

FIGURE 1

Table 1. Efflux-mediated resistance to non-fluoroquinolone antimicrobials

Antimicrobial	Efflux system	Pump family	Gene location	Organism(s)	Reference ^a
Chloramphenicol & florfenicol Chloramphenicol	Cml, CmlA, CmlB	MF	mostly plasmid; some chromosome	<i>P. aeruginosa</i> , <i>E. aerogenes</i> , <i>K. pneumoniae</i> , <i>S. enterica</i> serovar Typhimurium	48
	Cml, CmlV, Cml, CmlX, CmlA	?	plasmid & chromosome	<i>Streptomyces</i> spp., <i>Corynebacterium</i> spp., <i>Rhodococcus</i> spp.	48
	MdfA ^o	MF	chromosome	<i>E. coli</i>	74
	MexEF-OprN ^o ; variety of three-component RND pumps ^d	RND	chromosome	<i>P. aeruginosa</i> , several Gram-negative bacteria	74, 79
	OqxAB	RND	plasmid	<i>E. coli</i>	84
Chloramphenicol, florfenicol	Flo, FloR, pp-Flo	MF	plasmid & chromosome	<i>E. coli</i> , <i>K. pneumoniae</i> , <i>V. cholerae</i> , <i>S. enterica</i> serovar Typhimurium	48
	PexA	?	plasmid	<i>S. lentus</i>	70
	Mef(A)	MF	chromosome	<i>Streptococcus</i> spp., <i>Corynebacterium</i> spp., <i>Enterococcus</i> spp., <i>Micrococcus</i> spp., <i>Staphylococcus</i> spp., <i>Acinetobacter</i> spp., <i>Bacteroides</i> spp., <i>Neisseria</i> spp., several Enterobacteriaceae and Pseudomonadaceae commensals	146, 176
	Msr(A)	ABC	plasmid	<i>Staphylococcus</i> spp.	173, 175
	Msr(C)	ABC	chromosome	<i>E. faecium</i>	146, 189
Macrolides, lincosamides, streptogramins & ketolides Macrolides	Msr(D)	ABC	chromosome	<i>S. pneumoniae</i>	149
	MdeA	MF	chromosome	<i>S. aureus</i> , <i>S. hemolyticus</i> , <i>B. cereus</i> , <i>B. subtilis</i>	192
	Vga(A/B)	ABC	plasmid	<i>S. aureus</i>	173
	Lsa	ABC	chromosome	<i>E. faecalis</i>	173, 186
	Lsa(B)	ABC	plasmid	<i>S. sciuri</i>	187
Lincosamides, streptogramins Clindamycin	LmrB	MF	chromosome?	<i>B. subtilis</i>	189, 190
	LmrB	MF	chromosome	<i>C. glutamicum</i>	191
	Cme	MF	chromosome	<i>C. difficile</i>	172
	7 ^a	?		<i>S. pyogenes</i>	188
Macrolides, lincosamides, type B streptogramins Macrolides	MacAB-TetC	ABC	chromosome	<i>E. coli</i>	521
	MirCDE	RND	chromosome	<i>N. gonorrhoeae</i>	168, 197, 198
	AcrAB-TolC, Mex ^o , RND pumps in several Gram-negative bacteria ^a	RND	chromosome	<i>E. coli</i> , <i>E. aerogenes</i> , <i>P. aeruginosa</i> , other Gram-negative bacteria	74, 195, 196
	MdfA ^o	MF	chromosome	<i>E. coli</i>	74
	?	?	?	<i>Campylobacter</i> spp.	202, 480
Erythromycin Erythromycin, roxythromycin	MexCD-OptJ	RND	plasmid	<i>Pseudomonas</i> spp.	201
Tetracyclines & glycopeptides Tetracyclines	Tet(A), Tet(B), Tet(C), Tet(D), Tet(E), Tet(G), Tet(H), Tet(J), Tet(Y), Tet(Z), Tet(30), Tet(39)	MF	Plasmid	Gram-negative bacteria	47, 96, 522
	Tet(K), Tet(L)	MF	plasmid	Gram-positive bacteria	47, 522
	Tet38	MF	chromosome	<i>S. aureus</i>	94
	Tet(V)	MF	chromosome	<i>M. tuberculosis</i> , <i>M. fortuitum</i>	95
	Re1258/Tap	MF	chromosome	<i>M. tuberculosis</i> , <i>M. fortuitum</i>	129, 130

Table 1. (continued)

Glycylcyclines	P55/Rc1410	MF	chromosome	M. tuberculosis, M. bovis	131
	MdfA ^m	MF	chromosome	E. coli	74
	MexAB-OprM ^f , several three-component pumps of the RND family				74
β-Lactams	AcrAB-TolC, MexXY-OprM, MexAB-OprM, MexCD-OprJ	RND	chromosome	P. mirabilis, E. coli, K. pneumoniae, M. morganii	460-464a
	MepA	MATE	chromosome	P. aeruginosa	464a
				S. aureus	
Aminoglycosides	AcrAB-TolC ^j	RND	chromosome	H. influenzae	331
	MexAB-OprM ^k , several three-component pumps of RND family ^l	RND	chromosome	P. aeruginosa; several Gram-negative bacteria	74, 250
	LmrA ^m	ABC	chromosome	L. lactis	85
	AcrAD-TolC	RND	chromosome	E. coli	74, 523
	BpeAB-OprB	RND	chromosome	B. pseudomallei	292
	AmrAB-OprA	RND	chromosome	B. pseudomallei	524
	MexXY-OprM	RND	chromosome	P. aeruginosa	74, 306, 307
Oxazolidinones	MexAB-OprM ⁿ	RND	chromosome	P. aeruginosa	74
	EmrE ⁿ	RND	chromosome	P. aeruginosa	74
	MdfA ^m	MF	chromosome	E. coli	74
	LmrA ^m	ABC	chromosome	L. lactis	85
	AcrAB-TolC, AcrEF-TolC	RND	chromosome	E. coli	196

^aWhere efflux systems have been described in earlier review articles, these are highlighted here, otherwise original articles are cited.

^bThis multidrug efflux system was originally identified as the Cmr/CmlA chloramphenicol exporter.

^cMutant strains of *P. aeruginosa* overexpressing MexEF-OprN are readily selected in vitro using chloramphenicol. 78–80

^dWhere tested, RND-type efflux systems that promote resistance to chloramphenicol also promote florfenicol resistance (e.g. AcrAB-TolC75 and AcrEF-TolC86 in *S. enterica* serovar Typhimurium).

^eEfflux has been demonstrated although an efflux system has not been identified.

^fThe efflux gene(s) has not been identified though its mobility has been confirmed.

^gMutant strains of *P. aeruginosa* overexpressing MexCD-OprJ can be selected in vitro using erythromycin (Poole, unpublished results).

^hExport of macrolides, lincosamides and streptogramins by three-component RND type multidrug efflux systems may explain the insusceptibility of many Gram-negative bacteria to these agents.

ⁱMutant strains of *P. aeruginosa* overproducing MexAB-OprM can be selected in vitro using tetracycline. 78, 132, 133

^jAssociated with resistance to ampicillin in clinical strains. 331

^kImplicated in resistance to meropenem 322 and ticarcillin 323, 324 in clinical isolates.

^lWhile many RND-type multidrug efflux systems accommodate β-lactams (see text), few are implicated as primary determinants of resistance, in laboratory or clinical isolates.

^mCloned gene promotes very modest increases in MICs to the indicated antimicrobial.

ⁿShow a modest contribution to intrinsic aminoglycoside resistance but only seen in low ionic strength media.

Table 2. Efflux-mediated resistance to fluoroquinolones^a

Efflux system	Pump family	Antimicrobial ^b	Organism(s)	Reference
Gram-positive				
NorA	MF	NOR, CIP	<i>S. aureus</i>	209, 525
NorB	MF	NOR, CIP, MOX, SPR	<i>S. aureus</i>	94
γ^c	?	NOR, CIP, MOX, GAT, SPR	<i>S. aureus</i>	212
PmrA	MF	NOR, CIP	<i>S. pneumoniae</i>	209, 526
γ^d	?	NOR, CIP, MOX	<i>S. pneumoniae</i>	213
EmeA	MF	NOR, CIP	<i>E. faecalis</i>	235, 235a
Lde	MF	NOR, CIP	<i>L. monocytogenes</i>	233
EfrAB	ABC	NOR, CIP	<i>E. faecalis</i>	352
γ^e	?	FQ	<i>B. anthracis</i>	237, 527
Bmr	MF	FQ	<i>B. subtilis</i>	209
Blt	MF	FQ	<i>B. subtilis</i>	209
Bmr3	MF	FQ	<i>B. subtilis</i>	528
MD1, MD2 ^f	ABC	CIP	<i>M. hominis</i>	240
LfrA	MF	FQ (CIP, NOR?)	<i>M. smegmatis</i>	242, 529
EfpA	MF	CIP, NOR	<i>M. smegmatis</i>	242
Rv1634	MF	FQ	<i>M. tuberculosis</i>	129
Rv1258c	MF	OFL	<i>M. tuberculosis</i>	245
Rv2686c-Rv2687c-Rv2688c ^g	ABC	FQ	<i>M. tuberculosis</i>	243
LmrA	ABC	CIP, OFL	<i>L. lactis</i>	85
Mmr	SMR	CIP, NOR	<i>M. smegmatis</i>	242
Gram-negative				
AcrAB-TolC, AcrEF-TolC	RND	FQ	<i>E. coli</i>	74
MexAB-OprM, MexCD-OprJ,	RND	FQ	<i>P. aeruginosa</i>	74, 250
MexEF-OprN, MexXY-OprM ^h				
AcrAB-TolC	RND	FQ	<i>Enterobacter</i> spp.	74, 258, 530
AcrAB-TolC	RND	FQ	<i>Klebsiella</i> spp.	74, 76, 263, 531
AcrAB-TolC	RND	FQ	<i>S. enterica</i> (Typhimurium, Enteritidis)	75, 270-272, 532
AcrEF-TolC	RND	FQ	<i>S. enterica</i> serovar Typhimurium	86
SmeABC, SmeDEF	RND	FQ	<i>S. maltophilia</i>	74, 277, 289, 533, 534
CmeABC, CmeDEF	RND	FQ	<i>C. jejuni</i>	74, 256, 257, 535
SdeAB	RND	FQ	<i>S. marcescens</i>	194, 276, 535a
SdeXY	RND	NOR	<i>S. marcescens</i>	74
MtrCDE	RND	FQ	<i>N. gonorrhoeae</i>	210, 280
CeoAB-OpcM	RND	FQ	<i>B. cepacia</i> (ceenocepacia)	82
AcrAB	RND	CIP	<i>P. mirabilis</i>	74
AdeABC	RND	FQ	<i>A. baumannii</i>	74
VcaM	ABC	CIP, NOR	<i>V. cholerae</i>	290
Orf12-Orf11-Orf10 (plasmid) ⁱ	ABC	NAL, NOR	<i>Pseudomonas</i> spp.	193
MdfA	MF	FQ	<i>E. coli</i>	210, 291
?	?	FQ	<i>A. salmonicida</i>	255
?	?	FQ	<i>C. freundii</i>	536, 537
?	?	OFL	<i>P. vulgaris</i>	538
?	?	CIP, NOR	<i>B. fragilis</i>	209, 539

- ^aExcluding MATE family multidrug exporters.
- ^bNOR, norfloxacin; CIP, ciprofloxacin; MOX, moxifloxacin; GAT, gatifloxacin; SPR, sparfloxacin; OFL, ofloxacin; NAL, nalidixic acid; FQ, fluoroquinolones.
- ^cEfflux-mediated resistance observed but the specific determinant has not been identified; not NorA.
- ^dEfflux-mediated resistance observed but the specific determinant has not been identified; not PmrA.
- ^eEfflux-mediated resistance observed but the specific determinant not identified.
- ^fCytoplasmic membrane-associated ABC type efflux system assembled from 2 subunits.
- ^gCytoplasmic membrane-associated ABC type efflux system assembled from 3 subunits.
- ^hAccommodates fluoroquinolones although no reports of fluoroquinolones selecting for MexXY-overproducing mutants in vitro or in vivo.
- ⁱEncodes an ABC-MFP component of a probable ABC-MFP-OMF multidrug export system.

Figure 2

Transfection experiments

Decoy targets

Bacterium	ATCC/Strain	Classification	Indication	Target	Description
<i>Mycobacterium smegmatis</i>	MC2 155	Gram-positive/ Actinobacteria/ Lipid-rich cell wall	Considered non- pathogenic model for TB	WhiB7 consensus (396)	Transcriptional regulator of antibiotic resistance genes
<i>Staphylococcus aureus</i>	6538NA (FDA test strain)	Gram-positive/ Firmicutes/ coccus- golden balls	Many: TSS/ pneumonia/ septicemia	sigma-54 (601) WaiR consensus (448) GISA consensus Agra consensus	Major controller of adaptive response 2CS regulating antibiotic sensitivity, particularly wall structure. Also known as YYCG consensus Genes upregulated in glycopeptide- intermediate strains, candidate TFDs identified by bioinformatics Regulator of virulence, candidate sequence identified by bioinformatics
<i>Clostridium difficile</i>	BAA-1382	Gram-positive/ Firmicutes/ commensal gut bacterium	Diarrhoea to toxic PMC	TcdR consensus (506)	Alternative sigma factor that is autoregulated and drives expression of two exotoxins
<i>Pseudomonas aeruginosa</i>	-	Gram-negative/ Proteobacteria/ facultative anaerobe	Lung infection in CF patients/ Model for biofilm formation	Vfr consensus (508)	Global regulator of virulence factors
<i>Escherichia coli</i>	K12	Gram-negative/ Proteobacteria/ facultative anaerobe	Many: pneumonia/ septicemia	sigma-54 (601) fadR consensus (511)	Major controller of adaptive response Regulator of essential enzymes required for fatty acid synthesis
<i>Streptococcus pneumoniae</i>	-	Gram-positive/ Firmicutes/ in nasopharynx	Several: meningitis Now vaccinated against	fur (609)	Regulator of iron uptake
<i>Klebsiella pneumoniae</i>	GG4	Gram-negative/opportunistic pathogen	Septicemia/Crohn's /Ankylosing spondylitis	sigma-54 (601) NtrC (556)	Major controller of adaptive response Down regulates an essential gene, glnA
				sigma-54 (601)	Major controller of adaptive response

Figure 3

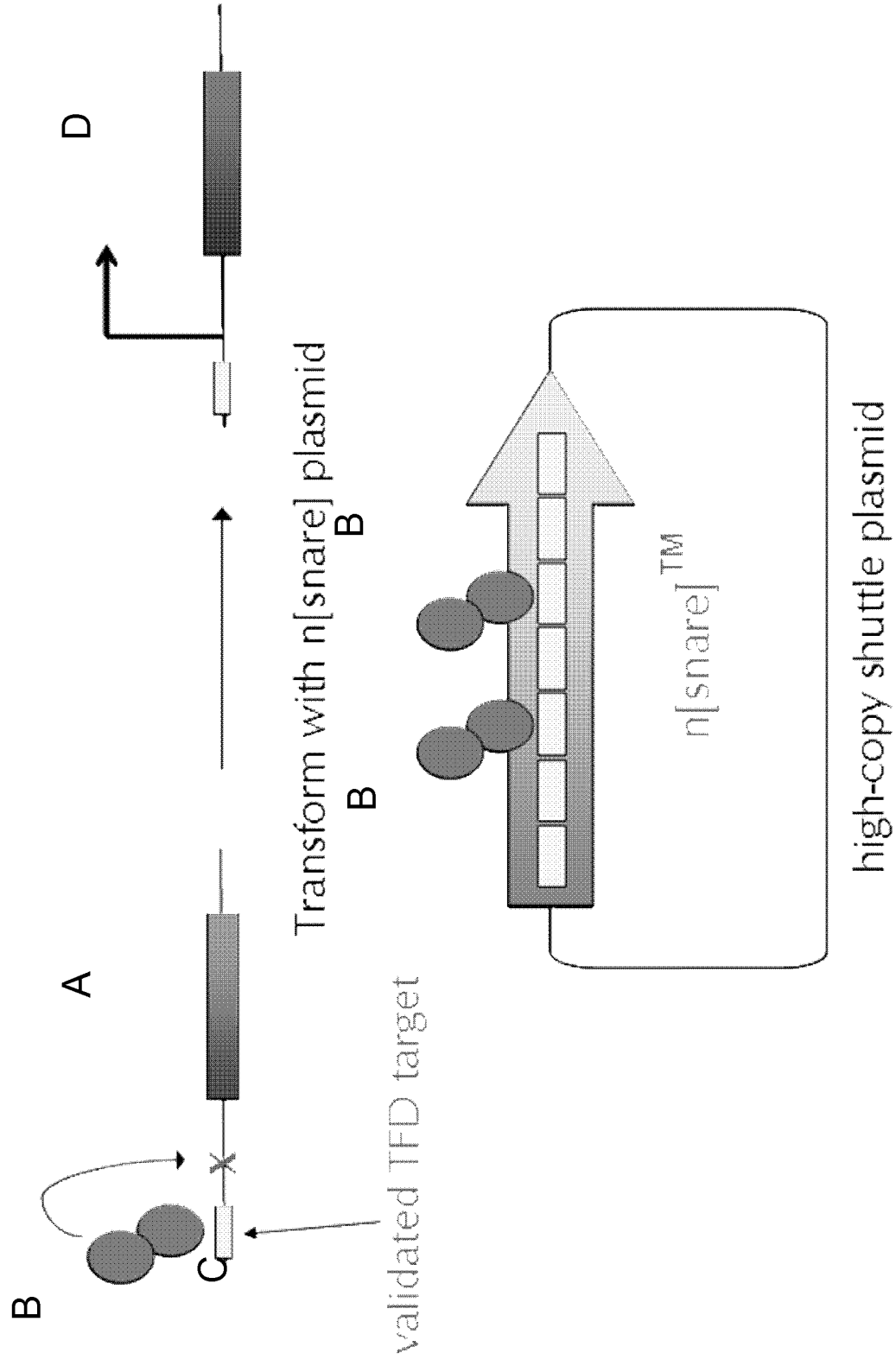


Figure 4

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GAACC AAAAA GGTTC TCTTCTCG ggc ggt acc gcc ggc gcc ctt aag nnn nnn AGT GAT CAC TTA AGC GCC GGC GGA CGGAGAGC GGC AGT TTT TCT GCC

T WITH Nt.BspQI (NEB: R0644L)

CTTGG TTTT CCAAG AGGAGAGC ccg cca tgg cgg ccg cgg gaa ttc nnn nnn TCA CTA GTG AAT TCG CGG CGG CCT GCTCTTCG
          TCTTCTCG ggc ggt acc gcc ggc gcc ctt aag nnn nnn AGT GAT CAC TTA AGC GCC GGC GGA CGGAGAGC GGC AGT TTT TCT GCC

E WITH T4 DNA POLYMERASE
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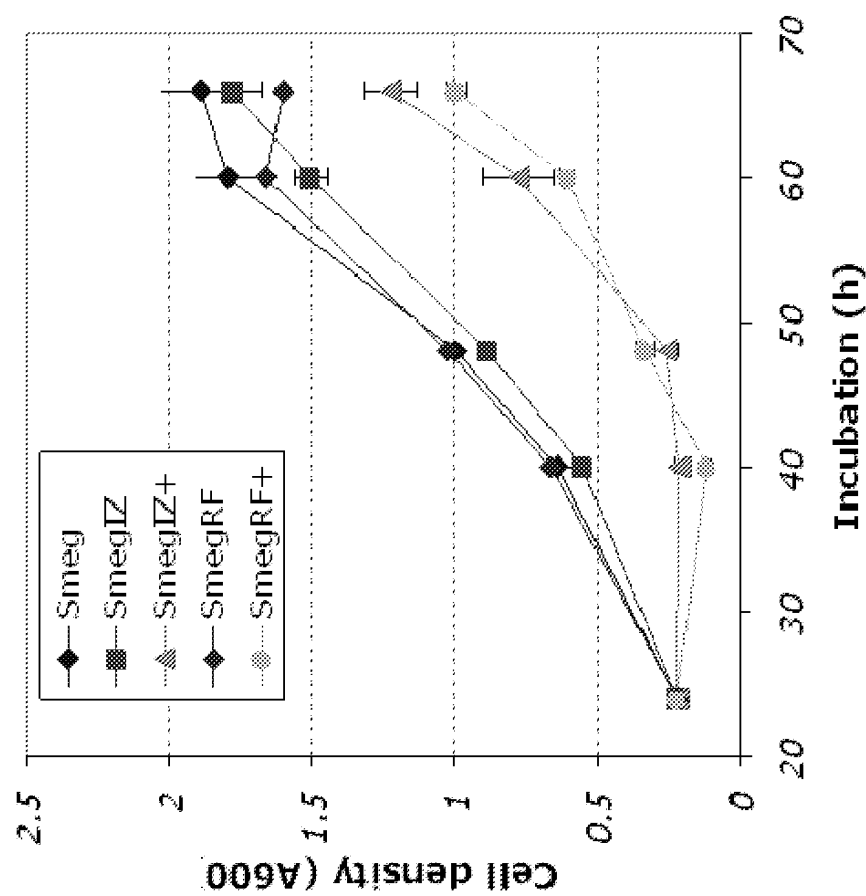


Figure 5

Figure 6

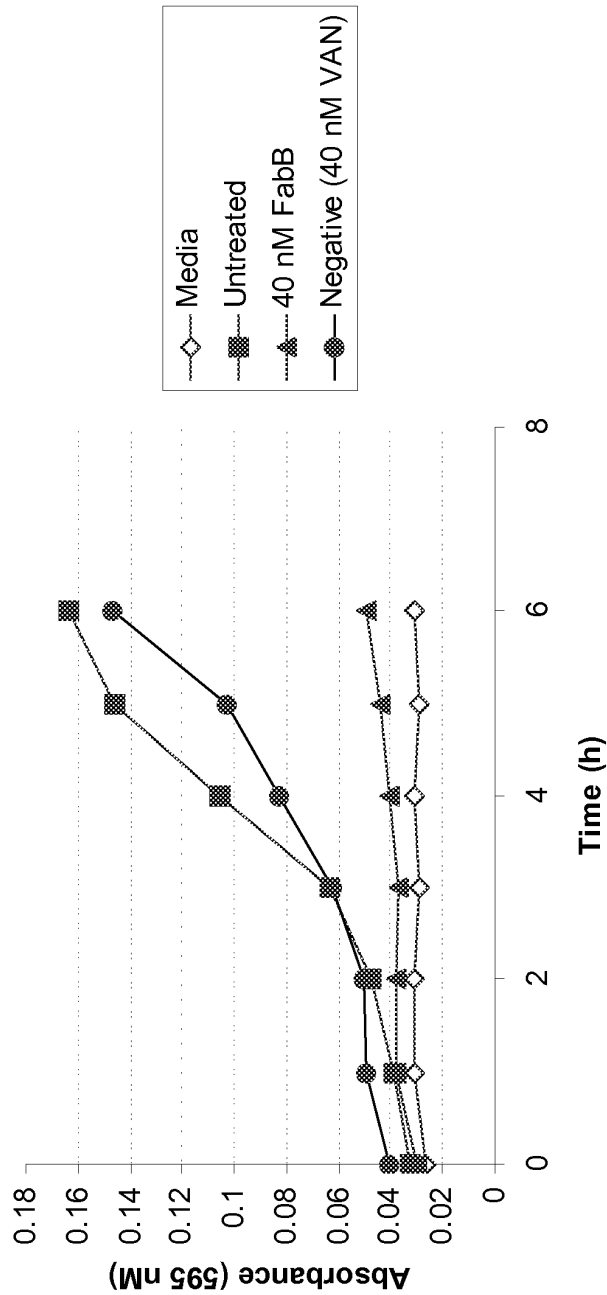


Figure 7

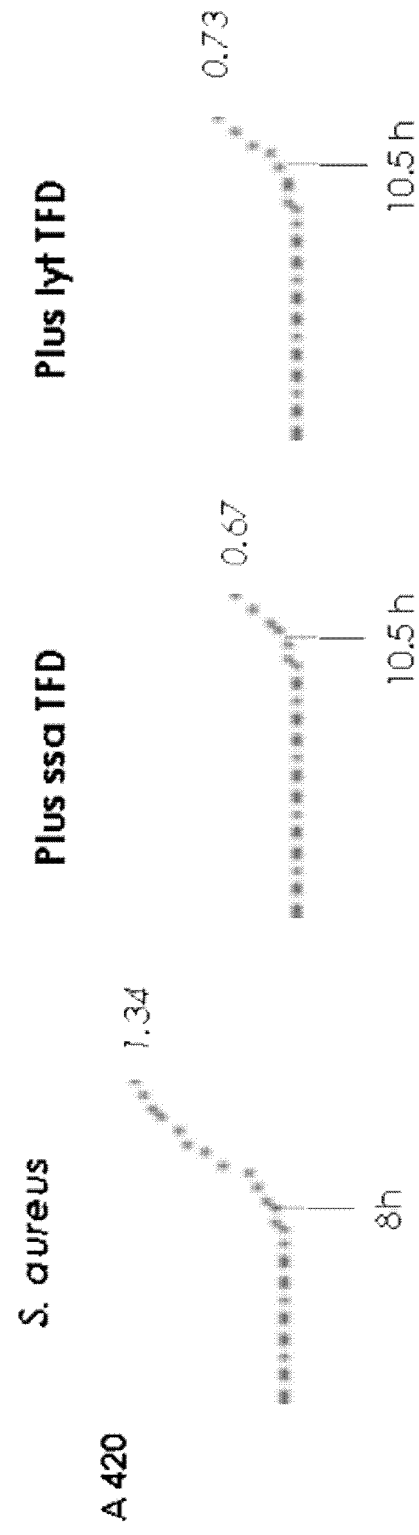


Figure 8

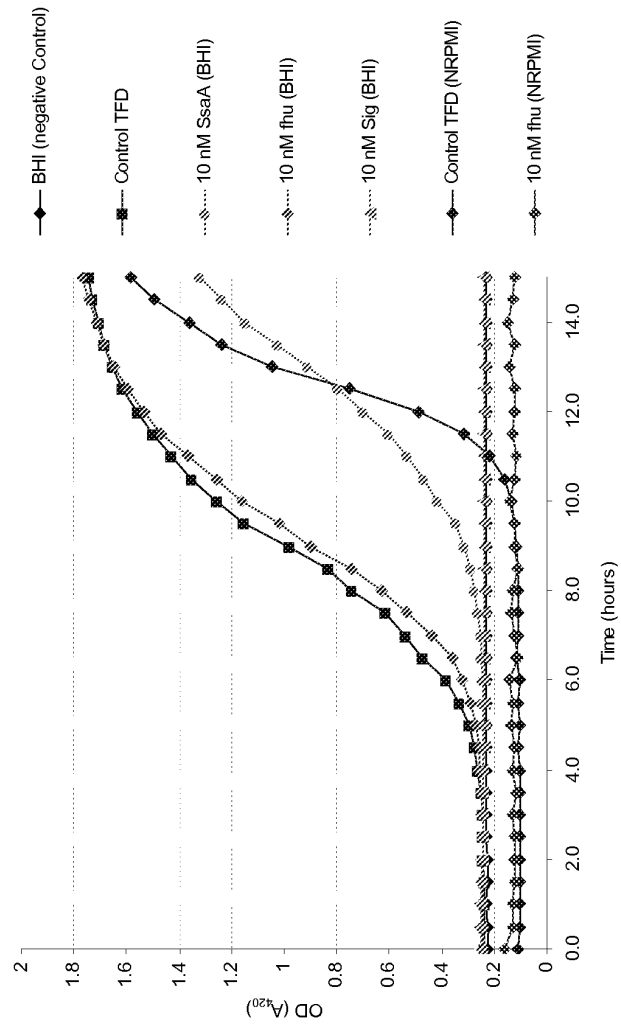
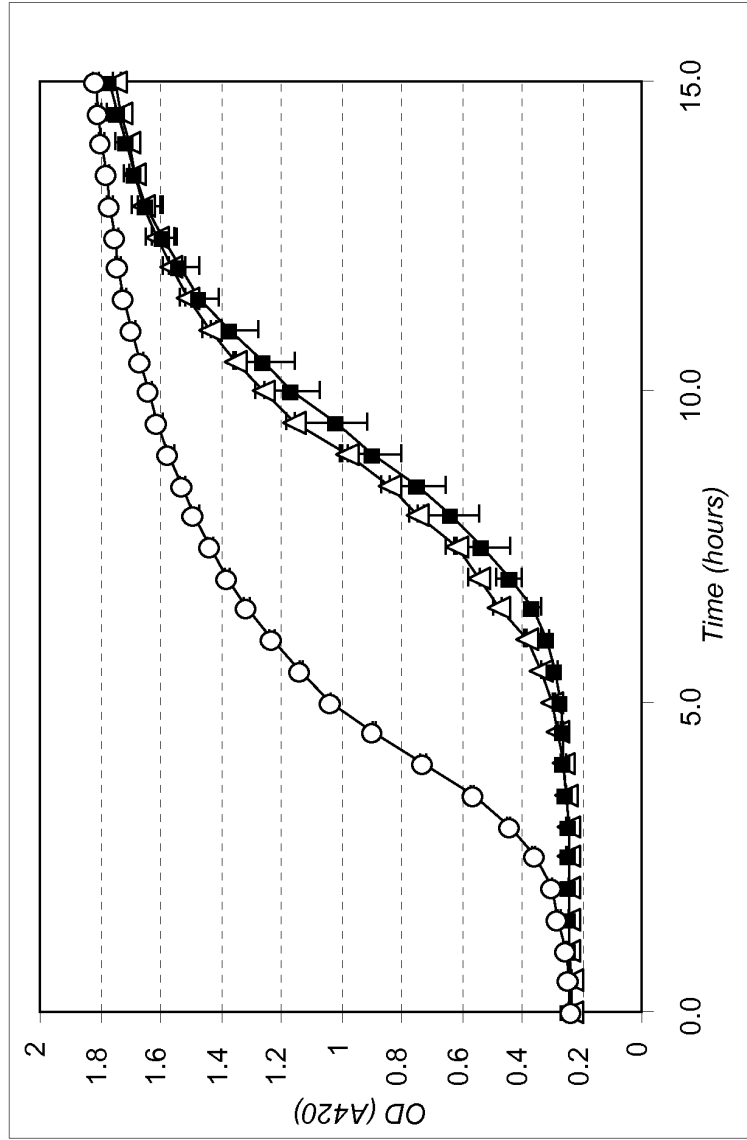


Figure 9



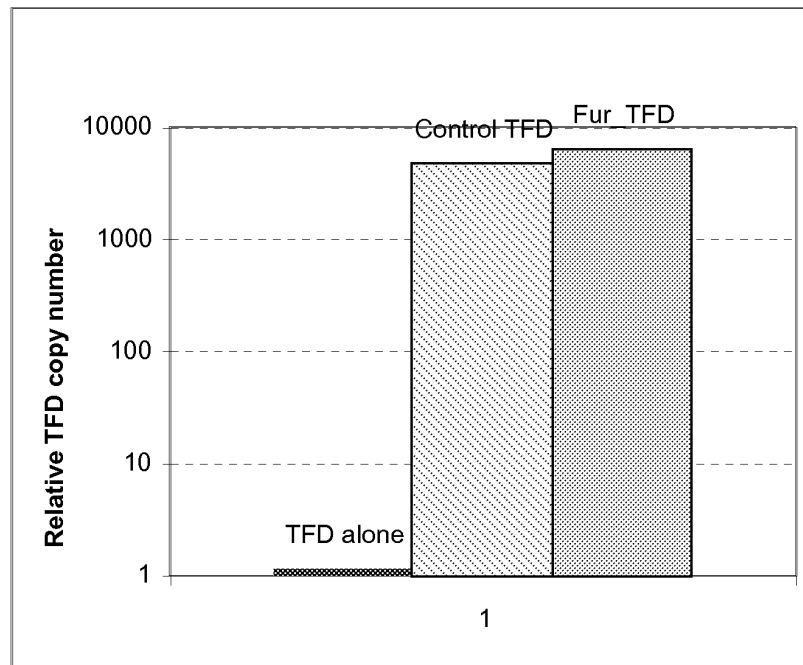


Figure 10A

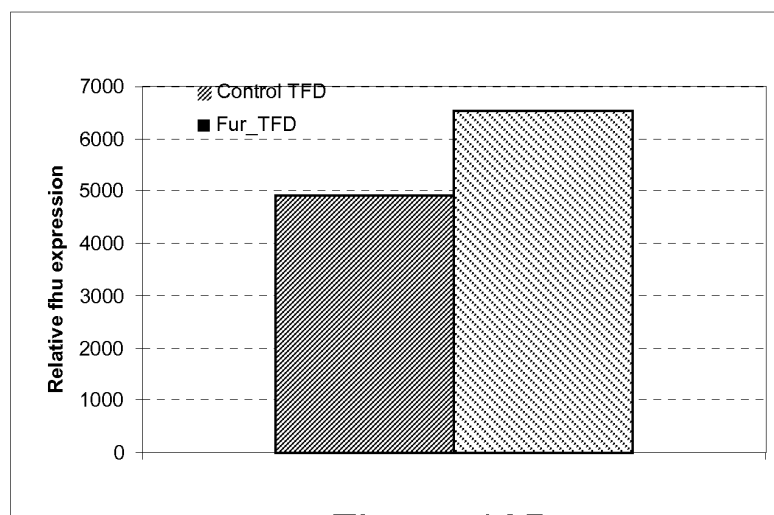


Figure 10B

Figure 11

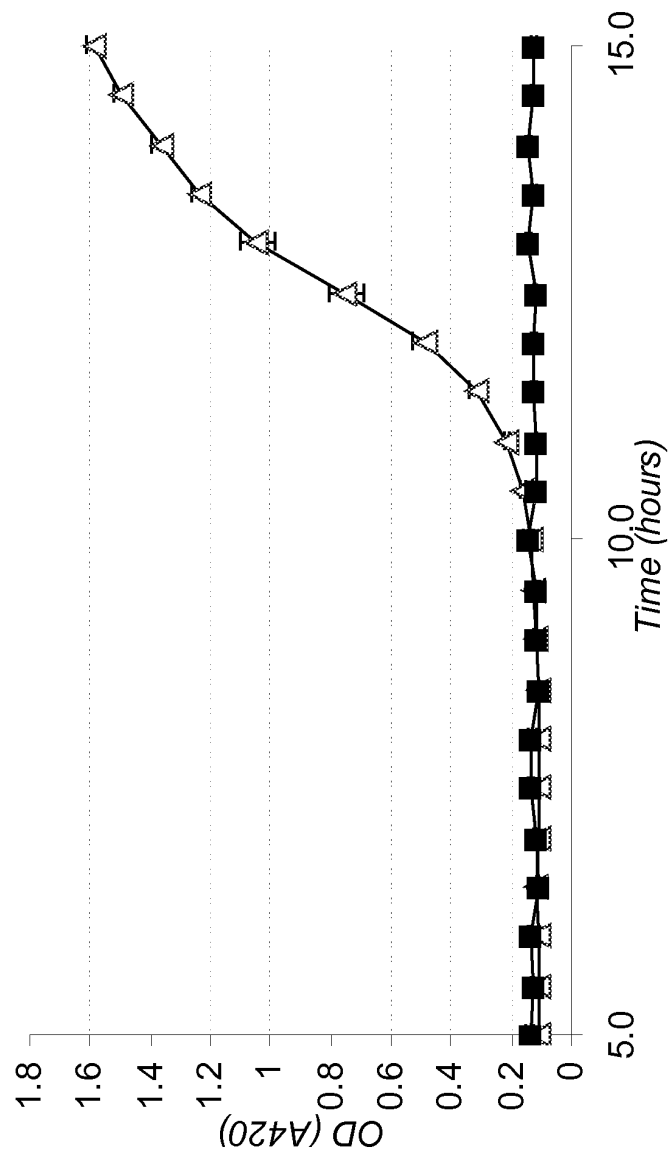
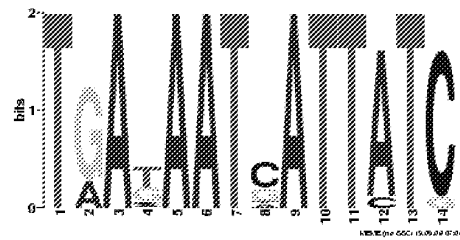


Figure 12



<u>Safur consensus</u>	(1)	<u>TGACATTCATTATC</u>
Banthracis_GBAA1093	(1)	TGACATTCATTATC
Banthracis_BA4651	(1)	TGACATTCATTATC
Banthracis_BA51021	(1)	TGACATTCATTATC
Banthracis_GBAA4651	(1)	TGACATTCATTATC
Bcereus_PCAB820_1177	(1)	TGACATTCATTATC
Bcereus_PCAB820_4500	(1)	TGACATTCATTATC
Bcereus_PCB4264_A4540	(1)	TGACATTCATTATC
Bcereus_BCG9842_B0695	(1)	TGACATTCATTATC
Bcereus_BCZK4165	(1)	TGACATTCATTATC
Saureus_SAOUHSC_00329	(1)	TGACATTCATTATC
Banthracis_BAS4317	(1)	-GACATTCATTATC
Bcereus_BCZK4166	(1)	-GACATTCATTATC
Banthracis_GBAA4652	(1)	-GACATTCATTATC
Lmonocytogenes_LMHCC_1523	(1)	-GACATTCATTATC
Lmonocytogenes_LMOF2365_1136	(1)	-GACATTCATTATC
Saureus_MW0088_A	(1)	-GACATTCATTATC
Saureus_NWMN_0059_A	(1)	-GACATTCATTATC
Saureus_SA0111_A	(1)	-GACATTCATTATC
Saureus_SAB0054c_A	(1)	-GACATTCATTATC
Saureus_SACOL0099_A	(1)	-GACATTCATTATC
Saureus_SAHV_0114_A	(1)	-GACATTCATTATC
Saureus_SAR0118_A	(1)	-GACATTCATTATC
Saureus_SAS0089_A	(1)	-GACATTCATTATC
Saureus_SaurJH1_0106_A	(1)	-GACATTCATTATC
Saureus_SAUSA300_0117_A	(1)	-GACATTCATTATC
Saureus_SAV0115_A	(1)	-GACATTCATTATC
Saureus_USA300HOU_0126_A	(1)	-GACATTCATTATC
Bcereus_BCG9842_B3605	(1)	-GACATTCATTATC
Bcereus_BCQ_4208	(1)	-GACATTCATTATC
Saureus_SAB0685_A	(1)	-GACATTCATTATC
Saureus_SAOUHSC_00746_A	(1)	-GACATTCATTATC
Lmonocytogenes_LMHCC_0596_A	(1)	TGACATTCATTATC
Saureus_MW0323_A	(1)	TGACATTCATTATC
Saureus_SaurJH9_0395_A	(1)	TGACATTCATTATC
Lmonocytogenes_LMOF2365_1990_A	(1)	TGACATTCATTATC
Lmonocytogenes_lmo1960_A	(1)	TGACATTCATTATC
Banthracis_BAS5233_A	(1)	-GACATTAATTTC
Bcereus_BC5383_A	(1)	-GACATTAATTTC
Bcereus_PCAB187_A5561_A	(1)	-GACATTAATTTC
Bcereus_PCB4264_A5506_A	(1)	-GACATTAATTTC
Bcereus_BCE_5512_A	(1)	-GACATTAATTTC
Bcereus_BCG9842_B5445_A	(1)	-GACATTAATTTC
Bcereus_BCQ_5223_A	(1)	-GACATTAATTTC
Lmonocytogenes_LMHCC_1524_A	(1)	-GACATTAATTTC
Lmonocytogenes_LMHCC_0597_A	(1)	TGACATTCATTATC
Lmonocytogenes_lmo1959_A	(1)	TGACATTCATTATC
Lmonocytogenes_LMOF2365_1989_A	(1)	TGACATTCATTATC
Lmonocytogenes_lmo0484	(1)	TGACATTCATTATC
Lmonocytogenes_lmo1131	(1)	TGACATTCATTATC
Saureus_MW0089_A	(1)	TGACATTCATTATC
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Saureus_SA0112_A	(1)	TGACATTCATTATC
Saureus_SACOL0100_A	(1)	TGACATTCATTATC
Saureus_SAHV_0115_A	(1)	TGACATTCATTATC
Saureus_SAR0119_A	(1)	TGACATTCATTATC
Saureus_SAS0090_A	(1)	TGACATTCATTATC
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Saureus_SaurJH9_0103_A	(1)	TGACATTCATTATC
Saureus_SAUSA300_0118_A	(1)	TGACATTCATTATC
Saureus_SAV0116_A	(1)	TGACATTCATTATC
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Consensus	(1)	TGATAT ATTTATC

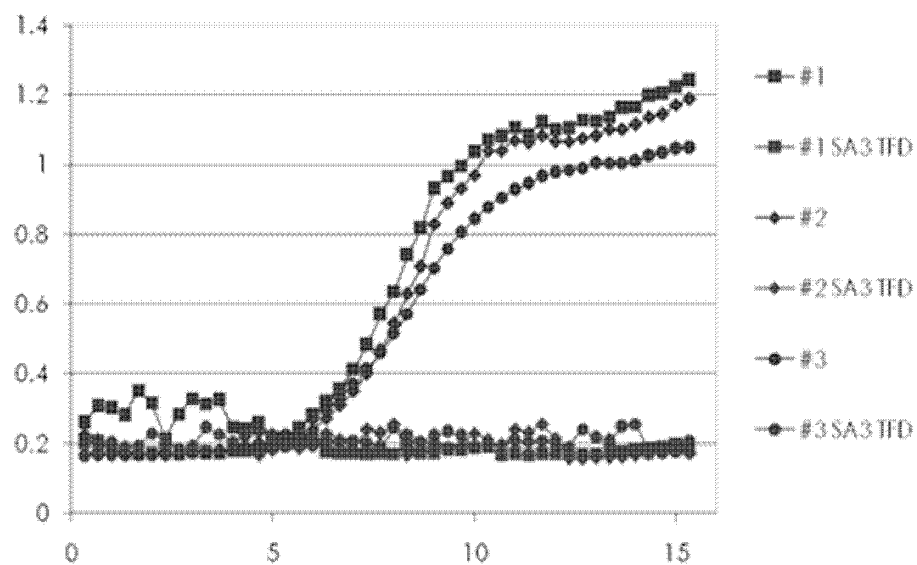


Figure 13

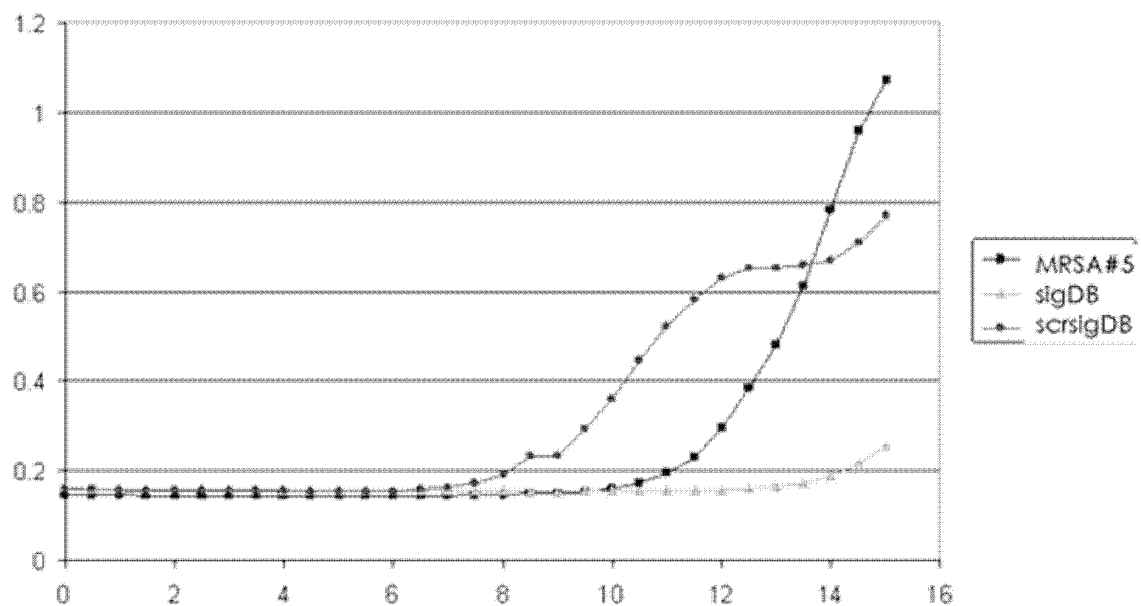


Figure 14

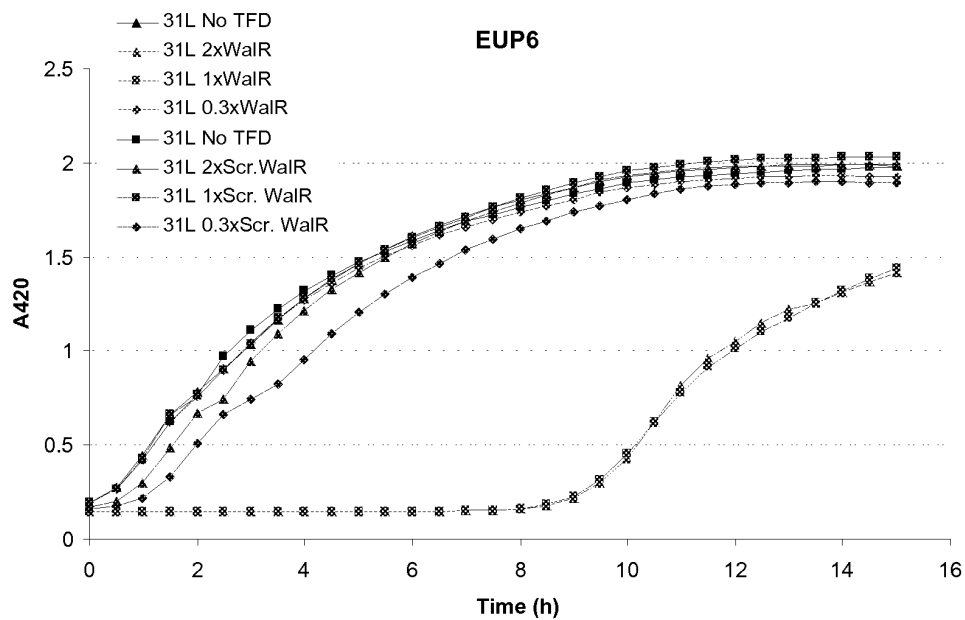


Figure 15

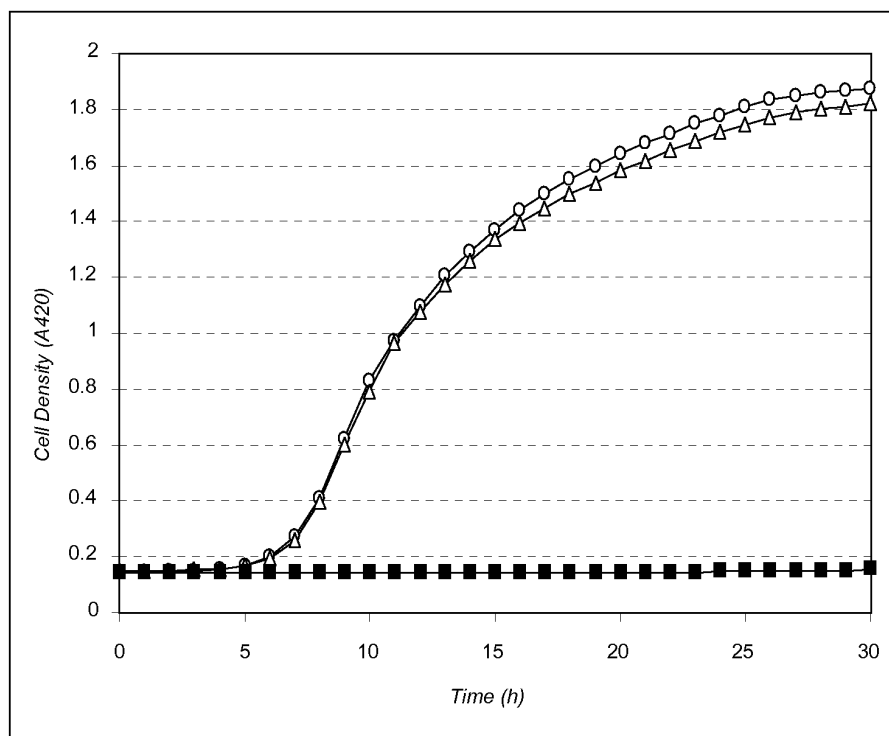


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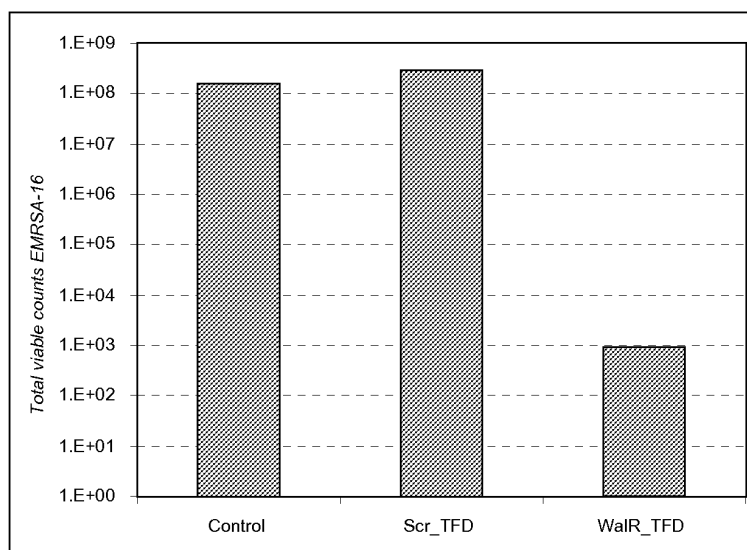


Figure 17A

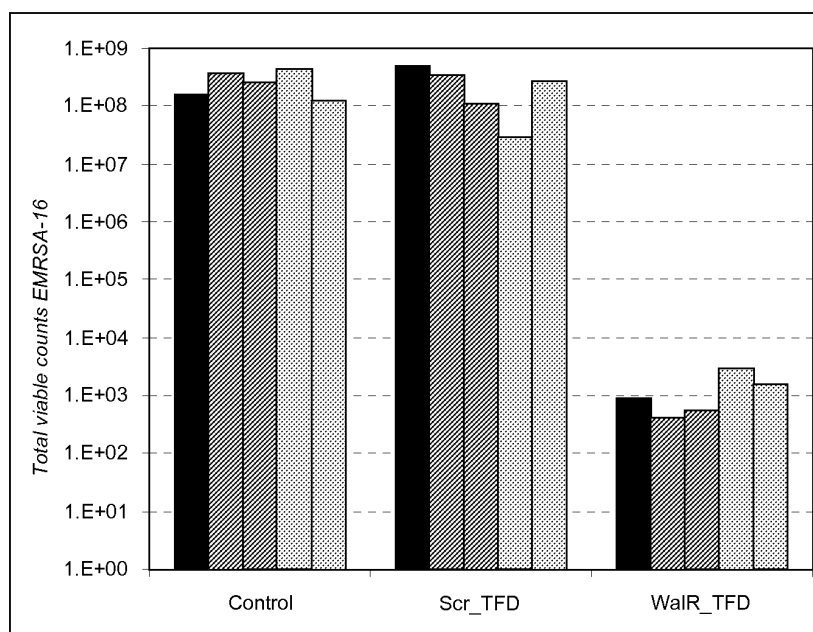
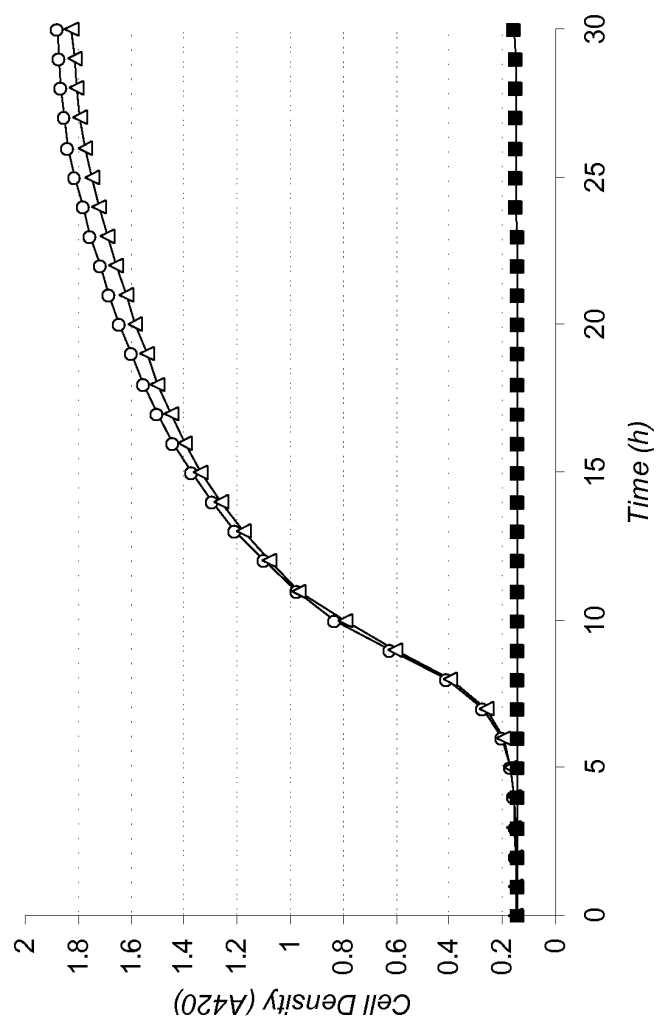


Figure 17B

Figure 17C



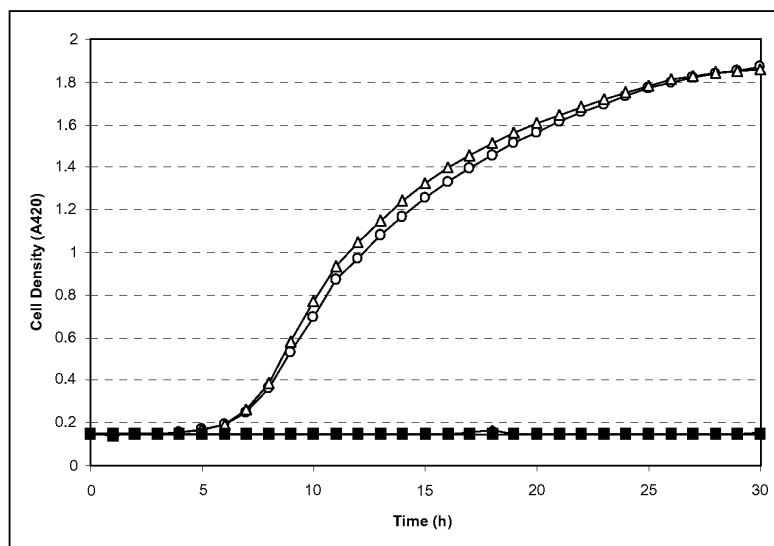


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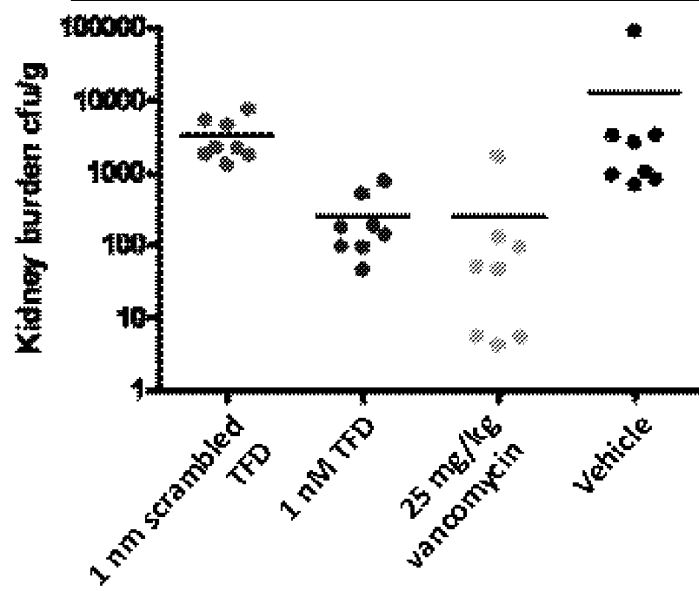


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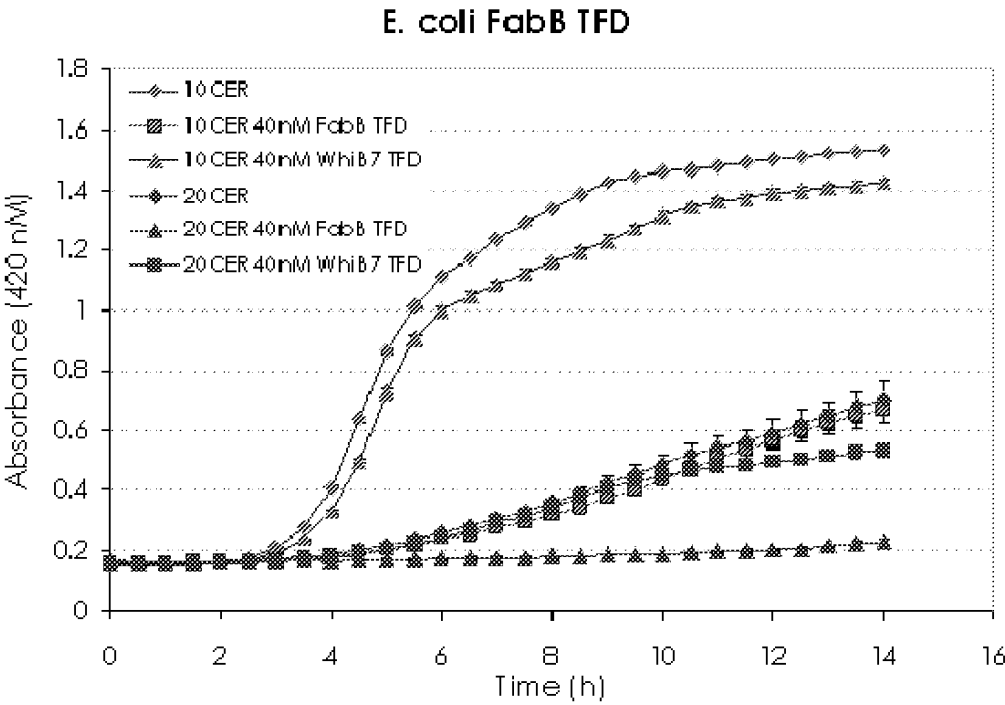


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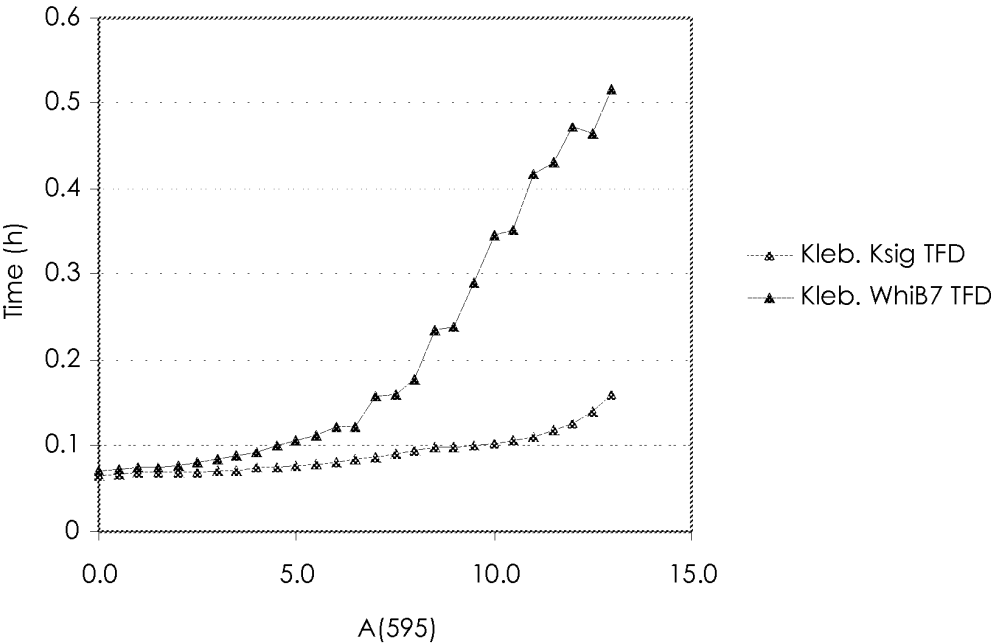
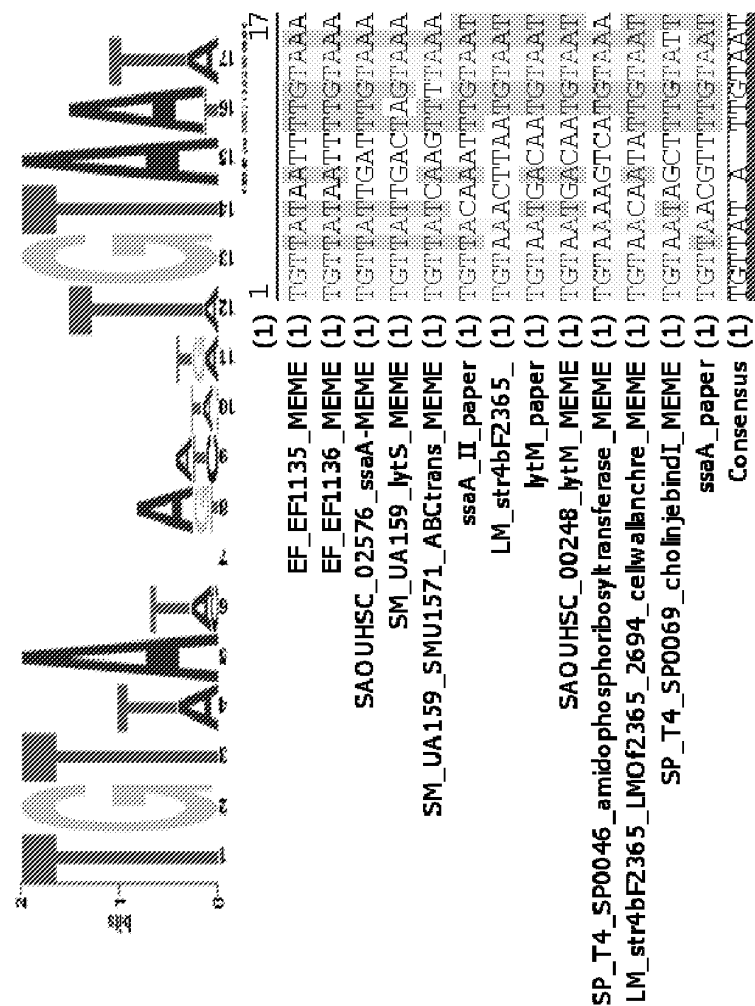
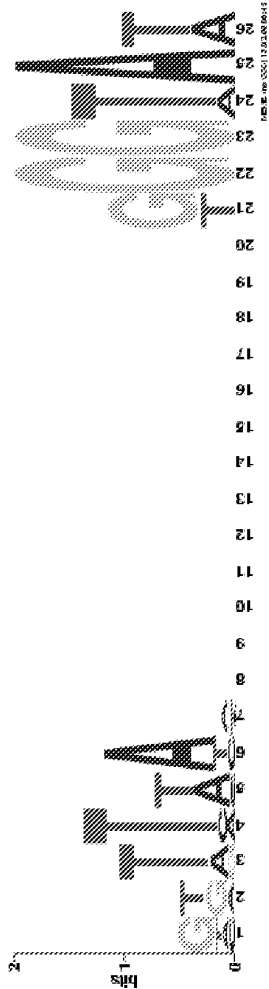


Figure 21

Figure 22



A.



B.

Sequence Name	Description	E-value	Length
NC_010079_USA300HOU_0495	1 5723	1.9	5724
NC_006582_ABC3117	-1 18	5.1	121
NC_006322_BLI03319	-1 202	7.9	203
NC_006270_BLI02593	-1 202	7.9	203
NC_007530_GBAA1815	1 4	10	121
NC_005945_BAS1680	1 4	10	121
NC_003997_BA1815	1 4	10	121
NC_010079_USA300HOU_0701	1 136	11	137
NC_009782_SAHV_0675	1 136	11	137
NC_009641_NWMN_0647	1 136	11	137
NC_009632_SaurH1_0718	1 136	11	137
NC_009487_SaurH9_0702	1 136	11	137
NC_007795_SAOUHSC_0686	1 136	11	137
NC_007793_SAUSA300_0664	1 136	11	137
NC_007622_SAB0627	1 136	11	137
NC_003923_MW0640	1 136	11	137
NC_002953_SAS0643	1 136	11	137
NC_002952_SAR0731	1 136	11	137
NC_002951_SAC010738	1 136	11	137
NC_002758_SAV0678	1 136	11	137
NC_002745_SAO633	1 136	11	137
NC_011969_BCQ_1823	1 4	20	121
NC_011773_BCAH820_1860	1 4	20	121
NC_011658_BCAH187_A1936	1 4	20	121
NC_008600_BALH_1592	1 4	20	121
NC_006274_BCZK1626	1 4	20	121
NC_003210_lm01940	-1 79	34	121
NC_009004_lmng_1109	-1 5	37	121
NC_011773_BCAH820_1667	1 71	41	121
NC_011773_BCAH820_1666	-1 71	41	121
NC_011725_BCB4264_A1632	1 71	41	121
NC_011725_BCB4264_A1631	-1 71	41	121
NC_011658_BCAH187_A1743	1 71	41	121
NC_011658_BCAH187_A1742	-1 71	41	121

Sequence Name	Description	E-value	Length
NC_007530_GBAA1597	1 71	41	121
NC_007530_GBAA1596	-1 71	41	121
NC_006274_BCZK1453	1 71	41	121
NC_006274_BCZK1452	-1 71	41	121
NC_005957_BI9727_1453	1 71	41	121
NC_005957_BI9727_1452	-1 71	41	121
NC_005945_BAS1480	1 71	41	121
NC_005945_BAS1481	-1 71	41	121
NC_004722_BC1574	1 71	41	121
NC_004722_BC1573	-1 71	41	121
NC_003997_BA1597	1 71	41	121
NC_003997_BA1596	-1 71	41	121
NC_003909_BCE_1703	1 71	41	121
NC_003909_BCE_1702	-1 71	41	121
NC_003923_MW2356	1 256	44	257
NC_003923_MW2355	-1 256	44	257
NC_002953_SAS2324	1 256	44	257
NC_002953_SAS2323	-1 256	44	257
NC_009004_lmng_2123	-1 5	48	121
NC_008527_LACR_1793	-1 5	48	121
NC_002662_L44970	1 5	48	121
NC_010999_LCABL_28620	1 33	48	121
NC_008526_LSEL_2672	1 33	48	121
NC_009725_RBAM_029740	1 135	49	136
NC_002570_BH4025	-1 5	49	121
NC_010382_Baph_RNA055S1	1 191	52	192
NC_002570_BH1834	1 33	53	121
NC_009782_SAHV_2416	1 266	53	267
NC_009782_SAHV_2415	-1 266	53	267
NC_009632_SaurH1_2507	1 266	53	267
NC_009632_SaurH1_2506	-1 266	53	267
NC_009487_SaurH9_2458	1 266	53	267
NC_009487_SaurH9_2457	-1 266	53	267
NC_002758_SAV2432	1 266	53	267

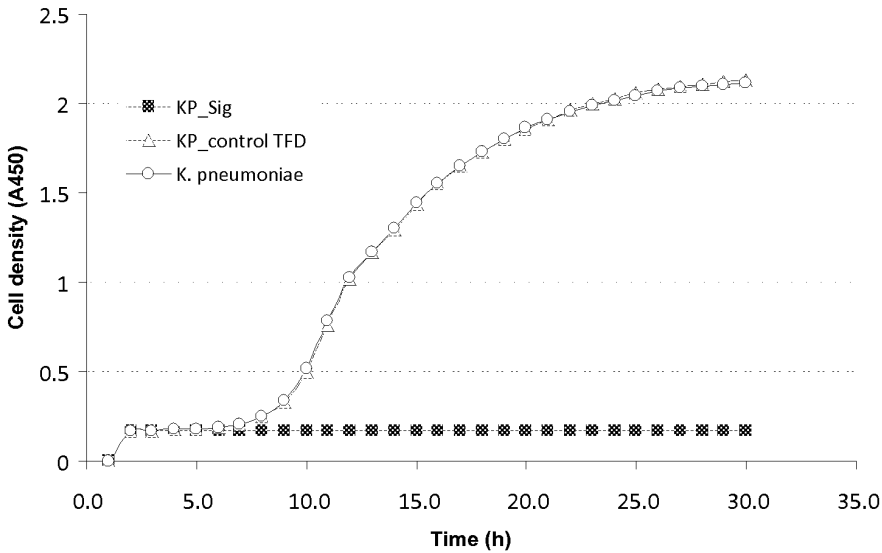


Figure 24A

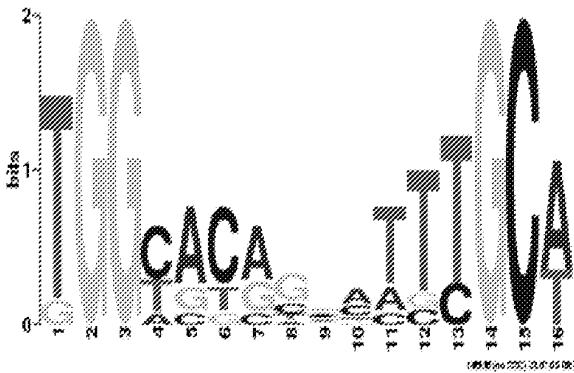


Figure 24B