Supplementary Table S1. Interactions between the N- (D1-D2) and C- (D3-D4) terminal modules of the IC5-4D molecule in the crystals.

Interface A: $\mathrm{P}_{3} 22\left(840 \AA^{2}\right)$

| D1 | Arg 33 Glu 37 Arg 74 | $\begin{aligned} & \hline \text { Asp } 221 \\ & \text { Arg } 201 \\ & \text { Asp } 249 \end{aligned}$ | D3 |
| :---: | :---: | :---: | :---: |
| D2 | Arg 112 | Asp 353 | D4 |
|  | Arg 119 | Asp 357 |  |
|  |  | Thr 362 |  |
|  | Arg 144 | Glu 361 |  |
|  | Arg 146 | Thr 362 |  |

Interface C: P2 ${ }_{1}\left(600 \AA^{2}\right)$

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

Interface B: P2 $1_{1}\left(570 \AA^{2}\right), \mathrm{R} 3\left(470 \AA^{2}\right)$

| D1 | Glu 32 | Ser 349 |  |
| :--- | :--- | :--- | :--- |
|  | Asp 345 |  |  |
|  | Leu 36 | Asn344 |  |
|  |  |  |  |
|  | Glu 343 |  |  |
| Thr 45 | Glu 343 |  |  |
| Arg 47 | Tyr375 |  |  |
| Gly48 | Arg347 |  |  |
| Arg 54 | Glu 343 |  |  |
|  | Arg 71 | Asn 344 |  |

Interface D: P2 $1_{1}\left(500 \AA^{2}\right)$

| D1 | Glu 15 | Arg 372 <br> Tyr 375 <br> Ser 304 | D4 |
| :--- | :--- | :--- | :--- |
|  | Ser 19 | Din |  |
| D2 | Arg 88 | Asp 346 <br> Val 373 <br> Arg 372 |  |
|  | Asp 90 |  |  |

Intermolecular interfaces A to D in the IC5-4D crystals, with buried surface areas (parenthesis) over $500 \AA^{2}$ 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 Fig. S3.


Supplementary Figure S1. Two-domain modules in the ICAM subfamily. (a) Superposition of the D1-D2 modules of ICAM-5 (D1 blue and D2 cyan), ICAM1 (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) Ribbon diagram of the D3-D4 interdomain regions in ICAM-5 and ICAM-1, with conserved residues shown in stick. ICAM-5 residues labeled.

(b)


Supplementary Figure S2. Structure of the N-terminal five domain fragments of ICAM-5 and ICAM-1. Ribbon diagrams of the models prepared as described in Methods. (a) The IC5-5D fragment is shown on the left with D1-D4 fragment structure represented in Fig. 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.


(d)


Supplementary Figure S3. Interactions between the $\mathbf{N}$ 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 ( $\mathrm{BSA} \geq 500 \AA^{2}$ ) in the IC5-4D crystal structures are show. Intermolecular interaction in the P 4322 (interface A) and $\mathrm{P} 2_{1}$ (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 $\mathrm{P} 2_{1}$ 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 symmetryrelated molecules, so that $\sim 1000 \AA^{2}$ of its accessible surface is buried. Buried surface areas and residues in the interfaces are included in Supplementary Table S1. Details of the interfaces A to C are shown in Fig. 5.

