



CARBOHYDE
REVOLUTION OF
CYCLODEXTRINS

Cyclodextrins

Uses as active ingredients



Uses of cyclodextrins

Traditional pharma applications

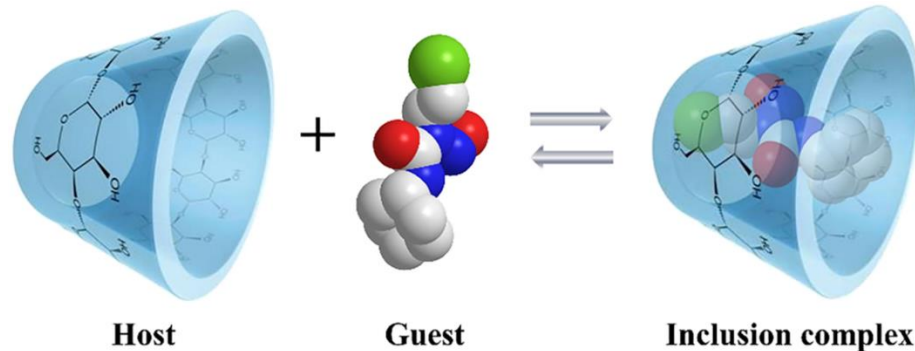
- CDs as drug complexing agents in drug delivery
- Nanosizing, solubilizing, stabilizing, etc.
- Summary of results: >100 marketed products in 2022

Novel applications

- **Active ingredients**
 - Monoclonal antibodies
 - Gene therapy
 - Targeted drug delivery
 - Diagnostics & Theranostics
 - Biotechnology

Common Advantages

- Cyclodextrins may increase
 - Drug solubility
 - Wetting, dissolution rate
 - Drug stability
 - Absorbed quantity
- Cyclodextrins may decrease
 - API's dose for same efficacy
 - Taste
 - Side effects
 - Smell





What are the "therapeutic" cyclodextrins?

Antidote-type cyclodextrins

- 2,6-di-*O*-methyl-BCD in hypervitaminosis (NIH)



Life Sciences

Volume 32, Issue 7, 14 February 1983, Pages 719-723



Rescue from hypervitaminosis A or potentiation or retinoid toxicity by different modes of cyclodextrin administration

Josef Pitha, Lajos Szenté

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[https://doi.org/10.1016/0024-3205\(83\)90304-1](https://doi.org/10.1016/0024-3205(83)90304-1)

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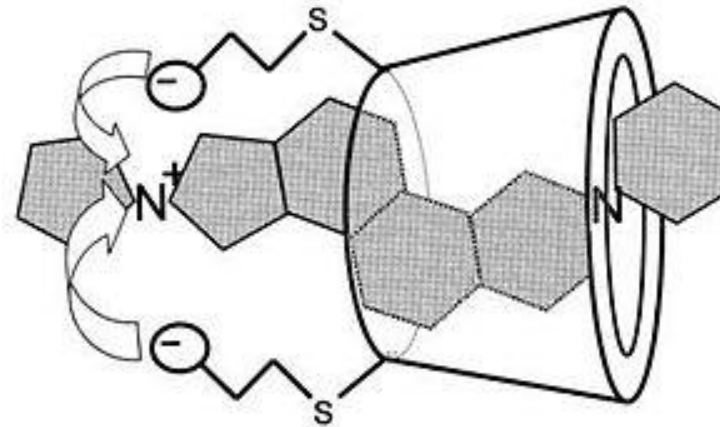
**Proof of his concept: first clinical life saving action:
rescue from retinoid intoxication in 1987**



What are the "therapeutic" cyclodextrins?

Antidote-type cyclodextrins

- 2,6-di-O-methyl-BCD in hypervitaminosis (NIH)
- Sugammadex (MSD + generics)

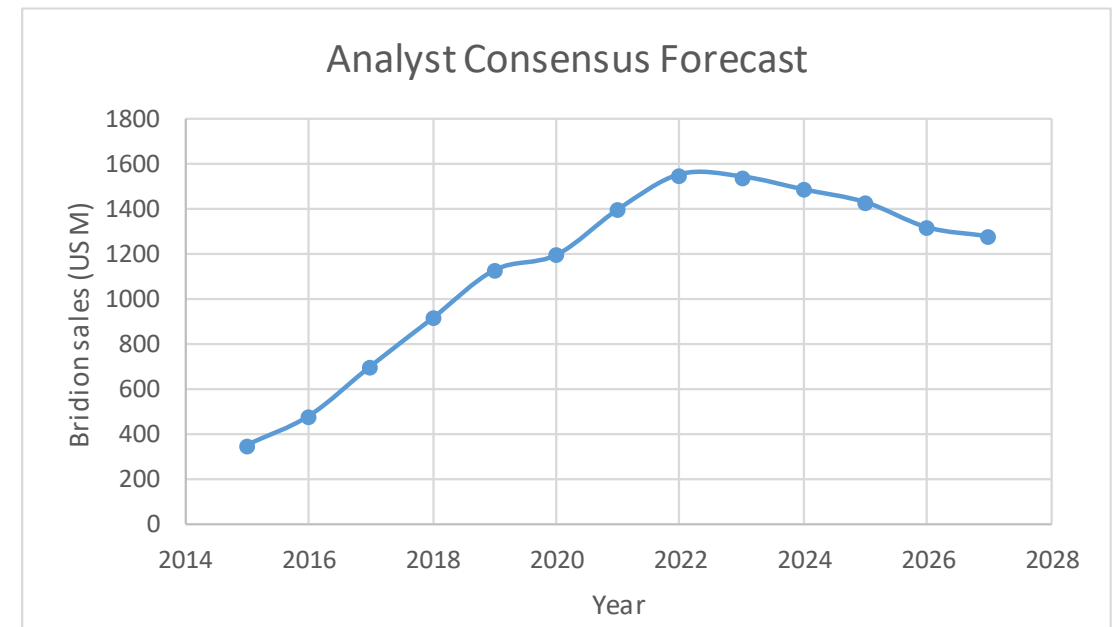


Concept: Release of neuromuscular blockade induced by rocuronium via selective removal

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



MSD
INVENTING FOR LIFE



No. of companies with SGM-related patent: 50+



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- Sugammadex (MSD + generics)
- SBECD (REV-0100) in Stargardt disease - lipofuscin removal (Revision - Aequus)



**Weill Cornell
Medicine**





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- LMWH antidote - OKL-1187 (Alveron Pharma)



MoA: undisclosed (reverse the anticoagulant effects of currently used direct-acting oral anticoagulants (DOACS), vitamin K antagonists, platelet inhibitors, (low molecular weight) heparins and heparin-like compounds)

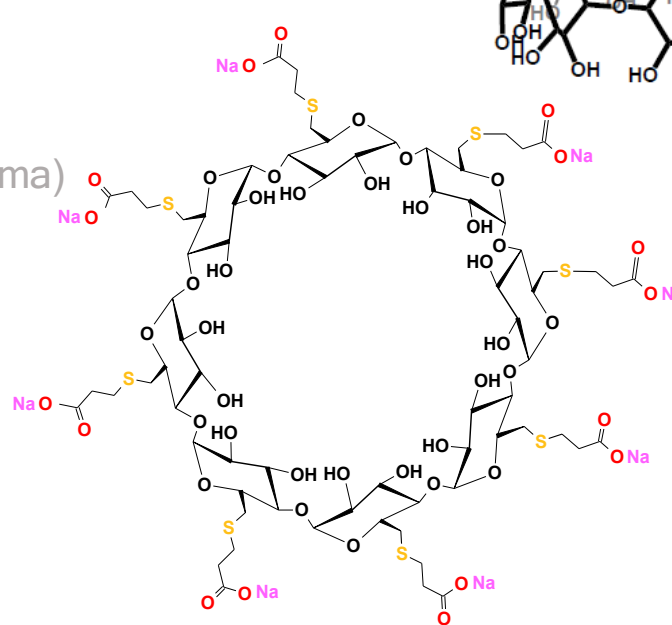
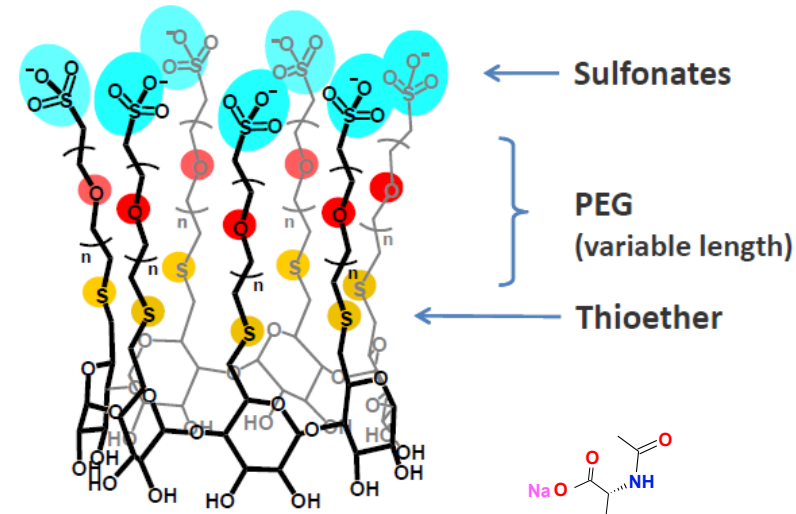




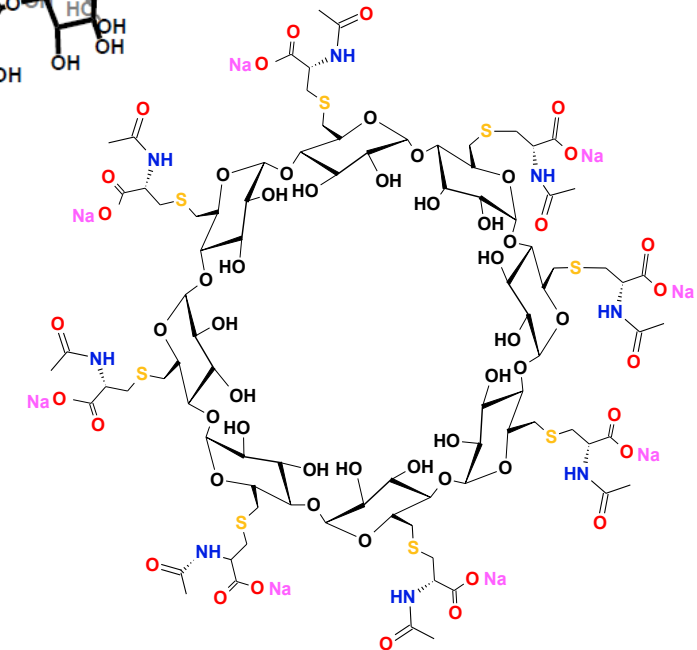
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- LMWH antidote - OKL-1187 (Alveron Pharma)
- Sugammadex follow-ups



Sugammadex (Bridion®)



Adamgammadex

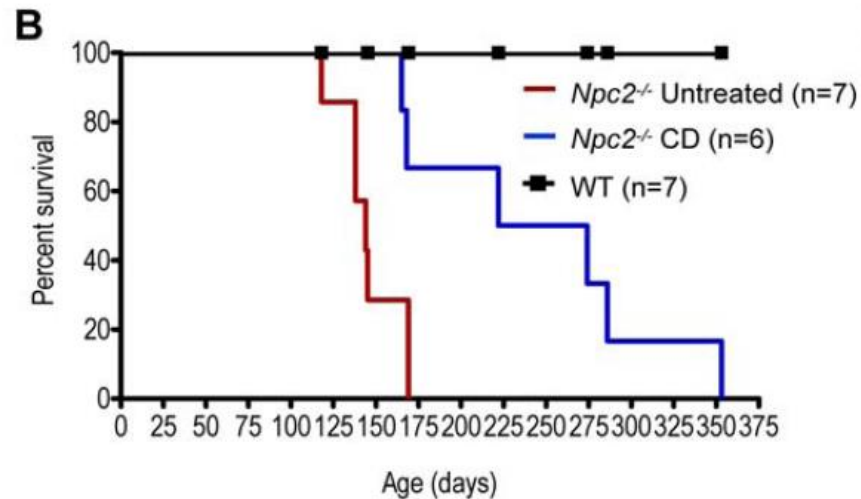




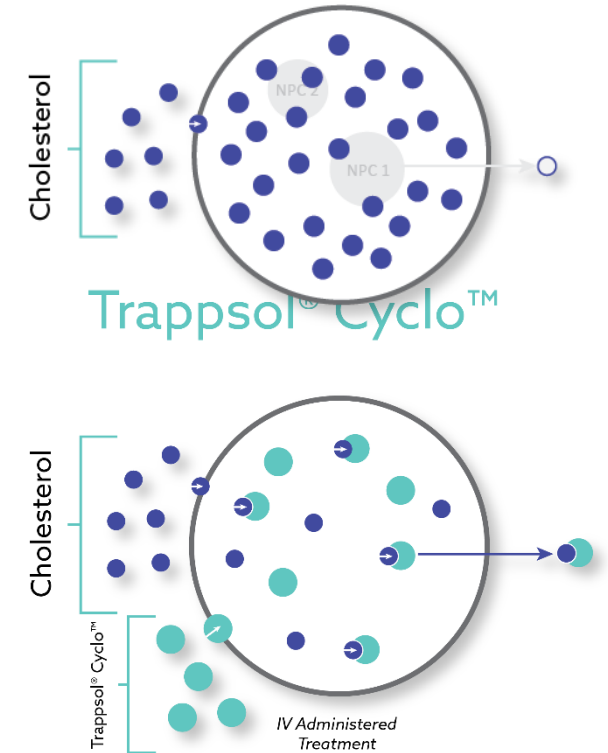
What are the "therapeutic" cyclodextrins?

Cholesterol(?) -targeting CDs

- Hydroxypropyl-BCD
 - in Niemann-Pick type C (Mandos / Cyclo Tx)
(Adrabetadex / Trappsol Cyclo)



Non-Functioning Lysosome



Mandos





What are the "therapeutic" cyclodextrins?

Cholesterol(?) -targeting CDs

- Hydroxypropyl-BCD
 - in Niemann-Pick type C
 - in Alzheimer's (Cyclo Tx)
 - in Parkinson's (Organo Tx)
 - in familial hypercholesterolemia (Berent Tx)
 - as poison/venom antidotes (Sydney Univ)
 - FSGS (Zyversa)



Beren Therapeutics (stealth)

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.

RESEARCH ARTICLE | ATHEROSCLEROSIS



Cyclodextrin promotes atherosclerosis regression via macrophage reprogramming

SEBASTIAN ZIMMER, ALENA GREBE, SIRIL S. BAKKE, NIKLAS BODE, BENTE HALVORSEN, THOMAS ULAS, MONA SKJELLAND, DOMINIC DE NARDO, LARISA I. LABZIN, [...], AND

EICKE LATZ [+15 authors](#) [Authors Info & Affiliations](#)

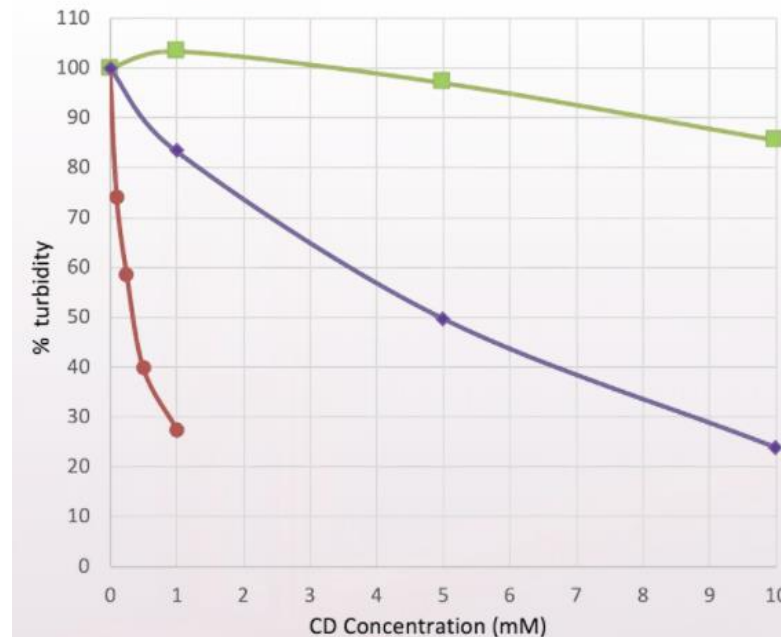
SCIENCE TRANSLATIONAL MEDICINE • 6 Apr 2016 • Vol 8, Issue 333 • p. 333ra50 • DOI: 10.1126/scitranslmed.aad6100



What are the "therapeutic" cyclodextrins?

Cholesterol(?)-targeting CDs

- Hydroxypropyl-BCD
 - in Niemann-Pick type C
 - in Alzheimer's
 - in Parkinson's
 - in atherosclerosis
 - as poison/venom antidotes
 - FSGS
- CD-dimers in atherosclerosis



- Normal cyclodextrins measured against binding to cholesterol
- ◆ Normal cyclodextrins measured against binding to 7KC
- Underdog-engineered cyclodextrins binding to 7KC (approx. 10x potency vs normal CDs)

Underdog has now created proprietary, custom-engineered, nontoxic cyclodextrins designed to achieve **high affinity** and **high specificity** for the 7KC target.

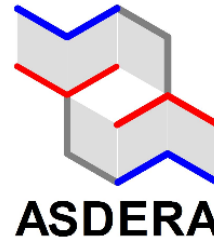


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Cholesterol(?) -targeting CDs

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- "Next generation" CDs in Niemann Pick C
 - HPACD
 - Sugar-appended CDs
 - Peptide-CD conjugates

HPGCD
polyrotaxanes
CD polymers





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 - FSGS
- CD-dimers in atherosclerosis
- „Next generation” CDs in Niemann Pick C
- Methyl-BCD (S-1229) in pulmonary inflammation (CF, asthma, etc)

MoA: reverse the surfactant dysfunction in conditions such as CF, ventilator-induced lung injury (VILI) asthma, COPD, bronchiolitis, ALI & ARDS via cholesterol sequestering





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 - FSGS
- CD-dimers in atherosclerosis
- „Next generation” CDs in Niemann Pick C
- Methyl-BCD in pulmonary inflammation (CF, asthma, etc)
- Methyl-BCD and derivatives in cancer therapy



**HACETTEPE
ÜNİVERSİTESİ**



熊本大学
Kumamoto University



**UNIVERSITÄT
DES
SAARLANDES**



MoA:

**triggering apoptosis, lower cell proliferation rate,
hinder MDR**

**Affecting cholesterol homeostasis → cell growth
inhibition → apoptosis**

Targeted therapy, tumour growth inhibition



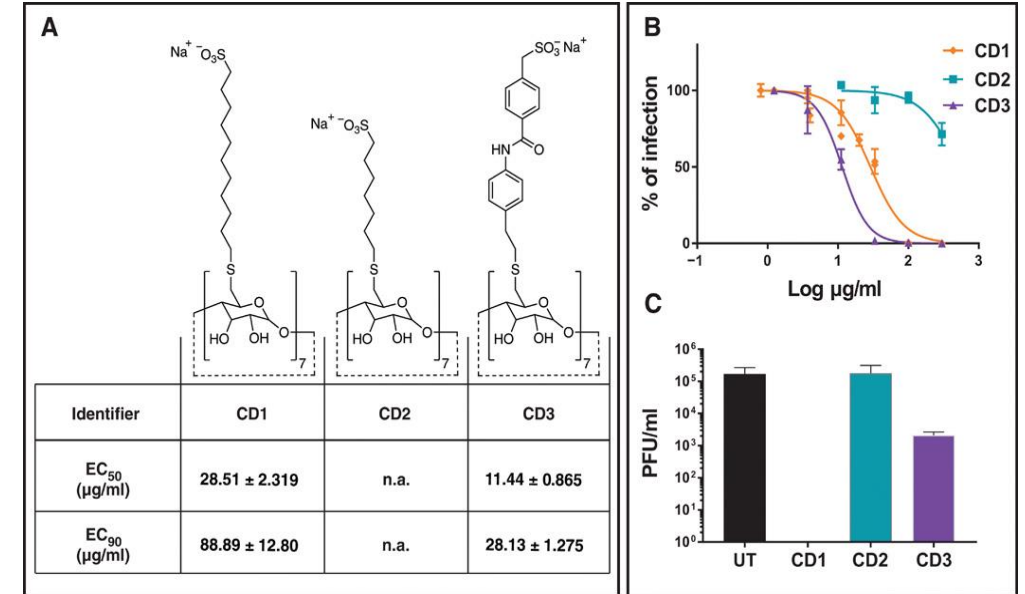
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- „Next generation" CDs in Niemann Pick C
- Methyl-BCD in pulmonary inflammation (CF, asthma, etc)
- Methyl-BCD and derivatives in cancer therapy
- Sulfated CDs as antivirals



ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE



- Evaluating modified, tailor-made CD against HSV-2
- Candidate proved to be active against several HS-dependent [heparan sulphate-dependent] viruses
- „exhibits a broad-spectrum virucidal, irreversible mechanism of action, presents a high barrier to viral resistance, and is biocompatible"



Thank you!

Take Home Message

- CDs are widely evaluated in therapy
- Real challenges are in upcoming areas
 - Vaccines
 - mAbs
 - Gene therapy
 - Targeted drug delivery / therapy
 - Biotechnology
 - NCE development

Reality & Next steps

- No novel cyclodextrin on the pharma market for almost 20 years
- New applications pose two big challenges
 - Understanding MoA
 - Designing new CDs
- Forming new consortia and collaborate with an industrial mindset



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For any questions:

info@carbohyde.com