

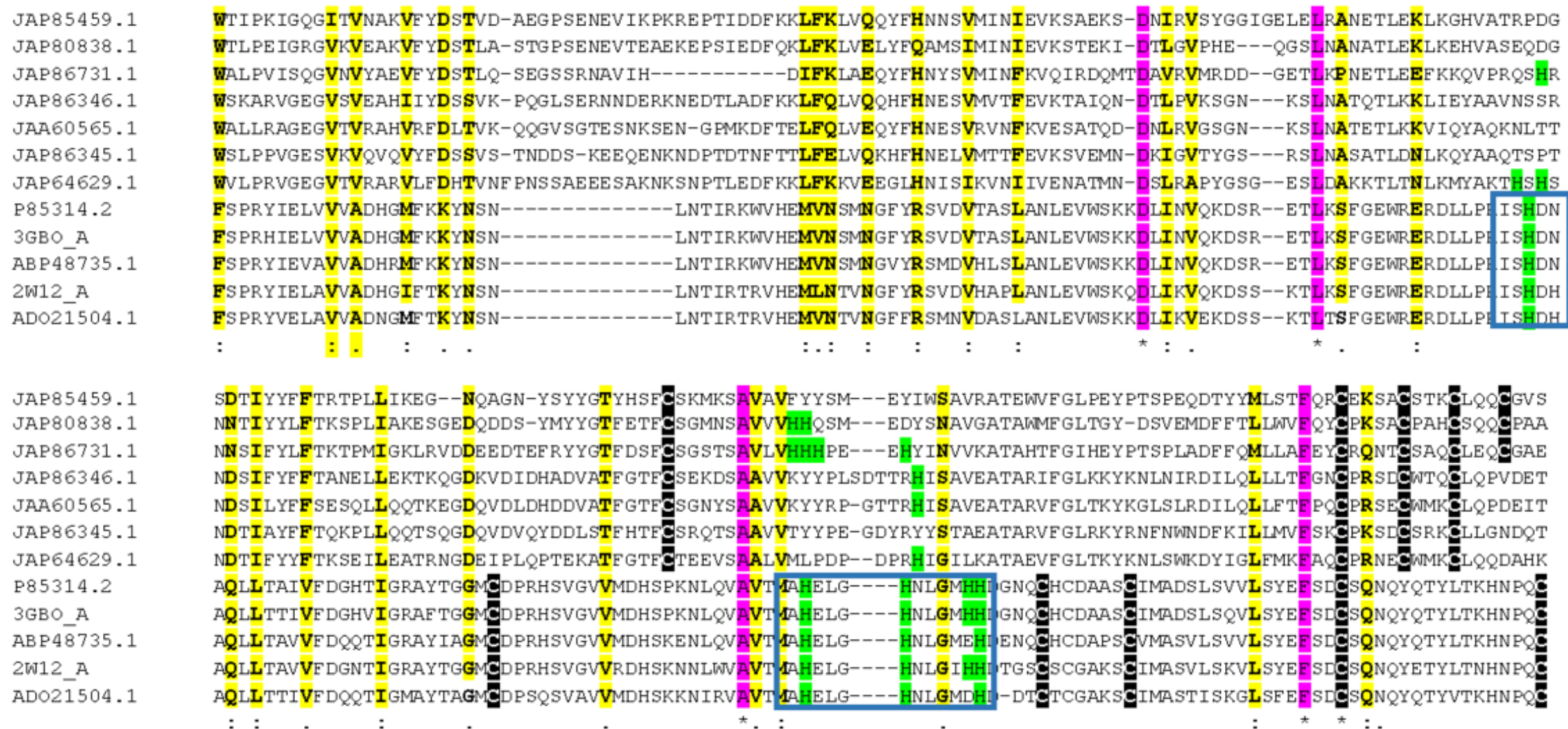


Figure S1: Alignment of members of the 28 kDa family with Zn metalloproteinases. The boxes show conserved histidines in green background. associated with the Zn binding function. The pink background displays identical amino acids, and in yellow the conserved sites. Cysteines are shown in black background. The sequences are named by their NCBI or PDB accessions.



Figure S2: Metalloproteoid JAA55829.1 predicted AlphaFold structure (Brown color) superimposed to the metalloprotease leucurolysin-a (PDB 4q1l-A) (Blue color).

[illegible]

Figure S3: Metalloproteoid subgroup Amblyomma. A) Alignment of two tick protein sequences with two metalloproteases. B) Superimposition of the AlphaFold structure prediction for JAG2448.1 (brown color) to the snake metalloprotease structure PDB:3gbo (Blue color).

A

JAP79473.1_Rhapp	--MKP---TYFCALFLIYAYA--CG-----EAMQEE--ERRDEVIRLGLYFVYD-----NAFSSRALFK-----VNG-SYNAYFAALTRAAEFF---KLHYDPKILLTLVG	85
JAG92707.1_Amame	--MRPQSFGFLVICLLVVFVASRA-----EHSEEDHVEMEEDKIILGIYIVYD-----DAFIKNFLFN-----KGDKPFNDYFTALCNAAEAYF---KDLRDPVRMLALAG	91
pdb_2DW1_Catrocollastatin	HQKYN--PFRFVELVLVVDKAMVTKNNGDLDKIKTRMYEIVNTVNEIYRYMYIH-----VALVGLEIWSNEDK-ITVKPEAGYTLNAFGEWRKTDLLT---RKKHDNAQLLTAID	104
pdb_3DSL_Bothropasin	QKYN--PFRYVELFIVVDQGMVTKNNGDLDKIKARMYELANIVNEILRLYLYMH-----AALVGLEIWSNGDK-ITVKPDVDYTLNSFAEWRKTDLLT---RKKHDNAQLLTAID	103
JAR89508.1_Ixric	--MSPVAMTITILTLLVTASQLVR-----ARESKPSSIPKVNLAHVHFVYD-----RYFEQISKFR-----DESGRYLDYFTTFLNIVELWF---RSSKLPHIKLTLHA	88
pdb_2RJQ_Adamts-5	--SIS--RARQVELLLVADASMARLYG---RGLQHYLLTLASIANRLYSHASINENHRLAVVRKVVLGDKDKSLEVSKNAAATLKNPCKWQHQNQLGDDHEEHYDAAILFTRED	108
JAP79473.1_Rhapp	SSQL---QEEDIVENTTTSDDK--LNASDTLDKL-----GTIMT-----WNNSLDPSVDVVFLATGMPLYIKE--SWMTGEWYGLSYRRSICYGNAT----VGII	169
JAG92707.1_Amame	TSRL---EEKNIITTLKDRKTYVDGEKTLDKF-----YDINT-----WNESLPEGVDVVFLVTGTETWITE--EAVTNEWKGLAAPKSLICFSAKITVQAKAVGIV	181
pdb_2DW1_Catrocollastatin	LDR----VIGLAYVGSMDCHPKRSTGIIQDYSEI-----NLVVAVIMAHMGMHNLGINHDSGYCSCGDYACIMR--PEISPEPSTFFSNCSYFECWDFIMNHNEPCI	199
pdb_3DSL_Bothropasin	FNGP----TIGYAYIGSMCHPKRSVAIVEDYSPI-----NLVVAVIMAHMGMHNLGIHHDIDFCSCGDYPCIMG--PTISNEPSKFFSNCSYIQCWDFIMKENPQCI	199
JAR89508.1_Ixric	ATEGPLNDIDNEPDGDEKSVDRMTSDESSQEEENFDKSETPYQPCRNRSVTKMKLKYHVETQDAYRGADVIFVTGLCINLEA--DAN-KEWEGFSKPGLICTKSAV-----GVV	194
pdb_2RJQ_Adamts-5	LCGHHSCTLTGMADVGTICSPERSCAVIEDD-----GLHAAFTVAHEIGHLGLSHD--OSK-FCEETFGSTEDKRLMSILTSIDASKPWSKCTSATITTEFLDDG	206
JAP79473.1_Rhapp	HDDGATFNGVR-LTALQIALVLGAYKDNGRWGECPQNEEEYLTNSNRGGRIPLYLSECSRESVRNFYFRDNDICWNDI--PKPAIEHDIGFPSDFYKLFDCDQCHVSEHFRNN	282
JAG92707.1_Amame	YDDGKNFNGVP-VLALQVAMLLGASKDSKRKYCPSSQG--YLTSSKDGGSRPALSACSRSALEFYFKNKDKDYICWNDF--PKAAQPGNKRLPVDFYLEKDHIDICES-----	285
pdb_2DW1_Catrocollastatin	LNEPLGTDIISPPVCGNELLEVGEEDCGTPENCQNECCDAATCKLKSGSQCGHGDCEQCKFSKSGTECRAS--MSECDP-AEHCTGQSSECPADV FHKNGQPCLDNYGYCYNG	311
pdb_3DSL_Bothropasin	LNEPLGTDIVSPPVCGNELLEVGEEDCGTPENCQNECCDAATCKLKSGSQCGHGDCEQCKFSKSGTECRAS--MSECDP-AEHCTGQSSECPADV FHKNGQPCLDNYGYCYNG	311
JAR89508.1_Ixric	HDDGKTFNGTR-SAALQLALMLGANEDAKTN--CSDMER--YLLNLMNGESLSELSCTKNAISFFKKPKTN--KCGKRT-PTPAKHNNMLAKYEYEAKNTECQVSSSGTQR	301
pdb_2RJQ_Adamts-5	HGSKFCEETFGSTEDKRLMSSILTSIDASKPWSKCTSATITEFLDDHGNCLLDLPRKQILGPEELPGQTYDATQCCNLTFGPEYVSCPMDVCARLWCAVVRQGMVCLKKLP	321
JAP79473.1_Rhapp	TATGKPINCLLSTINRNIPHWPSRKPTHWDWAACKRYRQWYRKHTTTVSPYQTCTQSCC--RFMRHTEITRAKGGWWD CWDTRAAD-----GTVCDSTRVCLDKCEA-----	381
JAG92707.1_Amame	-----ESTRRRTLYTCENIANAKRLLDQCVAAC--DYWQNREWFQKR-----VAAPD-----GTSCGKNTICLRGQCV-----	346
pdb_2DW1_Catrocollastatin	NCPIMYHQCYDLFG----ADVVEAEDSCFERNOKGNYYGYCRKENGKNIKPAEDVKCG--RLYCKDNSPGQNNPCKMFYSNDEHKGMVLPGTKCADGKVCNNGHCVDVATAY	419
pdb_3DSL_Bothropasin	NCPIMYHQCYALFG----ADVVEAEDSCFKDNOKGNYYGYCRKENGKNIKPAEDVKCG--RLYCKDNSPGQNNPCKMFYSNDDDEHKGMVLPGTKCADGKVCNNGHCVDVATAY	419
JAR89508.1_Ixric	VKKCKPNKVSYPKNK--RQATCKVTCCNQSGERDQNYTINLADGTPCKNMKVTVHTQS--LYGRVRFFFSLQLLDVLICGAPSR--MLVINTHCNWQSTVNNTNSSLYESIL	408
pdb_2RJQ_Adamts-5	AVEGTPCG-----KGRICLQGGKCVDKTKKKYVSTSSHGNGWSWSWGQCSRS CGGGVQFAYRHCNNAPRNNGRYCTGKRAIYRSCSLMPCPPNGKSFGSAWSHPGFEK	425

B

JAP79473.1_Rhapp	GTIMT-----WNNSLDPSVDVVFLATGMPLYIKE--S
JAG92707.1_Amame	YDINT-----WNESLPEGVDVVFLVTGTETWITE--E
pdb_2DW1_Catrocollastatin	NLVVAVIMAHMGMHNLGINHDSGYCSCGDYACIMR--P
pdb_3DSL_Bothropasin	NLVVAVIMAHMGMHNLGIHHDIDFCSCGDYPCIMG--P
JAR89508.1_Ixric	SVTMKKLKYHVETQDAYRGADVIFVTGLCINLEA--D
pdb_2RJQ_Adamts-5	GLHAAFTVAHEIGHLGLSHD--OSK-FCEETFGSTEDKR

Figure S4: Alignment of three tick metalloprotease protein sequences previously identified as metalloproteases, with three snake metalloproteases. A) Full ClustalW alignment. B) Detail of the alignment in the region of the Zn binding domain essential for catalytic activity. The boxes on the two figures delimit this domain. The snake proteases are indicated by their PDB accession, followed by their names. The tick sequences are identified by their NCBI accession, followed by the first two letters of their genus name and the first three letters of their species name.

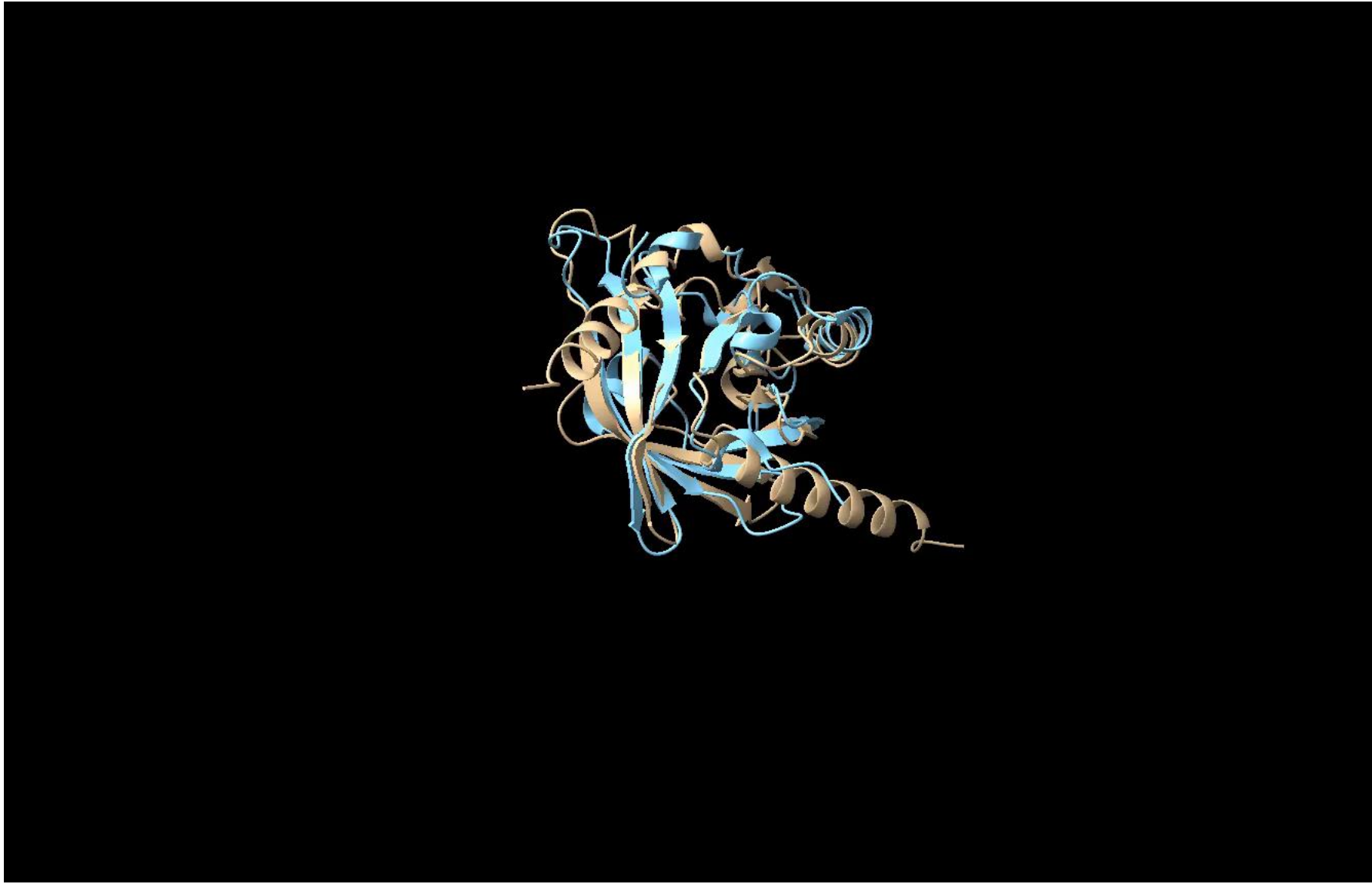


Figure S5: Superimposition of the AlphaFold structure prediction for JAC28582.1 (brown color) to the lipocalin structure PDB:4boe (Japanin) (Blue color).



Figure S6: Former 17.7 kDa family matches Niemann-Pick proteins. AlphaFold structure prediction for ABI52703.1 (brown color) superimposed to PDB:1nep-A (Bovine Niemann-Pick protein C2) (Blue color).

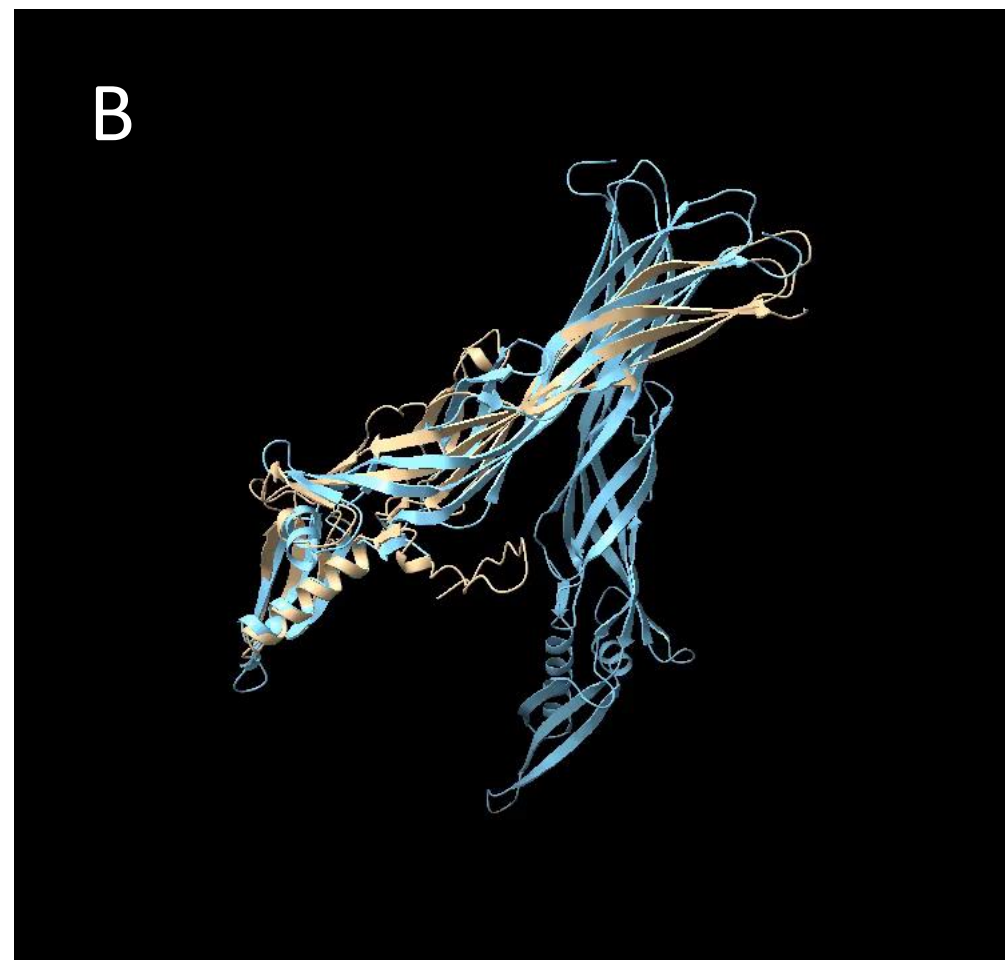
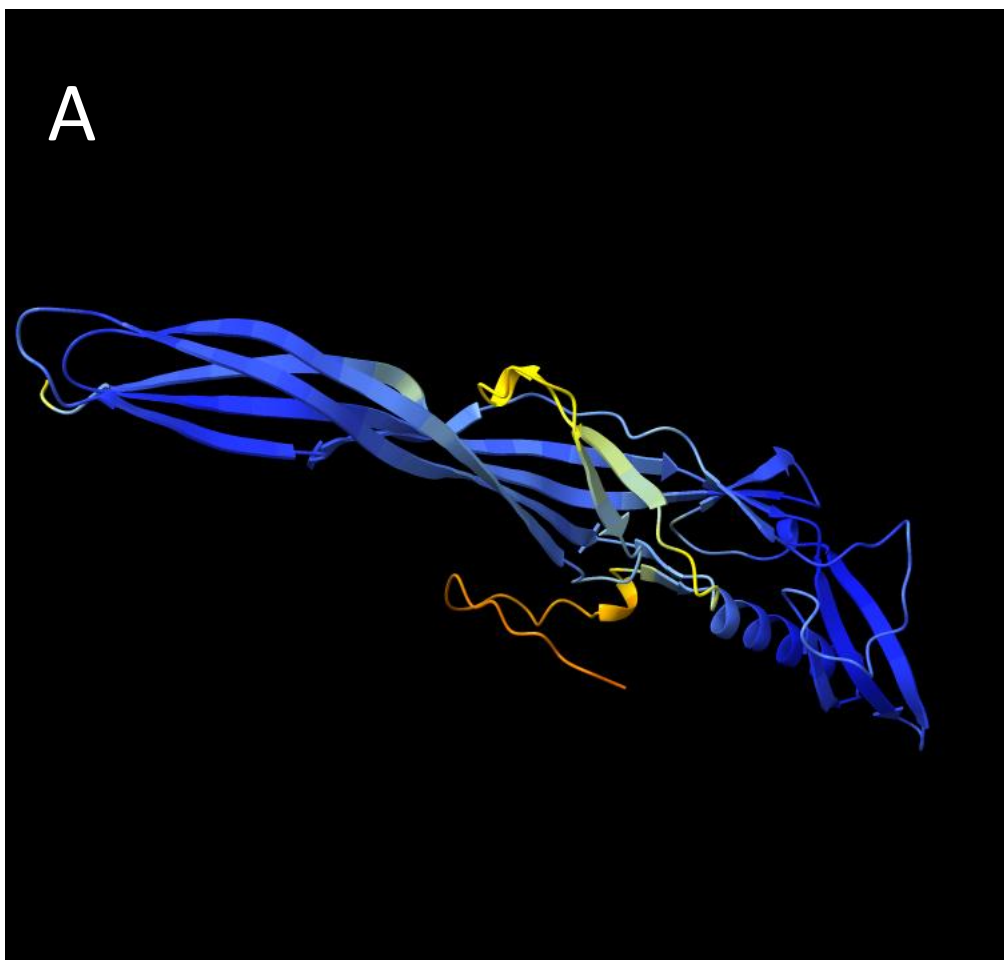


Figure S7: Tick Cytotoxin proteins: A) AlphaFold predicted structure for *Ixodes ricinus* JAB71021.1. The ribbon color indicates the B factor confidence value where blue=highest and red the lower values. B) Comparison of JAB71021.1 with the dimeric bacterial protein PDB:2d42.

A

JAB72190_Ix_ric	DSIVSTVLP	TNARSLG--	LDSDVLP	SYAFIVKSTS--	LTNRDL	HAEEHGGKLVGLVSPGLVRWGDC	SAPGWQ--	GF-N--	VTLC	GYLSLDNLHLSYVG
JAG92562_Amb_am	DGLFSTLV	PLYARSLG--	LENASVEN	CAFNVASTS--	VTNRD	VNVELHGGRLGLVIGPLARRGQC	SAPGWL--	GL-N--	VTLC	GYVSLDNAHLSYAG
JAC24281_Amb_caj	DLVLEQHLP	PLVRGSHALYPGARIP	DFHFKILKTG--	ITNRDL	LKANI	SEGFIHGFDN-GVHRLGNC	DPPLI-DG--	N--	TTVNC	VNLNMTGIGATLTA
JAC26824_Amb_par	DLVLEQHLP	PLVRGSHQLYPGARIP	DFHFKILKTG--	ITNRDL	LKANI	SEGFIHGFDN-GVHRLGNC	EPPLI-EG--	N--	TTVNC	VNLNMTGIGATLTA
JAA60568_Rh_pul	DVLLQRM	PALIRETPGLFPAAPI	PHYFKVYKTS--	ITNRDL	LKVN	TRGGIRNFDT-AIHRVGD	CIP-ALV-AG--	N--	TSV	SCTLSFDGILAEVA
JAP85995_Rh_app	DVLLQRM	PALIRETPGLFPAAPI	PHYFKVYKTS--	ITNRDL	LKVN	TRGGIRNFDT-AIHRVGD	CIP-ALV-AG--	N--	TSV	SCTLSFDGILAEVA
AEO36255_Amb_mac	DVLLQRM	EMLIRDTPGLYPTAPI	PFTFKVYKTA--	ITNRDL	LKVN	TRGGIKNFDT-AVRRVGD	CDP-KVV-AG--	N--	TSV	TCVISFDGIASDMVA
JAC28147_Amb_tr	DFIIDQV	LAGAG-----	VDVLDL	DISFDVDNQHNWTF	SGYVEFHL	QNGTLGNLRR-RVRRVGD	CGLRGDQDAG--	SPL	VEI	WCNINLRGVVARYDV
pdb 3UV1 A	NKAIDDA	IAAEQSET--	IDPXKV	EDHADKE	ERHVG---	ILDFK	GLAXRNIEARGLKQXKRQGD	ANVKGEE--	GIVK--	AHLIGVHDDIVSXEYDL
	:	.	:	:	*	.	:	.	:	:
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JAB72190_Ix_ric	SAKGD	SVLNTN	RTLSL	NVVPVKSSA-FIEVTSGS--	GGIPSL	LKTWLRPL	NFSVG-VTKPL	TLNNQRKTAF	QSEIA	KHSQAALLNVLLAS	FKEAVERS
JAG92562_Amb_am	SAKGD	SVLNTN	RSIVL	QAMPVNAS-LLEVTSTP--	GGAPRV	RTWLRPL	NFSVG-VTKPL	TLNNQRKTAF	QSEIA	KHSQAALLNVLLAS	FKEAVERS
JAC24281_Amb_caj	TTKGD	SLVGTIR	TIWVNV	TLKKETVLRVGV	TALA--	GRTASL	QTFFMEKLLKTK-YDSHLS	LNDDREDQ	EELIEEK	VRDILISAVYN	PKDLFARA
JAC26824_Amb_par	TTKGD	SLVGTIR	TIWVNV	TLKKETVLRVGV	TALA--	GRTASL	QTFFMEKLLKTK-YDSHLS	LNDDREDQ	EELIEEK	VRDILISAVYN	PKDLFARA
JAA60568_Rh_pul	VTKGD	NLLNIVK	SV	DVEALVYNTTG-RLEVTAAP--	NRPGF	VRTL	FVEGVNFDVR-PGSNLD	NEVRMNNEK	THIANFL	REELYMNIYGN	YQILLNHA
JAP85995_Rh_app	VTKGD	NLLNIVK	SV	DVEALVYNTTG-RLEVTAAP--	NRPGF	VRTL	FVEGVNFDVR-PGANLD	NEVRMNNEK	THIANFL	REELYMNIYGN	YQILLNHA
AEO36255_Amb_mac	VTKGD	NLLGTIR	DVG	VQAVVYNTTG-TMEVTAAR--	NRPGF	VRTL	FVEGVNFDVR-PGANLD	NEVRMNNEK	THIANFL	REELYMNIYGN	YQILLNHA
JAC28147_Amb_tr	EVIVD---	DRSKSV	VAELLVD	TGNVYFKFESRQDN	CTE	CSHFTDFQ	TDVTARLKPLG	VALDYAPDVIQ	QENEVVS	RAPKHISYAFTAAY	KRALAKM
pdb 3UV1 A	AYKLG	DLHPTT	V	ISDIQDFVVALSLEIPDEGN--	ITXTS	FEVRQ	ANVNVNHIGGLS	ILDPIFGVLS	DVIT	AIQD	TVRKEXTKVLAPAFKRELEKN
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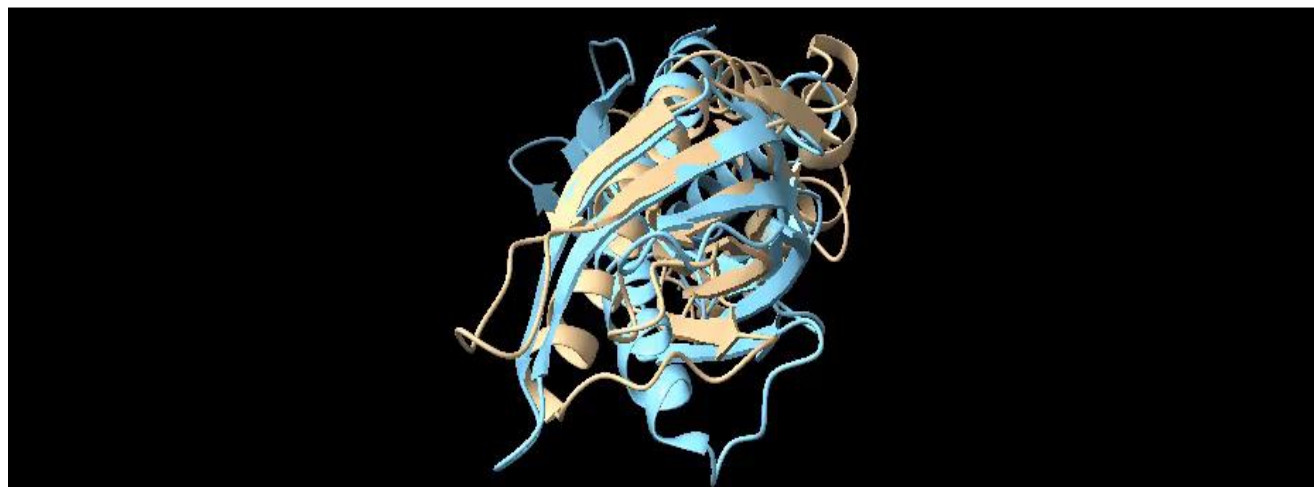


Figure S8: A subset of formerly assigned Cytotoxin proteins are most similar to Der f 7 allergen. A) Clustal alignment of tick salivary proteins with PDB:3uv1-A (Der f 7 allergen). Cysteines are shown in black background. Identical and similar amino acids are shown in green background. B) Superimposition of the AlphaFold predicted structure of JAB72190 to PDB:3uv1-A.

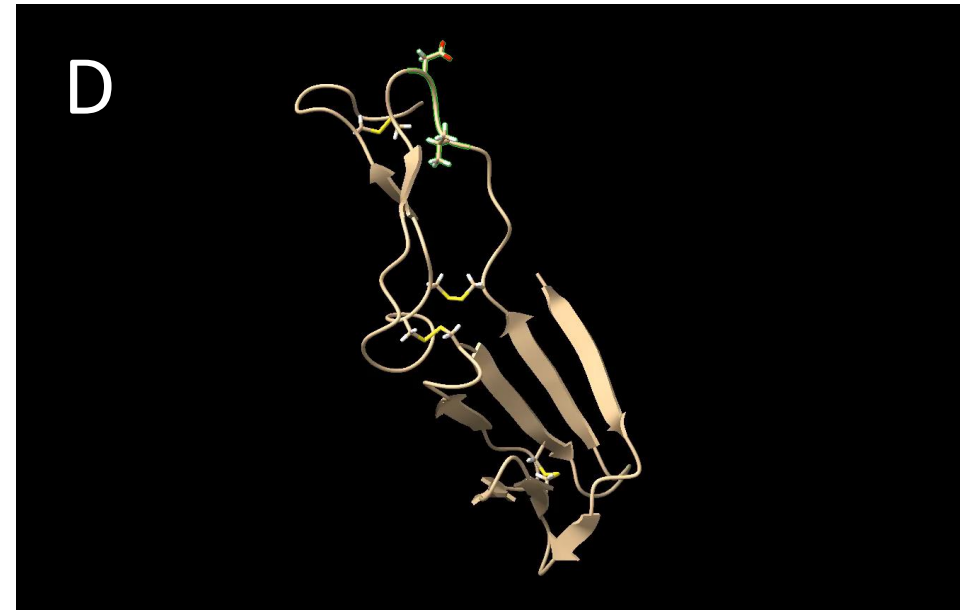
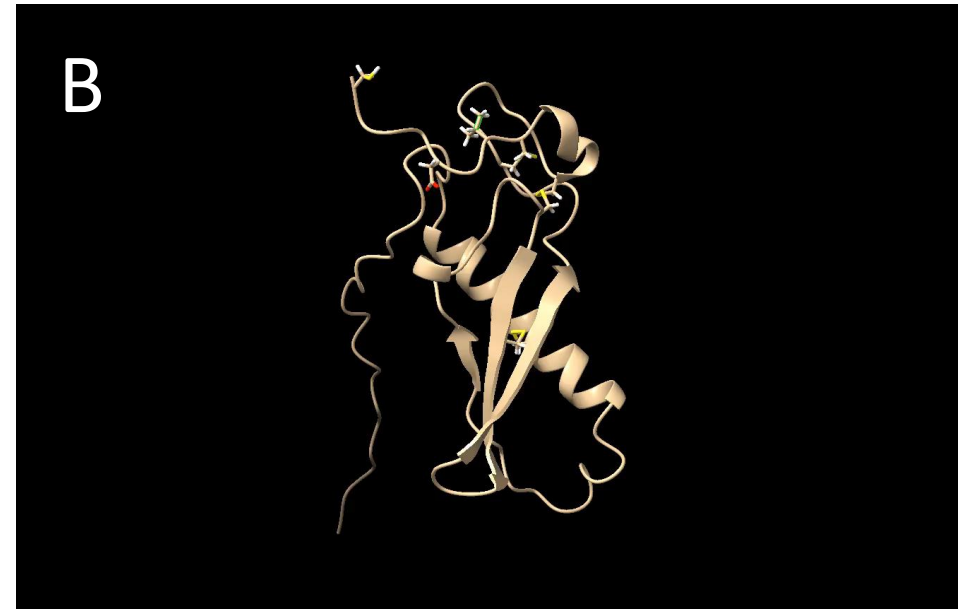
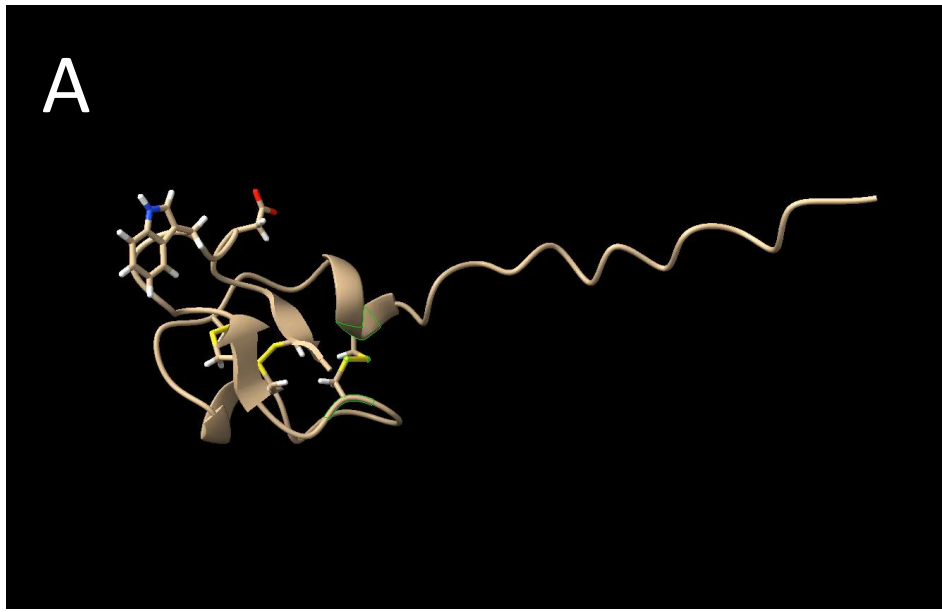


Figure S9: Tick salivary proteins with disintegrin motifs. A) 5.3 kDa AAY66640.1 with WGD domain. B) 8.9 kDa AEO35167.1 with VGD domain. C) Antigen-5 JAA67471.1 with RTS domain. D) Salp15 ABI97200.1 with VGD domain. Disulfide bonds are shown in yellow.

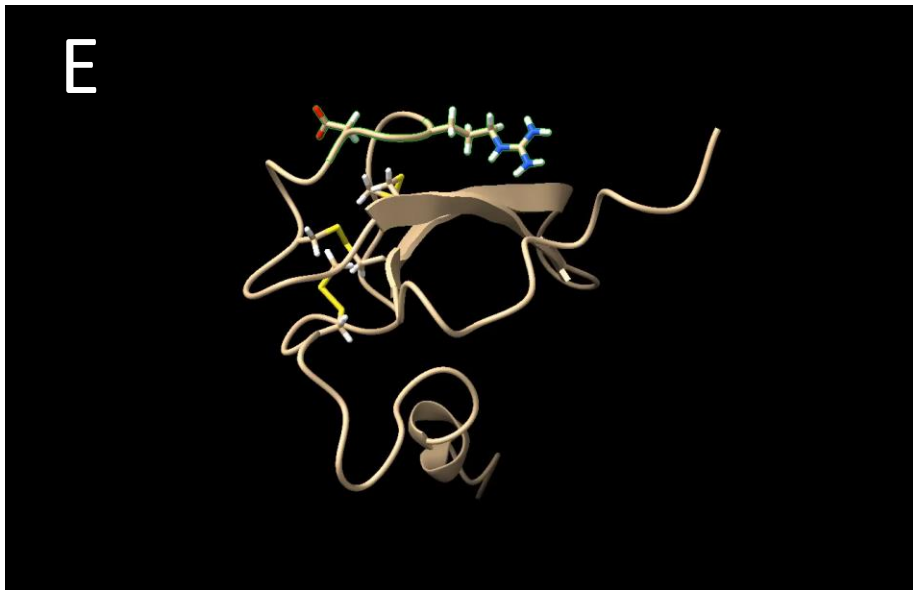


Figure S9: (Continuation): Tick salivary proteins with disintegrin motifs. E) Defensin JAP78020.1 with RGD domain. F) Basic Tail JAR94714.1 with KTS domain. G) Derf7/JHBP JAB71528.1 with KTS domain. H) Ixodegrin JAA69873.1 with RGD domain. Disulfide bonds are shown in yellow

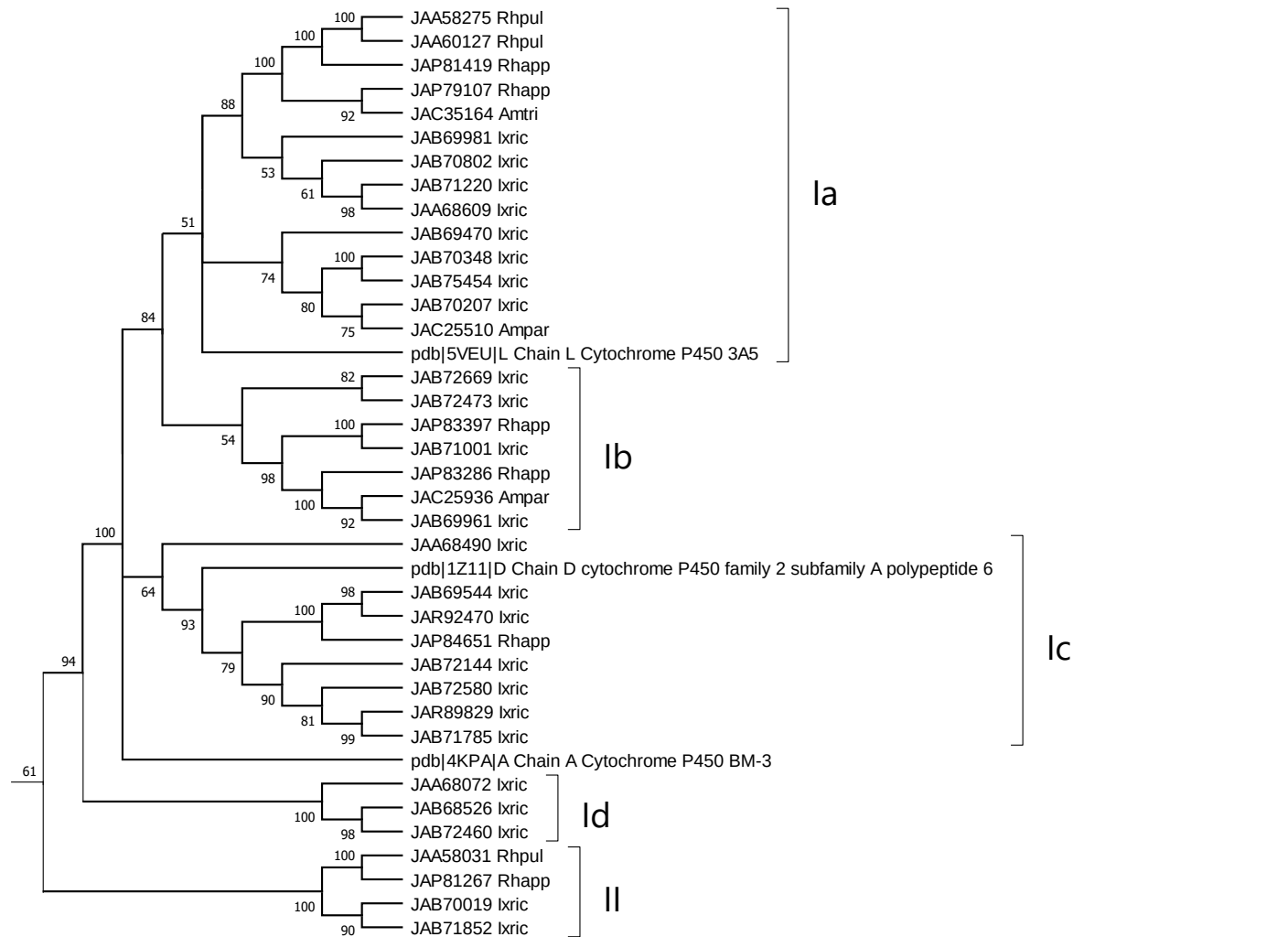


Figure S10: The tick salivary secreted cytochrome P450 family of proteins. Evolutionary analysis by Maximum Likelihood method. The evolutionary history was inferred by using the Maximum Likelihood method and JTT matrix-based model [1]. The bootstrap consensus tree inferred from 500 replicates [3] is taken to represent the evolutionary history of the taxa analyzed [3]. Branches corresponding to partitions reproduced in less than 50% bootstrap replicates are collapsed. The percentage of replicate trees in which the associated taxa clustered together in the bootstrap test (500 replicates) are shown next to the branches [3]. Initial tree(s) for the heuristic search were obtained automatically by applying Neighbor-Join and BioNJ algorithms to a matrix of pairwise distances estimated using the JTT model, and then selecting the topology with superior log likelihood value. This analysis involved 42 amino acid sequences. All positions with less than 50% site coverage were eliminated, i.e., fewer than 50% alignment gaps, missing data, and ambiguous bases were allowed at any position (partial deletion option). There were a total of 492 positions in the final dataset. Evolutionary analyses were conducted in MEGA X [2]

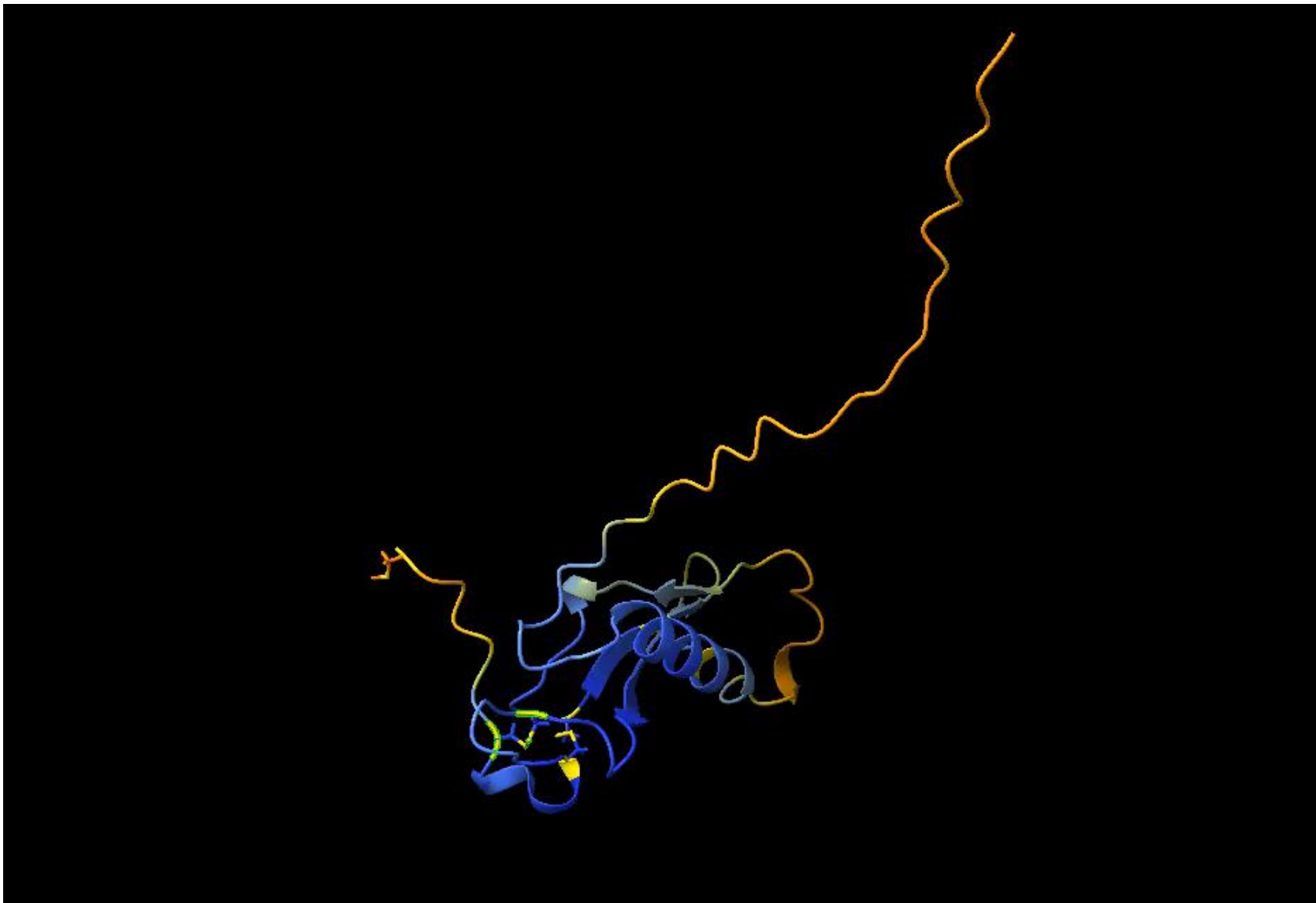


Figure S14: Predicted alphaFold structure of Salp15 showing disulfide bonds. The structure is colored according to the B factors, where blue represents higher confidence and red lower confidence. Cysteine residues are colored in yellow.

JAA65951.1_Ixric ----MQLALFMVILTFTHLSC-----GEQSEYI PDVHEQLNYLPRDCKENLIDQAEKCMRS-F SHKL--IEFKCEQFI CGSEDKSSGLRLKSRQTFYLEDGT FCGHSRVCINRQOVDTCGMRFVKT SG-----
 JAA68590.1_Ixric ----MQLAHFMVILTFTHLSC-----BAQSESI PDVHEQLNYLPRDCKQNLIDQAEKCMQS-FNHKL--IEFKCEQFI CGSEDKSSGLRLKSRQMFYLEDGT FCGHSRVCINRQOVDTCGMRFVKT SG-----
 JAA65958.1_Ixric ----MQLAHFMVIVTFTHLSY-----BAQSEYI PDVVDQLNYLPHDCKENLINQAEQKCMQS-FNHKL--IEIKCEEFKCGSEESTGVRLKSRQTFYLEDGT FCGHSRVCINRQOVDTCGMRFVKT SG-----
 JAR95043.1_Ixric ----MQLALFMVILTFTHLSS-----DAQSEYI PDVVDQLNYLPHDCKENLITQAEQKCMQS-FNHKL--IEIKCEEFKCGSEESTGVRIKSSQTFYLEDGT FCGHSRVCINRQOVDTCGMRFVKT SG-----
 JAA66032.1_Ixric ----MQLAHFMVILTFTHLSS-----BEQSEYI PDVHEQLEYLSDECKENLISQAEAKCMQS-F SHKL--IEINKCEQFKCGSKSTAGLKLTSSTQFGLKDGTF CGDRRVCIMGQCIDTCRMTFV-----
 JAA68720.1_Ixric ----MQLALFMVILTFTHLSS-----BEQSEYI PDVVDQLNYLPQECKENLIRQAEHKCMLS-FDHKL--IEFKVQCFI CGSKGTSAGLKLTSRQTFGLMDGT FCGDSRVCIRGQOVDTCRMTFV-----
 JAA71040.1_Ixric ----MQLAHFMVILTFTHLSS-----BAQSEYS PDVVEQLNYLSEICKESLISQAEQKCMLS-F SHKL--IEIKGCTIKCGSVDKNAGMKLTSSQTFRLKDGTF CGHRKVCIMGQCIDTCRMTFV-----
 JAA65899.1_Ixric ----MQLPLFVVIVAFVHLSC-----BEESEPS PDMYGELKYL PKDCKNNLKI QIQDRCEGHKFPQPEL--QWVTECQFKCGSENENDGYLMIKAGQIYHLKDGTF CGHSRVCITGKQVDTCENMFVPIKA-----
 JAA65885.1_Ixric ----MQLTLFIVIVTF AHLSC-----BGESEPS PDT SGLWKYL PKDCKNNLQIQI EAKCDGHRFPQPEL--QWVTECQFKCGYENDNGYLKITSQGTYNLKDGT FCGHSRVCITGROVDTCENMFVPSKA-----
 AAT92207.1_Ixpac ----MQLALLMVMVTFTHLSC-----BEQSQAS ENIFGEMNYL PKDCKDRLKAQIEDQCEGHKFPQPEL--QWVTECQFKCGYENNDGYIKTTTGQTYNLKDGT FCGHSRVCINGDOVDTCSMRFV-----
 JAA68686.1_Ixric ----MQLTLFIVIVTF AHLSC-----BAQSQVS PGIFGEMNYL PKDCKDRLKAQIEDKCSGHKFPQLL--VESTVCKFKCGDEHNNGYTQAQTAQIFFLKDGTF CGHSRVCIKGNOVDTCQMTFV-----
 AAM93641.1_Ixsca ----MQLALFMIMVTFTHLSC-----BEQSEAS PDIFGVMKYL PDCKNNLKKQIEDKCSGNPYQPQL--LEVNDCTIICGDWHDNGVT KATRHI INLKDGTF CGHSRVCIKGKCFDTCQMTFV-----
 CAX36743.1_Ixsca ----MQLALFMIMVTFTHLSC-----BEQSEAS PDIFGVMKYL PDCKNNLKKQIEDKCSGNPYQPQL--LEVNDCTIICGDWHDNGVT KATRHI INLKDGTF CGHSRVCIKGKCFDTCQMTFV-----
 AAY66646.1_Ixsca ----MQLALFMVILTFTHLSC-----BEQSEAS PDIFGDMKYL PDCKNNLKEQIQNKCSGHYQPLL--LEVNDCTIICGDWHDNGVT KAKTRHT INLKDGTF CGHSRVCIKGEOVDTCQMTFV-----
 AAY66699.1_Ixsca ----MQLALFIVILTFALLSC-----BEELEAS PDIFGEMKHL PDCKNTNKEQIQNKCSGHKYQPLL--LEVNDCKIVCGDWHNGVT KATRHT INLKDGTF CGHSRVCYKGEVDTCRMTFV-----
 JAA68683.1_Ixric ----MQLAYFMAIVTFMHLSC-----BEQSEAS PDIFGEMKYL PDCKDKLKEQIQNKCSGHIFQPLL--VKVSECTFRCGDEHDNGFT QAKTGQIYNNKDGTF CGHSRVCINGKQVDTCRMTFV-----
 JAA68682.1_Ixric ----MQLALFMVMVTFKLLSC-----BEQSASS PDIFGEMKDL PPGCKDNLKKQIKDNCEGNPYQPPEL--VEFRGQFTCEYKNNDYIFTKLTSRRITNLKDGT FCGQNKVCIGGNOVEACQMTFV-----
 JAA65900.1_Ixric ----MQLAYFMVIVTFTHLSC-----BVQSESI PDIPGKMKDLSQECKATLEKQIVDRCHGNPYQPLL--VQVSECOQFKCGYENNNGLRKITTGQTYNLKEGT FCGHSMVCINGQOVEKCDLDFVWANA-----
 JAB71687.1_Ixric MNVKMQLTLFVVIVTF SHLSC-----BVQWESGPFVIGEIDSLPQCKENLIKQMHCQCSGNPYQPQL--AEVNDCTFTCGDWHNGVT KAKTRHT INLKDGTF CGYSKMCVGGKQVQTCRSDYVKI SG-----
 JAB76908.1_Ixric ----MQLTLFVVIVTF SHLSC-----BVQWESGPFVIGEIDSLPQCKENLIKQMHCQCSGNPYQPQL--AEVNDCTFTCGDWHNGVT KAKTRHT INLKDGTF CGYSKMCVGGKQVQTCRSDYVKI SG-----
 JAA65880.1_Ixric ----MQLTLFIVFVTLAHLSC-----GVQSESI PVIIGEMNKL PDDCKEKLINEMKDCQSGHKFPQPTL--VEVNDCTFTCGYWHNGVT QAKTRHTIYLYKDGTF CGYSRMCVGGKQVQTCRSDYVKI SG-----
 JAB76907.1_Ixric ----MQLTLFIVIVTFVHLSC-----BVQSESS PKIVGEMNNLPEYCKESLISKEMKDCQSGHLFPQPTL--VEVSDCTFTCGDWHNGVT RAKTRHT INLKDGTF CGYSKVCISGNQVQTCRSDYVKI GAKKGVYK-----
 JAA68651.1_Ixric ----MQLALFVVIVAFVHLSC-----BVQSESS PKIVGEINNLNPNCKENITAQMEQRCHENKFPQPL--KEVNDCTFTCGDWHNGVT QAKTRHTIYLYKDGTF CGYSRVCINGKQVERCNLDENA-----
 JAA68560.1_Ixric ----MQLTLFIVIVTF AHLSC-----BVQSESI PNIVGEMSKLPEDCKANLIKQMRDECSGNHFPHTQL--VEVSECOQYKCEEHNNNGKIMGTFSQSFPKDGTF CGHSKVCIKGKQVQTCNLDPMKTD-----
 JAB68547.1_Ixric ----MQLTLFVVVTFVHLSC-----BVQLESSSGISGEMNYLTKKCKDNLKEQVQKQRCNAHKFPQPTL--VQVSECKYKCGEHDNGVT RGTSGQTFYRNKGT FCGHSKVCINGNOVEKCDLDFVWNTIA-----
 JAA68304.1_Ixric ----MQLVLFIVIVTFPLSCDNLQPGLEBVQSESI PVIYEEFKDL PPECKIKLENEMKERNEDSYHPHL--LEVSECKFKCGDKNNNGKTLILTHSQSFTLKDGTF CGKKNKICIDGKCI PRCSMPFVKLGRK-----
 JAA68392.1_Ixric ----MQLVLFIVIVTFPLSCDNLQPVLEBVSESI PVIYKEFKDL PPECKKNLENEMEQRCHEDSYHPQL--LEVSECKFKCGDKNNNGKTLILTHSQSFTLKDGTF CGKKNKICIDGQCI PRCSMPFVN-LRG-----
 JAA68559.1_Ixric ----MQLVLFIVIVTFPLSCBELS---VSS---PNFYREFESLPLQCKTNLKI QMEQRGGHSYQPLL--LEVSECEFKCGDKNNNGKTLILTHSQSFTLKDGTF CGKKNKICIDGQCI PRCSMPFVK-LRG-----
 JAA68430.1_Ixric ----MQLVLFIVIVTFTHLSC-----BVQSESI PDYKLEAL PPECKNNLKNQMERRCSEDYPQPLREVKLKCEEFKCGDDHNNGRTMGTHGQSFFLKDGTF CGQNEVCIDGICTDRCSMPVKMLKGRK-----
 JAB76930.1_Ixric ----MQLVLFIVIVTFPLSC-----BVQSESI PVIYKEFEDLPPECKNNQKNQMERRCSEDYHPRL--LKVSCEEFKCGDEHNNGRTMGTHGQSFFLKDGTF CGQNEVCIDGICTDRCSMPVKMLKRAKIASLQT-----
 JAA73786.1_Ixric ----MQLVLFIVIVTFPLSCDNLQPVLEBVQSESI PDYKLEVL PPECKNNLKNQMERRCSEDPHPRLEVLKLKCEEFKCGDDHNNGRTMGTHGQSFFLKDGTF CGKDMVCMQGIQINQCSLSEFVKGL-----
 AAM93642.1_Ixsca ----MQLALFLVVATFIYVSC-----CEKSESGLVYKEFESLQEGCKQKLRDEMEQRCSEHPFQPEL--VEVLQCKFKCGNEHSNGKTLILISGQYINLNDGT FCGENKICIDGQOVPRCMSPFVKLKGRI-----
 CAX36742.1_Ixsca ----MQLALFLVVATFIYVSC-----CEKSESGLVYKEFESLQEGCKQKLRDEMEQRCSEHPFQPEL--VEVLQCKFKCGNEHSNGKTLILISGQYINLNDGT FCGENKICIDGQOVPRCMSPFVKLKGRI-----
 AAY66757.1_Ixsca ----MQLVLFIVILTFTHLSR-----BELPESI PHFYREFESLQPECKDKLKT EMIQRSEHLYQPLL--VEVLECTFKCGNEHNNNGKTLILTSQYIKLNDGT FCGENKICIDGQOVSRCMSPFVKLKGRI-----
 JAA68436.1_Ixric ----MQLVLFIVIVTFPLSC-----BVQSESI SDIREKMKDL PGCKENLIDKMDQFCNGNLFQTQLVGLKLLECKFT CGEEHNNNGKTRGTSVQDFTLNDGT FCGPSKVCIDGICTGRCSMPVKMLKGRK-----
 JAA68113.1_Ixric ----MQLVLFIVIVTFPLSCDNLQTVLEBVQSESI TDIFEKIDYMSKCKVSLRDQLVKKCGES PFQTLVAV--SECKYKCGEKNHNGQT RAETSLEFSLNDWT FCGKDKVCRDGOQIDRCLLPFN-LKEDKVT LGT GNS
 JAA65955.1_Ixric ----MQLVLFIIIT---PLSC-----BVQSESI TDIFKKIDYMSKCKASLRDQLVKKCGES PFQTLVDV--TECKYKCGEQHNNNGRT KARTVQEFNLNDWT FCGQDKVCREGICFDRCSLPFN-LRE-----
 JAA70870.1_Ixric ----MQLVLFIVIVTFPLSC-----BLQSESI TDIFKKIDYMSKCKASLRDQLVKKCGES PFQTLVDNLSCKYKCGEQHNDNGTKGTGQEFVNDWT FCGKYKVCRRDRQMDRCLLPFN-LKGE-----
 JAA68532.1_Ixric ----MQLVLFIVIVTFPLSC-----BVQSESI QDIFKKIDYMSKCKDKLRDQLLEKCGES PFQTLVDV--SECTYKCGEQHNNNGTKGTGQEFVNDWT FCGKDKVCRDRQMDRCLLPFN-LKGE-----
 JAB71697.1_Ixric ----MQLVLFIVIVTFPLSC-----BVQSESI PAIFGNIDYMSKCKDKLRDQLLEKCGES LYQTQFVVV--SECTYKCGEEHNNGLT KATTGQEFRLNDWT FCGHDMVCRDGOQIDRCLLPFN-LKGDVSL-----
 JAA70884.1_Ixric ----MQLVLFIVIVTFPLSC-----BVQSESI PDIFENIDYMSKCKDKLRDQLLEKCGES SYQTQFVLV--SECTYKCGEEHNNNGTKAKTSQQFRNLNDWT FCGHDRVCRDGOQIDRCLLPFN-LKDDKVT-----
 JAA65892.1_Ixric ----MQLALFMVILTFVYLFSC-----BVQSKSS PDIFEMRYLPPVCKDNLKNQLVQRCEENPYQTQLVEVEVSKRFGKCGEEHNNNGTKRGTGQYFDLNDGT FCGPDMVCIDGQICINRCNM PFVN-LRG-----
 JAA65898.1_Ixric ----MQLTLFIVFVTFVHLSC-----BEQSEAS PDIFREMTYLSQCKANLKEQLVERCGEHRFPQTLVDI--SECHFKCGEEHNNNGQTRVRTSQEFKLNNDGT FCGQGVKICIDGTCTETCRMPVAK-QIG-----

Figure S15: Clustal alignment of members of the Ixostatin family of proteins. The eight conserved cysteines are shown in black background. The remaining identical sites are shown in green background. The red box delineates the signal peptide region. The sequences coding for ISL929 (CAX36743.1) and ISL1373 (CAX36742.1) are shown in yellow background.

The proposed disulfide bridges are: |C:1 C:3|C:2 C:5|C:4 C:6| The resulting prosite block is: PA C-x(11)-C-x(13,16)-C-x(3)-C-x(22)-T-P-C-G-x(4)-C-x(4)-C-x(3)-C.

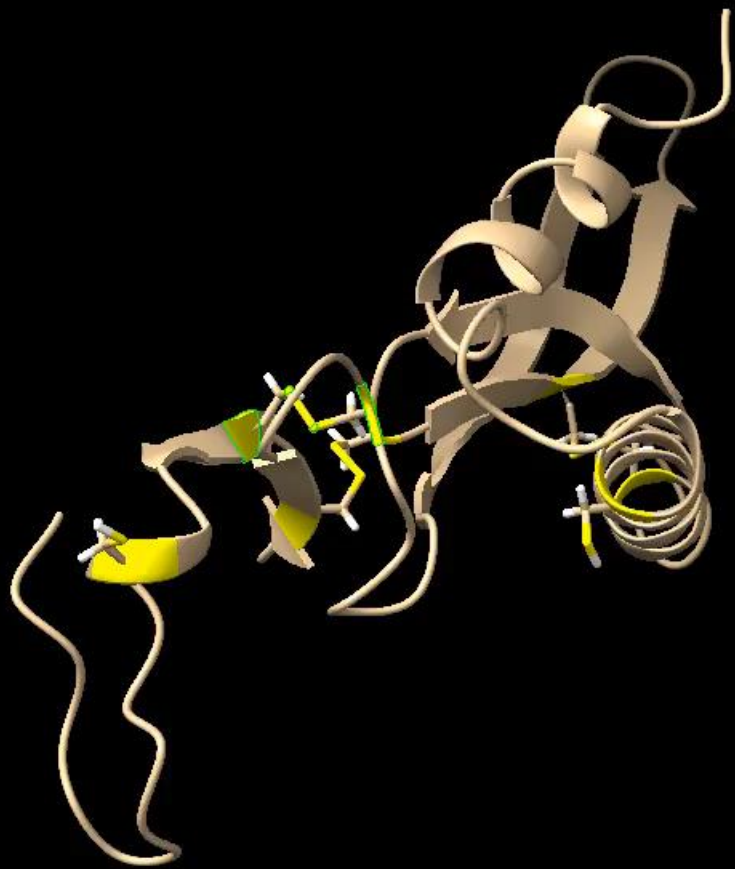
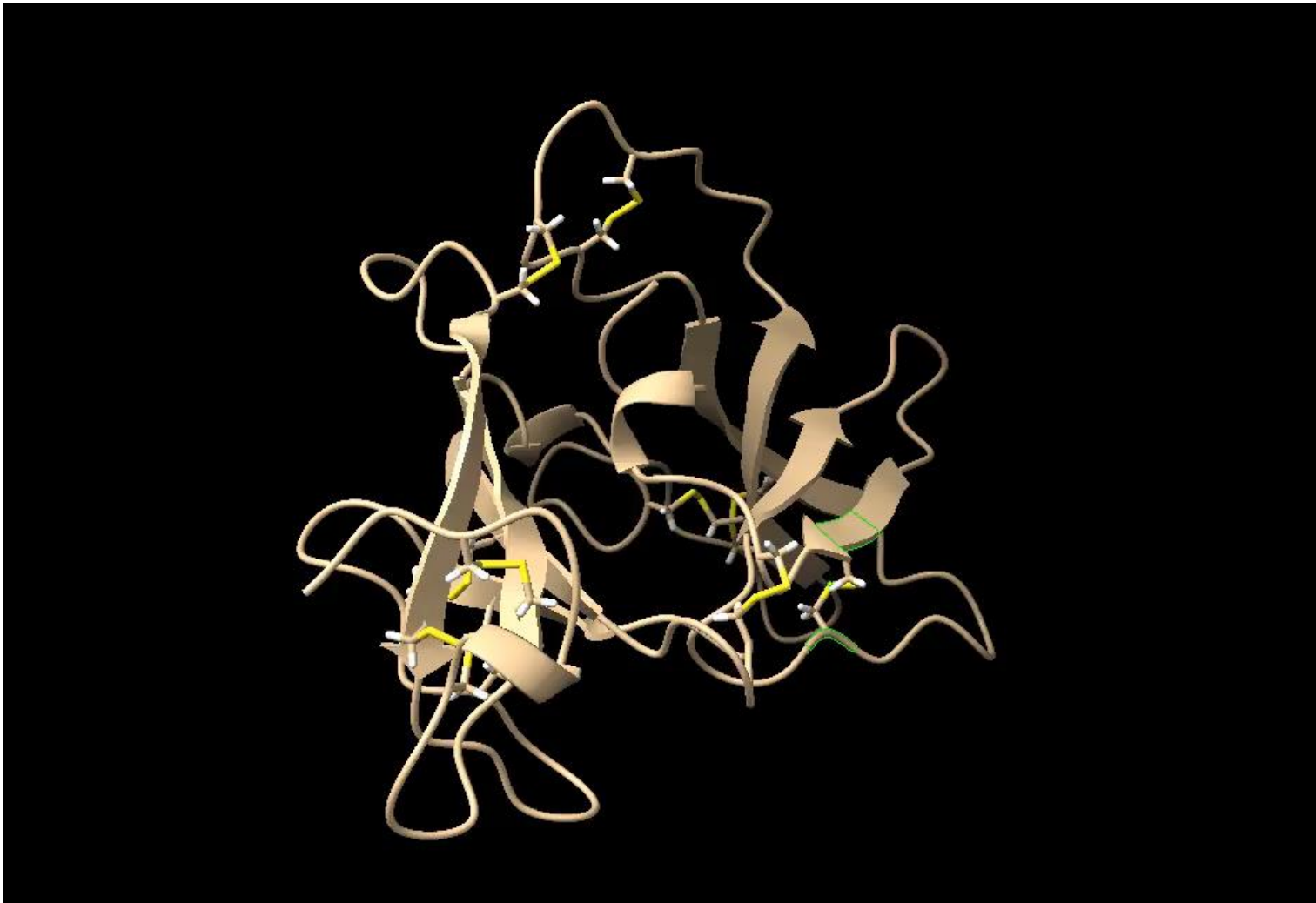
A**B**

Figure S16: Predicted AlphaFold structure for the Ixostatin CAX36742.1. A) Monomer with disulfide bonds |A:2 A:4 |A:3 A:6 |A:5 A:7|
B) Dimer with disulfide bonds |A:2 A:4 |A:3 A:6 |A:5 A:7 |B:2 B:4 |B:3 B:6 |B:5 B:7 |A:1 B:8 |A:8 B:1

JAA65485.1_Ixric	MDASSVLLAIACLSVAISSGVFGQAPTSCES	DAD	CIRGQRCVLHGNFSQNANC	ETYHTCI						
JAB69816.1_Ixric	MDASSVLLAVACVGVAISSGVFGQAPTSCES	DAD	CIRGQRCVLHGNFSQSANC	ETYHTCI						
JAA60721.1_Rhpul	MGSFHLMLAA----	LAVLGCGMAVSAATCQS	DAD	CSGGQRCVLHYNYS	SSGNC	ETDRRCI				
JAP85737.1_Rhapp	MGSFNLTLAA----	LAVLGCGMVVGATSCQS	DAD	CSRGQRCVLHSNFSSSANC	ESDRRCI					
JAC30670.1_Amtri	MDCFRLLTLAT----	VFLLEYALTVSATTCQS	DAD	CSGGQRCVLHRNFSSSANC	ETDRRCI					
JAC30671.1_Amtri	MGCFRLILAT----	VFLLGyALTVSATTCQS	DAD	CAGGQRCVLHRNFSSSANC	ETDRRCI					
JAC30673.1_Amtri	MSRSVSVLAFLVFAYAAVPSCLQSLVTT	CQT	DAD	CSNTQRCVWHYNYASSANC	ESAKYCI					
JAP81263.1_Rhapp	MLGYAFLVCILIALLA	VPHR--	CDDEITCTT	DAD	CTNMKCI	AHHNYGKDSMC	ETHKYCI			
	*	:	:	*	:	:	*			
JAA65485.1_Ixric	PVANDGCTCNPGYAC	YMKFCIQAP	FE	ECLVLEDLNS	RCGG	SEGP	KCSSNEVC	GYRRTFLNC		
JAB69816.1_Ixric	PVANDGCTCNPGYAC	YMKFCIQAP	FE	ECLVLEDLNS	RCGG	SEGP	KCSSNEVC	GYRRTFLNC		
JAA60721.1_Rhpul	SVSSTSCSCDPGFQ	CRLKDCPSS	PYE	ECLVLEHQNT	RCGG	TSGP	QCGPNQVC	GYKKTGLAC		
JAP85737.1_Rhapp	AVSSTSCSCDPGFQ	CRLKDCPSS	PYE	ECLVLEHQNT	RCGG	RNGP	KCGTNQVC	GYQKTGLTC		
JAC30670.1_Amtri	SGTPTTCTCEQGFQ	CFVRDCPTS	PYE	ECVVLEHQDT	RCGG	SNGP	QCGPDQVC	GYKDTGLRC		
JAC30671.1_Amtri	SGTPTTCAEQGFQ	CFVRDCPTS	PYE	ECVVLEHQNT	RCGG	SNGP	QCGPDQVC	GYKDTGLRC		
JAC30673.1_Amtri	SVSKTSCSCKAGYT	CRLKDCPAS	PYE	CLIIENQDT	RCGG	SQAPT	CLSTQIC	GYKLTGLVC		
JAP81263.1_Rhapp	AVNETSCVCRGEYK	CRVMD	CQES	PF	ECLILDNLET	RCGG	SKAPK	CALNEYC		
	.	*	*	:	*	:	*	:		
JAA65485.1_Ixric	IKPC	PCYG	THEAV	CVPRDPENT	CHRD	SMVQVGRGGT	PGYVCKD	CASPAS	SVLT	ARNRPSCK
JAB69816.1_Ixric	IKPC	PCYG	THEAV	CVPRDPENT	CHRD	SMVQVERGGT	SGYVCKD	CASPAS	SVLT	ARNRPSCK
JAA60721.1_Rhpul	IKPC	PCYGT	DRAVC	VDKQPGV	CGPNS	IIVQVNP	PD--	NSYVCKG	CASAT	SVLTR-----
JAP85737.1_Rhapp	IKPC	PCYGT	DRAVC	VDKQPGV	ECGPNS	IIVQVNP	PD--	NSYVCKG	CASAT	SVLTR-----
JAC30670.1_Amtri	IKPC	PCYGT	DLATC	VNKKPTIAC	GPNS	IIIRVTGDG	-QDY	EC	DGCASVT	SVLTALLH----
JAC30671.1_Amtri	IKPC	PCYGT	DLATC	VNKKPTIAC	GPNS	IIIRVTRDG	-QDY	EC	DGCASVT	SVLTALLH----
JAC30673.1_Amtri	IKPC	PCYGT	THKAV	CVTRKSTT	SCGAN	SIVTV	DQKG--	GYTC	NGCASAV	SVLTG-----
JAP81263.1_Rhapp	NKPC	PCYGS	HQATC	IRKKYNN	LCSPY	SIVRLDKEM	-GYT	CD	SCITAA	SVLTGMT-----
	*	*	*	*	*	:	:	:	*	:

Figure S17: Alignment of the 20cys subgroup of the Salp15/Ixostatin group of tick salivary proteins. The conserved cysteines are shown in black background. Other conserved amino acids are shown in green background. The red box delineates the signal peptide region.

A

B |A:1 A:3|A:2 A:5|A:4 A:15|A:6 A:8|A:7 A:10|A:9 A:20|A:11 A:13|A:12 A:17|A:14 A:16|A:18 A:19|

Figure S18: A) Predicted AlphaFold structure of JAA60721.1, a 20cys subgroup member of the Salp15/Ixostatin group of tick salivary proteins. The 20 cysteines form disulfide bonds as indicated in B.

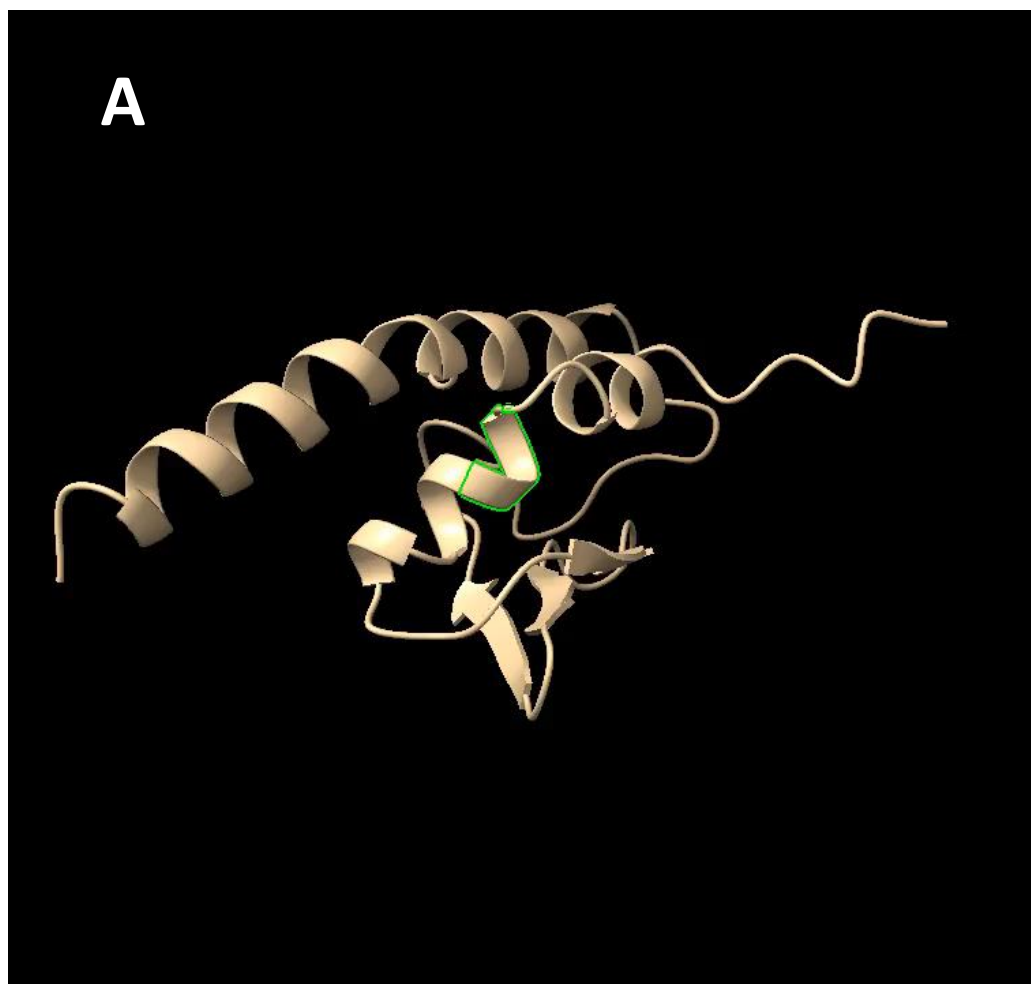


Figure S20: Predicted structure of the 10kDa-WC family. A) Monomer B) Dimer.

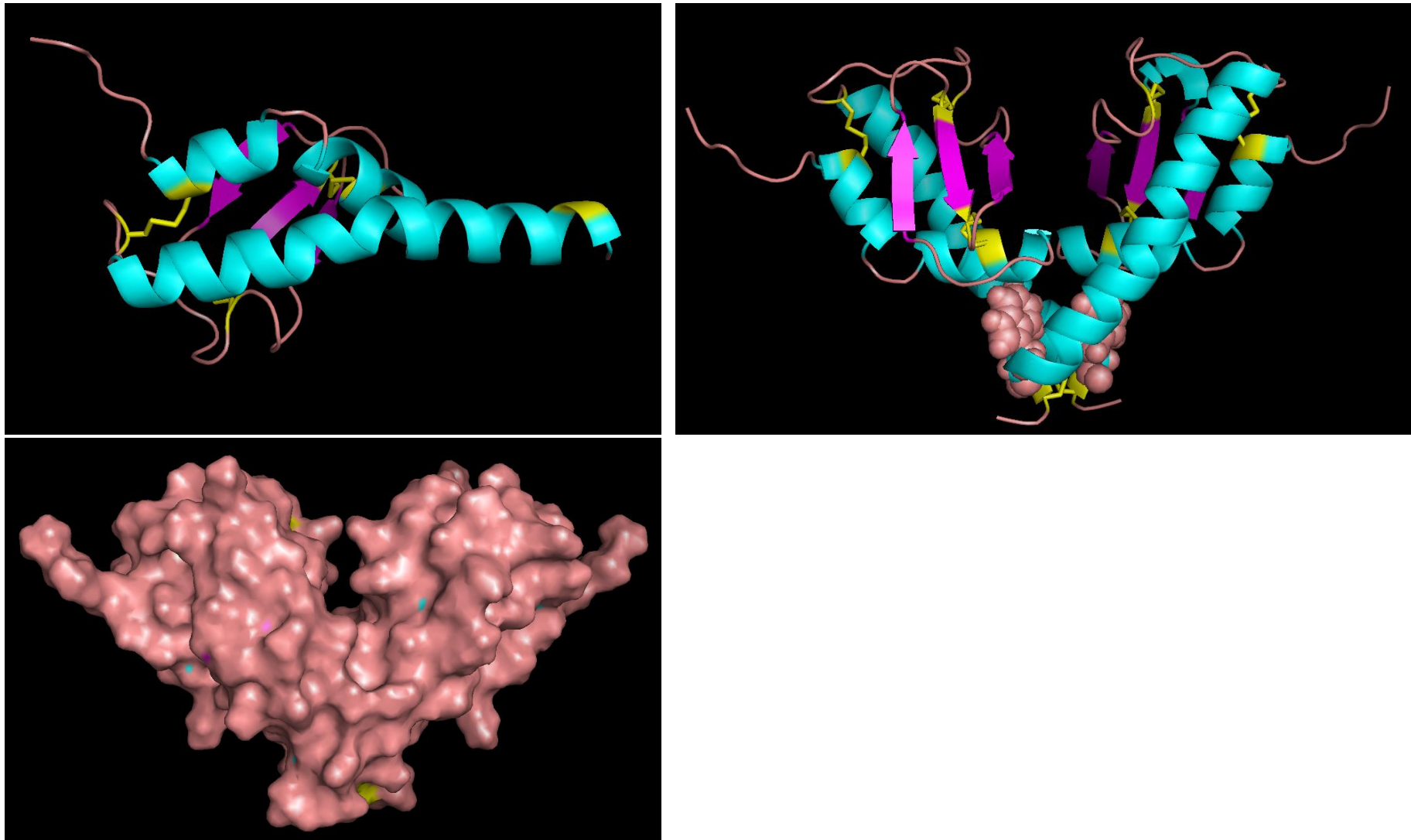


Figure S21: Predicted structure of the 10kDa-WC family. Top left are the N-terminal alpha-helices (top), the central anti-parallel beta-sheet (purple) and the C-terminal alpha-helix. disulfide bonds and cysteines are highlighted in yellow. Top right indicate the predicted homodimer with the formation of a disulfide bond by the C7 cysteines of each monomer at the bottom of the structure and the potential binding cleft at the top. Also indicated are the tryptophanes of the WC motif. The bottom right indicate a surface model of the dimer that indicates the binding cleft formed.

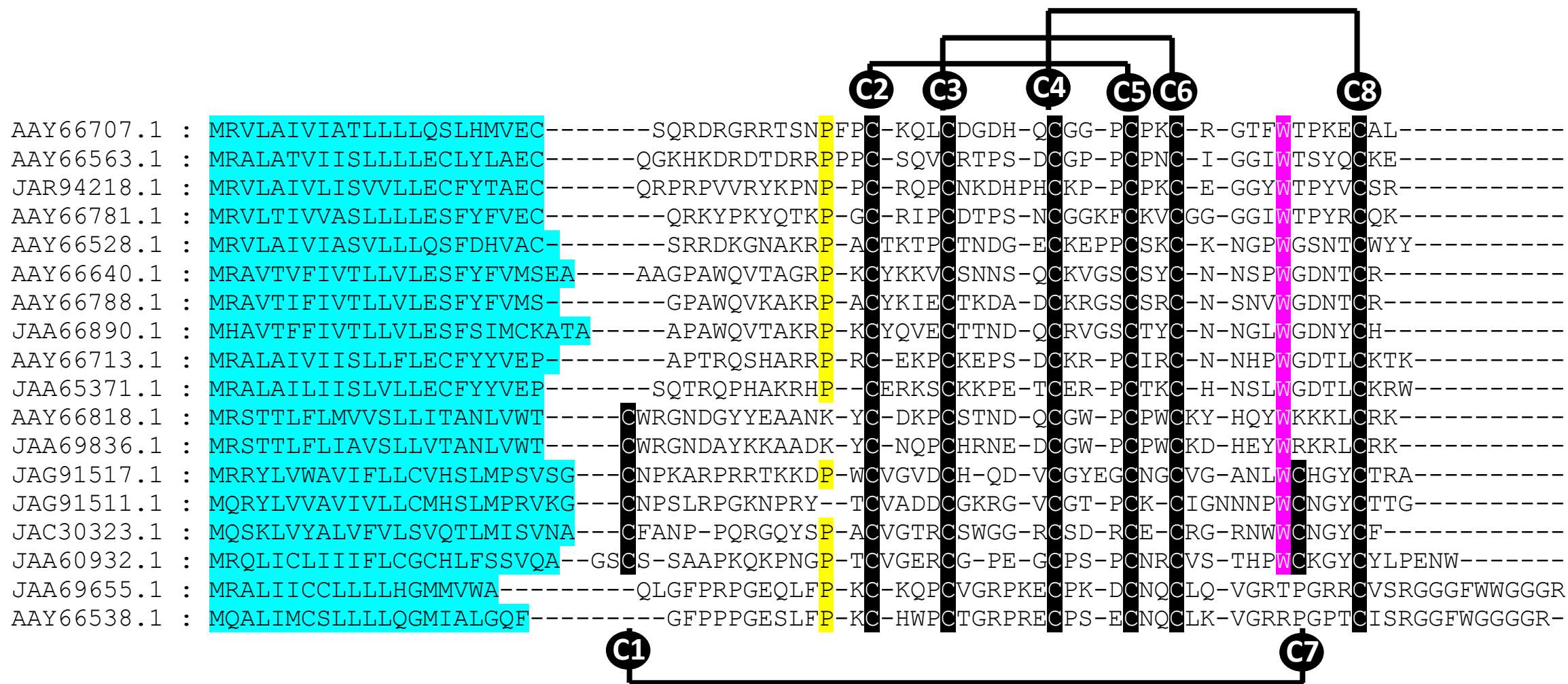


Figure S22: Alignment of selected members of the 5.3kDa family. Indicated are the conserved cysteines and their disulfide bond pattern. Conserved residues are highlighted in yellow, while a conserved W is highlighted in purple. The predicted signal peptides are highlighted in light blue.

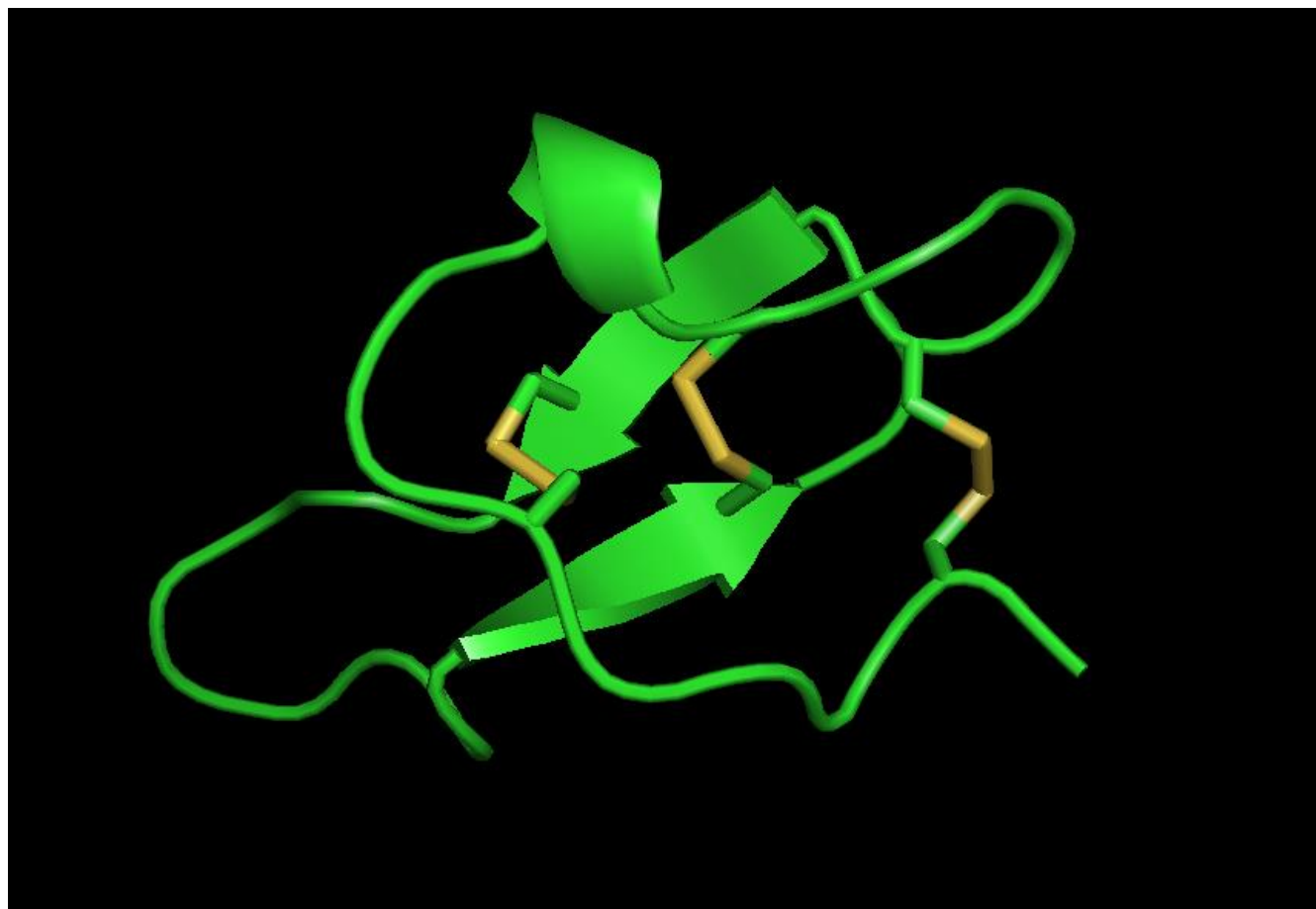


Figure S23: Predicted structure of the 5.3kDa family. Indicated are the central fold composed of two anti-parallel beta-sheets linked with three disulfide bonds that forms a cysteine knot.

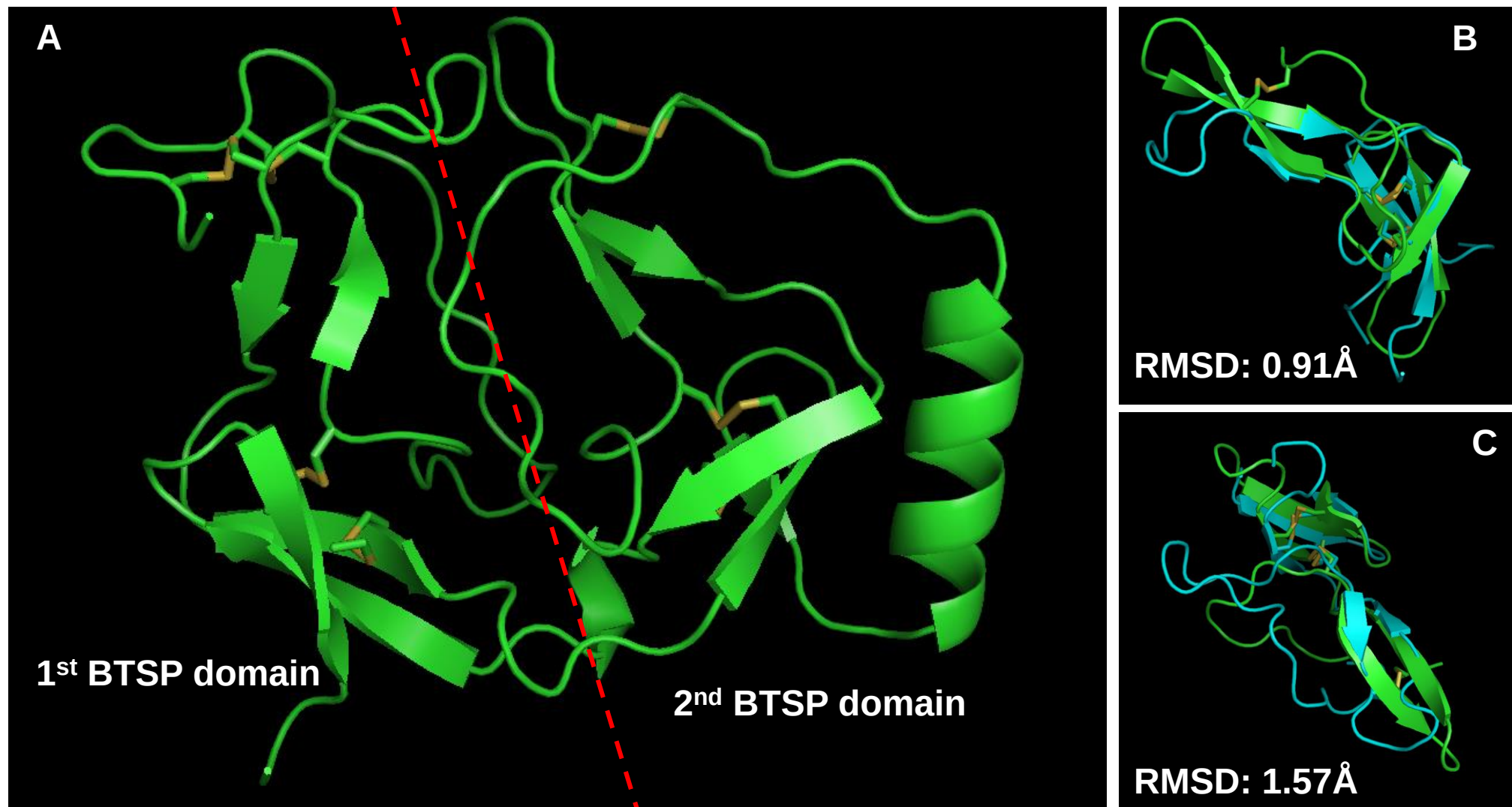


Figure S24: Predicted structure of the 7 disulfide bond family. A) The N-terminal start top left and the C-terminal end bottom left. The two BTSP-like domains are separated by the dashed red line. B) Superposition of the BTSP BSAP1 and the first 7DB-domain. C) Superposition of the BTSP BSAP1 and the second 7DB-domain.

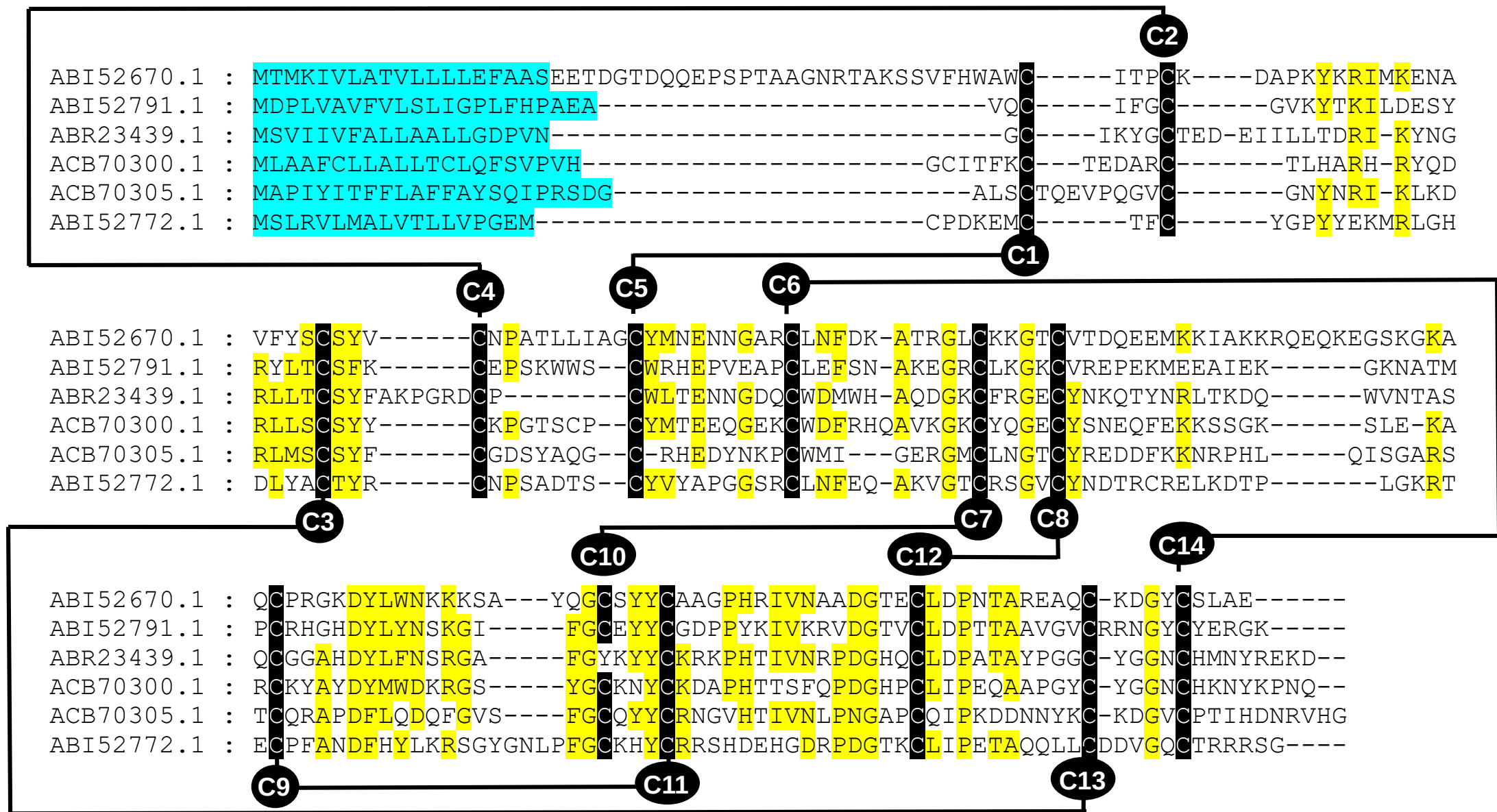


Figure S25: Alignment of selected members of the 7 disulfide bond family. Indicated are the conserved cysteines and their disulfide bond pattern. Conserved residues are highlighted in yellow. Signal peptides are highlighted in blue.

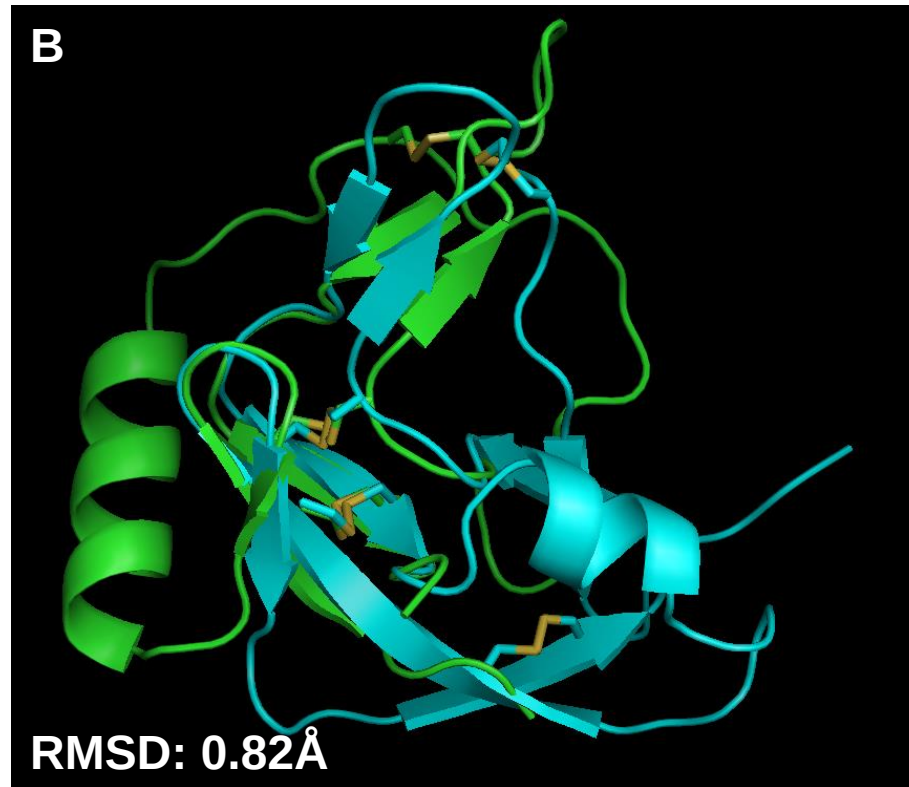
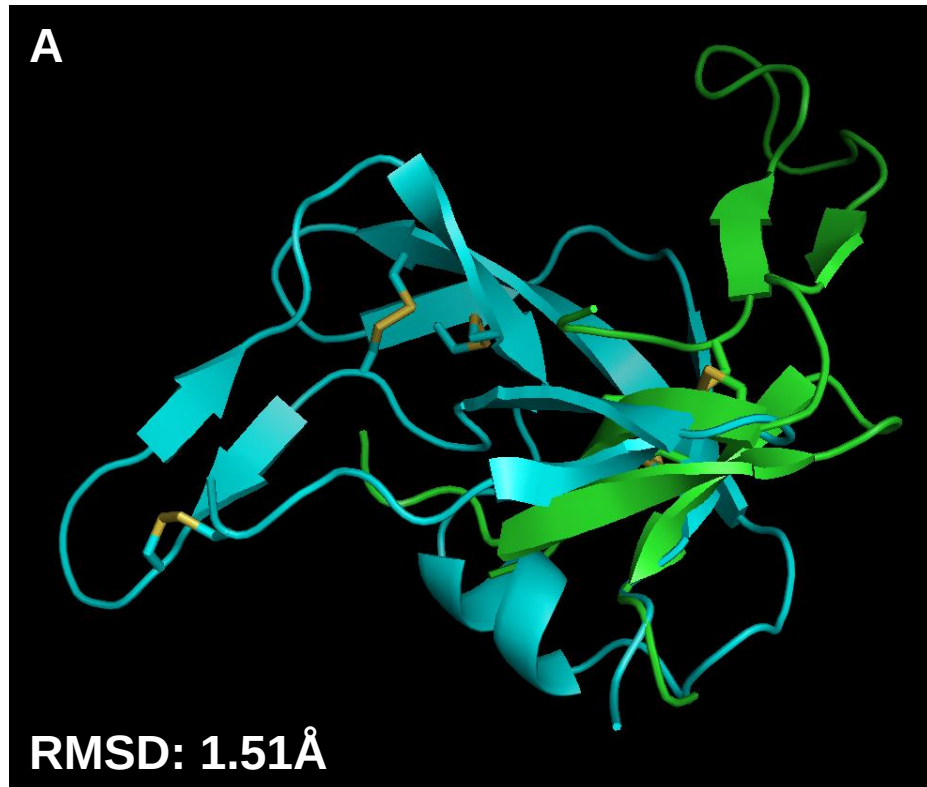


Figure S26: A) Superposition of the “first” 7DB-domain and the Evasin-1 fold. B) Superposition of the “second” 7DB-domain and the Evasin-1 fold.

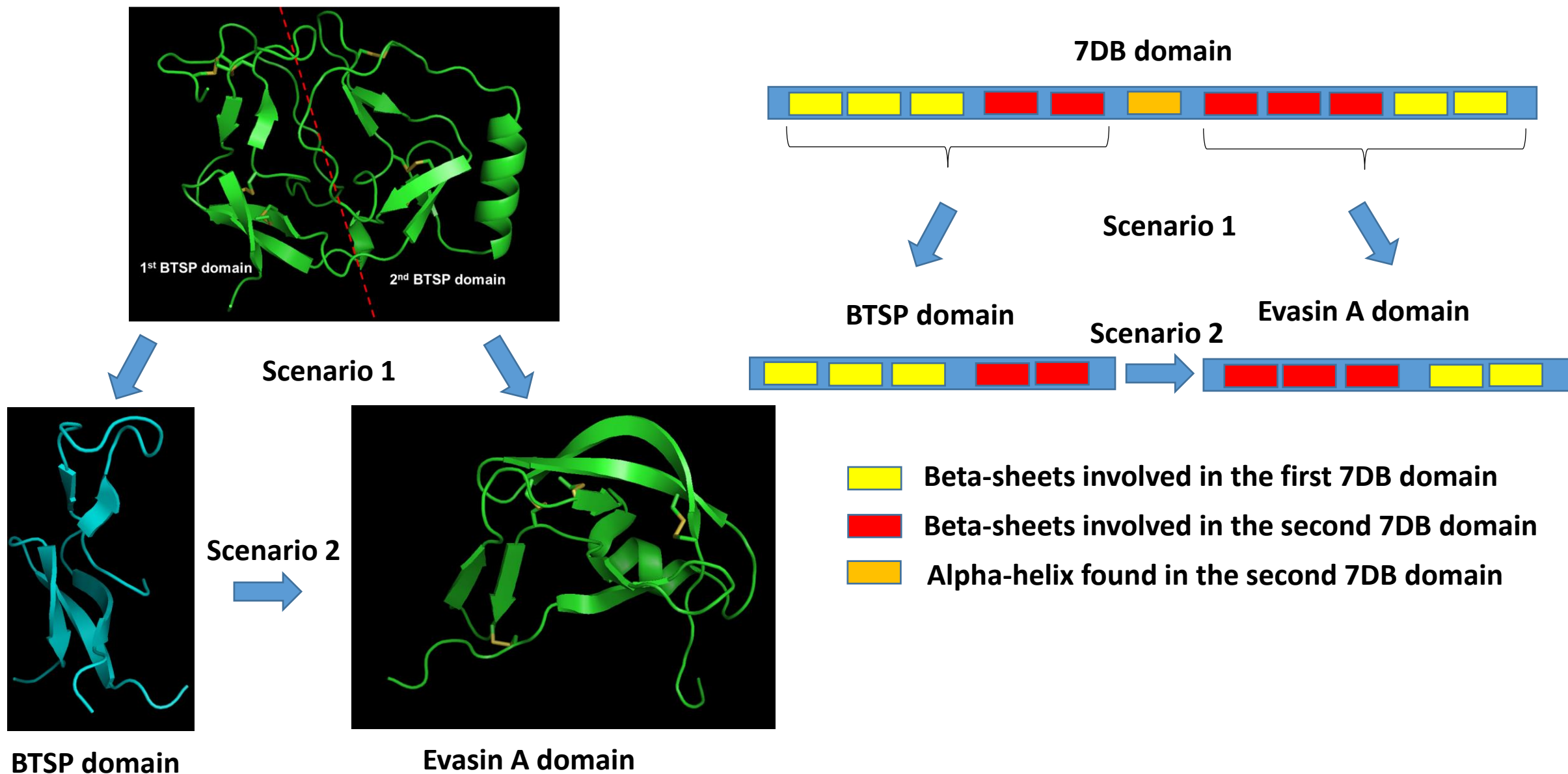


Figure S27: Model for the evolution of the 7DB, BTSP and Evasin A families. Indicated are the first and second domains of the 7DB family and how duplication of respective beta-sheet configurations may have resulted in the different BTSP and Evasin A domains.

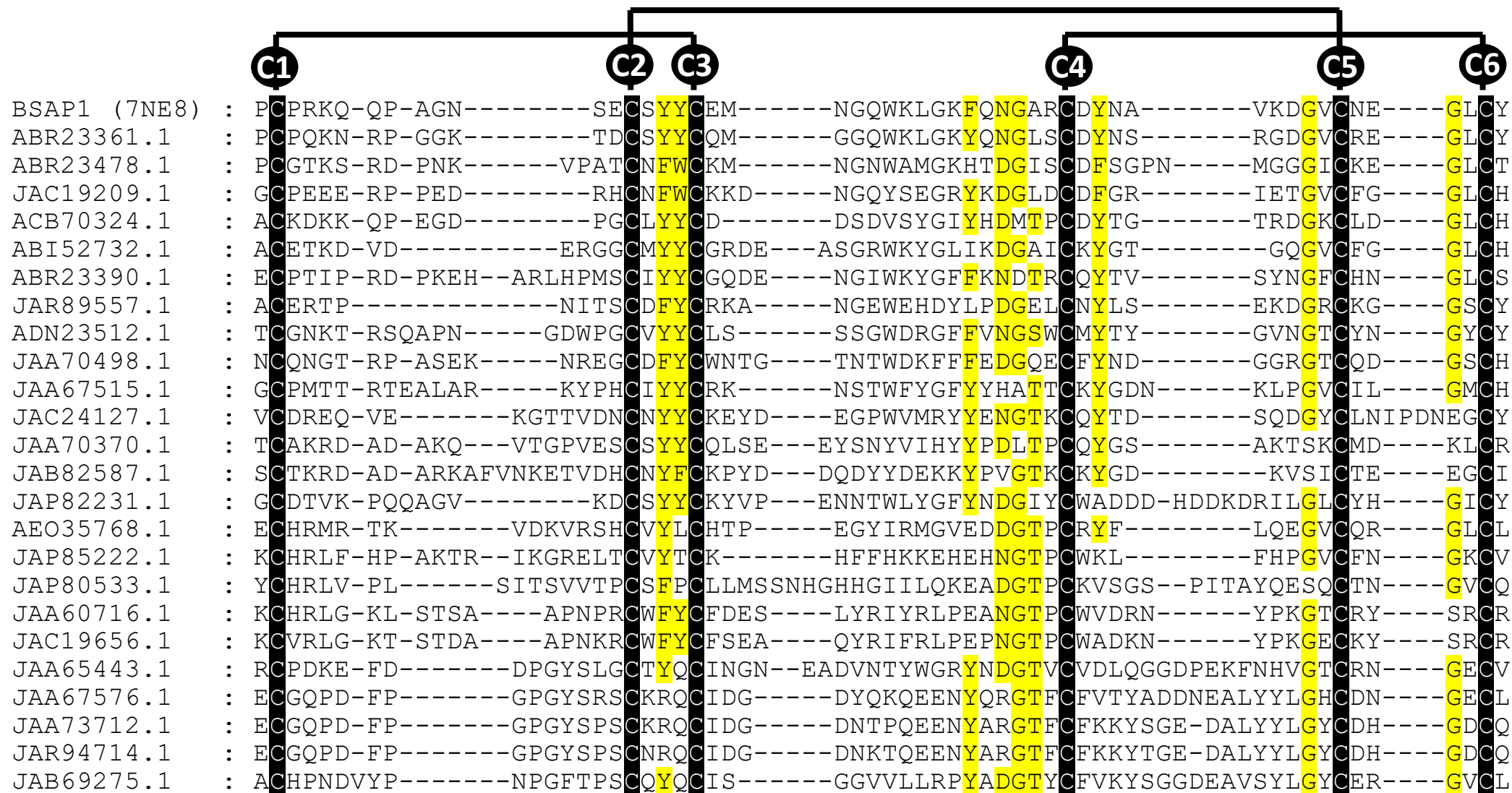


Figure S28: Alignment of selected members of the BTSP family. The alignment has been trimmed to the core domain. Indicated are the conserved cysteines and their disulphide bond pattern. Conserved residues are highlighted in yellow.

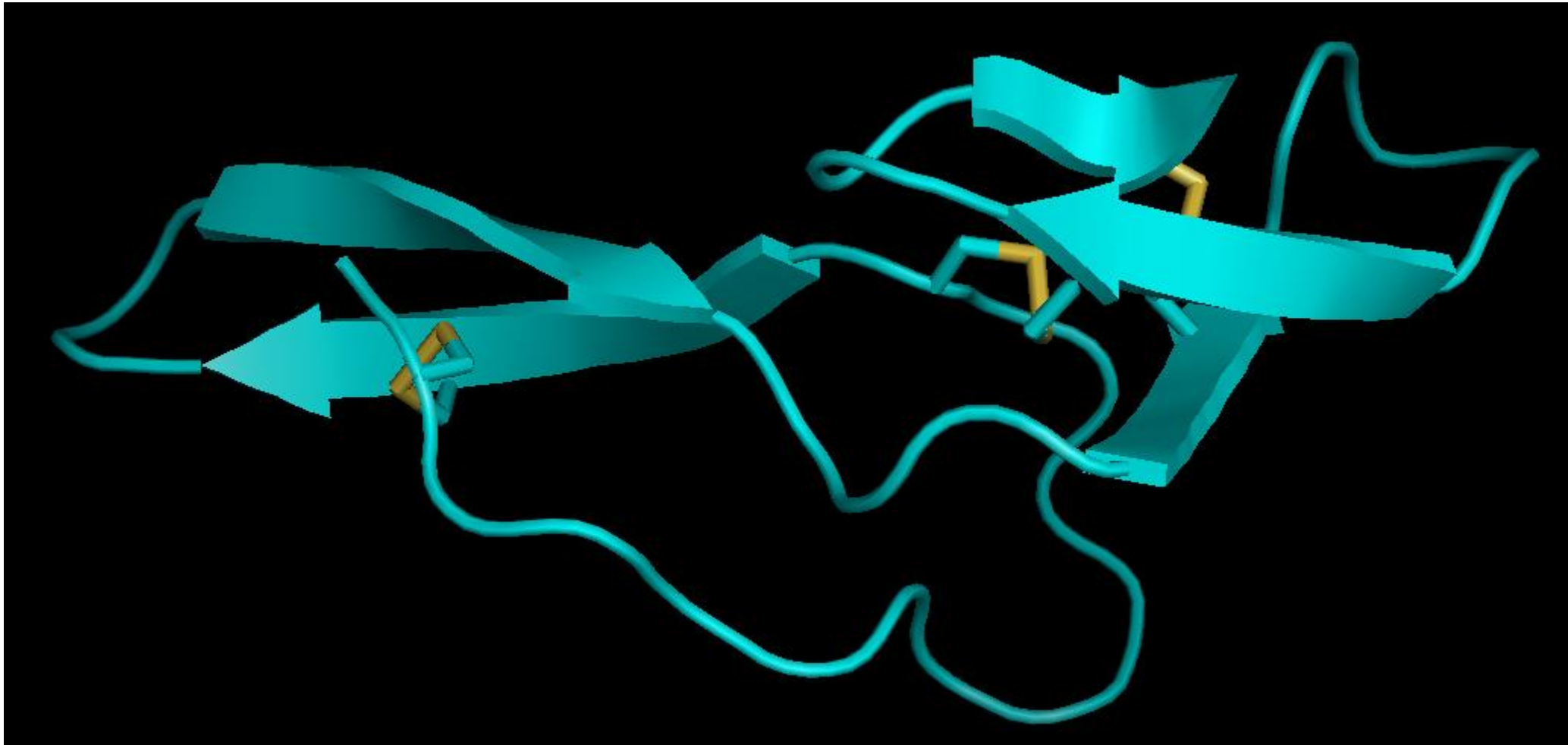


Figure S29: Predicted structure of the BTSP family. Indicated are the central fold composed of two domains, an N-terminal domain (left) composed of two anti-parallel beta-sheets and a C-terminal domain (right) composed of three anti-parallel beta-sheets. Disulphide bonds stabilize the fold by linking the N-terminal to the first domain, while remaining disulphide bonds stabilize the C-terminal domain.

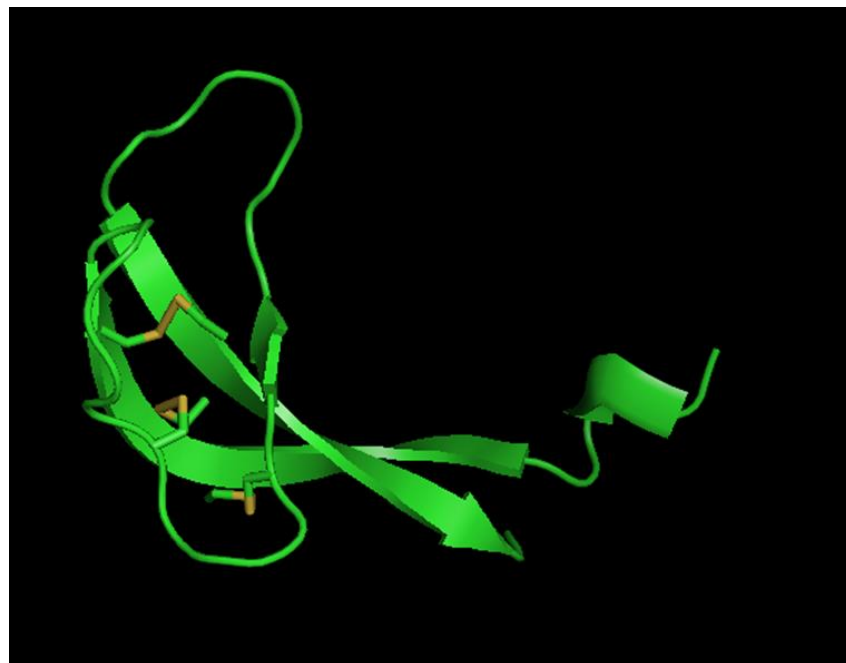
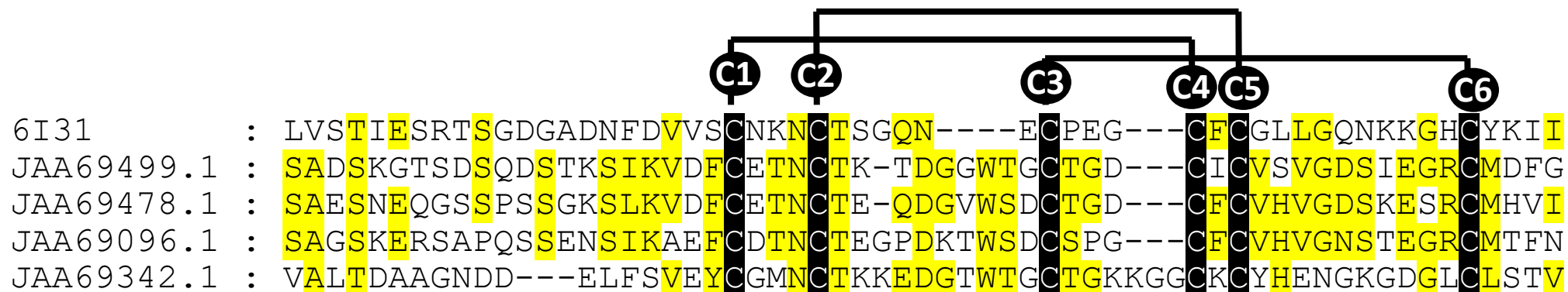


Figure S31: Alignment of selected members of the Evasin B family. Evasin-3 is included (6I3L). Indicated are the conserved cysteines and their disulfide bond pattern. Conserved residues are highlighted in yellow. The alignment was trimmed to represent the core domain. The structure of Evasin-3 with disulfide bonds is also indicated below the alignment.

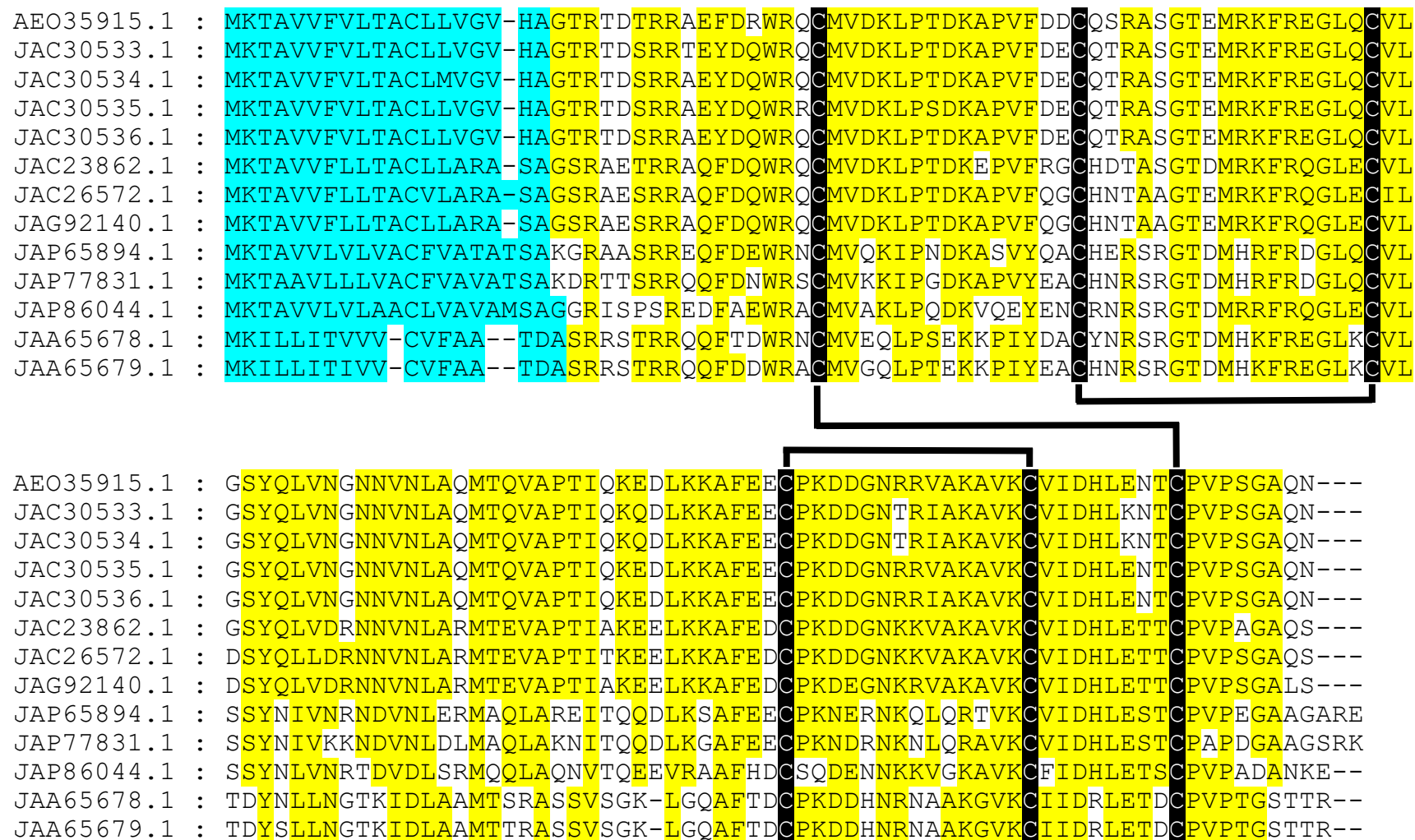


Figure S32. Alignment of the 13kDa-basic family. Conserved residues are highlighted in yellow and the signal peptides in light blue. Conserved cysteines with their predicted disulphide pattern is indicated.

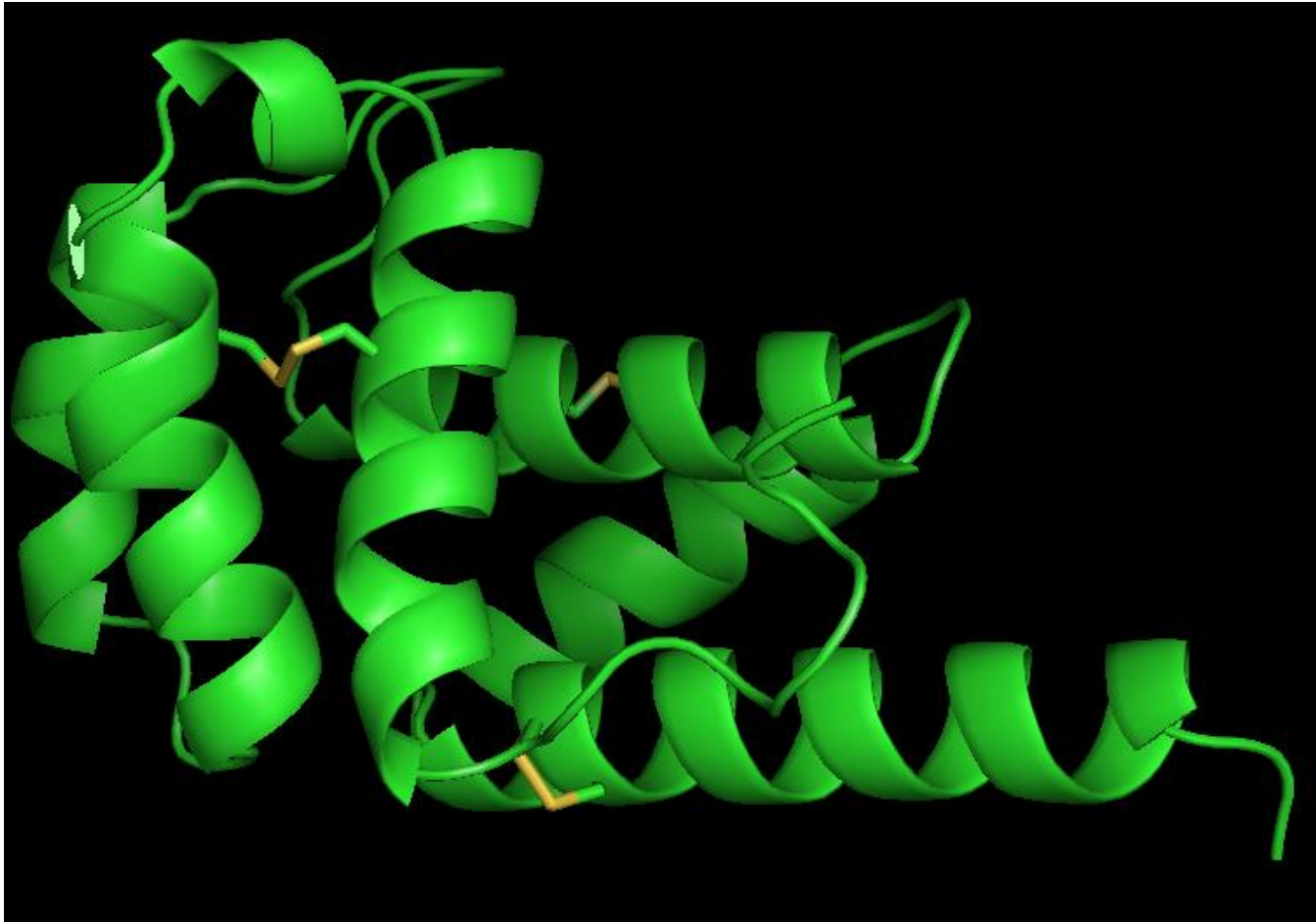


Figure S33. Predicted structure of the 13kDa-basic family. Disulfide bonds are indicated in yellow.

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HBP2_O77421 : -----NQPDWADEAANGAHQDAWKS LKADVENVYVMVKATYKNDP-VWGNDFTCVGVMANDVN-EDEKSIQAEFLFMNADTNMQF---ATEKVTAVKMYGY----- : 92
HBP3_O77422 : -----NPTWANEAKLGSYQDAWKS LQDQNKRYLLAQATQTDDG-VWGEEFTCVSVTAEKIG---KKKLNATILYKNKHLTDLKE---SHETITVWKAYDY----- : 89
SHBP_AAL56644 : ETTSAKAGENPLWAHEELLGKYQDAWKSIDQGVSVTVYLAKTTYENDTGSWGSQFKCLQVQEIERK-EEDYTVTSVFTFRN-ASSPIKY-YNVTETVKAVFQYGYK---- : 103
TSGP4_AAN76831 : -----ANDVWNVLKGS DSKELMVKRTYERGA-----NKCVMKRTSMD-ESSHTLEVLMGYSK-AGTTTDFVEPSKYTVTATSE-GA----- : 74
AM33_ABI52653 : -----ASAVENELPLNVWKAISKGTYYVLIQRSYQKVG-----ATCTYAKIKTKD-QSTHSYTAEMGFTL-NGKKMKN---TYNMYAAKETGK----- : 77
OMCI_2CM4 : -----DSESDCTGSEPVDAFQAFSEGKEA-----YVLVVRSTDPAK-----RDCLKGEPAGEK--QDNTLPVMMTFKQ-GTDWAST--DWTFTL----- : 73
TSGP2_AAN76829 : -----DCPTGKPTDAYVAFNEGQGA-----YILVKSTD LLD-----RDCLKGSATGKK--EGNKVPVMAAFKN-EGQWVSL--PWTFTL----- : 69
TSGP3_AAN76830 : -----DCPTGKPTDAYVAFNEGKGA-----YILVVRSTNLNA-----RDCLKGATGKK--EGNTLPVMAAFKD-EGKWVSL--PWTFTL----- : 69
Moubatin_A46618 : -----QSGCSVSDPLDALKA FKDGAGT-----YLLQKSTDPA-----RDCLKGT PGNR--DGNTLPVTMTYKD-DSKWVSL--NWMFTL----- : 71
Monotonin_ABI52654 : -----SAPCNFNGPFQAWRSVNGPGSGG-----YYMVKT TDPQT-----PDCPYVLVPRTRLTEGDAVEFTYGSLE-DGELTRR--TATVSG----- : 74
Monomine_ABI52634 : -----QQQCDTVSAWQSLRPGTGG-----YYLFKTTTEGGK-----TDCTYVKGSNFN-DAAQTATYTYGNLGSNGQLTQQ--TASASI----- : 71
TSGP1_AAN76828 : -----GPDGCVGSTEAKVAVFEGEGNAGSPTIGYSYLVKTTYPDE-----HACVYILPPYGTADASGRYPYRMGYKDSNDQWVKL--DGKIKT----- : 81
CirpA1_7B2D : ---EDQETDFSSTDGAELIAKEPEVYPIDQFMNTEIWWFNTTQPDP-----PNCKKDKSKSMT-QTATSFVRSHVK---NGNIIENLVGNFTYFNDKE----- : 88
Japanin_AGF70149 : -----TPSMPAINTQTLLYLAGHSSKL--FERNVGCVKTRYLNQT-GDWVTRSLIYVETFDTEPWVTQ--AGAFQV---KWEFYSPLLR : 75

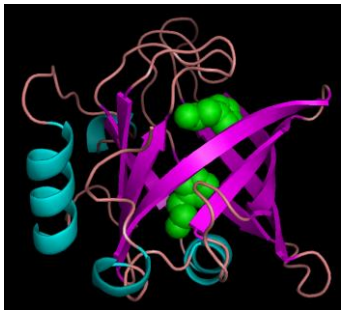
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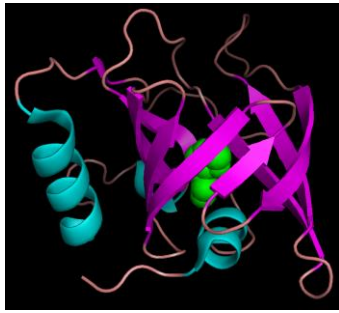
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HBP3_O77422 : -TTENGIKYETQGT-----RTQTFEDVFVFS-DYKNCDVIFVPKERGSDEG----DYELWVSEDKIDKIP-----DCCKFTMAYFAQQQEKTVRNVTDSCKPAPAQN- : 182
SHBP_AAL56644 : -NIRNAIEYQVGG-----GLNITDTLIFT-DGELCDVFYVPNAD---QG---CELWVKKSHYKHVP-----DYCTFVNVFCADRK-TYDIEN-ECVYNGEPWL : 189
TSGP4_AAN76831 : -STYNMMTVRRGPAS----HGVK-FE-LVYS-DDQGCN LQMKTSP--FPG--KCELWAPEGKAKNVE-----SSCSGKEKELCGDA--VETPYA-EGCRVP----- : 156
AM33_ABI52653 : -NTRNVLSISSKPLTDPL-QGEL-YF-LIYR-DGKGCN LFAQNKTTTRKDL--ECMWEKKNVADNIS-----EDCKHYNDRCMAV--VETHYS-KACKIP----- : 164
OMCI_2CM4 : -DGAKVTATL-GQ-----LTQN-RE-VVYDSQSHHCHVDKVEKEVPD-----YEMWMLDAGGLEVE-----VECCRQKLEELASGRN--QMYPHL-KDC----- : 150
TSGP2_AAN76829 : -DGPKVTATD-GQ-----RTLK-RE-VVYDVASHHCHVEKLASGA-----YEMWMLEAGGLEVD-----IECNKKYDELTSQGV--VIRPQD-KDC----- : 144
TSGP3_AAN76830 : -DGPKVTATH-GQ-----RTLK-GE-VVYDVPSHHCHIEKLES GA-----YDMWMLEAGGLEVD-----IECNKRYDELTSQGV--VIRPQD-KDC----- : 144
Moubatin_A46618 : -EGANIVATLEGK-----RKQR-GE-LVYDVQSHDCHITKLSSGV-----YQQWQSNGSADDDK-----IKCCDEKFKELTSGID--YTKPQE-KCETS AK--- : 152
Monotonin_ABI52654 : -QGSNIVVTGGDNPG-----TTTLIFS-DYQTCDDVVRGPTGG-----YELWVHADNVHDSS---HGCCDTKFYQVTGGNG--IRDVYQ-ETCPPLPTQ-- : 154
Monomine_ABI52634 : -SG-NAIVVGTDH-----SE-VLYS-DGSTCDVVR LINGQ-----IELWIHSSATSNTGN--LNSCCTDKENQEGSRP--EHVVYR-STCPNL PQ--- : 147
TSGP1_AAN76828 : -EGSKIIDNDPEY-----GDTVTT-VLYTHLGGGCDVTLFEGQKGQSKVQGPFLLELWYHSGASEESM-----RCCEEEERKNLKEGTA-VRKVN--KNCDYGDVA-- : 171
CirpA1_7B2D : -KVYDGIYISGES-----SGVY-AEHLIYVSEDKKGLFQVFAHVND-----KTTIWRDVRVSRPEEGVPLELNTKEDEYVKLVNATSKSPYT-SECQ----- : 176
Japanin_AGF70149 : VKASDYVRDNLGAKPDYFIRTYD-NDFLILS-DLKEV-----RSTCSLWVTLKYVDRI P-----ETINRTYITICPDP--VPVPFD-ERCYP----- : 152

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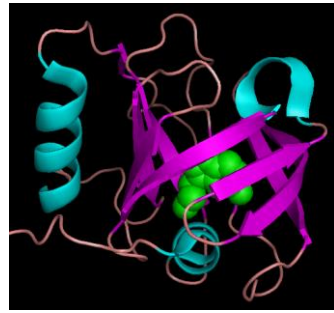
Figure S34. Alignment of lipocalins for which structures and/or functions has been determined. Indicated are conserved disulfide bonds. Also indicated are the names and accession numbers of the proteins. Functions include histamine and serotonin binding (HBP1, HBP2, HBP3, SHBP, Monomine, Monotonin, TSGP1), leukotriene B4 scavenging (OMCI, TSGP2, TSGP3, moubatin), complement inhibition (OMCI, CirpA1), leukotriene C4 scavenging (AM-33, TSGP4) and cholesterol binding and immune regulation (Japanin).



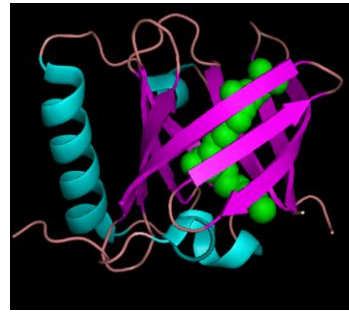
HBP1
Histamine



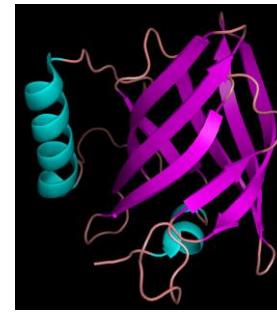
Monomine
Histamine



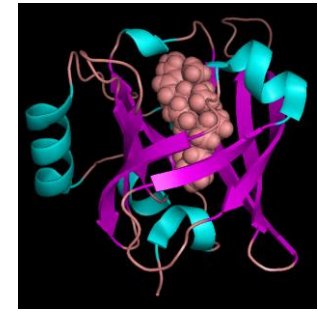
Monotonin
Serotonin



OMCI
Leukotriene B4
Complement C5

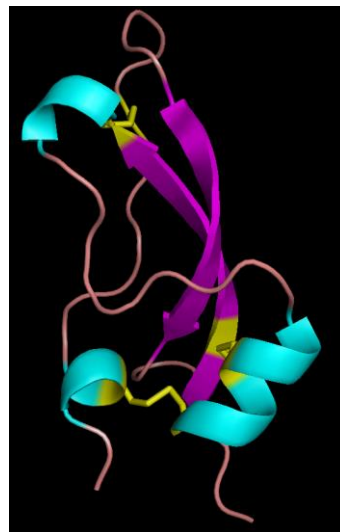
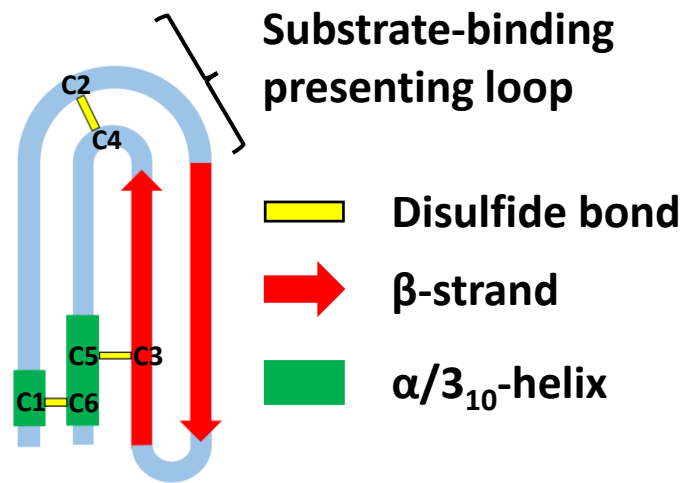


Cirp1
Properdin

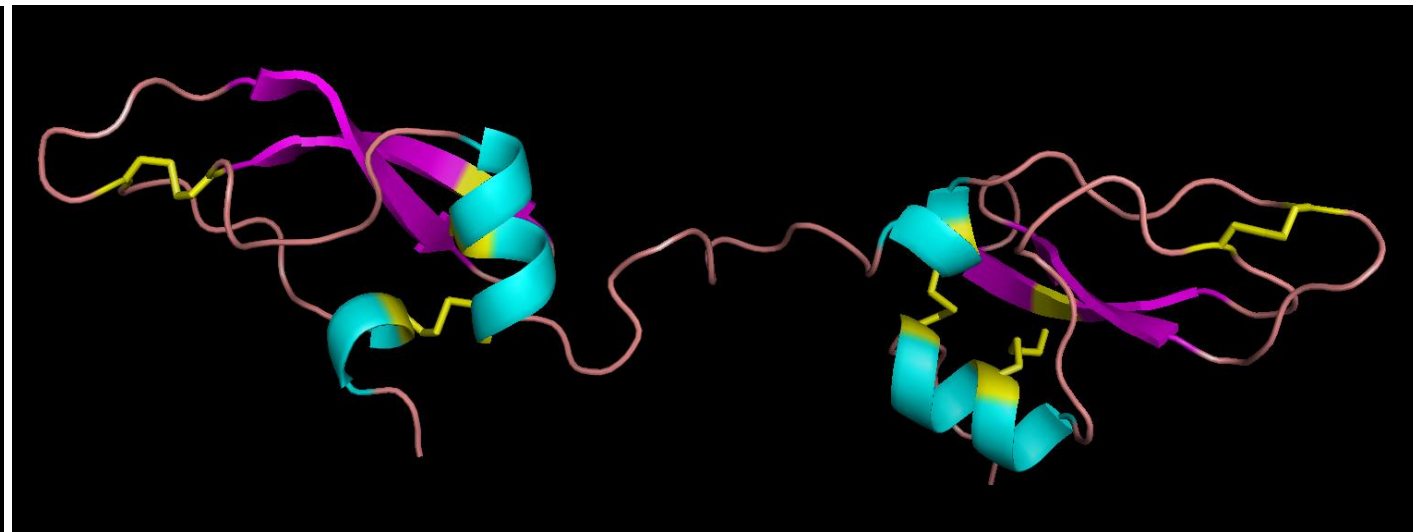


Japanin
Dendritic cells
Cholesterol

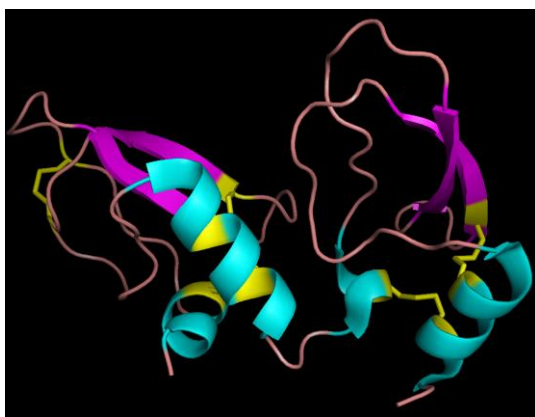
Figure S35: Structures for lipocalins whose functions has been determined. Indicated are the names of the proteins. Ligands scavenged or functions are indicated below names.



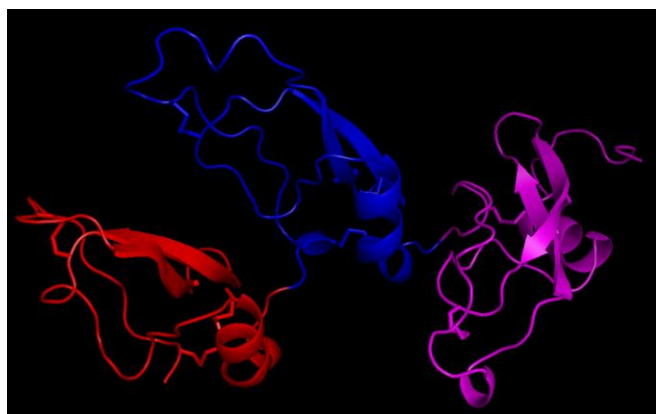
Savignygrin



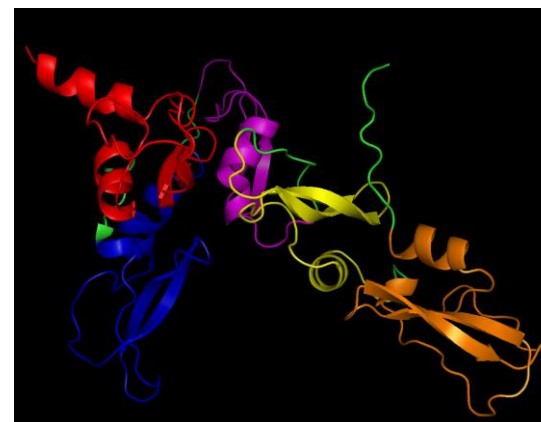
Ornithodorin (double-domain)



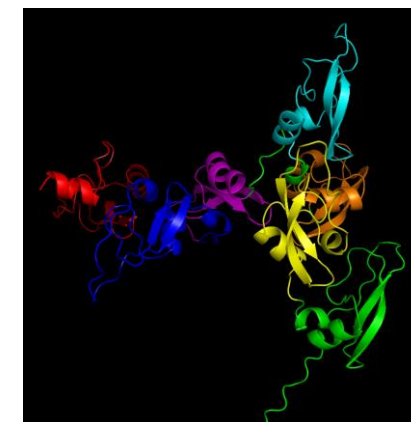
Ixolaris (double-domain)



Four domain



Penthalaris (Five domain)



Seven-domain

Figure S36: Summary of the Kunitz-BPTI fold. Top left indicate a schematic representation of the secondary structure, disulfide bonds and substrate-binding presenting loop. Also indicated are representatives for single, double-domain (ornithodorin-like), double-domain (bikunin-like), three-domain, five-domain and seven-domain models. For the single and double domain proteins, secondary structure is colored, while for the four, five and seven domain proteins, domains are colored individually.

JAA66710.1	MNIFIVCIVI	ANVVISQSNV	EEAGKTNFEI	QEQSLLIFDH	HEKYLGYK.	MQNGEEKKLT	DPEVFWTDLA	NQTQLLVQGC
JAA66714.1	MNIIIVCIVI	ANVVISQGNV	EEAGKTNFEI	QEQSLLVYDH	REKYLGYK.	MKNGEVKTLO	TPKVKWTLA	NQTQLLVQGC
JAA69601.1	MNIIIVCIVI	ANVVISYGNV	EEAGKTEHEI	QAQSLLIFDQ	QEGYLGYT.	MKNGEVKNLS	NPEVVRWTLA	NESQLLVQGC
JAA69608.1	MNIIIVCIVI	ANVVISQGNV	KEDGKTDSEV	QEQSLLVYDR	QEKYLGHK.	MQNGEVKTLO	NPEVKLTDLA	NQTQLLVQGC
JAA69610.1	MNIIIVCIVI	ANVVISQGNV	KENGKLLYKI	QEQSLVIYDH	REKYLGYR.	MHNGEVKELS	DPEVFWTDLA	TQSQLLVQGC
JAA69611.1	MNIIIVCIVI	ANVVISQGNV	KEAGKTNSEI	QEQSLLVYDR	QEKYLGYK.	MKNGEVKTLO	NPEVFWTDLA	NQTQLLVQRC
JAA71455.1	MNIIIVCIVI	ANVVISQGNV	EEAGRTNSEI	QERSLLIFDH	QEKYLGYK.	MKNGEVKELT	DPEVFWTDLA	NQTQLLVQGC
JAA72383.1	MNIIIVCIVI	ANVVISHGNV	EEAGKNEYEI	QAQSLLIFDQ	QEGYLGYT.	MKNGEVKNLS	DPEVFWTDLA	NQSQLLVQGC
JAB69725.1	MNIIIVCIVI	ANVVISQSNV	KEAGKTDSEI	QEQSLRVYDR	QEKYLGYR.	MKNGEVTLE	NPEVRLTDLA	NQTQLLVQRC
JAB70273.1	MNIIIVCIVI	VHVVISQGNV	EEAGKSRYKI	QEQSLVVDH	QVKYLGYQ.	MHNGEVKELL	VPEVFWTDLA	TQSQLLVQGC
JAB71105.1	MNIIACILI	ANVVISQGNV	KENGKSRYKI	QEQSLLIYDN	QEKYLGYK.	MKNGEVKELS	DPEVFWTDLA	TQSQLLVQGC
JAB71107.1	MNIIIVCIVI	ANVVISQGNV	KEAEKTNSEI	QEQSLLVYDR	QEKYLGYKN	AKRRSKKVL	DPEVFWTDLA	NQAQLLVQGC

Figure S37A: Amino acid sequence alignment of *Ixodes ricinus* four-cysteine 8.9 kDa family members. Conserved cysteine residues are highlighted in black.

CAJ20018.1	..MRKIVLLA	VIALGGVSLI	LGDTNHRHPY	G....VSFEN	GTGKYRDQTL	ENGGFETFQY	PEELWIDNVT	AKTILTVFGIS	VR....RYGS	..IHEHNPDYY
JAA65306.1	..MLFPAALV	LGLAAFFSVW	KVSQAAPPFS	D....VVIVD	GKATYGNHSV	AHGESLTWAD	PEQIWEENVE	ERSFGVLPNG	LVA...IPAG	..EMVRGTGP
JAA66153.1	..MKLPTALL	LGLVVSVSIF	KVSLAEPFES	D....VEIVD	GKATYGNYSV	ADGERLNLAD	PEQTWQEEVK	ERRFSVLSNG	YVI...KPSN	..ELERGTGV
JAA66164.1	..MRTIVLLA	VIALGGVSLI	TGDANHHHLY	G....VSFEE	GKATYRNQTL	KDGGSETFQF	PEEQWIDNVT	AKTVTIHGN	VA....SYGS	..MVPVHYPIYY
JAA68879.1	..MKLPTALL	LGLMVSTSIL	EISLAEPPTS	D....VKIVD	GKATYGNHSV	ADGEQLNLAD	PEQTWQEEVK	EKRFSVLSNG	YVF...NPAI	..ELRRGSGV
JAA68924.1	.MKGILAAFT	LVCVLAQQTF	GAGQAEVTSS	NRDGSLLTDQ	GTGYYRGMNI	PNGQTVKLSN	PEQWTEIST	AQKVTVNGW	APR...NYGD	..PSHFKEGE
JAA68936.1	MNSKELVGAV	LVLICIGAA	TSAAVFVQP.	VDVKN	KGIWKYVI	PDGGHLNLAN	PEISLTDAK	LEYLRGASG	RIAHEGIPKN	..TLGKGKGI
JAA68957.1	.MHAFPAIV	S..AGLLLLS	RCSDGYTGKS	E....ASIQD	GKATYQGVET	AHNRTAHNVS	PEESWTEQVN	EGTVHIVGIV	TWG...APEN	..LLEKKIKP

CAJ20018.1	WPRCCPGRPI	
JAA65306.1	YPCCTY.RAV	
JAA66153.1	YPCCTY.RTK	
JAA66164.1	WPGCCPRRMI	
JAA68879.1	YPCCTD.RVF	CPGIPL...
JAA68924.1	YPCCTP.GIL	
JAA68936.1	YPCCTQTLT	CH.....
JAA68957.1	HPGCTP.KVV	PPVRT....

Figure S37B: Amino acid sequence alignment of *I. ricinus* eight-cysteine 8.9 kDa family members.

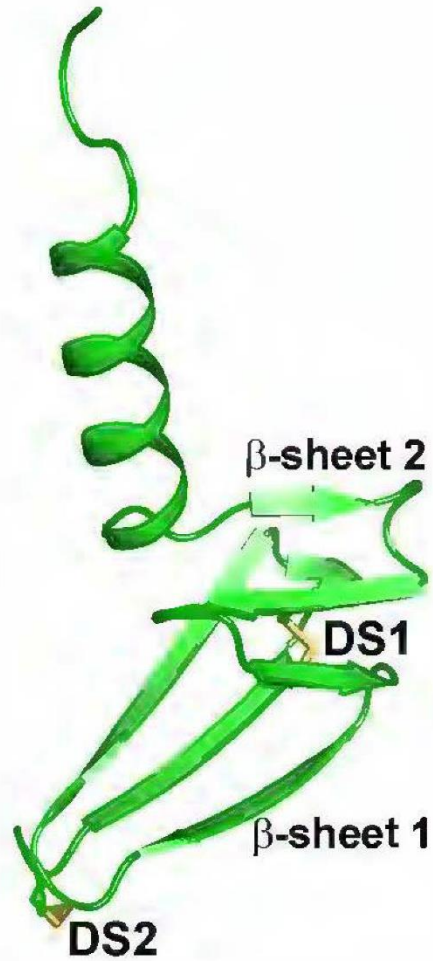
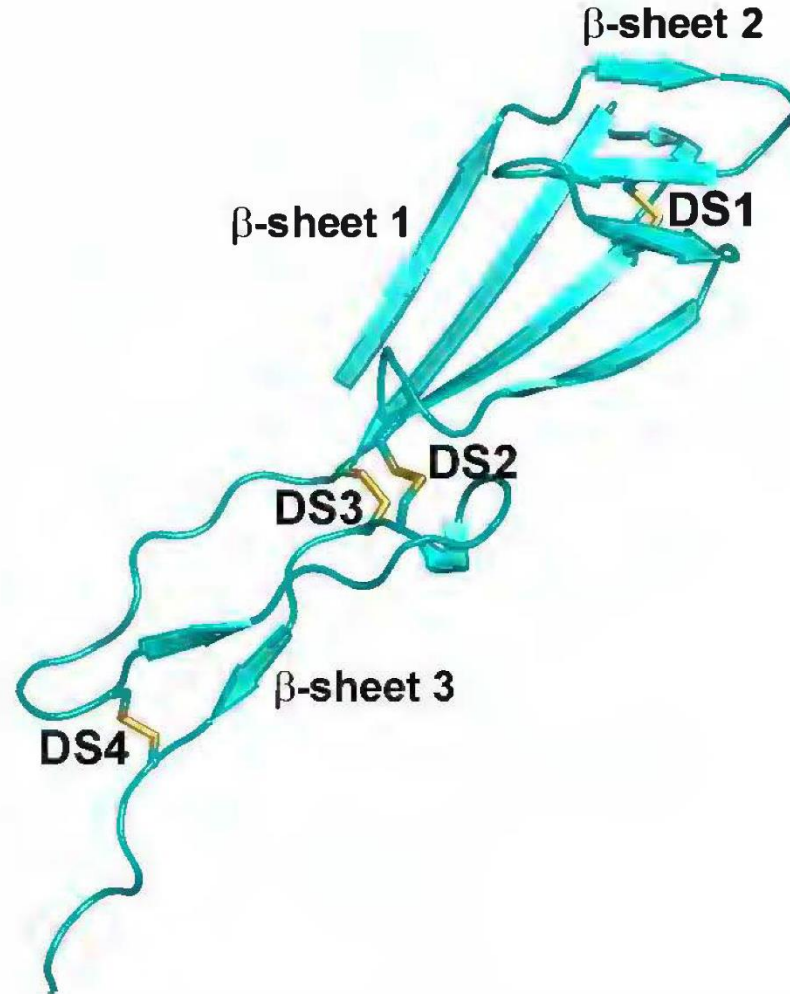
A**B**

Figure S38: Structural models of four- (A) and eight- (B) cysteine 8.9 kDa family members from *Ixodes ricinus*. Cysteine side chains are shown as sticks with sulfur atoms colored yellow. Beta sheet structures described in the text are labeled.

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AEO35217.1 ...MKKVPML LLIFGAEVAM ATRFSMMRDE SLHCQDGECCF FRGYEVKVGVV PVSMEKPCEEQ WNRRESVEYPP EVFVK.GCDM KIVSERTLPE .YIEQDESNL
AEO35215.1 ...MKKVSVL LFVFGVEVAI ATRFSMMRDE SLHCQDGECCF FRGYEVKVGVV PVDMENPCEEE WNRQKSVQYPP EVFVK.GCDV KIVSERTLPK .HIDQNESNL
AEO35216.1 ...MKKVPML LLIFGAEVAM ATRFSMMRDE SLHCQDGECCF FRGYEVKVGVV SVEMEKPCEEE WDLQKSEQYPP EVFVK.GCDG KVVSERTLPK .YIDQNETNV
AEO36432.1 MASVCKAIKL IVLFGPLCLT SGVKYVSKQY ALTFEDGCCK FEGLNMPYGG EGFLFG.CVF LKCCDYEN..K TVTMY.GCPP ...PPYVLPL SDYGADSNDI
AEO36553.1 .....MNIL FFVICLLCPV YTTL.YNTDD DQRVDGKACV IGPLSLSAGD TRYSNRPCVVK AQCIANP..PP QLIIT.GCSA DGVNDYTLS. ...EGKNIVV
AEO36758.1 .....MHTL LLCLAIFLTL AVIYCDGKKN GGKSK.GNCE YGDRTIPNGQ SRNLQNPCVK VKCNDGT..PP TVTECPGASV K.LEERRRGK .RSGKRKEGV

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AEO35217.1 WPKCCKK... .
AEO35215.1 WPFCCCQK... .
AEO35216.1 WPSCCCQK... .
AEO36432.1 WPNCCCPGYEV E
AEO36553.1 WPGCCCDRDD. .
AEO36758.1 FPQCCEEDSS .

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Figure S39A: Amino acid sequence alignment of *Amblyomma maculatum* six-cysteine forms having two alternative disulfide bonding patterns

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AEO35167.1 ....MSMLVA LLCTLASFTL IICGTPDVVG RTYVVKNVKV IN.GSCIYVG NQIPDGEQKS LHYPCENVTC NAEEREVTAV MCKDFGVGDG CTLKLINEGV
AEO35493.1 ....MMQLMV LSFVLLHSM GAT...HAE VFNSTGSLVF VN.GTCWYNG LKIDDDTYQS FKKPCSQLWC SASKGYLTFY GCMRPLEKPY CGVP..VDQV
AEO35708.1 ....MRIIVA SLCALVVFAT VICDIQEH.G QSYLTRNVTI VD.GSCIFER NTLPDGETKA LHEPCVIATC YAERREVNAT CCRNFGVDPG CRVHWTPDGV
AEO35865.1 MLEVKKLSTS KDMLTFLIT ITLGAHIVDG EDVEVSSLLF VN.GTCLYRN VQLSDGESQA QNEPCENWTC DNKNKRLKVQ GCNLENKYGS CVYTNSGRRT
AEO35866.1 MLEVKKLSTS KDMLRFLLIA ITLGAHIVDG EDVEVSSLLF VN.DTCHYRD TVISDGESQA QYEPCENWTC DISKKHLKVQ GCNLEDKYGS CVYTNRGTWP
AEO35932.1 ....MCSKLS LAVYAIVAVT GTLWH..ISE AYSGQVHVEV LN.GTCIYAN RTLGHRSIQ LKEPCEGWYC DANRRIIFVG WCSPVALLGH CRTVK.GNGT

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AEO35167.1 FPACCP..RQ ECPDGKKTV
AEO35493.1 YPKCCS.YTR TC.....
AEO35708.1 YPECCP..RQ VCDRTD...
AEO35865.1 WPYCCRY.ER TC.....
AEO35866.1 WPYCCSY.QR TC.....
AEO35932.1 YPNCCP..RM VCN.....

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Figure S39B: Amino acid sequence alignment of *A. maculatum* eight cysteine forms

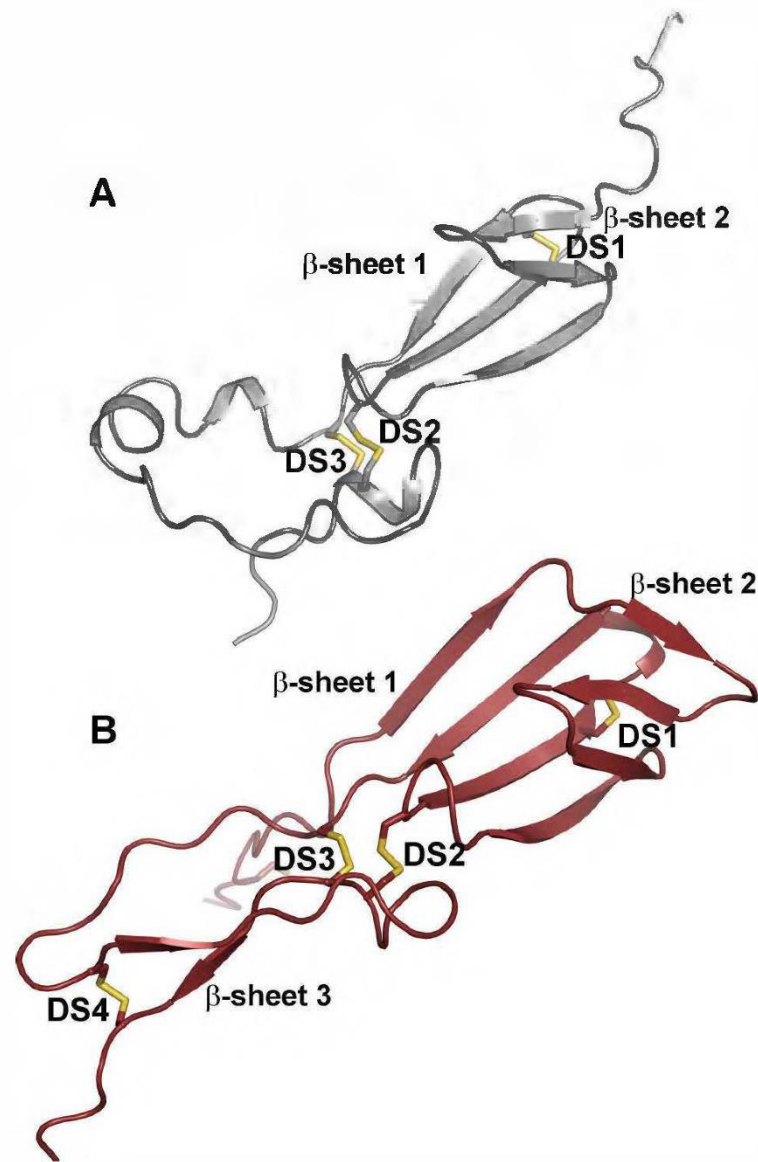


Figure S40: Six- (A) and eight- (B) cysteine 8.9 kDa family members from *Amblyomma maculatum*. Cysteine side chains are shown as sticks with sulfur colored yellow. Disulfide bonds are labeled (DS). Beta sheet structures are labeled as in the text.

AE035686.1	...MLVRALL	CGLILPMANS	FDS..SDLNI	LTVS.VTMEG	GK..CVYKNH	TFPSYYDPSG	DNCELWTCNK	PKHTVSVMGC	SPLPPGQERK	PKANSTFPKC	16 Cys
AE036153.1	MCTMLHYLLF	CGIVLLVLHN	HGS..SGLKL	VEVSSVKVEN	GN..CVYGSV	SFPTYFQTNG	SLCEDWTCEP	KKHTLTIVGC	SPPRPGCRRN	TSVDLRFPCV	
AE036311.1	...MFASVLL	FGCISHLVDC	ASN..SDMKI	VVAT.ATVVG	DK..CVYKDK	TFSSIFVPDA	PVCEQWTCDE	KRGTVNILGC	SDPSPGQTRI	ASGGAKEFPC	
AE036678.1	MRNRGSNILP	CAMLSLLSLG	RANILENVKY	VYVQNVKVE	IKHTCEYRNY	TFNSTLVLT	.POMSLECYW	RKQEVVISEC	KQPKRNCVQR	PSEGKVFPEC	
AE036727.1	...MLQRILL	FGLALELATS	FDN..SDLKT	WLAT.VQMDG	DK..CIYRNY	TFALYYNPKE	.ACEDWTCNK	REKTVSVVGC	SDPPTGCIRN	ASSDAAFPEC	
AE036739.1	...MLLCGLL	SALLLVPR	RAEDVSNVKQ	VEIKNPQLDK	GY..CAYHTS	AFNGAILPSG	.LCERWTCKY	NEGKILKEEC	KALEHCCNR	SNPKARFPEC	12 Cys
AE036783.1	...MLAFPLL	GALLAWLCLP	SVEGIHSIRR	IISTSPNIPK	GI..CVHYPY	FINGTLTVPG	.ECRTLTQYY	HQGQVLIIEC	QPLEHDCQR	VNSSAPFPEC	
AE036784.1	...MLAFPLL	GALLAWLCLL	SVEGIHSIRR	IIATSPNIPK	GI..CVHYPY	FINGTLTVPG	.ECRTLTQYY	HQGQVLIIEC	QPLEHDCQR	VNSSAPFPEC	
AE036785.1	...MRAFTLL	GALLAWLSHR	PVEGIHNLRR	ITVSNPNIPR	GI..CAYYPY	FINGTLDPG	.KQCKLTQYY	RQGRIEIEEC	QLEHGCVR	VKPDAAFPEC	
AE036864.1	...MLLCGLL	ITLLLVPLS	RAEDVSNVKQ	VEIQNPQLDK	GY..CAYHTT	AFNGAIIPPE	.ACERWTCKS	NEGKILKEEC	KELEHGCER	KNPKAKFPEC	
AE036918.1	...MNRVMAI	MSILLRLAHA	QAP..EDLEK	VEFTNVTLHE	DEY..CEYKNS	TFRNKEVEAA	PVCKTITCLH	SQKVRISEC	APLKPGCERD	PEPMSFYPEC	
AE035686.1	CEKSCVRLTD	ATCTTPNNIL	LADGQAYNST	DP..CVRYPE	NNKTITTVR	CS.EPP...P	GCTRDSTRSS	YGYPTCCETR	..CVETASP		16 Cys
AE036153.1	CEKSCVRLTD	ATCTTPNNIL	LADGQAYNST	DP..CVRYPE	NNKTITTVR	CS.EPP...P	GCTRDSTRSS	YGYPTCCETR	..CVETASP		
AE036311.1	CEKSCVRLTD	ATCTTPNNIL	LADGQAYNST	DP..CVRYPE	NNKTITTVR	CS.EPP...P	GCTRDSTRSS	YGYPTCCETR	..CVETASP		
AE036678.1	CEKSCVRLTD	ATCTTPNNIL	LADGQAYNST	DP..CVRYPE	NNKTITTVR	CS.EPP...P	GCTRDSTRSS	YGYPTCCETR	..CVETASP		
AE036727.1	CEKSCVRLTD	ATCTTPNNIL	LADGQAYNST	DP..CVRYPE	NNKTITTVR	CS.EPP...P	GCTRDSTRSS	YGYPTCCETR	..CVETASP		
AE036739.1	CEKSCVRLTD	ATCTTPNNIL	LADGQAYNST	DP..CVRYPE	NNKTITTVR	CS.EPP...P	GCTRDSTRSS	YGYPTCCETR	..CVETASP		12 Cys
AE036783.1	CEKSCVRLTD	ATCTTPNNIL	LADGQAYNST	DP..CVRYPE	NNKTITTVR	CS.EPP...P	GCTRDSTRSS	YGYPTCCETR	..CVETASP		
AE036784.1	CEKSCVRLTD	ATCTTPNNIL	LADGQAYNST	DP..CVRYPE	NNKTITTVR	CS.EPP...P	GCTRDSTRSS	YGYPTCCETR	..CVETASP		
AE036785.1	CEKSCVRLTD	ATCTTPNNIL	LADGQAYNST	DP..CVRYPE	NNKTITTVR	CS.EPP...P	GCTRDSTRSS	YGYPTCCETR	..CVETASP		
AE036864.1	CEKSCVRLTD	ATCTTPNNIL	LADGQAYNST	DP..CVRYPE	NNKTITTVR	CS.EPP...P	GCTRDSTRSS	YGYPTCCETR	..CVETASP		
AE036918.1	CEKSCVRLTD	ATCTTPNNIL	LADGQAYNST	DP..CVRYPE	NNKTITTVR	CS.EPP...P	GCTRDSTRSS	YGYPTCCETR	..CVETASP		
AE035686.1	KNRKRKRSSE	KNL									
AE036153.1	..KRRRR...	...									
AE036311.1	...GRF....	...									
AE036678.1		...									
AE036727.1	...PEALANK	PG.									
AE036739.1		...									
AE036783.1		...									
AE036784.1		...									
AE036785.1		...									
AE036864.1		...									
AE036918.1		...									

Figure S41: Amino acid sequence alignments of *A. maculatum* twelve- and sixteen-cysteine 8.9 kDa family members.

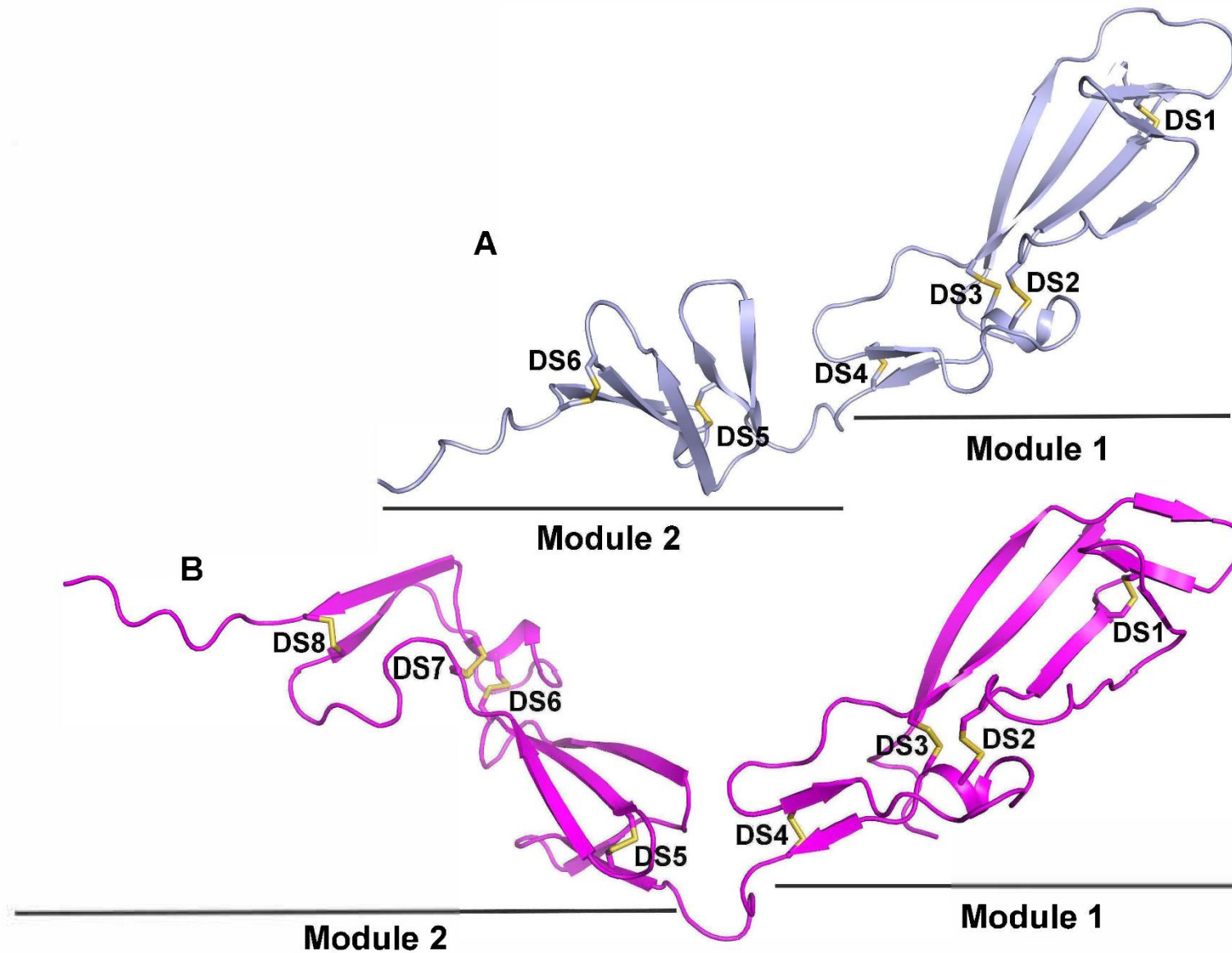


Figure S42: Structural models of *A. maculatum* twelve- (A) and sixteen- (B) cysteine forms. Cysteine side chains are shown as sticks with sulfur atoms colored in yellow. Disulfide bonds are labeled DS. Repeated modules are indicated by bars under the models.

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JAP77261.1 .MSTALVILF AACAAASVVGQ FYDPCPQRE HRHG C DFLG RIIGRGLTVS LRI C LRV C HPDGS.VTSI GCPREAG.SN PHPGAPPTR. .GVWCC DM
JAP77703.1 MKCLFAAIVV LLIVSLLRRS FA.IKCPARF DRQGCH VFG LTVPRGHTVA VPNPCV SV C NHNG.HMLVK GCINFAGNME VHPGSPDEAR VLPYCC PR
JAP80461.1 MKYSLLVISL VAYVAVVKC.VF...CPARF ANGR C FIFG RVILDGLAWT FNNPCV QV C NYHGRTITIK GCPGNE.... .AP.GAP.QP MNRYCC HN
JAP84679.1 MKLSAALLIL VASFSAKRR PG.ITCPARH TPVG C FFLG HFIPAGESSA SWNPCV FV C SRNGQTVSIT GCPVAE.PR QHAASAPTTL PQGYCC ER
JAP84931.1 MNIPAVGILL AVQVALVMTQ V...QCPVRY GQRG C TAFG QTIPAAGSAN LRNPCV HV C SANRHRVTVT GCQDVAG.LN QHPPGAPGGP WGDWPC SR
JAP86317.1 MMISALAILF SAWAALVLCQ YYDPCPVRN HPIC C QFMG RLLFPDTSQL WRLPCLIVSC AVDGS.VTTQ GCPRTTG.RN PHPGAAPGP. .GVWCC DM
JAP85507.1 .MTTALVILF AACAAASVVGQ FYDPCPQRE HRHG C DFLG RIIGRGLTVS LRI C LRVTC HPDGS.VTSI GCPREAG.SN PHPGAPPTR. .GVWCC DM
JAP85780.1 MKMLTVALAL ISLSVLVACH IR.. C PVRS VRGA CW YDG RLYPAGSHVS SINPCA FIT C SHTGQTLTIT GCPGTAG.GD EHPPGAAGVP LLFYPC SR

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JAP77261.1 C G.....
JAP77703.1 C GPAPRFR
JAP80461.1 CD IL....
JAP84679.1 C RPV....
JAP84931.1 C PALPRG.
JAP86317.1 C S.....
JAP85507.1 C G.....
JAP85780.1 C PRIR...

```

Figure S43A: Amino acid sequence alignment of *R. appendiculatus* eight-cysteine 8.9 kDa family members with alternative disulfide bonding pattern. Conserved cysteine residues are highlighted in black.

```

JAP86702.1 ..MMIPVILI CSVLHLFLVF EIVP..GQSV NTYK.VNTTD EGQCH FNGTY YPNGNFSTWE PCYMALCN T ...TARELTL WCN ARRIPG .C LMPKAPKD
JAP77355.1 ....MHTFGA SLFVLVVISV VYADVSEGRH TYVTKNVTVE DGACV YLRNV IPNGETKALN NPCV LSC YA ...ADRKVNS TLCPNIGVDE GCHVEWTPDG
JAP81018.1 ....MTKLLT CFVIFITGTL FQVDI.SWQA LYPD.PSAYR NGKCYFRGGV YKPGENMYDQ PCMKWGC SK INSTSGSMVG VSCGVVASP PCKVTPLTTG
JAP81333.1 ....MTKLRT CLVLFITSVL CLVEV.SWQA .....TPYK EGKCYFEGKF YEPGENIYTK .RCSMWSC IK TNSTHTYMHE KCV RPLVQM GCRRLPGKEG
JAP81374.1 ....MSLVHK CLMVTMSVLC AGCGI.CNGY MGRT.PVEIK NGHCTLDGRT IRVNQSVSLQ DC EEWC DY ...VSKSVVI ACSPTTEAGP DC KMVDGK.G
JAP85717.1 ....MWFRS FLLFTATVVL AEWHA.ANGY VSIA.EVPVE NGECDFNGTK VAPGHPLNLE EC EEWC ST REGQTGHL SI ACGAVGAGA GC RKVKGT.G
JAP86658.1 MSGAVSVLAL CVVATLFIFD PWMAC.GQLV TVIKEVNVTD QGQCH YNGTY YPKGNESTWI PC YMAIC KS ...ARKVLKI IC DAKPVHG .C PLPPVPQD

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JAP86702.1 GYACC V EPI C.....
JAP77355.1 VYPNCCPKHV C PSASATS
JAP81018.1 IYPKCCPRRV C P.....
JAP81333.1 IYPKCCPRFL C P.....
JAP81374.1 DYPDCCPQML C Y.....
JAP85717.1 VYPDCCEKVI C D.....
JAP86658.1 GYPACCPEPV C.....

```

Figure S43B: Amino acid sequence alignment of *R. appendiculatus* eight-cysteine 8.9 kDa family members with conventional disulfide bonding pattern. Conserved cysteine residues are highlighted in black.

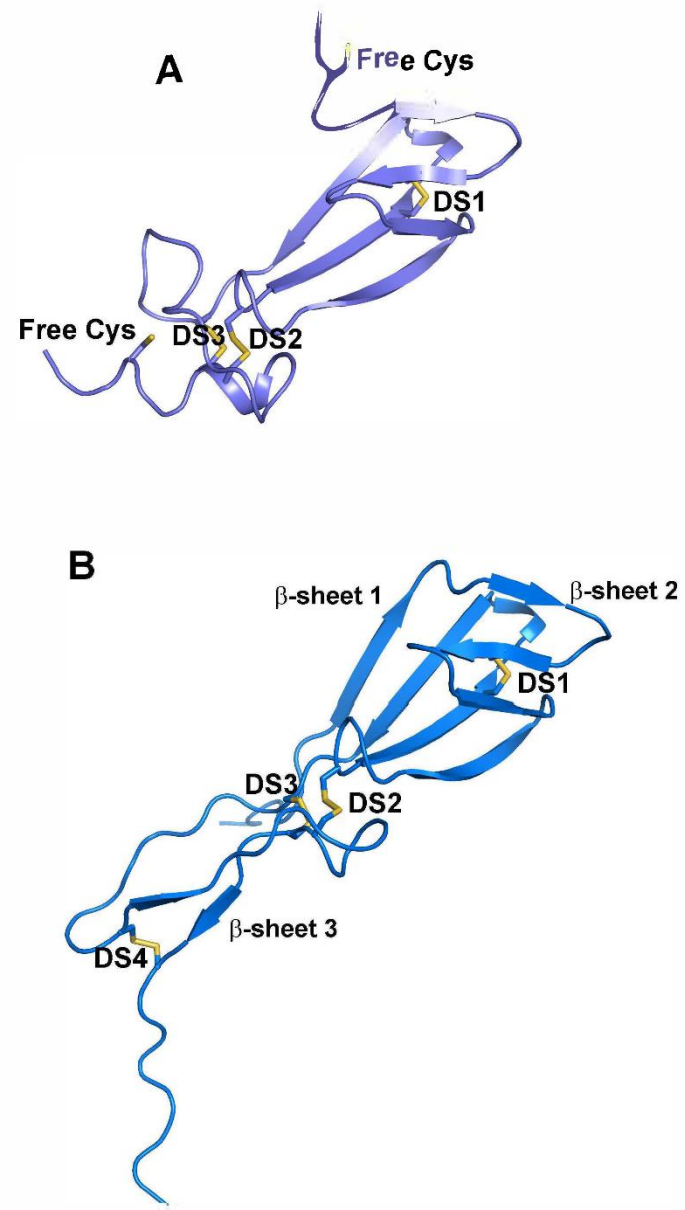


Figure S44: Eight-cysteine cysteine 8.9 kDa family members from *R. appendiculatus* with alternative (A) and standard (B) disulfide bonding pattern. Cysteine side chains are shown as sticks with sulfur colored yellow. Disulfide bonds are labeled (DS). Beta sheet structures are labeled as in the text.

JAP77355.1	MHTFGASLFV	LVVISVVYAD	VSERGHTYVT	KNVTVEDGAC	VYLRNVIPNG	ETKALNNPCV	LSTCYAADRK	VNSTLCPNIG	VDEGCHVEWT	PDGVYPNCCP
AEO35708.1	MRIIVASLCA	LVVFATVICD	IQEHGQSILT	RNVTIVDGSC	IFERNTLPDG	ETKALHEPCV	IATCYAERRE	VNATLCRNFG	VDPGCRVHWT	PDGVYPECCP
AEO35710.1	MRILVASLCA	LVVLATVICD	IEEHGHSYLT	RNVTVVDGSC	VFERNTLPDG	ETKALHEPCV	IATCYAERRE	VNATLCRNFG	VDPGCRVHWT	PDGVYPECCP
JAG91758.1	MRALVS.FCA	LSAFATVICD	IQEHGHSYLT	RNVTVENGAC	IFEHNTLPDG	ETKALHDPCV	IATCNAARRE	VNATLCRNFG	VDPGCRFHWR	FVGVYPECCP
JAG91783.1	MRAFVASLCA	LVAFATVICD	IQEHGHSYLT	RNVTVENGAC	IFERNALPDG	ETKALHDPCV	IATCYAARRE	VDATELCRNFG	VDPGCRFHWR	NDGVYPQCCP
JAG91784.1	MRVLVASLCA	IVAFSIVTCD	IQEHGHSYLT	RNVTVENGAC	IFERNTLPDG	ETKSLHDPCV	IATCYAARRE	VNATLCRNFG	VDPSCRFHWR	NDGVYPQCCP
JAC23742.1	MRAFTASFCA	LVAFATVICD	VQEHGHSYLT	RNVTVENGAC	IFERNTLPDG	ETKALHDPCV	IATCYAARRE	VNATLCRNFG	VDPGCRVQWT	PDGVYPQCCP
cirpt1		D	VQERGHTYVT	KNVTVEDGAC	VYLRNVIPNG	ETKALNNPCV	LSTCYAADRK	VNSTLCPNIG	VDEGCHVEWT	PDGVYPNCCP
cirpt2	MRTLVASLCV	FAVFSAVCCD	VQERGHTYRT	RNVTVEDGAC	VFERNVIPDG	ETKALNSPCV	LSTCYAAARE	VNSTLCPNIG	VEQGCRVEWT	PVGEYPNCCP
cirpt3	MRTLGVSLFV	LVGISAVYCD	VQERGHTYVT	KNVTVENGAC	VFERNVIPDG	ETKALNSPCV	LSTCYAADRK	VNSTLCPNFG	VAEGCHVEWT	PDGEYPNCCP
cirpt4	MRAFVALFCT	LVAFATVICD	IQEHGHSYLT	RNVTVENGAC	IFERNTLPDG	ETKALHDPCV	IATCYAARRE	VNATLCRNFG	VDPGCRFHWR	NDGVYPQCCP

JAP77355.1	KHVCPSASAT	S.
AEO35708.1	RQVCDRTD..	..
AEO35710.1	RQVCDRTD..	..
JAG91758.1	RQVCDGTD..	..
JAG91783.1	TQVCDGTD..	..
JAG91784.1	RQVCDGTD..	..
JAC23742.1	RQVCDGTN..	..
cirpt1	KHVCPSATAS	S.
cirpt2	KHVCPTTS..	..
cirpt3	KHVCPAAPAT	S.
cirpt4	TQVCDGTD..	..

Figure S45: Amino acid sequence alignment of sequences from *Amblyomma* and *Rhipicephalus* species grouping with C5-binding complement inhibitors CirpT1-4. The sequence block containing selected residues contained in the interaction interface with complement factor C5 are highlighted in green. CirpT1 is from *Rhipicephalus pulchellus*, CirpT2 is from *Dermacentor andersonii*, CirpT3 is from *Rhipicephalus sanguineus* and CirpT4 is from *Amblyomma americanum*.

JAG91563.1	..MMASAKLL	SFALLVLTTV	AMIGVPSADT	SSVPYGPDVI	LPC.RGNYIC	FIHTD..G..	RQYGC	CPQ...	GGKCIPNGNY	DQHGYAQGKC	FCAHG.....
JAC19583.1				YSGHFFDEAI	YQC.YPRVDC	FRHKD..G..	WQS.CPAHLP	GAQCIPNRRF	NERGFASGVC	FCRGR.....	
JAA60894.1			.RPGPPG...	SAGVM	LVC...GDPC	YIRND..G..	VAKGC	CPE...	ECRCVSNKFA	RGIYTGEGIC	WIERWRNSTP
JAG91534.1	...MTLNKLL	SFALLAVTIV	MMMGRCs...	...AYHDNAF	WQC.YNAGPC	YRYPN..G..	TQQGC	CPP...	YCGCVSRRYY	EGIIYYGLGNC	VALPQYG...
JAU03243.1	...MTLTKLL	YFALFAVTIM	AMMGRCs...	...AYGNDVI	RQCPITPGPC	YIHHN..G..	MQEGC	CPW...	TCRCISNKYN	QGIYNGWGRC	FTNRRTG...
JAG91532.1	...MTSAKRL	SYPVYVVALL	AMIGICSQ..	VAQGYGNDAI	GLC.PESGVC	FIRSD..G..	RQAGC	SG...	DCRCISDRYN	EGIYDGWGH	YG.....
Raci1	...MNAMLVL	.FIASALFIS	EHNTEEV...	..KTTPIP.N	HQC..VNATC	ERKLDALGNA	VITKC	CPQ...	GCLCVVRG.A	SNIVPANGTC	FQLATTKPPM
Raci2	...MNAVTVL	AFTAFALIVH	DCYSEEA...	..NTTPISVK	DQC..ANVTC	RRTVDNRGKR	HIDGC	CPP...	GCLCVLKG.P	DSKDNLDGTC	YLLATTPKST
Raci3	MAALNGLVLL	LLTISAMFIS	ECYSSGE...	..SQS.IQRK	GQC..EEVIC	HRKLNHLGER	VTSC	CPT...	GCLCVIRE.P	DNVDNANGTC	YALMSSTTTT

JAG91563.1		
JAC19583.1		
JAA60894.1		
JAG91534.1		
JAU03243.1		
JAG91532.1		
Raci1	APGDNKDNKE	EESN
Raci2	TTSTEQSFNM	EE..
Raci3	TTTPDGTITS	EEEE

Figure S46: Alignment of 8kDa family members. Raci1-3 are known inhibitors of the complement pathway from *Rhipicephalus appendiculatus*. Cysteine residues are highlighted in black.

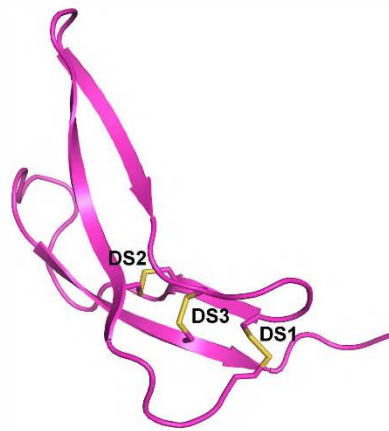
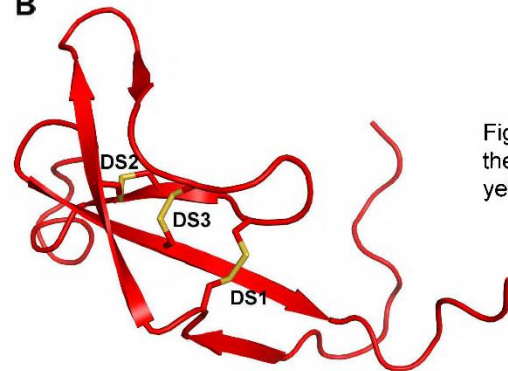
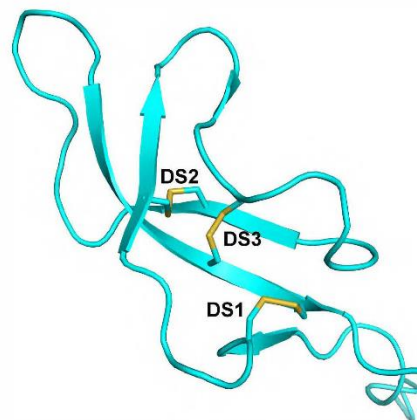
A**RaCl3****B****JAA60894.1****C****JAA19583.1**

Figure S47: AlphaFold2 models of two uncharacterized 8 kDa family members compared to the crystal structure of RaCl3. Cysteines are shown in stick format with sulfur colored yellow. Disulfide bonds are labeled DS1-3

JAG92232.1	.MNV....AL	FLLFSLGIL	NLAE.....	ASSSQSGTTT	TKVAE C HGTE	C ISS.ADGQT	RCPPG C ECYY	YEEYG....G	NY C V...QAG	AGSGDYVYG.
JAC19098.1	.MKG....AL	VCLLSVLSLI	TTAE.....	SSGSSP....	P.AKTVT C D.	.A C Q..DEQY	RCQAG C ECAA	YDYEG..TEV	YY C SLPDGTA	DYANTYNGG.
JAC27161.1	.MKS....VL	VCLLS.LQFL	TITE.....	ASGSSS....	S.AKAVT C CP.	.EE C ..DGNY	GCGDD C ECVT	DEDE....IE	YF C TQAGGGS	..TADYNGG.
JAC27594.1	.MKS....SW	ILLPFALGIL	DVA.....	GRIILQ....	..SS S CGGT.	.. C NPYENDG	WCSEDCY C EL	G.....FP	...LPMQGY C	TPAEYASASV
JAC27201.1	.MKY....AL	LFILSVVGSL	H.KT.....	ASGSHS....	..YDACHQA.	...CHLEKGV	SCPTGC S CAE	YGTG.....A	YRGR...GV C	QLNRGWTSEQ
JAC27947.1	.MKT....AL	GIVLFAVGFI	LTVR.....	ASGSSR....	.SPAACVGQ.	.V C DAYDSQA	GCP P PC F CQP	YDAG...DGT	VVSYCITGNG	DYGDSGSGGG
JAG92094.1	.MKS....AL	LLLLSVLGSL	R.NE.....	ASGSQS....	..YDVCHQT.	...CNTDRGL	RCEVGC S CGE	Y.....	YHGW...GV C	QLKPGWTAER
JAC27126.1	.MKY....PL	LFILSVVGSL	H.KI.....	ASGSHS....	..YDACHQS.	...CHTDRKV	YCPTGC S CAE	YGTG.....H	YQGR...G I C	VLKPGWTSE
JAG92061.1	.MKA....AL	LLLLSIIGSL	R.KE.....	ATGSQS....	..VDVCAQR.	...CVCRLGL	YCDYGC S CGE	Y.....	YYGE...GV C	HIKPGFTQEQ
JAC27906.1	MMKI....AY	YIMMSVLGFI	QIAE.....	SGSQK.SAP	TPKTVFT C QE	SACNPYNEGP	QCGPH C ECA	YEEDG....Q	YLG V CTTADG	VDGGDYQP..
JAC27858.1	.MKA....SL	ILFLFTIGFL	QHAL.....	GSPREQ....	..KNT C GGT.	.. C NPYEGDG	WCSEECY C EM	D.....FP	...LPLWGY C	TRAEYASIGT
JAC19077.1	.MRS....VL	LILLLLVDVL	HLSK A NG C E	RNAKDA....	..YQ G CLGT.	..CDPDEPFK	GCSKG C LCYD	GGT.....YP	.DGTPWGG I C	YAAPEGGVED
JAC27917.1	.MPGKWGYLY	FLLVMQHLL	RVSQ S CDW C D	RSADP....	..YQ G CLGT.	..CDPYKPYE	GCGSG C WCYH	GGT.....HP	VEGYDMGG F C	YEADE.DNEP
JAG92276.1				.SSSS..ST	TKQPT C AGQW	C SRDQSTEEY	SCGPG C ACY	YESDGDSDG	GYV C SAYAAG	AANTDYS
JAG92164.1	.MLR....FE	YFLLHMLSLA	HASH.....	RNAKEP....	..CQ G CLGT.	.. C NPDKPFE	GCGSN C LCYD	GGI.....HP	VEKYEIG G I C	YDAPEFGDDD

JAG92232.1	SS.....	.QRVDPNVAV	QASTQLISDA	LQVAAYS	SRGS	...LPSIKKP	SLKL P KMKLP	KFKMPNVK..	...LPRLRMP	RIRFRGRR..	
JAC19098.1	PG.....	.GATDPAYVA	QTVSSMLTDT	VQMASS	LRRP	...SGLAKKP	S..FLSKMK S	RISLRKVR..	...LPKVKSS	DSDFQDAAED	LPLTF
JAC27161.1	GG.....	.GGVDPTAIV	QSATSLAGEA	INMASL	MRRP	...KEVSR..	DH	HVSRR.....			
JAC27594.1	D.....	...VEF....	.VAKSSEHDA	KQS.....	..QNYIENKN	GTD	DIA.....				
JAC27201.1	VQ.....	.ALLDAQDVM	ETVTEVG	GEL	VKKVYKKLRN	L....KITKK	MSKAI	KAGMKI I KK.	...LVKALKG	LVRFRG....	
JAC27947.1	GG.....	.TGIDPNTAL	MSSTGLAGNL	LNTVPYWKLP	KIKKPSLPSL	P....KLNLP	KVGLSKV S FG	KNLLSKIKRP	KFKMPRIG..		
JAG92094.1	VT.....	.AVIEAQAVM	EAVLEASGDA	VKHGMSKVSK	IK.MPKIKLP	KMKGL	RFGIGRLMK.	...LLKTL S R	ILRFRG....		
JAC27126.1	VQ.....	.AEIDAQEVV	ETVVEVG	GQL	VKKVLKN...						
JAG92061.1	VA.....	.AAIDANAVI	EAVTQISGDL	LKKGINKMSK	V....KIKLP	KIKMT	RFGVSKIMK.	...LIK I IKK	LLRFRG....		
JAC27906.1	YS.....	.SGVDPNVAA	QSGTELAGSV	VQALAIARPK	...SSPLKK.	LKIP	LQKM K SS...	...IK K IRP	KLSIRKQK..		
JAC27858.1	DTMDALMDLG	ELKAEMP	KTP	KL	GASSNTA	KSPKISAPTV	RFPKFTAPKM	P....RLSLP	KITLP.....	...K...VFT	RG.....
JAC19077.1	IDY.....	TT	AHTAVAATGL	ALQSAVAVSS	AVRRVSFGSS	AARKAVSSAL	SK..VKVRMP	RIKI...R..	...IPR F KLS	RG.....	
JAC27917.1	KE.....	DN	SQTAATAIQ L	TATT L QAGAA	VASRIPISKV	KIGRAAAKFA	A....KIRMP	KIKL...R..	...IPR F KLS	RG.....	
JAG92276.1	YQ.....	SSIDPNVAL	TSATSIFGDV	MNAALSGKP	SFKTPSF I KN	IRRVSLPKMP	SIKMPKLK..	...IPK F TRP	KLRLRIRG..		
JAG92164.1	KR.....	QG	GVNKEGLQKF	TEEITKSGGE	ITRIPWSKT	ALARATSKWA	T....AVRVP	RIKL P KFR..	...IPR I RTS	RG.....	

Figure S48:Amino acid sequence alignment of 15 kDa basic proteins. Cysteine residues are highlighted in black.

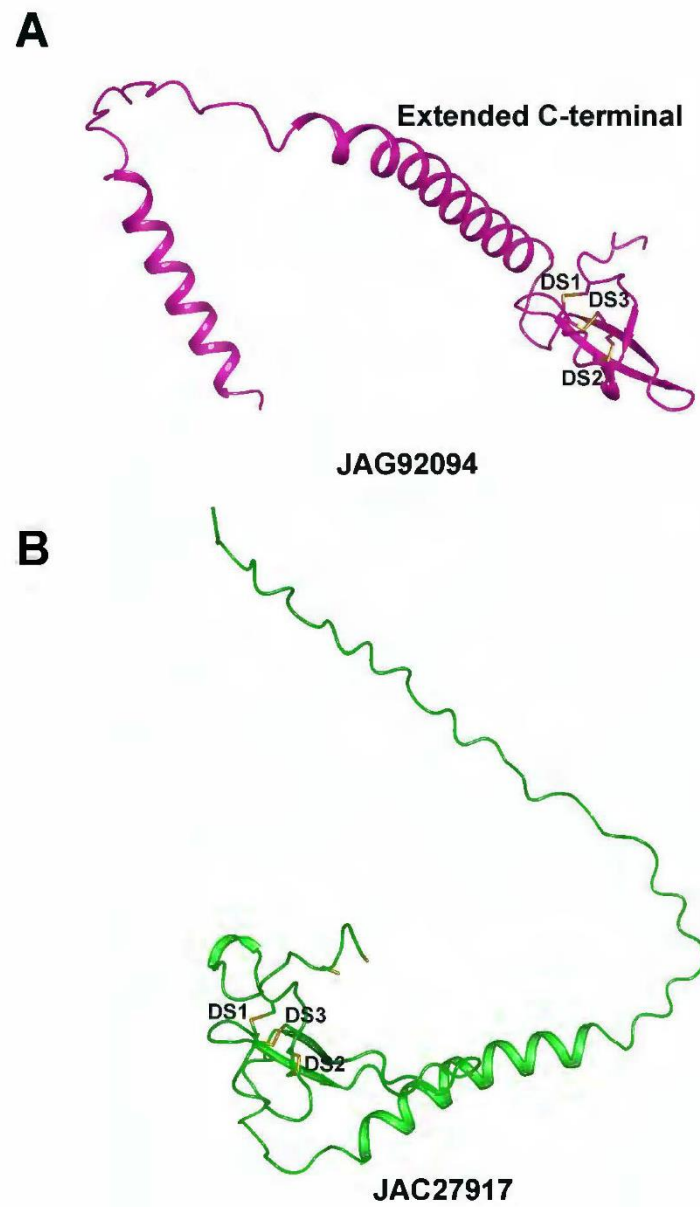


Figure S49: AlphaFold2 models of 15 kDa basic proteins. The proteins contain a small domain similar to the 8 kDa proteins with a long C-terminal portion that does not fold into a distinguishable domain.

jar89651.1	MGACFDGSDR	SPRCGCGRVV	CLVGYLMALL	ALISTTAAQC	PNPAVPVYAK	ATFSNDDRRA	GTVVITYSCDD	GYELFGTATR	TQSEKRRWVG	ELPYCAVNVA
T.urticae	MKF	KPLFGLLCIL	QFIR.ISSGR	RYSNQYGFEC	PNPAVPLYAQ	VNLSDD.LQP	GSKATYTCDD	GYELFGPSVR	TQFDGKWTG	DLPYCAVNVA
L.polyphemus				..FPIAATCC	PLPAVSLYSK	VSLSQN.KNP	GSFATYTCDD	GYELFGGQSR	VQSPDGTWKG	EVPICATNVA
jar89651.1	YGKPTNQSSST	VRGGDSKNAN	DGDLTTLHEN	RFCCTETKLEN	APWQVVDLLQ	PYEVRVIRLL	TRCCGHQPL	HDLEIRVSNR	SDLQNSRICA	WYPGTLEDGV
T.urticae	YGKPSQSSST	IRGGESRNAN	DGNIVTIHEN	RFCCTETKNEN	SPWQVVDLLQ	PYEIRVVRII	TRCCGHQPL	HDLEIRVGNS	SVVSGNRICA	WYPGTLDGCV
L.polyphemus	YGKPANQSSST	SRGGKPQMAN	DGDTTTFHED	KFCCTETKQDN	SPWQVVDLLQ	EYEVRVVRIF	TRCCGHQPL	HDLEIRVGNS	SVIQGNRICA	WYPGTIEDGT
jar89651.1	SKDFSCAYPI	MGRYVYVHMV	GGEGSLSCGE	VMVFTTQEFS	PEKCGNRVEP	LELTTFIRFC	YEFQGSRRGS	FQDASAVCQT	RGGLLVHGVD	DLILPFISAE
T.urticae	TKDLSCAHPI	SGRYVYIQMV	GVEASLSLGE	VLVFTTKEFS	EDFCGTQMEH	QQLISFNQIC	YEFQTQGGGS	FNDAENYOKA	RGGLVVNSVG	DVTQNFLQYE
L.polyphemus	TKDFFCAYPI	KGRYVYVQMV	GIEGSLSLGE	VMVFSTQEFS	AQFCGNQLEP	LKLTTFNHTC	YEFQGEKGGT	FKDADRYCDD	HGGQIAHSMS	NVTHNFLSTE
jar89651.1	LERRRDKLKS	KLVMGAQRR	TGIGLNKRG.	WYWN	GDPVREFLWA	EDQPNNYNGQ	QNCVVIDGGR	KWRWNDVTCDD	LDYLPWICQY	NPSNCGSPDK
T.urticae	LQRLKAKLKS	RLVWLGAKRE	IPANQPVTHR	SRSNVWRWVN	GGLITQFLWA	DDQPNNYNGQ	QNCIVLDGGR	KWQWNDVTCDD	LDYLPWICQY	TPSNCGSPDK
L.polyphemus	LERLKGQLKS	KLVLGAQRE	PGIVSQK...	XHWID	KQVVVDFLWA	PDQPNNYNGQ	QNCVVDGGR	KWQWNDVTCDD	LDYLPWICQY	SPSNCGSPDR
jar89651.1	KENSTTTGQD	YRVGQEVSYD	CPTGSLLVGS	RTRKCAVSGF	WTGSAPSCKY	MDCGNPESVE	NGQFVLLHR.	RTTFNATVEY	VCDANYTLVG	KPRRVCGEDG
T.urticae	AENSTILEKD	YRVGREINMYR	CPIGHVVVGN	ESRHCESNGF	WSGSPPTCKY	VWCGALNDIE	HGRVLLVNQS	RTTFNATARY	VCDQDYTIVG	NDSRVCLANG
L.polyphemus	KENSTILGNS	FTLGQKVITYT	CPVGNMLVGD	AIRTCRADGF	WTGAAPSCKY	VCCGPLSDIE	NGKVRYLES.	RTTFNASAQY	VCDQNYTLIG	DGIQVCLGSS
jar89651.1	RWNGSQPACL	LSFCSELAPT	PSSSVQVQGL	RFGDRARYTC	KMGHKLIGND	TRVCLGGNW	SGDEPTCKYI	CGEPRPLDD	GEVLLVNGTS	TFLSVVKYSC
T.urticae	SWSDTEPACL	YSACPELLPI	PNGILNVTNR	TLNGVASYS	LKGHKLISNG	TRVCLGGKW	TGEEPTCKYI	CGMPLDLRF	GRYLLNSST	TYESLVKYFC
L.polyphemus	SWKGDVACL	FNCCPQLKTP	ANSILEVTGQ	SAGSQAKYS	EKGYRLIGKD	TRVCLGGMW	TDSEPTCKFI	CGCKPDPLTN	GDHVLNQTT	TYLSKVKHTC
jar89651.1	HDNFTLSGVD	TRSCLETGLW	SDVEPSCOMI	SCGEPEIPLG	GYVVEEDFQV	HDTVHYFCHP	GHVMAGHETR	.TCLRDGTWS	GSAFTCSFVD	CGRVPPILKG
T.urticae	NPNYILTGNE	TRCCTEHATW	SGVEPVORMI	DCGPPEIPSG	ADLIGDTFSI	DSVIEYCQRP	GHLMSNGESK	RTCGSDGKWT	GVPPSCRFID	CGRVTTIFNG
L.polyphemus	HQNFSLVGDE	VRTCLETKLW	SGKQPVCKLI	FCGEPDVRPG	SYVEGGGLTV	HSVVEYFCET	GHVMISSSR	RVCGLDGKWM	GEAAICHFVD	CGRVPPIPRG
jar89651.1	EVAYENGTTT	LGSRIVHGCS	AGYRLTGVRV	RICGLEGRWS	GTPPICEEIR	GPPEVPKNA	TVVYGDNDRS	SAESFKIAST	VQYFCVTGHI	VQGESLRTCD
T.urticae	EVKYLNGTTS	LGSQISYSQS	YGYRVKGFSV	RECAVDGKWT	GSTPICEEIR	CLPPEKPKNS	SVVYSGNDRS	TSDSFKVGST	VQYFCASGHI	VSGQSLRTCE
L.polyphemus	AVHYINETTF	LHSIISYKGS	FGYRLIGDRM	RICLEDGHWN	GSTPICEEIR	CPVPQVPHNA	SIIYTGNDRS	LAVSFKIGSN	AQYFCVGHV	LKGVSLRACL
jar89651.1	VTGEWTGEVP	ECVYVSCSFP	LPIGNHALL	STNSTHYGAT	VEYFCDRNYQ	LDGAPRRICL	ENGTSWGPEP	ICLEVFCACP	KASDSKTVIK	F.SDDSVGSS
T.urticae	ADGSWDGSQP	ICVYIICGLP	GFIPIQGRWLL	SSNSTHYGST	VEYFCSSNFR	LEGPARRICL	ENGTSWNVAP	ICSLVNCCKP	PVRDDKTIVE	GGFTFAVGK
L.polyphemus	QTGVWSGEVP	ICVYVSCGLL	MPVAHGHWLL	PNNATFYGTS	VEYFCDENYK	VVGPSRRICL	ENGTSWGQDP	ICIEISCGVP	DTLDTMTFVE	G.SVFTIGRM
jar89651.1	VEYSCQGYE	LOGLTTTRICQ	SNGLWSGDAS	TICALVCGRP	SVIGNRGQQL	LNGSTTFGSL	VEYCLHEFK	LVGEALRTCG	ADGQWSGQEP	FCFDVPVRDS
T.urticae	VSYSQVNGYE	LVGEEQRQCA	SDGLWTNOTP	YCRIVNCGKP	PIPVNRGVVL	LNGSTTYGSL	VEYHCLPDFK	TIGEETRFQI	SSGVWSGSLP	FCFDRKLMOM
L.polyphemus	VVYSCVNGYE	VIGQNIKSC	KSGQWSGQTP	FCR...CKYS	IMFEPLKGKY	LTN.....	.FYAC.....			
jar89651.1	..NDVEG.AD	SNRADFT...	..YDSSRTVG	IAIAVGAGAL	LVIAIVVAIV	WMRTKAQR.V	KNTENVEVNR	NVEKD NATVM	SFSRLALEAA	EANSAPYHNG
T.urticae	EKNEVDGDFD	LSTSSFTNHS	PIYQSSKAIG	IGISVAIGVI	LVLIIITITIV	CLKTKKPKPV	KNTENVEITR	PPDKDTATVM	SYSRLSLESE	AAAAASLPAS
L.polyphemus										
jar89651.1	PGIRHNPNGL	VTFAAGPQPI	YANVTVNGQS	LSTSNSSGRG	NLGVPSPPPH	A.PPRHNGNPA	GNNHHSSSHN	SSHNGSHNGN	HNSGHNRGSH	GGNGSLTANG
T.urticae	GPIRHHNPGL	VTFSAPSANS	TANNHPNNQP	IYANTNGYRA	ASNPGSTVSV	AVRNSHGLSN	G...TTTPRF	MAAAANRXGN	NNS.....	
L.polyphemus										

Figure S50, Amino acid sequence alignment of sushi domain-containing proteins having lectin domains at the N-terminal end from a variety of arthropod species. Numerous cysteine residues are all predicted to participate in disulfide bonds. These are highlighted in black, *T.urticae*: *Tetranychus urticae*, *L.polyphemus*: *Limulus polyphemus*.

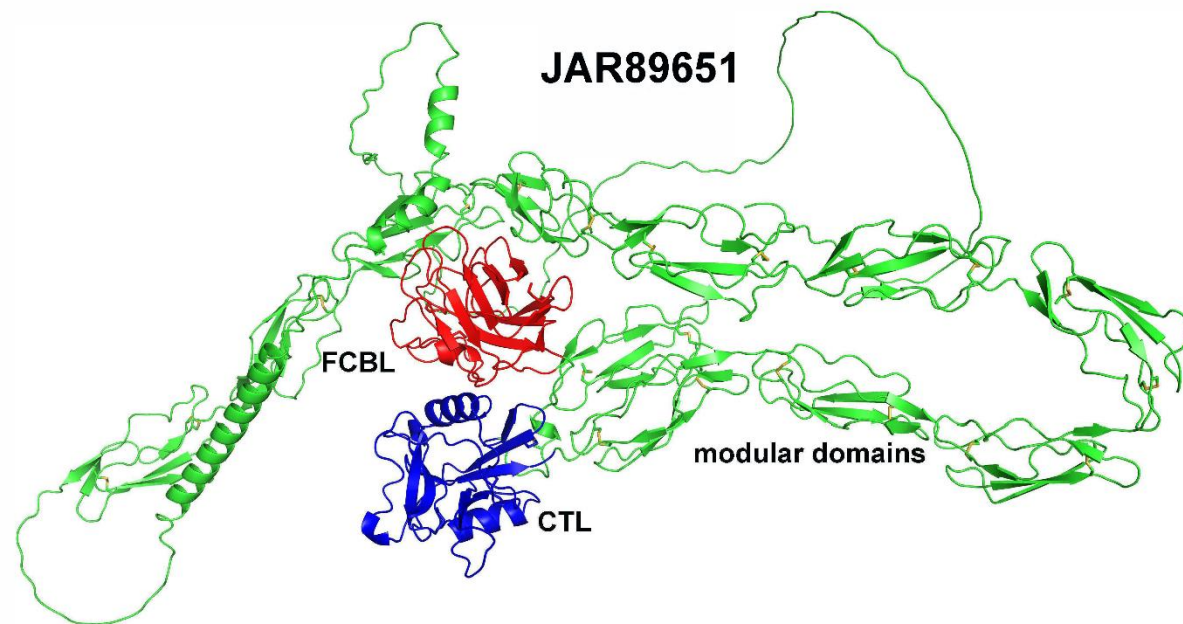
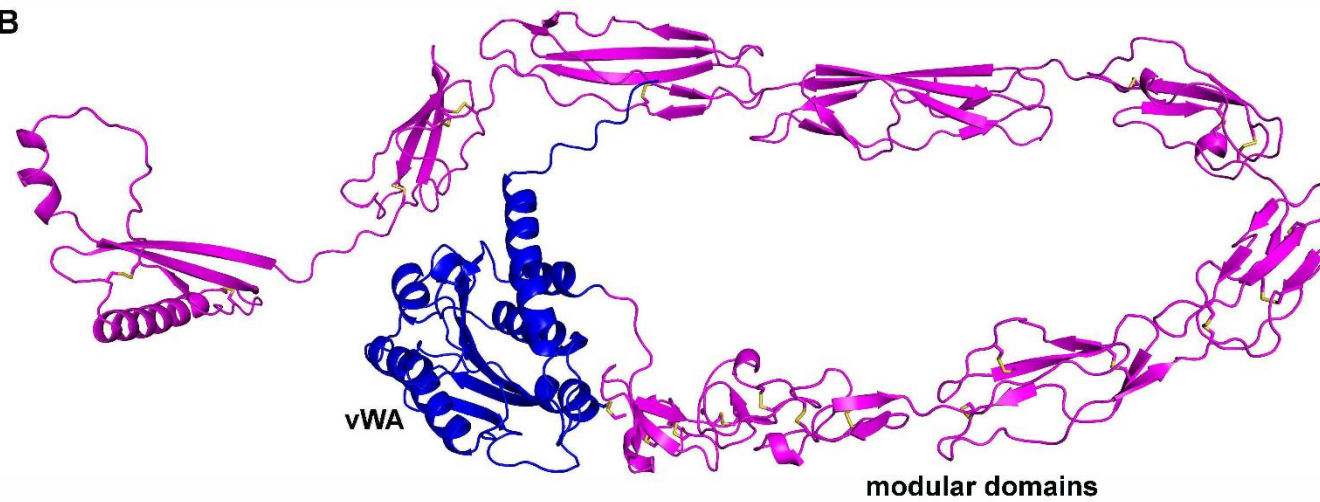
A**JAR90946****B**

Figure S51. Structures predicted by AlphaFold2 of JAR90946 containing lectin domains and JAR89651 containing a von Willebrand A domain at the N-terminal end.

JAR90946.1	ME	VLKLLCSFSL	LLLVPVDVAD		A	QPVKTFPEAT	E...DSERMD	QLGAVLKRHV	AKLRSTAR..	AELVFLVDSS
L.polyphemus	MN	IFWYLVGLLF	VAAGLSQAAS	SGGYRHTRNK	EYEQFFNSGA	KPSFTSNERL	PNQLKKNKVE	ELGNILKQHV	AALRRTPNKQ	VELVFLVDSS
V.destructor	MYFSSESATN	RWVFFLAIFY	IARVSSTLN.			EIVEYPLSTI	DATIDIKKLE	QQSERLKSSL	GALHNNYEHG	IDIAFLVDSS
P.vannamei	MRAKASYPEG	RRRLMLAVLS	FLSLMVLAPV	AVAQYKTERP	PYPDFLNYGK	KKFTKPGIEL	ENEIISKVE	VLGEILKSHV	HQLRQAPGQR	VELVFLVDAS
JAR90946.1	ASVGAGNFLN	ELRFVRKLLA	DFTVS...LD	ATRVALVTFS	SKKRVLREVD	HITRPTD...	.TNHKCLLLN	TQLAHVKYAG	GGTFTLGAVL	EAQDILKSAR
L.polyphemus	ASVGSENFN	ELKFVKLLA	DFTVS...YE	ATRVAVITFS	SRRERVVKD	HLSNPSE...	.NNHKCALLR	DQLPSINYTG	GGTYTLGAVL	KAQEVLYKYAR
V.destructor	LSVGLANFKL	ELRFVKKILA	DFSISHLRKN	TTRVTLVTFS	SPDKVVTHVD	FISPNGSSQI	LNHRHCSLMA	.ELAQIQYVG	GLTYTLGAMK	IADRVLGASN
P.vannamei	ASVGAENFFN	EIKFVKLLA	DFAVS...YN	QTRVAVITFS	SKSKVIRHID	HVTQASP...	.DNHKCTLLE	TELPRIKYSG	GGTYTLGAML	EAQSVLALAR
JAR90946.1	EDAVKVVFLV	TDGYSNGGDP	RPAAQELRDA	GTLVYTFGVR	NGNVRELDRM	ASLPADHECY	ILNSFEEFEA	LARRALHEDM	HVGPHQNLNS	SDCDGLCK.E
L.polyphemus	PESTKAIFLV	TDGYSNGGDP	RPAAKDLRDQ	GVQIFTFGIK	NGNVRELHDM	ASEPSKEHCY	ILDSFEEFEA	LARRALHEDL	QIGSYLPQKS	EACLRICQGE
V.destructor	RSVPQVVFLV	TDGFSNGGDP	KPIARKLKSR	GVTIFTFGIK	NGNVKELQDM	AT.TRKEHCF	IVNSFEEFEA	LARRALHQDL	SVGDFEPLDL	SQCNGLC.PA
P.vannamei	NDARKAVFLV	TDGYSNGGDP	RPAAAFQLAR	GVTIFTFGIR	NGNVKELYDM	ASVPKEEHSY	ILDTFEEFEA	LARRALHEDL	HSGFLIHQPP	RTCGKLC.E
JAR90946.1	GSECCSHGAQ	CTCGIYSGQY	SCLCPKGYHYG	SGMRGECHEC	PQGTYPQSVS	SGDKGICLFC	PNAHQNSAPG	STSVMOCHCR	RGYSAEGHS.	...CRVHHCQ
L.polyphemus	SKSCCDARAQ	CTCGTHTGHY	ACLCQPGYYG	TGLQGNCEPC	PEGTYHVGSG	PGDISSCQSC	PDAQHTSPLA	STSPNQCTCK	PGYVTNGKK.	...CEVIECP
V.destructor	GQLCCQSGAR	CACGTTSGYF	SCLCPRGQYG	TGLKGECRCP	PKGTYPQRFV	HGGIEECLFC	PGSHQTSPSG	SHSKQQCSCK	SGFTTLITGN	SSVCMPPVACP
P.vannamei	GTGCCDADAA	CTCDTHTGHY	ACTCRKGYYG	TGILGDCRPC	PPGTYRTHQG	PGDVSSCSFC	PDPHMVSDAA	STSAQQCYCK	RGFKQVQGE.	...CLMLCCQ
JAR90946.1	KLRPPANGYL	VNSDCGVVFN	AACGFRCNPG	YRLIGNSIRV	CQQSGTWSGS	DPVCEKKKCC	TLGAPFHGSI	KCSTEAFDFE	TVCEFECCQRG	YVLIGSRKRS
L.polyphemus	PLSPPEHGYF	VNGICSSVIH	AACGIRPCDSG	YKLVGSSVRL	CTVDGTWSGT	NVACEKKKCS	SLSAPHHGSV	LCTTDSNVFE	TKCHFSCDPG	YKLVGSKIRT
V.destructor	ALVAPLNGFL	VNEKCESVFN	AACGVACETG	YKLSGSPILV	CNQDGRWSGE	MPKCHKRKCC	ELTAPNSGWM	KCTTRSYPQFE	TECEFGCSEG	FVLVGSKRRN
P.vannamei	VLAPPENGYF	VRNTCNNVFN	AACGVRCNPG	YTLKSSSIRM	CGENGEGWTG	NACVCMKSCC	KLKPMAGTGM	VCTQPTPIMD	TECHFTCCDPG	YQLVGSKMRT
JAR90946.1	CLSIALWDGL	PTLCRPVSCP	PLLAPANGIF	SPAHCSETKS	AFGETCYLAC	NDGFASPHQA	SRECVHPGLW	SGNDTAINCM	DLEPPTIRNC	PEDMEVDSEP
L.polyphemus	CLAIALWDGL	PALCRPVDGP	PLSPIFNHGV	SPAKCTESKM	RYGDVCIYTC	KPGFVVRGPA	TRACEDQGVW	GNEEKKTVCI	DVEPPVLR.C	PEDIVVDAEE
V.destructor	CLAVAHWDGL	PATCRQIYCP	ALDIPANGRI	FPLSCNASRT	TFGDQCRYAC	QEGYRLTGPS	SRECIYPGVW	TDHQLVTRCV	DTKPPSIE.C	PDNILVPADP
P.vannamei	CLPVAMWDGI	PAYCKPIFCP	RLPPLLNTRI	RPGSCSSSKS	KYGSACEFAC	DPGYQISGPI	KTTCIDPGVW	SEGHKSPPCV	DITPPVIQ.C	PENITTETEP
JAR90946.1	GYAEALVDWE	LLEASDNSG.	ESLMLSVVPA	VMPPQLFPIG	T.SDITYWAE	DAAGNKACCN	FSVVVRDREP	PMDDSCITSPS	DAFSNGSPSA	VVTWDEPVFS
L.polyphemus	NERDYMVTWN	VPQIDNSG.	EIPSVSVLPA	VIPRRFAIG	T.ATITYTAE	DRSHNTASCS	FMVTVRDVQP	PTIDKCVSPP	KFLSREAP.V	TVFWEEPIFS
V.destructor	GEPYATVDFS	LPSIQDNSGF	QEITLTVSPA	VEPPLPFFIG	DPMNITYTAT	DSQENKNSCT	FSVTVIDEEP	PTVDRCESPA	VTLSSDGQGA	KVVWEEPLFS
P.vannamei	NEVYANVTWN	PPHVKDNSK.	GKIKLHTVPA	TSQPMKMIG	N.HTITYVAM	DKLGNKASCE	FSVTVVDKEP	PRIDECLSP	VFLSYEEV.V	DVYWEEPVFS
JAR90946.1	DNSGIDPVVW	QSHQGTTFP	VGETLVTYVA	SDASGNNASC	ILRVVVRDHR	CIMPVAPANG	DVDCRKTSSG	IACRITCLQG	YGLQPRVPSE	YTCAFDGSWS
L.polyphemus	DNSGSPVNIR	RSHSPG.LFP	LGETVVTYEA	VDEAGNNNTC	NLTITVQEHA	CSIPSPDPVNG	KANCTESDSG	VNCSLSCCEG	YAFVTSPPYN	YFCAYDGVWL
V.destructor	DNSNEDVFIW	SSHKPGQYFP	INDTVVTYNA	ADNSGNNASC	TFNITVKATK	CEPSFSVLNG	KLNCITVDALQ	TLCHIQCDRG	FTLLPNLP.N	YLCYIDGVWN
P.vannamei	DNSGVDVKIT	RSKEPG.QFP	QGDTMVEYWA	EDAAGNVATC	NITITVQKHA	CQMPVDPING	AANCTENPDA	VFTLTLCDDS	YAFAMRPQQD	YFCAYDGMWL
JAR90946.1	P.HSIHSFPD	CSESSPP...	...SSATVKA	RLFYSA.FGI	SCGDRLTQKE	LREHLLRRLS	MQAAR.CPDG	VDCSVGDLHI	ECPTVQAEPN	DAESSE.LHR
L.polyphemus	P.RDRFPFPD	CAVTQLS...	...NAISQTG	IITISS.DGG	DCDDQFLLNQ	VKSHLHRKIE	KKVASLCKEN	MLCNVNNFAT	MCNTEFEETE	EETNAI.ISR
V.destructor	ISDIDLPSCT	TVVTSSSGSS	SKLTSSSAST	PVVLPSGTMF	ECTNEFLSQ	LSVVLKKRIS	MKNVIKCRAK	PKCYKEKLKP	ICEVTQRNML	PISSHA..AR
P.vannamei	PDENMPFPD	CSVTSVS...	...NSISQYG	EMAMGEEDDS	ICDDIFFMGQ	VENQLEKKLE	DALTANCSDD	VVCEVAAVEA	VCECILADAE	EEFNISIGFFR
JAR90946.1	ERRSKRAEDI	EVSFDITG								
L.polyphemus	KKRNAVFLTK	T								
V.destructor	KRRS.VS...									
P.vannamei	RRRSAAEDAL	NRYWPQRH								

Figure S52. Comparison of vWA domain containing protein JAR89651 with representatives from non-blood feeding arthropod species. Cysteine residues are highlighted in black and all are involved in disulfide bonds in modeled proteins. *L.polyphemus*: *Limulus polyphemus*, *V.destructor*: *Varroa destructor*, *P.vannamei*: *Penaeus vannamei*.

JAC30591.1	MKTVAVPSVL	AFLLLLEIVS	GGYICQDPRP	YLSTYRVRSD	GHECTSLVKN	MSTVLGDYTT	NSWVAGVRVR	DNC	.DIPRWT	AIATFLGPGG	KYNTGAVNDM
AEO34830.1			..ISCSNPES	LKGNWVIGVD	GKECVALVKE	KCSGMRQYST	HSWRRGKHVR	SN	CGSIPRWT	AIATFLDG.S	KY.....
ACX53960.1	MKGFVI.SVG	LLLLGMTVVT	QAIRCADPTG	FKGGWVIGVD	RKECVALVKE	KCKGLRQYTT	HRWRRGLQVR	SN	CRKVPRWS	AIATFLDG.K	SY.....
JAP80515.1	MKGFVV.SLG	LLLLGMAVVI	QAIRCANPTS	FKGRWVIGVD	RKECVALVKE	KCKGLRRYTT	HRWRRGIRVR	GN	CRKVPRWS	AIATFLDG.R	SY.....
JAC30544.1	MNGFLL.CAA	LLVLGMAVGS	QAISCSNPES	LKGNWVIGVD	GKECVALVKE	KCSGMRQYST	HSWRRGKHVR	SN	CGSIPRWT	AIATFLDG.T	KY.....
JAA60761.1	MKGFVV.SVG	LLLLGMAIVI	QAIRCVNPTR	FKGRWVIGVD	RRECVALVKE	KCNGLRRYTT	HRWRRGIRVR	GN	CRKVPRWS	AIATFLDG.R	SY.....
JAP66903.1	MNTSVV.FAA	LLVLSMDIAI	QAIRCADPSR	YKGRWVIGVD	GRECVALVKE	KCKGLRRYTT	HRWRRGLHVR	KN	CAKVPRLS	AIATFLDGKG	RY.....
JAC30591.1	AKQHAAIFDT	CESNGLWVYD	QNRNRPVNRT	FFKDLGGDDT	TSNARNYRVI	ELR					
AEO34830.1	.RGHAAIFES	CAPDGIWVYD	QWNTAKVDRR	KIR.YGNSKP	NYNGDNFYVI	EL.					
ACX53960.1	.RGHAAIFES	CAKDGIWVYD	QWNTAPIKRR	KIY.YGYRKL	NYNGNNFYMI	KL.					
JAP80515.1	.RGHAAIFES	CAKDGIWVYD	QWNTAPVKRR	KIH.FGYRMP	NYNGNNFYMI	KL.					
JAC30544.1	.RGHAAIFES	CAPDGIWVYD	QWNTAKVDRR	KIR.YGNSKP	NYNGDNFYVI	EL.					
JAA60761.1	.RGHAAIFES	CAKDGIWVYD	QWNTAPVQRR	KIR.FGYRMP	NYNGNNFYMI	KL.					
JAP66903.1	.RGHAAIFLS	CASDGIWVYD	QWNTAPLKRR	KIR.YGYKAP	NYNGNNFYMI	KL.					

Figure S53. Amino acid sequence alignment of Dae-2 protein family members. The catalytic cysteine and histidine residues are highlighted in green. Disulfide bonding cysteines are highlighted in black.

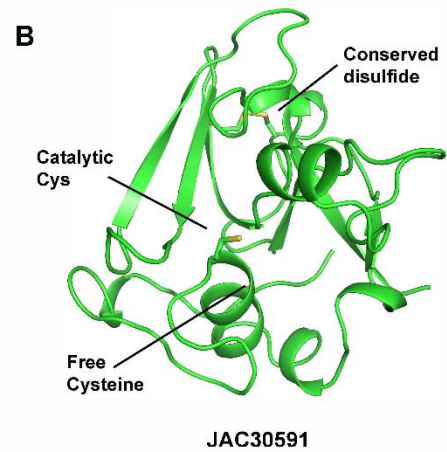
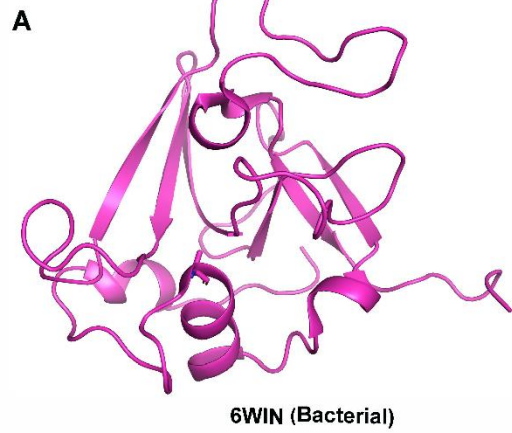


Figure S54. Structure of bacterial Tae-2 (PDB 6WIN) compared to AlphaFold2 models of tick salivary proteins (Dae-2). The catalytic cysteine and additional conserved cysteines are shown in stick representation and sulfur is colored in yellow

