

F. nucleatum 1 MMNFVKKMEIMMSLKM-MKI~~K~~TL~~L~~VFF~~L~~LSAS--~~I~~YPASKSVK~~D~~-M~~N~~K~~R~~L~~K~~N-----~~I~~
F. periodonticum 1 MKT-----~~K~~T~~L~~L~~T~~FF~~L~~LSAS--~~I~~YPASNSVK~~D~~-M~~N~~K~~R~~L~~K~~N-----~~I~~
E. coli 1 MTRAVKPRR-----FAIRPIT~~I~~YASV~~L~~SAGV-~~L~~LCAFSAHAD-ERDQ~~L~~K~~S~~-----~~I~~
P. aeruginosa 1 MLRL~~L~~P-----~~L~~LL~~S~~-LACLAP--~~A~~FA--~~D~~ERAD-TQRQ~~L~~E~~Q~~-----~~T~~
M. tuberculosis 1 MAHKHVFRT--HSRRVSPGVRT~~L~~LAAL~~L~~LPVSFAVSAANTTADASKNEL~~L~~K~~N~~-----~~L~~
S. pneumoniae 1 MLRFGVNQ-----~~K~~TSS~~L~~L~~T~~ALL~~S~~CGL-~~L~~IF--~~S~~PV-S-QSSDL~~N~~Q-----~~I~~
S. oneidensis 1 MSTR~~L~~PV-----~~K~~AS~~I~~TAGFM~~L~~SFS--~~V~~YA--~~S~~NLEK-RQSEL~~L~~K~~S~~-----~~I~~
C. botulinum 1 MKKSLIKI-----~~V~~T~~I~~IS~~L~~S~~C~~F~~F~~ESPI-~~V~~YA--~~I~~NSD-~~I~~KDQ~~I~~NNNNQ~~A~~IDN~~L~~
V. fischeri 1 MNIS~~L~~LNNS-----~~F~~SCRR~~L~~ATTAL~~V~~CLA--~~F~~SSPILAH-A-SDAEL~~K~~G-----~~M~~

F. nucleatum 50 DK~~E~~I~~E~~K~~K~~N~~R~~I~~K~~AIDTETS~~K~~L~~E~~K~~M~~I~~K~~E~~L~~E~~E~~E~~I~~K~~K~~L~~E~~H~~E~~R~~K~~E~~I~~E~~D~~E~~I~~TV~~V~~K~~K~~N~~I~~D~~Y~~S~~R~~K~~N~~
F. periodonticum 34 DK~~E~~I~~E~~K~~K~~N~~R~~I~~K~~AIDTETS~~K~~L~~E~~K~~M~~I~~K~~E~~L~~E~~E~~E~~I~~K~~K~~L~~E~~H~~E~~R~~K~~E~~I~~E~~D~~E~~I~~TV~~V~~K~~K~~N~~I~~D~~Y~~S~~R~~K~~N~~
E. coli 44 QAD~~I~~A~~A~~K~~E~~R~~A~~V~~R~~Q~~Q~~Q~~R~~A~~S~~L~~L~~A~~L~~K~~K~~Q~~E~~A~~I~~SEATR~~K~~RETQNT~~L~~NQ~~L~~N~~K~~Q~~I~~DE~~N~~AS~~I~~
P. aeruginosa 33 QKD~~I~~G~~E~~L~~K~~K~~L~~D~~G~~I~~Q~~Q~~E~~K~~S~~G~~V~~Q~~K~~Q~~L~~K~~S~~T~~E~~M~~G~~D~~L~~E~~K~~Q~~I~~K~~A~~L~~Q~~D~~E~~L~~D~~K~~S~~E~~A~~E~~L~~K~~R~~I~~D~~G~~E~~K
M. tuberculosis 52 QLN~~I~~A~~E~~K~~E~~K~~S~~V~~K~~E~~Q~~Q~~G~~K~~R~~A~~N~~L~~L~~T~~O~~L~~K~~N~~Q~~E~~K~~I~~A~~A~~A~~G~~R~~E~~L~~Y~~S~~T~~Q~~K~~T~~L~~K~~Q~~I~~D~~S~~E~~I~~T~~T~~L~~S~~A~~E~~I
S. pneumoniae 39 QK~~Q~~I~~K~~Q~~Q~~E~~S~~K~~T~~E~~K~~Q~~K~~R~~E~~Q~~A~~K~~L~~Q~~A~~N~~L~~K~~K~~H~~E~~S~~K~~I~~N~~S~~V~~E~~G~~E~~L~~E~~T~~E~~I~~S~~I~~K~~E~~I~~R~~K~~Q~~I~~A~~D~~A~~D~~K~~Q~~L~~
S. oneidensis 38 QA~~Q~~I~~N~~Q~~Q~~S~~A~~L~~K~~N~~T~~S~~K~~Q~~R~~E~~K~~L~~L~~A~~L~~L~~S~~D~~E~~A~~T~~A~~A~~A~~A~~K~~K~~V~~N~~S~~T~~K~~T~~S~~L~~A~~Q~~I~~D~~N~~T~~I~~A~~E~~L~~K~~Q~~R~~Q~~
C. botulinum 47 Q~~N~~E~~K~~D~~K~~I~~Q~~N~~Q~~V~~N~~N~~V~~N~~K~~E~~L~~D~~K~~I~~T~~E~~Q~~M~~E~~A~~K~~N~~K~~E~~L~~E~~K~~S~~S~~K~~K~~V~~N~~E~~F~~Q~~S~~K~~I~~D~~S~~I~~Q~~A~~E~~I~~D~~S~~V~~Q~~A~~K~~I~~
V. fischeri 42 K~~Q~~E~~I~~S~~R~~Q~~S~~V~~I~~N~~K~~Q~~K~~K~~E~~L~~S~~S~~L~~Q~~N~~S~~L~~K~~K~~H~~E~~V~~S~~I~~A~~N~~A~~S~~K~~K~~I~~R~~N~~A~~E~~Q~~E~~L~~T~~T~~L~~K~~S~~S~~I~~S~~S~~I~~K~~Q~~Q~~

F. nucleatum 110 E~~I~~S~~E~~V~~E~~H~~N~~K-----~~E~~S~~E~~-~~F~~V~~A~~K~~I~~I~~A~~W~~D~~K~~Y~~S~~K~~I~~H~~R~~E~~I~~D~~E~~K~~V~~L~~L~~T~~K~~-~~NYRE
F. periodonticum 94 E~~I~~S~~E~~V~~E~~H~~G~~R~~K~~-----~~E~~S~~E~~-~~F~~V~~A~~K~~I~~I~~A~~W~~D~~K~~Y~~S~~K~~I~~H~~G~~A~~D~~I~~D~~E~~K~~V~~L~~L~~T~~K~~-NYRE
E. coli 104 --AK~~L~~E~~Q~~Q~~K~~A-----~~A~~Q~~E~~R~~S~~L~~A~~A~~Q~~L~~D~~-~~A~~A~~F~~R~~Q~~--~~G~~E~~H~~T~~G~~T~~Q~~L~~T~~L~~S~~G--~~E~~S~~Q~~
P. aeruginosa 93 --K~~K~~L~~Q~~D~~A~~R~~I~~-----~~E~~Q~~R~~L~~L~~A~~I~~Q~~A~~R-~~A~~A~~V~~Q~~S~~--~~G~~R~~E~~E~~Y~~K~~L~~L~~L~~N~~Q~~--~~E~~H~~P~~E
M. tuberculosis 112 --K~~Q~~L~~D~~A~~K~~Q~~K~~-----~~A~~Q~~R~~A~~L~~L~~S~~Q~~L~~D-~~A~~A~~F~~R~~Q~~--~~G~~R~~H~~Q~~G~~E~~L~~I~~F~~K~~G~~--~~E~~G~~Q~~
S. pneumoniae 99 --K~~Q~~L~~E~~K~~Q~~R-----~~E~~Q~~K~~A~~R~~L~~A~~Q~~I~~D-~~I~~I~~Y~~R~~S~~--~~G~~I~~N~~P~~S~~I~~E~~R~~M~~F~~A~~-~~Q~~D~~P~~T
S. oneidensis 98 --E~~E~~L~~S~~L~~K~~V-----~~S~~Q~~N~~T~~L~~S~~K~~Q~~L~~S-~~S~~A~~Y~~L~~A~~--~~G~~N~~H~~D~~Y~~T~~K~~M~~M~~L~~N~~Q--~~Q~~S~~P~~A
C. botulinum 107 --N~~E~~A~~E~~E~~E~~I~~V~~K~~K~~E~~L~~I~~V~~Q~~K~~E~~N~~E~~A~~E~~R~~E~~N~~M~~L~~C~~L~~R~~I~~R-~~N~~Y~~Y~~K~~N~~--~~D~~M~~T~~S~~Q~~M~~L~~A~~F~~L~~V~~S~~S~~~~G~~L~~S~~
V. fischeri 102 --S~~E~~L~~T~~Q~~Q~~Q~~I~~-----~~G~~Q~~T~~E~~I~~L~~K~~D~~L~~I~~V~~-~~N~~Y~~Y~~L~~T~~--~~S~~I~~N~~Q~~L~~S~~N~~V~~L~~S~~G~~--~~D~~V~~T~~

F. nucleatum 154 MLHGD~~L~~Q~~R~~M~~G~~~~I~~T----~~E~~K~~V~~T~~G~~S~~I~~K~~E~~V~~K~~E~~K~~I~~E~~A~~E~~K~~R~~K~~L~~D~~R~~L~~E~~A~~E~~L~~R~~E~~N~~I~~R~~K~~S~~D~~I~~K~~K~~E~~Q~~K~~K~~
F. periodonticum 138 MLHGD~~L~~Q~~R~~M~~G~~~~I~~T----~~E~~K~~V~~T~~G~~S~~I~~K~~E~~V~~K~~E~~K~~I~~E~~A~~E~~K~~R~~K~~L~~D~~R~~L~~E~~A~~E~~L~~R~~E~~N~~I~~R~~K~~S~~D~~A~~K~~K~~E~~Q~~K~~K~~
E. coli 144 R~~G~~Q~~R~~L~~Q~~A~~Y~~F~~G~~Y~~N~~Q~~A~~R~~Q~~E~~T~~I~~A~~Q~~L~~K~~Q~~T~~R~~E~~E~~V~~A~~M~~Q~~R~~A~~E~~L~~E~~E~~K~~Q~~S~~E~~Q~~Q~~T~~L~~L~~Y~~-----~~E~~Q~~R~~A
P. aeruginosa 133 K~~F~~S~~R~~T~~L~~T~~Y~~D~~Y~~I~~N~~K~~A~~R~~L~~E~~Q~~L~~A~~S~~F~~N~~E~~L~~R~~Q~~L~~A~~N~~V~~E~~Q~~D~~I~~S~~A~~Q~~K~~A~~E~~Q~~L~~S~~K~~Q~~G-----~~E~~L~~D~~S
M. tuberculosis 152 R~~D~~E~~R~~I~~L~~A~~Y~~T~~Y~~I~~G~~A~~A~~R~~E~~K~~T~~I~~A~~E~~L~~E~~E~~T~~Q~~Q~~L~~H~~A~~R~~R~~Q~~T~~E~~Q~~K~~R~~A~~B~~H~~K~~S~~L~~I~~G~~-----~~K~~Q~~Q~~T
S. pneumoniae 139 K~~A~~E~~R~~M~~K~~V~~Y~~Q~~H~~I~~N~~Q~~V~~R~~I~~E~~M~~I~~N~~N~~L~~K~~A~~I~~Q~~A~~Q~~L~~A~~V~~Q~~K~~K~~A~~V~~L~~S~~Q~~Q~~K~~N~~H~~R~~N~~Q~~L~~S~~-----~~T~~Q~~K~~K
S. oneidensis 138 T~~I~~E~~R~~V~~L~~A~~Y~~Q~~Y~~I~~N~~K~~A~~R~~M~~K~~S~~I~~N~~E~~L~~K~~Q~~I~~T~~E~~L~~D~~E~~I~~K~~V~~T~~Q~~T~~S~~K~~Q~~K~~Q~~L~~T~~T~~L~~M~~A-----~~E~~Q~~Q~~V
C. botulinum 162 S~~F~~I~~G~~N~~I~~Y~~N~~M~~K~~L~~L~~D~~T~~D~~K~~K~~L~~I~~D~~E~~V~~N~~S~~I~~K~~E~~A~~L~~N~~N~~E~~K~~K~~L~~E~~E~~K~~I~~V~~E~~L~~D~~E~~E~~K~~V-----~~E~~I~~K~~N
V. fischeri 142 K~~M~~D~~R~~M~~T~~Q~~M~~A~~Q~~I~~S~~E~~A~~R~~V~~G~~A~~I~~S~~Q~~L~~E~~F~~I~~N~~M~~Q~~L~~E~~E~~K~~E~~A~~D~~L~~L~~K~~K~~Q~~Q~~R~~Q~~N~~E~~L~~I~~A~~-----~~Q~~Y~~K~~K

F. nucleatum 210 L~~K~~E~~K~~L-----~~C~~V~~E~~K~~K~~G~~H~~Q~~S~~S~~I~~E~~K~~L~~K~~E~~K~~Q~~R~~I~~S~~-----~~K~~E~~I~~E~~R~~I~~I~~R-----~~E~~N~~A~~R~~A~~A
F. periodonticum 194 L~~K~~E~~Q~~L-----~~C~~V~~E~~K~~K~~G~~H~~Q~~S~~S~~I~~E~~K~~L~~K~~E~~K~~Q~~R~~I~~S~~-----~~R~~E~~I~~E~~R~~I~~I~~R-----~~E~~N~~A~~R~~A~~A
E. coli 197 Q~~Q~~A~~K~~L-----~~T~~Q~~A~~L~~N~~E~~R~~K~~K~~T~~L~~A~~G~~L~~E~~S~~S~~I~~Q~~Q~~G~~Q~~Q~~L~~S~~E~~L~~R~~A~~N~~E~~S~~R~~L~~R~~-----~~N~~S~~I~~A~~R~~A
P. aeruginosa 186 R~~R~~E~~A~~L-----~~A~~A~~T~~R~~K~~E~~R~~Q~~Q~~A~~L~~A~~K~~I~~N~~S~~D~~Y~~R~~E~~R~~D~~Q~~K~~L~~K~~S~~R~~Q~~Q~~D~~Q~~A~~R~~E~~A~~A~~A~~A~~A~~E~~R~~E~~R~~Q~~A
M. tuberculosis 205 E~~K~~K~~K~~L-----~~D~~R~~A~~Q~~T~~A~~R~~K~~S~~T~~L~~T~~E~~L~~E~~R~~S~~L~~K~~A~~D~~Q~~K~~D~~L~~L~~V~~M~~R~~E~~N~~E~~S~~Q~~L~~R-----~~N~~K~~I~~A~~K~~A
S. pneumoniae 192 Q~~Q~~A~~L~~-----~~C~~K~~A~~Q~~Q~~E~~H~~Q~~S~~T~~N~~E~~L~~N~~N~~L~~A~~L~~D~~Q~~D~~K~~L~~N~~A~~L~~K~~A~~N~~E~~Q~~A~~L~~R-----~~Q~~E~~I~~Q~~A~~A
S. oneidensis 191 Q~~S~~K~~R~~L-----~~N~~Q~~E~~Q~~D~~Q~~R~~Q~~L~~T~~N~~E~~L~~Q~~R~~T~~N~~T~~K~~G~~A~~E~~L~~E~~Q~~L~~I~~E~~B~~A~~S~~L~~K~~-----~~R~~V~~V~~E~~Q~~A
C. botulinum 215 K~~Q~~Q~~E~~L~~V~~N~~A~~Q~~K~~E~~F~~V~~D~~E~~Q~~N~~K~~Y~~L~~A~~Q~~M~~N~~D~~L~~K~~G~~I~~E~~S~~K~~K~~Q~~S~~M~~I~~N~~S~~L~~S~~D~~K~~R~~E~~R~~L~~Q~~-----~~E~~K~~I~~G~~D~~L
V. fischeri 195 E~~K~~V~~T~~L-----~~C~~T~~S~~Q~~N~~K~~R~~K~~K~~T~~V~~S~~S~~I~~R~~R~~T~~I~~S~~N~~E~~N~~S~~Y~~L~~S~~E~~L~~Q~~Q~~N~~E~~K~~R~~L~~K-----~~T~~A~~T~~A~~K~~A

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F. nucleatum      252  EKAA--R-EAAK EAAKNKGG-S-KRSGG TKVTTTT-VDPMK SNPE----AY-KRIG
F. periodonticum236 EKAA--R-EAAK EAAKNKGS-AGKSGE TKVTTTT-VDPMK SNPE----AY-KRIG
E. coli          244  EAAAKARAE EAE EAQAVRD RQKEATRKGTT-YKPT E-SEKSLN SRTG----GLGAPRG
P. aeruginosa    238  LAAE-----RERARQQQAAPGRVT-SPPREPAPGPTL SGTGAVYGGAFGSA RG
M. tuberculosis  252  EREAKARAE EAE EAARIREKQAQAKKGGST-YTPTQ-DERSLN SRTG----GLGRPAG
S. pneumoniae   239  EQAAHEQE-KRE EEA LAQRQKA-EEKRTSKP-YQPTV-QERQLN STS----GLGAAKK
S. oneidensis   238  LKAM-----RD-----N-----PSMEGFDK QGG
C. botulinum    269  TDFN-----Q--DLQNK-----DDLFLNGLDGGNSGNSQG
V. fischeri     242  KAKN--N-----VPM-----GIGRQKG

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F. nucleatum      300  K-TIKP NG-QLVVYFGQKK---AG--VV-ESNGIEIKKLGPNV VASKAGTVIYADKFQ
F. periodonticum285 K-TIKP NG-QLVVYFGQKK---AG--VV-ESNGIEIKKLGPNV VASKAGTVIYADAFQ
E. coli          297  Q-AFWP RG-PTLHRYGEQL---QG--EL-RWKG MVI GASEGTVKATADGRVILADWLQ
P. aeruginosa    285  K-LPWP NG-RVVARFGSQR---GDDPRA-KWDGVLISASAGS TVRAVHCGRRVVFADWLR
M. tuberculosis  305  Q-AIWP RG-PLLHRFGDSI---SG--EL-RWKG MVI GAPEGTQVKA VADGRVLLADWLQ
S. pneumoniae   290  Q-YSLP VSG-SILHTFGSIQ---AG--EV-RWKG MVI GASAGTPVKA TAAGR VILAGYLN
S. oneidensis   256  K-LKWP TKG-RV SASFGSPR---SG--QV-VWKG TMLSAPEGONIRAVSGGKVIYADWLK
C. botulinum    297  ETFLRPTSC-RV TSEYGP RTHPI SC--QSGFHTCIDL ASPSGTPKASKS GTVVYSGWQG
V. fischeri     258  R-LPWP TSNPKT IHSFGTKQ---TG--QI-TWKG MVL AGDYGTPVKA VYS GKVVFADWLR

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F. nucleatum      352  GLGKVV IDYCGGI IGVYGNLLA KVN NSKVSSGQTIGVIGLSSD-KEPNLYEIRANL
F. periodonticum337 GLGKVV IDYCGGI IGVYGNLLA KVN NSKVSSGQTIGVIGLSSD-KEPNLYEIRANL
E. coli          349  GYGLVV VVEHCKGDM SLYGYNQSA VSVGSQVRAGQPIA VGS SGGQGRPSLYFEIRRG
P. aeruginosa    339  GAGLVI IDHCGGYL SLYGHNQSLK DACDTVKAGDPIATVGTSGGQSSPAVYFAIRHCG
M. tuberculosis  357  GYGLMV VVEHCKGDM SLYGYNQSA VNVGDQVKAGQPIA VGS SGGQERPGLYFEIRRG
S. pneumoniae   342  GYGYMV IVKHGETDLSLYGFNQTVSVKVGQLVSAGQVIAQVGN IGEISRSALYFGISRKG
S. oneidensis   308  GFGMVV IDHCKGYS SLYGHAQTLKSPGEMVKTGEAIA VGRSGGQTEPGLYFEIRYKG
C. botulinum    354  GYGQVV IDHCGGYRTLYAHCSKLVN VKNQKVS RGOVVA VGSIGNSTGPHLHFVVRVNN
V. fischeri     311  GYGLMV IDHCKGDM TLYGYNQSLMKKEGDKVRAGETIAVGD SGGQDRPSLYFEIRNS

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F. nucleatum      411  RPIDPIPTF----
F. periodonticum396 RPIDPIPTF----
E. coli          409  QAVNPQPWLG--R
P. aeruginosa    399  RPADPTTWCRAQG
M. tuberculosis  417  RTVNPQPWLG--R
S. pneumoniae   402  TPVNPAGWV---R
S. oneidensis   368  QAVDPAKPCR---
C. botulinum    414  KHQNPRKYVPI--
V. fischeri     371  KAQNPRSWLR--R

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Figure S4: Wu et al.

Bacterial EnvC homologs. Shown is an alignment of amino acids of EnvC-like proteins. The GenBank accession codes are as follows: EFG94960.1 (*Fusobacterium nucleatum*); WP_099960967.1 (*Fusobacterium periodonticum*); WP_061354207.1 (*Escherichia coli*); WP_043091244.1 (*Pseudomonas aeruginosa*); SGD49707.1 (*Mycobacterium tuberculosis*); CVP50706.1 (*Streptococcus pneumoniae*); WP_011070463.1 (*Shewanella oneidensis*); WP_049177113.1 (*Clostridium botulinum*); WP_026029412.1 (*Vibrio fischeri*). The multiple sequence alignment is generated using T-coffee (<http://tcoffee.crg.cat/apps/tcoffee/do:regular>).