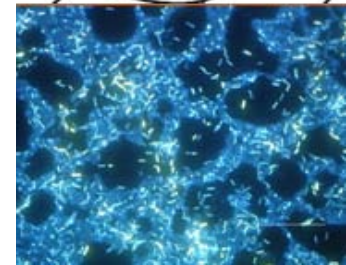
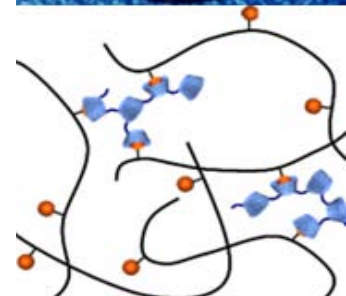
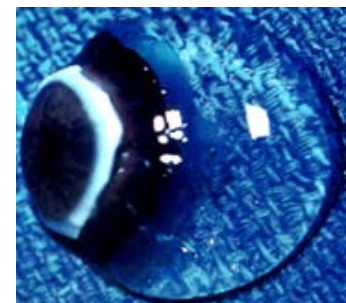
NANOSCIENCE 2009

9<sup>th</sup> Leibniz Conference of Advanced Science,  
1<sup>st</sup> German-Russian Symposium on Nanobiotechnology,  
Lichtenwalde, October 15 – 17, 2009

Lothar Heinrich

Center for Nanotechnology/marcotech oHG

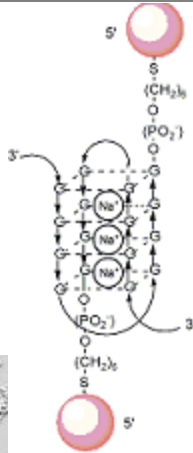
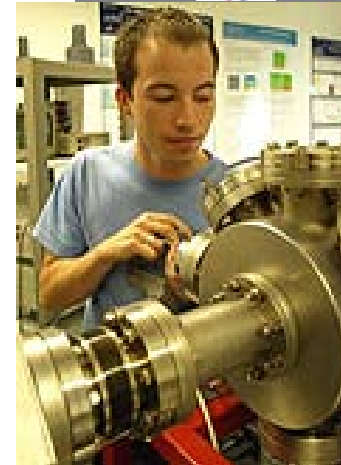
Westphalian Wilhelms University Muenster, Institute for Biochemistry



Established as interdisciplinary nano technological research centre targeted to application and commercialization, as well as acquisition of for public grants, providing educational events and organizing international conferences



Building of CeNTech ([www.centech.de](http://www.centech.de))  
= Centre for academic research (12 teams)  
and small enterprises (7)





# 1. Examples of structured gels in medical technology

Decubitus



Gel mattress pads



Artificial sinovia



Diapers and hygienic article



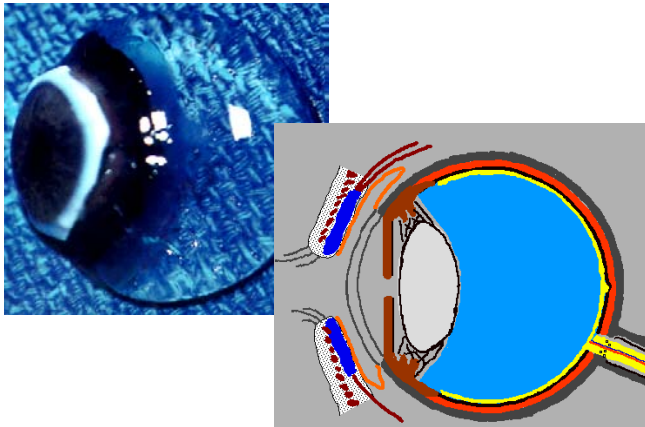
Breast implants of cohesive silicon



Wound management systems

## 2. Vitreous body of the eye

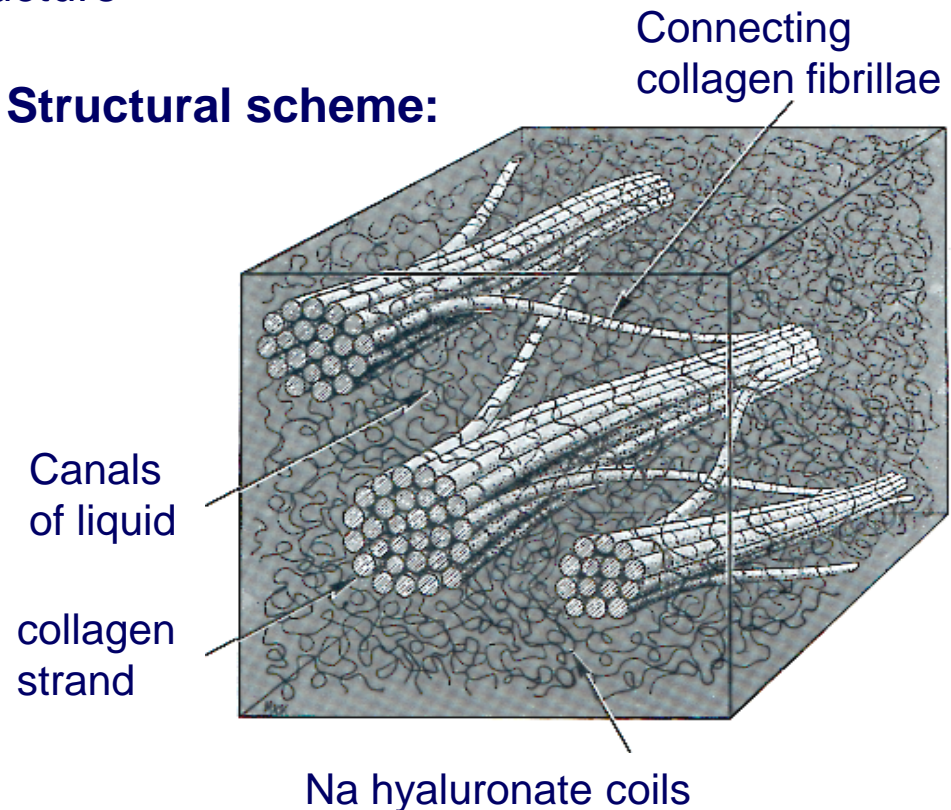
= complex, well arranged gel structure  
containing  $\geq 98\%$  water



### Requirements:

- Large transparency
- Insignificant light scattering
- Oxygen barrier
- Barrier against cytokine transport
- Form stability, visco-elasticity
- Corresponding osmolarity

### Structural scheme:



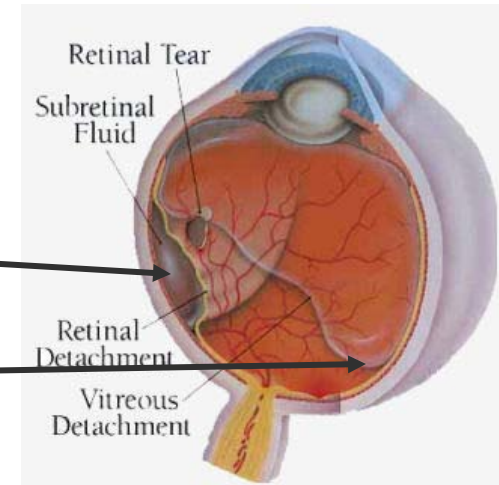
Source: J. Sebag, The Vitreous, Springer 1989



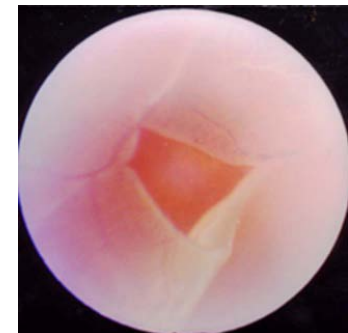


## 2.1. Indications to remove the vitreous = vitrectomy

- **retinale traction** (--> detachment)  
caused by  
**age-related degeneration**  
of the vitreous

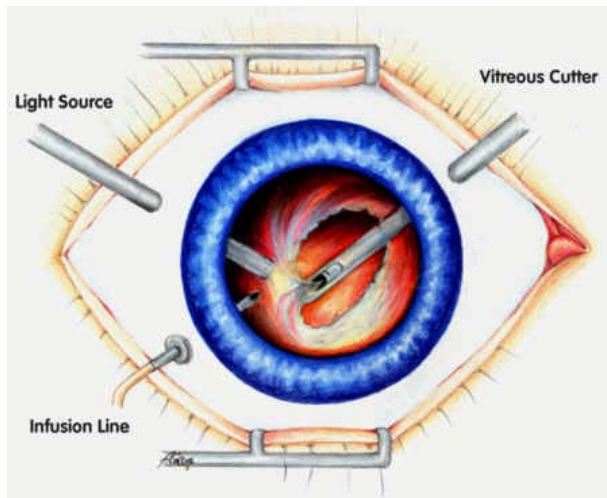


- **proliferative retinopathy** (proliferative vitreoretinopathy = PVR)
- **proliferative diabetic retinopathy** (PDVR)
- age-related **macula degeneration** (AMD)
- **opacity** caused by blood penetration (Hämorrhagie) or increasing inclusion of cellular or non-cellular species)

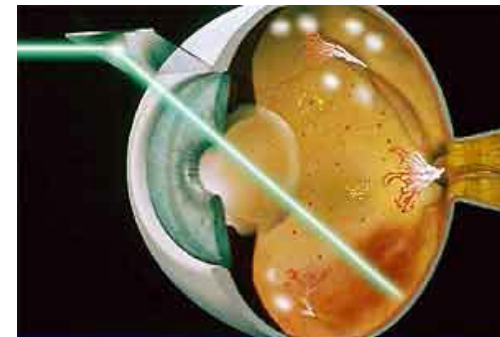
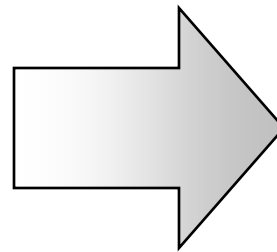


retinal hole

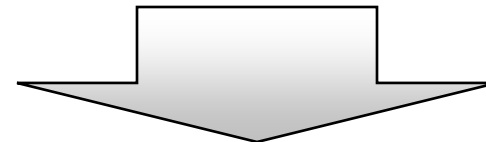
## 2.1.2. Vitrectomy, re-attachment & support of the retinal attachment



Pars-plana vitrectomie



Retina re-attachment  
by argon laser treatment



Filling with **tamponades**  
in order to support  
the attachment of  
the repaired retina



**Materials as artificial vitreous body are not available !**



## 2.1.3. Reasons for a total replacement of vitreous instead of the use of **tamponades** like silicon oils or perfluoreted hydrocarbon liquids

### vitrectomy



- increased oxygen transport
- significant transport of VEGF \*)
- tamponade liquid can access the anterior eye chamber

- emulsification with eye chamber water
- insufficient mechanical support for retina and eye bulb

- neovascularization of iris
- cataract (clouding of the lens); statistically after 2 years
- dysfunctions of feeding the cornea

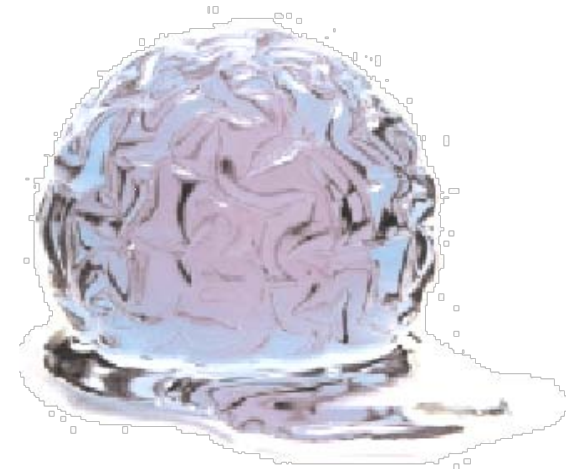
- frequent exchange of the tamponade liquid
- incidence of further retinal lesions

\*) VEGF = Vascular Endothelial Growth Factor

## 2.2. Requirements to an artificial vitreous material

### Biocompatibility and **exchangeability** !

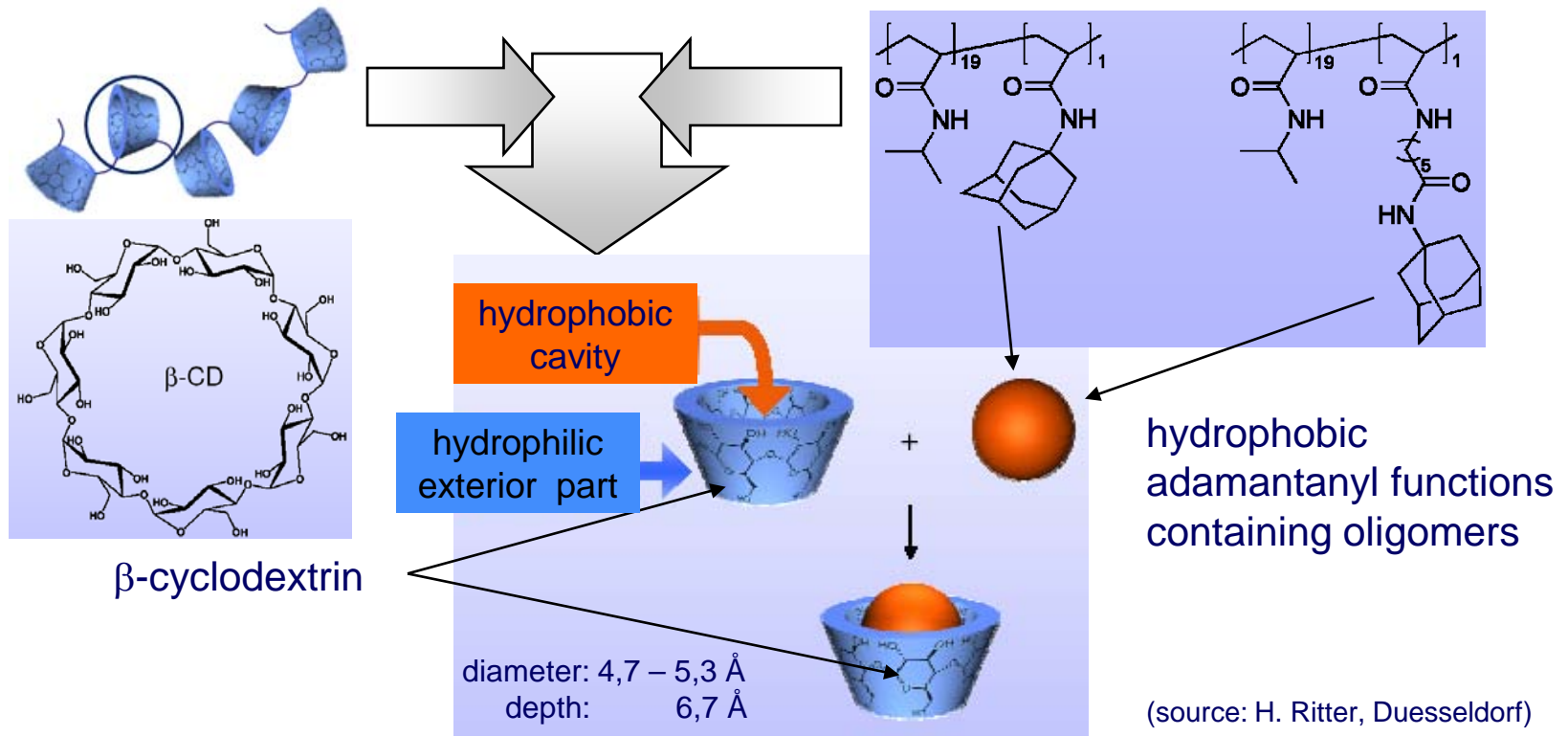
- Tamponade effect and large interfacial tension
- Sufficient pressure to support the retina attachment, but limited pressure to avoid any dysfunctions or damage of glial cells and visual nerv
- Physiologically adjusted osmotic tension
- Reasonable viscosity before and after application, and forming cohesive gel within the bulb (viscoelasticity)
- Transparency and stability of light refraction
- Circulation of metabolism, but tansport limitation for oxigen and growth factor VEGF
- Inhibition of any cell proliferation



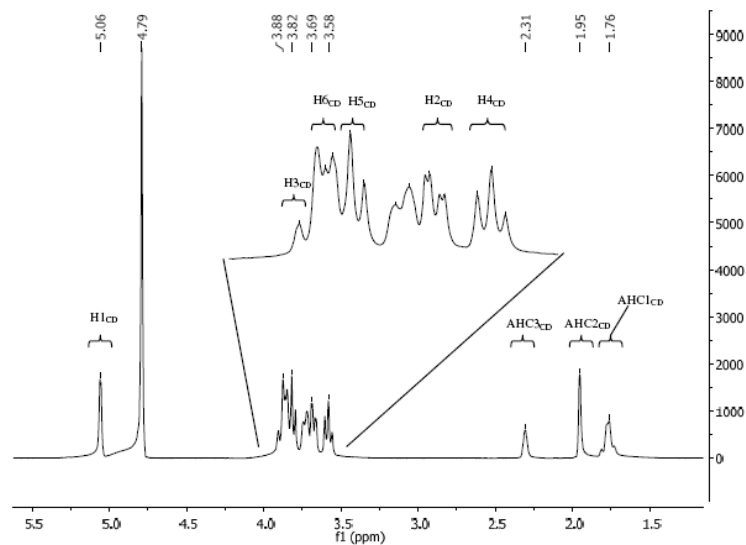
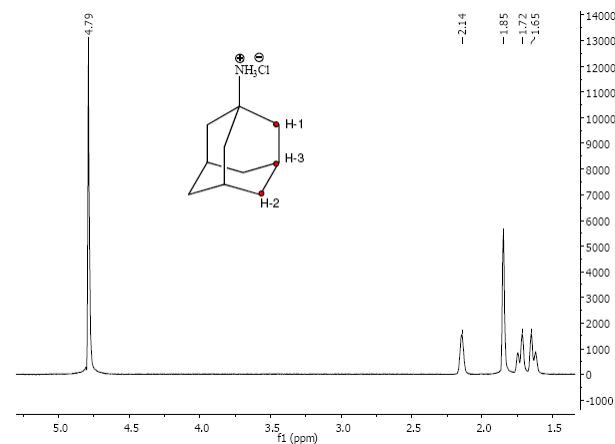
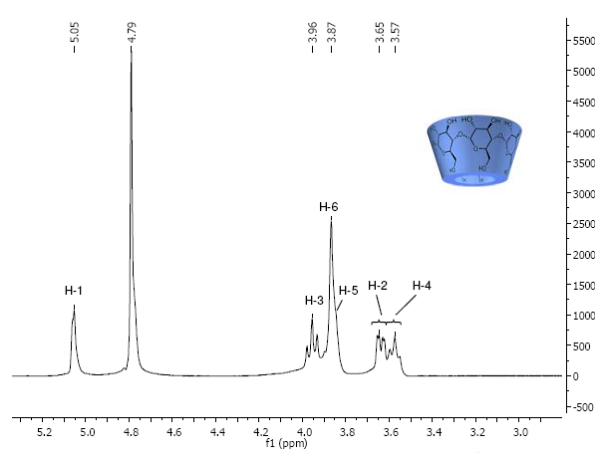
Refractive index: 1,336  
 Optical scattering loss: 1-2%  
 Vitreous- smolality:  
                                   ca. 330 mosm/kg H<sub>2</sub>O  
 Surface energy: ca. 70 mN/m  
 Intraocular pressure:  
 10 ... 20 mm Hg = 1,33 ... 2,66 kPa



### 3. Construction principle of the supramolecular polymer complexes based on associative host-guest interactions



# <sup>1</sup>H NMR studies



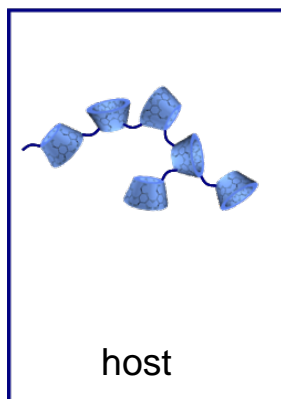
$\beta$ -cyclodextrin : adamantyl complex

[Sporenberg, Muenster 2008]

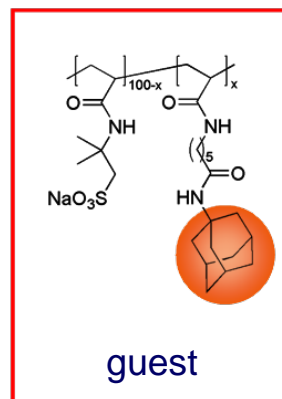
### 3.1. Supramolecular polymer complex has been formed as transparent gel within the bulb



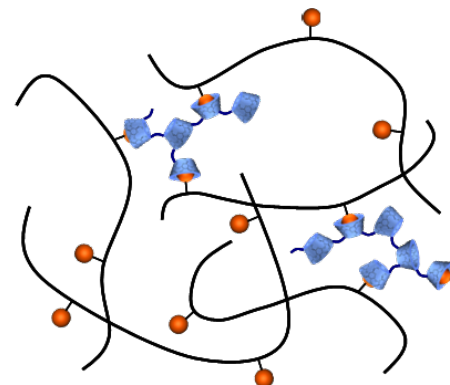
mixing



+



$H_2O$



Liquid oligomers

gel forming  
by supramolecular interaction  
without heat excess

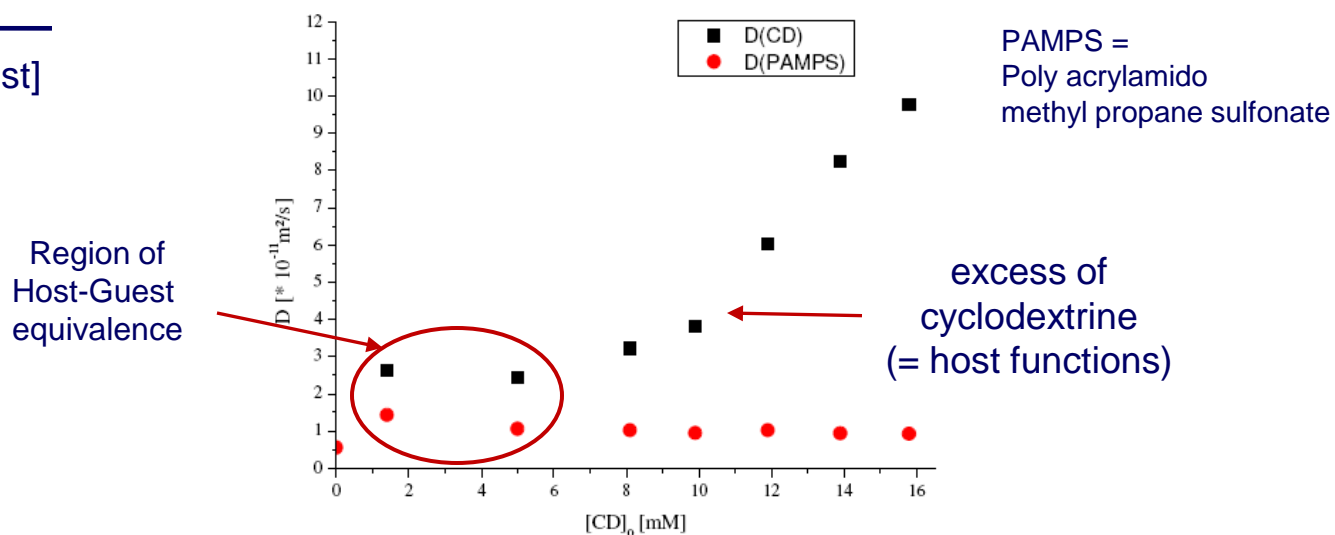
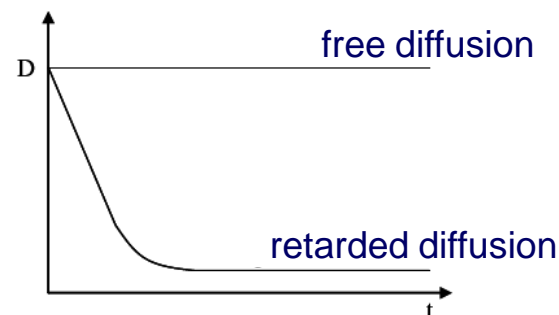


## 3.2. Stability of the supramolecular polymer complex

Diffusion experiments by Pulsed Field Gradient (PFG)-NMR



$$K_S = \frac{[\text{HGC}]}{[\text{Host}] \cdot [\text{Guest}]}$$



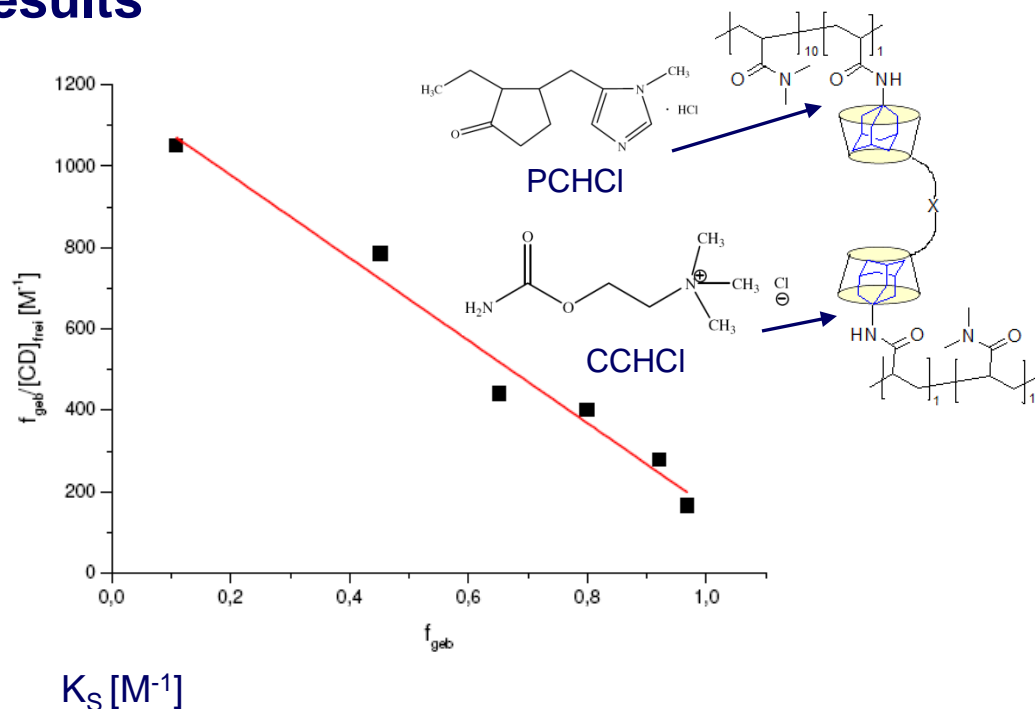




## Examples of experimental results

$$f_{\text{bound}} = \frac{D_{\text{free, guest}} - D_{\text{measured, guest}}}{D_{\text{free, guest}} - D_{\text{bound, guest}}}$$

$$f_{\text{bound}} = \frac{K_S \cdot [\text{Host}]}{1 + K_S \cdot [\text{Host}]}$$



Poly[(AMPS-Na)-co-(AAHA)]<sup>\*)</sup>

$4500 \pm 200$

(Host Guest Complex)

Carbamoyl cholin hydrochlorid e (CCHCl)

$70 \pm 4$

Interaction with

Pilocarpine hydrochloride (PCHCl)

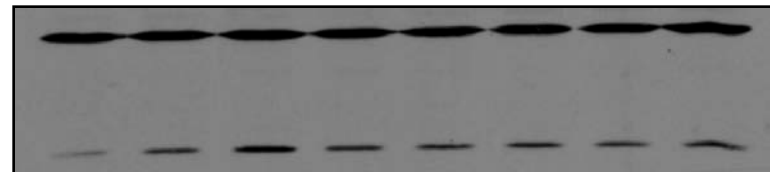
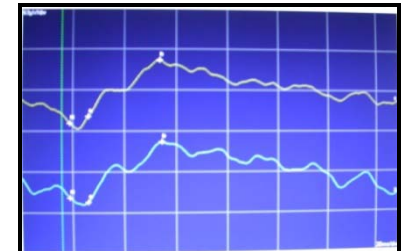
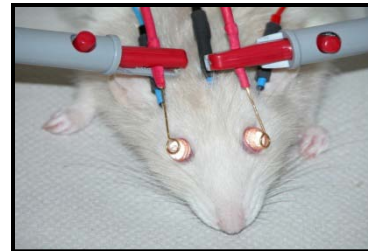
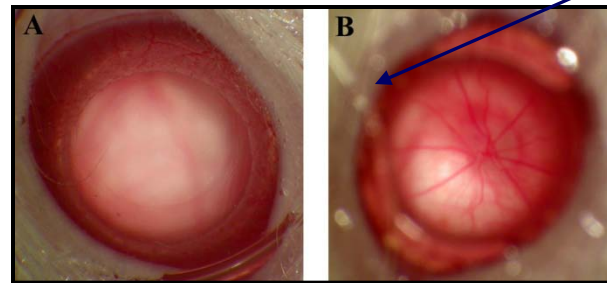
$90 \pm 4$

potential pharmaceuticals

## In-vivo tests (rat model)

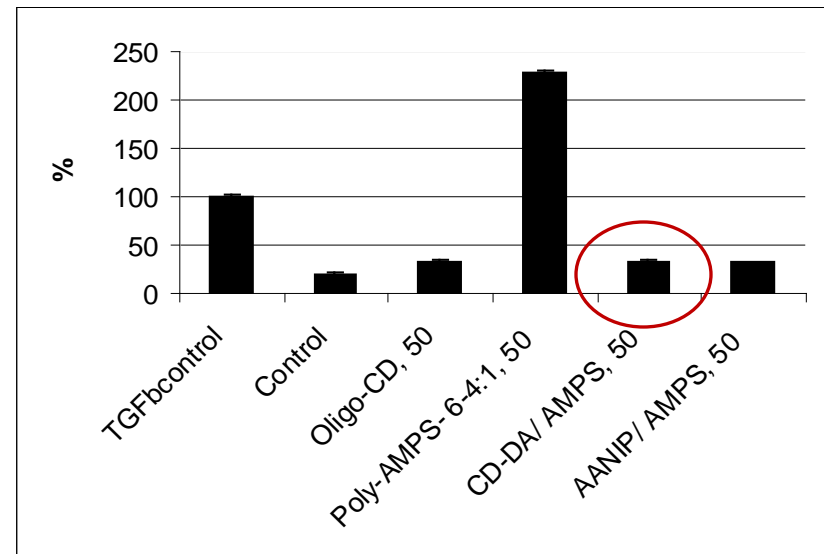
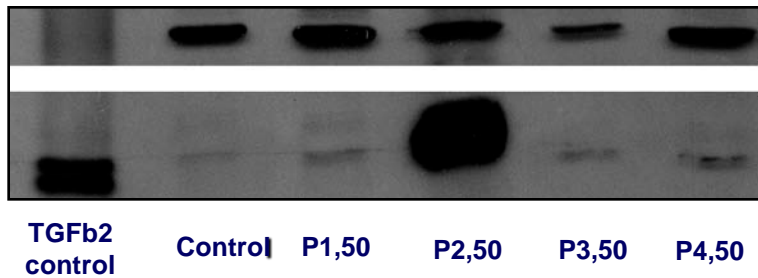
- Vitrectomy
- Fundoscopy (optical integrity)
- Electrophysiology (ERG)  
= detection of  
outer retinal cell function
- Westernblot (inflammation, TGF 2b)

glas microcapillary



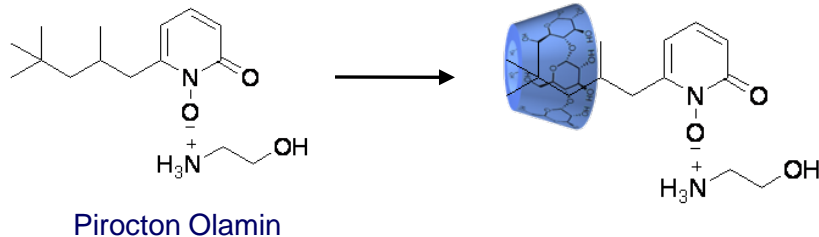
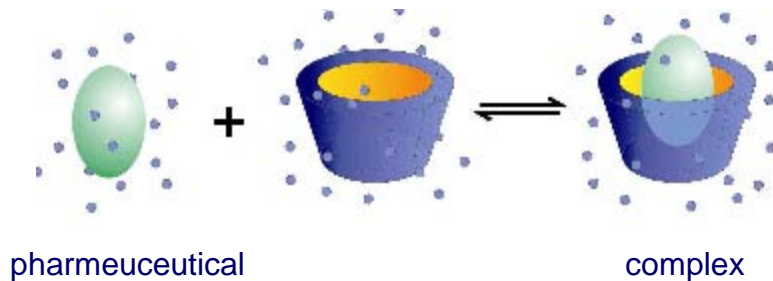
## Expression of tumor growth factor TGFb2 after 1 month

### WB-Vitreous



### 3. Medical artificial toenails

Fungal infections like onychomycosis:  
15 -20% of the human population  
> 70% of seniors older than 70 years  
mostly associated with  
nail bed infections and psoriasis



Alternatively: Terbinafin, ciclopirox & tretinoin (antipsoriatica)



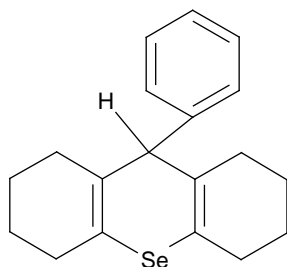
Polymer matrix containing  
antifungal, antipsoriatic and antibacterial  
agents as CD complex







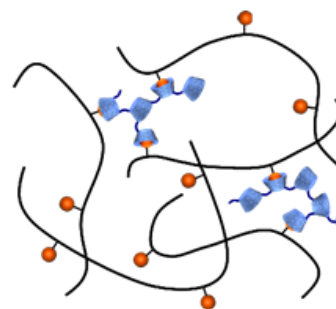
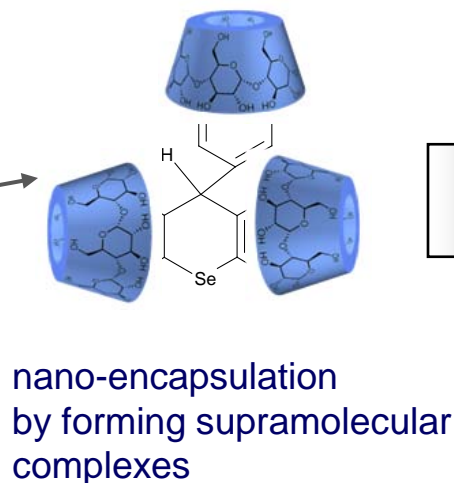
## 4. Nano-encapsulation for oral or directly injectable drug



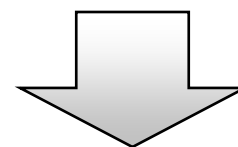
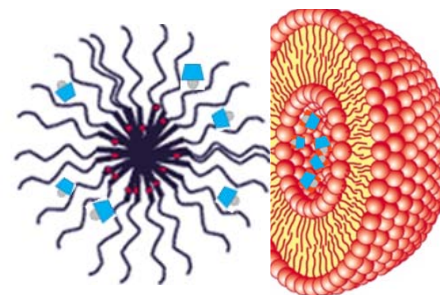
9-Phenyl *sym* octahydro seleno xanthene

Anticancer and radioprotecting pharmaceutical : CD complex

- a) hydrophobic nanoscaled particles
- b) hydrophilic/lipophilic gel particles
- c) nanoparticles containing
  - micelles
  - liposomes



copolymers or composites  
forming host-guest complex by linked CD





## 5. Conclusion & Outlook

- Supramolecular polymer complexes on the base of cyclodextrin “baskets” are promising gel forming systems usable for
  - forming gel body from two liquid oligomer components
  - acting as container for drug delivery
- Equilibrium of the host and guest complex is for the drug delivery properties
- Optimizations of drug delivery and bioavailability by modification of the polymer chains and functionalizing the guest molecule (CD)
- similar supramolecular structures are useful for medicine, cosmetics, as well as food/feed engineering



## Partners of the presented joint projects, and acknowledgment

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Institute of Macromolecular Chemistry

**Helmut Ritter et al**

Westphalian Wilhelms University Muenster

**Hans-Joachim Galla et al**, Institute for Biochemistry

**Solon Thanos et al**, Experimental Ophthalmology

**Monika Schoenhoff et al**, Institute for Physical Chemistry

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