Supplementary Tables

Supplementary Table S1: Interface parameters C-subunit and IP20 peptide (PDB ID: 1ATP)

	Catalytic Subunit		IP20 peptide	
Number of atoms				
interface	126	4.50%	92	58.60%
surface	1502	54.10%	138	87.90%
total	2777	100.00%	157	100.00%
Number of residues				
interface	40	11.90%	17	85.00%
surface	317	94.30%	20	100.00%
total	336	100.00%	20	100.00%
Solvent-accessible area, Å				
interface	963.7	6.30%	1143.5	47.90%
total	15344.9	100.00%	2388.6	100.00%
Solvation energy, kcal/mol				
isolated structure	-328.7	100.00%	-7.8	100.00%
gain on complex formation	-3.1	1.00%	-2.2	28.70%
average gain	-2.6	0.80%	-2.8	35.80%
P-value	0.451		0.537	

1.1 Hydrogen bond profile for C-subunit and IP20 peptide (PDB ID: 1ATP)

##	Catalytic Subunit	IP20 peptide	H-bond distance
1	E:ASP 241[OD1]	I:GLY 14[N]	2.82
2	E:GLU 203[OE2]	I:ARG 15[NH1]	2.70
3	E:GLU 127[OE2]	I:ARG 18[NE]	2.82
4	E:THR 51[O]	I:ARG 18[NH1]	3.14
5	E:GLU 127[OE2]	I:ARG 18[NH2]	2.94
6	E:THR 51[O]	I:ARG 18[NH2]	2.93
7	E:GLU 170[OE2]	I:ARG 19[N]	2.52
8	E:GLU 170[OE2]	I:ARG 19[NE]	2.78
9	E:GLU 230[OE1]	I:ARG 19[NH1]	3.46
10	E:GLU 230[OE2]	I:ARG 19[NH1]	3.31
11	E:GLU 230[OE1]	I:ARG 19[NH2]	3.46
12	E:GLU 230[OE2]	I:ARG 19[NH2]	3.42
13	E:GLU 170[OE1]	I:ARG 19[NH2]	2.96
14	E:SER 53[OG]	I:ALA 21[N]	3.48
15	E:GLY 200[O]	I:ILE 22[N]	2.80
16	E:ARG 133[NH1]	I:THR 16[O]	3.09
17	E:SER 53[OG]	I:ALA 21[O]	2.77

1.2 Salt Bridge profile for C-subunit and IP20 peptide (PDB ID: 1ATP)

##	Catalytic Subunit	IP20 peptide	Dist. [Å]
1	E:GLU 203[OE2]	I:ARG 15[NE]	3.59
2	E:GLU 203[OE1]	I:ARG 15[NH1]	2.95

3	E:GLU 203[OE2]	I:ARG 15[NH1]	2.70
4	E:GLU 127[OE1]	I:ARG 18[NE]	3.37
5	E:GLU 127[OE2]	I:ARG 18[NE]	2.82
6	E:GLU 127[OE2]	I:ARG 18[NH2]	2.94
7	E:GLU 170[OE1]	I:ARG 19[NE]	3.54
8	E:GLU 170[OE2]	I:ARG 19[NE]	2.78
9	E:GLU 230[OE1]	I:ARG 19[NH1]	3.46
10	E:GLU 230[OE2]	I:ARG 19[NH1]	3.31
11	E:GLU 230[OE1]	I:ARG 19[NH2]	3.46
12	E:GLU 230[OE2]	I:ARG 19[NH2]	3.42
13	E:GLU 170[OE1]	I:ARG 19[NH2]	2.96
14	E:GLU 170[OE2]	I:ARG 19[NH2]	3.62
15	E:LYS 83[NZ]	I:ASP 24[OD1]	3.22
16	E:LYS 83[NZ]	I:ASP 24[OD2]	3.64

Supplementary Table S2: Interface parameters C-subunit and CNBA(73-244)of RIA (PDB ID: 3PVB)

	Catalytic Subunit		CNBA RIA	
Number of atoms				
interface	171	6.20%	151	12.40%
surface	1515	54.60%	773	63.50%
total	2774	100.00%	1218	100.00%
Number of residues				
interface	49	14.20%	36	22.50%
surface	324	93.90%	154	96.20%
total	345	100.00%	160	100.00%
Solvent-accessible area, Å				
interface	1510	9.60%	1592	16.10%
total	15773.1	100.00%	9906.3	100.00%
Solvation energy, kcal/mol				
isolated structure	-317.4	100.00%	-123.4	100.00%
gain on complex formation	-8.3	2.60%	-3.6	2.90%
average gain	-5.5	1.70%	-5.1	4.10%
P-value	0.273		0.621	

2.1 Hydrogen bond profile for C-subunit and CNBA(73-244)of RIA (PDB ID: 3PVB)

##	Catalytic Subunit	**CNBA RIA**	**Dist. [Å]**
1	A:GLU 203[OE2]	B:ARG 92[NH1]	3.49
2	A:GLU 230[OE2]	B:ARG 92[NH2]	2.47
3	A:GLY 234[O]	B:ARG 92[NH2]	3.36
4	A:GLU 127[OE1]	B:ARG 94[NH1]	2.49
5	A:THR 51[O]	B:ARG 94[NH2]	2.46
6	A:GLU 170[OE2]	B:ARG 95[N]	3.22
7	A:GLU 170[OE2]	B:ARG 95[NE]	2.49
8	A:GLU 230[OE1]	B:ARG 95[NH1]	3.38
9	A:GLU 230[OE2]	B:ARG 95[NH1]	3.14

10	A:GLU 203[OE2]	B:ARG 95[NH1]	3.76
11	A:GLU 170[OE1]	B:ARG 95[NH2]	3.42
12	A:GLU 230[OE1]	B:ARG 95[NH2]	3.20
13	A:GLU 230[OE2]	B:ARG 95[NH2]	3.05
14	A:SER 53[OG]	B:ALA 97[N]	2.74
15	A:GLY 200[O]	B:ILE 98[N]	2.44
16	A:LEU 198[O]	B:SER 99[OG]	3.31
17	A:LEU 198[O]	B:ALA 100[N]	2.98
18	A:TYR 247[OH]	B:TYR 205[OH]	2.63
19	A:SER 212[OG]	B:TYR 229[OH]	3.79
20	A:TRP 196[O]	B:ARG 230[NH1]	2.45
21	A:LYS 168[NZ]	B:ARG 95[O]	2.91
22	A:SER 53[OG]	B:ALA 97[O]	2.70
23	A:GLY 200[N]	B:ILE 98[O]	2.54
24	A:GLN 84[NE2]	B:SER 99[O]	3.52
25	A:LYS 213[NZ]	B:HIS 138[O]	3.22

2.2 Salt Bridge profile for C-subunit and CNBA(73-244)of RIA (PDB ID: 3PVB)

##	Catalytic Subunit	**CNBA RIA**	**Dist. [Å]**
1	A:GLU 230[OE2]	B:ARG 92[NH1]	3.25
2	A:GLU 203[OE2]	B:ARG 92[NH1]	3.49
3	A:GLU 230[OE2]	B:ARG 92[NH2]	2.47
4	A:GLU 127[OE2]	B:ARG 94[NE]	3.99
5	A:GLU 127[OE1]	B:ARG 94[NH1]	2.49
6	A:GLU 127[OE2]	B:ARG 94[NH1]	2.96
7	A:GLU 170[OE1]	B:ARG 95[NE]	3.91
8	A:GLU 170[OE2]	B:ARG 95[NE]	2.49
9	A:GLU 203[OE2]	B:ARG 95[NE]	3.98
10	A:GLU 230[OE1]	B:ARG 95[NH1]	3.38
11	A:GLU 230[OE2]	B:ARG 95[NH1]	3.14
12	A:GLU 203[OE2]	B:ARG 95[NH1]	3.76
13	A:GLU 170[OE1]	B:ARG 95[NH2]	3.42
14	A:GLU 170[OE2]	B:ARG 95[NH2]	3.37
15	A:GLU 230[OE1]	B:ARG 95[NH2]	3.20
16	A:GLU 230[OE2]	B:ARG 95[NH2]	3.05

Supplementary Table S3: Interface parameters C-subunit and CNBA(102-265)of RIIB (PDB ID: 3IDC)

	Catalytic Subunit		CNBA RIB	
Number of atoms				
interface	175	6.40%	148	13.00%
surface	1527	55.80%	815	71.70%
total	2736	100.00%	1136	100.00%
Number of residues				
interface	51	14.90%	35	21.90%

surface	321	93.60%	159	99.40%
total	343	100.00%	160	100.00%
Solvent-accessible area, Å				
interface	1430.4	9.30%	1653.3	15.80%
total	15433.5	100.00%	10473.8	100.00%
Solvation energy, kcal/mol				
isolated structure	-316	100.00%	-69.4	100.00%
gain on complex formation	-9.4	3.00%	-9.8	14.10%
average gain	-4.2	1.30%	-9.7	14.00%
P-value	0.096		0.491	

3.1 Hydrogen bond profile for C-subunit and CNBA(102-265)of RIIB (PDB ID: 3IDC)

##	Catalytic Subunit	**CNBA RIIB**	**Dist. [Å]**
1	A:ASP 241[OD2]	B:ARG 106[NH1]	2.69
2	A:GLU 127[OE2]	B:ARG 109[NE]	2.63
3	A:GLU 127[OE2]	B:ARG 109[NH2]	2.54
4	A:GLU 170[OE1]	B:ARG 110[N]	2.89
5	A:GLU 170[OE1]	B:ARG 110[NE]	2.71
6	A:GLU 230[OE1]	B:ARG 110[NH1]	2.89
7	A:GLU 230[OE2]	B:ARG 110[NH2]	3.20
8	A:GLU 170[OE2]	B:ARG 110[NH2]	2.96
9	A:GLY 200[O]	B:VAL 113[N]	2.70
10	A:LEU 198[O]	B:ALA 115[N]	2.94
11	A:TPO 197[O3P]	B:TYR 118[N]	3.79
12	A:TPO 197[OG1]	B:TYR 118[N]	3.88
13	A:TYR 247[OH]	B:TYR 226[OH]	3.21
14	A:SER 212[O]	B:ASN 258[ND2]	3.27
15	A:LYS 168[NZ]	B:ARG 110[O]	3.75
16	A:THR 201[OG1]	B:ALA 111[O]	3.47
17	A:GLY 200[N]	B:VAL 113[O]	2.94
18	A:ARG 194[NH1]	B:ALA 259[O]	3.17

3.2 Salt Bridge profile for C-subunit and CNBA(102-265)of RIIB (PDB ID: 3IDC)

##	Catalytic Subunit	CNBA RIIB	Dist. [Å]
1	A:ASP 241[OD1]	B:ARG 106[NE]	3.73
2	A:ASP 241[OD1]	B:ARG 106[NH1]	3.41
3	A:ASP 241[OD2]	B:ARG 106[NH1]	2.69
4	A:ASP 241[OD1]	B:ARG 106[NH2]	3.93
5	A:ASP 241[OD2]	B:ARG 106[NH2]	3.27
6	A:GLU 127[OE1]	B:ARG 109[NE]	2.87
7	A:GLU 127[OE2]	B:ARG 109[NE]	2.63
8	A:GLU 127[OE2]	B:ARG 109[NH2]	2.54
9	A:GLU 170[OE2]	B:ARG 110[NE]	3.81

10	A:GLU 170[OE1]	B:ARG 110[NE]	2.71
11	A:GLU 230[OE2]	B:ARG 110[NH1]	3.59
12	A:GLU 230[OE1]	B:ARG 110[NH1]	2.89
13	A:GLU 230[OE2]	B:ARG 110[NH2]	3.20
14	A:GLU 230[OE1]	B:ARG 110[NH2]	3.21
15	A:GLU 170[OE2]	B:ARG 110[NH2]	2.96
16	A:GLU 170[OE1]	B:ARG 110[NH2]	3.31

Supplementary Table S4: Interface parameters C-subunit and CNBA + CNBB (91-379) of RIA (PDB ID: 4X6R)

	Catalytic Subunit		CNBA + CNBB RIA	
Number of atoms				
interface	220	7.70%	203	8.80%
surface	1573	55.20%	1419	61.90%
total	2851	100.00%	2294	100.00%
Number of residues				
interface	60	17.10%	51	17.60%
surface	323	92.30%	283	97.60%
total	350	100.00%	290	100.00%
Solvent-accessible area, Å				
interface	1959.8	11.80%	2043.8	11.90%
total	16633.2	100.00%	17129.8	100.00%
Solvation energy, kcal/mol				
isolated structure	-338.6	100.00%	-259.4	100.00%
gain on complex formation	-8.9	2.60%	-0.5	0.20%
average gain	-3.7	1.10%	-2.7	1.00%
P-value	0.136		0.656	

4.1 Hydrogen bond profile for C-subunit and CNBA + CNBB (91-379) of RIA (PDB ID: 4X6R)

##	Catalytic Subunit	CNBA + CNBB RIA	Dist. [Å]
1	A:ASP 328[OD1]	B:ARG 92[NH1]	2.94
2	A:ASP 328[OD2]	B:ARG 92[NH1]	2.95
3	A:ASP 328[OD1]	B:ARG 92[NH2]	2.81
4	A:GLU 203[OE2]	B:ARG 93[NH1]	3.50
5	A:GLU 127[OE2]	B:ARG 94[NE]	3.22
6	A:GLU 127[OE1]	B:ARG 94[NE]	2.93
7	A:THR 51[O]	B:ARG 94[NH1]	3.28
8	A:THR 51[OG1]	B:ARG 94[NH1]	3.77
9	A:GLU 127[OE1]	B:ARG 94[NH2]	2.88
10	A:THR 51[O]	B:ARG 94[NH2]	3.27
11	A:GLU 170[OE2]	B:ARG 95[N]	2.87
12	A:GLU 170[OE2]	B:ARG 95[NE]	2.74
13	A:GLU 230[OE1]	B:ARG 95[NH1]	3.02
14	A:GLU 230[OE2]	B:ARG 95[NH1]	2.98
15	A:GLU 230[OE2]	B:ARG 95[NH2]	3.12
16	A:GLU 170[OE1]	B:ARG 95[NH2]	2.88

17	A:SER 53[OG]	B:ALA 97[N]	3.47
18	A:GLY 200[O]	B:ILE 98[N]	2.79
19	A:LEU 198[O]	B:SER 99[OG]	3.85
20	A:LEU 198[O]	B:ALA 100[N]	2.86
21	A:TYR 247[OH]	B:TYR 205[OH]	2.77
22	A:TRP 196[O]	B:ARG 230[NH1]	2.74
23	A:LYS 213[O]	B:ARG 241[NH2]	3.20
24	A:ASP 276[OD1]	B:ARG 352[NH1]	2.90
25	A:ASP 276[OD2]	B:ARG 352[NH2]	3.67
26	A:THR 278[O]	B:ARG 355[NE]	2.86
27	A:THR 278[OG1]	B:ARG 355[NH2]	2.93
28	A:LYS 168[NZ]	B:ARG 95[O]	2.91
29	A:SER 53[OG]	B:ALA 97[O]	2.91
30	A:GLY 200[N]	B:ILE 98[O]	3.02
31	A:LYS 213[NZ]	B:HIS 138[O]	3.35
32	A:LYS 213[NZ]	B:GLU 143[OE1]	2.99
33	A:ARG 194[NH2]	B:ASP 267[OD2]	2.48
34	A:LYS 285[N]	B:ARG 355[O]	2.96

4.2 Salt Bridge profile for C-subunit and CNBA + CNBB (91-379) of RIA (PDB ID: 4X6R)

##	Catalytic Subunit	CNBA + CNBB RIA	Dist. [Å]
1	A:ASP 328[OD1]	B:ARG 92[NH1]	2.94
2	A:ASP 328[OD2]	B:ARG 92[NH1]	2.95
3	A:ASP 328[OD1]	B:ARG 92[NH2]	2.81
4	A:GLU 203[OE2]	B:ARG 93[NH1]	3.50
5	A:GLU 127[OE2]	B:ARG 94[NE]	3.22
6	A:GLU 127[OE1]	B:ARG 94[NE]	2.93
7	A:GLU 127[OE1]	B:ARG 94[NH2]	2.88
8	A:GLU 170[OE1]	B:ARG 95[NE]	3.61
9	A:GLU 170[OE2]	B:ARG 95[NE]	2.74
10	A:GLU 230[OE1]	B:ARG 95[NH1]	3.02
11	A:GLU 230[OE2]	B:ARG 95[NH1]	2.98
12	A:GLU 230[OE1]	B:ARG 95[NH2]	3.33
13	A:GLU 230[OE2]	B:ARG 95[NH2]	3.12
14	A:GLU 170[OE1]	B:ARG 95[NH2]	2.88
15	A:GLU 170[OE2]	B:ARG 95[NH2]	3.46
16	A:ASP 276[OD1]	B:ARG 352[NH1]	2.90
17	A:ASP 276[OD2]	B:ARG 352[NH1]	3.77
18	A:ASP 276[OD1]	B:ARG 352[NH2]	3.74
19	A:ASP 276[OD2]	B:ARG 352[NH2]	3.67
20	A:LYS 83[NZ]	B:GLU 101[OE2]	3.56
21	A:LYS 213[NZ]	B:GLU 143[OE1]	2.99
22	A:LYS 213[NZ]	B:GLU 143[OE2]	3.80
23	A:ARG 194[NE]	B:ASP 267[OD2]	2.91
24	A:ARG 194[NH2]	B:ASP 267[OD2]	2.48

Supplementary Table S5: Interface parameters C-subunit and CNBA + CNBB (108-416) of RIIB (PDB ID: 4X6Q)

	Catalytic Subunit		CNBA + CNBB RIIB	
Number of atoms				
interface	212	7.60%	182	8.50%
surface	1551	55.70%	1295	60.70%
total	2787	100.00%	2132	100.00%
Number of residues				
interface	59	17.50%	47	17.40%
surface	315	93.50%	259	95.90%
total	337	100.00%	270	100.00%
Solvent-accessible area, Å				
interface	1885.6	11.40%	2042.9	12.50%
total	16490.8	100.00%	16317.5	100.00%
Solvation energy, kcal/mol				
isolated structure	-335.7	100.00%	-227.8	100.00%
gain on complex formation	-8.9	2.70%	-5.5	2.40%
average gain	-3	0.90%	-4.9	2.20%
P-value	0.105		0.464	

5.1 Hydrogen bond profile for C-subunit and CNBA + CNBB (108-416) of RIIB (PDB ID: 4X6Q)

##	Catalytic Subunit	CNBA + CNBB RIIB	Dist. [Å]
1	C:ARG 133[NE]	B:ARG 106[O]	2.87
2	C:LYS 168[NZ]	B:ARG 110[O]	2.98
3	C:SER 53[OG]	B:SER 112[O]	3.12
4	C:LYS 168[NZ]	B:SER 112[OG]	3.00
5	C:THR 201[OG1]	B:SER 112[OG]	3.90
6	C:GLY 200[N]	B:VAL 113[O]	3.30
7	C:TYR 247[OH]	B:TYR 226[OH]	2.65
8	C:ARG 194[NE]	B:ASP 288[OD1]	3.12
9	C:ARG 194[NH1]	B:ASP 288[OD2]	2.48
10	C:LYS 285[N]	B:ARG 381[O]	3.17
11	C:LYS 285[N]	B:LEU 382[O]	3.30
12	C:ARG 133[O]	B:ARG 106[NH1]	3.03
13	C:GLU 127[OE1]	B:ARG 109[NE]	2.57
14	C:TYR 330[OH]	B:ARG 109[NH1]	3.03
15	C:ASP 328[OD2]	B:ARG 109[NH1]	2.69
16	C:GLU 127[OE1]	B:ARG 109[NH2]	2.70
17	C:SER 130[OG]	B:ARG 109[NH2]	3.56
18	C:GLU 170[OE1]	B:ARG 110[N]	2.85
19	C:GLU 170[OE1]	B:ARG 110[NH1]	2.95
20	C:GLU 170[OE2]	B:ARG 110[NH1]	2.79
21	C:GLU 230[OE1]	B:ARG 110[NH2]	2.19
22	C:ASP 166[OD2]	B:SER 112[OG]	2.56
23	C:GLY 200[O]	B:VAL 113[N]	2.63
24	C:LEU 198[O]	B:ALA 115[N]	2.85

25	C:SER 212[O]	B:ASN 258[ND2]	2.73
26	C:LYS 213[O]	B:ARG 262[NE]	2.94
27	C:GLY 214[O]	B:ARG 262[NH2]	3.30
28	C:ASN 283[O]	B:LYS 285[NZ]	2.70
29	C:THR 278[O]	B:ARG 381[NE]	3.03
30	C:THR 278[OG1]	B:ARG 381[NH2]	2.98

5.2 Salt Bridge profile for C-subunit and CNBA + CNBB (108-416) of RIIB (PDB ID: 4X6Q)

##	Catalytic Subunit	CNBA + CNBB RIIB	Dist. [Å]
1	C:ARG 194[NE]	B:ASP 288[OD1]	3.12
2	C:ARG 194[NH1]	B:ASP 288[OD1]	3.60
3	C:ARG 194[NE]	B:ASP 288[OD2]	3.14
4	C:ARG 194[NH1]	B:ASP 288[OD2]	2.48
5	C:GLU 127[OE1]	B:ARG 109[NE]	2.57
6	C:GLU 127[OE2]	B:ARG 109[NE]	3.55
7	C:ASP 328[OD2]	B:ARG 109[NH1]	2.69
8	C:ASP 328[OD2]	B:ARG 109[NH2]	3.03
9	C:GLU 127[OE1]	B:ARG 109[NH2]	2.70
10	C:GLU 127[OE2]	B:ARG 109[NH2]	3.91
11	C:GLU 170[OE1]	B:ARG 110[NH1]	2.95
12	C:GLU 170[OE2]	B:ARG 110[NH1]	2.79
13	C:GLU 230[OE2]	B:ARG 110[NH2]	2.88
14	C:GLU 230[OE1]	B:ARG 110[NH2]	2.19