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CYCLODEXTRINS IN THE PHOTODYNAMIC THERAPY

The photodynamic therapy was introduced to the cyclodextrin researchers at the Sixth International Cyclodextrin Symposium (Chicago, 1992) by Prof. Morgan who studied synthetic chlorophyll-type sensitizer, tin etiopurpurin dissolved in γ CD and HP γ CD to replace the synthetic surfactant, Chremophore [1]. Both CDs gave efficient concentration of this photosensitizer in the tumor in *in vivo* experiments. Since that, about 100 papers and conference publications have been published on CD application in photodynamic therapy, 20 of them in 2012, according to the *Cyclodextrin News Database*. The dynamics of the publications are shown in *Fig. 1*.

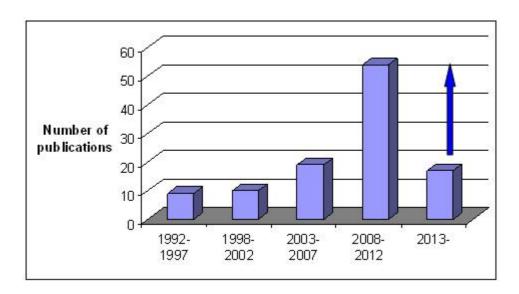


Fig. 1 Number of publications on CDs in photodynamic therapy in 5 year periods

Photodynamic therapy (PDT) is a new anticancer, antimicrobial therapy using light-sensitive compounds, which have anticancer/antibiotic effect only when irradiated by low power laser light. The photosensitizers produce reactive oxygen species (singlet oxygen or other oxygen radical species) which destroy the tissues/pathogens exposed to light. The therapy can be selectively targeted by applying either the photosensitizer or the light onto the target area. PDT is used for the skin disorders, such as acne, psoriasis and skin tumor applying both the photosensitizer and the light locally to the injured skin surface. When internal tumors are treated, either the PDT is used during surgery or the

photosensitizer is administered intravenously and the light is delivered through endoscopes or optical fibers. Nowadays when antibiotic resistance makes the conventional antibiotic therapies useless, PDT is one of the novel antimicrobial strategies because resistance will not readily develope against antibiotic PDT.

Photochemical internalization (PCI) is the novel technology for light-induced release of endocytosed macromolecules (proteins, plasmids, adenovira, nanoparticles) into the cytosol.

Cyclodextrins as carriers of various drug molecules can be vehicles of photosensitizers via complexation (*Fig. 2*). The complexes usually show improved solubility, stability, and changed aggregation behavior. In addition to complexation, there is another possibility: using photosensitizers conjugated to CDs (*Fig. 3*). In this case, the CD cavity can accommodate another anticancer or antibiotic compound making possible a two-way attack against cancer or pathogens.

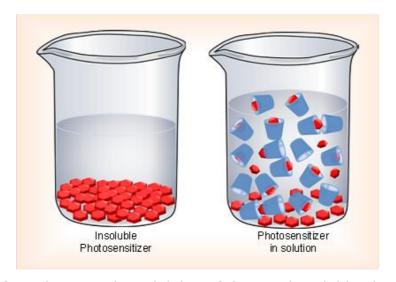


Fig. 2 CD for enhancing the solubility of the poorly soluble photosensitizer

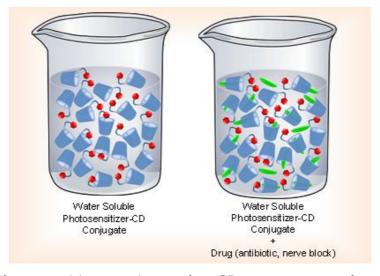


Fig. 3 Photosensitizer conjugated to CD can accommodate another anticancer drug or antibiotic

The conference on "Application of Nanodrugs in Photodynamic Therapy" (NanoPDT) held in Gothenburg (Sweden) in this month (April 11-12) gave an overview on the latest achievements and developments in both diagnostics% and therapy using various laser techniques. The interdisciplinary approach of the conference organized in the frame of Cyclon project (Marie Curie Initial Training Network 237962) by contribution of Center of Skin Research (SkinResQU) of Gothenburg University gave a platform for clinical researchers as well as for chemists and pharmacists. Out of the approx. 40 presentations 14 was related with cyclodextrins covering the following topics [2]:

- multifunctional CD-based nanoconstructs able to produce both singlet oxygen and nitric oxide on the effect of light and providing super-resolution imaging simultaneously;
- nanoparticles such as metal-organic frameworks (MOFs) surface-modified with CD derivatives as proper carriers for azidothimidine model drug;
- self-assembling CDs and CD polymers able to penetrate through biological barriers;
- CD-porphyrin conjugate multimodal drug delivery system of a NO photodonor studied by multiphoton microscopy;
- fluorescent labeling of CD-based nanoconstructs;
- alginate foams containing curcumin complexed with HPBCD or HPGCD;
- supersaturated solutions of curcumin solubilized with various CDs and CDcontaining polymers;
- hybrid gold nanoparticles with lactose and BCD as bio recognizable vector for methotrexate delivery to cancer cells.

The CD-assisted photodynamic therapy is a dynamically developing option for anticancer and antimicrobial treatment.

É. Fenyvesi and M. Malanga



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 - S. Sortino: Photoactivated nanoconstructs for bimodal phototherapy and super-resolution imaging (S2-KL1 Keynote lecture)
 - N. Kandoth, V. Kirejev, R. Gref, M. Ericson, S. Sortino: Cyclodextrin based nanoparticles for light controlled nitric oxide release and two-photon fluorescence reporting in cells (S2-3 Oral presentation)
 - R. Gref: Design and control of drug delivery using nanoparticles (S4-KL1 Keynote lecture)
 - T. Loftsson: Cyclodextrins as nanocarriers for pharmaceutical applications (S5-KL1 Keynote lecture)
 - V. Kirejev, R. Goncalves, I. Manet, K. Yannakopoulou, M. B. Ericson: Multiphoton microscopy and spectroscopy of cyclodextrin-porphyrin multimodal drug delivery system (S5-1 Oral presentation)
 - M. Malanga, L. Jicsinszky, K. Tuza, E. Fenyvesi: Fluorescent labelling of cyclodextrin-based nanoconstructs (S5-2 Oral presentation)
 - A. B. Hegge, N. Vukicevic, K. O. Wikene, E. Bruzell, H. H. Tonnesen: Supersaturation and supersaturated drug delivery systems to surpass the outer membrane barriers of gram negative bacteria in antimicrobial photodynamic therapy (aPDT) (S6-1 Oral presentation)
 - H. H. Tonnesen, A. Bee Hegge, E. Bruzell: Application of nanovehicles in preparations for antimicrobial photodynamic therapy (aPDT) (S6-2 Oral presentation)
 - C. Aggelidou, T. A. Theodossiou, K. Yannakopoulou: Protoporphyrin IX-cyclodextrin conjugate: a nanosized drug carrier and photosensitizer (PS-1 Poster presentation)
 - A. Aykac, M. C. Martos-Maldonado, J. M. Casas-Solvas, I. Quesada-Soriano, L. Garcia-Fuentes, A. Vargas-Berenguel: Novel B-cyclodextrin-lactose hybrid gold nanoparticle as specific drug delivery system towards cancer cells (PS-2 Poster presentation)
 - A. Fraix, A. R. L. Goncalves, V. Cardile, A. C. E. Graziano, K. Yannakopoulou, T. A. Theodossiou, S. Sortino: A multifunctional bichromophoric nanoaggregate for imaging and photoactivated therapy of melanoma cells (PS-6 Poster presentation)
 - R. Anand, F. Manoli, I. Manet, S. Monti, M. P. Donzello, E.Viola, M. Malanga, E. Fenyvesi: Study of the association of a water soluble Zn(II) porphyrazine octacation to fluorescent cyclodextrin derivatives by spectroscopic techniques (PS-11 Poster presentation)
 - Y. Wang, B. Cohen, L. Jicsinszky, A. Aykac, A. Vargas-Berenguel, A. Douhal: Second studies of a water-soluble porphyrin derivative in chemical and biological nanocavities: relevance to photodynamic therapy (PS-13 Poster Presentation)



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3. CDs in Drug Formulation

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porphirin, NO-releasing agent, fluorescent nanoscopy

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Cyclodextrin based nanoparticles for light controlled nitric oxide release and twophoton fluorescence reporting in cells

cancer cells, two-photon fluorescence

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Design and control of drug delivery using nanoparticles

metal-organic frameworks (MOFs), modified by CDs, engineered nano-MOFs, azidothimidine

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Cyclodextrins as nanocarriers for pharmaceutical applications

skin surface, hair follicles, eye surface, retina

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Fluorescent labelling of cyclodextrin-based nanoconstructs

HPBCD, carboxymethyl-BCD, RAMEB, rhodaminyl-, fluoresceinyl-, nitro-benzofurazanyl and coumarinyl-CD derivatives

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Supersaturation and supersaturated drug delivery systems to surpass the outer membrane barriers of gram negative bacteria in antimicrobial photodynamic therapy (aPDT)

E.coli, nanocarriers, PEG, PEG-CD polymers, MeBCD

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Application of nanovehicles in preparations for antimicrobial photodynamic therapy (aPDT)

alginate foams, curcumin, HPBCD, HPGCD, sterilization

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5-aminolevulinic acid, tamoxifen, phototoxicity

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bio recognizable vector, lectins, methotrexate

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A multifunctional bichromophoric nanoaggregate for imaging and photoactivated therapy of melanoma cells

porphyrin covalently bound with BCD, nitric oxide photodonor, nanoassembly, singlet oxygen and nitric oxide

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carboxymethyl-BCD, nitro-benzofurazan-triazolyl chromophore, carboxymethyl-BCD-epichlorohydrin crosslinked oligomer, rhodaminyl moiety

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quaternary ammonium modified BCD, hexa-2,4-diynediyl briged BCD dimer, human serum albumin, singlet oxygen, stopped-flow spectrometer

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cytokine, siRNA, macrophage, PCR, IL-6

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high speed counter-current chromatography, HPBCD

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