Development of a Rapid Complement Array for Detection of Shunt Infection and Failure

James M. Johnston, MD, Theresa Ramos, PhD., Anastasia Arynchyna, MPH, Curt Rozzelle, MD, Scott Barnum, Ph.D.
Departments of Neurosurgery and Microbiology
University of Alabama at Birmingham

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Children's of Alabama

UAB IMMUNOLOGY

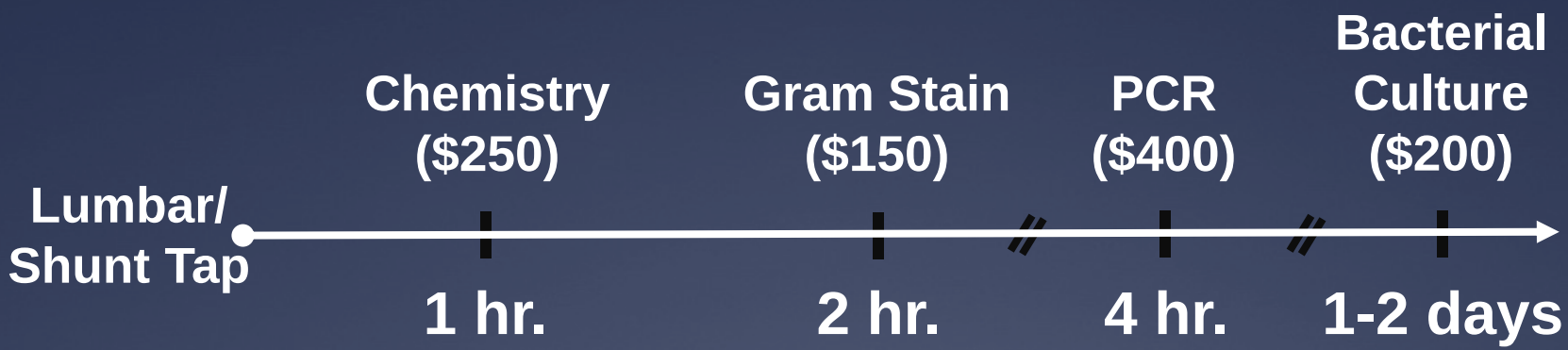
Bacterial Meningitis

- Induces a massive host immune response in the CNS – including complement production and activation
- Requires rapid diagnosis and treatment – 30% mortality rate, significant morbidity
- Diagnosis is expensive, difficult and slow
- Significant childhood mortality worldwide

Shunt Infection

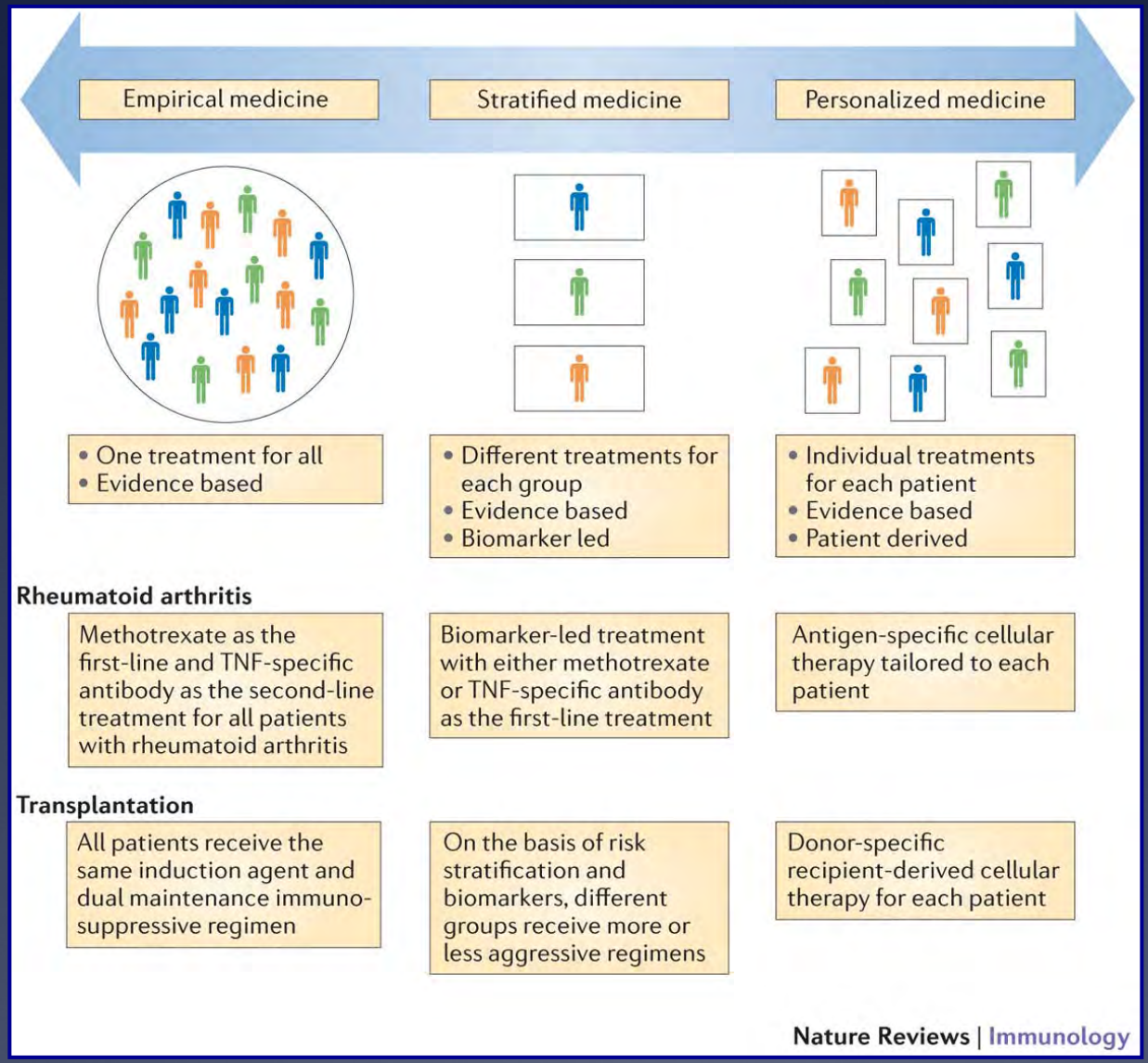
- Shunt infection (SI) is common and associated with shunt failure and significant morbidity
- Symptoms of SI vary with pathogen type, often leading to delayed diagnosis and treatment or more commonly overtreatment
- Associated with significant costs: hospital admission days, antibiotics, microbiology

The Problem



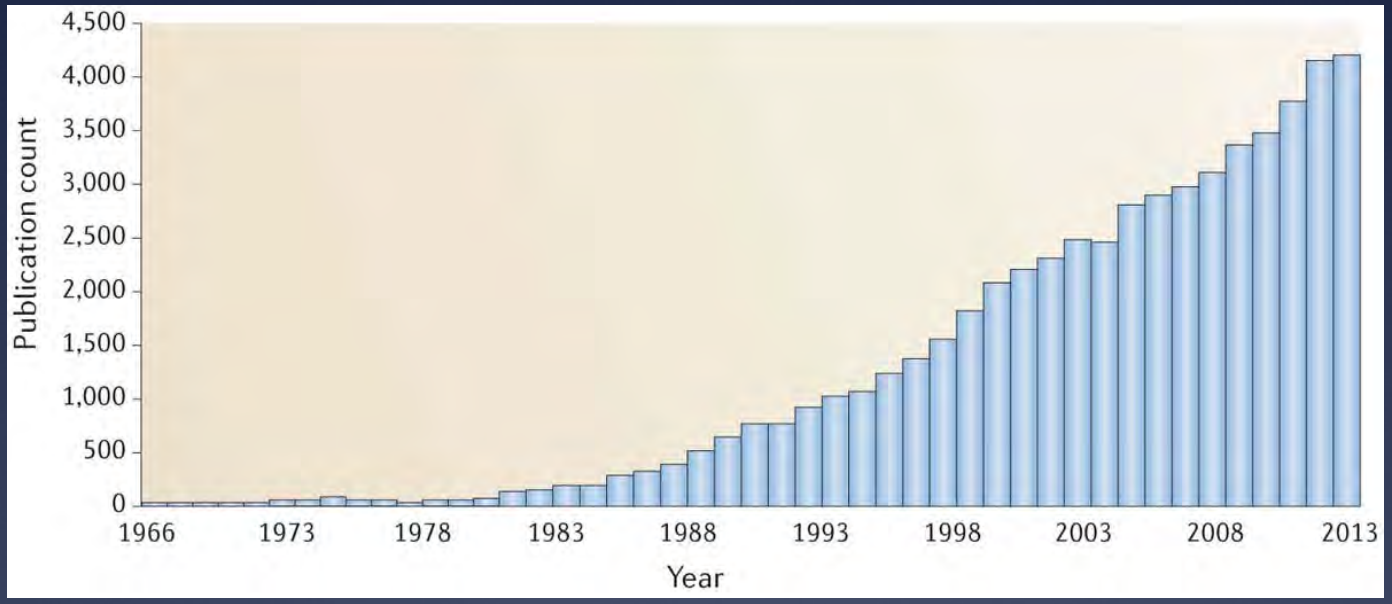
Total Cost: ~$1,000+Hospitalization+Abx

The Promise of Biomarkers



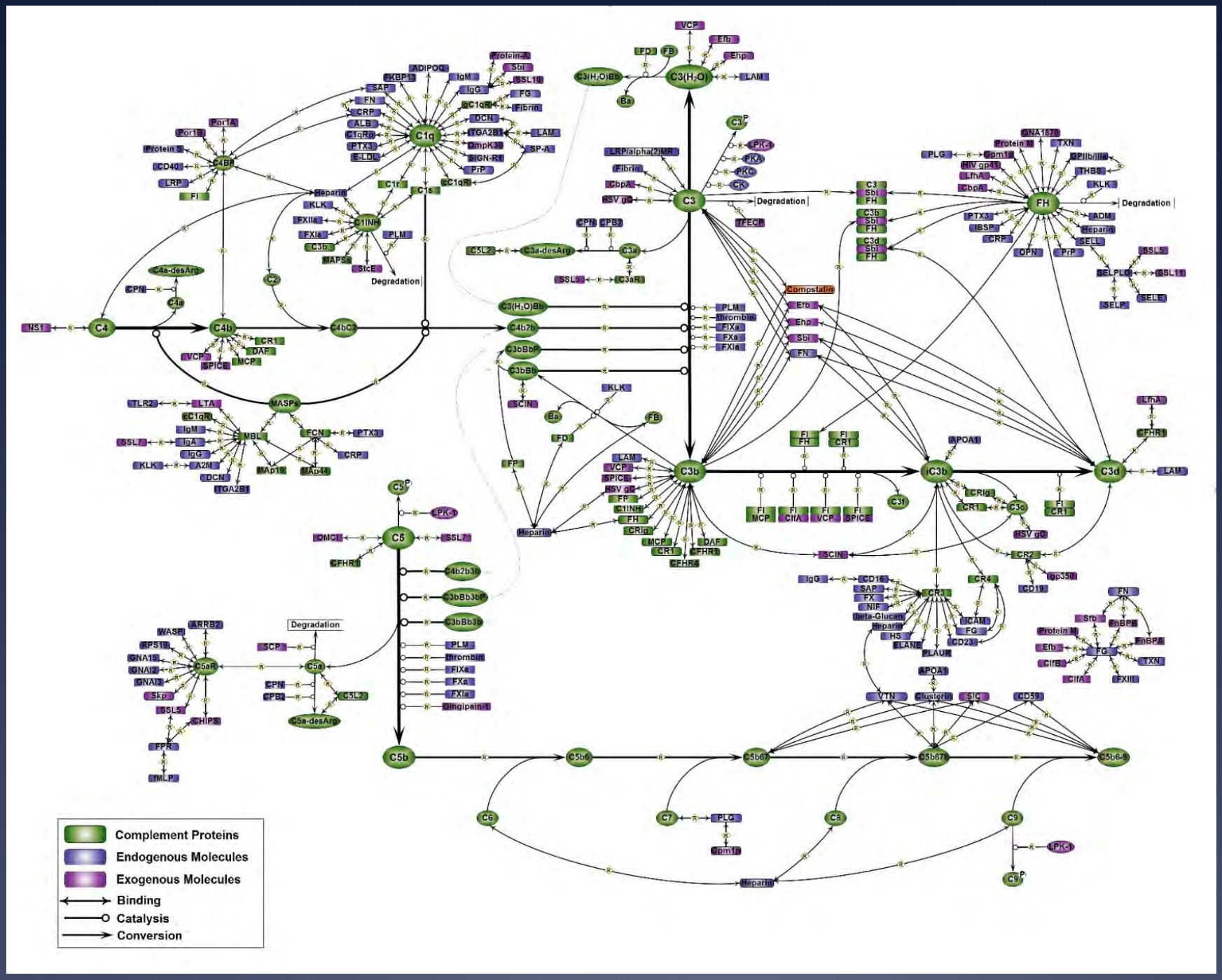
Willis & Lord, Nat. Rev. Immunol. 15:323, 2015

The Road to Biomarker Development is Crowded

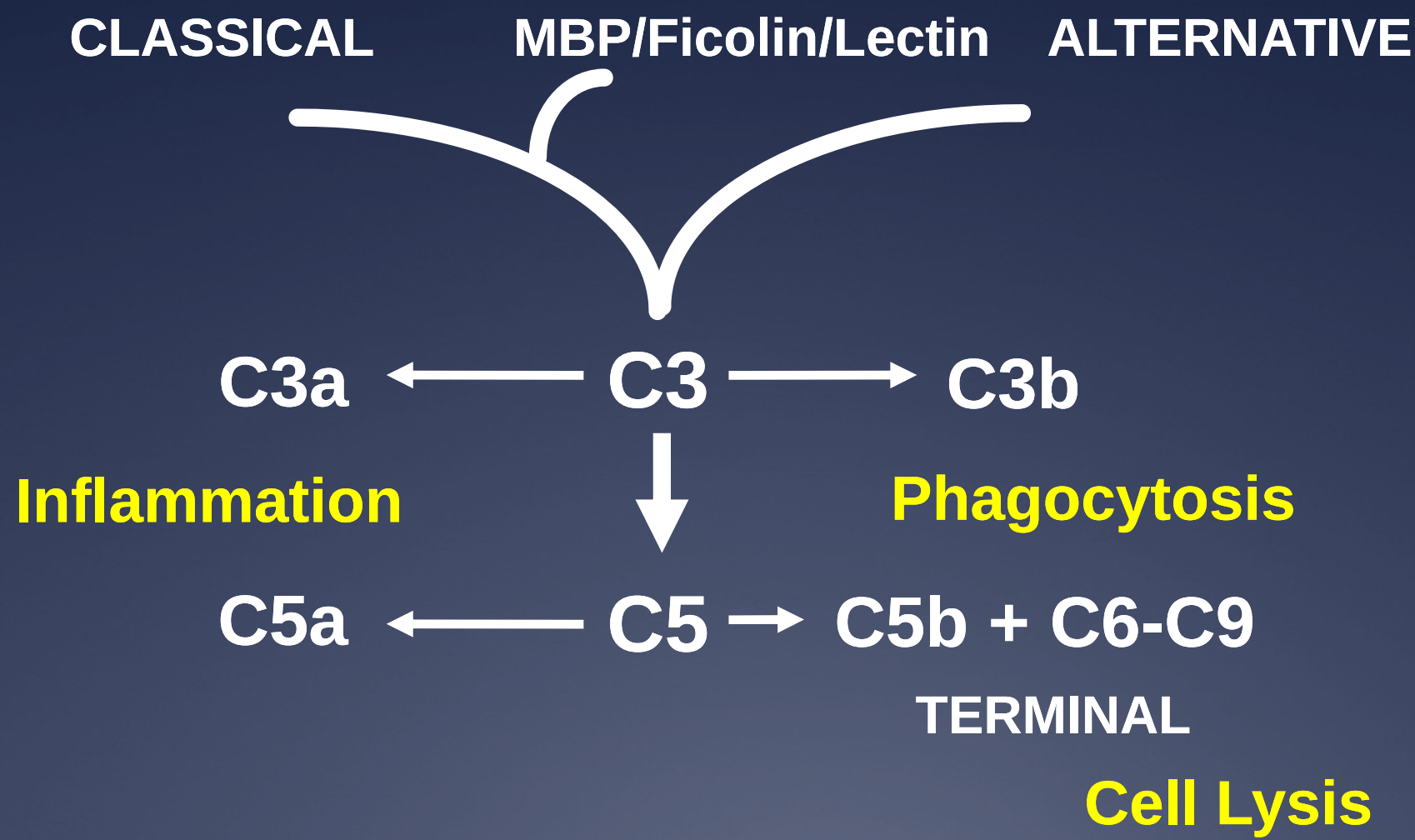


Biomarker: "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention"
(NIH Biomarker Definitions Working Group)

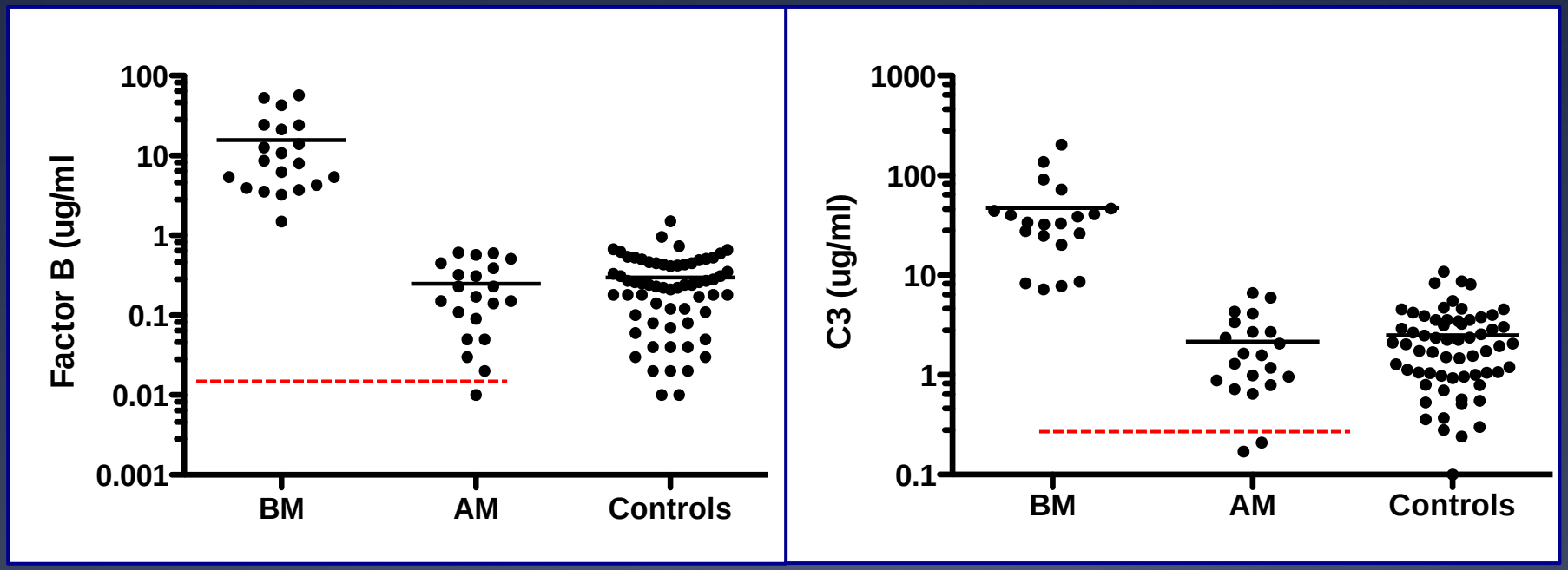
Willis & Lord, Nat. Rev. Immunol. 15:323, 2015


C1q
C4BP
C4
C4b
C4bC2
C4b2b
C3(H2O)Bb
C3(H2O)
C3
C3b
iC3b
C3d
C3c
C3f
C3a-desArg
C4a-desArg
C2
C1r
C1s
C1INH
MASPs
MBL
FCN
PTX3
CRP
CR1
DAF
MCP
VCP
SPICE
Degradation
Compstatin
FH
FI
FB
Ba
FD
Properdin
C5
C5b
C5a
C5a-desArg
C5aR
C5L2
C5b6
C5b67
C5b678
C5b6-9
C6
C7
C8
C9
PLG
Heparin
Complement Proteins
Endogenous Molecules
Exogenous Molecules
Binding
Catalysis
Conversion

COMPLEMENT PATHWAYS



Elevation of terminal complement pathway distinguishes bacterial from viral infection in mice

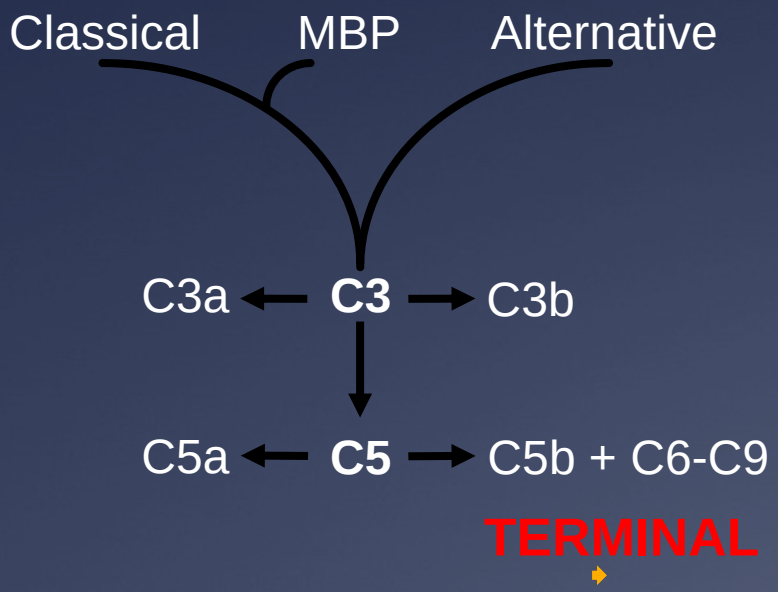


Bacterial Viral Non inf.

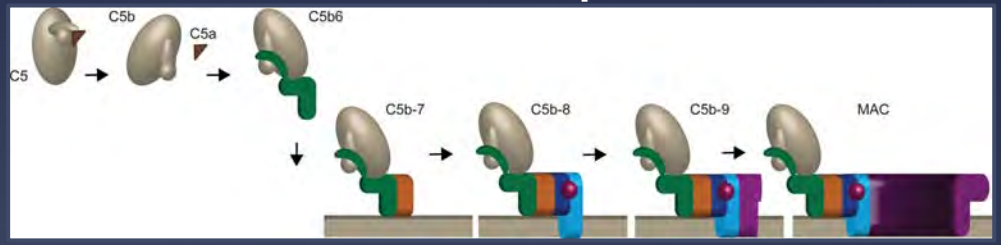
Bacterial Viral Non inf.

Membrane Attack Complex (C5a-C9)

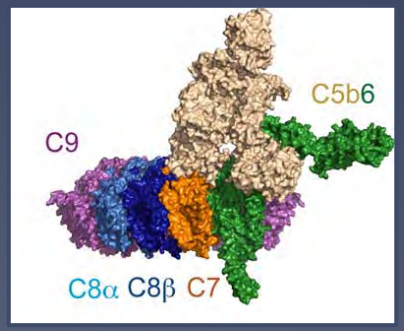
-aka Terminal Complement Complex (TCC) forms on the surface of bacterial cells, forms transmembrane channels that disrupt the phospholipid bilayer leading to cell death

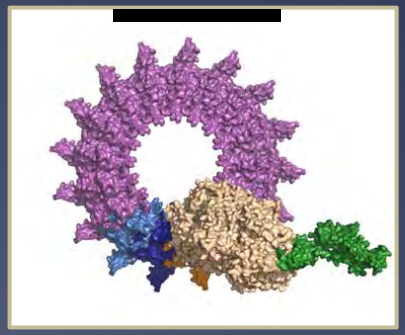


Membrane Attack Complex Formation

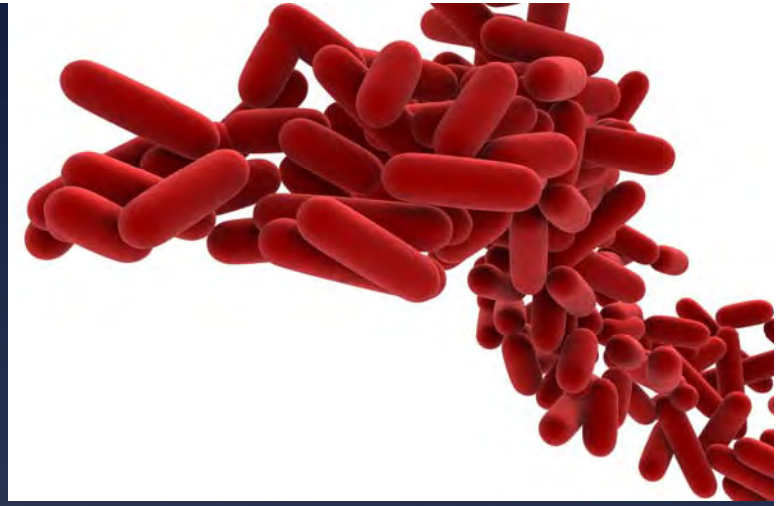


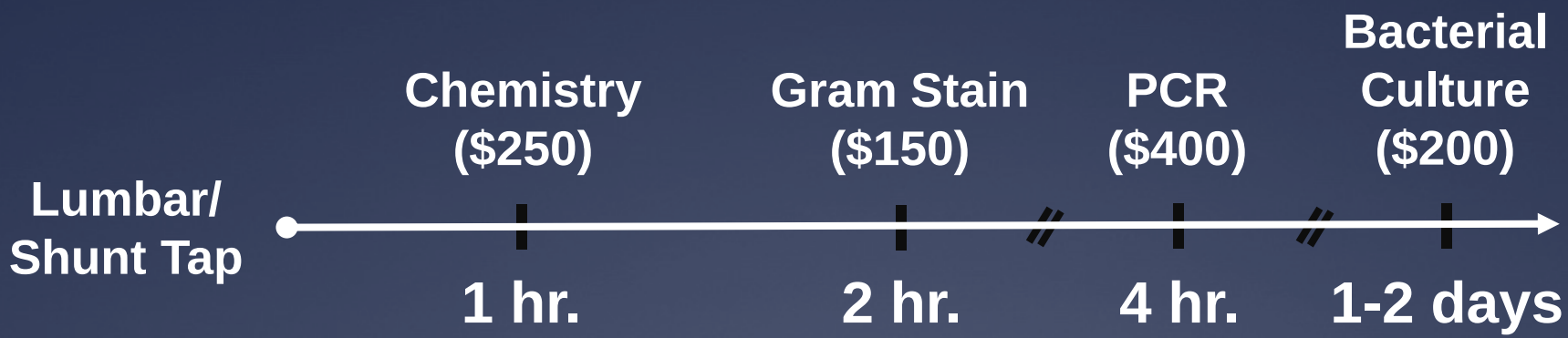
MAC





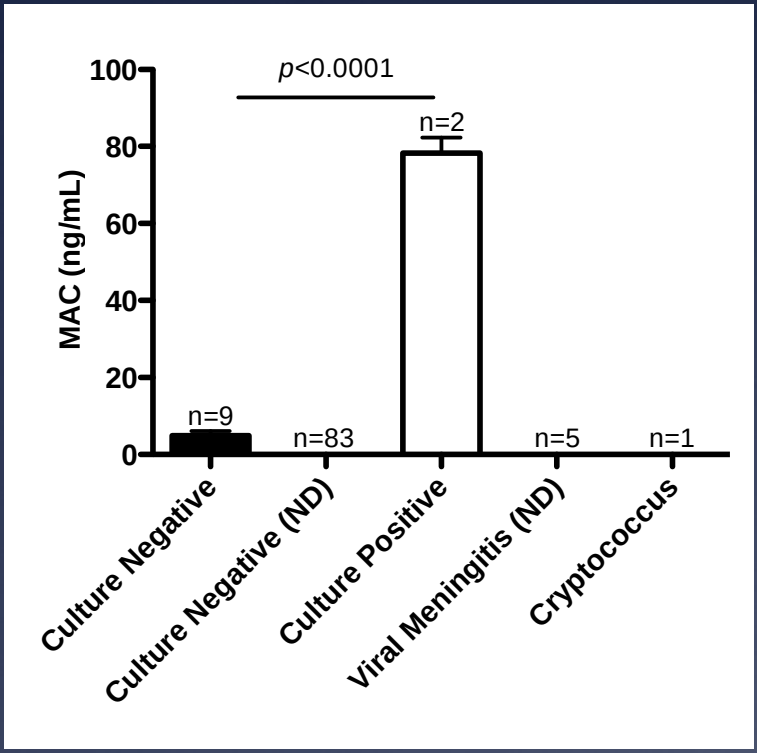
The Problem



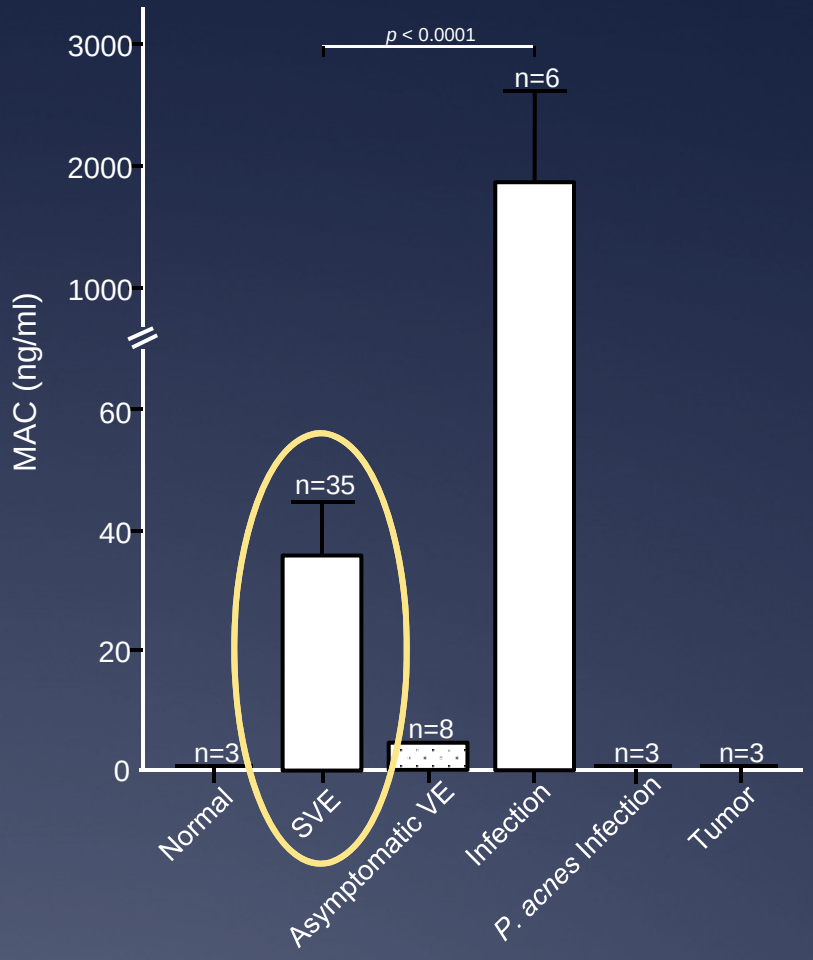


Total Cost: ~$1,000+Hospitalization+Abx

MAC is Sensitive and Specific for Infection



n = 100
ND = not detected
2 confirmed bacterial meningitis
5 confirmed viral meningitis
1 cryptococcal infection



n = 61 pts.
ND = not detected
SVE = symptomatic ventricular enlargement

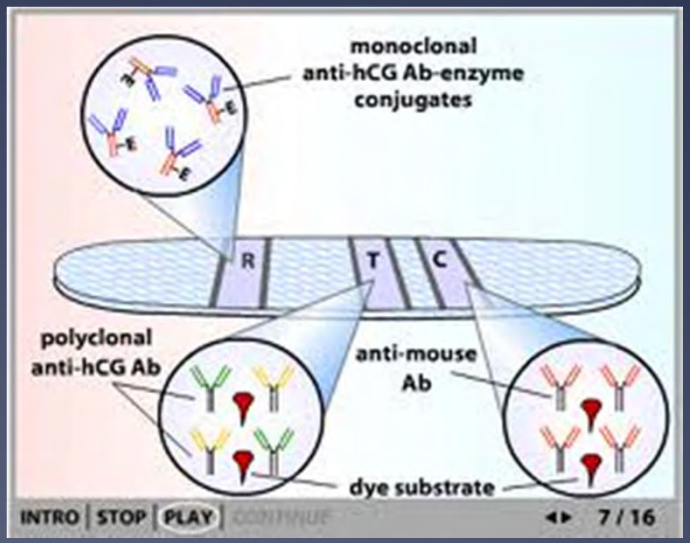
The Solution

Lateral Flow Assay for MAC:

rapid - 15-20 minutes

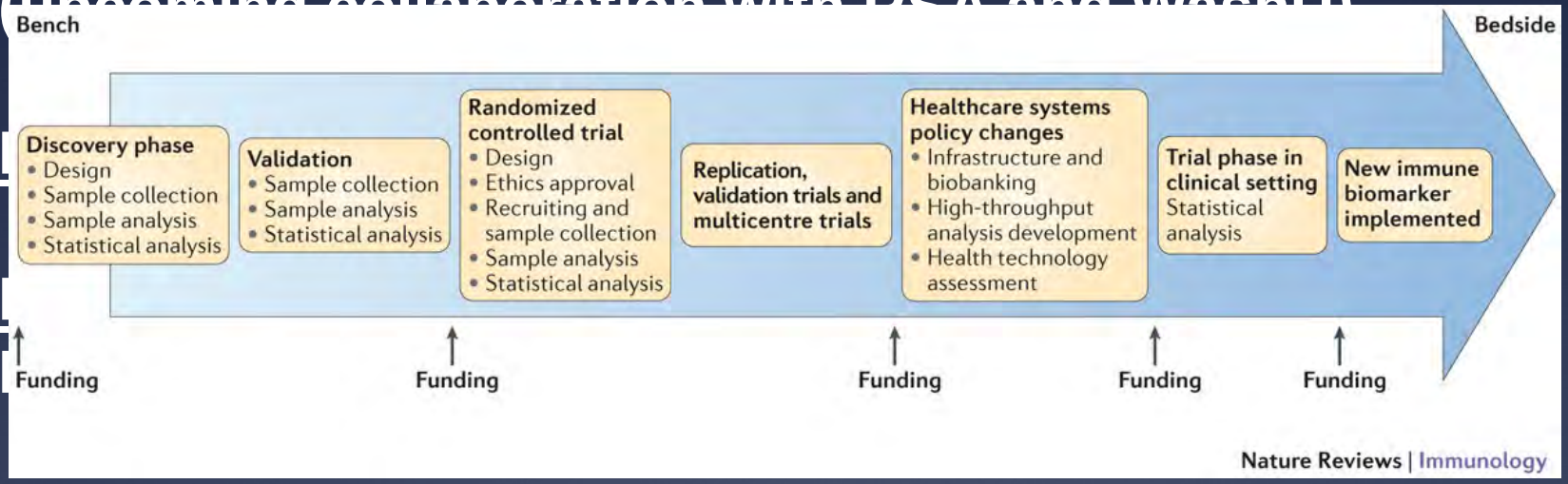
inexpensive - $25-100

sensitive - nanogram detection



Research & Business Strategy

- **<u>Biomarker Validation</u>: complement proteins in CSF samples from patients at UAB and Children's hospitals (upcoming collaboration with BSA and WashU)**



- **<u>License:</u> diagnostic companies focused on inflammatory biomarkers using an established POC/LFA platform – possible multi-platform applications**

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