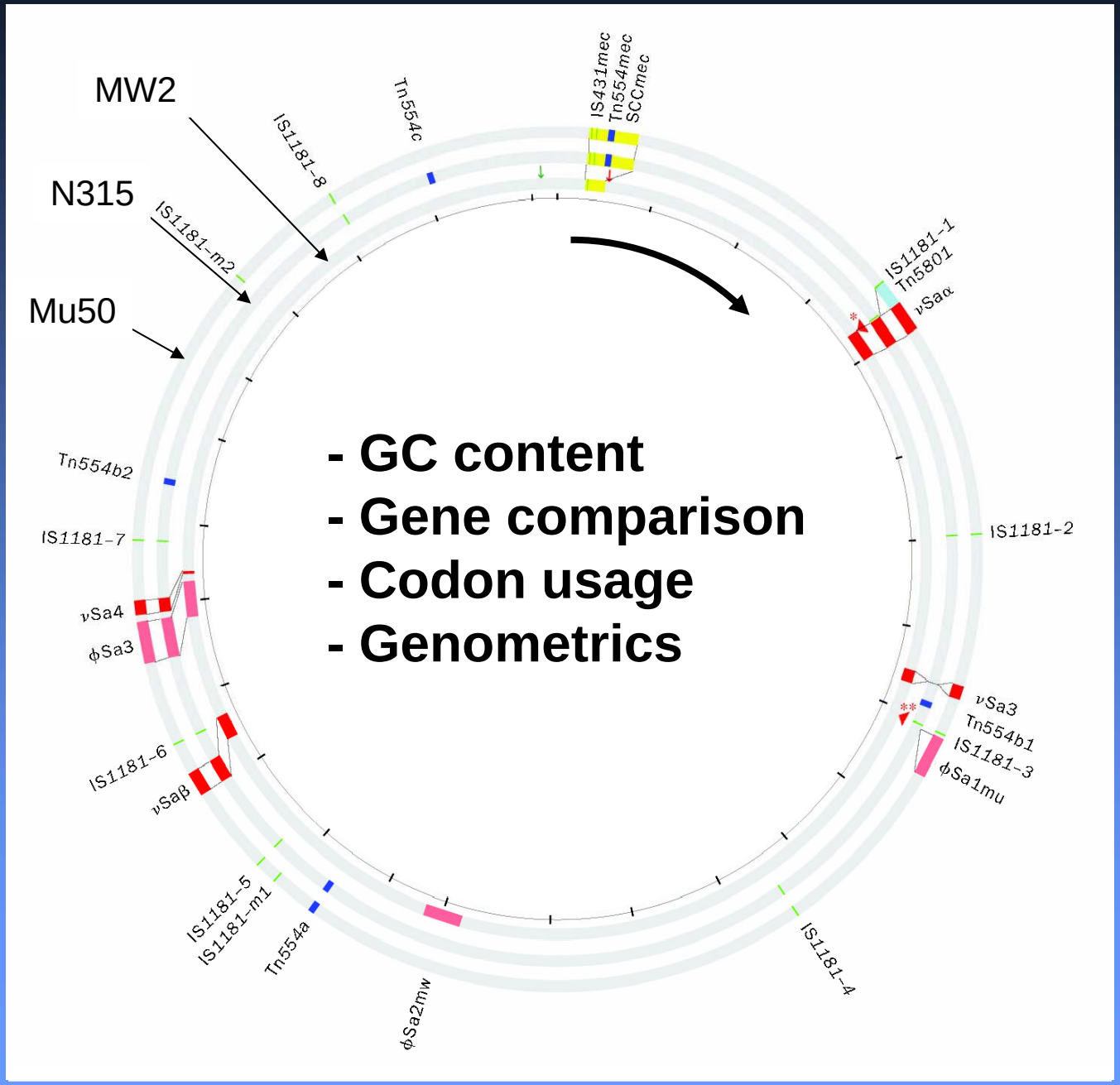
Staphylococcus aureus Pathogenesis

- Gene exchanges
- Gene regulation
- Gene products
- Gene product cooperation

Some Staphylococcal Species from Mammals

Host	Species	Coagulase	Clumping factor	Virulence
Human and other primates	*S. aureus*	++	++	+++
	S. epidermidis	-	-	+
	S. capitis	-	-	(+)
	S. caprae	-	-	(+)
	S. saccharolyticus	±	-	-
	S. warneri	-	-	-
	S. pasteuri	-	-	-
	S. haemolyticus	-	-	+
	S. hominis	-	-	(+)
	S. lugdunensis	-	±	+
	S. auricularis	-	-	(+)
	S. saprophyticus	-	-	+
	S. cohnii	-	-	-
	S. xilosus	-	-	-
	S. simulans	-	-	-
	S. schleiferi	±	+	+
Carnivores	*S. intermedius*	+	-	++
	S. felis	-	-	++

Whole genomes of *S. aureus* MW2, N315 and Mu50



Baba T et al. Lancet 2002;359:1819

From Linguistics to Genometrics

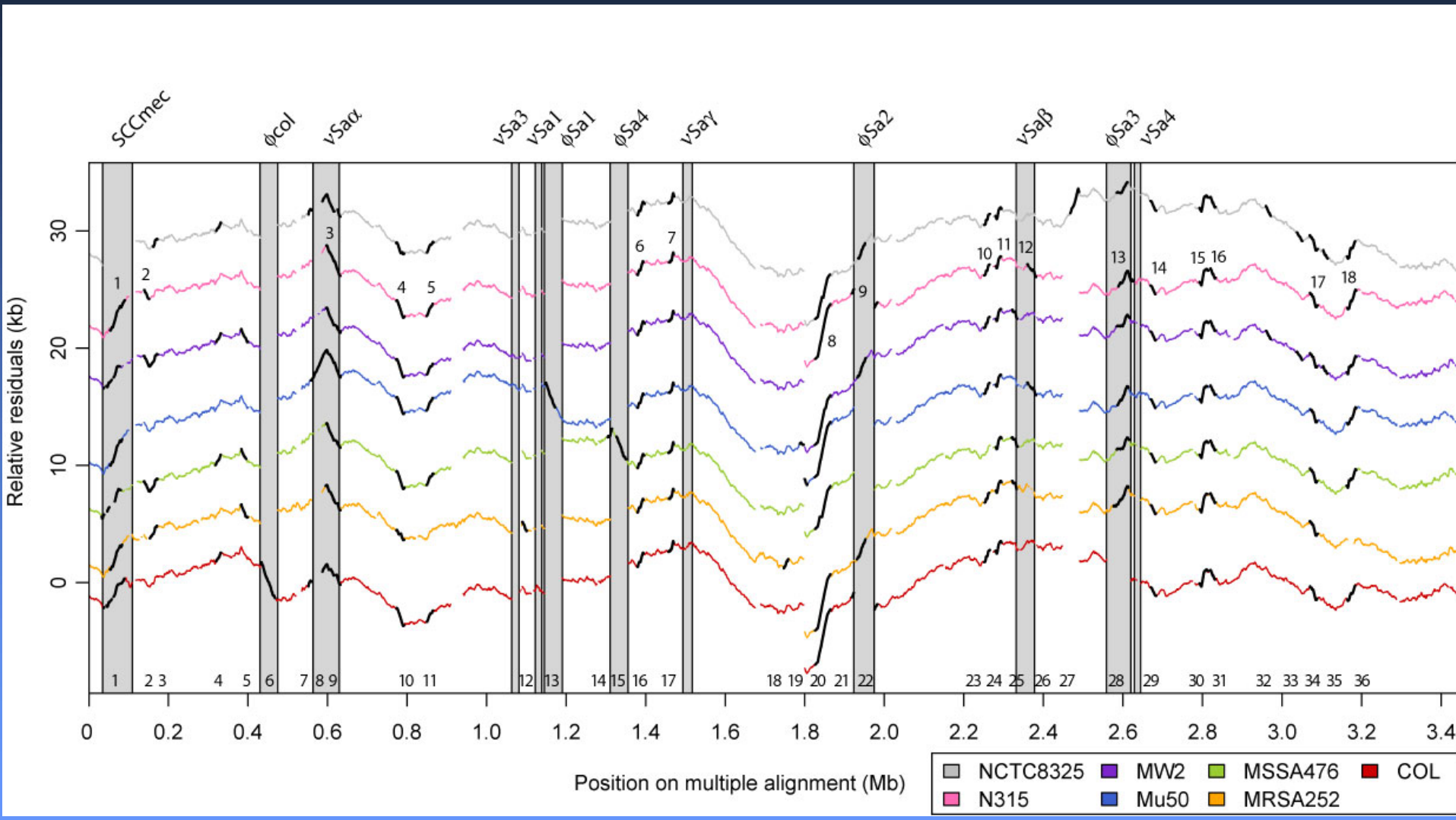
theicaacisagreatconférenceparcequellegathermanygreatscientists

theicaacisagreatconférenceparcequellegathermanygreatscientists

http://www2.unil.ch/comparativegenometrics/

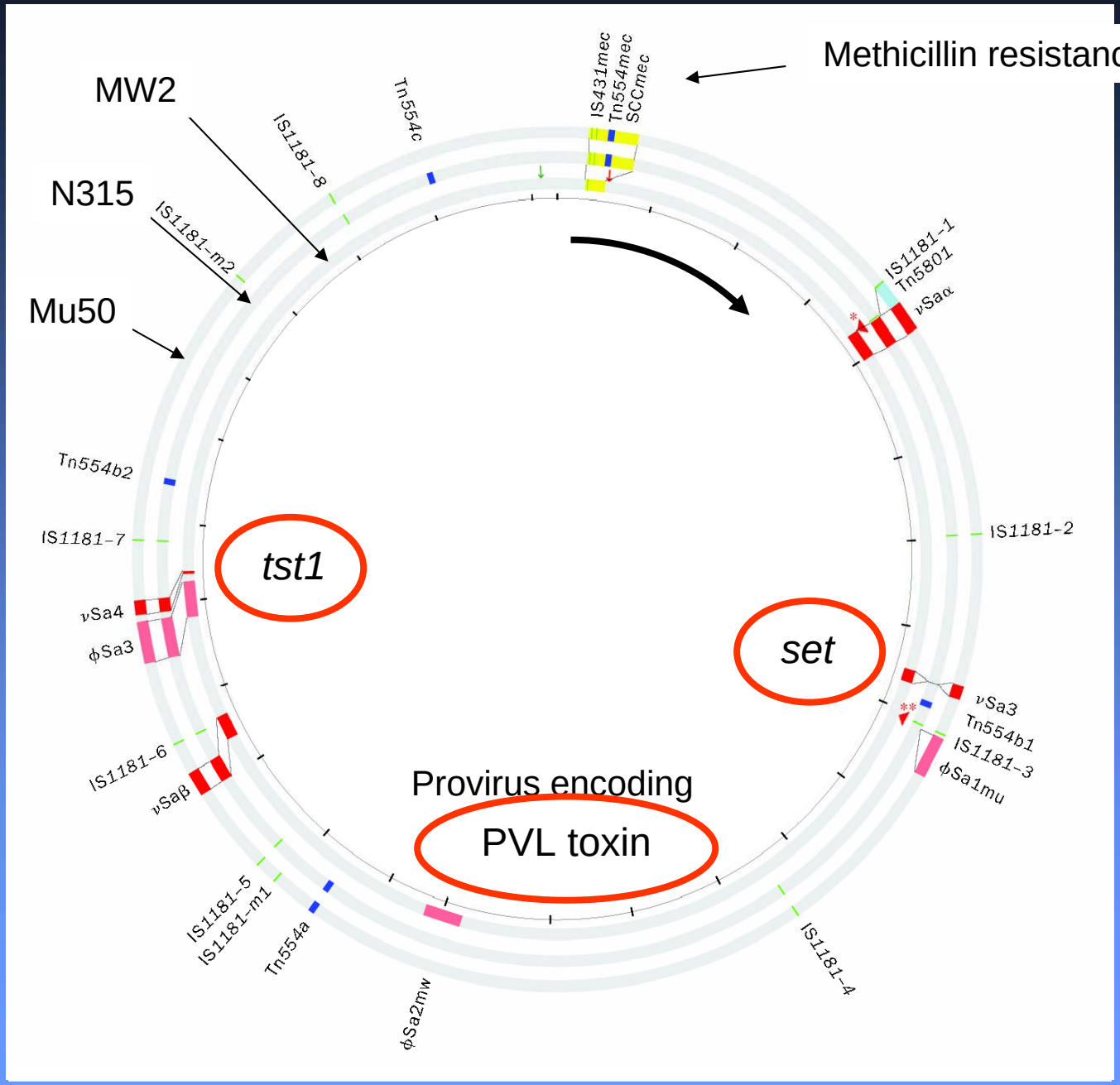
CA Roten and L. Guy

S. aureus Genometric Analysis



Guy Lionel, Thesis 2007

Whole genomes of S. aureus MW2, N315 and Mu50



Baba T et al. Lancet 2002;359:1819

Define Pathogenicity Islands

- **DNA region (up to 200 kb) of foreign origin**
- **Contain pathogenic genes**
- **May have a different GC content**
- **Flanked by direct repats of IS**
- **Associated with tRNA genes**
- **Contain relics of integrase/excisase genes or of phage genes**

Hacker J et al. Mol Microbiol 1997; 23:1089-97

How do they move ?

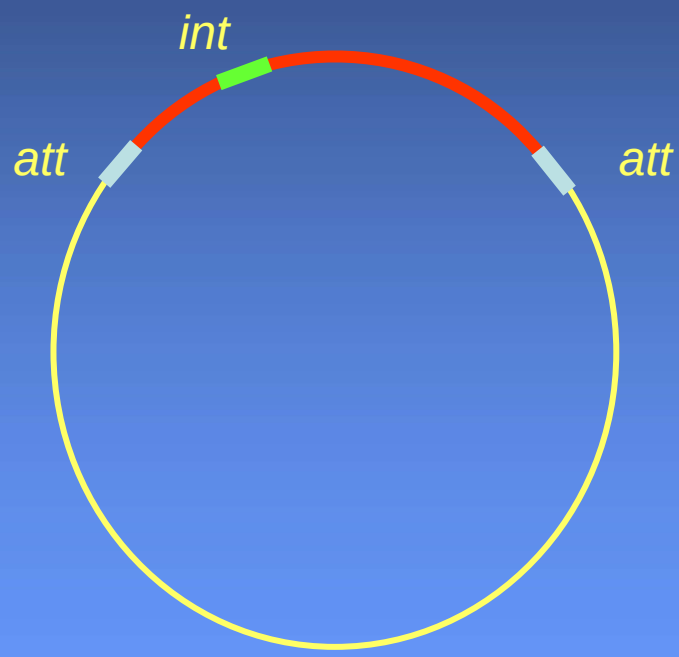
- **Transformation**

- **Conjugation**

- **Transduction (generalized)**

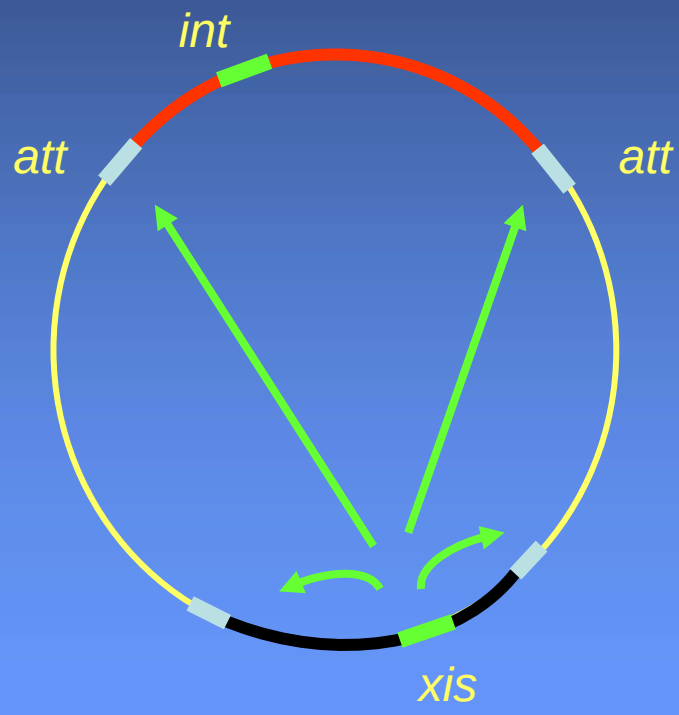
Moving Genes Around

The example of SaPI1



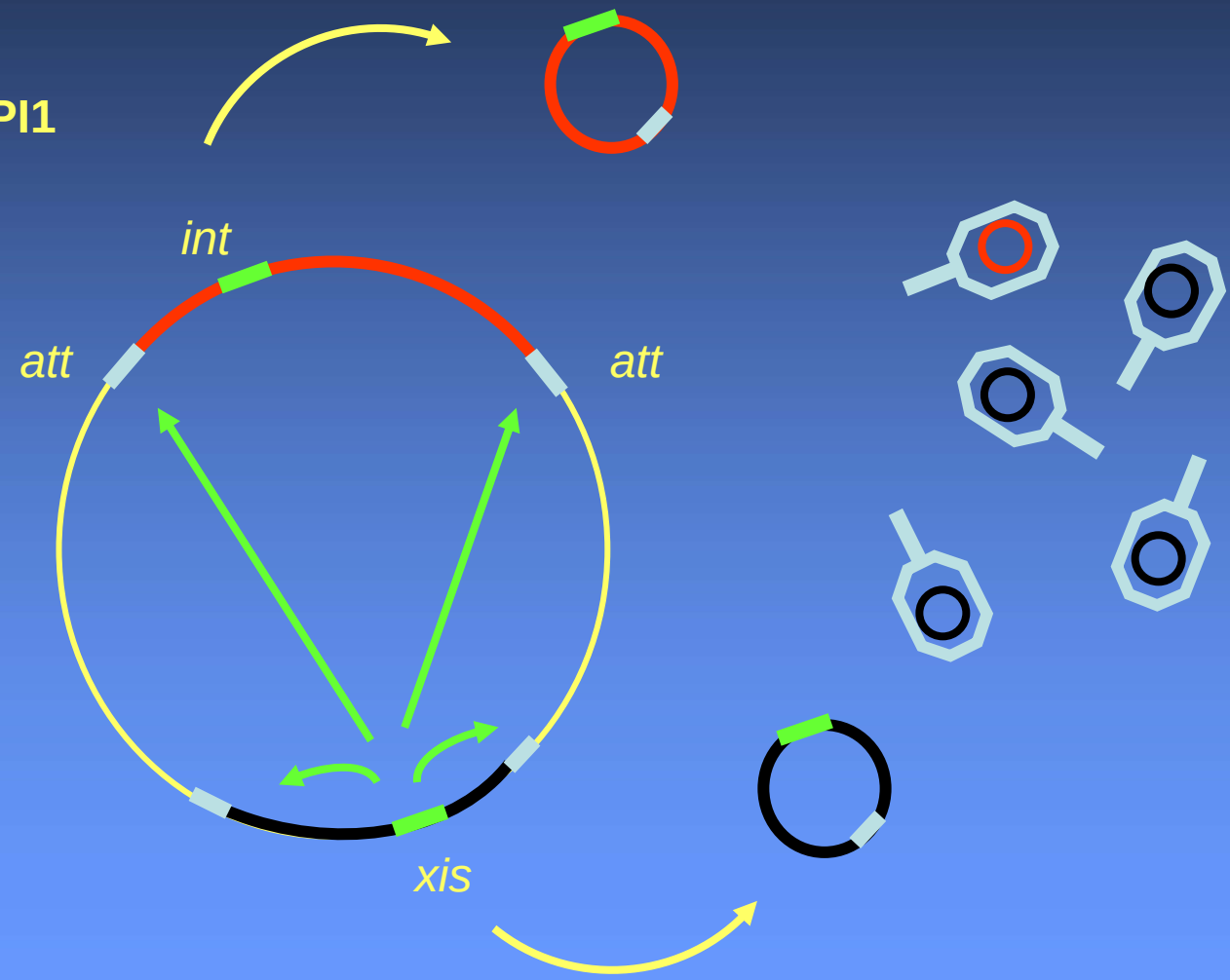
Moving Genes Around

The example of SaPI1



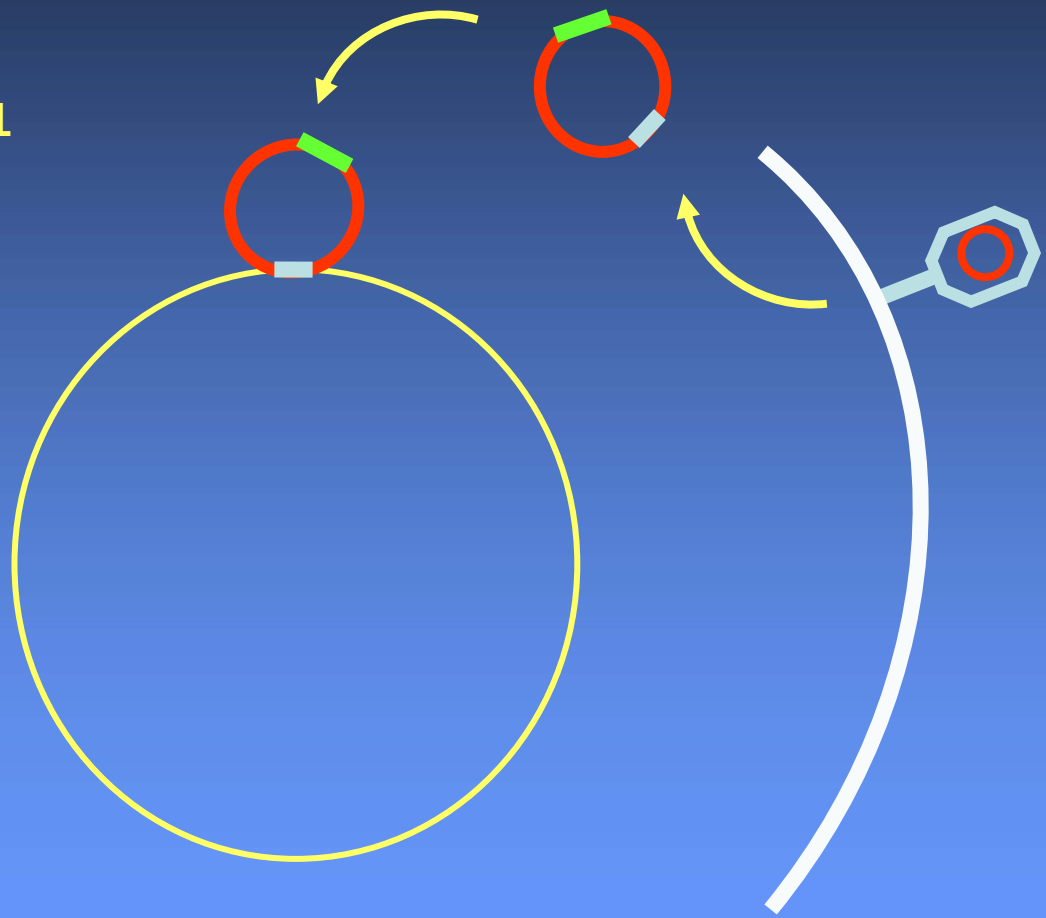
Moving Genes Around

The example of SaPI1



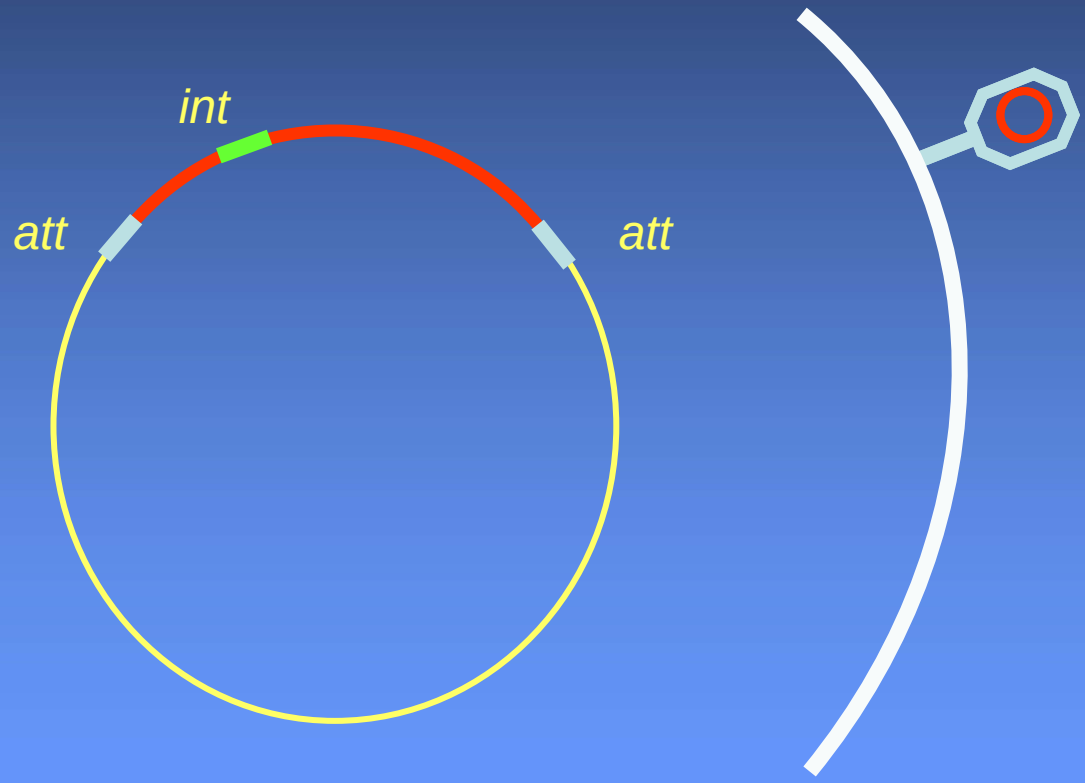
Moving Genes Around

The example of SaPI1

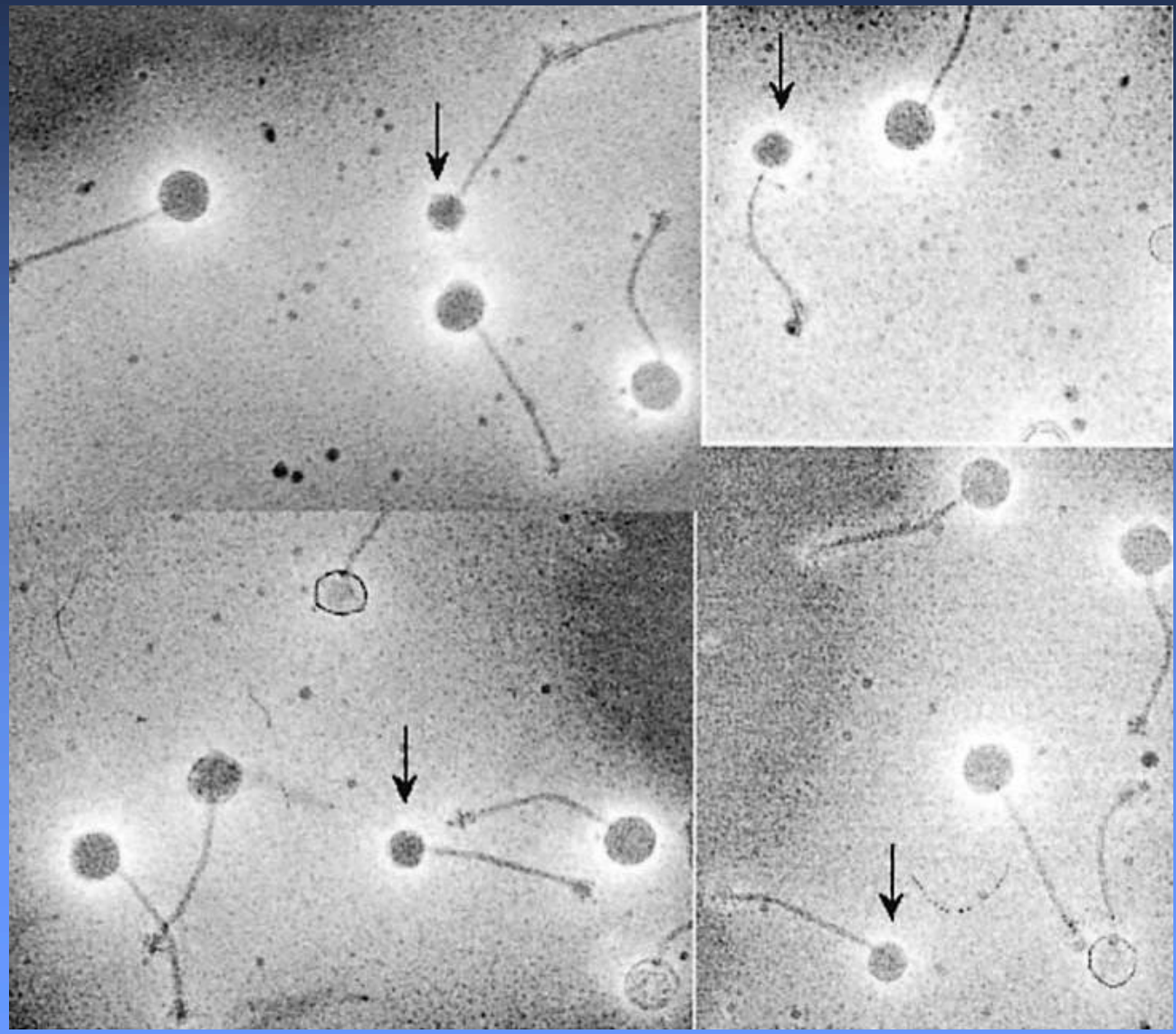


Moving Genes Around

The example of SaPI1



Moving SaPI1 with Phage 80α

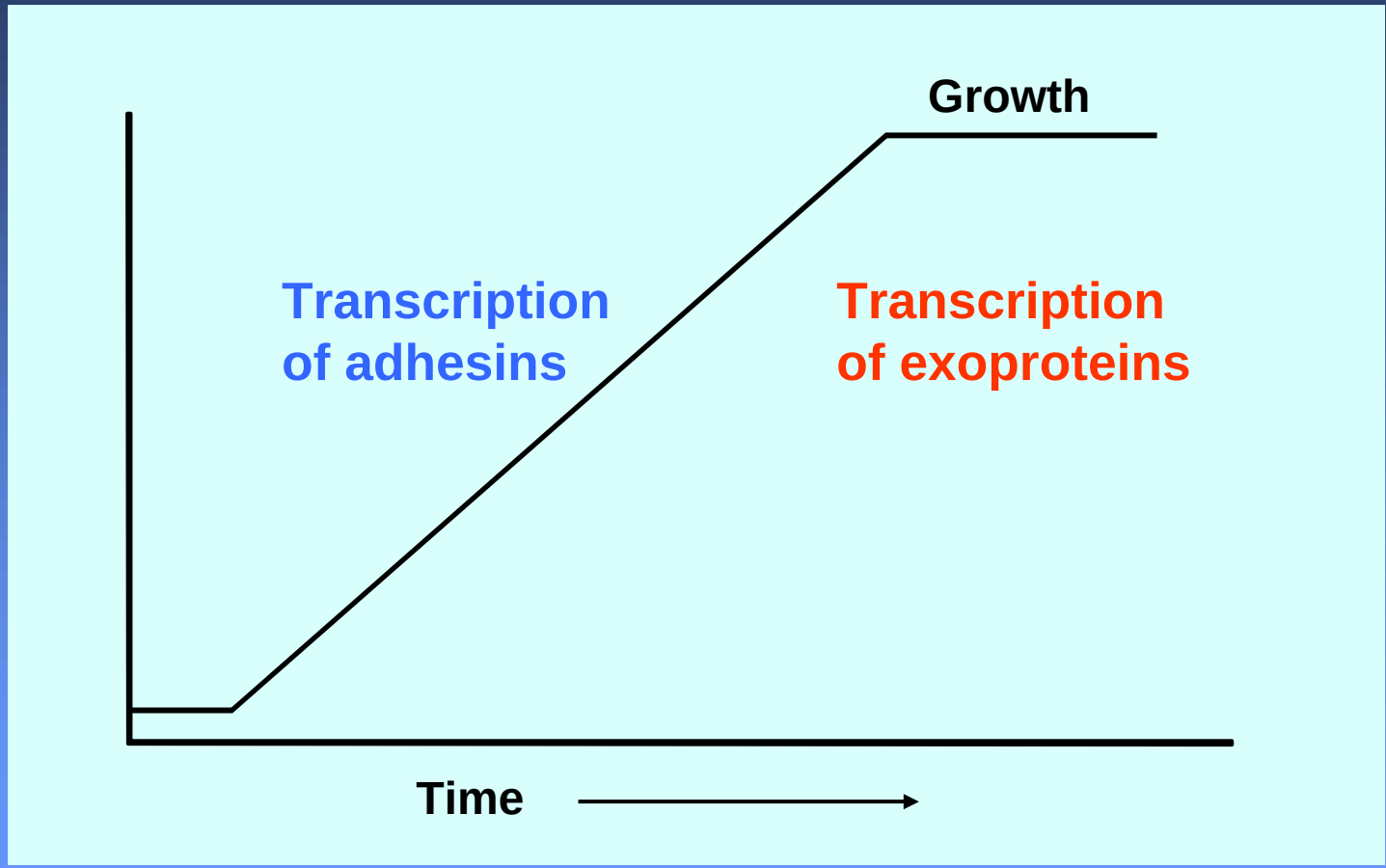


Novick, Schlievert, Ruzin. Microbes and Infect 2001; 3:585

***Staphylococcus aureus* Pathogenesis**

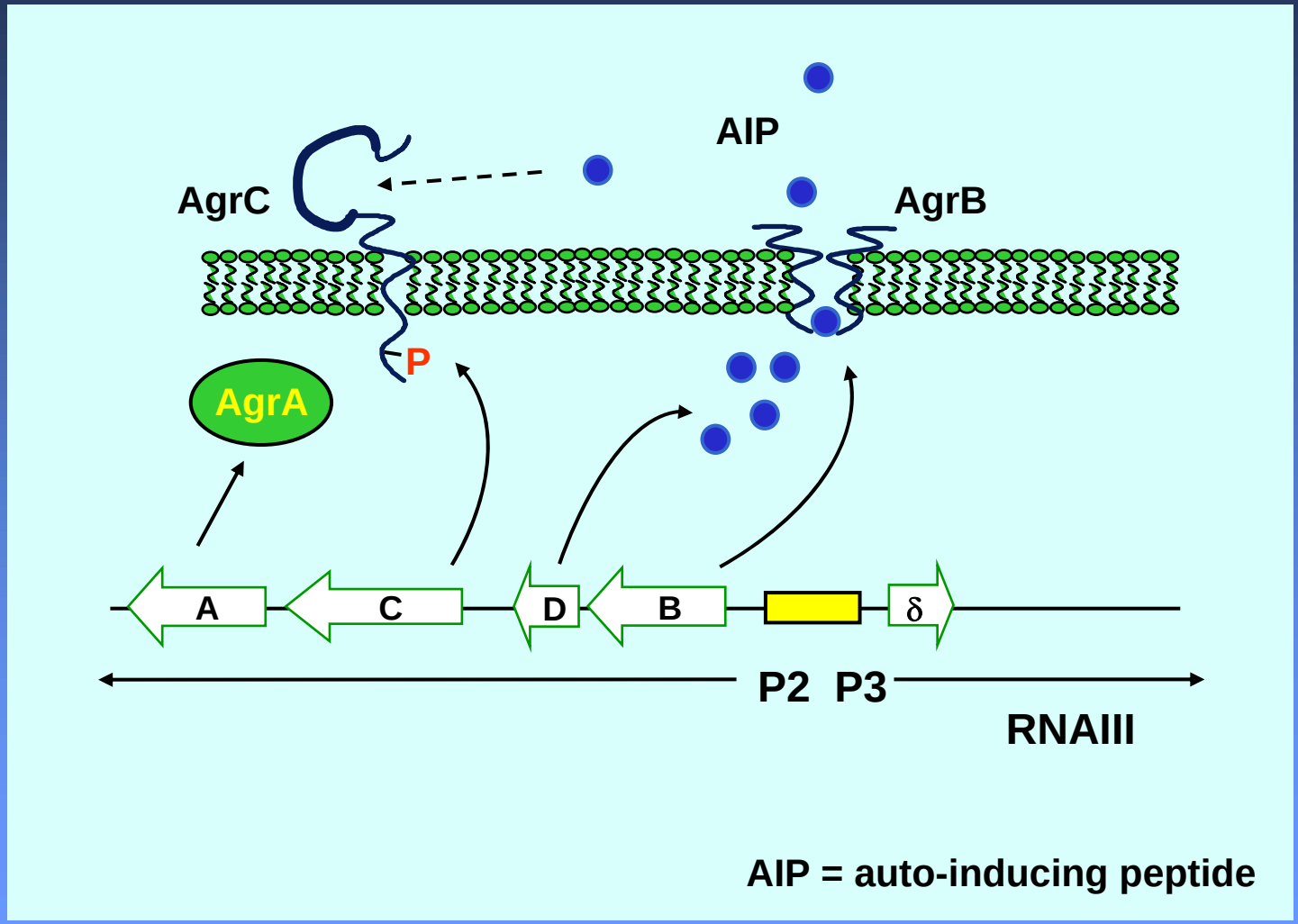
- **Gene exchanges**
- **Gene regulation**
- **Gene products**
- **Gene product cooperation**

agr-Regulation of Virulence Determinants During in vitro Growth of S. aureus (1)



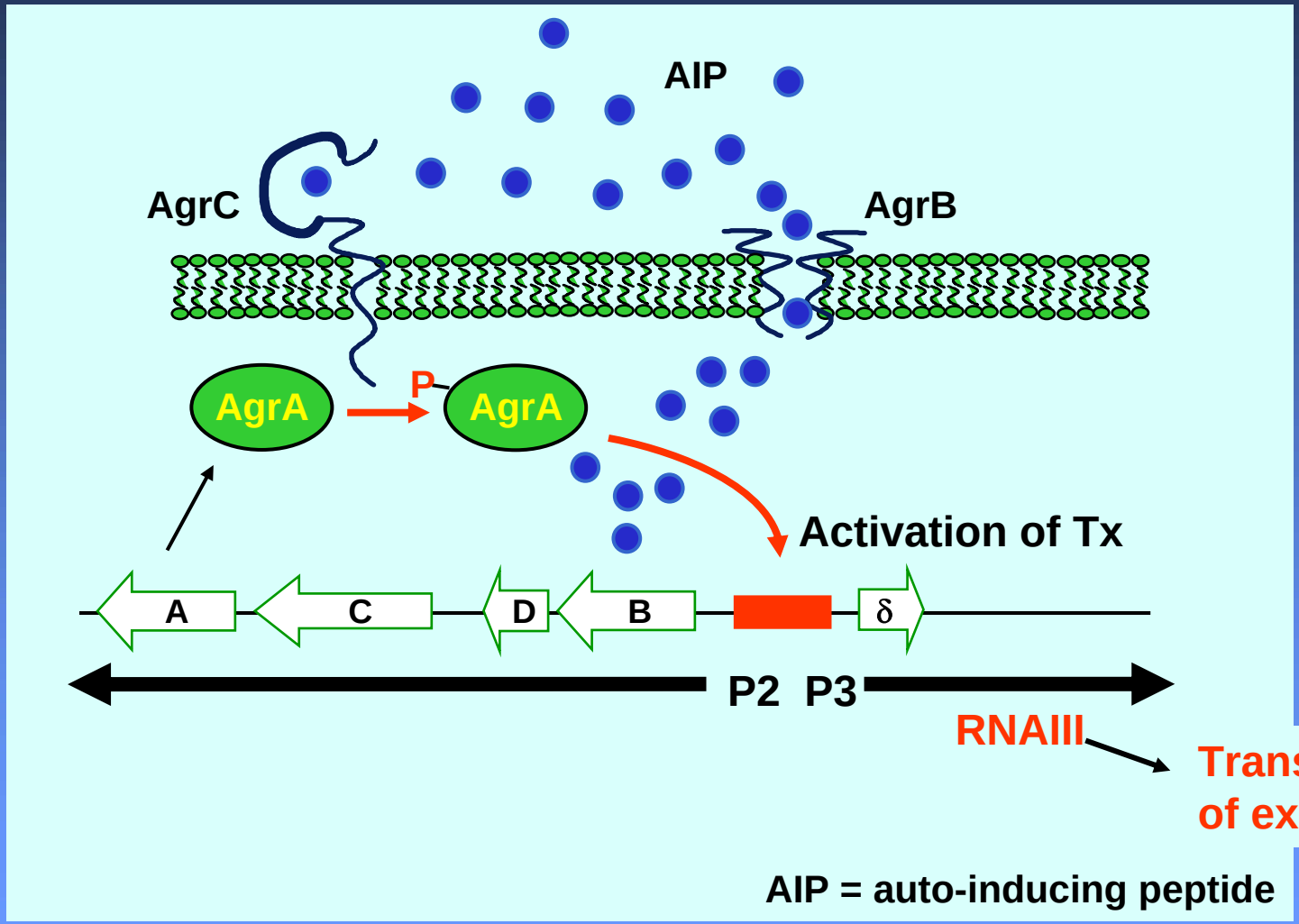
Adapted from R.P. Novick ASM press, 2000

Virulence Gene Regulation by Peptides in S. aureus (1)



Novick et al. Curr. Op. Microbiol. 1999;2:40-45

Virulence Gene Regulation by Peptides in S. aureus (2)



Novick et al. Curr. Op. Microbiol. 1999;2:40-45

Regulation of S. aureus super-antigens

			Action of regulatory genes						
Gene	Product	Activity/function	*agr*	*Sae-RS*	*rot*	*sarA*	*sarS*	*sarT*	*tst*
Superantigens									
sea	Enterotoxin A	Food poisoning, TSS	0						0
seb	Enterotoxin B	Food poisoning, TSS	+			b			-
sec	Enterotoxin C	Food poisoning, TSS	+						
sed	Enterotoxin D	Food poisoning, TSS	+						
eta	Exfoliatin A	Scalded skin syndrome	+						
etb	Exfoliatin B	Scalded skin syndrome	+						
tst	Toxic shock toxin-1	Toxic shock syndrome	+	-		b			-

0, no effect of gene on expression; +, upregulated; -, downregulated.
b. Controversial.

Conditions for Developing Toxic Shock Syndrome

Host:

- Lack of anti-TSST antibodies

Environment:

- High protein concentration
- Neutral pH
- High pCO_2
- High pO_2

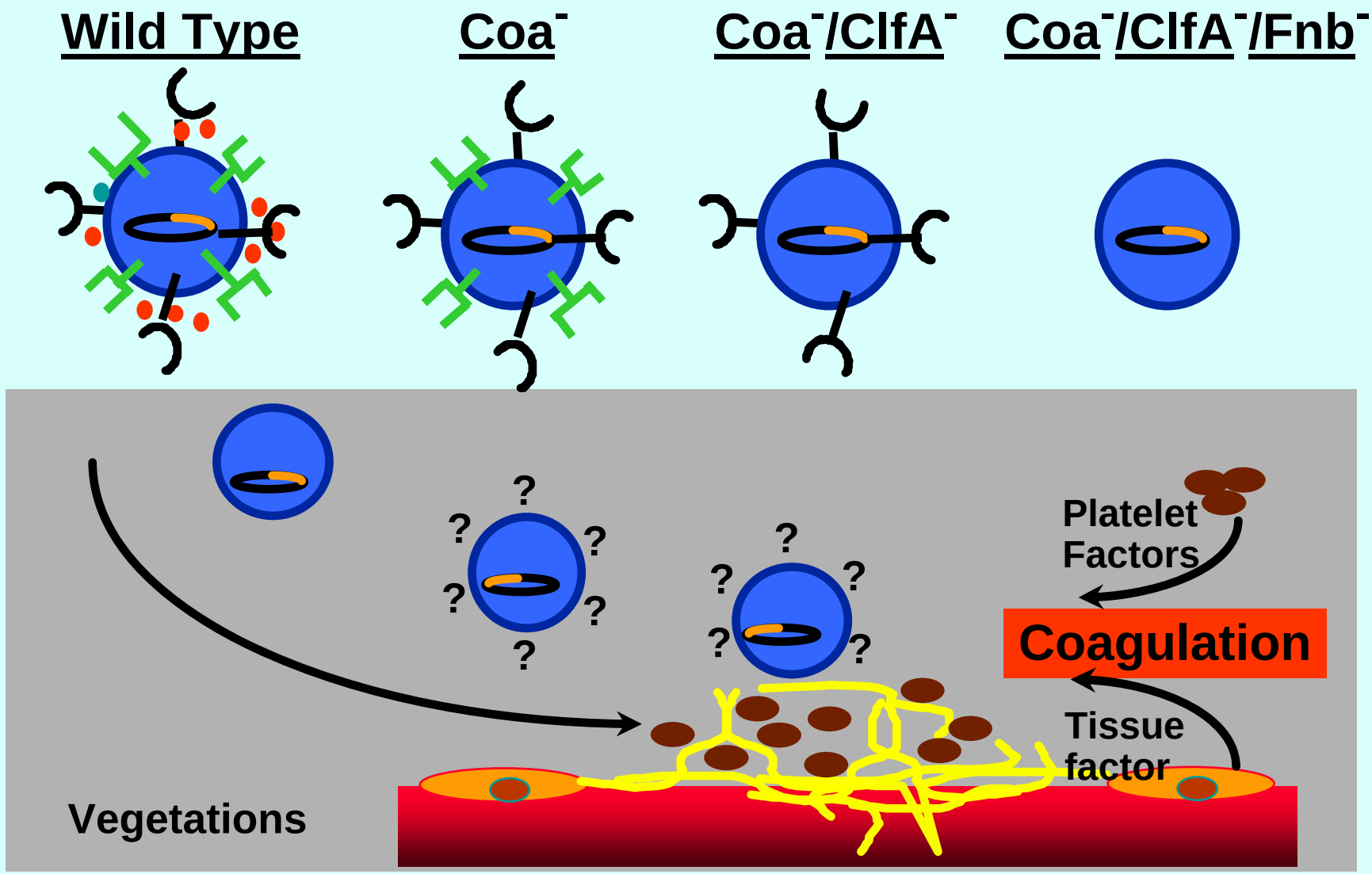
Altered Ecology !

***Staphylococcus aureus* Pathogenesis**

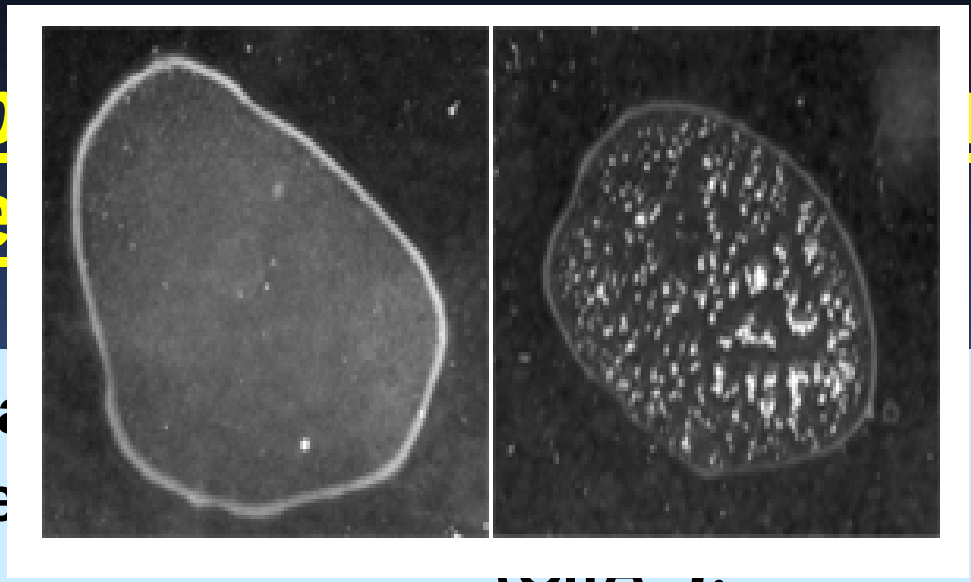
- **Gene exchanges**
- **Gene regulation**
- **Gene products**
- **Gene product cooperation**

Gene	Protein	Function	Implication in disease
spa	Protein A	Binds Fc fragment	Sepsis, osteoarthritis
clfA	Clumping factor A	Binding to fibrinogen	Endocarditis
clfB	Clumping factor B	Binding to fibrinogen	-
cna	Collagen binding protein	Binding to collagen	Osteomyelitis
fnA	Fn-binding protein A	Binding to fibronectin	Endocarditis, persistence
fnB	Fn-binding protein B	Binding to fibronectin	-
sdrC	Serine-aspartate repeat prot	Binding to fibrinogen	-
sdrD	Serine-aspartate repeat prot	Binding to fibrinogen ?	-
sdrE	Serine-aspartate repeat prot	Binding to fibrinogen ?	-
pls	Plasmin-sensitive protein	Binding to nasal mucosa	Nasal colonization?
fmtB	Methicillin resistance	Putative cell-wall building	Expression of methi-R
sasA	*S. aureus* surface protein A	Undetermined	-
sasB	*S. aureus* surface protein B	Undetermined	-
sasC	*S. aureus* surface protein C	Undetermined	-
sasE	*S. aureus* surface protein E	Undetermined	-
sasF	*S. aureus* surface protein F	Undetermined	-
sasG	*S. aureus* surface protein G	Binding to nasal mucosa	Invasive disease
sasH	*S. aureus* surface protein H	Undetermined	Invasive disease
sasI	*S. aureus* surface protein I	Undetermined	-
sasJ	*S. aureus* surface protein J	Undetermined	-
sasK	*S. aureus* surface protein K	Undetermined	-

Understanding Pathogenic Factors

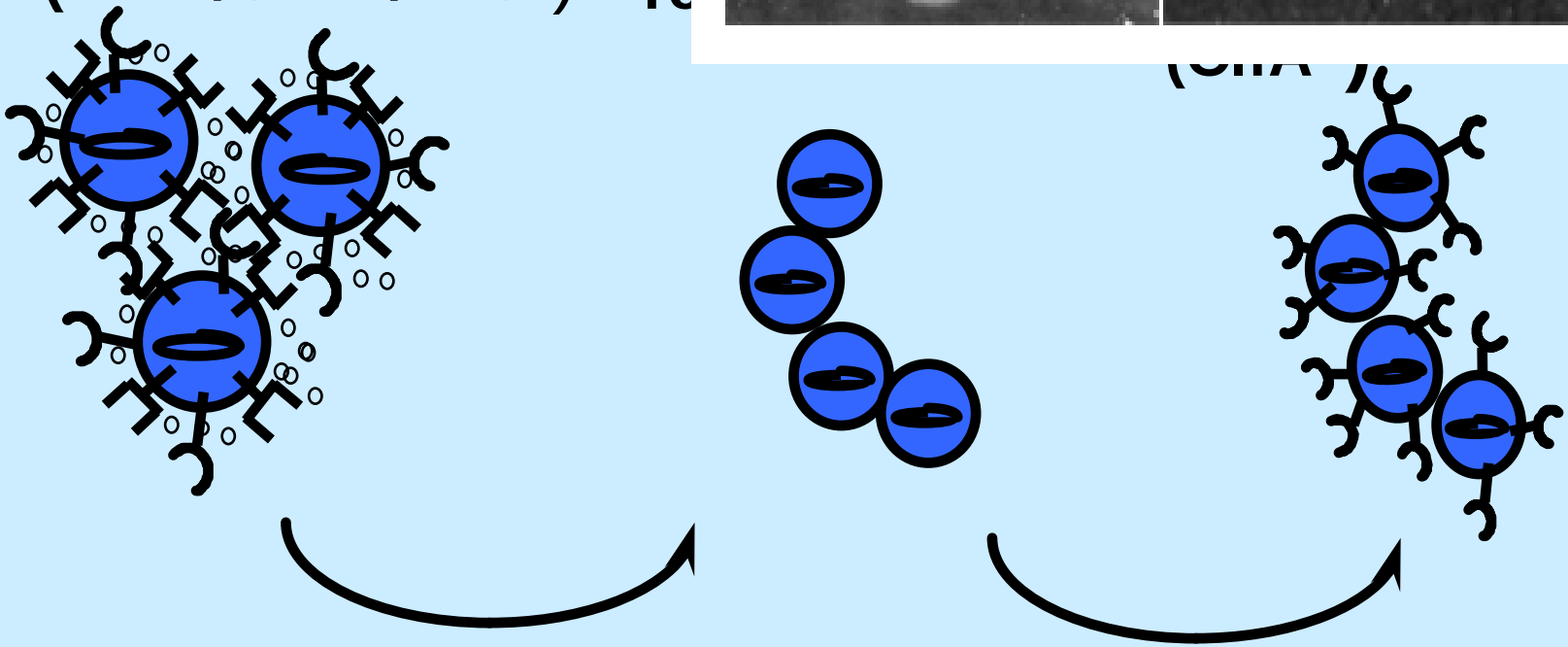


Transfer or Stap… …ic genes into le…



S. aureus donor (Coa$^+$/ClfA$^+$/Fnb$^+$)

La… re…

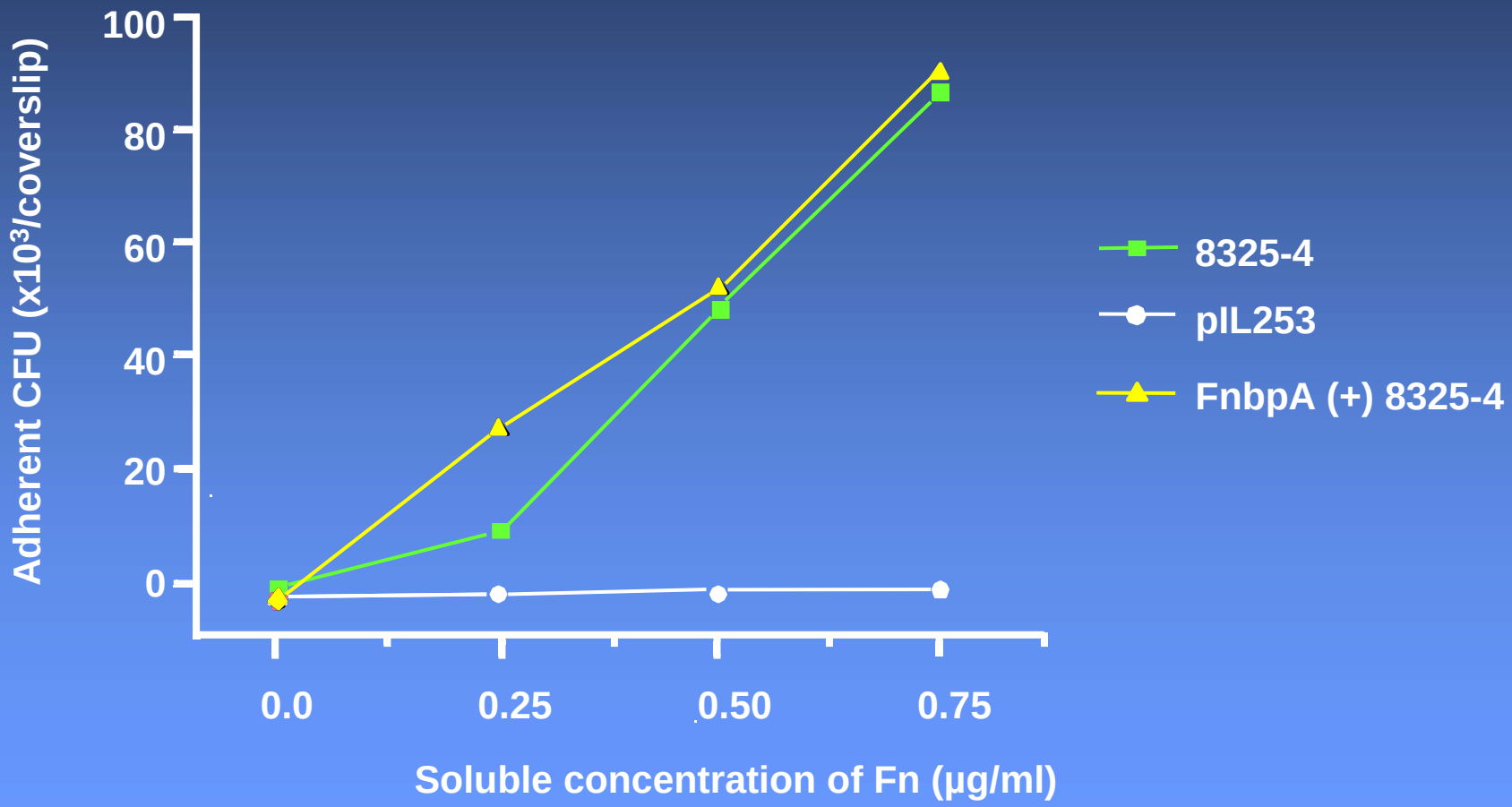


1: Transfer of *S.aureus clfA* gene into viridans group streptococcus

2: Select clumping-positive recombinants

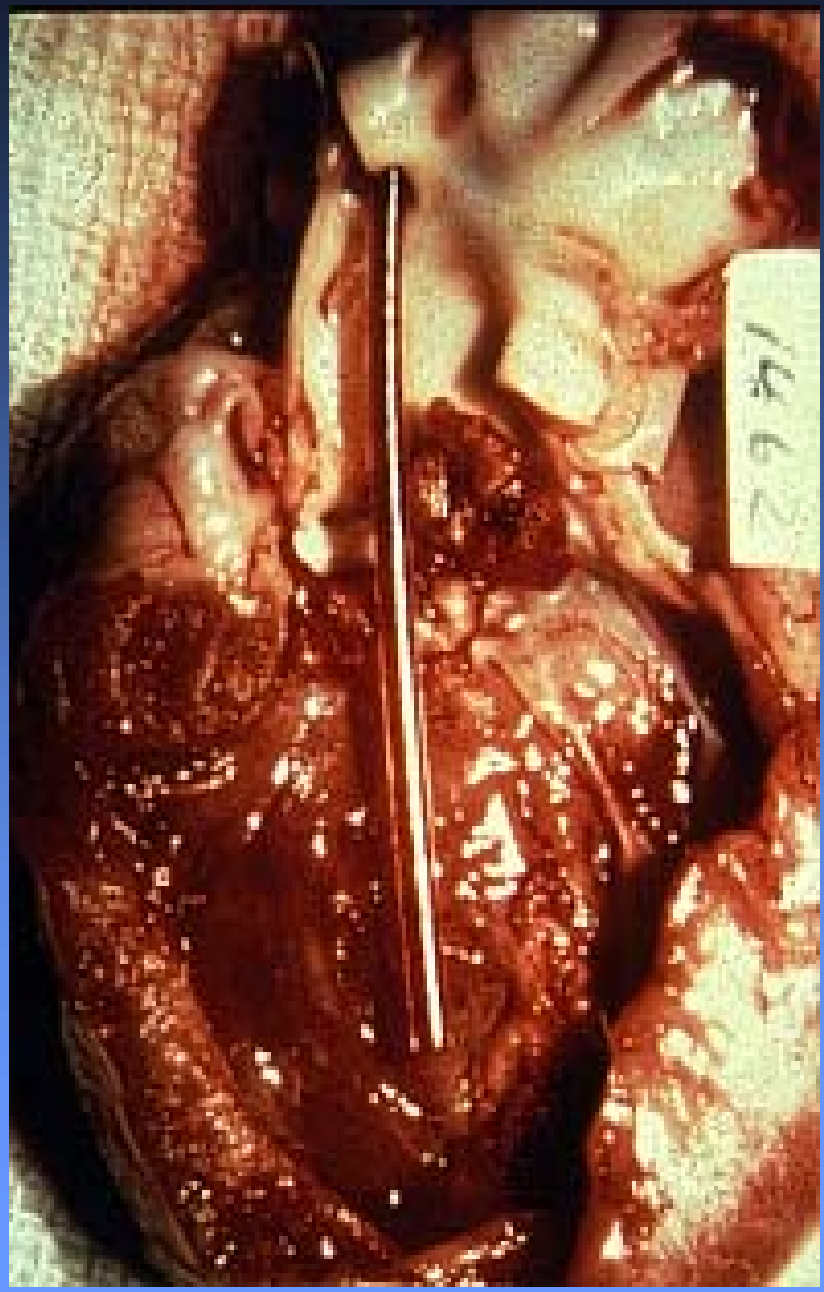
Que et al. I&I 2000; 68:3516-22

Adherence of L. lactis to PMMA coverslips coated with fibronectin

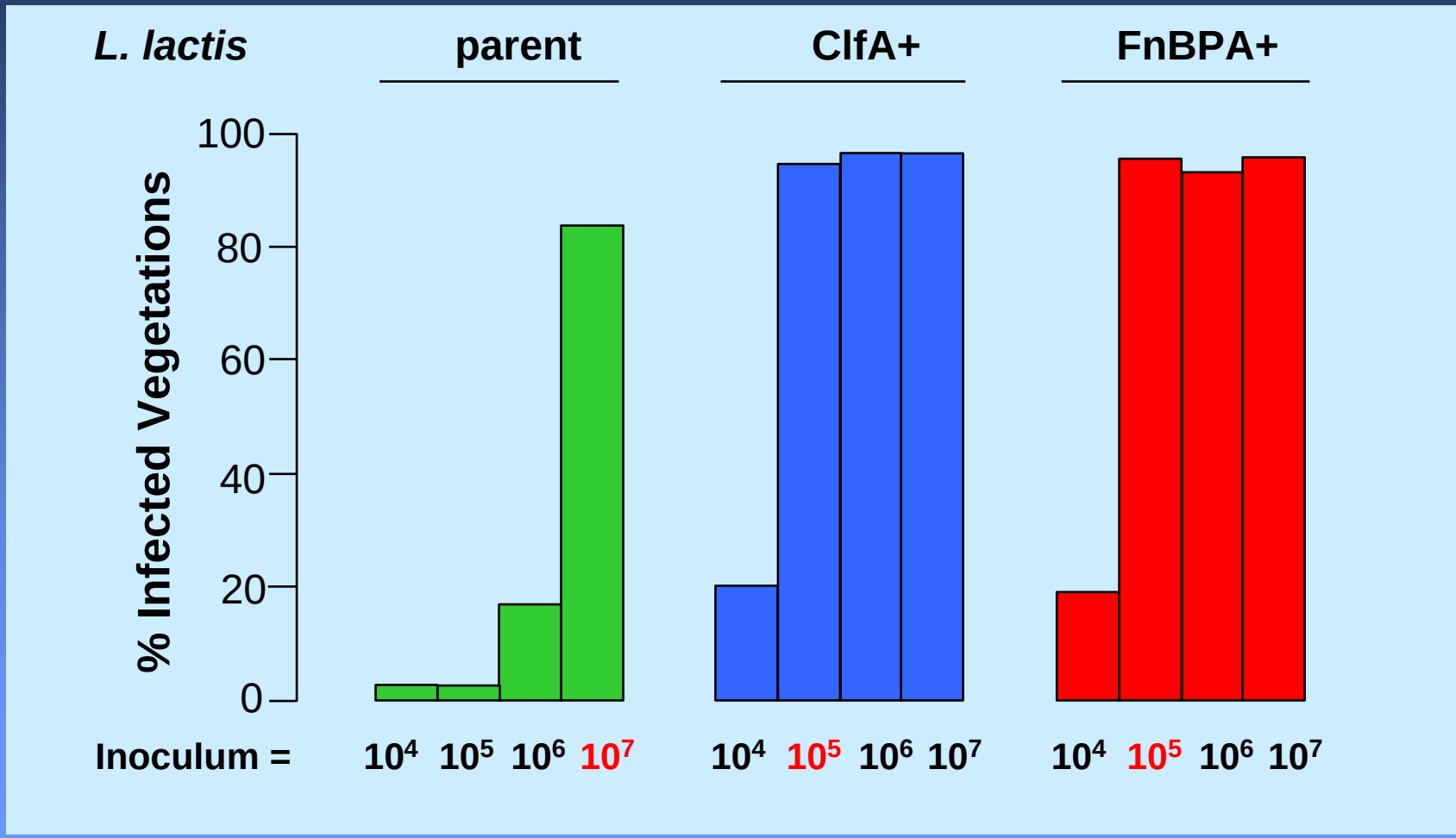


Que et al, I&I 2001; 69:6296-302

Experimental Endocarditis

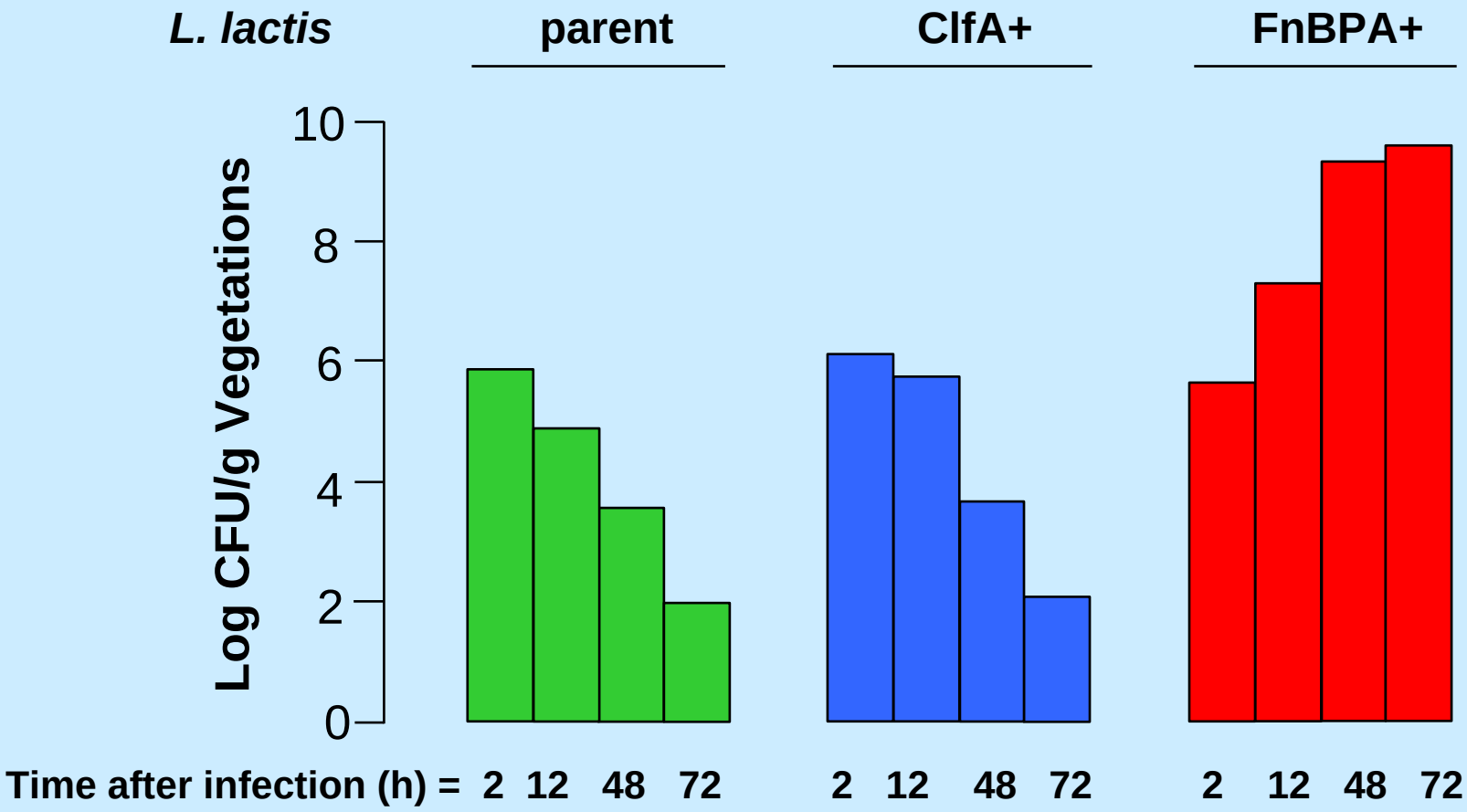


Infectivity of L. lactis Recombinants Binding to Fibrinogen or Fibronectin



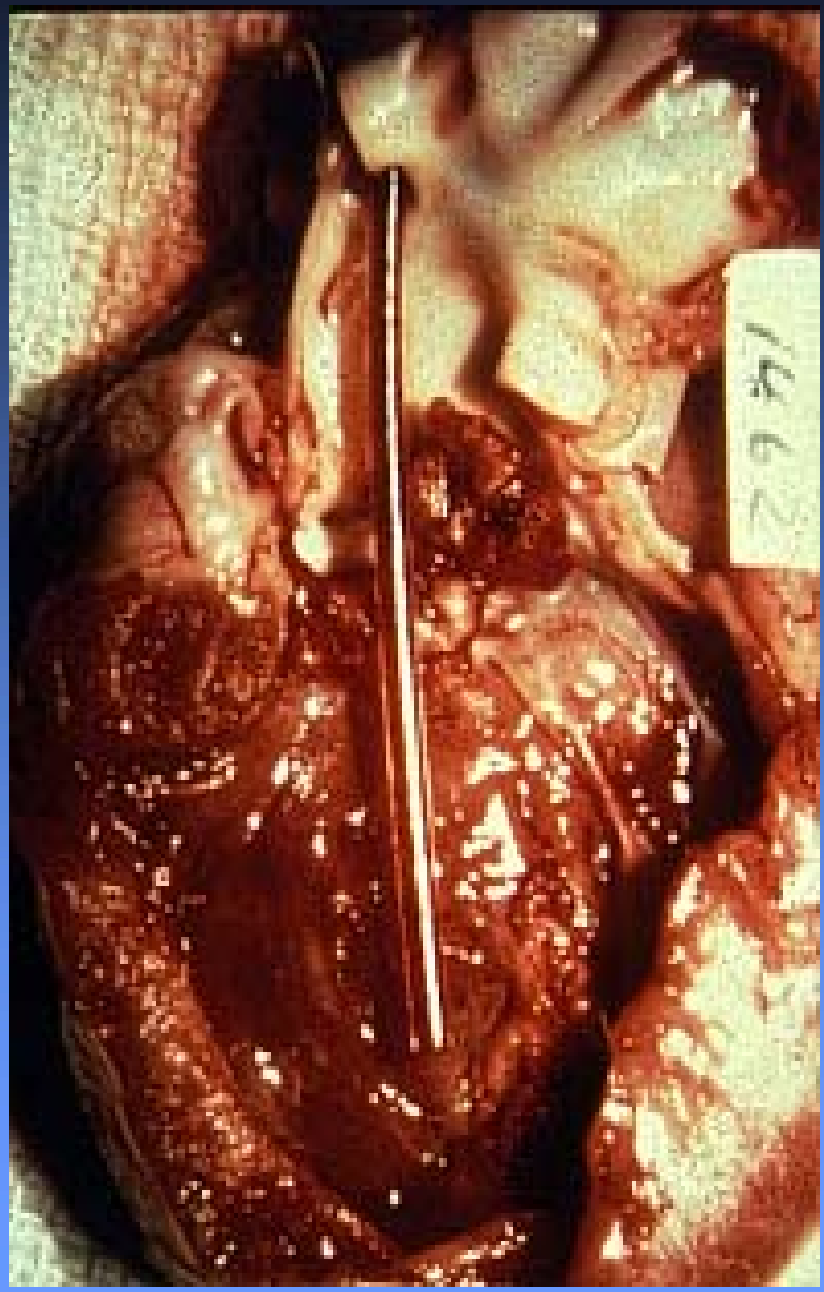
Que et al. Infect. Immun. 2001

Dynamic of L. lactis Endocarditis

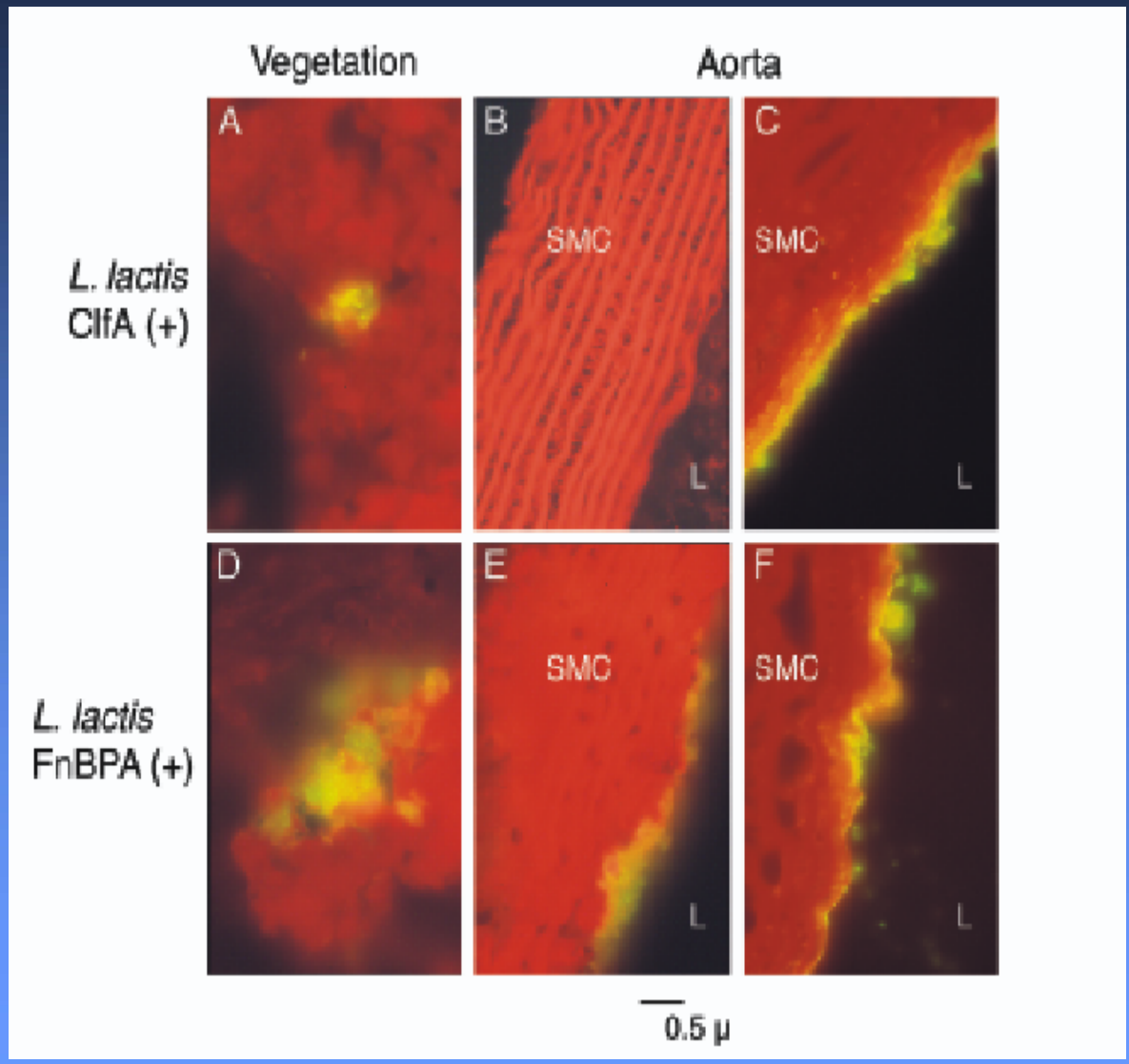


Que et al. J. Exp. Med . 2005

Experimental Endocarditis

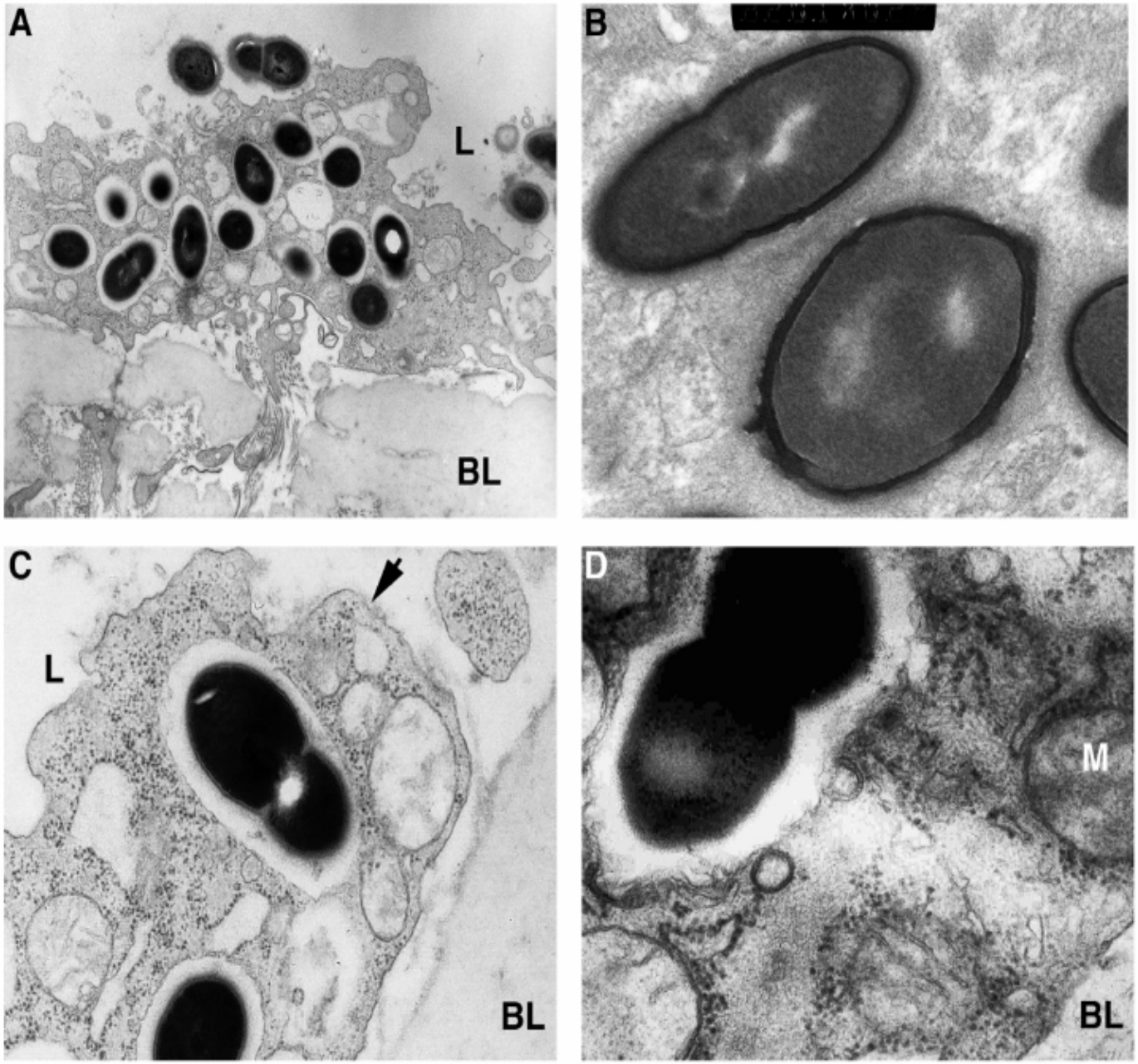


Neighboring Aorta of Valves Infected with ClfA-positive Lactococci /Gram Stain



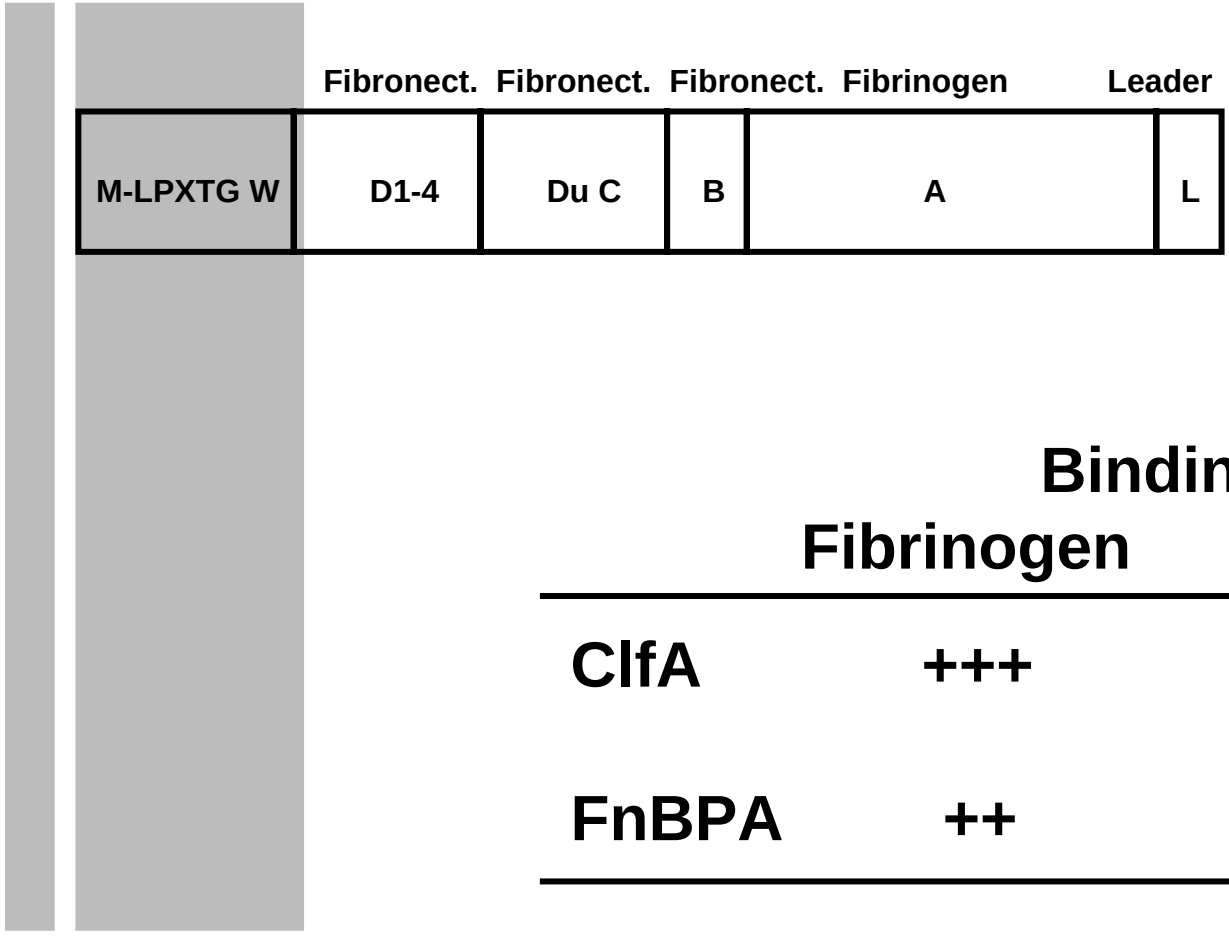
Que YA, J. Exp. Med 2005;201:1627

L. lactis FnBPA (+)



Que YA, J. Exp. Med 2005;201:1627

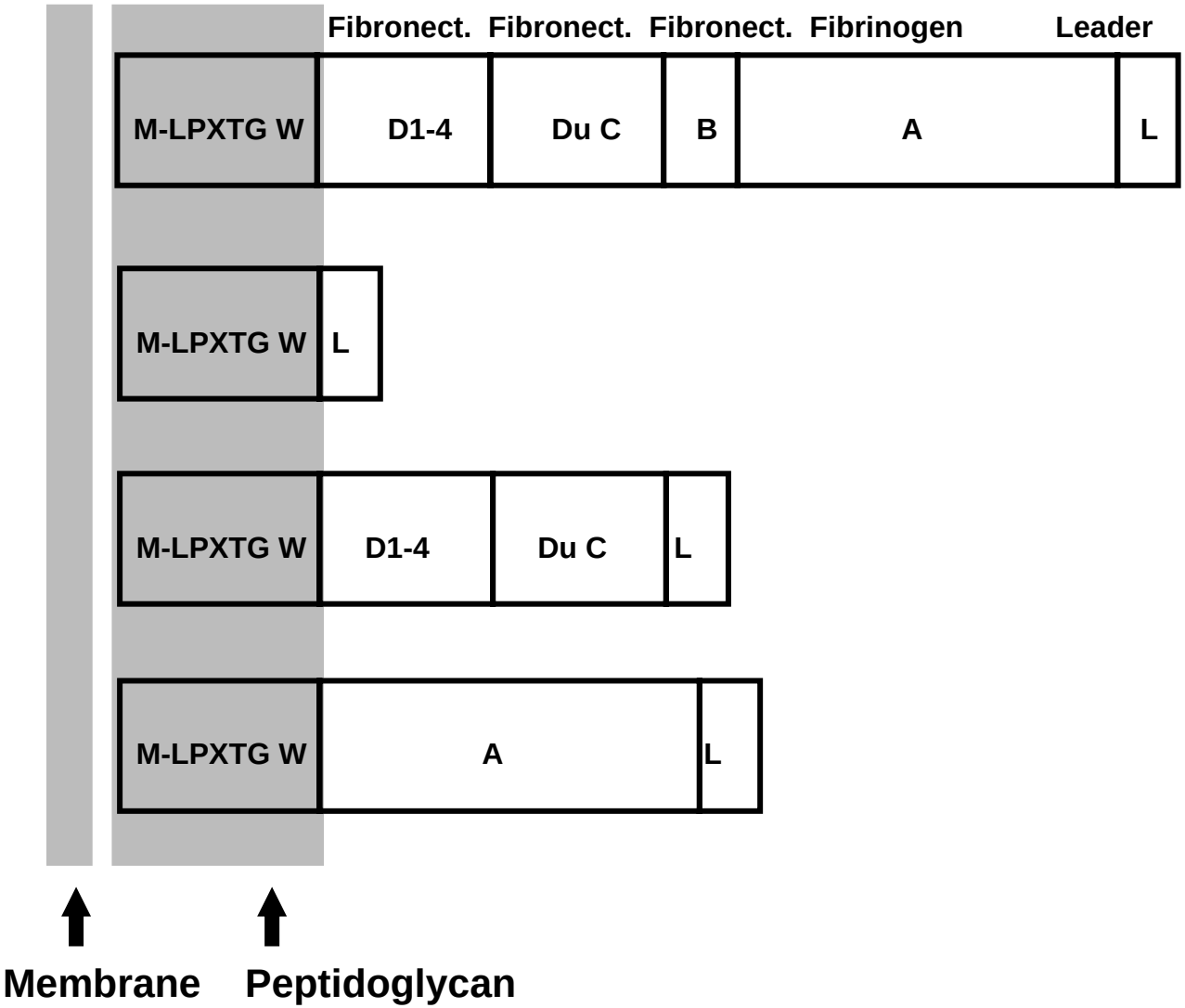
Binding Domains of FnBPA



	Binding to Fibrinogen	Binding to Fibonectin
ClfA	+++	-
FnBPA	++	+++

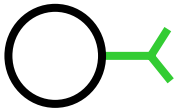
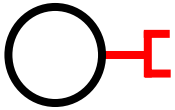
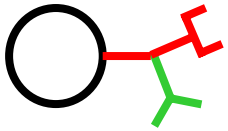
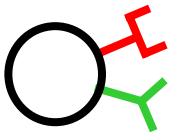
Que YA, J. Exp. Med 2005;201:1627 and Piroth et al. 2007, submitted

Binding Domains of FnBPA



Que YA, J. Exp. Med 2005;201:1627 and Piroth et al. 2007, submitted

Binding Domains of FnBPA

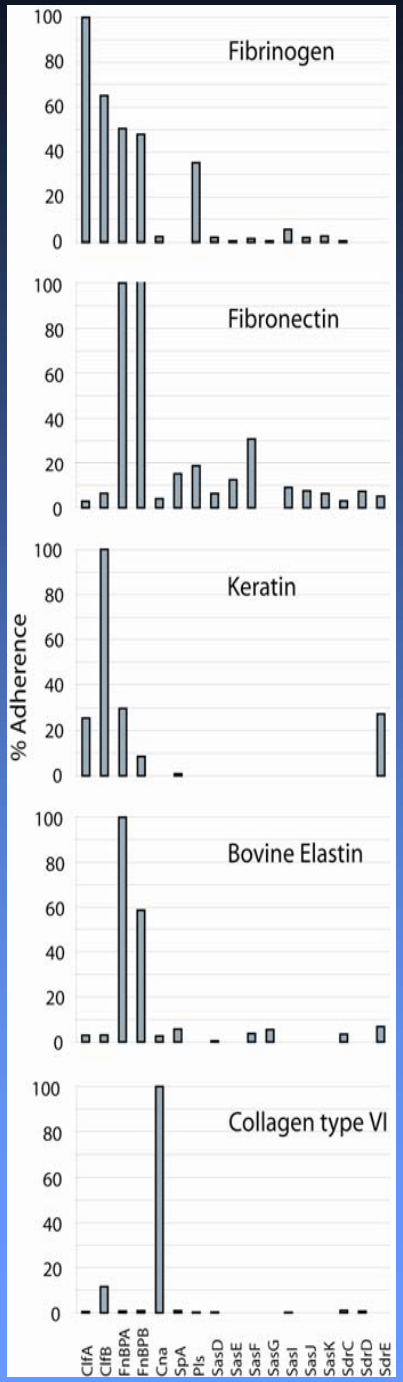
Surrogate recombinant	Binding	Infection	Internalization	Persistence
	Fg	+++	---	---
	Fn	---	+++	---
	*cis* Fn/Fg	+++	+++	+++
	*trans* Fn/Fg	+++	+++	+++

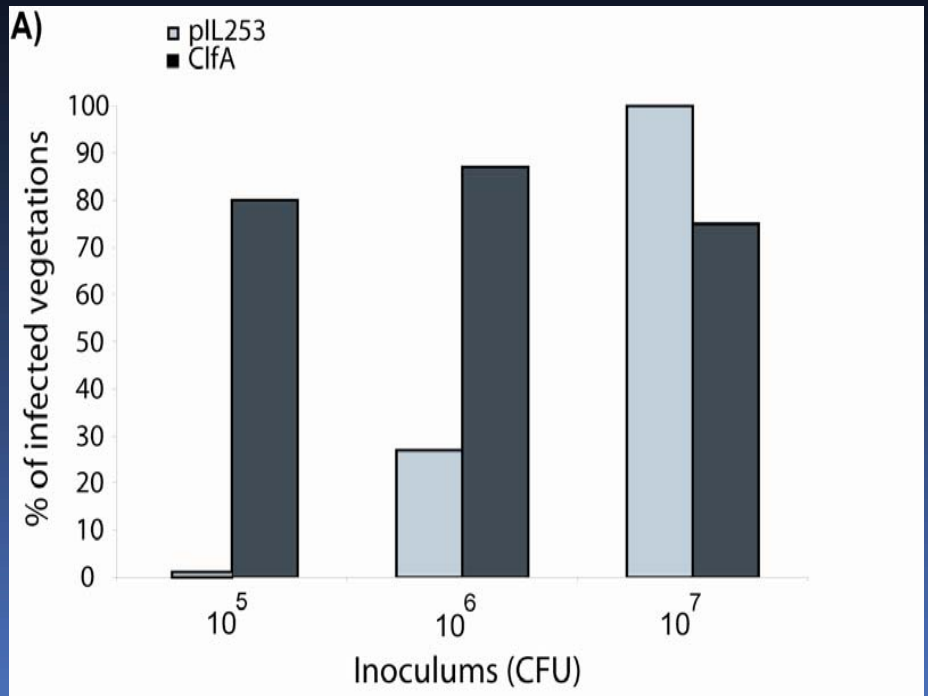
Que YA, J. Exp. Med 2005;201:1627 and Piroth et al. 2007, submitted

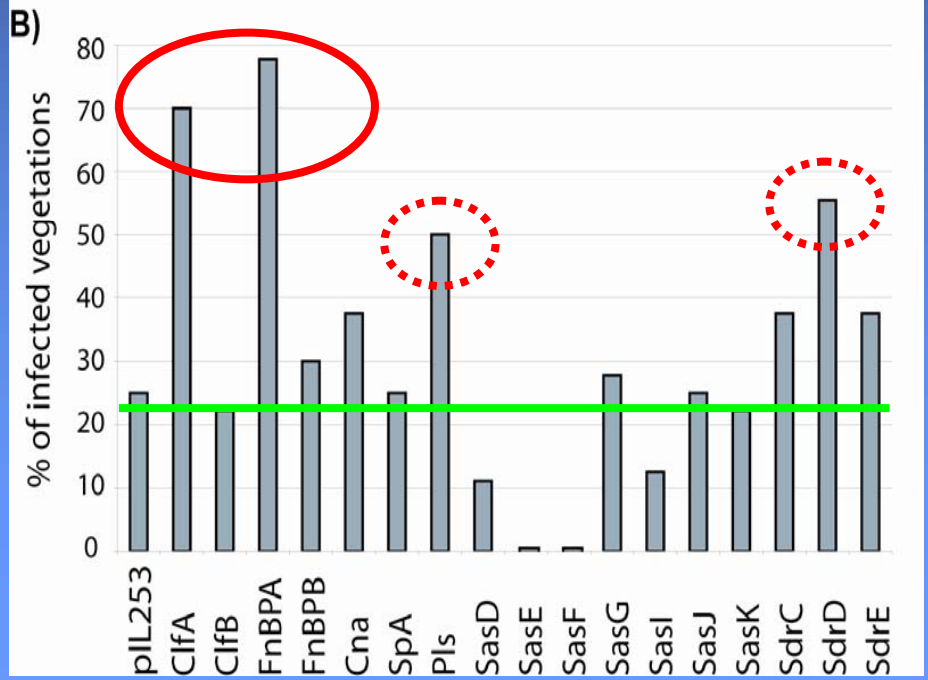
- *S. aureus* needs both fibrinogen- and fibronectin-binding domains to be fully infective

- Fibronectin-binding protein represents an example of *intra-molecular* domain cooperation

- Fibronectin- and fibrinogen-binding represent an example of *inter-molecular* domain cooperation

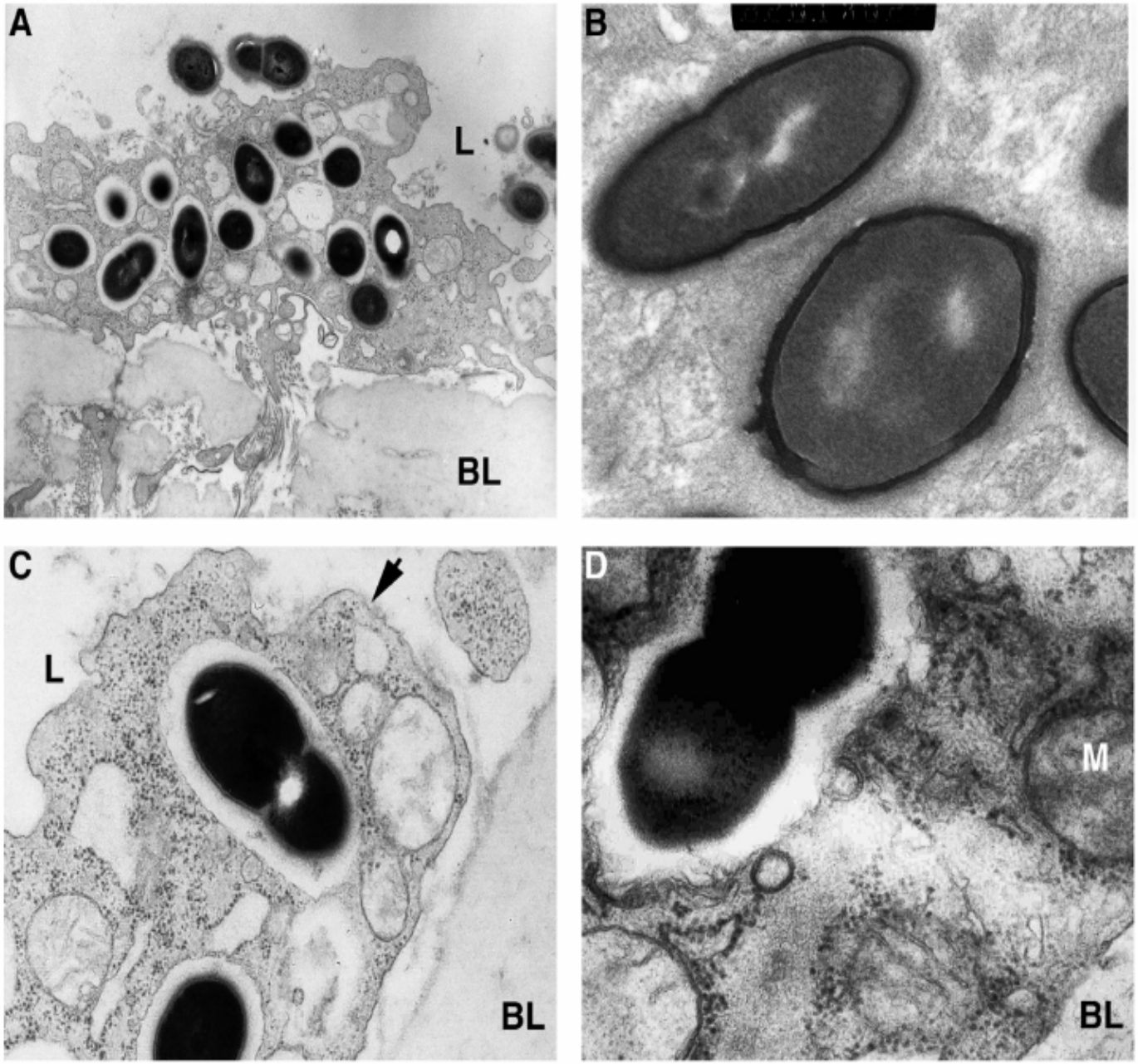






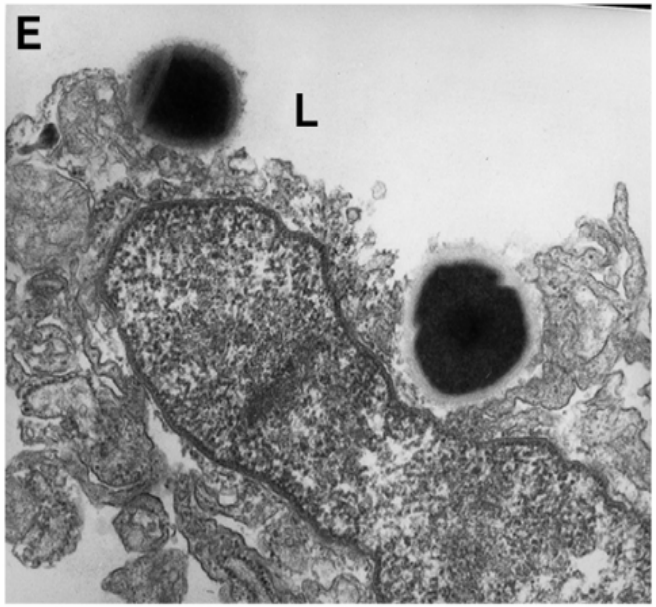
E. Widmer et al. I&I , submitted

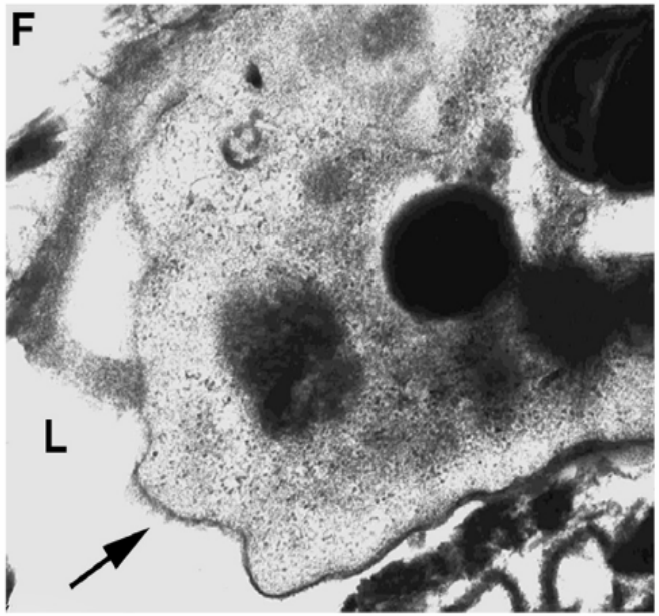
L. lactis FnBPA (+)

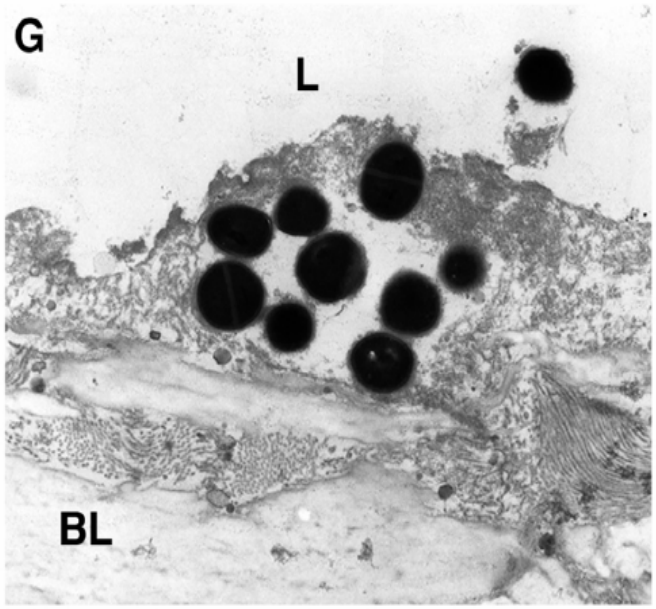


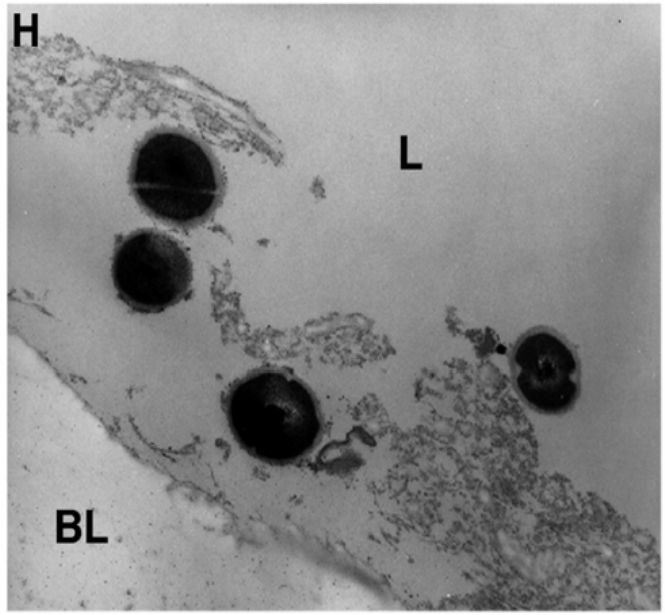
Que YA, J. Exp. Med 2005;201:1627

S. aureus Cowan

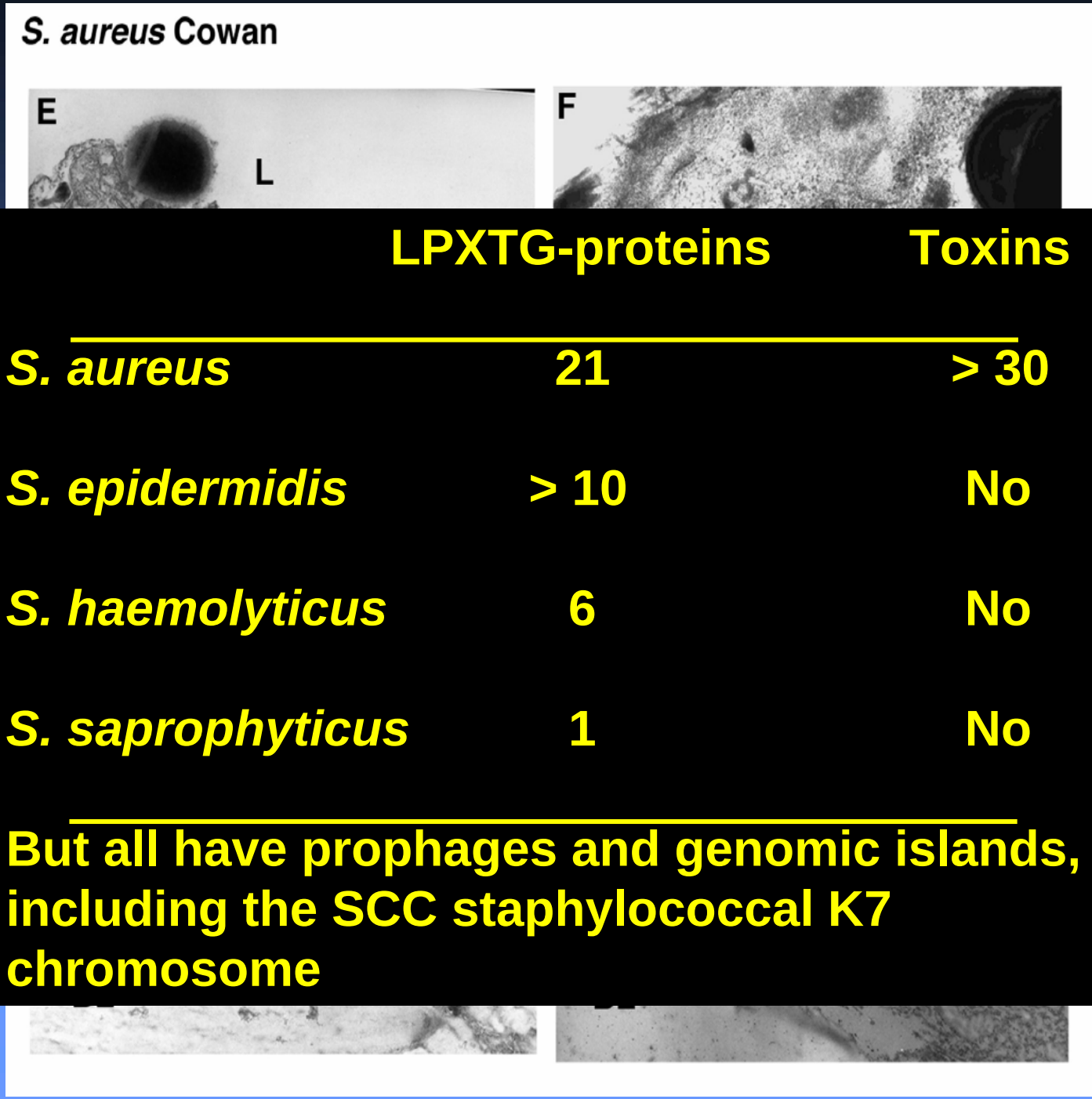








Que YA, J. Exp. Med 2005;201:1627



	LPXTG-proteins	Toxins
S. aureus	21	> 30
S. epidermidis	> 10	No
S. haemolyticus	6	No
S. saprophyticus	1	No

But all have prophages and genomic islands, including the SCC staphylococcal K7 chromosome

Que YA, J. Exp. Med 2005;201:1627

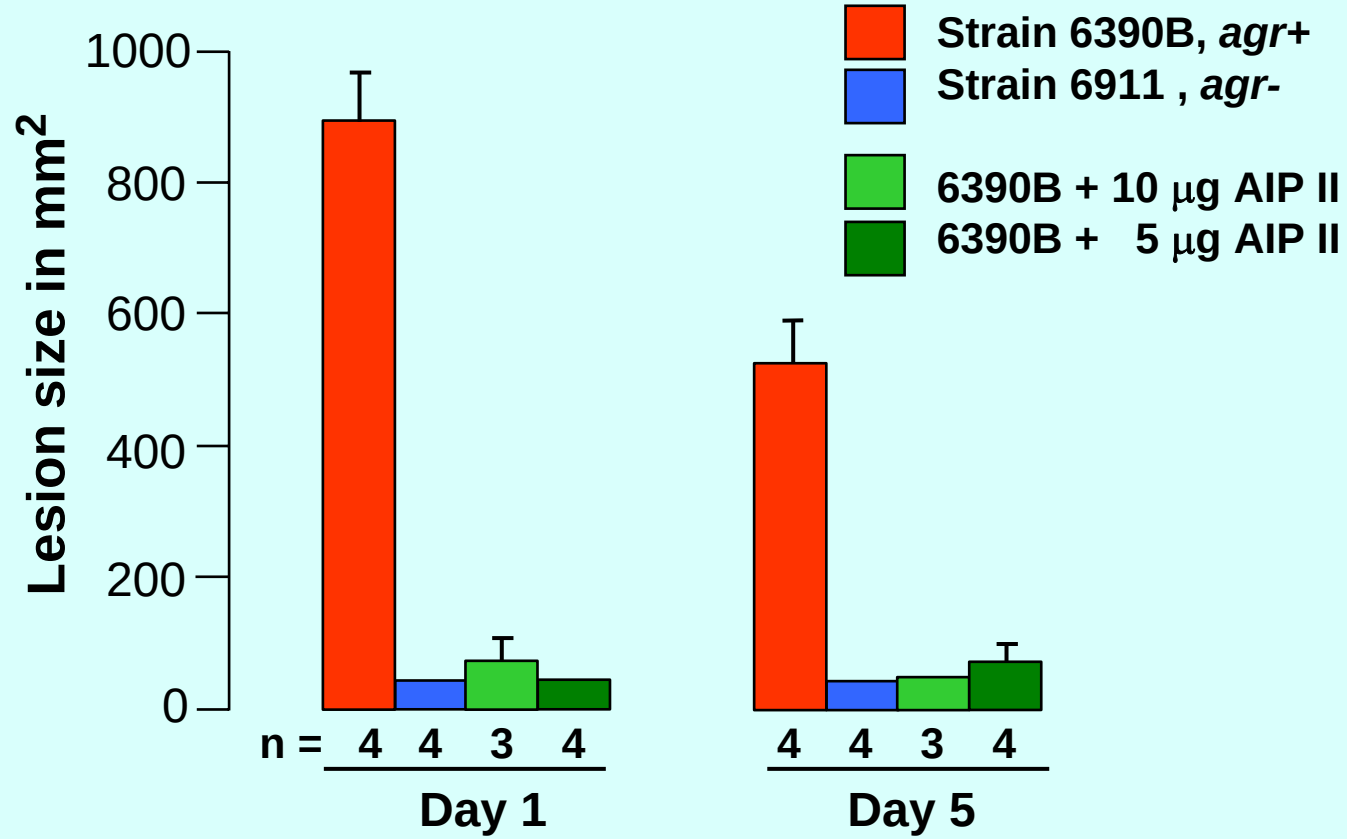
Staphylooccus aureus

a paradigm of host-parasite evolution

N. Widmer
M. Giddey
J. Entenza
S. Piu
J. Vouillamoz

YA Que
L Piroth
CA. Roten
L. Guy
F. Collyn

Subcutaneous Infection of Mice with 10^8 CFU of AIP I *S. aureus* supplemented or not with AIP II



Mayville et al. PNAS 1999; 96:1218-1223

Is agr a Virulence Factor ?

- No, not *sensu stricto*

- All *Staphylococcus* spp. carry an *agr*

- *agr* is also required for regulation of house-keeping genes