

The peritoneal membrane: an open window to local inflammation



Systems Immunity
Research Institute

Sefydliad Ymchwil
Systemau Imiwedd

Matthias Eberl

„I was terrified of the possibility of peritonitis”

“The high possibility of infection reported amongst PD patients was a significant factor in my decision to opt for haemodialysis from the outset.

“Self-testing for PD patients will be a major advantage.”

– **Janet Williams** –

Renal transplant patient



Diagnosis of infection largely depends on microbiological culture results



Robert Koch
(1843-1910)

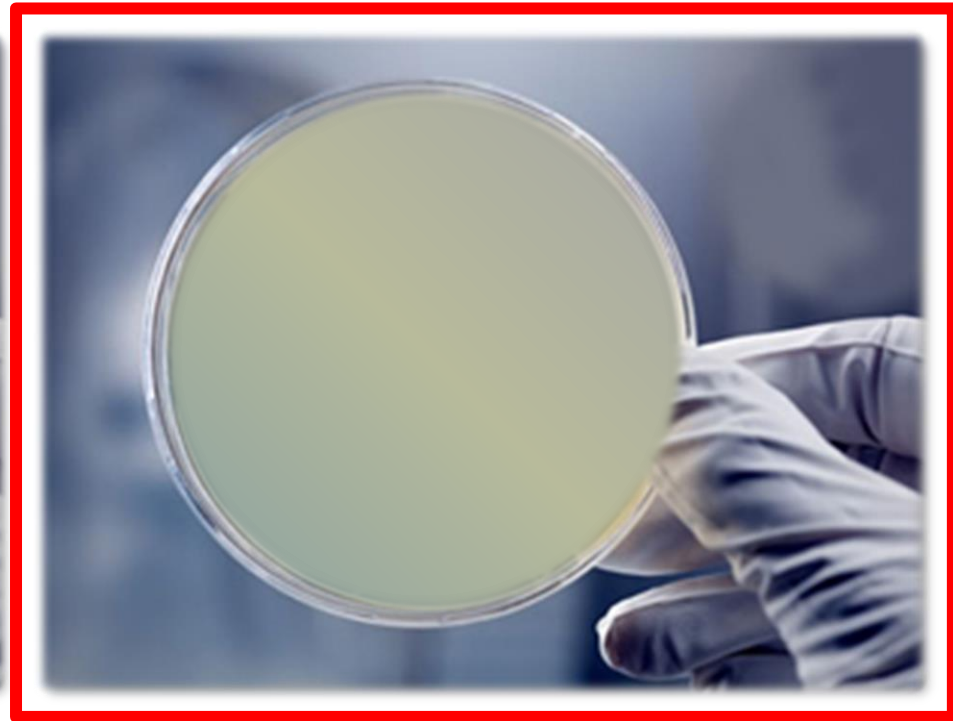
Diagnosis of infection largely depends on microbiological culture results



Causative organism or contamination?



No growth or no infection?



Delayed antibiotic-treatment increases the risk of treatment failure

The Relationship Between *Presentation* and the Time of Initial Administration of Antibiotics With *Outcomes* of *Peritonitis* in Peritoneal Dialysis Patients: The PROMPT Study



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**In the absence of rapid and reliable diagnostics,
treatment of infections is largely empirical**



„No patient wants to take unnecessary drugs”

“Having to take a lot of drugs, with the side effects they give, is a matter of concern to all patients with a long term chronic illness.”

– **Gloria Owens** –

Renal transplant patient



**Can we improve
the current diagnosis
of microbial infection
in PD patients ?**

Features of an ideal diagnostic test

Sensitivity and Specificity

- Detect all true positive
- Identify true negatives
- Minimal false positive/negative

Currently: 20% culture negative

Time to Result

- Clinically relevant timeframes
- ID and AST profile
- 4 hours total

Currently: 2-5 days

Ease of Performance

- No specialist training
- Minimal sample preparation
- Minimal biosafety concerns

Currently: Specialist staff in labs

Accessibility

- Comprehensive laboratory tests
- Rapid screening for ED testing
- Point of care for rural/remote
- Acceptable cost-per-test

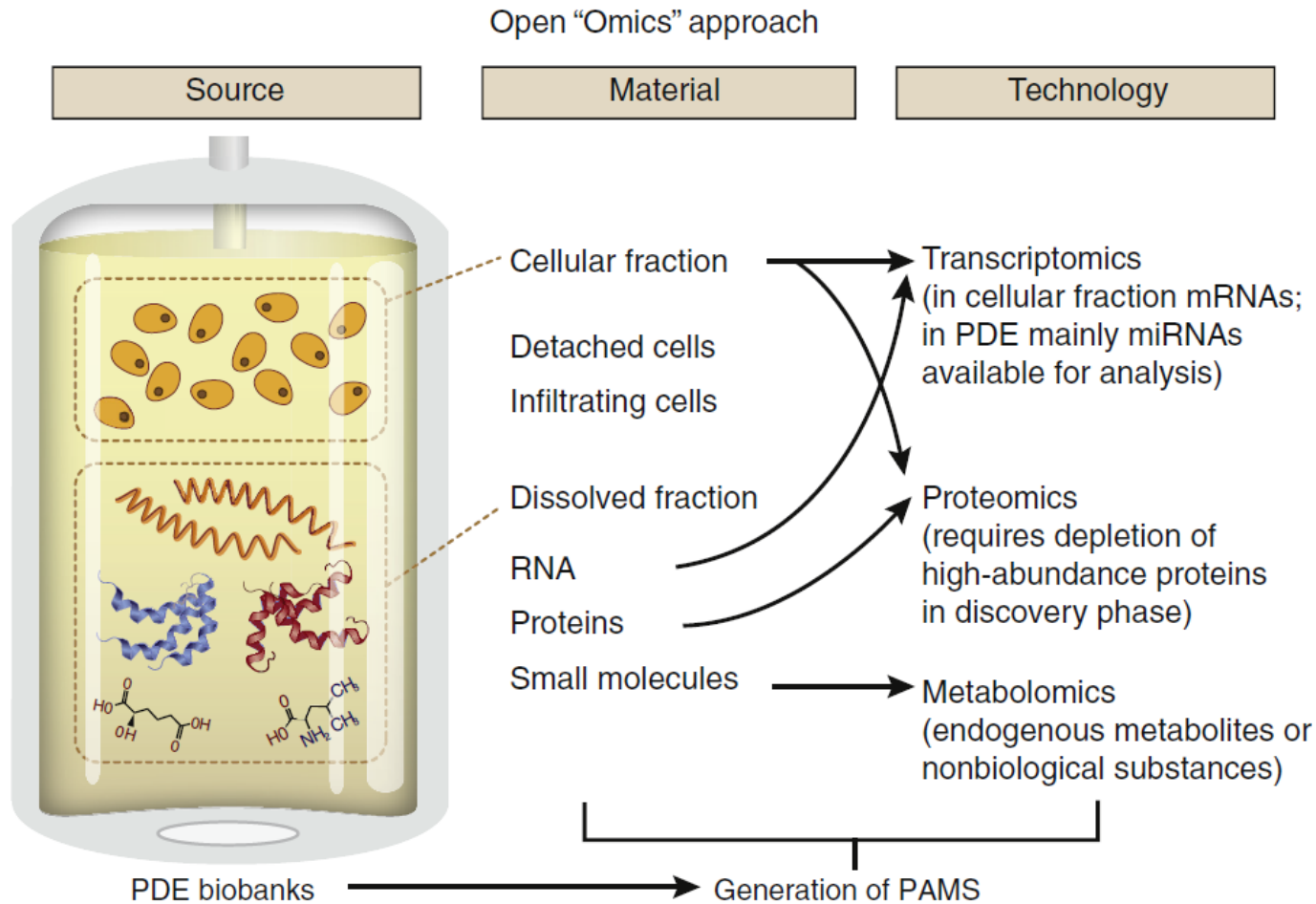
Currently: Laboratory tests only

**Can we exploit the
inflammatory response
for diagnostic purposes ?**

Analysis of local inflammatory biomarkers during acute peritonitis



Analysis of local inflammatory biomarkers during acute peritonitis

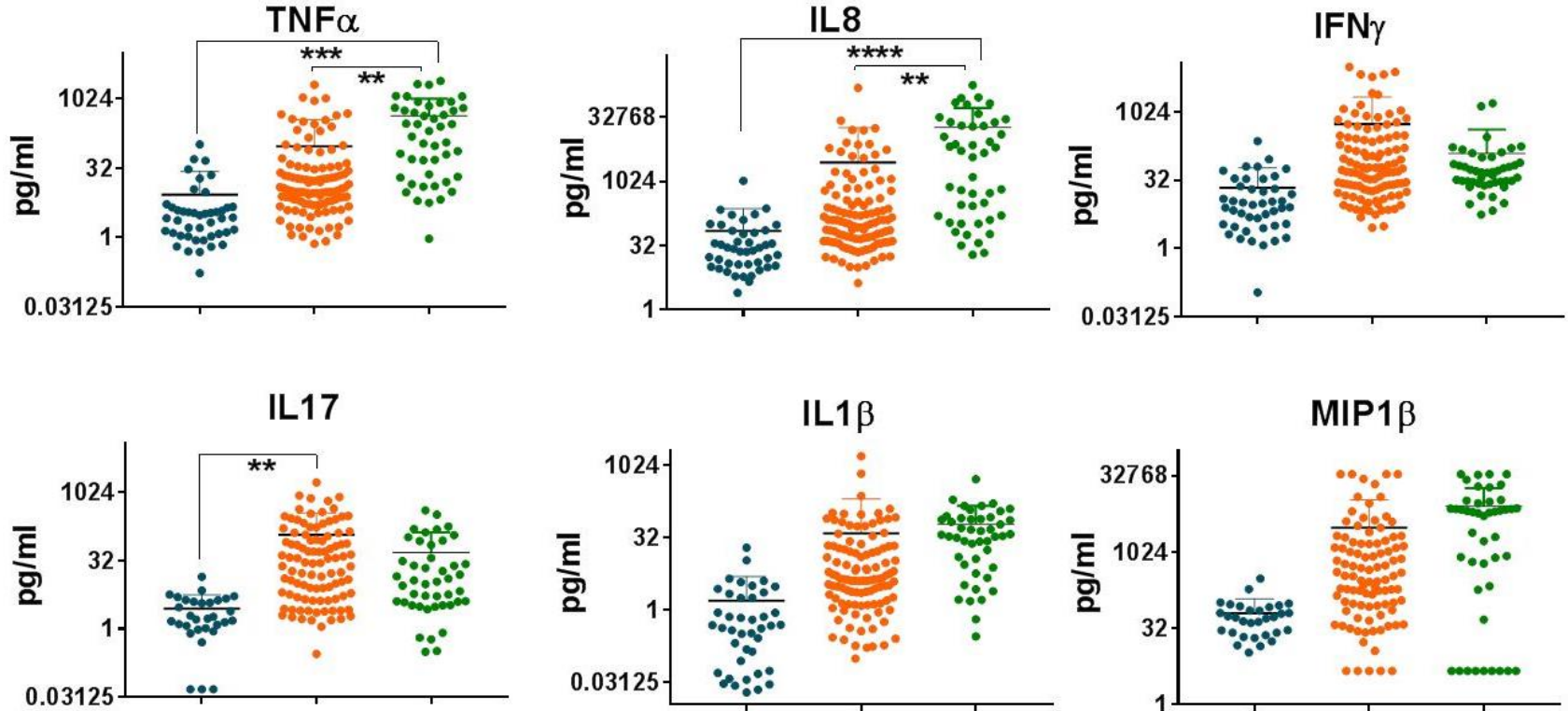


Analysis of local inflammatory biomarkers during acute peritonitis

- 281 patients
 - 169 with confirmed bacterial infection
 - 30 with culture-negative peritonitis
 - 82 stable controls
- Parameters measured:
 - cytokines, chemokines and other immune mediators
 - microRNAs
 - number, proportion and activation status of immune cells

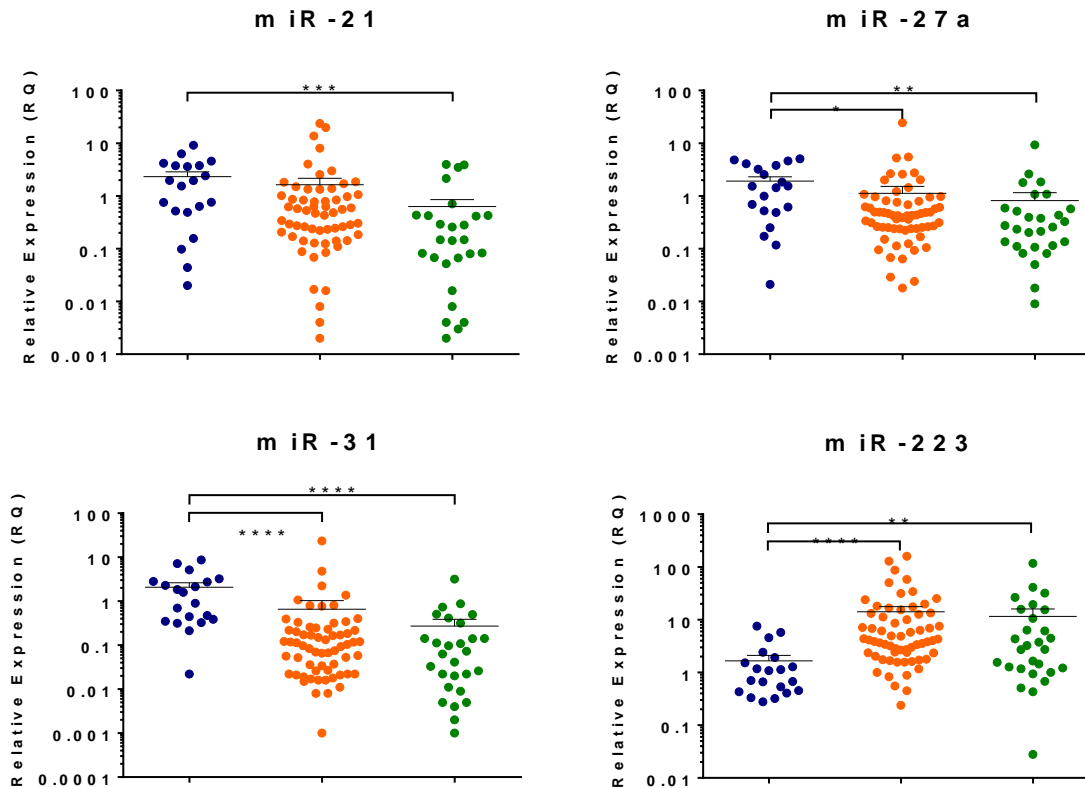
Local levels of cytokines and chemokines during acute peritonitis

● Stable ● Gram-positive ● Gram-negative



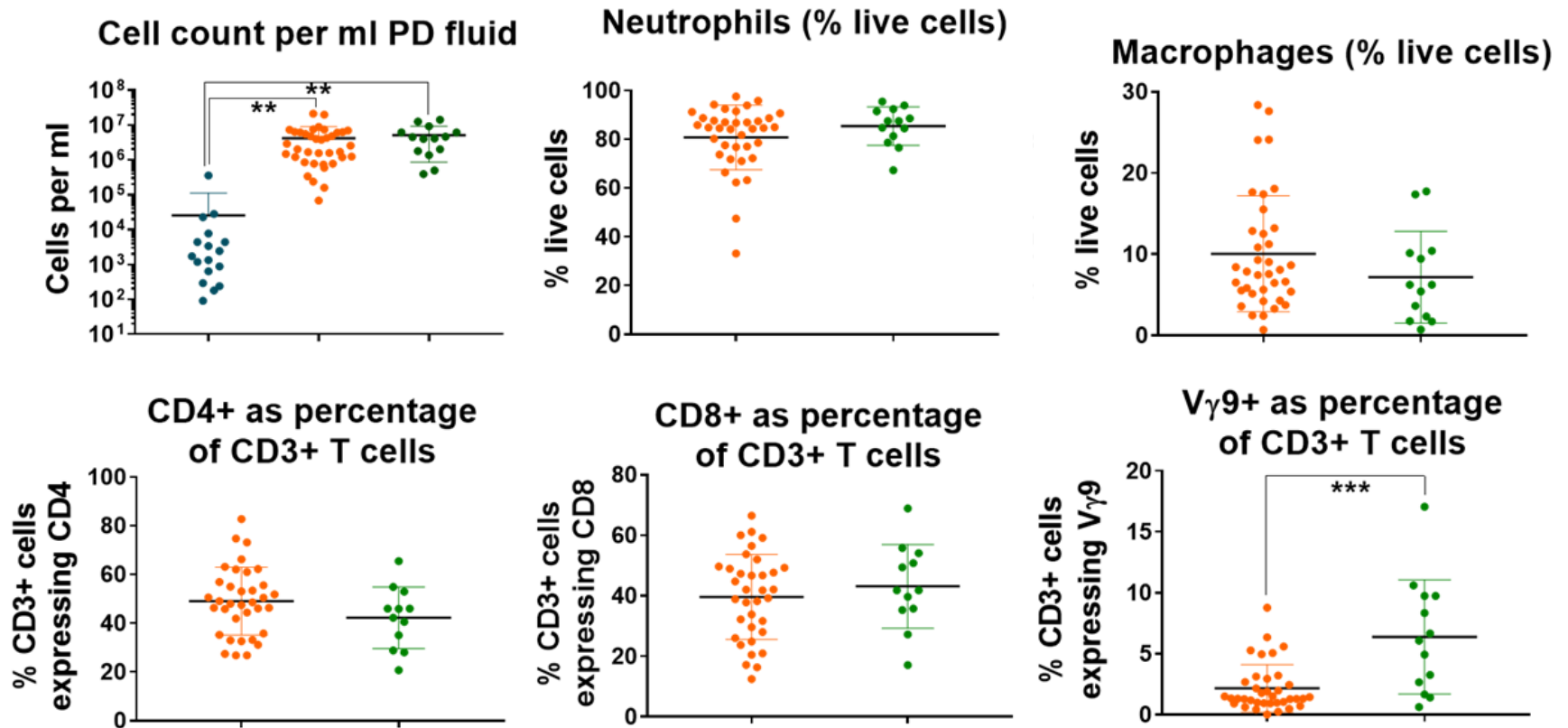
Local levels of microRNAs during acute peritonitis

● Stable ● Gram-positive ● Gram-negative



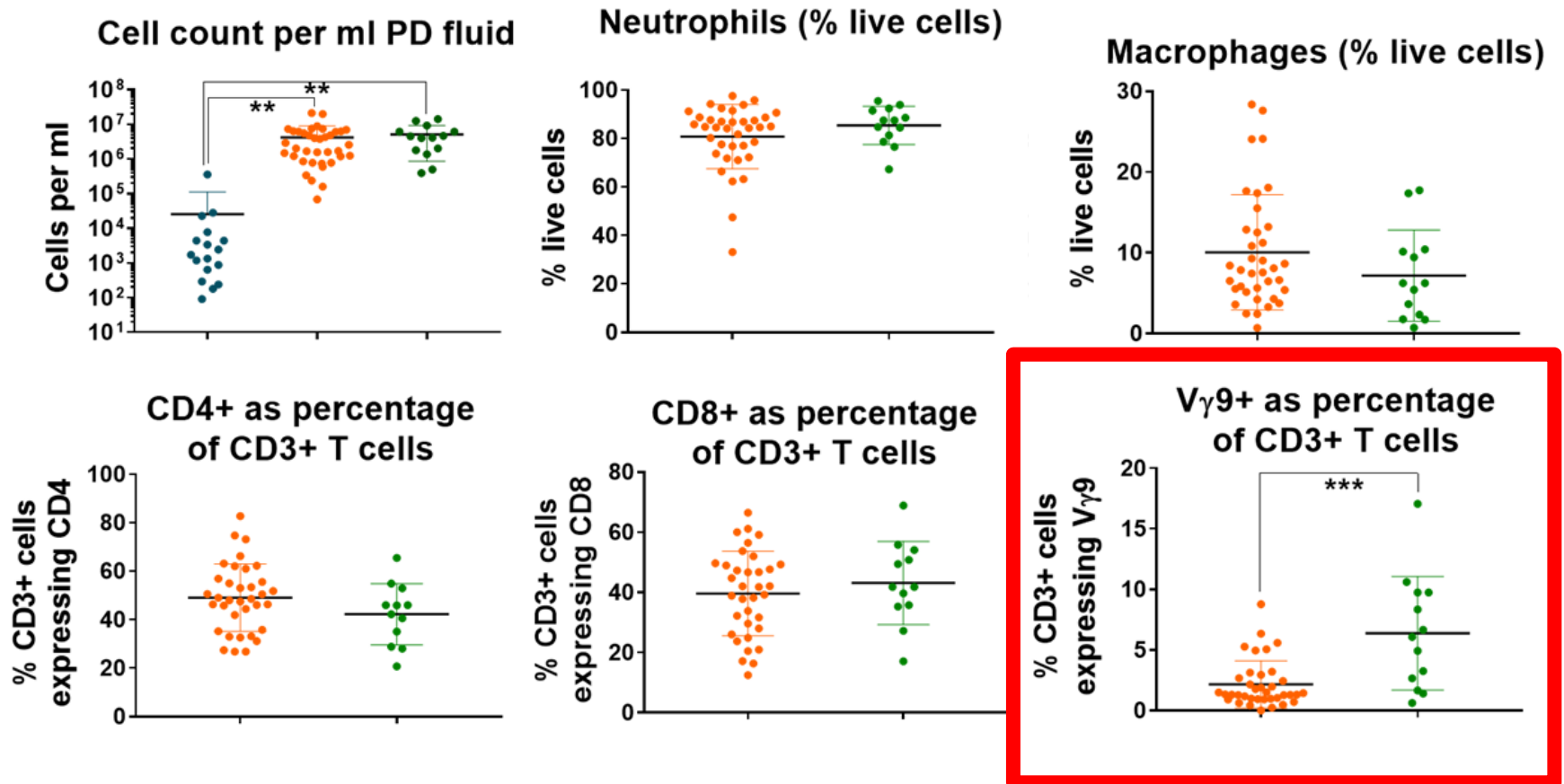
Composition of the inflammatory infiltrate during acute peritonitis

● Stable ● Gram-positive ● Gram-negative

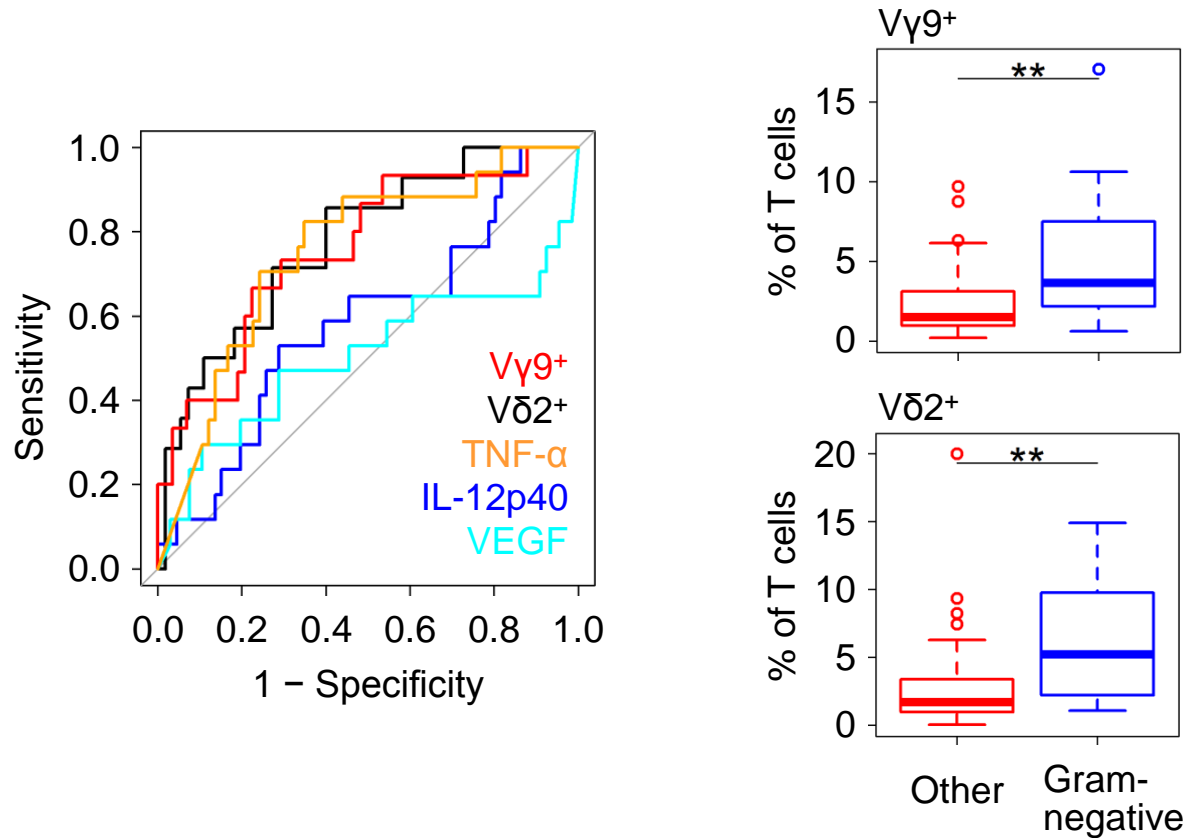


Composition of the inflammatory infiltrate during acute peritonitis

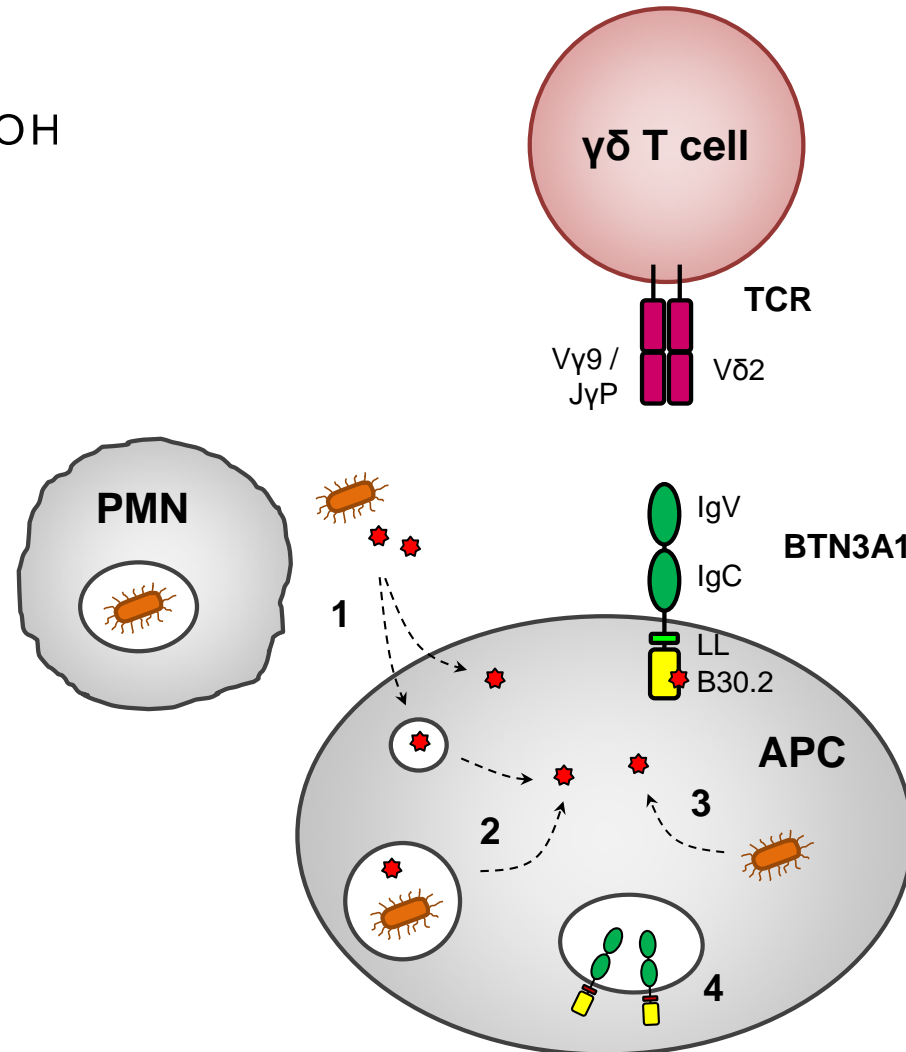
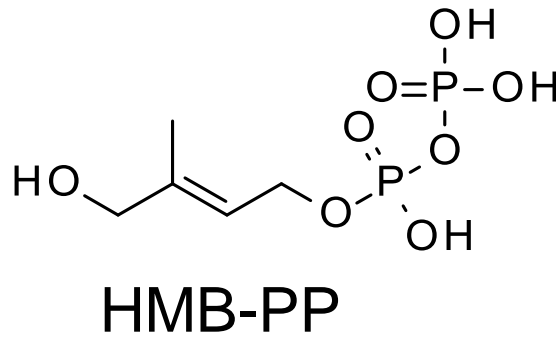
● Stable ● Gram-positive ● Gram-negative



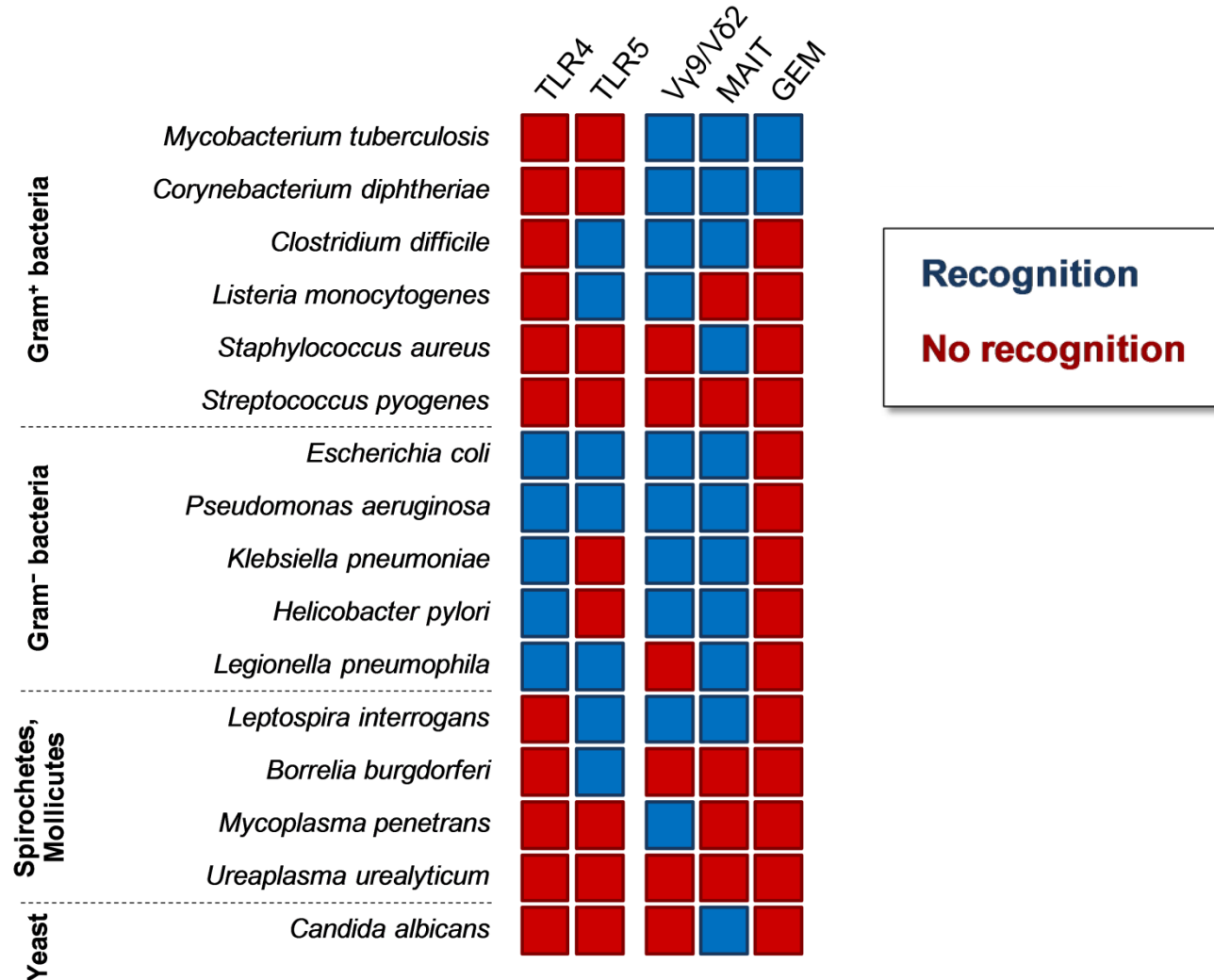
Elevated levels of peritoneal $\gamma\delta$ T cells predict Gram-negative infections on the day of presentation



Pattern recognition by human unconventional T cells



The immune system responds to pathogen-associated molecular patterns



The immune system responds to pathogen-associated molecular patterns

Staphylococcus aureus



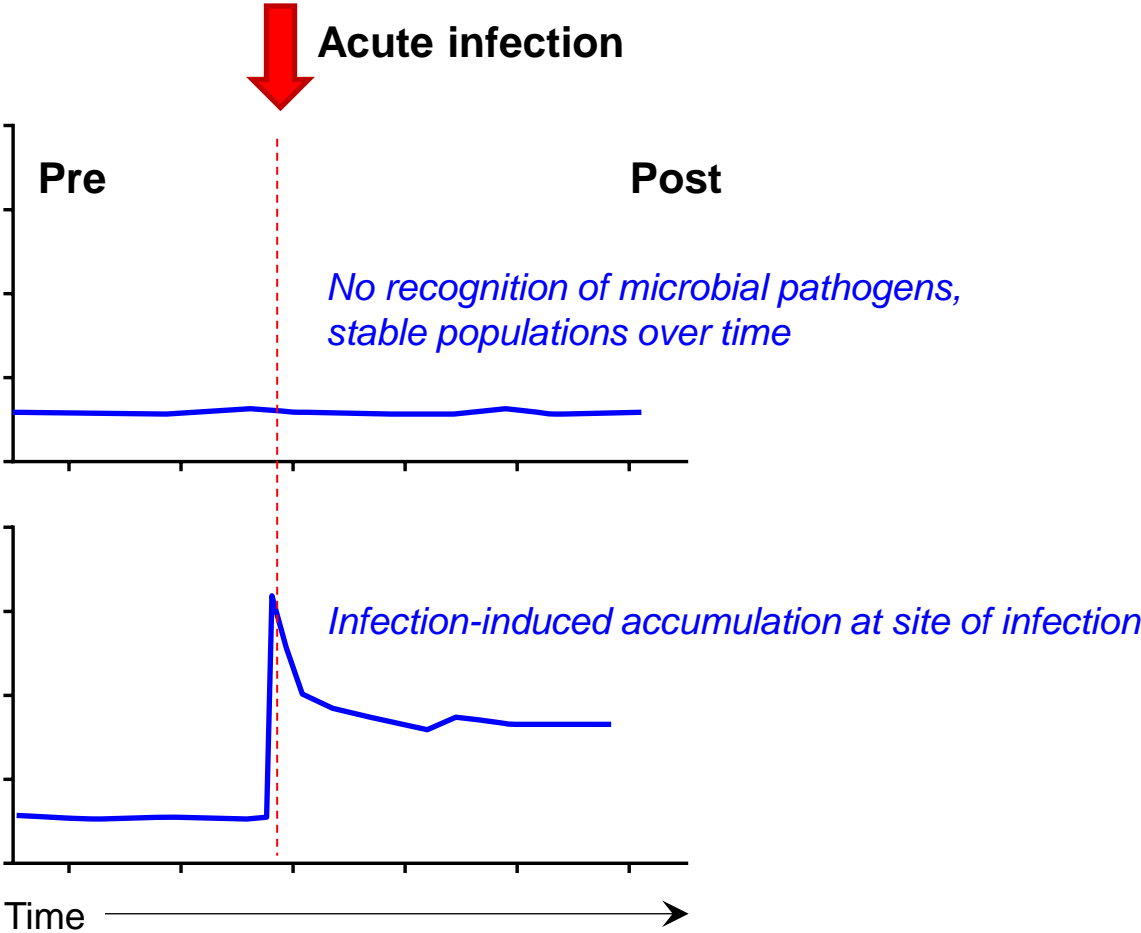
Escherichia coli



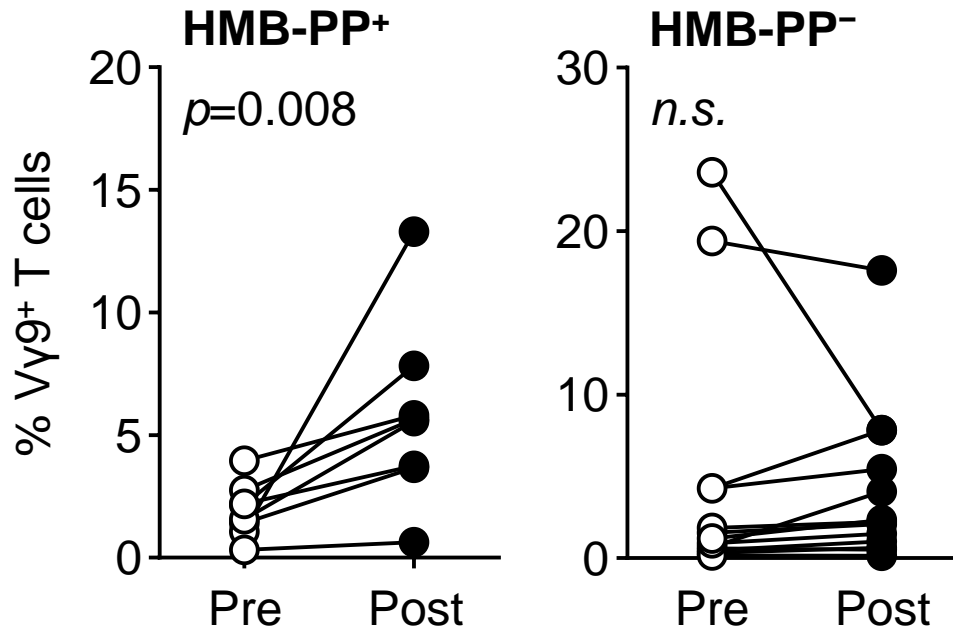
Recognition

No recognition

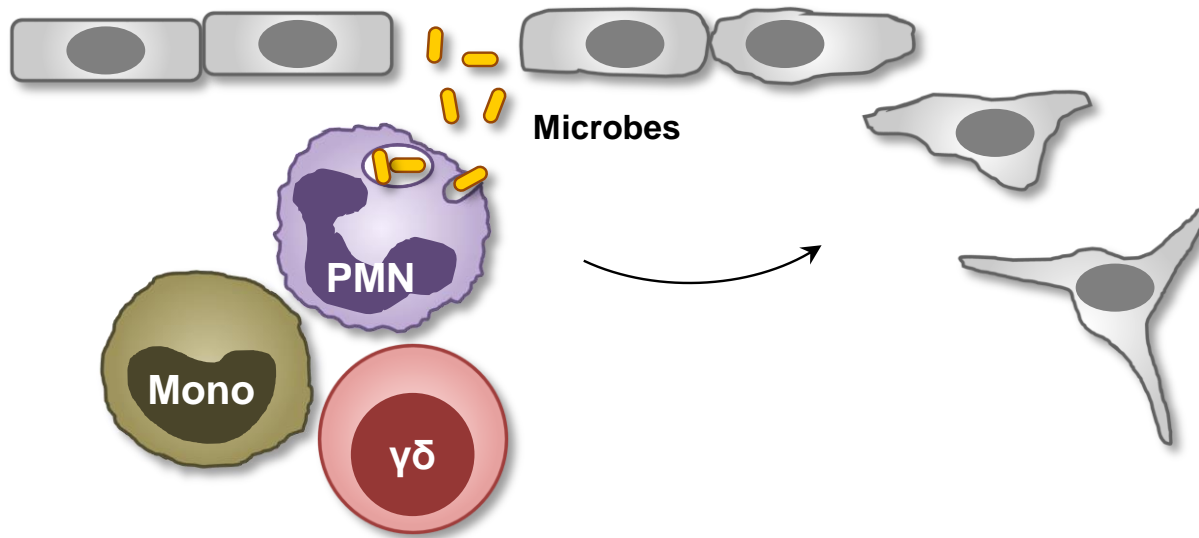
Longitudinal immune profiling of PD patients



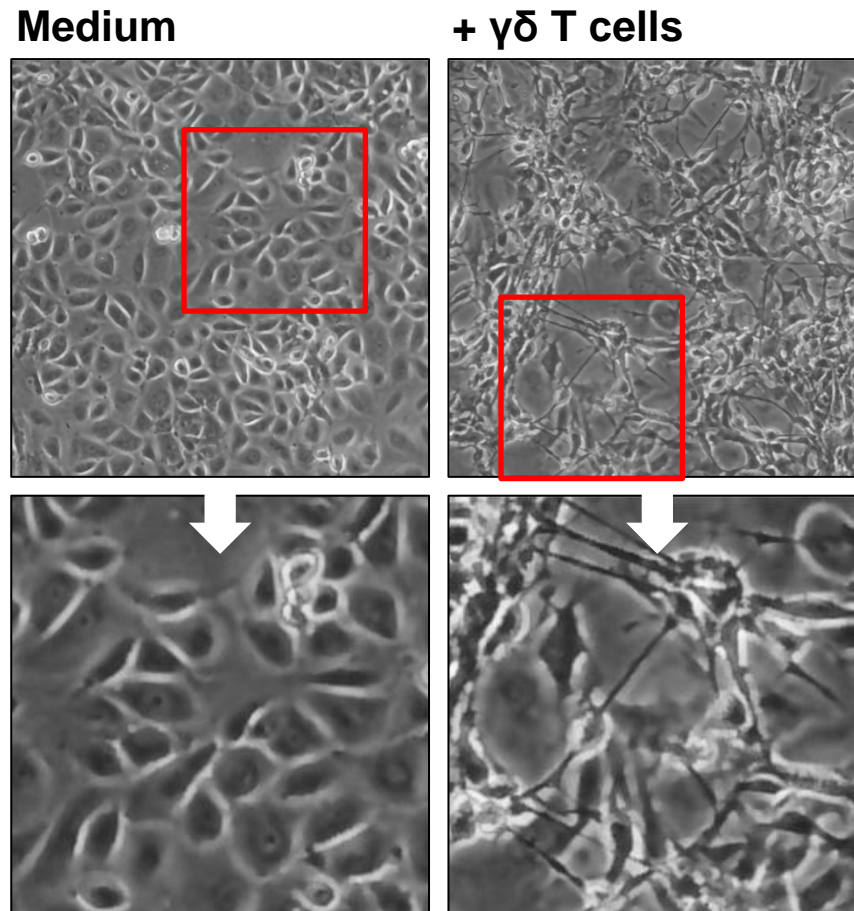
Local enrichment of $\gamma\delta$ T cells in acute infections caused by HMB-PP⁺ but not HMB-PP⁻ organisms



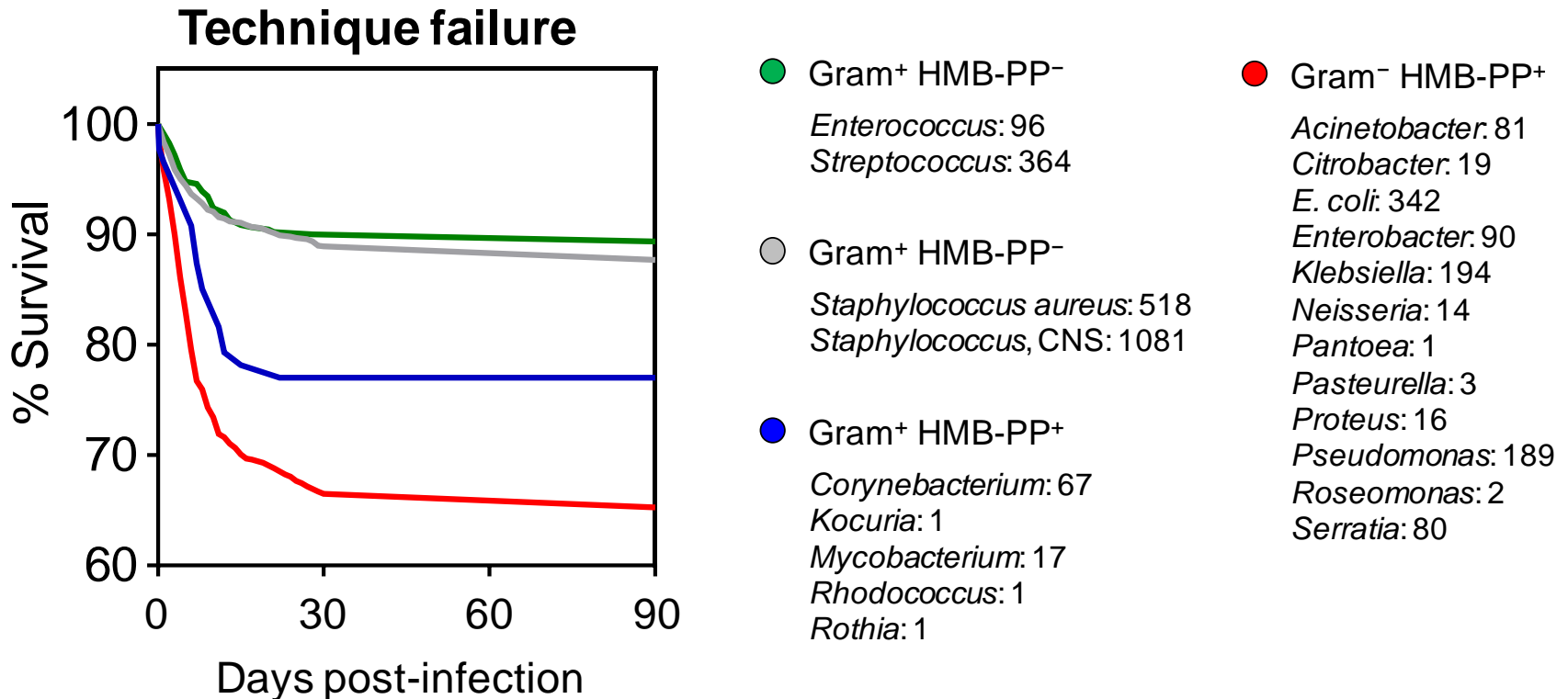
Unconventional T cells induce damage of peritoneal tissue cells



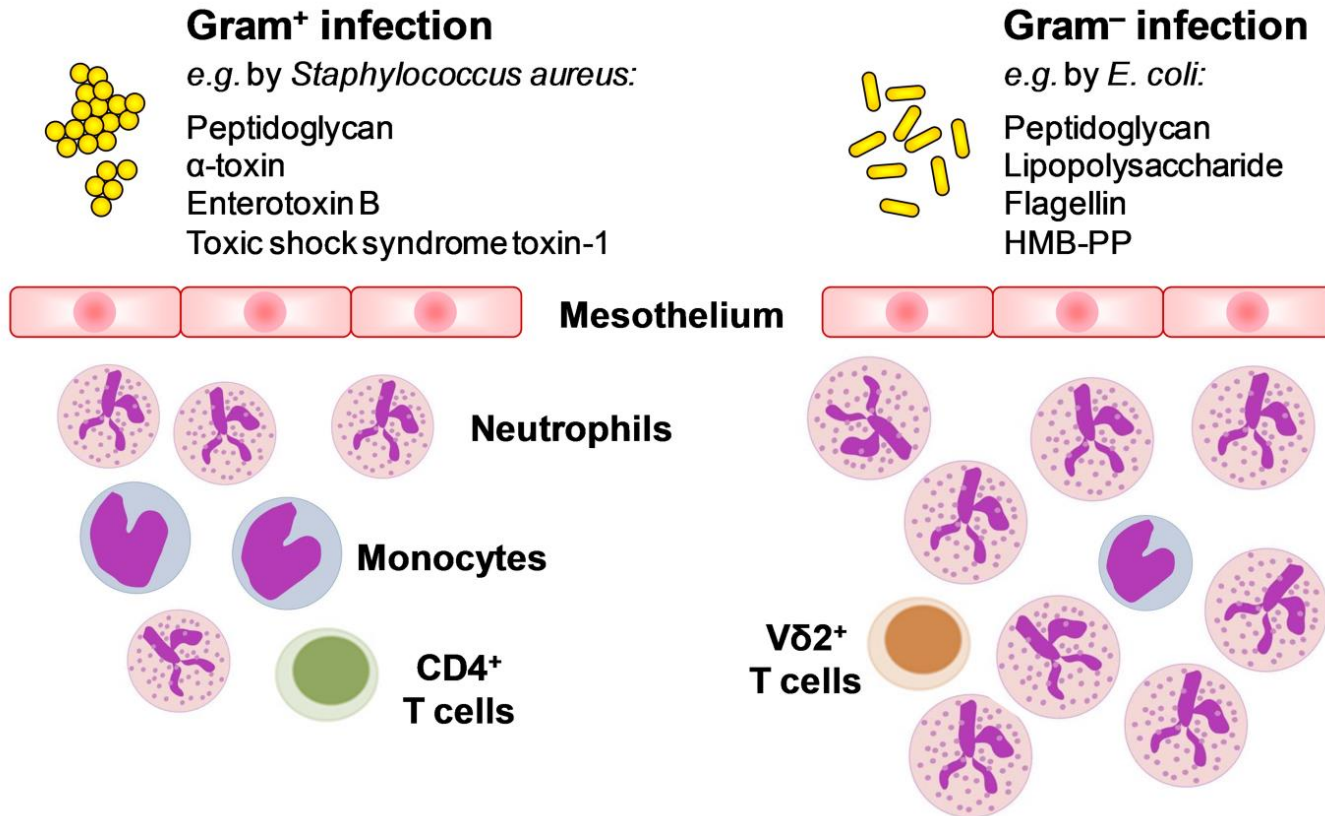
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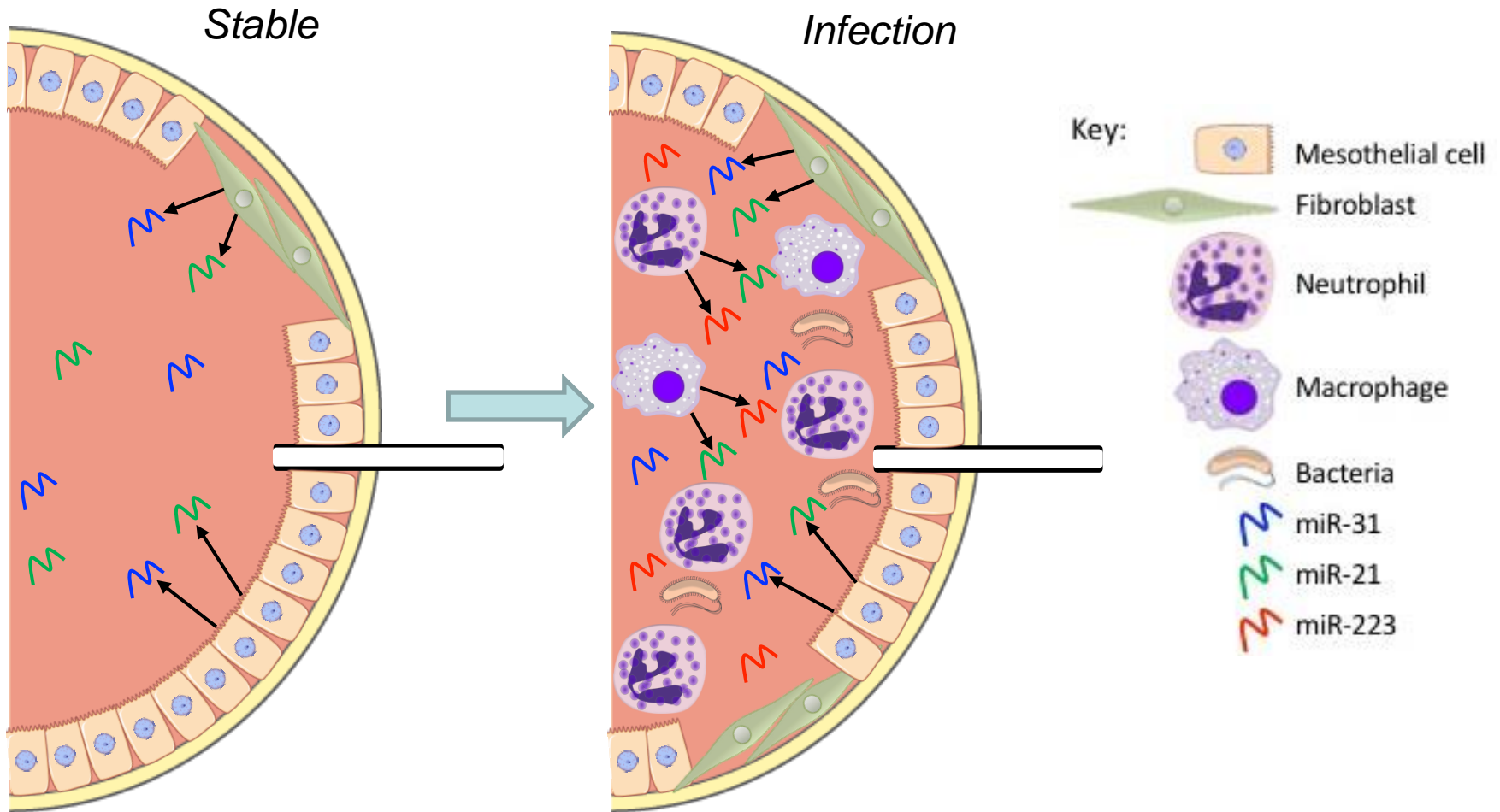
Unconventional T cell activating pathogens are associated with worse clinical outcomes



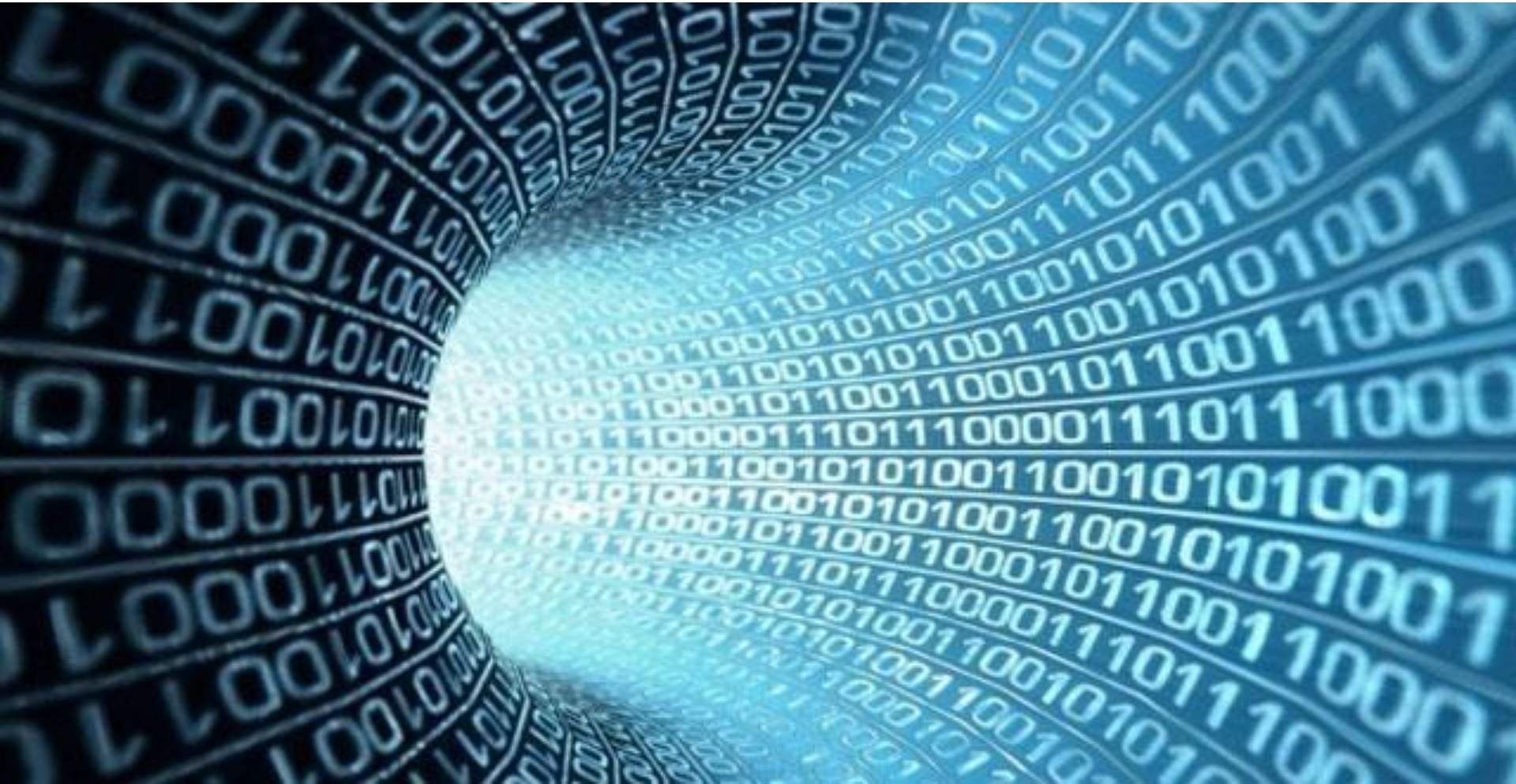
The peritoneal membrane: a window to local inflammation



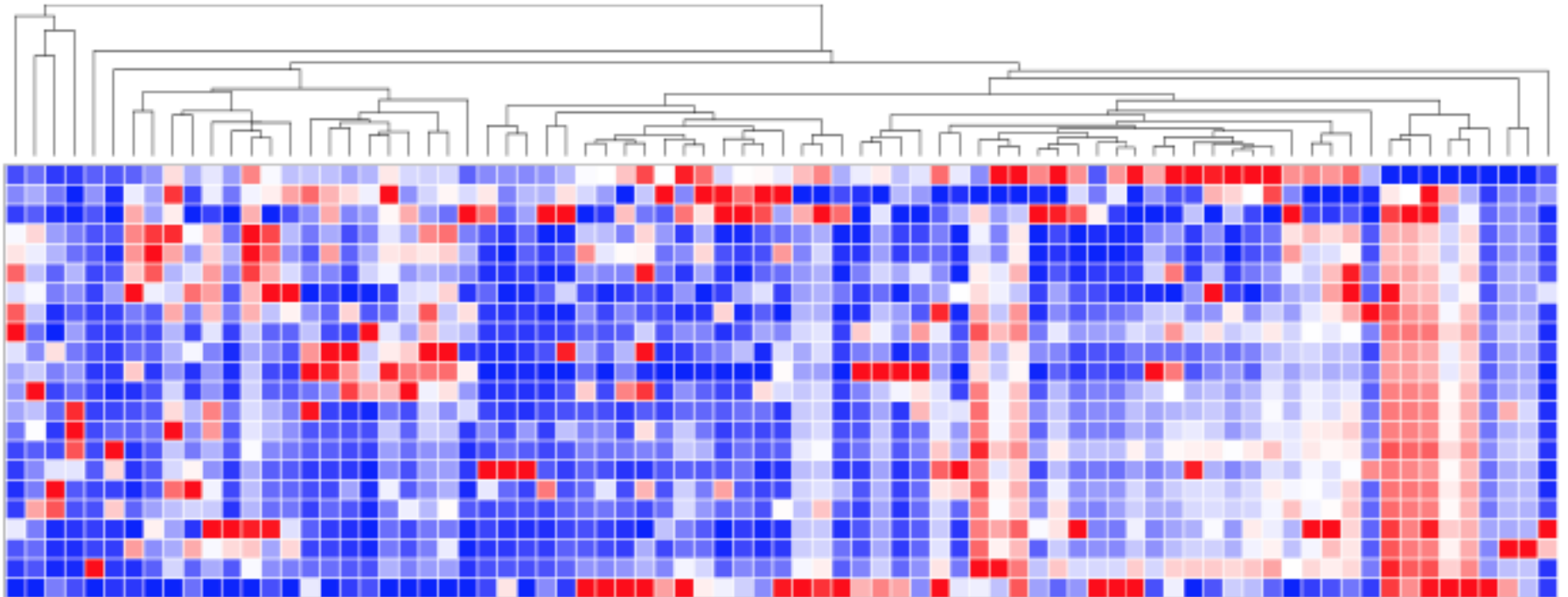
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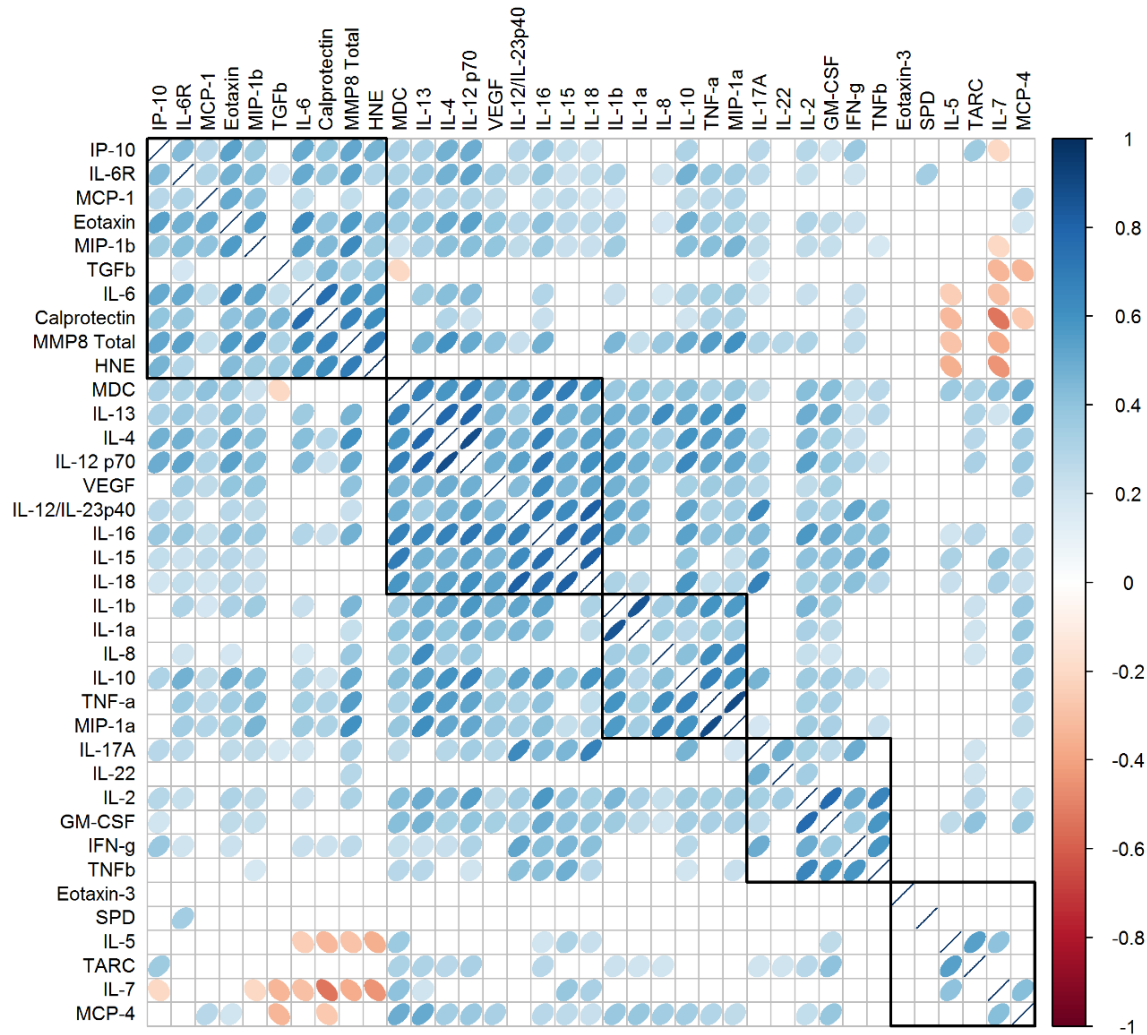
Machine-learning algorithms enhance the predictive power of biomarker signatures



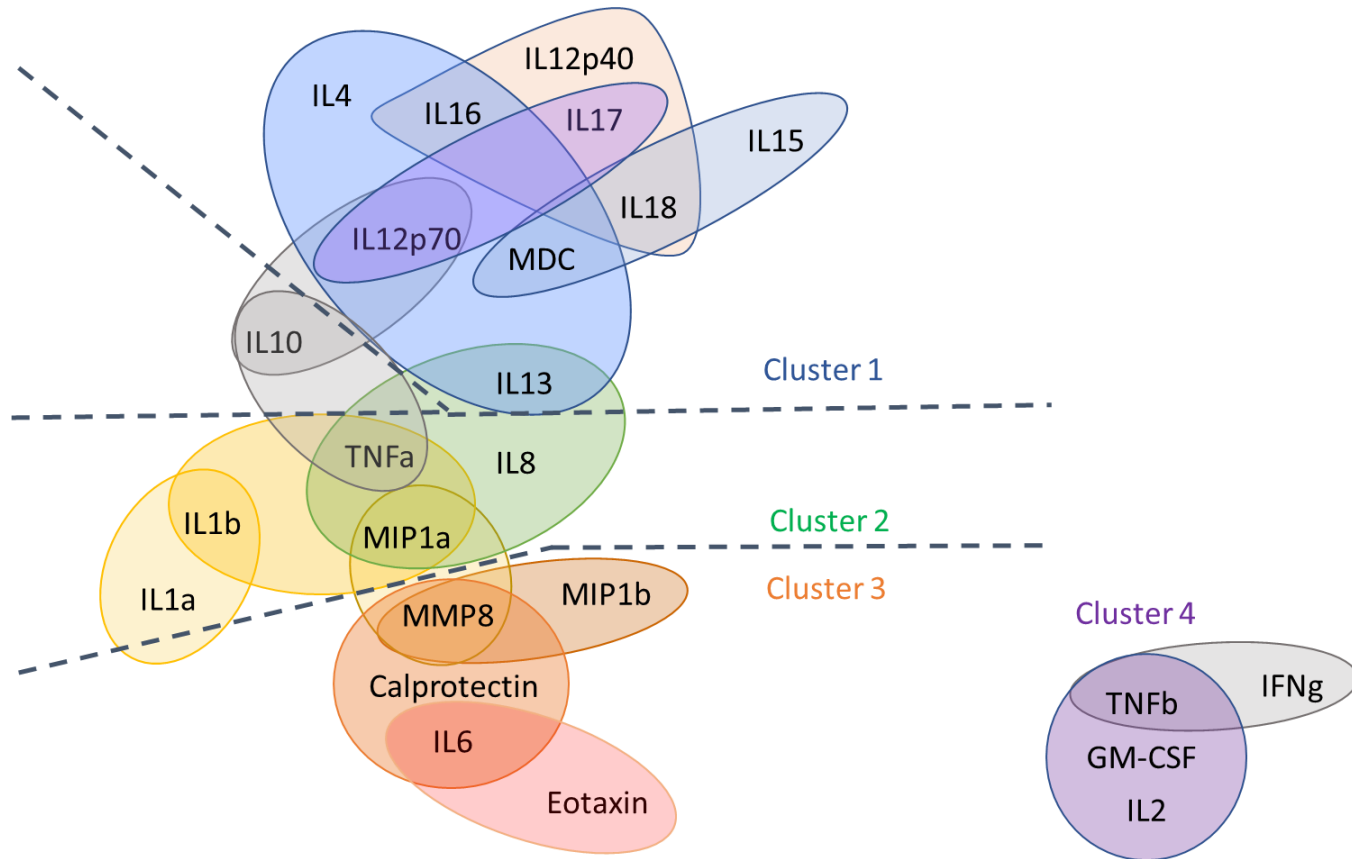
Cluster analysis of cellular and soluble biomarkers in patients presenting with acute peritonitis



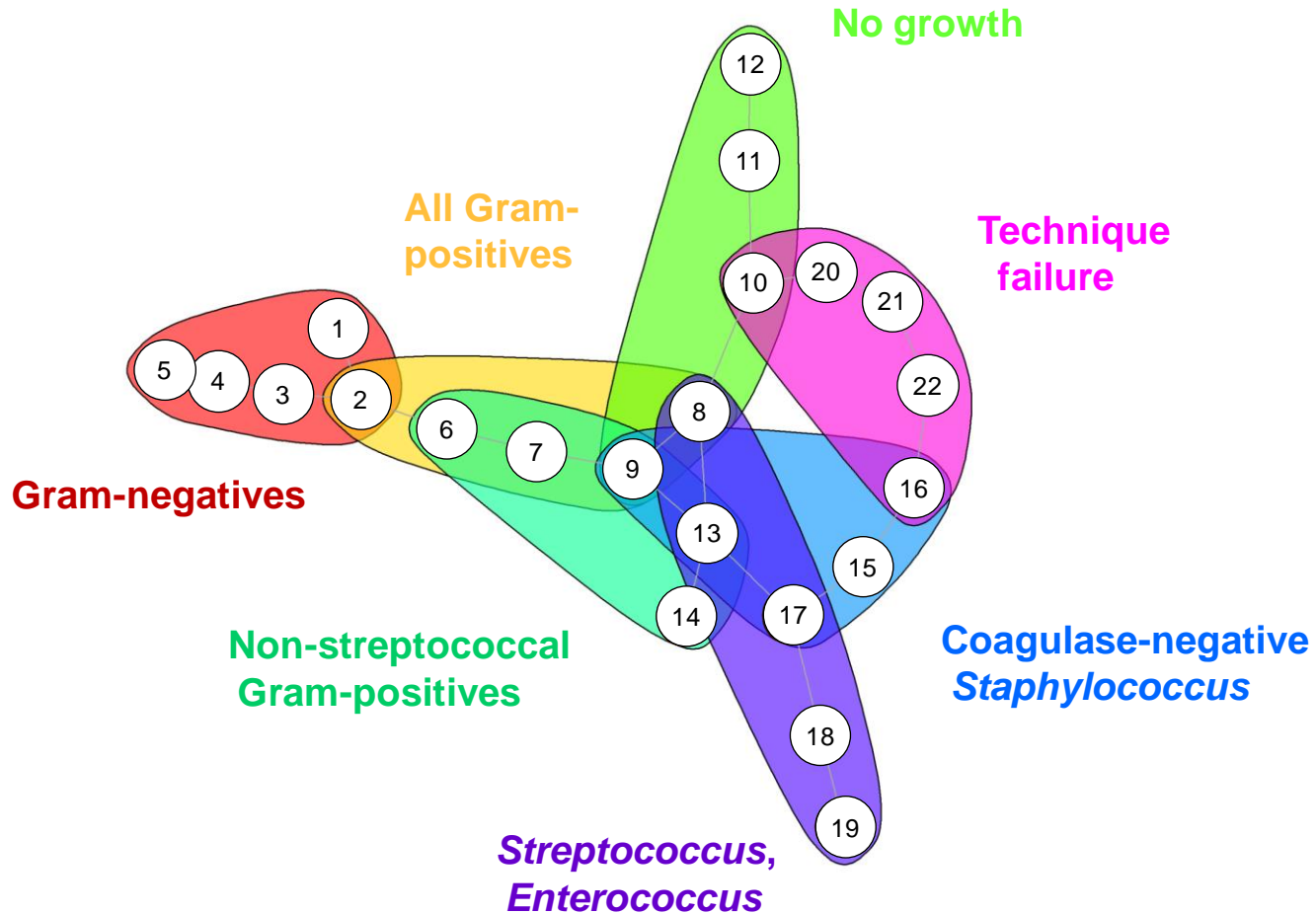
Cluster analysis of cellular and soluble biomarkers in patients presenting with acute peritonitis



Cluster analysis of cellular and soluble biomarkers in patients presenting with acute peritonitis



Pathogen-specific local immune fingerprints in patients with acute peritonitis



Immune fingerprint-based diagnosis of acute infection

Model	Sensitivity	Specificity
Random Forest: Cytokines only	0.800 ± 0.100	0.333 ± 0.365
with $\gamma\delta$ T cells	0.775 ± 0.215	0.850 ± 0.050
Support Vector Machine: Cytokines only	0.775 ± 0.215	0.850 ± 0.050
with $\gamma\delta$ T cells	0.925 ± 0.070	0.775 ± 0.146

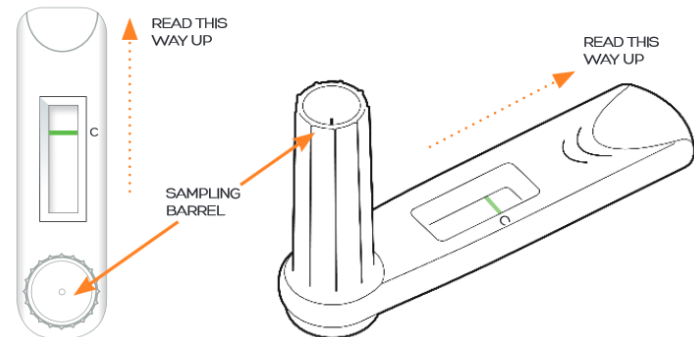
Immune fingerprint-based diagnosis of acute infection



- ✓ Diagnostic assays for hospital laboratories
- ✓ Point-of-care devices for primary/secondary care
- ✓ Home tests for high risk patients

SIEMENS
Healthineers

MOLOGIC
BIG IN TINY SCIENCE

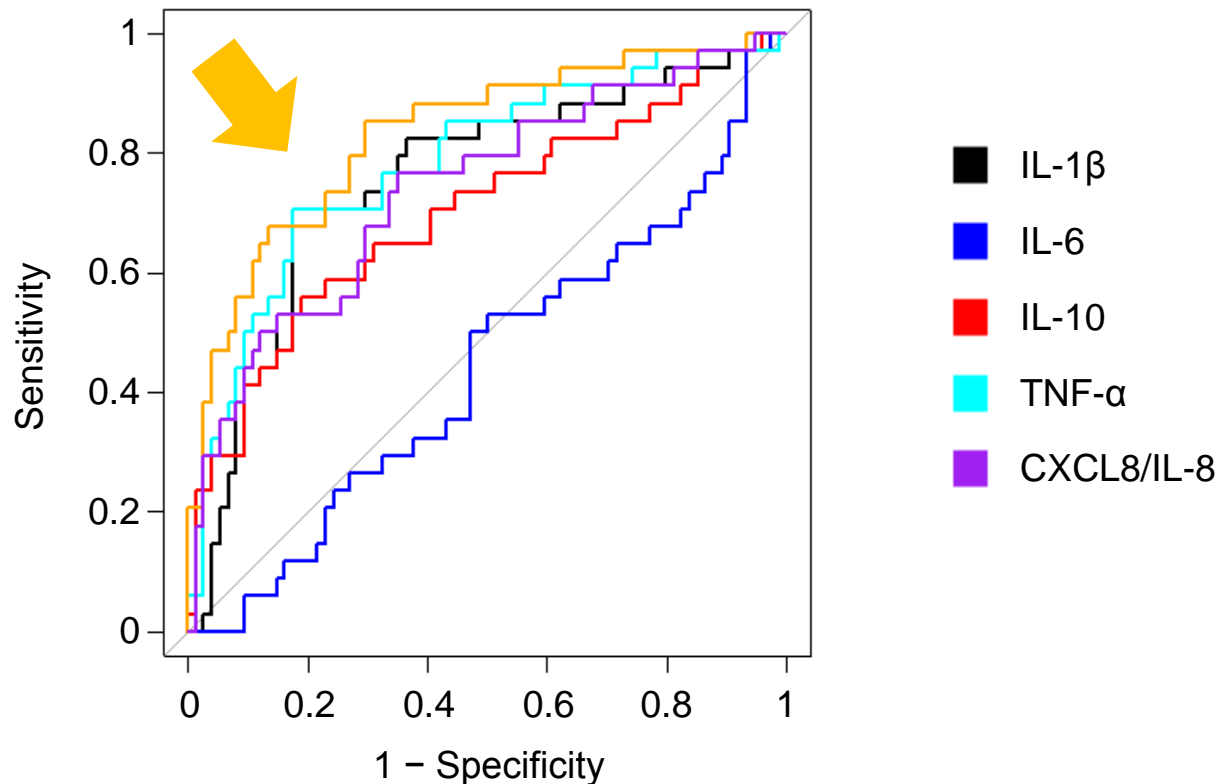


Organism-specific diagnosis of early peritonitis using clinical immunoanalysers



Organism-specific diagnosis of early peritonitis using clinical immunoanalysers

→ *Discrimination of Gram-positive vs Gram-negative infections*



PERIT-PD:

**„Patient immune responses
to infection in peritoneal dialysis“**



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SEVENTH FRAMEWORK
PROGRAMME



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