**Supplementary Figures** 



**Fig. S1** Disulfide cross-linking between A323C or E325C in DrrA and S23C in DrrB. Two different cross linkers were used: CuPhe and DTME. *Panel* A, anti-DrrA. *Panel* B, anti-DrrB. *Panels* A and B, *lanes* 1, 2: A(Y89C)B(S23C). *Lanes* 3-5: A(S319C)B(S23C). *Lanes* 6-8: A(A323C)B(S23C); *Lanes* 9-11: A(E325C)B(S23C). The plus or minus indicates the presence or absence of the cross linker.

LDEADQLA

S.p.DrrA	199	LD EADQ LAD RIAVIDHGRVIA EGT TG ELKSS LGSNVLRL RLHDAQS RAEAE RLLSA ELG	257
S.a.ABV97910	199	LD RADQMADDL TLIDHGRVVA RGT PAELKTGRADGVLEVLL TDSSRRAEAGRLLTRAIG	257
S.t.ABP53097	195	LE KADRFAD RIAVI KHOWVLAGGT PD ELKDQVGGHRLEVTL SRPAD LSRARSVLAPVAA	253
M.e.CalT5	199	LD EADHLAD EL TLIDHGRIVA QGT PP ELKAS RAAGVLDVRL RDP ER RAD AGAL LAKAVG	257
N.f.BAD59995	200	LD RADQLAD RIAVIDRGRVIADGTAD ELKAS IGGSSLHLTLADRALLEQARRVIGELLG	258
G.k.BAD75195	206	LQ RADE LAD RIAVIDHGRVVA EGT PD ELKAS IGQ SS LQVKL QHP GEIETAKRI IERVLH	264
R.o.BAH55073	199	LD RADQ LAD RVAVIDHCKV IA EGT TO ELKAS VOS GALHV RV TD I AT RPAAAAL LRD VL E	257
G.o.EEI31000	199	LE RADQ LAD GIVVIDHGRVIA EGT PGQLKASVGT GSLHVRL LDP AQ RABAA RVLKAAVG	257
A.s.ACG75227	195	LD RADRLAB RMAVIDHGRVIA EGT SRELKASVGSNALRL RLADAGQ RLAAQ QVITRVLG	253
B.c.BAD64015	200	LE RADQ LAD RIAVINHERT IA BET SS ELKASVETNT LHL TL QHASD QERAI QL LABDON	258
M.s.ABG63493	209	LE RADQLAARIAVIDHGRKIAEGT SRELKAAIGS GF LHVAP ADQ SQLDEAAAILEARLG	267
L.i.ABJ72056	195	LD RADQ LAD RIAIIDHGSVIA QGT PSELKNILGE TT FELSLIKS SQIKQAK EMI EQKFN	253
J.s.EAP97255	196	LD RADQLADNI VVIDQ GRI IAQGT PLELKNQ SGAAS LVV TV SRHDEVHQAA EL LRGVVG	254
A.e.ABI58055	195	LE RADA LAD LIVVLDQ GRV IA EGT SA QLK SRVGA RT LYVTV SDPA-LAP RT AE RVT AV T	252
P.s.KDS54065	206	LD RADQ LAD RIAVIDR GHVVA EGTVD ELKQSVGT SSLQL RVLDQ SD IEI ARHTVEHVLQ	264
0.g.KAR51498	196	LE RADQ LAD RIAVIDHGRKIA EGT SRELKAQ TGSGVLQVVP AAAGEAEAA LAV-LG	250
L.b.ABJ65324	197	LD RADA LAD RIAVIDHCKLIKLGT PTALKOOIGGAT LTL SLAKA TO GPLAO RL LAOALH	255
S.t.EEP40806	201	LD EADOLAE RLATIDRGRVIAEGT VD RIKASVGSGVLHI RLGDPARRPEAEAVLARSLD	259
S.s.KDX84899	202	LE RADALAD OT WITCHGOV TA EGT VD RLKDRVGGKF CEL RLANLAD VPKVKKL LFD IGD	260
C.m.ACL16820	221	LD RADO LADNI WUIDKGRWVANDT PD GLKRSVGSSSLHL TVKDADNAANAA OI IERILD	279
F.s.ABW09842	198	LD BADO LAD RI GVLDGGRL VA EGT AA KLKRRVPGGHVSVOF TDAAGLAAAAAAHPKAT T	2.56
M. g. ABP44416	197	LE RADO LADAT WAT DEGET TA RESPLIE AND AGE AS LWATVADA AD LES ARGULARTEA	2.55
M.v. ABM15569	216	LE RADO LADNI WUIDRCHI IA EGS PLELKOOAGRAS LWUTVCDAAD LEGARTL LGOTGA	274
T.b. KDY41301	195	MD RAROLAD RIATIDHGRI IA RGT SERLEKLVCNDV IYI RIANGKREVECLNAD FIR	251
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C a David	250 1	EDEVFL	21.5
S.p.DrrA	258 V	LDEVFL 7T IHPD -SD PTALSAR IDD PROGMPALAR LSRTH-LEVRSF SLGOSSLD EVFLALT GHPA	315
S.p.DrrA S.a.ABV97910	258 V 258 A	LDEVFL JT IHRD - SD PTALSAR IDD PROGMRALAELS RTH - LEVRSF SLGOS SLD EVFLALT GHPA AGVAAR - SD PS PLLVKITD AD QAARALGE LA RAG - I SWEDF TLGOP TLD TVFLALT GHST	315 315
S.p.DrrA S.a.ABV97910 S.t.ABP53097	258 V 258 A 254 G	LDEVFL JT IHRD-SD PTALSAR IDD PROGMRALAELS RTH-LEVRSF SLGOS SLD EVFLALT CHPA AGVAAE-SD PS RLLVKIPD AD QAA RALGE LA RAG-I SVEDF TLGOP TLD TV FLALT CHTS JEAVSD EAE CRLAV TV AAADG VLVDG I RILDAAG-I EVIDASLREP TLDDVFLALT CHTA	315 315 312
S.p.DrrA S.a.ABV97910 S.t.ABP53097 M.e.CalT5	258 V 258 A 254 G 258 A	LDEVFL VT IHRD -SD PTALSAR IDD PROGMRALAELS RTH-LEVRSF SLGOS SLD EVFLALT CHPA AGVAAE -SD PS RLLVKIPD AD QAA RALGE LA RAG -I SVEDF TLGOP TLD TVFLALT CHST JEAVSD EAE GRLAVTVAAADGVLVDG IRRIDAAG -I EVIDA SLRRP TLDDVFLALT CHIA AAD LD -SD PARLSVRVTD PD RAALALGE LA RAG -I HVDDF TLGOP SLD TVFLALT CHST	315 315 312 312
S.p.DrrA S.a.ABV97910 S.t.ABP53097 M.e.CalT5 N.f.BAD59995	258 V 258 A 254 G 258 A 259 V	LDEVFL VT IHRD -SD PTALSAR IDD PRQCMPA LAE LS RTH-L EVRSF SLGQS SLD EVFLALT CHPA AGVAAE -SD PS RLLVKIPD AD QAA RALGE LARAG-I SVEDF TLGQP TLD TV FLALT CHPA BRAVSD EAE GRLAV TV AAADGVLVDG IRRIDAAG-I EVIDA SLRP TLDDV FLALT CHIA VAAD LD -SD PARLSVRVTD PD RAA LALGE LARAG-I HVDDF TLGQP SLD TV FLALT CHST VEAQ IT -PEAGRLTAP LREAGLTTDL LIRLREHD -I AID EI SVSKP SLD EVFL TIT CHPA	315 315 312 315 316
S.p.DrrA S.a.ABV97910 S.t.ABP53097 M.e.CalT5 N.f.EAD59995 G.k.BAD75195	258 V 258 A 254 G 258 A 259 V 265 V	LDEVFL VT IHRD -SD PTALSAR IDD PRQCMPALABLS RTH-LEVRSF SLGQS SLD EVFLALT CHPA AGVAAB -SD PS RLLVKIPD AD QAARALGE LARAG-I SVEDF TLGQP TLD TVFLALT CHTA BAAV SD BABEGRLAWT WAAAD GVLWDG IRRID AAG-I EVIDA SLRRP TLDD VFLALT CHTA AAD LD -SD PARLSVRVTD PD RAALALGE LARAG-IHVDD FTLGQP SLD TVFLALT CHTS VEAQ IT -PEAGRLT AD LREAGLTTDL LIRLREHD -IAID EI SVSKP SLD EVFL TIT CHPA VRPT VS -LE TGNIT APMAD PD HVTDL LVALRQEG-IHLT EL SVQKP TLD EVFL TIT CHGV	315 315 312 315 316 322
S.p.DrrA S.a.ABV97910 S.t.ABP53097 M.e.CalT5 N.f.BAD59995 G.k.BAD75195 R.o.BAH55073	258 V 258 A 254 G 258 A 259 V 265 V 258 V	LDEVFL JT IHRD -SD PTALS AR IDD PROGMRALAELS RTH -L EVRSF SLGOS SLD EVFLALT GHPA AGVAAE -SD PS RLUNKITD AD QAARALGE LA RAG -I SWEDF TLGOP TLD TVFLALT GHST BEAVSD EAE GRLAWTWAAAD GVLWDG IRRLD AAG -I EVIDAS LRRP TLD DVFLALT GHST AAAD LD -SD PARLS VRVTD PD RAALALGE LA RAG -I HVDDF TLGOP SLD TVFLALT GHST YEAQ IT -PEAGRLT AP LREAGLTTDL LIRLEEHD -I ATD EI SVSKP SLD EVFL TIT GHPA /RPTVS -LE TGNIT APMAD PD HVTDL LVALRQEG -I HLT EL SVQKP TLD EVFL TIT GHGW /PVT EE -AD PAALT AR IDD PARVS RALPALDDAG -I AVS TFALGOP SLD EVFL SLT GRPT	315 315 312 315 316 322 315
S.p.DrrA S.a.ABV97910 S.t.ABP53097 M.e.CalT5 N.f.BAD59995 G.k.BAD75195 R.o.BAH55073 G.o.EKI31000	258 V 258 A 254 G 258 A 259 V 265 V 258 V 258 -	LDEVFL VT IHRD -SD PTALSAR IDD PRQGMRALABLS RTH-LEVRSF SLGQS SLD EVFLALT GHPA AGVAAB -SD PS RLLVKTPD AD QAA RALGE LA RAG-I SVRDF TLGOP TLD TV FLALT GHST BRAVSD RAB GRLAV TVAAADGVLVDG IRR LDAAG-I EVIDASLR RP TLDD VFLALT GHST VBAQ IT -PBAGRLAV TVAAADGVLVDG IRR LDARG-IHVDDF TLGOP SLD TVFLALT GHST VBAQ IT -PBAGRLT AP LREAGLTTDL LIRLR RHD -I AID BI SVSKP SLD EVFL TIT GHGV VPT VS -LB TCNIT AP MAD PD HVTDL LVALRQ BG-IHLT BL SVORP TLD EVFL TIT GHGV VPVT EE -AD PAALT AR IDD PARVS RALPALDDAG-I AVS TF ALGOP SLD EVFL SLT GR PT -TVVLE -PD PAALS AVCPD AR LGALGMGE LGRAG-L GIA BF SLGOP SLD EVFL GLT GHAA	315 315 312 315 316 322 315 314
S.p.DrrA S.a.ABV97910 S.t.ABP53097 M.e.CalT5 N.f.BAD59995 G.k.BAD75195 R.o.BAH55073 G.o.EEI31000 A.s.ACG75227	258 V 258 A 254 G 258 A 259 V 265 V 258 V 258 - 258 D	LDEVFL VT IHRD -SD PTALSAR IDD PRQCMPA LAE LS RTH-L EVRSF SLGQS SLD EVFLALT CHDA AGVAAE -SD PS RLLVKIPD AD QAARALGE LARAG-I SVEDF TLGQP TLD TV FLALT CHDA SRAVSD EAECRLAV TVAAADGVLVDG IRRIDAAG-I EVIDASLRP TLDDV FLALT CHDA AAAD LD -SD PARLSVRVTD PD RAALALGE LARAG-I HVDDF TLGQP SLD TV FLALT CHDA VERTVS -LETCNIT AD MAD PDHVTDL LVALRQEG-IHLT EL SVGRP TLD EVFL TIT CHDA VRPTVS -LETCNIT AD MAD PDHVTDL LVALRQEG-IHLT EL SVGRP TLD EVFL SLT CHTO VPVT EE -AD PAALT AR IDD PARVS RALDAG-L GRAG-LCTAEF SLGQ PSLD EVFL SLT CHTA OCMPG-SE PAKVAARLEKAAQAGAV LTALS EGG-I ELAKV TVGNP SLD EVFLALT CRDA	315 315 312 315 316 322 315 314 311
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S.p.DrrA S.a.ABV97910 S.t.ABP53097 M.e.CalT5 N.f.BAD59995 G.k.BAD75195 R.o.BAH55073 G.o.EEI31000 A.s.ACG75227 B.c.BAD64015 M.s.ABG63493 L.i.ABJ72056	258 V 258 A 254 G 259 V 259 V 258 V 258 J 258 J 258 J 258 I 259 T 259 T 254 I	LDEVFL VT IHRD -SD PTALSAR IDD PROCMRALAELS RTH -L EVRSF SLGOS SLD EVFLALT CHPA AGVAAE -SD PS PLLVKIPD AD QAARALGE LARAG -I SVEDF TLGOP TLD TVFLALT CHST BEAVSD EAE GRLAVTVAAAD GVLVDG IRRLD AAG -I EVIDASLRRP TLDD VFLALT CHST YRAQ IT -PEACPLT AP LPEAGLTTDL LIRLFEHD -I ATD EI SVSKP SLD EVFL ITT CHPA YRPT VS -LE TCNIT APMAD PD HVTDL LVALRQEG -I HLT EL SVQKP TLD EVFL TIT CHGV YPVT EE -AD PAALT AR IDD PARVS RALPALDDAG -I AVS TF ALGOP SLD EVFL SLT GRPT -TVVLE -PD PAALSAVCPD ARLGALGMCE LGPAG -L GTAEF SLGOP SLD EVFL SLT GRPT -TVVLE -DD PAALSAVCPD ARLGALGMCE LGPAG -L GTAEF SLGOP SLD EVFL GLT CHAA )GVMPG -SE PA EVAARLEKAAQAGAVLTALS EGG -I EIAEV TVGNP SLD EVFL ALT GERV WVQ PS -AEGAQLSVVACSAR EAMEALAALT SAG -I ELSDF SMGSP SLD EVFFLATT GAPA LEVIVL -PE FATLS IKVTD TK IMT QI LLLLE TEH -I AINEF ETRKP TLD EV FL BLT CK	315 312 315 316 322 315 314 311 316 325 309
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S.p.DrrA S.a.ABV97910 S.t.ABP53097 M.e.CalT5 N.f.BAD59995 G.k.BAD75195 R.o.EAH55073 G.o.EAH55073 G.o.EA131000 A.s.ACG75227 B.c.BAD64015 M.s.ABG63493 L.i.ABJ72056 J.s.EAP97255 A.e.ABI58055 P.s.EDS54065 O.g.EAR51498 L.b.ABJ65324 S.t.EXP40806 S.s.EDX84899 C.m.ACL16820 F.s.ABW09842 M.g.ABP4416	258 V 258 A 258 A 258 V 258 V 258 V 258 V 258 V 258 V 258 V 259 V 259 V 259 I 268 N 255 E 255 V 255 E 256 A 256 A 256 A 257 - 250 E 257 - 256 E	LDEVFL VT IHRD -SD FTALSAR IDD PROCMPALAELS RTH-LEVRSF SLGOS SLD EVFLALT CHPA AGVAAE -SD PS RLLVKIPD AD QAARALGE LARAG-I SVEDF TLGOP TLD TVFLALT CHFA AAAD LD -SD PARLSVRVTD PD RAALALGE LARAG-I EVIDAS LRPP TLDDVFLALT CHTA AAAD LD -SD PARLSVRVTD PD RAALALGE LARAG-I HVDD FTLGOP SLD TVFLALT CHTA AAAD LD -SD PARLSVRVTD PD RAALALGE LARAG-I HVDD FTLGOP SLD EVFL TTT CHPA ARAT LD -SD PARLSVRVTD PD RAALALGE LARAG-I HVDD FTLGOP SLD EVFL TTT CHPA VEAQ IT -PEAGRLT AP LREAGLTTDL LIRLREHD -I AID EI SVSKP SLD EVFL STIT CHGV VPVT SE -AD PAALTAR IDD PARVS PA LPALDDAG-I AVS TFALGOP SLD EVFL SLT GRPT -TVVLE -PD PAALS AVCPD ARLGALGMGE LGRAG-L GTAEF SLGOP SLD EVFL SLT GRPT -TVVLE -PD PAALS AVCPD ARLGALGMGE LGRAG-I ELSDF SMGSP SLD EVFL SLT GRPA IMVHPG-KD PT SLT AQ TCNPP VAAAAVCKLASAN -I AVRTF SLGOP SLD EVFL ALT CRPA INVHPG-KD PT SLT AQ TCNPP VAAAAVCKLASAN -I AVRTF SLGOP SLD EVFLALT GRPA INVHPG -KD PT SLT AQ TCNPP VAAAAVCKLASAN -I AVRTF SLGOP SLD EVFLALT GRPA INVHPG -KD PT SLT AQ TCNPD VAAAAVCKLASAN -I AVRTF SLGOP SLD EVFLALT GRPA INVHPG -KD PT SLT AQ TCNPD VAAAAVCKLASAN -I AVRTF SLGOP SLD EVFLALT GRPA INVHPG -KD PT SLT AQ TCNPD VAAAAVCKLASAN -I AVRTF SLGOP SLD EVFLALT GRPA INVHPG -VD CEQISAPVQD PG LLPAVLRALD QAG -I EVABL GUC RASLDD VFLALT CHSG VQAT LT -SEAAKIT APMANAD LITDL LIALEKEG-I TLS EVS VQRP TLD EVFLALT CHSG VQAT LT -SEAAKIT APMANAD LITDL LIALEKEG -I TLS EVS VQRP TLD EVFLALT CHSG VQAT LT -SEAAKIT APMANAD LITDL LVQ LQAAD -I SLANT AVQ EPS SLDD VFFALT CKFL SQTYS -AEGGRIS LPVTGAA EARARLAALEAAG -I EVAEF SLGSP SLD EVFFALT CKFL TYTSE -CD PARLSARVSE GE EVARALAVLS HG -I ANJ SLRPP SLDD VFFALT CHTT NVT GEMCNGP LAIAAPKGANT LT EVVLR LE RAG -I ALADI SLRPP SLDD VFFALT CHTT NVT GEMCNGP LAIAAPKGANT LT EVVLR LE RAG -I ALADI SLRPP SLDD VFFALT CHTT NVT GEMCNGP LAIAAPKGANT LT EVVLR LE RAG -I ALADI SLRPP SLDD VFFALT CHTT NVT D-AGARPLT AT DON ID KUTDVLTT LKDAG -I ALS GVNIL OP TLDE VFMALT CHTT NVTDAGARPLT AT AD CLDD MVT VAGWLDDSG -I TVDDI GLS PPS SLDD VFFALT CHTT NVTD- AGARPLT AT AD DON ID KUTDVLTT LKDAG -I ALS GVNIL OP	315 315 312 315 316 322 314 311 316 325 309 311 309 322 308 310 317 318 336 308 312
S.p.DrrA S.a.ABV97910 S.t.ABP53097 M.e.CalT5 N.f.BAD59995 G.k.BAD75195 R.o.EAH55073 G.o.EXI31000 A.s.ACG75227 B.C.EAD64015 M.s.ABG63493 L.i.ABJ72056 J.s.EAP97255 A.e.ABI58055 P.s.EDS54065 0.g.EAR51498 L.b.ABJ65324 S.t.EEP40806 S.s.EDX84899 C.m.ACL16820 F.s.ABW09842 M.g.ABP44416 M.v.ABM15569	258 V 258 A 258 A 259 V 258 V 258 V 258 V 258 V 259 V 259 V 259 I 259 I 259 I 253 G 253 B 253 B 255 E 256 A 256 A 256 A 256 A 256 A 256 A 256 A 257 E 256 A 257 E	LDEVFL VT IHRD -SD FTALSAR IDD PROCMPALAELS RTH-LEVRSF SLGOS SLD EVFLALT CHPA AGVAAE -SD PS PLLVKIPD AD QAARALGE LARAG-I SVEDF TLGOP TLD TVFLALT CHFA AGAD LD -SD PARLSVRVTD PD RAALALGE LARAG-I EVTDAS LRRP TLDDVFLALT CHTA AAAD LD -SD PARLSVRVTD PD RAALALGE LARAG-I HVTDAS TLGOP SLD TVFLALT CHTA VEAQ IT -PEAGRLT AP LREAGLTTDL LIRLREHD -I AID EI SVSKP SLD EVFL TIT CHPA VRPTVS -LE TGNIT APMAD PDHVTDL LVALRQEG-IHLT EL SVQKP TLD EVFL TIT CHPA VRPTVS -LE TGNIT APMAD PDHVTDL LVALRQEG-IHLT EL SVQKP TLD EVFL SLT CRPT -TVVLE -PD PAALS AVCPD AR LGALGMGE LGRAG-LGTAEF SLGOP SLD EVFL SLT GRPT -TVVLE -PD PAALS AVCPD AR LGALGMGE LGRAG-LGTAEF SLGOP SLD EVFL ALT GRPA IMVHPG-KD PT SLT AQT TON PD VAAAAVCKIASAM-I AVRTF SLGQP SLD EVFL ALT GRPA INVHPG-KD PT SLT AQT TON PD VAAAAVCKIASAM-I AVRTF SLGQP SLD EVFL ALT GRPA INVHPG-KD PT SLT AQT CN PD VAAAAVCKIASAM-I AVRTF SLGQP SLD EVFL ALT GRPA INVHPG-KD PT SLT AQT CN PD VAAAAVCKIASAM-I AVRTF SLGQP SLD EVFL ALT GRPA INVHPG-KD PT SLT AQT CN PD VAAAAVCKIASAM-I AVRTF SLGQP SLD EVFL ALT GRPA INVHPG-KD PT SLT AQT CN PD VAAAAVCKIASAM-I AVRTF SLGQP SLD EVFL ALT GRPA INVHPG-KD PT SLT AQT CN PD VAAAAVCKIASAM-I AVRTF SLGQP SLD EVFL ALT GRPA INVHPG-KD PT SLT AQT CN PD VAAAAVCKIASAM-I AVRTF SLGQP SLD EVFL ALT GRPA INVHPG-KD PT SLT AQT CN PD VAAAAVCKIASAM-I AVRTF SLGQP SLD EVFL ALT GRPA INVHPG-KD PT SLT AQT CN PD VAAAAVCKIASAM-I AVRTF SLGQP SLD EVFL ALT GRPA ISVIVL -PERATLS IKVTD TK IMT QI LLLE TEH-I AINEF ETRKP TLD EVFL FLT GK EVAND- AD ARKLT AP GCD VP ALT RI AAQ LD BAG-I EVABL GLGA SLD VFL ALT CHCKS AQAQ - VD GE QI SAPVQD PG LLP AVLRALD QAG-I EVABL SLGS SLD VFFALT CHCS AQAQ - VD GE QI SAPVQD PG LLP AVLRALD QAG-I EVABL SLGSP SLD EVFFALT CHCS AQAQ - LT SHAKIT AP MANAD LITTDL LLAIREKG-I TIS EVSVQRP TLD EVFL ALT CHCY HUT CEMMENPELATAPERSAR EE EVARALAVLS SHG-I PVT TF SFGOP SLD VFFALT CHCY MVTC EMALT GEN SALD AVSE GE EVARALAVLS SHG-I PVT TF SFGOP SLD DVFFALT CHCY MVTLA - AAA PKGAN ILT RIVLT VLTL KERAG-I ALS CVNIL OP TLD EVFLALT CHCY MVVDL - AGARRLT AT ADGLD DMVKVAGWLRDSG-I TVDDI GLS RP SLD DVFMALT GERS 	315 315 312 315 316 322 314 311 316 325 309 311 309 309 310 310 310 317 318 336 336 3308 312 331
S.p.DrrA S.a.ABV97910 S.t.ABP53097 M.e.CalTS N.f.BAD59995 G.k.BAD75195 R.o.BAH55073 G.o.EKI31000 A.s.ACG75227 B.c.BAD64015 M.s.ABG63493 L.i.ABJ72056 J.s.EAP97255 A.e.ABI58055 P.s.EDS54065 O.g.EAR51498 L.b.ABJ65324 S.t.EKP40806 S.s.EDX84899 C.m.ACL16820 F.s.ABW09842 M.g.ABP44416 M.v.ABM15569 T.b.EDY41301	258 V 258 A 258 A 258 V 258 V 258 V 258 V 258 I 259 I 259 I 259 I 253 G 253 G 253 G 253 A 251 E 256 A 256 A 256 A 256 A 257 E 257 E 257 E	LDEVFL VT IHRD -SD PTALSAR IDD PRQCMRALAB LS RTH-L EVRSF SLGQS SLD EVFLALT CHPA AGVAAB -SD PS RLLVKIPD AD QAARALGB LARAG-I SVEDF TLGQP TLD TVFLALT CHTS GEAVSD EAE GRLAWTVAAAD GVLVDG IRR LD AAG-I EVTDAS LRRP TLDD VFLALT CHTA AAAD LD -SD PARLSVRVTD PD RAALALGB LARAG-I HVDD ST LGQP SLD TVFLALT CHTA VEAQ IT -PEAGRLT AP LREAG LTTDL LIRLREHD -I AID EI SVSKP SLD EVFL TIT CHPA VRPTVS -LE TCNIT APMAD PD HVTDL LVALRQEG-IHLT EL SVQKP TLD EVFL TIT CHPA VRPTVS -LE TCNIT APMAD PD HVTDL LVALRQEG-IHLT EL SVQKP TLD EVFL TIT CHPA VRPTVS -LE TCNIT APMAD PD HVTDL LVALRQEG-IHLT EL SVQKP TLD EVFL SLT GRPT -TVVLE -PD PAALSAN CPD AR USALGALGMGE LGRAG-LGIA EF SLGQP SLD EVFL GLT CHPA OGVMPG -SE PA EVAARLEKAA QAGAV LTALS EGG-I ELSDF SMG SP SLD EVFL ALT GRPA NVVQ PS -AE GAQLS VVACS AR EAN KA LAALI SAG-I ELSDF SMG SP SLD EVFL ALT GRPA IEVIVL -PE FATLS IKVTD TK IMT QI LLL LE TEH-I AINEF ETRKP TLD EVFL BLT CK KVHVD - ADARKLT AP GGD VP ALT FLAAQ LD EAG-I EVABLG RGA SLDD VFLALT CHKA AQAQ - VD GEQ IS AP VQD PGLLPAV LRALQ AG-I EVABLG RGA SLDD VFLALT CHSG VGAT LT -SEAAKIT APMANAD LITDL LIALREKG-I TLS EVSVQKP TLD EVFFLATT CHGV EGAQYS -AE GGP IS LP VTGAA RAARARLAALEAAL SAG-I EVABLG RGA SLDD VFLALT CHSG VGAT LT -SEAAKIT APMANAD LITDL LIALREKG-I TLS EVSVQ RP TLD EVFFLATT CKFL AQPT LH -GAQ - LT AHLEN PNQITDL LVQ LQAAD -I SLANI AVQ EP SLDD VFFLATT CKFL TY YS = CD PARLSARVSE GE EVARALAVLS SHG-I PVT TF SFGOP SLD EVFFLATT CHCT WVT GEMCNGG LAI AAPRGANTIT EI VLRLE EAG-I ATADI SLRPP SLDD VFFLATT CECT YVYUD - AGARRLT AT DGGLD MITVL WLT LKDAG-I ALS CVNIL QP TLD EV FMALT GECT YVYUD - AGARRLT AT DGGLD MITVL WAEWLRDSG-I TVDDI GLS RP SLDD VFLALT CHTT YVFVD - AGARRLT AT ADGLD MIT RVAEWLRDSG-I TVDDI GLS RP SLDD VFLALT CHTT YVFVD - AGARRLT AT ADGLD MIT WAEWLRDSG-I TVDDI GLS RP SLDD VFLALT CHTT YVFVD - AGARRLT AS ADGLD MIT RVAEWLRDSG-I AVDDI GLS RP SLDD VFLALT CHTT YVFVD - AGARRLT AS ADGLD MIT RVAEWLRDSG-I AVDDI GLS RP SLDD VFLALT CHTT YVFVD - AGARRLT AS ADGLD MIT RVAEWLRDSG-I AVDDI GLS RP SLDD VFLATT GHTT	315 312 315 316 322 315 314 311 316 325 309 311 309 322 308 310 317 318 336 308 312 331 331 331

**Fig. S2** ClustalW alignment of the C terminal sequence (residues 199-315) of DrrA with the C-terminal sequences of bacterial homologs identified by BLAST search. Sequences in LDEADQLA and LDEVFL motifs are highlighted.

LDEADQLA

S.p.DrrA ABCA1_human ABCA2_human ABCA3_human ABCA3_human ABCA8_human Ced-7	199 1081 1182 723 635 737	LDEAD QLADRIAVIDHG RVI AR GTT GE LKS SLGS-NVLPL PLHDA242 242   MDEAD VLGDRIAIISHGKLCCVGSSLF LKNQLGTGYYLTLVKKDVESSLSSCPNSSSTV 1139   MDEAD LLGDRIAIISHGKLKCCGSPLFLKGTYGDGYRLTLVKRPAEPGGP
S.p.DrrA	243	QSRAEAERLLSAELGVTIHRDSDPTAL 269
ABCAl_human	1140	SYLKKED SVSQSSSDAGLGSDHESDTLTID VSAISNLIRKHVSEARLVEDIGHELTYVLP 1199
ABCA2_human	1232	QEPGLASSPPGRAPLSSCSELQVSQFIRKHVASCLLVSDTSTELSYILP 1280
ABCA3_human	768	ISQLVHHHVPNATLESSAGAELSFILP 799
ABCA8_human	680	ITSLVKQHIPDAKLSAKSEGKLIYTLP 711
Ced-7	782	GDKRKMAVILTDVCTHYVKEAERGEMHGQQIEIILP 817
		LDEVFL
S.p.DrrA	270	SARIDDPRQCMRALAELSRTHLEVRSFSLGQSSLDEVFLAL 310
ABCA1 human	1200	YRAAKEGAFVELFHEIDDRLSDLGISSYGISETTLEEIFLKV 1241
ABCA2 human	1281	SEAAKKGAFERLFOHLERSLDALHLSSFGLMDTTLEEVFLKV 1322
ABCA3 human	800	RESTHRFEGLFAKLEKKOKELGIASFGASITTMEEVFLRV 839
ABCA8 human	712	LERTNKFPELYKDLD-SYPDLGIENYGVSMTTLNEVFLKL 750
Ced-7	818	EARKKEFVPLFQALEAIQDRNYRSNVFDNMPNTLKSQLATLEMRSFGLSLNTLEQVFITI 877 : * : * ::::::*::
S.p.DrrA	311	TCHPADD RST EEAAE EEKVA 330

5.p.DrrA	311	IGHPADD KSI KEAAR KEKVA	330
ABCAl human	1242	AEESGVDAE	1250
ABCA2 human	1323	SEEDQSLENSEADVKESFKD	1342
ABCA3_human	840	GKLVDSSMDIQAIQLPALQYQ	860
ABCA8_human	751	EGKSTINESD	760
Ced-7	878	GDKVDKAIASRONSRISHNSRNA	900

**Fig. S3** ClustalW alignment of the last 132 amino acids of DrrA with the C-terminal sequences of NBDI of eukaryotic homologs identified by TC-Blast search. Their homology in LDEADQLA and LDEVFL motifs are highlighted.

## LDEADQLA

S.p.DrrA ABCA2 human ABCA1 human ABCA3 human ABCA3 human ABCA8 human Ced-7	199 2247 2104 1574 1438 1563	LDEAD QLADRIAVIDHGRVIAEGTIGELKSSLGSN-VLRLRLHDAQS RAKAERLLS MEECKALCTRLAIMVNGRLRCLGSIQHLKNRFGDGYMITVRTKSQSVKDVVRFFN MEECKALCTRMAIMVNGRFRCLGSVQHLKNRFGDGYTIVVRIAGSNPDLKPVQDFFG MEECKALCTRLAIMVQGQFKCLGSPQHLKSKFGSGYSLRAKVQSEGQQEALEEFKAFVD MABARAVCDRVAIMVSGRLRCIGSIQHLKSKFGKDYLLEMKVKNLAQVEPLHAEIL MDECKALCSRIAVLNRGSLIAIGSSQELKSLYGNNYTMTLSLYEPNQRDMVVQLVQ : *.: :. *:*:: * *:*	253 2301 2160 1630 1493 1618
			-
S.p.DrrA	254	AEL GVTIHRD SD PTALSARIDDP ROGMRALAEL SR THLEVRSF SL GOSSLDEVF	<mark>1</mark> 308
ABCA2_human	2302	RNF PEAMLKERHHTKVQYQLKSEHIS-LAQVFSKMEQVSGVLGIEDYSVSQTLDNVF	2359
ABCA1_human	2161	LAFPGSVLKEKHRNMLQYQLPSSLSS-LARIFSILSQSKKRLHIEDYSVSQTTLDQVF	7 2218
ABCA3_human	1631	LTF PGSVLED EHQGMVHYHLPG RD LS-WAKVFGILEKAK EKYGVDDYSVSQISLEQVF	6 1691
ABCA8_human	1494	RLF PQAARQE RYSSLMVYKLPVED VQP LAQAF FKLEKVKQSFDLEEYSLSQSTLEQVF	L 155Z
Ced-7	1619	TRL PNSVLKTTSTNKTLNLKWQIPKEKEDCWSAKFEMVQALAKDLGVKDFILAQSSLEETF	L 1679
		: : . : : : : : : : : : : : : : : : : :	:
S.p.DrrA	309	ALT CHPADDRST EE	330
ABCA2 human	2360	NFAKKOSDNLEOOET EP PSALOSPLGCLLSLL RPRSAPTELRALVAD EPEDLDT KDEG	2418
ABCAL human	2219	NFAKD QSDDDHLKDLSLHKNQ TV-VDVAVLT S	2251
ABCA3 human	1692	SFAHL QP PTA EEGR	1706
ABCAS human	1553	ELSKEQELCOFEEDFDPSVKWKLLPQ	1580
Ced-7	1680	RLAGLDEDQLDTHS	1704
		::	
S.p.DrrA	0.410		
ABCAZ numan	2419	LISFREERAULSFNIDTLC 2434	
ABCAL numan	2252	FLQDERVRESIV 2261	
ABCAS_numan	1.501	IF04	
ABCAS_numan Ced-7	1281	<u>kk</u> / 1584 	

**Fig. S4** ClustalW alignment of the last 132 amino acids of DrrA with the C-terminal sequences of NBDII of eukaryotic homologs identified by TC-BLAST search. Their homology in LDEADQLA and LDEVFL motifs are highlighted.



Fig. S5 Effect of LDEVFL or CREEM mutations on doxorubicin efflux. E.coli LE392/JuncIC cells containing the indicated plasmids were grown in TEA medium and induced with IPTG at OD=0.6, as described under Methods. Washed cells were de-energized with 5mM DNP and loaded with 10 µM doxorubicin for 11 hours. Loaded cells were washed twice, and doxorubicin fluorecence was measured for 100 seconds. Doxorubicin efflux by the cell suspension was then initiated by providing 20 mM glucose, shown with an arrow. The fluorescence was monitored for additional 400 seconds. The linear region of each curve was used for calculation of the slope of the curve. Panel A, effect of L303V, D304N or V306A/F307A/L308A mutation on doxorubicin efflux by DrrAB. The slopes obtained were: vector, 82; wild type DrrAB, 331; DrrA(L303V)DrrB, 63; DrrA(D304N)DrrB, 229; DrrA(V306A/F307A/L308A)DrrB, 84. Panel B, effect of L310A/T311A/G312A mutation or  $\Delta$ LDEVFL in DrrA on doxorubicin efflux by DrrAB. The slopes were: vector, 172; wild type DrrAB, 558; DrrA(L310A/T311A/G312A)DrrB, 220; DrrA(ΔLDEVFL)DrrB, 143. Panel C, effect of E(321, 322, 325)G, E(321, 322, 325, 326, 327)G mutation or  $\triangle$ CREEM on doxorubicin efflux by DrrAB. The slopes were: vector, 233; wild type DrrAB, 930; DrrA(E(321, 322, 325)G)DrrB, 832; DrrA(E(321, 322, 325, 326, 327)G)DrrB, 507; DrrA(ΔCREEM)DrrB, 429.



**Fig. S6** Docking analysis of the predicted structures of DrrA and DrrB. DrrA protein was modeled using AMMP modeling software and the known structure of MalK as a template. DrrB protein was modeled using the Phyre modeling software (27), as described under Methods. The coordinates obtained for the predicted structures of DrrA and DrrB were then used for docking analysis of DrrA and DrrB by Rosetta Docking server (28). *Panel* A, wild type DrrA and DrrB; *Panel* B, D304N and DrrB; *Panel* C, L303V and DrrB; *Panel* D, X306-308A and DrrB. In all panels, DrrA is shown in green and DrrB is shown in grey. The Walker A, Signature, and Walker B motifs of DrrA are shown in red. The LDEVFL and CREEM motifs in DrrA are shown in yellow and purple, respectively. The  $\beta$ -strands in the C-terminal domain of DrrA are shown in different colors following the same color scheme as seen in Fig. 9. The distances between S319 (shown in magenta) in DrrA and S23 (shown in blue) in DrrB are shown in angstroms.



**Fig. S7** A model showing various interactions between DrrA-DrrB and DrrA-DrrA during different stages of the catalytic cycle. Both DrrA and DrrB proteins are shown as dimers. DrrA protein contains two domains: an N-terminal nucleotide binding domain (abbreviated as N-ter, filled with blue) in the front, and a C-terminal domain (showing the CREEM motif) (abbreviated as C-ter) in the front. In Conformation I, the two nucleotide binding domains in the N terminus of the DrrA protein are in the open state, while the extreme C terminus of DrrA forms an interface with the N-terminal tail of DrrB. It is proposed that this interaction between the extreme C terminus of DrrA and the N-terminal cytoplasmic tail of DrrB plays a role in assembly and biogenesis of the DrrAB complex. Doxorubicin binding to DrrB produces a conformational change: the extreme C terminus of DrrA disengages from the N-terminal tail of DrrB, which is now involved in communicating conformational changes to the Q-loop region (represented by residue 89) in the N-terminal domain of DrrA (Confo. II). Simultaneously, the extreme C terminus of DrrA undergoes homodimerization. This is followed by the 'closed' state, produced by the head-to-tail dimerization of the NBDs (Confo. III). Hydrolysis of ATP returns the complex to the resting state.