CYCLOLAB

PIONEERS IN CYCLODEXTRIN-BASED INNOVATION

GETTING THE BEST OUT OF CYCLODEXTRINS

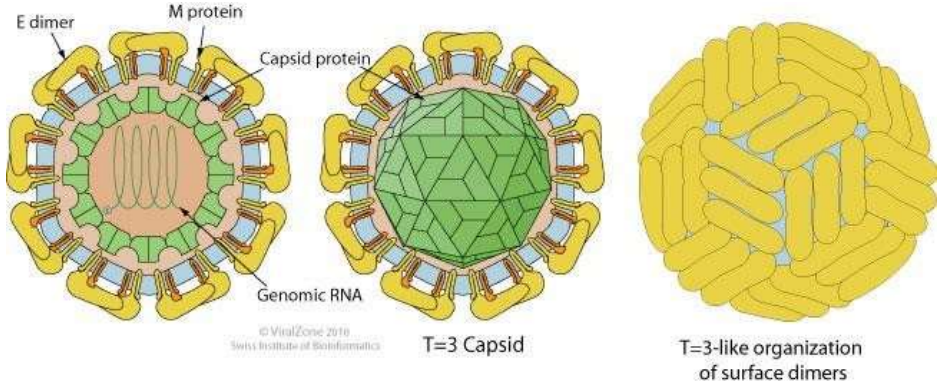
Technology presentation

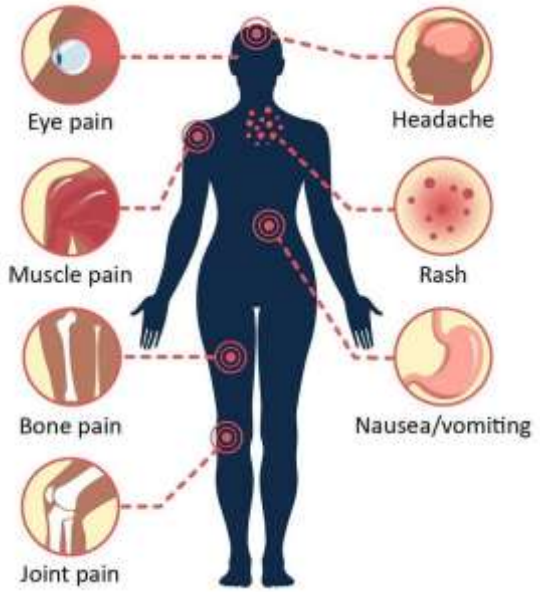
DEXOLVE™

CYCLODEXTRINS AGAINST DENGUE FEVER

DENGUE FEVER

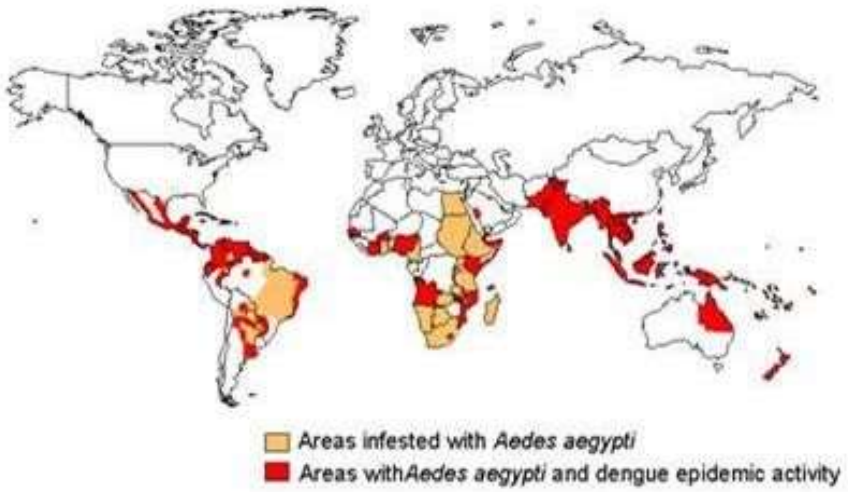
- Caused by Dengue virus (DENV), from *Flaviviridae* family, a **positive-sense, single stranded RNA virus** (+ssRNA)
- It is transmitted by **mosquitos**
- Dengue infections are caused by four closely related viruses named DEN-1, DEN-2, DEN-3, and DEN-4
- Dengue fever is **hard to diagnose** relying only on symptoms, because it has no specific ones





DENGUE FEVER

- According to the WHO the incidence of dengue has grown dramatically around the world in recent decades. A vast majority of cases are asymptomatic or mild and self-managed, and hence the actual numbers of dengue cases are under-reported. Many cases are also misdiagnosed as other febrile illnesses.
- The number of dengue cases reported to WHO increased **over 8 fold** over the last two decades, from 505.430 cases in 2000, to over 2.4 million in 2010, and 4.2 million in 2019.
- The most affected countries are **Vietnam, Colombia**, **Paraguay**, **Philippines**, **Sri Lanka**, **Bangladesh** and **Malaysia**.



DENGUE FEVER

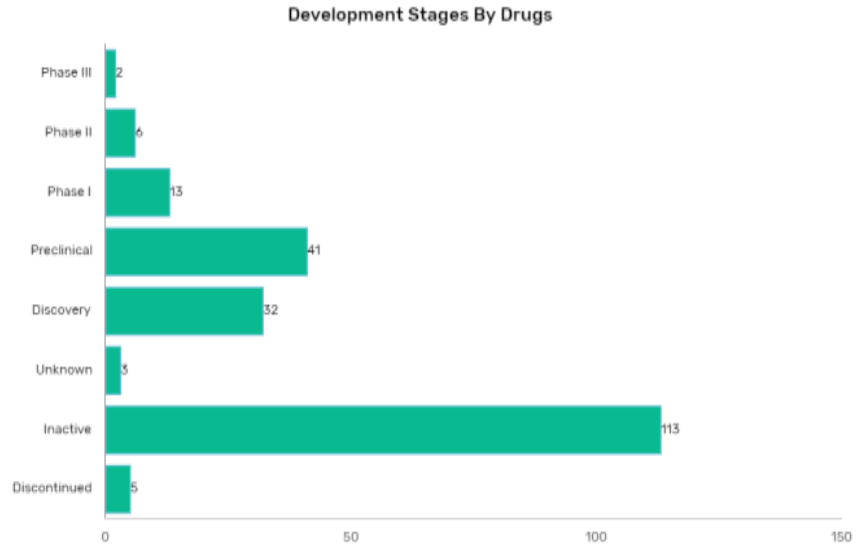
- Currently there **is no known treatment** for the disease
- OTC drugs can be used to ease the symptoms (e.g. paracetamol for fever)
- There is a vaccine against dengue fever, however it is **only** recommended in individuals who have had a prior dengue infection or in populations where most (>80%) of people have been infected by age 9[1]. For people who have not been infected yet with the virus it may worsen subsequent infections.

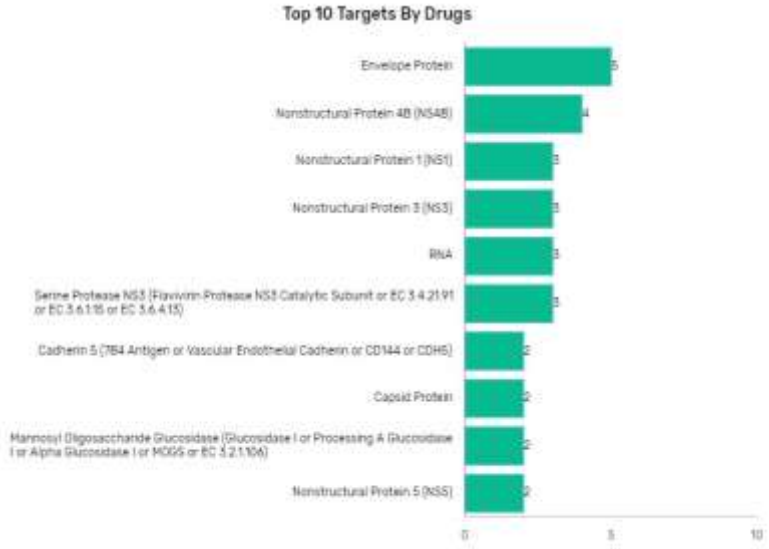
- **Since there is no known treatment and it is a global disease with increasing numbers of infected (according to ECDC[2]) there is an urgent need for the development of an effective drug against it.**

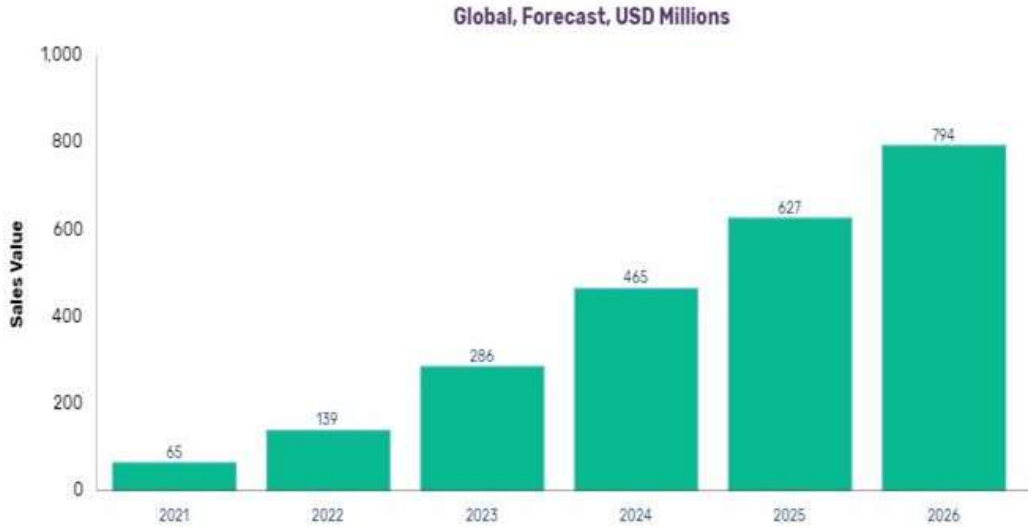
1 https://apps.who.int/iris/bitstream/handle/10665/274315/WER9336.pdf?ua=1
2 https://www.ecdc.europa.eu/en/dengue-monthly

DENGUE FEVER

- There are several molecules in different stages of development
- Also, the **market potential** is huge and exponentially increasing







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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

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CDS AS ANTIVIRAL AGENTS

- CDs have been shown to possess broad-spectrum antiviral activity against HIV, herpes simplex, influenza, RSV and Zika viruses with suggested mechanisms of action including:
- Inhibition of viral entry
- Inhibition of viral replication
- Cholesterol sequestering and virucidal activity[3]

methyl derivatives

methyl and sulphate derivatives

heparan-sulfate mimics[4]

[3]Martin-Acebes et al. Progress in Lipid Research 2016, 64, 123-137
[4]Jones, S.T. et al. Modified cyclodextrins as broad-spectrum antivirals. Science Advances 2020, 6(5), eaax9318

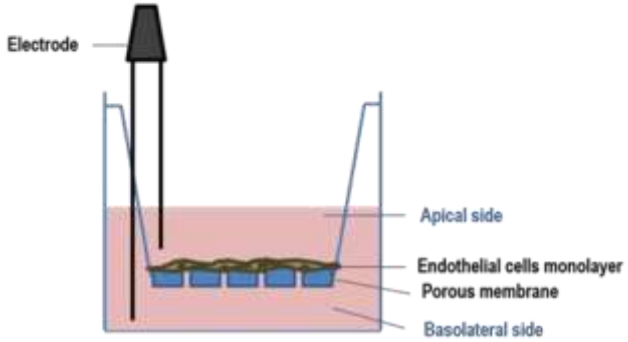
CYCLODEXTRINS AND CYCLOLAB

- Since 1991, Cyclolab has been at the forefront of introducing cyclodextrins to the pharmaceutical industry.
- The pipeline of the company focuses on inventing **novel applications of cyclodextrins**, such as their uses in formulation biologicals, applications in biotech processes and vaccines, creating drug delivery systems, or their uses as active ingredients in a wide range of diseases.
- **Recently University of California, Berkeley, Excivion and CycloLab teamed-up to develop the antiviral potential of cyclodextrins against Dengue and Zika viruses in NIH-supported studies.**

CDs AGAINST DENV

- A wide range of CDs were evaluated for the *in vitro* efficacy against **DEN2 NS1** (nonstructural protein 1)-mediated pathogenesis
- In an *in vitro* model of endothelial permeability, CDs, at concentrations that had zero anticoagulant effect, were added to human pulmonary microvascular endothelial cells (HPMECs) in the presence of DENV2 NS1.
- Endothelial disruption was quantified by measuring **Trans-Endothelial Electrical Resistance** (TEER). **No cytotoxicity** was observed for any CD tested up to 1500 µg/mL.

TEER measurement
(*Trans Endothelial Electrical Resistance*)



Source: http://www.itqb.unl.pt/

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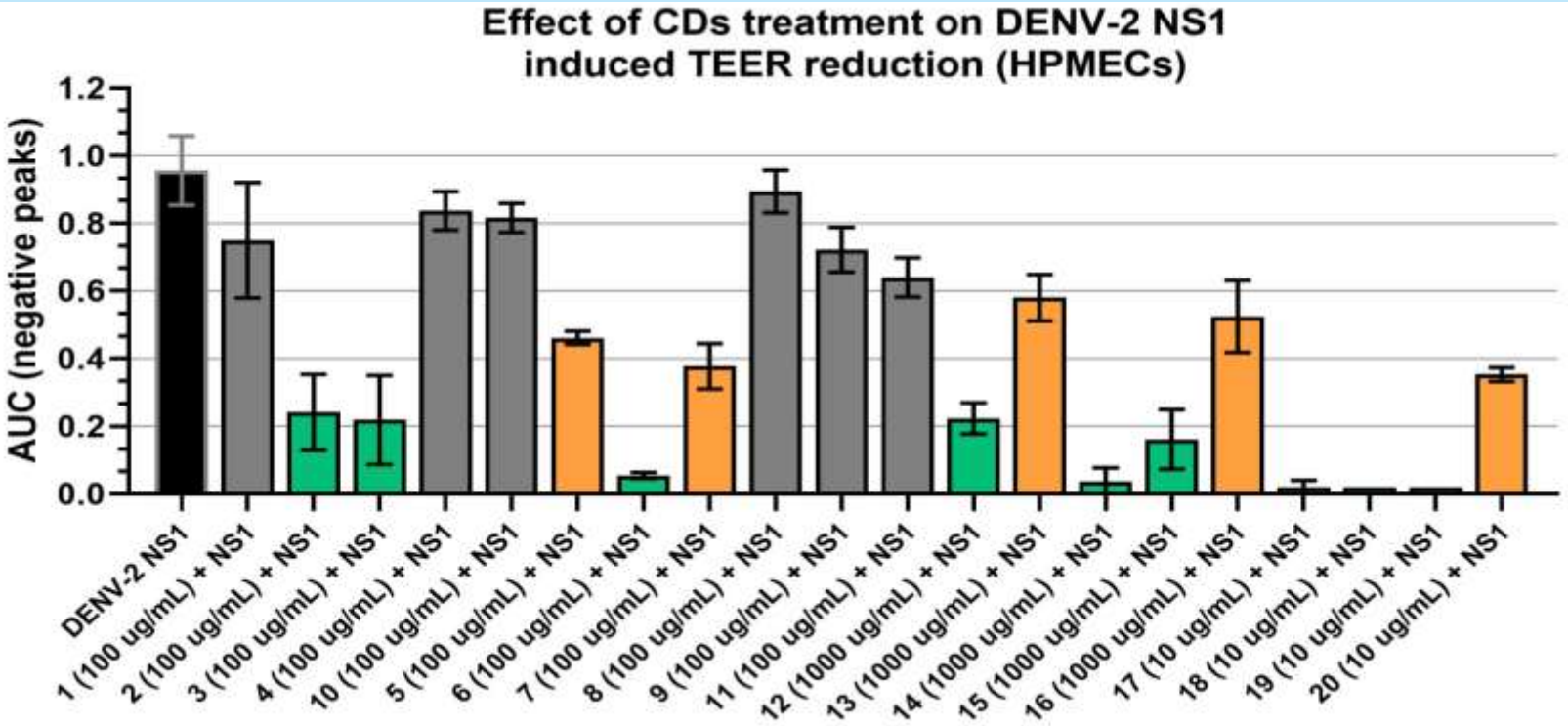
Inhibition of DENV NS1-induced hyperpermeability by CDs



- AUC of dengue NS1 alone in **black** compared to NS1 plus the compounds.
- **9 CDs have significant reduction as shown in the green bars.**

DEXOLVE™

CURRENT AND FUTURE ASPECTS

- We are currently assessing the inhibition of NS1 binding to HPMECs by CDs, their *in vitro* anti-DENV activity, and their *in vivo* efficacy in murine models of vascular leak.
- **PATENT:** Cyclodextrin derivatives reducing flavivirus NS1-induced endothelial hyperpermeability and vascular leak, United States Application Number: 17/097,977
- Evaluate CDs against other viral infections
- Candidate selection, scale-up, GMP production
- IND-enabling tox and efficacy studies planned through 2021

COMPANY CONTACTS

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