

BEYOND, TOGETHER

ADEBIOTECH : Cell Factories for Industrial Bioproduction

HTL's key figures



30 YEARS OF EXPERTISE



R&D AND MANUFACTURING PLATFORM



KEY MARKETS

#1

Global provider of pharma-grade Hyaluronic Acid

#1

Global manufacturer of biopolymers with 2 plants – GMP compliant

100+

Customers located in 30+ countries

1992

Company founded by Michèle Ranson, Pharmacist

2.3x

Capacity increase in 2021

100%

Health Care applications

193

Number of employees working daily with excellence to serve clients

15

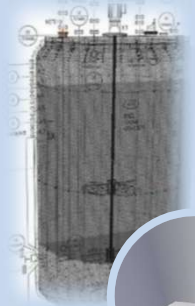
Projects in external R&D pipeline

200+ millions

Syringes containing HTL's hyaluronic acid have been safely used since 2006

Proprietary Manufacturing Process

HTL FERMENTATION TECHNOLOGY



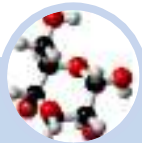
Our expertise:
dedicated fermentor,
medium composition,
stirring,
mass transfer...



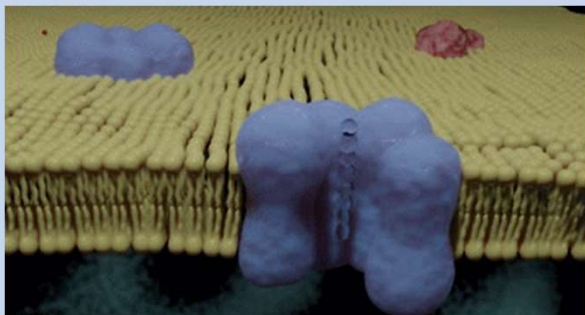
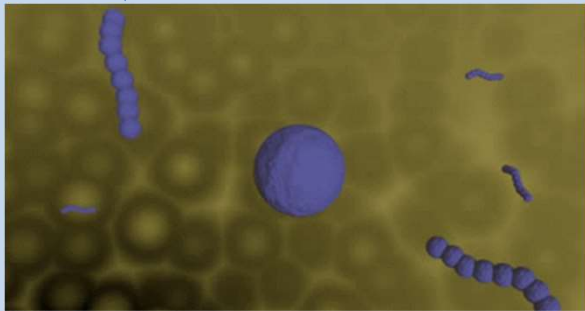
STREPTOCOCCUS
EQUI



NUTRIENTS

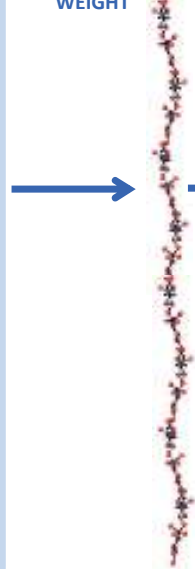


GLUCOSE

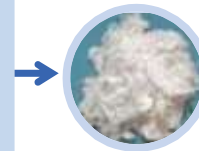
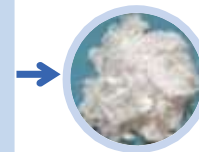


HYALURONIC ACID

HIGH
MOLECULAR
WEIGHT



HIGH PURITY
HYALURONIC ACID
FIBERS



WIDE RANGE
OF MOLECULAR
WEIGHT

DOWN-
STREAM
PROCESS

Proprietary
Know-How
of HTL

IMPACT ON VISCOSITY MODULATION



Heparosan

a new Glycosaminoglycan for pharmaceutical applications



Endogenous transitory molecule in the biosynthesis of heparin in mammals



- **Biocompatible**
- **Non-immunogenic**
- **Hyaluronidase resistance**
- **No accumulation of breakdown products in the body**



WELL TOLERATED

INCREASED STABILITY

SAFE ABSORPTION

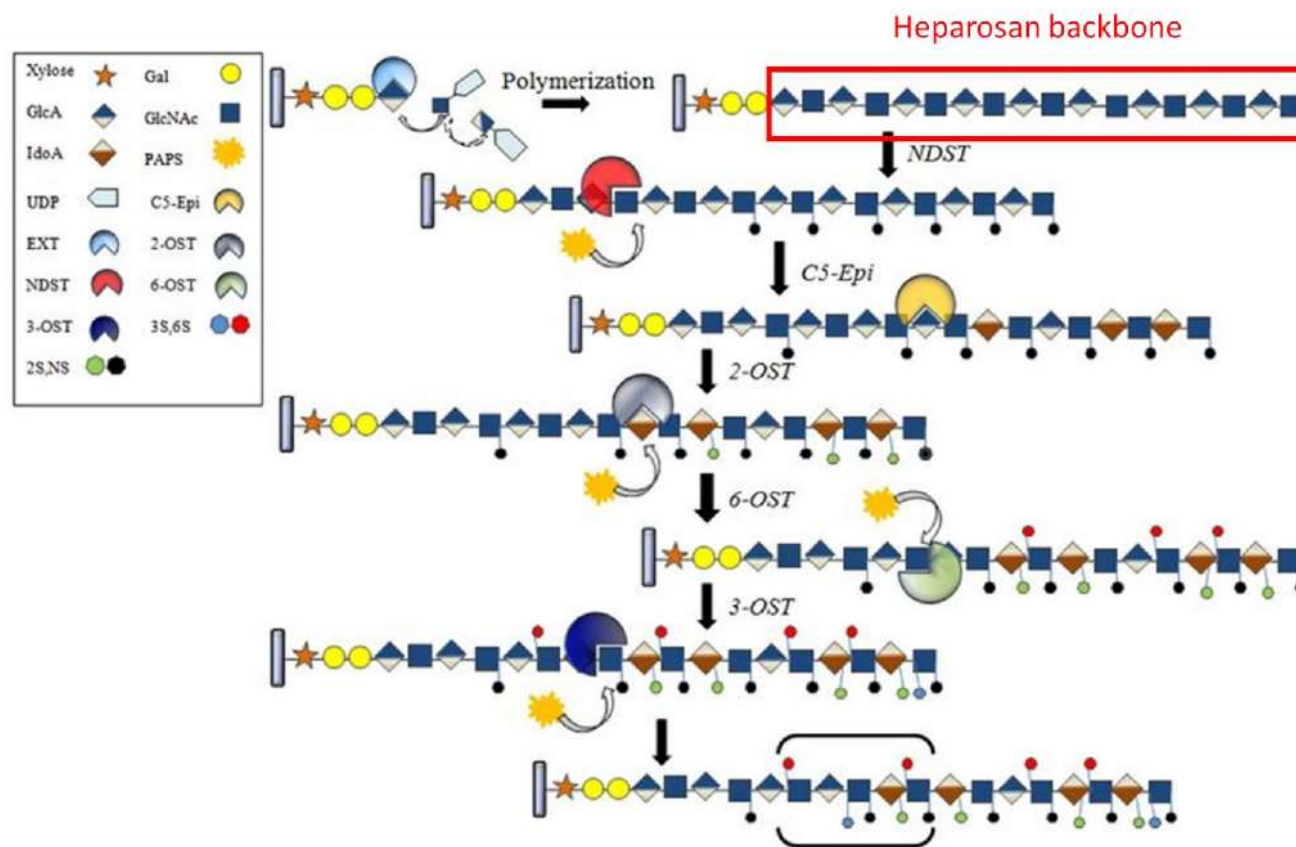


Biological, physical and chemical characteristics suited to prepare tissue engineering biomaterials as gels and scaffolds



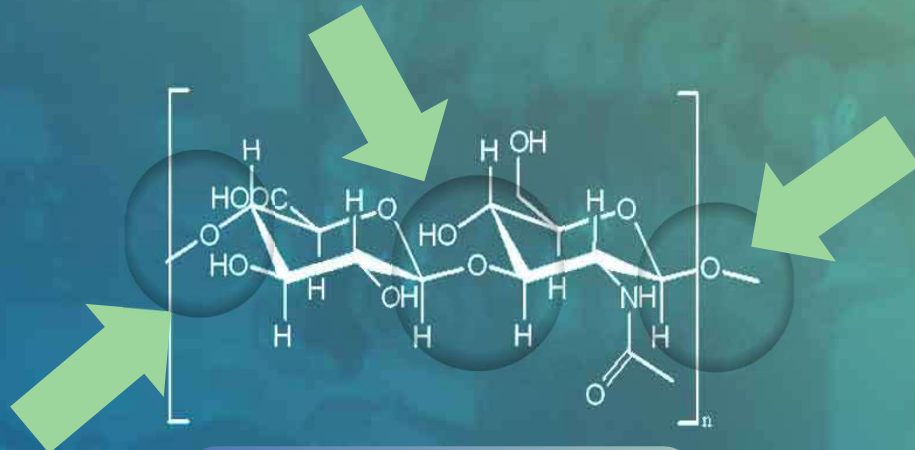
Our Heparosan pilot scale fermentation process enables to produce **MW of more than 2 MDa**

Origin of the molecule : heparan sulfate precursor

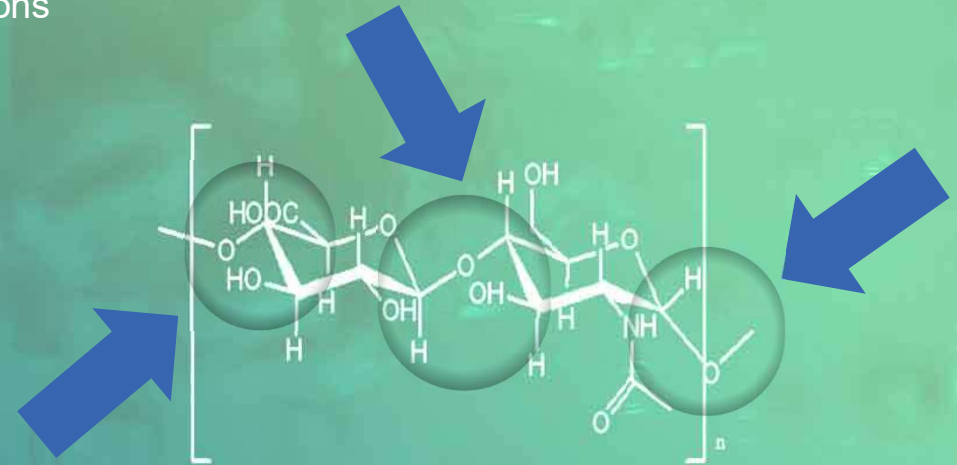


Heparosan

Heparosan, a new Glycosaminoglycan for pharmaceutical applications



HYALURONIC ACID STRUCTURE



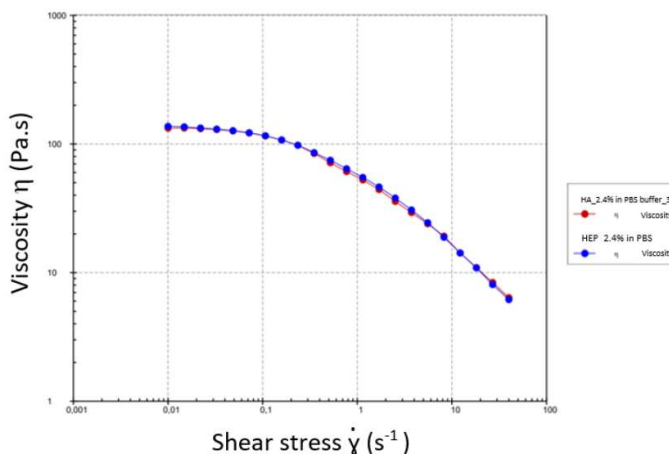
HEPAROSAN STRUCTURE

STRUCTURE, PHYSICAL AND CHEMICAL BEHAVIOURS CLOSE TO HYALURONIC ACID

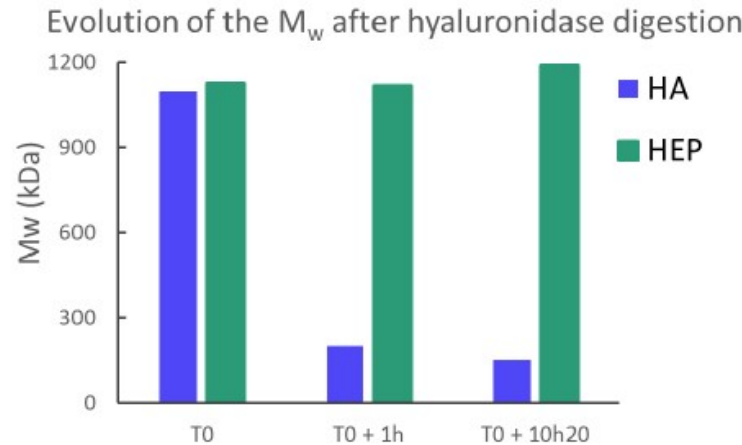
Repetitive unit similar to Hyaluronic Acid, but difference in glycosidic bonds

- The heparosan polysaccharide is comprised of a $[\rightarrow 4) \beta\text{-D-glucuronic acid (GlcA) (1\rightarrow 4) N\text{-acetyl-}\alpha\text{-D-glucosamine (GlcNAc) (1\rightarrow)}_n$ repeating disaccharide unit
- Hyaluronic acid is a polymer of disaccharides, themselves composed of D-glucuronic acid and N-acetyl-D-glucosamine, linked via alternating $\beta\text{-}(1\rightarrow 4)$ and $\beta\text{-}(1\rightarrow 3)$ glycosidic bonds

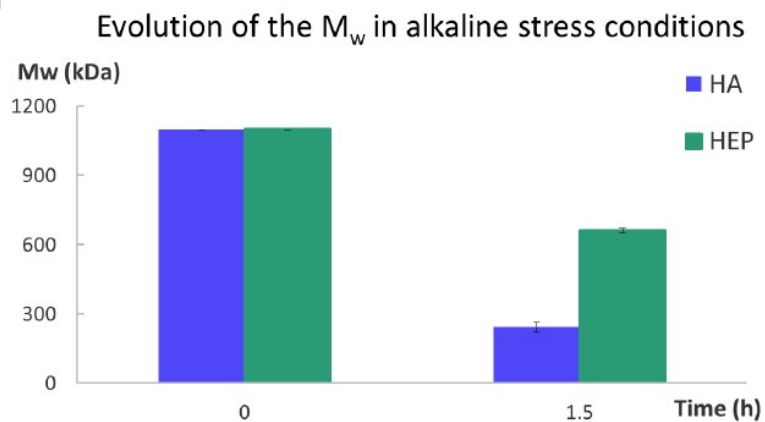
A new Glycosaminoglycan for medical applications



Similar rheological properties for Hyaluronic Acid and Heparosan (HPN) at the same MW



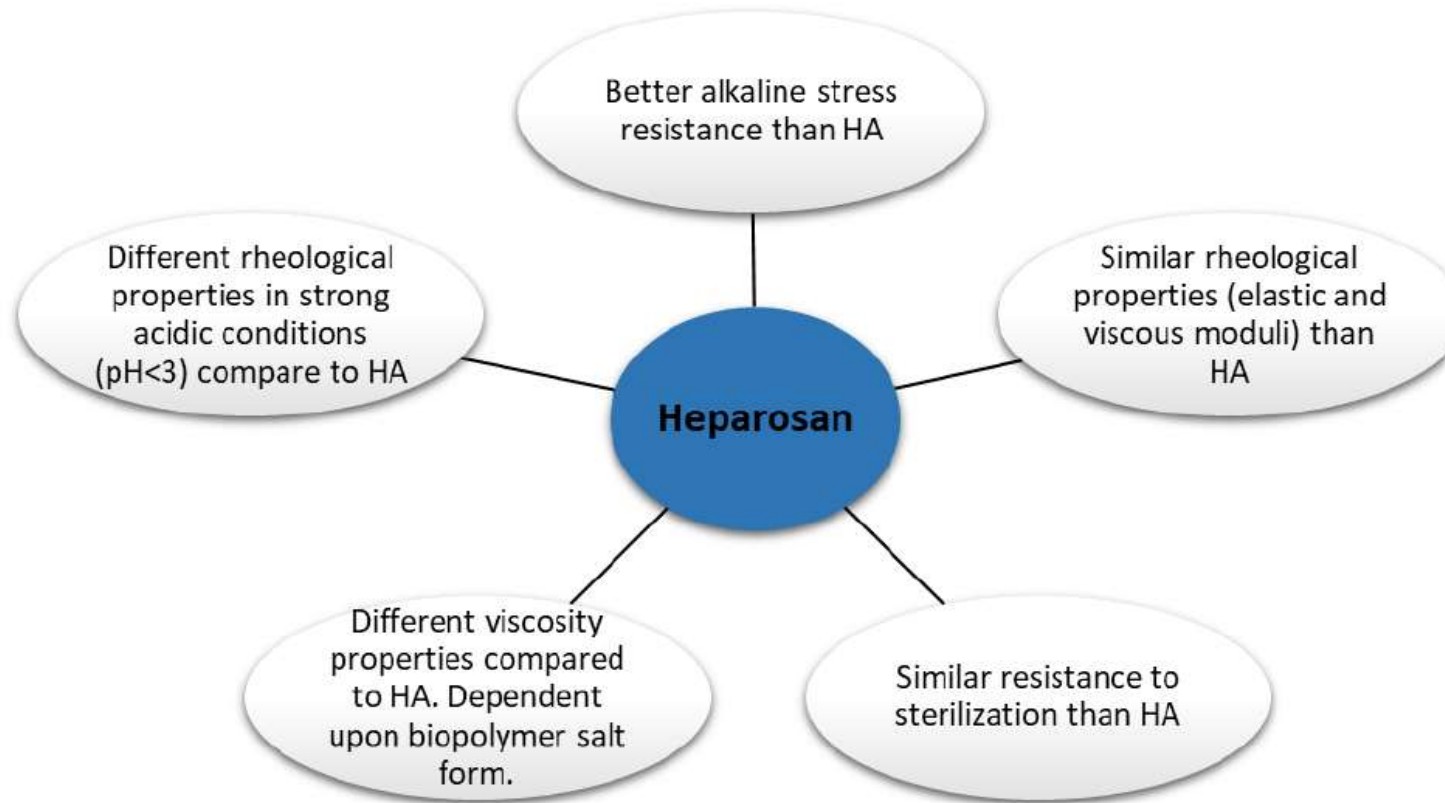
Hyaluronidase digests HA but not HPN



For close HA and HPN MW some properties could vary

Heparosan

Conclusions



Project specifications

1°) High molecular Heparosan targeted

2°) Molecule purity compliant with injectable use

3°) Quality by Design approach

4°) Natural or edited strain ?

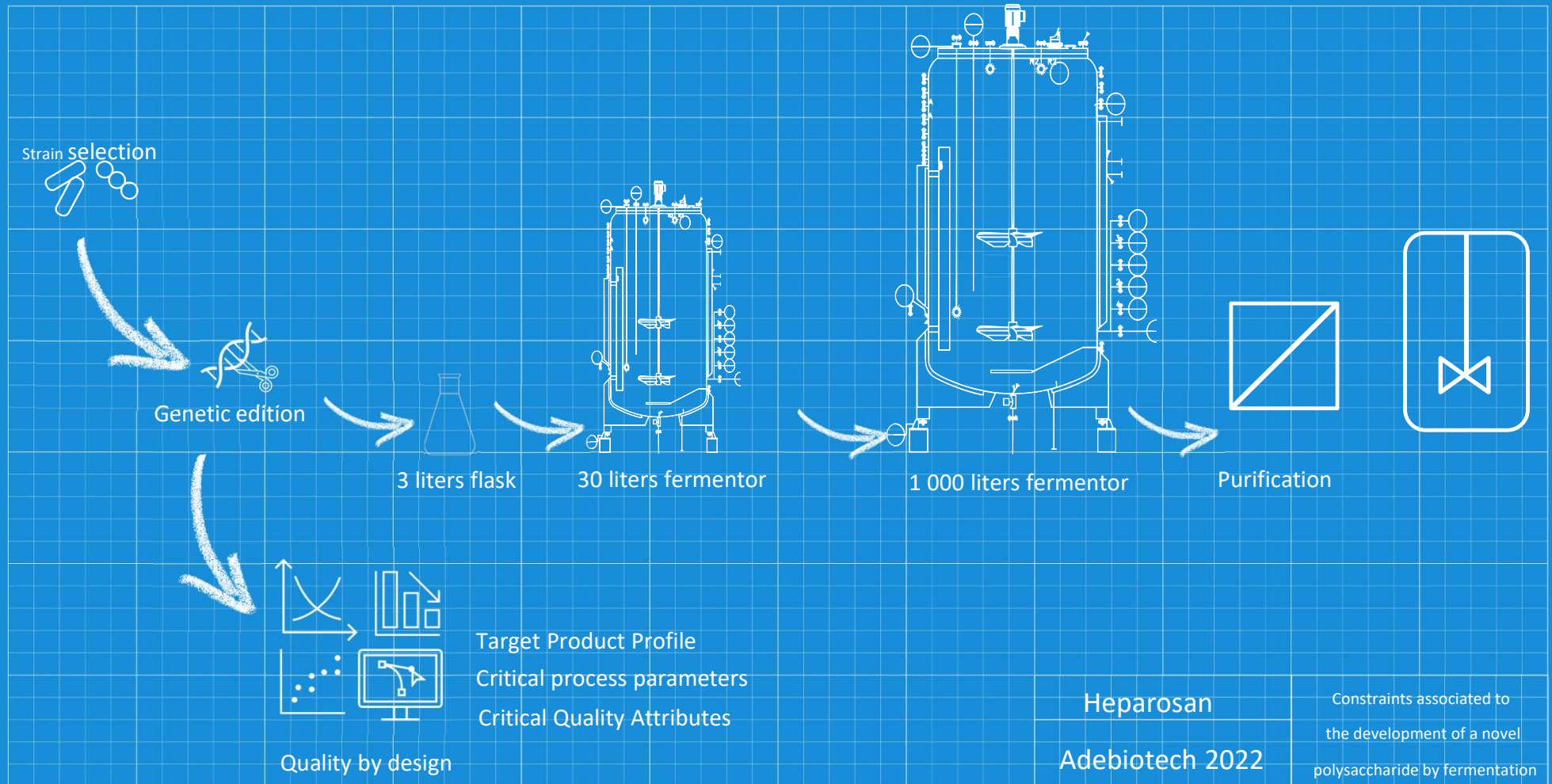
5°) cGMP process

6°) Low carbon footprint

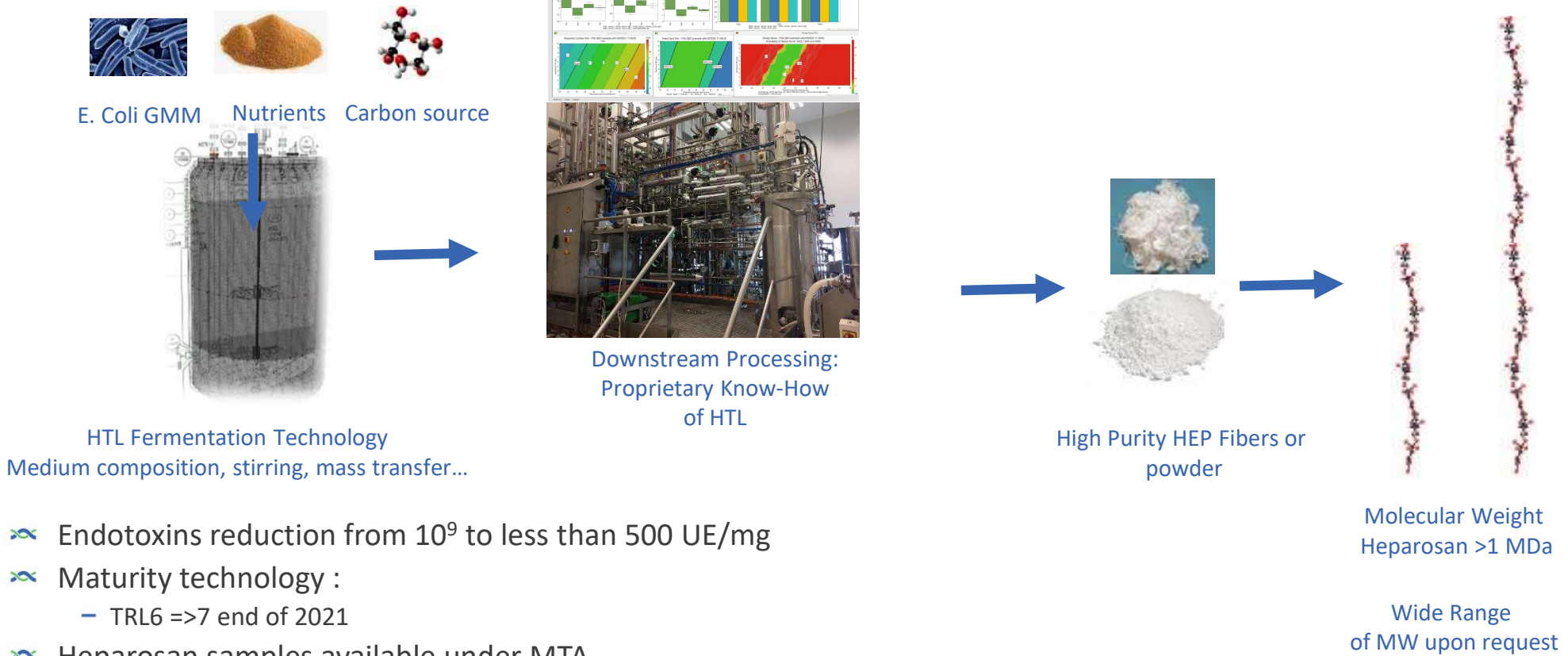
Heparosan

Adebiotech 2022

Constraints associated to
the development of a novel
polysaccharide by fermentation



HTL Heparosan production technology



- ✘ Endotoxins reduction from 10^9 to less than 500 UE/mg
- ✘ Maturity technology :
 - TRL6 =>7 end of 2021
- ✘ Heparosan samples available under MTA

Conclusions

Heparosan development process

- ✎ Designed a strain and additional modifications to integrate industrial constraints
 - Robustness
 - No antibiotics resistance markers remaining in the strain
 - No more induction

- ✎ Designed a state-of-the-art full cGMP compliant pilot facility
 - Fermentor up to 1 000 liters
 - Versatile DSP able to purify most of polysaccharides

- ✎ Development of a very efficient DSP
 - To reduce endotoxins level to an acceptable level for parenteral use
 - Remove most of impurities to maintain the good safety profile of Heparosan

- ✎ Implemented a QbD methodology to secure quality compliance and industrial performances



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