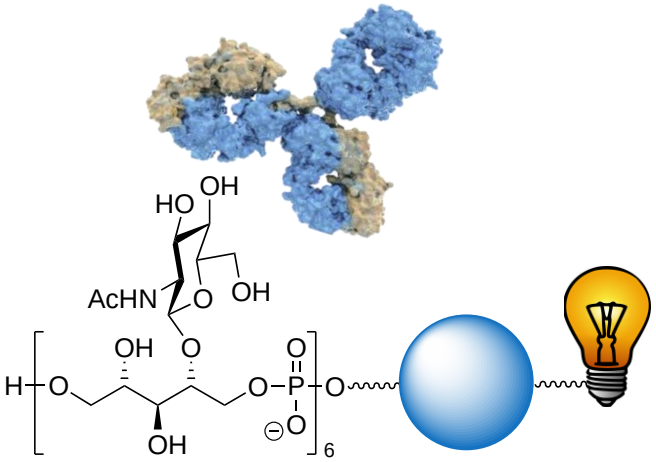
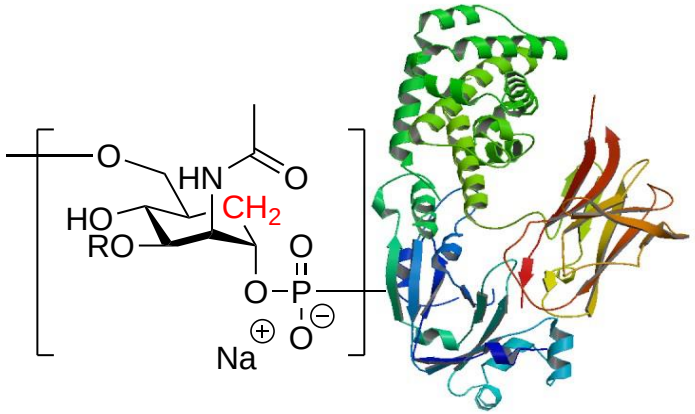
Sweet vaccines

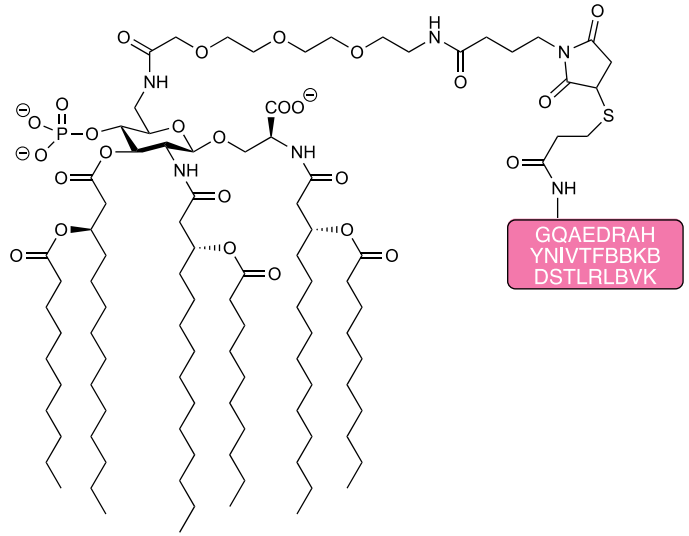
application of synthetic carbohydrates in conjugate vaccines

Jeroen Codée

Leiden Institute of Chemistry, Leiden University, Leiden, The Netherlands





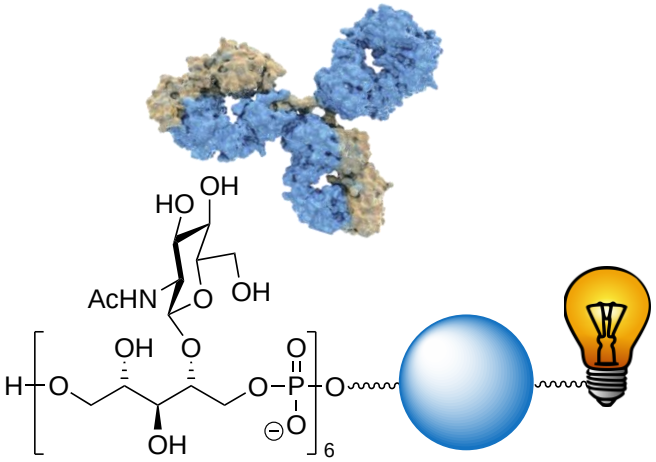


LEIDEN
DRUG DEVELOPMENT
CONFERENCE

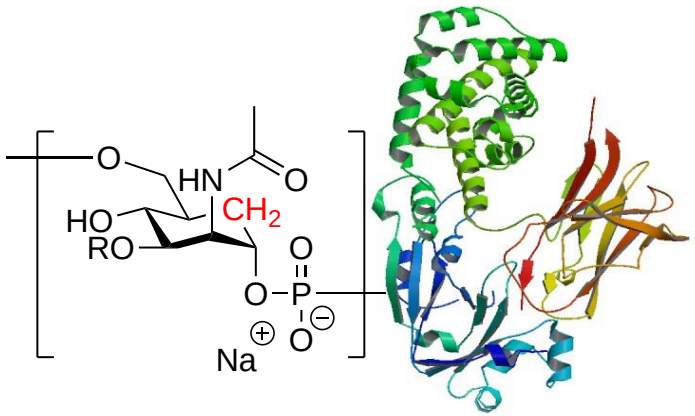
Sweet vaccines

application of synthetic carbohydrates in conjugate vaccines

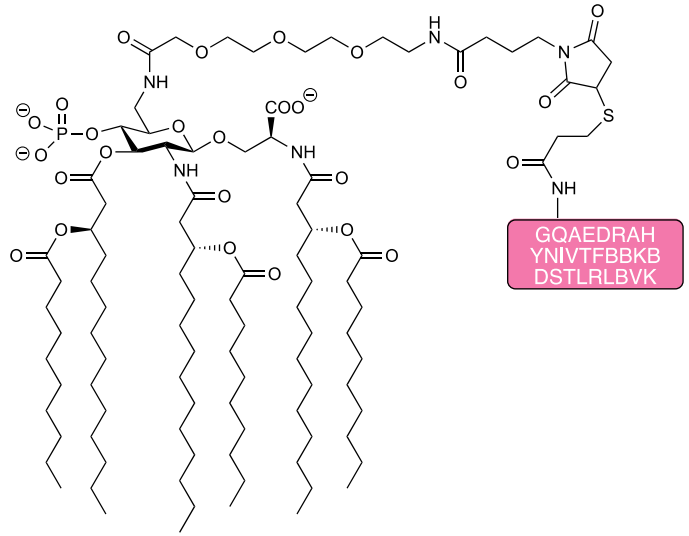
Synthetic *Staphylococcus aureus*
Wall Teichoic Acids
to unravel host-pathogen interactions



Antigen mimicry in the development of a
stabilized *Neisseria meningitidis*
conjugate vaccin



Self adjuvanting
anti-cancer vaccines



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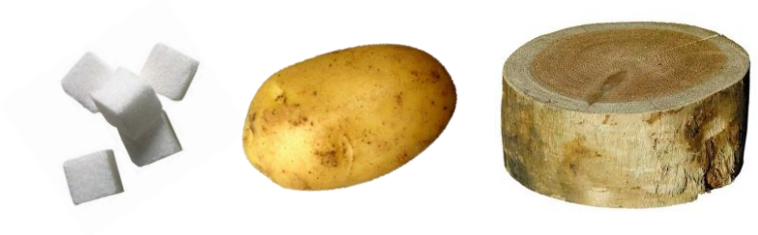
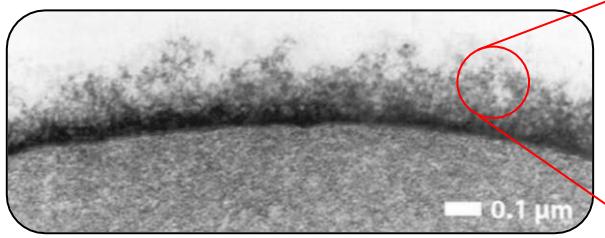
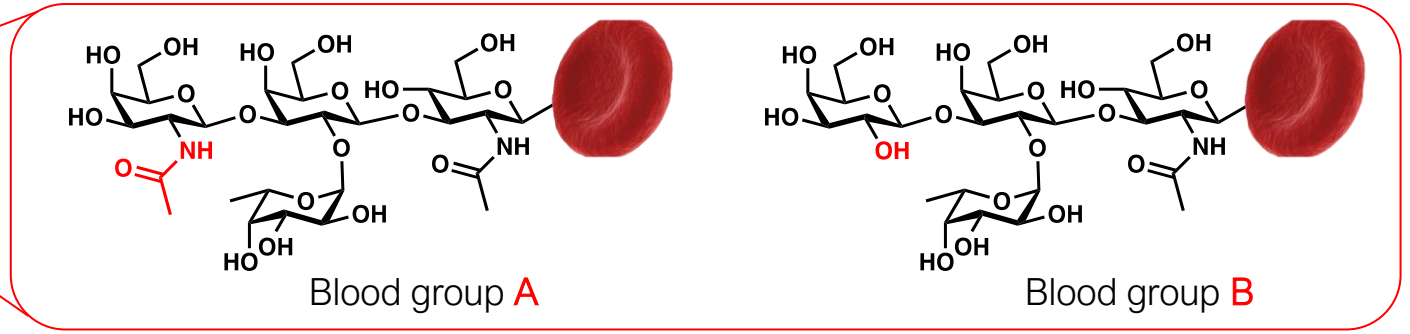
CARBOHYDRATES

Most abundant biopolymers on earth
Present in all kingdoms of life
Molecular insight required for new medicine, materials, biofuels…
Biosynthesis non-template driven
Gargantuan diversity

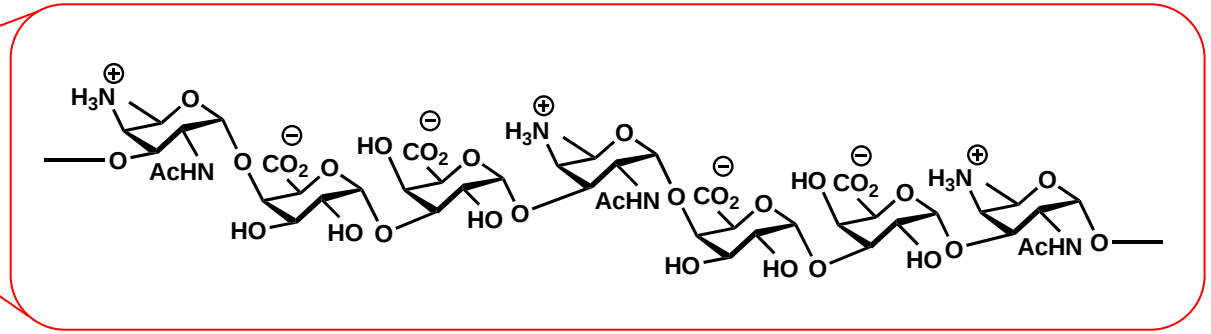




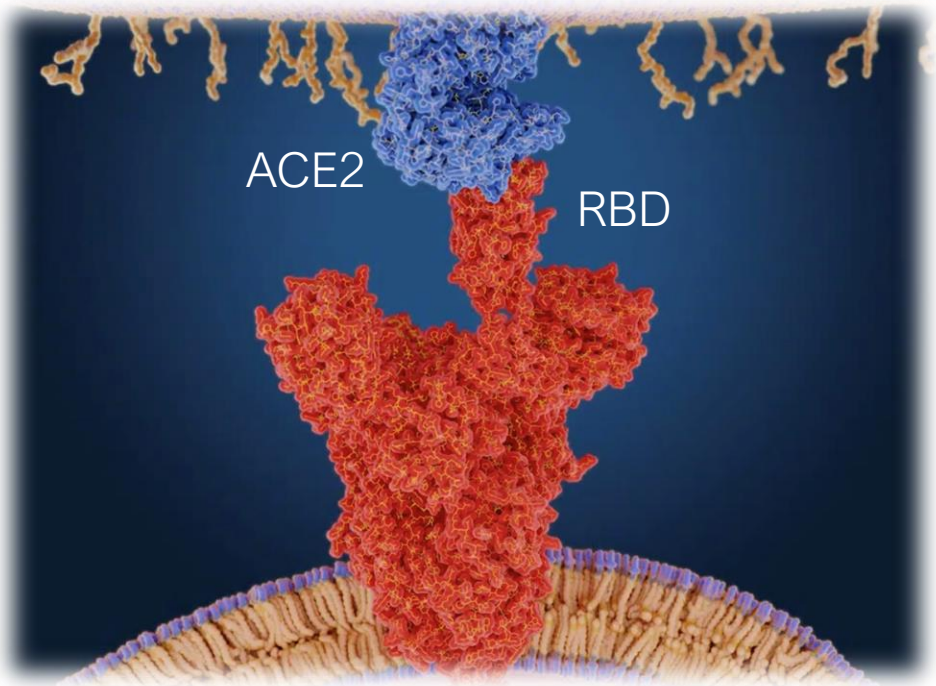
Red blood cell



S. pneumoniae

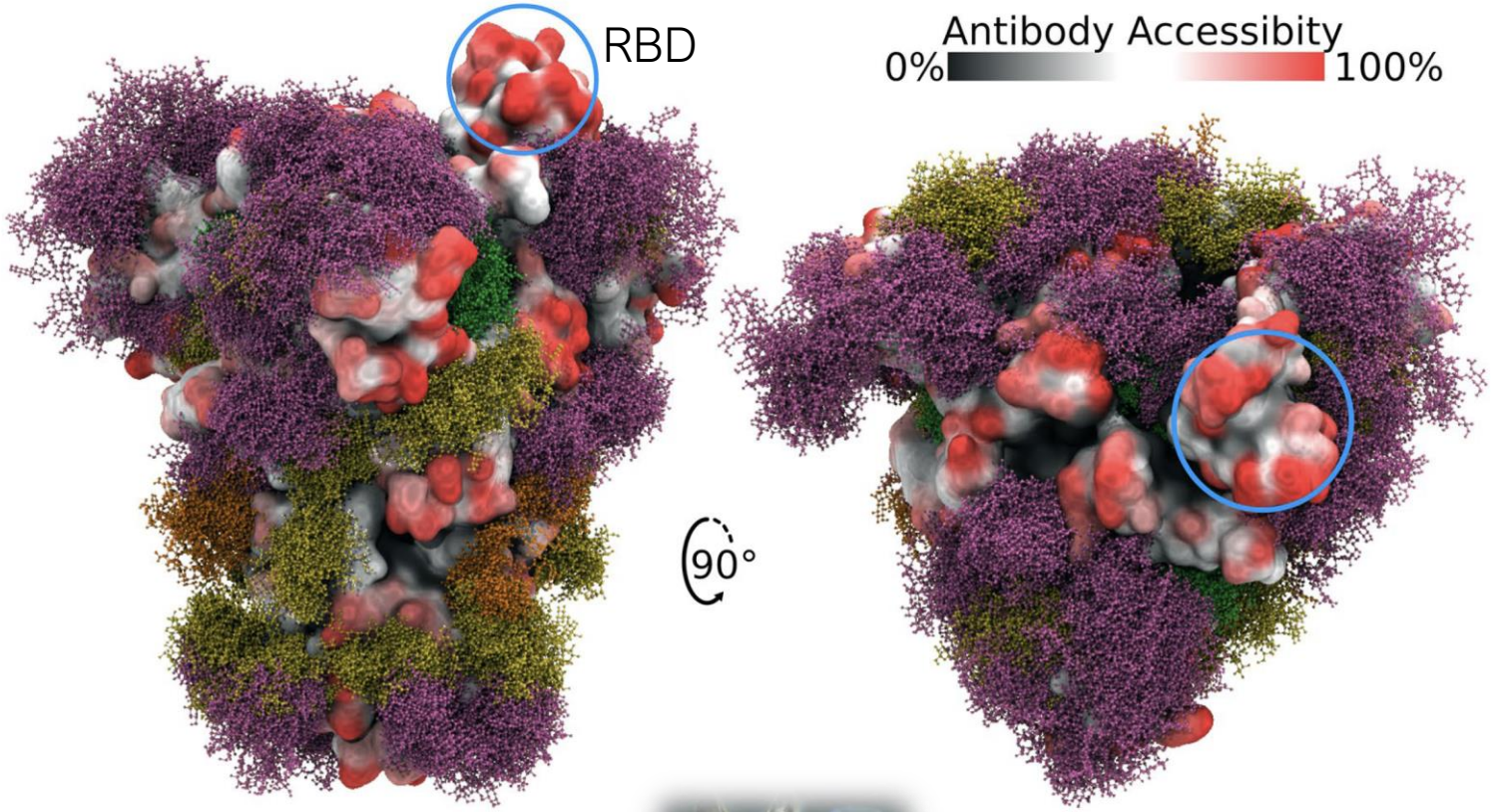


VIRAL GLYCAN SHIELD



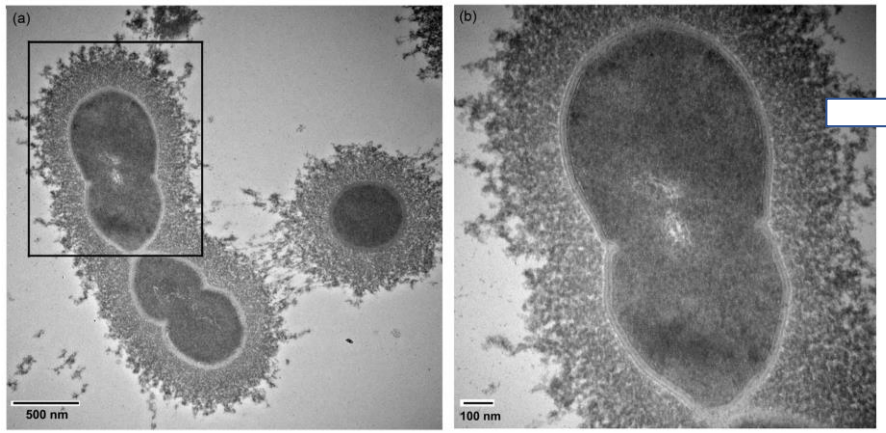
Corona spike protein

"Self glycans" to hide from our immune system



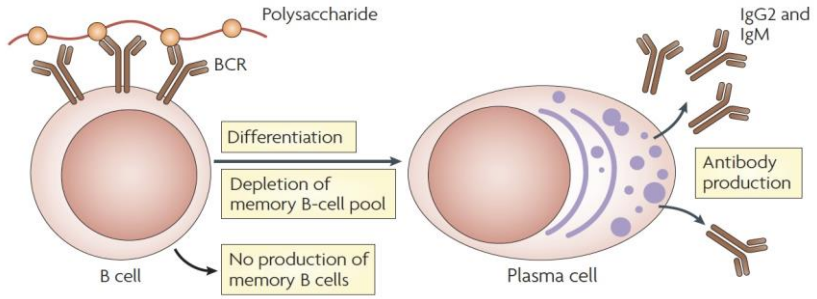
Woods, Sci rep 2020

GLYCOCONJUGATE VACCINES

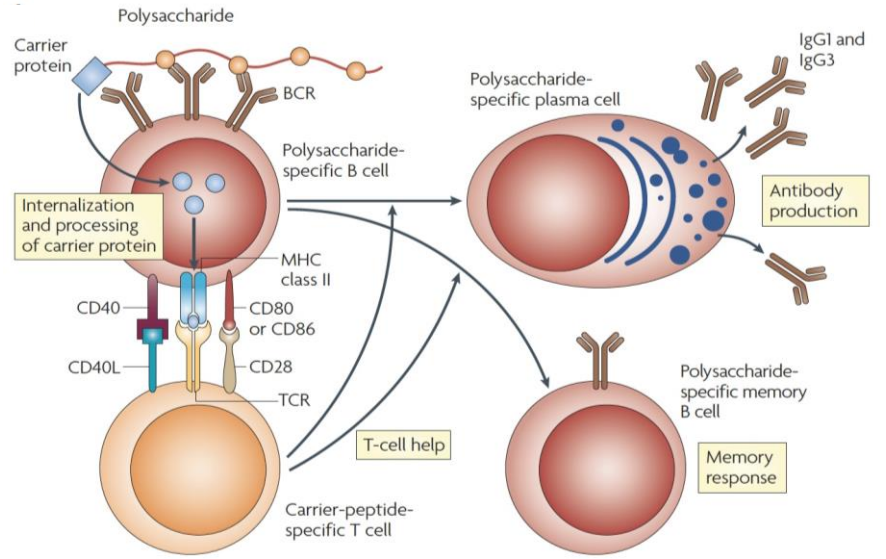


Wen, Mol Med Microbiol 2015, 1, 3-53.

Stand alone polysaccharide



Glyco conjugate vaccines



Polysaccharides are poorly immunogenic (in infants)
IgM response, no memory

Conjugation leads to class switching (high affinity IgG) and memory B-cells

Effective glycoconjugate vaccines have erradicated
H. influenza
N. meningitidis
S. pneumoniae
S. enterica s. typhi

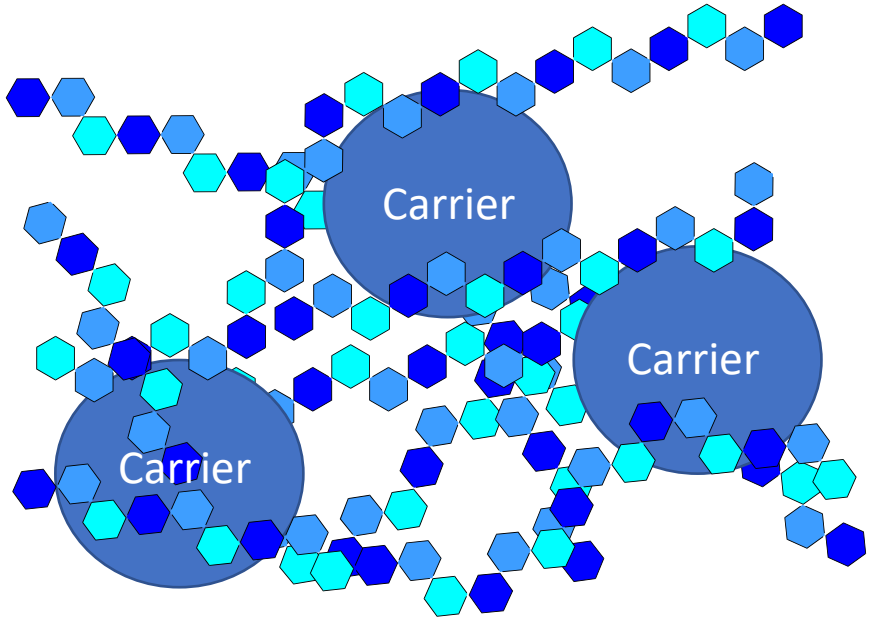
Pollard, Nat Rev Immunol 2009

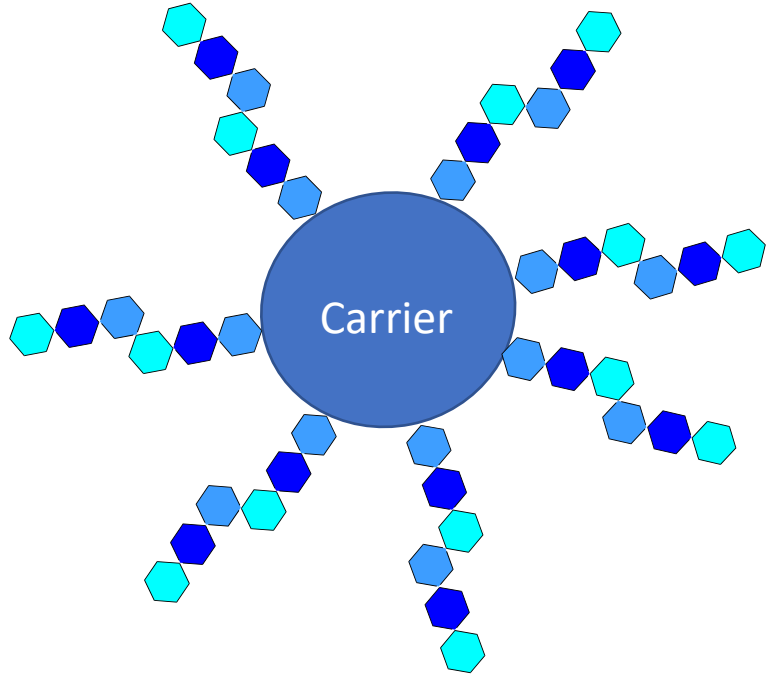
Why synthesis?

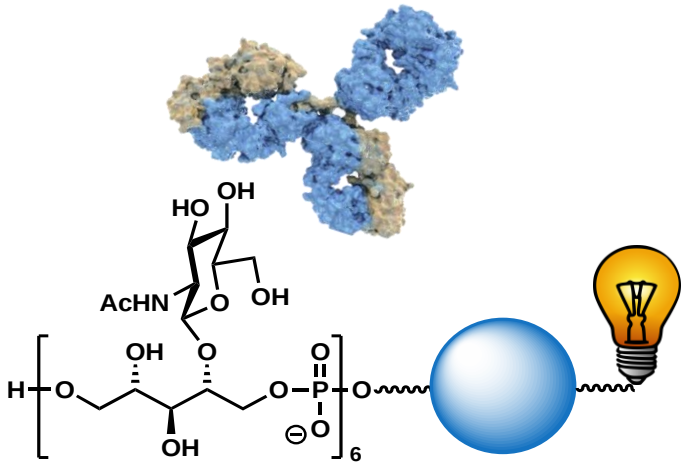
Minimal batch to batch variation
Well-defined structure
Length control
Composition control
Single conjugation site
Optimal loading control

Antigen mapping
Biosynthesis probes (Antibiotics?)

First synthetic vaccine: Quimihib (2004)
PNAG (Phase II)
Shigella (Phase I)



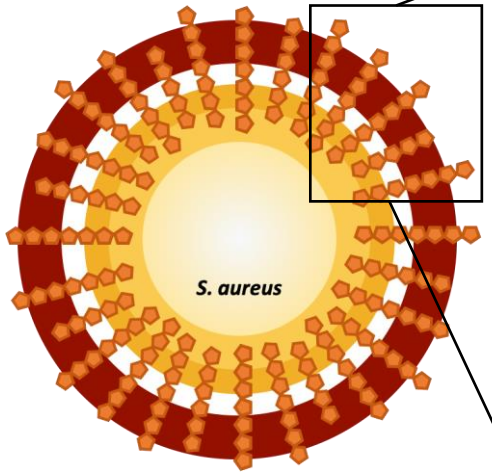


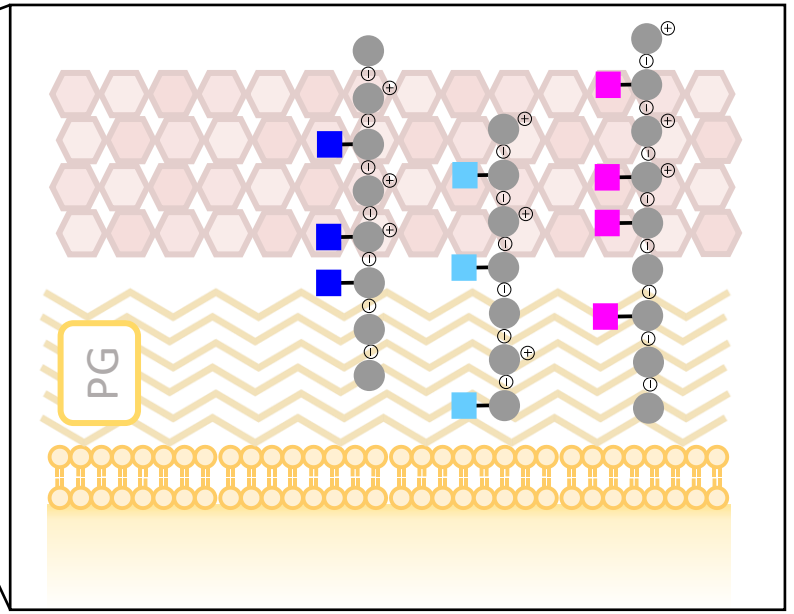


Synthetic Staphylococcus aureus Wall Teichoic Acids to unravel host-pathogen interactions

S. aureus

Commensal bacterium (skin, nasopharynx, gastrointestinal tract)
Gram-positive
ESKAPE pathogen
Methicilin Resistant *S. Aureus* (MRSA)
Novel treatments urgengtly needed
Passive or active vaccination?
Optimal antigen?

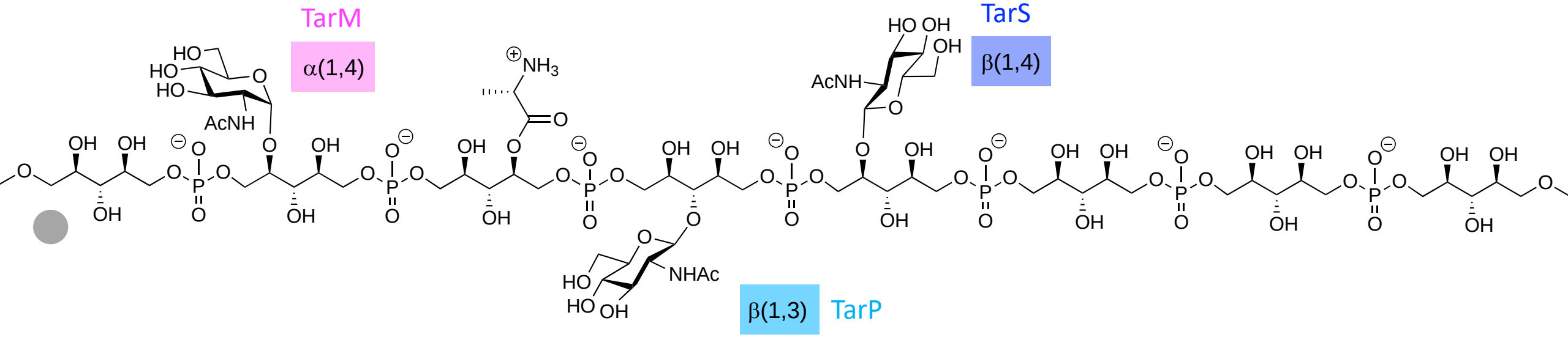




Wall teichoic Acid (WTA)

RboP
GlcNac
D-Ala
Very heterogeneous
Binding partners?
SAR?

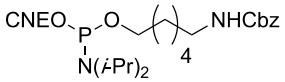
⇨ SYNTHESIS

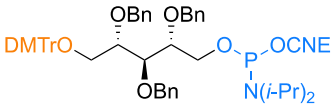


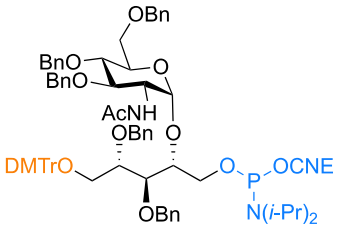
Gerlach, Nature, 2018, 563, 705.

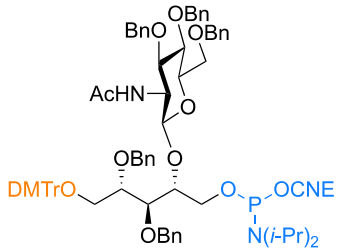
“DNA-style” chemistry

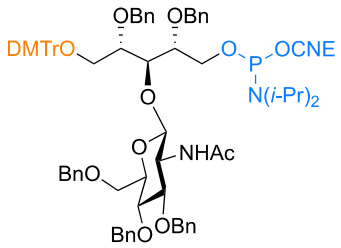
Tailor made building blocks



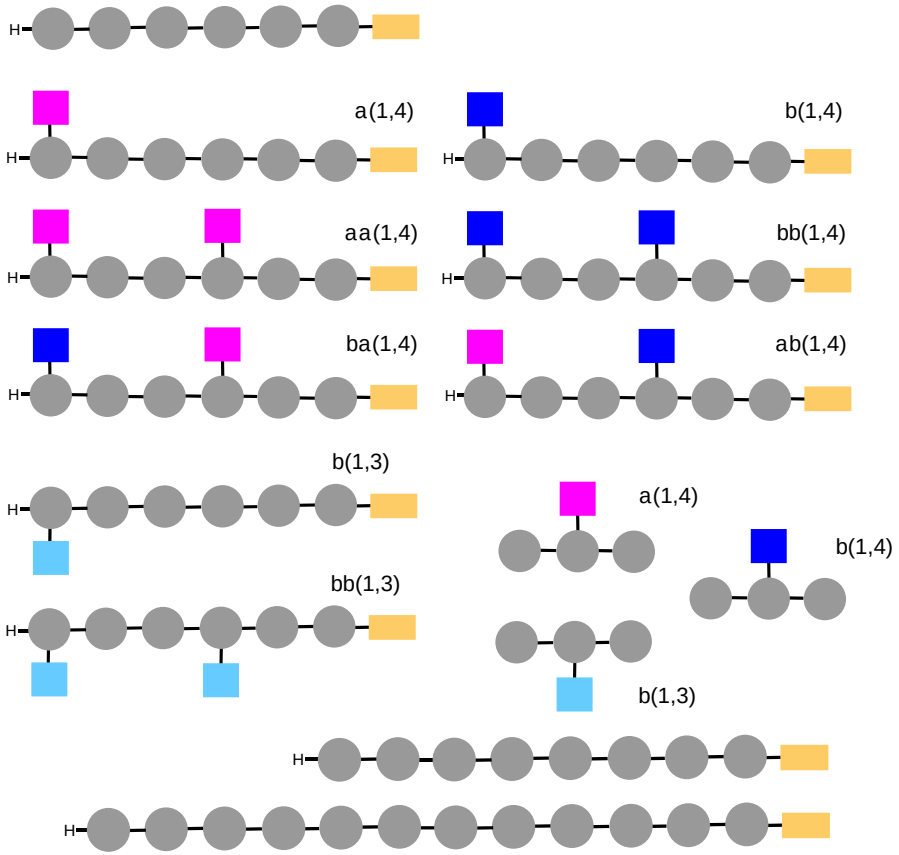


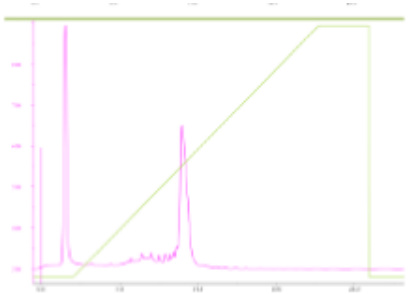




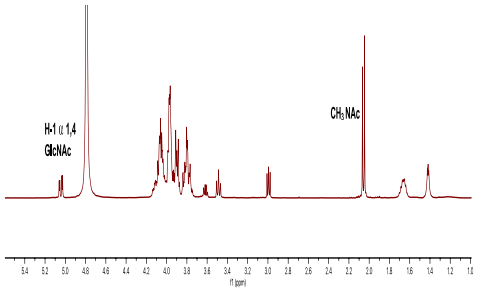


Library assembly



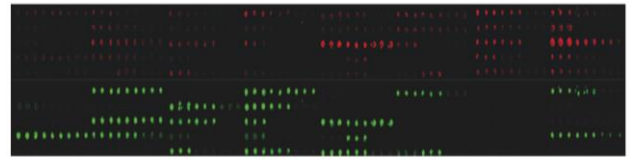


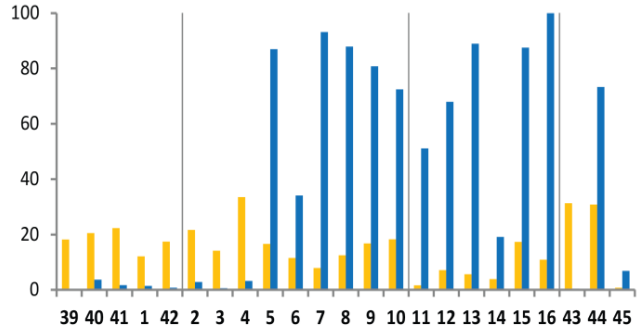
HPLC

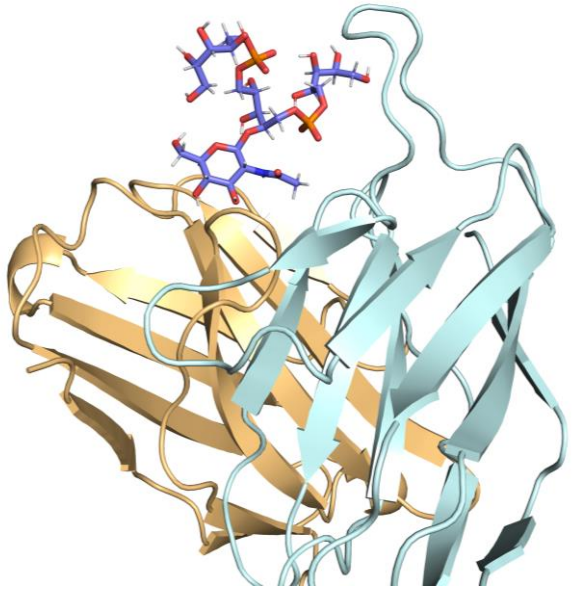


NMR

Interaction studies

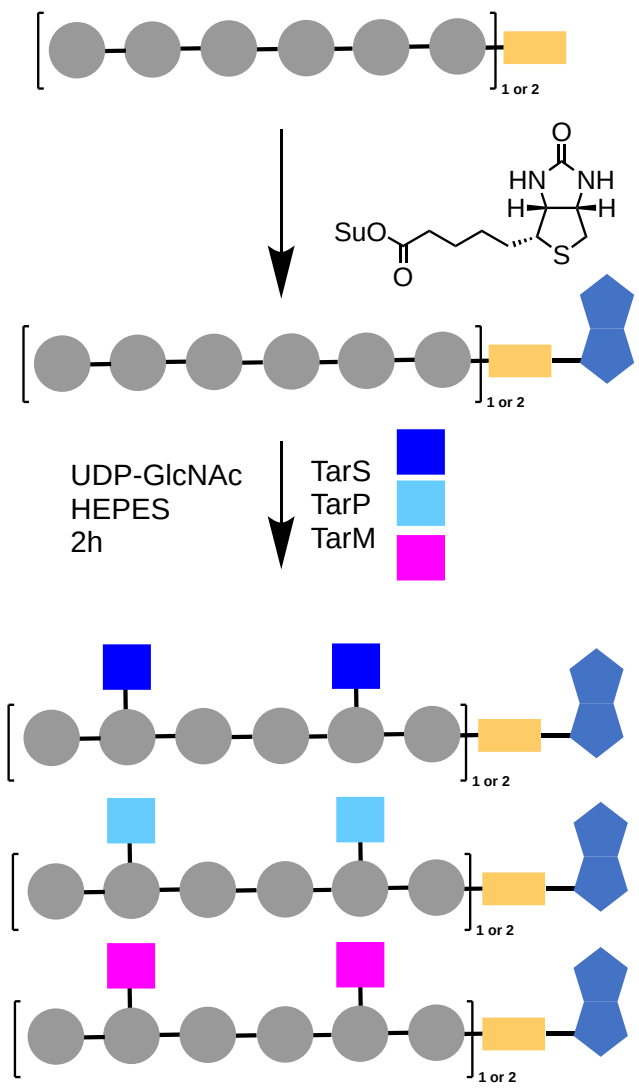


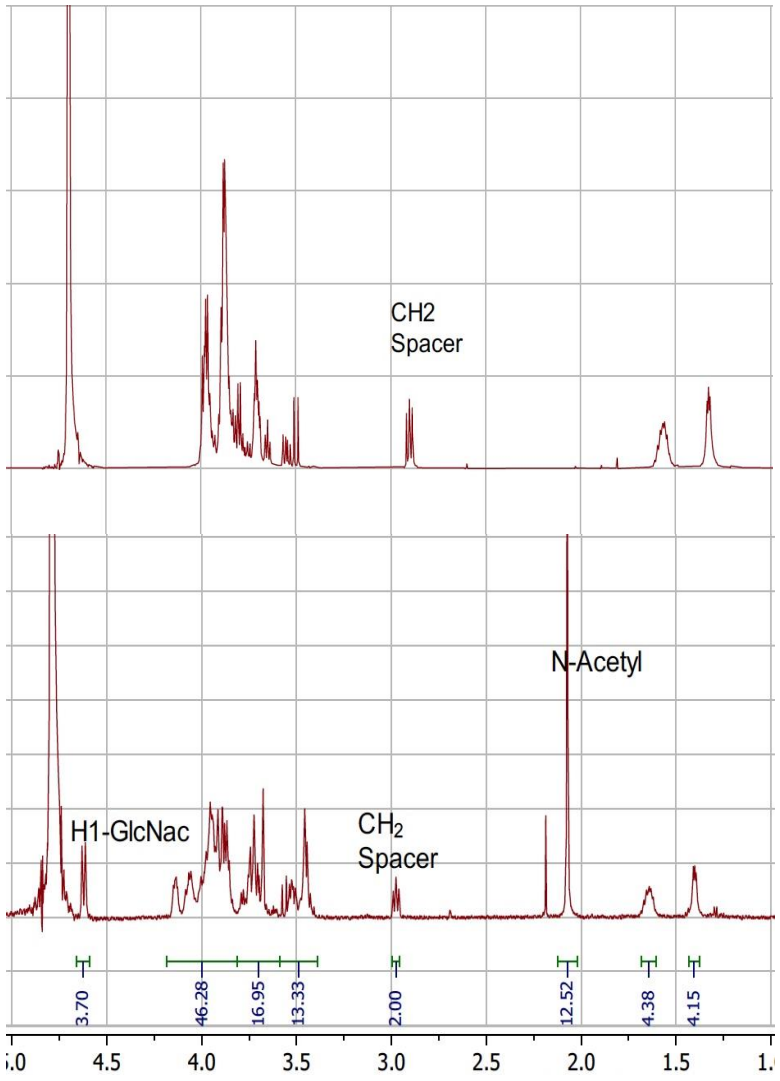




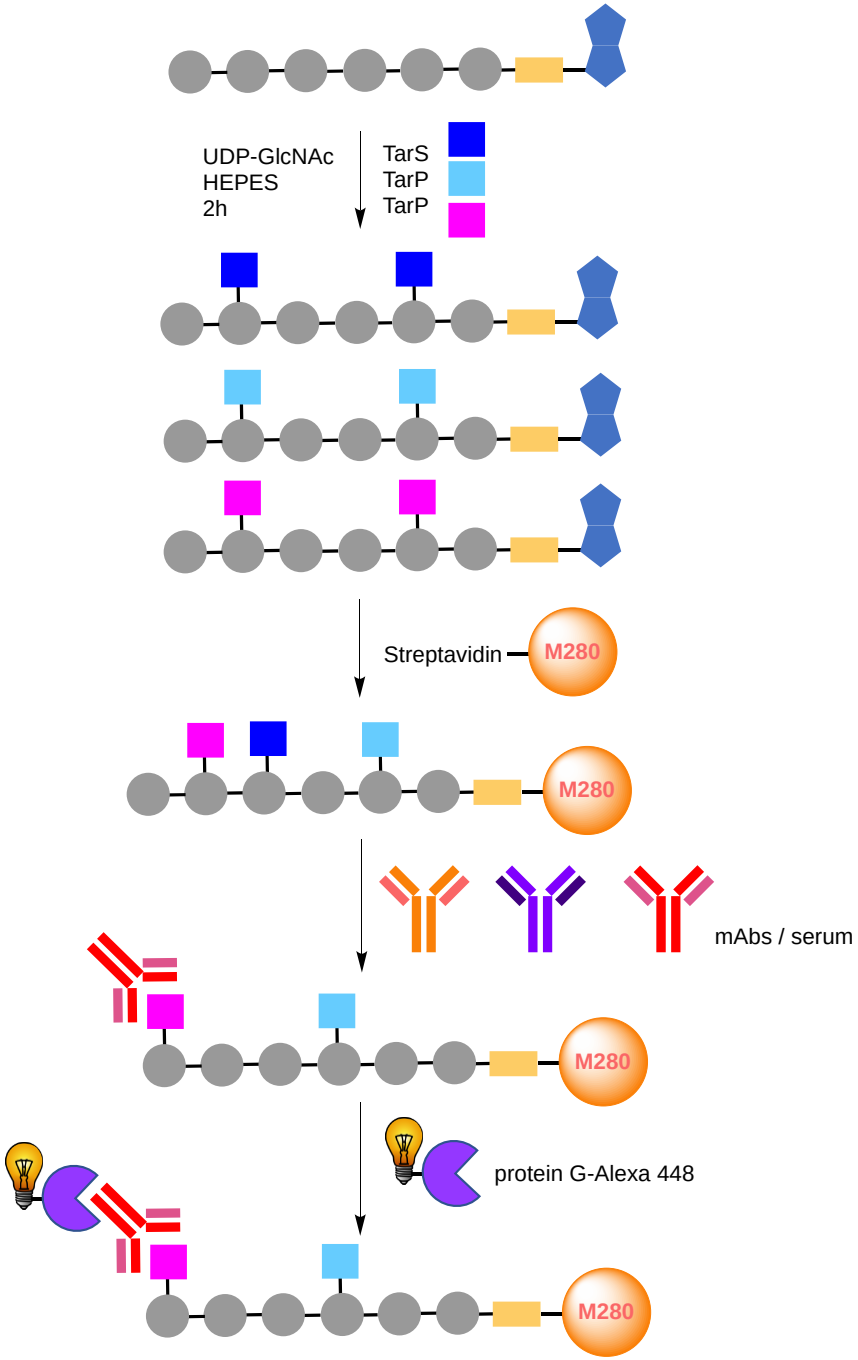
Ali, Chem Eur J, 2021, 27, 10461.
Di Carluccio, ACS Centr Sci, 2022.

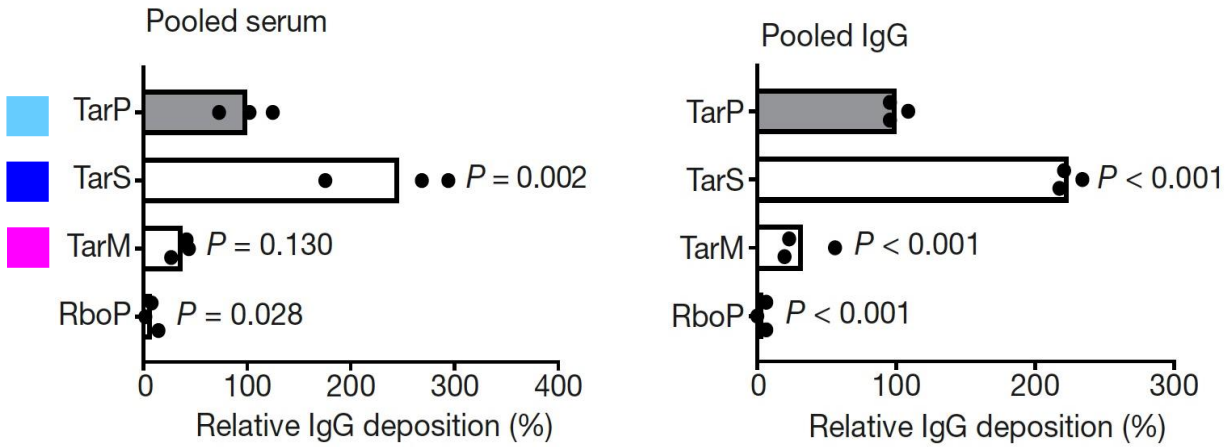
Enzymatic glycosylation





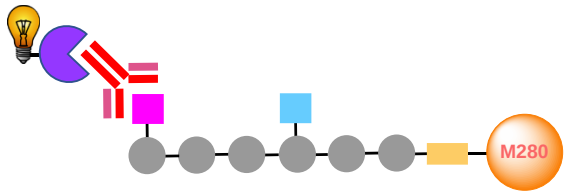
NMR, MALDI:
±3-4 GlcNAc per hexamer

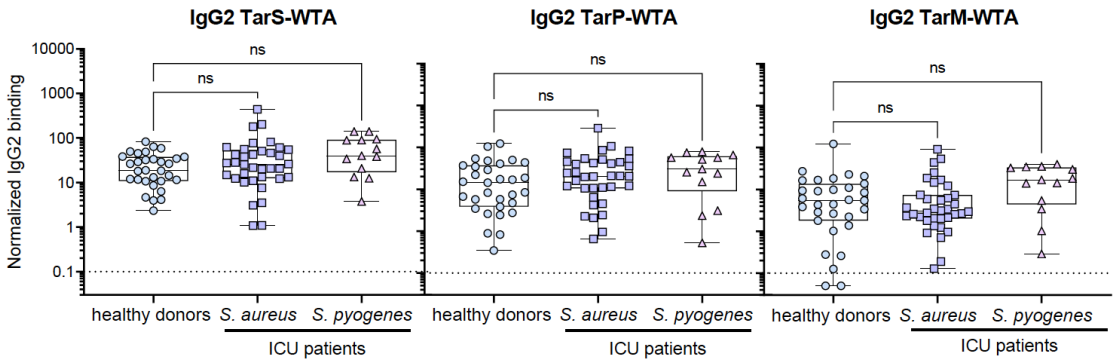




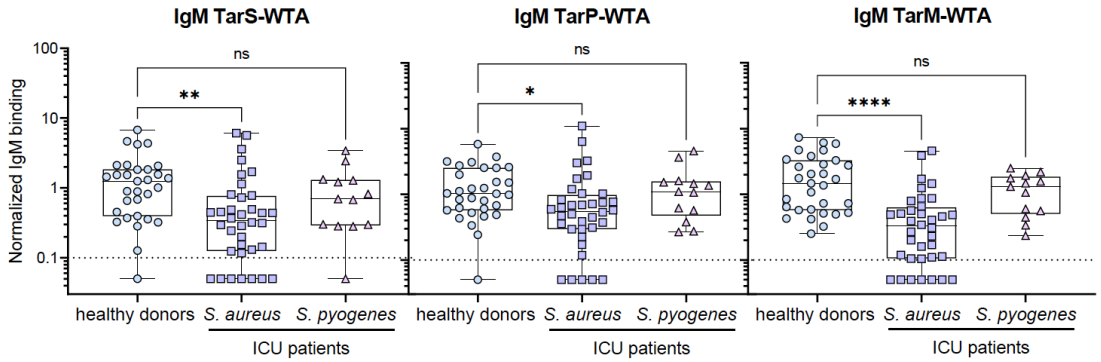
Different recognition of different glycoforms

Van Dalen, Nature, 2019, 572, E2-E5

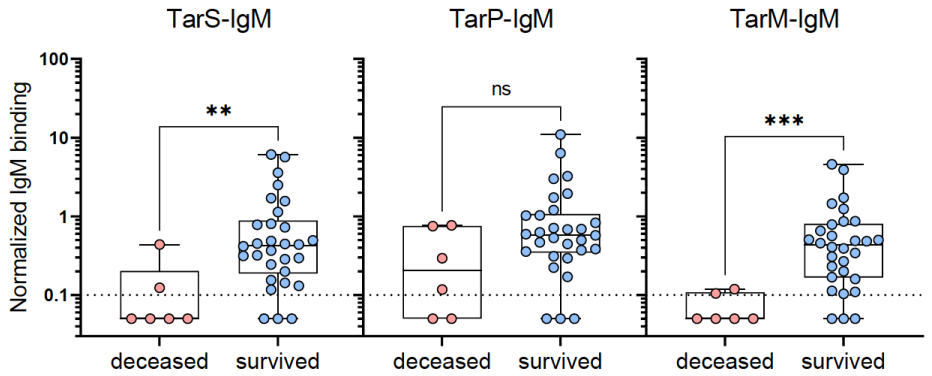




No difference in IgG levels between healthy and ICU



IgM (ICU) < IgM (healthy)



IgM (deceased) < IgM (survived)

Hendriks, *unpublished*

Organic, enzymatic and automated syntheses

Synthetic WTAs enable detailed SAR studies

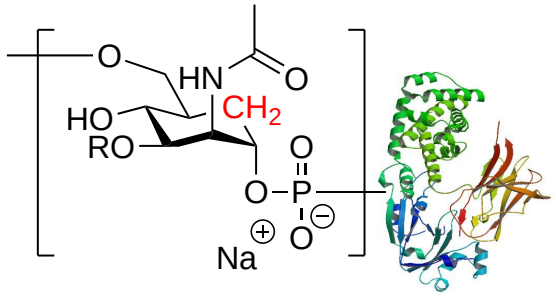
β-GlcNAc WTA (1,4 AND 1,3) is a target for opsonic antibodies

α-GlcNAc WTA: immune evasion?

Role of circulating antibodies (IgM!)?

WTA as antigen in conjugate vaccines?

Role of D-Ala?

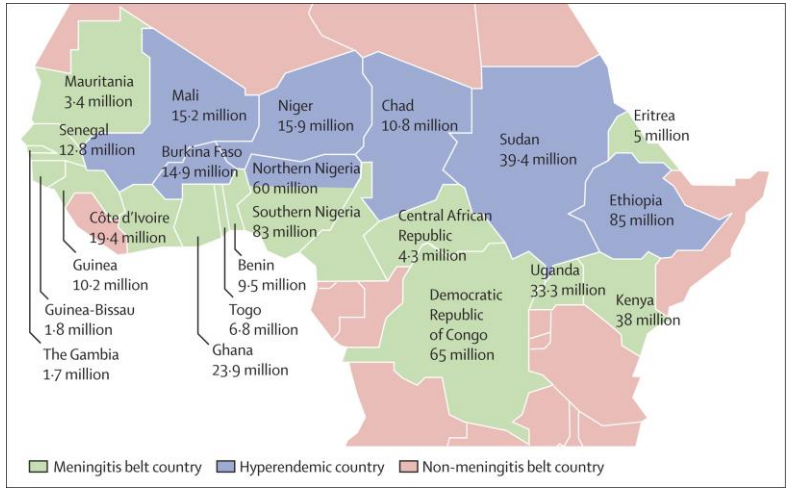


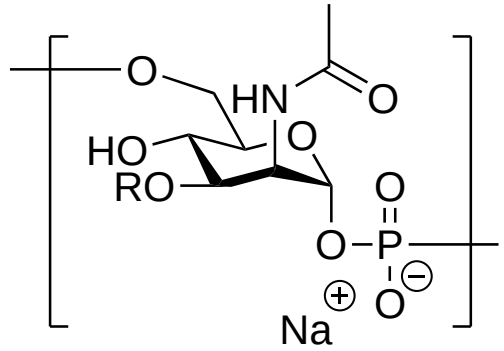
Antigen Mimicry in the Development of a Stabilized Neisseria meningitidis Conjugate Vaccin

Bioquell

Neisseria meningitidis

Gram-negative bacterium
170.000 death per annum
13 serotypes (A, B, C, Y, W135, X)
Different Capsular polysaccharides
MenA responsible for epidemic outbrakes
(especially African meninigitidis belt)
MenACWY vaccine available, but MenA unstable

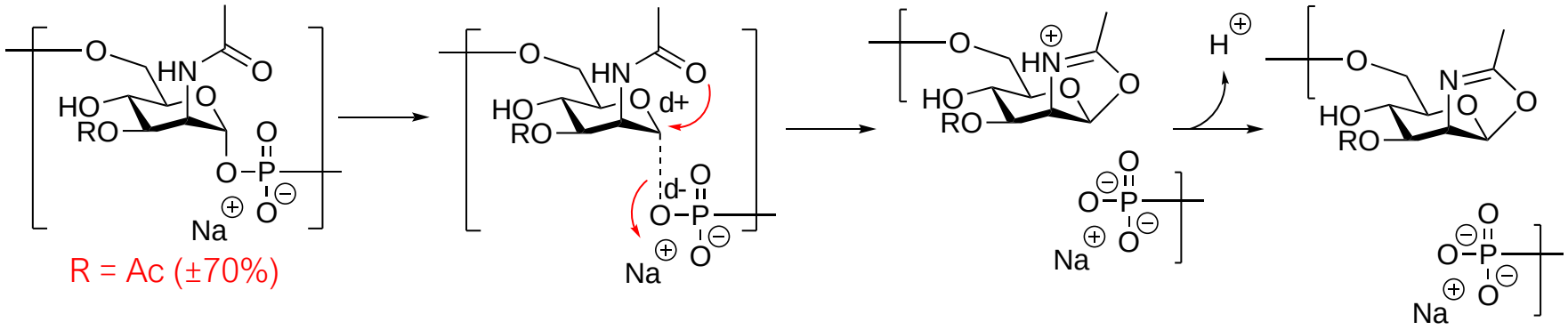




R = H
R = Ac

N. Meningitidis Serotype A

Intrinsically labile antigen:



N. Meningitidis Serotype A

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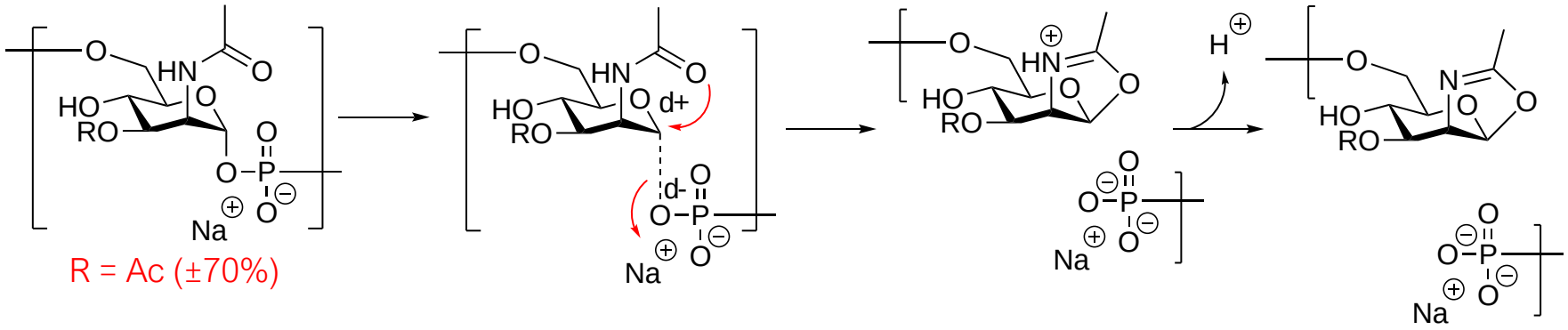
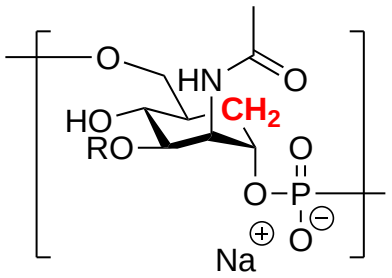


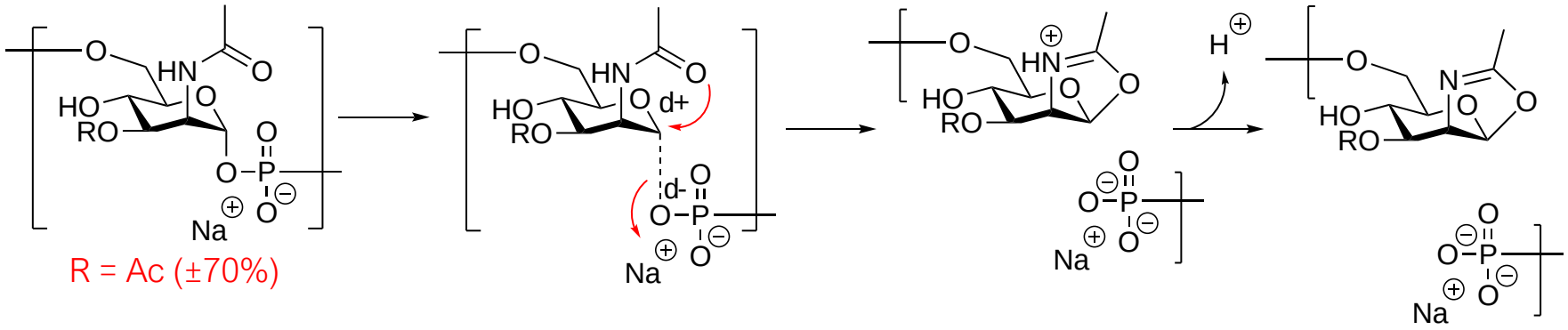
Carba MenA:



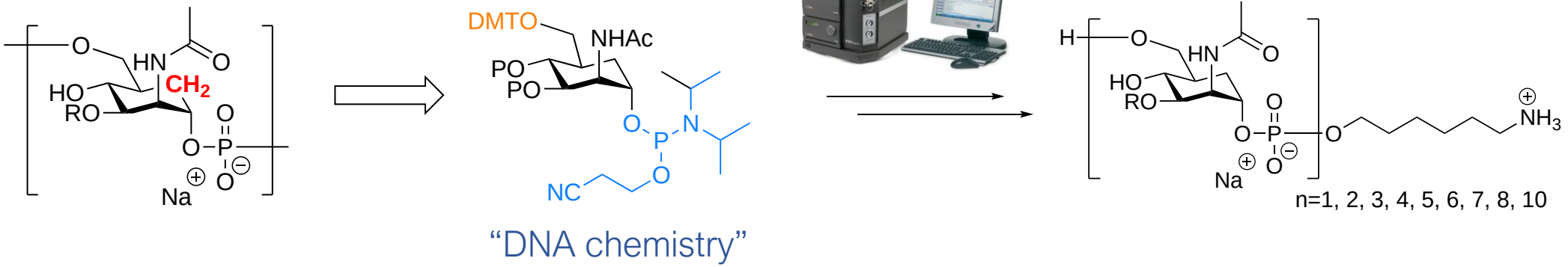
Luigi Lay (Univeristy of Milan)
Roberto Adamo (GSK)

N. Meningitidis Serotype A

Intrinsically labile antigen:

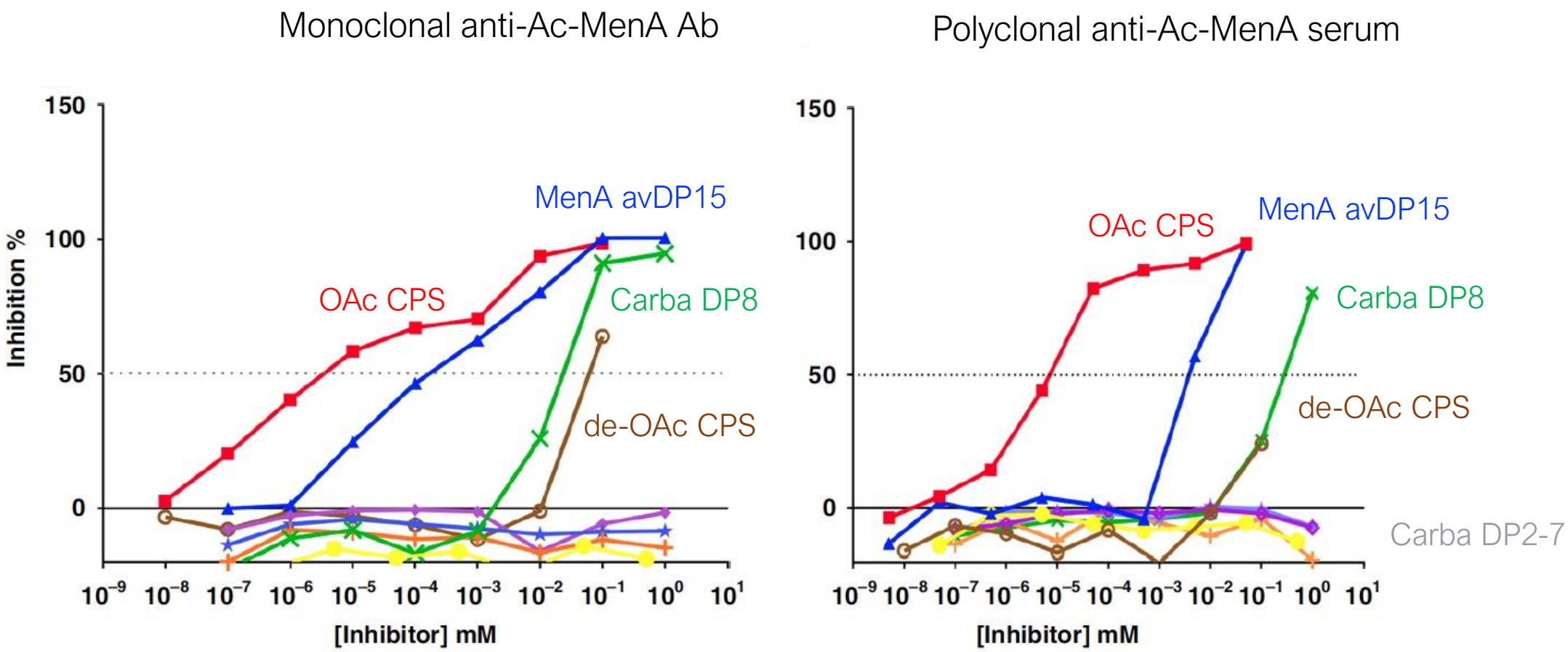


Carba MenA:

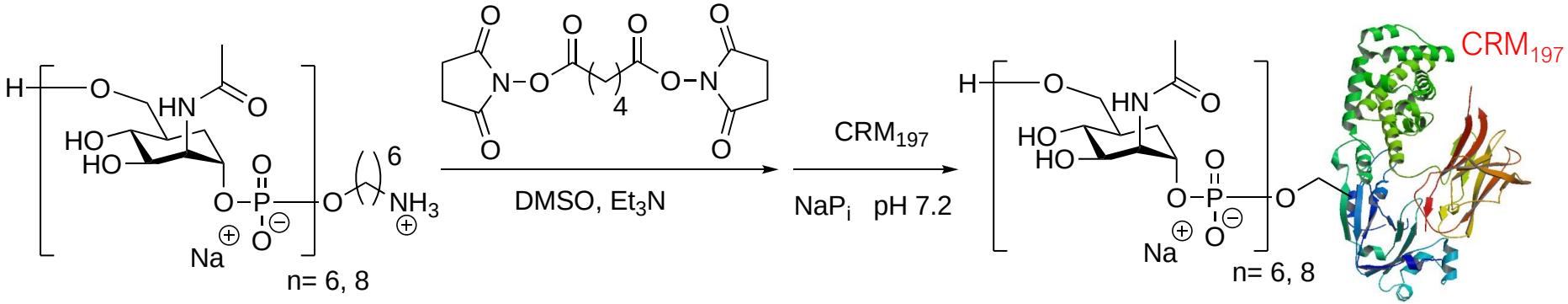


Luigi Lay (Univeristy of Milan)
Roberto Adamo (GSK)

Competitive ELISA: Antibody binding vs natural Ac-MenA PS

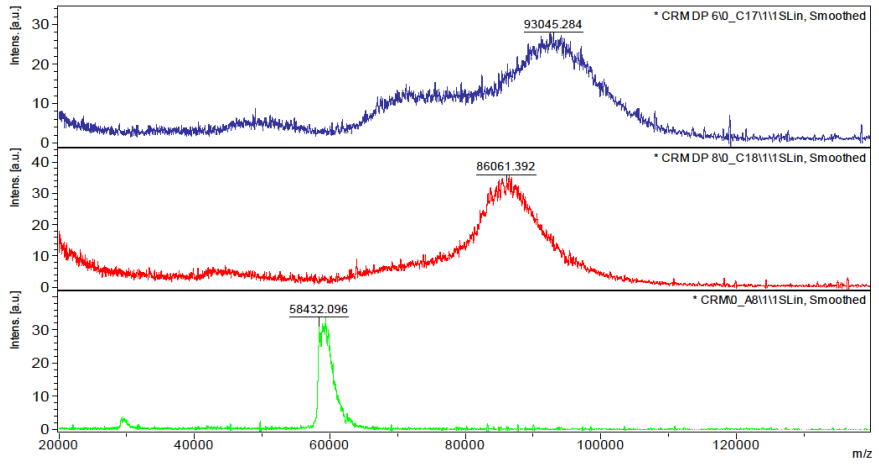


Carba MenA DP8 inhibits binding between a protective anti-MenA Ab and the CPS

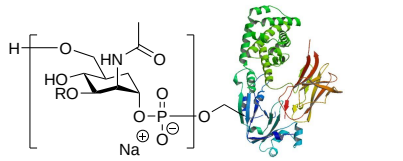


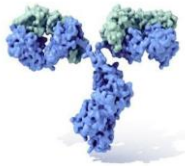
CarbaMenA per CRM_{197}:

DP 6 17
DP 8 10

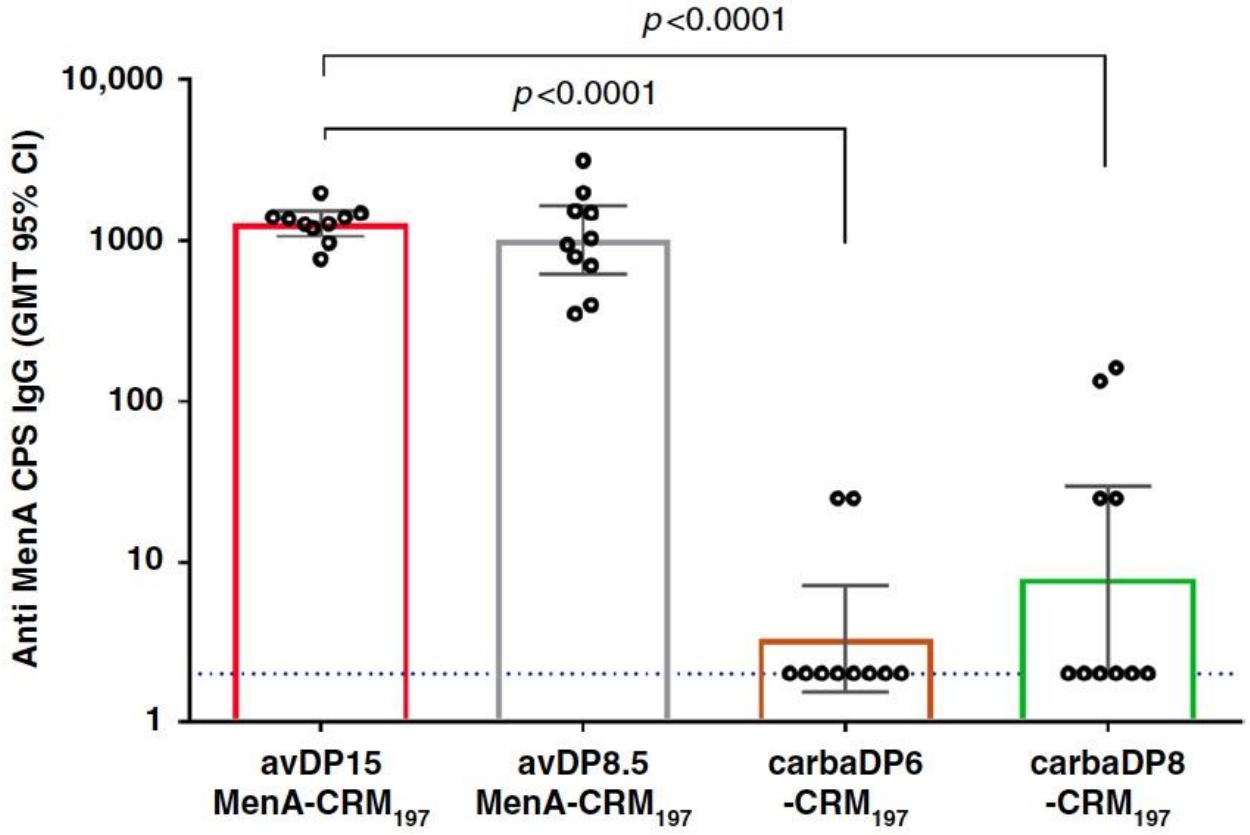


Poor titer against natural Ac-MenA



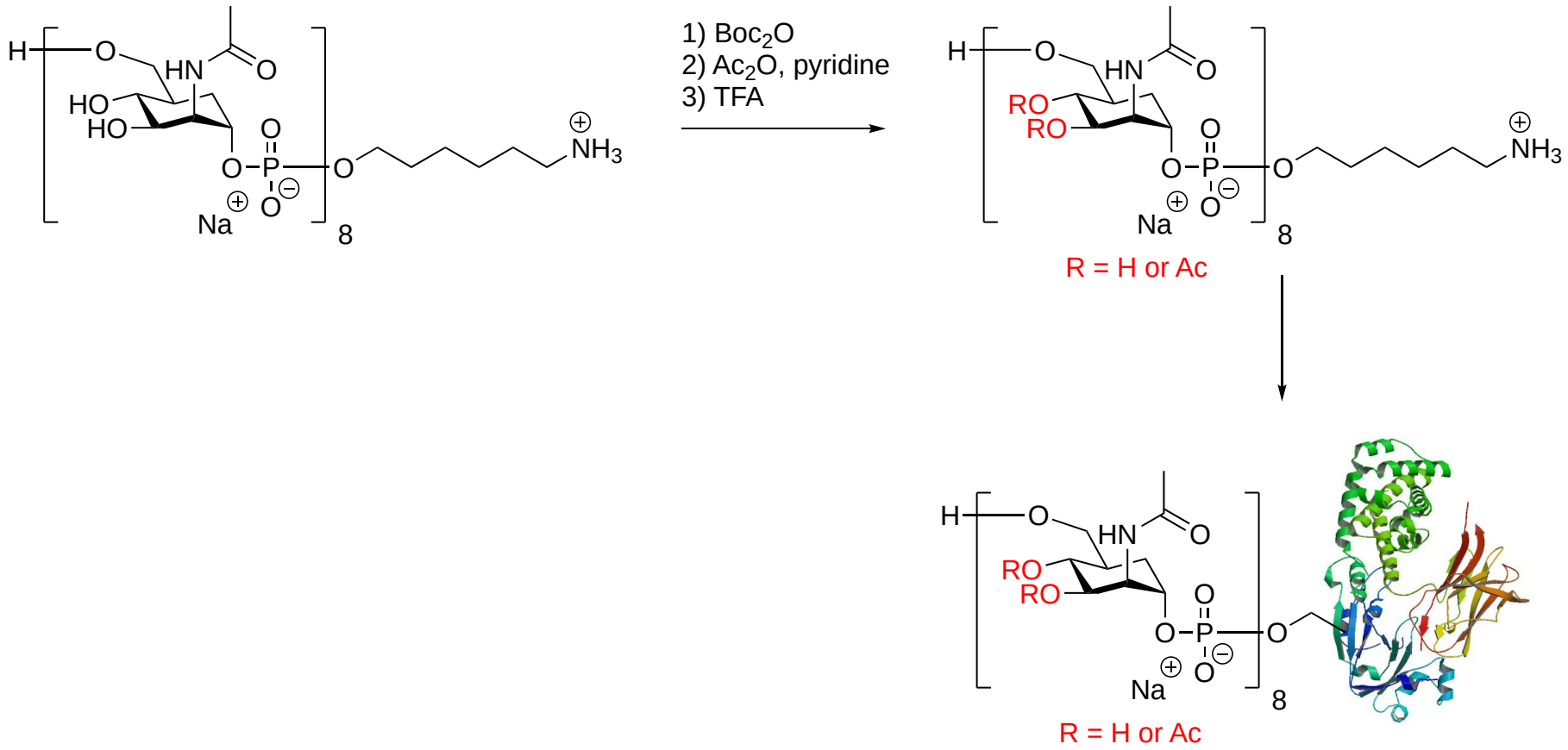


ELISA

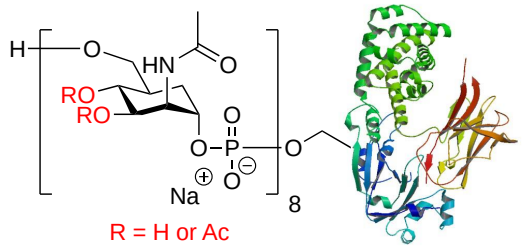


	avDP15 MenA-CRM$_{197}$	avDP8.5 MenA-CRM$_{197}$	carbaDP6 -CRM$_{197}$	carbaDP8 -CRM$_{197}$
rSBA	8192*	4096*	1024**	512**
hSBA	4096*	8192*	<16**	128**
Pre-immune	<16			

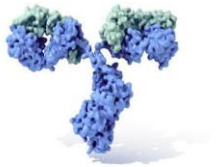
Enotarpi, Nat. Comm. 2020, 11, 4434



Enotarpi, Nat. Comm. 2020, 11, 4434

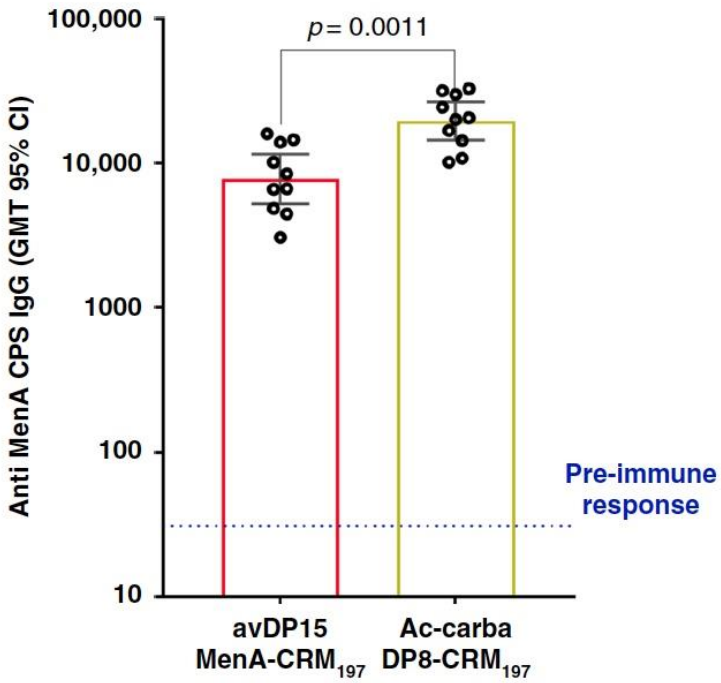


R = H or Ac

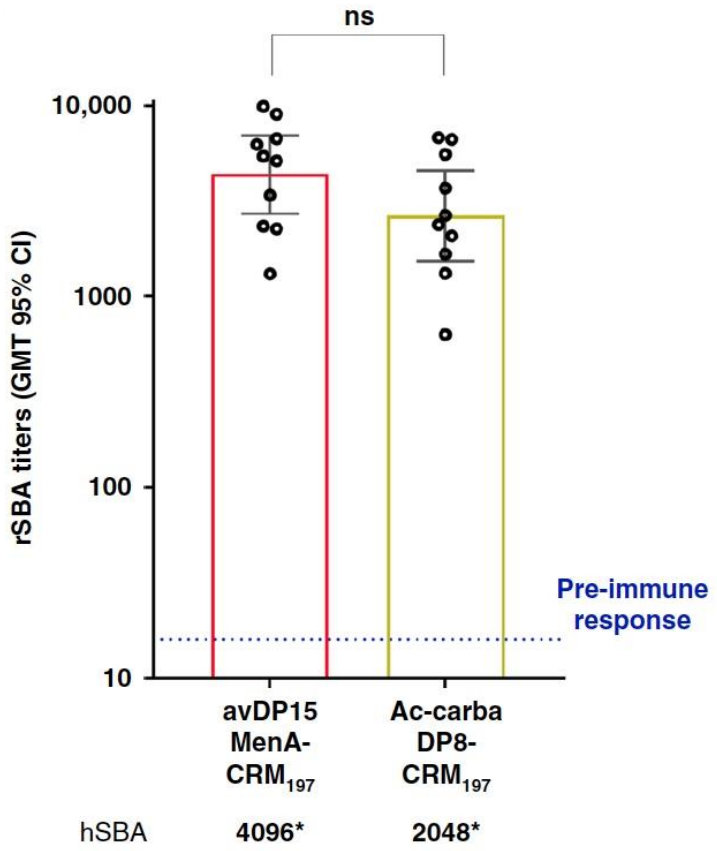


ELISA
and OPKA

Titer against natural Ac-MenA



Bacterial killing



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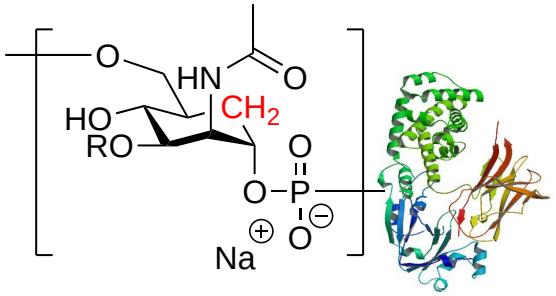
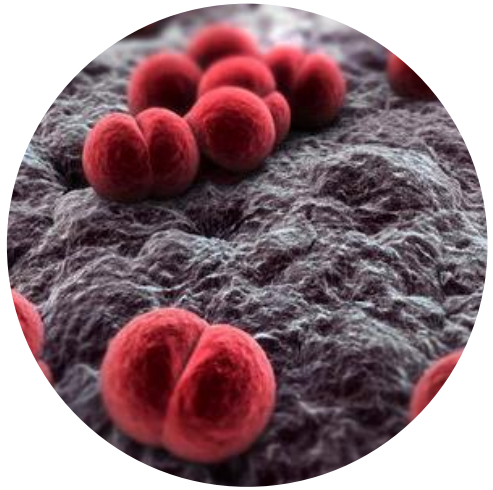


Antigen Mimicry in the Development of a Stabilized Neisseria meningitidis Conjugate Vaccin



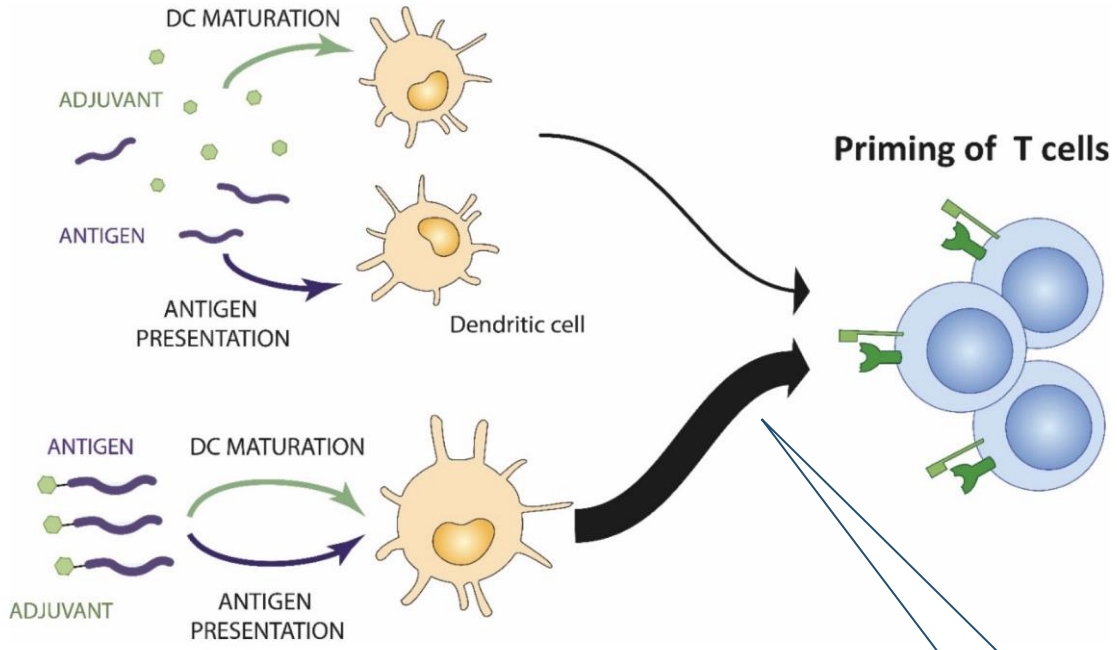
Effective (automated) synthesis of CarbaMenA oligomers

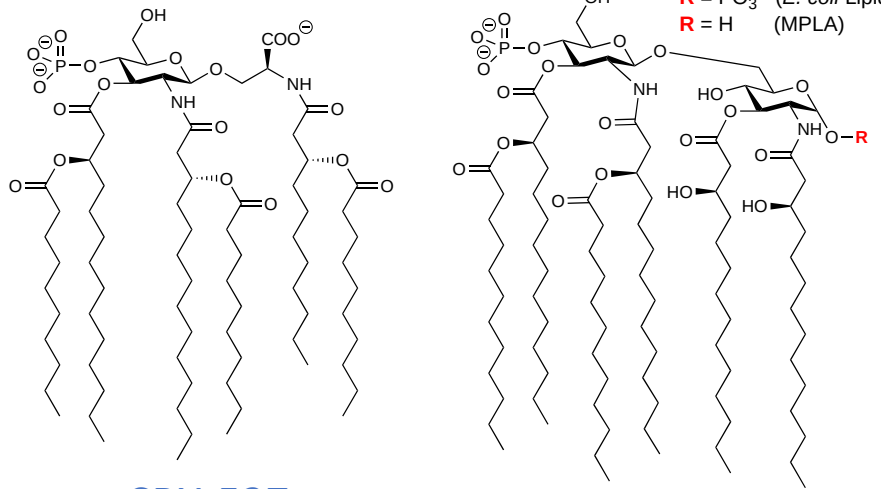
The first glycomimetic antigen used in an effective vaccine

Role/pattern of acetylation?

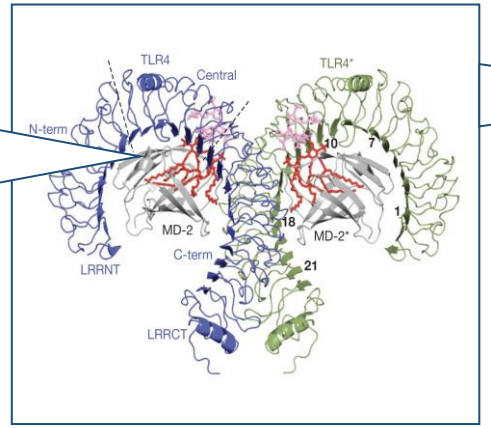
Enotarpi, Nat. Comm. 2020, 11, 4434

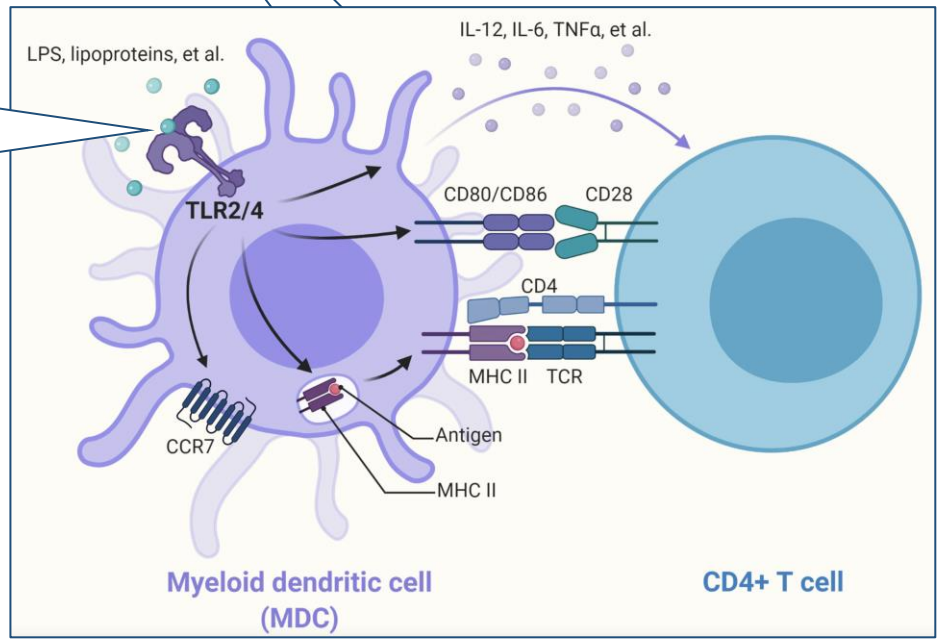
Self adjuvanting anti-cancer vaccines



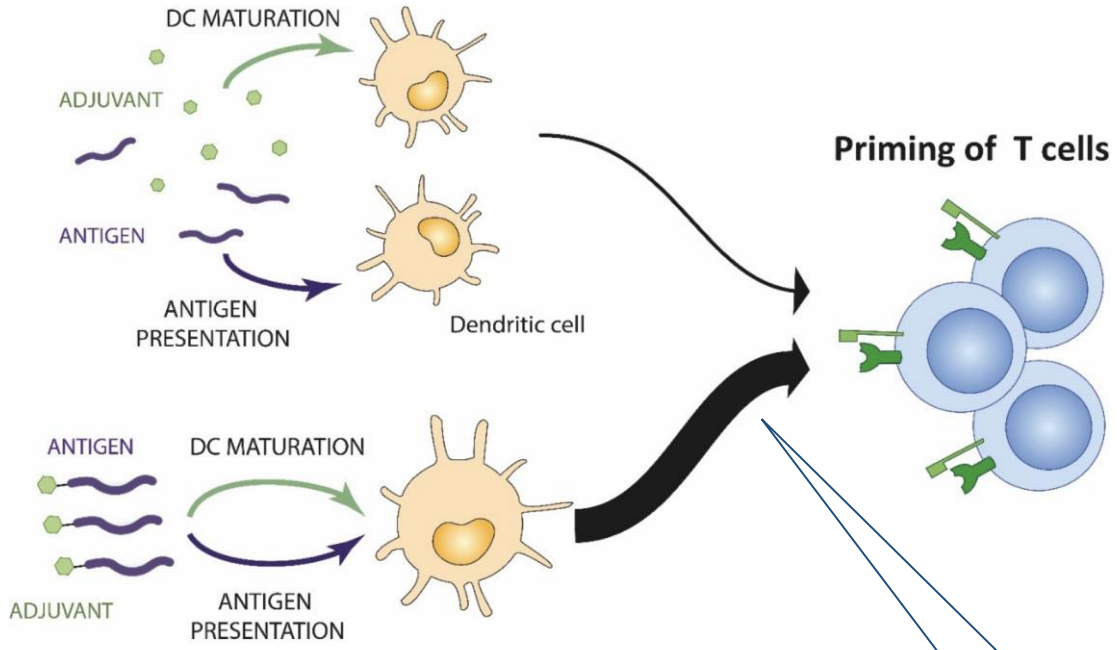


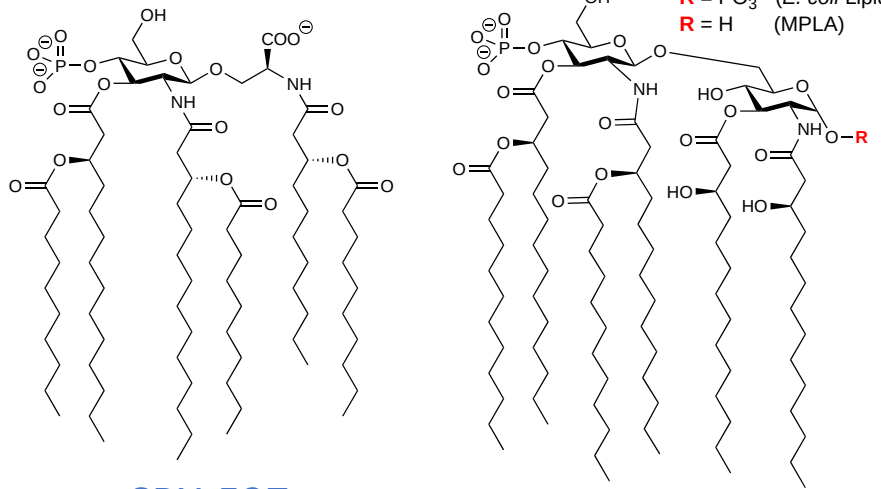
CRX-527





Self adjuvanting anti-cancer vaccines





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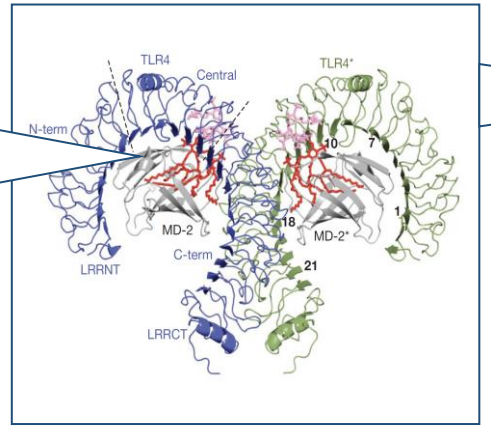
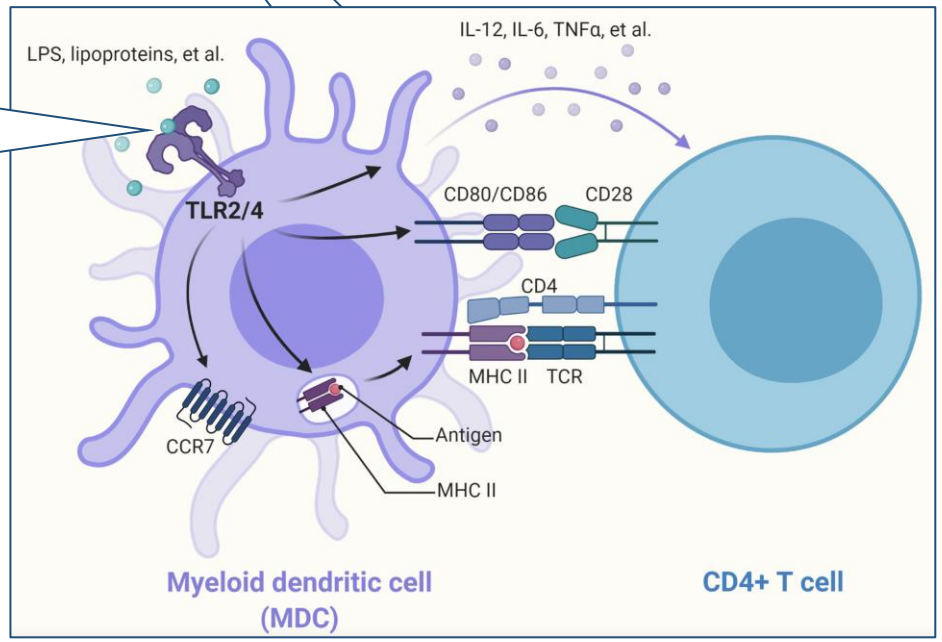
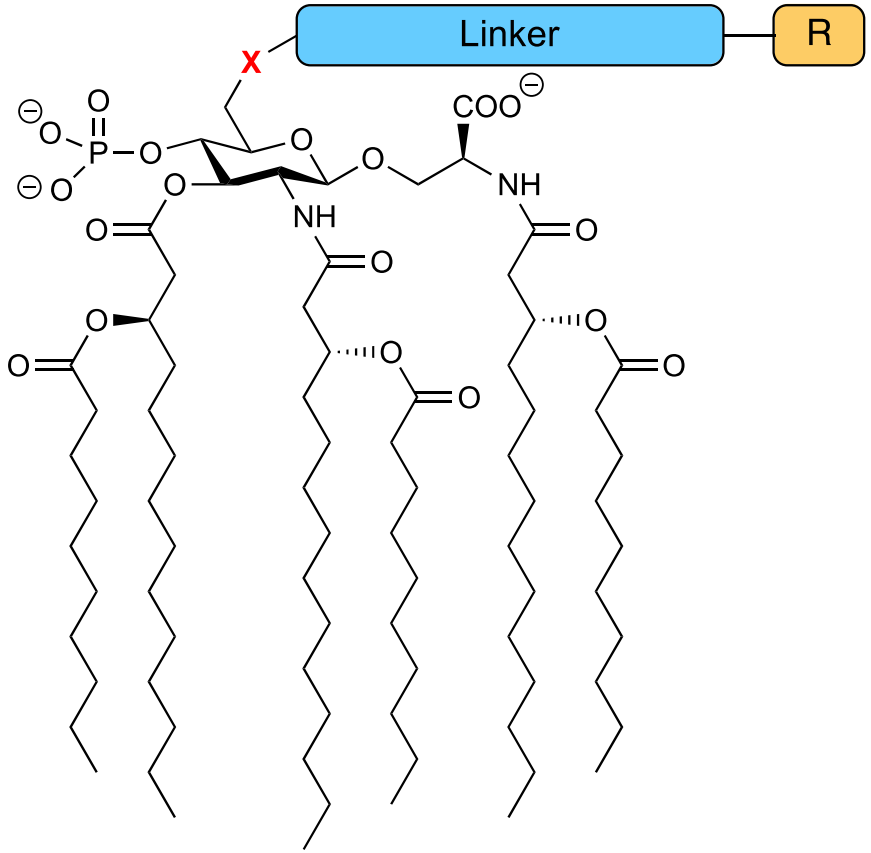
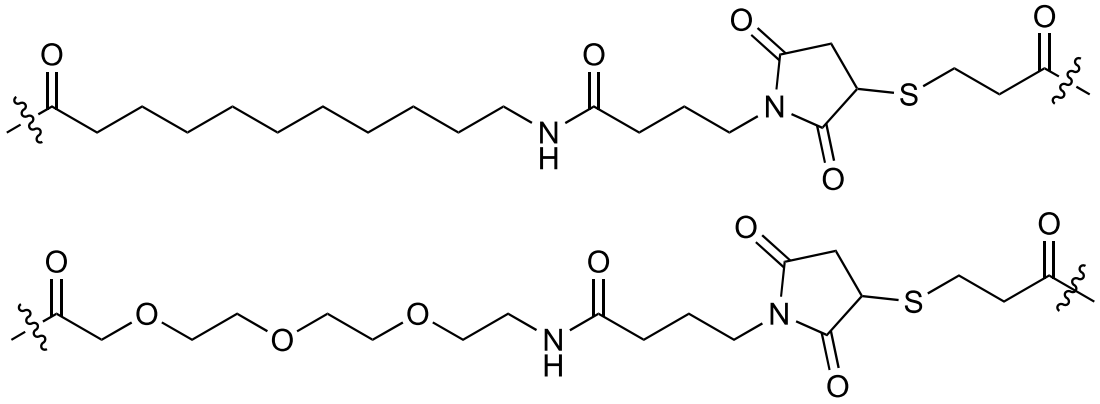






X = O or NH

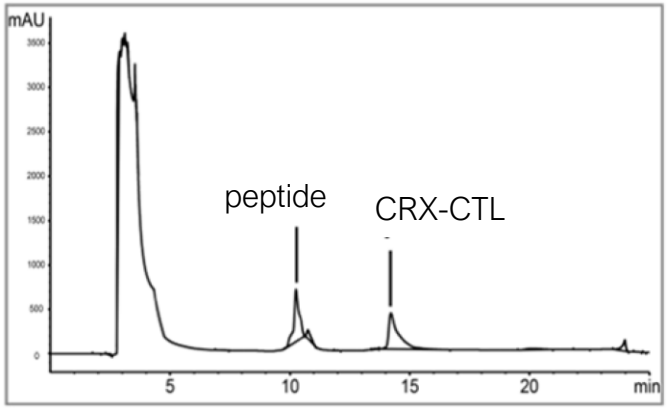
Linker

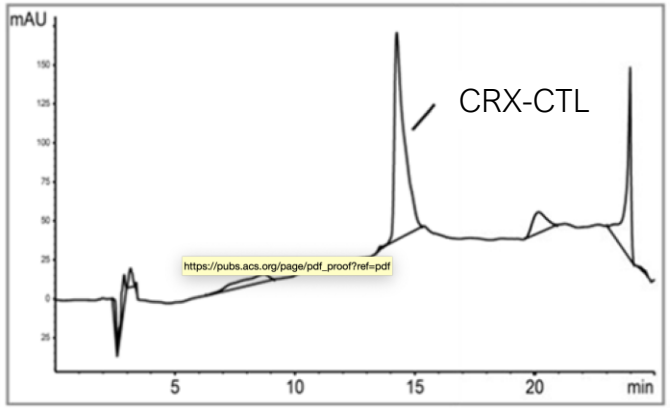


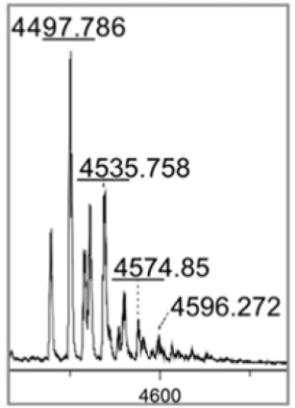
R

OVA CTL: DEVSGLEQLESIINFEKLAAAAAK
OVA HELP: ISQAVHAAHAEINEAGRK

HPV E7 CTL: GQAEDRAHYNIVTFBBKBDSTLRLBVK
MML CTL: EEPLTSLTPRBNTAWNRL







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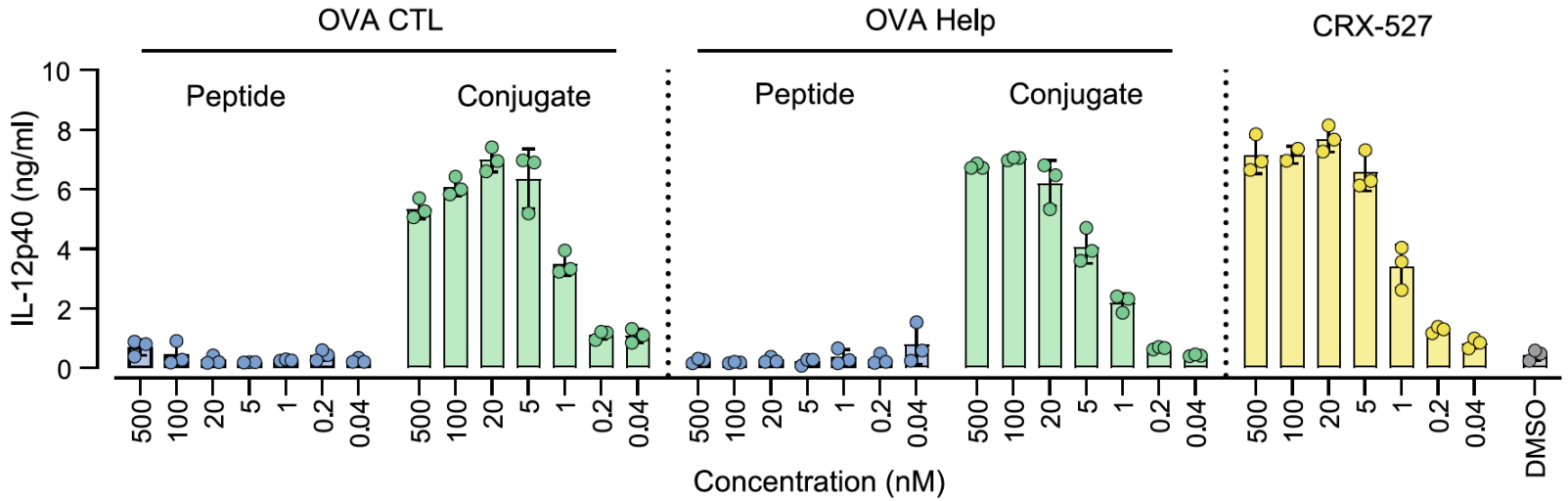
in vitro

TLR4 activation:



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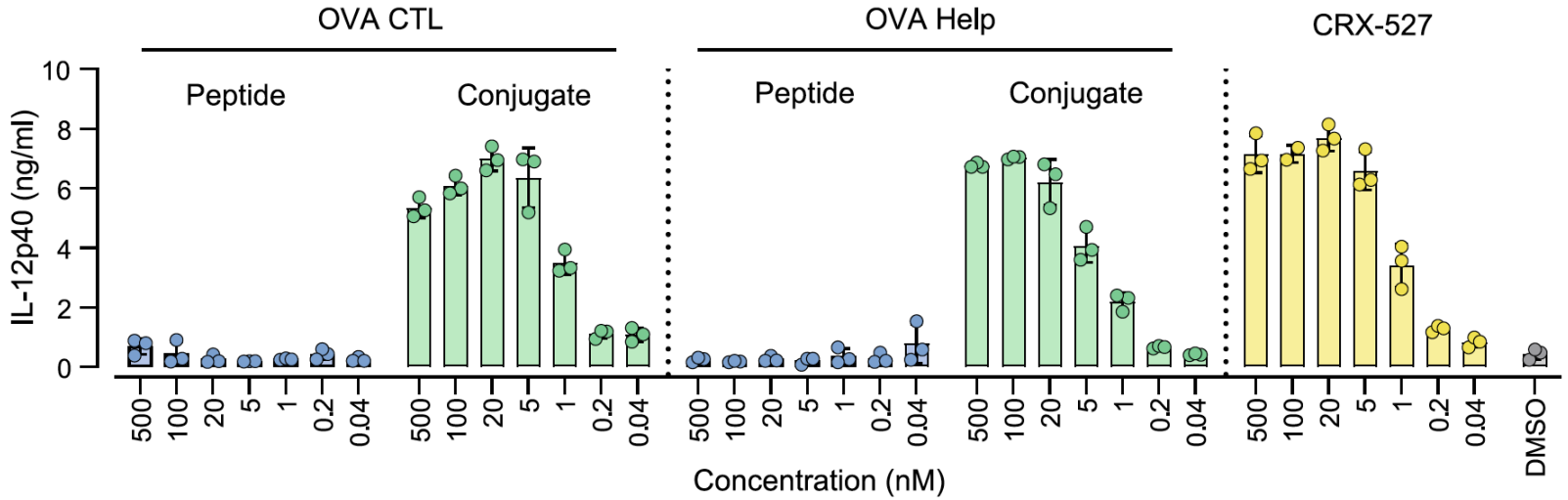
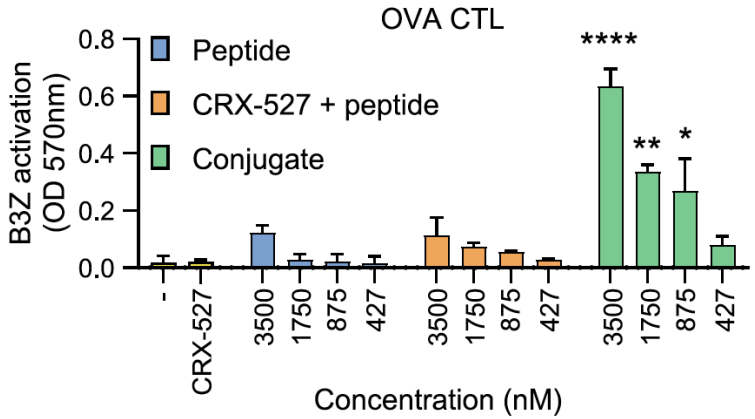
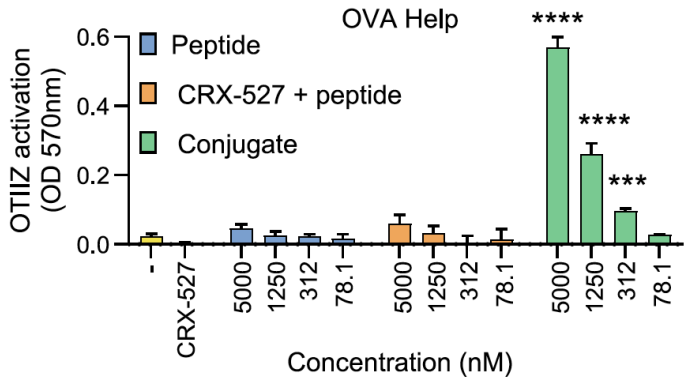
TLR4 activation:



MHC-I presentation:



MHC-II presentation:



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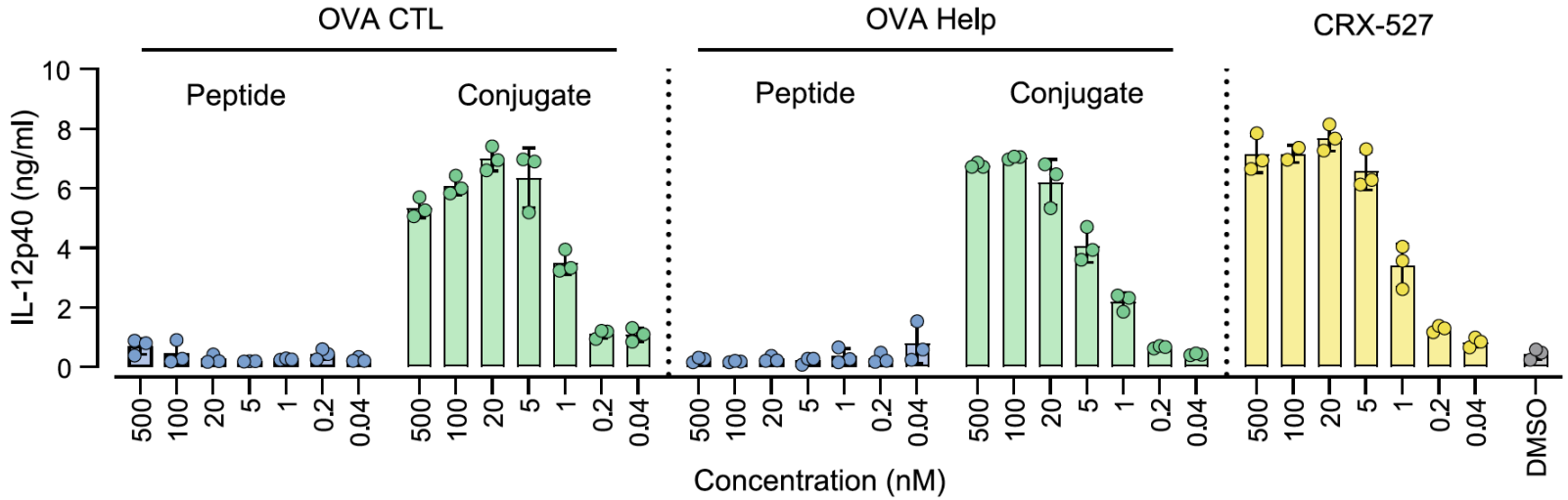
in vitro

TLR4 activation:



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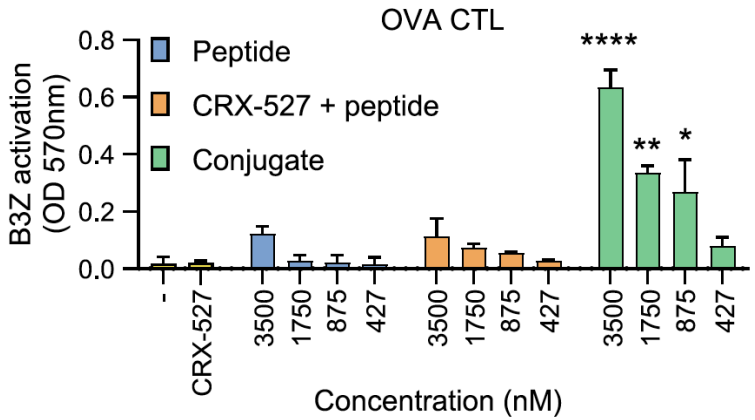

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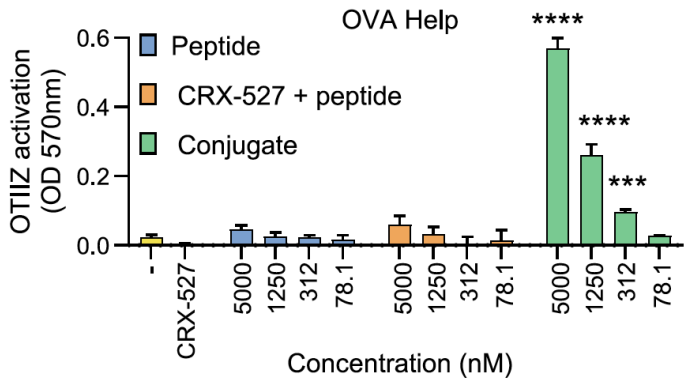
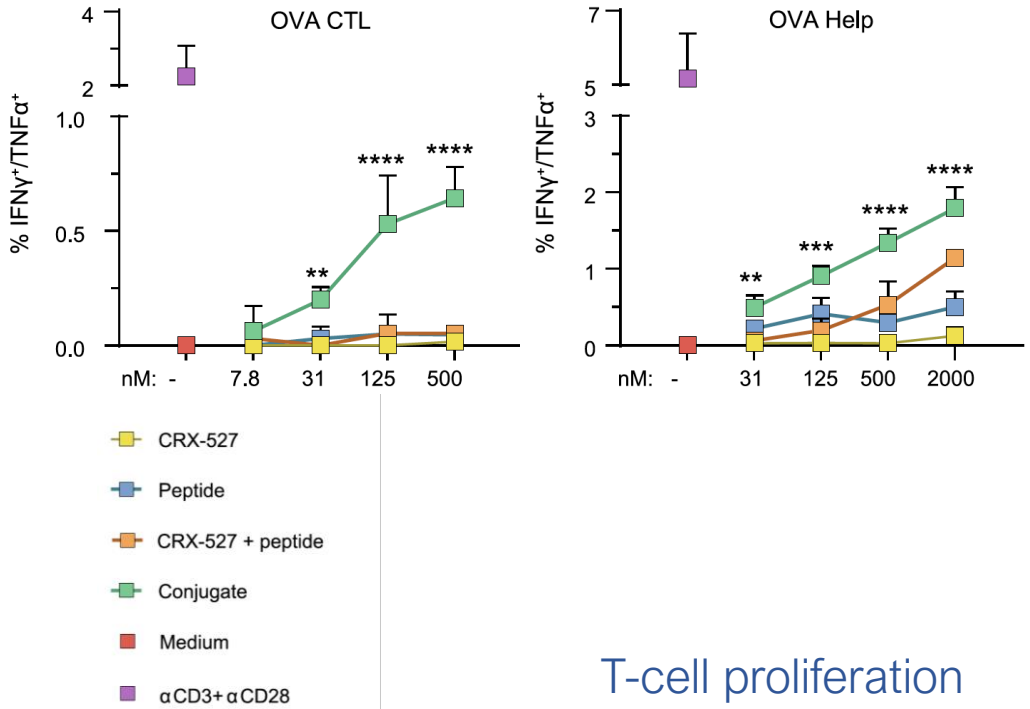
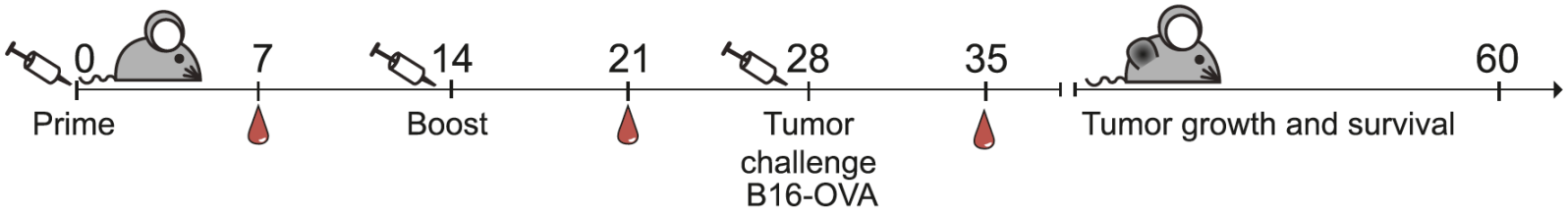
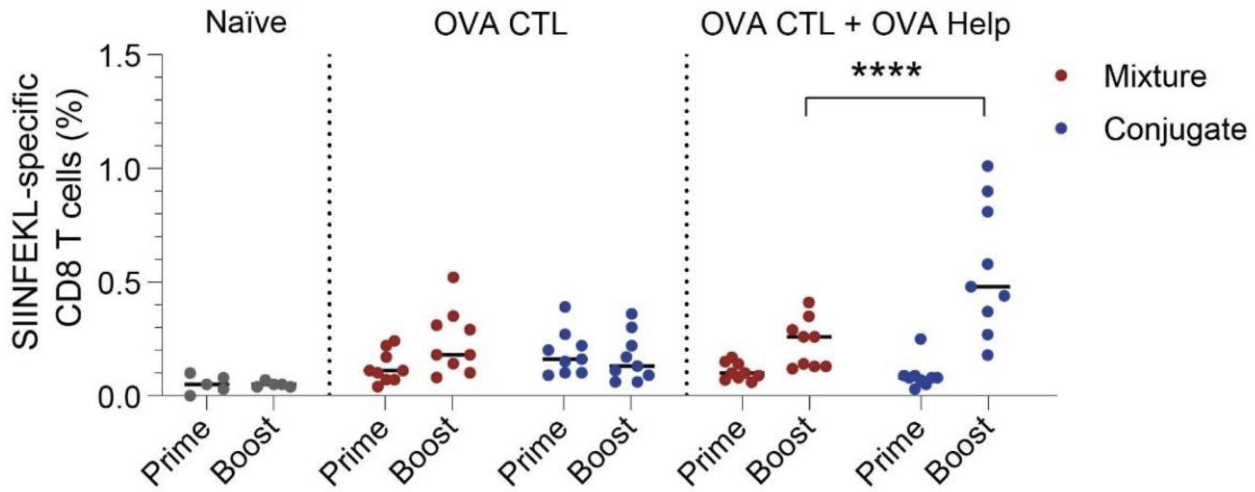




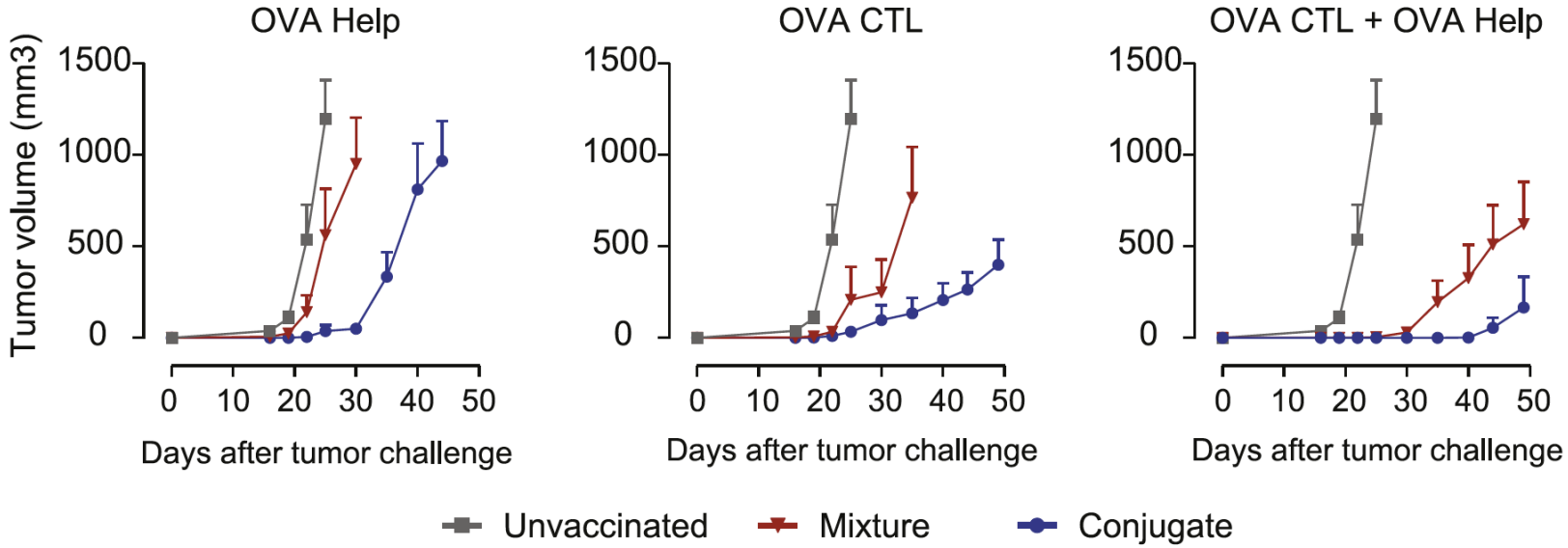
T-cell proliferation



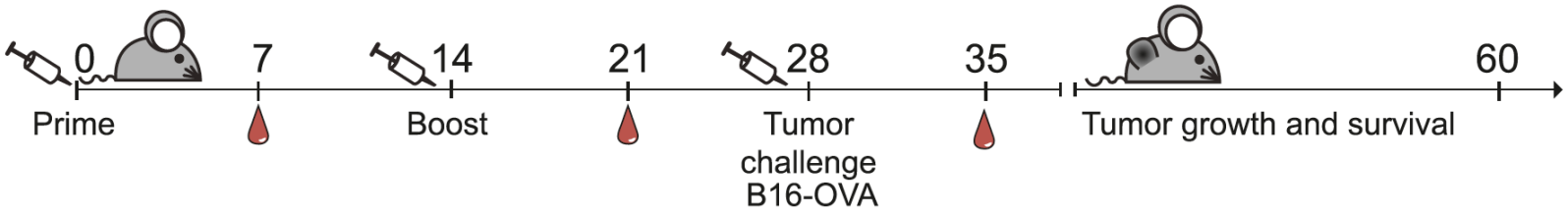
T-cell proliferation:



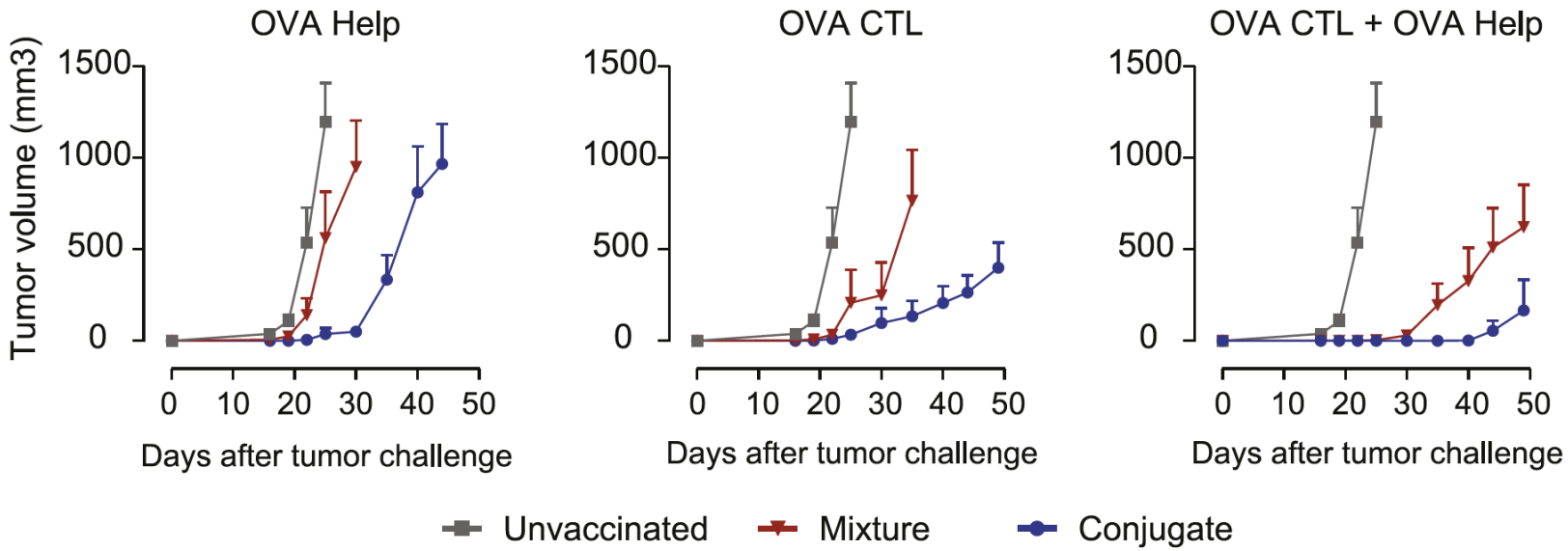
Tumor growth:



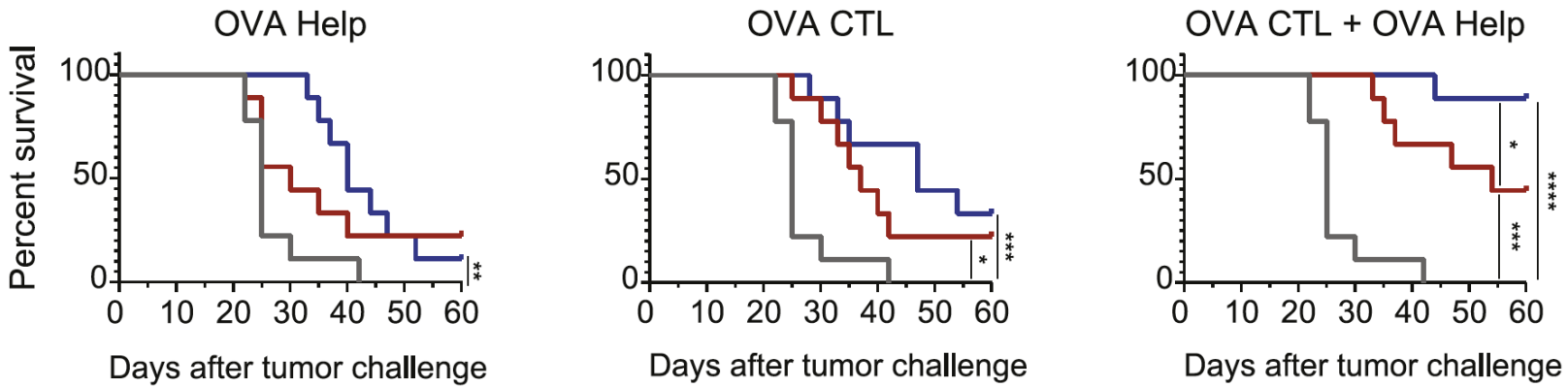
in vivo



Tumor growth:



Survival:



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Tondinin, NPJ Vacc. 2022, 7, 64

Biosyn

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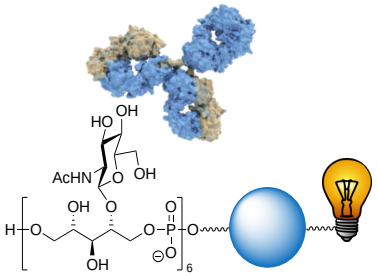
Francesca Berni
Sara Ali
Thijs Voskuilen
Niels Reintjes
Marjolein Isendoorn
Fabrizio Chiodo
Daan van der Es
Hans van den Elst
Nico Meeuwenoord

Sander van Kasteren
Hermen Overkleeft
Dima Filippov
Gijs van der Marel

S. aureus



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Utrecht Univeristy MC
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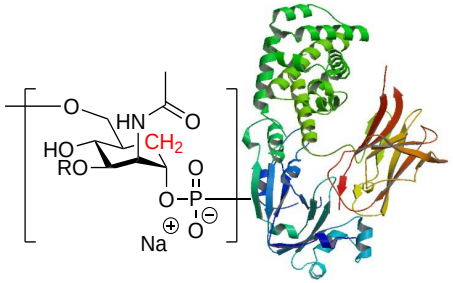
Alba Silipo
Tony Molinaro

CSIC Madrid
Pablo Soriano
Mark van Raaij

Carba-MenA



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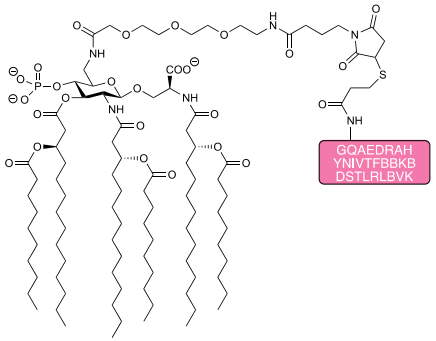
CRX-527



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