Supplementary Table 1. Interactions between the N- (D1-D2) and C- (D3-D4) terminal modules of the IC5-4D molecule in the crystals.

Interface A: $P4_322$ (840 Å^2)

D1	Arg 33 Glu 37 Arg 74	Asp 221 Arg 201 Asp 249	**D3**
D2	Arg 112 Arg 119 Arg 144	Asp 353 Asp 357 Thr 362 Glu 361	**D4**
	Arg 146	Thr 362	

Interface B: $P2_1$ (570 Å^2), R3 (470 Å^2)

D1	Glu 32 Arg 33 Leu 36 Arg 42 Thr 45 Arg 47 Gly48 Arg 54 Arg 71	Ser 349 Asp 345 Asn344 Asn 344 Glu 343 Glu 343 Tyr375 Arg347 Glu 343 Asn 344 Glu 324	**D4**

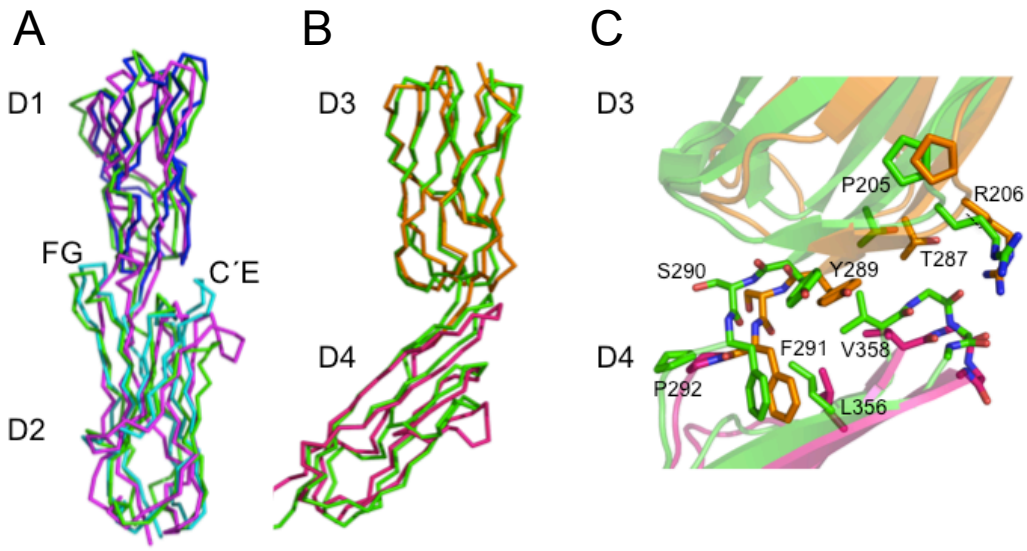
Interface C: $P2_1$ (600 Å^2)

D1	Arg 75	Asp 357	**D4**
D2	Arg 119 Arg 144	Asp 198 Glu 284	**D3**
D3	NAG 2851	Ser 39 Glu 61 Glu 63 Thr64 Gln 65 Arg 80 Arg 144	**D1** **D2**
	NAG 2852	Ser39 Glu61 Glu63 Thr64	**D1**
	BMA 2853	Ser 39 Leu 40 Arg 41	**D1**
	MAN 2854	Leu 40 Arg 41 Val 57 Asp 58 Arg 60 Glu 61	**D1**

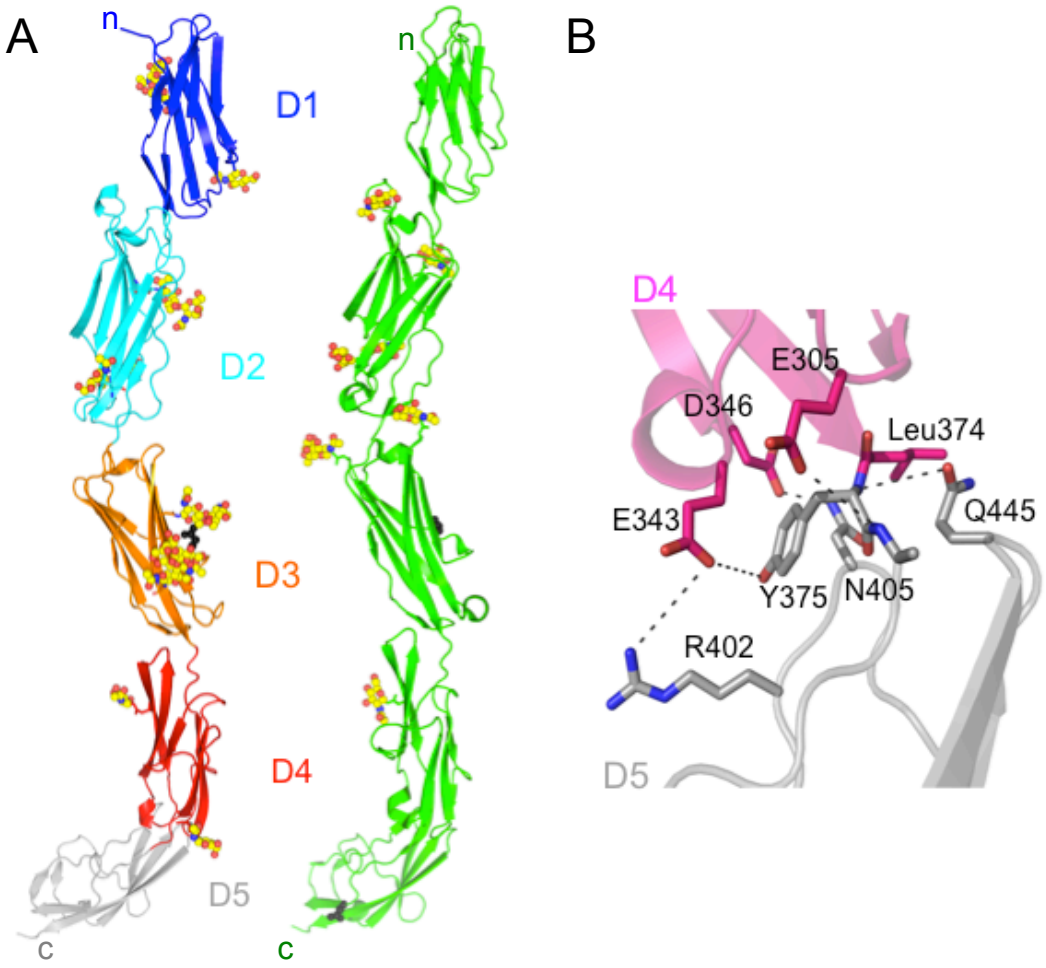
Interface D: $P2_1$ (500 Å^2)

D1	Glu 15 Ser 19	Arg 372 Tyr 375 Ser 304	**D4**
D2	Arg 88 Asp 90	Asp 346 Val 373 Arg 372	

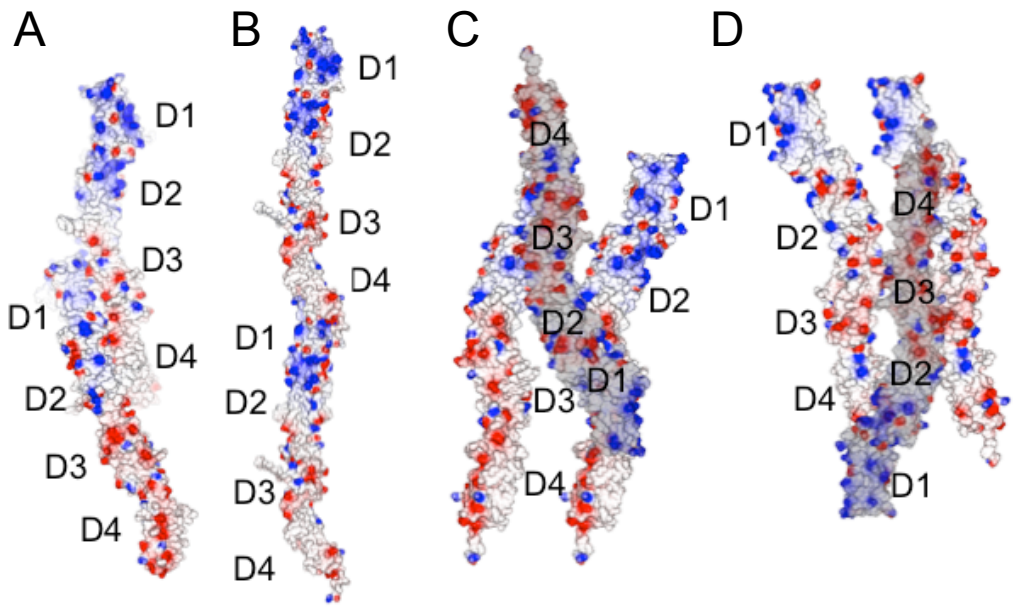
Intermolecular interfaces A to D in the IC5-4D crystals, with buried surface areas (parenthesis) over 500 Å^2 in each interacting molecule. Residues involved in polar interactions (salt bridges and hydrogen bonds) between IC5-4D molecules, computed with PISA. Residues in the N-terminal D1-D2 module and the interacting residues in the C-terminal D3-D4 module are on the same file of the table. Basic and acid residues are in blue and red, respectively. Interacting molecules are shown in Supplementary Figure 3.



Supplementary Figure 1. Two-domain modules in the ICAM subfamily. (A) Superposition of the D1-D2 modules of ICAM-5 (D1 blue and D2 cyan), ICAM-1 (green) and ICAM-2 (magenta). (B) Superposition of the D3-D4 modules of ICAM-5 (D3 orange and D4 red) and ICAM-1 (green). (C) View of the D3-D4 interdomain region in ICAM-5 and ICAM-1, with conserved residues shown in stick. ICAM-5 residues labeled.



Supplementary Figure 2. Structural models of the N-terminal five domain fragments of ICAM-5 and ICAM-1. Ribbon diagrams of models prepared as described in Methods. (A) The IC5-5D fragment is shown on the left with D1-D4 fragment structure represented in Figure 1, and the modeled D5 in grey. The ICAM-1 structure is green. Side chains of asparagines with N-linked glycosylations are shown in sticks, and the N-linked carbohydrates in the structures as spheres with carbon in yellow, nitrogen, blue and oxygen, red. Asparagine residues without any modeled carbohydrate in the structures (Asn239 in ICAM-5; Asn233 and Asn379 in ICAM-1) are shown in black. (B) View of the modeled D4-D5 interdomain region of ICAM-5, with conserved residues in ICAM-1 shown in stick.



Supplementary Figure 3. Interactions between the N and C-terminal portions of IC5-4D molecules in the crystals. Surface representation of interacting IC5-4D molecules showed with their electrostatic surface potential. Homodimers with the highest buried surface area (BSA $\geq$ 500 Å^2) in the IC5-4D crystal structures are show. Intermolecular interaction in the $P4_322$ (interface A) and $P2_1$ (interface B) crystal structures are shown in (A) and (B), respectively, where molecules follow head-tail parallel packing. Homodimers shown in (B) are similar to crystal contacts found in the R3 crystal structure. Two distinct antiparallel arrangements of the IC5-4D molecules in the $P2_1$ crystal structure, interfaces C and D, are shown in (C) and (D), respectively. The head (D1-D2) and tail (D3-D4) of one IC5-4D molecule (shaded) contacts two symmetry-related molecules, so that ~1000 Å^2 of its accessible surface is buried. Buried surface areas and residues in the interfaces are included in Supplementary Table 1. Details of the interfaces A to C are shown in Figure 5.