

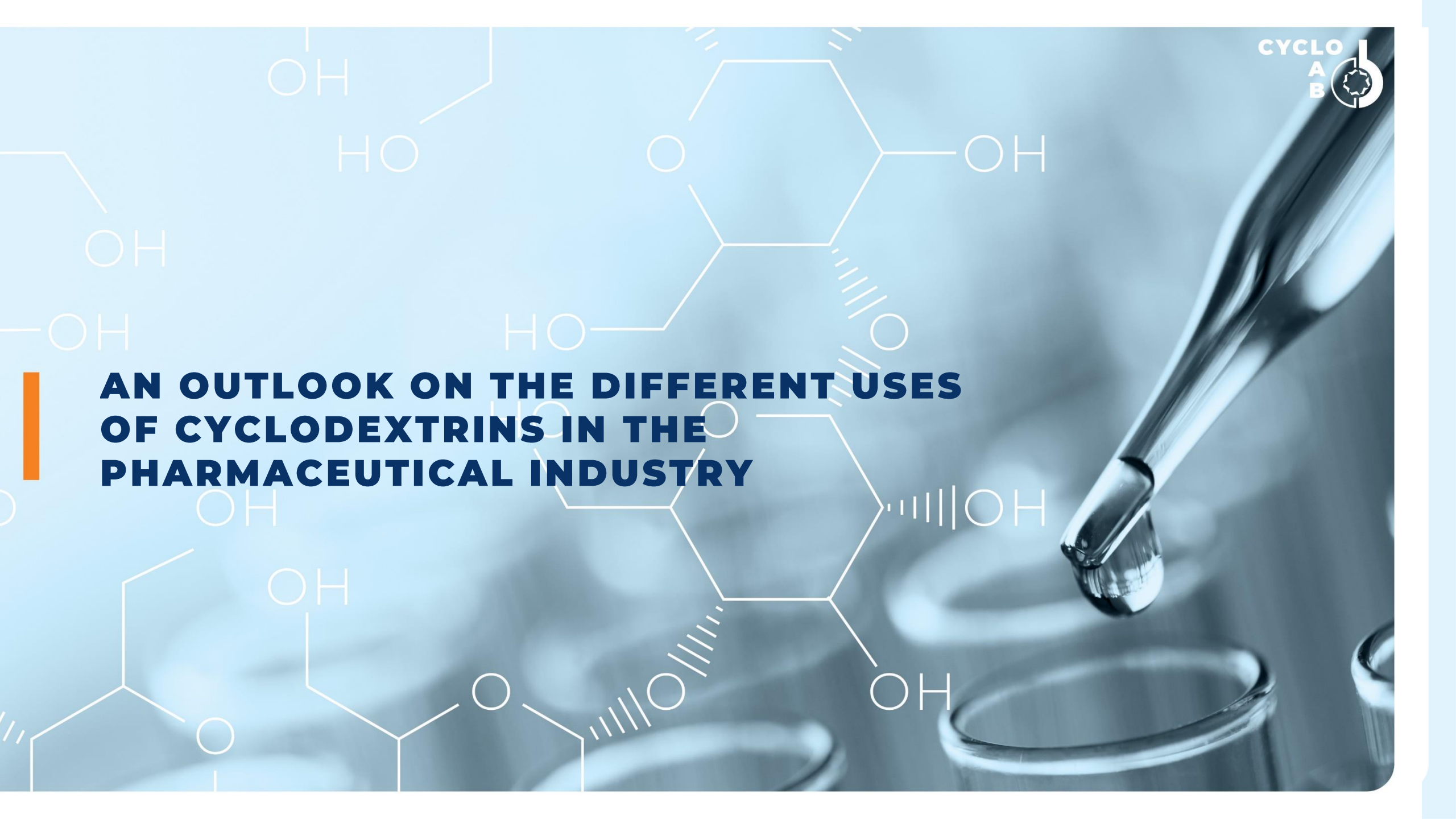
# GETTING THE BEST OUT OF CYCLODEXTRINS

Technology presentation



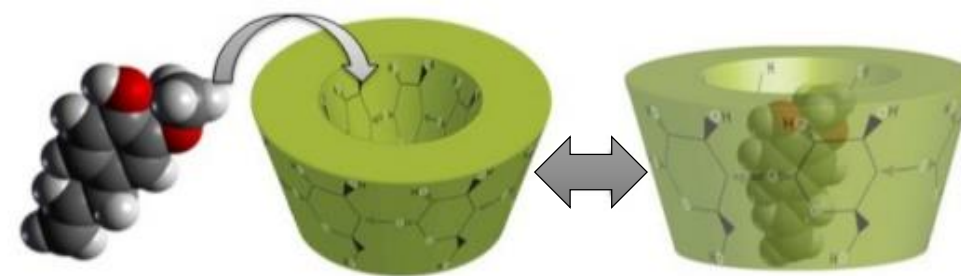
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# **AN OUTLOOK ON THE DIFFERENT USES OF CYCLODEXTRINS IN THE PHARMACEUTICAL INDUSTRY**



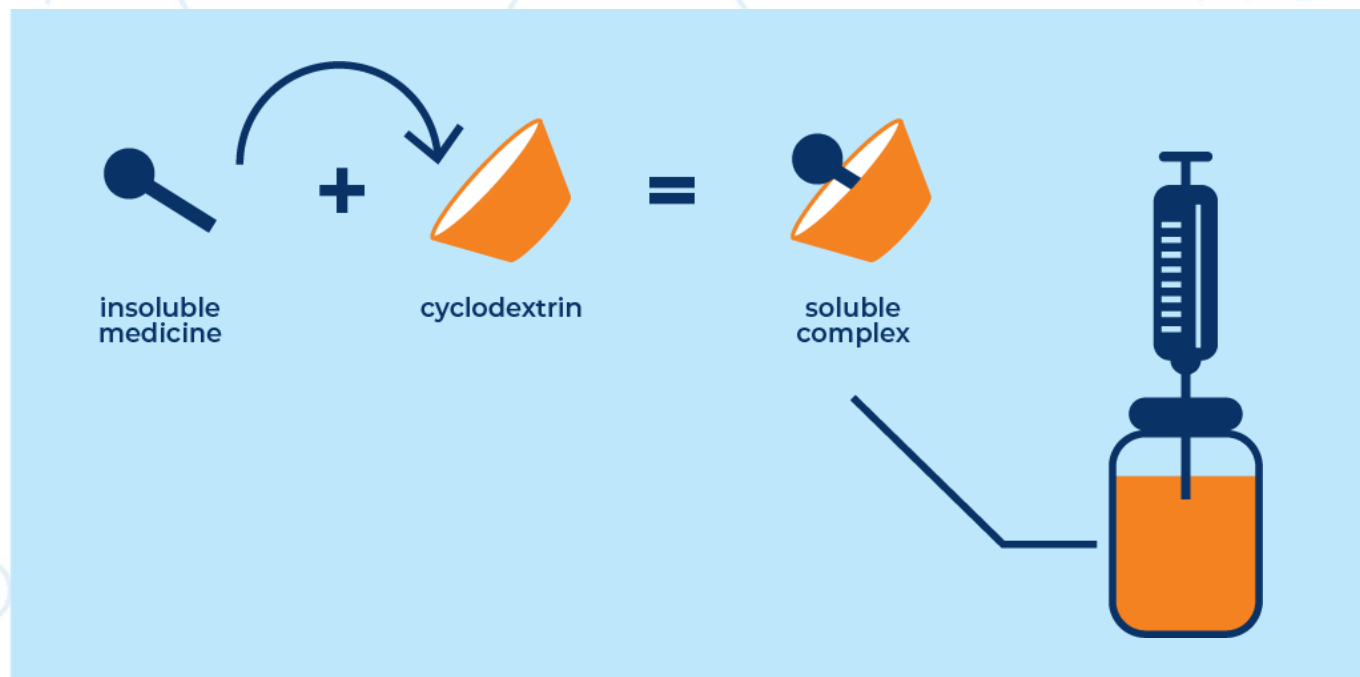
# WHAT ARE CYCLODEXTRINS?

- Composed of sugars
- Cyclic molecules
- Naturally occurring compounds
- Used in food, pharmaceuticals, drug delivery, chemical industries, agriculture, etc.
- **Sub-nanometer** sized molecular containers with hydrophilic outer phase and hydrophobic interior properties
- Reversible inclusion complex formation



## MAIN FUNCTIONAL PROPERTIES OF CDs

They form **NON-COVALENT** „host-guest” type inclusion complexes in a **reversible** manner (Szejtli,1980)



**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



## WHY USE CYCLODEXTRINS? POSSIBILITIES

- Significant **solubility enhancement** (10 to 100,000 fold)
- Improvement of **chemical stability**
- **Increased bioavailability**, facilitated delivery
- Reduced aggregation
- **Moderate irritation** or reduced side-effects
- Maximized patient safety, complete renal elimination
- Enables **formulation of water-insoluble APIs** in all dosage forms
- Lower API doses can be achieved



## CDs USED IN PHARMACEUTICALS

### Parent Native Unsubstituted

$\alpha$ -CD (Alfadex)  
EP, USP

$\beta$ -CD (Betadex)  
EP, USP

$\gamma$ -CD (Gammadex)  
EP, USP, JPC

### Derivatives Substituted

2-hydroxypropyl  $\beta$ -CD (HP- $\beta$ -CD,  
hydroxypropyl betadex)  
EP, USP

Sulfobutylether  $\beta$ -CD (SBE- $\beta$ -CD, betadex  
sulfobutyl ether sodium)  
EP, USP

Random methylated  $\beta$ -CD (RM- $\beta$ -CD)  
rare: nasal/ocular

2-hydroxypropyl  $\gamma$ -CD (HP- $\gamma$ -CD)

## CDs USED IN PHARMACEUTICALS

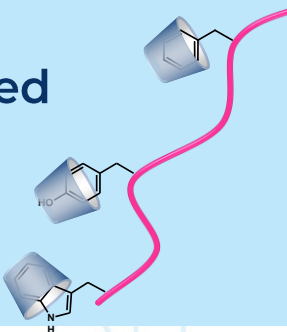
**>100 pharma products on the market containing cyclodextrins**



	$\alpha$ -CD	$\beta$ -CD	$\gamma$ -CD	HP- $\beta$ -CD	SBE- $\beta$ -CD	RM- $\beta$ -CD	HP- $\gamma$ -CD
ORAL		X	X	X	X		
NASAL						X	
RECTAL		X		X			
DERMAL		X	X	X			
OCULAR		X		X	X	X	X
PARENTERAL	X			X	X		X

## Why use CDs in protein and biological formulations?

- Safer than current excipients (e.g. Tween) – no peroxide formation, corresponding immunogenicity, degradation
- Prevention of aggregation, delayed folding
- Less protein adsorption onto container surface
- Reduced/maintained viscosity, improved injectability
- Life-cycle management



Protein without  
CD

Protein + CD1

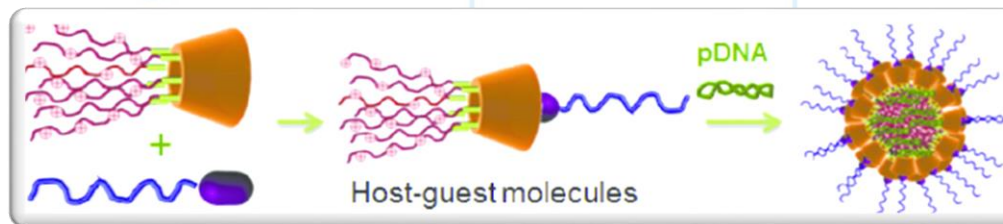
Protein + CD2

Protein + CD3

Cyclodextrins' effect on  
insulin aggregation after  
stirring

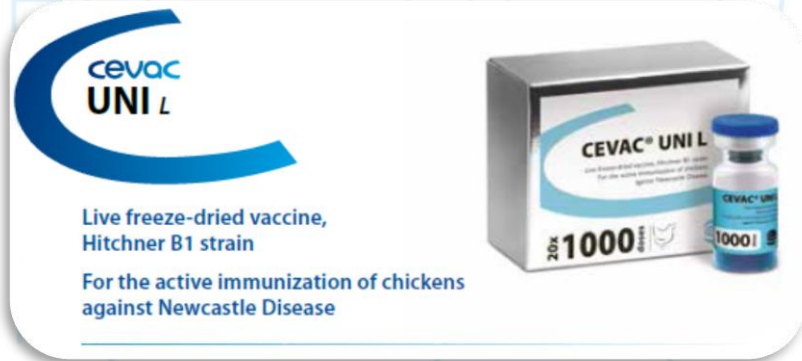


### Why use CDs in non-viral gene delivery?



- Novel approach with a lot of promise and potential to protect intellectual property
- The systems offer delivery of synthetic siRNA to target cells
- Act as gene delivery vectors by condensing DNA and forming liquid crystalline complexes with oligonucleotides
- Ability to self-assemble in aqueous solvent forming micelles or vesicles and can be used as hosts for the solubilization and/or stabilization of various compounds
- Nanoparticle system based on CD complexed siRNA has been effective in phase I clinical trials for the treatment of solid tumors

# FORMULATING VACCINES



As an excipient , (2-hydroxypropyl)-beta-cyclodextrin is used.



## Vaccine

Volume 34, Issue 27, 8 June 2016, Pages 3191-3198



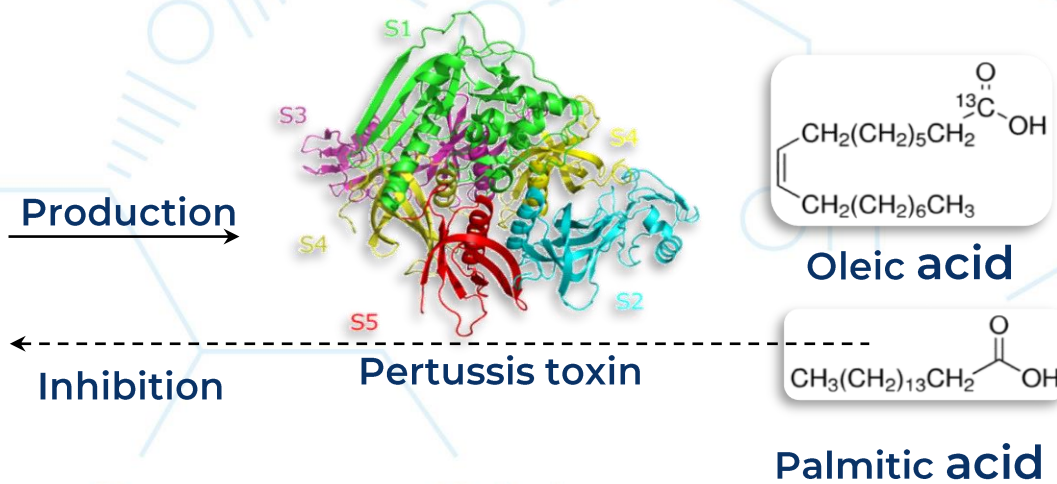
Intranasal hydroxypropyl- $\beta$ -cyclodextrin-  
adjuvanted influenza vaccine protects against  
sub-heterologous virus infection

Takato Kusakabe <sup>a, b</sup>, Koji Ozasa <sup>a</sup>, Shingo Kobari <sup>a</sup>, Masatoshi Momota <sup>a, b</sup>, Natsuko Kishishita <sup>a</sup>, Kouji Kobiyama <sup>a, b</sup>, Etsushi Kuroda <sup>b</sup>, Ken J. Ishii <sup>a, b</sup>

Suvaxyn PCV<sup>™</sup> contains inactivated recombinant Porcine Circovirus type 1, expressing the Porcine Circovirus type 2 ORF2 protein. This vaccine is used for the active immunization of pigs over the age of 3 weeks against Porcine Circovirus type 2 (PCV2).

Sulfolipo-cyclodextrin (SLCD) is used as an adjuvant.

# CYCLODEXTRINS AS „CATALYSTS” IN BIOTECHNOLOGY



Bordetella pertussis

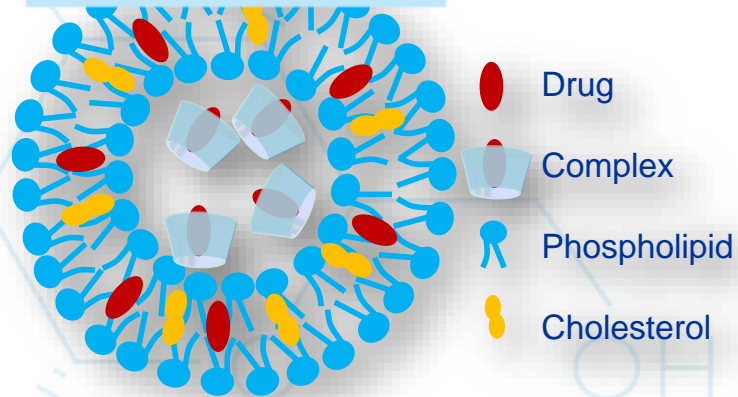
Inoculum size cells in 5 µL	0	α	β	γ	DIMEB
10 <sup>3</sup>	-	-	-	-	++
10 <sup>4</sup>	-	-	-	-	+++
10 <sup>5</sup>	-	-	-	-	+++
10 <sup>6</sup>	-	++	+	+	+++
10 <sup>7</sup>	-	+++	++	++	+++
- no growth	+ < 100 colonies	++ 10 <sup>2</sup> to 10 <sup>3</sup> colonies	+++ full growth		

Complexation of fatty acids (growth inhibitors) results in enhanced cell growth and toxin production

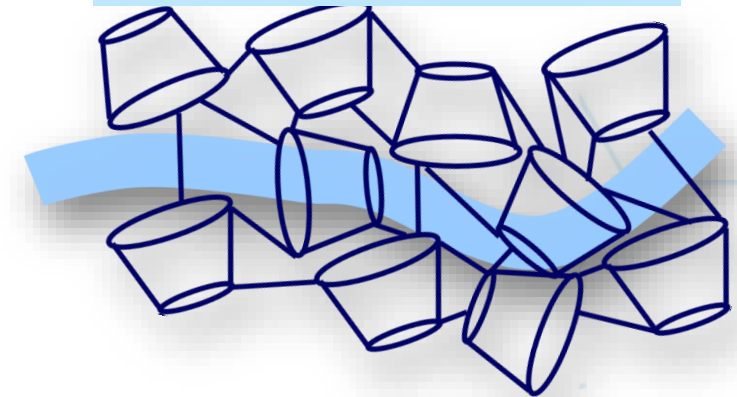
**DIMEB** increases pertussis toxoid production 100-fold

# CYCLODEXTRINS IN DDSs CONTROLLED AND TARGETED RELEASE

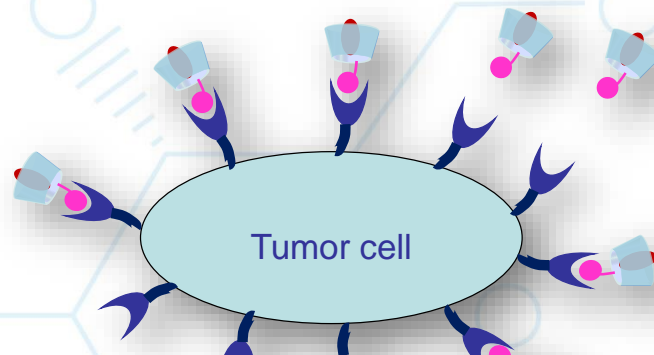
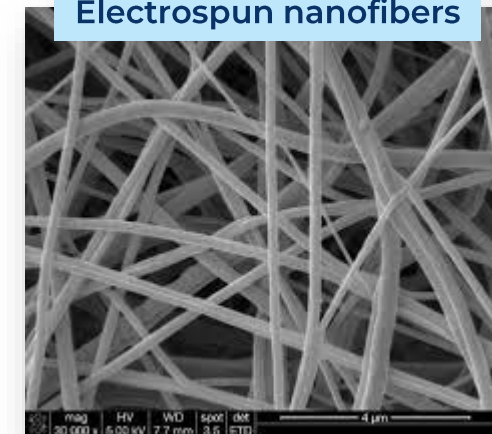
Drug in CD in liposome



CD is immobilized on polyester mesh for local and prolonged delivery



Electrospun nanofibers

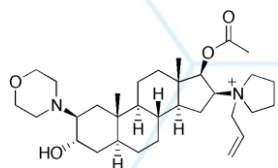


Tumor targeting by folate and/or mannoside moieties; cell-penetrating peptide-conjugated CD

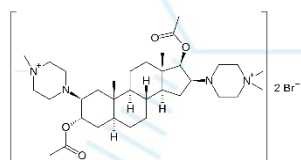


# CYCLODEXTRINS AS APIs

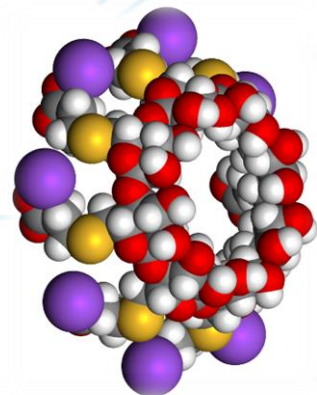
## SUGAMMADEX



Rocuronium



Pipecuronium



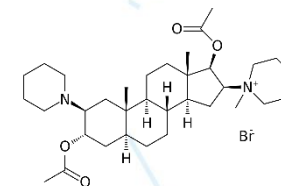
The 1<sup>st</sup> selective relaxant binding agent to reverse NMBA induced neuromuscular blockade

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

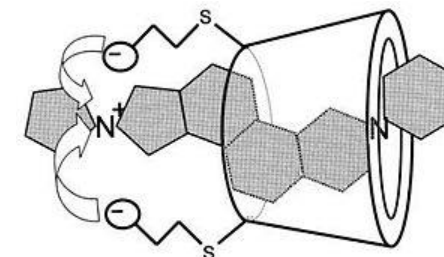
One of the strongest fits among CDs and guests – the rocuronium is unavailable to bind the receptor

Reduced/eliminated adverse effects compared to neostigmine

(lower) Affinity for vecuronium, pipecuronium and pancuronium, yet still working clinically



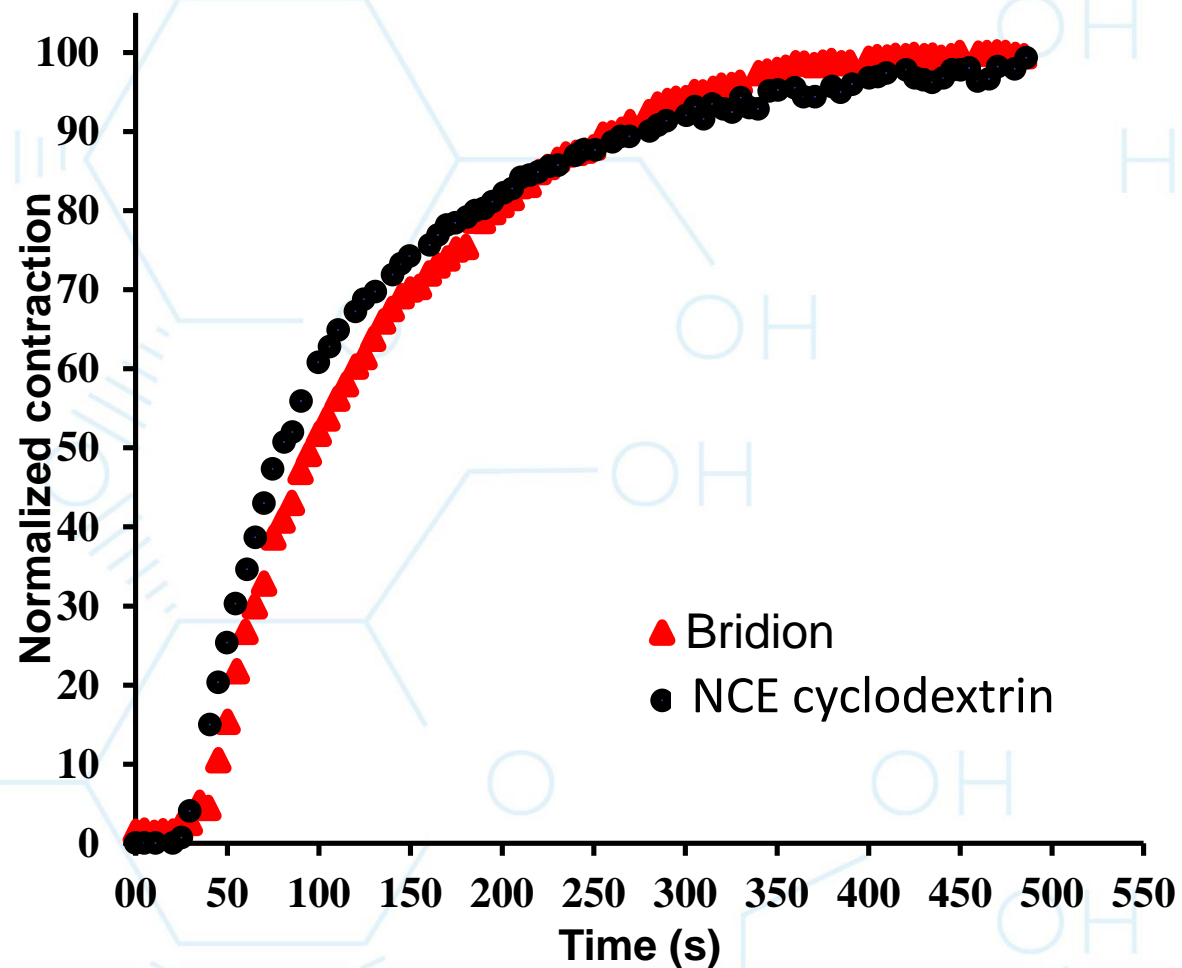
Vecuronium





## CYCLODEXTRINS AS APIs ANTIDOTES

Time elapsed until the reversal of neuromuscular blockade induced with pipecuronium



### Possibilities:

- LMWH antidote
- Toxin/poison antidotes (jellyfish, conotoxin, etc.)
- Retinoid intoxication
- AMD – lipofuscin removal

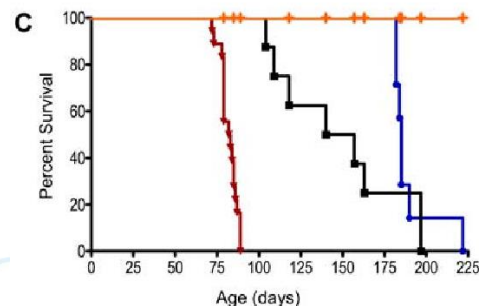
# CYCLODEXTRINS AS APIs NEURODEGENERATIVE DISEASES

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

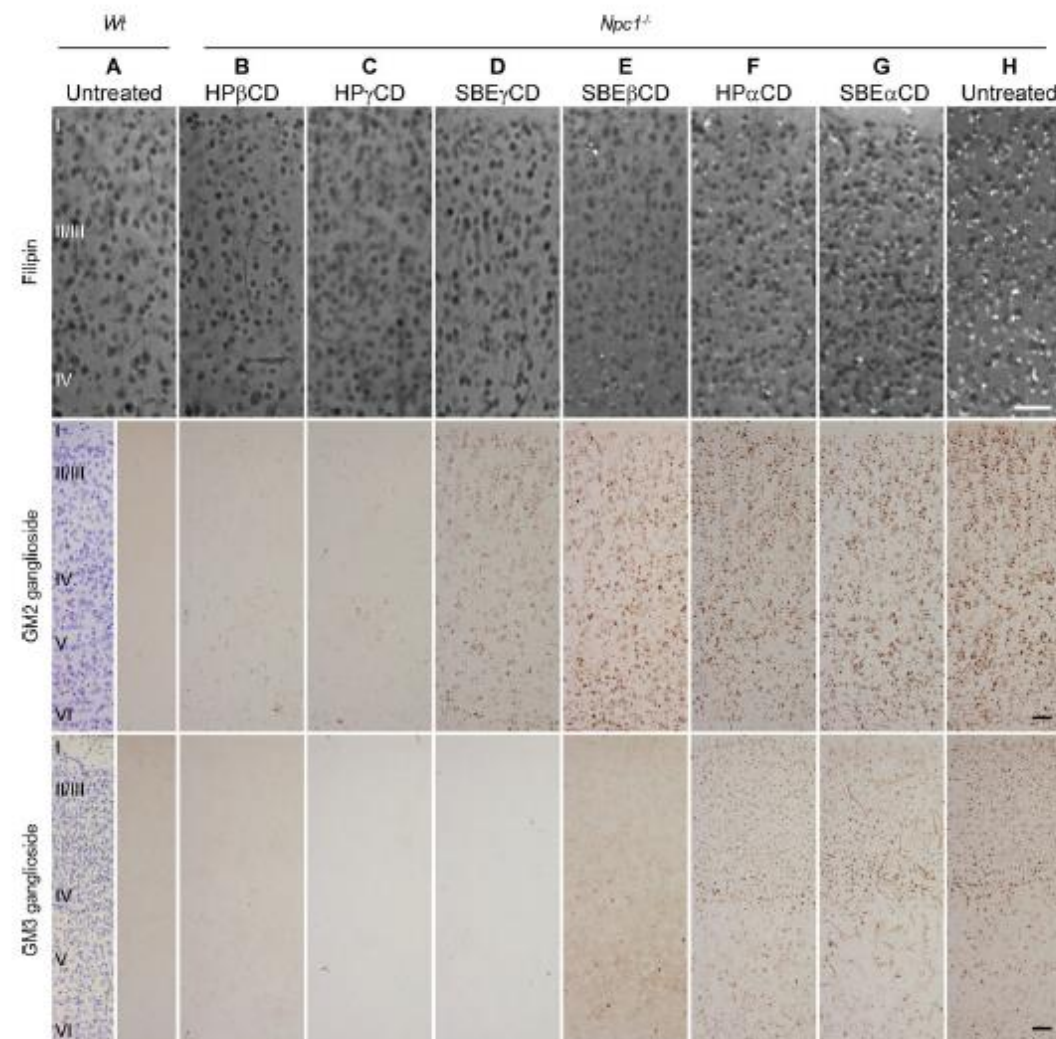
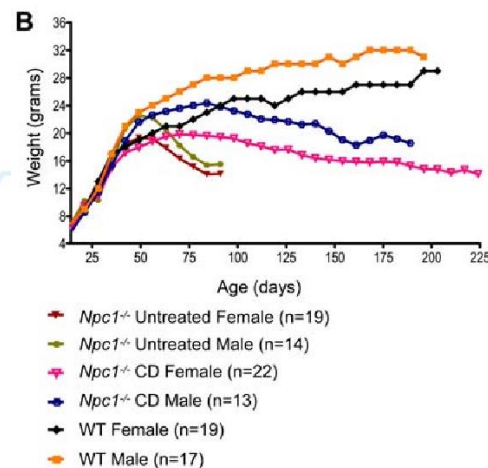
Lina Abi-Mosleh, Rodney E. Infante, Arun Radhakrishnan<sup>1</sup>, Joseph L. Goldstein<sup>2</sup>, and Michael S. Brown<sup>2</sup>

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)



- *Npc1*<sup>-/-</sup> Untreated (n=18)
- *Npc1*<sup>-/-</sup> CD start at P7 (n=7)
- *Npc1*<sup>-/-</sup> CD start at P21 (n=8)
- WT (n=22)



# CYCLODEXTRINS AS APIs PRECLINICAL DEVELOPMENTS

## CNS diseases

- Alzheimer's disease
- Parkinson's disease
- Neurodegenerative lysosomal storage diseases

## Cardiovascular diseases

- Atherosclerosis

## Oncology

- Anticancer agents

## Infectious diseases

- Antivirals (SARS-CoV-2, Zika, Dengue, HIV, Herpes, Influenza, RSV)
- Antibacterials (Anthrax, MRSA, Clostridium, Pseudomonas)

## Respiratory diseases

- Asthma
- COPD
- Cystic fibrosis

WHO ARE WE AT CYCLOLAB?



The world's only all-round **CYCLODEXTRIN** company with over

**40-year experience of CD-technology**

**in pharmaceutical-, cosmetics-, food-, environmental- and analytical applications**

### Experience

Over 490 technical/scientific papers  
and 950 technical reports to customers

200 different cyclodextrin derivatives  
130 patents/applications  
40 products on the market

Drug Master Files (USA type IV) and eCTD

Over 20,000 citations to CYCLOLAB's papers

### Expertise & Technology

Custom synthesis

Drug solubilization and stabilization

Further industrial applications

Cyclodextrin-related analytics

Stability testing

GMP-conform manufacturing

Feasibility studies



## GMP Manufacturing

Betadex Sulfobutyl Ether Sodium  
**Dexolve™**

Custom cGMP synthesis  
of CDs, CD complexes,  
investigational medicinal  
products

Preparation/filing of  
regulatory dossier

## Products

- Pharma grade CDs
- Fine chemical grade CDs
- Standard grade CDs
- Single isomer CDs
- Fluorescent derivatives
- Maltooligomers
- CD complexes
- Analytical standards
- Sugammadex impurities
- CD polymers
- Special HPLC columns





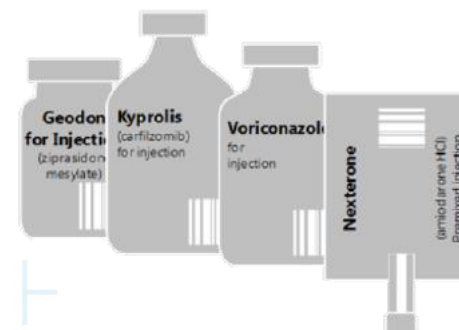
# CYCLOLAB PRODUCT PORTFOLIO DEXOLVE™



**>350 kg/batch USP N.F. / EP**

Global presence and distribution  
cGMP certified OGYÉI/57792-7/2018  
48 months stability data  
>200 batches manufactured  
Annual capacity over 30,000 kgs  
2<sup>nd</sup> manufacturing site established

**No down payment**  
**no royalty**  
**no milestone payment**



SAMPLES  
**FREE**  
SAMPLES



# CYCLOLAB SERVICE PORTFOLIO

## RELATED SERVICES – R&D



### Early phase drug development

Customization of CD enabled formulations

Investigation of changes in physico-chemical properties

Life cycle management

### IP services and consultation

### Custom cyclodextrin synthesis

Exclusive manufacture, unique synthetic routes

Self-tailored products and characteristics

30 years of experience in compilation of CD related patents (synthesis, application, etc.), patent claim analysis, consultancy in CD related projects

Over 62.000 CD related papers

### In vitro bioequivalence studies

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

### Analytical services

Method development, validation; cGMP release testing of pharma grade CDs

HPLC, GC, CE, UV, MS, NMR, IR, Micro and BET content methods

Stability studies

CD-guest interaction studies

CD-based chiral separations

Assay, impurity tests

Bioanalytical investigations



## CYCLOLAB SERVICE PORTFOLIO RELATED SERVICES – R&D



### 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



# PIPELINE FOR PARTNERING

## Formulations

Pediatric and geriatric reformulation  
Injectable panobinostat – various types of cancer  
Injectable lonafarnib – progeria  
Injectable repurposing: oral drugs reformulated as injectables

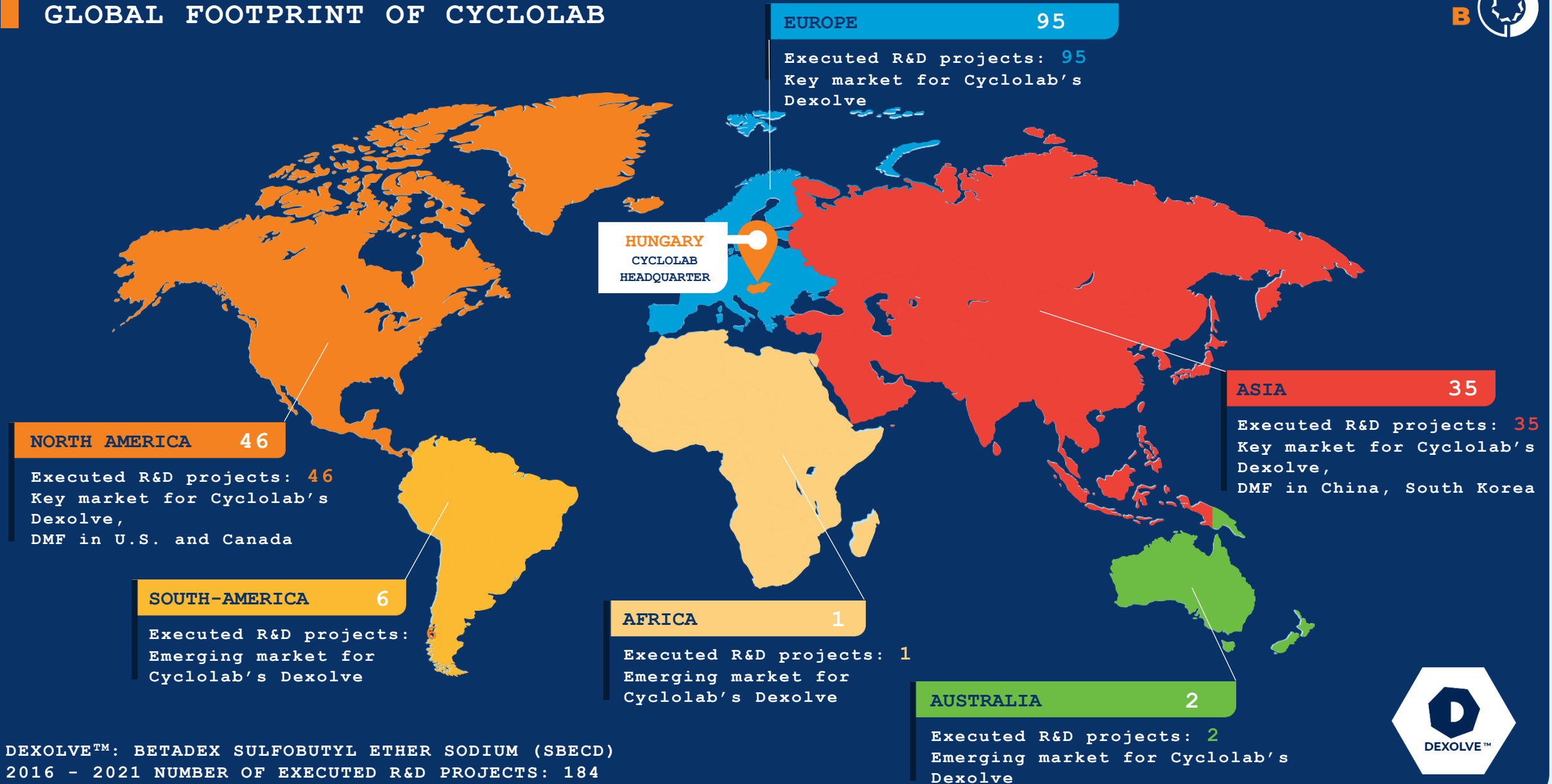
## Cyclodextrins as NCEs

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)

## Drug delivery systems

Platform for selective and targeted anticancer therapy with unmodified APIs  
Platform for improving BBB penetration

# GLOBAL FOOTPRINT OF CYCLOLAB



DEXOLVE™: BETADEx SULFOBuTYL ETHER SODIUM (SBECd)  
2016 - 2021 NUMBER OF EXECUTED R&D PROJECTS: 184



# CYCLOLAB

## 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](mailto:info@cyclolab.hu)

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

