Why structurally different cyclic peptides can be glycomimetics of the HNK-1 carbohydrate antigen

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Supporting Information

Figure 1S

Figure 1S. Compound **1** was added to compound **4**

(KGVSSRSYVGCIKNLEISRST) in a stepwise manner at $T = 300$ K. The Asn14 and Arg19 NH signals as well as the Tyr8 $\epsilon 1$ signal (b) of **4** are labelled. The first (bottom) trace (a, b) shows signals of **4** without any ligand. The second trace (a, b) corresponds to an equimolar ratio of **1** and **4**, the third trace (a, b) illustrates the two-fold molar excess of **1**, and in the fourth trace (a only) there is a three-fold molar excess.

Figure 2S

Figure 2S. Overlay of characteristic spectral parts of **4**

(KGVSSRSYVGCIKNLEISRST) demonstrating binding specificity by signal alteration (black without, red with compound **2**). Compound **2** was added in a two-fold molar excess to **4** at $T = 300$ K.

S3

2JD4	MOUSE LAMININ ALPHA1 CHAIN, DOMAINS LG4-5
Chains	A,B
E Value	5.9E-2
Characteristics	Release Date: 27-Feb-2007 Exp. Method: X Ray Diffraction
Classification	Resolution: 1.90 Å Metal Binding Protein
Compound	Polymer: 1 Molecule: LAMININ SUBUNIT ALPHA-1 Fragment: DOMAINS LG4-5, RESIDUES 2706-3084 Mutation: YES Chains: A,B
Authors	Harrison, D., Hussain, S.A., Combs, A.C., Ervasti, J.M., Yurchenko, P.D., Hohenester, E.
Alignment stats	initn: 42 init1: 42 opt: 52 Z-score: 152.8 bits: 32.8 E(): 0.059 Smith-Waterman score: 52 S-W identity: 0.5 S-W similarity: null Overlap length: 20
1CQ3	STRUCTURE OF A SOLUBLE SECRETED CHEMOKINE INHIBITOR, VCCI, FROM COWPOX VIRUS
Chains	A,B
E Value	1.3E0
Characteristics	Release Date: 12-Nov-1999 Exp. Method: X Ray Diffraction
Classification	Resolution: 1.85 Å Cytokine
Compound	Polymer: 1 Molecule: VIRAL CHEMOKINE INHIBITOR Fragment: NATIVE PROTEIN Chains: A,B
Authors	Carfi, A., Smith, C.A., Smolak, P.J., McGrew, J., Wiley, D.C.
Alignment stats	initn: 40 init1: 40 opt: 43 Z-score: 129.0 bits: 27.7 E(): 1.3 Smith-Waterman score: 43 S-W identity: 0.44 S-W similarity: null Overlap length: 25

Figure 4S. Sequence alignment of the 21mer laminin fragment (**4**) vs. PDB structures. 2JD4 (the murine laminin α -1LG4/G5) is the best target structure.

Figure 5S.

Mouse	25	QQRGLFPAILNLATNAHISANATCGEKGPEMFCKLVEHVPGRPVRAQCRVCDGNSTNPR	84
Human	18	+QRGLFPAILNLA+NAHIS NATCGEKGPEMFCKLVEHVPGRPV+ QCR+CDGNS NPR RQRGLFPAILNLASNAHISTNATCGEKGPEMFCKLVEHVPGRPVNPQCRICDGN SANPR	77
Mouse	85	ERHPISHAIDGTNNWWQSPSIQNGREYHWVTITLTLRQVFQVAYII IKAANAPRPGNWIL	144
Human	78	ERHPISHAIDGTNNWWQSPSIQNGREYHWVT+TLDLRQVFQVAY+IIKAANAPRPGNWIL	137
Mouse	145	ERSVDGVKFKPWQYYAVSDTECLTRYKITPRRGPPITYRADNEVICTSYYSKLVPLEHGEI	204
Human	138	ERS+DG F PWQYYAVSD+ECL+RY ITPRRGPPTYRAD+EVICTSYYS+LVPLEHGEI ERSLDGTTFSFWQYYAVSDSECLSRYNITPRRGPPITYRADDEVICTSYYSRLVPLEHGEI	197
Mouse	205	HTSLINGRPSADDPSPQLLEFTSARYIRLRLQRI RTLNADLMTLSHRDLRDLDPIVTRRY	264
Human	198	HTSLINGRPSADD SP+LLEFTSARYIRLRLQRI RTLNADLMTLSHR+ ++LDPIVTRRY HTSLINGRPSADDLSFKLLEFTSARYIRLRLQRI RTLNADLMTLSHREPKELDPIVTRRY	257
Mouse	265	YYSIKDISVGGMCICYGHASSCPWDEEAKQLQCQCEHNTCGESCDRCCPGYHQQPWRPGT	324
Human	258	YYSIKDISVGGMCICYGHASSCPWDE K+LQCQCEHNTCGESC+RCCPGYHQQPWRPGT YYSIKDISVGGMCICYGHASSCPWDETTKKLQCQCEHNTCGESCNRCCPGYHQQPWRPGT	317
Mouse	325	ISSGNECEECNCHNKA KDCYYDSSVAKERRSLNTAGQYSGGGVCVNC SQNTTGINCETCI	384
Human	318	+SSGN CE CNCHNKA KDCYYD SVAK+++SLNTAGQ+ GGGVC+NC QNT GINCETCI VSSGNTCEACNCHNKA KDCYYDESVAKQKSLNTAGQFRGGGVCINCLQNTMGINCETCI	377
Mouse	385	DQYYRPHKVPYDDHPCRPNCDPVGSLSSVCIKDDRHADLANGWPGQCPCRKYAGDK	444
Human	378	D YYRPHKVPY+D PCRPNCDPVGSLSSVCIKDD H+DL NGK PGQCPC++GY G+K DGYYRPHKVPYDEDEPCRPNCDPVGSLSSVCIKDDLHSDLHNGKQPGQCPCKEGYTGEK	437
Mouse	445	CDRCQFGYRGFPNCIPDCDRTVGS LNEDPCIEPCLCKKNVEGKNCDRCKPGFYNLKERNP	504
Human	438	CDRCQ GY+ +P C+ C C VGS +++PC PC+CK+NVEGK CDRCKPGFYNLKE+NP CDRCQLGYKDYPTCVSCGNPVG SASDEPCTGPCVCKENVEGKACDRCKPGFYNLKEKNP	497
Mouse	505	EGCSECFCFGVSGVCDSLTWSISQVTNMSGWLVTDL MSTNKIRSQQDVLGGHRQISINNT	564
Human	498	GCSECFCFGVS VC SL+W + QV +MSGWLVTDL+S KI SQQD LGG Q+SINNT RGCSECFCFGVSDVCSLSWFPVGQVNSMSGWLVTDLISPRKIPSQQDALGGRHQVSINNT	557
Mouse	565	AVMQRLTSTYYWAAPEAYLGNKLTAFGGFLKYTVSYDIPVETVDS LMSHADII IKG NGL	624
Human	558	AVMQRL YYWAAPEAYLGNKLTAFGGFLKYTVSYDIPVETVDS+LMSHAD+II IKG NGL AVMQRLAPKYWAAPEAYLGNKLTAFGGFLKYTVSYDIPVETVDSNLMSHADVII IKG NGL	617
Mouse	625	TISTRAEGLSLQPYEYFNVRVLVPENFRDFNTRREIDRQ LMTVLANVTHLLIRANYNS	684
Human	618	T+ST+AEGLSLQPYEY NVVRLVPENF+DF+++R+IDRQ LMTVLANVTHLLIRA YNS TLSTQAEGLSLQPYEYLVNVRVLVPENFQDFHSKRQIDRQ LMTVLANVTHLLIRATYNS	677
Mouse	685	AKMALYRLDSVSLDIASPNALDLA VADVEHCECPQGYTGTSCEACLPGYRVDGILFGG	744
Human	678	AKMALYRL+SVSLDIAS NAIDL VAADVEHCECPQGYTGTSCE+CL GYRVDGILFGG AKMALYRLSVSLDIASSNAIDLVAADVEHCECPQGYTGTSCE SCLSGYRVDGILFGG	737
Mouse	745	ICQPCECHGHASECDIHGICSVCTHNTTG DHC EQCLPGFYGTSPRGTPGDCQPCACPLSI	804
Human	738	ICQPCECHGHA+EC++HG+C C HNTTG HCEQCLPGFYG PSRGTPGDCQPCACPL+I ICQPCECHGHAAECNVHGVCIACAHNTTG VHC EQCLPGFYGEP SRGT PGDCQPCACPLTI	797
Mouse	805	DSNNFSPTCHLTDGEEVVCDQCAPGYSGSWCERCADGYGNPTVPGGTCVPCNCSGNVDP	864
Human	798	SNNFSPTCHL DG+EVVCD CAPGYSG+WCERCADGYGNPTVPG +CVPC+CSGNVDP ASNNFSPTCHLNDGDEVVCDWCAPGYSGAWCERCADGYGNPTVPGESCVPCDCSGNVDP	857
Mouse	865	LEAGHCDSVTGECLKCLWN TDGAHCERCADGFYGD AVTAKNCRACDCHENGSLSGVCHLE	924
Human	858	EAGHCDSVTGECLKCL NTDGAHCERCADGFYGD AVTAKNCRAC+CH GS S VCHLE SEAGHCDSVTGECLKCLGN TDGAHCERCADGFYGD AVTAKNCRACECHVKGSHSAVCHLE	917
Mouse	925	TGLCDCKPHVTGQQCDQCLSGYYGLDTGLGCVPCNCSVEGVSVDNCTE EGQCHCGPGVSG	984
Human	918	TGLCDCKP+VTGQQCDQCL GYYGLD+G GC PCNCSV GSVSD CT+EGQCHC PGV+G TGLCDCKPNVTGQQCDQCLHGYYGLDSGHGCRPCNCSVAGSVSDGCTDEGQCHCVPGVAG	977
Mouse	985	KQCDRCSHGFYAFQDGGCTPCDCAHTQNNCDPASGECLCPHTQGLKCEEC EAYWGLDP	1044
Human	978	K+CDRC+HGFYA+QDG CTPCDC HTQN CDP +GEC+CPHTQG KCEEC+ +WG D KRCDCRAHGFIYQDGSCTPCDCHPTQNTCDPETGECVCPHTQGGKCEECEDGHWGYDA	1037
Mouse	1045	EQGCQACNCSAVGSTSAQCDVLSGHCPCKKFGGQSCHQCSLGYRSFPDCVPCGCDLRGT	1104
		E GCQACNCS VGST +CDV++GHC CK FGG++C QCSLGYR FPDCVPC CDLRGT	

Human	1038	EVGCQACNCSLVGSTHHRCDVVTGHCHQCKSKFGRACDQCSLGYRDFPDCVPCDCDLRGT	1097
Mouse	1105	LPDTCDELEQGLCSCSEDSGTCSCKENVVGPQCSKCQAGTFALRGDNPQGCSPCFGLSQ	1164
Human	1098	D C+LEQGLC C E++G C CKENV GPQC++C+ GTFALR DNP GCSPCFGLS	1157
Mouse	1165	SGDACNLEQGLCGCVEETGACPCCKENVFGPQCNECREGTFALRADNPLGCSPCFCSGLSH	1224
Human	1158	LCSELEGYVRTLITLASDQPLLHVVSQSNLKGITIEGVHFQPPDITLLDAEAVRQHIYAEPF	1217
Mouse	1225	LCSELE YVRT +TL SDQPLL VVSQSNL+GT EGV++Q PD LLDA VRQHI AEPF	1284
Human	1218	LCSELEDYVRTPVTLGSDQPLLRVVSQSNLRGTTEGVYYQAPDFLLDAATVRQHIAEPF	1277
Mouse	1285	YWRLPKQFQGDQLLAYGGKLQYSVAFYSTLTGTSTNYEPQVLIKGGRRARKHVIYMDAPAP	1344
Human	1278	YWRLPQFQGDQLMAYGGKLKYSVAFYSLDGVGTSNFEPQVLIKGGRRIRKQVIYMDAPAP	1337
Mouse	1285	ENGVRQDYEVQMKEEFWKYFNSVSEKHVTHSDFMSVLSNIDYILIKASYGQGLQQSRIAN	1404
Human	1278	ENGVRQ+ EV M+E FWKYFNSVSEK VT DFMSVLS+I+YILIKASYGQGLQQSRI++	1337
Mouse	1345	ENGVRQEVEAMRENFWKYFNSVSEKPVTRDFMSVLSIDIEYILIKASYGQGLQQSRISD	1404
Human	1338	ISMEVGRKAVELPAEGEAALLLELCVCPPTAGHSCQDCAPGYREKLPESSGGRGPRPLL	1397
Mouse	1405	IS+EVGRKA +L E E A LLE CVCPPGT G SCQDCAPGY+R KLP RGRPL+	1464
Human	1398	ISVEVGRKAELHPEEEVASLLENCVCPPTGVGFSCQDCAPGYHGRKLPAGSDRGPRPLV	1457
Mouse	1405	APCVPNCNNHSDVCDPETGKCLSCRDHSTSGDHCELCASGYGKVTGLPGDCTPCTCPHH	1524
Human	1398	APCVPNCNNHSD CDP TGKCL+C D+T+GDHC++C SGYYGKVTG DC C CPH	1457
Mouse	1465	APCVPSCNNHSDTCDPNTGKCLNCGDNTAGDHCDVCTSGYYGKVTGSASDCALCACPHS	1517
Human	1458	PPFSFSPTCVVEGSDSDFRCNACLPYEGQYCERCSSAGYHGNPRAAGGSCQTCDCNPQGSV	1584
Mouse	1525	PP SFSPTCV+EGD DFRC+ACL GYEG++CERCSS+ Y+GNP+ GGSCQ CDCN GSV	1517
Human	1458	PPASFSPTCVLEGDHDFRCDAALLGYEGKHCERCSSSYGNPQTPGGSCQKDCNHRGVS	1584
Mouse	1525	HSDCDRASGQCVCKPGATGLHCEKCLPRHILMESDCVSCDDDCVGPLLLNDLSDVGDVLS	1577
Human	1518	H DCDR SGQCV+ GA+GL C++C PRHILME+DCVSCDD+CVG LLNDLD +GDVLS	1577
Mouse	1585	HGDCDRTSGQCVCRLGASGLRCDECEPRHILMETDCVSCDDECVGVLNDLDEIGDAVLS	1644
Human	1578	LNLTGVSPPYGIENLENTTKYFQRYLIKENAKKIRAEIQLEGIAEQTENLQKELTRVL	1637
Mouse	1645	LNLTG+ P PYGIL NLENTTKY Q L+KEN +K +I+LEG+AE+T+NLQK+LTR+L	1704
Human	1638	LNLTGIIIPVYGIENLENTTKYLQESLLKENMQDLGKIKLEGVAEETDNLQKKLTRML	1696
Mouse	1645	ARHQKVNAEMERTSNGTQALATFIEQLHANIKEITEKVATLNQTARKDFQPPVSALQSMH	1763
Human	1638	A QKVN ER +Q LA IE+L +I EI EK TLNQT +DF P S LQ+M	1696
Mouse	1705	ASTQKVNRAERIFKESQDLAVAIERLQMSITEIMEK-TTLNQTILDEDFLLPNSTLQNMQ	1756
Human	1697	QNISLLGLIKERNFTMQNATLELKAADLLSRIQKRFQKPKQEKLKALKEANS-LLSN	1823
Mouse	1764	QN +SLL +++ R+FT++ QNATLELKAA+DLLS+IQ+ +QKP E+L+ LKEA S +LS	1815
Human	1757	QNGTSLLEINQIRDFTQLHQNATLELKAEDLLSIIQENYQKPLEELEVLEKEAASHVLSK	1823
Mouse	1764	HSEKLQAAEELLKEAGSKTQESNLLLLLVKANLKEEFQEKLRVQEEQNVTSELIAGRE	1815
Human	1757	H+ +L+AAE L++EA +K QESN LLL+V ANL+ EF +KKL VQEEQN+TSELI +GR	1815
Mouse	1824	HNNELKAAEALVREAEAKMQESNLLLLMVNANLR-EFSDKKLHVQEEQNLTSELIVQGRG	1883
Human	1816	WVDAAGTHTAAAQDTLTQLEHHRDELLWARKIRSHVDDLVMQSKRRARDLVHRAEQHA	1875
Mouse	1884	+DAA T A QD L LE H+D+LLLW+ KIR H+DDLVM MS+R A DLV+RAE HA	1943
Human	1876	LIDAAAAQTDVQDALEHLEDHQDKLLLSAKIRHHIDDLVMHMSQRNAVLDLVYRAEDHA	1935
Mouse	1944	SELQSRAGALDRDLENVRNVSLSNATSAHVSNITLQTEEAEMLAADAHKTANKTDLISE	2003
Human	1936	+E Q A L LEN+RNVSLSNATSA+VH NIQ+L EE+E LA DAH+T +T L+SE	1995
Mouse	2004	TEFQRLADVLYSGLENIRNVSLNATSAAYVHYNIQSLIEESEELARDAHRTVTETSLISE	2063
Human	1996	SLASRGKAVLQRSSRFLKESVGTTRKQOGITMKLDELKNLTSQFQESVDNITKQANDSLA	2055
Mouse	2064	SL S GKA +QRSSRFLKE RK GI ++L EL+N T++FQE+ IT+Q N+SL	2123
Human	2056	SLVSNKAAVQRSSRFLKEGNNLSRKLPGLALELSELRNKTNRQENAVEITRQTNESLL	2115
Mouse	2004	MLRESPPGMMREKGRKARELAAAANESAVKTLEDVLALSRLRVNTSEDLRSRVNATVQETND	2183
Human	1996	+LR P G+R+KG K +ELA +A++SAV TL DV LS + NTS LSRVN T++ET+	2055
Mouse	2064	ILRAIPEGIRDKGAKTELATSASQSAVSTLRDVAGLSQELLNTSASLSRVNTTLRETHQ	2123
Human	2056	LLHNSTMTTLLAGRKMKDMEMQANLLLDRLKPLKLTLEENLSRNLSSEIKLLISARKQAAS	2115
Mouse	2124	LL +STM TLLAGRK+KD+E+QANLL DRKPLK LEENLSRNLSSEIKLLISARKQAAS	2183
Human	2116	LLQDSTMATLLAGRKVDVEIQANLLFDRLKPLKMLEENLSRNLSSEIKLLISQARKQAAS	2175
Mouse	2184	IKVAVSADRDCIRAYQPQTSSSTNYNTLLNVKTQEPDNLFLYLGSSSSSDFLAVEMRRGK	2243
Human	2116	IKVAVSADRDCIRAYQPQ SSTNYNTL LNVKTQEPDNLFLYLGSS++SDFLAVEMRRG+	2175
Mouse	2184	IKVAVSADRDCIRAYQPQISSTNYNTLLNVKTQEPDNLFLYLGSSSTASDFLAVEMRRGR	2243
Human	2116	VAFLWDLGSGSTRLEFPEVSIINNRRWHSIYITRFGNMGSLSVKEASAAENPPVRTSKSPG	2243
Mouse	2184	VAFLWDLGSGSTRLEFP+ I++NRWHSI++ RFGN+GSLSVKE S+ + P +TSKSPG	2243

Human	2176	VAFLWDLGSGSTRLEFFDFPIDDNRWHSIHVARFGNIGSLSVKEMSSNQKSPTKTSKSPG	2235
Mouse	2244	PSKVLDINNSTMFMVGGGLGGQIKKSPAVKVTHFKGCMGEAFLNGKSIGLWNYIEREGKCN	2303
Human	2236	TANVLDVNNSTMFMVGGGLGGQIKKSPAVKVTHFKGCLGEAFLNGKSIGLWNYIEREGKCR	2295
Mouse	2304	GCFGSSQNE DSSFHFDGSGYAMVEKTLRPTVTQIVILFSTFSPNGLLFYLASNGTKDFLS	2363
Human	2296	GCFGSSQNE DPSFHFDGSGYSVVEKSLPATVTQIIMLFNTFSPNGLLLYLSYGTKDFLS	2355
Mouse	2364	IELVRGRVKVMVDLGSGLTLMTDRRYNNGTWYKIAFQRNRKQGLLAVFDAYDTSKETH	2423
Human	2356	IELFRGRVKVMTDLGSGLTLMTDRRYNNGTWYKIAFQRNRKQGLLAVFDAYDTSKETH	2415
Mouse	2424	QGETPGAASDLNRLEKDLIYVGGPLPHSKAVKGVSSRSYVGCINKLEISRSTFDLLRNSY	2483
Human	2416	QGETPGAASDLNRLEKDLIYVGGPLPHSKAVKGVSSRSYVGCINKLEISRSTFDLLRNSY	2475
Mouse	2484	GVRKGGALEP IQSVSFLRGGYVEMPPKSLSPESLLATFATKNSSGILLVALGKDAEEAG	2543
Human	2476	GVRKGGLEP IIRSVSFLRGGYIELPPKSLSPESLWLTFTATNSSGIILAALGGDVEKRG	2535
Mouse	2544	G-AQAHVPFFSIMLLEGRIEVHVNSGDGTSIRKALLHAPTGSYSDGQEHHSISLVRNRRVI	2602
Human	2536	DREEAHVPFFSVMLIGGNIEVHVNSGDGTSIRKALLHAPTGTCSGQAHHSISLVRNRRII	2595
Mouse	2603	TIQVDENSPVEMKLGPLTEGKTIDISNLYIGGLPEDKATPMLKMRTSFHGCINKNVLDQAQ	2662
Human	2596	TVQLDENNPVEMKLGTLVESRTINVSNLYVGGIPEEGTSLTMRSSFHGCINKLIFNLE	2655
Mouse	2663	LLDFTHATGSEQVELDTCLLAEPMQSLHREHGEPLPEPPTLPQPELCAVDTPAGYVAGA	2722
Human	2656	LLDFNSAVGHEQVLDTCWLSERPKLAPDAEDS--KLLREPRAFPEQCVDAALEYVPGA	2713
Mouse	2723	HQFGLSQNSHLVPLNQSDVRKRLQVQLSIRTFASSGLIYYVAHQNM DYATLQLQEGRL	2782
Human	2714	HQFGLTQNSHFILPFNQSAVRKKSVELSIRTFASSGLIYYMAHQNQADYAVLQLHGGRL	2773
Mouse	2783	HFMFDLGKGRITKVSHFALLSDGKWHVKTETIKRKAFMTVDGQESPSVTIVGNATLTDVE	2842
Human	2774	HFMFDLGKGRITKVSHFALLSDGKWHVKTETIKRKAFMTVDGQESPSVTIVGNATLTDVE	2833
Mouse	2843	RKLYLGGLPSHYRARNIGTITHSIPACIGEIMVNGQQLDKDRPLSASAVDRCYVVADEGT	2902
Human	2834	GLFYLGGLPSQYQARKIGNITHSIPACIGDVTVNSKQLDKDSPVSAFTVNRCYAVADEGT	2893
Mouse	2903	FFEGSGYAAALVKEGYKVRDLNITILEFRITSKNGVLLGISSAKVDAIGLEIVDGKVLHFV	2962
Human	2894	YFDGSGYAAALVKEGYKVSQSDVNITILEFRITSSQNGVLLGISTAKVDAIGLEIVDGKVLHFV	2953
Mouse	2963	NNGAGRITATYQPRARALCDGKWHTLQAHSKSHRIVLTVDGNSVRAESPHSTSTADTN	3022
Human	2954	NNGAGRITATYQPRARALCDGKWHTLQAHSKSHRITLTVDGNAVGAESPHTQSTSTADTN	3013
Mouse	3023	DPIYVGGYPAAHIKONCLSSRASFRGCVRNLRLSRGSOVQSLDSRAFDLQGVFPHSCPGP	3082
Human	3014	NPIYVGGYPAGVKKQCLRSQTSFRGCLRLALIKSPQVQSFDFSRAFELHGVFLHSCPGT	3073
Mouse	3083	E 3083	
Human	3074	E 3074	

Figure 5S. Sequence comparison of the laminin $\alpha 1$ G2 domain mouse vs. man by a Blast-based alignment. Score = 4780 bits (12399), Expect = 0.0 Identities = 2336/3061 (76%), Positives = 2635/3061 (86%), Gaps = 6/3061 (0%).

Figure 6S. The three-dimensional structure of the G1, G2 and G3 domain (from left to right) of the $\alpha 2$ laminin subunit (ref 59) is shown as backbone structure (upper part) and in its surface representation (lower part). The overall structure of the laminin G-domains are similar, however, the G5 domain of the murine $\alpha 1$ domain (please see the right part of Figure 2 in the manuscript) is the best template for our homology modeled receptor structure.

Figure 7S. Computational calculation of **1** (VDW presentation) in a stable binding mode with **4**. Tyr8, Lys13 and Asn14 (VDW presentation) of **4** are displayed in red, blue and green, respectively. All three amino acid residues are in close contact with the 3-*O*-sulfo-GlcA-residue of HNK-1.

Figure 8S. Computational calculation of **3** in a stable binding mode with **4**. Arg1 (R1) of **3** is displayed in green, Glu16 (E16) of **4** is shown in orange.

Commentary (acceptor (A) and donor (D) groups are indicated in the following text-part below):

The interactions of compound **1** with the HNK-1 binding site of the laminin domain model establish a stable complex formation. The two negatively charged functional groups of 3'-sulfated glucuronic acid are in close contact with the positively charged Lys residue (at position 3026) of the HNK-1 binding site. These two functional groups (sulfate and carboxylic group) enclose the Lys residue. Furthermore, the C4 OH (D) group between the charged residues of 3'-sulfated glucuronic acid establishes a hydrogen bond to the Lys residue (A). The HNK-1 receptor binding is additionally supported by a hydrogen bond contact of the oxygen (A) at the *N*-acetyl C atom of GlcNAc to Ser (D) (at position 3038).

When comparing the negative binding energies of **2** and of **1** in complex with our model receptor we learn that the glycomimetic peptide **2** binds in a less favorable way (54.8 kJ/mol weaker) than the glycan (**1**). In this regard, we have to consider that in contrast to **1** compound **2** has only one negatively

charged group. Furthermore, fewer and weaker hydrogen bonds are established by **2** when interacting with the HNK-1 binding site in the modeled laminin domain. For example, a Thr residue of **2** forms via its NH (D) hydrogen atom a stable hydrogen bond with the carboxylic CO group (A) of Glu (at position 2904). The same nitrogen (A) atom is involved in a hydrogen bond to a water molecule (D). The N (A) atom of the Ser residue of **3** thus establishes a hydrogen bond to the Ser OH (D) (at position 3038) residue of the laminin domain. Furthermore, a hydrogen bond exists between the NH group (D) of the Arg residue of **3** and the CO group (A) of Lys (at position 3026). Two additional hydrogen bonds are present between Pro (A) and Thr (A) residues of **3** and two water molecules (D).

Complete author list of reference 43:

43. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery Jr., J. A.; Vreven, T.; Kudin, K. N.; J. C. Burant; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision B.03*, Gaussian, Inc.: Pittsburgh PA, 2003.