Why is *Neisseria meningitidis* so good at entering the CSF and causing meningitis?

Blood Brain Barrier

Control the exchange between the blood and cerebral compartment

Barriers:

-Blood vessels and CNS parenchyma

-Blood cerebrospinal fluid (BCSFB)

-CSF

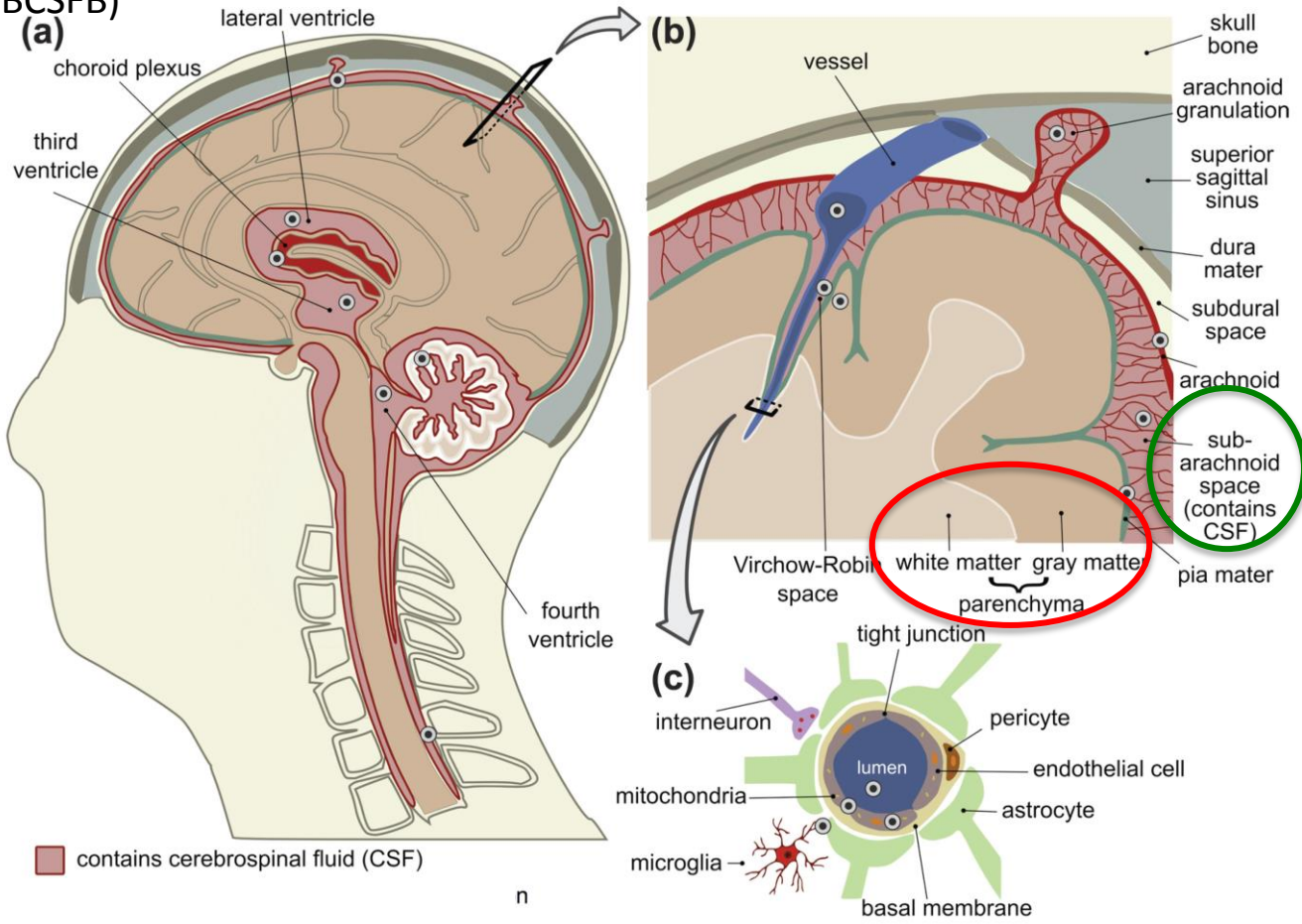
-Meningeal

Junctions:

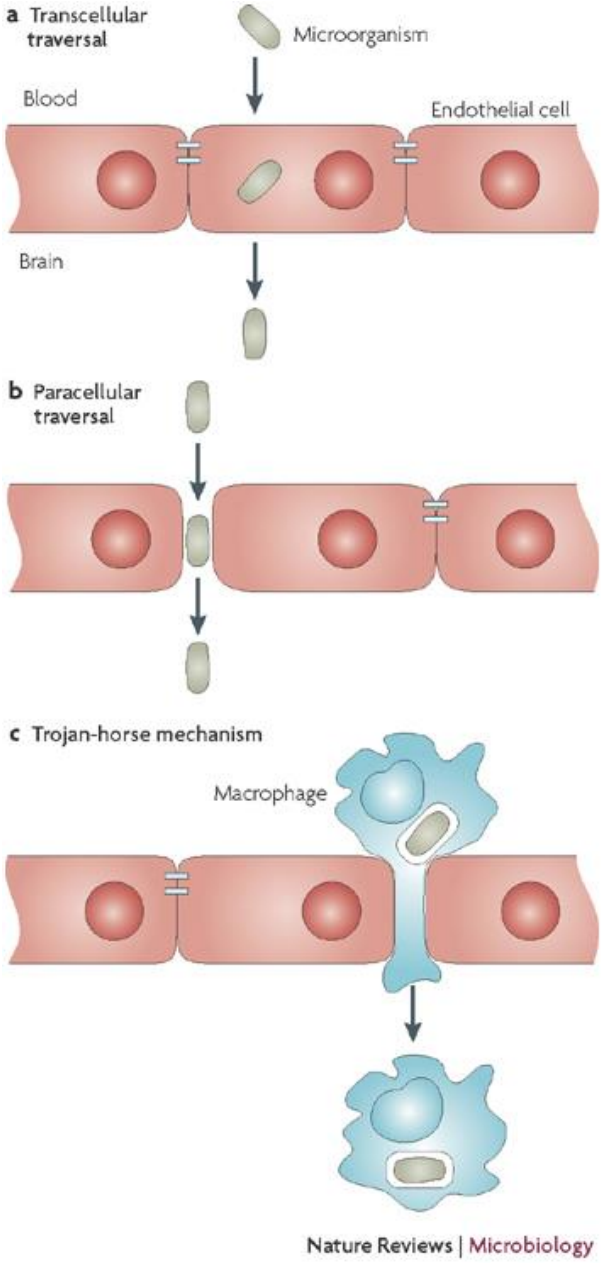
-Anchoring

-Gap

-Tight



Ways to cross the BBB



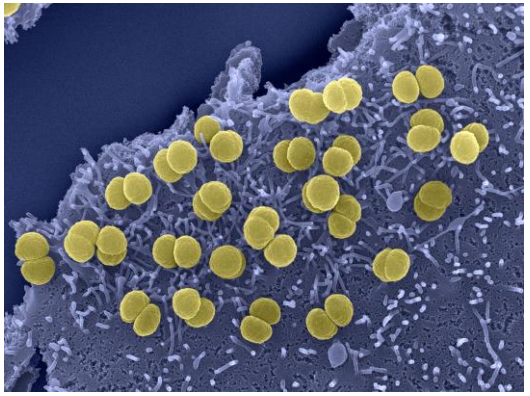
E. coli
S. agalactiae
N. meningitidis
S. pneumoniae
L. monocytogenes
M. tuberculosis
Borrelia spp
C. neoformans

N. meningitidis
Borrelia spp.

L. monocytogenes
M. Tuberculosis
C. neoformans

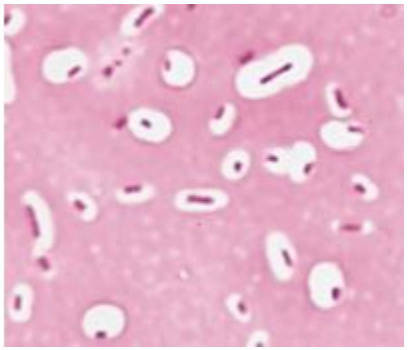
Neisseria meningitidis

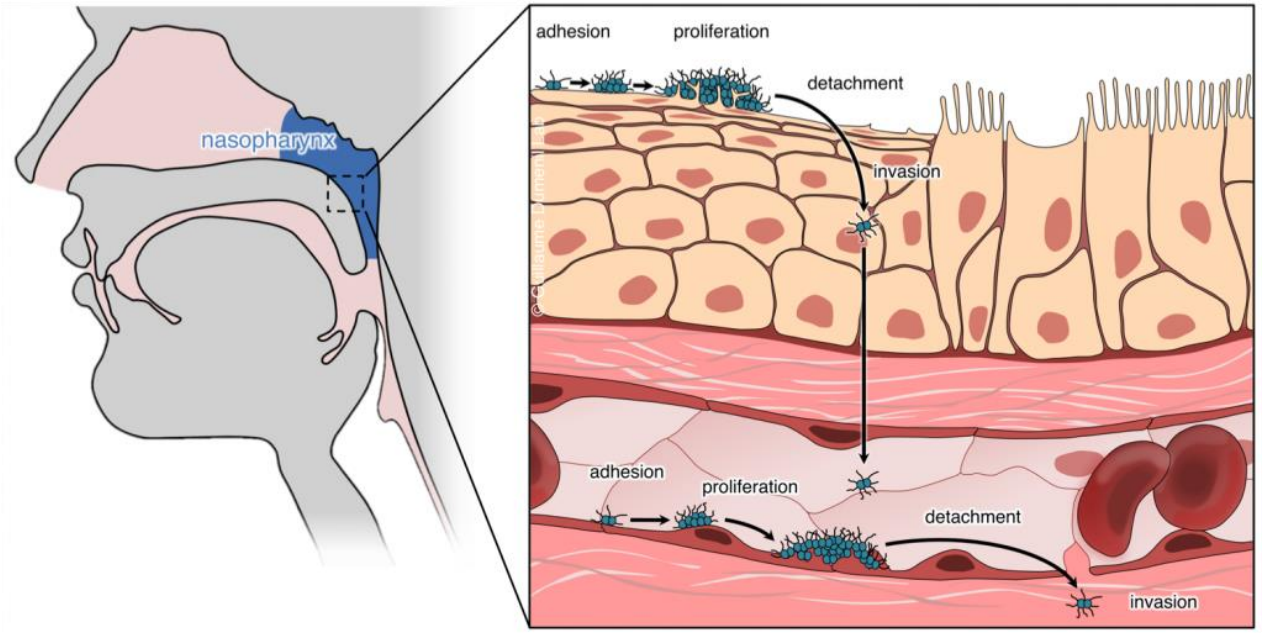
-Gram negative
~10-40% of population is colonized
-13 Serogroups
    -A-C, E-29, H, I, K, L, W-135, X-Z
    -A, B, C, W-135, and Y encapsulated
-Invasive vs carrier isolates
    -LPS-sialic acid
    -capsule
-Human only
-Meningitis lacks a relevant animal model



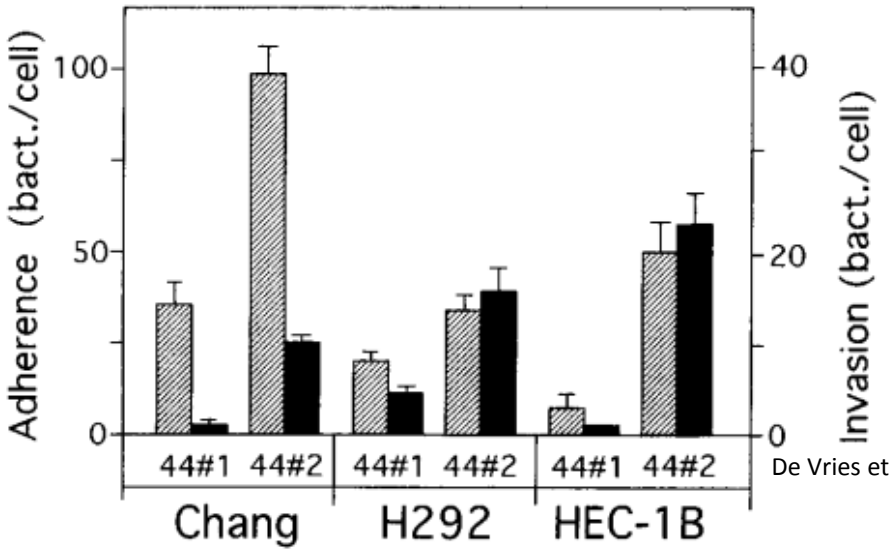
How does *N. meningitidis* get to the blood brain barrier?

-Crosses from the nasopharnyx to the blood
    N. meningitidis
        -LPS (sialyation prevents entry)
        -Opc play role in crossing nasal epithelial cells
    -Survive shear force
-Protect against complement
    -capsule
-Iron chelation



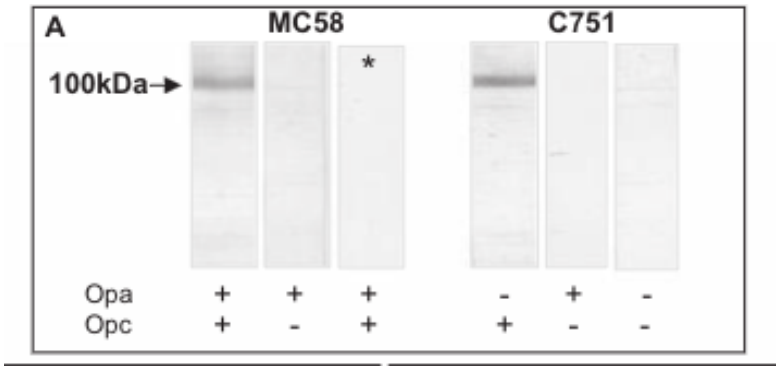


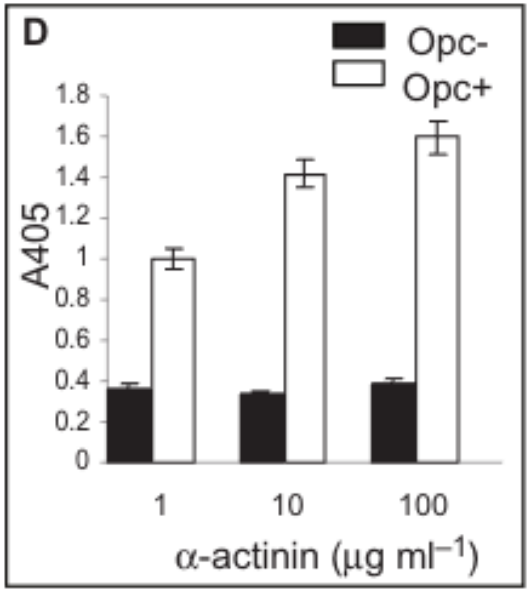
N. meningitidis Opc binds α-actinin to invade



De Vries et al., IAI 1996

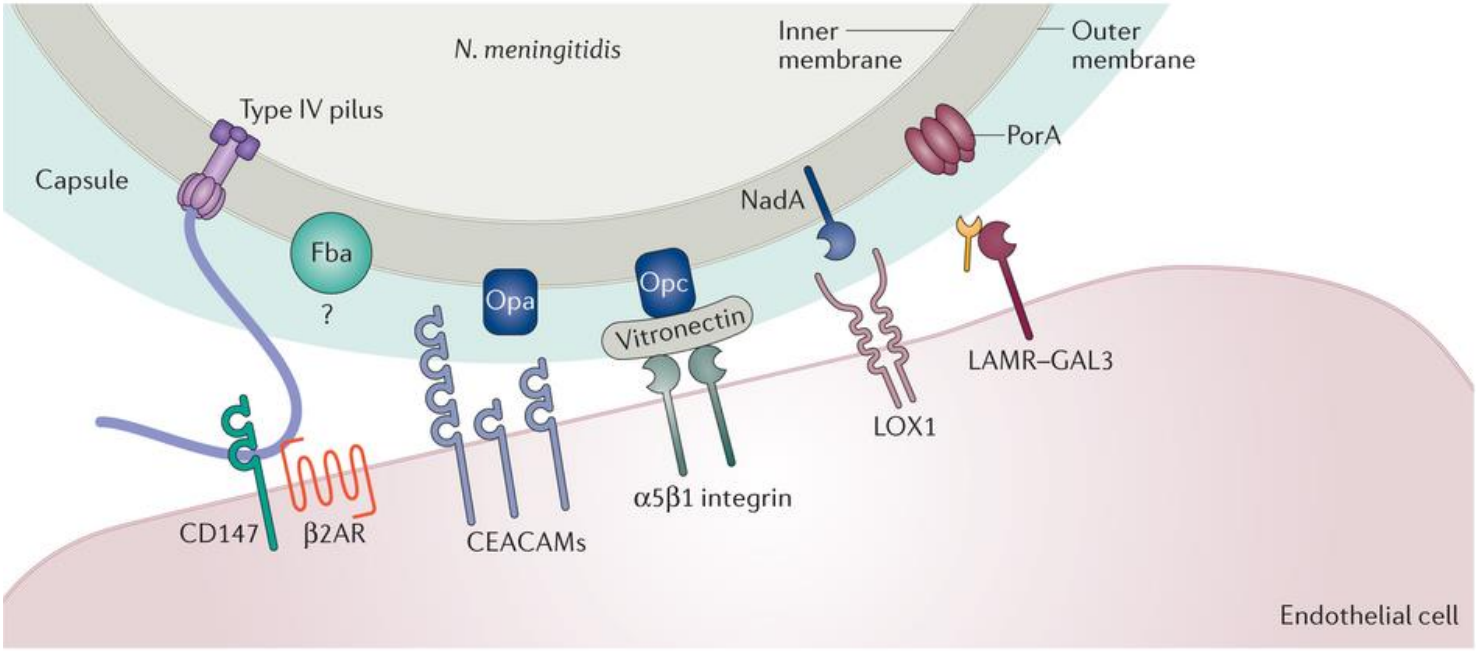
α-actinin





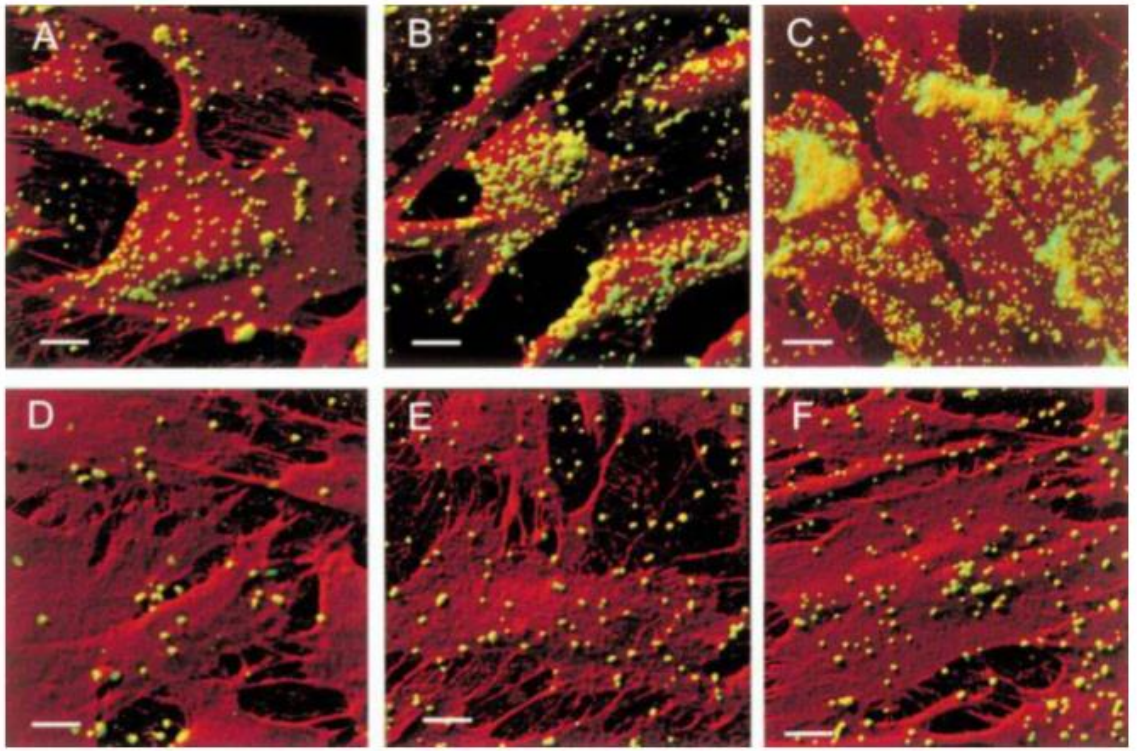
Cunha, et al,. Cell Micro 2008

How does *N. meningitidis* attach to endothelial cells?

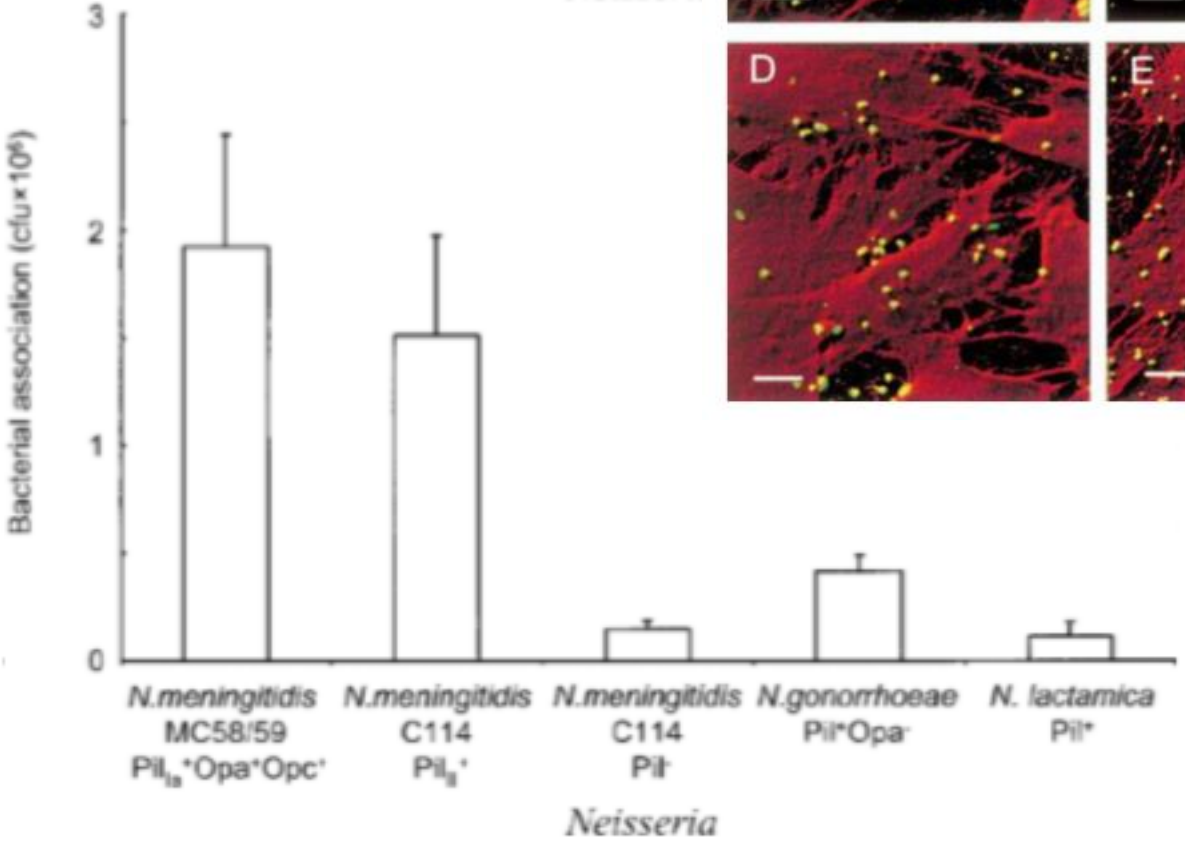


Nature Reviews | Microbiology

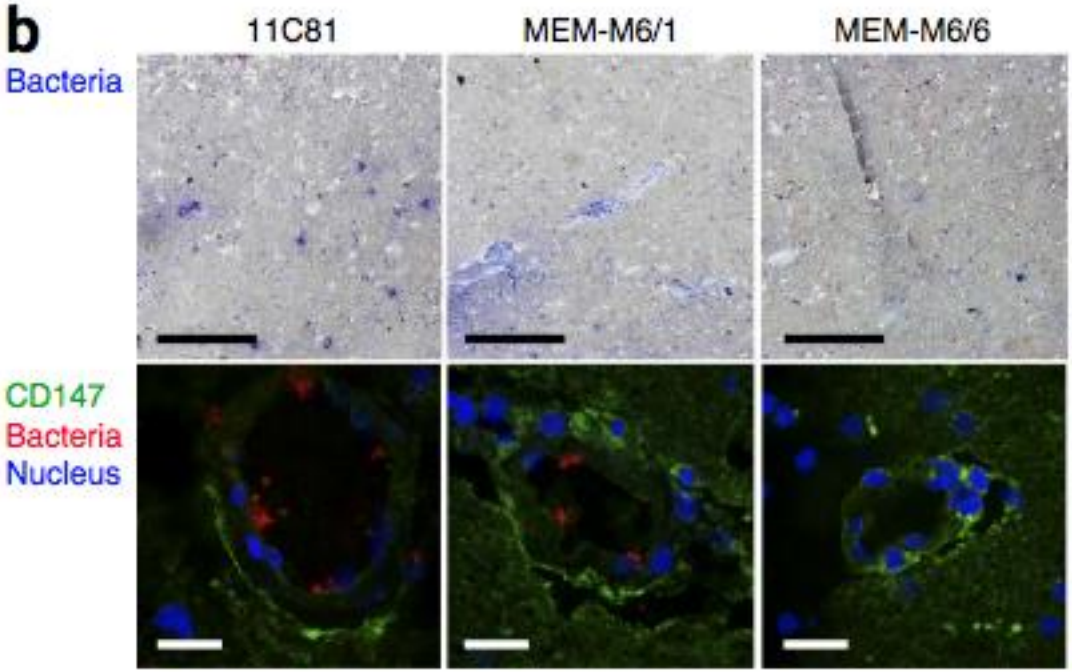
N. meningitidis attaches to endothelial cells using type 4 pili

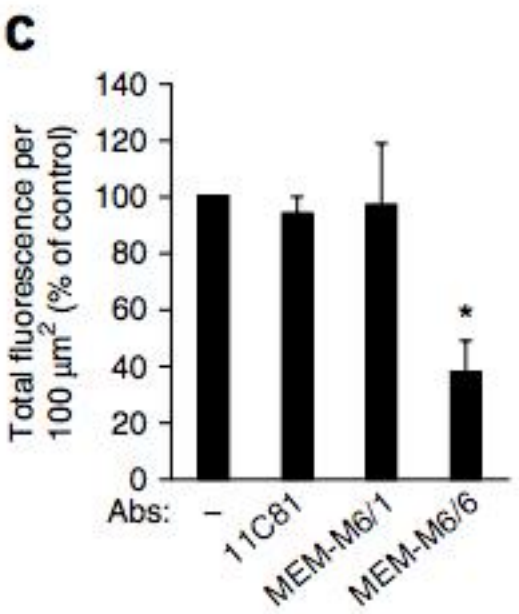


Hardy et al., Mol Micro 2000



Type 4 pili bind CD147



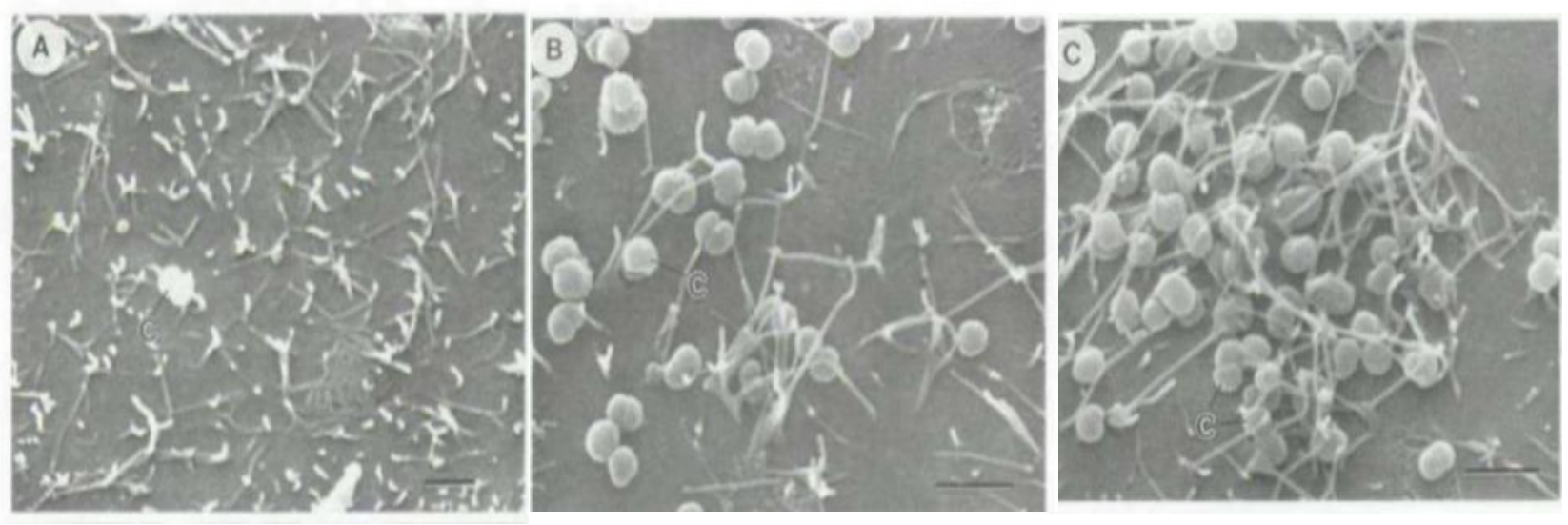


Bernard et al,. Nature 2014

Opacity proteins contribute to adhesion

Opa-opacity proteins

- -OpaA, OpaB, and OpaD
- -promote aggregation
- -antigenic variation
- -constitutively transcribed
- -pentameric repeat 5’-CTCTT-3’ within amino-terminal leader peptide



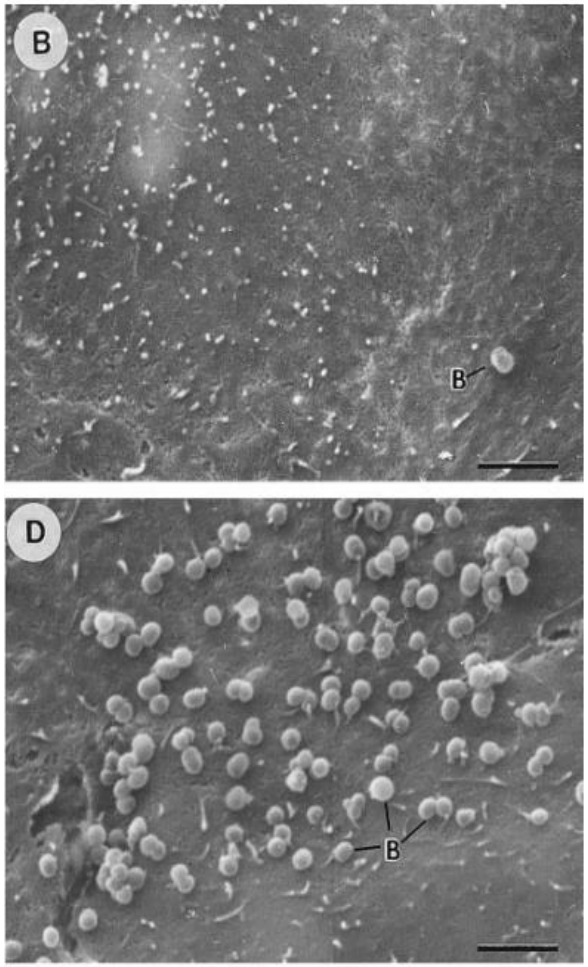
Virji, et al. Mol Micro 1993

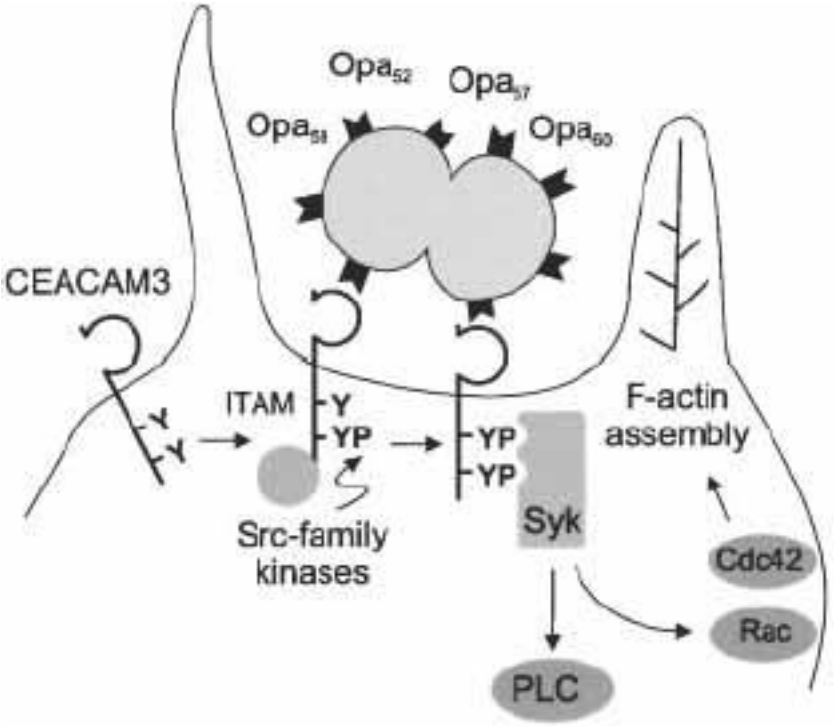
Opa interacts with CEACAM

-Carcinoembryonic antigen-related cell adhesion molecules (CEACAM)
-Mediates intracellular binding

CD33

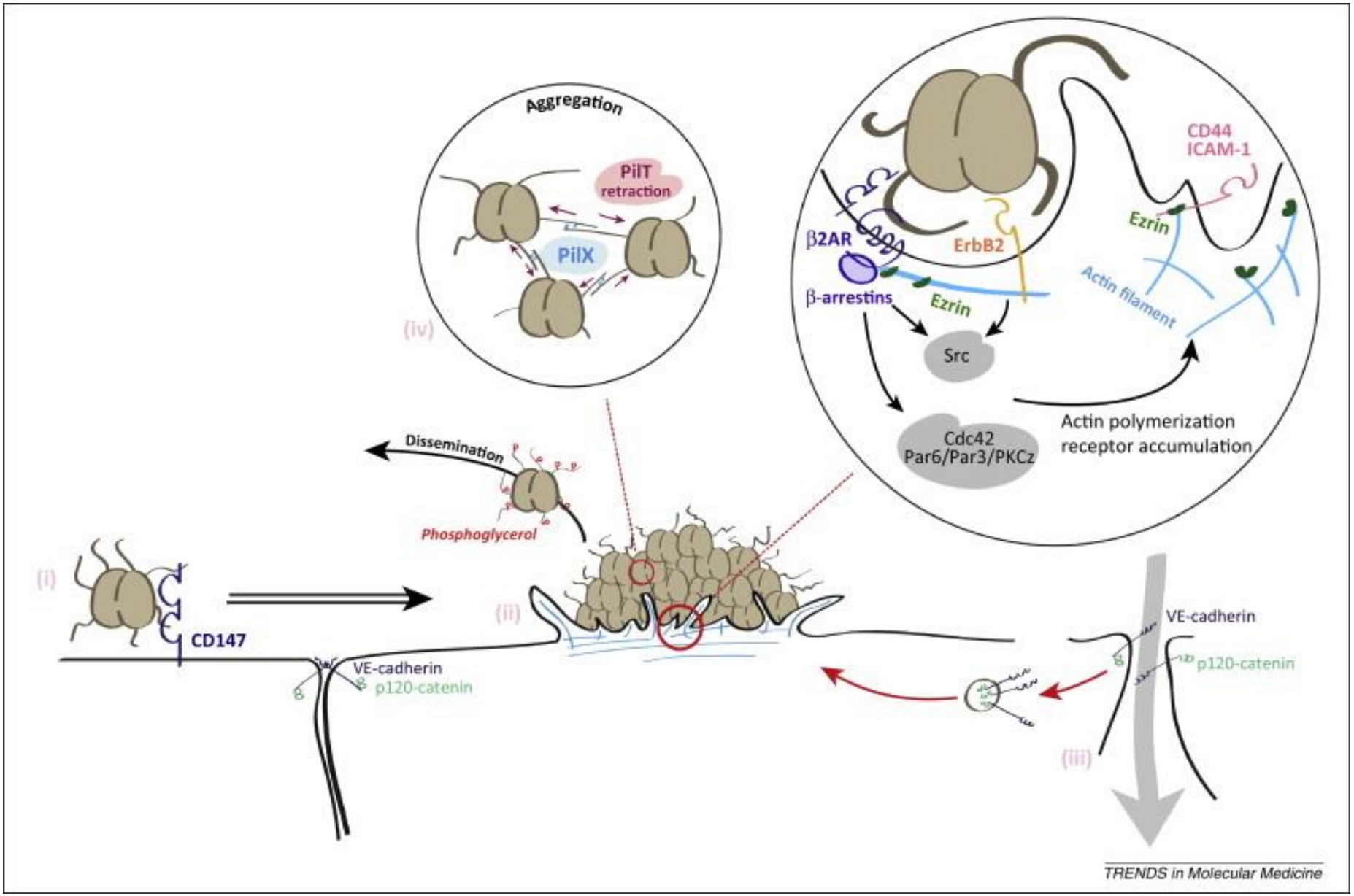
CEACAM





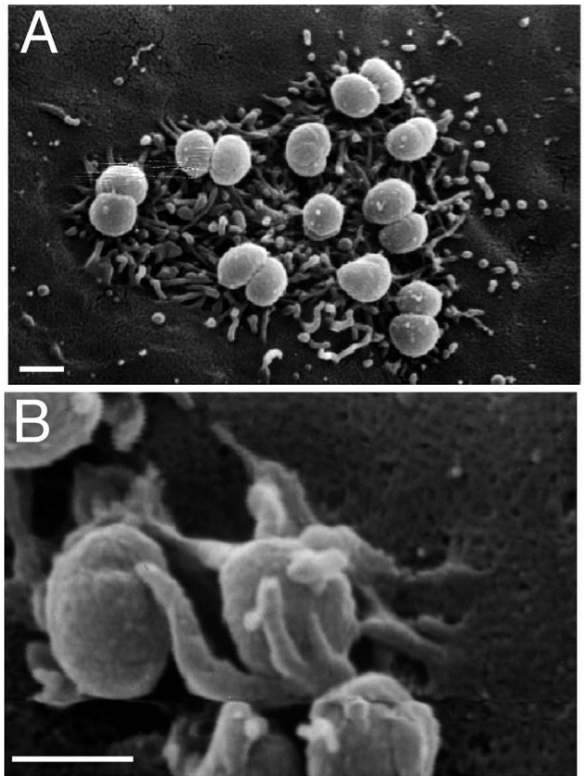
Virji, et al. Mol Micro 1996

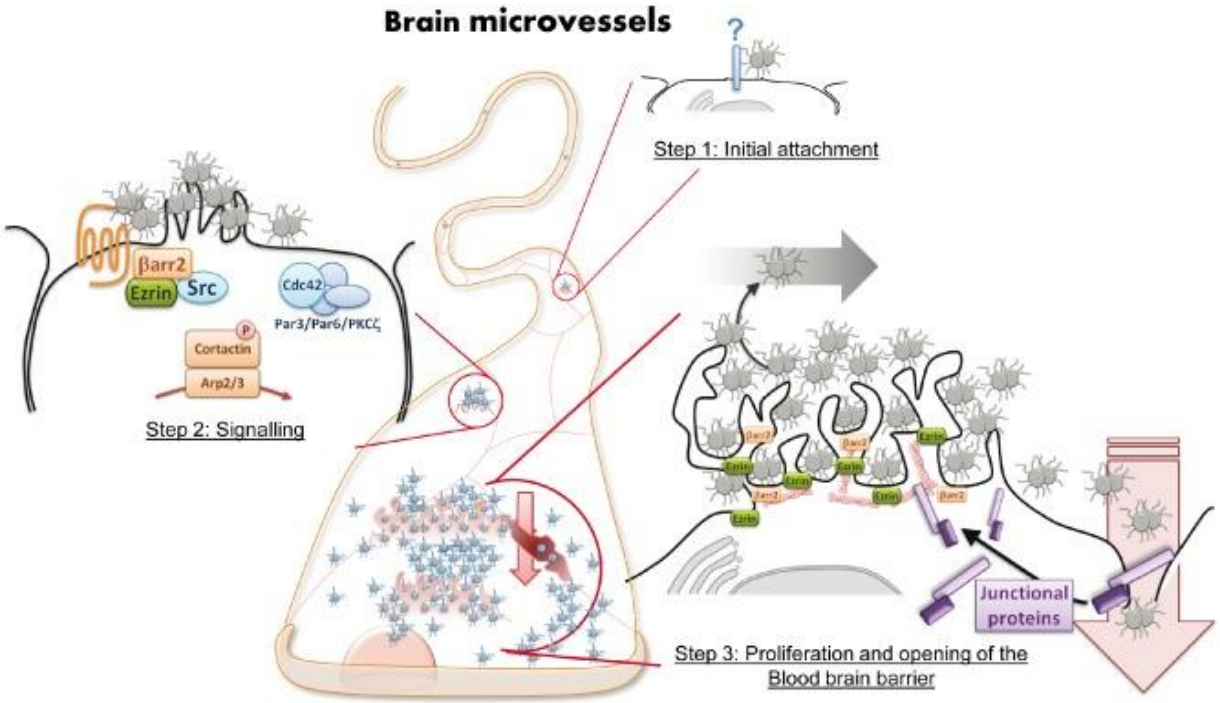
How does *N. meningitidis* invade



N. meningitidis forms cortical plagues

Recruitment of molecular linkers
Provide protection

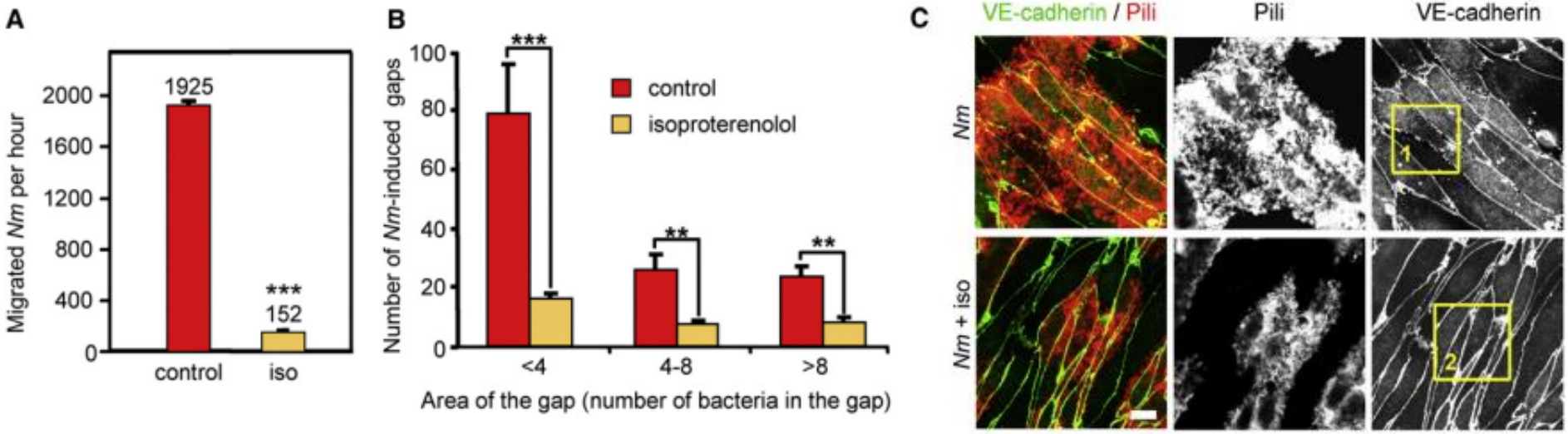




Eugene et al., Jcell Science 2002

N. meningitidis invades by binding ß2-adrenegic receptor

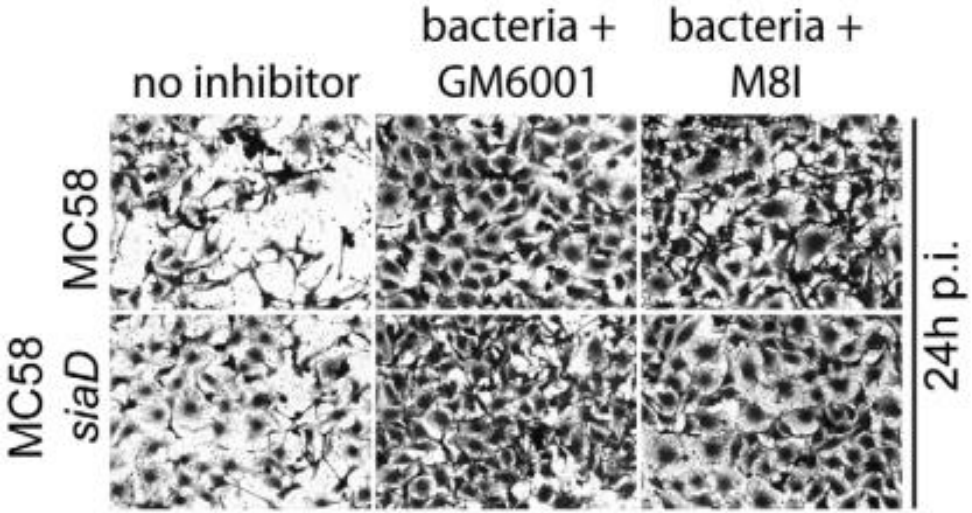
-G protein-coupled receptor
-scaffolds kinases resulting in actin polymerization

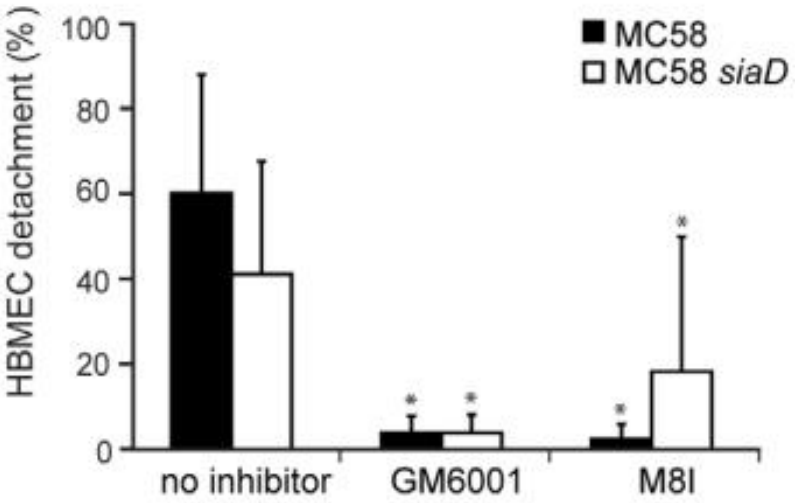


Coureuil et al., Cell 2010

N. meningitidis triggers release of matrix metalloproteinases-8

-Breakdown extracellular matrix at tight junctions

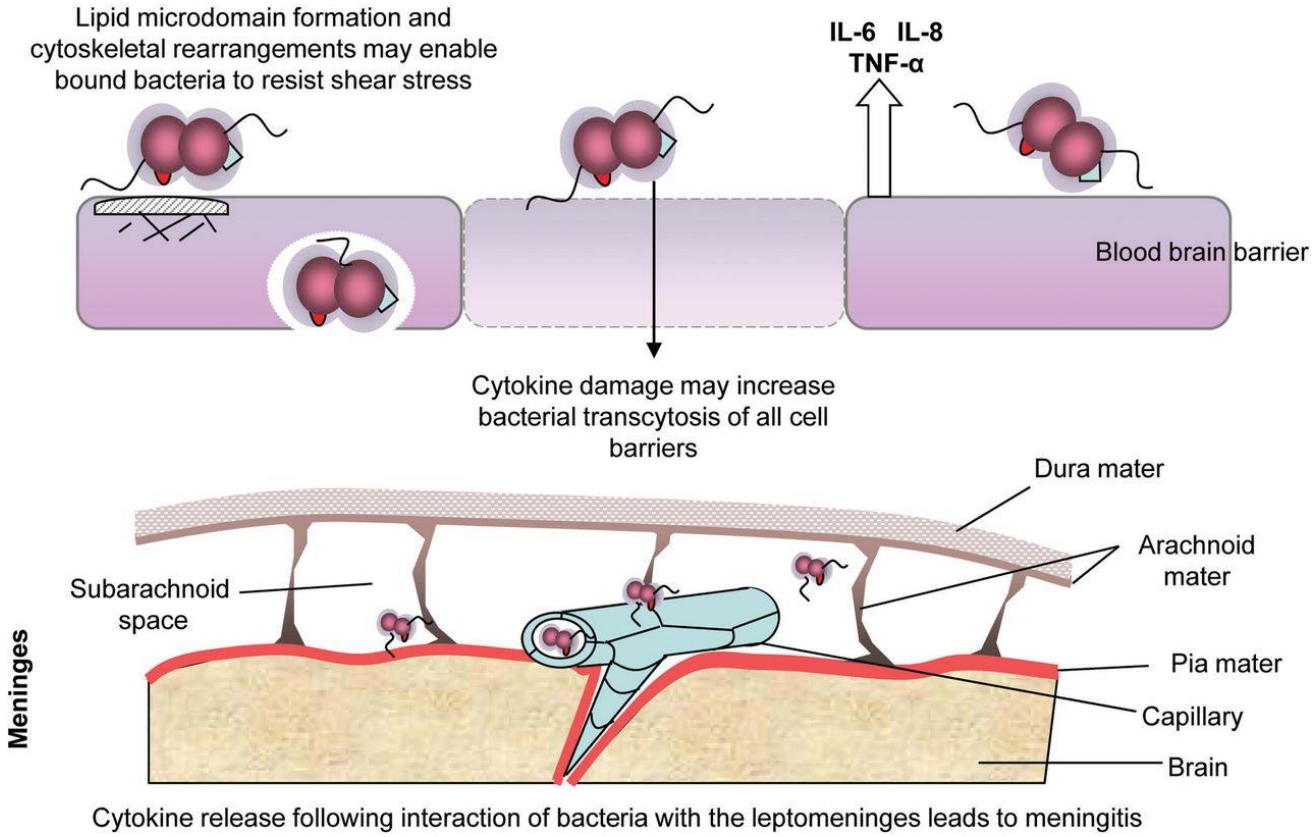




Schubert-Unkmeir et al., PLOSpath 2010

What is the host response to *N. meningitidis* infection?

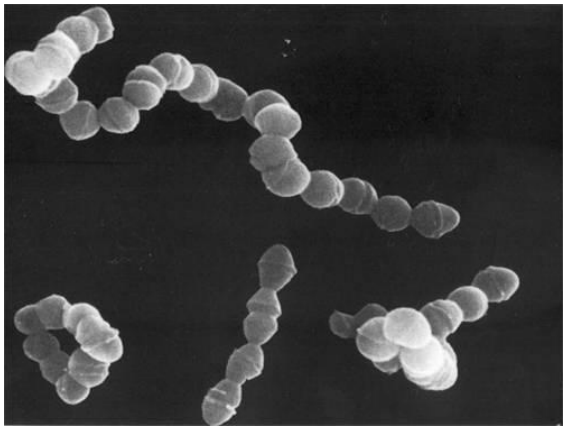
-edema, increased intracranial pressure and altered cerebral flow
-Septicemia
-TLR2 and TLR4
-NO production
-Higher levels of TNFα due to LOS



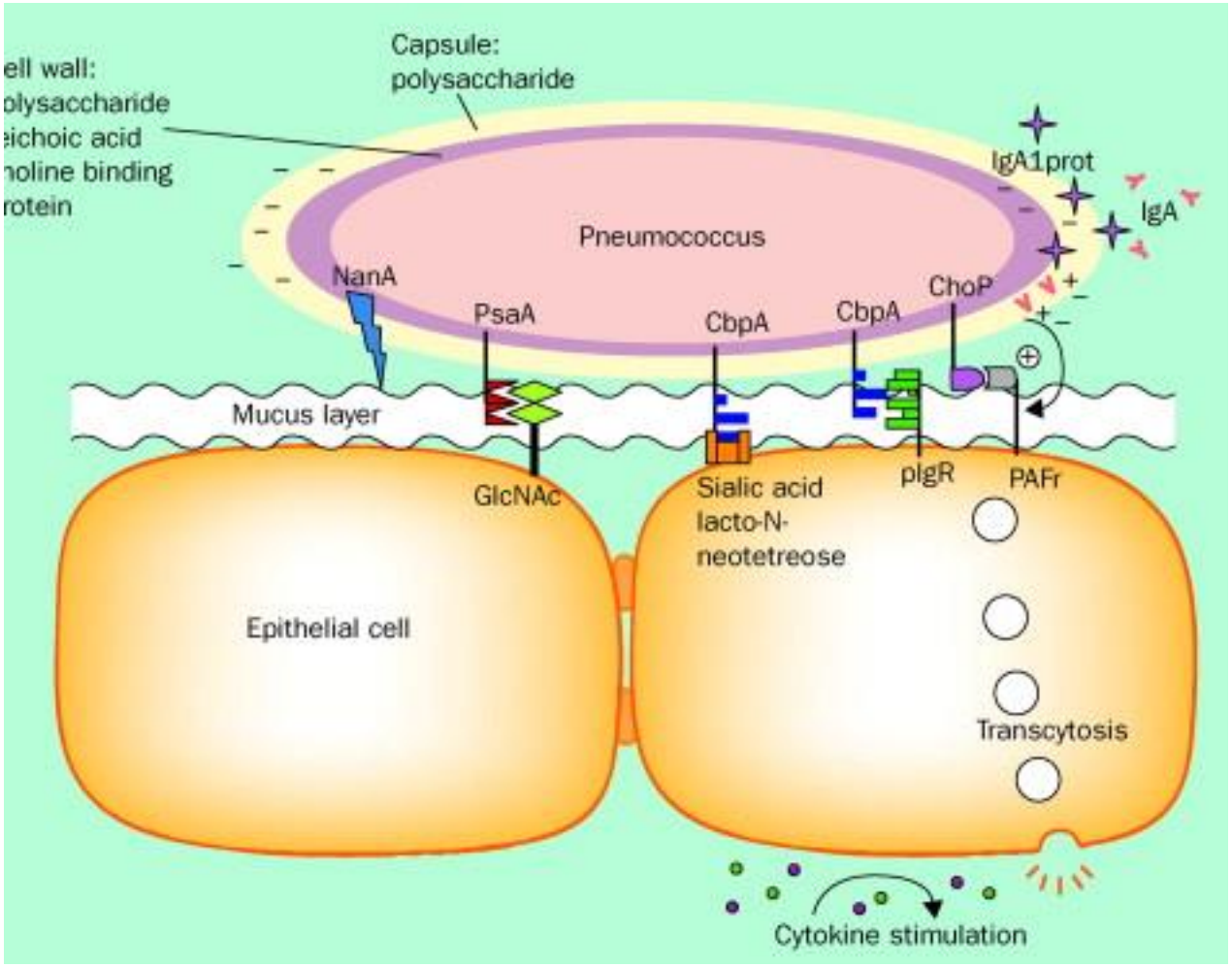
Cytokine release following interaction of bacteria with the leptomeninges leads to meningitis

Streptococcus pneumoniae

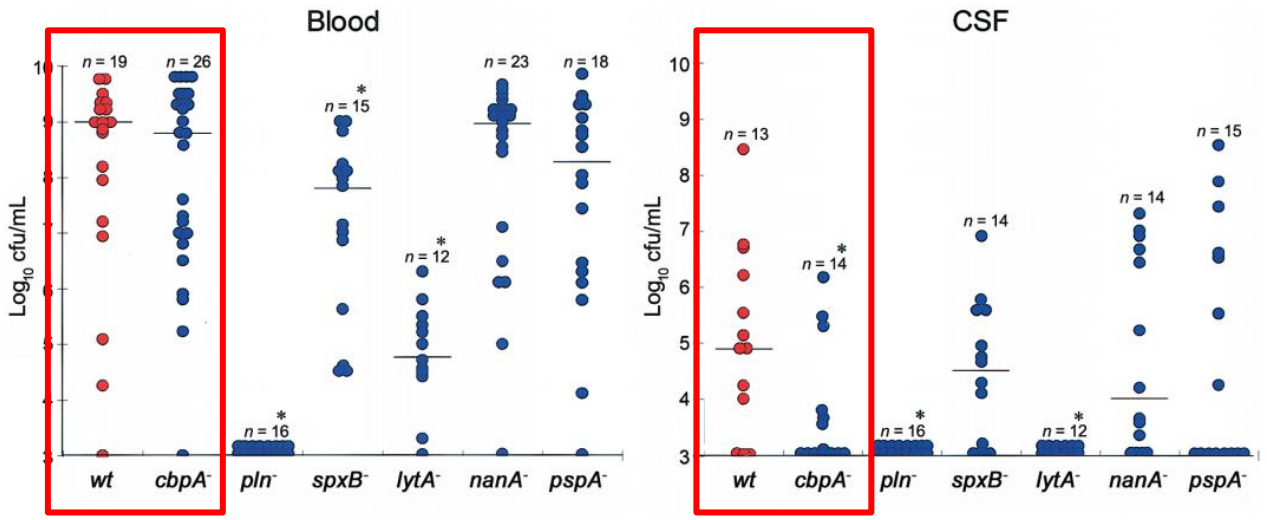
-Gram positive
90+serotypes based on capsule
    -essential for meningitis
    -thicker
~10% of adults and ~40% of children are carriers
-phase variation
    opaque vs translucent
-Human only



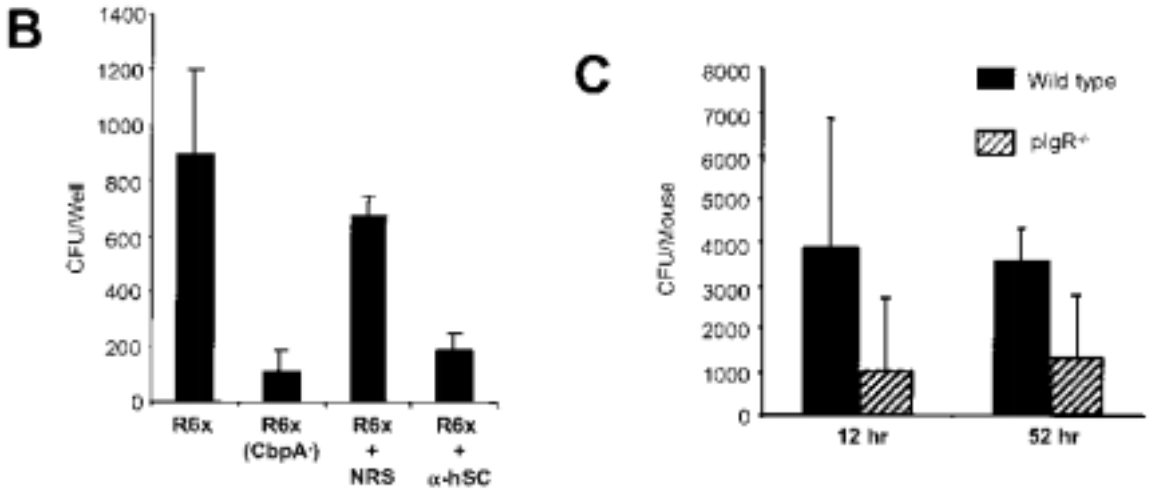
How does *S. pneumoniae* attach?



Choline binding protein (CbpA) interacts with plgR

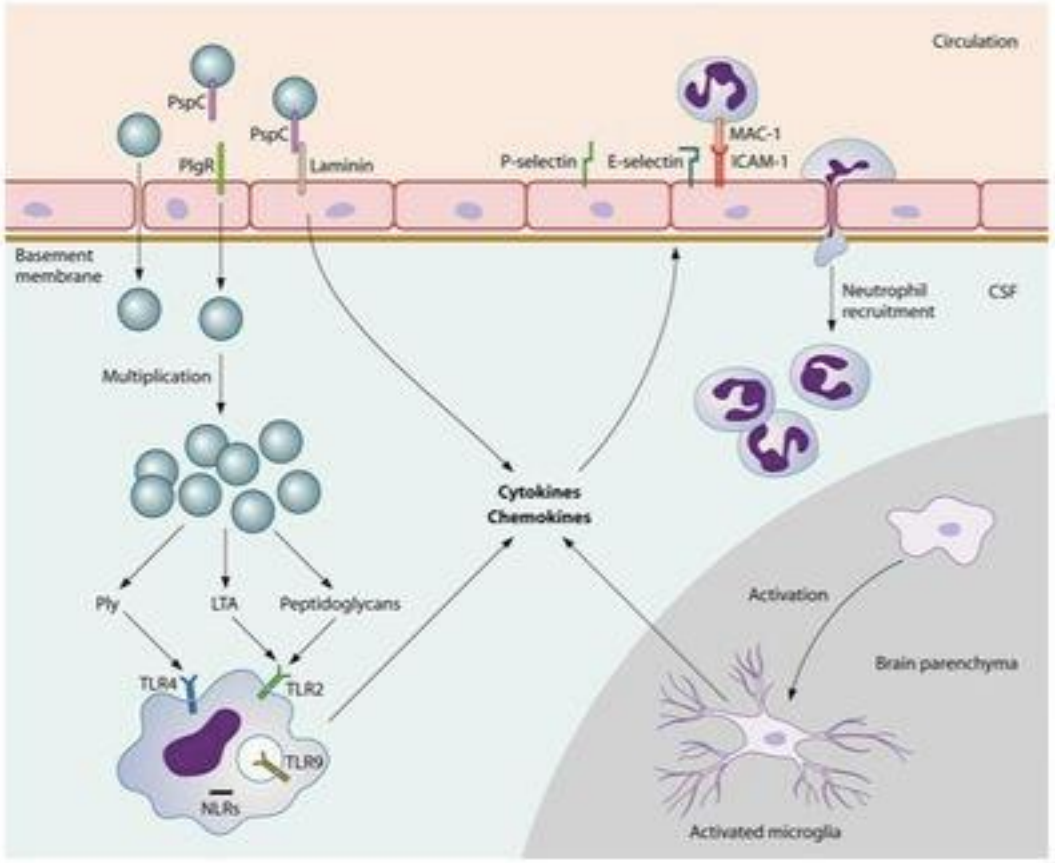


Orihuela et al., JofID 2003



Zhang et al., Cell 2000

How does *S. pneumoniae* invade?

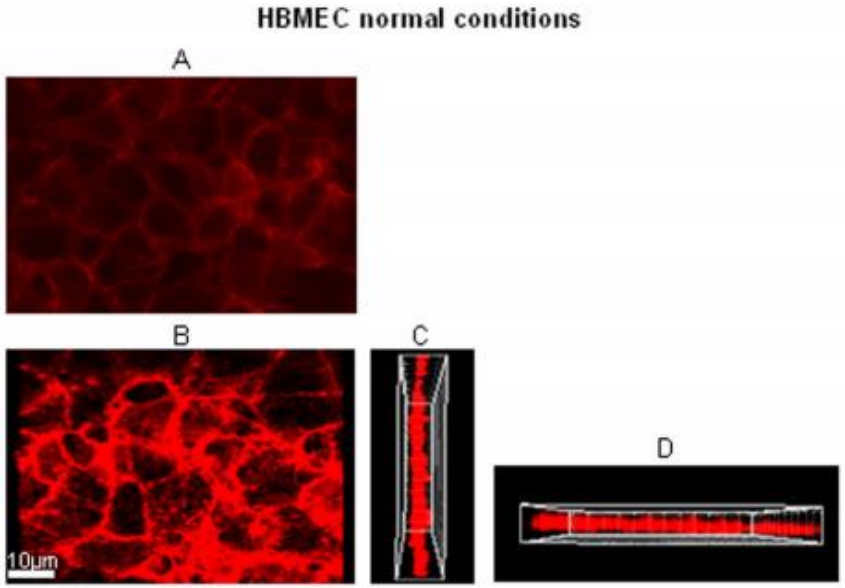


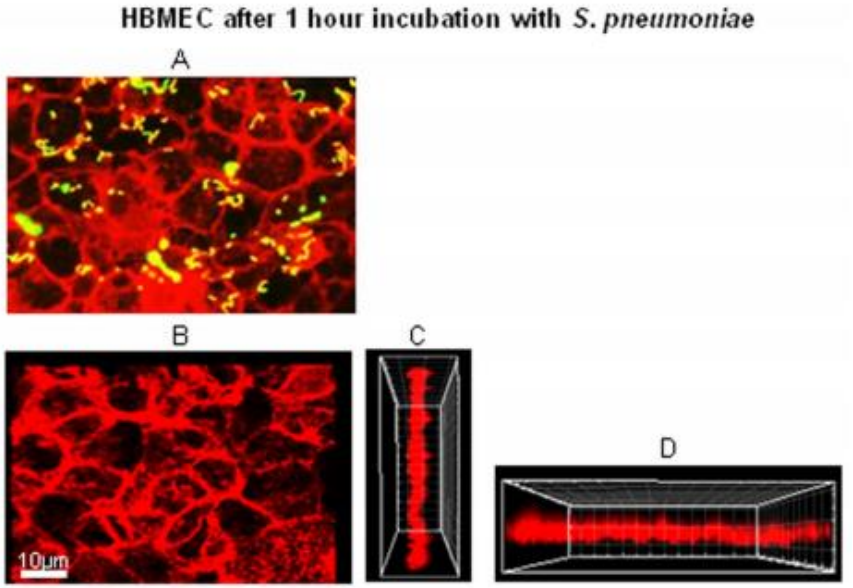
S. pneumoniae does not disrupt tight junctions

How is still up for debate

-transcytosis

Cross into the subarachnoid space

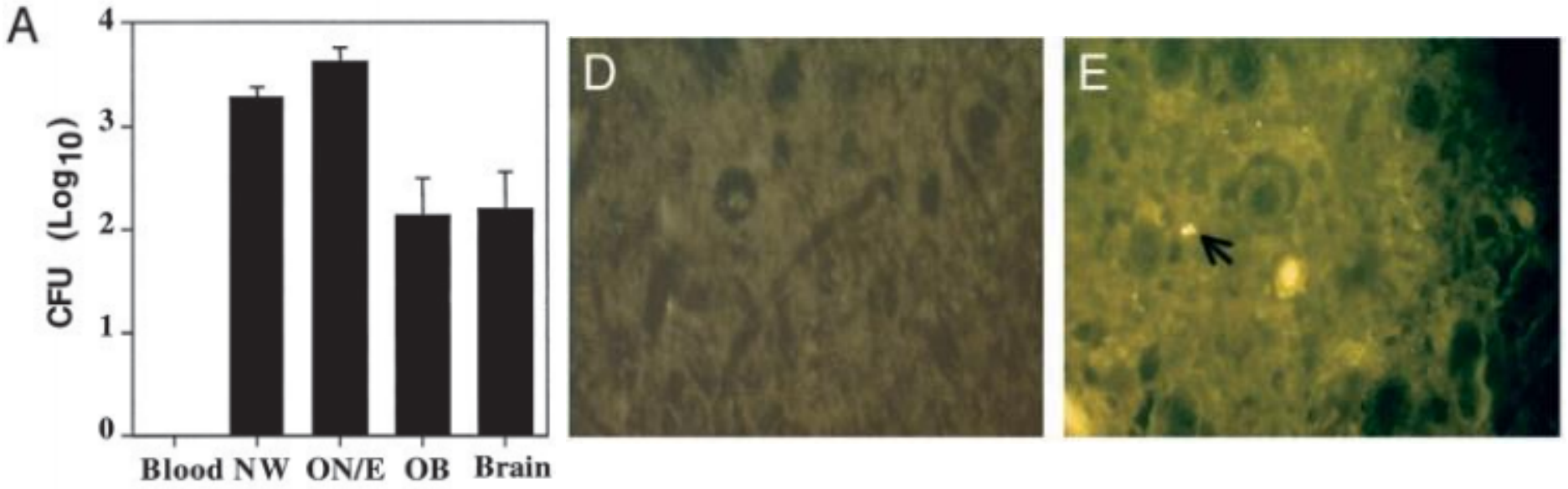




Iovino et al., PlosOne 2013

S. pneumoniae can infect the olfactory bulb

Teichoic acid interacts with gangliosides

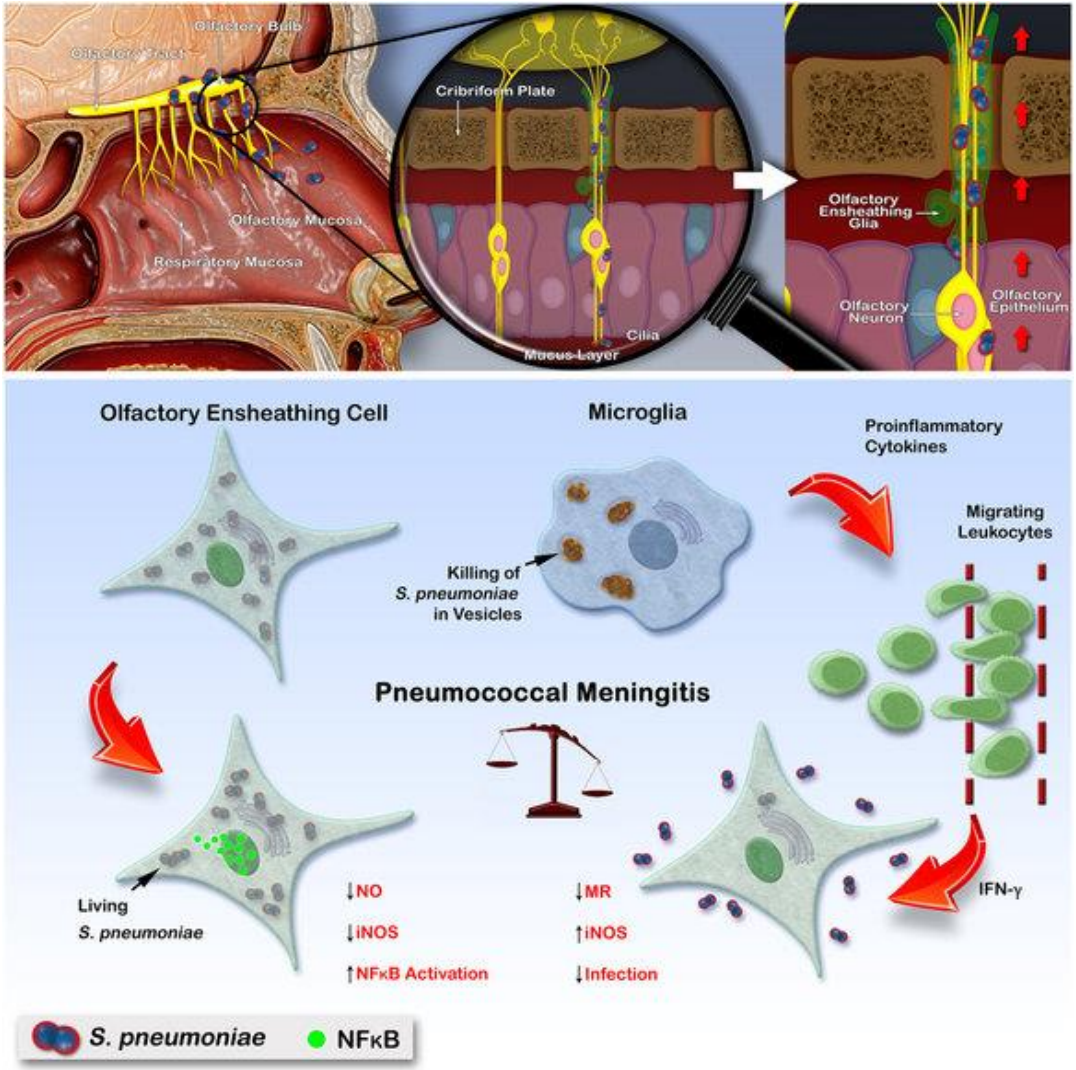


NW-nasal wash
ON/E-olfactory nerves and epithelium
OB-olfactory bulb

Ginkel et al., PNAS 2003

What is the host response to *S. pneumoniae* infection?

-Microglia express TLRs and produce pro-inflammatory cytokines
-ROS and NO



Comparison of *S. pneumoniae and N. meningitidis*

Table 1 Main similarities and differences of bacterial pathogens causing meningitis

	Streptococcus pneumoniae	*Neisseria meningitidis*
Nature of the pathogen	Gram-positive cocci, encapsulated, serotype diversity, extracellular	Gram-negative cocci, encapsulated, serogroup diversity, clonal complexes, extracellular
Site(s) of entry and colonization	Nasopharynx, Lung	Nasopharynx
Factors involved in bacterial adherence and invasion	Cell wall-anchored proteins, cytolysin, capsule	Capsule, type IV pili, outer membrane proteins (Opa, Opc, FBA, ACP, MspA)
Mechanisms of survival and dissemination in the blood	Capsule-dependent protection, complement inhibitors	Capsule-dependent protection, complement inhibitors
Mode(s) of entry into the CNS	Invasion across the BBB and B-CSFB	Invasion across the B-CSFB
Causes of tissue damage in the CNS (cerebral ischemia, edema, hydrocephalus, increased intracranial pressure)	Cytotoxin, cell wall-TLR2 induced inflammation, neuronal apoptosis, increased BBB permeability	Release of inflammatory mediators, increased BBB permeability, neuronal apoptosis, LPS
Pathology and clinical symptoms	Meningitis, sepsis, pneumonia	Meningitis, sepsis
Possible sequelae	Deafness, learning deficits, paralysis	Deafness, neuro-developmental deficits

Conclusion

What makes a pathogen successful at crossing the BBB?

- -invasive
- -survive in the blood
- -evade immune system (capsule)
- -antigenic variation

What separates *N. meningitidis* from other pathogens that can cross the BBB?

- -Adapted well to invade and cause disease
- -higher tropism
- -manipulation of the host

How is *Neisseria meningitidis* so good at entering the CSF and causing meningitis?

Background

- -BBB anatomy
- -Nm pathogenic isolates vs carriage isolates
- -Sp

Compare and contrast S. pneumoniae and N. meningitidis

- -How do they get to the BBB
- -How do they attach
- -How do they cross/entry
- -How do they cause disease once in the CSF/BBB

Conclude-what separates Nm from other pathogens