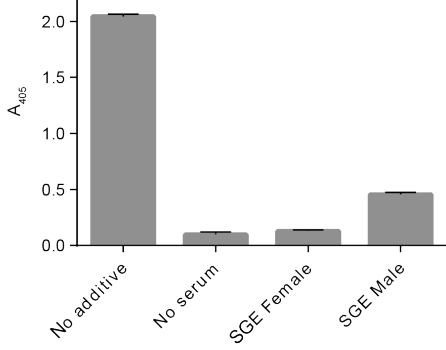
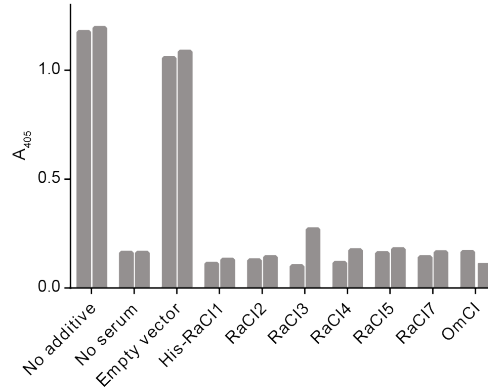
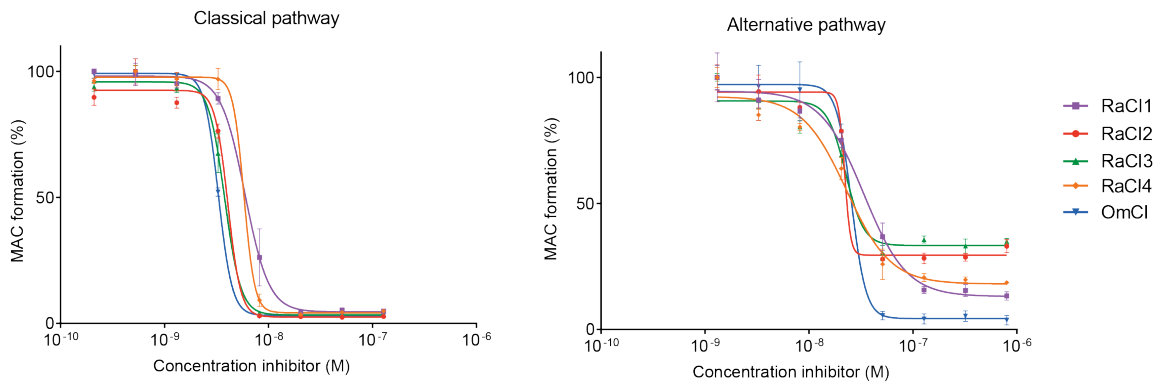
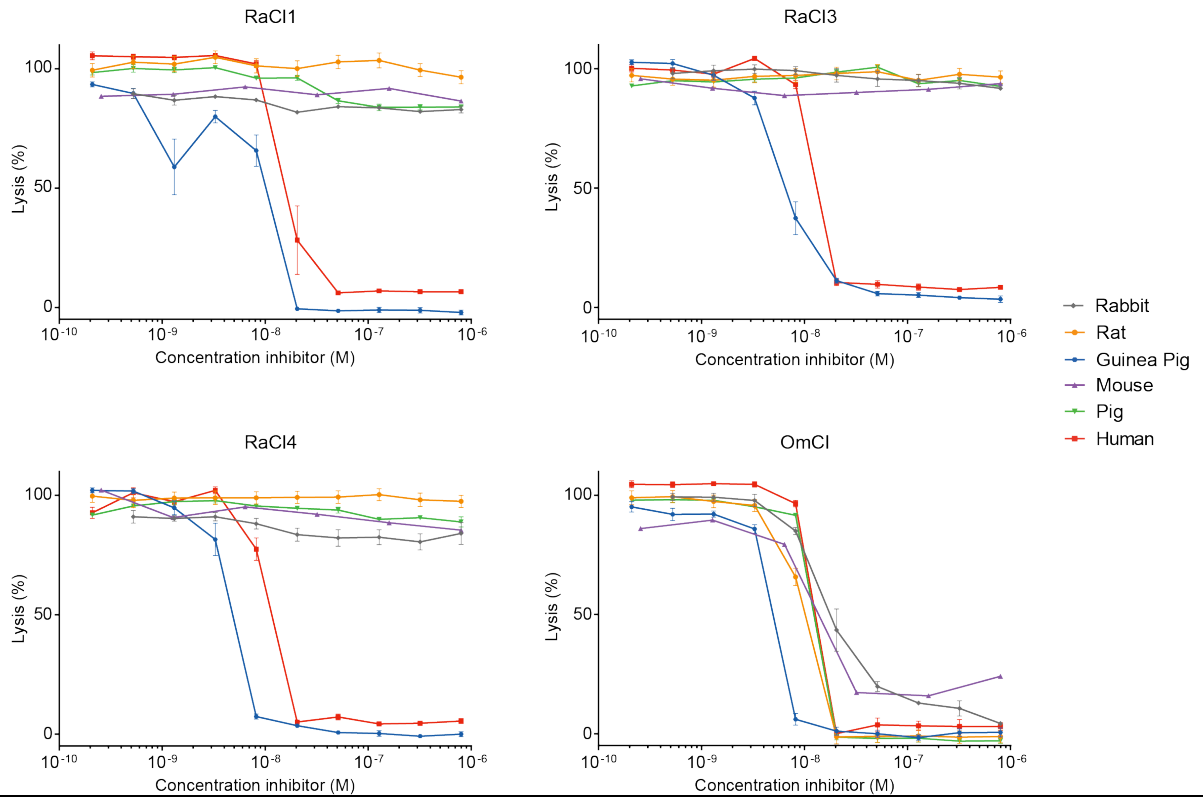
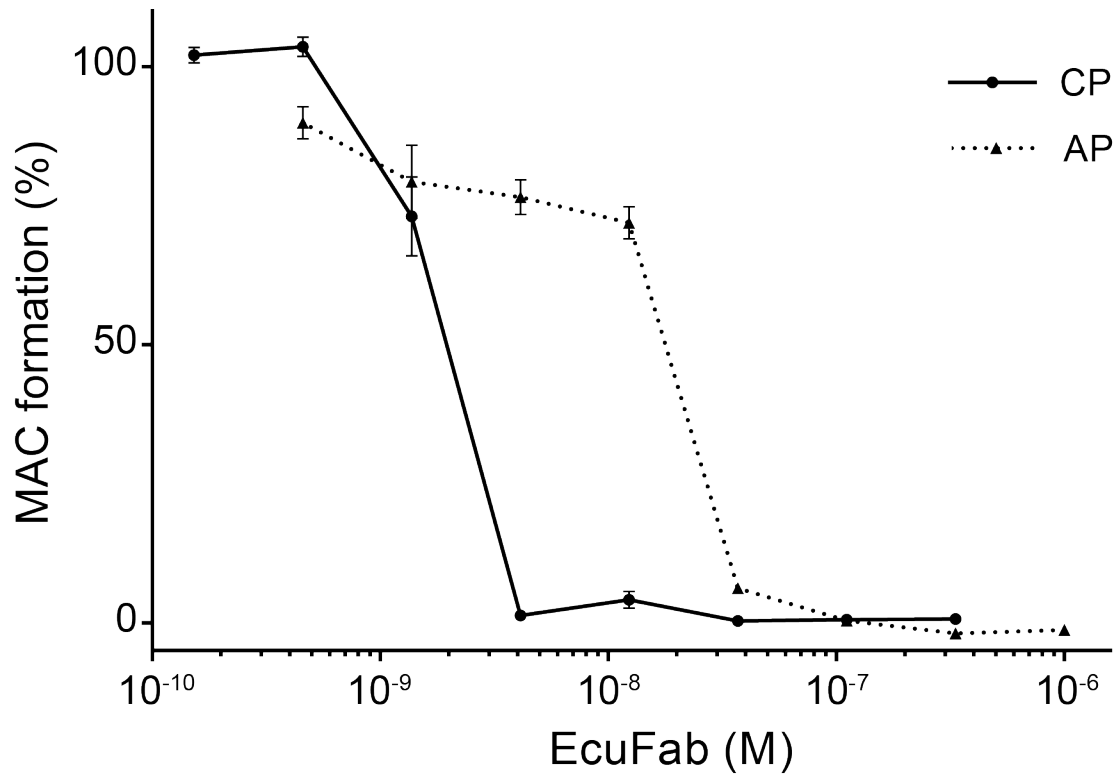


A**B****C****D**

Supplementary Figure 1

Complement inhibition by Salivary Gland Extract (SGE) and RaCI homologues.

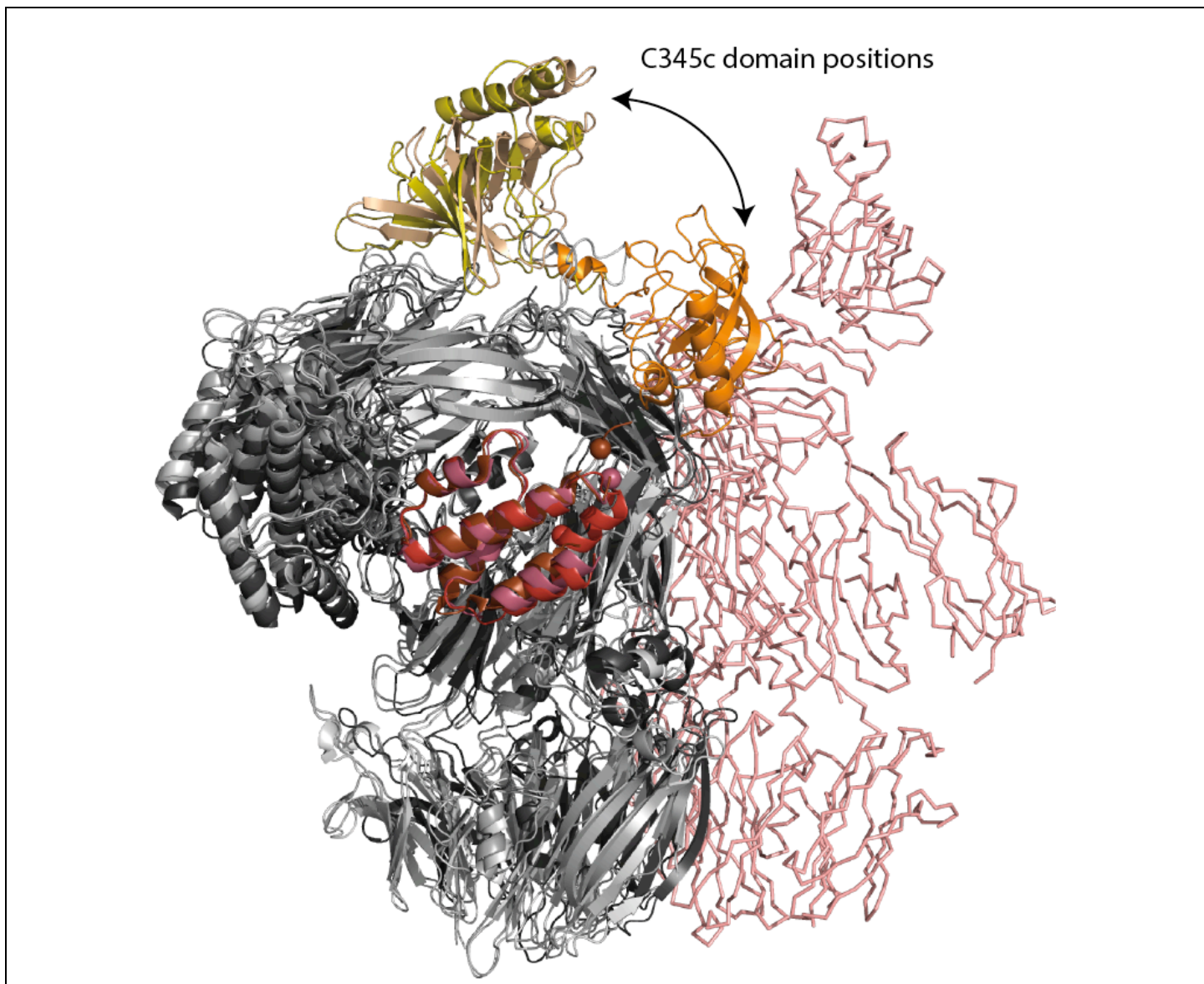
(A) SGE from both male and female ticks inhibit the classical pathway in a haemolysis assay. SGE equalling 2 glands (female) or 1 gland (male) were added to the haemolysis assay. Error bars, s.e.m. ($n = 3$ technical replicates). (B) Inhibition of classical pathway in a haemolysis assay with supernatants from stable transfected *Drosophila melanogaster* S2 cell lines. Individual values of two technical replicates are shown. (C) Classical and alternative pathway inhibition by RaCI family members and OmCI using an ELISA based activation assay, similar to the Wieslab assay used in Fig. 1b. The difference between the IC_{50} values for CP and AP inhibition likely reflects the difference in C5 concentrations used in the assays (1% serum in CP assay versus 10% serum in the AP assay). Error bars, s.e.m. ($n = 3$ technical replicates). (D) Cross-species reactivity of RaCI homologues and OmCI in a haemolysis assay. Error bars, s.e.m. ($n = 3$ technical replicates).



Supplementary Figure 2

The custom-made Fab (EcuFab), based on the sequence of Eculizumab, is a fully active complement inhibitor.

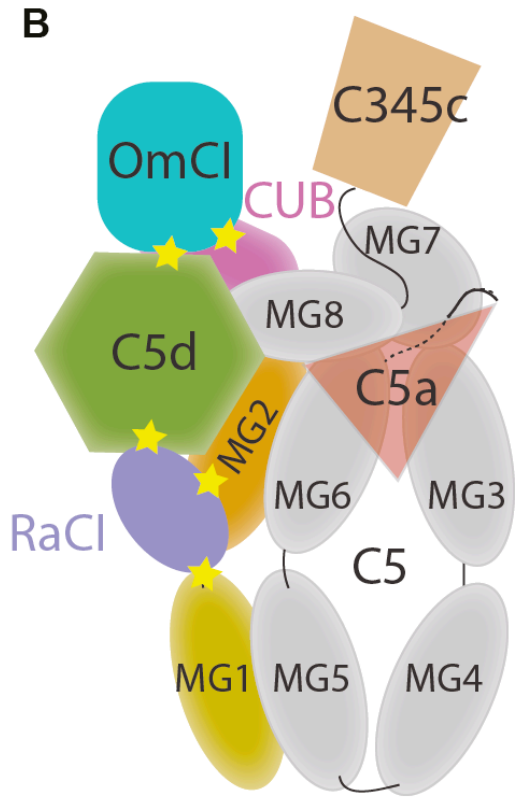
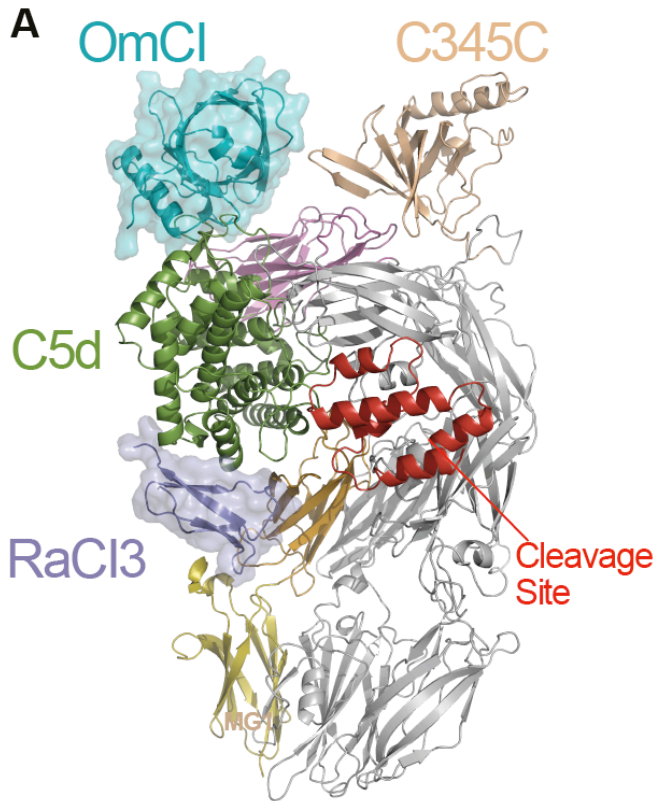
The custom-made Fab (EcuFab), based on the sequence of Eculizumab, is a fully active complement inhibitor. Classical (CP) and alternative (AP) pathway inhibition by the Fab fragment using an ELISA based activation assay show that the IC₅₀ values are similar to RaCIs and OmCI in Supplementary Figure 1. Error bars, s.e.m. (*n* = 3 technical replicates).



Supplementary Figure 3

Different location of C345c domain our new structures of inhibited C5 compared to apo-C5.

Different location of C345c domain with respect to the rest of C5 in our new structures of inhibited C5 (wheat) compared to the earlier structures of apo-C5 (orange; Fredslund *et al.*, *Nat. Immunol.* **9**, 753-760, 2011). The new location is consistent with that previously seen in the CVF-C5 complex (olive; Laursen *et al.*, *EMBO J.* **9**, 606-616, 2011). The CVF component of the C5-CVF complex is shown in a salmon ribbon representation highlighting the clash with the C345c domain in the apo-C5 like position. The residues that will form the anaphylatoxin C5a are coloured in shades of red and the overall view is the same as in the close-up of this region shown in Figure 3. The structures are overlaid by superposition of the C5a domain in each structure.



Supplementary Figure 4

Overviews of ternary complex

(A) Front view of C5-OmCl-RaCl3 complex. (B) Cartoon showing domain organisation of C5 and interaction sites for both tick-inhibitors (yellow stars)

MG1 - MG2

<i>Homo_sapiens</i>	20	EQTYVISAPKIFRVGASENIVIQVYGYTEAFDATISIKSYDPDKKFSYSSGHVHLSSENKFQNSAILTI	87
<i>Macaca_mulatta</i>	20	EQTYVISAPKIFRVGASENIVIQVYGYTEAFDATISIKSYDPDKKFSYSSGHVHLSSENKFQNSAVLTI	87
<i>Canis_lupus</i>	20	EQTYVISAPKIVFRVGASENVIQVYGYTEEFDATISIKSYDPDRKFSYSSGYVTLSPENKFQNNVVLTI	87
<i>Felis_catus</i>	20	EQTYVISAPKIFRVGASENIVIQVYGYTEAFDATISLKSYPDKKFSYSSGYVTLSMENKFQNSAVLTV	87
<i>Sus_scrofa</i>	20	EQTYVISAPKILHVGAENIVVQVYGYTEAFVTVSVKSYDPDKKITYSSMYVILSTENKFQNSAFLTI	87
<i>Cavia_porcellus</i>	20	EQTYVISASKVLRVGASENIVIQVYGYTEAFDATISLKSYPDKKFSYASEYVNLSPENKFQNSAFLTI	87
<i>Oryctolagus_cuniculus</i>	20	EQTYVISAPKIVLRVGASENIVIQVYGYTEAFDSTISIKSYDPDKKFSYSSGYVLSSENKFQNSATLTI	87
<i>Rattus_norvegicus</i>	25	EQTYVISAPKIFRVGSSENVVIQAHGYTEAFDATISLKSYPDKKVITYSSGYVNLSPENKFQNSALLTL	92
<i>Mus_musculus</i>	25	EQTYVISAPKILRVGSSENVVIQVHGYTEAFDATLSLKSYPDKKVTFSSGYVNLSPENKFQNAALLTL	92
<i>Homo_sapiens</i>	88	QPKQLP GGQ NPVSYVYLEVSKHFSKSKRMPITYDNGFLFIHTDKPVYTPDQSVKVRVYSLNDDLKPA	155
<i>Macaca_mulatta</i>	88	QPKQLP GGQ QVSYVYLEVSKHFSKSKKIPITYDNGFLFIHTDKPVYTPDQSVKVRVYSLNDDLKPA	155
<i>Canis_lupus</i>	88	QPKQL SGGQ GPVSHVYLEVSRHFSKSKKVPITYDNGFLFIHTDKPIYTPQSVKVRVYSLNDDLKPA	155
<i>Felis_catus</i>	88	QPKQL SGGQ NPVSHVYLEVSKHFSRSKSKVPITYDNGFLFIHTDKPVYTPQSVKVRVYSLNDDLKPA	155
<i>Sus_scrofa</i>	88	QPKQL L L GKPN SVSHVYLDIVSKHFSRSKSKIPVITYDNGFLFIHTDKPVYTPHQSVKVRVYSLNDELKPA	155
<i>Cavia_porcellus</i>	88	QPKQL SGGQ NSVSHVYLEVSKHFSKSKKMPITYDNGFLFIHTDKPVYTPHQSVKVRVYSLNDDLKPA	155
<i>Oryctolagus_cuniculus</i>	88	QPKQL STGQ NAPSHVYLEVSKHFSRSKSKMPITYDNGFLFIHTDKPVYTPHQSVKVRVYSLNDDLKPA	155
<i>Rattus_norvegicus</i>	92	PPKQ F PRDENPVSHVYLEVSMHFSKSKKIPITYDNGFLFIHTDKPVYTPDQSVKIRVYSLSDDLKPA	160
<i>Mus_musculus</i>	92	QPNQ V PREESPVSHVYLEVSKHFSKSKKIPITYNNGILFIHTDKPVYTPDQSVKIRVYSLGDDLKPA	160
<i>Homo_sapiens</i>	156	KRETVLTFIDP EGSE EVDMEVEIDHIGIISFPDFKIPSNPRYGMWTIKAK YKED FSTTGTAFFEVKEYV	223
<i>Macaca_mulatta</i>	156	KRETVLTFIDP EGSE IDMVEEIDHIGIISFPDFKIPSNPRYGMWMIQAK YKED FSTTGTAFFEVKEYV	223
<i>Canis_lupus</i>	156	KRETVLTYIDP EGSE EVDIVEENDYTGIIISFPDFKIPSNPKYGVWTIRAK YKED FSTTGTTQFEVKEYV	223
<i>Felis_catus</i>	156	KRETVLTYIDP EGSE EVDIMEENDYTGIIISFPDFKIPSNPKYGVWTIRAK YKED FSTTATAYFEIKEYV	223
<i>Sus_scrofa</i>	156	KRETVLTFIDP QGS EVEVLEENDYTGIIISFPDFKIPSNPKYGVWTIQAK YRE DFSTTGTAFFEVKEYV	223
<i>Cavia_porcellus</i>	156	KRETVLTFIDP EGSE EVDMEVEENDYTGIIISFPDFKIPPNPKYGMWTIKAK YKED FSTSGTTHFEIKEYV	223
<i>Oryctolagus_cuniculus</i>	156	KRETVLVFIDP EGSE EVDMEVEENDYTGIIISFPDFKIPSNPKYGVWTIKAK YKED FSTTGTTYFEVKEYV	223
<i>Rattus_norvegicus</i>	161	KRETVLTFVDP EGT EVDIVEENDYTGIIISFPDFKIPSNPKYGVWTIKAK YKED FTTTGTAYFEVKEYV	228
<i>Mus_musculus</i>	161	KRETVLTFIDP EGSE EVDIVEENDYTGIIISFPDFKIPSNPKYGVWTIKAN YKED FTTTGTAYFEIKEYV	228

Supplementary Figure 5

RaCI contacts mapped onto cross-species sequence alignment of the MG1 and MG2 domains of C5.

C5 residues that make contact with one or more RaCIs in the crystal structures are highlighted in black (van der Waals interaction) and red (salt or hydrogen bonds).

C5d

<i>Homo_sapiens</i>	982	LLVGEILSAVLSQEGINILTHLPGGSAEAEELMSVVPVFYVFHYLETGNHWNIFHSDPLIEKQKLLK	1047
<i>Macaca_mulatta</i>	982	LLVGEILSAVLSREGINILTHLPGGSAEAEELMSVVPVFYVFHYLETGNHWNIFHSDPLIEKRNLEK	1047
<i>Canis_lupus</i>	982	MLMGEVMSAVLSQEGIDILTHLPGGNAEAEELMSVVPVFYVFHYLEAGSNWNIFSPNSLMKKQSLKN	1047
<i>Felis_catus</i>	983	LLIGEVMSTVLSQEGIDILTHLPGGNAEAEELMSIVPVFVFYVFHYLEAGKNWNIFSTNSLIQNQLRK	1048
<i>Sus_scrofa</i>	982	LLIGEVMSTVLSQEGIDILTHLPGGNAEAEELMSIVPVFVFYVFHYLEAGNNWNIFSSNSLAQRQNLQK	1047
<i>Cavia_porcellus</i>	982	MLMGEVLSTVLSKEGIDIITHLPRGNAEAEELMSIVPVFVFYVFHYLEAGNNWNIFYPHSLTKKQYLK	1047
<i>Oryctolagus_cuniculus</i>	982	LLIGEVLSTVLSQEGINILTHLPGGSAEAEELMSVAPVFVFYVFHYLETGNHWDIFSPNSLIKKQDLK	1047
<i>Rattus_norvegicus</i>	991	LLIGEFLLSTVLSKEGIDILTHLPGGSAEAEELMSIVPVFVFYVFHYLEAGNHWNIFHPDTLARKQSLQK	1056
<i>Mus_musculus</i>	991	LLVGEFLSTVLSKEGINILTHLPGGSAEAEELMSIAPVFVFYVFHYLEAGNHWNIFYPDTLSKRQSLK	1056
<i>Homo_sapiens</i>	1048	KLKEGMLSIMSRYRNADYSYSVWKGGSASTWLTAFALRVLGQVNKYVEQNQNSICNSLLWLVENYQL	1113
<i>Macaca_mulatta</i>	1048	KLKEGMVSIMSRYRNADYSYSVWKGGSASTWLTAFALRVLGQVHKYVEQNQNSICNSLLWLVENYQL	1113
<i>Canis_lupus</i>	1048	QLKQGMVSIITSYRNADYSYSMWKGGDASTWLTAFALRVLGQVQKYIGQNQNSICNTLLWLTENCQL	1113
<i>Felis_catus</i>	1049	KLKEGMVSIMSRYRNADSSYSMWKGGDASTWLTAFALRVLGQLNKYIEQNQNSICNTLLWLVENCQL	1114
<i>Sus_scrofa</i>	1048	KLREGVVSVMFSRNADHSYSMWKGGDASTWLTAFALRVLGQASKYIDQDLNSICNSLLWLVEKQCL	1113
<i>Cavia_porcellus</i>	1048	KIKEGMVSIMSRYRNADYSYSMWKGGDASTWLTAFALRVLGQVNKYVEQNQNSICNSLLWLVEKQCL	1113
<i>Oryctolagus_cuniculus</i>	1048	KLKEGIVSIMSRYRNADHSYSMWKGGDASTWLTAFALRVLGQVNKYVEHNQNLICNSLLWLVEKQCL	1113
<i>Rattus_norvegicus</i>	1057	KIKEGLVSVMSRYRNADYSYSMWKGASSAWLTAFALRVLGQVNKYVKQDQYSTICNSLLWLIEKQCL	1122
<i>Mus_musculus</i>	1057	KIKQGVVSVMSRYRNADYSYSMWKGASASTWLTAFALRVLGQVAKYVKQDENSTICNSLLWLVEKQCL	1122
<i>Homo_sapiens</i>	1114	DNGSFKENSQYQPIKLQGTLPVEARENLYLTAFTVIGIRKAFDICPLVKIDTALIKADNFLLNT	1179
<i>Macaca_mulatta</i>	1114	DNGSFKENSQYQPIKLQGTLPVEARENLYLTAFTVIGIRKAFDICPLVKINTALIKADTFLLNT	1179
<i>Canis_lupus</i>	1114	ENGSFKENSQYQPVKLQGTLPTEAHEHSLYLTAFAVIGIRKSFDLCPQLKINAALTRADAFLLLEGA	1179
<i>Felis_catus</i>	1115	ENGSFKENSQYQPIKLQGTLPVEARENTLYLTAFAVIGIRKAFDICSMLKINTAITKADTFLLNT	1180
<i>Sus_scrofa</i>	1114	GNGSFKENSEYQPIKLQGTLPVEAQENTLYLTAFAVIGIRKAFDLCPLMKISMALTKADTFLLNT	1179
<i>Cavia_porcellus</i>	1114	ENGSFKENSHYQPVKLQGTLPVEAENVLYLTAFTVIGIRKAFDICPLVKISAAVTKADTFLLNT	1179
<i>Oryctolagus_cuniculus</i>	1114	ENGSFKDSDSKYQPIKLQGTLPVEAKENLYLTAFTVIGIRKAFDLCPLKISTALTKAENFLLNT	1179
<i>Rattus_norvegicus</i>	1123	ENGSFKENSQYLPKIKLQGTLPVEAENTLYLTAFTVIGIRKAFDLCPLKISTALTKAENFLLERT	1188
<i>Mus_musculus</i>	1123	ENGSFKENSQYLPKIKLQGTLPVEAENTLYLTAFTVIGIRKAFDLCPLKISTALTKAENFLLERT	1188
<i>Homo_sapiens</i>	1180	LPAQSTFTLAIASAYALSLGDKTHPQFRSIVSALKREALVK-GNPPPIYRFWKDNLQ-HKDSSVPNTG	1243
<i>Macaca_mulatta</i>	1180	LPAQSTFTLAIASAYALSLGDKTHPQFRSIVSALKREALVK-GNPPPIYRFWKDSLQ-HKDSSVPNTG	1243
<i>Canis_lupus</i>	1180	PSARSTFTLAIASAYALSLGDRTHPQFYSIVSGLKRRKALVK-GTARS-----	1224
<i>Felis_catus</i>	1181	LSAQSTFTLAIASAYALSLGDKTHPQFRSIVSALKKKALVK-GDPVIYRFWKDDLQ-ESTSTPSPS	1244
<i>Sus_scrofa</i>	1180	RSTRSTFALAIASAYALSLGDKSHPQFRSIVSALKKEALVK-GNPPPIYRFWKDDLQ-KDRSVPNTG	1243
<i>Cavia_porcellus</i>	1180	VLSQNTFTLAIIVTYALSLGDRTHPQLRSIVSALKRRASVK-GNPPPIYRFWKDSLQ-EGSFAPNAA	1243
<i>Oryctolagus_cuniculus</i>	1180	LPAQSTFTLAIASAYALSLGDRTHPQFRAIASALKRAASVKGSPPIYRFWKDGLQHKDTSAPNAG	1245
<i>Rattus_norvegicus</i>	1189	LPSKSTFTLAIIVAYALSLGDRTHPKFRSIVSALKREALVK-GDPPPIYRFWRDLQR-PDSSAPNSG	1252
<i>Mus_musculus</i>	1189	LPSKSTFTLAIIVAYALSLGDRTHPRFRLIVSALRKEAFVK-GDPPPIYRYWRDLQR-PDSSVPSSG	1252
<i>Homo_sapiens</i>	1244	TARMVETTAYALLTSLNLKDINYNPVIKWLSEEQRYGGGFYSTQDTINAIEGLTEYSLLVKQ	1306
<i>Macaca_mulatta</i>	1244	TARMVETTAYALLTSLNLKDINYNPVIKWLSEEQRYGGGFYSTQDTINAIEGLTEYSLLVKQ	1306
<i>Canis_lupus</i>	1225	-----CPRRRDTINAIEGLTEYSLLIKQ	1247
<i>Felis_catus</i>	1245	TAHVETTAYALLTSLSLKDINYNPVIKWLSEEQRYGGGFYSTQDTINAIEGLTEYSLLIKQ	1307
<i>Sus_scrofa</i>	1244	TARMVETTAYALLTSLNLKDMNYPVIKWLSEEQRYGGGFYSTQDTINAIEGLTEYSLLIKN	1306
<i>Cavia_porcellus</i>	1244	TATMVETTSYALLTSLNLKDMNYPVIKWLSEEQRYGGGFYSTQDTINAIEGLTEYSLLIKQ	1306
<i>Oryctolagus_cuniculus</i>	1246	TAGMVETTAYALLTSLNLKEMNYPVIKWLSEEQRYGGGFYSTQDTINAIEGLTEYSLLVKQ	1308
<i>Rattus_norvegicus</i>	1253	TAGMVETTAYALLTSLNLKETSYPVIKWLSEEQRYGGGFYSTQDTINAIEGLTEYSLLVKQ	1315
<i>Mus_musculus</i>	1253	TAGMVETTAYALLASLKLKDMNYANPVIKWLSEEQRYGGGFYSTQDTINAIEGLTEYSLLKQ	1315

Supplementary Figure 6

RaCI contacts mapped onto cross-species sequence alignment of the C5d domain of C5.

C5 residues that make contact with one or more RaCIs in the crystal structures are highlighted in black (van der Waals interaction) and red (salt or hydrogen bonds). The large deletion in the *Canis lupus* sequence is likely due to sequencing or assembly errors and may not represent the actual sequence.

CUB - C5d

<i>Homo sapiens</i>	932	EGVKRESYSGVTLDPGGIYGT ISRRKE FPYRIPLDLVPKTEIKRILSVKGLLVGEILSAVLSQE	995
<i>Macaca mulatta</i>	932	EGVKRESYSGITLDPGGIYGT ISRRKE FPYRIPLDLVPKTEIKRILSVKGLLVGEILSAVLSRE	995
<i>Canis lupus</i>	932	EGIKKESYAGVTLDPGGIYGV ISRRKE FPYRIPLDLVPKTEVKRIVSVKGMLMGEVMSAVLSQE	995
<i>Felis catus</i>	933	EGIKKESYAGVTLDPGGIYGVV SRRKE FPYRIPLDLVPKTKVKRIVSVKGLLIGEVMSVTLVLSQE	996
<i>Sus scrofa</i>	932	EGVKRESYAGITLDPGGIYGAMT RRKE FPYRVPLDLVPKTKVKRIVSVKGLLIGEVMSAVLSQE	995
<i>Cavia porcellus</i>	932	EGVKRESYAGVTLDPGGIYGT TRRKE LPYKIPDLVPKTNVKRILSVKGMLMGEVLSTVLSKE	995
<i>Oryctolagus cuniculus</i>	932	EGVKRETHAGVTLDPGGIYGVV SRRKE FPYRIPLDLVPKTNVERIVSVKGLLIGEVLSAVLSKE	995
<i>Rattus norvegicus</i>	941	EGIKKESYAGVTLDPGGVYGV RRKE FPYRIPLDLVPKTNVKRILSVKGLLIGEFVLSVLSKE	1004
<i>Mus musculus</i>	941	EGVKRESYAGVILDPKGIIRGIVN RRKE FPYRIPLDLVPKTKVERILSVKGLLVGEFLSTVLSKE	1004
<i>Homo sapiens</i>	996	GINILTHLPGKSAEAEELMSVVPVYFVYFHYLETGNHWNIFHSDPLIEKQKLLKLLKEGMLSIMS	1059
<i>Macaca mulatta</i>	996	GINILTHLPGKSAEAEELMSVVPVYFVYFHYLETGNHWNIFHSDPLIEKRNLEKLLKEGMSIMS	1059
<i>Canis lupus</i>	996	GIDILTHLPGKNAEAEELMSVVPVYFVYFHYLEAGSNWNIFSPNSLMKKQSLKNQLKQGMVITSY	1059
<i>Felis catus</i>	997	GIDILTHLPGKNAEAEELMSIVPVYFVYFHYLEAGKNWNIFSTNSLIQNQLRKKLKEGMSIMS	1060
<i>Sus scrofa</i>	996	GIDILTHLPGKNAEAEELMSIVPVYFVYFHYLEAGNNWNIFSSNSLAQRQNLQKLLREGVSVMSF	1059
<i>Cavia porcellus</i>	996	GIDIITHLPRGNAEAEELMSIVPVYFVYFHYLEAGNNWNIFYPHSLTKKQYLKLLKEGMSIMS	1059
<i>Oryctolagus cuniculus</i>	996	GINILTHLPGKSAEAEELMSVAPVYFVYFHYLETGNHWDIFSPNSLIKKQDLKLLKEGIVSIMS	1059
<i>Rattus norvegicus</i>	1005	GIDILTHLPGKSAEAEELMSIVPVYFVYFHYLEAGNNWNIFHPDTLARKQSLKQKIKKEGLVMSY	1068
<i>Mus musculus</i>	1005	GINILTHLPGKSAEAEELMSIAPVYFVYFHYLEAGNNWNIFYPDTLSKRQSLKLLKEGIVSIMS	1068
<i>Homo sapiens</i>	1060	RNADYSYSVWKGGSASTWLTAFALRVLGQVNYVEQNQNSICNSLLWLVENYQLDNGSFKENSQ	1123
<i>Macaca mulatta</i>	1060	RNADYSYSVWKGGSASTWLTAFALRVLGQVHYVEQNQNSICNSLLWLVENYQLDNGSFKENSQ	1123
<i>Canis lupus</i>	1060	RNADYSYSMWKGGDASTWLTAFALRVLGQVQYIGQNNQNSICNTLLWLVENCQLENGSFKENSQ	1123
<i>Felis catus</i>	1061	RNADSSYSMWKGGASASTWLTAFALRVLGQLNKYIEQNQNSICNTLLWLVENCQLENGSFKENS	1124
<i>Sus scrofa</i>	1060	RNADHSYSMWKSGSASTWLTAFALRVLGQASKYIDQDLNSICNSLLWLVKQCQLGNGSFKENSE	1123
<i>Cavia porcellus</i>	1060	RNADYSYSMWKGGASASTWLTAFALRVLGQVNYVEQNQNSICNSLLWLVENCQLENGSFKENS	1123
<i>Oryctolagus cuniculus</i>	1060	RNADHSYSMWKGGASASTWLTAFALRVLGQVNYVEHNQNLICNSLLWLVENCQLENGSFKDSSK	1123
<i>Rattus norvegicus</i>	1069	RNADYSYSMWKGGASASTWLTAFALRVLGQVNYVVKQDQYSICNSLLWLVKQCQLGNGSFKENSQ	1132
<i>Mus musculus</i>	1069	RNADYSYSMWKGGASASTWLTAFALRVLGQVAKYVVKQDENSCNSLLWLVKQCQLGNGSFKENSQ	1132
<i>Homo sapiens</i>	1124	YQPIKLGQTLPEARENSLYLTAFTVIGIRKAFDICPLVKIDTALIKADNFFLENTLPAQSTFT	1187
<i>Macaca mulatta</i>	1124	YQPIKLGQTLPEARENSLYLTAFTVIGIRKAFDICPLVKINTALIKADTFLENTLPAQSTFT	1187
<i>Canis lupus</i>	1124	YQPVKLGQTLPEAHEHSLYLTAFAVIGIRKSFDLCPKINAALTRADAFLLLEGAPSARSTFT	1187
<i>Felis catus</i>	1125	YQPIKLGQTLPEARENTLYLTAFAVIGIRKAFDICSLMKINTAITKADTFLENTLSAQSTFT	1188
<i>Sus scrofa</i>	1124	YQPIKLGQTLPEAQENTLYLTAFAVIGIRKAFDLCPKIMKINTAITKADTFLENTLRSTRSTFA	1187
<i>Cavia porcellus</i>	1124	YQPVKLGQTLPEAQENVLYLTAFTVIGIRKAFDICPLVKISAATKADTFLENTVLSQNTFT	1187
<i>Oryctolagus cuniculus</i>	1124	YQPIKLGQTLPEAKENSLYLTAFTVIGIRKAFDLCPKIKISTALTKAENFFLENTLPAQSTFT	1187
<i>Rattus norvegicus</i>	1133	YLPKLGQTLPEAQENTLYLTAFSVIGIRKAFDICPLVKISTALTKAENFFLENTLPSKSTFT	1196
<i>Mus musculus</i>	1133	YLPKLGQTLPEAQEKTLYLTAFSVIGIRKAFDICPTMKIHTALDKADSFLENTLPSKSTFT	1196
<i>Homo sapiens</i>	1188	LAI SAYALSLGDKTHPQFRSIVSAL KREALVK -GNPPIYRFW KDNLQ -HKD SSVPNT TGTARMVE	1249
<i>Macaca mulatta</i>	1188	LAI SAYALSLGDKTHPQFRSIVSAL KREALVK -GNPPIYRFW KDNLQ -HKD SSVPNT TGTARMVE	1249
<i>Canis lupus</i>	1188	LAI AAYALSLGDRTHPQFYSIVSGL KRALVK -GTARS-----	1224
<i>Felis catus</i>	1189	LAI AAYALSLGDKTHPQFRSIVSAL KKALVK -GDPVIYRFW KDDLQ -EST STP SPSTAHVVE	1250
<i>Sus scrofa</i>	1188	LAI AAYALSLGDKSHPQFRSIVSAL KREALVK -GNPPIYRFW KDDLQ -KDR SVPN TGTARMVE	1249
<i>Cavia porcellus</i>	1188	LAI VTYALSLGDRTHPQLRSIVSAL KRASVK -GNPPIYRFW KDNLQ -EG SFAPNA AATATMVE	1249
<i>Oryctolagus cuniculus</i>	1188	LAI AAYALSLGDRTHPQFRAIASAL KRAASVK GGSPPIYRFW KDQLQ HKDTS APNA GATAGMVE	1251
<i>Rattus norvegicus</i>	1197	LAI VAYALSLGDRTHPKFRSIVSAL KREALVK -GDPPIYRFW RDTLQR -PDS SAPNS GTAGMVE	1258
<i>Mus musculus</i>	1197	LAI VAYALSLGDRTHPRFRLIVSAL KEAFVK -GDPPIYRFW RDTLKR -PDS SSVP SSGTAGMVE	1258
<i>Homo sapiens</i>	1250	TTAYALLTSLNLKDIYVNPVIKWLSEEQRYGGGFYSTQDTINAIEGLTEYSLLVQKRLRSM	1313
<i>Macaca mulatta</i>	1250	TTAYALLTSLNLKDIYVNPVIKWLSEEQRYGGGFYSTQDTINAIEGLTEYSLLVQKRLRNM	1313
<i>Canis lupus</i>	1225	-----CPRRRDINAIEGLTEYSLLIKQLHLNMDV	1254
<i>Felis catus</i>	1251	TTAYALLTSLSLKDIYVNPVIIRWLSEEQRYGGGFYSTQDTINAIEGLTEYSLLIKQLHLNMD	1314
<i>Sus scrofa</i>	1250	TTAYALLTSLNLKDMNYVNPVIKWLSEEQRYGGGFYSTQDTINAIEGLTEYSLLIKNQLNMDV	1313
<i>Cavia porcellus</i>	1250	TTSYALLTSLNLKDMNYVNPVIKWLSEEQRYGGGFYSTQDTINAIEGLTEYSLLIKQHLNMDI	1313
<i>Oryctolagus cuniculus</i>	1252	TTAYALLTSLNLKEMNYVNPVIKWLSEEQRYGGGFYSTQDTINAIEGLTEYSLLVQKQLDMDI	1315
<i>Rattus norvegicus</i>	1259	TTAYALLTSLNLKETSIVNPVIKWLSEEQRYGGGFYSTQDTINAIEGLTEYSLLVQKHLDM	1322
<i>Mus musculus</i>	1259	TTAYALLASLKLKDMNYANPVIKWLSEEQRYGGGFYSTQDTINAIEGLTEYSLLKQIHLDM	1322
<i>Homo sapiens</i>	1314	DVSYKHKHGALHNYKMTDKNFLGRPVEVLLNDDLIV-STGFGSGLATVHVTTVVHKTSTSE	1372
<i>Macaca mulatta</i>	1314	DVAYKHKHGALHNYKMTDKNFLGRPVEVLLNDDLIV-STGFGSGLATVHVTTVVHKTSTSE	1372
<i>Canis lupus</i>	1255	KISYKHKGDLHYHKMTEKNFLGRPIEVPLNDDLIV-STGFSNGLATVHVTTVVQKTSTSE	1313
<i>Felis catus</i>	1315	NVSYKHKGDLHRYKMTETNFLGRPIEVPLNDDLIV-STGYSNGLATVHVTTVVQKTSTSD	1373
<i>Sus scrofa</i>	1314	KVSYKHRGDFYHYKITEKNFLGRPVEVPLNDDLIVVSTGQNSGLATVHVKTVVHKTSTSE	1373
<i>Cavia porcellus</i>	1314	NVSYKHKGDFYHYKVTDKNFLGRPVEVPLNDDLI-STGHSNGLATVHVKTVVHKTGTSE	1372
<i>Oryctolagus cuniculus</i>	1316	NVSYKHKGNFQYKITEKNFLGKPEVPLDDDLVI-STGHSNGLATVHVATVVHKTSTSE	1374
<i>Rattus norvegicus</i>	1323	NVSYKHKGDFYQYKTEKNFLGRPVEVPLNDDLIV-TTGYSSGLATVYKVVHKTVAE	1381
<i>Mus musculus</i>	1323	NVAYKHEGDFHYKYTEKNFLGRPVEVPLNDDLIV-STGYSSGLATVYKVVHKTVAE	1381

Supplementary Figure 7

OmCI contacts mapped onto cross-species sequence alignment of the CUB and C5d domains of C5.

C5 residues that make contact with OmCI in the crystal structures are highlighted in black (van der Waals interaction) and red (salt or hydrogen bonds). The large deletion in the *Canis lupus* sequence is likely due to sequencing or assembly errors and may not represent the actual sequence.

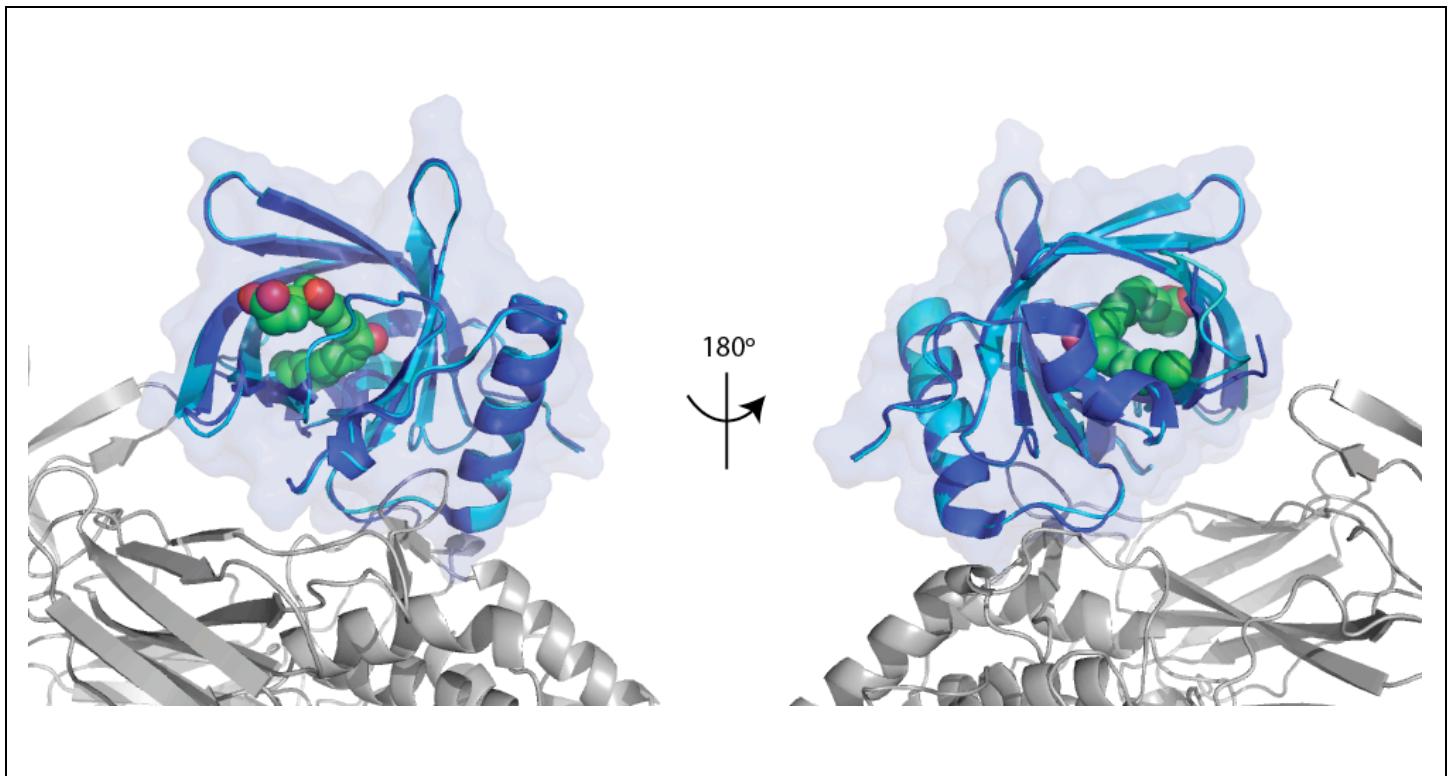
C345c

<i>Homo_sapiens</i>	1503	KQCTMFYSTSNIKIQKVCEGAACKCVEADCGMQQEELDLTISAETRKQTACKPEIAYAYKVSIT	1566
<i>Macaca_mulatta</i>	1503	KQCTMFYSTSNIKIQKVCEGATCKCIEADCGMQKELDLTISAETRKQTACNPEIAYAYKVIIT	1566
<i>Canis_lupus</i>	1444	KQCTMFYSPSGSKLQKVCEGVTCKCIEADCGMQAELDLTISADARKETACKPDIAYAYKVHIT	1507
<i>Felis_catus</i>	1504	KQCTMFYNPFDARLQKVCEGVTCKCIEADCGMQTELDLTISADTRKETACKPDIAYAYKVRIT	1567
<i>Sus_scrofa</i>	1501	KQCTMFYSMSQTKLQKVCEGVTCKCIEADRGQMTEVDLTISVNTRKETACKPEIAYVYKVKII	1564
<i>Cavia_porcellus</i>	1503	KQCTMFYSASDTKLQKVCEEATCKCIEADCGQMEKELDLTISADARKEIACKPEIAYVYKVSIT	1566
<i>Oryctolagus_cuniculus</i>	1502	KQCTMFYSTSNTKLQRVCEGTLCKCIEADCGQMEKELDLTISAETRKEKACKPEIVYAYKVSIT	1565
<i>Rattus_norvegicus</i>	1512	KQCTMIYSTSDTNLQRVCEGAACKCVEADCGQLQAELDLAISADTRKETACKPEIAYAYKVRIT	1575
<i>Mus_musculus</i>	1512	KQCTMIYSISDTRLQKVCEGAACCTCIEADCAQLQAEVDLAISADSRKEKACKPETAYAYKVRIT	1575
<i>Homo_sapiens</i>	1567	SITVENFVKYKATLLDIYKTGEAVAEKDSEITFIKKVTCTNAELVKGRQYLIMGKEALQIKYN	1630
<i>Macaca_mulatta</i>	1567	SITTFENFVKYKATLLDIYKTGEAVAEKDSEITFIKKVTCTNAELVKGRQYLIMGKEALQIKYN	1630
<i>Canis_lupus</i>	1508	SITKENVFIKYATLLDVYKAGEAAAQKDSEITFIKKATCANAELEKGRHYLIMGKEALQIKHN	1571
<i>Felis_catus</i>	1568	SITKENVFKYTATLLDIYKAGEAVAQKDSVTFIKKVTCANADLEKGRQYLIMGKEALQIKYN	1631
<i>Sus_scrofa</i>	1565	AMTEESAFVKYTASLLDVYKAGEAVAEGSEITFIKKTTCTNANLEKGRQYLIMGKEALQIKHN	1628
<i>Cavia_porcellus</i>	1567	SMMKENAFVKYTATLLDIYKAGDAVAEKGEITFIKKVSCANADLEKGRQYLIMGKEALQIKHN	1630
<i>Oryctolagus_cuniculus</i>	1566	SITEENFVKYTATLLDVYKTGEAIAEKGEITFIKKTTCANADLLKGRQYLIMGKEALQIKHN	1629
<i>Rattus_norvegicus</i>	1576	SATEENIFVKYTATLLDIYKTGEAAAQKDSEITFIKKISCTNANLVKGRQYLIMGKEALQIKHN	1639
<i>Mus_musculus</i>	1576	SATEENFVKYTATLLVTYKTGEAAD-ENSEVTFIKKMSCTNANLVKGRQYLIMGKEVLQIKHN	1638
<i>Homo_sapiens</i>	1631	FSFRYIYPLDSLWIEYWPRD-TTCSSCQAFLANLDEFAEDIFLNGC---	1676
<i>Macaca_mulatta</i>	1631	FTFRYIYPLDSLWIEYWPRD-TTCSSCQAFLANLDEFAEDIFLNGC---	1676
<i>Canis_lupus</i>	1572	FSFKYIYPLDSSTWIEYWPTADAACPACPAFLANLDEFAEDIFLNGCENS	1621
<i>Felis_catus</i>	1632	FSFKYLYPLDSSTWIEYWPTN-AMCPSCQAFLANLDEFAEDIFLNGCENP	1680
<i>Sus_scrofa</i>	1629	FNFKYIYPLDSSTWIEYWPTD-TACPSCQTFLANLDEFTEDI FLNNCENA	1677
<i>Cavia_porcellus</i>	1631	FSFKYIYPLDSSTWIEYWPS--VTCSSCQAFLANLDEFAEDIFLNGCENA	1678
<i>Oryctolagus_cuniculus</i>	1630	FSFKYIYLLDSWTWIEYWPSD-TTCPSCQAFSANLDEFAEDIFLNGCENA	1678
<i>Rattus_norvegicus</i>	1640	FSFKYIYPLDSSTWIEYWPTD-TTCPSCQAFVANLDEFAEDIFLNGCENA	1688
<i>Mus_musculus</i>	1639	FSFKYIYPLDSSTWIEYWPTD-TTCPSCQAFVENLNNFAEDLFLNSCE--	1685

Supplementary Figure 8

OmCI contacts mapped onto cross-species sequence alignment of the C345c domain of C5.

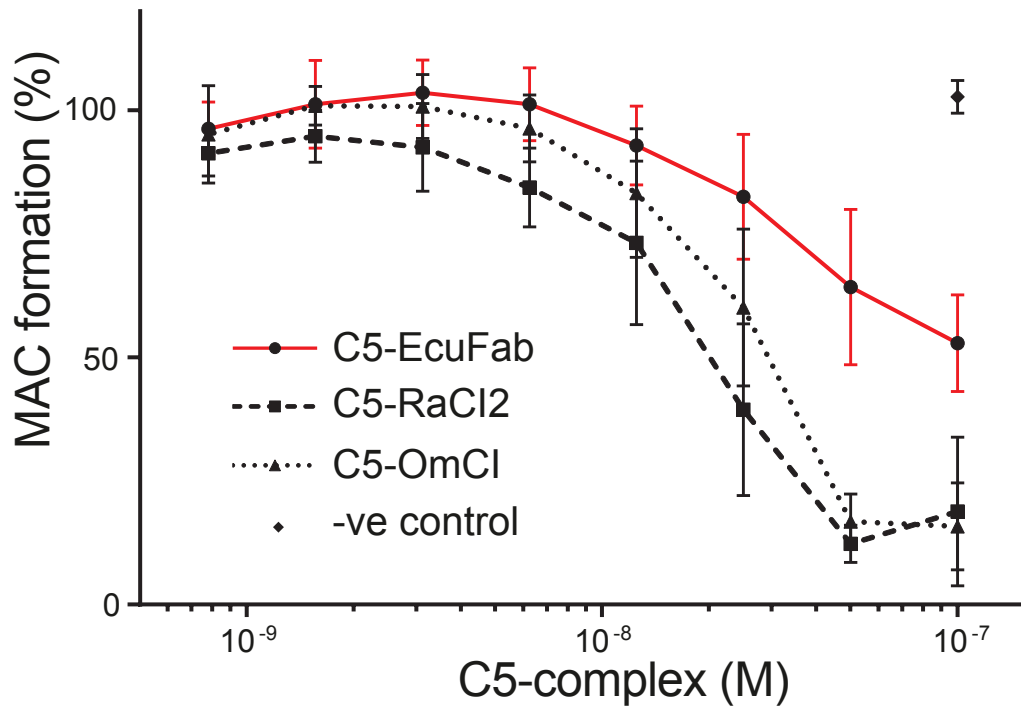
C5 residues that make contact with OmCI in the crystal structures are highlighted in black (van der Waals interaction) and red (salt or hydrogen bonds).



Supplementary Figure 9

OmCI can bind C5 and LTB4 simultaneously

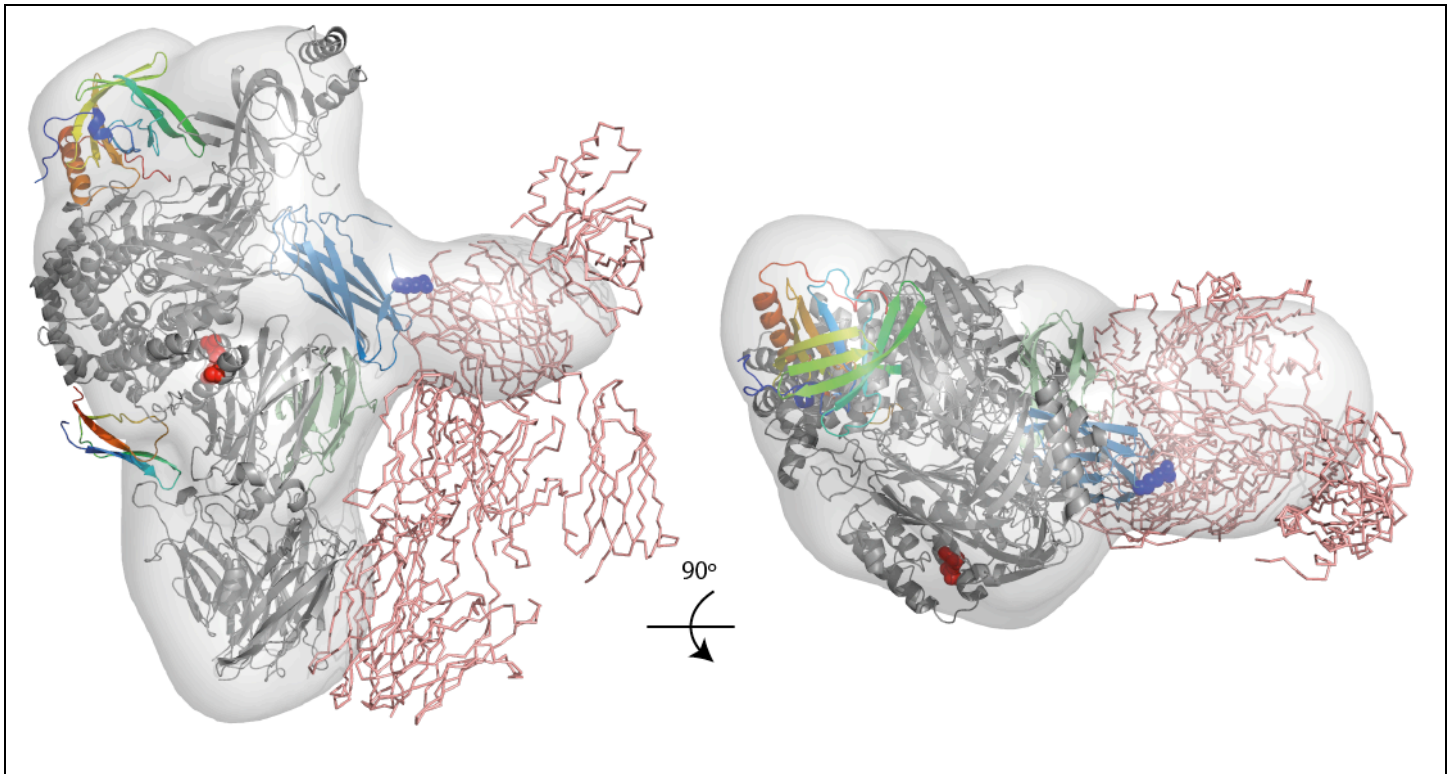
An overlay of the structure of OmCI (blue cartoon) in complex with LTB4 (VDW spheres, carbon-green, oxygen-red) (PDB ID 3zuo; Roversi et al., J. Biol. Chem 288, 18789-18802, 2013) onto OmCI (cyan cartoon) in complex with C5 (grey cartoon) demonstrates that LTB4 binding and exchange are both compatible with C5 binding. Two views related by a rotation of 180 degrees are shown with the view on the right hand side being equivalent to the views of the complex shown in Fig. 2.



Supplementary Figure 10

The binary inhibited C5 complexes are competitive inhibitors of further C5 cleavage by the native convertase

Purified binary C5 complexes with any of OmCl, RaCl or EcuFab compete with C5 at an initial stage of the activation pathway. -ve control is histamine-binding protein 2. Error bars, s.e.m. ($n = 6$; 2 independent experiments with 3 technical replicates each).



Supplementary Figure 11

Eculizumab sterically hinders the binding of CVF to C5.

Crystal structure of C5-OmCI-RaCI fitted in the EM envelope as in Figure 5E. Superposition of C5-CVF complex (Laursen *et al.*, *EMBO J.* **9**,606-616, 2011) on the C5-OmCI-RaCI structure results in a steric clash between CVF (salmon ribbon) and the EM volume where the Fab is positioned.