Assessing contribution of *B. burgdorferi* genomic diversity to disseminated infection and persistent symptoms of LD

Research for Lyme Infection-Associated Chronic Illnesses Treatment

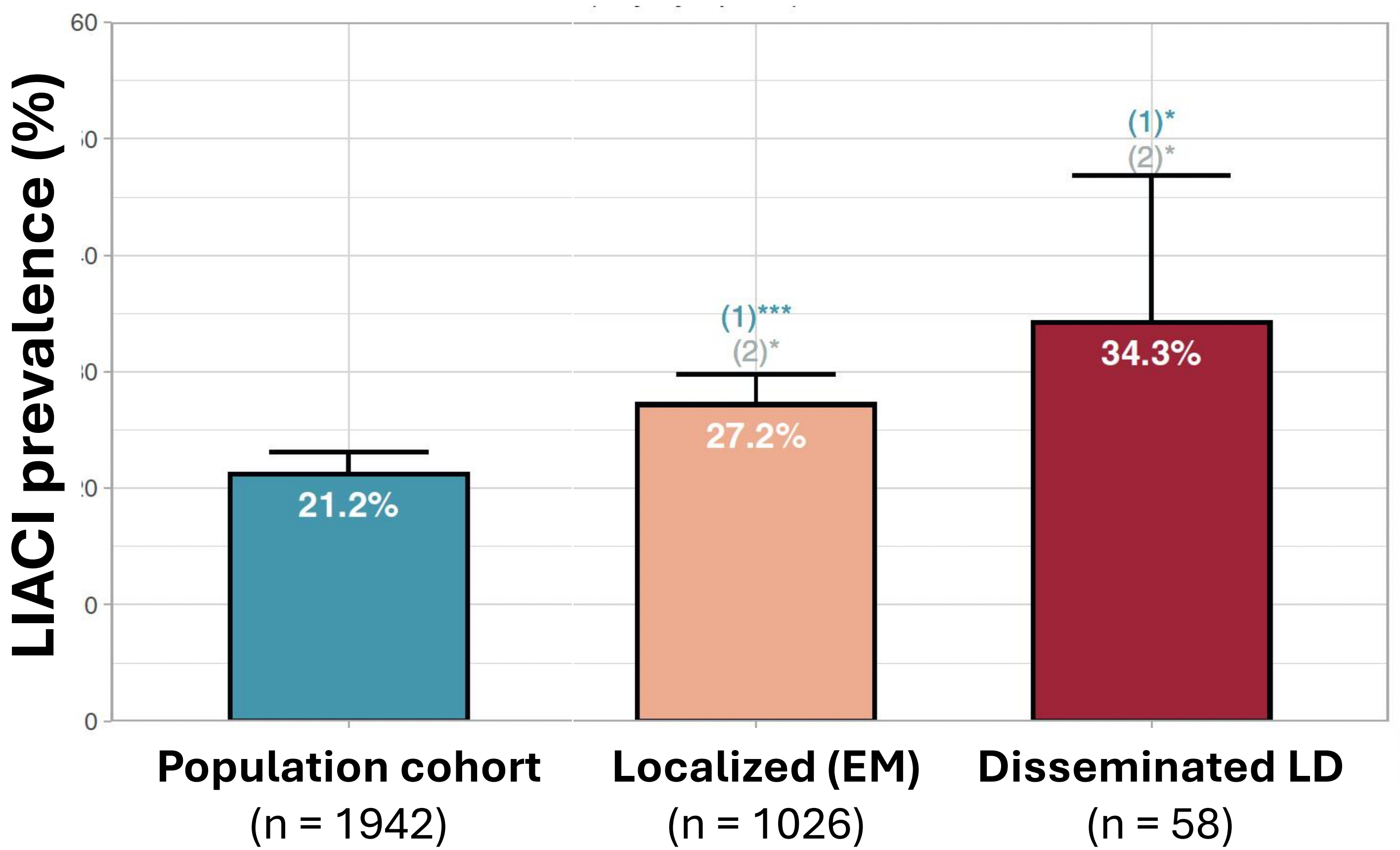
Broadening the Lens – Committee Meeting 2

July 11, 2024

John Leong, MD, PhD

Disseminated LD is associated with:

A. Persistent symptoms



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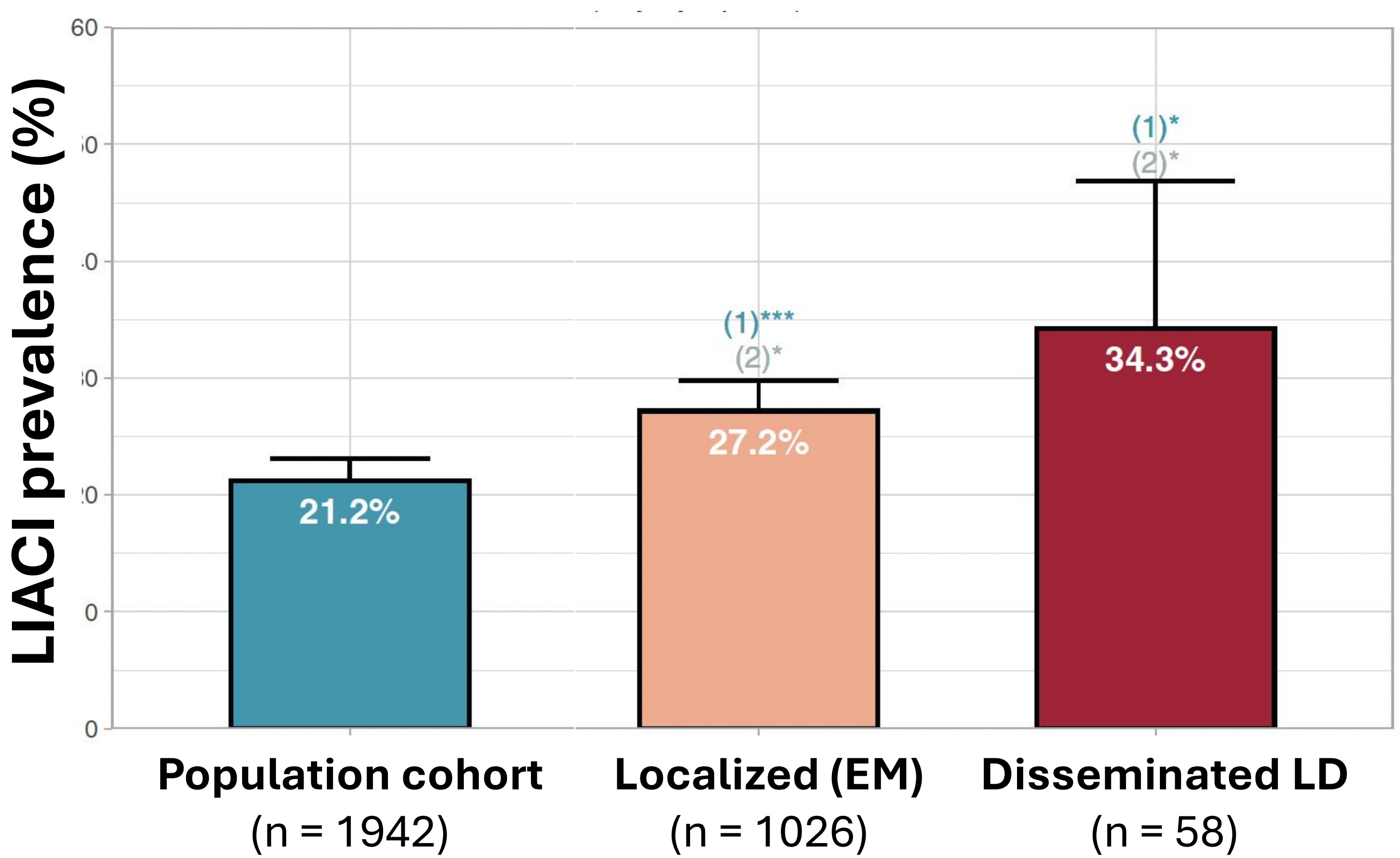

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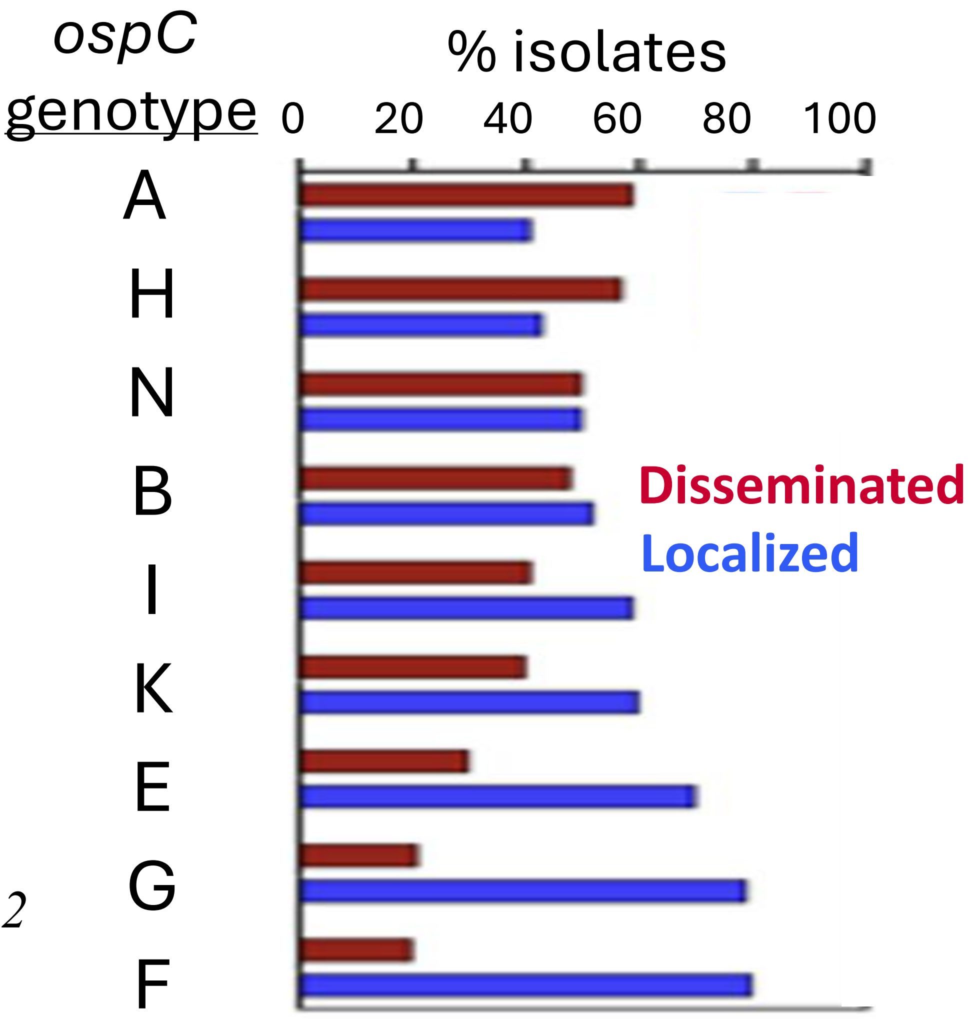
B. Specific *Bb* genotypes



Strle and coworkers

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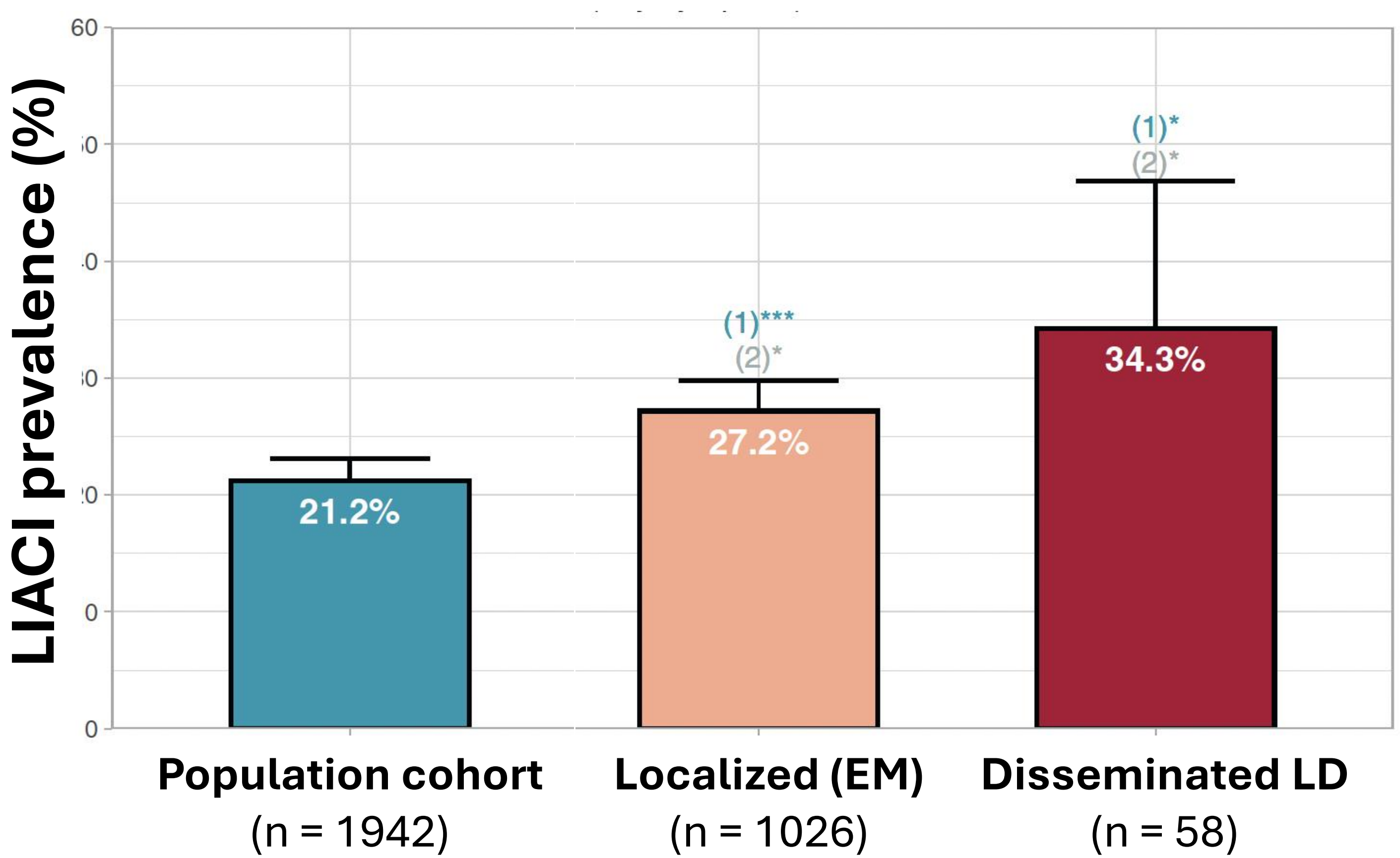

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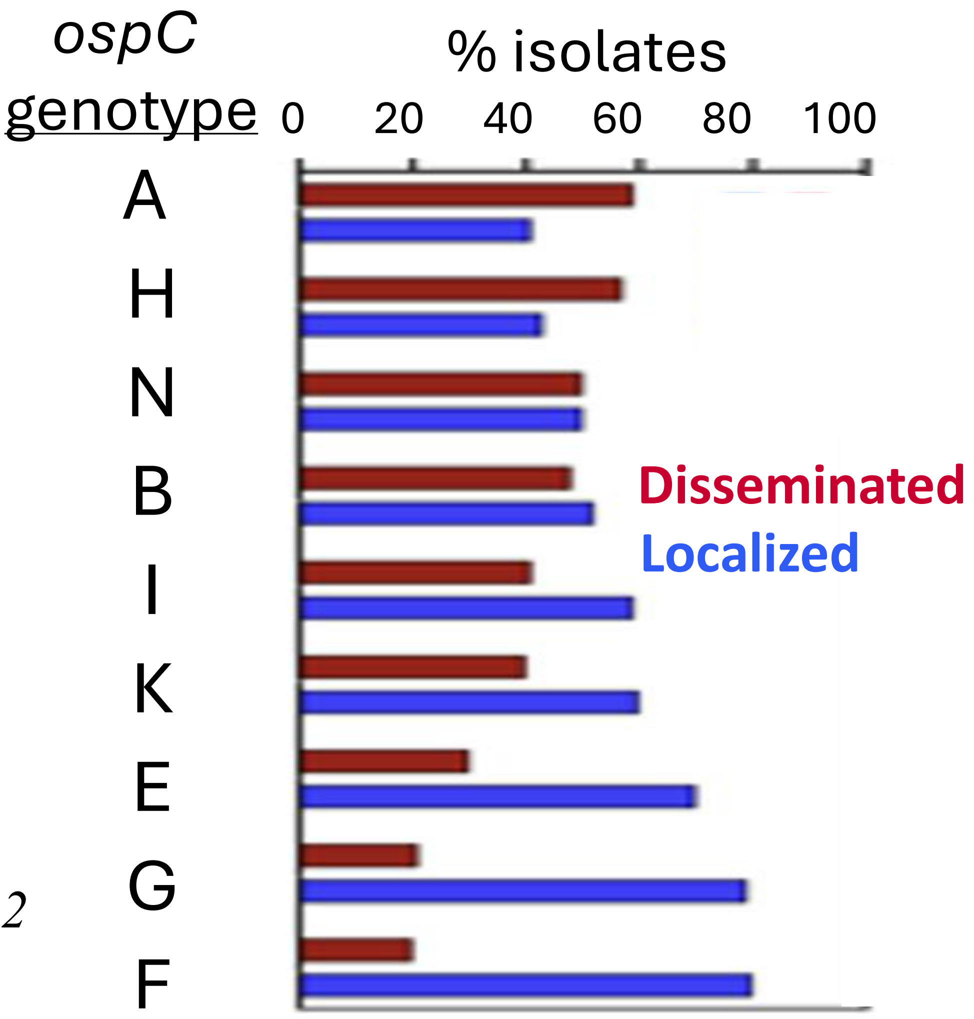

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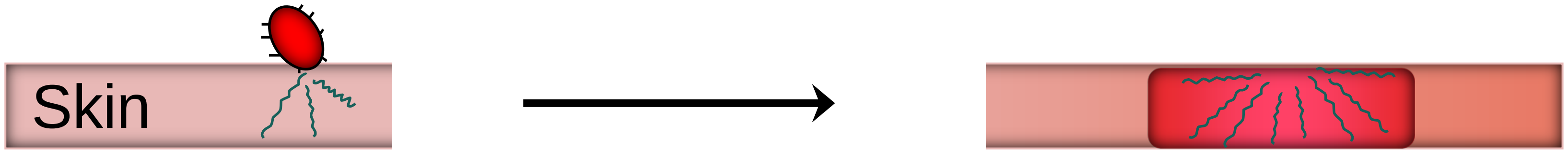
Does microbial genotype contribute to Lyme IACI and if so, how?

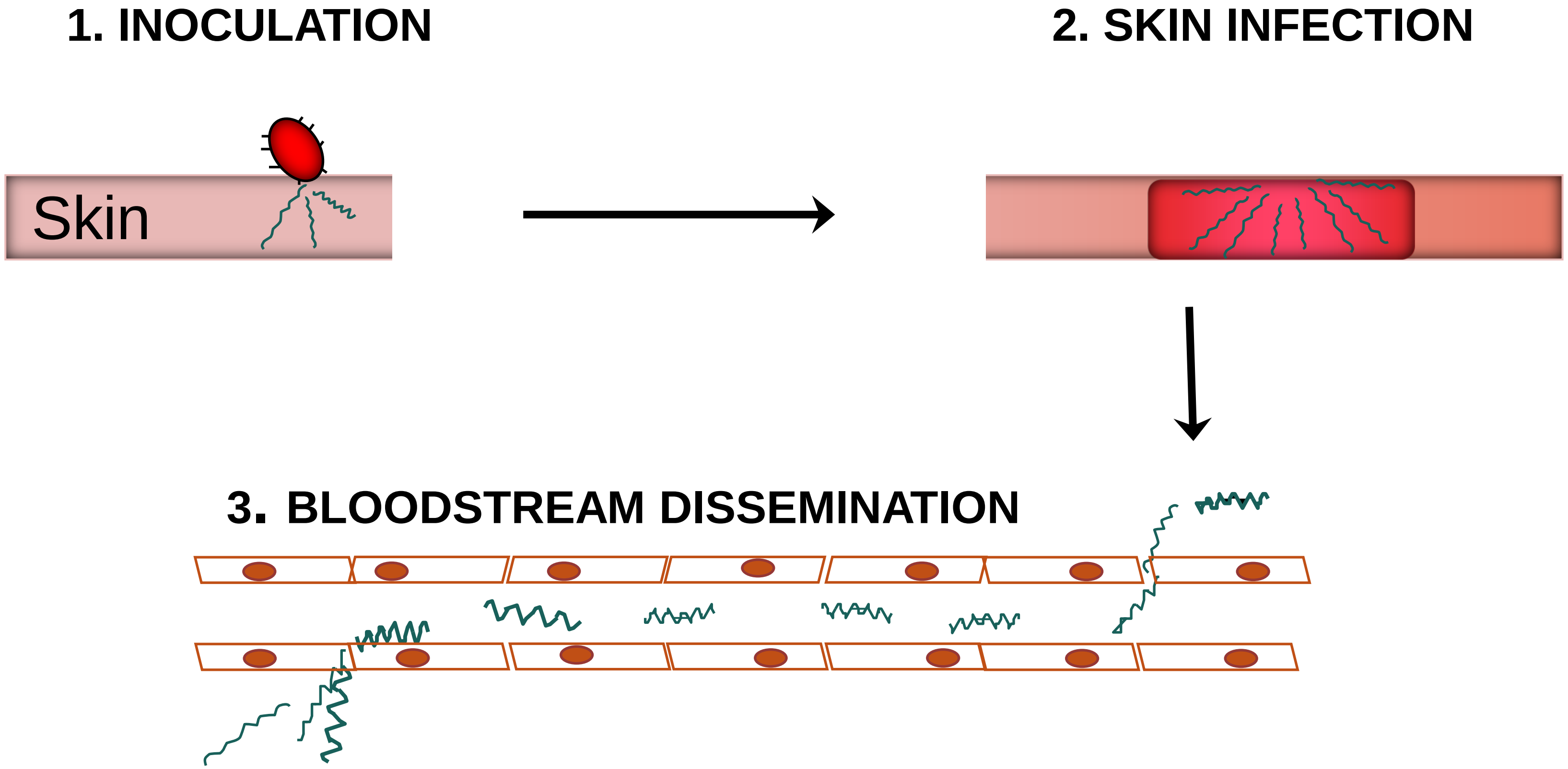
Disseminated LD



1. INOCULATION

2. SKIN INFECTION

Disseminated LD



1. INOCULATION

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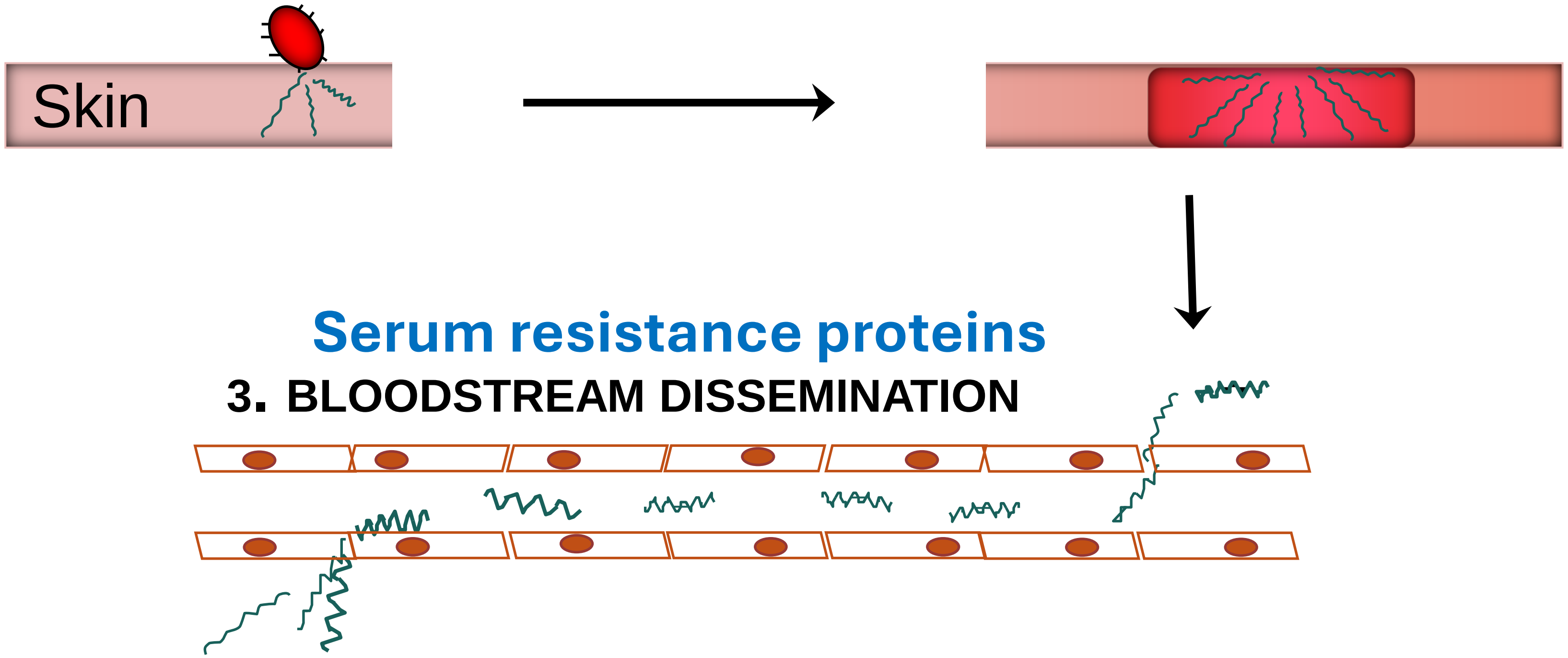
3. BLOODSTREAM DISSEMINATION

Disseminated LD



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Serum resistance proteins

3. BLOODSTREAM DISSEMINATION

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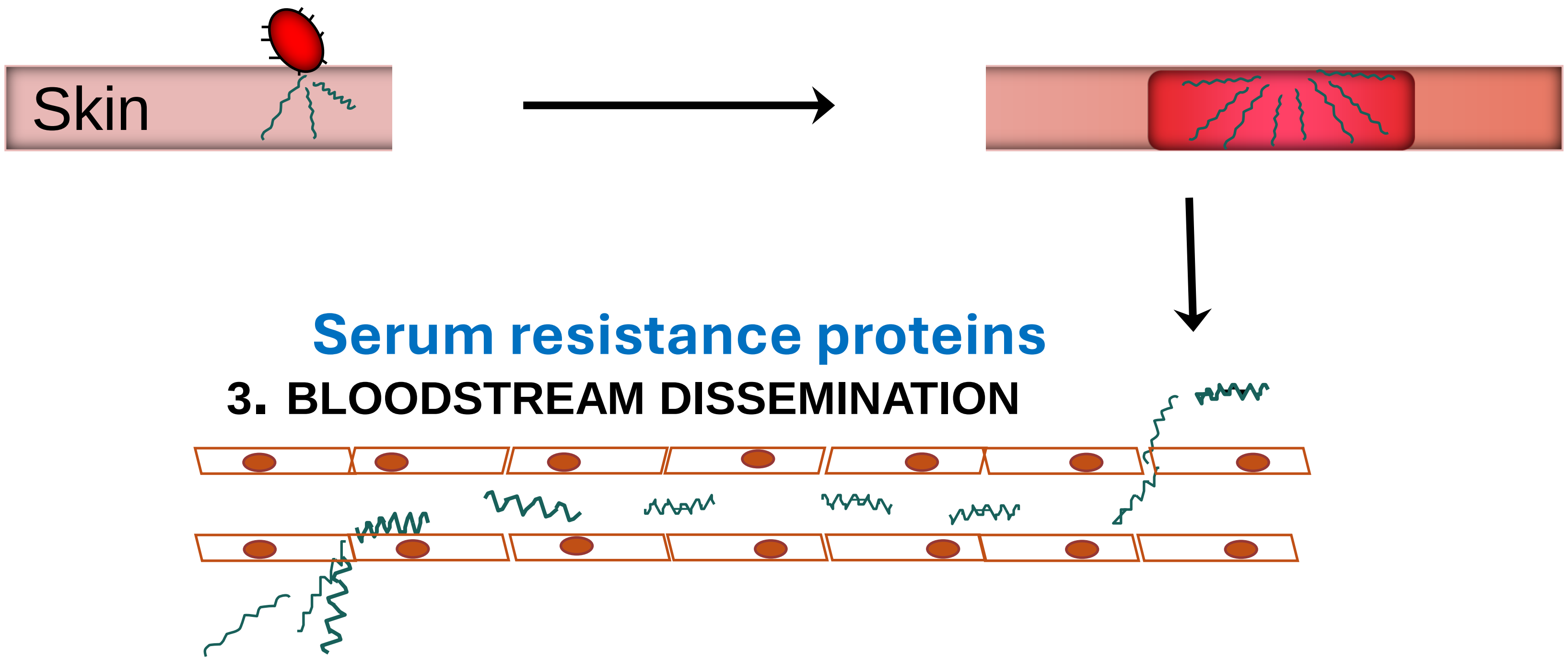


1. INOCULATION

Skin

2. SKIN INFECTION

Serum resistance proteins

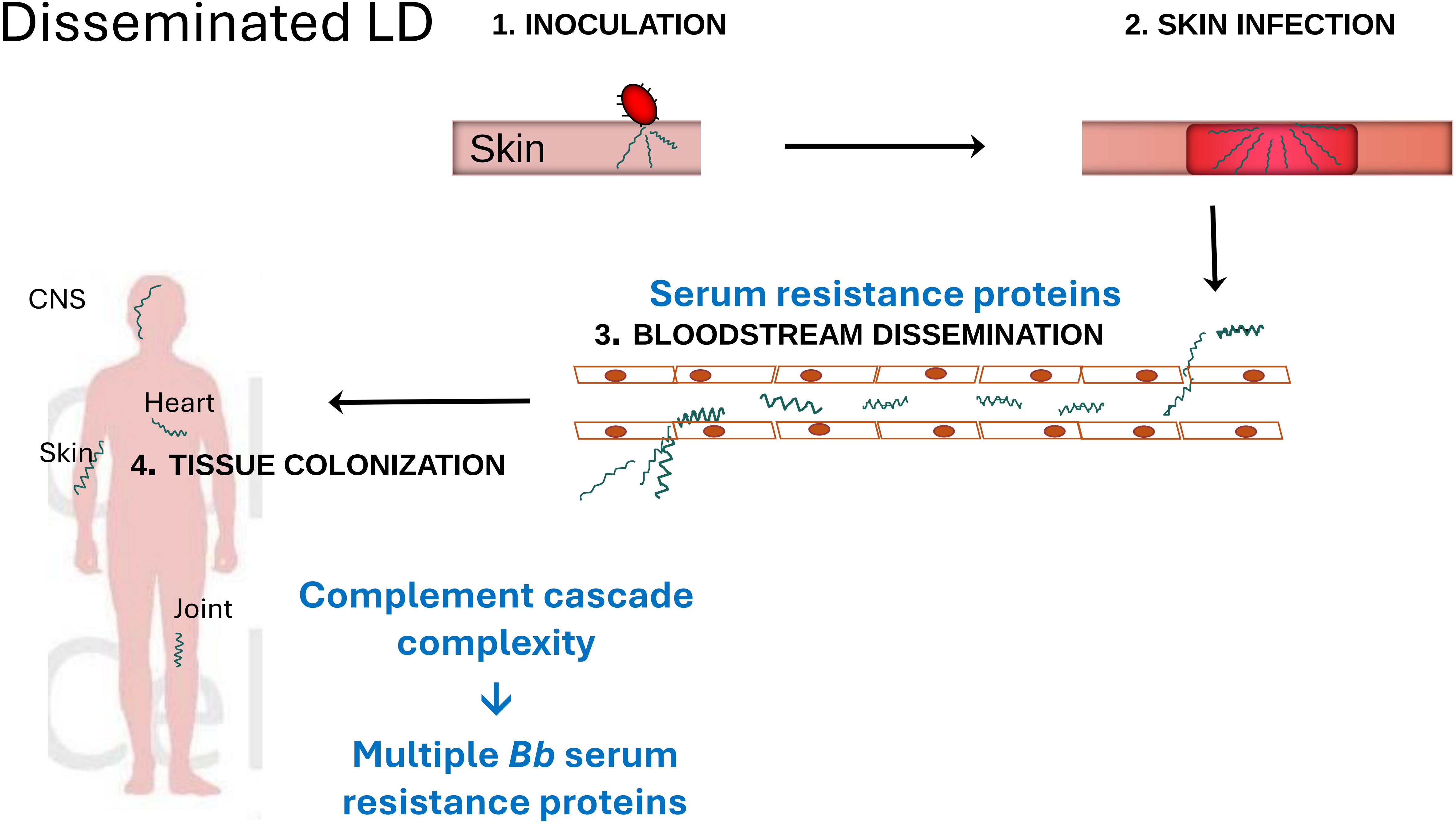
3. BLOODSTREAM DISSEMINATION

Complement cascade complexity

↓

Multiple *Bb* serum resistance proteins

Disseminated LD



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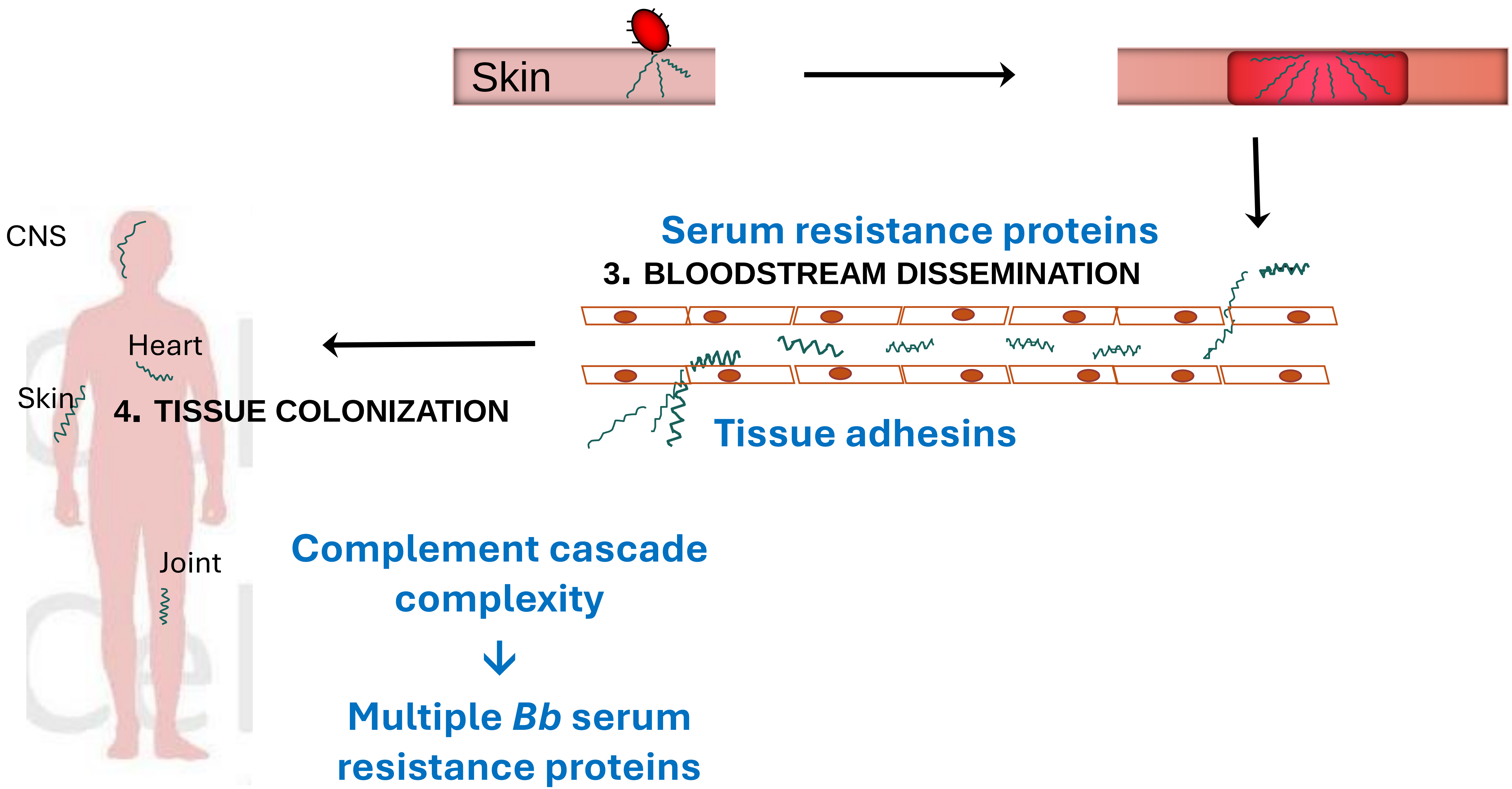

1. INOCULATION

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Serum resistance proteins

3. BLOODSTREAM DISSEMINATION

Tissue adhesins

4. TISSUE COLONIZATION

Complement cascade complexity

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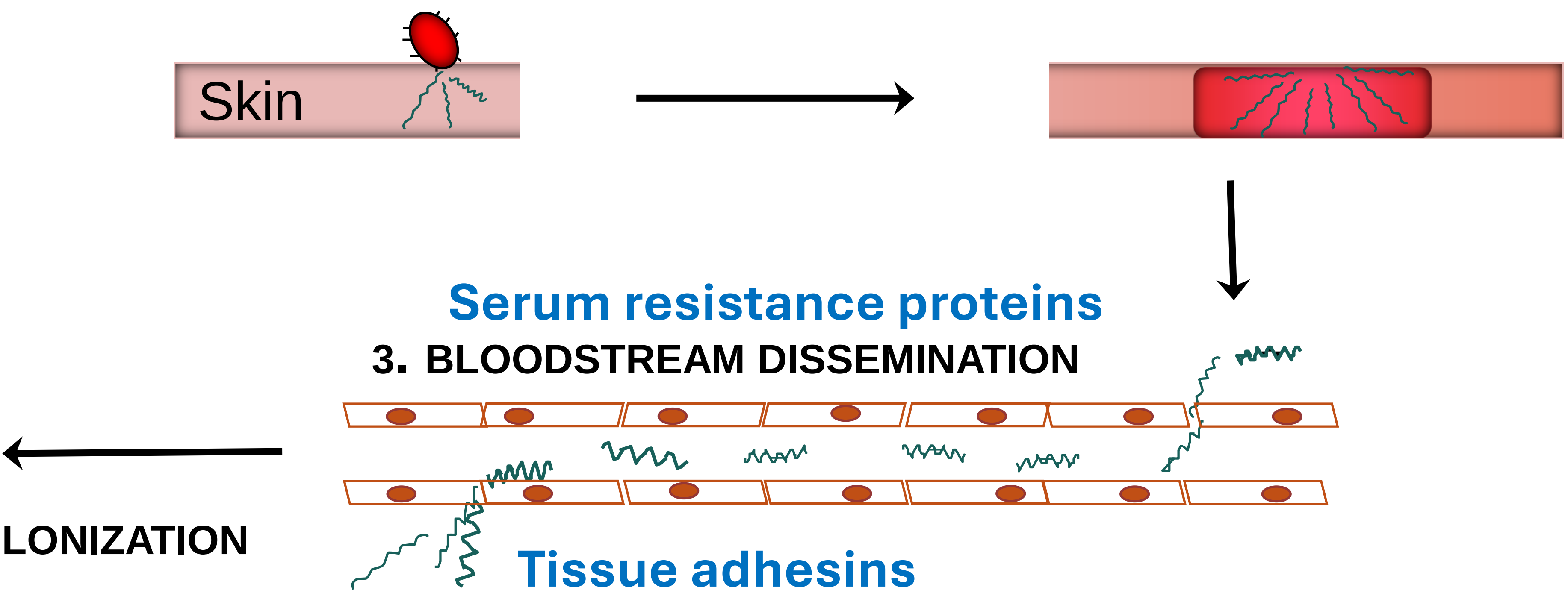

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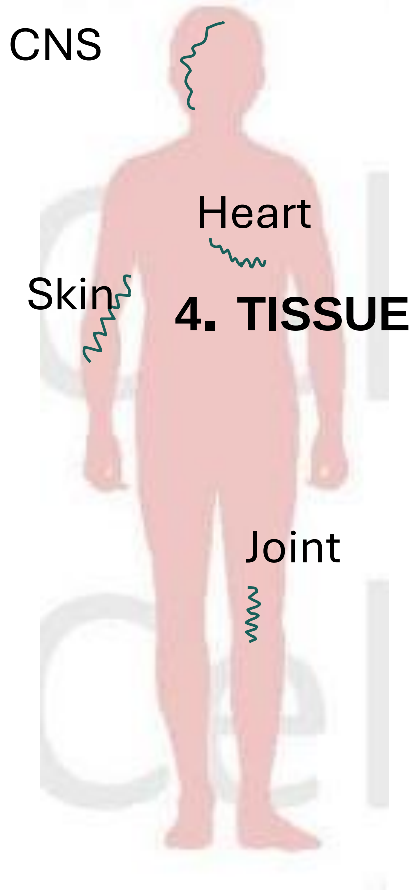

4. TISSUE COLONIZATION

Complement cascade complexity

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Multiple *Bb* serum resistance proteins

Multistep invasion process

↓

Multiple *Bb* adhesive proteins

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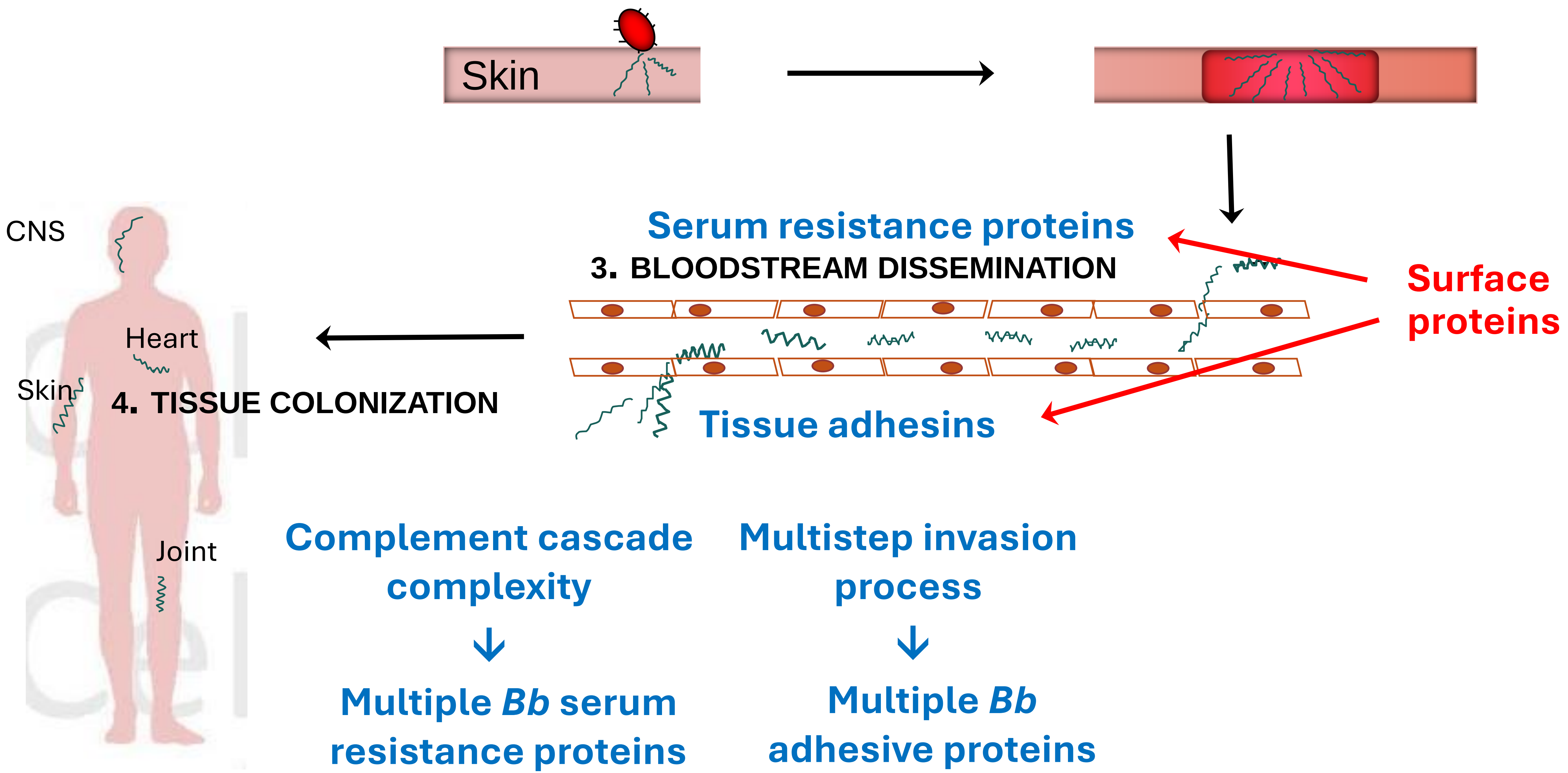

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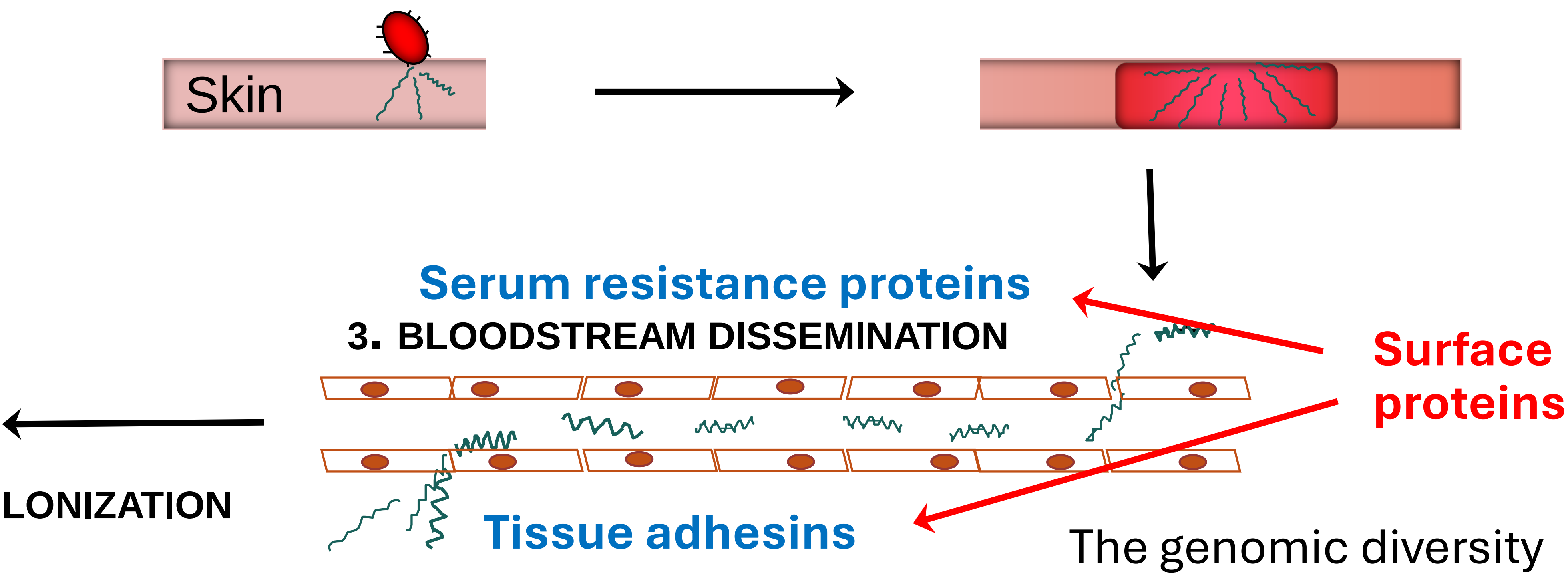

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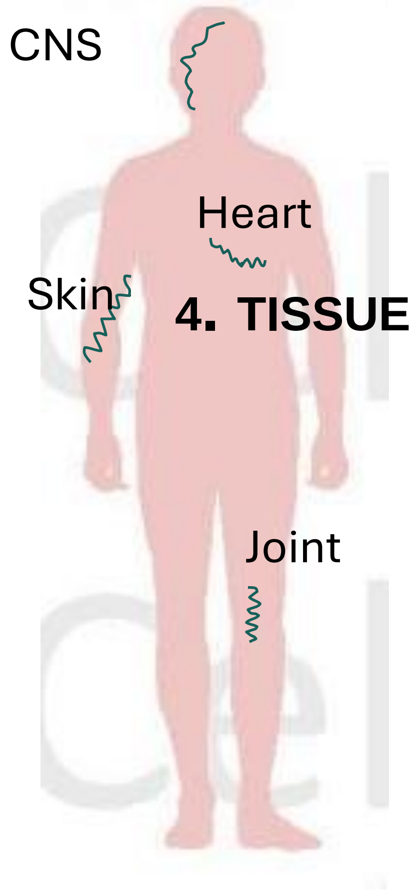

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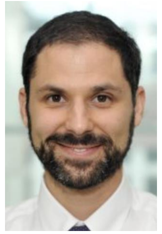
Multiple *Bb* adhesive proteins

The genomic diversity of *Bb* largely reflects the diversity of the surface lipoproteome



Jake Lemieux

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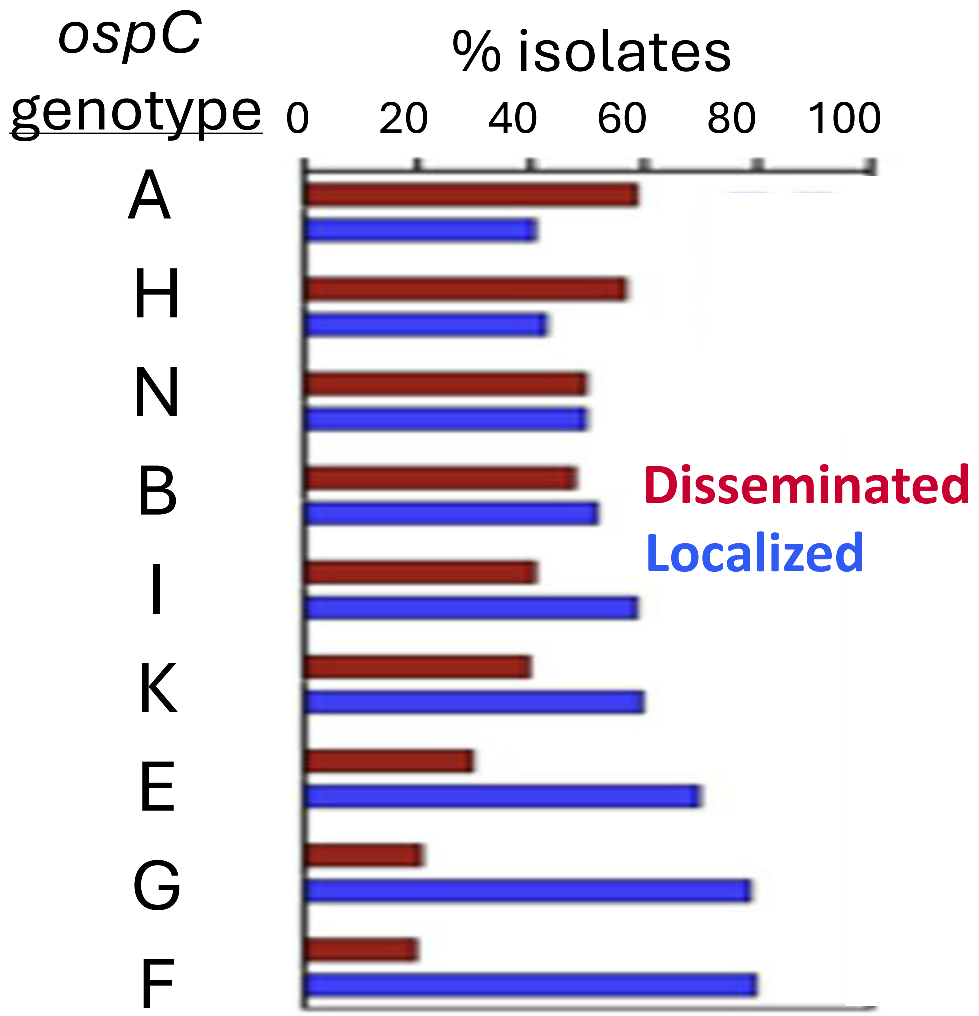

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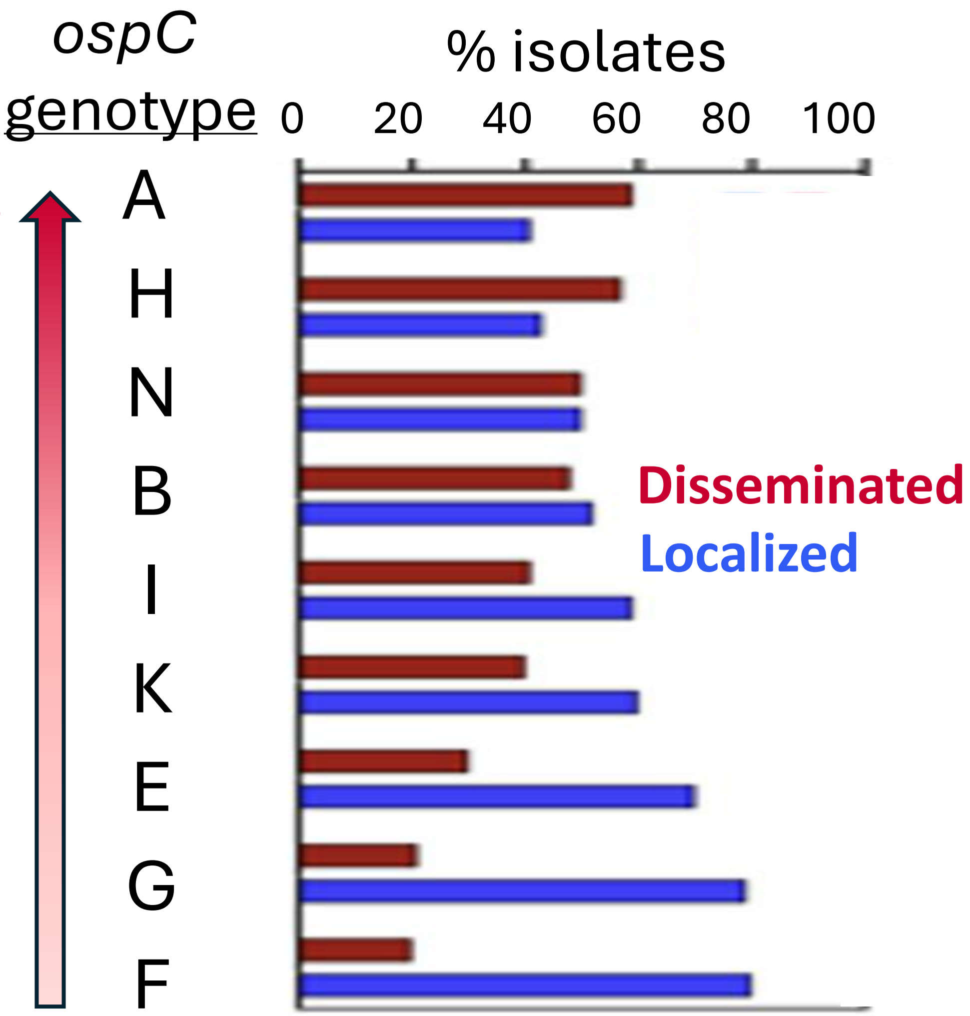

Serum resistance proteins?

Disseminated

Localized

Strle and coworkers

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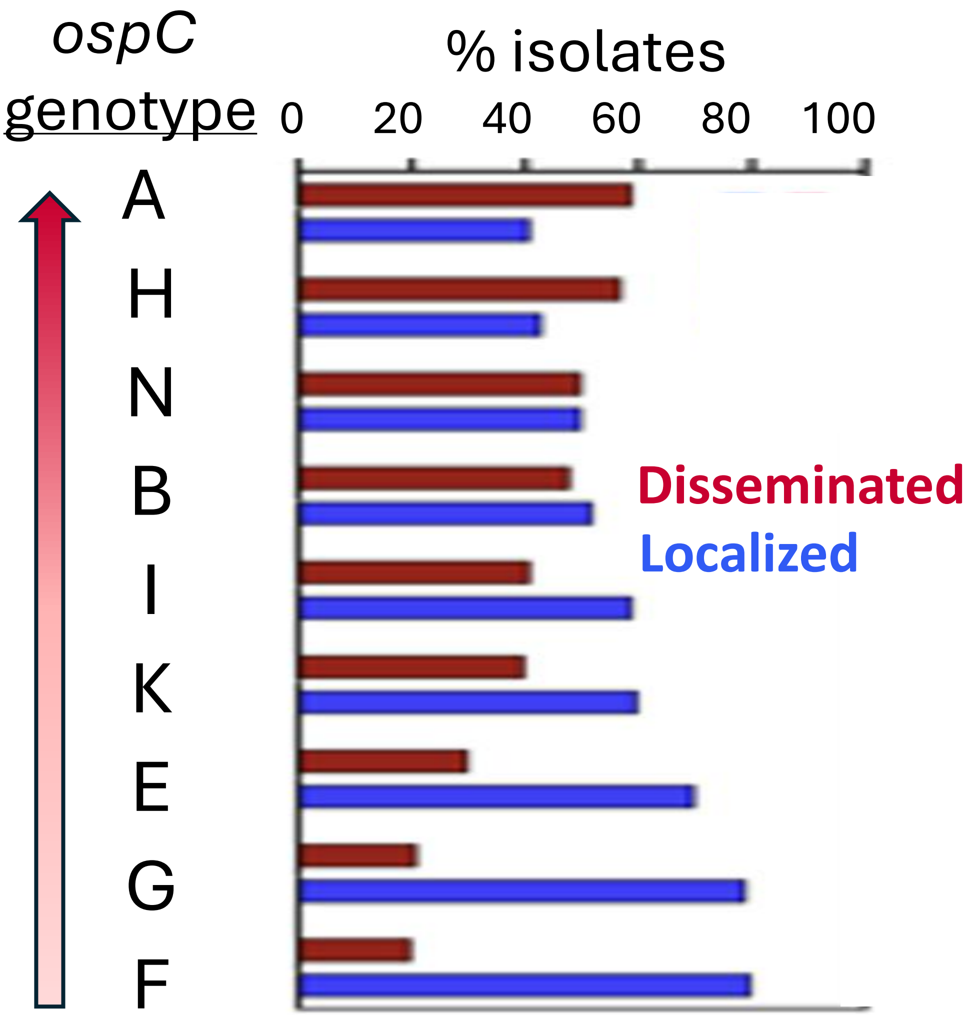
Serum resistance proteins?

Adhesins?



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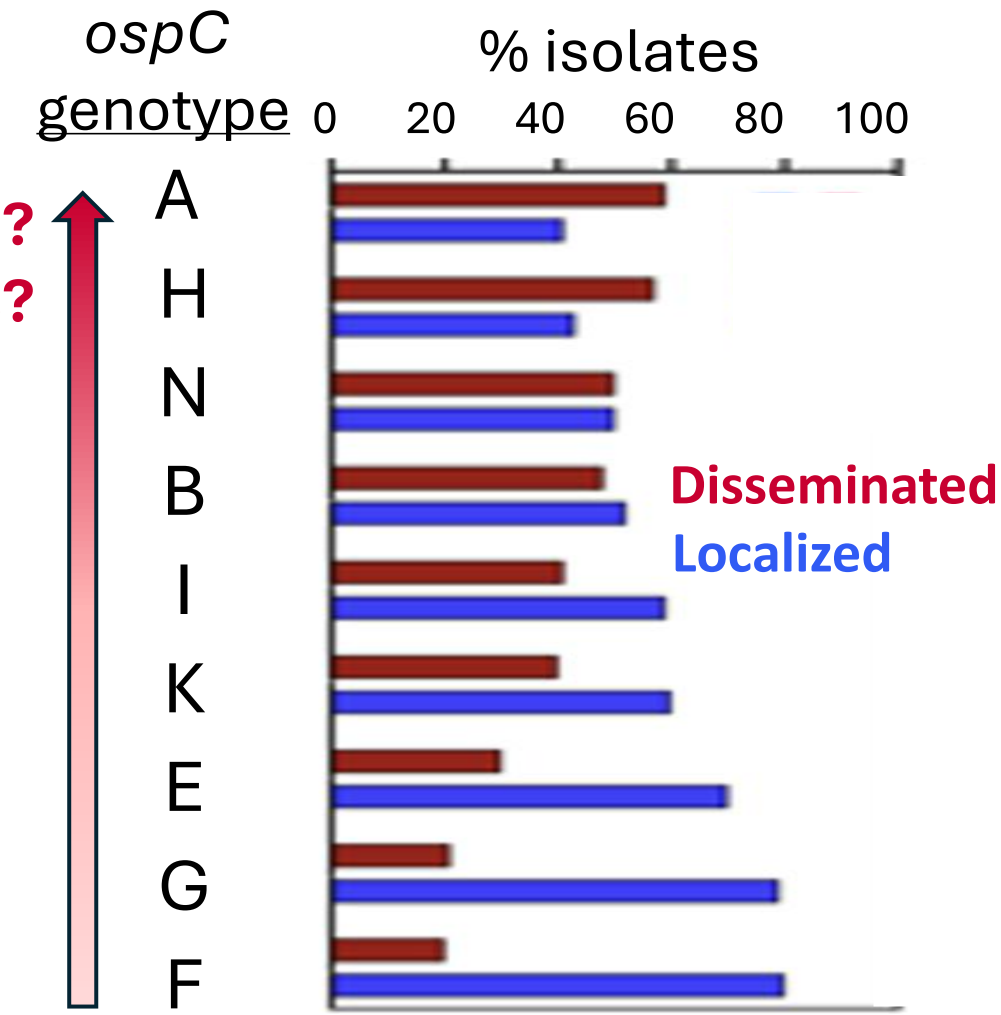

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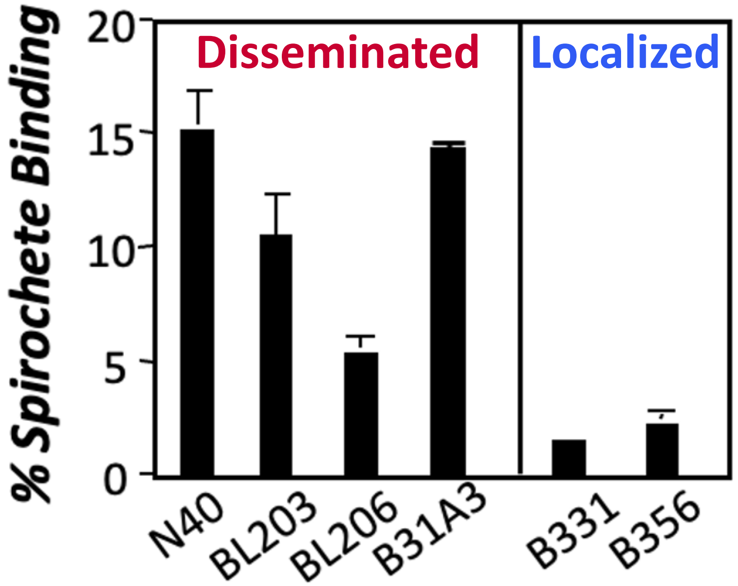


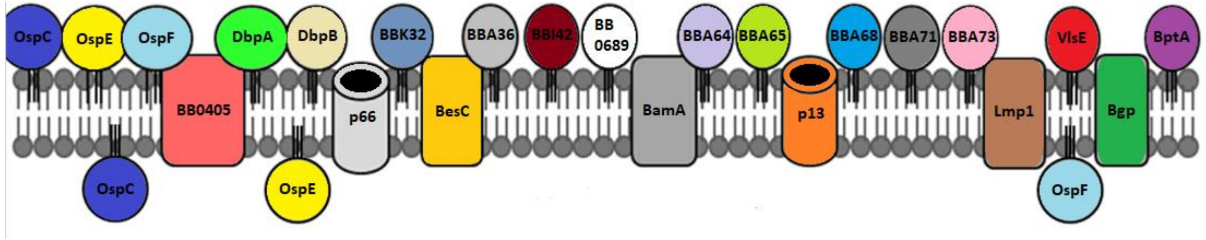

Ira Schwartz


Nikhat Parveen

Identification of serum resistance and adhesive *Bb* proteins

Experimental Challenges

- >80 surface lipoproteins, many with multiple functions, leading to functional redundancy



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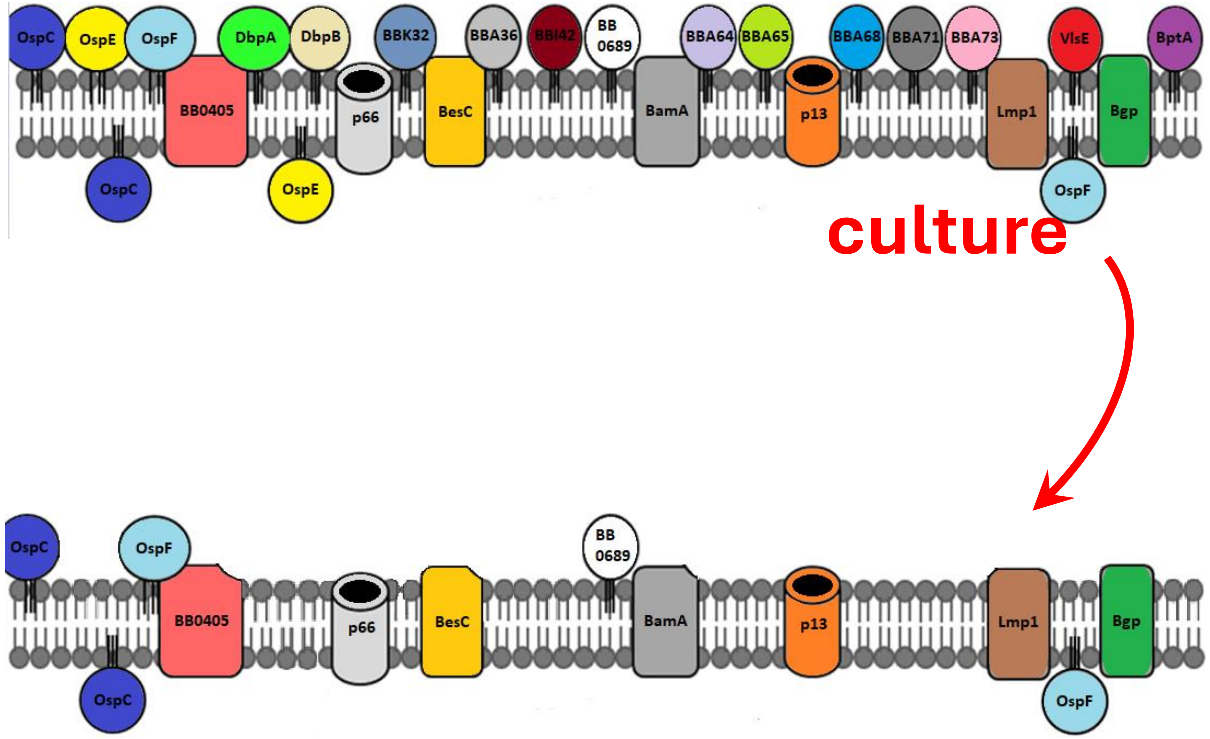

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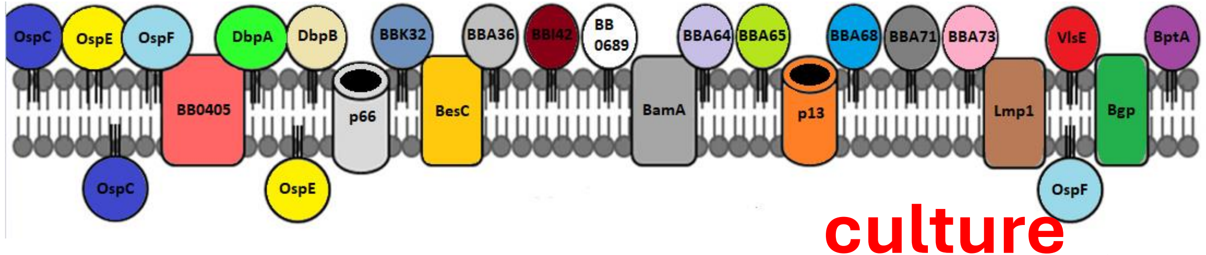
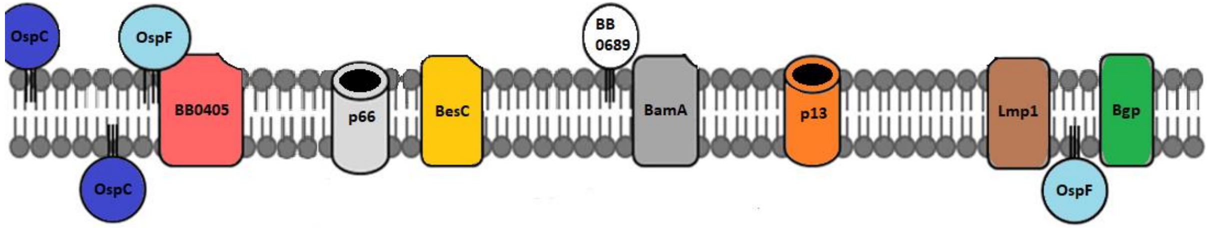


culture

- Complex genome, with multiple lipoprotein-encoding plasmids, many of which are unstable.



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Approaches

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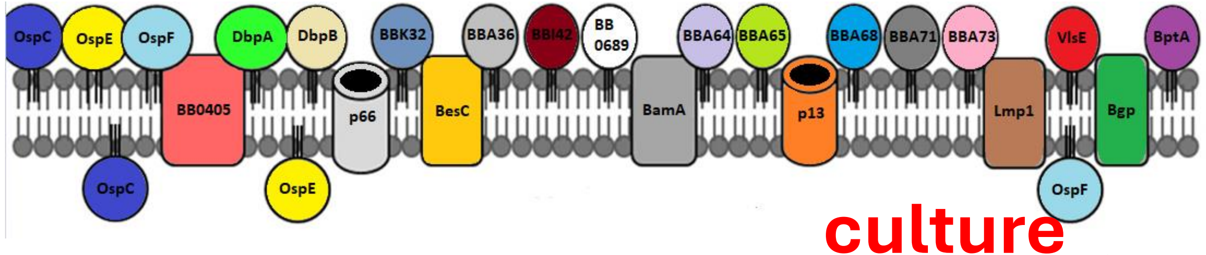

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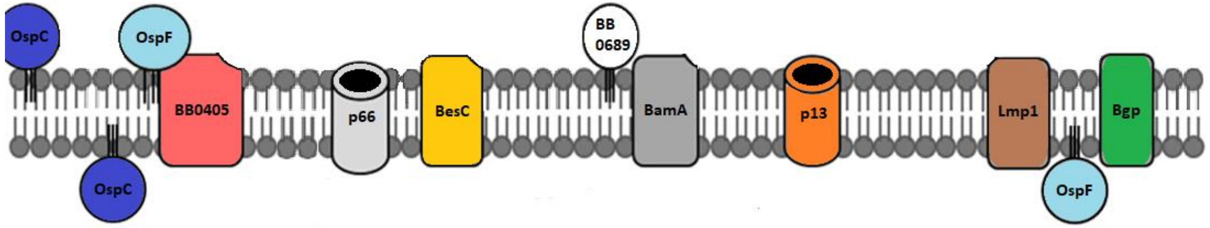

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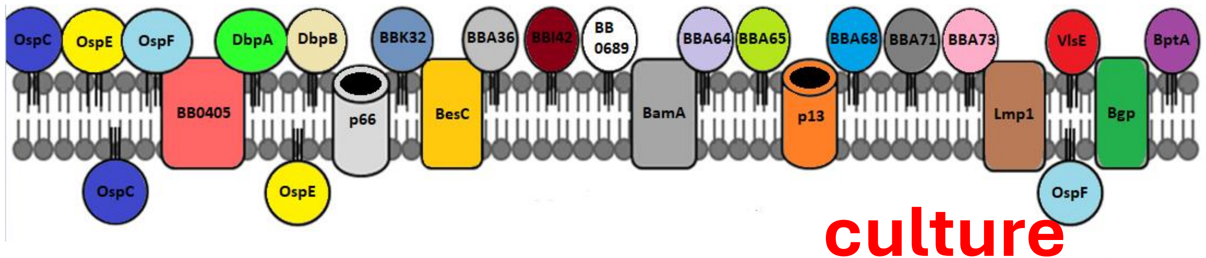

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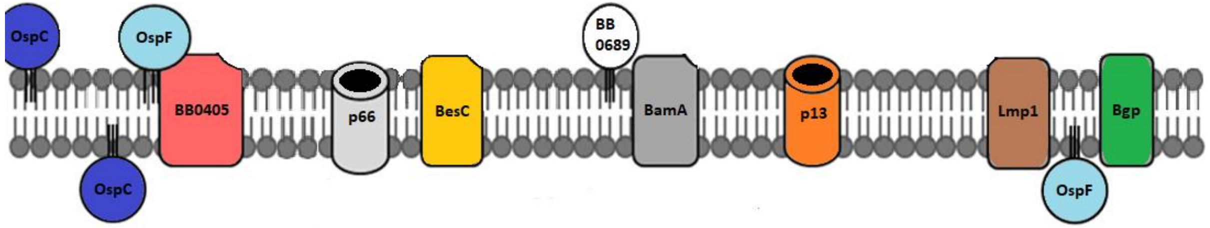
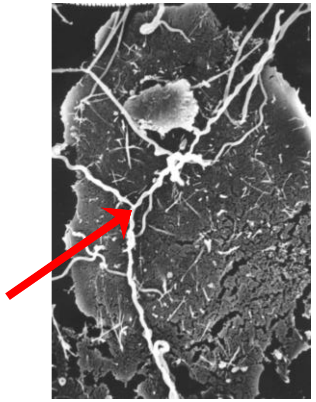


Approaches

- *In vitro* cell binding assays



Bound *Bb*

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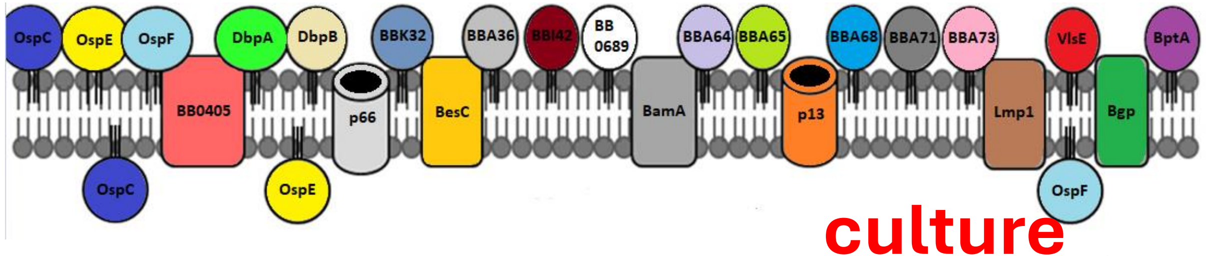

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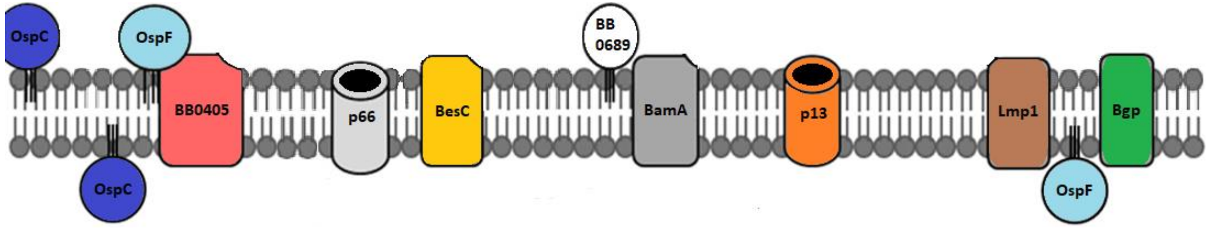
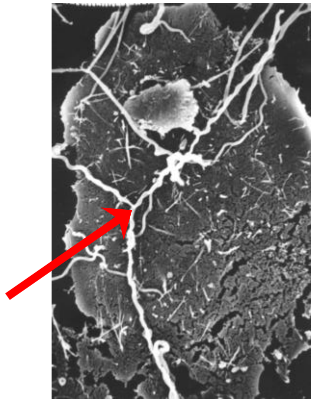


Approaches

- *In vitro* cell binding assays

- *In vitro* serum killing assays



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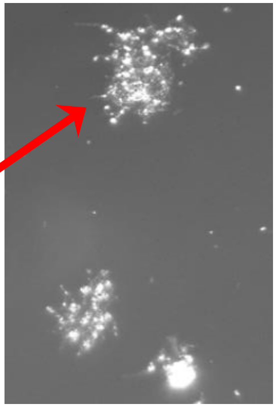

Dead *Bb*

Identification of serum resistance and adhesive *Bb* proteins

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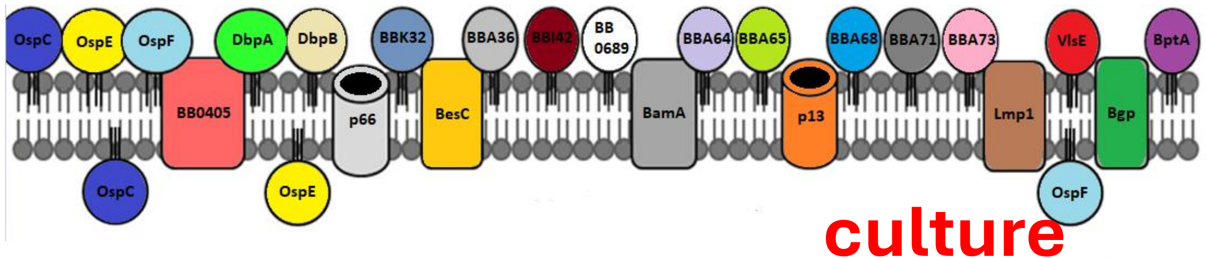

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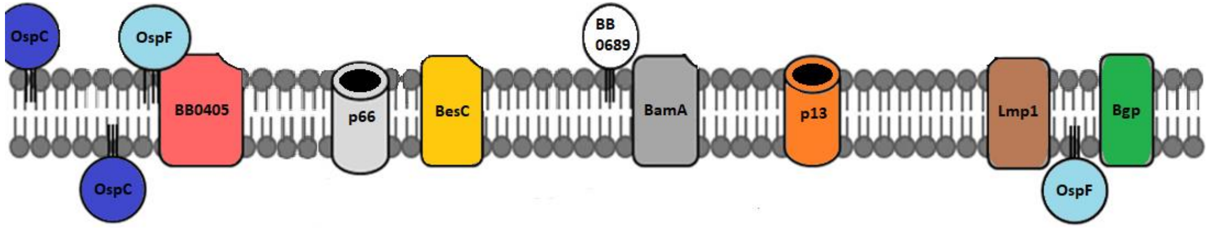

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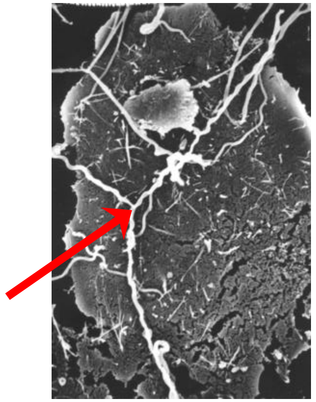
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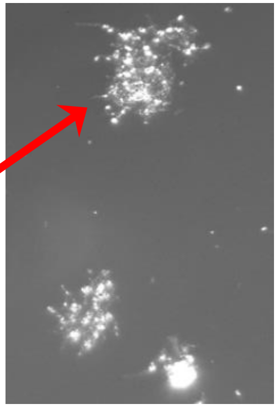
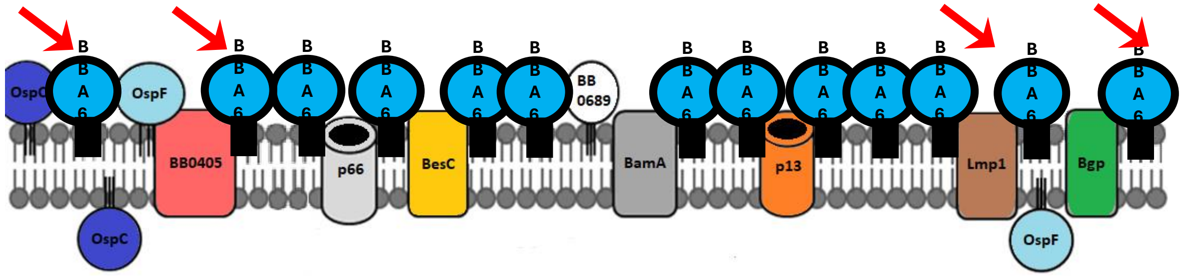
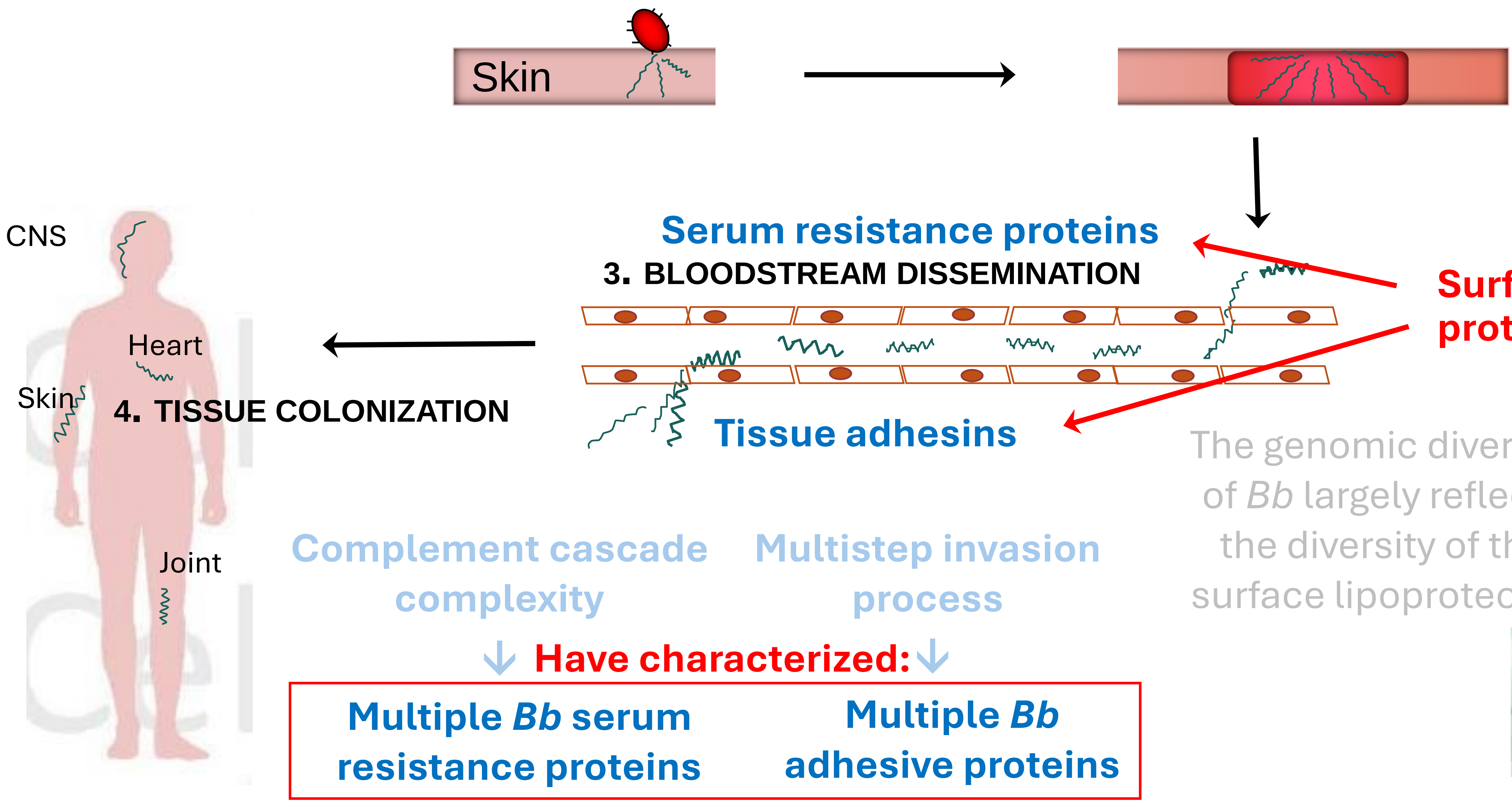

Dead *Bb*

Ectopic production

- "Gain-of-function" *Bb* strains



Disseminated LD



1. INOCULATION

Skin

2. SKIN INFECTION

Serum resistance proteins

3. BLOODSTREAM DISSEMINATION

Surface proteins

Tissue adhesins

4. TISSUE COLONIZATION

CNS

Heart

Skin

Joint

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Complement cascade complexity

Multistep invasion process

↓ **Have characterized:** ↓

Multiple *Bb* serum resistance proteins

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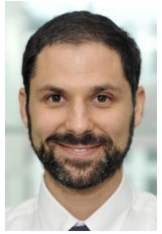


Jake Lemieux

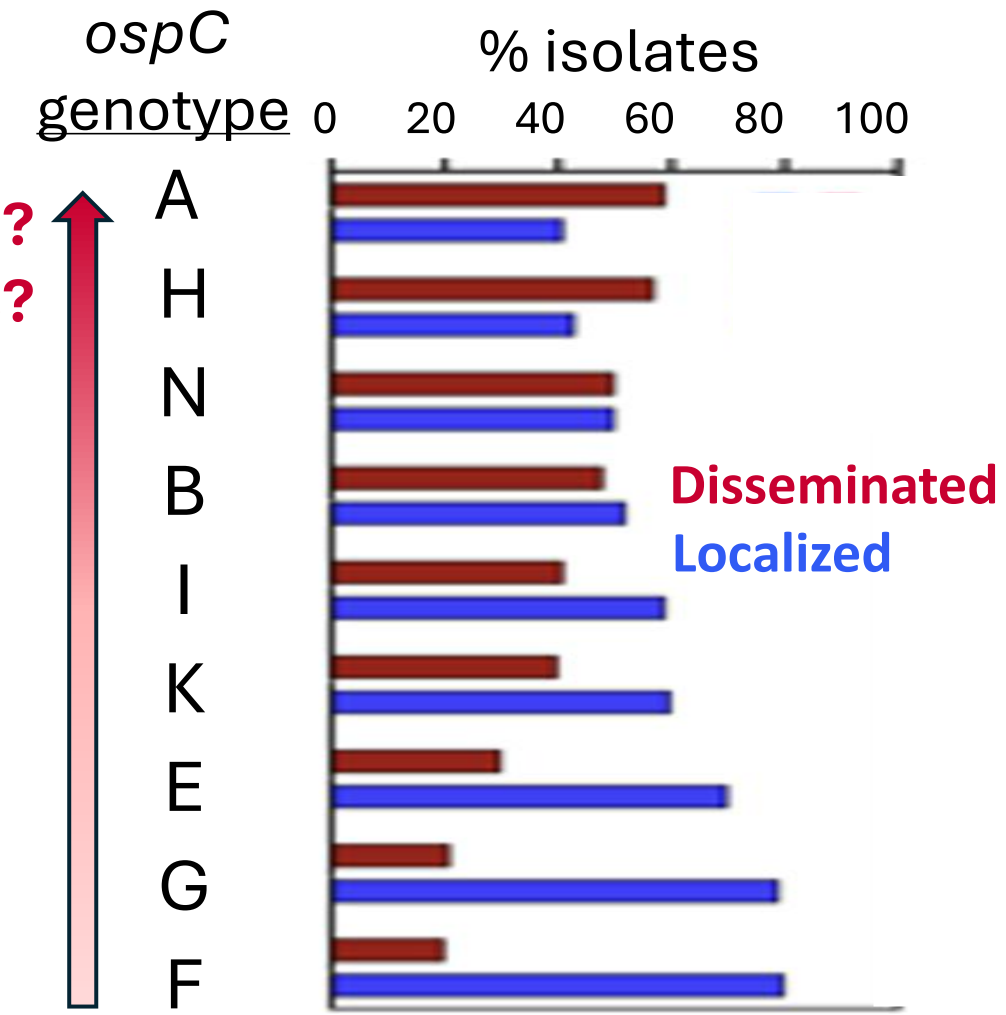
Disseminated LD is associated with:

Serum resistance proteins?

Adhesins?

Comprehensive assessment

Specific *Bb* genotypes



Strle and coworkers

Development of large-scale screening methods

Experimental Challenges

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- Enumeration of *Bb* is labor intensive.
  - Plating efficiency variable.
  - Staining/OD-based methods unreliable.

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Approaches

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Loranne Magoun

Linda Xu

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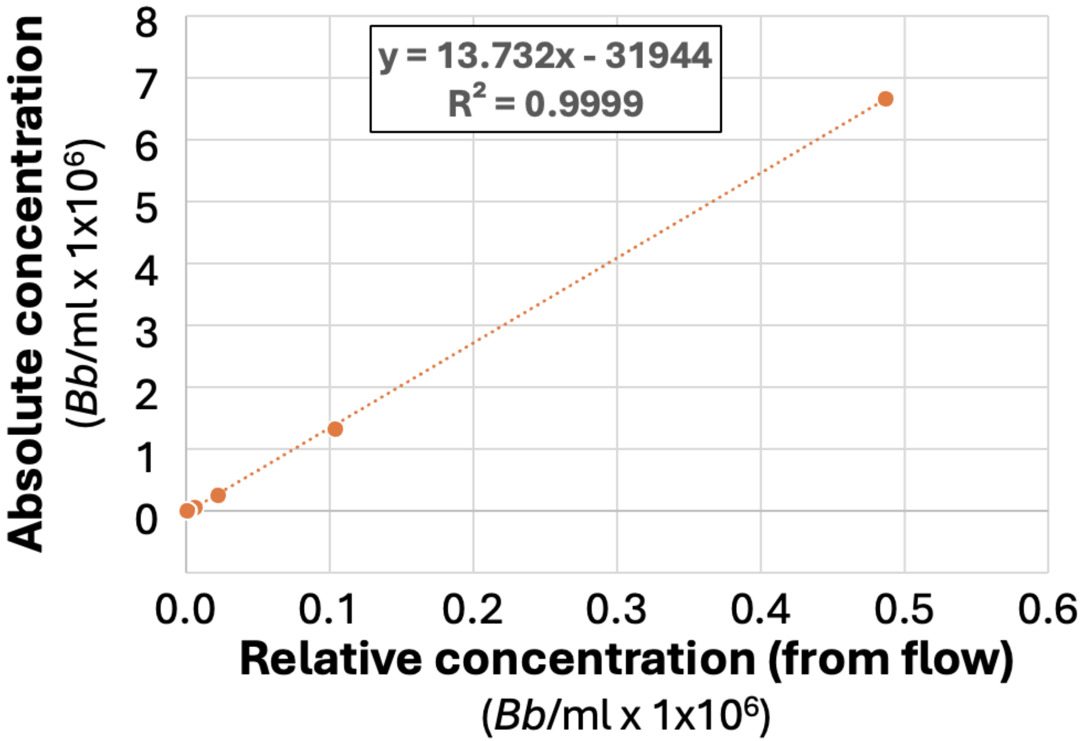

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Permits rapid, large-scale, microtiter well-based screening of surface proteins for serum resistance or adhesive activity

Approaches

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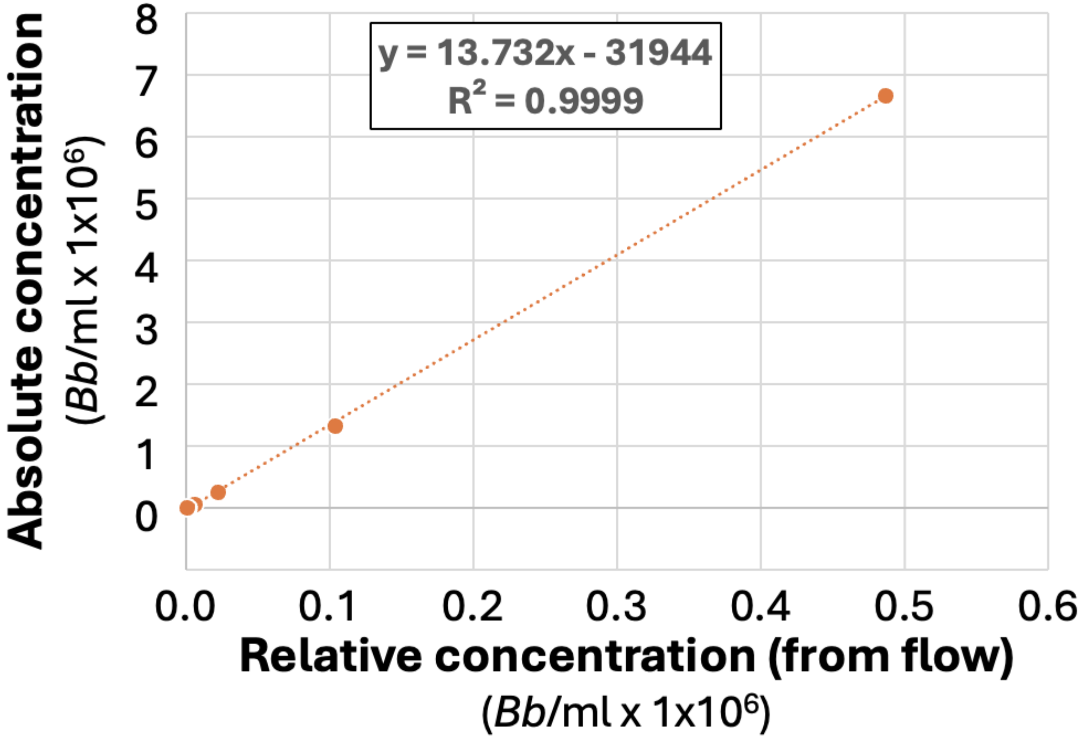

Loranne Magoun

Linda Xu

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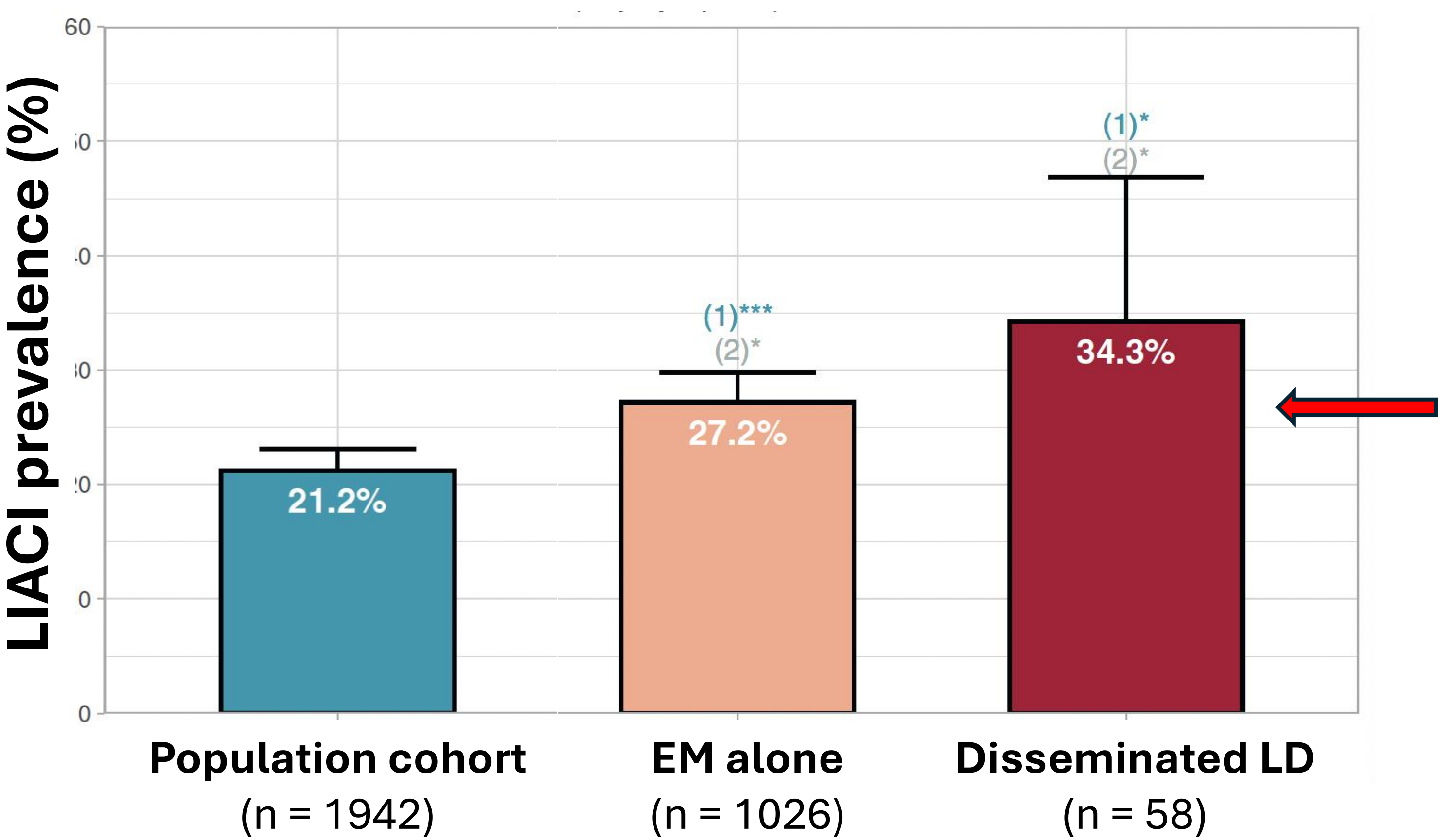

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Does microbial genotype contribute to Lyme IACI and if so, how?

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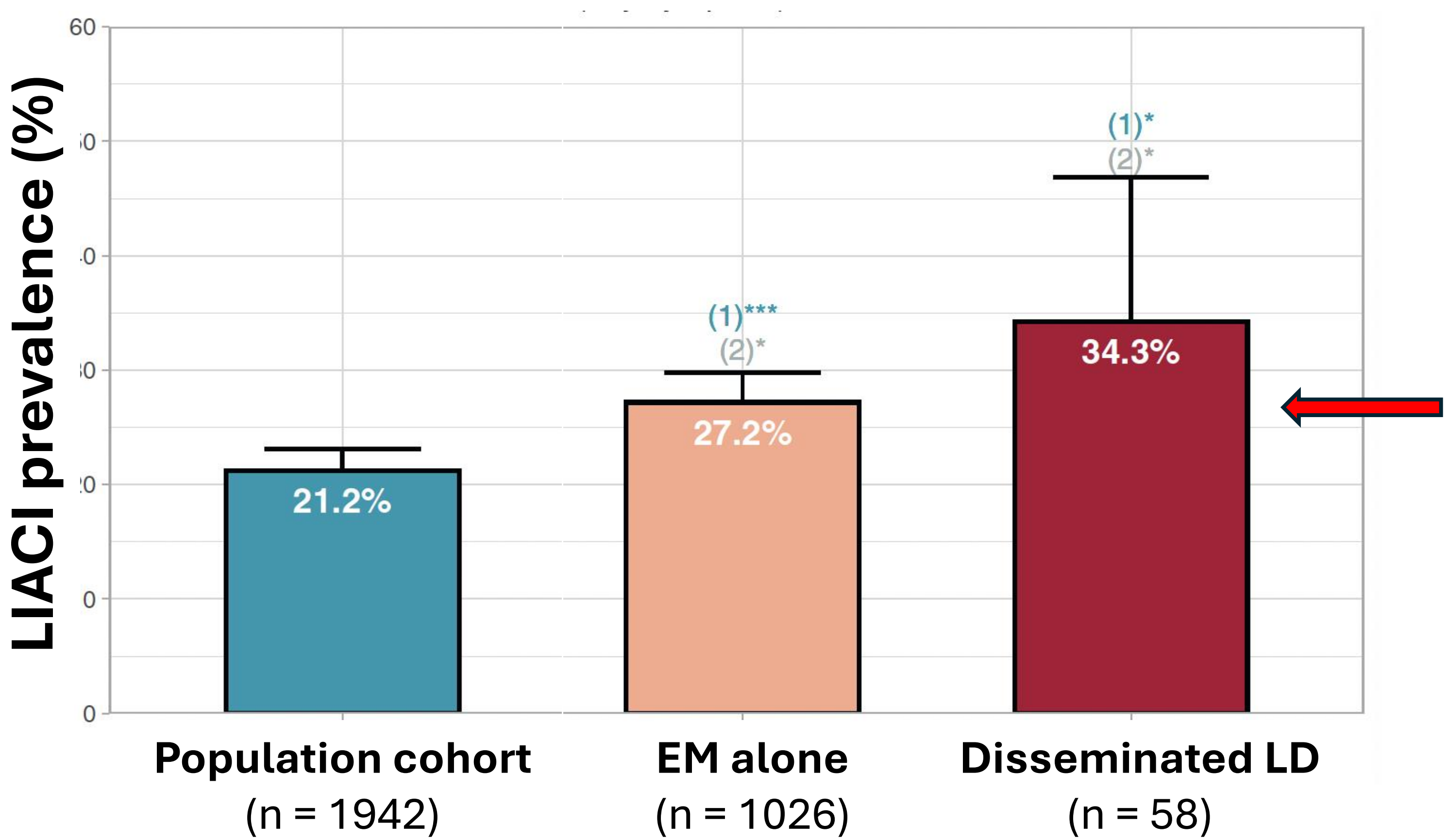

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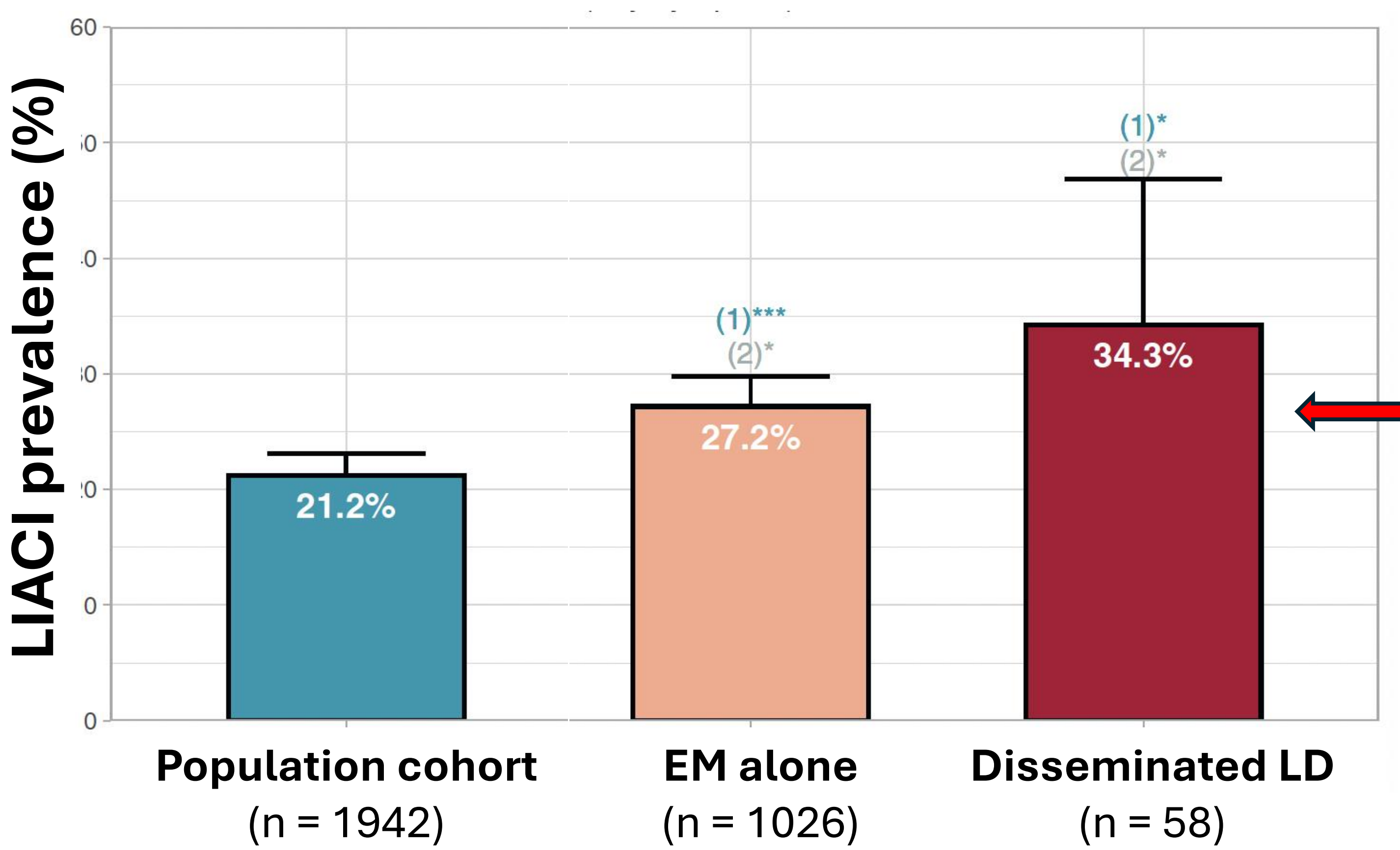

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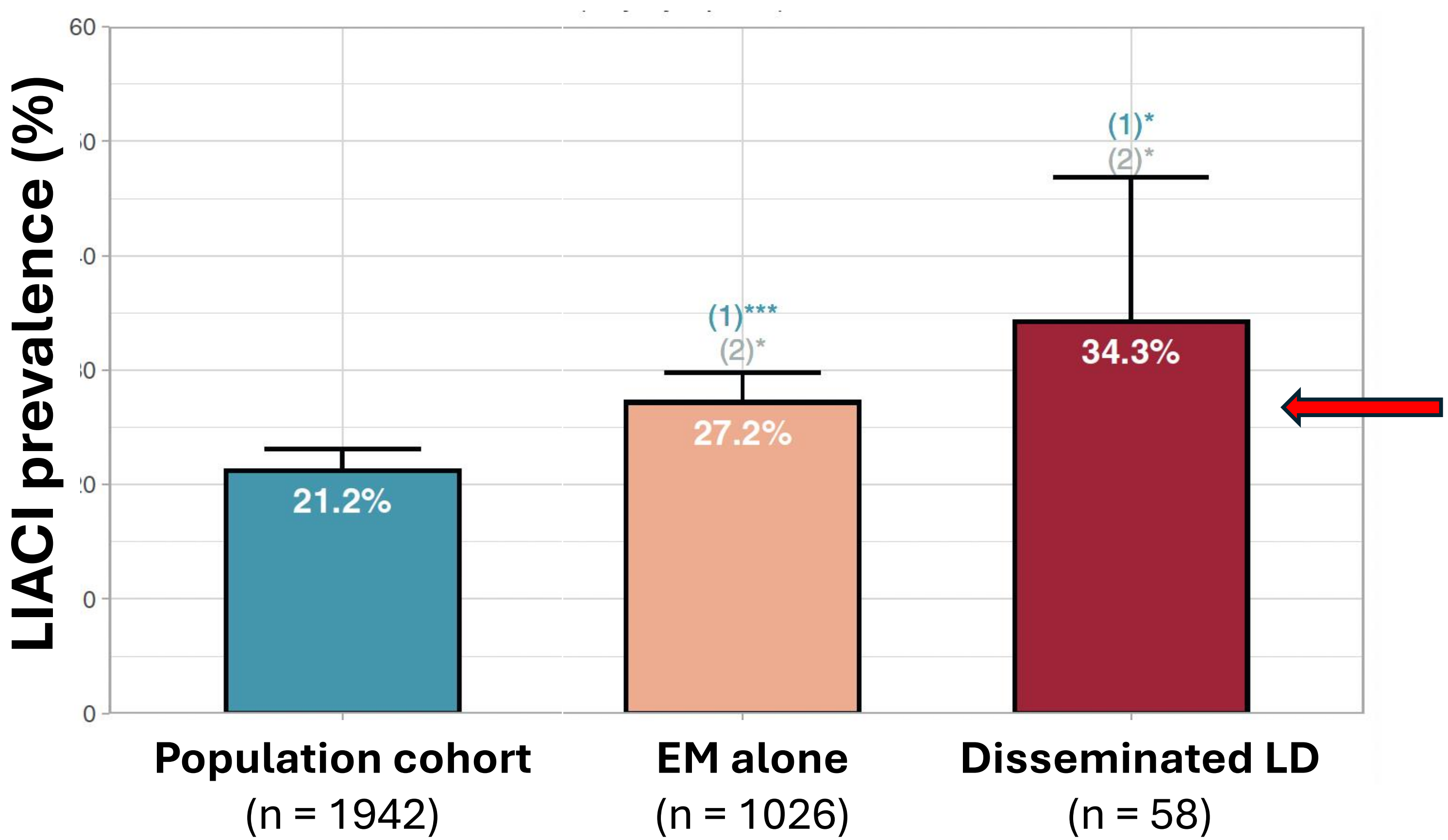

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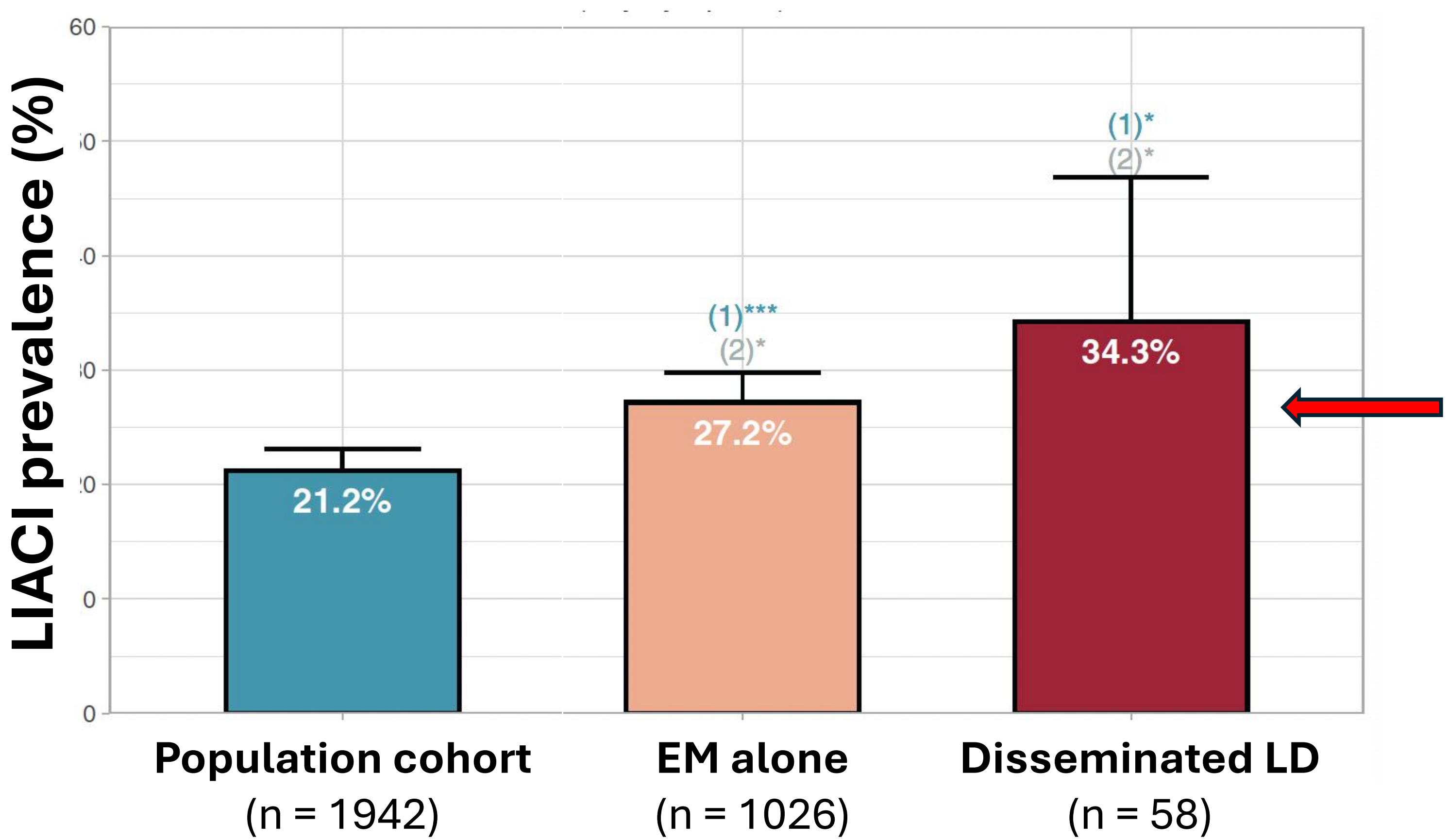

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Tufts
UNIVERSITY

Mass General Hospital
Harvard University

Loranne
Magoun

Linda
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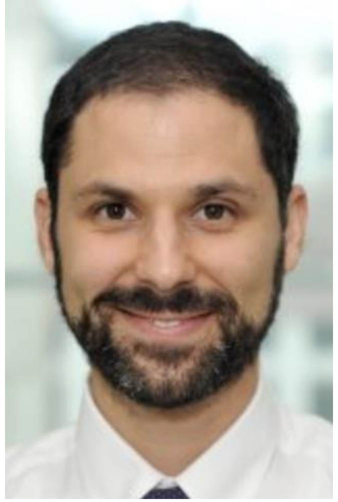

Jake
Lemieux

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Carol Lyn Piazza and Graham Willsey
in the Mantis lab, Wadsworth Institute