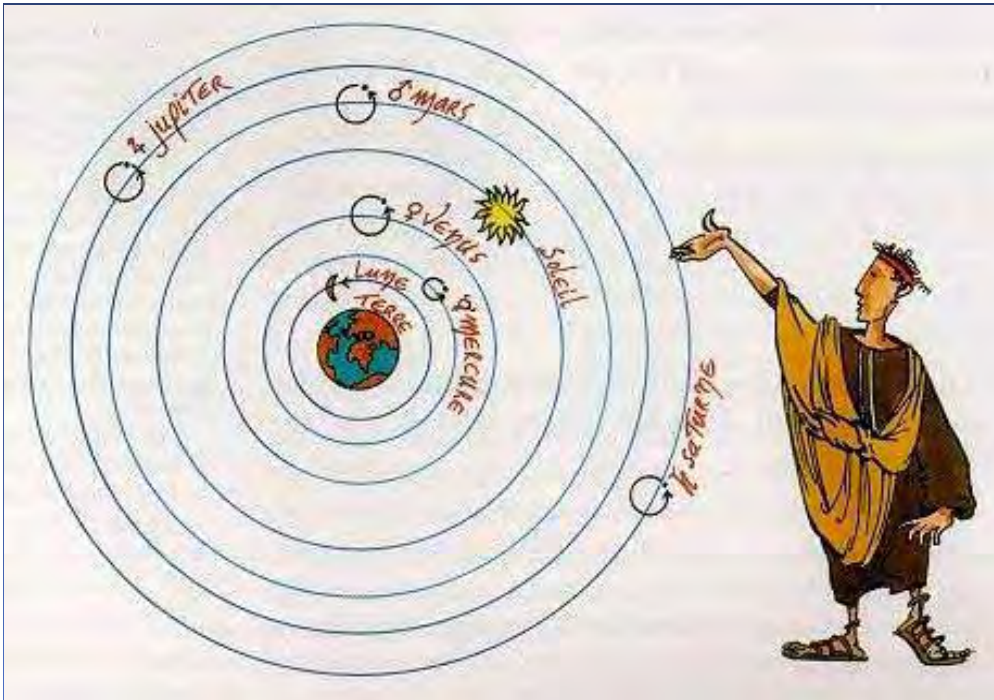


Recherche

Appliquée - Fondamentale



Ptolémée - 3000 avant JC

Copernic - 1472 - 1543

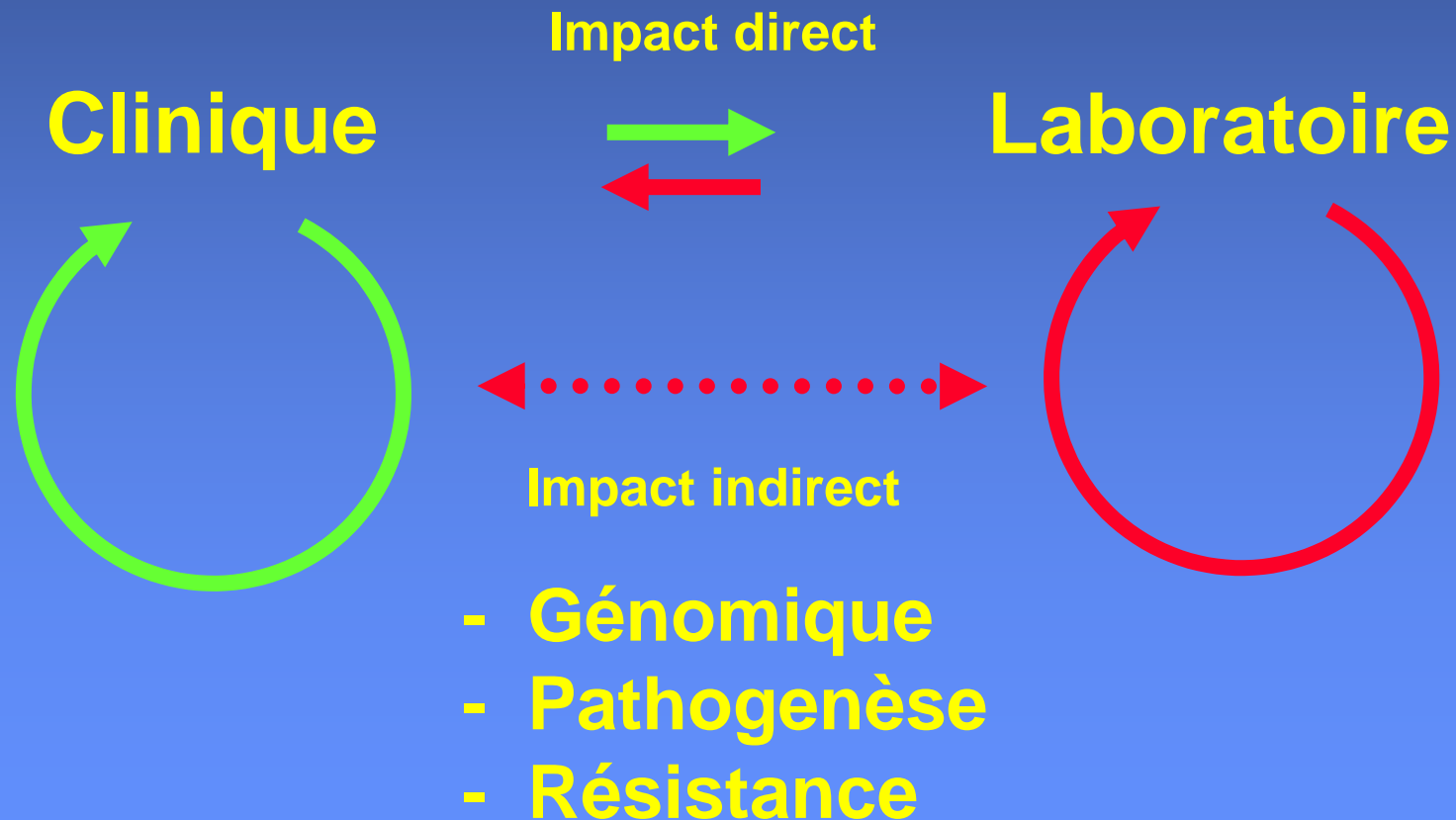


Recherche

Appliquée - Fondamentale

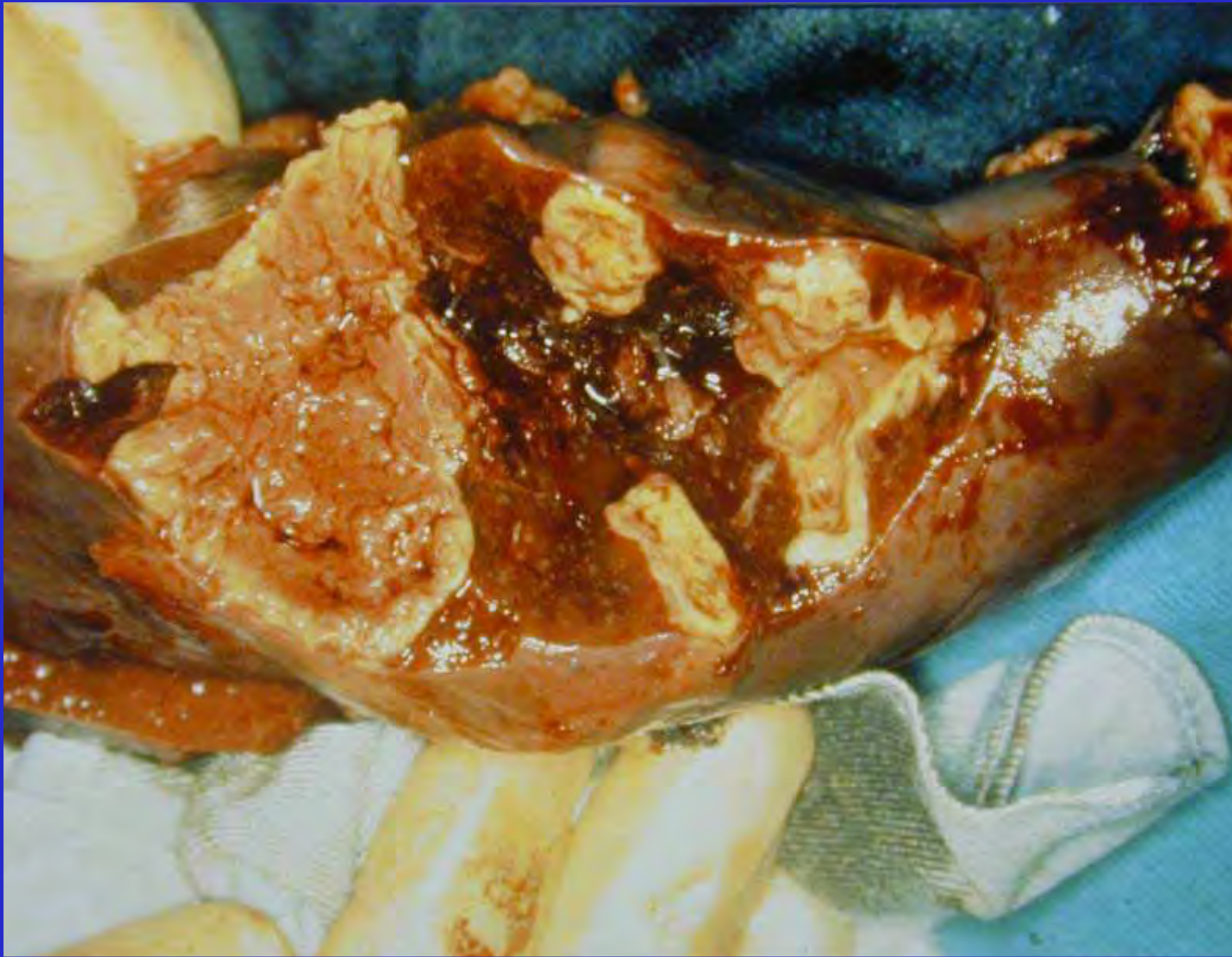
Médicale - Biologique

Dialogue entre le Clinicien et le Chercheur L'exemple des Staphylocoques dorés



Some Staphylococcal Species from Mammals

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



S. aureus
Scalded-Skin
Syndrome due
to Phage Type
71 Encoded
Toxin

*Adapted from Infect. Dis. Atlas,
Pfizer 1995*



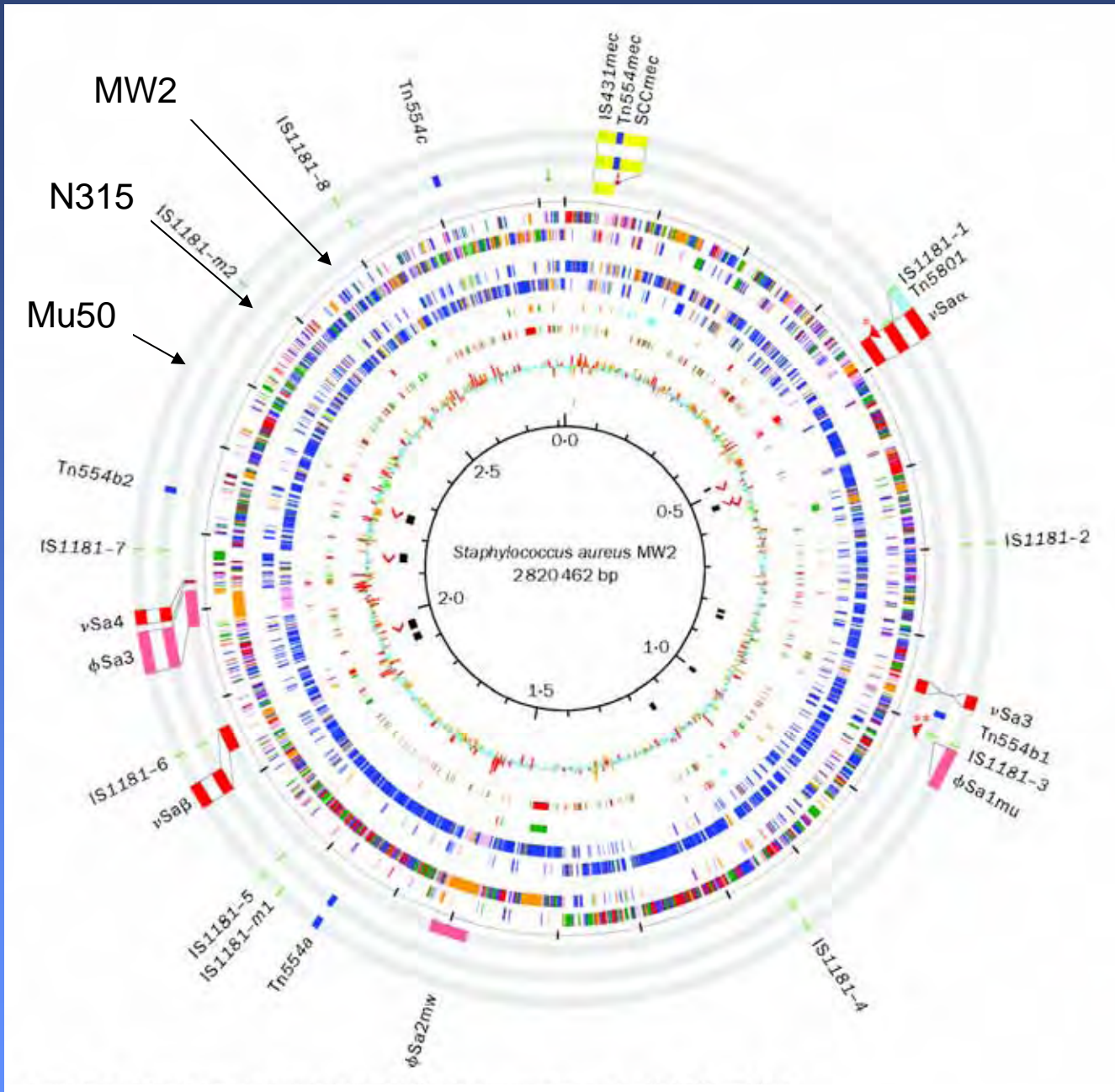
The Staphylococcal Toxic Shock Syndrome



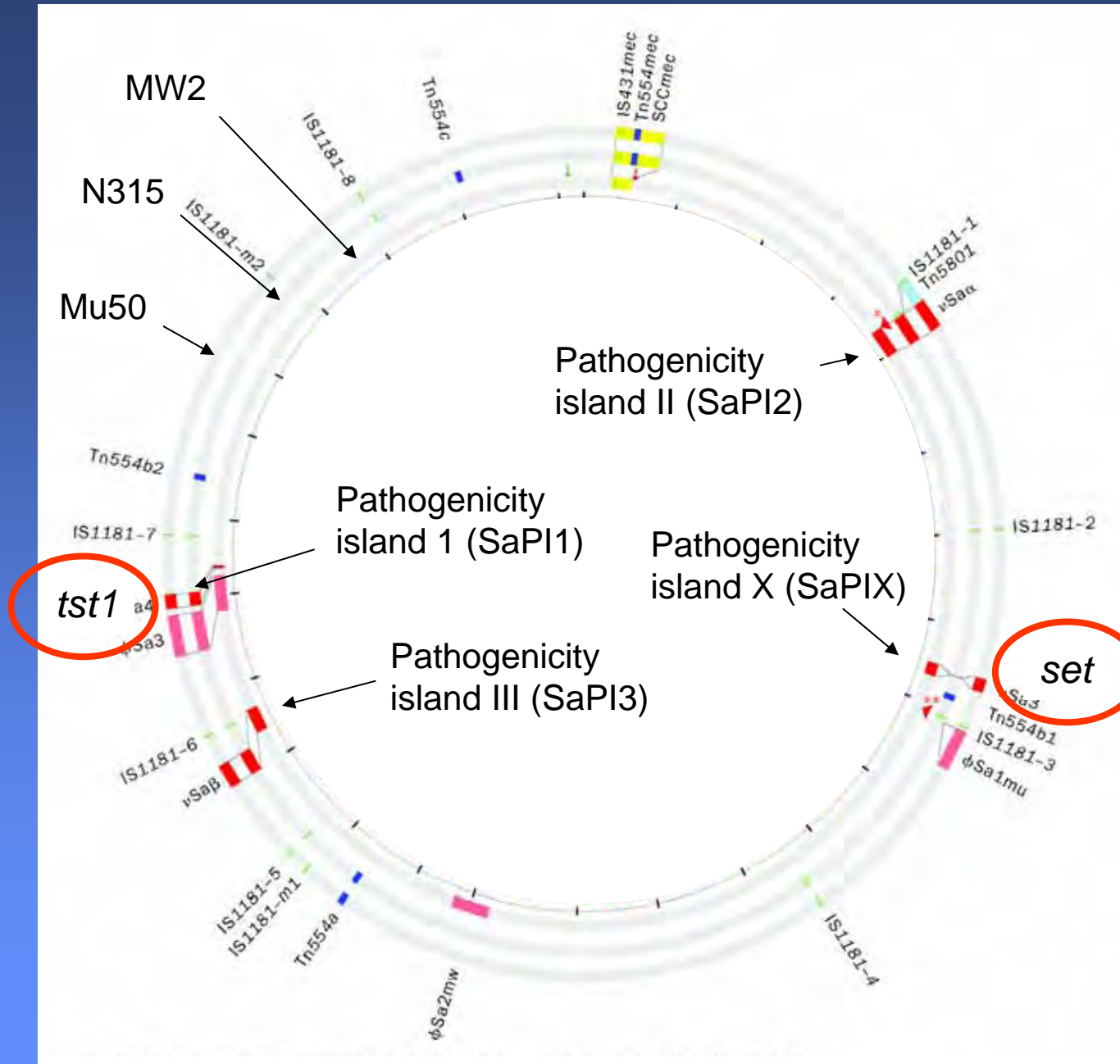
- Skin rash
- Blood cultures usually negative
- Not invasive
- Relatively low mortality (10%)
- Due to TSST-1 toxin

Skin rash during staphylococcal TSS

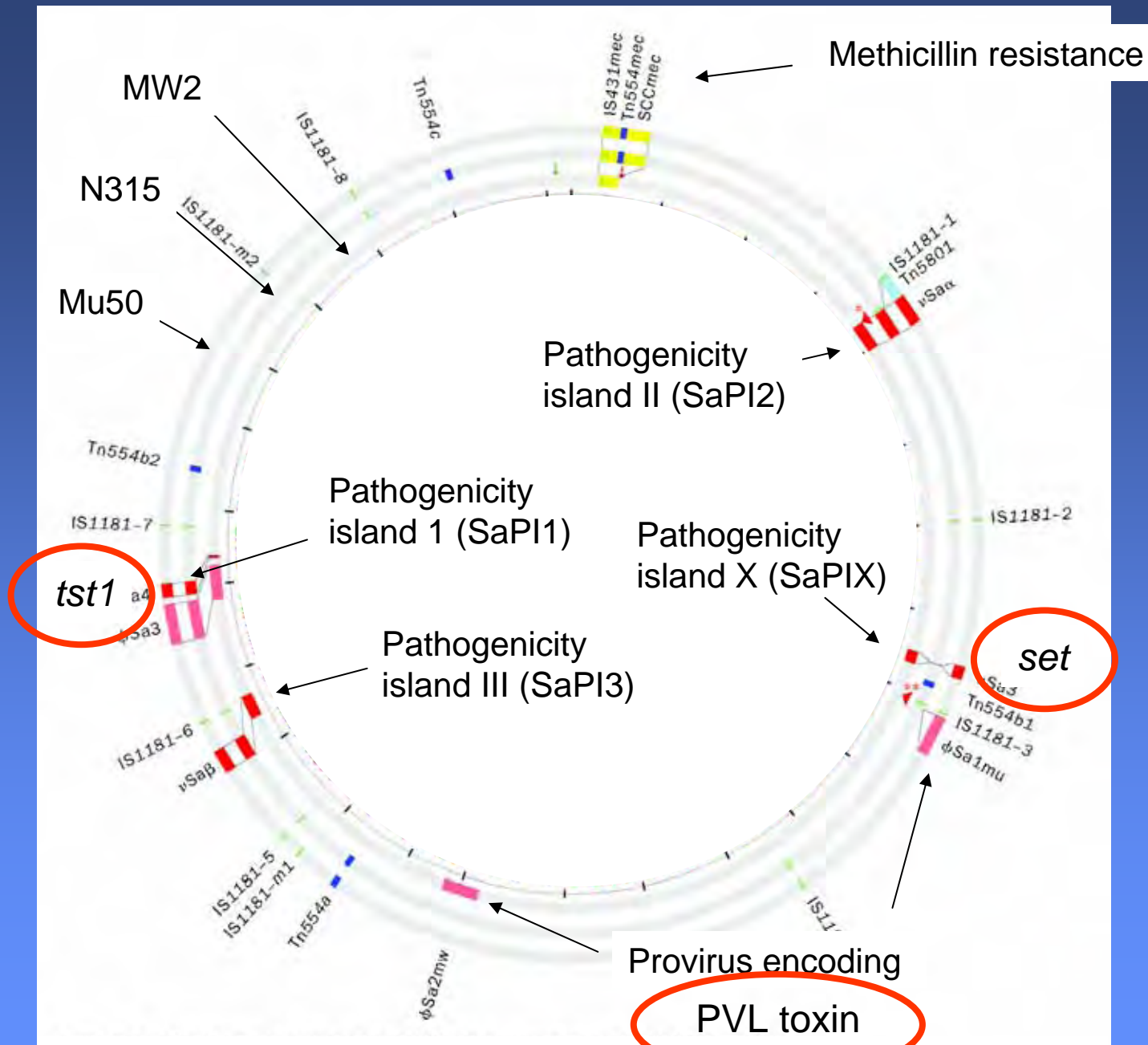
Whole genomes of *S. aureus* MW2, N315 and Mu50



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

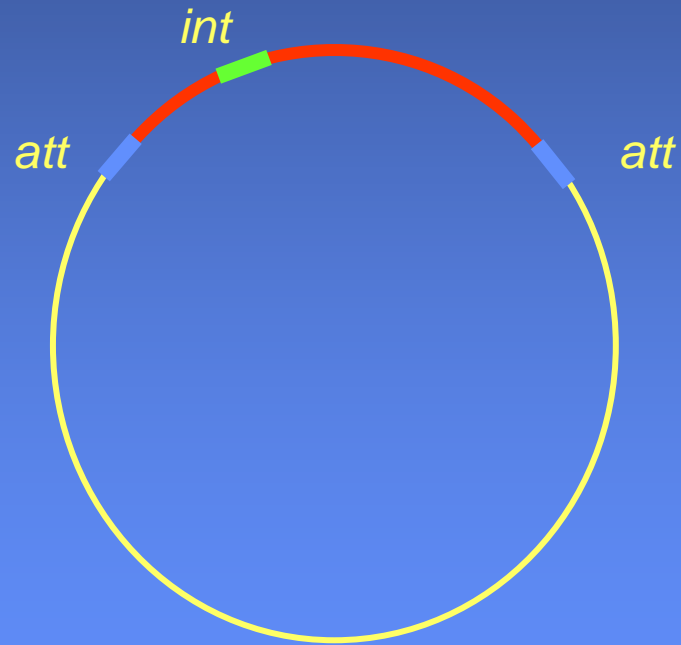


Whole genomes of *S. aureus* MW2, N315 and Mu50



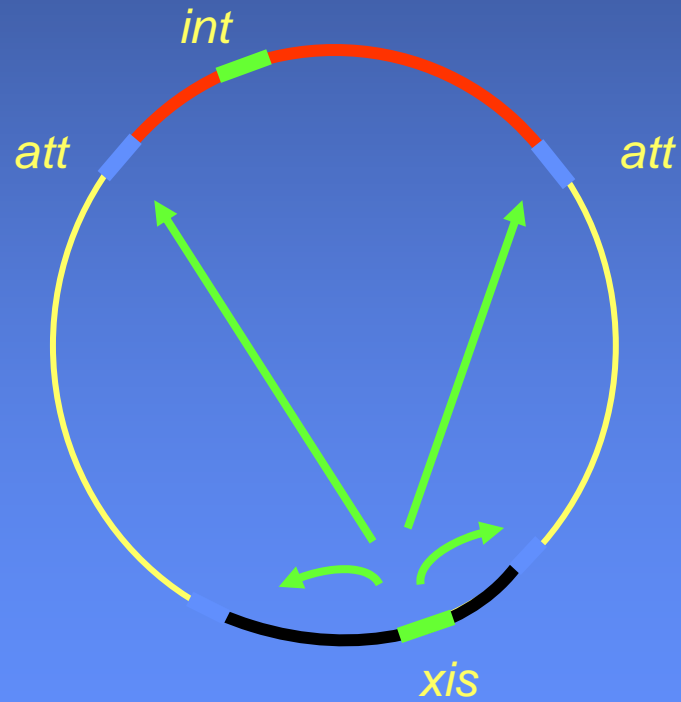
Moving Genes Around

The example of SaPI1



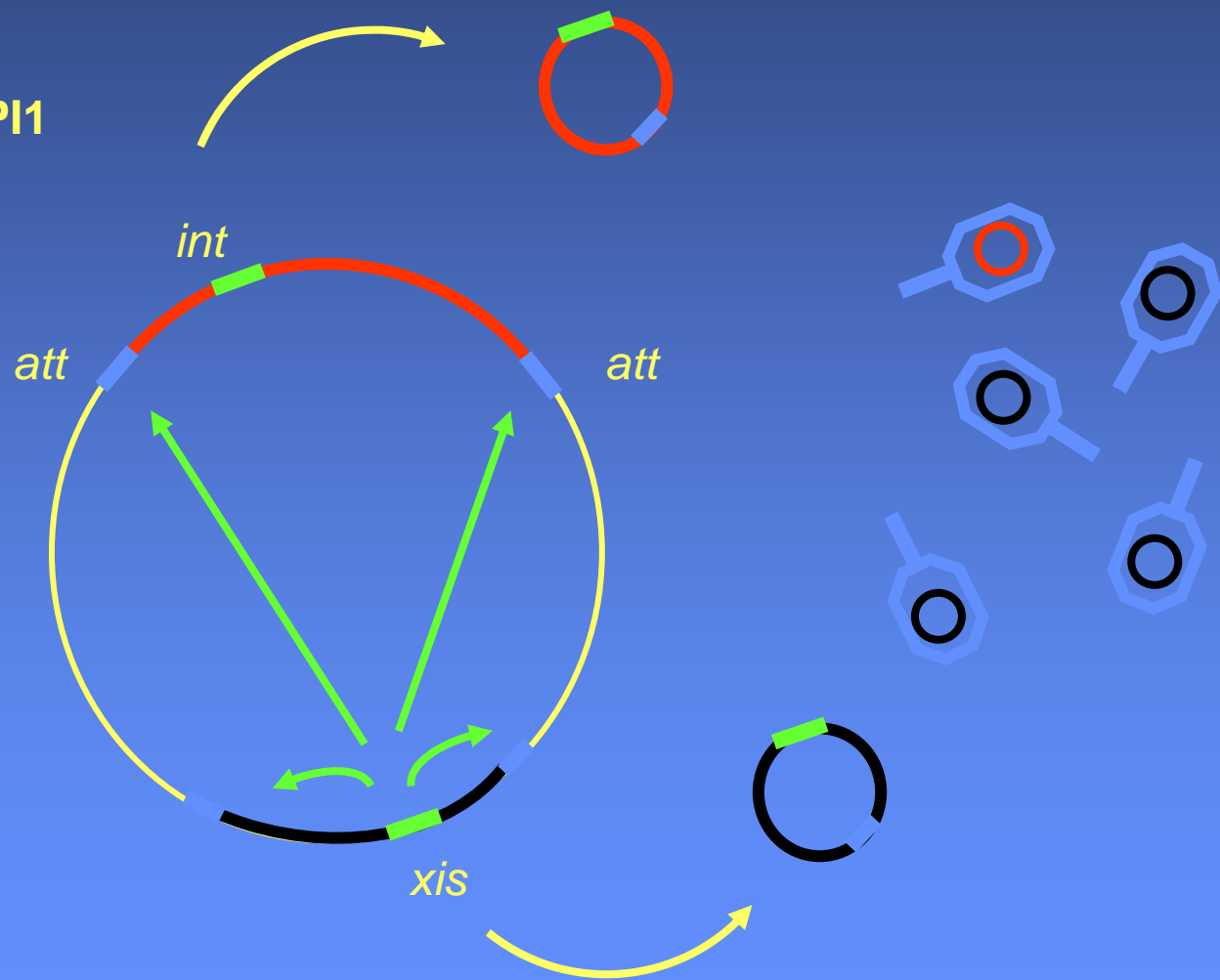
Moving Genes Around

The example of SaPI1



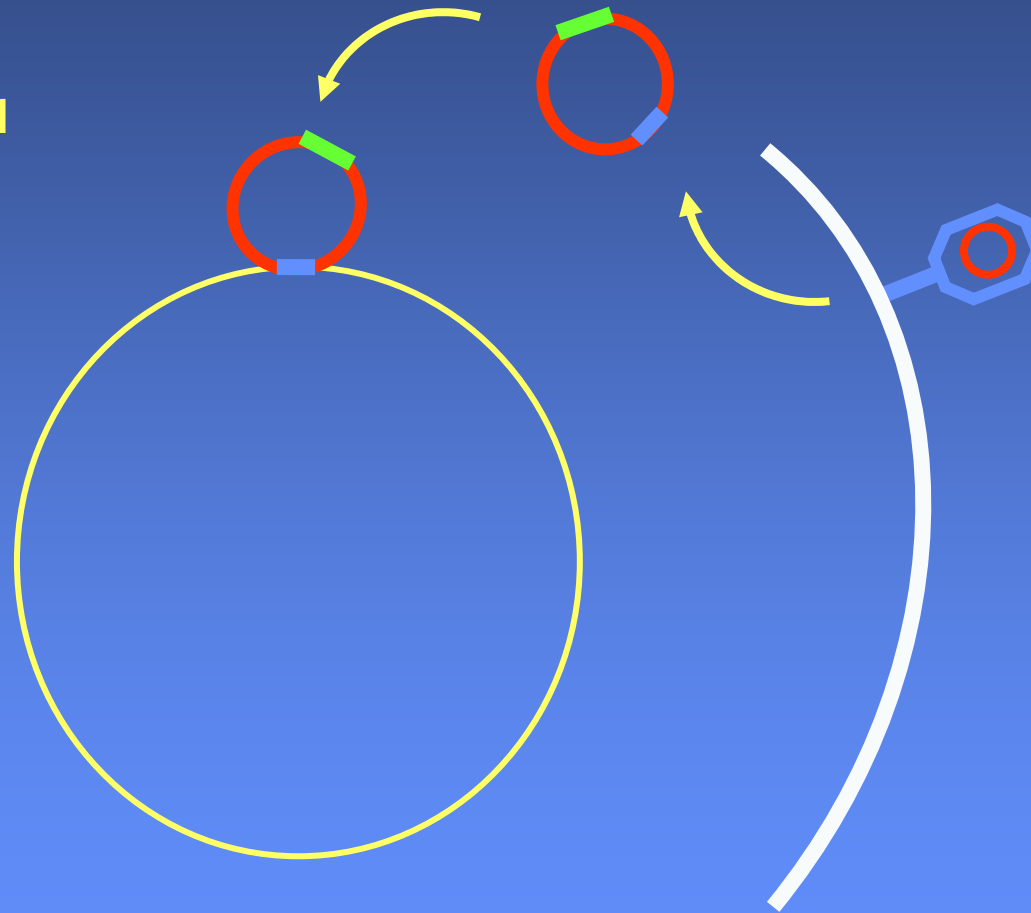
Moving Genes Around

The example of SaPI1



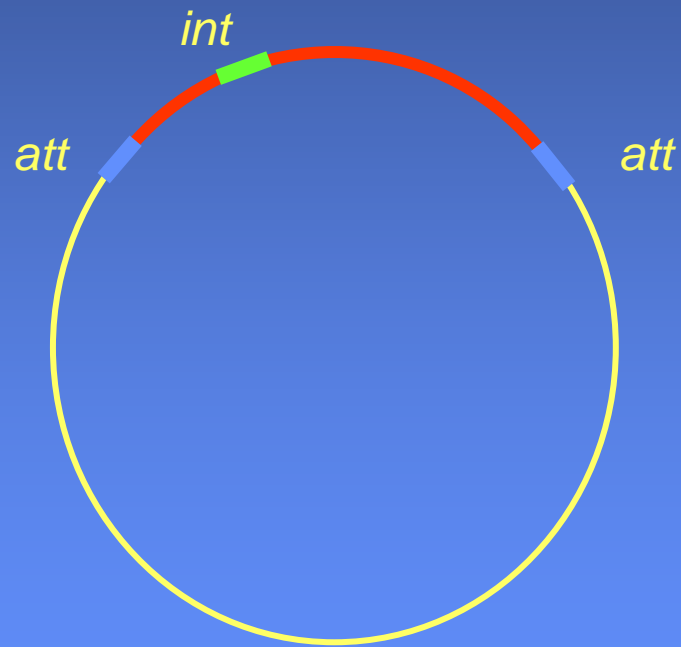
Moving Genes Around

The example of SaPI1

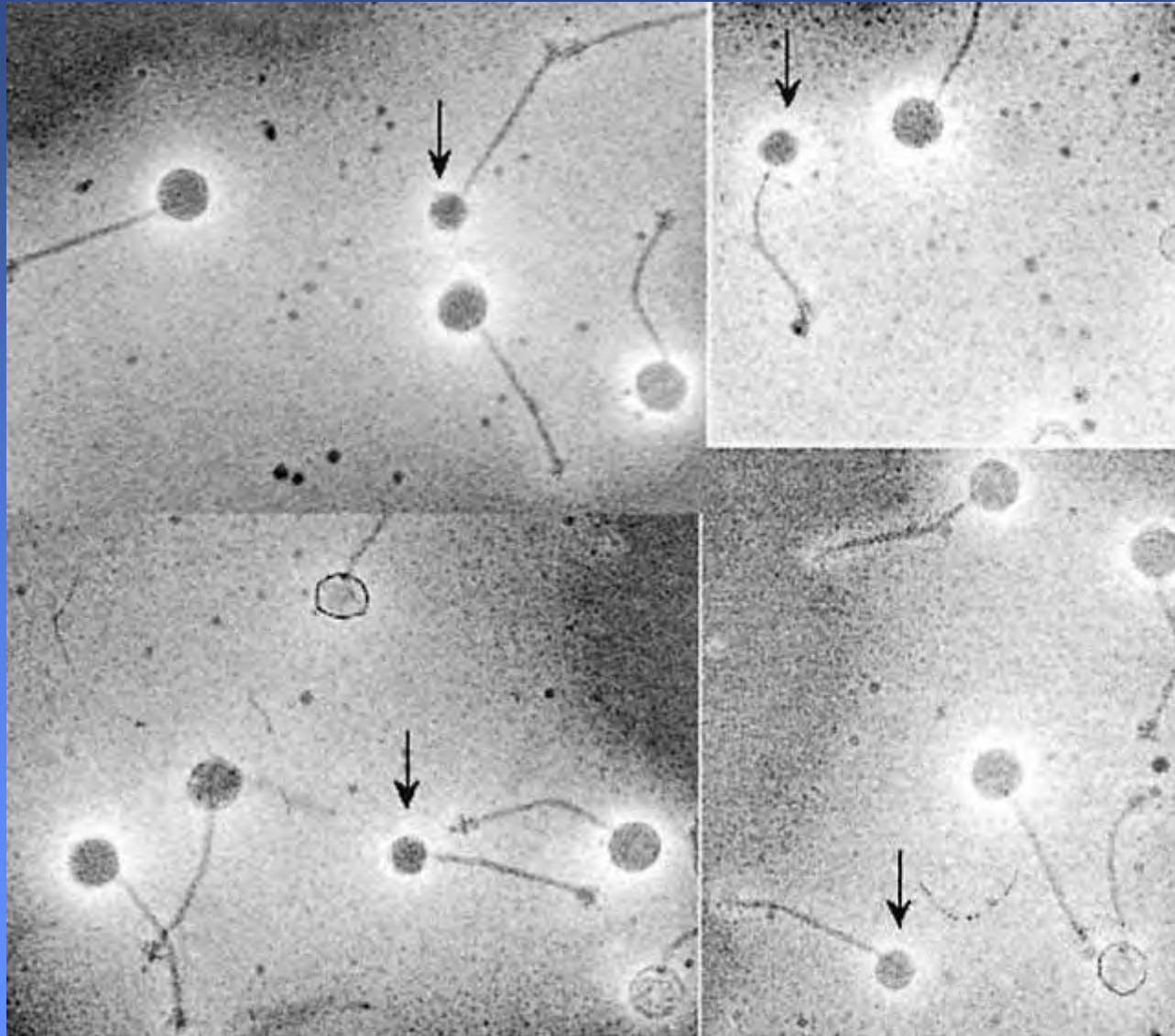


Moving Genes Around

The example of SaPI1



Moving SaPI1 with Phage 80 α



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

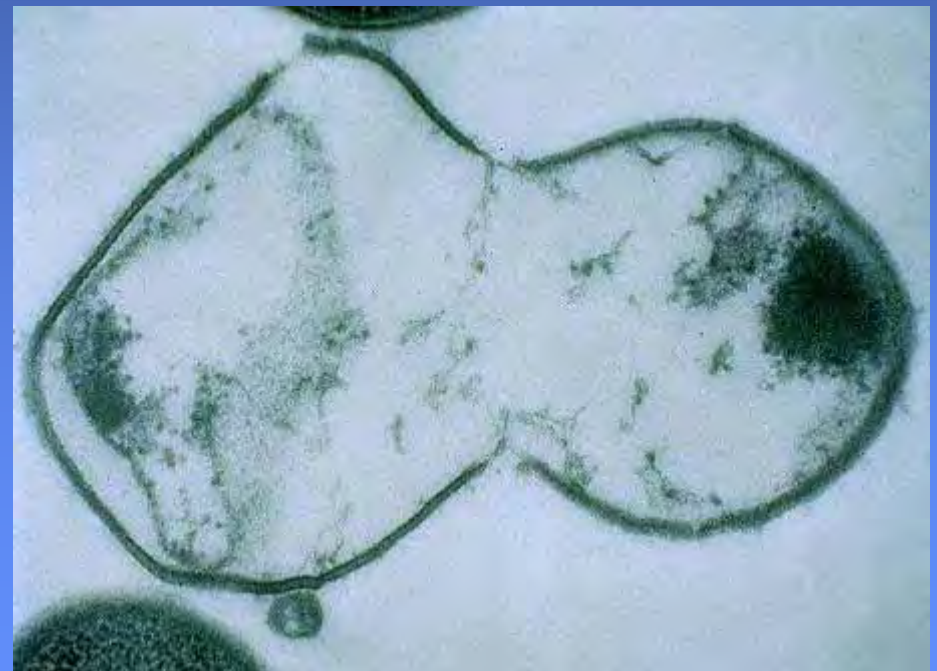
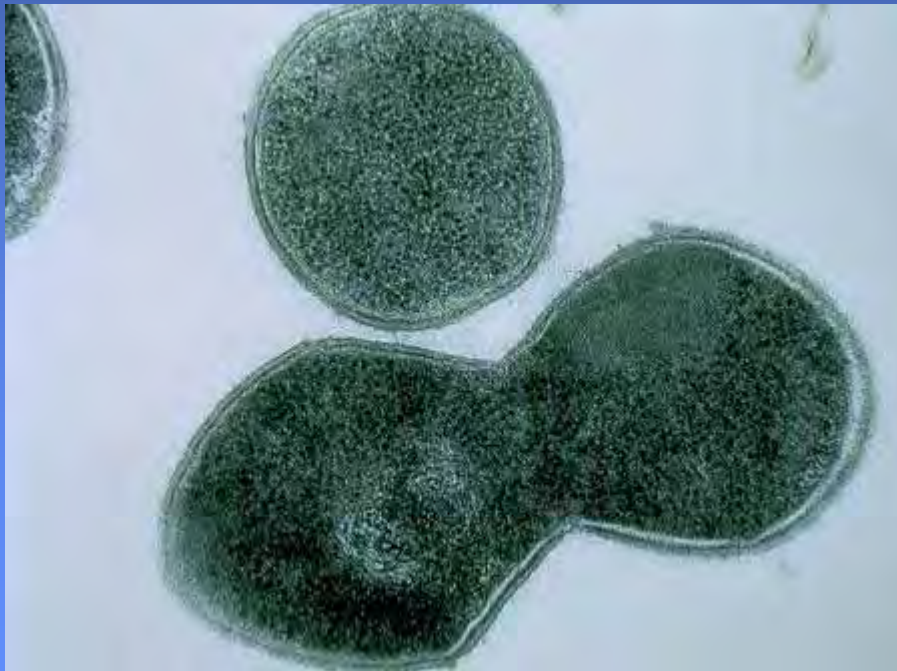
D'Herelle

J. Monod et F. Jacob

**H. Bruessow
V. Fischetti**

Implication Actuelles des Phages

1. Transferts génétiques
2. Phago-thérapie



Entenza et al. AAC 2005; 49:4789

Enseignements Acquis pas les Phages

Concernant la régulation

- Opérateurs,
 - Répresseur,
 - Trans-activateur,
 - Anti-terminateur,
 - ARN anti-sens
 - Rétro régulation
 - Coopération protéique
 - Régulation via protéase spécifiques
 - Détection des conditions environnementales
-
- Connexions étroites entre deux individus réplicatifs (virus et bactéries) phylogénétiquement très éloignés

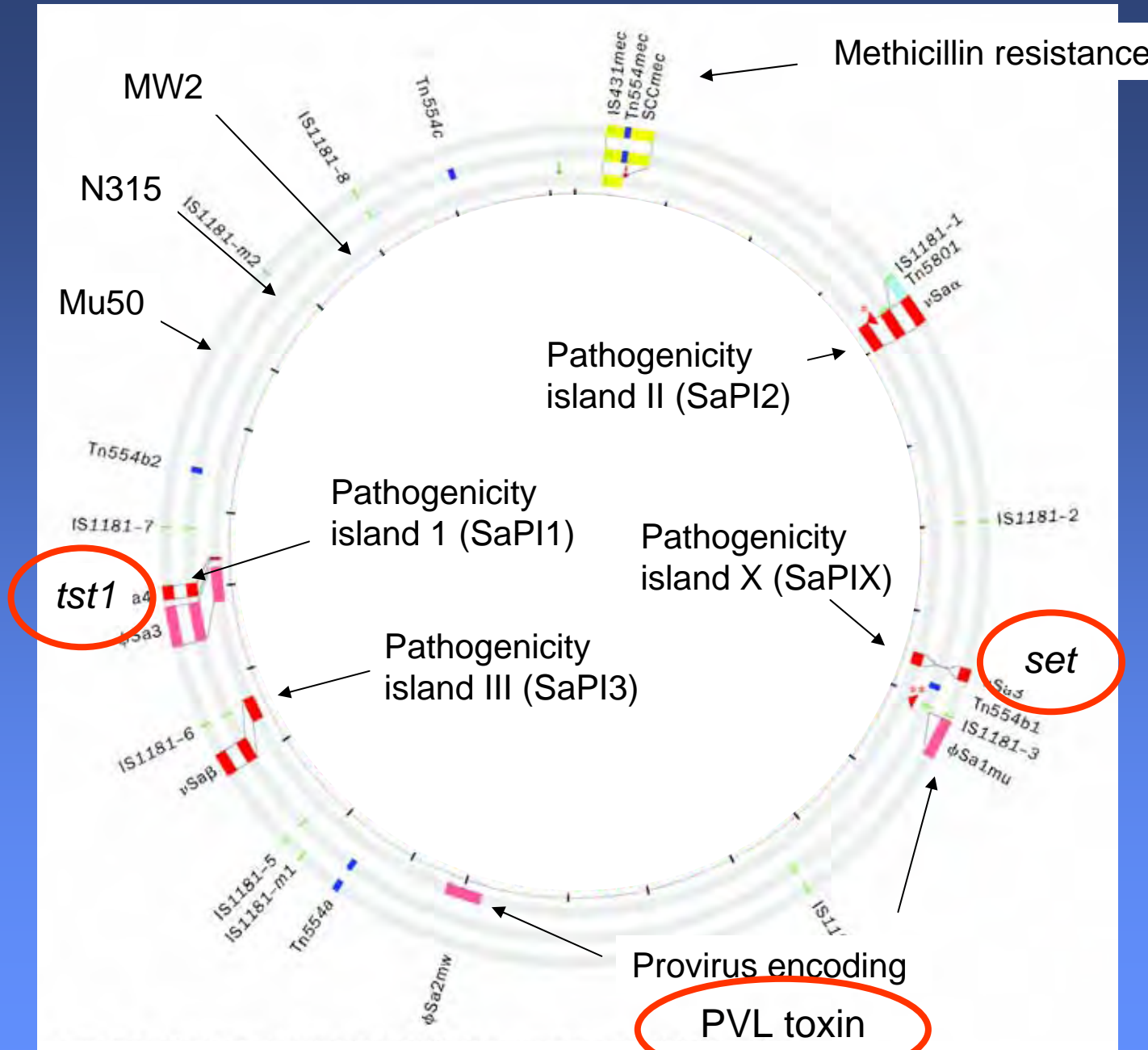
Concernant l'implication biologique

- Évolution des génomes
- Transfert horizontal de matériel génétique

Concernant la biotechnologie

- Typage bactérien; phagemides; cosmides; mutagenèse; séquençage; phage display etc...

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



De la Linguistique à la Génométrie

theicaacisagreatconférenceparcequeellegathermanygreatscientists

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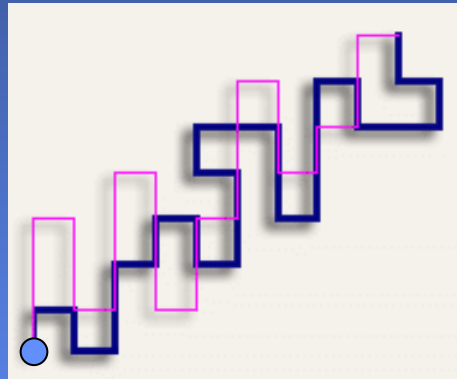
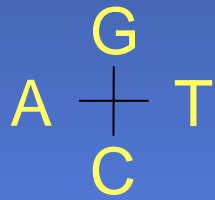
theicaacisagreatconférenceparcequeellegathermanygreatscientists

theicaacisagreatconférenceparcequeellegathermanygreatscientists



Génométrie: le DNA walk

4 directions, 4 bases: to each particular base is assigned a direction

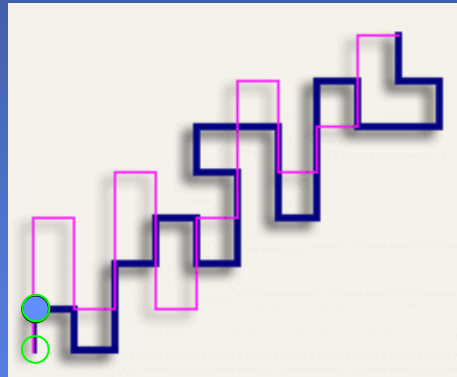
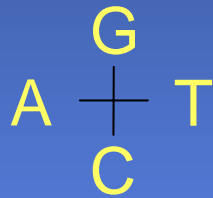


GTCTGGTGTCTGGAGTTCCTGGGTCTTGAG **ACCACAGGACCCACCAGGGACCCAGGACCC**

Jean Lobry: DNA walk

Génométrie: le DNA walk

G: one step to the top

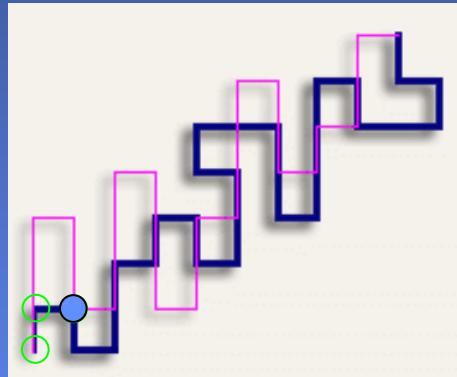
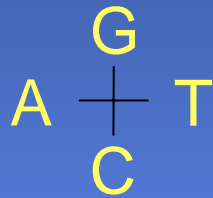


GTCTGGTGTCTGGAGTTCCTGGGTCTTGAGACCACAGGACCCACCAGGGACCCAGGACCC

Jean Lobry: DNA walk

Génométrie: le DNA walk

T: one step rightwards

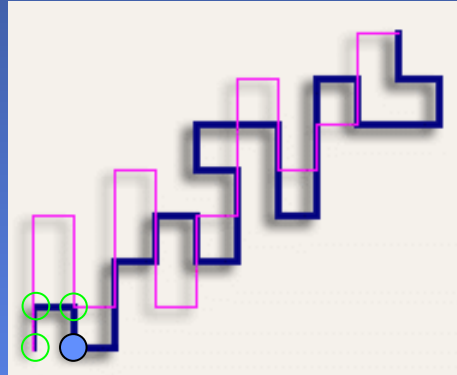
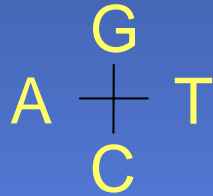


GTCTGGTGTCTGGAGTTCCTGGGTCTTGAG ACCACAGBACCCACCAGGGACCCAGBACCC

Jean Lobry: DNA walk

Génométrie: le DNA walk

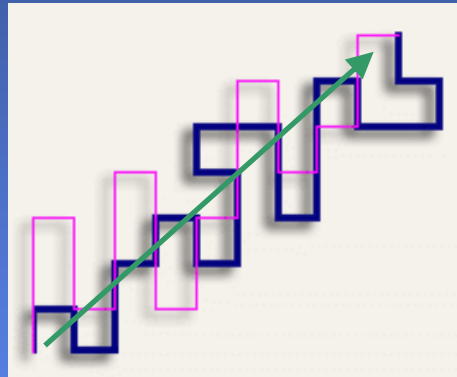
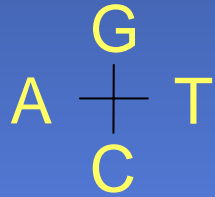
C: one step to the bottom



GTCTGGTGTCTGGAGTTCCTGGGTCTTGAGACCAACAGGACCCACCAGGGACCCAGGACCC

Jean Lobry: DNA walk

Génométrie: le DNA walk

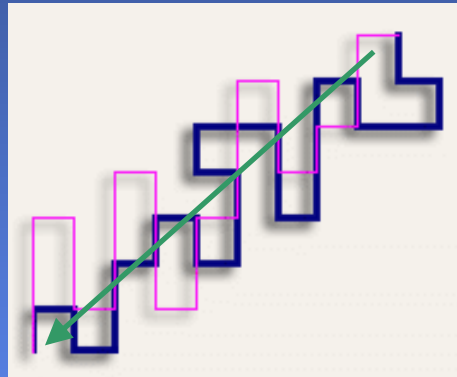
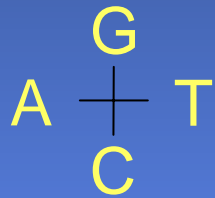


GTCTGGTGTCTGGAGTTCCTGGGTCTTGAG ACCACAGBACCCACCAGGBACCCAGBACCC



Jean Lobry: DNA walk

Génométrie: le DNA walk

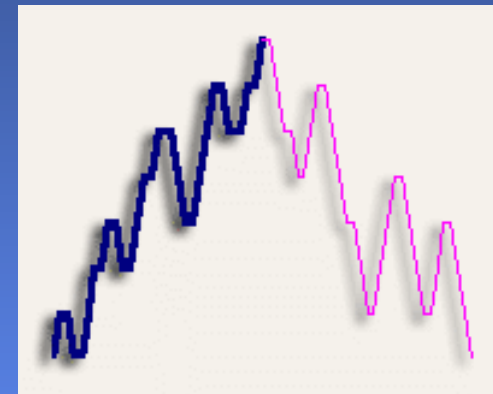
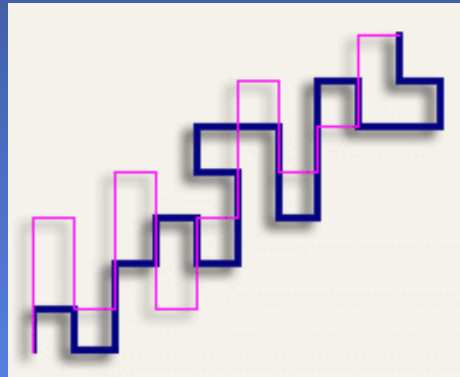
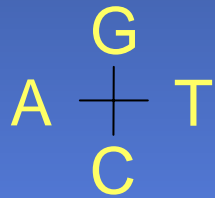


GTCTGGTGTCTGGAGTTCCTGGGTCTTGAG **ACCACAGGACCCACCAGGGACCCAGBACCC**



Jean Lobry: DNA walk

Cumulative nucleotide skew

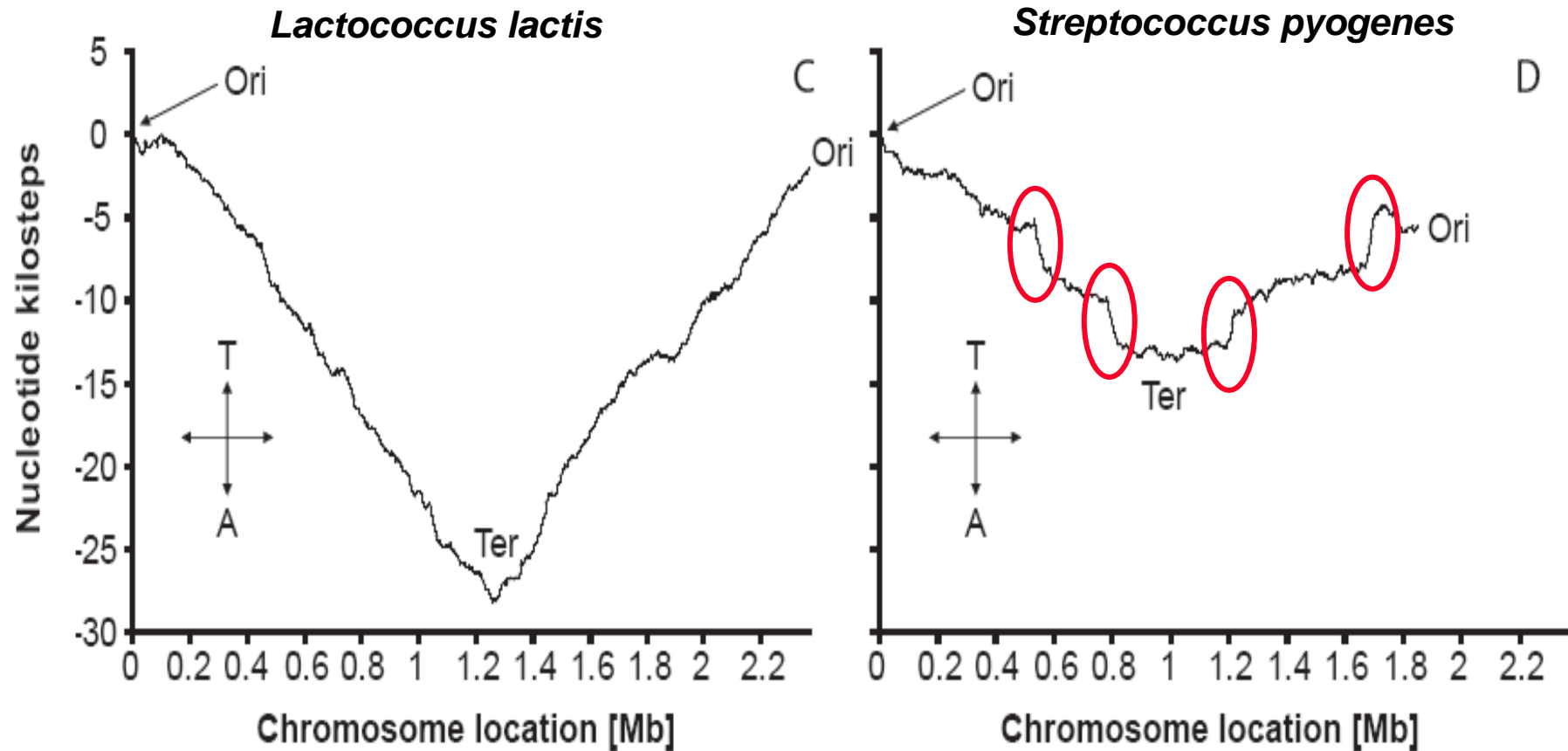


Position

GTCTGGTGTCTGGAGTTCCTGGGTCTTGAGACCACAGGACCCACCAGGGACCCAGGACCC

To each base, a step rightwards. If G, one
Supplementary step to
the top, If C, to the bottom.

Detection of PAIS: cumulative TA skew



Le Code Génétique est Redondant

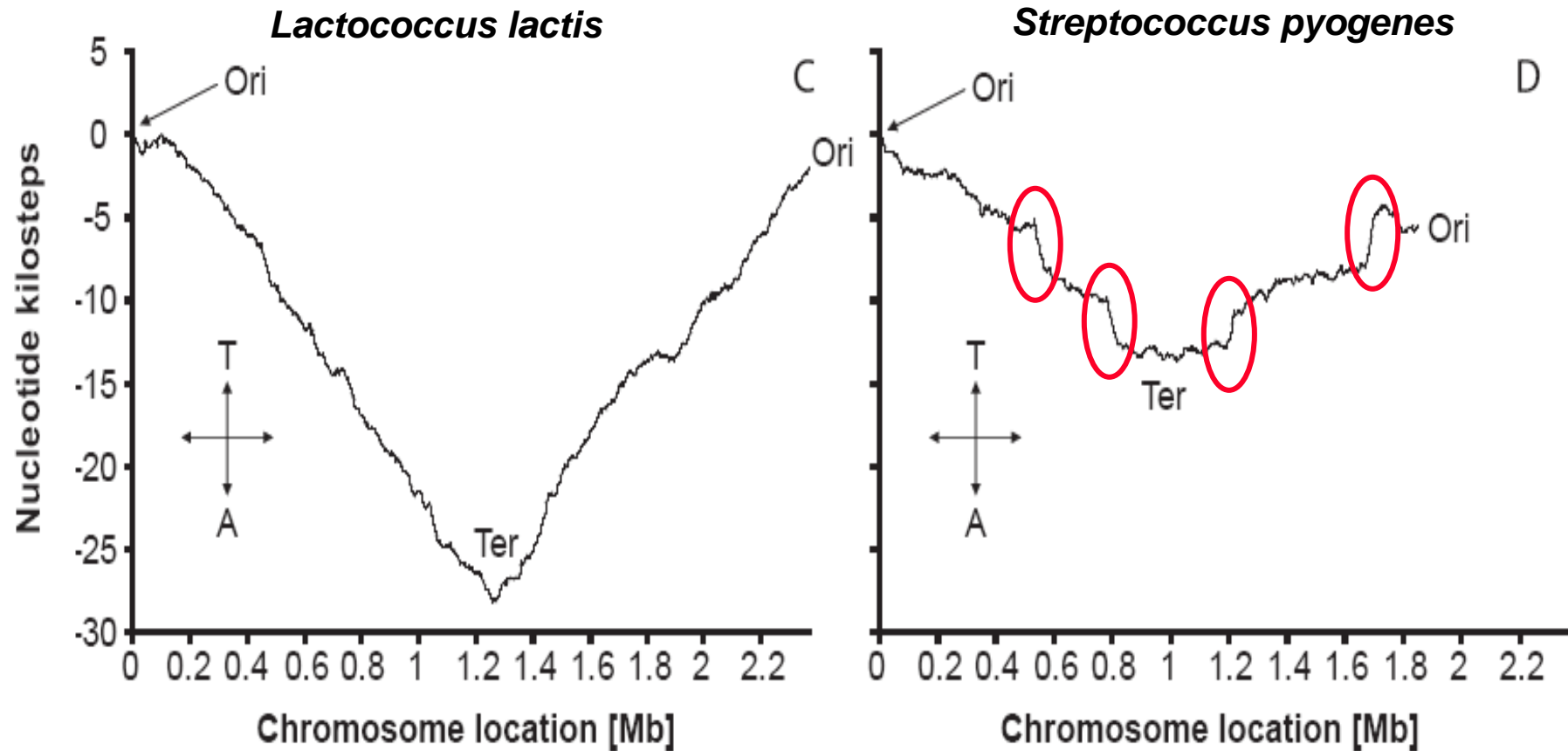
LE CODE GENETIQUE

Deuxième lettre

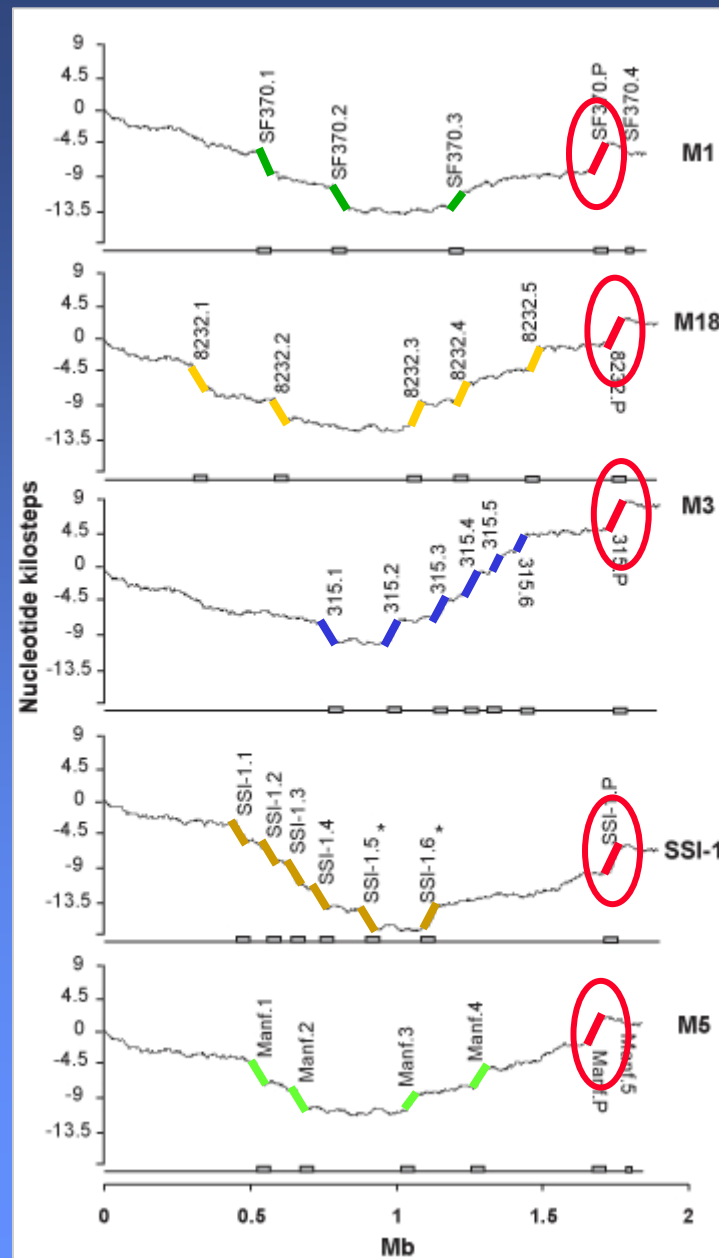
		<i>Deuxième lettre</i>			
		U	C	A	G
<i>Première lettre</i>	U	UUU phe (F)	UCU ser (S)	UAU tyr (Y)	UGU cys (C)
		UUC	UCC	UAC	UGC
		UUA leu (L)	UCA	UAA STOP	UGA STOP
		UUG	UCG	UAG STOP	UGG trp (W)
	C	CUU leu (L)	CCU pro (P)	CAU HIS (H)	CGU arg (R)
		CUC	CCC	CAC	CGC
		CUA	CCA	CAA gln (Q)	CGA
		CUG	CCG	CAG	CGG
	A	AUU ile (I)	ACU thr (T)	AAU asn (N)	AGU ser (S)
		AUC	ACC	AAC	AGC
		AUA	ACA	AAA lys (K)	GA arg (R)

Il existe une flexibilité orthographique pour la première et SURTOUT pour la dernière lettre des codons

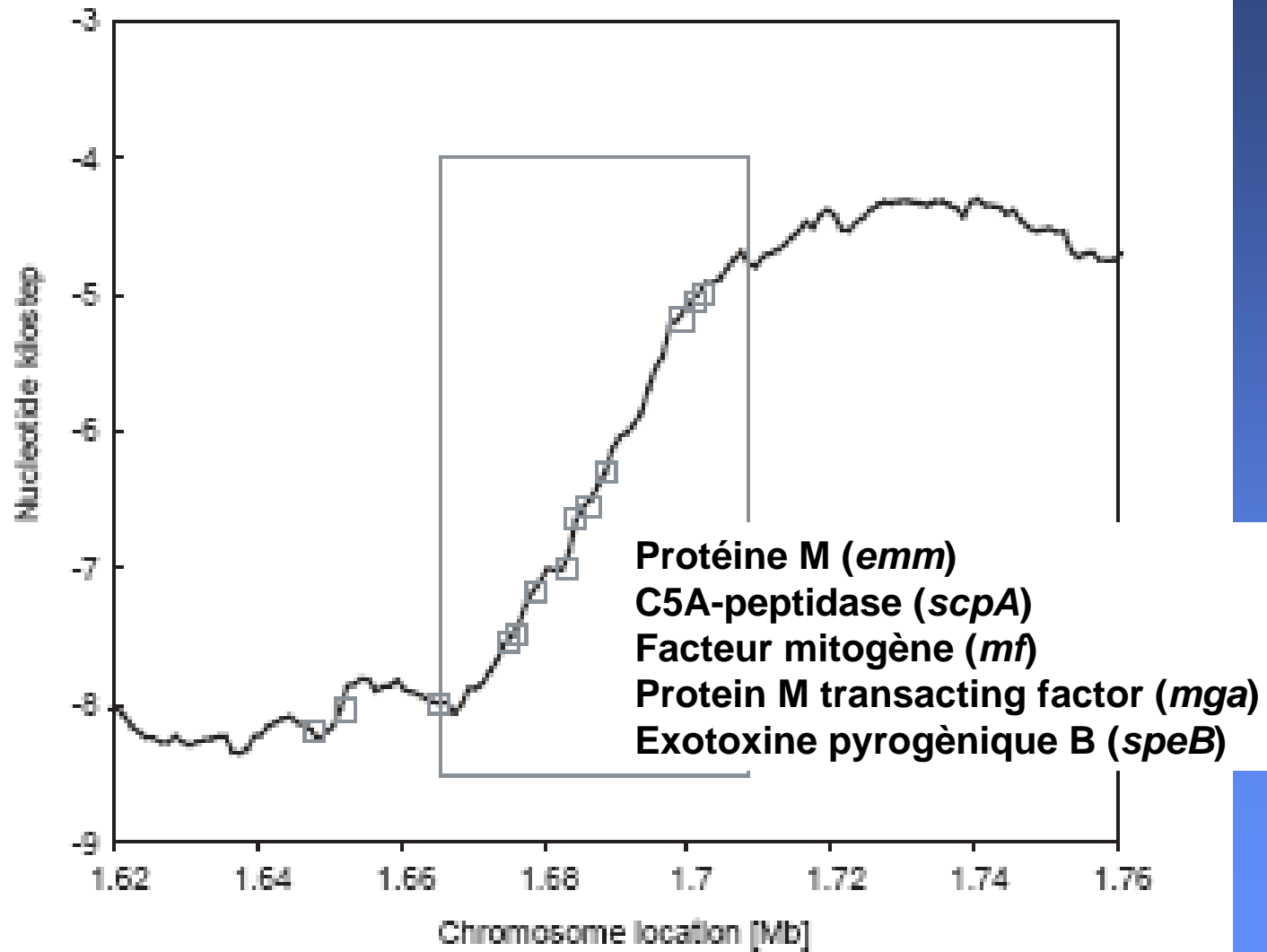
Detection of PAIS: cumulative TA skew



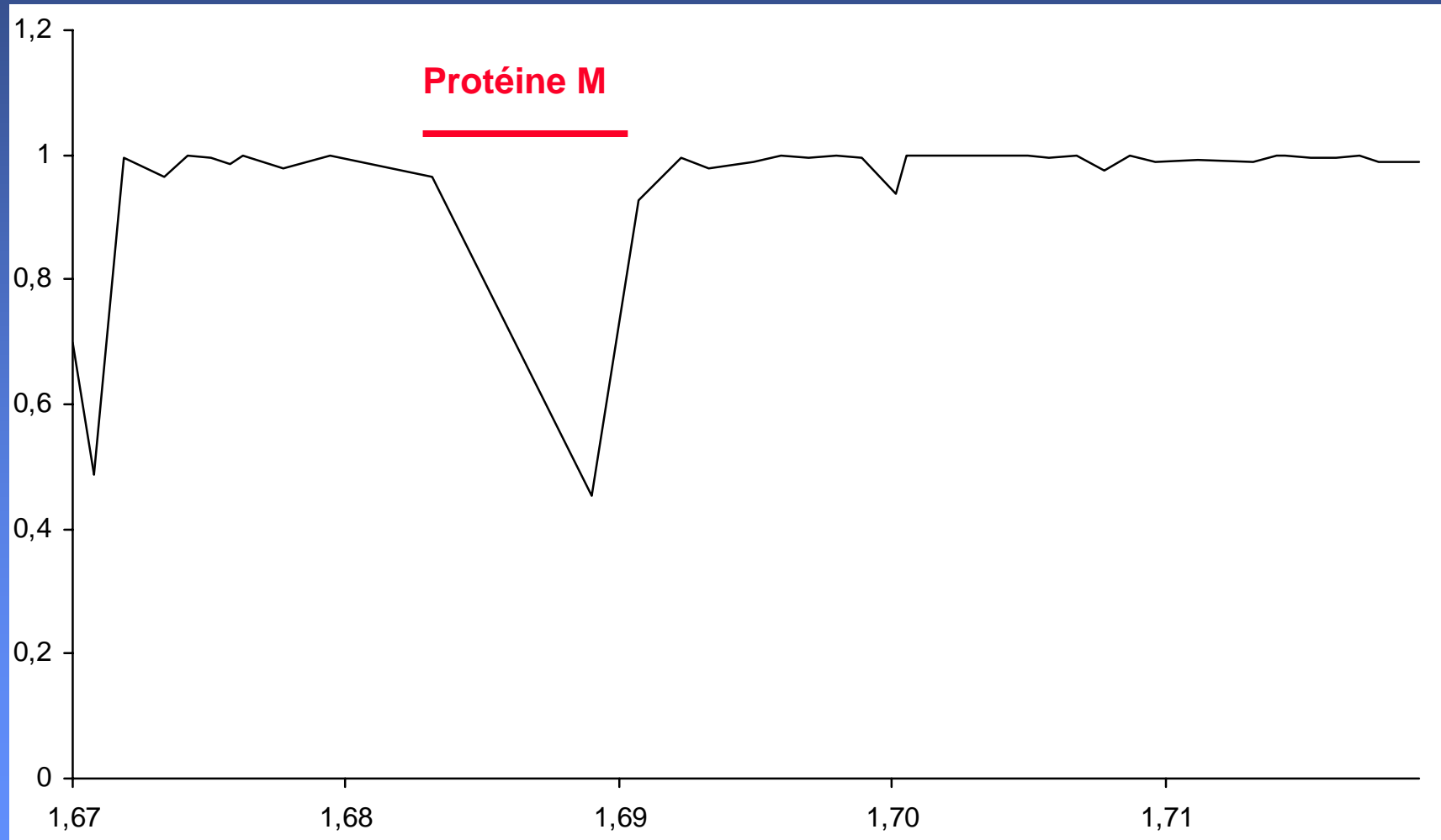
Genomic landscape: 5 strains of *S. pyogenes*



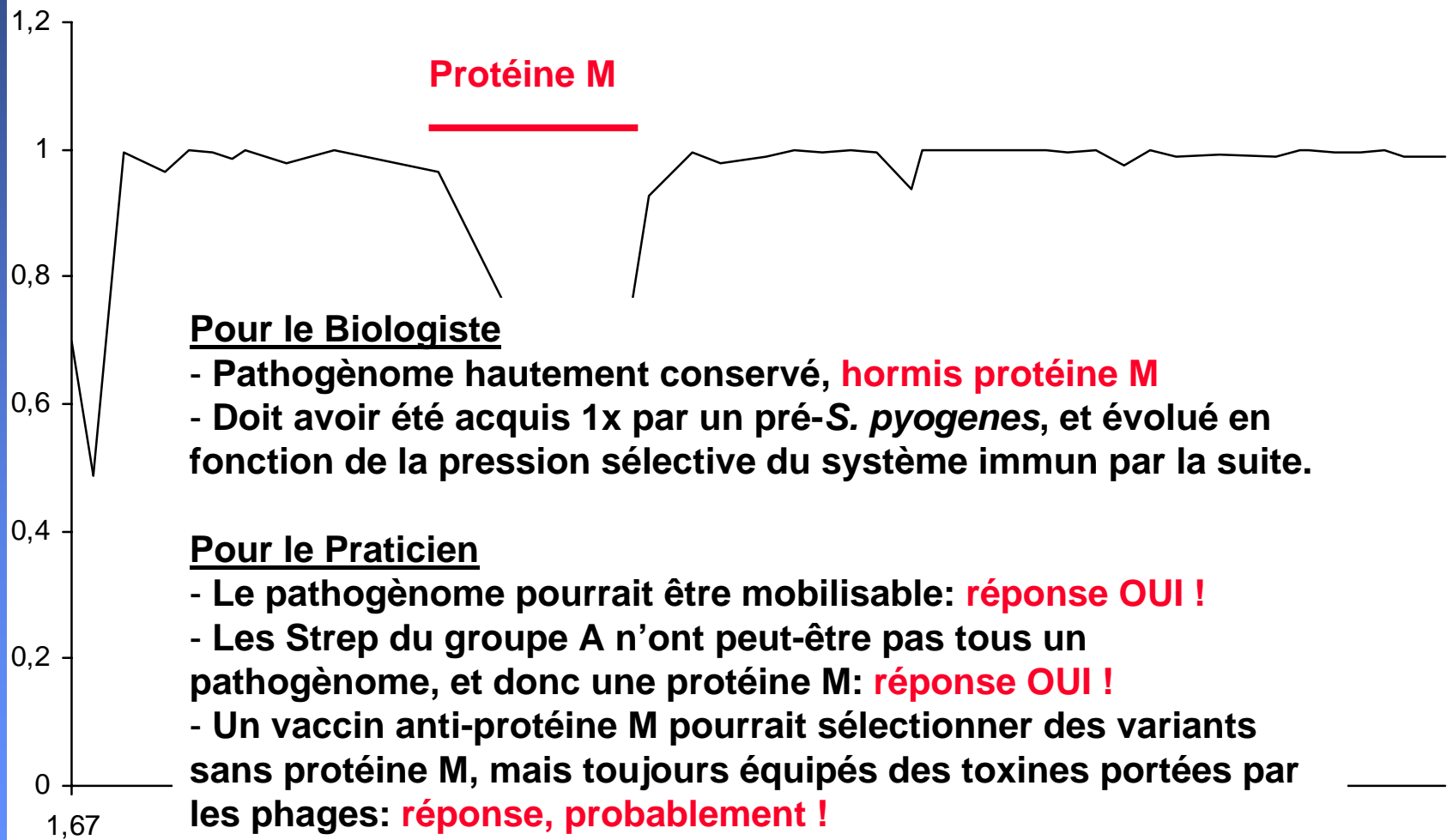
The *Streptococcus pyogenes* "Pathogenome"



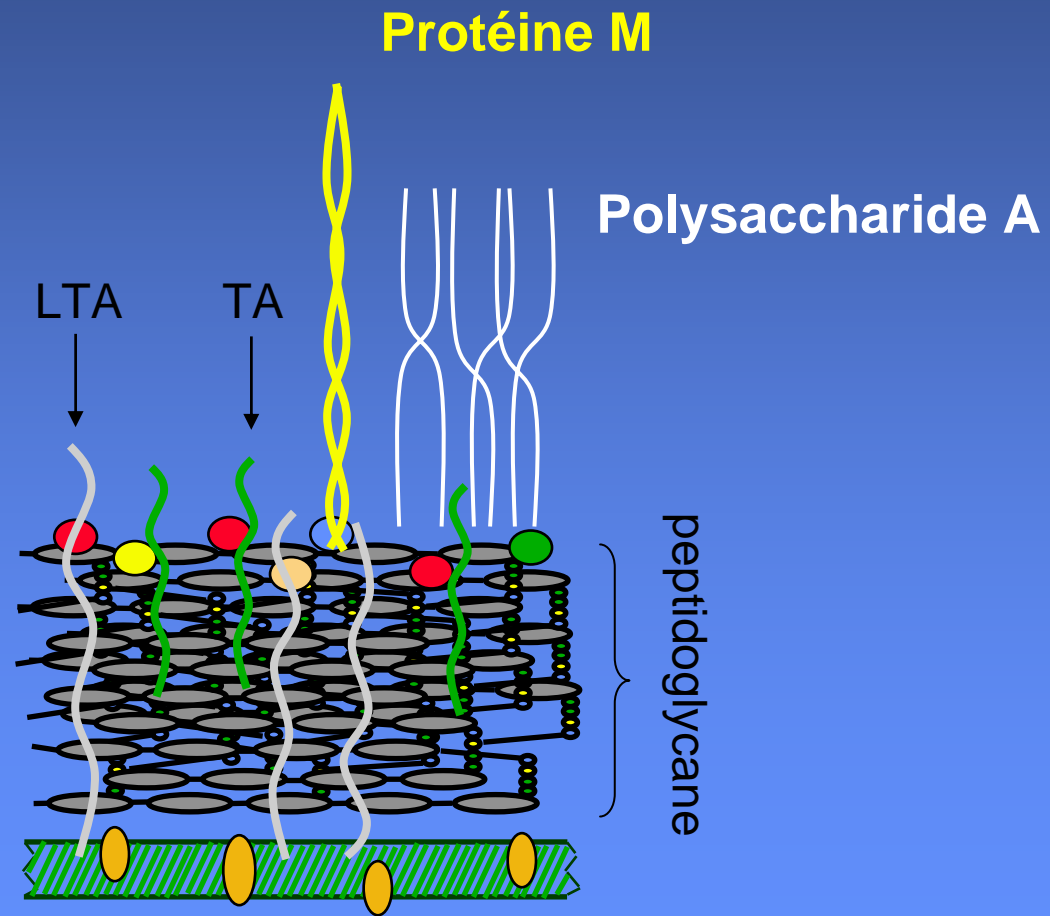
Comparaison des Séquence des Pathogènes Des *S. pyogenes* Séquencés



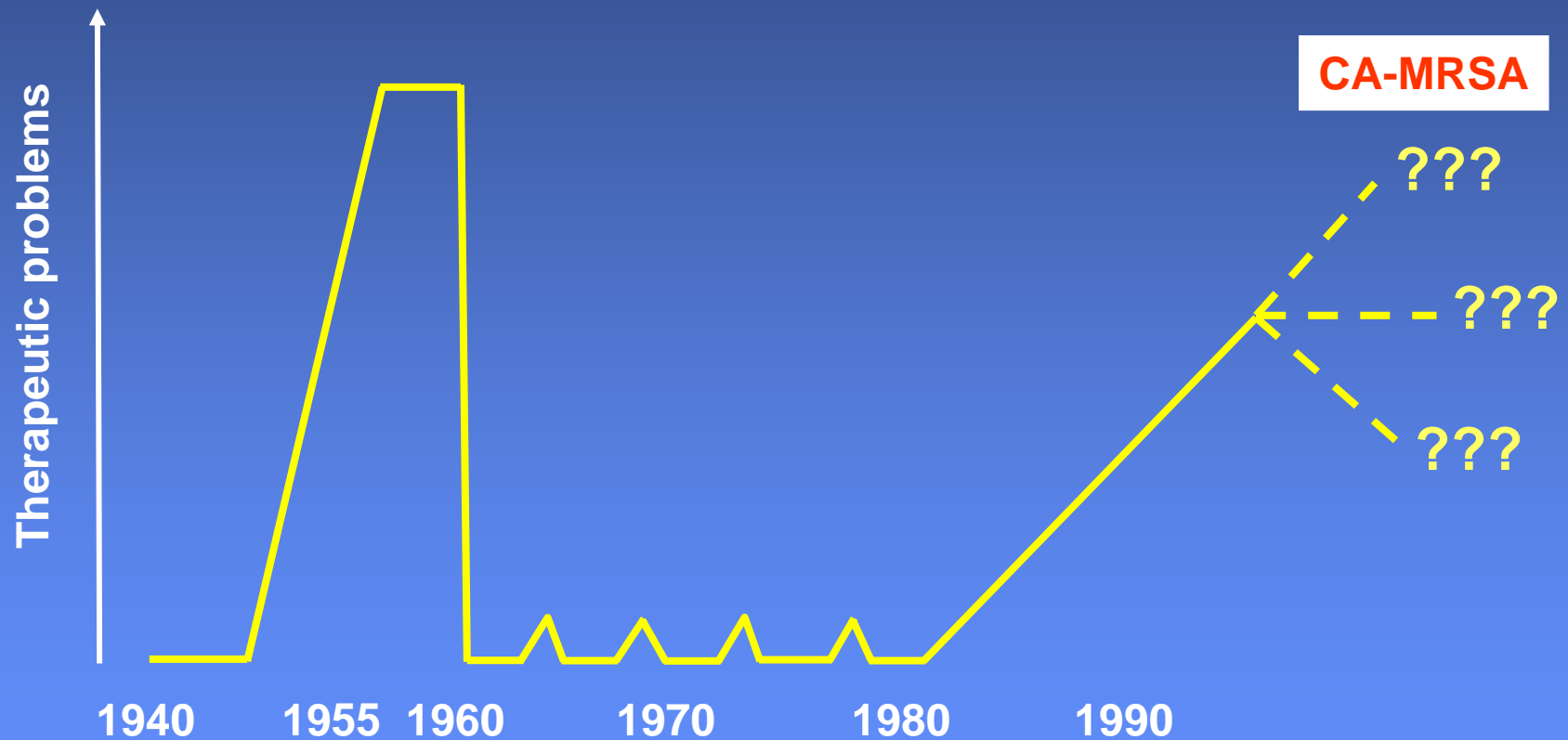
Comparaison des Séquence des Pathogénomés Des *S. pyogenes* Séquencés



Constituants de la Paroi de *S. pyogenes*

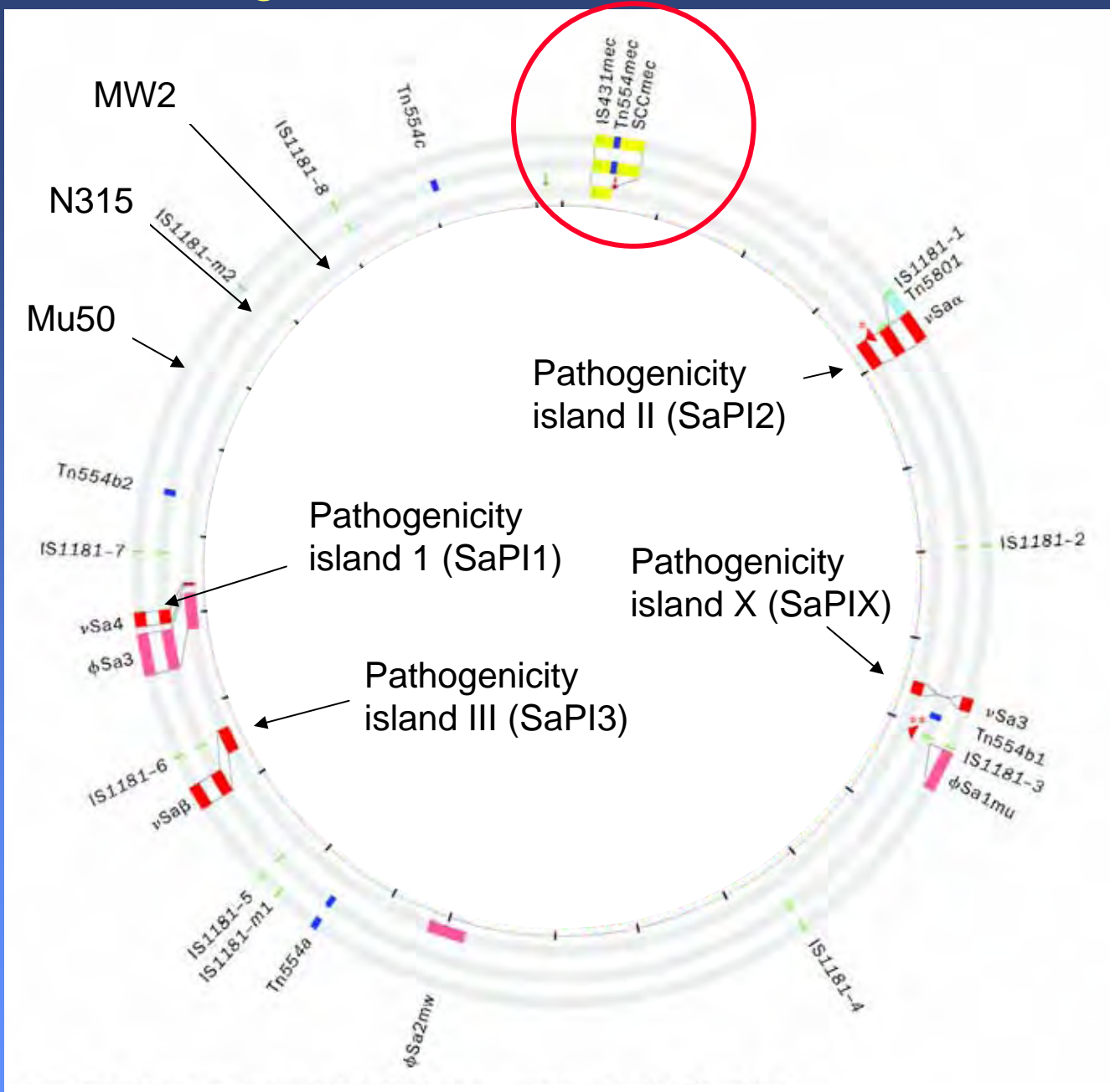


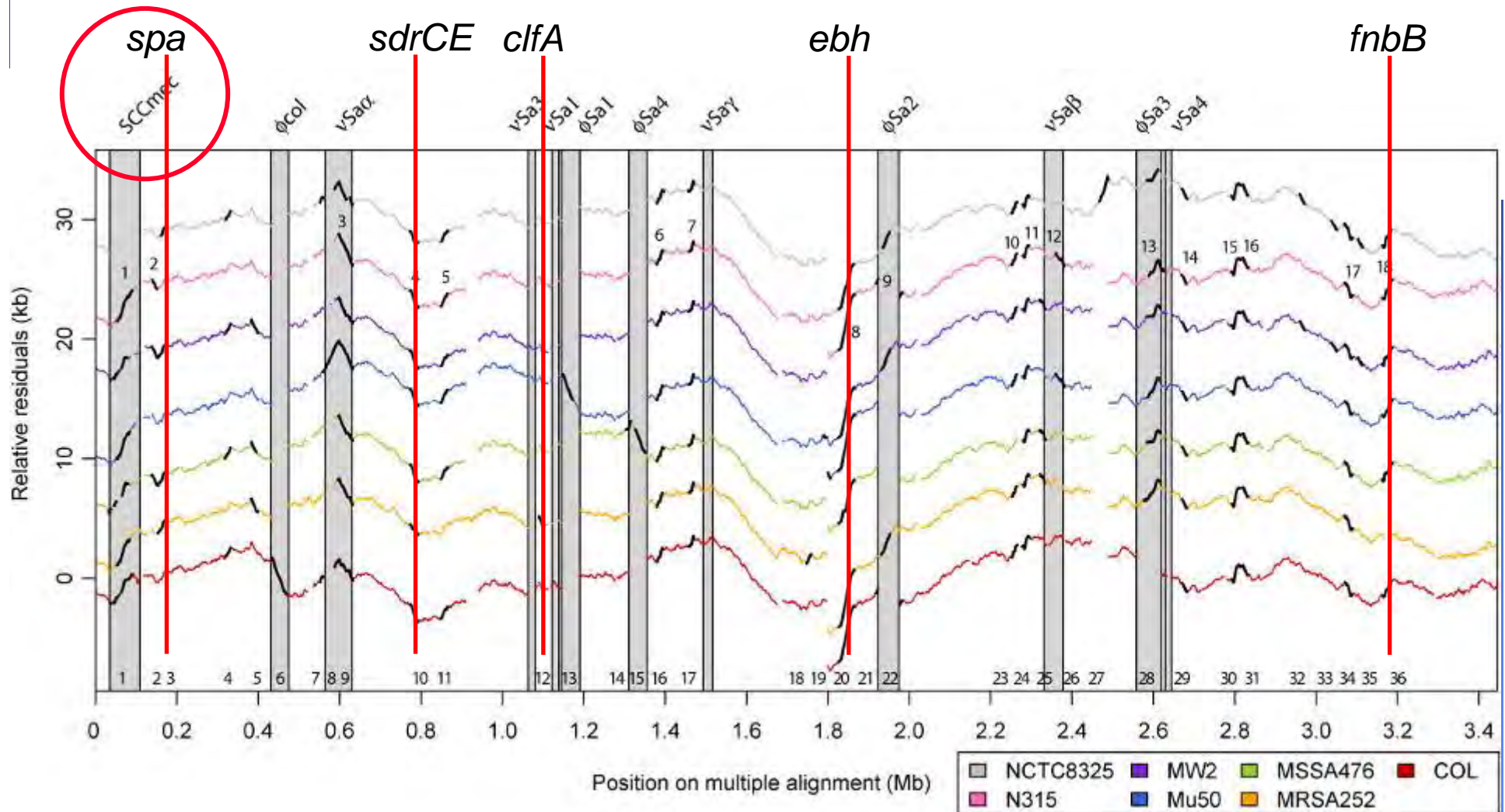
Evolution of Beta-lactam-Resistance in Staphylococcus aureus



Adapted from Maple PA et al. Lancet 1989; i:1989

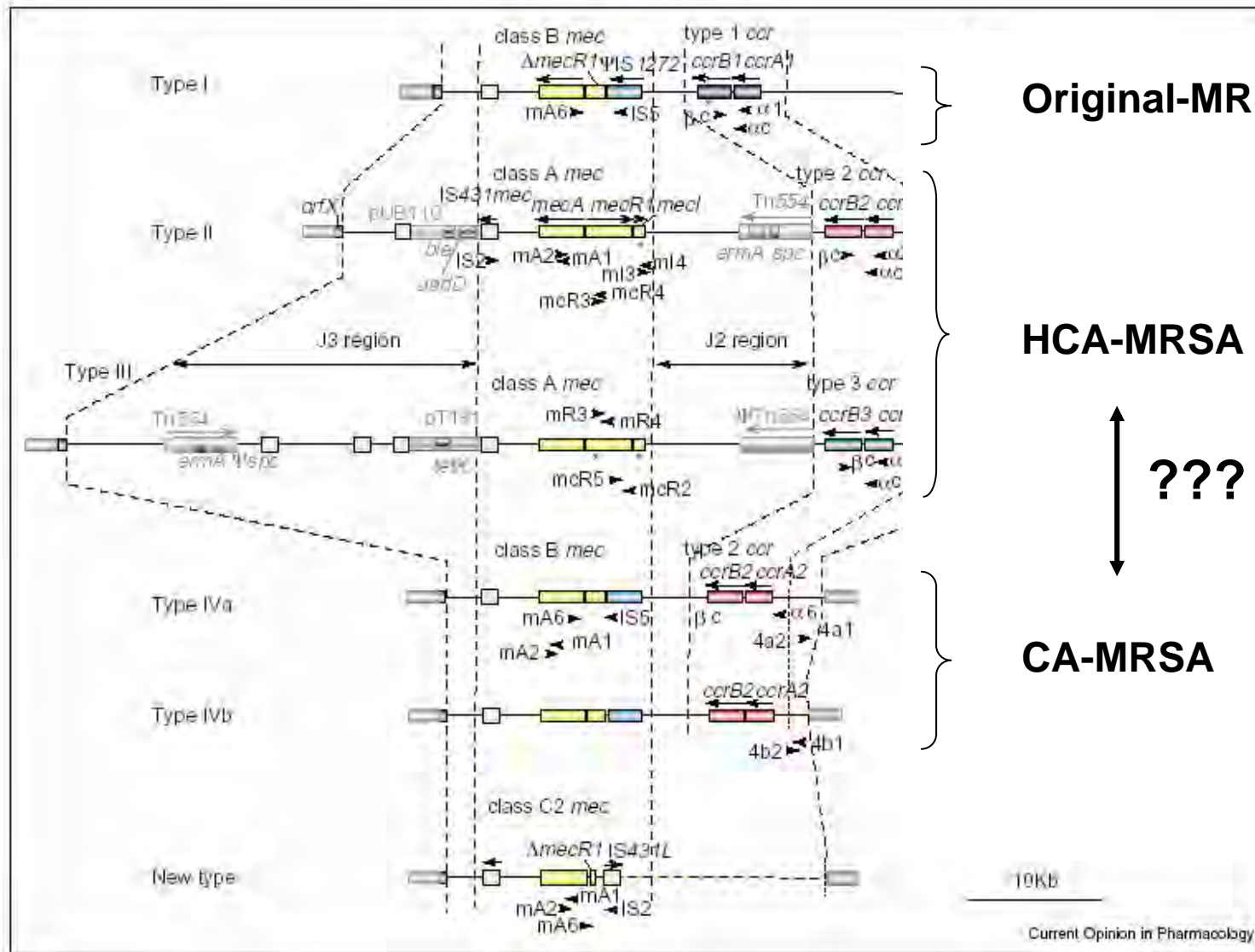
Whole genomes of *S. aureus* MW2, N315 and Mu50



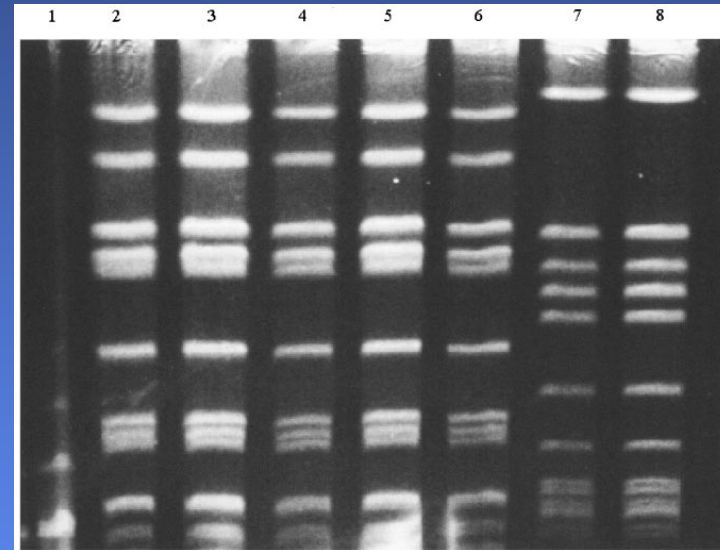
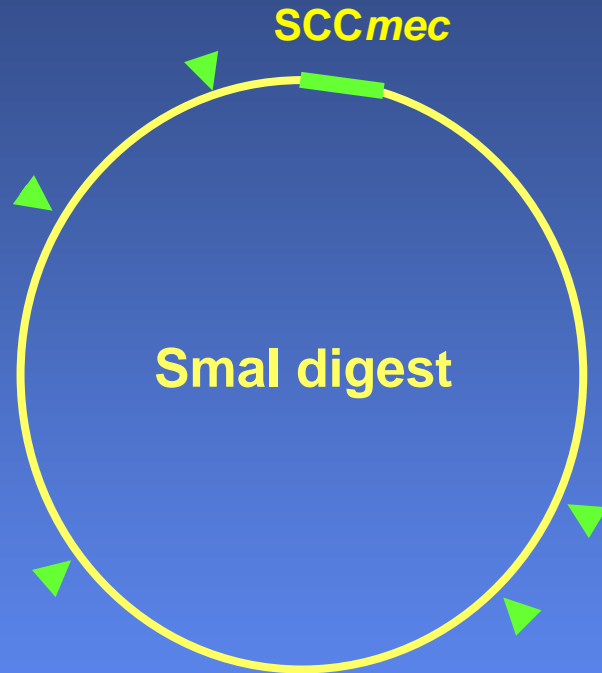


The SCCmec elements

Figure 1



Pulse-Field Gel Electrophoresis

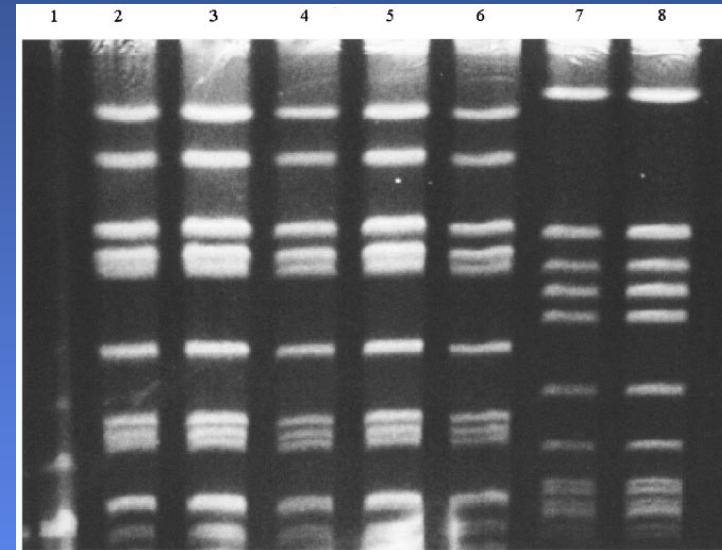
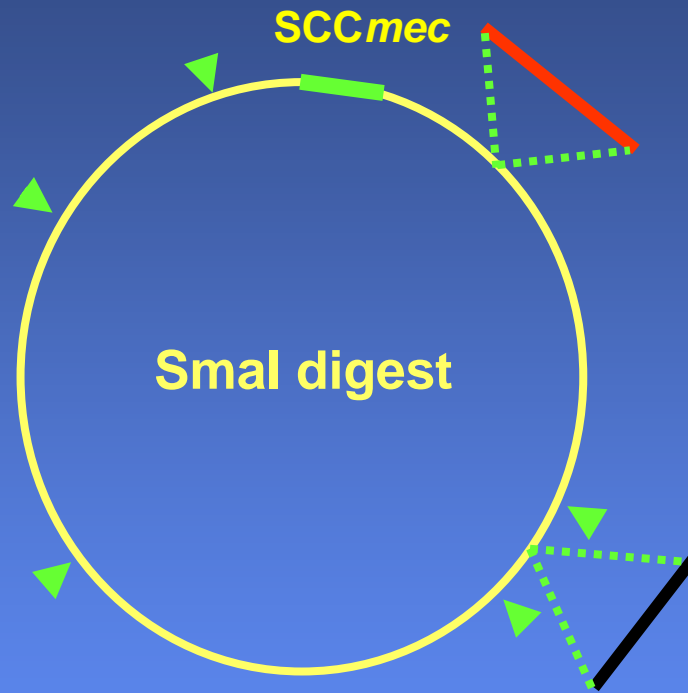


- Lineages:
- Iberian
 - Bresilian
 - Hungarian
 - NY/Japan
 - pediatric pandemic

Que le SARM le plus fort gagne !

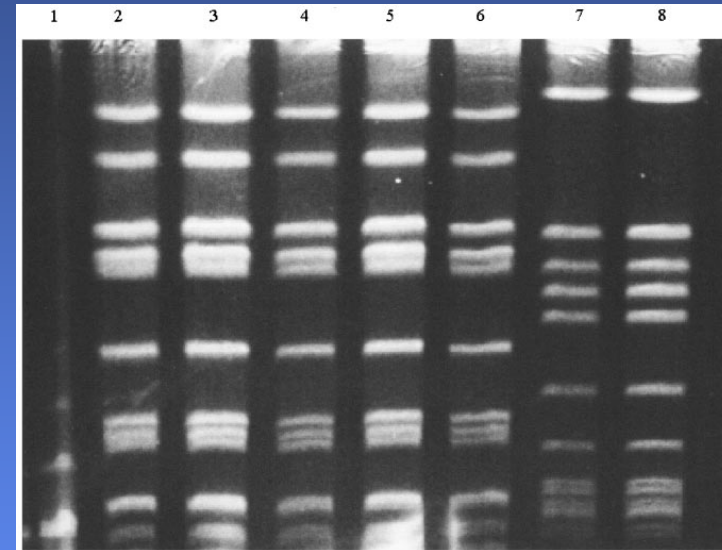
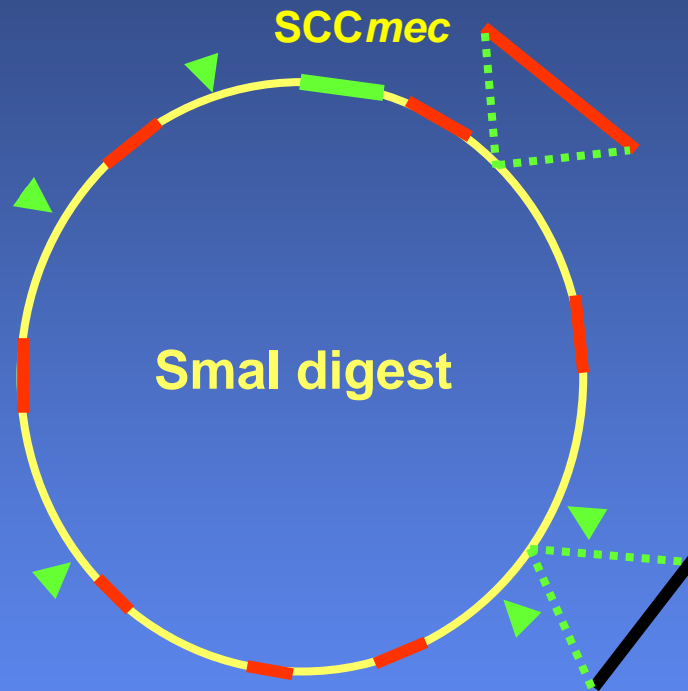
Peut-être, mais d'où vient-il ?

Pulse-Field Gel Electrophoresis



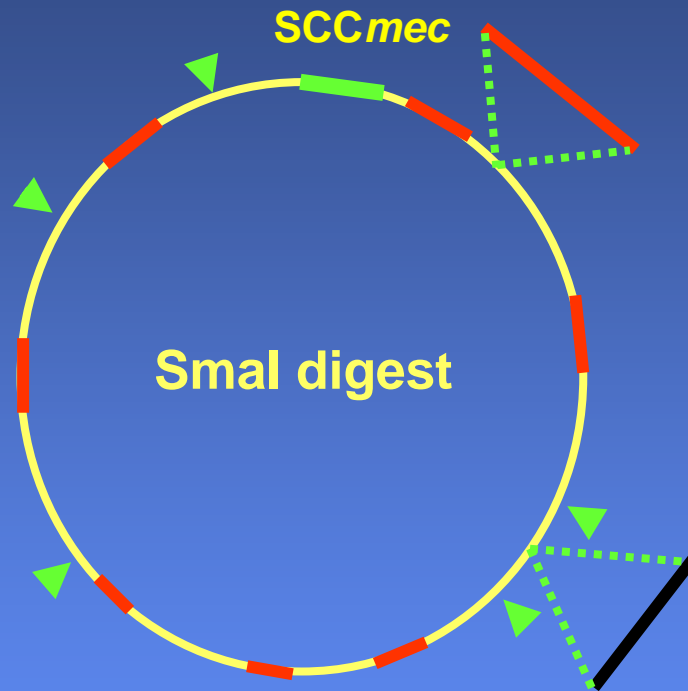
- Lineages:
- Iberian
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 - NY/Japan
 - pediatric pandemic

Multi-Locus Sequence Typing



- Lineages:
- Iberian
 - Bresilian
 - Hungarian
 - NY/Japan
 - pediatric pandemic

Multi-Locus Sequence Typing



House-keeping genes:

- *arcC*
- *aroE*
- *glpF*
- *gmk*
- *pta*
- *tpi*
- *yqiL*

www.mlst.net

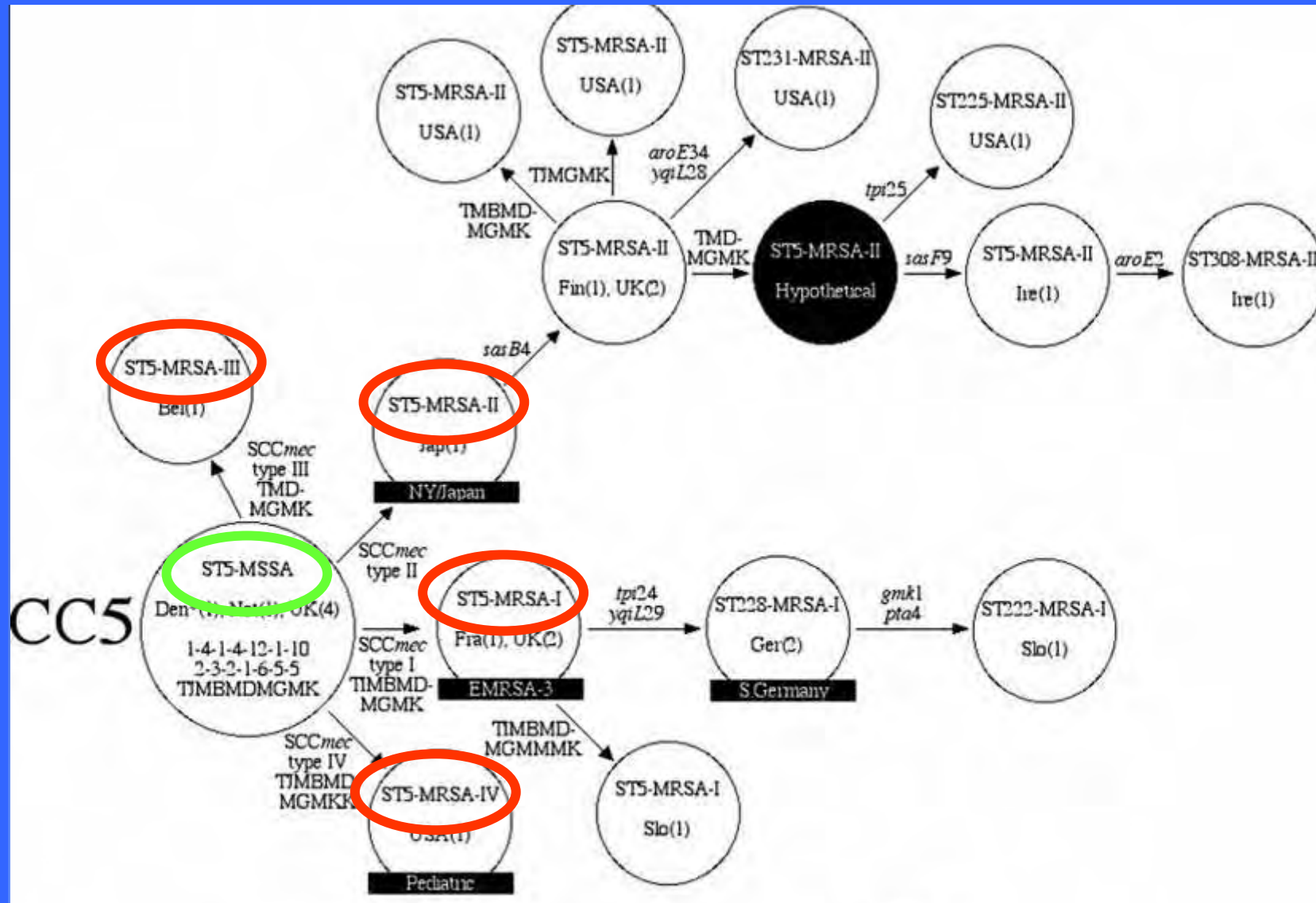
7/7 = clone

5/7 = clonal complex

< 5/7 = unrelated

5 clonal complexes: CC5, CC8, CC22, C30, CC45

MSSA Clonal Clusters and SCCmec Acquisition



*Que le SASM le plus fort gagne !
... et devienne SARM*

Soit, mais d'où vient son SCCmec?



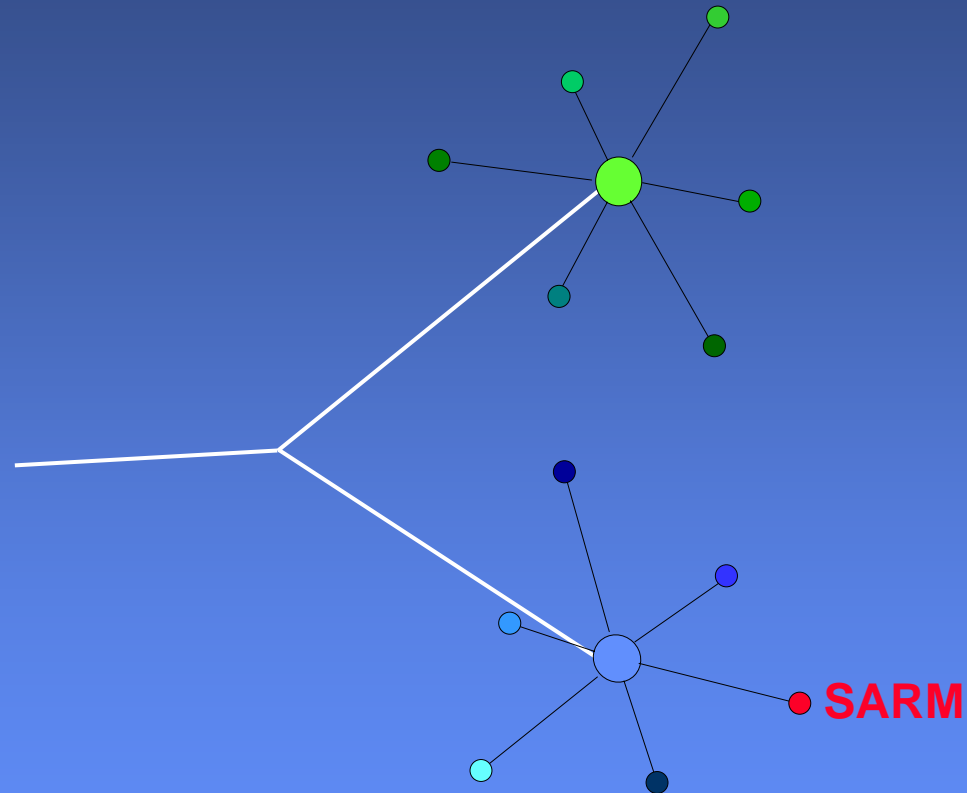
Protocole

- 500 volontaires en bonne santé
- frottis nez
- rechercher *S. aureus* et *S. coag nég*
- déterminer phylogénie
- tester résistance antibio

Résultats

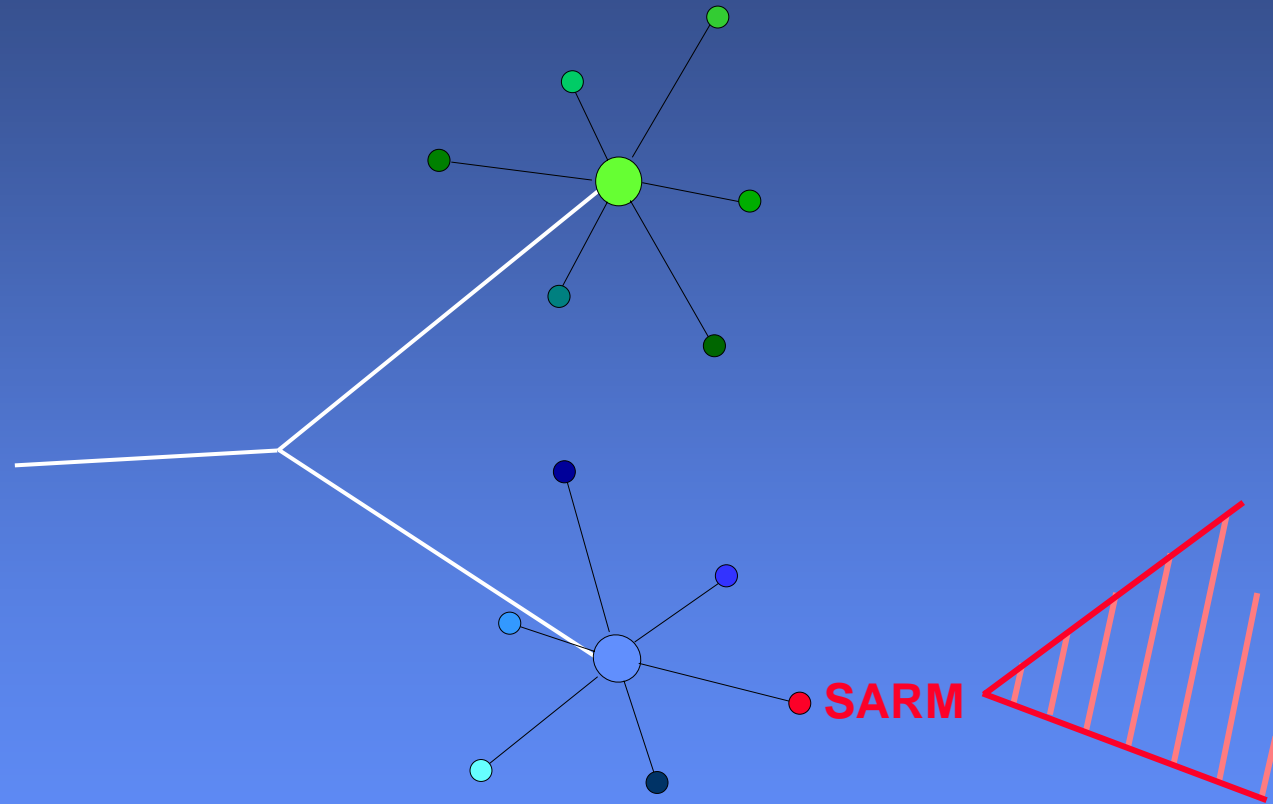
- 135 (27%) porteurs
- SARM (0.66%)
- colonisation *S. aureus* unique, non clonale
- colonisation coag neg générale, et polyclonale
- ca. 20% coag neg résistants méticilline

Phylogénie des *S. aureus* chez les Porteurs Sains



- Acquisition et perte de *SCC_{mec}* = phénomène fréquent (mais non quantifié)
- Les clones se font et se défont *in situ* sur la base de SASMs pré-existants

Phylogénie des *S. aureus* chez les Porteurs Sains



- Acquisition et perte de *SCCmec* = phénomène fréquent (mais non quantifié)
- Les clones se font et se défont *in situ* sur la base de SASMs pré-existants

Infection par SARM à l'hôpital

1. Si souche épidémique = gagneur établi...
Mesures d'hygiène

2. Si souche sporadique = nouvelle (?)

- acquisition sur le patient ?
- quid donneur ?
- quid mécanisme d'acquisition ?
- quid conditions de développement ?

3. Hypothèse:

- Staph coag nég autochtone
- transduction généralisée
- favorisée par stress (fièvre ? antibio ?)

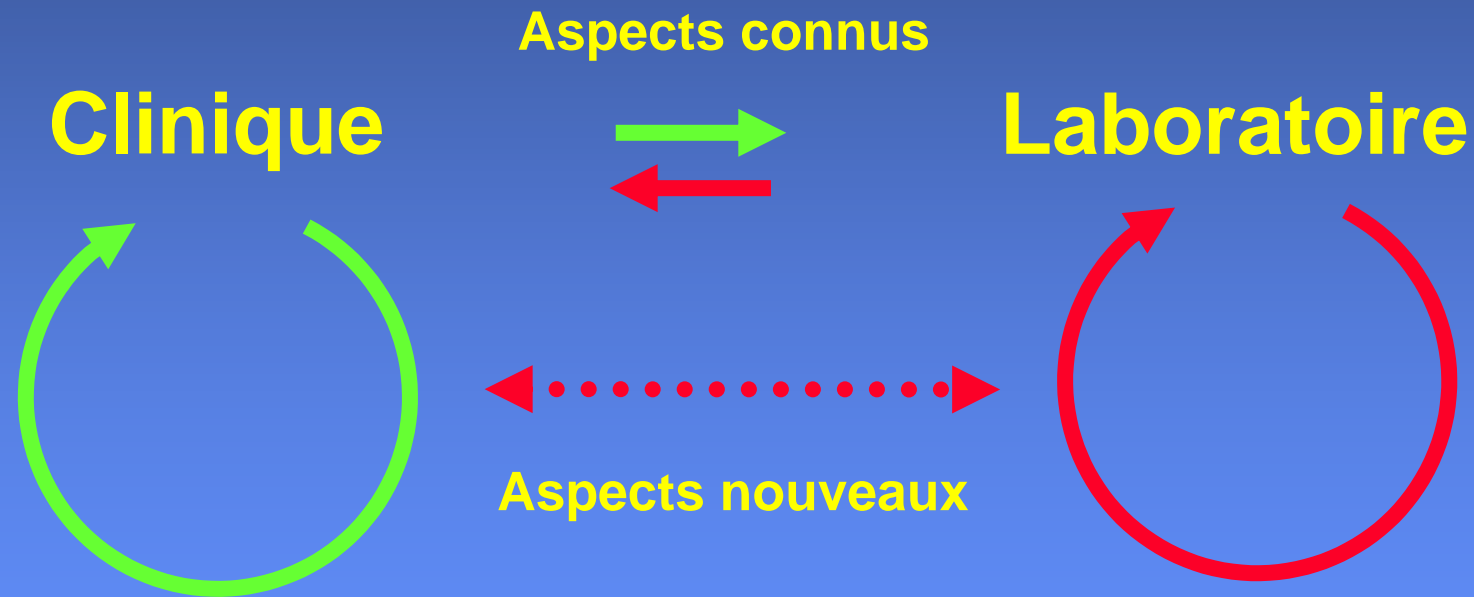
Problème

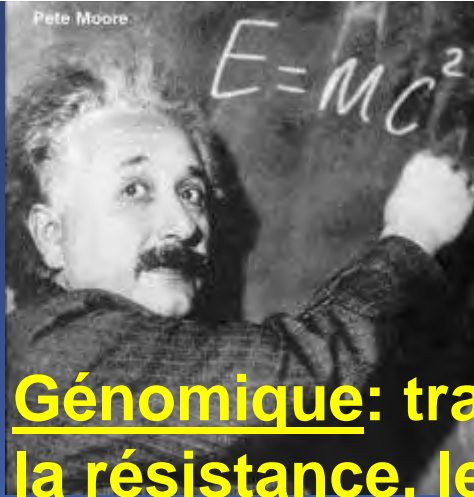
- Le modèle prédit que même avec un très bon contrôle d'infection, de nouvelles souches de SARMs apparaîtrons constamment !!!

Les Mesures Potentielles

- Prévenir la transmission de SCCmec
 - molécules interférant avec phages?
- Décoloniser de leurs S. coag négatifs du nez tous les patients soumis à un traitement antibiotique
- Suivre les résultats de l'intervention

Dialogue entre le Clinicien et le Chercheur L'exemple des Staphylocoques dorés





1. Génomique: transferts de gènes, pathogénèse la résistance, le traitement par le phages
2. Mathématiques: génomique, épidémiologie, vaccins
3. ... compréhension de l'évolution des SARMs, et l'établissement de nouvelles mesures de prévention
4. Quid: biologie moléculaire, biologie organismique, chimie, physique, technologie de l'information, ingénierie ... et toutes les sciences humaine ?