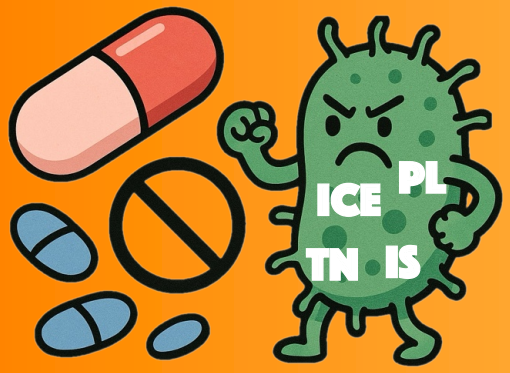
UER MG 2 : Microbiologie générale 2 : bactériologie



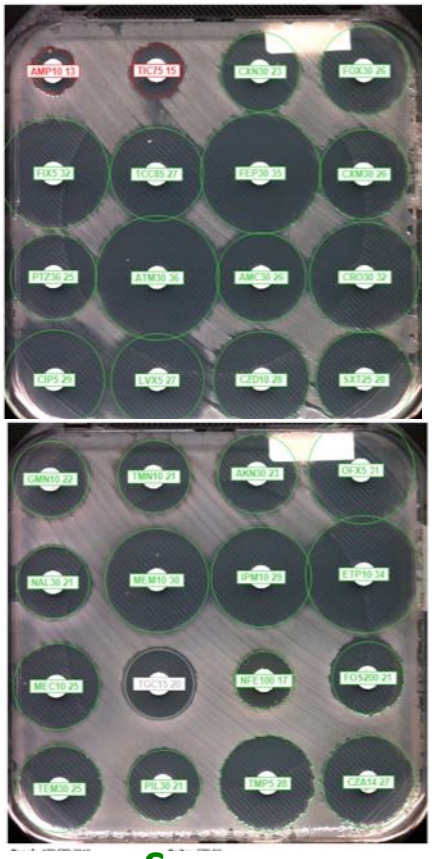
Mobilité des gènes de résistance aux antibiotiques

22 Octobre 2026

Dr Léa BIENTZ

Laboratoire de Bactériologie - CHU Bordeaux
Laboratoire MFP, équipe ARMYNE - Université de Bordeaux

Exemple : *Klebsiella pneumoniae*



Sauvage



BLSE



Carbapénémase (EPC)

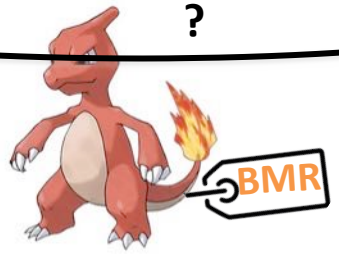
Par quels mécanismes une bactérie peut-elle devenir résistante aux antibiotiques ?

?

?

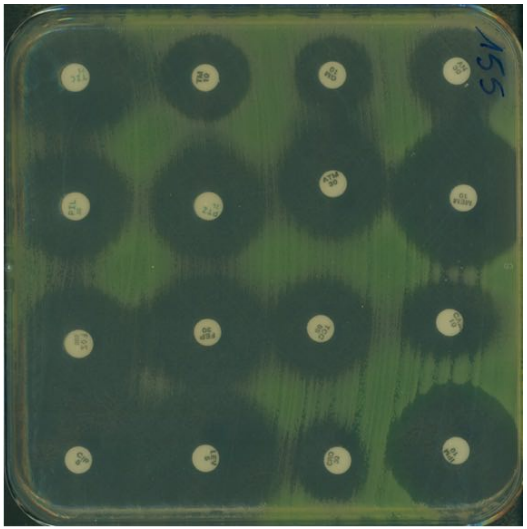
?



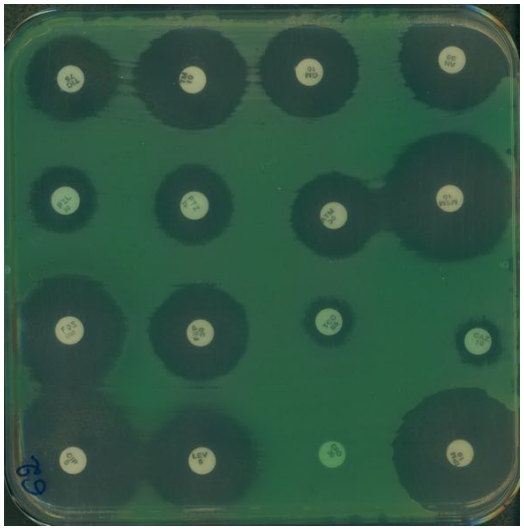




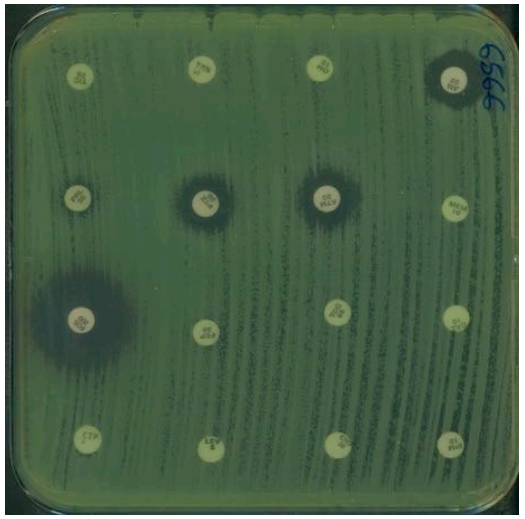
Exemple : *Pseudomonas aeruginosa*



Sauvage



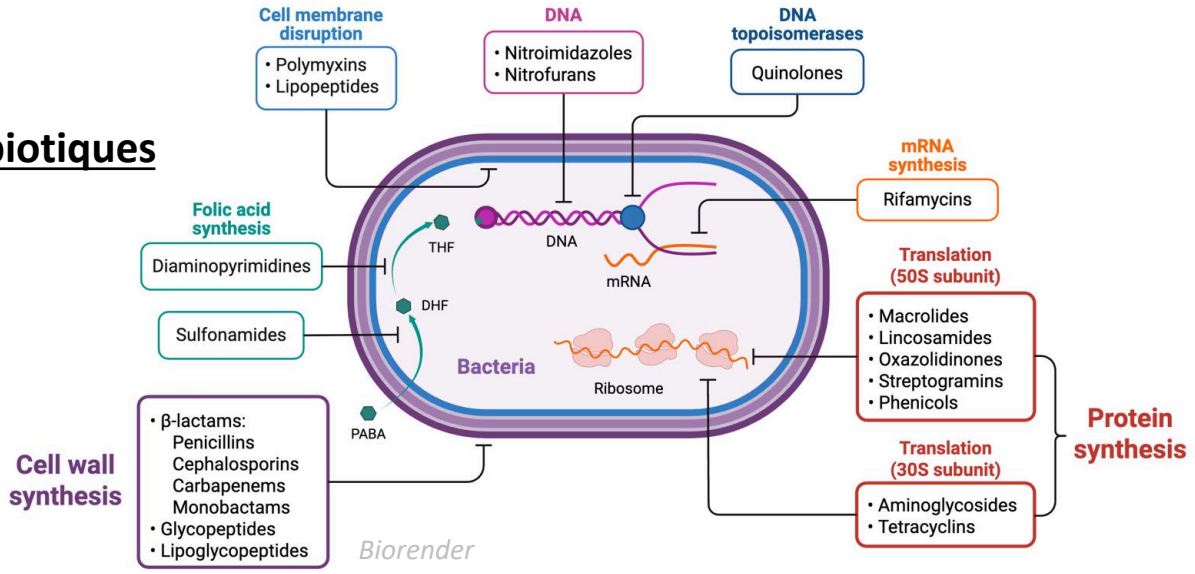
MDR



XDR

Mécanismes de résistance aux AB

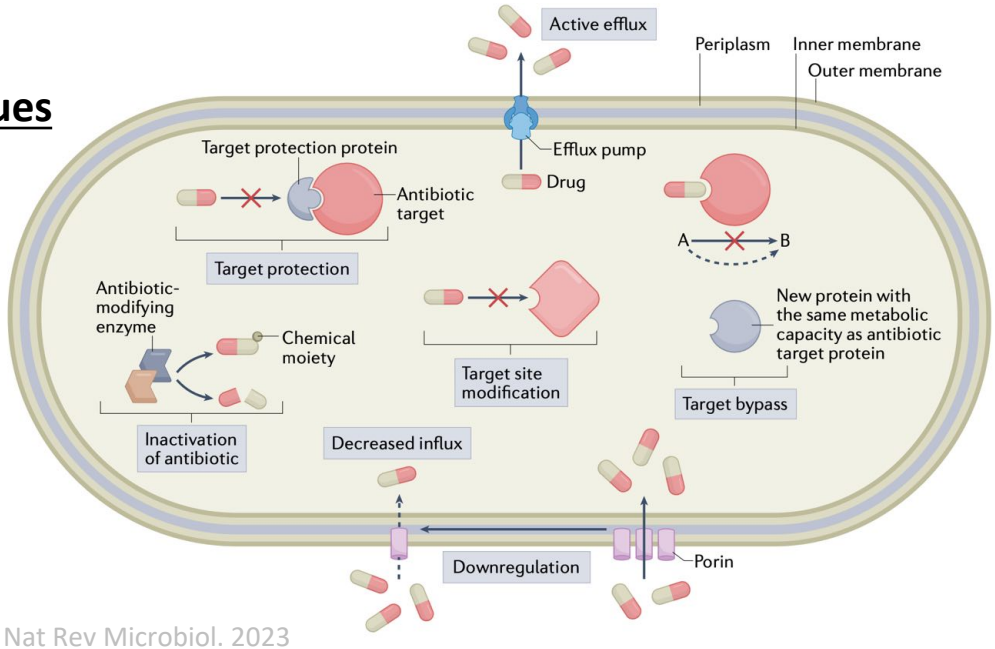
Mécanismes d'action des antibiotiques



Mécanismes de résistance aux antibiotiques

- Défaut d'accumulation +
- Détoxification enzymatique +++
- Défaut de cible ++

EGM



 Darby EM. Molecular mechanisms of antibiotic resistance revisited. Nat Rev Microbiol. 2023

Support génétique

- **Résistances naturelles**
  - affectent toutes les souches d'une même espèce
  - support chromosomique

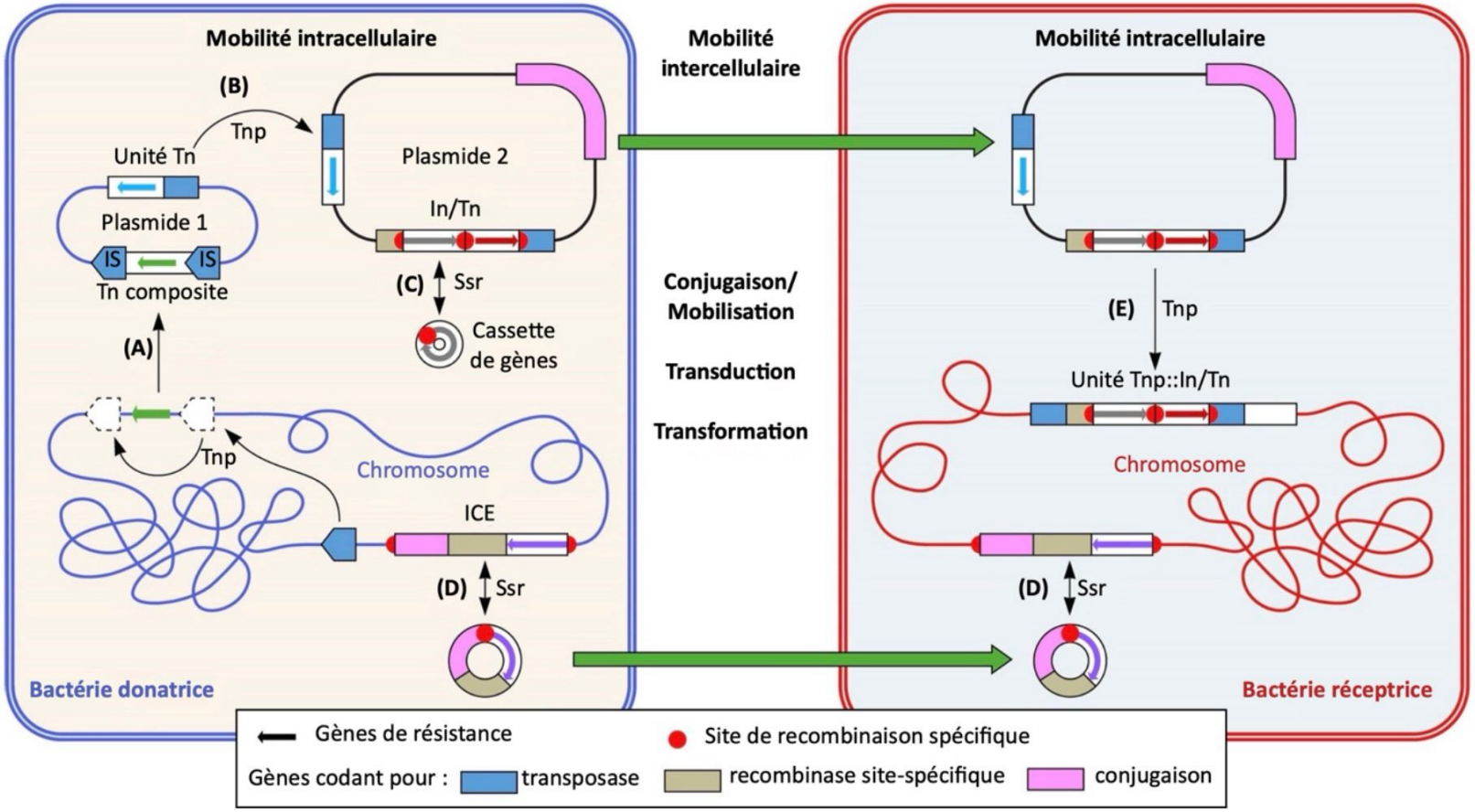
- **Résistances acquises**
  - affectent une partie des souches
  - supports chromosomiques ou extra-chromosomiques
  - **Mutations chromosomiques**
  - **Acquisition de gènes**
    - Mobilisation entre bactéries (inter-cellulaire)
      - Transformation
      - Conjugaison ← **Plasmide, ICE**
      - Transduction
    - Mobilisation des gènes (intra-cellulaire)
      - Eléments transposables
        - Autonomes, EGM ← **Plasmide, ICE, IS**
        - Non-autonomes (ex : Intégrons)

Mécanismes de résistance aux AB

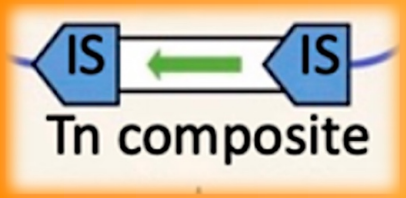
Famille ou groupe d'antibiotiques	Principaux gènes - exemples	Mécanisme de résistance
β-lactamines : pénicillines	blaTEM-1, blaSHV-1, blaZ	Pénicillinases
β-lactamines : céphalosporines à spectre étendu	blaCTX-M, certains variants de blaTEM et blaSHV, blaPER, blaVEB	β-lactamases à spectre étendu — BLSE
β-lactamines : céphalosporines	blaCMY, blaDHA, blaFOX, blaACC, blaACT, blaMIR	Céphalosporinases de classe C
β-lactamines : Carbapénèmes	blaOXA-48-like, blaOXA-23-like, blaOXA-24/40-like, blaOXA-58-like, blaNDM, blaVIM, blaIMP, blaKPC	Carbapénémases à sérine
Méticilline et β-lactamines chez les staphylocoques	mecA, mecC	Production d'une protéine liant les pénicillines de faible affinité
Aminosides : enzymes modificatrices	aac(3)-IIa, aac(6')-Ib, ant(2")-Ia, aadA, aph(3')-IIIa, aph(3")-Ib, aph(6)-Id	Acétylation, adénylation ou phosphorylation ; spectre variable selon l'enzyme
Aminosides : méthylation de la cible	armA, rmtA à rmtH, npmA	Méthylation de l'ARNr 16S
Quinolones : protection de la cible	qnrA, qnrB, qnrS, qnrC, qnrD, qnrVC	Protection de l'ADN gyrase et de la topoisomérase IV
Quinolones : modification ou efflux	aac(6')-Ib-cr, qepA, oqxAB	Modification de certaines fluoroquinolones ou efflux
Glycopeptides	vanA, vanB, vanC, vanD, vanM	Modification du précurseur du peptidoglycane
Macrolides, lincosamides et streptogramines B	erm(A), erm(B), erm(C), erm(F)	Méthylation de l'ARNr 23S : phénotype MLS_B
Macrolides	mef(A), mef(E) ; mph(A), mph(B) ; ere(A), ere(B)	Efflux ou inactivation enzymatique
Tétracyclines : efflux	tet(A), tet(B), tet(K), tet(L)	Diminution de la concentration intracellulaire par efflux
Tétracyclines : protection ribosomique	tet(M), tet(O), tet(Q), tet(S), tet(W)	Protection de la cible ribosomique
Sulfamides	sul1, sul2, sul3	Dihydroptéroate synthase résistante
Triméthoprime	dfrA, dfrB	Dihydrofolate réductase résistante
Phénicolés	catA, catB ; cmlA, floR, fexA	Acétylation ou efflux
Oxazolidinones	cfr, optrA, poxtA	Méthylation de l'ARNr 23S pour cfr ; protection ribosomique pour optrA et poxtA
Fosfomycine	fosA, fosB, fosX	Inactivation enzymatique
Polymyxines	mcr-1 à mcr-10	Modification du lipide A par ajout de phosphoéthanolamine
Acide fusidique	fusB, fusC, fusD	Protection du facteur d'élongation EF-G

Support génétique

- **Echanges inter- et intra-cellulaires**



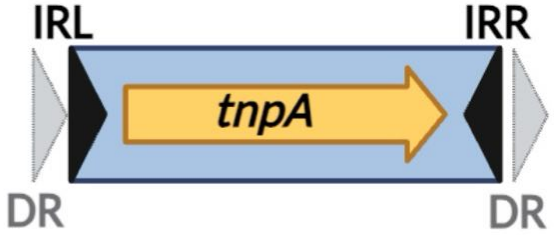
 Partridge SR. Mobile Genetic Elements Associated with Antimicrobial Resistance. Clin Microbiol Rev. 2018.



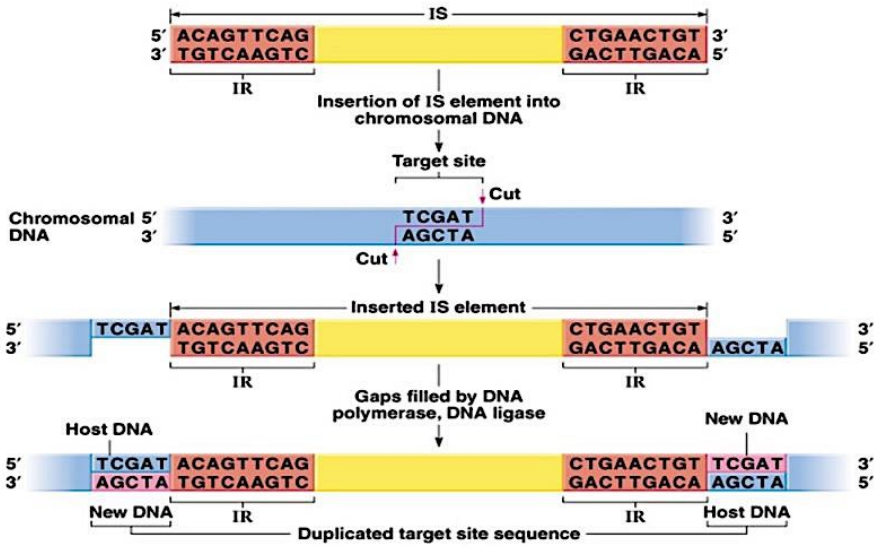
IS : Séquences d'insertions

IS : Séquences d'insertions

IS : Séquence d'insertion



- **Eléments transposables les + simples**
- **Taille** < 2,5 kb
- **Structure**
  - Transposase
  - Séquences répétées : IRL/IRR
  - ADN cible : DR



IS : Séquences d'insertions

- **30^aines de familles**

Families	Sub-groups	Typical size-range	DR (bp)	Ends	IRs	No. of ORF	Frameshift	Catalytic residues	Comments	Mechanism
IS1	–	740–1,180	8–9	GGnnnTG	Y	2	ORFAB	DDE		copy-and-paste and cointegrate
	single ORF	800–1,200	0–9			1				
	ISMhu11	900–4,600	0–10		Y	2	ORFAB			
IS1595	ISPna2	1,000–1,150	8	GGCnnTG	Y	1		DDNK		copy-and-paste ?
	ISPna2+pass	1,500–2,600	8							
	ISH4	1,000	8	CGCTCTT		1		DDNK		
	IS1016	700–745	7–9	GGGgctg		1		DDEK		
	IS1595	900–1,100	8	CcTGATT		1		DDNK + ER4R7		
	ISSod11	1,000–1,100	8	nnnGcnTATC		1		DDHK + ER4R7		
	ISNwi1	1,080–1,200	8	ggnnatTAT		1		DDEK + ER4		
	ISNwi1+pass	1,750–4,750	8			1				
	ISNha5	3,450–7,900	8	CGGnnTT		1		DDER/K		
IS3	IS150	1,200–1,600	3–4	TG	Y	2	ORFAB	DDE		copy-paste
	IS407	1,100–1,400	4	TG						
	IS51	1,000–1,400	3–4	TG						
	IS3	1,150–1,750	3–4	TGa/g						
	IS2	1,300–1,400	5	TG						
IS481	–	950–1,300	4–15	TGT	Y	1		DDE		copy-paste ?
ISNCY	IS1202	1,400–1,700	5	TGT	Y	1		DDEQ		
IS4	IS10	1,200–1,350	9	CT	Y	1		DDE	Hairpin intermediate	cut-and-paste
	IS50	1,350–1,550	8–9	C					Hairpin intermediate	
	ISPepr1	1,500–1,600	7–8	-T-AA					?	
	IS4	1,400–1,600	10–13	-AAT					?	
	IS4Sa	1,150–1,750	8–10	CA					?	
	ISH8	1,400–1,800	10	CAT					?	
	IS231	1,450–5,400	10–12	CAT		1 or + *			* Passenger genes	
IS701	–	1,400–1,550	4		Y	1		DDE		
	ISAba11				Y	1		DDE		
ISH3	–	1,225–1,500	4–5	C-GT	Y	1		DDE		
IS1634	–	1,500–2,000	5–6	C	Y	1		DDE		
IS5	IS903	950–1,150	9	GG	Y	1		DDE		
	ISL2	850–1,200	2–3			1				
	ISH1	900–1,150	8	-GC		1				
	IS5	1,000–1,500	4	Ga/g		1				
	IS1031	850–1,050	3	GAa/g		1				
	IS427	800–1,000	2–4	Ga/g		2	ORFAB			

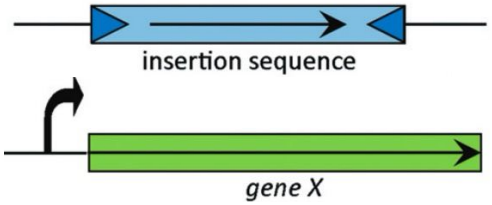
Families	Sub-groups	Typical size-range	DR (bp)	Ends	IRs	No. of ORF	Frameshift	Catalytic residues	Comments	Mechanism
IS1182	–	1,330–1,950	0–60		Y	1		DDE		
ISNCY	ISDol1	1,600–1,900	6–7		Y	1		DDE		
IS6	–	700–900	8	GG	Y	1		DDE		co-integrate
IS21	–	1,750–2,600	4–8	TG	Y	2 *		DDE	* istB: transposition helper	
IS30	–	1,000–1,700	2–3		Y	1		DDE		copy-and-paste
IS66	–	2,000–3,000	8–9	GTAA	Y	3 *		DDE *	* TnpC has the DDE domain	
	ISBst12	1,350–1,900	8–9	GTAA	Y	1		DDE		
IS256	–	1,200–1,500	8–9	Ga/g	Y	1		DDE		copy-paste
	IS1249	1,300	0–10	GG	Y	1		DDE		
	ISC1250	1,250	0–9	GG	Y	1		DDE		
ISH6	–	1,450	8	GGT	Y	1		DDE		
ISLre2	–	1,500–2,000	9		Y	1		DDE		
ISKra4	ISAzba1	1,400–2,900	0		Y	1 or + *		DDE	* Passenger genes	
	ISMich2	1,250–1,400	8	GGG	Y	1 or 2	ORFAB	DDE		
	ISKra4	1,400–3,700	9	GGG	Y	1 or + *		DDE	* Passenger genes	
IS630	–	1,000–1,400	2 *		Y	1 or 2	ORFAB	DDE	* Target site : often NTAN with duplication of the TA	cut-and-paste
IS982	–	1,000	3–9	AC	Y	1		DDE		
IS1380	–	1,550–2,000	4–5	CC	Y	1		DDE		
ISAs1	–	1,200–1,500	8–10	CAGGG	Y	1				
ISL3	–	1,300–2,300	8	GG	Y	1				
Tn3	–	>3,000	0	GGGG	Y	>1		DDE		co-integrate
ISAzo13	–	1,250–2,200	0–4	Ga/g	Y	1				
IS110	–	1,200–1,550	0		N	1		DEDD		
	IS1111				Y *				* IRs not at the termini of the IS	
IS91	–	1,500–2,000	0		N	1		HUH/Y2	Target site GAAC( ) CAAG	rolling circle
IS200/IS605	IS200	600–750	0		N	1 *		HUH/Y1	* TnpA	peel-and-paste
	IS605	1,300–2,000				2 *		HUH/Y1 **	* TnpA + TnpB ; ** Y1 on TnpA	
	IS1341	1,200–1,500				1 *			* TnpB	
IS607	–	1,700–2,500	0		N	2 *		Serine **	* TnpA + TnpB; ** TnpA	
ISNCY	IS892	1,600	0–8	CTAG	Y	2	ORFAB			
	ISLbi1	1,400–1,500	5		Y	1				
	ISMae2	1,400–2,400	9	CAG	Y	1				
	ISPlu15	800–1,000	0		N	1				
	ISA1214	1,000–1,200	8–12		Y	2				
	ISC1217	1,200	6–8	TAG	Y	1				
	ISM1	1,300–1,600	8–9		Y	1				

- Type de transposase : site actif DDE, DEDD, HUH
- Mécanisme de transposition : couper-coller, copier-coller
- Taille

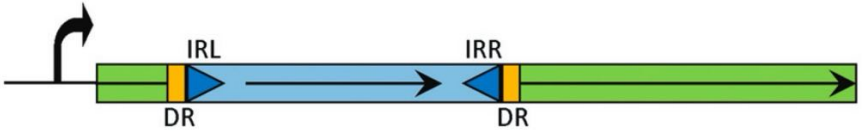
Siguier P. et al. (2006) ISfinder: the reference centre for bacterial insertion sequences. Nucleic Acids Res.
http://www-is.biotoul.fr

IS : Séquences d'insertions

- **Modulation des gènes de résistance**
  - Inactivation du gène



(a) Inactivation of gene product by IS insertion within a target host gene

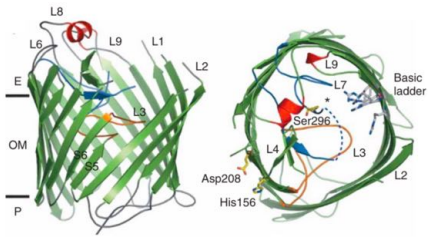


(b) Inactivation of gene expression by IS insertion that disrupts or deletes a target host gene promoter



Table 1. IS-mediated gene inactivation affecting virulence, resistance, and metabolism.

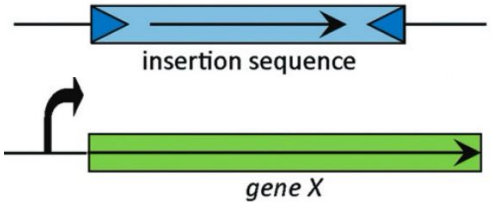
Phenotype affected	Gene	IS element	IS family	Organism	Reference
Antibiotic/xenobiotic resistance					
β-lactam^R	*ampD*	IS*1669*	IS*5*	*P. aeruginosa*	Bagge et al. (2002)
	mexR	IS*21*	IS*2*	*P. aeruginosa*	Boutoille et al. (2004)
Carbapenem^R	*carO*	IS*Aba125*	IS*30*	*A. baumannii*	Mussi et al. (2005)
		IS*Aba825*	IS*982*	*A. baumannii*	Mussi et al. (2005)
	ompE36	IS*903*-like	IS*903*	*E. aerogenes*	Chen et al. (2008b)
	ompK36	IS*5*	IS*5*	*K. pneumoniae*	Lee et al. (2007)
	oprD	IS*Pa133*	IS*13*	*P. aeruginosa*	Ruiz-Martinez et al. (2011)
		IS*Pa1328*	IS*256*	*P. aeruginosa*	Al-Bayssari et al. (2015) and Wolter et al. (2004)
		IS*Pa46*	IS*256*	*P. aeruginosa*	Diene et al. (2013)
		IS*Ppu22*	IS*3*	*P. putida*	Kalantar-Neyestanaki et al. (2015)
		IS*Pa1635*	IS*4*	*P. aeruginosa*	Wolter et al. (2004)
		IS*Pa45*	IS*4*	*P. aeruginosa*	Rojo-Bezares et al. (2014)
		IS*Pa26*	IS*5*	*P. aeruginosa*	Evans and Segal (2007)
		IS*Pa8*	IS*5*	*P. aeruginosa*	Fowler and Hanson (2014)
		IS*Pre2*-like	IS*5*	*P. aeruginosa*	Al Bayssari et al. (2014)
Cefoxitin^R	*ompK36*	IS*26*	IS*6*	*K. pneumoniae*	Hernandez-Alles et al. (1999)
		IS*903*	IS*5*	*K. pneumoniae*	Hernandez-Alles et al. (1999)
		IS*1*	IS*1*	*K. pneumoniae*	Hernandez-Alles et al. (1999)
		IS*5*	IS*5*	*K. pneumoniae*	Hernandez-Alles et al. (1999)
Colistin^R	*lpxA/lpxC*	IS*Aba11*	IS*701*	*A. baumannii*	Moffatt et al. (2011)
	mgrB	IS*1F*-like	IS*1*	*K. pneumoniae*	Cannatelli et al. (2014)
		IS*Kpn14*	IS*1*	*K. pneumoniae*	Cannatelli et al. (2014), Poirel et al. (2015)
		IS*5*-like	IS*5*	*K. pneumoniae*	Cannatelli et al. (2014) and Poirel et al. (2015)
		IS*Kpn13*	IS*5*	*K. pneumoniae*	Poirel et al. (2015)
		IS*Kpn26*-like	IS*5*	*K. oxytoca*	Jayol et al. (2015)



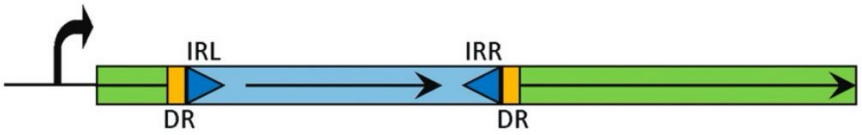
 Vandecraen J. The impact of insertion sequences on bacterial genome plasticity and adaptability. Crit Rev Microbiol. 2017

IS : Séquences d'insertions

- **Modulation des gènes de résistance**
  - Inactivation du gène



(a) Inactivation of gene product by IS insertion within a target host gene

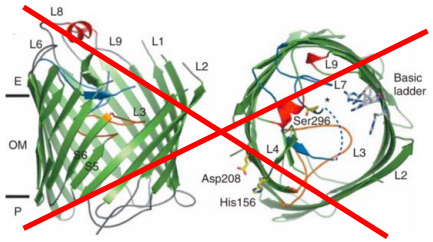


(b) Inactivation of gene expression by IS insertion that disrupts or deletes a target host gene promoter

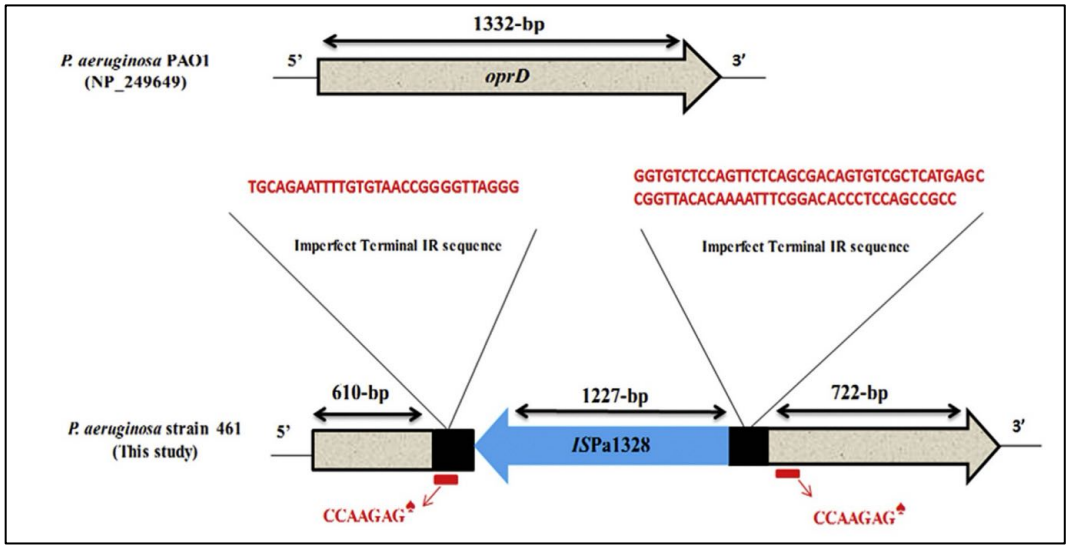


Table 1. IS-mediated gene inactivation affecting virulence, resistance, and metabolism.

Phenotype affected	Gene	IS element	IS family	Organism	Reference
Carbapenem^R	*oprD*	IS*Pa1328*	IS*256*	*P. aeruginosa*	Al-Bayssari et al. (2015)



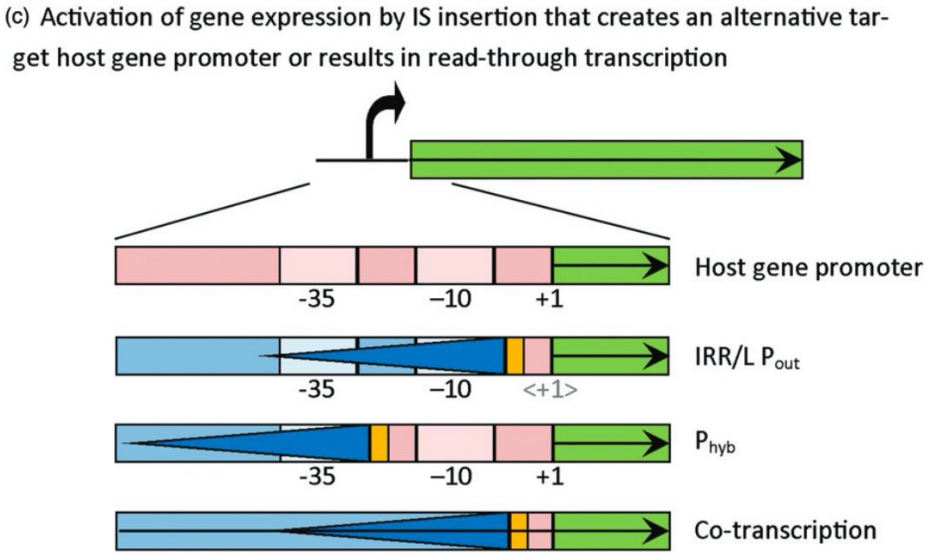
Imipénème-R
Méropénème-R



 Vandecraen J. The impact of insertion sequences on bacterial genome plasticity and adaptability. Crit Rev Microbiol. 2017

IS : Séquences d'insertions

- **Modulation des gènes de résistance**
  - Modulation de l'expression des gènes



 Vandecraen J. The impact of insertion sequences on bacterial genome plasticity and adaptability. Crit Rev Microbiol. 2017

IS : Séquences d'insertions

Table 2. Modulation of expression of neighbouring genes by IS elements carrying a complete outward-directed promoter.

IS family	IS element	IRx[a]	Phenotype affected	Gene	Organism
IS*1380*	IS*Ecp1*	R	β-Lactam^R	$bla_{CTX-M-15}$	*Enterobacteriaceae*
				$bla_{CTX-M-17}$	*K. pneumoniae*
				$bla_{CTX-M-19}$	*K. pneumoniae*
				$bla_{CTX-M-2}$	*K. ascorbata*
			Aminoglycoside^R	*rmtC*	*E. coli*
	IS*1170*	L	5-Nitroimidazole^R	*nimC*	*Bacteroides*
	IS*1188*	L	Carbapenem^R	*cfiA*	*B. fragilis*
	IS*612*	L		*cfiA*	*B. fragilis*
	IS*613*	L		*cfiA*	*B. fragilis*
	IS*614*	L		*cfiA*	*B. fragilis*
	IS*942*	L		*cfiA*	*B. fragilis*
IS*3*	IS*Pst4*	R	Effective host range expression	*oriV*	*P. stutzeri*
	IS*3*	R	Arginine biosynthesis	*argE*	*E. coli*
		R	Citrate utilization	*citT*	
		R	Acetate utilization	*acs*	
	IS*407*	R	Lactose utilization	*lac*	*B. cepacia*
	IS*6110*	R	Genes activated during infection	Rv2280/Rv1468c	*M. tuberculosis*
IS*4*	IS*Aba1*	L	Ceftazidime^R	bla_{ampC}	*A. baumannii*
			Carbapenem^R	$bla_{OXA-51-like}$	*A. baumannii*
				bla_{OXA-23}	*A. baumannii*
	IS*Pa12*	L	Ceftazidime^R	bla_{PER-1}	*A. baumannii*
					P. aeruginosa
					S. enterica
	IS*10*	L	Fluoroquinolone^R	*acrEF pump*	*S. enterica*
			Histidine biosynthesis	*hisD*	*S. enterica*
	IS*1999*	L	Ceftazidime^R	bla_{VEB-1}	*P. aeruginosa*
				bla_{OXA-48}	*K. pneumoniae*
	IS*942*	L	β -lactam^R	*ccrA*	*B. fragilis*
IS*481*	IS*Rme5*	R	Zinc^R	*cnrCBAT*	*C. metallidurans*
	IS*481a*	L	Catalase activity	*katA*	*B. pertussis*
			Type III cytotoxic effector protein	*bteA*	*B. pertussis*
IS*5*	IS*Bf6*	L	5-nitroimidazole^R	*nimE*	*Bacteroides*
	IS*1168*	R		*nimA nimB*	*Bacteroides*
	IS*1169*	R		*nimD*	*B. fragilis*
	IS*1186*	R	Carbapenem^R	*cfiA*	*B. fragilis*
IS*6*	IS*S1*	L	Restriction-Modification system	*abi-416*	*Lactobacillus lactis*
	IS*257*	L	Tetracycline^R	*tetA*(K)	*S. aureus*
IS*982*	IS*1187*	L	Carbapenem^R	*cfiA*	*B. fragilis*
IS*L3*	IS*1411*	L	Phenol degradation	*pheBA*	*P. putida*

Table 3. Modulation of expression of neighbouring genes by IS elements carrying an outward-directed -35 promoter component.

IS family	IS element	Phenotype affected	Gene	Organism
IS1	IS*1*	Erythromycin^R		*E. coli*
		Extended-spectrum β-lactamase	bla_{TEM-1}	
	IS*1*	Fluoroquinolone^R	*acrEF pump*	*S. enterica*
	IS*1*-like	Extended-spectrum β-lactamase	*blaT-6*	*E. coli*
IS*21*	IS*Bf1*	High-level β-lactam ^{R}	*cepA*	*B. fragilis*
	IS*Kpn7*	Extended-spectrum β-lactamase	bla_{KPC}	*K. pneumoniae*
IS*256*	IS*1490*	2,4,5-trichlorophenoxyacetic acid catabolism	*tftA*	*B. cepacia*
	IS*256*	Methicillin^R	*llm*	*S. aureus*
			mecA	*S. sciuri*
	IS*406*	Lactose utilization	*lac*	*B. cepacia*
IS*3*	IS*2*	Ampicillin^R	*ampC*	*E. coli*
		Fluoroquinolone^R	*acrEF pump*	*E. coli*
		Erythromycin^R		
		Galactose utilization	*gal*	*E. coli*
		Arginine biosynthesis	*argE*	
			xis/int	Bacteriophage λ
	IS*981*	Lactate production	*ldhB*	*L. lactis*
IS*30*	IS*18*	Aminoglycoside^R	*aac(6')-Ij*	*Acinetobacter*
	IS*30*	Spectinomycin^S	*cmr/mdfA*	*E. coli*
		Galactose utilization	*galK*	*E. coli*
IS*6*	IS*1008*	Carbapenem^R	bla_{OXA-58}	*A. baumannii*
	IS*140*	Gentamycin^R	*aac*(3)-III and IV	
	IS*257*	Tetracycline^R	*tetA*(K)	*S. aureus*
		Trimethoprim^R	*thyE-dfrA-orf140*	*S. aureus*
	IS*26*	Aminoglycoside^R	*aphA7*, bla_{SHV-2a}	*K. pneumoniae*
		SHV-type extended-spectrum β-lactamase	bla_{SHV-2a}	*P. aeruginosa*
IS*5*	IS*Va1*	Ferric anguibactin transport and biosynthesis	*fatDCBAangRT*	*V. anguilarum*
IS*982*	IS*982*	Citrate transport	*citQRP*	*L. lactis*

 Vandecraen J. The impact of insertion sequences on bacterial genome plasticity and adaptability. Crit Rev Microbiol. 2017

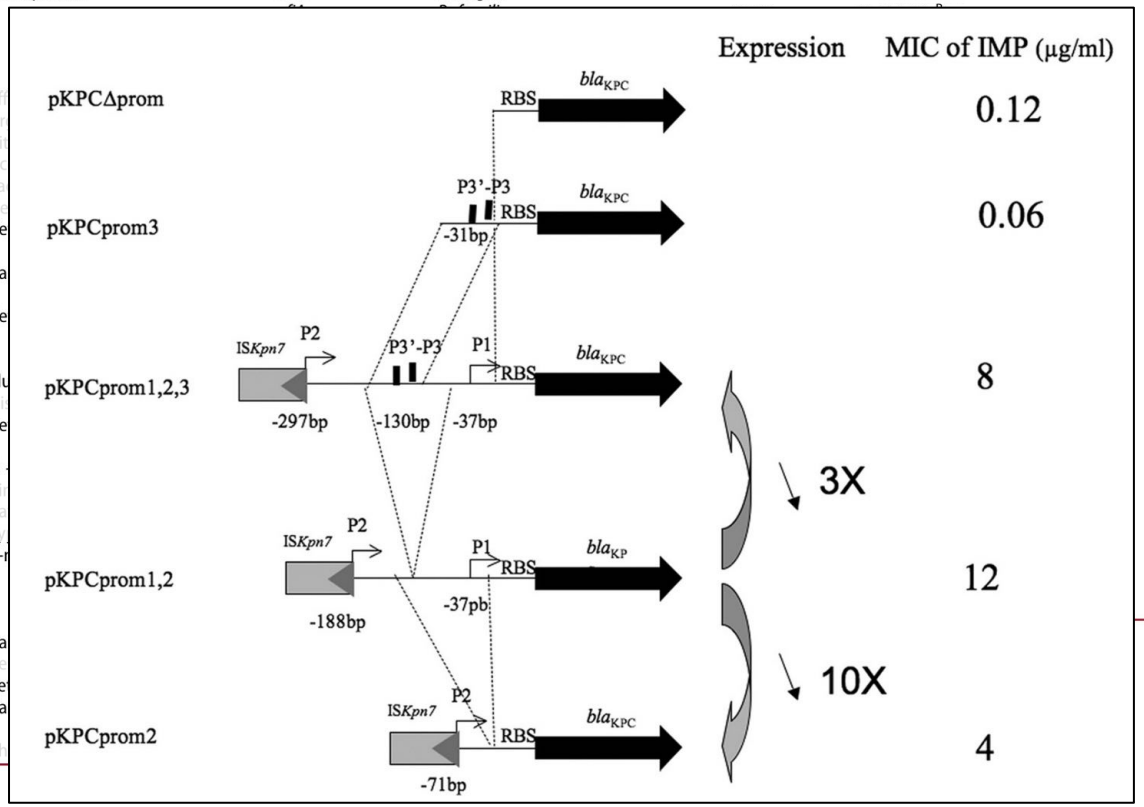
IS : Séquences d'insertions

Table 2. Modulation of expression of neighbouring genes by IS elements carrying a complete outward-directed promoter.

IS family	IS element	IRx[a]	Phenotype affected	Gene	Organism
IS*1380*	IS*Ecp1*	R	β-Lactam^R	$bla_{CTX\text{-}M\text{-}15}$	*Enterobacteriaceae*
				$bla_{CTX\text{-}M\text{-}17}$	*K. pneumoniae*
				$bla_{CTX\text{-}M\text{-}19}$	*K. pneumoniae*
				$bla_{CTX\text{-}M\text{-}2}$	*K. ascorbata*
			Aminoglycoside^R	*rmtC*	*E. coli*
	IS*1170*	L	5-Nitroimidazole^R	*nimC*	*Bacteroides*
	IS*1188*	L	Carbapenem^R	*cfiA*	*B. fragilis*
	IS*612*	L			
	IS*613*	L			
	IS*614*	L			
	IS*942*	L			
IS*3*	IS*Pst4*	R	Ef		
	IS*3*	R	Ar		
		R	Cl		
		R	Ac		
	IS*407*	R	La		
	IS*6110*	R	Ge		
IS*4*	IS*Aba1*	L	Ce		
			Ca		
	IS*Pa12*	L	Ce		
	IS*10*	L	Flu		
			Hi		
	IS*1999*	L	Ce		
	IS*942*	L	β -		
IS*481*	IS*Rme5*	R	Zi		
	IS*481a*	L	Ca		
			Ty		
IS*5*	IS*Bf6*	L	5-r		
	IS*1168*	R			
	IS*1169*	R			
	IS*1186*	R	Ca		
IS*6*	IS*S1*	L	Re		
	IS*257*	L	Te		
IS*982*	IS*1187*	L	Ca		
IS*L3*	IS*1411*	L	Ph		

Table 3. Modulation of expression of neighbouring genes by IS elements carrying an outward-directed -35 promoter component.

IS family	IS element	Phenotype affected	Gene	Organism
IS1	IS*1*	Erythromycin^R		*E. coli*
		Extended-spectrum β-lactamase	$bla_{TEM\text{-}1}$	
	IS*1*	Fluoroquinolone^R	*acrEF pump*	*S. enterica*
	IS*1*-like	Extended-spectrum β-lactamase	*blaT-6*	*E. coli*
IS*21*	IS*Bf1*	High-level β-lactam ^{R}	*cepA*	*B. fragilis*
	IS*Kpn7*	Extended-spectrum β-lactamase	bla_{KPC}	*K. pneumoniae*
IS*256*	IS*1490*	2,4,5-trichlorophenoxyacetic acid catabolism	*tftA*	*B. cepacia*
			llm	*S. aureus*
			mecA	*S. sciuri*
			lac	*B. cepacia*
			ampC	*E. coli*
			acrEF pump	*E. coli*
			gal	*E. coli*
			argE	
			xis/int	Bacteriophage λ
			ldhB	*L. lactis*
			aac(6')-Ij	*Acinetobacter*
			cmr/mdfA	*E. coli*
			galK	*E. coli*
			$bla_{OXA\text{-}58}$	*A. baumannii*
			aac(3)-III and IV	
			tetA(K)	*S. aureus*
			thyE-dfrA-orf140	*S. aureus*
			aphA7, $bla_{SHV\text{-}2a}$	*K. pneumoniae*
			$bla_{SHV\text{-}2a}$	*P. aeruginosa*
			fatDCBAangRT	*V. anguilarum*
			citQRP	*L. lactis*

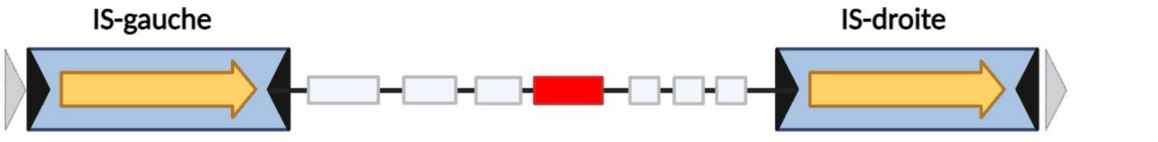


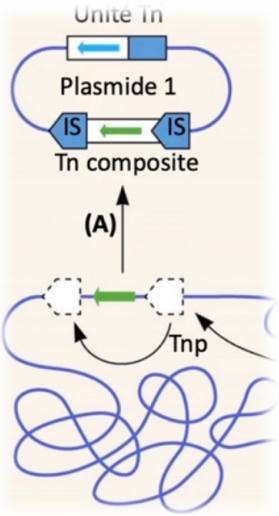
Naas T. Role of ISKpn7 and deletions in blaKPC gene expression. Antimicrob Agents Chemother. 2012

 Vandecraen J. The impact of insertion sequences on bacterial genome plasticity and adaptability. Crit Rev Microbiol. 2017

IS : Séquences d'insertions

- **Mobilisation des gènes de résistance**
  - Transposon composite





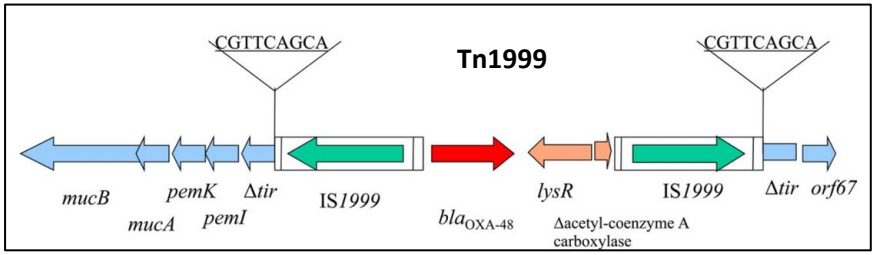


TABLE 1 Examples of IS and composite transposons associated with resistance genes in Gram-negative bacteria

IS[a]	Tn[b]	Determinant	Resistance(s)[c]
IS*1*	Tn*9*	*catA1*	Chloramphenicol
IS*10*	Tn*10*	*tet*(B)	Tetracycline
IS*26*[d]	Tn*4352*	*aphA1*	Kanamycin
	Tn*6020*	*aphA1*	Kanamycin
		tet(C)	Tetracycline
		tet(D)	Tetracycline
		catA2	Chloramphenicol
	Tn*2003*	bla_{SHV}	β-Lactams
		cfr	Phenicols/lincosamides/oxazolidinones/ pleuromutilins/streptogramin A
IS*256*[e]		*cfr*	Phenicols/lincosamides/oxazolidinones/ pleuromutilins/streptogramin A
IS*50*	Tn*5*	*aph*(3′)-*IIa*-*ble*-*aph*(6)-*Ic*	Kanamycin, bleomycin, streptomycin
IS*903*	Tn*903*	*aphA1*	Kanamycin
IS*1999*	Tn*1999*	bla_{OXA-48}-like	Carbapenems
IS*Apl1*	Tn*6330*	*mcr-1*	Colistin
IS*Ec69*		*mcr-2*	Colistin
IS*As2*		bla_{FOX-5}	BLBLI
IS*Aba14*	Tn*aphA6*	*aphA6*	Kanamycin
IS*Aba1*	Tn*2006*	bla_{OXA-23}	Carbapenems
		$bla_{OXA-237}$	Carbapenems
IS*Aba125*	Tn*125*	bla_{NDM}	Carbapenems

TABLE 2 IS and composite transposons associated with resistance genes in staphylococci and enterococci

IS[a]	Tn	Determinant	Associated resistance(s)	Host[b]
IS*16*	Tn*1547*	*vanB1*	Vancomycin	E
IS*256*		*cfr*	Phenicols/lincosamides/oxazolidinones/ pleuromutilins/streptogramin A	S
	Tn*1547*	*vanB1*	Vancomycin	E
	Tn*4001*	*aacA-aphD*	Gentamicin/kanamycin/tobramycin	S
	Tn*5281*	*aacA-aphD*	Gentamicin/kanamycin/tobramycin	E
	Tn*5384*	*aacA-aphD*	Gentamicin/kanamycin/tobramycin	E
	Tn*5384*	*erm*(B)	MLS antibiotics	E
IS*257*[c]		*aadD*	Kanamycin/neomycin/paromomycin/tobramycin	S
		aphA-3	Kanamycin/neomycin	S
		bcrAB	Bacitracin	S
		ble	Bleomycin	S
		dfrK	Trimethoprim	S
		erm(C)	MLS antibiotics	S
		fosB5	Fosfomycin	S
		fusB	Fusidic acid	S
		ileS2 (*mupA*)	Mupirocin	S
		qacC	Antiseptics/disinfectants	S
		sat4	Streptothricin	S
		tet(K)	Tetracycline	S
		tet(L)	Tetracycline	S
		vat(A)	Streptogramin A	S
		vga(A)	Streptogramin A/pleuromutilins/lincosamides	S
		vgb(A)	Streptogramin B	S
	Tn*924*	*aacA-aphD*	Gentamicin/kanamycin/tobramycin	E
	Tn*4003*	*dfrA*	Trimethoprim	S
	Tn*6072*	*aacA-aphD*	Gentamicin/kanamycin/tobramycin	S
	Tn*6072*	*spc*	Spectinomycin	S
IS*1182*	Tn*5405*	*aadE*	Streptomycin	S, E
	Tn*5405*	*aphA-3*	Kanamycin/neomycin	S, E
	Tn*5405*	*sat4*	Streptothricin	S, E
IS*1216*		*cfr*	Phenicols/lincosamides/oxazolidinones/ pleuromutilins/streptogramin A	E
		str	Streptomycin	E
	Tn*5385*	*aacA-aphD*	Gentamicin/kanamycin/tobramycin	E
	Tn*5385*	*aadE*	Streptomycin	E
	Tn*5385*	*blaZ*	Penicillins	E
	Tn*5385*	*erm*(B)	MLS antibiotics	E
	Tn*5385*	*tet*(M)	Tetracycline/minocycline	E
	Tn*5482*	*vanA*	Vancomycin	E
	Tn*5506*	*vanA*	Vancomycin	E
IS*1272*	Tn*Sha1*	*fabI*	Triclosan	S
	Tn*Sha2*	*fabI*	Triclosan	S
IS*21-558*		*cfr*	Phenicols/lincosamides/oxazolidinones/ pleuromutilins/streptogramin A	S
		lsa(B)	Lincosamides	S
IS*Enfa4*		*cfr*	Phenicols/lincosamides/oxazolidinones/ pleuromutilins/streptogramin A	S, E
IS*Sau10*		*aadD*	Kanamycin/neomycin/paromomycin/tobramycin	S
		dfrK	Trimethoprim	S
		erm(C)	MLS antibiotics	
		erm(T)	MLS antibiotics	S
		tet(L)	Tetracycline	S

Poirel L. Genetic features of the widespread plasmid coding for the carbapenemase OXA-48. Antimicrob Agents Chemother. 2012

IS : Séquences d'insertions

- **Mobilisation des gènes de résistance**
  - IS « atypiques »

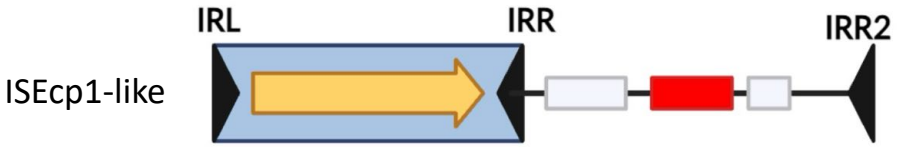
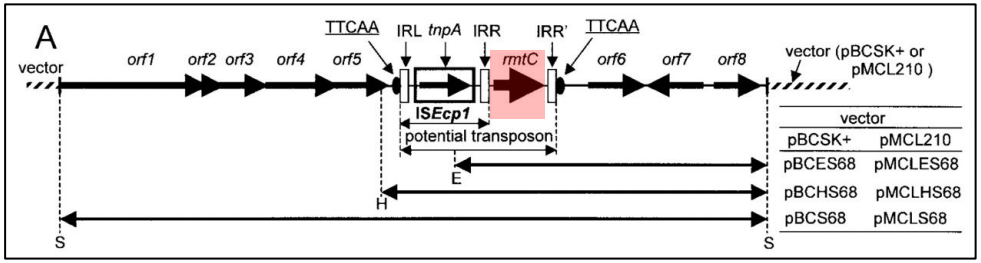


TABLE 3 Examples of resistance genes associated with IS*Ecp1* and related elements

IS[a]	Determinant(s)	Resistance(s)[b]
IS*Ecp1*[c]	$bla_{CTX-M-1}$ group	3GC
	$bla_{CTX-M-2}$ group	3GC
	$bla_{CTX-M-9}$ group	3GC
	$bla_{CTX-M-25}$ group	3GC
	bla_{ACC}	3GC, BLBLI
	bla_{CMY-2}-like genes	3GC, BLBLI
	$bla_{OXA-181}$-like genes	Carbapenems
	$bla_{OXA-204}$	Carbapenems
	Some *qnrB* genes	Fluoroquinolones (low level)
	qnrE1	Fluoroquinolones (low level)
	rmtC	Aminoglycosides (high level)
IS*1247*	*aac(3)-IIf-arr*	(Aminoglycosides, rifampin[d])
IS*Kpn23*	bla_{BKC}	Carbapenems
	aac(3)-IIb	GEN, TOB
IS*Enca1*	*aph(2″)-Ie*	GEN, TOB, KAN



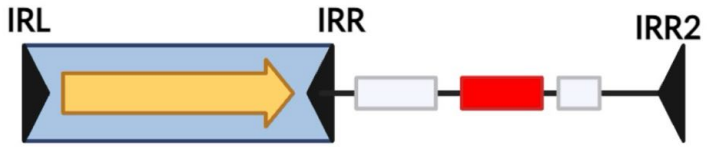
Wachino J. Mode of transposition and expression of 16S rRNA methyltransferase gene rmtC accompanied by ISEcp1. Antimicrob Agents Chemother. 2006.

 Partridge SR, Kwong SM, Firth N, Jensen SO. Mobile Genetic Elements Associated with Antimicrobial Resistance. Clin Microbiol Rev. 2018.

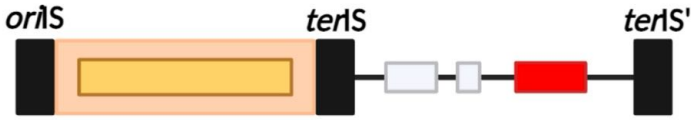
IS : Séquences d'insertions

- **Mobilisation des gènes de résistance**
  - IS « atypiques »

ISEcp1-like



IS91-like
ISCR-like



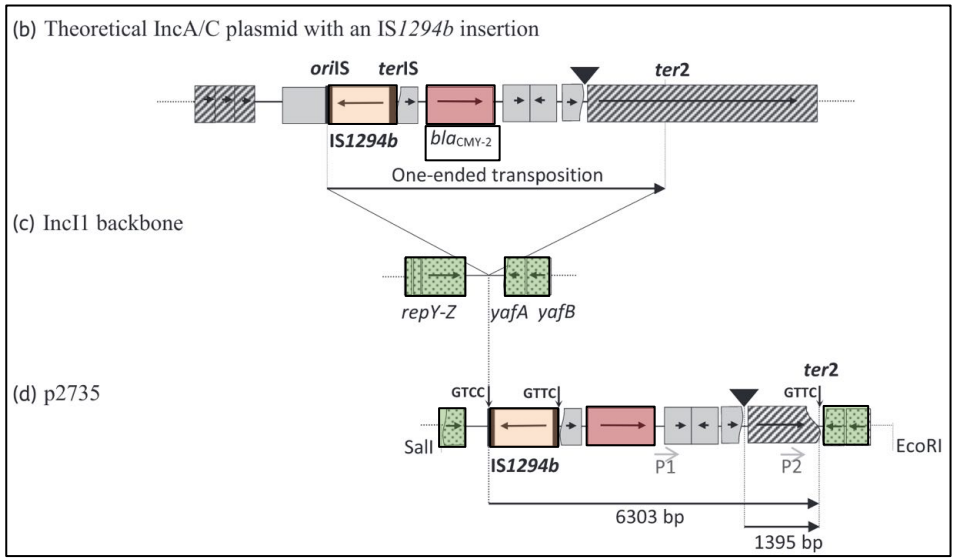


TABLE 3 Examples of resistance genes associated with IS*Ecp1* and related elements

IS[a]	Determinant(s)	Resistance(s)[b]
IS*Ecp1*[c]	$bla_{CTX-M-1}$ group	3GC
	$bla_{CTX-M-2}$ group	3GC
	$bla_{CTX-M-9}$ group	3GC
	$bla_{CTX-M-25}$ group	3GC
	bla_{ACC}	3GC, BLBLI
	bla_{CMY-2}-like genes	3GC, BLBLI
	$bla_{OXA-181}$-like genes	Carbapenems
	$bla_{OXA-204}$	Carbapenems
	Some *qnrB* genes	Fluoroquinolones (low level)
	qnrE1	Fluoroquinolones (low level)
	rmtC	Aminoglycosides (high level)
IS*1247*	*aac(3)-IIf-arr*	(Aminoglycosides, rifampin[d])
IS*Kpn23*	bla_{BKC}	Carbapenems
	aac(3)-IIb	GEN, TOB
IS*Enca1*	*aph(2″)-Ie*	GEN, TOB, KAN

TABLE 4 Examples of resistance genes associated with IS*CR* elements

IS[a]	Determinant(s)	Resistance(s)[b]
IS*CR1*	*dfrA10*	Trimethoprim
	catA2	Chloramphenicol
	armA	Aminoglycosides (high level)
	bla_{DHA}	3GC, BLBLI
	$bla_{CMY/MOX}$-like genes	3GC, BLBLI
	Some *qnrB* genes	Fluoroquinolones (low level)
IS*CR2*	*sul2*	Sulfonamides
	tet(31)	Tetracycline
IS*CR3* family elements		
IS*CR3*	*floR*	Florfenicol
IS*CR4*	bla_{SPM-1}	Carbapenems
IS*CR5*	bla_{OXA-45}	3GC
IS*CR6*	*ant(4′)-IIb*	TOB, AMK
IS*CR14*	*rmtB, rmtD*	GEN, TOB, AMK
IS*CR15*	bla_{AIM-1}	Carbapenems
IS*CR27*	bla_{NDM}	Carbapenems

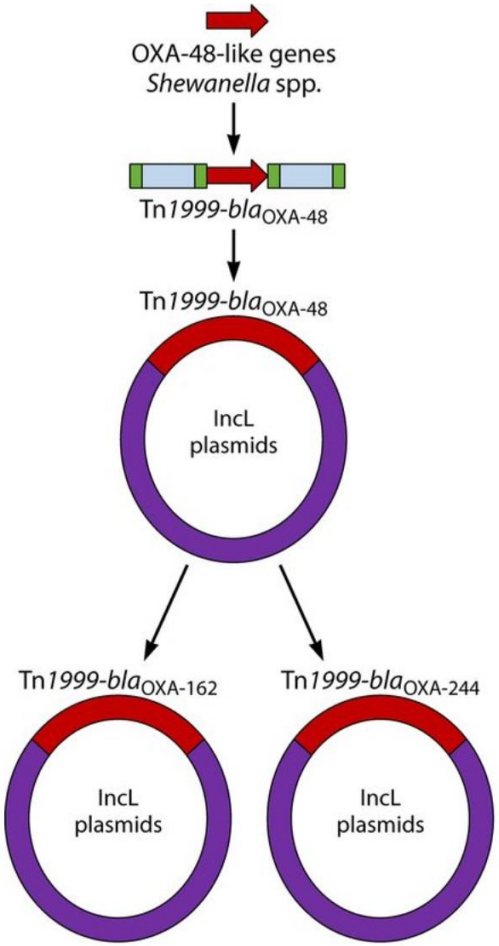
Yassine H. Experimental evidence for IS1294b-mediated transposition of the blaCMY-2 cephalosporinase gene in Enterobacteriaceae. J Antimicrob Chemother. 2015.

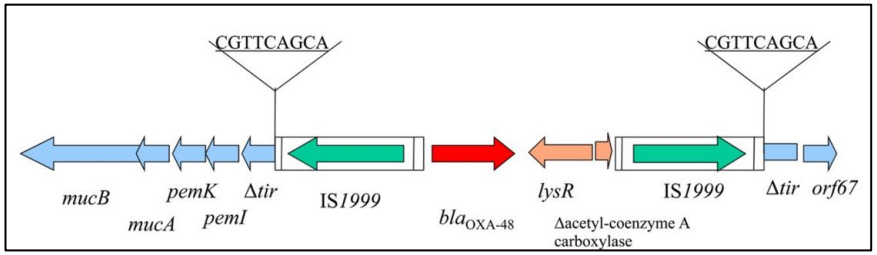
 Partridge SR, Kwong SM, Firth N, Jensen SO. Mobile Genetic Elements Associated with Antimicrobial Resistance. Clin Microbiol Rev. 2018.

IS : Séquences d'insertions

- **Mobilisation des gènes de résistance**

Origine des carbapénémases *bla*$_{\text{OXA-48-like}}$ chez les *Enterobacterales*





2004 : 1er description en Turquie, OXA-48 chez *K. pneumoniae*

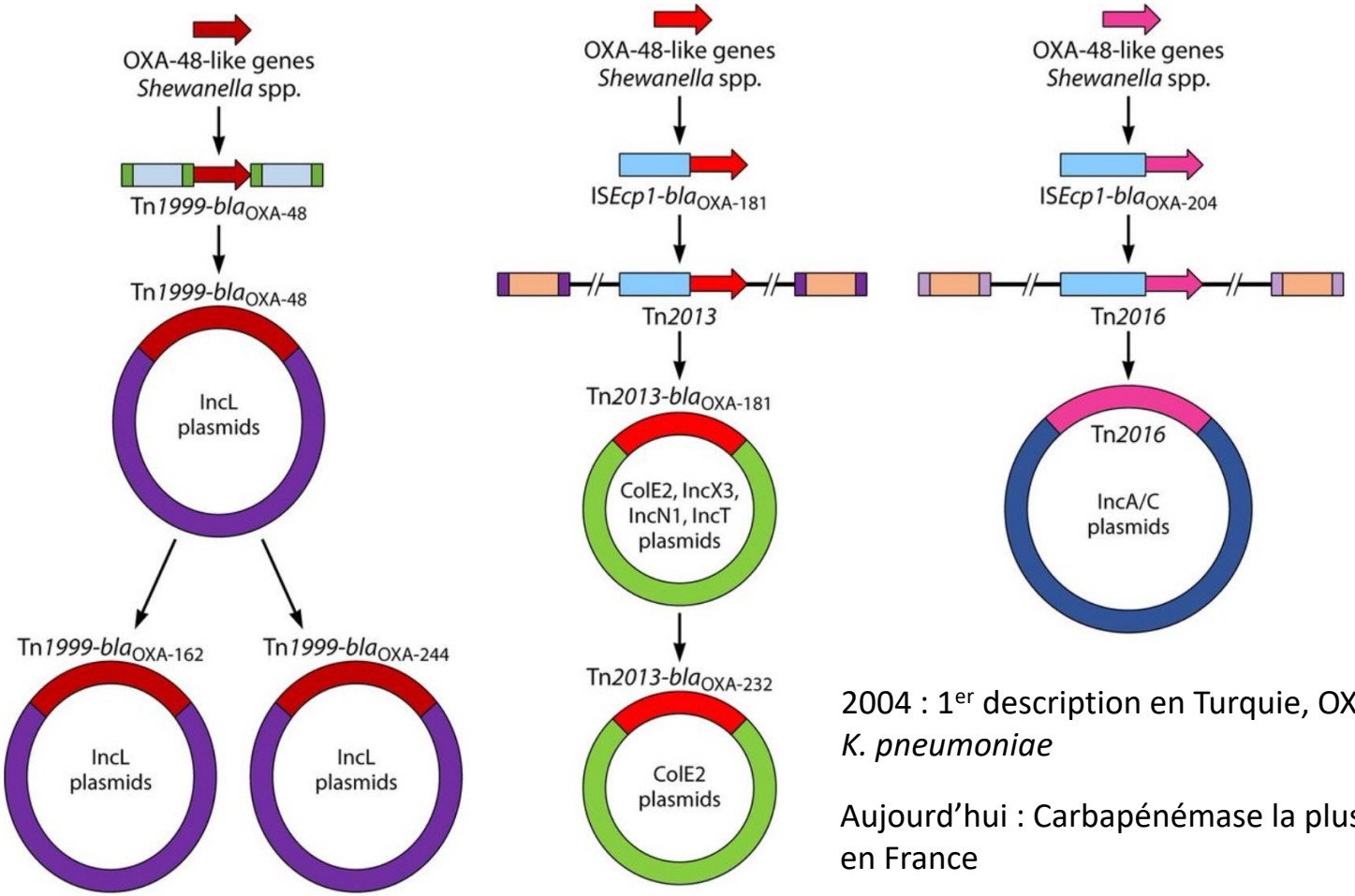
Aujourd'hui : Carbapénémase la plus fréquente en France

Pitout JDD. The Global Ascendency of OXA-48-Type Carbapenemases. Clin Microbiol Rev. 2019

IS : Séquences d'insertions

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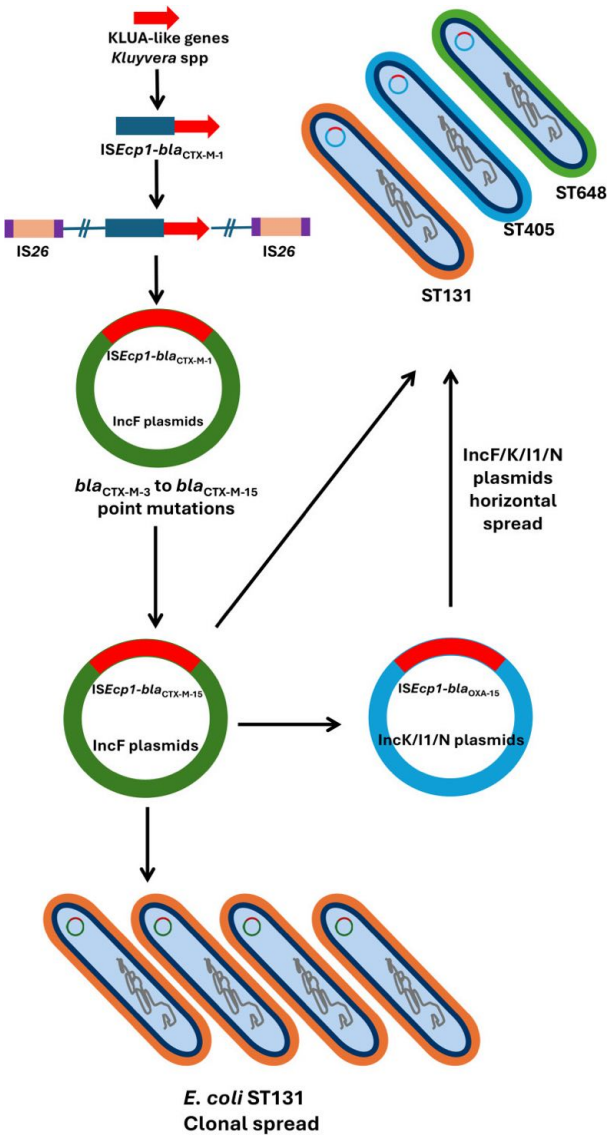
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IS : Séquences d'insertions

- **Mobilisation des gènes de résistance**

  Origine *bla*$_{CTX-M}$ chez les *Enterobacterales*

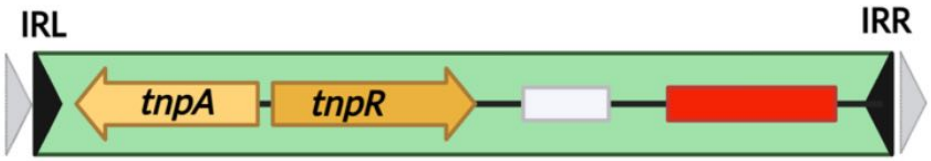


Peirano G, Endimiani A, Pitout JDD. CTX-M-Producing Escherichia coli: History, Molecular Epidemiology and Laboratory Detection. Infect Drug Resist. 2025 Dec 10;18:6549-6560. doi: 10.2147/IDR.S553853. PMID: 41399812; PMCID: PMC12702286.



Transposon unitaire

Transposon unitaire



- **Eléments transposables**
- **Structure**
  - Transposase (*tnpA*)
  - **Résolvase (*tnpR*)** => persistance
  - Séquences répétées : IRL/IRR
  - ADN cible : DR
  - ± gènes de résistance

Transposon unitaire

TABLE 5 Unit transposons associated with resistance in staphylococci and enterococci[a]

Transposon	Family	Determinant	Associated resistance(s)	Host[b]
Tn*551*	Tn*3*	*erm*(B)	MLS antibiotics	S
Tn*917*		*erm*(B)	MLS antibiotics	E
Tn*1546*		*vanA*	Vancomycin/teicoplanin	S, E
Tn*552*	Tn*7*	*blaZ*	Penicillins	S, E
Tn*5404*		*aadE*	Streptomycin	S
		aphA-3	Kanamycin/neomycin	
Tn*554*	Other	*erm*(A)	MLS antibiotics	S, E
		spc	Spectinomycin	
Tn*558*		*fexA*	Chloramphenicol/florfenicol	S
Tn*559*		*dfrK*	Trimethoprim	S
Tn*5406*		*vga*(A)*v*	Streptogramin A/pleuromutilins/lincosamides	S
Tn*6133*		*erm*(A)	MLS antibiotics	S
		spc	Spectinomycin	
		vga(E)	Streptogramin A/pleuromutilins/lincosamides	

[a]See reviews by Firth and Skurray (494), Hegstad et al. (412), and Clewell et al. (16) for references. Also see the work of Kehrenberg and Schwarz (496), Kadlec and Schwarz (510), and Schwendener and Perreten (511).
[b]S, *Staphylococcus*; E, *Enterococcus*.

 Partridge SR, Kwong SM, Firth N, Jensen SO. Mobile Genetic Elements Associated with Antimicrobial Resistance. Clin Microbiol Rev. 2018.

Transposon unitaire

Enterococcus faecium résistant aux glycopeptides (ERG) = BHR

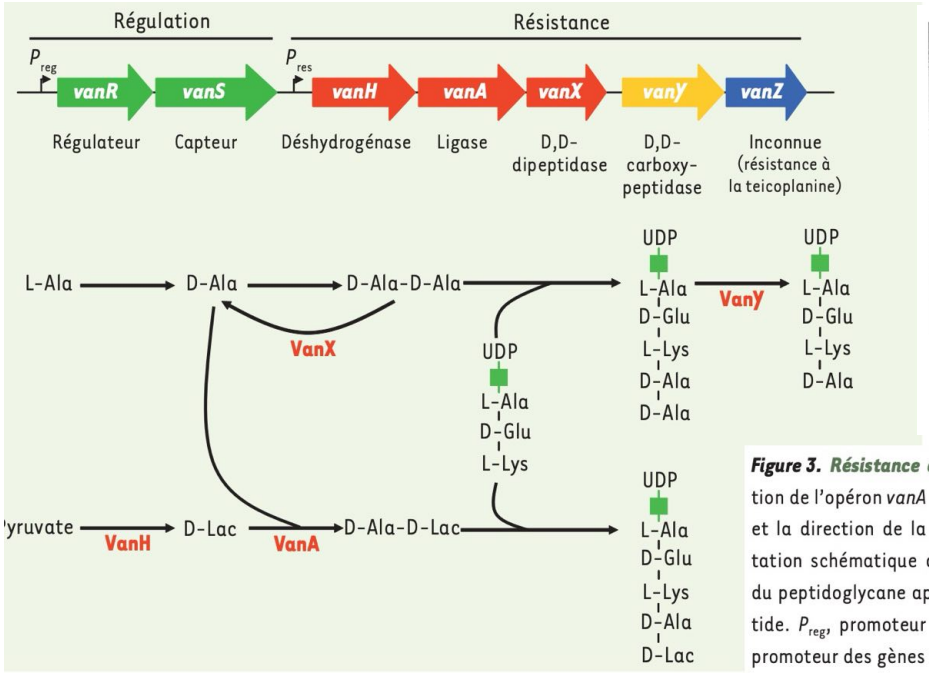
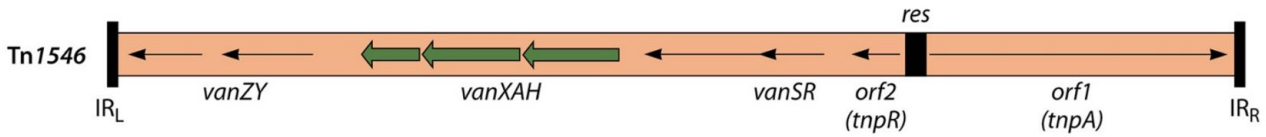
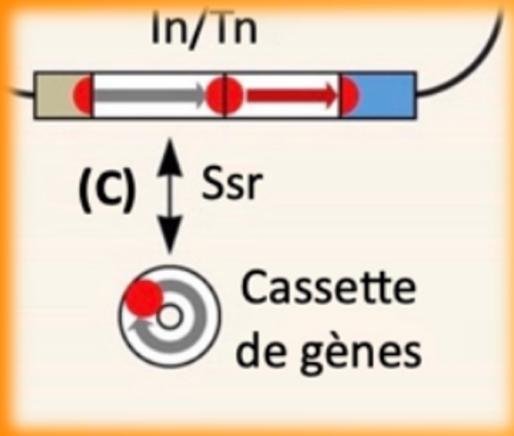


Figure 3. ***Résistance de type VanA.*** Haut : organisation de l'opéron *vanA* (les flèches indiquent les gènes et la direction de la transcription). Bas : représentation schématique de la synthèse des précurseurs du peptidoglycane après induction par un glycopeptide. P_{reg}, promoteur des gènes de régulation ; P_{res}, promoteur des gènes de résistance (d'après [6]).

Antibiotiques	Résultats	Diamètres	Seuils
AMPICILLINE 2µg	Résistant	6	8 - 10
IMIPENEME 10µg	Résistant	6	18 - 21
ERYTHROMYCINE 15µg	Résistant	6	14 - 23
QUINUPRISTINE + DALFOPRISTINE 15µg	SENSIBLE	22	20 - 22
PRISTINAMYCINE 15µg	SENSIBLE		20 - 22
GENTAMICINE 30µg	Haut niveau de résistance	6	8 - 8
VANCOMYCINE 5µg	Résistant	6	12 - 12
TEICOPLANINE 30µg	Résistant	14	16 - 16
NORFLOXACINE 10µg	Résistant	6	12 - 12
TIGECYCLINE 15µg	SENSIBLE	27	15 - 18
LINEZOLIDE 10µg	SENSIBLE	21	19 - 19
RIFAMPICINE 5µg	Résistant	6	17 - 20



Cattoir V, Leclercq R. Les entérocoques résistants aux glycopeptides [Enterococci resistant to glycopeptides]. Med Sci (Paris). 2010 Nov;26(11):936-42. French. doi: 10.1051/medsci/20102611936. PMID: 21106175.



Intégrons

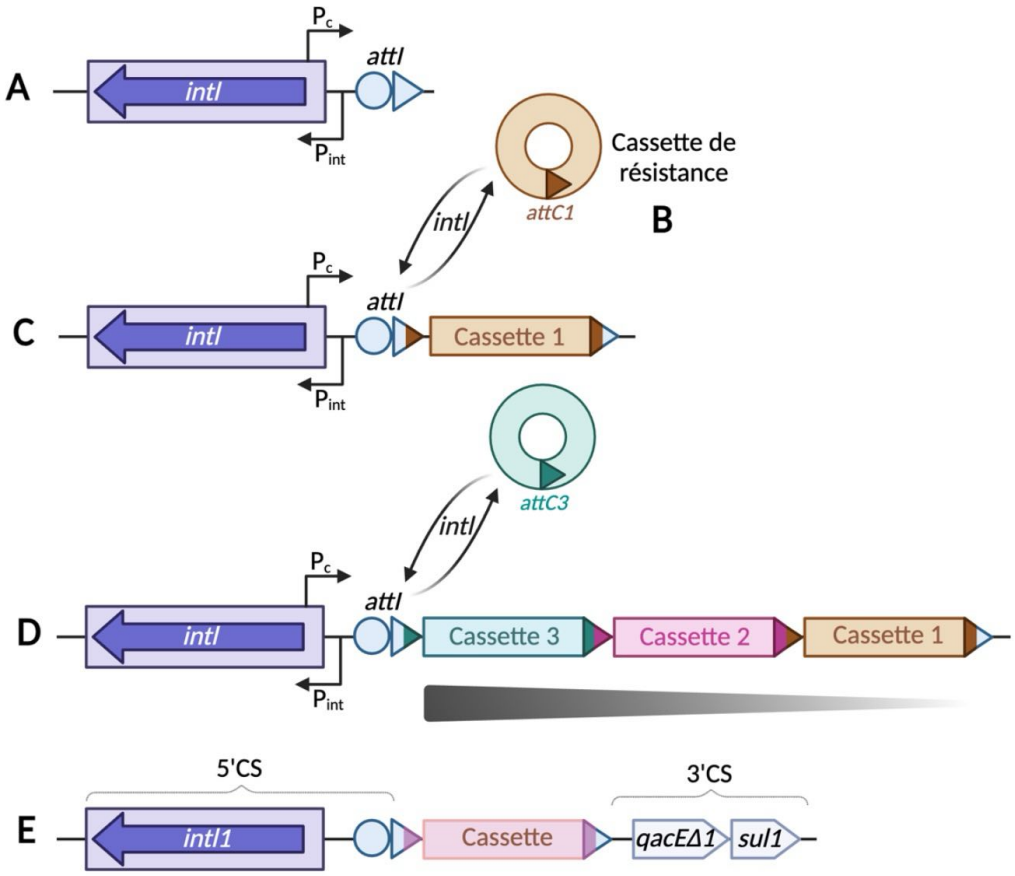
Intégrons

Intégrons

- Eléments génétiques qui capturent des cassette de gène et assurent leur expression
- Constitué
  - intégrase *intI*
  - site de recombinaison *attI*
  - deux promoteurs P_{int}, P_c

Cassette de gène

- Petits éléments mobiles (< 1kb)
- Constitué
  - d'un gène dépourvu de promoteur
  - d'un site de recombinaison *attC*

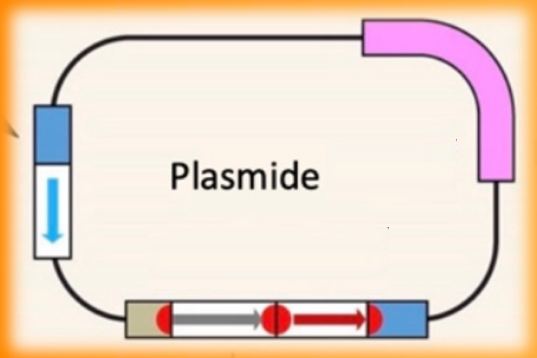


Plusieurs cassettes de gènes peuvent être capturées par le même intégron. Niveau expression maximal au plus proche de Pc

Intégrons = **non mobilisables** => insérés dans éléments transposables, plasmides ou ICE

Intégron de Classe 1, les plus répandus : deux parties conservées 5'CS avec l'intégrase et 3'CS constituée d'un gène tronqué qacEΔ1 (résistance aux ammoniums quaternaires) et sul1 (résistance aux sulfonamides)

Léa Bientz. Résistance aux antibiotiques de dernier recours chez Pseudomonas aeruginosa et nouvelles stratégies diagnostiques et thérapeutiques. Microbiologie et Parasitologie. Université de Bordeaux, 2024. Français.



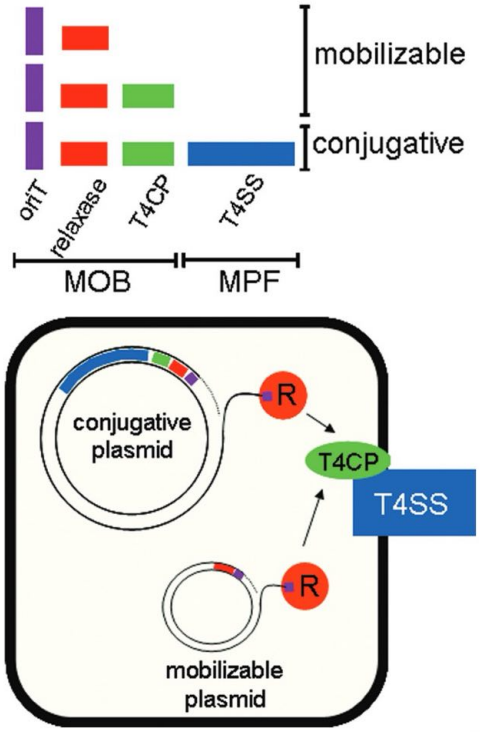
Plasmides

Plasmides

- **ADN circulaires surenroulés négativement, extra-chromosomiques**
- **Capable d'auto-réplication**
- **Taille** quelques kb à plusieurs centaines de kb

- **Structure**
  - Origine de réplication (*oriV*) => classe d'incompatibilité
  - MOB (système de mobilité), constitué :
    - de la relaxase,
    - d'une origine de transfert *oriT,*
    - ± d'un système de couplage de type IV (T4CP)

  La relaxase catalyse les étapes initiales (clivage initial de l'oriT) et finales de la conjugaison. T4CP est impliqué dans la connexion entre le relaxosome et le système de sécrétion de type IV (T4SS). Il existe différentes classes de MOB
  - MPF (mating pair formation, système de formation du pore de conjugaison) composé d'un T4SS *permettant de relier les bactéries entre elles et le passage de l'ADN plasmidique. Il existe différentes classes de MPF*



- **Différents types de plasmides**
  - Conjugatifs : Auto-transférables par conjugaison (MOB + MPF)
  - Mobilisables : Transférables via un plasmide conjugatif (MOB)
  - Non conjugatifs et non mobilisables

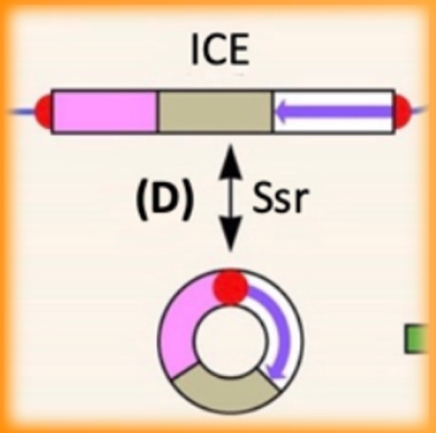
Smillie C, Garcillán-Barcia MP, Francia MV, Rocha EP, de la Cruz F. Mobility of plasmids. Microbiol Mol Biol Rev. 2010 Sep;74(3):434-52. doi: 10.1128/MMBR.00020-10. PMID: 20805406; PMCID: PMC2937521.

Plasmides

Table 1. Summary of plasmid features

Replicon type	Relaxase type	Size (kb)	Copy number	Transferability	Host range
IncF	MOB_F	45–200	low	conjugative	Enterobacteriaceae
IncI	MOBP	50–250	low	conjugative	narrow
IncK, IncB/O and IncZ	MOB_P	80–150	low	conjugative	narrow
IncA/C	MOB_H	18–230	low	conjugative	narrow
IncH	MOB_H	75–400	low	conjugative	wide host range (Enterobacteriaceae, several Gram-negative organisms such as *Aeromonas salmonicida*, *Vibrio anguillarum* and *Yersinia ruckeri*)
IncP	MOB_P	70–275	low	conjugative	broad
IncL/M	MOB_P	50–80	low	conjugative	broad
IncN	MOB_F	30–70	low	conjugative	broad
Col	MOB_P	6–40	1–20	mobilizable	
IncX	MOB_P	30–50			narrow
IncR	not included	40–160		mobilizable	broad
IncW	MOB_F	up to 40	low	conjugative	broad
IncQ	MOB_Q	8–14	medium (4–12 copies/ cell)	mobilizable	broad (including Alpha- Beta- Delta- and Gammaproteobacteria and Cyanobacteria)
IncT	MOB_H	~217	low	conjugative	narrow
IncU	MOB_P	29–60	low	conjugative	broad (Alpha-, Beta- and Gammaproteobacteria)

Rozwandowicz M, Brouwer MSM, Fischer J, Wagenaar JA, Gonzalez-Zorn B, Guerra B, Mevius DJ, Hordijk J. Plasmids carrying antimicrobial resistance genes in Enterobacteriaceae. J Antimicrob Chemother. 2018 May 1;73(5):1121-1137. doi: 10.1093/jac/dkx488. PMID: 29370371.

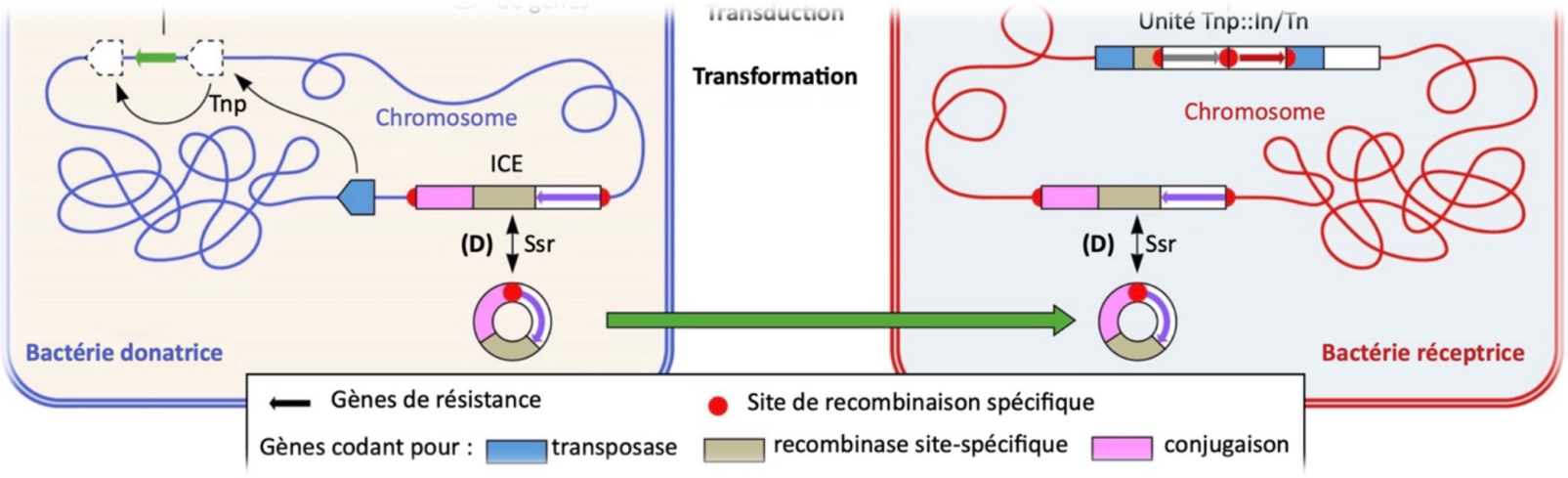


ICE : Eléments intégratifs et conjugatifs

ICE : Eléments intégratifs et conjugatifs

- **Synonymes** : transposons conjugatifs, îlots génomiques, îlots de pathogénicité, îlots de résistance = **ICE** (2002)

- **Caractéristiques**
  - Intégré dans le chromosome
  - Excision sous forme extra-chromosomiques circulaire
  - Autotransfère par conjugaison
  - Réintégration dans un autre chromosome pour se répliquer



 Bellanger X. Conjugative and mobilizable genomic islands in bacteria: evolution and diversity. FEMS Microbiol Rev. 2014

ICE : Eléments intégratifs et conjugatifs

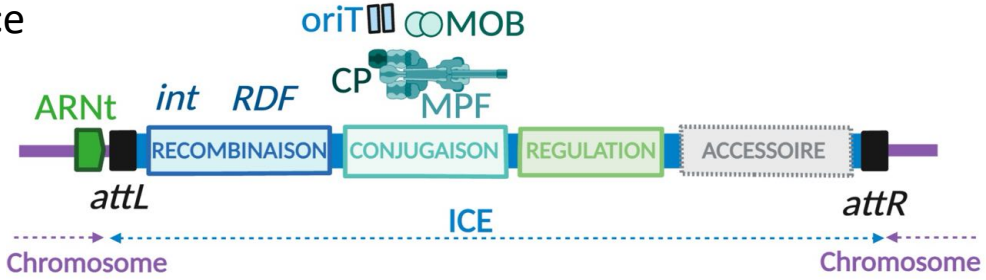
- **Structure**

3 modules essentiels

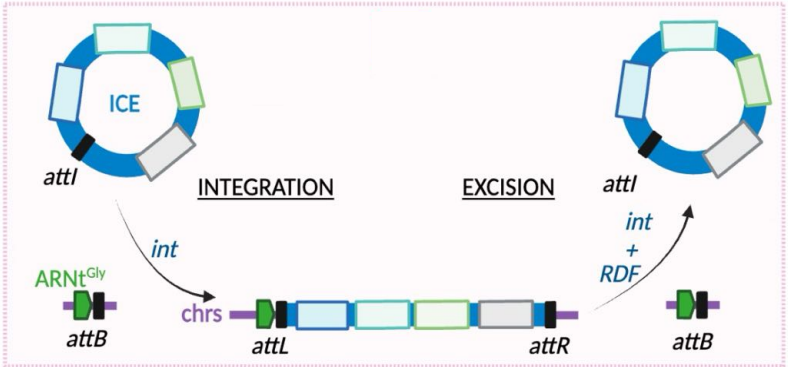
- module recombinaison (intégration/excision) **:** intégrase (int), excisionase (RDF)
- module conjugaison : origine de transfert (oriT), relaxase (MOB), T4SS (MPF), protéine de couplage (CP)
- module régulation/maintenance

Modules accessoires

- résistance aux antibiotiques
- virulence
- fonctions cataboliques



ICE inséré dans le chromosome au niveau d'un site d'insertion spécifique *attB*, encadré par des régions répétées *attL* et *attR*



- **Taille** : 18 kb (Tn916, *Enteroccocus faecalis*) à > 500 kb (ICEMlSymR7A *Mesorhizobium loti*)

ICE : Eléments intégratifs et conjugatifs

- **Différentes familles**

Famille	Intégrase	Site insertion	Module de conjugaison	Exemples d'espèces
SXT/R391	Tyrosine recombinase	5' *prfC*	MPF_F, MOB_H	*Vibrio cholerae, Proteus mirabilis*
pKLC102	Tyrosine recombinase	3' ARNt Lysine	MPF_G, MOB_H	*Pseudomonas aeruginosa*
ICE*Hin*1056	Tyrosine recombinase	3' ARNt Leucine	MPF_G, MOB_H	*Haemophilus influenzae*
ICE*Bs1*	Tyrosine recombinase	3' ARNt Leucine	MPF_{FA}, MOB_T	*Bacillus subtilis*
ICE*clc*	Tyrosine recombinase	3' ARNt Glycine	MPF_G, MOB_H	*P. aeruginosa, P. putida, P. knackmussii,* autres non fermentants
Tn4371	Tyrosine recombinase	5'-TTTTTCAT-3'	MPF_T, MOB_L	*P. aeruginosa*
Tn916	Tyrosine recombinase	Riche en A+T	MPF_{FA}, MOB_T	*Clostridium difficile, Enterococcus sp. Staphylococcus aureus, Streptococcus pneumoniae*
Tn5253	Tyrosine recombinase	5' *rbgA*	MPF_T, MOB_P	*S. pneumoniae*
TnGBS1	DDE	15-17 bp en-35 amont σ^A promoteur	MPF_I, MOB_P	*Streptococcus sp.*
ICE*6013*	DDE	Multiples sites	MPF_{FA}, MOB_T	*S. aureus*

2065 ICE (Base de données ICEBerg3.0) => 356 porteurs de gène(s) de résistance aux AB

Bellanger X. Conjugative and mobilizable genomic islands in bacteria: evolution and diversity. FEMS Microbiol Rev. 2014
Wang M. ICEberg 3.0: functional categorization and analysis of the integrative and conjugative elements in bacteria. Nucleic Acids Res. 2024

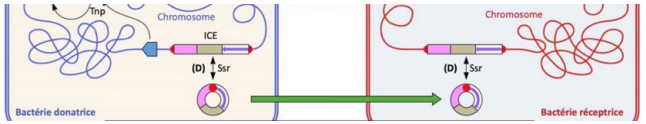
ICE : Eléments intégratifs et conjugatifs

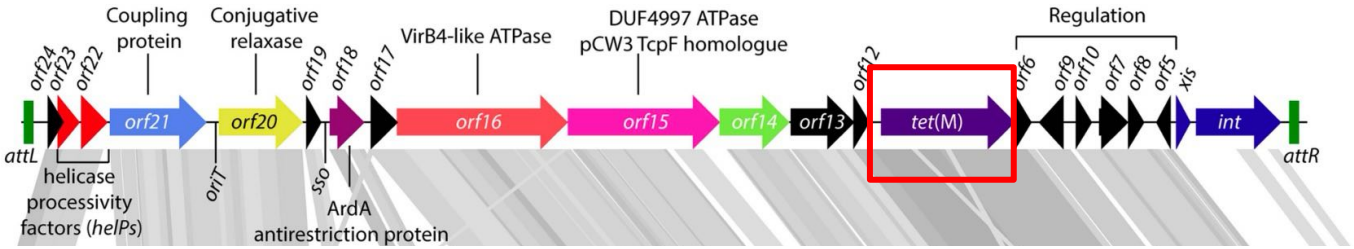
Exemples

S. aureus

Tn*916*
S. aureus S0385 (ST398)

Tn*916* Taux de conjugaison entre Gram négatif et positif : 4,6 x 10^{-4} - 1,4x10^{-8} Tc/donneur





Firth N. Staphylococcal Plasmids, Transposable and Integrative Elements. Microbiol Spectr. 2018

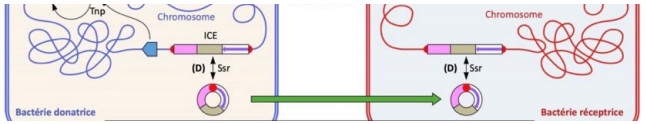
Sansevere EA. Staphylococci on ICE: Overlooked agents of horizontal gene transfer. Mob Genet Elements. 2017.

ICE : Eléments intégratifs et conjugatifs

Exemples

S. aureus

Tn*916* Taux de conjugaison entre Gram négatif et positif : 4,6 x 10^{-4} - 1,4x10^{-8} Tc/donneur



Tn*916*
S. aureus S0385 (ST398)

Coupling protein
Conjugative relaxase
VirB4-like ATPase
DUF4997 ATPase pCW3 TcpF homologue
Regulation
orf24 orf23 orf22 orf21 orf20 orf19 orf18 orf17 orf16 orf15 orf14 orf13 orf12 tet(M) orf6 orf9 orf10 orf7 orf8 orf5 xis int
attL
attR
helicase processivity factors (*helPs*)
oriT
sso
ArdA antirestriction protein

Tn*5801*
S. aureus Mu50

sav415 sav414 sav413 orf22 orf23 orf24 sav410 orf21 orf20 sav406 orf18 sav404 orf17 orf16 orf15 orf14 orf13 tet(M) orf9 orf10 orf7 orf8 xis int
attR
attL
guaA ->

ICE*Bs1*
B. subtilis JH642

Regulation
Pheromone production and regulation
int immA immR xis ydzL ydcO helP conQ nicK conB conC conD conE conG cwlT yddF yddI yddJ yddK rapI phrL yddM
attL
attR
oriT
sso ydcS ydcT ydcA
Interacting membrane proteins
VirB6-like ATPase
Cell wall hydrolase

ICE*6013*
S. aureus HDG2

orf15 orf14 orf13 orf12 orf11 orf10 orf9 orf8 orf7 orf6 orf5 orf4 orf3 orf2 blaZ blaR1 blaI blnL tnsB orf271 orf1
DUF961 helicase processivity
pCW3 TcpC-like VirB8-like protein
Putative mating-channel protein
CHAP-domain cell-wall lysis
IS*30*-like DDE recombinase
Immobilising Tn*552* insertion
IS*30*-like DDE recombinase
1 Kbp
21%
tblastx
100%

ICE*6013* Taux de conjugaison entre *S. aureus* : 1,16x10^{-7} ± 7,2x10^{-8} Tc/donneur

Firth N. Staphylococcal Plasmids, Transposable and Integrative Elements. Microbiol Spectr. 2018
Sansevere EA. Staphylococci on ICE: Overlooked agents of horizontal gene transfer. Mob Genet Elements. 2017.

ICE : Eléments intégratifs et conjugatifs

Exemples

ICEs porteurs de carbapénémases chez *P. aeruginosa*

Nom	Famille	Taille	Principaux gènes de résistance
ICE décrits dans ICEberg3.0 (version juin 2023)			
ICE*6440*	ICE*clc*	83	***bla*$_{VIM-2}$**, aac(6')-II, aac(3)-Ia, aac(6')-Ib
ICE*6441*	ICE*clc*	88	***bla*$_{VIM-2}$**
ICE*6660*	ICE*clc*	112	***bla*$_{NDM-1}$**, *bla*$_{PME-1}$, rmtD3
ICE*Pae*690	ICE*clc*	86	***bla*$_{GES-6}$**, aac(6')-II
ICE$_{Tn4371}$6061	Tn$_{4371}$	43	***bla*$_{SPM-1}$**
ICE$_{Tn4371}$6385	Tn$_{4371}$	74	***bla*$_{NDM-1}$**
Tn*6413*	Tn$_{6417}$	114	***bla*$_{VIM-4}$**, ant(3'')-Ia, aac(6')-II
Tn*6585*	Tn$_{6417}$	100	***bla*$_{GES-6}$**, aph(3')-XV
Tn*6586*	Tn$_{6417}$	100	***bla*$_{GES-15}$**, aac(6')-Ib4, aph(3')-XV
Tn*6953*	Tn$_{6417}$	-	***bla*$_{VIM-2}$**, *bla*$_{CARB-2}$, ant(2'')-Ia, aac(6')-IIa, aph(3')-VI
Tn*6956*	Tn$_{6417}$	123	***bla*$_{VIM-2}$**
ICE décrits			
PAGI-15	ICE*clc*	118	***bla*$_{GES-24}$**, *bla*$_{OXA-2}$, aac(6')-Ib-cr, aph(3')-Ib
PAGI-16	ICE*clc*	95	***bla*$_{IMP-6}$**, *bla*$_{OXA-1}$, aac(6')-Ib-cr
PAGI-16	ICE*clc*	96	***bla*$_{IMP-10}$**, *bla*$_{OXA-1}$, aac(6')-Ib-cr
GI2	ICE*clc*	93	***bla*$_{GES-5}$**, aac(6')-Ib, aph(3')
ICE prédits uniquement par bio-informatique			
-	ICE*clc*	-	***bla*$_{IMP-1}$**, ant(2'')-Ia, ant(3'')-Ia
-	ICE*clc*	-	***bla*$_{IMP-13}$**, aac(6')-Ib4
-	ICE*clc*	-	***bla*$_{IMP-14}$**, *bla*$_{OXA-10}$, ant(2'')-Ia, aac(6')-Ib
-	ICE*clc*	-	***bla*$_{DIM-1}$**
-	ICE*clc*	-	***bla*$_{VIM-1}$**, *bla*$_{OXA-2}$, ant(3''), aac(6')-Ib

Botelho J. Carbapenemases on the move: it's good to be on ICEs. Mob DNA. 2018.

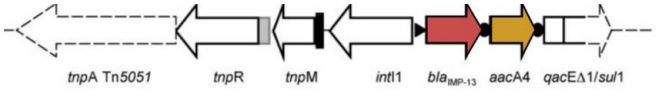
ICE : Eléments intégratifs et conjugatifs

Exemples

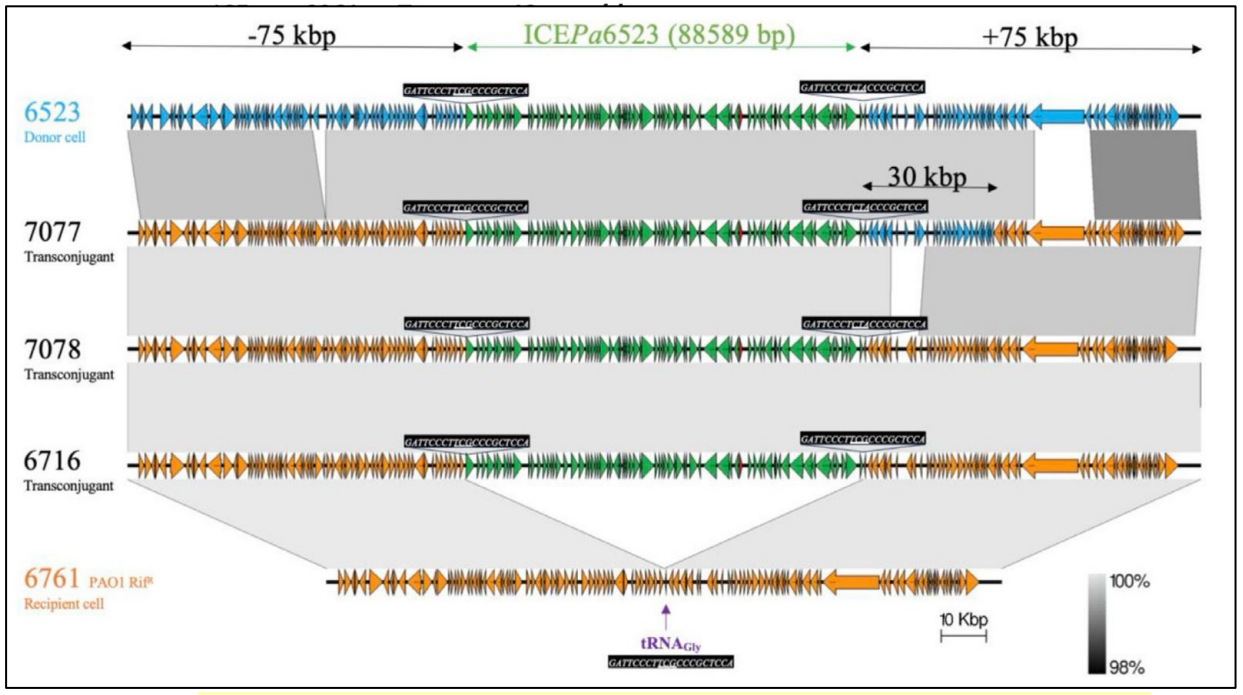
ICEs porteurs de carbapénémases chez *P. aeruginosa*

Nom	Famille	Taille	Principaux gènes de résistance
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ICE*6441*	ICE*clc*	88	***bla*$_{VIM-2}$**
ICE*6660*	ICE*clc*	112	***bla*$_{NDM-1}$**, *bla*$_{PME-1}$, rmtD3
ICE*Pae*690	ICE*clc*	86	***bla*$_{GES-6}$**, aac(6')-II

ICE*Pa*6523 Taux de conjugaison entre *P. aeruginosa* : 10^{-8} Tc/donneur



Bientz L. Mobilization of an ICEclc-Like Element as a Potential Mechanism for the Spread of IMP-13 Carbapenemase in Pseudomonas aeruginosa. J Glob Antimicrob Resist. 2025.



-	ICE*clc*	-	***bla*$_{IMP-13}$**, aac(6')-Ib4
-	ICE*clc*	-	***bla*$_{IMP-14}$**, *bla*$_{OXA-10}$, ant(2'')-Ia, aac(6')-Ib
-	ICE*clc*	-	***bla*$_{DIM-1}$**
-	ICE*clc*	-	***bla*$_{VIM-1}$**, *bla*$_{OXA-2}$, ant(3''), aac(6')-Ib

Botelho J. Carbapenemases on the move: it's good to be on ICEs. Mob DNA. 2018.

En pratique

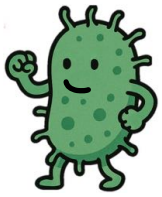
Exemple : *Pseudomonas aeruginosa*

Résistances naturelles

- AMP, C1-3G, ETP… *(non visibles sur cet ATB)*
- Céphalosporinase, Efflux
- Support chromosomique

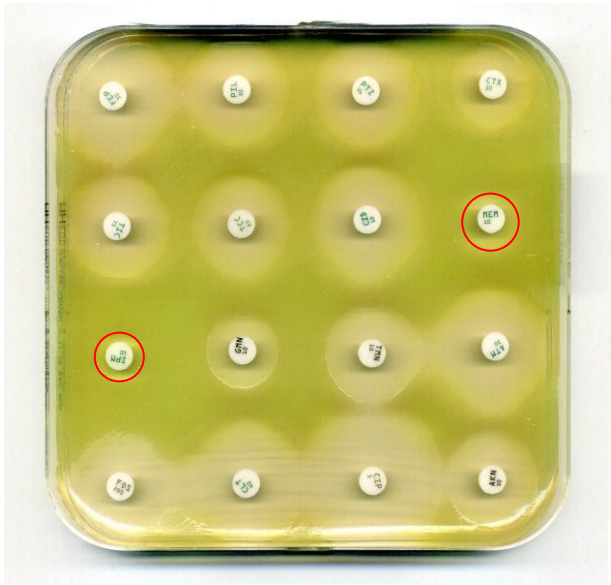


100 %
des souches

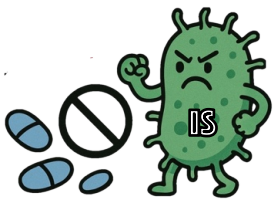


Résistances acquises

- IPM, MEM
- IS dans gène *oprD*



15 %
des souches

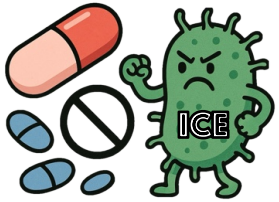


Résistances acquises

- IPM, MEM, C/T, GEN, TOB
- Carbapénémase, bla_{IMP-13}
- Support : ICE



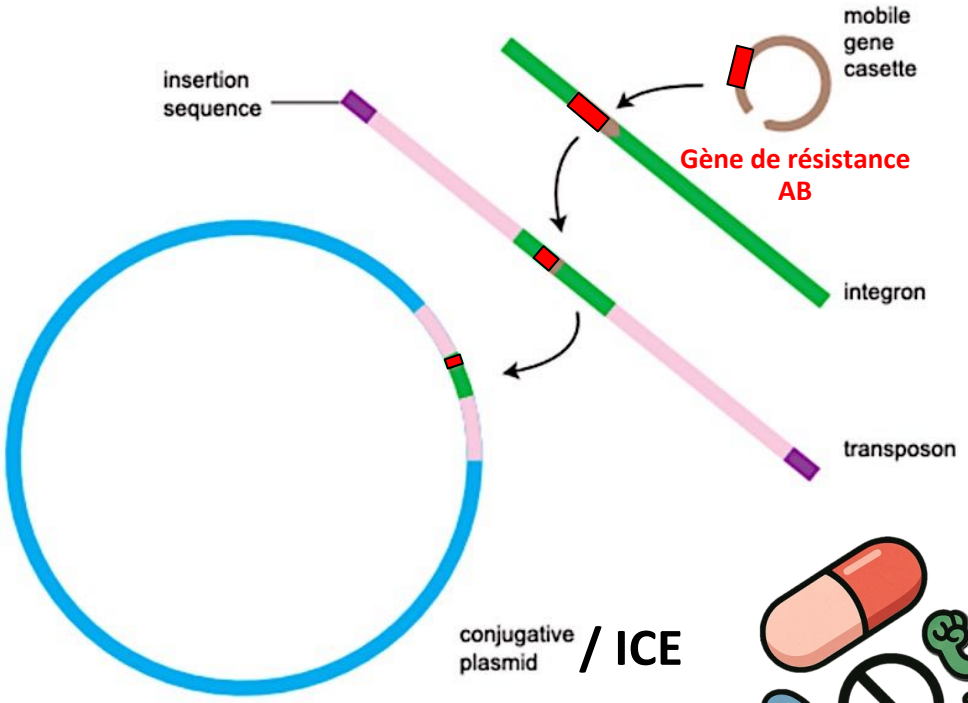
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des souches

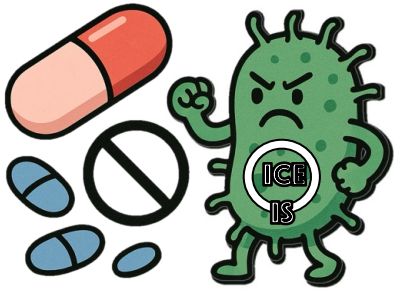


CONCLUSION

- **Résistance aux antibiotiques ⇔ Eléments génétiques mobiles**
- **Nombreux gènes et familles d'antibiotiques**
- **IS : simple, transposon composite, atypiques => Inactivation, modulation et mobilisation de gènes**
- **ICE : support d'autres EGM, mobilisation possible entre bactéries**







CONCLUSION

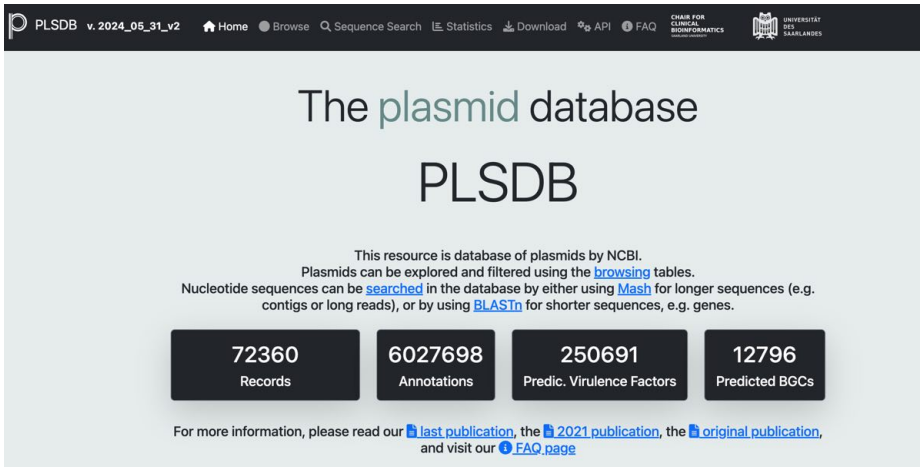
ISFinder

https://www-is.biotoul.fr/index.php



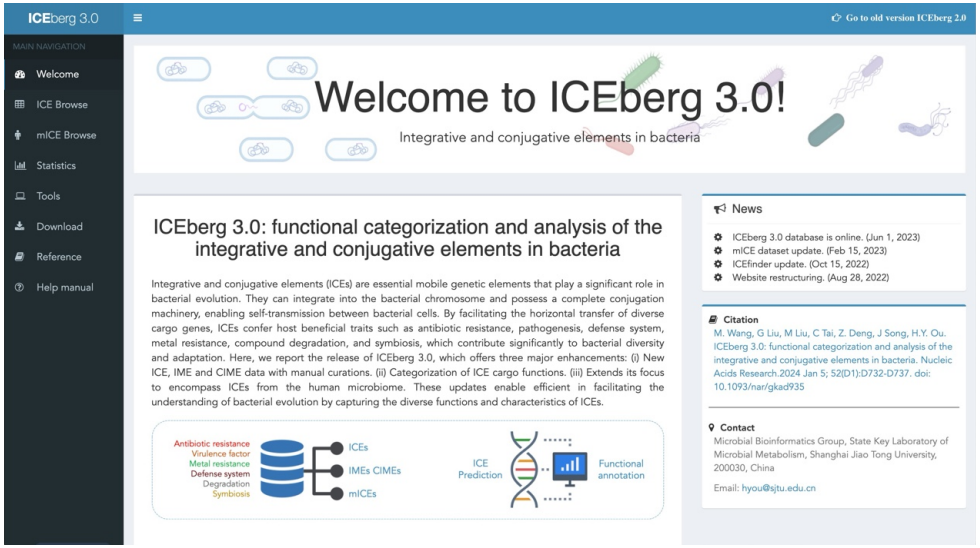
PLSDB

https://ccb-microbe.cs.uni-saarland.de/plsdb2025/



ICEberg 3.0

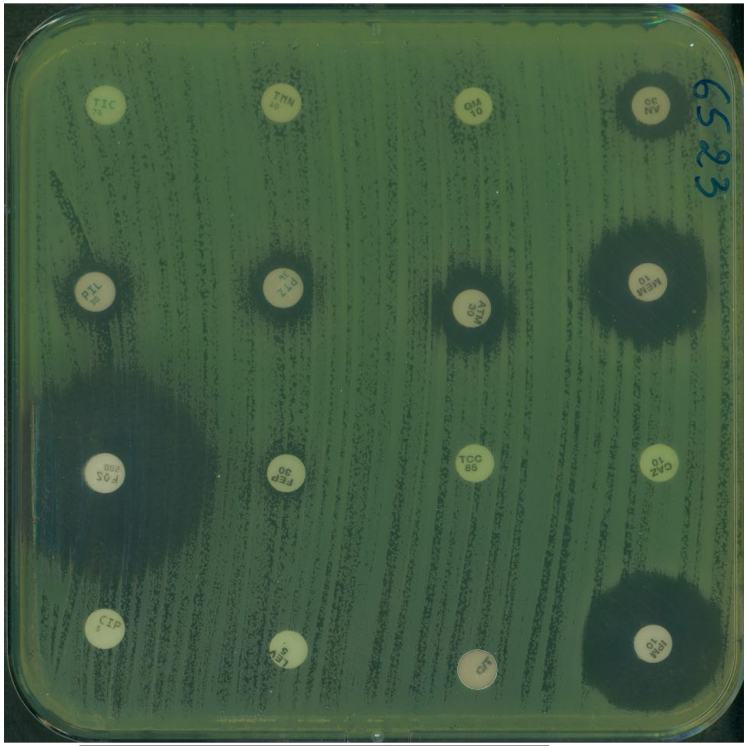
https://tool2mml.sjtu.edu.cn/ICEberg3/jobstat.php?job=CuttgUa44H



Mise en pratique

Résistance au Ceftolozane/tazobactam par acquisition d'une carbapénémase

Contexte



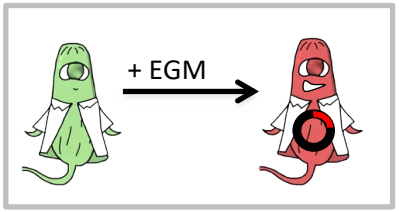
Antibiotiques	Résultats
TICARCILLINE 75µg	Résistant
TICARCILLINE + AC.CLAVULANIQUE 75-10	Résistant
PIPERACILLINE 30µg	Résistant
PIPERACILLINE + TAZOBACTAM 30-6µg	Résistant
CEFTRIAXONE 30µg	Résistant
CEFEPIME 30µg	Résistant
CEFTAZIDIME 10µg	Résistant
CEFTOLOZANE + TAZOBACTAM 30-10µg	Résistant
AZTREONAM 30µg	Résistant
IMIPENEME 10µg	SENSIBLE
MEROPENEME 10µg	SENSIBLE
TOBRAMYCINE 10µg	Résistant
GENTAMICINE 10µg	Résistant
AMIKACINE 30µg	Résistant
CIPROFLOXACINE 5µg	Résistant
LEVOFLOXACINE 5µg	Résistant

Etude rétrospective 2010-2020,
***P. aeruginosa* producteur de carbapénémase IMP-13**

Isolate	Collection date	Sample	Unit
Pa5247	Nov. 2011	Urine	Private laboratory
Pa5957	Sep. 2015	Urine	Cardiology
Pa6466	Aug. 2019	Sputum	Hematology
Pa6523* (D)	Jan. 2020	Stool	Hematology
Pa6567*	Mar. 2020	Stool	Hematology
Pa6536	May 2020	Urine	Orthopedic traumatology
Pa6566	Jun. 2020	Stool	Hematology
Pa6559	Jul. 2020	Blood	Hematology

8 isolats cliniques

- **Etudier le support génétique du gène *bla*$_{IMP-13}$**
- **Evaluer le risque de diffusion de la résistance aux carbapénèmes**



Réflexion

Carbapénémase
IMP-13



Description dans la littérature ?

Sur le chromosome, ou sur des plasmides

Support génétique ?

Extraction plasmides

Séquençage

Epidémie ?

Souche clonale ?
Transfert du gène ?

Mobilité/transférabilité ?

Conjugaison,
Transformation

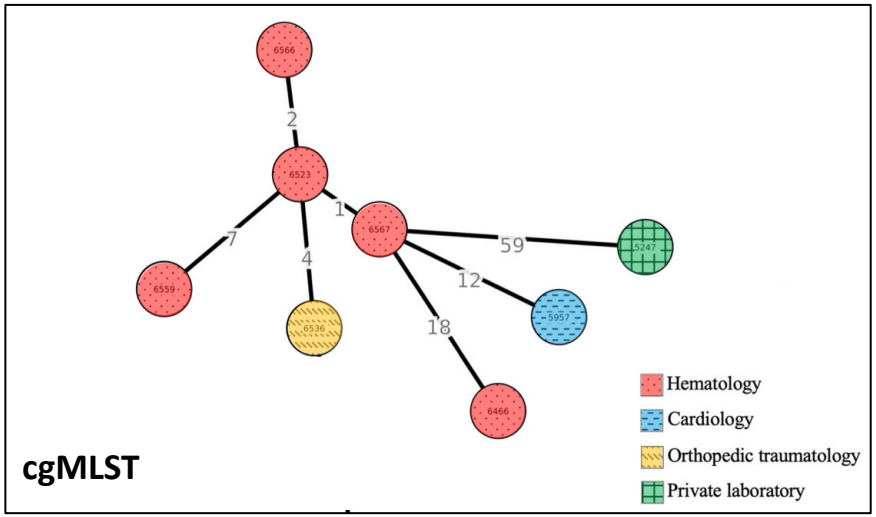
Isolats cliniques

CMI

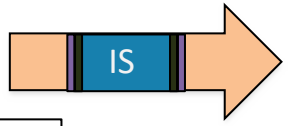
Séquençage Illumina

Isolate	Collection date	Sample	Unit	Diameter (mm) TIC	TCC	PIP	PTZ	FEP	CAZ	ATM	IPM	MER	TOB	AMK	CIP	LVX	MIC (mg/L) C/T	CZA	IPM	I/R	FDC	CST
Pa5247	Nov. 2011	Urine	Private laboratory	6	6	21	22	11	6	29	21	20	6	22	6	6	>256	>256	8	4	1	1
Pa5957	Sep. 2015	Urine	Cardiology	6	6	16	16	11	6	25	24	23	6	20	6	6	>256	>256	8	4	2	2
Pa6466	Aug. 2019	Sputum	Hematology	6	6	6	6	6	6	6	6	6	6	10	6	6	>256	>256	>32	>32	0,5	1
Pa6523* (D)	Jan. 2020	Stool	Hematology	6	6	11	12	8	6	19	20	22	6	14	6	6	>256	>256	16	8	1	1
Pa6567*	Mar. 2020	Stool	Hematology	6	6	10	11	6	6	19	21	21	6	14	6	6	>256	>256	8	4	1	2
Pa6536	May 2020	Urine	Orthopedic traumatology	6	6	10	14	8	6	24	22	22	6	21	6	6	>256	>256	16	4	1	1
Pa6566	Jun. 2020	Stool	Hematology	6	6	10	12	6	6	19	6	6	6	14	6	6	>256	>256	>32	>32	1	1
Pa6559	Jul. 2020	Blood	Hematology	6	6	11	14	9	6	15	6	6	6	12	6	6	>256	>256	>32	>32	1	2

Isolate	ST	Acquired antibiotic resistance genes		ß-lactamases PDC	OXA	Modifications** associated with resistance *gyrA*	*gyrB*	*parC*	*parE*	*oprD*
Pa5247	621	bla_{IMP-13}, *aac(6')-Ib4, qacEΔ1, sul1*	*crpP*	PDC-5	OXA-914	T83I	WT	S87L	WT	oprD_5
Pa5957	621	bla_{IMP-13}, *aac(6')-Ib4, qacEΔ1, sul1*	*crpP*	PDC-5	OXA-914	T83I, D87H	WT	S87L	WT	oprD_5
Pa6466	621	bla_{IMP-13}, *aac(6')-Ib4, qacEΔ1, sul1*	*crpP, aph(3')-VIa, aac(3)-IIIb*	PDC-5	OXA-914	T83I, D87H	WT	S87L	WT	oprD_5 (IS insertion)
Pa6523* (D)	621	bla_{IMP-13}, *aac(6')-Ib4, qacEΔ1, sul1*	*crpP, aph(3')-VIa, aac(3)-IIIb*	PDC-5	OXA-914	T83I, D87H	WT	S87L	WT	oprD_5
Pa6567*	621	bla_{IMP-13}, *aac(6')-Ib4, qacEΔ1, sul1*	*crpP, aph(3')-VIa, aac(3)-IIIb*	PDC-5	OXA-914	T83I, D87H	WT	S87L	WT	oprD_5
Pa6536	621	bla_{IMP-13}, *aac(6')-Ib4, qacEΔ1, sul1*	*crpP*	PDC-5	OXA-914	T83I, D87H	WT	S87L	WT	oprD_5
Pa6566	621	bla_{IMP-13}, *aac(6')-Ib4, qacEΔ1, sul1*	*crpP, aph(3')-VIa, aac(3)-IIIb*	PDC-5	OXA-914	T83I, D87H	WT	S87L	WT	oprD_5 (IS insertion)
Pa6559	621	bla_{IMP-13}, *aac(6')-Ib4, qacEΔ1, sul1*	*crpP, aph(3')-VIa, aac(3)-IIIb*	PDC-5	OXA-914	T83I, D87H	WT	S87L	WT	oprD_5 (IS insertion)



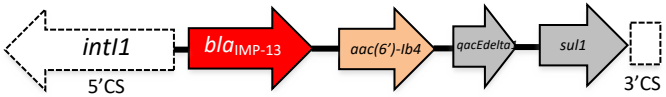
ST 621



Diffusion clonale

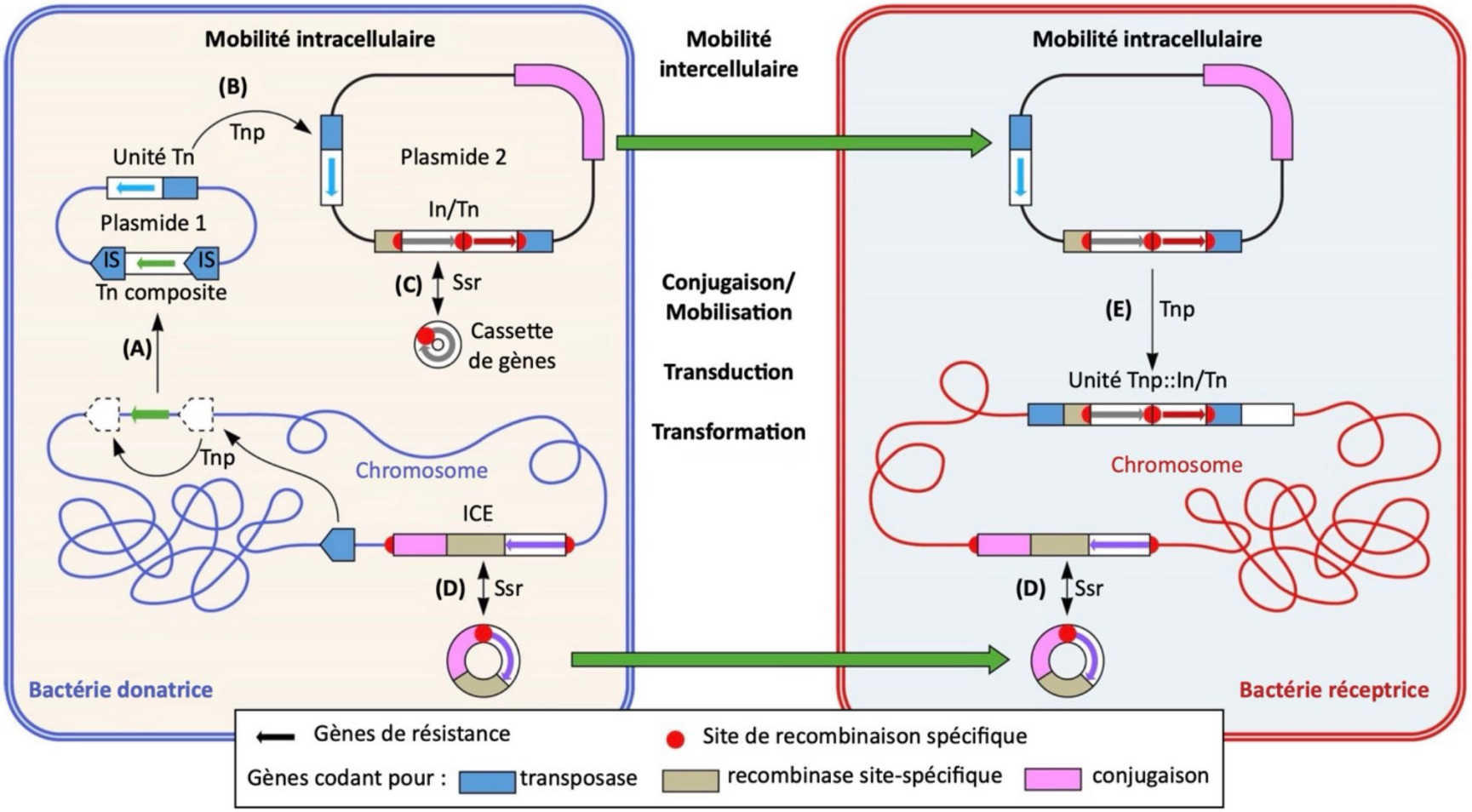
bla_{IMP-13} + aac(6')-Ib4

intégron de classe I



Éléments génétiques mobiles

Supports génétiques de la résistance ? *bla*$_{\text{IMP-13}}$

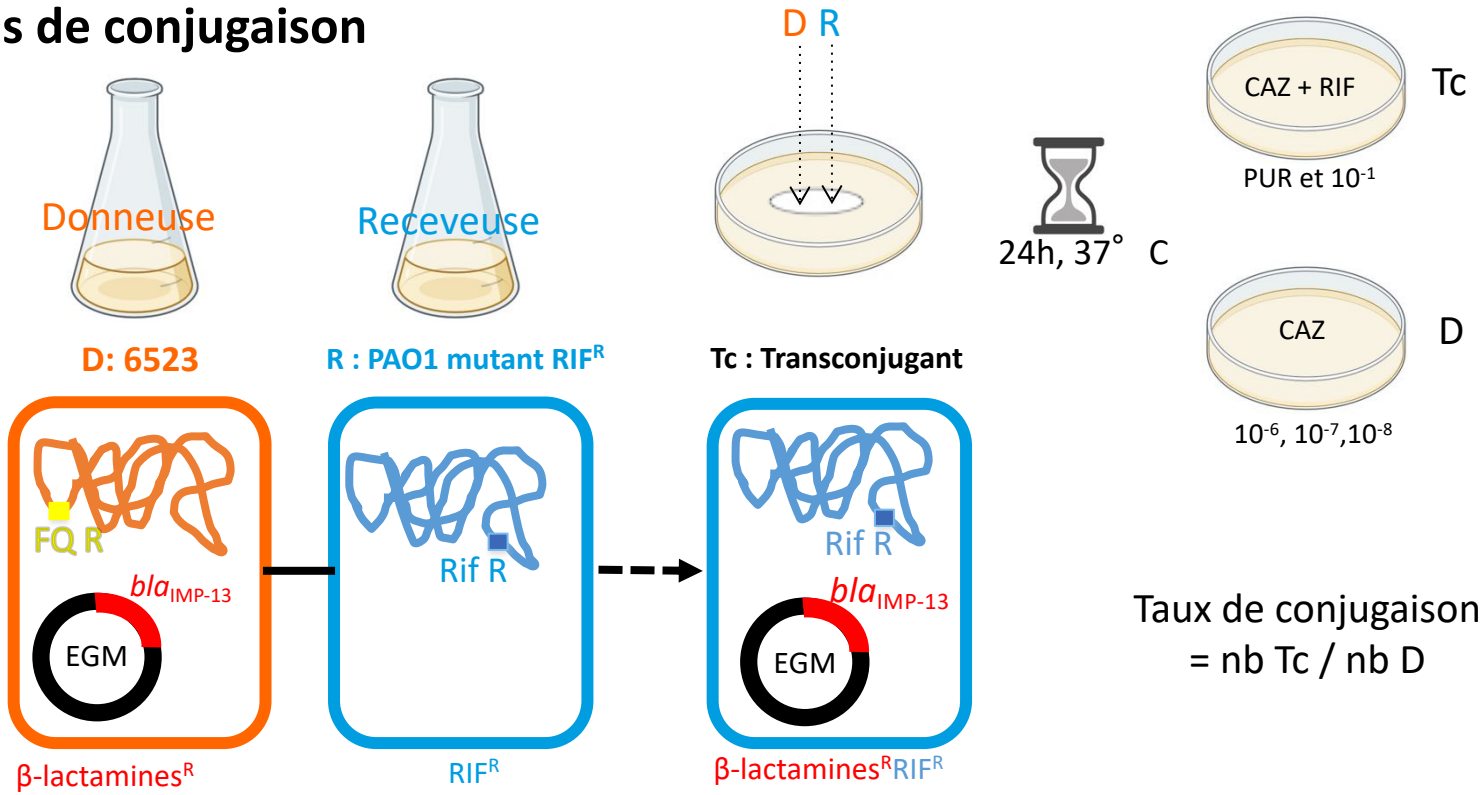


IS : séquence d'insertion, Tn : transposon, In : intégron, ICE : élément intégratif et conjugatif, Tnp : transposase, Ssr :recombinase site-spécifique

Partridge SR, Kwong SM, Firth N, Jensen SO. Mobile Genetic Elements Associated with Antimicrobial Resistance. Clin Microbiol Rev. 2018;31(4).

Etude support génétique / mobilité

➔ Expériences de conjugaison



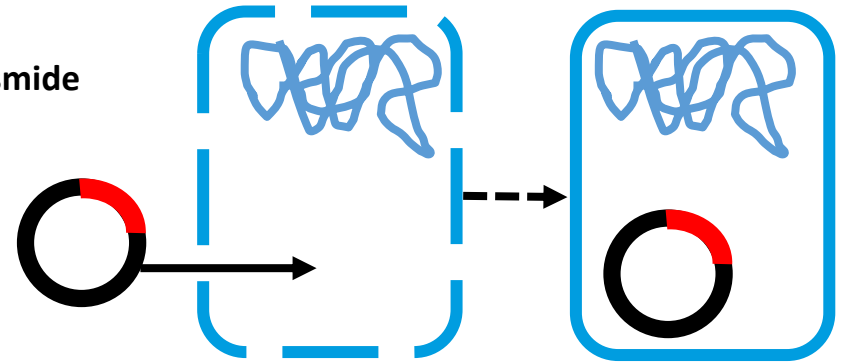
Taux de conjugaison
= nb Tc / nb D

➔ Extraction plasmidique



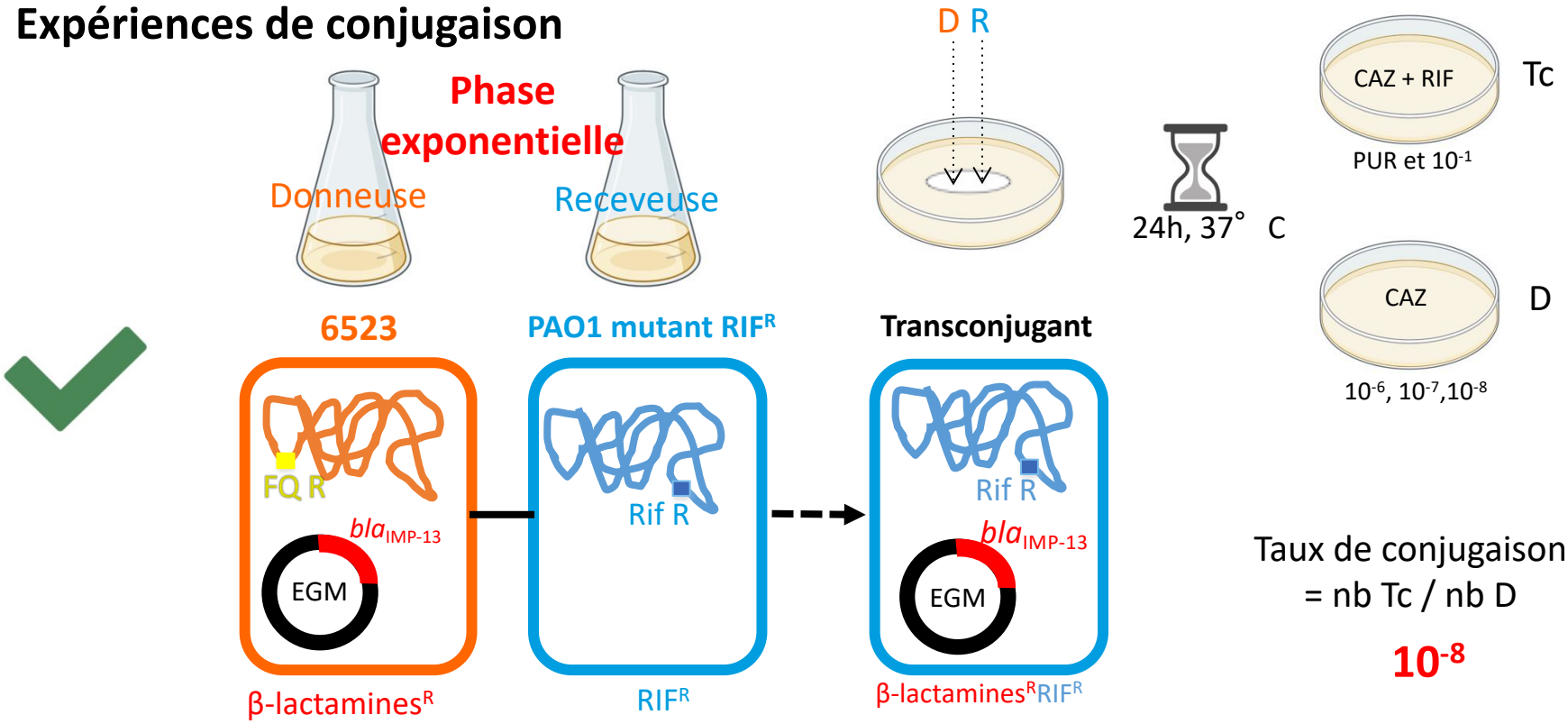
Plasmide

➔ Expériences de transformation



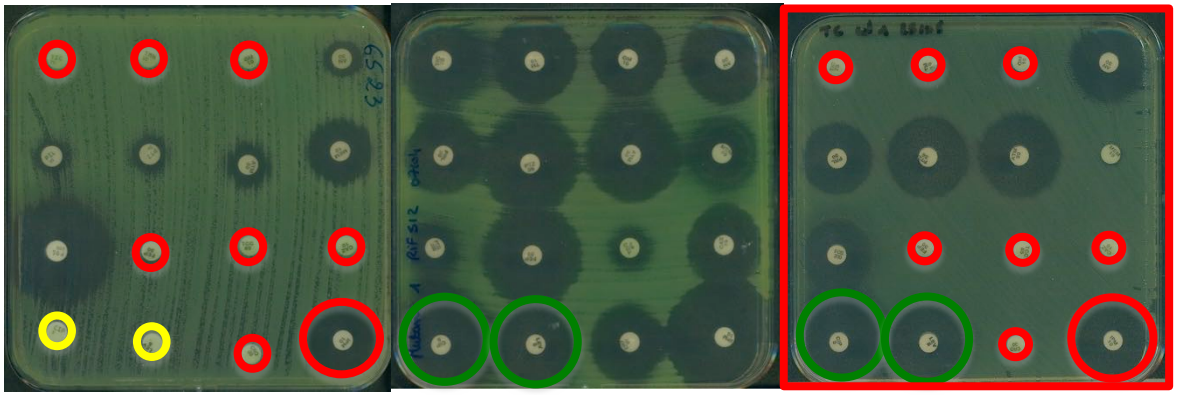
Etude support génétique / mobilité

➔ Expériences de conjugaison



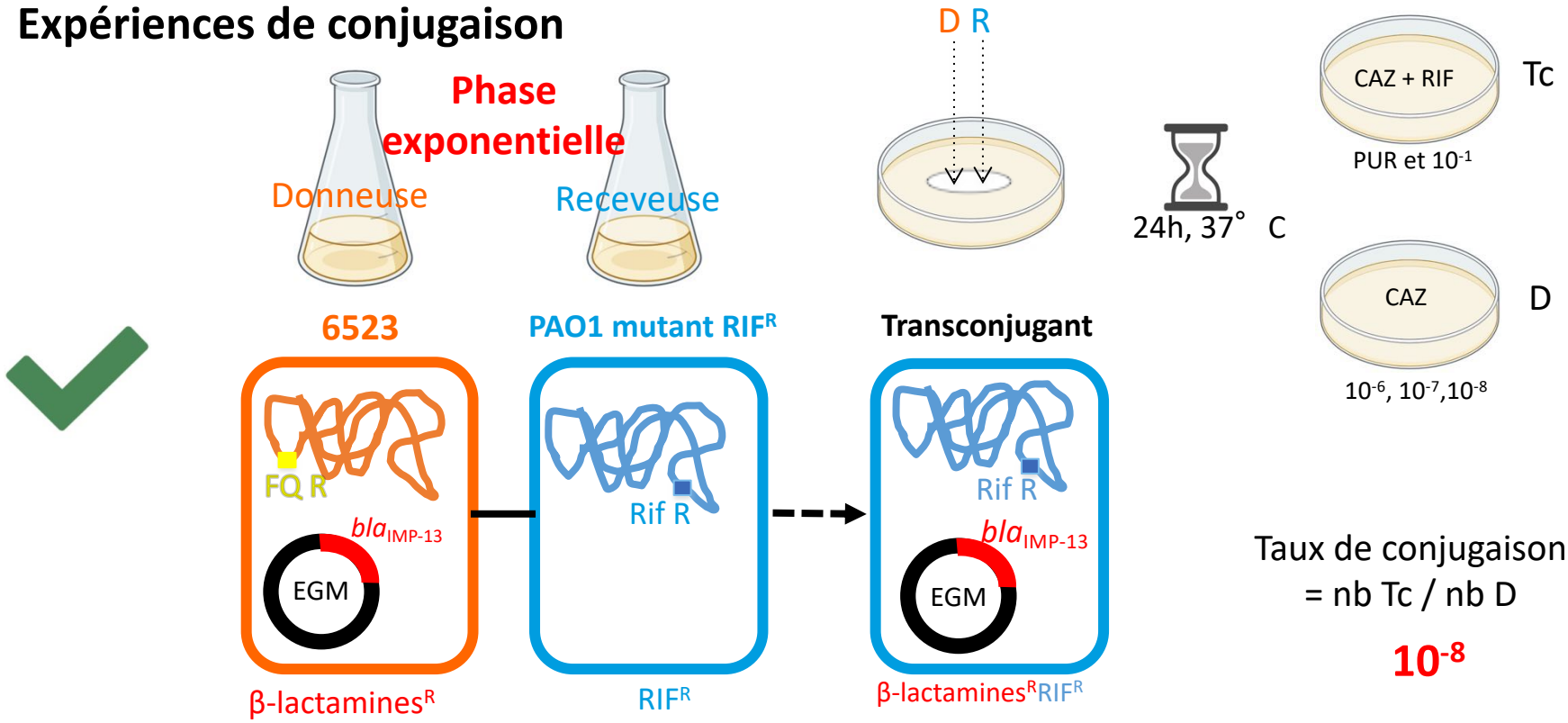
Taux de conjugaison
= nb Tc / nb D

10^{-8}



Etude support génétique / mobilité

➔ **Expériences de conjugaison**



Taux de conjugaison
= nb Tc / nb D

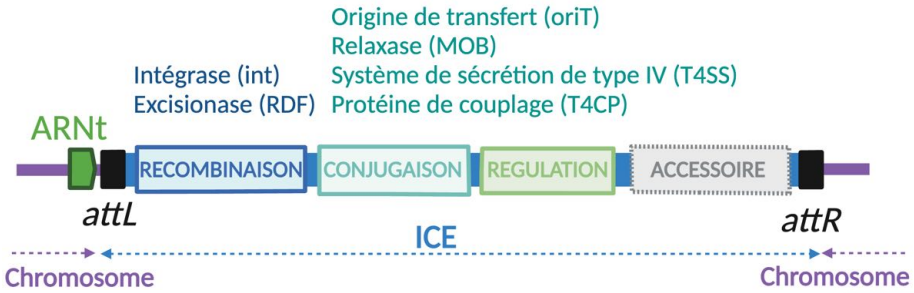
10^{-8}

➔ **Extraction plasmidique**

EGM chromosomique = ICE ?

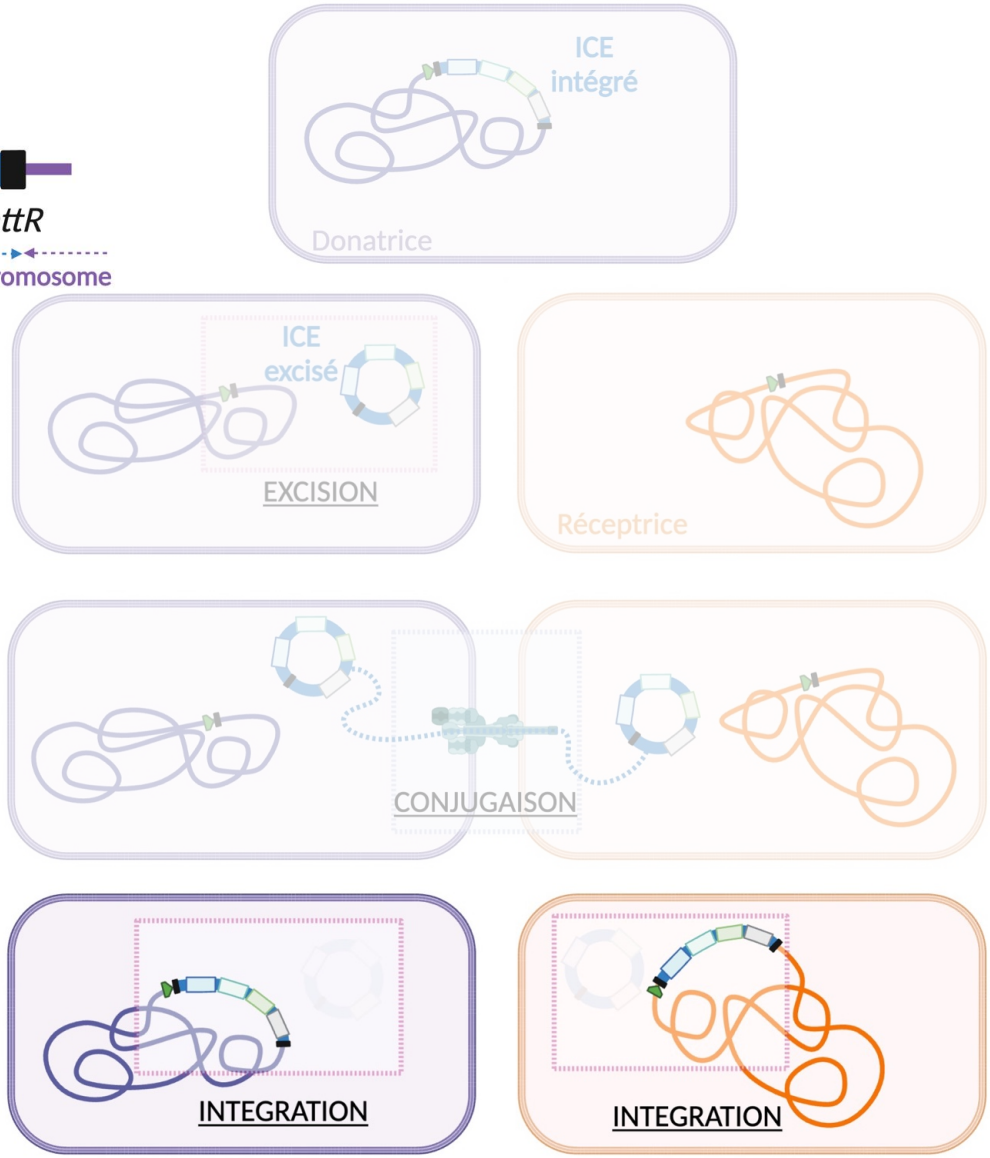
➔ **Expériences de transformation**

ICE : Elément intégratif et conjugatif



Mobilisation - Transfert - Intégration

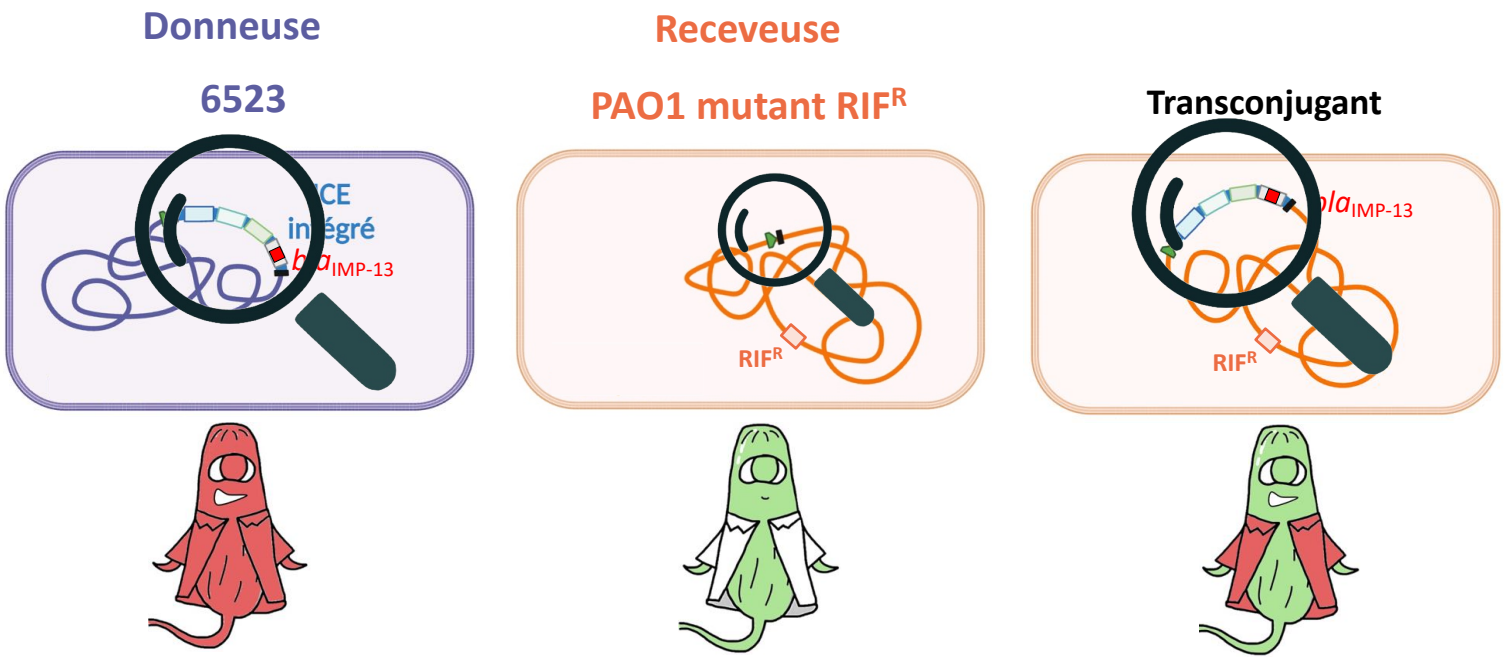
- 3 modules
  - Recombinaison (intégration, excision)
  - Conjugaison
  - Régulation
- Gènes accessoires
  - Gènes de résistance aux antibiotiques
  - Gènes de virulence



Created with BioRender.com.

Support génétique

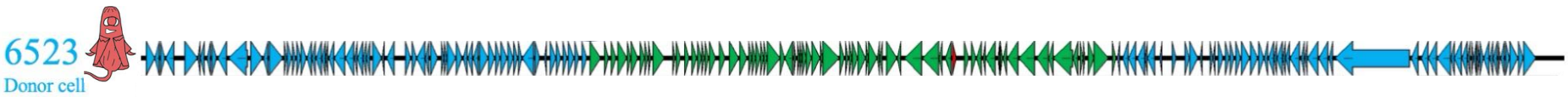
Séquençage nanopore



Séquençage nanopore

Support génétique

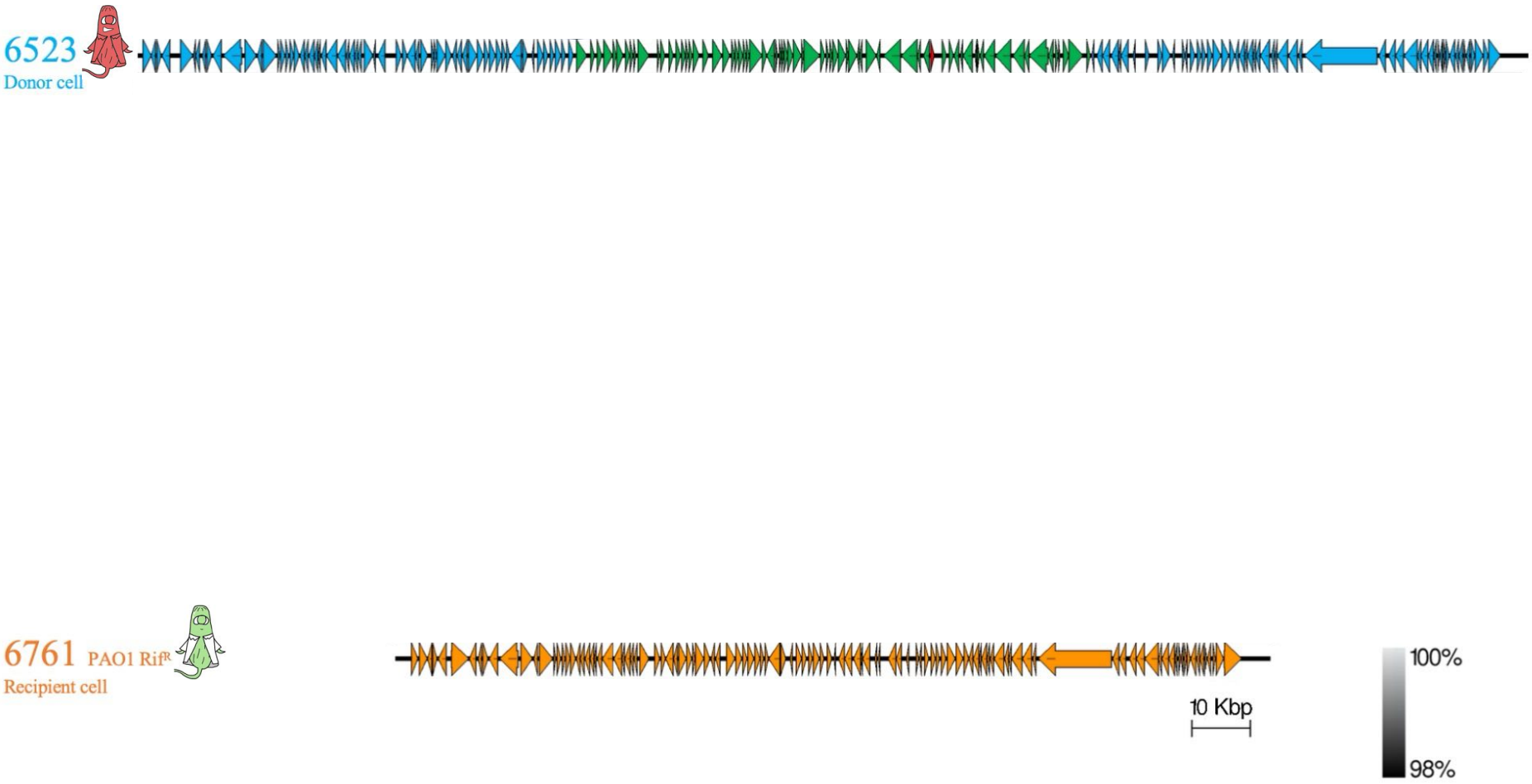
Séquençage nanopore





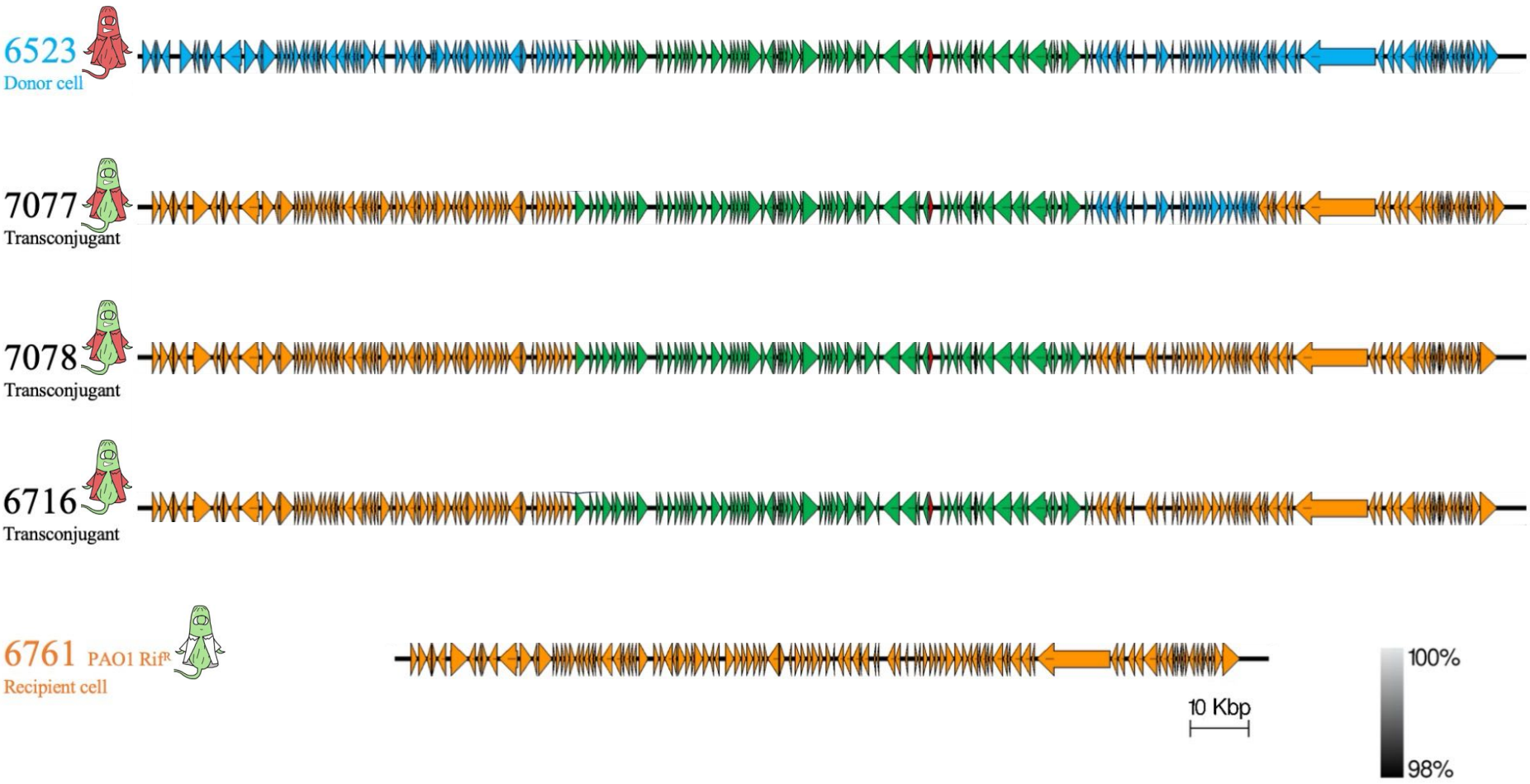
Support génétique

Séquençage nanopore



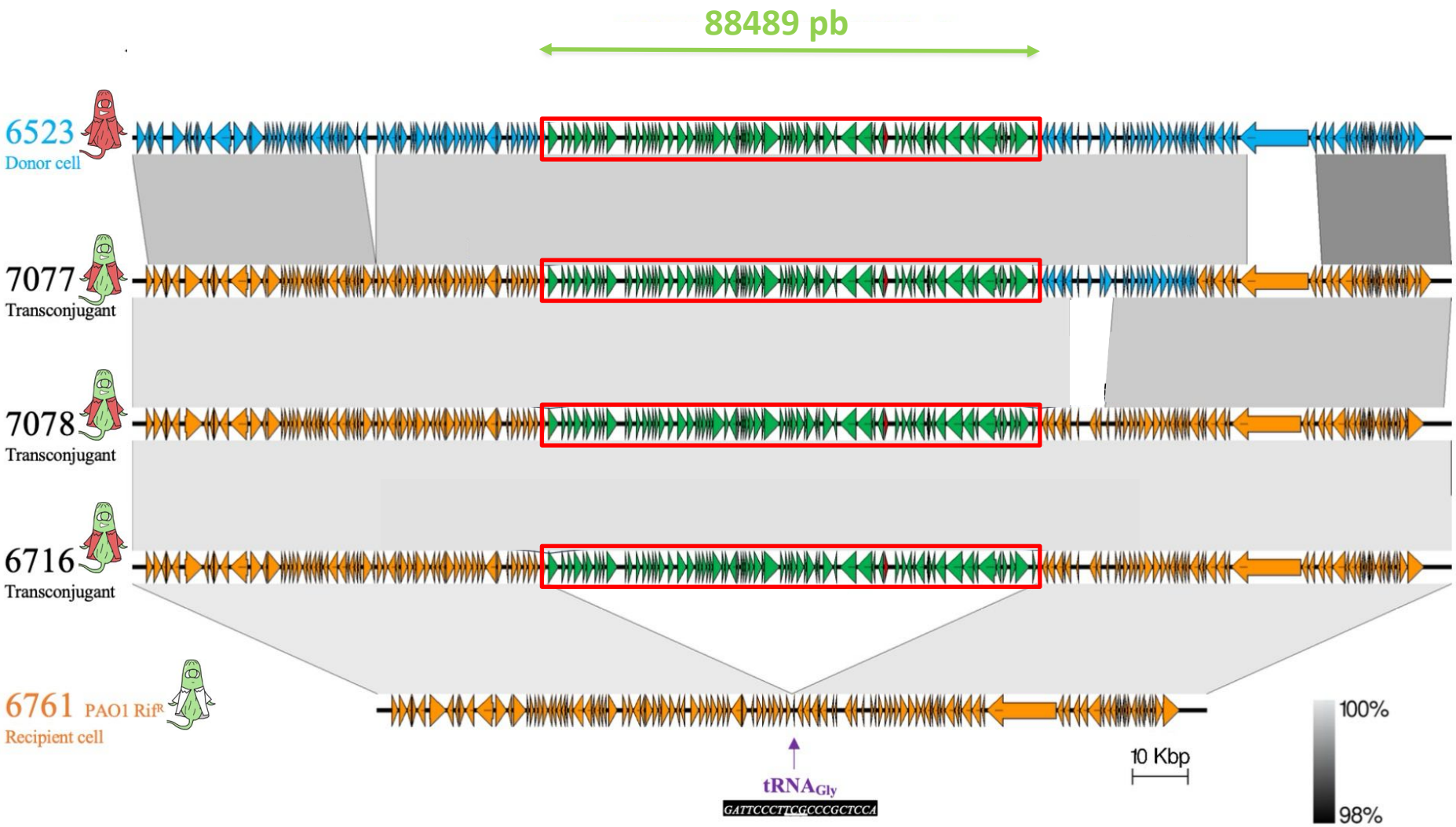
Support génétique

Séquençage nanopore



Support génétique

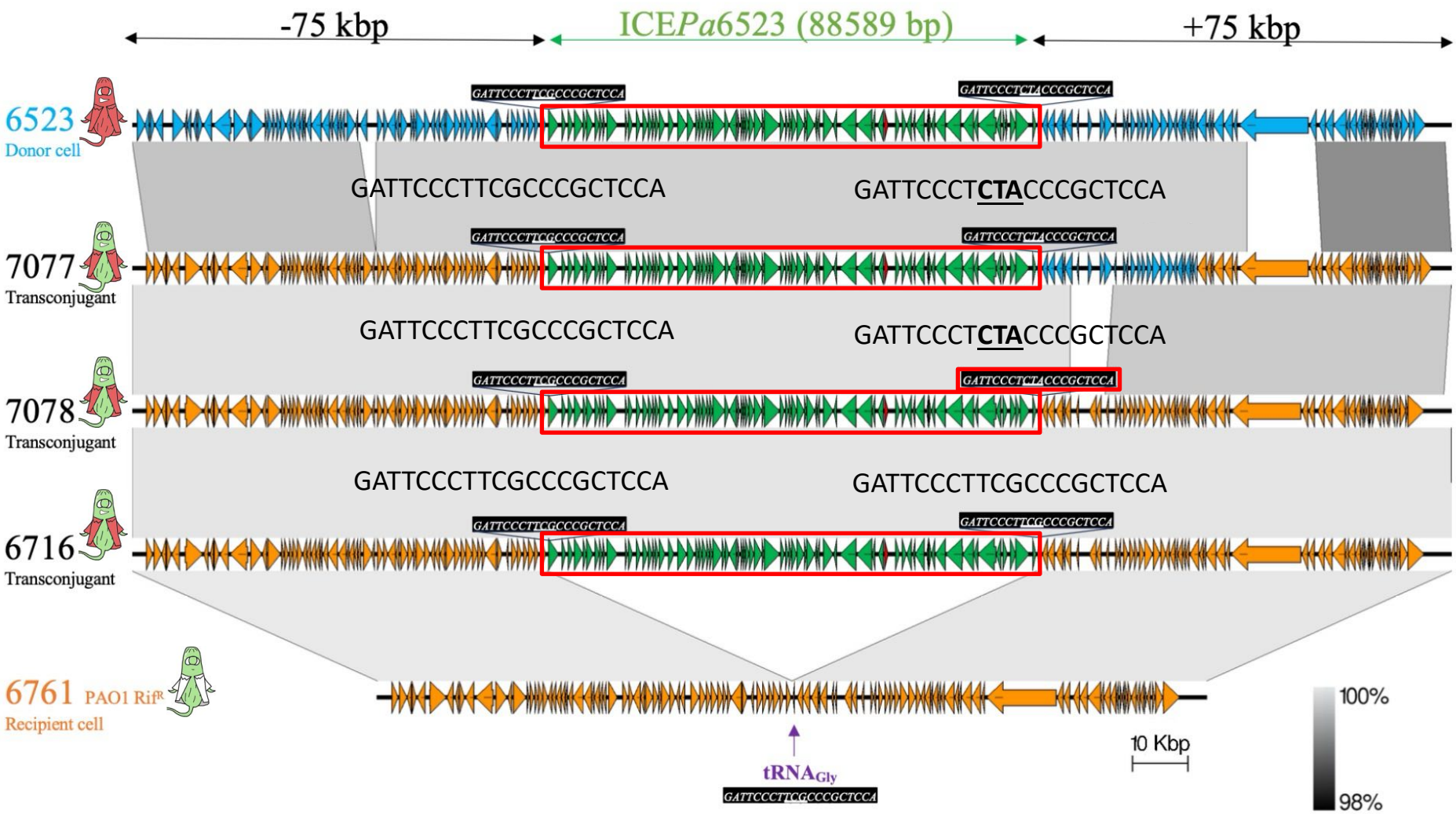
Séquençage nanopore



☑ Site d'insertion : 3' ARNt^{Gly} PA0729.1

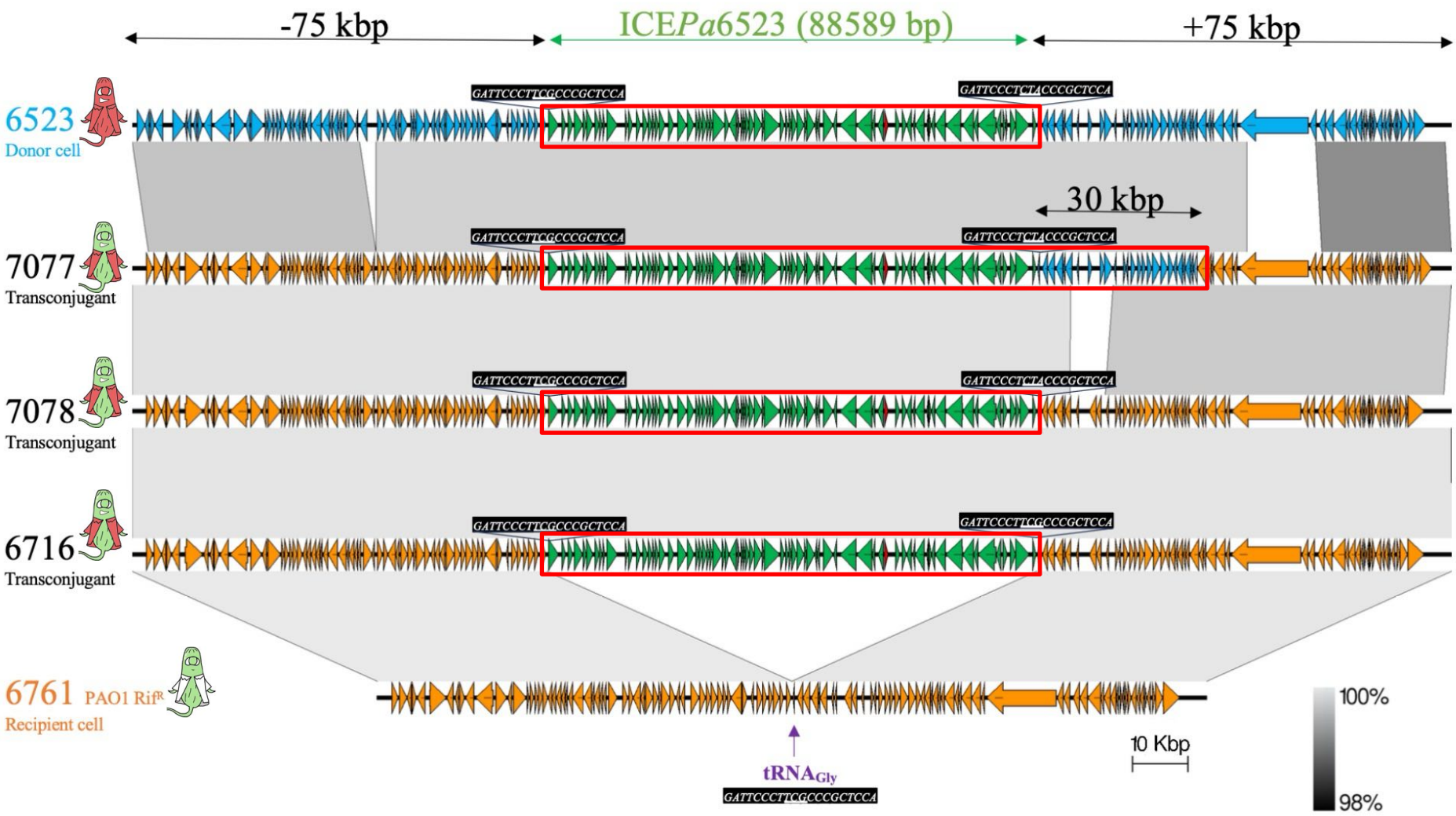
Support génétique

Séquençage nanopore



Support génétique

Séquençage nanopore



Conclusion

Support génétique carbapénémase IMP-13

ICE*Pa*6523 **Fonctionnel**

89 kb

Insertion 3' ARNtGly PA0729.1

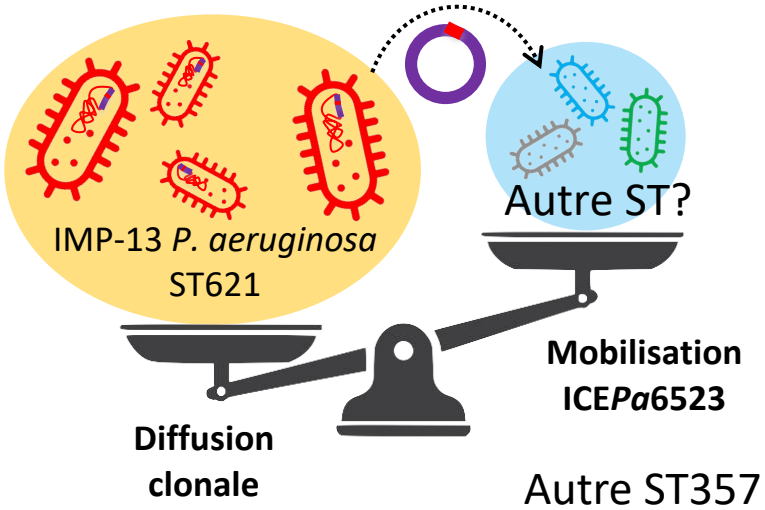
Mécanisme et régulation du transfert de l'ICE

Mobilisation gènes adjacents ?

Gènes régulateurs ?

=> Améliorer le taux de conjugaison

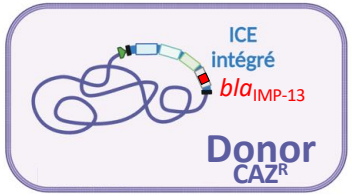
Mode de diffusion carbapénémase IMP-13

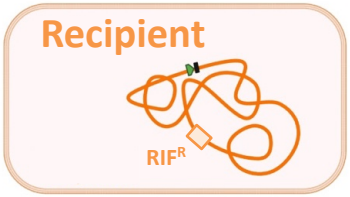


Séquençage illumina	**CMI**
Séquençage nanopore	**Conjugaison**

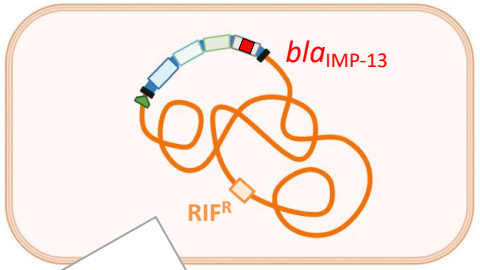
Recipe : Mating assay

Ingredients





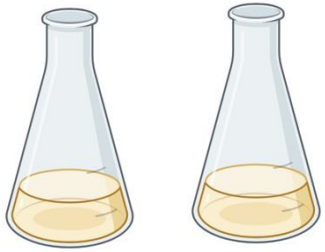
Tc



CAZ^R
RIF^R

Directions

Very low conjugation rate



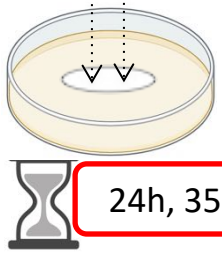
D: 6523 R: PAO1 RIF^R

Exponential phas
OD600nm

0,5 mcF, 1/200e 50 mL MH
Incubation 35°C±2°C

Thermal stress
10 min -20°C
5 min -20°C
10 min 20°C
5 min 50°C
10 min 50°C

500 µL D + 500 µL R (1:1)
Centrifugation
100 µL => 0.45 µm nitrocellulose filter on MH agar plate



24h, 35°C±2°C

Thermal stress
24h 20°C
48h 20°C
24h 37°C
48h 37°C

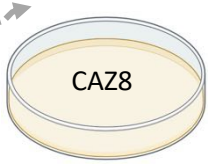
Filter => 1 mL MH
100 µL on selective media

ctive antibiotic GEN25 Ø



Tc

PUR and 10^{-1}

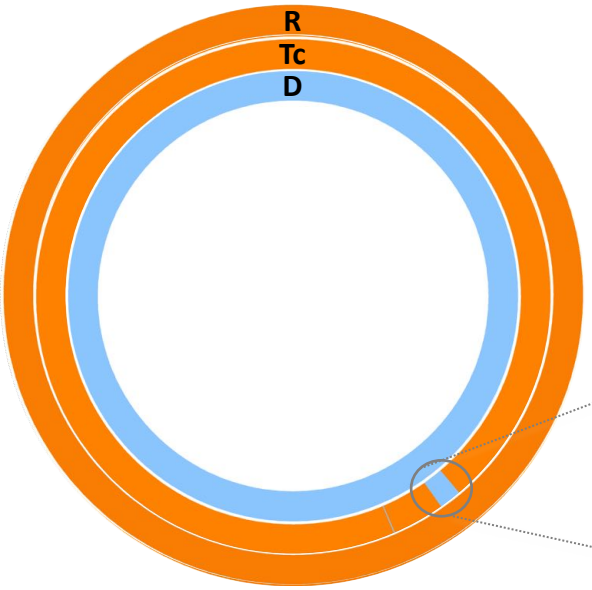


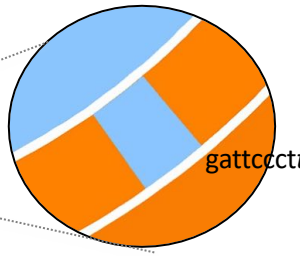
D

10^{-6}, 10^{-7},10^{-8}

Conjugation rate
= nb Tc / nb D

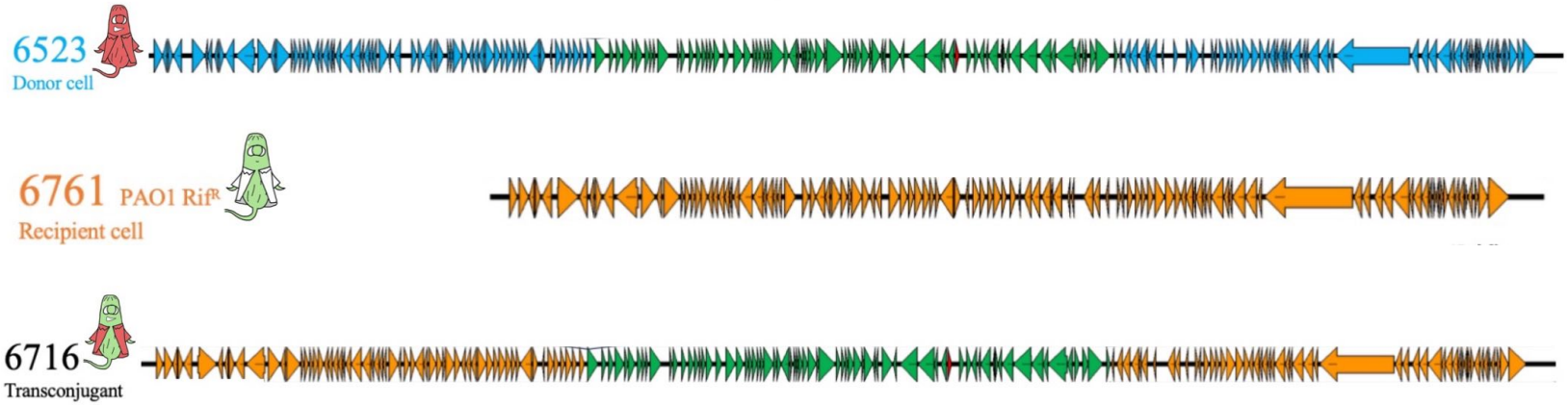
Transconjugants : Only ICE transfert





gattcc*ctt**cg*cccgctcca

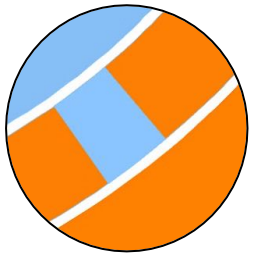
- Nanopore
- Read alignment: Minimap2
- Coverage of the R reads on **Tc**
- Regions not covered by R
- Comparison with D coverage
- Regions transferred by conjugation
- Circos plot



Transconjugants : Only ICE transfert



gattccct***tcg***cccgctcca



ICE*Pa6523* 88589 bp





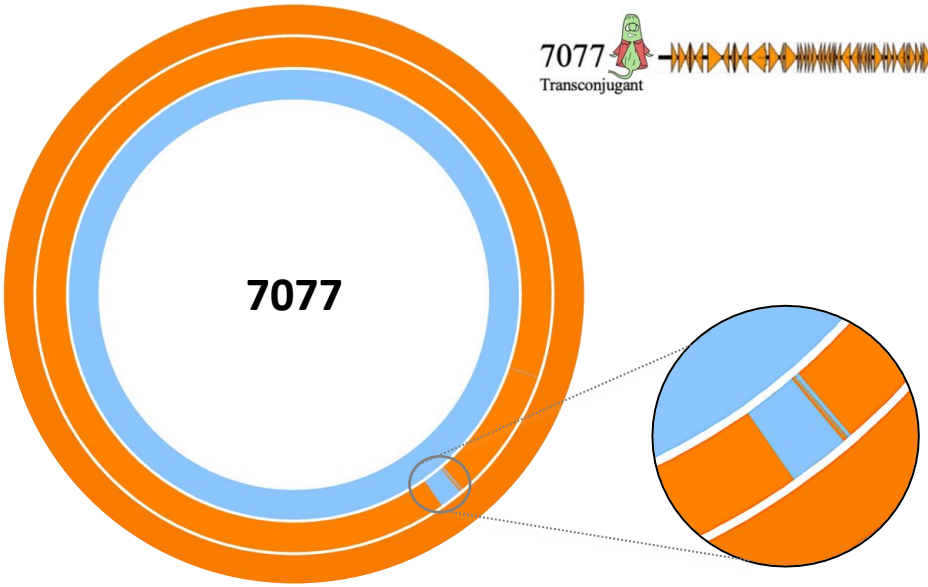




gattccct***cta***cccgctcca

Transconjugants obtained from independent experiments

Transconjugants : ICE and other regions

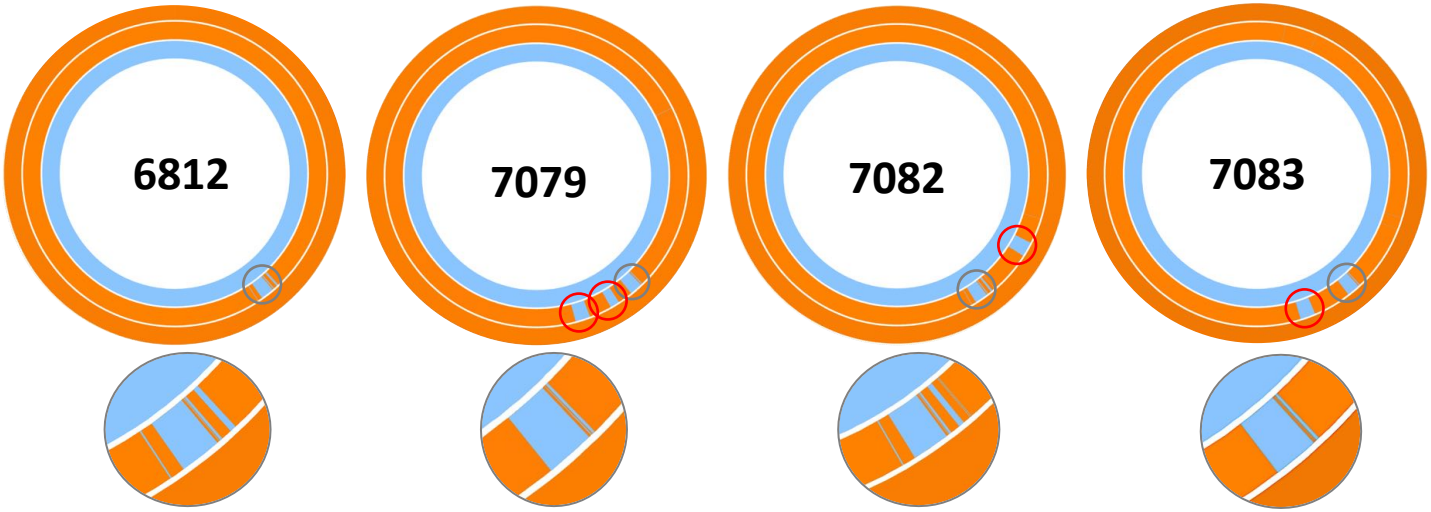




ICE*Pa6523* with rearrangements

Other transfert region

Conjugation ± recombinaison



Transconjugants obtained from independent experiments

Mise en pratique

Résistance au Ceftolozane/tazobactam par acquisition d'une carbapénémase

Mobilisation d'un ICE*clc*-like comme mécanisme potentiel de propagation de la carbapénémase IMP-13 chez *Pseudomonas aeruginosa*

Bientz L, Guyet U, Guiraud J, Metifiot M, Moulieras M, Aillerie S, Coulange-Mayonnove L, Boureima-Abdou B, Groppi A, Nikolski M, Bébéar C, Pereyre S, Dubois V. **Mobilization of an ICE*clc*-Like Element as a Potential Mechanism for the Spread of IMP-13 Carbapenemase in *Pseudomonas aeruginosa*.** J Glob Antimicrob Resist. 2025 Mar;41:44-51. doi: 10.1016/j.jgar.2024.12.006. Epub 2024 Dec 18. PMID: 39706477.