CYCLOLAB

PIONEERS IN CYCLODEXTRIN-BASED INNOVATION

GETTING THE BEST OUT OF CYCLODEXTRINS

Cyclodextrins as APIs

Outline

Cyclodextrins as antidotes

- Retinoid intoxication
- Sugammadex (Bridion®)
- LMWH antidotes
- Poison antidotes

Cyclodextrins as classical APIs

- Neurodegenerative (NPC, Alzheimer's, Parkinson's)
- AMD treatment
- Cancer
- Cardiovascular
- Infectious

Cyclodextrin-assisted detoxification

Pioneering role of an eminent NIH scientist: Josef Pitha

J. Pitha and L. Szente: Rescue from hypervitaminosis A or potentiation of retinoid toxicity by different modes of cyclodextrin administration, Life Sci., 32 (7), 719-23, 1983.

Proof of his concept: first clinical life saving action: rescue from retinoid intoxication in 1987

J. Pitha and Carpenter T.: Hypervitaminosis A in Siblings, J. of Pediatrics 111 507, 1987.

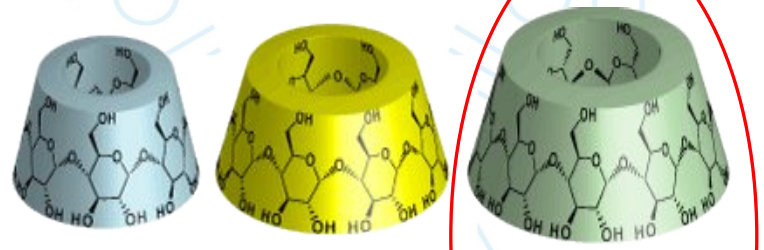
Father of CD-based clinical detoxification

Sugammadex – Bridion®

The API is a cationic aminosteroid, with approx. 1.6 nm x 0.9 nm size

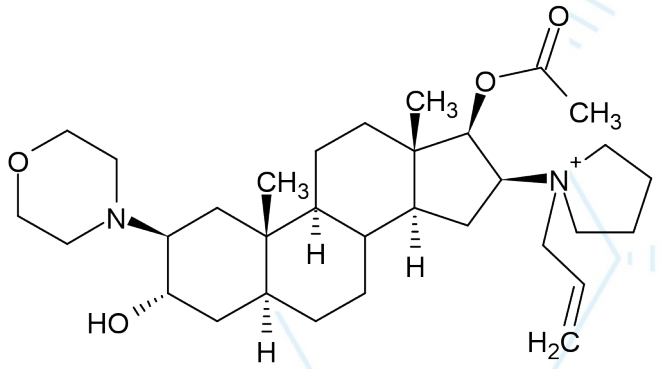
To form a highly stable non-covalent complex:

- The gamma-CD cavity size is OK, nice fit
- Cavity height is not enough→ should be extended
- Need a negative charge on the CD surface to have electrostatic interaction besides inclusion



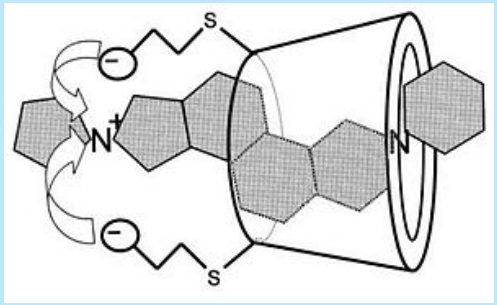
	α-CD	β-CD	γ-CD
No. of Glucose Units	6	7	8
Cavity Diameter (nm)	0.47	0.60	0.75
Height of Torus (nm)	0.79	0.79	0.79

Removal of neuromuscular blockade induced by rocuronium



Sugammadex – Bridion®

The 1st selective relaxant binding molecules to reverse neuromuscular blocking agents (NMBA) induced paralysis of skeletal muscles

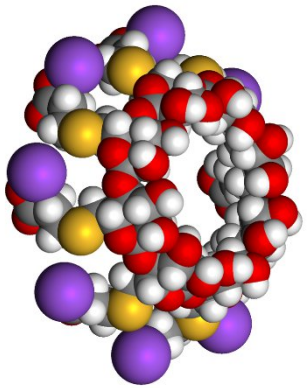


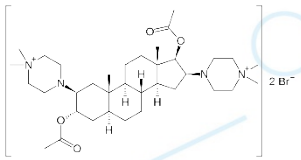
Approved in the EU (2008) and US (2015)

One of the strongest fits among CDs and guests – thus rocuronium is unavailable to bind to the receptor

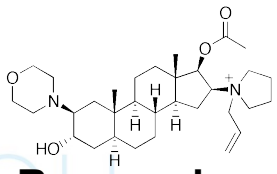
Reduced/eliminated adverse effects compared to neostigmine (no systemic side effects)

(Lower) affinity for vecuronium, pipecuronium and pancuronium, yet still of clinical significance

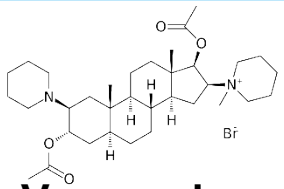




Pipecuronium

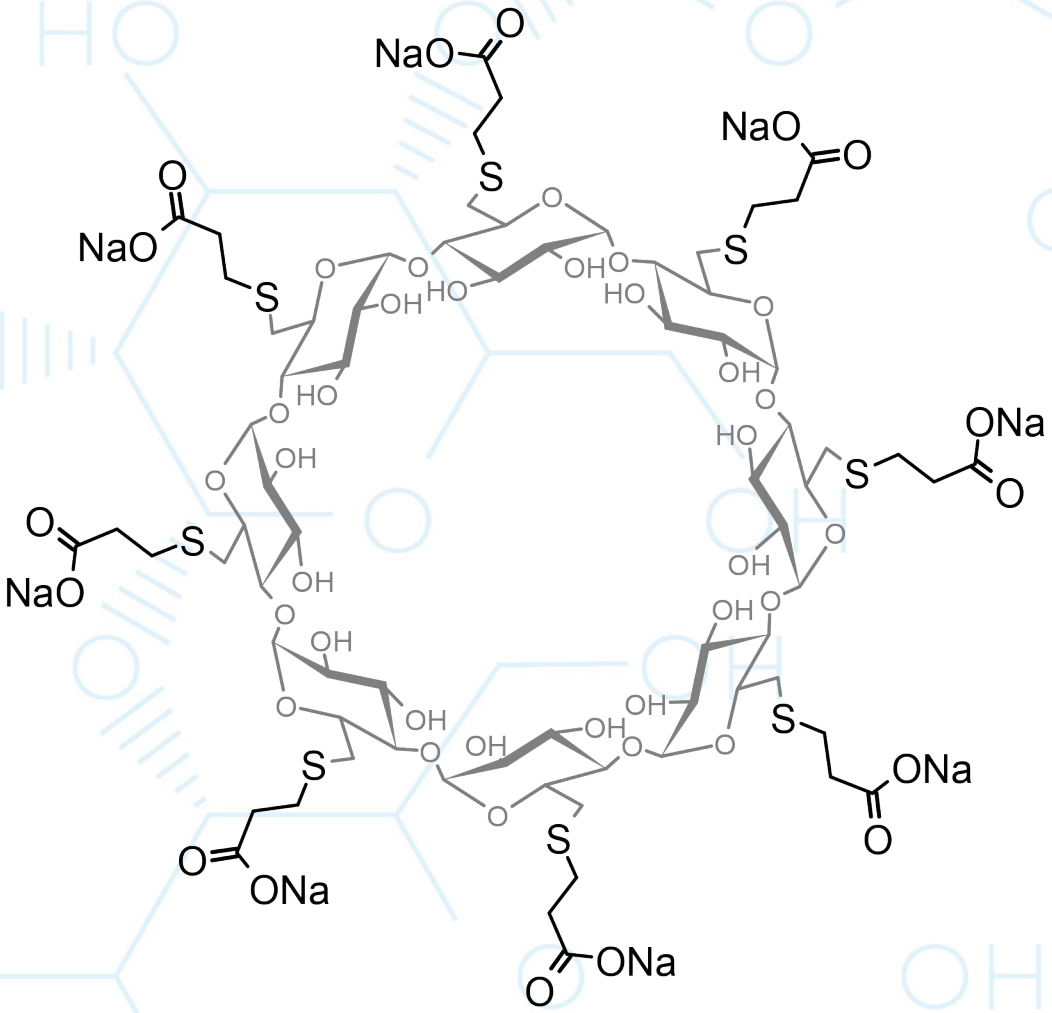


Rocuronium



Vecuronium

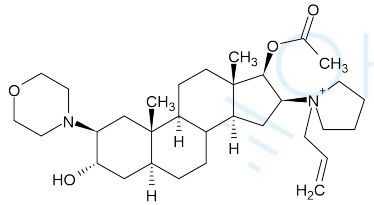
Sugammadex – Bridion®



Molecular mass: 2178.01

Clinical efficacy of Sugammadex

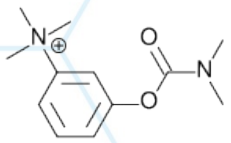
Normal neuromuscular function



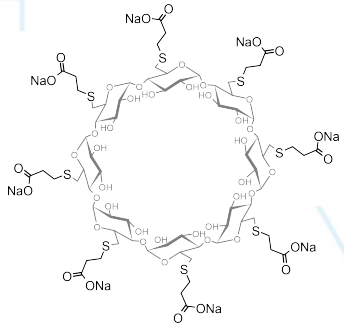
Normal neuromuscular blocade

Common antidote: Neostigmine

Sugammadex reversal

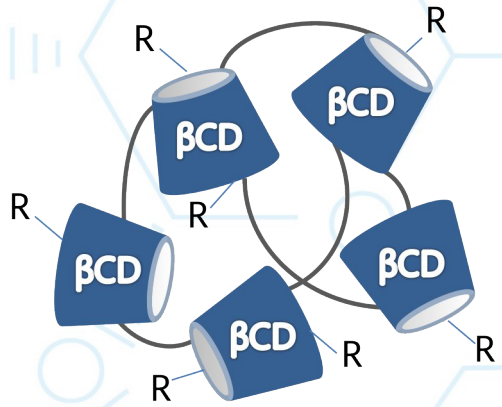


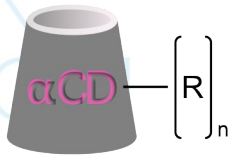
Neostigmine has systemic side effects, while Sugammadex is excreted in the urine

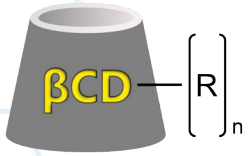


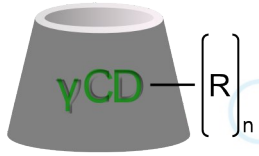
Antidotes - LMWH

CycloLab developed a new family of cyclodextrins having huge affinity for different types of low molecular weight heparins









Interaction studies

NMR TLC

CE ITC

Dynamic Light Scattering

Ex vivo human blood

Antidotes - LMWH

Application-1

Sensors in bedside detection of heparin levels

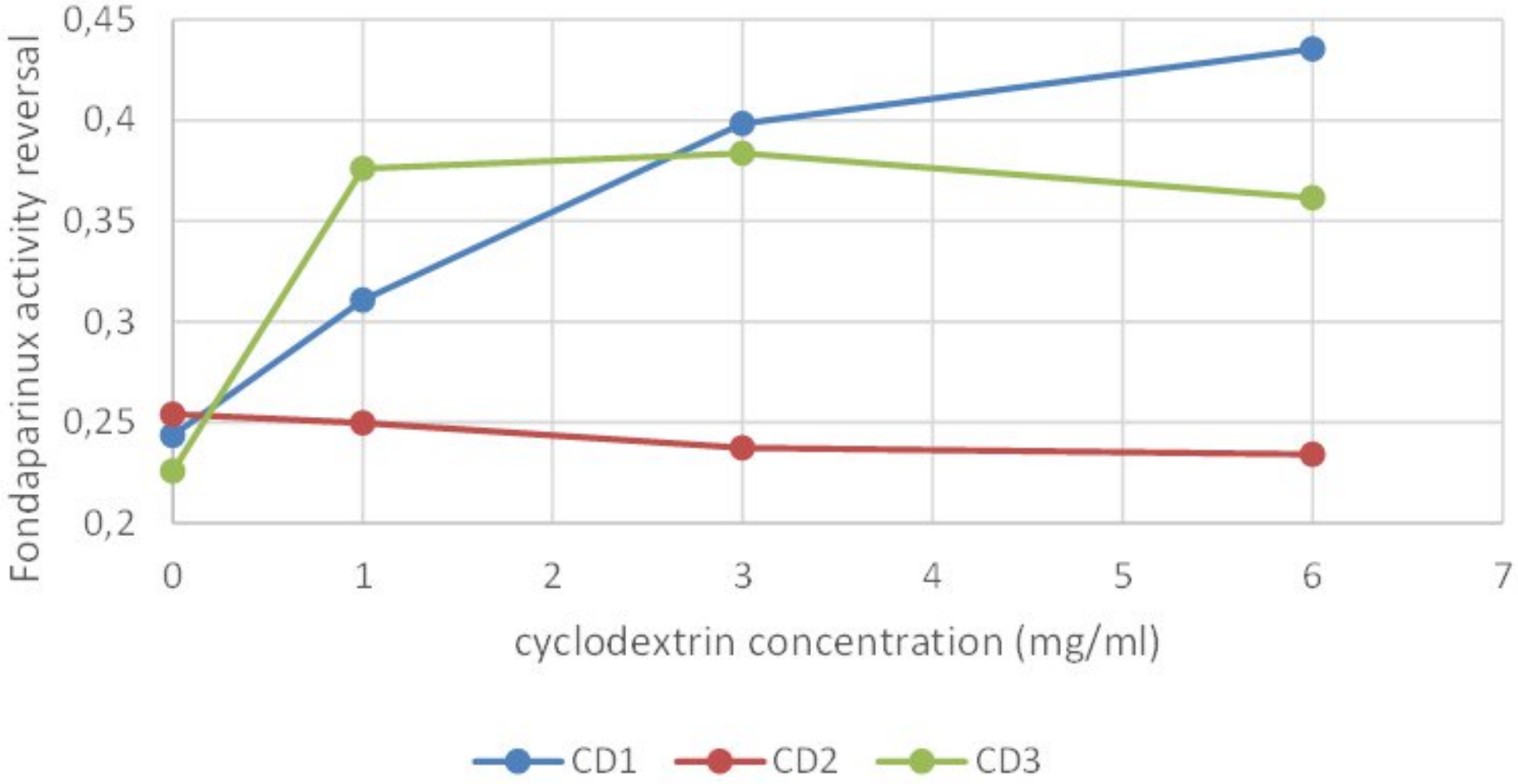
Application-2

Heparin traps, as reversal agents for surgical procedures

- Promising market size, as heparins are the second most prescribed drugs after insulin
- The effective and selective universal heparin antidote would address an unmet clinical need
- Affinity of CDs towards several LMWHs is in the same range as that of other drug candidates
- The designed CD family has excellent toxicological profile and it is well tolerable
- Capability of highly selective binding and this kind of „antagonizing” effect of cyclodextrins has already been proven (Sugammadex)

Antidotes - LMWH

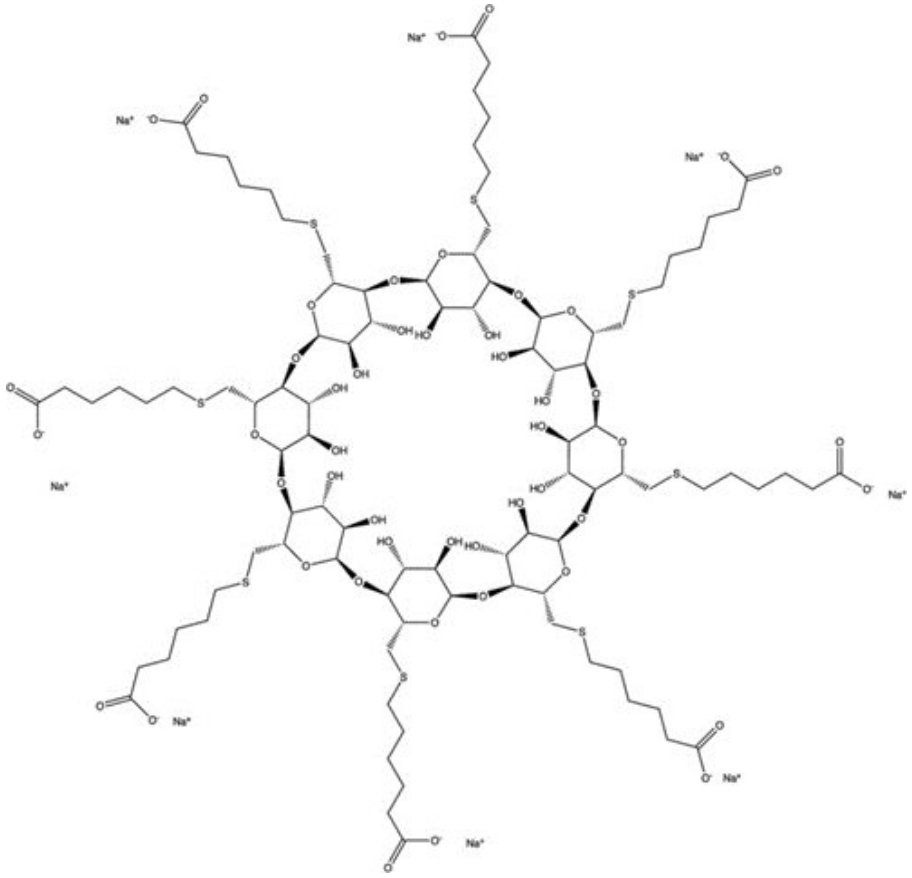
Whole blood experiments on antagonizing Fondaparinux (3 cyclodextrins shown)



Antidotes - universal reversal agent for anticoagulants

Reversing the effects in vitro of all direct oral anticoagulants and vitamin K antagonists, such as warfarin and platelet aggregation inhibitors, such as clopidogrel

- Concentration dependent reversing effect
- developed as a ready-to-use solution for injection so eliminating a time-consuming preparation step
- Under clinical development by Alveron Pharma (Phase I)



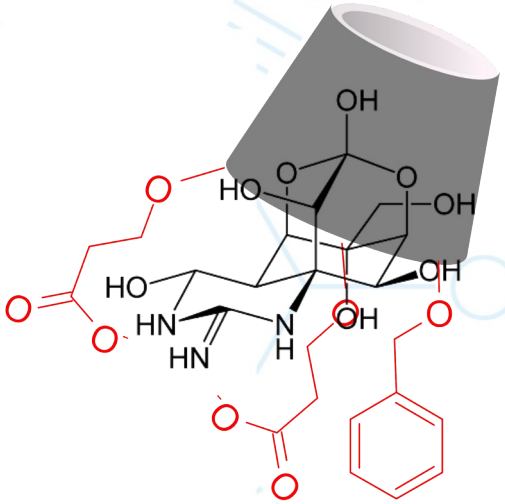
Joost C.M. Meijers, Kamran Bakhtiari, Alex Zwiers, Stephan L.M. Peter: OKL-1111, A modified cyclodextrin as a potential universal reversal agent for anticoagulants. Thrombosis Research 227. 2023, 17-24. https://doi.org/10.1016/j.thromres.2023.05.003

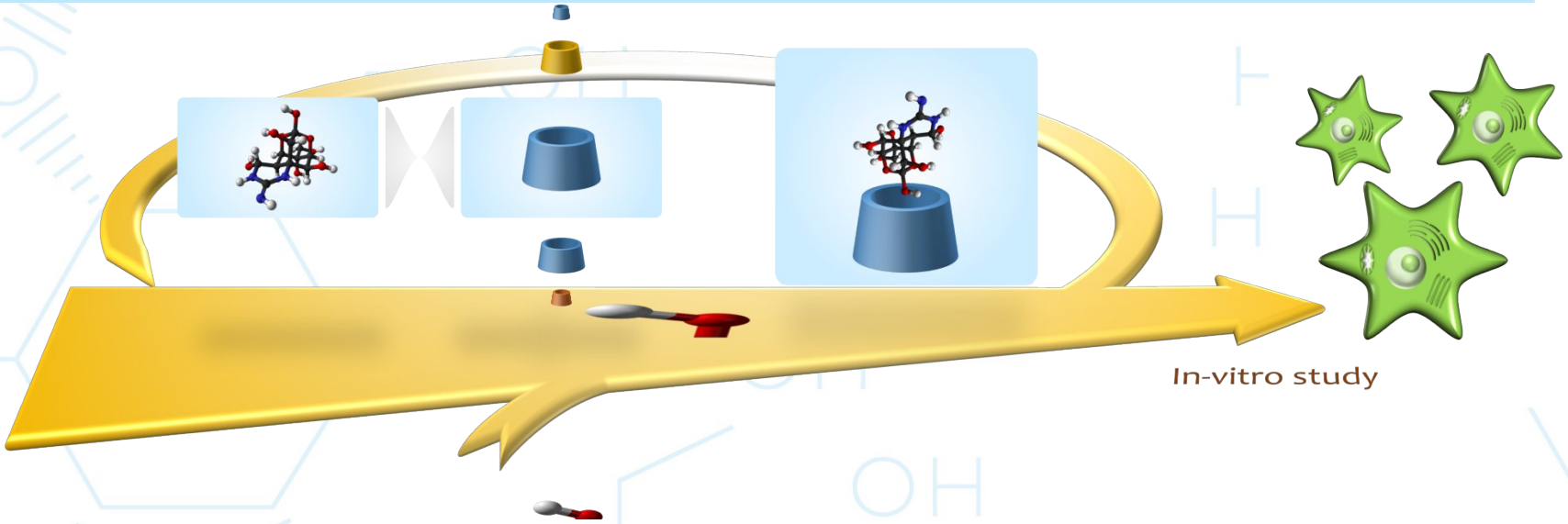
Antidotes - tetradotoxin

Selective and efficient antidotes could be developed for a wide variety of toxins

Cyclodextrins have shown great safety profile for all types of administration

Unique CDs can be designed for each toxin with a selective binding





Antidotes – conotoxin, box jellyfish poison

Box jellyfish: Australian researchers find antidote for world's most venomous creature

Jellyfish's sting carries enough venom to kill more than 60 people

▲ University of Sydney researchers have found a 'molecular antidote' that blocks the symptoms of a box jellyfish sting if applied to the skin within 15 minutes. Photograph: Melanie Stetson Freeman/Christian Science Monitor/Getty Images

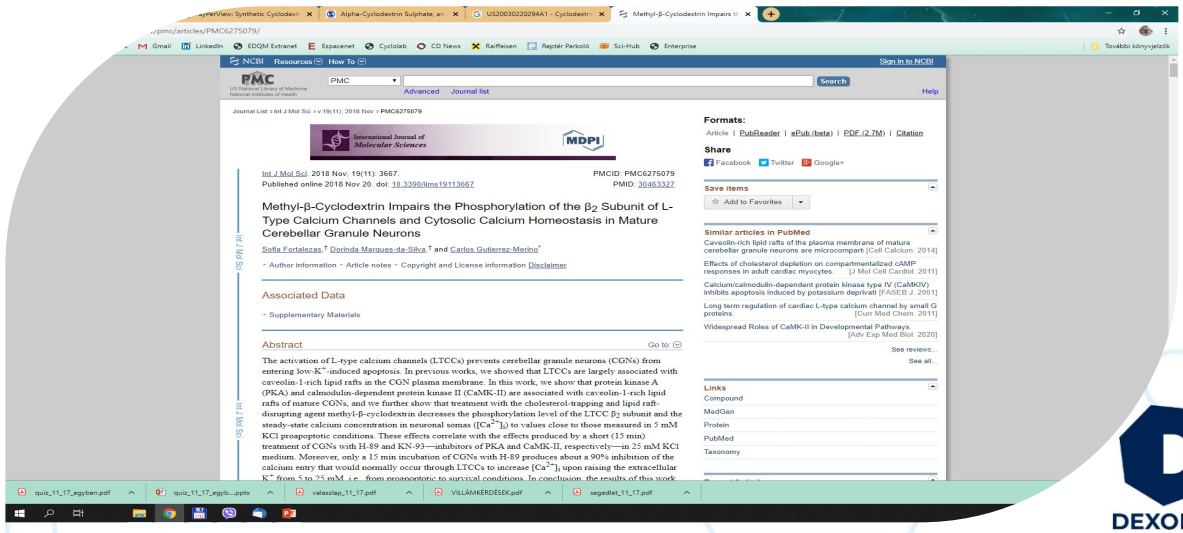
An antidote has been discovered for the world's most venomous creature, the Australian box jellyfish.

nature communications

Article | Open Access | Published: 30 April 2019

Molecular dissection of box jellyfish venom cytotoxicity highlights an effective venom antidote

Man-Tat Lau, John Manion, Jamie B. Littleboy, Lisa Oyston, Thang M. Khuong, Qiao-Ping Wang, David T. Nguyen, Daniel Hesselson, Jamie E. Seymour & G. Gregory Neely



PNAS

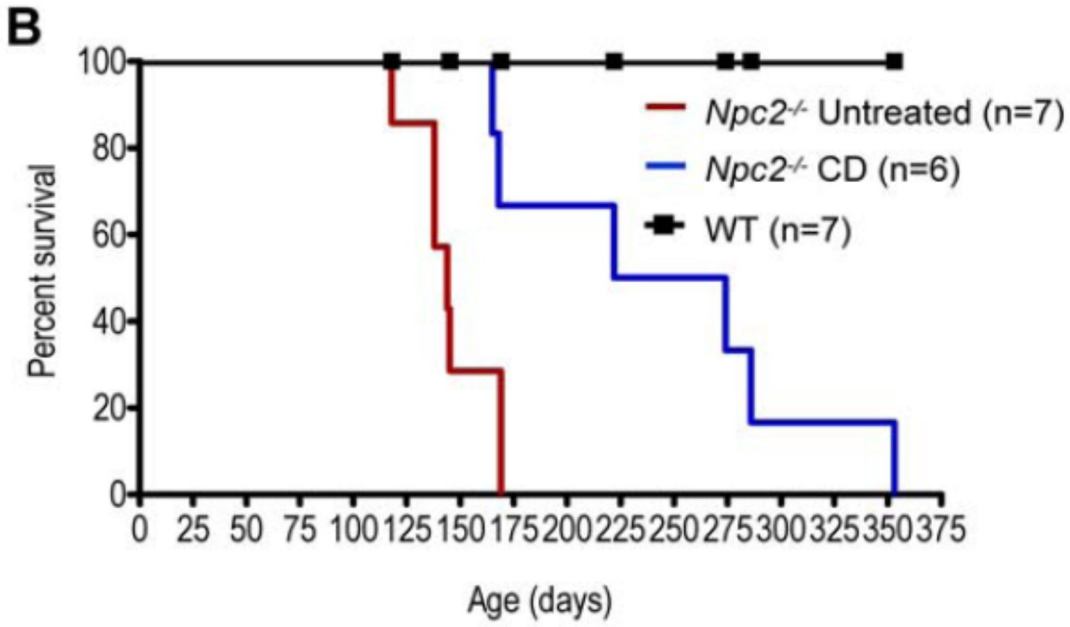
Cyclodextrin overcomes deficient lysosome-to-endoplasmic reticulum transport of cholesterol in Niemann-Pick type C cells

Lina Abi-Mosleh, Rodney E. Infante, Arun Radhakrishnan[1], Joseph L. Goldstein[2], and Michael S. Brown[2]

Department of Molecular Genetics, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-9046

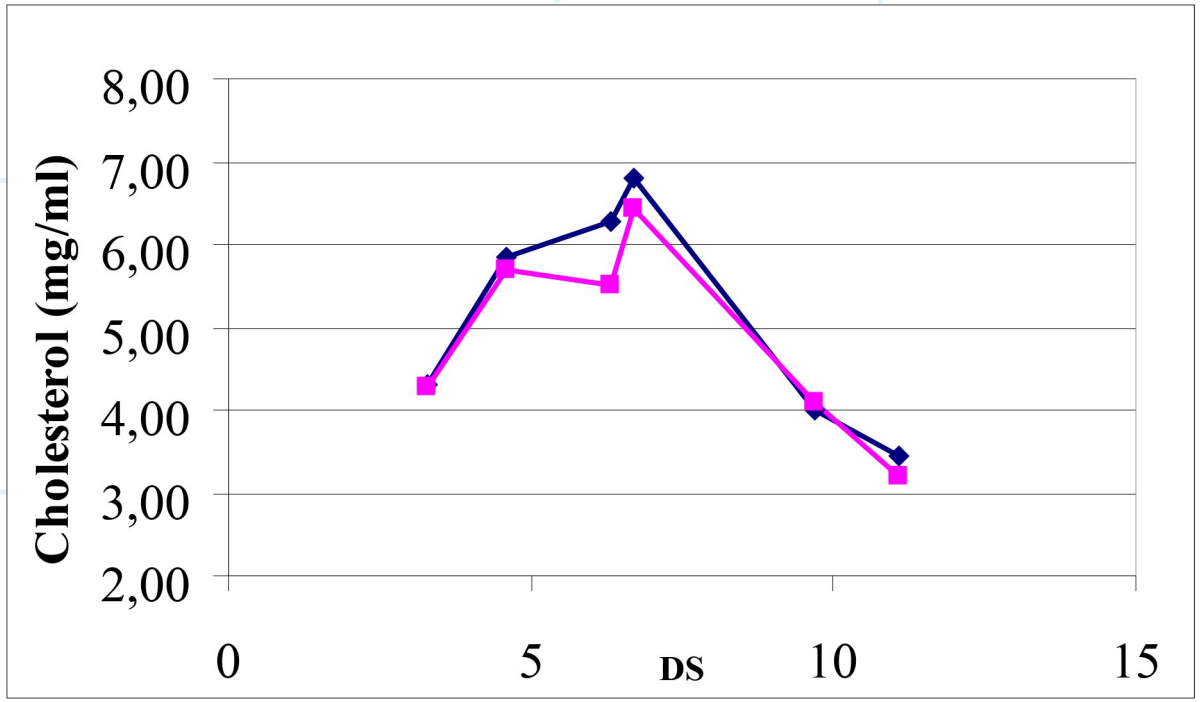
Contributed by Joseph L. Goldstein, September 23, 2009 (sent for review September 15, 2009)

The Nobel Prize in Physiology or Medicine 1985 was awarded jointly to Michael S. Brown and Joseph L. Goldstein "for their discoveries concerning the regulation of cholesterol metabolism”



Is cholesterol the therapeutic target in the therapy of NPC?

Aqueous solubility of Cholesterol in the presence of 10% HPBCD of different DS



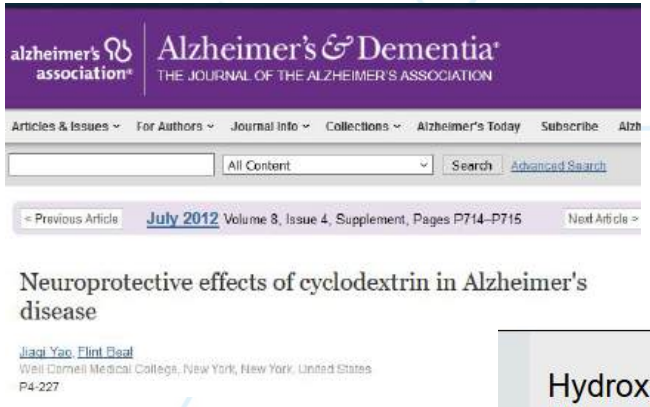
Malanga, M., Szemán, J., Fenyvesi, É., Puskás, I., Csabai K., Gyémánt Gy., Fenyvesi, F., Szente, L.
“BACK TO THE FUTURE”: A NEW LOOK AT HYDROXYPROPYL BETA-CYCLODEXTRINS
Journal of Pharmaceutical Sciences, Volume 105, Issue 9, 2921–2931 (2016)

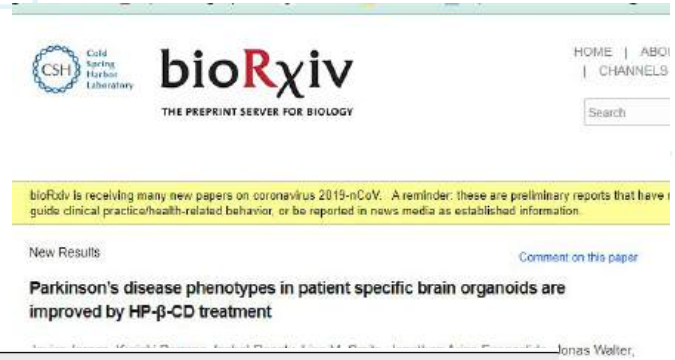
Neurodegenerative

The success of NPC therapy opened up a lot of opportunities for other diseases like Alzheimer's, lysosomal and several neurodegenerative diseases

Ongoing clinical trials for NPC treatment:

- Mallinckrodt (VTS-270)
- Cyclo Therapeutics (Trappsol)

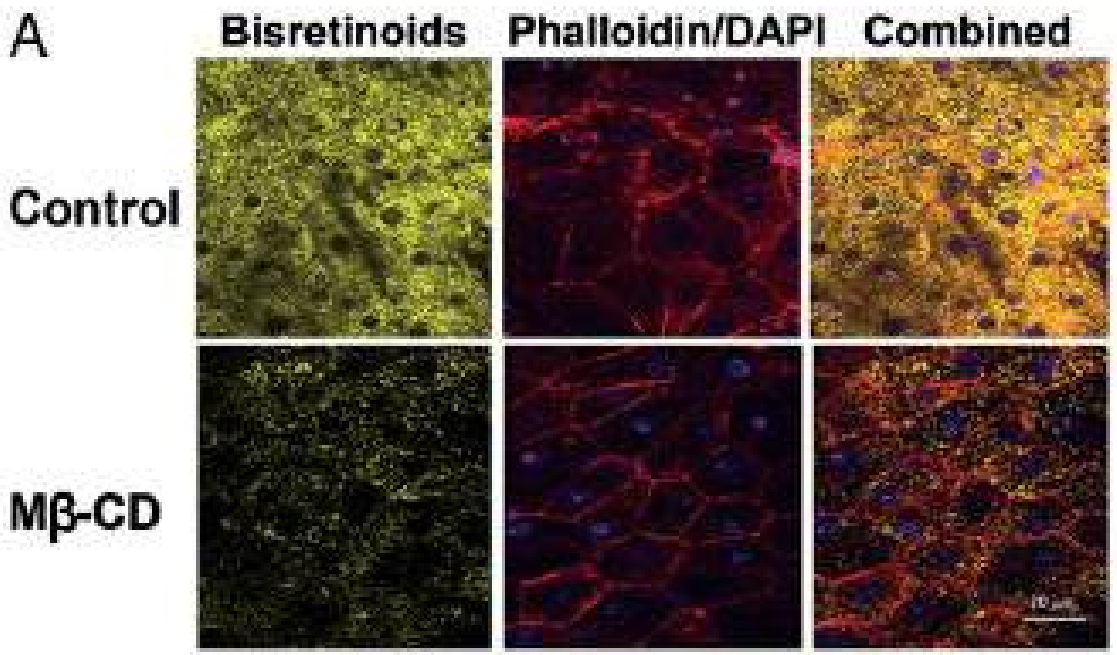




DEXOLVE™

AMD – Lipofuscin removal

Cyclodextrins have been shown to efficiently remove lipofuscin (bisretinoids) from the eye and thus treat lysosomal storage diseases, like age-related macula degeneration



PNAS

Beta cyclodextrins bind, stabilize, and remove lipofuscin bisretinoids from retinal pigment epithelium

Marcelo M. Nociari[a,1], Guillermo L. Lehmann[a], Andres E. Perez Bay[a], Roxana A. Radu[b], Zhichun Jiang[b], Shelby Goicochea[a], Ryan Schreiner[a], J. David Warren[c], Jufang Shan[d], Ségolène Adam de Beaumais[e], Mickaël Ménand[e], Matthieu Sollogoub[e], Frederick R. Maxfield[c], and Enrique Rodriguez-Boulan[a,1]

[a]Margaret Dyson Vision Research Institute, [c]Department of Biochemistry, and [d]Department of Physiology, Weill Cornell Medical College of Cornell University, New York, NY 10065; [b]Stein Eye Institute, Department of Ophthalmology, University of California, Los Angeles, CA 90095; and [e]Sorbonne Universités, Université Pierre et Marie Curie Paris 06, Centre National de la Recherche Scientifique, Unité Mixte de Recherche 8232, Institut Parisien de Chimie Moléculaire, 75005 Paris, France

Edited by Janet R. Sparrow, Columbia University, New York, NY, and accepted by the Editorial Board February 27, 2014 (received for review January 14, 2014)

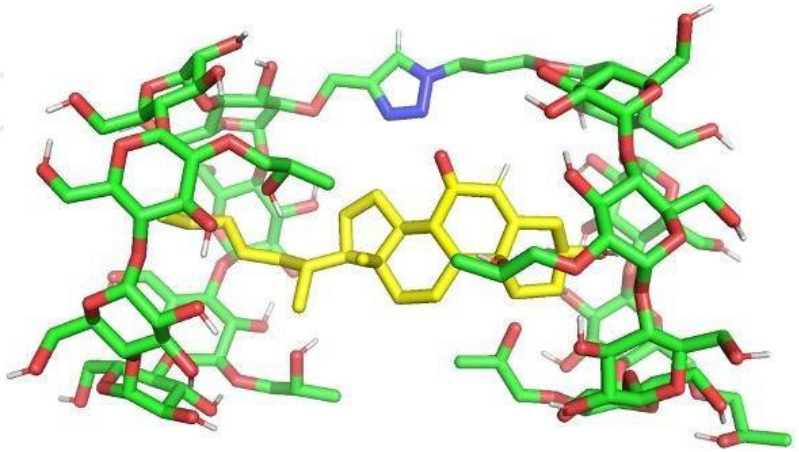
Accumulation of lipofuscin bisretinoids (LBs) in the retinal pigment epithelium (RPE) is the alleged cause of retinal degeneration in genetic blinding diseases (e.g., Stargardt) and a possible etiological agent for age-related macular degeneration. Currently, there are no approved treatments for these diseases; hence, agents that efficiently remove LBs from RPE would be valuable therapeutic

Here we report that a family of modified cyclic oligosaccharides, beta cyclodextrins (β-CDs), formed by seven D-glucose units, can encapsulate the hydrophobic arms of A2E within their nonpolar cavity, protect A2E from oxidation, and remove A2E from RPE cells. Our data demonstrate a direct correlation between the ability of β-CDs to perform these protective functions and their

Cardiovascular diseases - atherosclerosis

Cyclodextrin dimers against 7-ketocholesterol (7-KC)

- **7-KC is the major oxidation product of cholesterol, and one of the most toxic metabolites is associated with several diseases, like cardiovascular diseases, age-related macular degeneration, and Alzheimer's disease. 7-KC can be found in high amount in human atherosclerotic plaque.**
- **A custom-tailored cyclodextrin dimer was designed to specifically bind 7-KC. Several studies were preformed to better understand the complex of CD and 7-KC.**



Ghazaiel et al. 7-Ketocholesterol: Effects on viral infections and hypothetical contribution in COVID-19. The Journal of Steroid Biochemistry and Molecular Biology 212, 2021, 105939. doi: 10.1016/j.jsbmb.2021.105939

Anticancer agent

Journal List › Biomed Res Int › v.2015; 2015 › PMC4637021

BioMed Research International — IMPACT FACTOR 2.48

Biomed Res Int. 2015; 2015: 198268. Published online 2015 Oct 25. doi: 10.1155/2015/198268 PMCID: PMC4637021

A Comprehensive Review on Cyclodextrin-Based Carriers for Delivery of Chemotherapeutic Cytotoxic Anticancer Drugs

Bina Gidwani and Amber Vyas*

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BEILSTEIN JOURNAL OF NANOTECHNOLOGY

Development of polycationic amphiphilic cyclodextrin nanoparticles for anticancer drug delivery

Gamze Varan[1], Juan M. Benito[2], Carmen Ortiz Mellet[3] and Erem Bilensoy*[1,4]

Full Research Paper — Open Access

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Beilstein J. Nanotechnol. **2017,** *8,* 1457–1468. doi:10.3762/bjnano.8.145

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Guest Editor: V. Sivakov

SCIENTIFIC REPORTS

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Potential use of Folate-appended Methyl-β-Cyclodextrin as an Anticancer Agent

Risako Onodera, Keiichi Motoyama, Ayaka Okamatsu, Taishi Higashi & Hidetoshi Arima

Scientific Reports 3, Article number: 1104 (2013)
doi:10.1038/srep01104
Download Citation

Received: 27 September 2012
Accepted: 10 December 2012
Published online: 22 January 2013

Cancer immunotherapy Drug development Targe

Back to Journals » International Journal of Nanomedicine » Volume 12

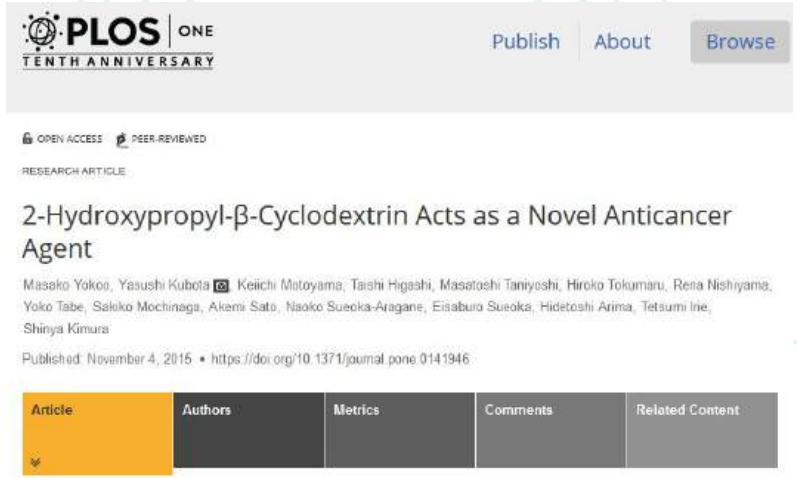
ORIGINAL RESEARCH

Induction of mitophagy-mediated antitumor activity with folate-appended methyl-β-cyclodextrin

Abstract Fulltext Metrics Get Permission

Authors Kameyama K, Motoyama K, Tanaka N, Yamashita Y, Higashi T, Arima H

Received 30 January 2017



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RESEARCH ARTICLE

2-Hydroxypropyl-β-Cyclodextrin Acts as a Novel Anticancer Agent

Masako Yokoo, Yasushi Kubota, Keiichi Motoyama, Taishi Higashi, Masatoshi Taniyoshi, Hiroko Tokumaru, Rena Nishiyama, Yoko Tabe, Saioko Mochinaga, Akemi Sato, Naoko Sueoka-Aragane, Eisaburo Sueoka, Hidetoshi Arima, Tetsumi Irie, Shinya Kimura

Published: November 4, 2015 • https://doi.org/10.1371/journal.pone.0141946

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RESEARCH ARTICLE VIROLOGY

Modified cyclodextrins as broad-spectrum antivirals

Samuel T. Jones[1,2,*], Valeria Cagno[1,3,*], Matej Janeček[1], Daniel Ortiz[4], Natalia Gasilova[4], Jocelyne Piret[5], Matteo Gasbarri[1],...
+ See all authors and affiliations

Science Advances 29 Jan 2020:
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Article Figures & Data Info & Metrics eLetters PDF

US 20030220294A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2003/0220294 A1**

Wallace et al. (43) **Pub. Date: Nov. 27, 2003**

(54) **CYCLODEXTRIN COMPOSITIONS AND METHODS OF TREATING VIRAL INFECTIONS**

(76) Inventors: **Kendall B. Wallace**, Duluth, MN (US); **Muhammad A. Khan**, Duluth, MN (US); **Robert M. Carlson**, Duluth, MN (US); **Stephen Rice**, Minneapolis, MN (US); **Mervin Kent Froberg**, Danbury, WI (US)

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Minneapolis, MN 55402 (US)

(21) Appl. No.: **10/394,449**

(22) Filed: **Mar. 21, 2003**

Related U.S. Application Data

(60) Provisional application No. 60/366,429, filed on Mar. 21, 2002. Provisional application No. 60/456,112, filed on Mar. 19, 2003.

Publication Classification

(51) **Int. Cl.**[7] **A61K 31/724**; A61K 31/522
(52) **U.S. Cl.** **514/58**; 514/263.31

(57) **ABSTRACT**

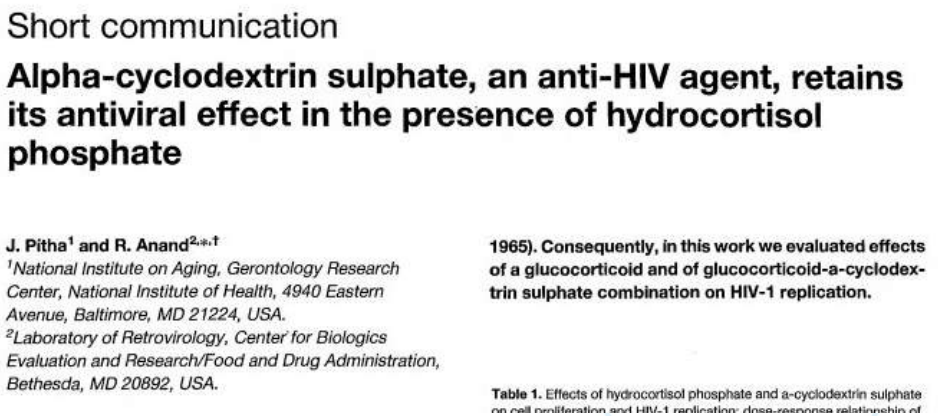
The present invention provides methods and therapeutic compositions for treating viral infections.

Pathobiology 1992;60:206–212
(DOI:10.1159/000163724)

Synthetic Cyclodextrin Derivatives Inhibit HIV Infection in vitro

Weiner D.B.[a] · Williams W.V.[b] · Weisz P.B.[c] · Greene M.I.[d]
Author affiliations

[a]Wistar Institute, [b]Department of Medicine, [c]Department of Chemical Engineering, and [d]Department of Pathology and Laboratory, University of Pennsylvania, Philadelphia, Pa., USA



Antiviral Chemistry & Chemotherapy (1993) 4(1), 65–66

Short communication

Alpha-cyclodextrin sulphate, an anti-HIV agent, retains its antiviral effect in the presence of hydrocortisol phosphate

J. Pitha[1] and R. Anand[2,*,†]
[1]National Institute on Aging, Gerontology Research Center, National Institute of Health, 4940 Eastern Avenue, Baltimore, MD 21224, USA.
[2]Laboratory of Retrovirology, Center for Biologics Evaluation and Research/Food and Drug Administration, Bethesda, MD 20892, USA.

1965). Consequently, in this work we evaluated effects of a glucocorticoid and of glucocorticoid-a-cyclodextrin sulphate combination on HIV-1 replication.

Table 1. Effects of hydrocortisol phosphate and a-cyclodextrin sulphate

Antibacterial effect

US 2006024 7208A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2006/0247208 A1**

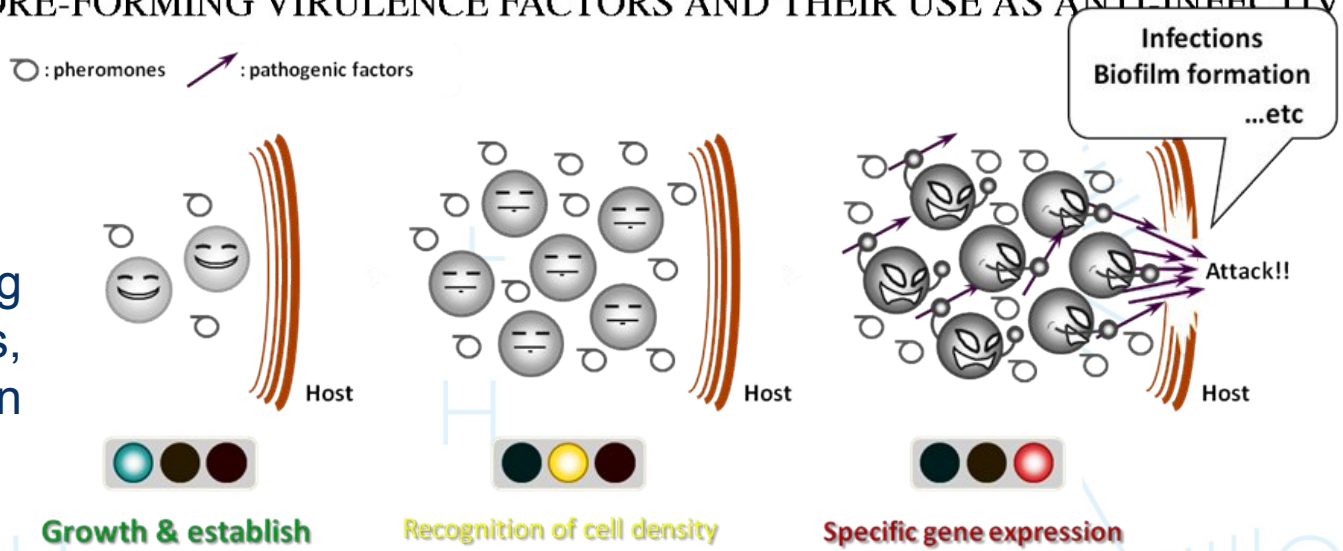
Karginov et al. (43) **Pub. Date: Nov. 2, 2006**

(54) **B-CYCLODEXTRIN DERIVATIVES AND THEIR USE AGAINST ANTHRAX LETHAL TOXIN**

Publication Classification

(54) Title: BLOCKERS OF PORE-FORMING VIRULENCE FACTORS AND THEIR USE AS ANTI-INFECTIVES

The use of cyclodextrins is possible in inhibiting quorum sensing by binding the signal molecules, thus preventing microbes to reach the population density



Cell density dependent gene expression in quorum sensing
(e.g. virulence expression)

Antibacterial effect

The cell wall has negative charge due to the dissociation of acidic groups such as carboxyl and phosphate. Chemicals with positive charge can penetrate into the cell wall disturbing its functions (amino- and thiadiazole CDs showed broad spectrum or narrow spectrum antibacterial activity).

Per- 6-(4-methoxylbenzyl)-amino-6-deoxy-beta-CD HCl salt combined with methicillin showed 30–60-time enhancement in efficacy against MRSA (reduced MIC values) compared to the drug alone or to its HPBCD complex.

Published: 29 May 2013

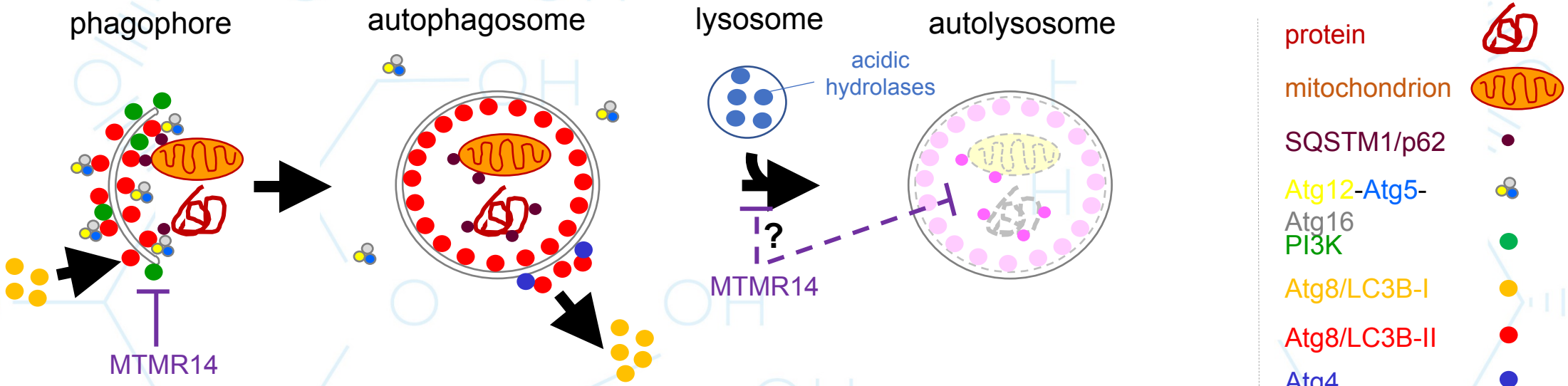
Methicillin/per-6-(4-methoxylbenzyl)-amino-6-deoxy-β-cyclodextrin 1:1 complex and its potentiation *in vitro* against methicillin-resistant *Staphylococcus aureus*

Jing-Zhen Deng

The Journal of Antibiotics **66**, 517–521(2013) | Cite this article

Inducing autophagy

- Autophagy (cellular self-eating) is a highly conserved, lysosome-mediated, self-degradation process of essentially all eukaryotic cells.
- Defects in autophagy can lead to various degenerative diseases, such as cancer, neuronal demise, tissue atrophy and fibrosis, and immune deficiency, as well as an accelerated rate of aging
- Cyclolab explores the effect of selected cyclodextrins and cyclodextrin derivatives, which have the potential to be widely used in the pharma industry as delivery compounds of drugs and other active substances, on autophagic activity.



CycloLab service portfolio and pipeline programs related to NCE development

Early phase drug development

Customization of CD enabled formulations

Investigation of changes in physico-chemical properties

In vitro bioequivalence studies

Design in vitro studies to support bioequivalence of a CD enabled formulation.

IP services and consultation

Analytical services

Method development, validation

HPLC, GC, CE, UV, MS, NMR, IR

Stability studies

CD-guest interaction studies

Assay, impurity tests

PIPELINE FOR PARTNERING

Antivirals (SARS-CoV-2, Zika, Dengue), protective gear

Lysosomal storage diseases (Niemann Pick C)

Neurodegenerative diseases (Alzheimer's)

Antibacterials (Quorum quenching)

Sugammadex (technology, analytical support and impurity supply)

CycloLab service portfolio

Feasibility study

Running a short feasibility study with your molecule free of charge

Proof of concept to consider CD based formulations

CycloLab Grant

CycloLab offers a unique possibility to collaborate on creating novel and interesting cyclodextrins under the terms of the CycloLab Grant

The proposal after application is thoroughly evaluated by CycloLab

If the application is approved, the cyclodextrin is provided free of charge for the beneficiary

GLOBAL FOOTPRINT OF CYCLOLAB

EUROPE 97

Executed R&D projects: 97
Key market for Cyclolab's Dexolve

HUNGARY
CYCLOLAB HEADQUARTER

NORTH AMERICA 48

Executed R&D projects: 48
Key market for Cyclolab's Dexolve,
DMF in U.S. and Canada

SOUTH-AMERICA 9

Executed R&D projects: 9
Emerging market for Cyclolab's Dexolve

AFRICA 1

Executed R&D projects: 1
Emerging market for Cyclolab's Dexolve

ASIA 44

Executed R&D projects: 44
Key market for Cyclolab's Dexolve,
DMF in China, South Korea

AUSTRALIA 2

Executed R&D projects: 2
Emerging market for Cyclolab's Dexolve

DEXOLVE™: BETADEX SULFOBUTYL ETHER SODIUM (SBECD)
2016 - 2022 NUMBER OF EXECUTED R&D PROJECTS: 201

Getting the best out of cyclodextrins

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