

GETTING THE BEST OUT OF CYCLODEXTRINS

Cyclodextrins as APIs



Cyclodextrins as antidotes

- Retinoid intoxication
- Sugammadex (on the market)
- 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

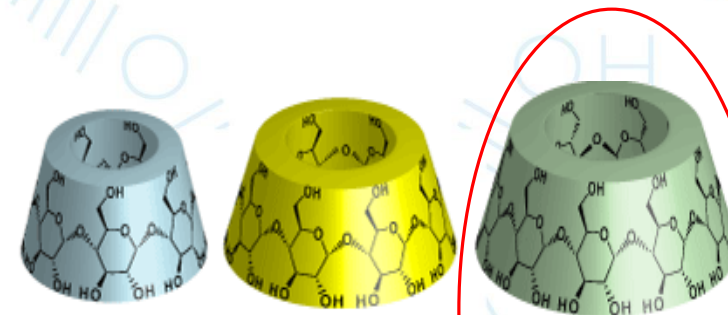


Sugammadex – Bridion®

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

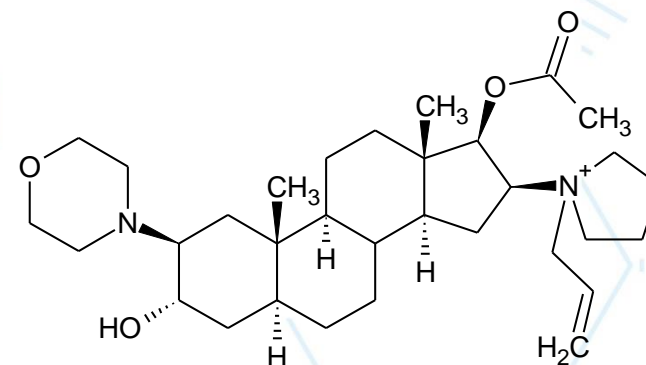
To form a highly stable non-covalent complex:

- 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®

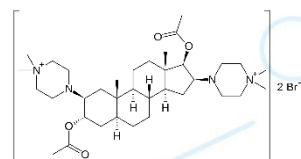
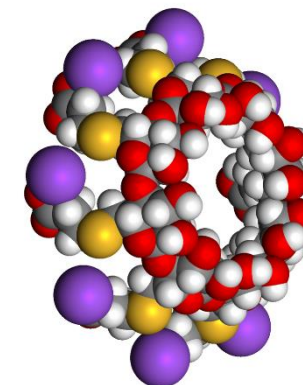
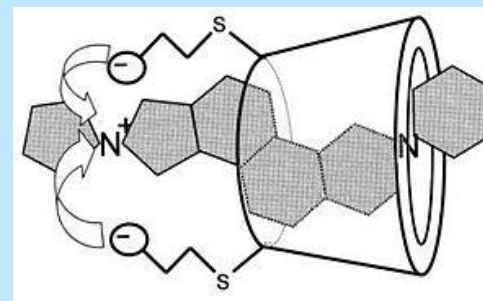


The 1st selective relaxant binding molecules to reverse neuromuscular blocking agents (NMBA) induced paralysis of skeletal muscles

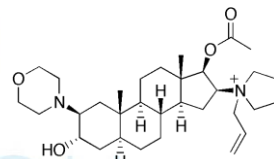
Approved in the EU (2008) and US (2015)

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

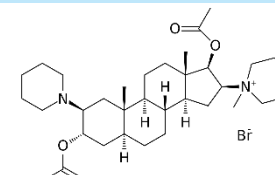
Reduced/eliminated adverse effects compared to neostigmine
(lower) affinity for vecuronium, pipecuronium and pancuronium, yet still working clinically



Pipecuronium



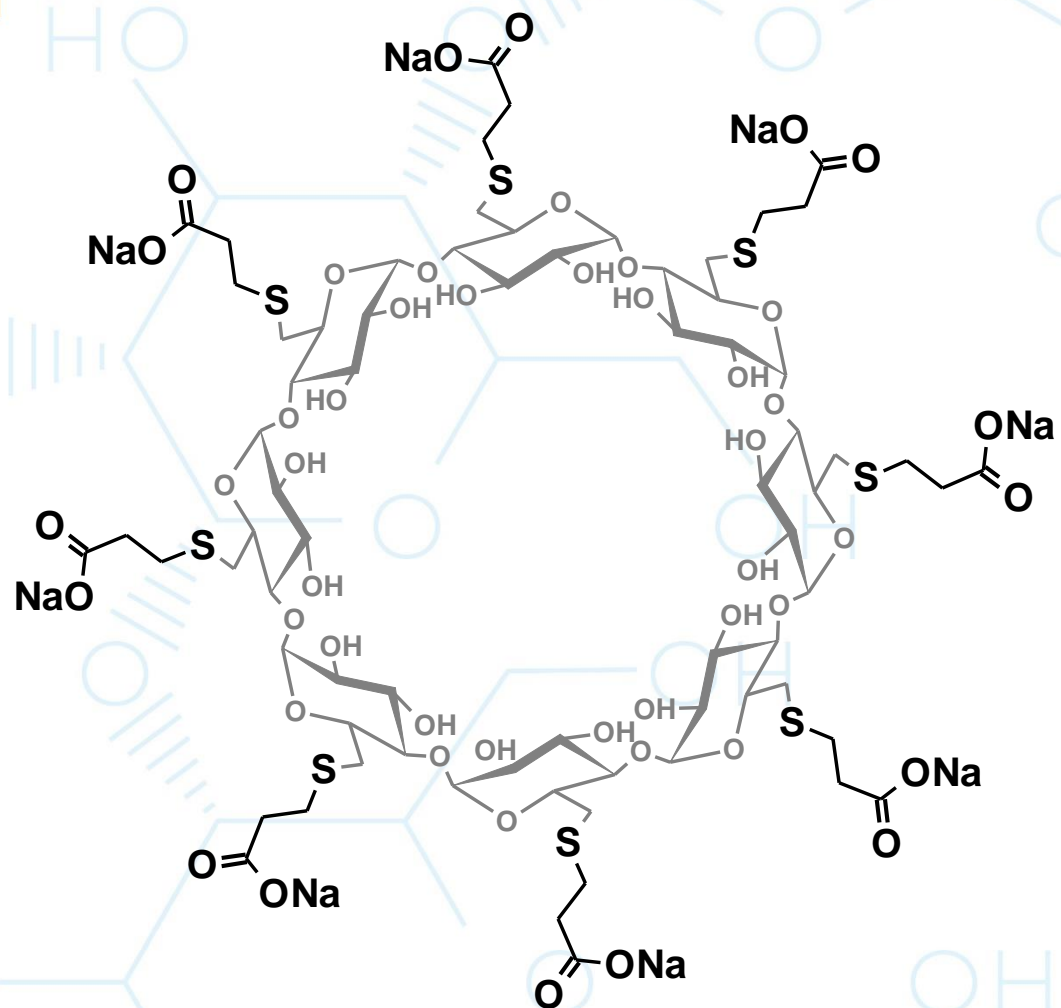
Rocuronium



Vecuronium



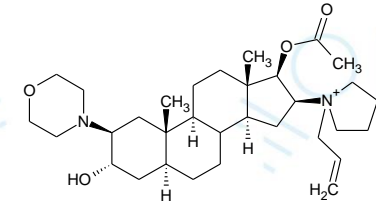
Sugammadex – Bridion®



Molecular mass: 2178.01



Clinical efficacy of Sugammadex



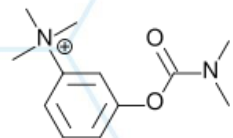
Normal neuromuscular function

Normal neuromuscular blockade

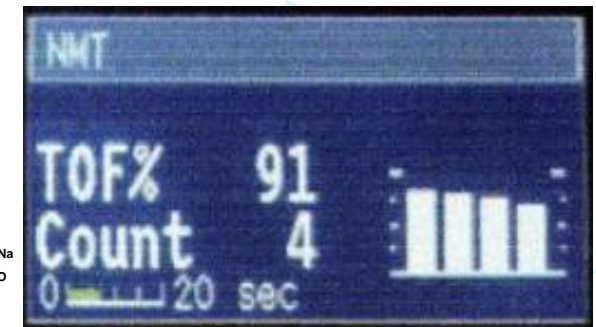
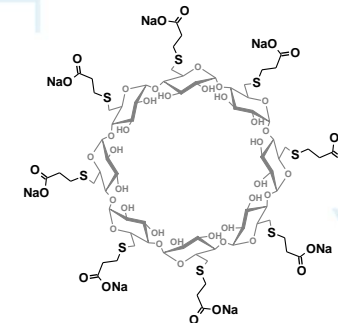


Common antidote: Neostigmine

Sugammadex reversal

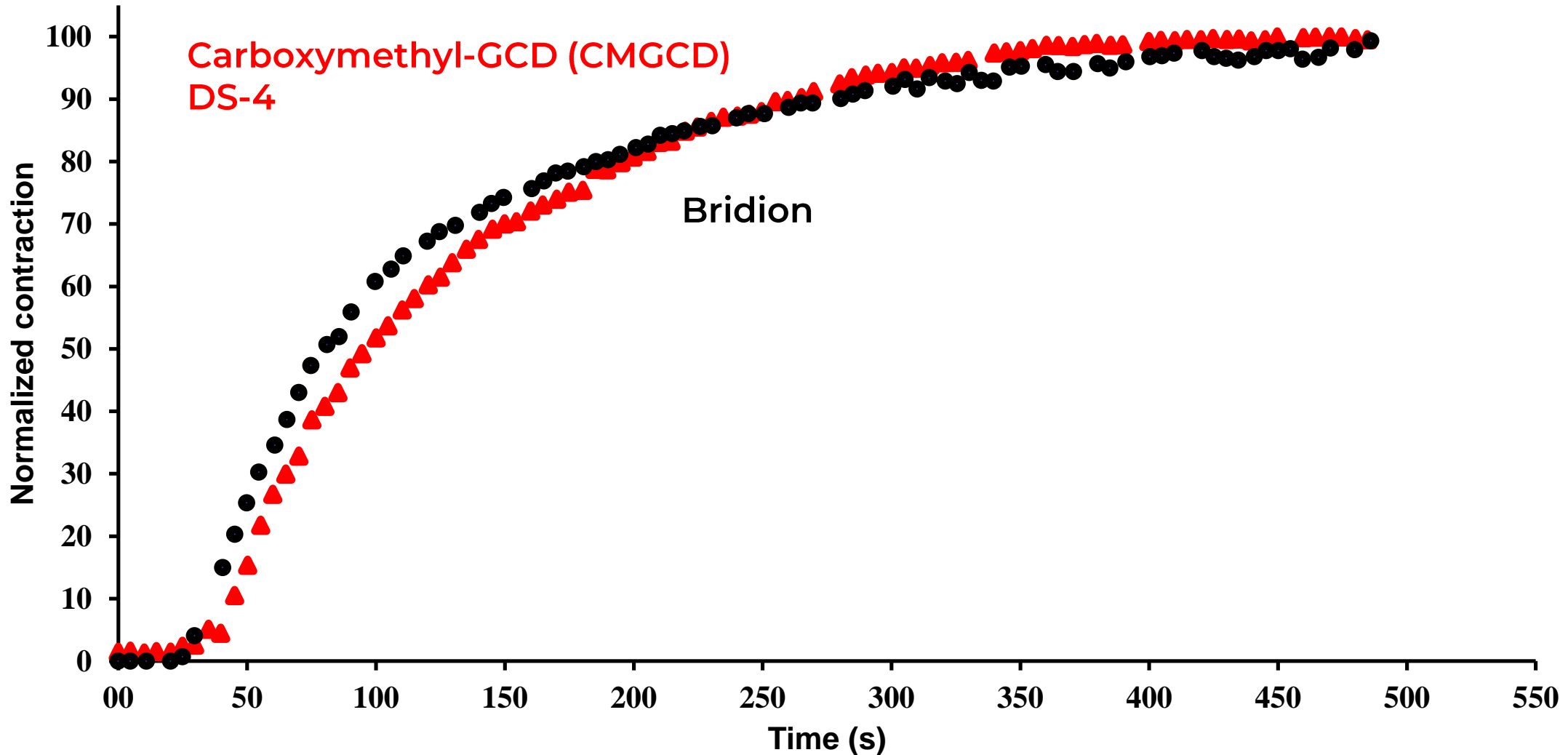


Neostigmine has systemic side effects, while Sugammadex is excreted in the urine

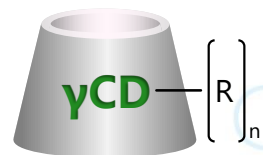
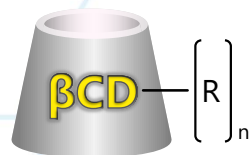
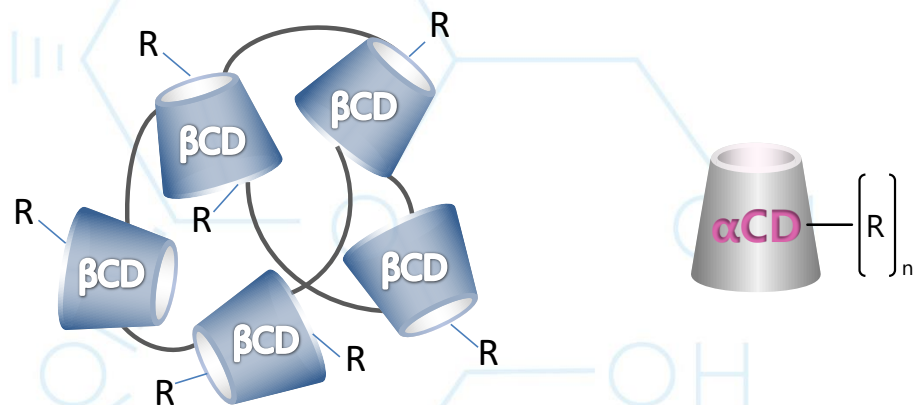


Sugammadex follow-ups

Time elapsed until the reversal of neuromuscular blockade induced with pipecuronium



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

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

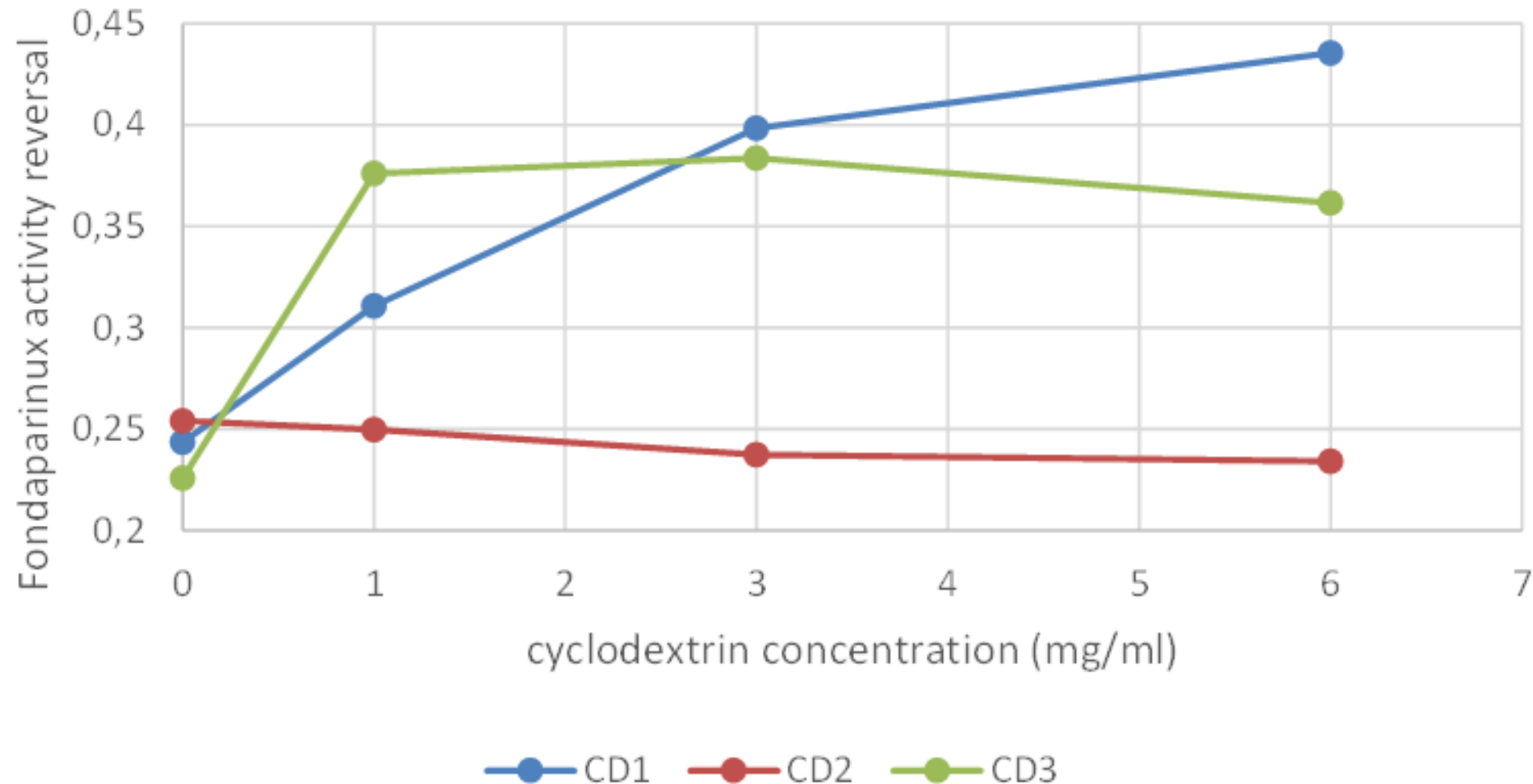
Affinity of CDs towards several LMWHs is in the same range as that of other drug candidates

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)



Whole blood experiments on antagonizing Fondaparinux (3 cyclodextrins shown)

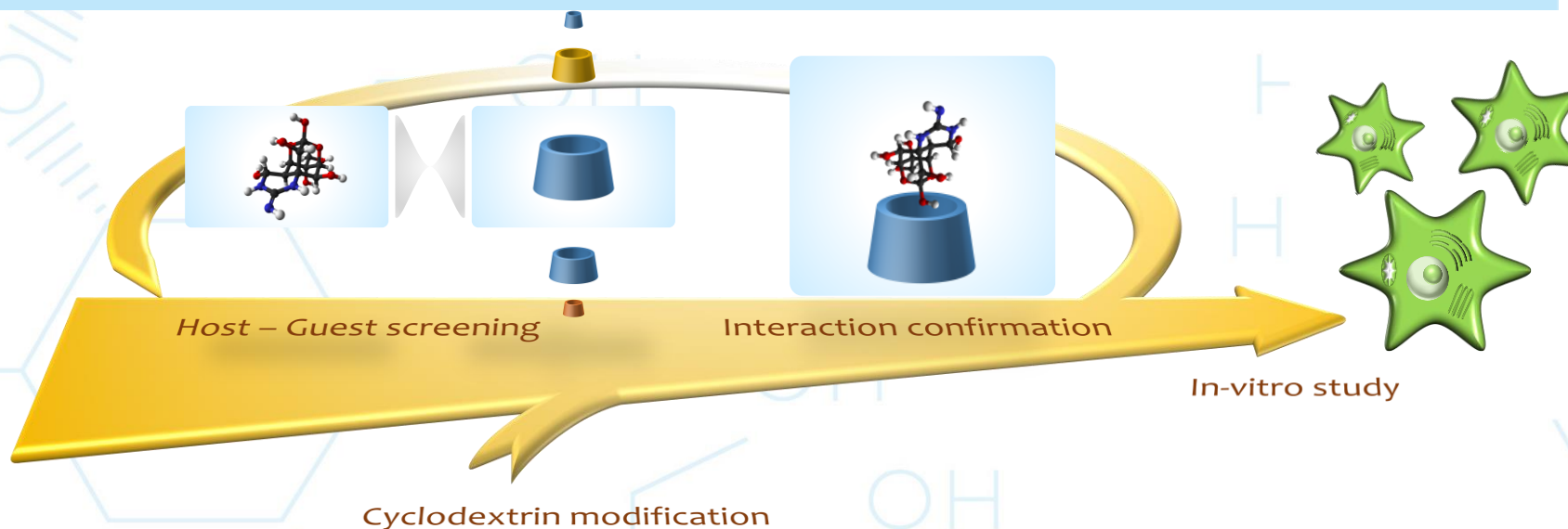
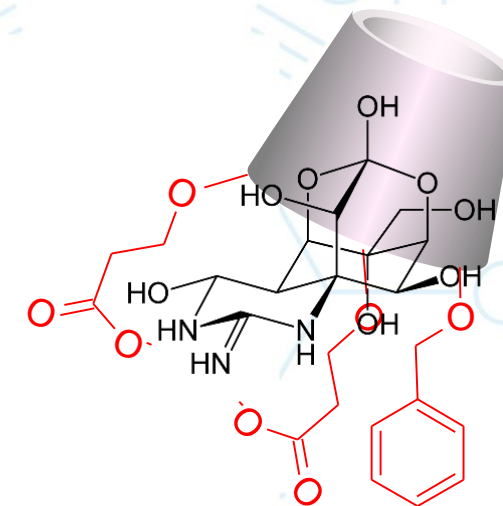


Antidotes - tetradoxin

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



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



International Journal of
Molecular Sciences



Int J Mol Sci. 2018 Nov; 19(11): 3667.
Published online 2018 Nov 20. doi: [10.3390/ijms19113667](https://doi.org/10.3390/ijms19113667)

PMCID: PMC6275079
PMID: [30463327](https://pubmed.ncbi.nlm.nih.gov/30463327/)

Methyl- β -Cyclodextrin Impairs the Phosphorylation of the β_2 Subunit of L-Type Calcium Channels and Cytosolic Calcium Homeostasis in Mature Cerebellar Granule Neurons

Sofia Fortalezas,[†] Dorinda Marques-da-Silva,[†] and Carlos Gutierrez-Merino^{*}

► Author information ► Article notes ► Copyright and License information [Disclaimer](#)



IPNAS

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

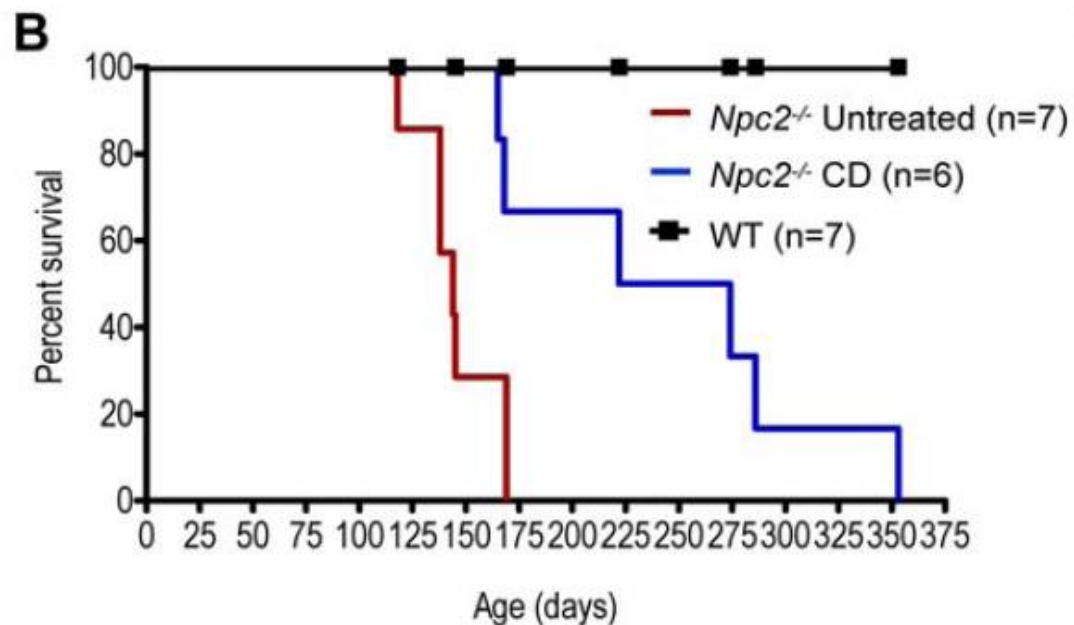
Lina Abi-Mosleh, Rodney E. Infante, Arun Radhakrishnan¹, Joseph L. Goldstein², and Michael S. Brown²

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)

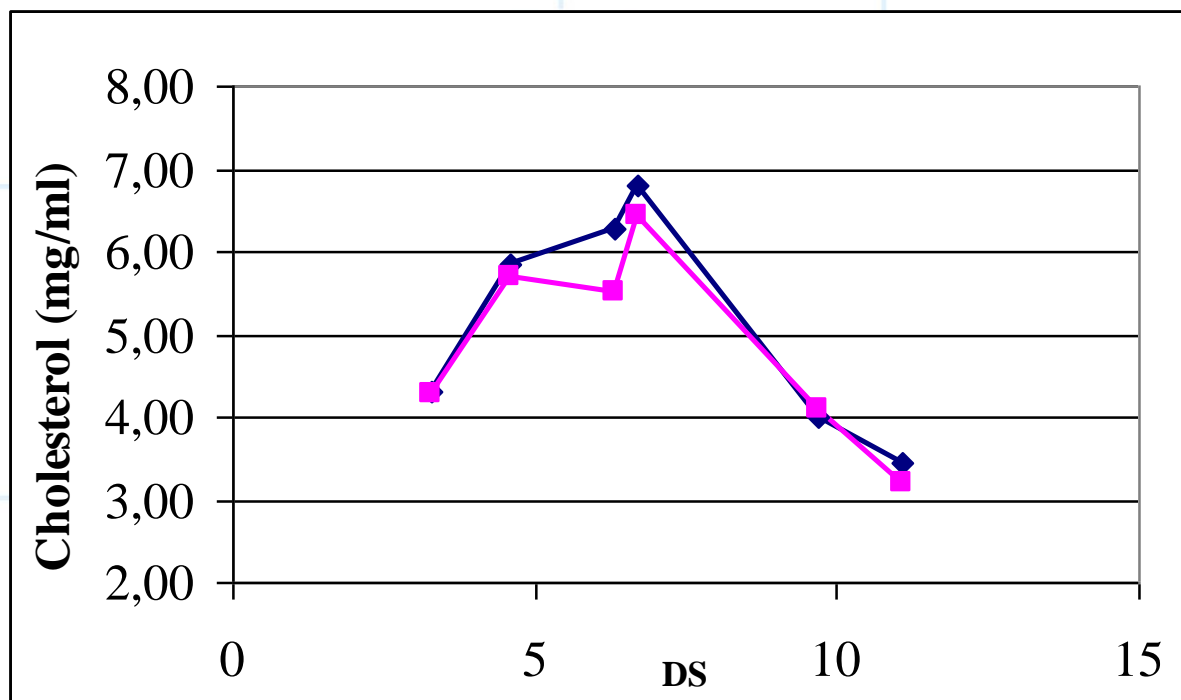


The Nobel Prize in Physiology or Medicine 1985 was awarded jointly to Michael S. Brown and Joseph L. Goldstein "for their discoveries concerning the regulation of cholesterol metabolism"



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)



Review

Cyclodextrins as Emerging Therapeutic Tools in the Treatment of Cholesterol-Associated Vascular and Neurodegenerative Diseases

Caroline Coisne^{1,*}, Sébastien Tilloy², Eric Monflier², Daniel Wils³, Laurence Fenart¹ and Fabien Gosselet^{1,*}

Alzheimer's & Dementia
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

Articles & Issues | For Authors | Journal Info | Collections | Alzheimer's Today | Subscribe | Alzh

All Content Search Advanced Search

< Previous Article July 2012 Volume 8, Issue 4, Supplement, Pages P714-P715 Next Article >

bioRxiv
THE PREPRINT SERVER FOR BIOLOGY

HOME | ABOUT | CHANNELS

Search

bioRxiv is receiving many new papers on coronavirus 2019-nCoV. A reminder, these are preliminary reports that have not yet been peer reviewed and should not be used to guide clinical practice/health-related behavior, or be reported in news media as established information.

New Results Comment on this paper

Parkinson's disease phenotypes in patient specific brain organoids are improved by HP-β-CD treatment

Jiaqi Yao, Daniel Ho, Noel Y. Calingasan, Nina H. Pipalia, Michael T. Lin, M. Flint Beal

Neuroprotective effects of cyclodextrin in Alzheimer's disease

Jiaqi Yao, Flint Beal
Weill Cornell Medical College, New York, New York, United States
P4-227

Hydroxypropyl-β-cyclodextrin Formulated in Nasal Chitosan Microspheres as Candidate Therapeutic Agent in Alzheimer's Disease

(E-pub Ahead of Print)

Author(s): Giovanna Rassu, Elisabetta Gavini, Antonio Carta, Antonella Obinu, Elena Piera Porcu, Paolo Giunchedi*

Journal Name: Current Drug Delivery

Rockefeller University Press JCB JEM JGP

JEM Journal of Experimental Medicine

search Advanced Search

Home Articles Reviews & Opinions Alerts About Submit Subscriptions

JEM Home » 2012 Archive » 17 December » 209 (13): 2501

Article

Neuroprotection by cyclodextrin in cell and mouse models of Alzheimer disease

Jiaqi Yao, Daniel Ho, Noel Y. Calingasan, Nina H. Pipalia, Michael T. Lin, M. Flint Beal

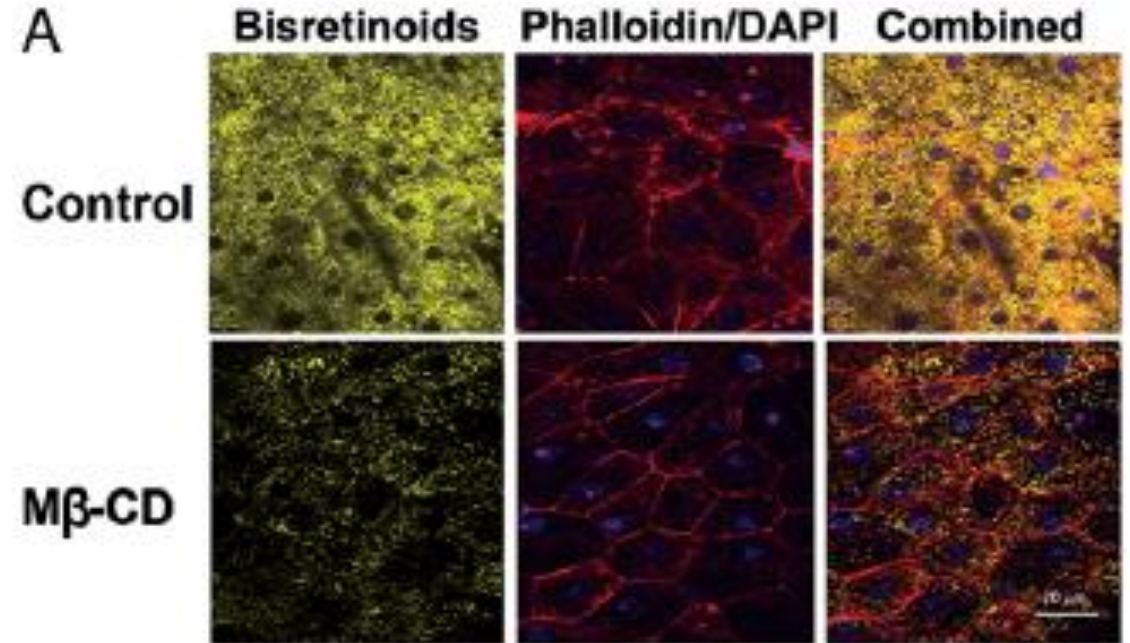
DOI: 10.1084/jem.20121239 | Published December 3, 2012 Check for updates

Article Figures & Data Info Metrics

Preview PDF Download PDF Alerts

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



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}

^aMargaret Dyson Vision Research Institute, ^bDepartment of Biochemistry, and ^cDepartment of Physiology, Weill Cornell Medical College of Cornell University, New York, NY 10065; ^dStein Eye Institute, Department of Ophthalmology, University of California, Los Angeles, CA 90095; and ^eSorbonne 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



Since the mechanism of action is not completely clarified, this leads to a lot of successful research in other areas

Article | [OPEN](#)

2-Hydroxypropyl-beta-cyclodextrin (HPβCD) reduces age-related lipofuscin accumulation through a cholesterol-associated pathway

Jason Gaspar, Jacques Mathieu & Pedro Alvarez

Scientific Reports 7, Article number: 2197 (2017)

doi:10.1038/s41598-017-02387-8

Download Citation

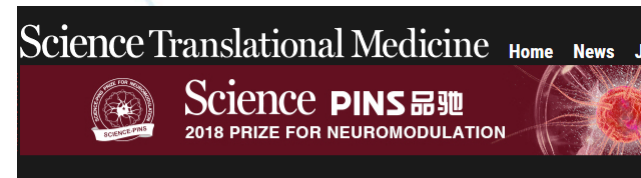
Drug development Lysosomes

Molecular medicine

Received: 27 October 2016

Accepted: 26 April 2017

Published online: 19 May 2017



SHARE RESEARCH ARTICLE | ATHEROSCLEROSIS

Cyclodextrin promotes atherosclerosis regression via macrophage reprogramming

Sebastian Zimmer^{1,*}, Alena Grebe^{2,*}, Siril S. Bakke^{2,3,4}, Niklas Bode¹, Bente Halvorsen⁵, ...
+ See all authors and affiliations

Science Translational Medicine 06 Apr 2016:
Vol. 8, Issue 333, pp. 333ra50
DOI: 10.1126/scitranslmed.aad6100

Article Figures & Data Info & Metrics eLetters PDF

You are currently viewing the abstract.

[View Full Text](#)

ScienceDaily

Your source for the latest research news

Follow

Just In:
Brain St

Will physicians ever really trust pharma as a knowledge source?
See 8 big pharma CEOs pitch their solutions to you.

Click here to be a part of EYEFORPHARMA BARCELONA
...join 1300+ senior executives
Europe's biggest Pharma

SD Health Tech Enviro Society Quirky

Science News

from research organizations

Cyclodextrin dissolves away cholesterol crystals
Drug used for rare disease may be able to treat heart disease

Date: April 8, 2016

Source: Norwegian University of Science and Technology

Summary: Cyclodextrin has been shown in mice to dissolve cholesterol crystals and prevent plaque formation. The drug is already approved for use in humans and could be tested in patients to treat atherosclerosis.

Share: f t G+ p in e

RELATED TOPICS

FULL STORY



MEDICAL HOME

LIFE SCIENCES HOME

Become a M

About News Health A-Z Drugs Medical Devices Thought L

Will physicians ever really trust pharma as a knowledge source?
See 8 big pharma CEOs pitch their solutions to you.

Click here to EYEFORPHARMA
...join 1300+ senior executives
Europ

Cyclodextrin offers potential new therapy for cardiovascular disease

Download PDF Copy

April 19, 2016

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](https://doi.org/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 *

[Author information](#) [Article notes](#) [Copyright and License information](#)

This article has been cited by other articles in PMC.



Development of polycationic amphiphilic cyclodextrin nanoparticles for anticancer drug delivery

Gamze Varan¹, Juan M. Benito², Carmen Ortiz Mellet³ and Erem Bilensoy^{*1,4}

Full Research Paper

Open Access

Address:
¹Department of Nanotechnology and Nanomedicine, Graduate School of Science and Engineering, Hacettepe University, Ankara, 06800, Turkey, ²Institute for Chemical Research, CSIC - University of Sevilla, Av. Américo Vespucio 49, Sevilla, 41092, Spain, ³Department of Organic Chemistry, University of Sevilla, C/ Prof García González 1, Sevilla, 41012, Spain and ⁴Department of Pharmaceutical Technology, Faculty of Pharmacy, Hacettepe University, Ankara, 06100, Turkey

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

Received: 30 March 2017
Accepted: 14 June 2017
Published: 13 July 2017

This article is part of the Thematic Series "Nanomaterial-based cancer theranostics".

Guest Editor: V. Sivakov

Email:

SCIENTIFIC REPORTS

Altmetric: 3 Citations: 26

[More detail](#)

Article | OPEN

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](#)

[Cancer immunotherapy](#)

[Drug development](#) [Target](#)

Received: 27 September 2012

Accepted: 10 December 2012

Published online: 22 January 2013

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



Publish About Browse

OPEN ACCESS PEER-REVIEWED

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, Sakiko 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>

Article	Authors	Metrics	Comments	Related Content
---------	---------	---------	----------	-----------------



Antiviral HIV, HSV, Zika, Dengue



ScienceAdvances

Contents News Careers Journals

Advertisement

Employer Profiles

Learn more about jobs at top organizations

Science
Careers

SHARE RESEARCH ARTICLE VIROLOGY

Modified cyclodextrins as broad-spectrum antivirals

Samuel T. Jones^{1,2*}, Valeria Cagno^{1,3*}, Matej Janeček¹, Daniel Ortiz⁴, Natalia Gasilova⁴, Jocelyne Piret⁵, Matteo Gasbarri¹, ...
+ See all authors and affiliations

Science Advances 29 Jan 2020:
Vol. 6, no. 5, eaax9318
DOI: 10.1126/sciadv.aax9318

Article Figures & Data Info & Metrics eLetters PDF

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

^aWistar Institute, ^bDepartment of Medicine, ^cDepartment of Chemical Engineering, and ^dDepartment of Pathology and Laboratory, University of Pennsylvania, Philadelphia, Pa., USA



US 20030220294A1

(19) United States

(12) Patent Application Publication
Wallace et al.

(10) Pub. No.: US 2003/0220294 A1

(43) Pub. Date: Nov. 27, 2003

(54) CYCLODEXTRIN COMPOSITIONS AND METHODS OF TREATING VIRAL INFECTIONS

(22) Filed: Mar. 21, 2003

Related U.S. Application Data

(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)

(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

Correspondence Address:
Schwegman, Lundberg, Woessner & Kluth, P.A.
P.O. Box 2938
Minneapolis, MN 55402 (US)

(57) ABSTRACT

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

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

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. Pitha¹ and R. Anand^{2,*†}

¹National Institute on Aging, Gerontology Research Center, National Institute of Health, 4940 Eastern Avenue, Baltimore, MD 21224, USA.

²Laboratory 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- α -cyclodextrin sulphate combination on HIV-1 replication.

Table 1. Effects of hydrocortisol phosphate and α -cyclodextrin sulphate on cell proliferation and HIV-1 replication: dose-response relationship of



DEXOLVE™

Antibacterial effect

US 20060247208 A1

- (19) **United States**
- (12) **Patent Application Publication** (10) **Pub. No.: US 2006/0247208 A1**
Karginov et al. (43) **Pub. Date: Nov. 2, 2006**

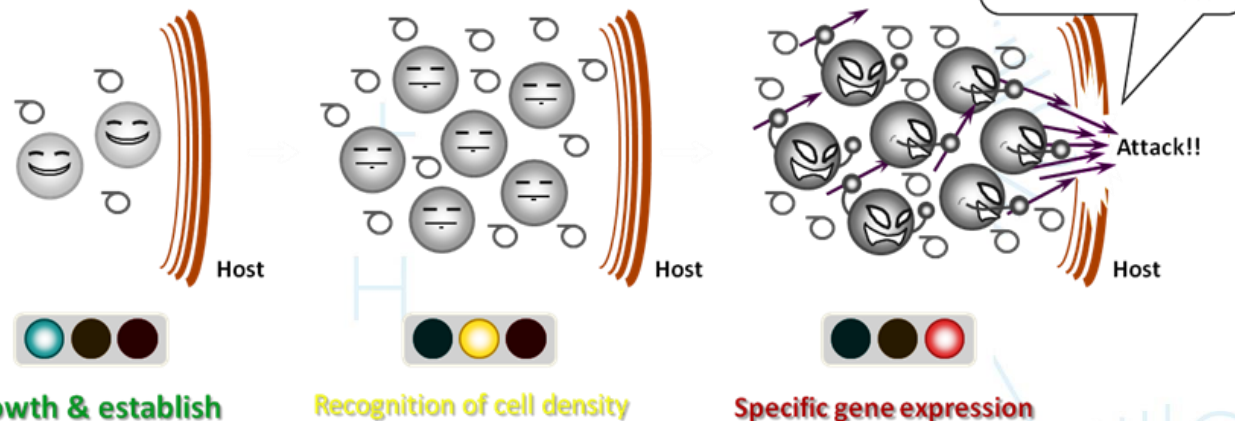
(54) **B-CYCLODEXTRIN DERIVATIVES AND THEIR USE AGAINST ANTHRAX LETHAL TOXIN**

Publication Classification

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

The use of cyclodextrins is possible in inhibiting quorum sensing by binding the signal molecules

○ : pheromones ↗ : pathogenic factors



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-methoxybenzyl)-amino-6-deoxy-beta-CD HCl salt combined with methoxycillin 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-methoxybenzyl)-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

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)

Feasibility study

Running a short feasibility study with your molecule free of charge

Proof of concept to consider CD based formulations



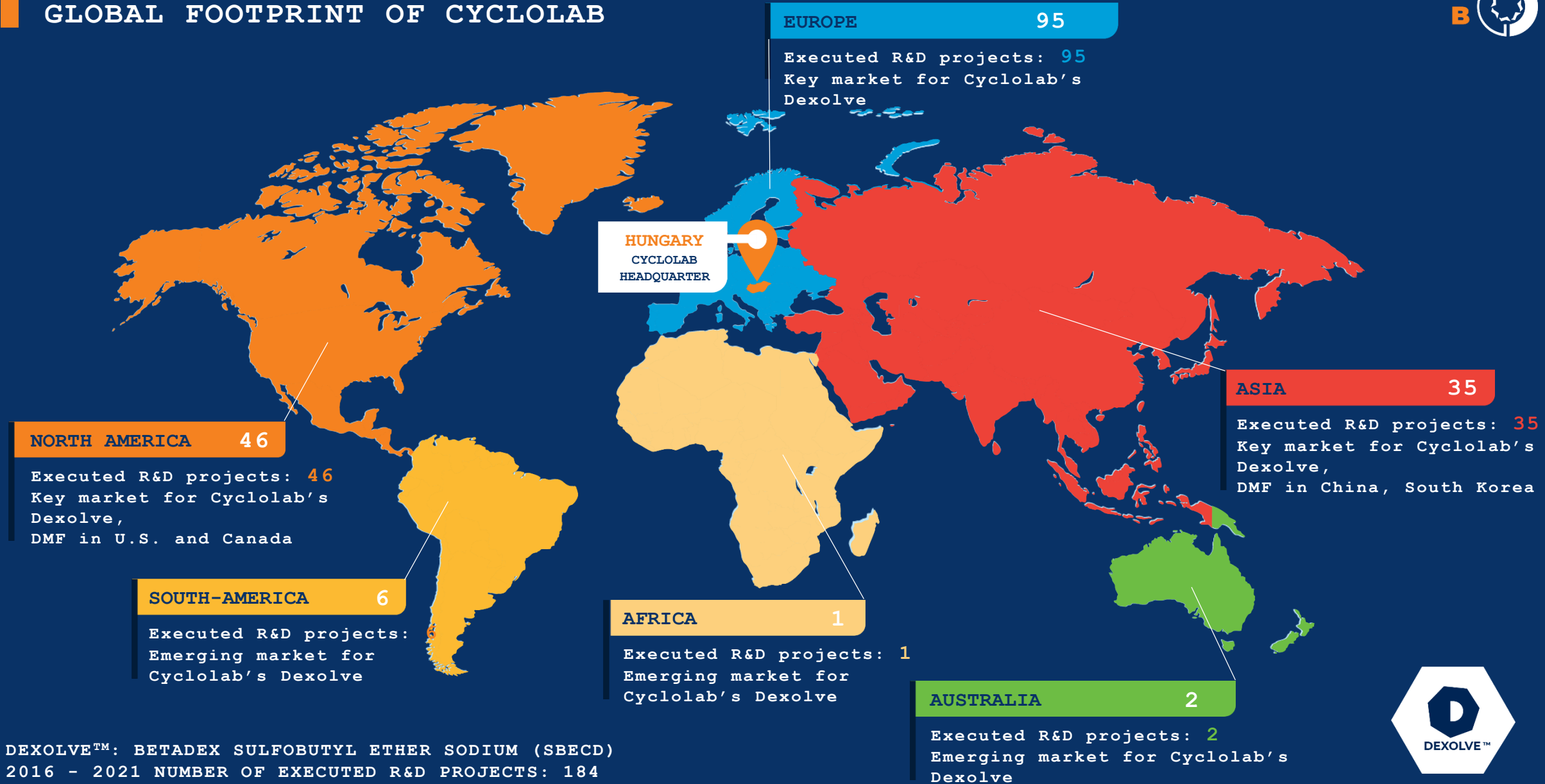
CycloLab Grant

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



DEXOLVE™: BETADEX SULFOBUTYL ETHER SODIUM (SBECD)
2016 - 2021 NUMBER OF EXECUTED R&D PROJECTS: 184



Getting the best
out of cyclodextrins

COMPANY CONTACTS

CYCLOLAB CYCLODEXTRIN RESEARCH & DEVELOPMENT LABORATORY LTD.

Budapest, P.O. Box 435, H-1525 Hungary

Location: Illatos út 7., Budapest, H-1097- Hungary

Tel: (+36) 1-347-60-70

E-mail: info@cyclolab.hu

Web: <http://www.cyclolab.hu>

CONTACT PERSON

Tamas Sohajda

CEO

sohajda@cyclolab.hu

(+36) 30-315-70-38

ASK FOR
A FREE
SAMPLE

