Therapeutic and Diagnostic Utility of Cyclodextrins

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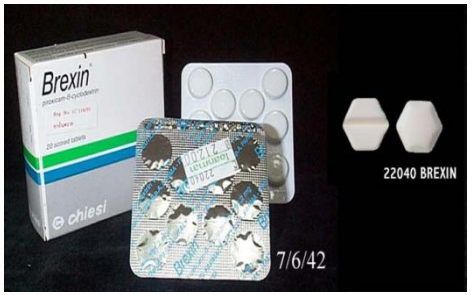
CYCLOLAB
The Cyclodextrin Company

Traditional Therapeutic Use of Cyclodextrins:
Enabling Pharmaceutical Excipients
(more than 60 approved products in 2017)



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This talk focuses on Non-excipient type Therapeutic Utility

Therapeutic and Diagnostic applications are based on selective molecular recognition/complex formation of cyclodextrins (CDs):

- **Cyclodextrins themselves act as active drugs, artifical receptors („empty” CDs as antidotes)**
- **Diagnostic use of molecular recognition of CDs: new DNA sequencing methods**

A concept was born in 1983: Cyclodextrin-assisted Detoxication

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**.)*

Cyclodextrin as a Pharmaceutical Active

as a follow up Pitha's concept:

Development and Application of Sugammadex-BRIDION®

Sugammadex-BRIDION® Story

The Cyclodextrin Company

Purpose of project:

Design and optimization of an artificial receptor cyclodextrin which:

- **Selectively and efficiently reverses effect of muscle relaxing agents used in anesthesia**
- **Is non-toxic, well tolerated**
- **Improves patient safety, minimizes side effects**
- **Simplifies postoperative care, reduces costs**

The design of Sugammadex: Cavity size matters!

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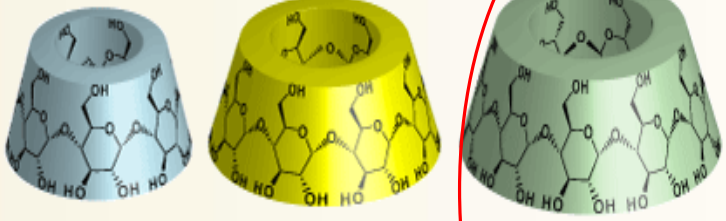
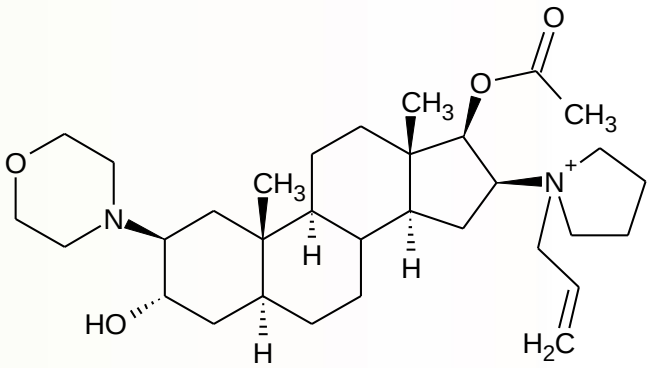


	α-CD	β-CD	γ-CD
No. of Glucose Units	6	7	8
Cavity Diameter (nm)	0.47	0.60	0.75
Height of Torus (nm)	0.79	0.79	0.79

Target API: rocuronium

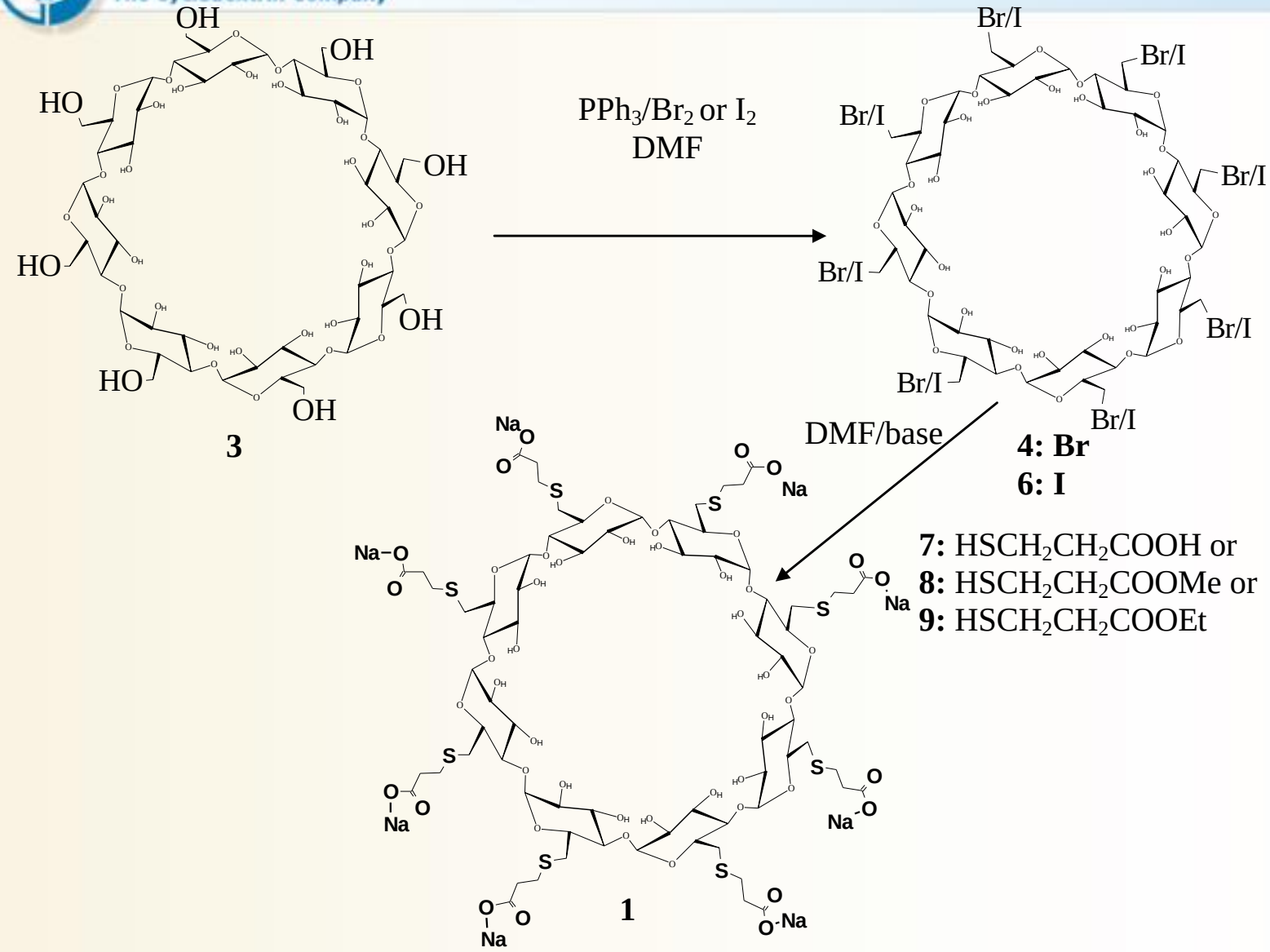


API is a cationic aminosteroid, with approx. 1.6 nm x 0.9 nm size

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**

Chemical „optimization” of gamma-cyclodextrin



Scheme 1.: **Preparation of Org25969**

Purification of crude Sugammadex: toward Bridion®

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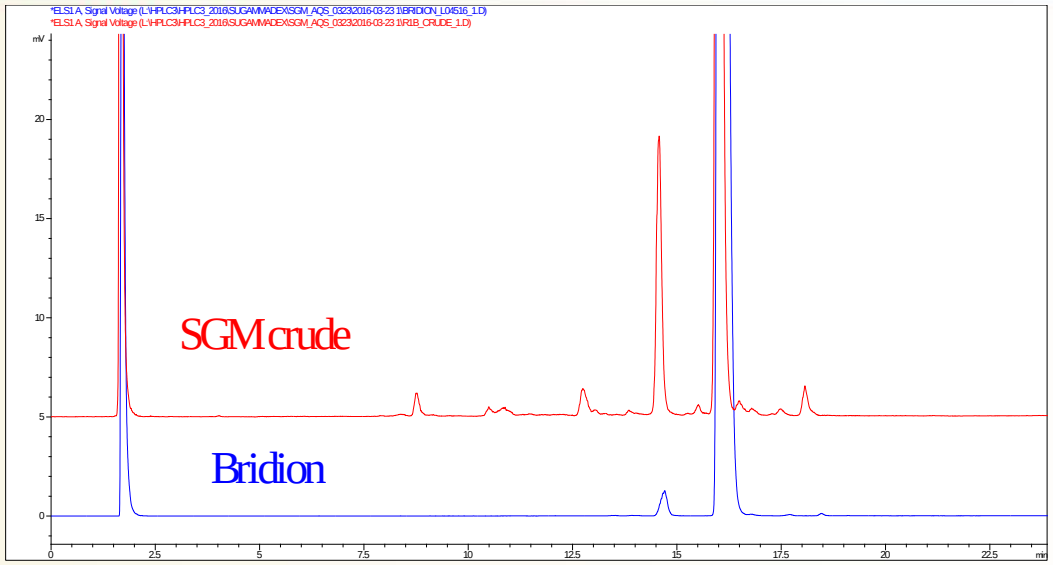


Several potential impurities (challenging purification)

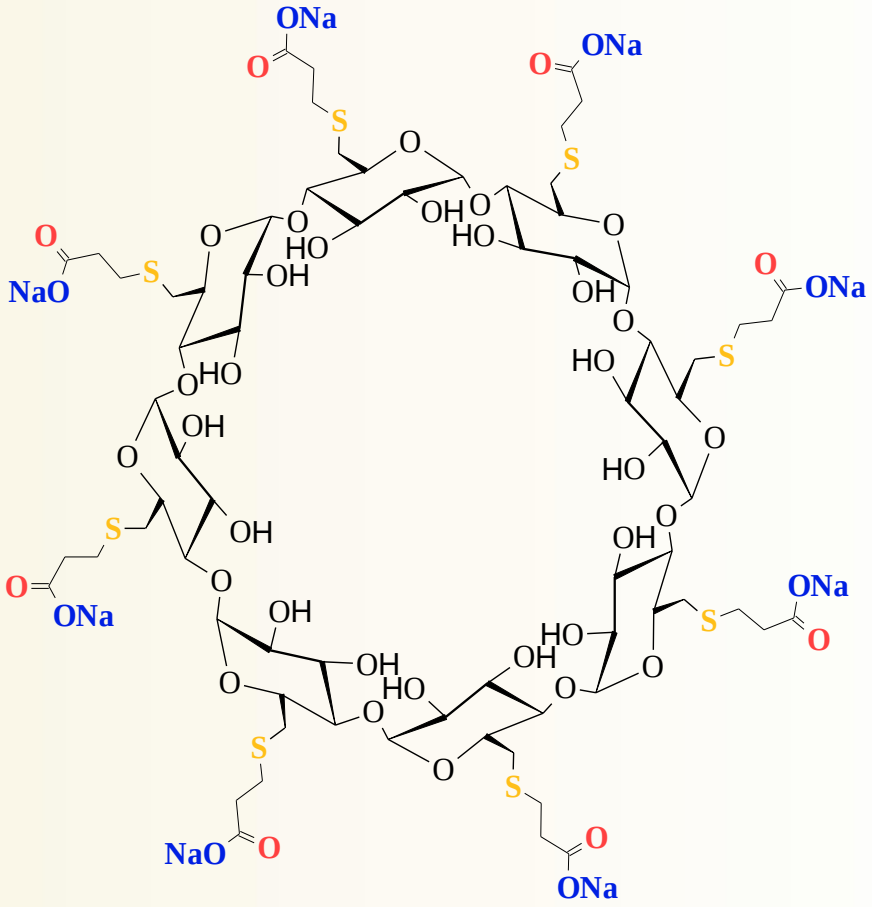
Over 30 potential impurities depending on synthesis route altogether

(Mono-SO-Prop)-SGM
SGM isomer
(Mono-SO-Et)-SGM
(Mono-OH)-SGM
(Mono-anhydro)-SGM/1
(Mono-Formyl)-SGM
(Mono-anhydro)-SGM/2
(SS)1-SGM
(OCH3)2-SGM
(Mono-Cl)-SGM
(Mono-S-Prop)-SGM
(Di-SH)-SGM

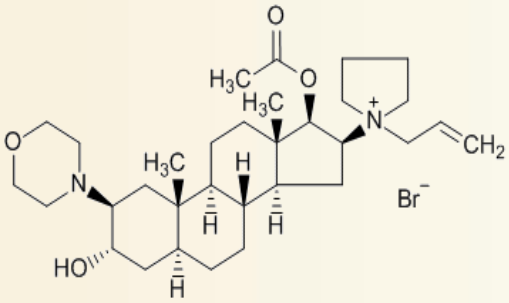
Sugammadex: the first CD derivative approved as API

6A,6B,6C,6D,6E,6F,6G,6H-Octakis-S-(2-carboxyethyl)-6A,6B,6C,6D,6E,6F,6G,6H-octathio-Gamma-cyclodextrin-Na

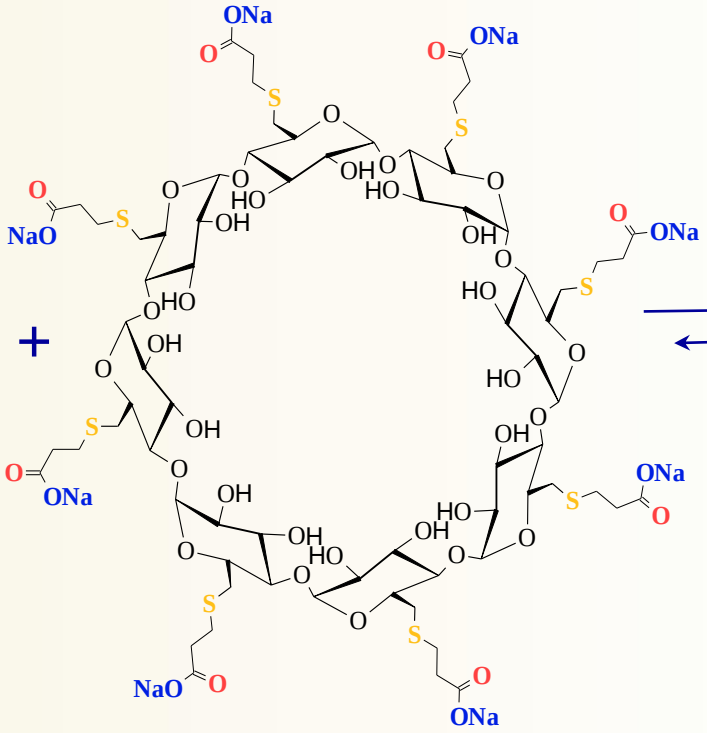
Molecular mass: 2178.01



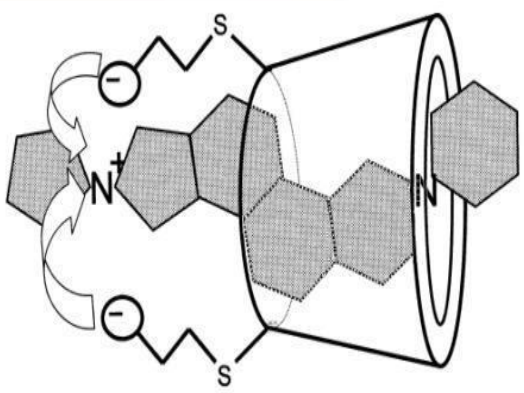
Mechanism of action: Sugammadex is an artificial receptor for rocuronium



Rocuronium Br (to be entrapped)



Sugammadex, (Bridion®) binding host for Rocuronium

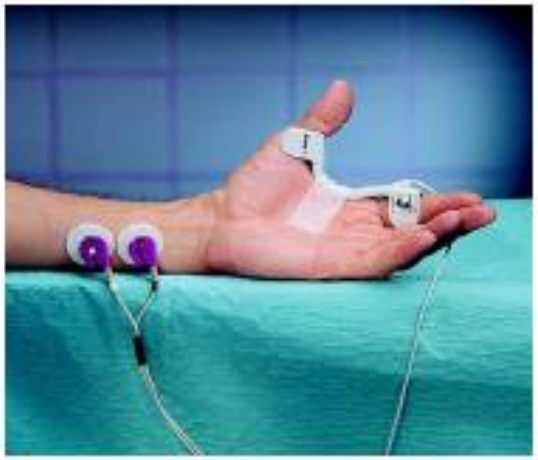


K_a=10.000.000 1/M* complex (extreme binding constant!)

** Schaller S. J., Fink H., Core Evidence, 2013*

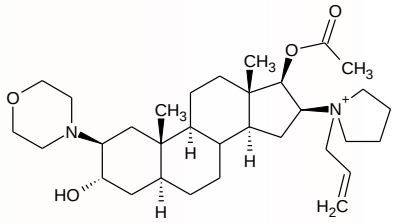
Clinical efficacy of Sugammadex

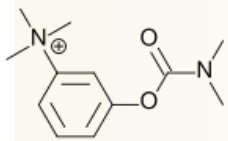
(Naguib et al Anesthesiology 2008)



← Normal NM function

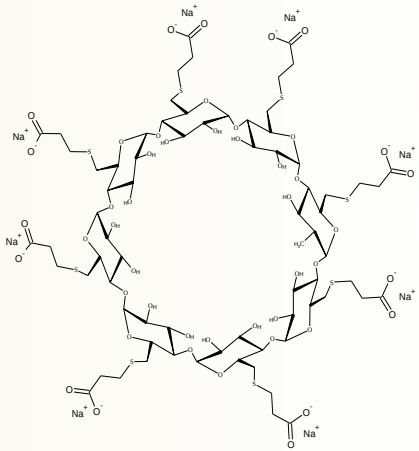
← NM blocade

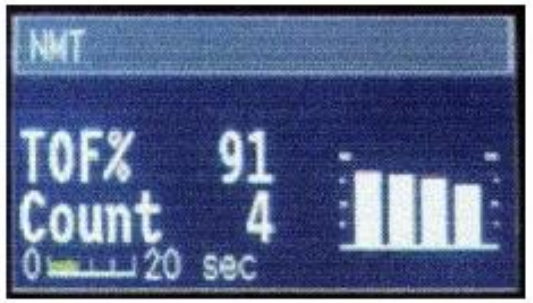




common antidote

Neostigmin





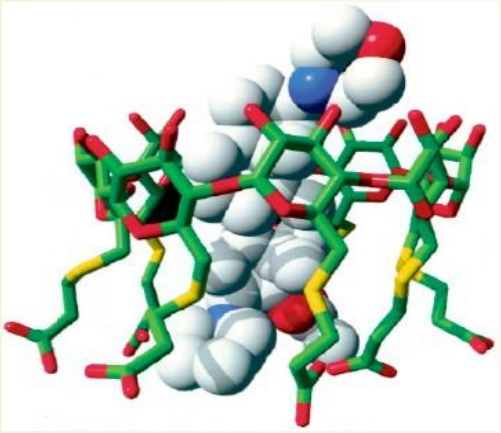
Sugammadex reversal

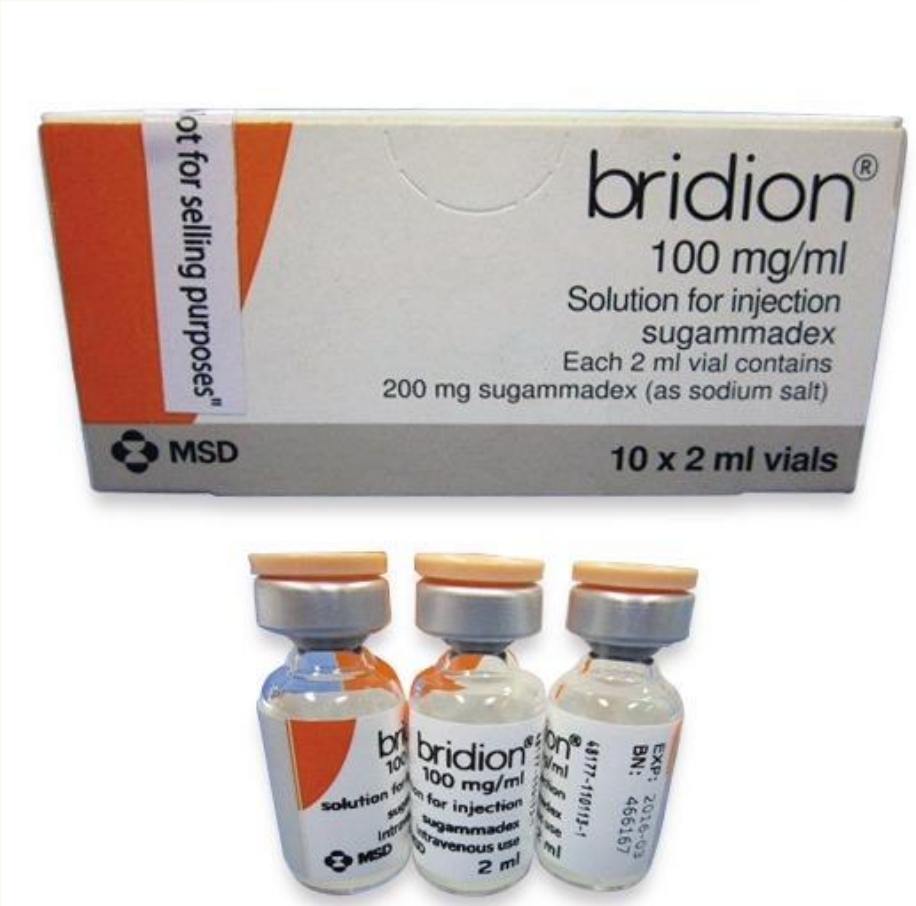
A Sugammadex-BRIDION® on the market since 2008

Approved

in Europe: 2008

in the United States: 2015





Summary of Sugammadex Uses and Value

Naguib, M: Sugammadex: Another Milestone in Clinical Neuromuscular Pharmacology Anesthesia & Analgesia 2007. Vol. 104 p.575

Miller, Ronald D. MD : Sugammadex: An Opportunity to Change the Practice of Anesthesiology? Anesthesia & Analgesiaa 2007 Vol. 104. 477

Kopman A. Sugammadex: A Revolutionary Approach to Neuromuscular Antagonism Anesthesiology 4 2006, Vol.104, 631

Kusha, N et al Sugammadex: A Revolutionary drug in neuromuscular pharmacology Anesth Essays Res. 2013 Sep-Dec; 7(3): 302–306

….”globally in excess of 9 million patients have been exposed to sugammadex without significant reported adverse events showing it to be a safe, effective and important new drug”

Future of Sugammadex?

Currently many attempts for Sugammadex follow-up:

- **Sugammadex will soon be generic**
- **Other macrocycles (cucurbiturils, in USA)**
- **Other Cyclodextrins (in CycloLab's pipeline)**
- **Other novel CDs as antidotes (for heparinoids, in CycloLab's pipeline)**

Diagnostic Utility of cyclodextrins

Cyclodextrin-assisted DNA sequencing

A *„pore in the hole„* concept by Hagan Bayley (Oxford Univ.)

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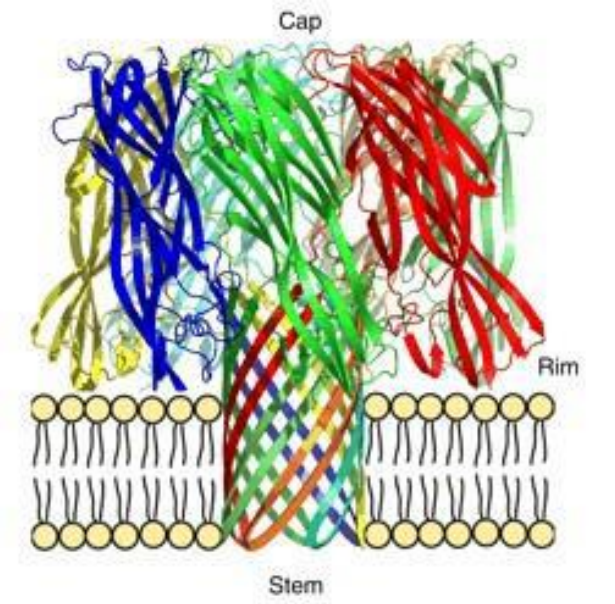

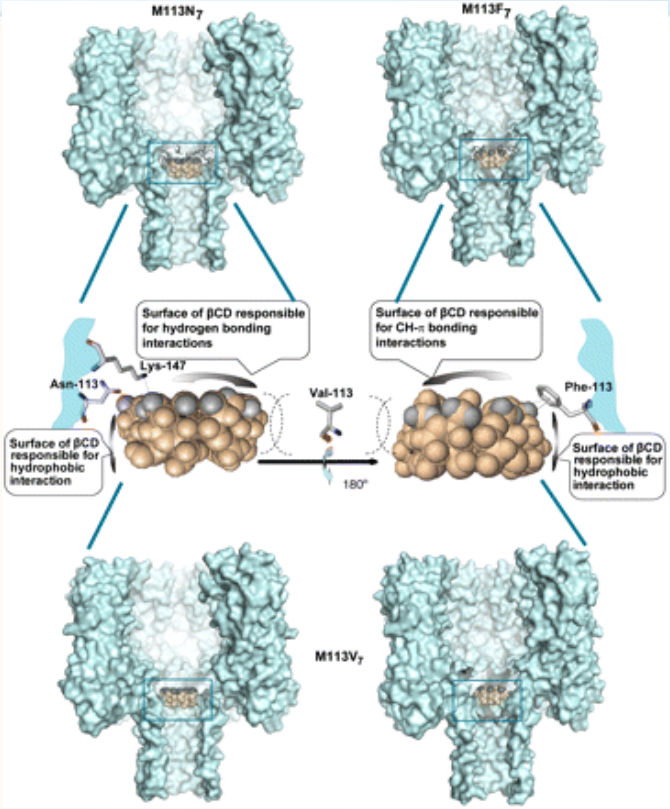

nature nanotechnology

ARTICLES

PUBLISHED ONLINE: 22 FEBRUARY 2009 | DOI: 10.1038/NNANO.2009.12

Continuous base identification for single-molecule nanopore DNA sequencing

James Clarke[1], Hai-Chen Wu[2], Lakmal Jayasinghe[1,2], Alpesh Patel[1], Stuart Reid[1] and Hagan Bayley[2]*

DNA sequencing process *(Oxford Nanopore, Ltd.)*

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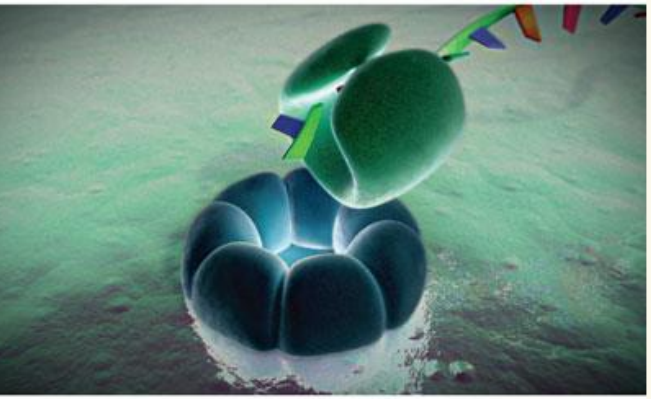
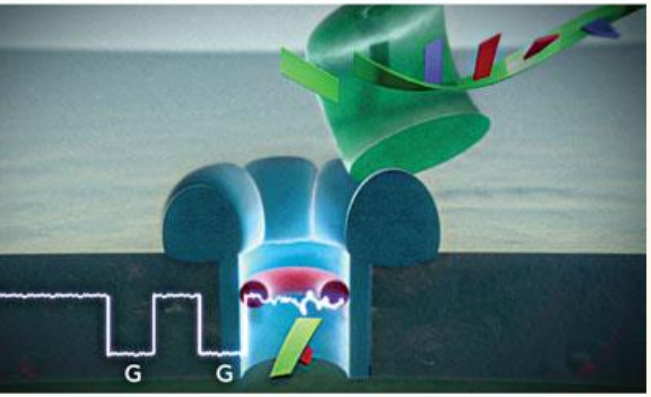
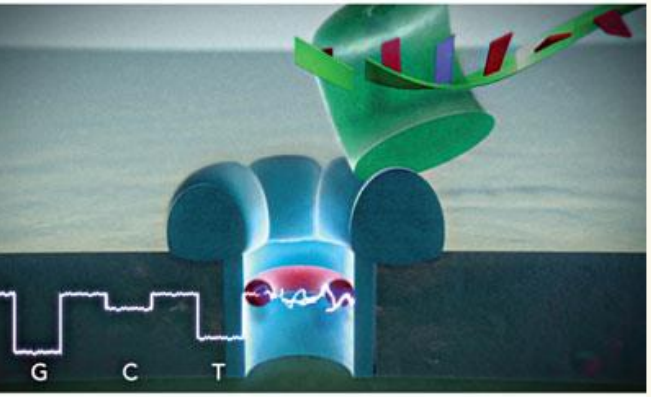


Protein nanopore in silica layer with continupous ion current (exonuclease enzyme splits DNA sample to fragments)



Enzyme-split DNA fragments move through nanopore where *red molecular adapter* recognizes them and stops ion current giving a signal



Each nuclein base gives characteristic signal enabling base identification.
(the molecular dapter is a betaCD derivative)

Significant extent of miniaturization

(A) A 860 kgs weigh setup of Pacific Biosciences RSII
(B) MinION sequencing device 120 gram
(C) Genapsys cross flow cell prototype
(D) A commodity digital camera-chip for mobil phones

(Ehrlich, Y. Genom Research 2015)

Oxford Nanopore's sequencing products

MINION® 2014 (left) and 2016 SmidgION® (right)
(Source: Oxford Nanopore)

The Minion® Sequencer in action in Guinea during Ebola outbreak, in 2015

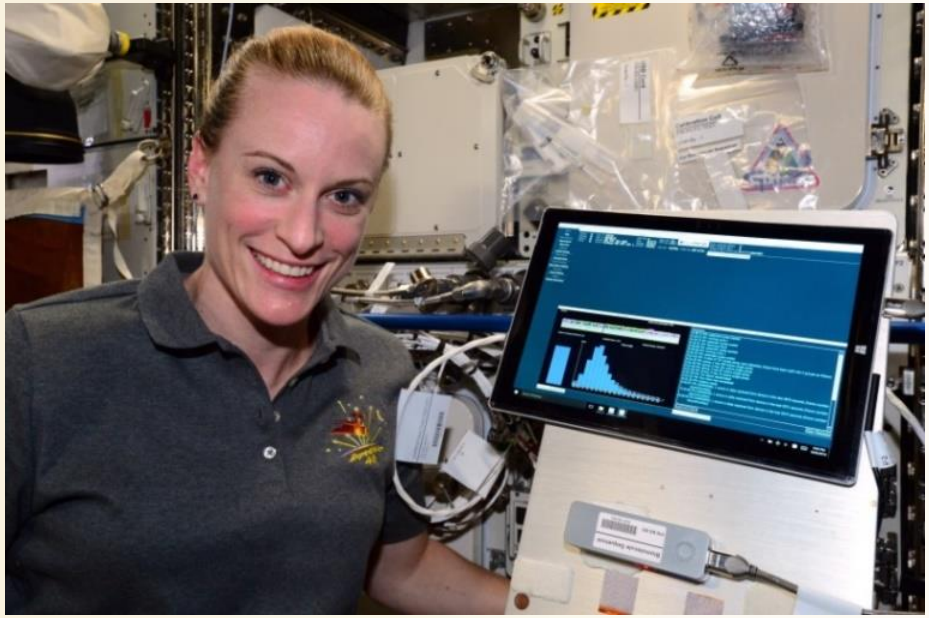
Quick, J. et al: Real-time, portable genome sequencing for Ebola surveillance

(Nature 530, 228–232. 2016)

*„ ..to generate **results** **less than 24 h** after receiving an Ebola-positive sample, with the sequencing process taking as little as **15–60 min.** We show that real-time genomic surveillance is possible in **resource-limited settings** and can be established rapidly to monitor outbreaks.”*

The very first DNA sequencing in microgravity

(NASA, August, 22. 2016.)



„For the first time ever, DNA was successfully sequenced in microgravity as part of the Biomolecule Sequencer experiment performed by NASA astronauts this weekend aboard the International Space Station" *NASA Johnson Space Center, August, 22. 2016.*

The first results

New Results first posted online Sep. 27, 2016.

Nanopore DNA Sequencing and Genome Assembly on the International Space Station

*Sarah L Castro-Wallace, Charles Y Chiu, Kristen K John, Sarah E Stahl, Kathleen H Rubins, Alexa B. R. McIntyre, Jason P Dworkin, Mark L Lupisella, David J Smith, Douglas J Botkin, Timothy A Stephenson, Sissel Juul, Daniel J Turner, Fernando Izquierdo, Scot Federman, Doug Stryke, Sneha Somasekar, Noah Alexander, Guixia Yu, Christopher Mason, Aaron S Burton**

doi: http://dx.doi.org/10.1101/077651

**To whom correspondence should be addressed: aaron.burton@nasa.gov*

Summary

Novel uses of „old" cyclodextrins resulted in:

- Development and clinical application of Bridion® where CD itself, acts as API
- Similar product developments currently in preclinical progress such as Heparinoid antidote CDs (CycloLab),
- The automatized and sensitive real-time DNS sequencing devices enabling diagnostic DNA analysis for about 1000 USD

Thank you!