

Supporting Information for

**An ensemble docking approach for analyzing and designing
aptamer heterodimers targeting VEGF₁₆₅**

Yeon Ju Go ^{1,2}, Mahroof Kalathingal ^{1,*} and Young Min Rhee ^{1,*}

¹ Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST),

Daejeon 34141, Republic of Korea

² Department of Chemistry, Pohang University of Science and Technology (POSTECH), Pohang

37673, Republic of Korea

Supporting Figures

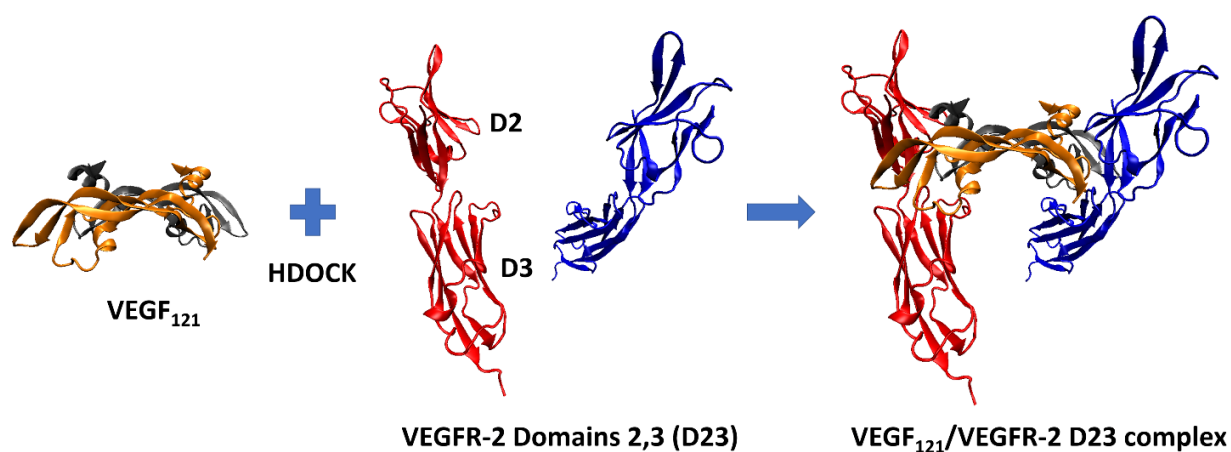


Figure S1. Schematic illustration of the testing process of the HDOCK performance. VEGF₁₂₁ and VEGFR-2 D23 were docked, and the resulting pose was cross-checked against the X-ray crystal structure of the VEGF-A/VEGFR-2 D23 complex. Indeed, they showed a good agreement. The two monomers of VEGF₁₂₁ are shown in orange and gray, while those of VEGFR-2 are shown in red and blue.

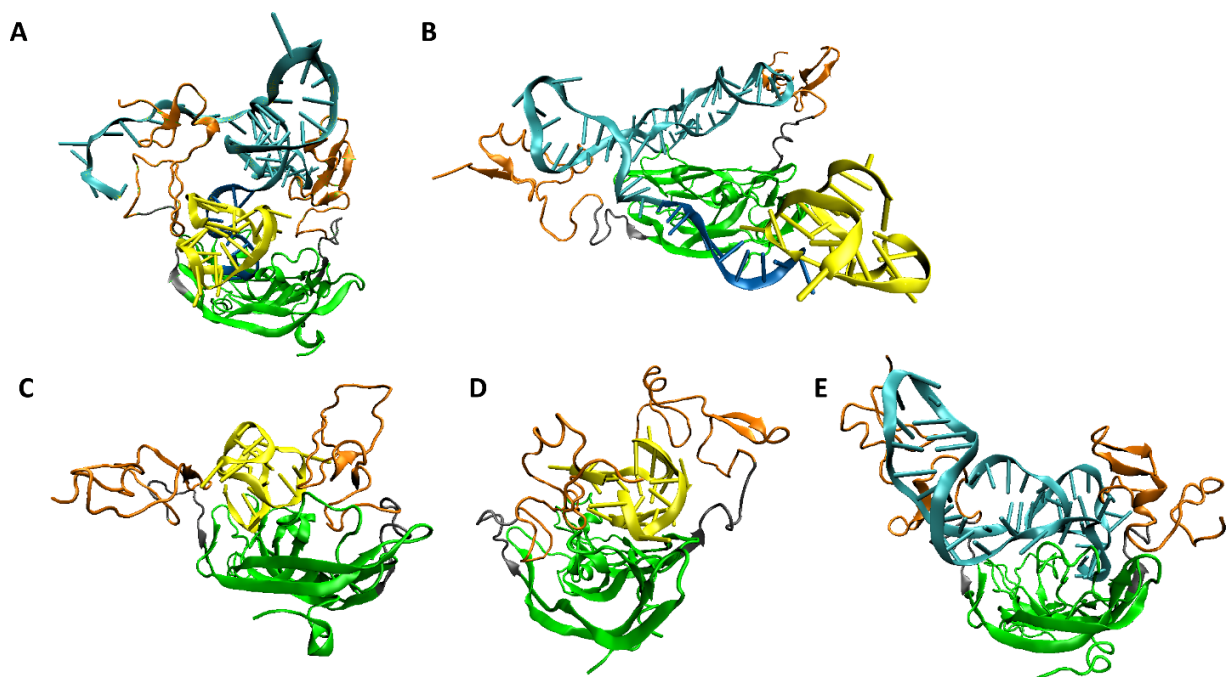


Figure S2. Representative structures of the sandwich poses for (A) VEGF₁₆₅/RNV66:del5-1, (B) VEGF₁₆₅/V7t1:del5-1, (C) VEGF₁₆₅/RNV66, (D) VEGF₁₆₅/V7t1, and (E) VEGF₁₆₅/del5-1. For the aptamers, RNV66 and V7t1 are shown in yellow while del5-1 is in cyan, with the linker in blue. For VEGF₁₆₅, RBD is in green while HBD is in orange, with the linker in gray.

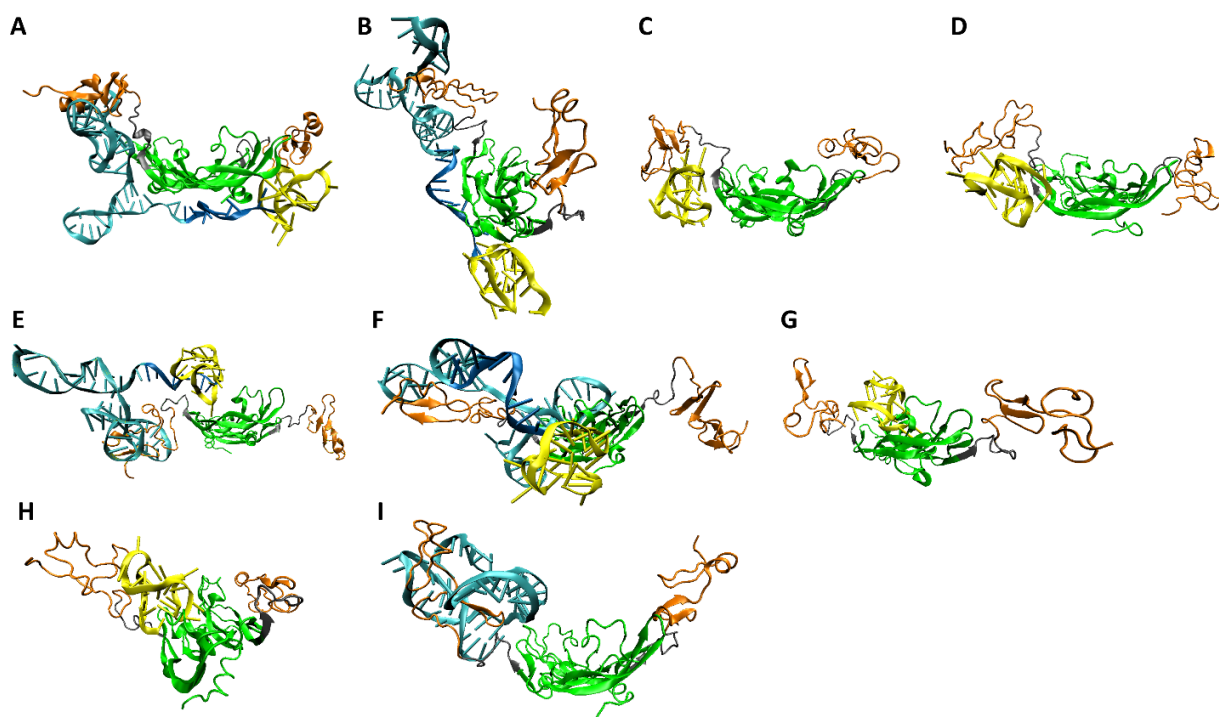


Figure S3. Side and hug poses of VEGF₁₆₅/aptamer complexes: (A) a side pose of VEGF₁₆₅/RNV66:del5-1, (B) a side pose of VEGF₁₆₅/V7t1:del5-1, (C) a side pose of VEGF₁₆₅/RNV66, (D) a side pose of VEGF₁₆₅/V7t1, (E) a hug pose of VEGF₁₆₅/RNV66:del5-1, (F) a hug pose of VEGF₁₆₅/V7t1:del5-1, (G) a hug pose of VEGF₁₆₅/RNV66, (H) a hug pose of VEGF₁₆₅/V7t1, and (I) a hug pose of VEGF₁₆₅/del5-1. No side pose was seen in the complexes of del5-1 with VEGF₁₆₅. RNV66 and V7t1 are shown in yellow and del5-1 is in cyan, with the linker between them in blue. RBD is in green and HBD is in orange with the linker between them in gray.

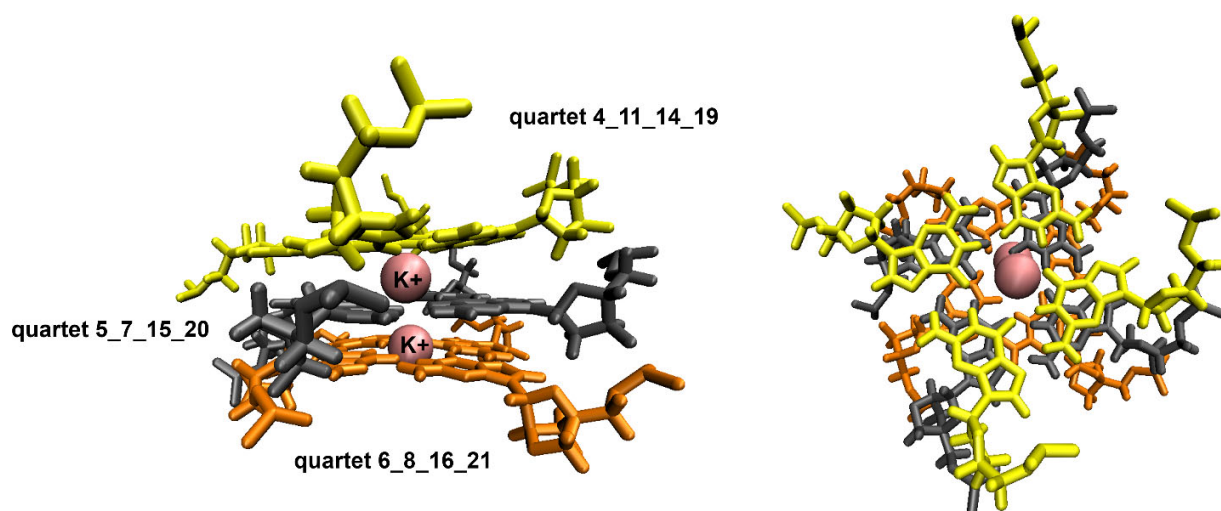


Figure S4. Schematic illustration of the G-quadruplex structure of RNV66. Three quartet planes are represented by 4-11-14-19 (yellow), 5-7-15-20 (gray), and 6-8-16-21 (orange), where the numbers represent the indices of guanine nucleotides forming the G-quartet plane. The right panel shows the structure viewed from the top.

Supporting Tables

Table S1. Docking scores for VEGF₁₆₅/RNV66:del5-1 and VEGF₁₆₅/V7t1:del5-1. For each of the 84 variants composed of 12 aptamer and 7 VEGF₁₆₅ conformations, the pose with the highest docking score was selected.

Pose no.	Aptamer variant (nm)	VEGF ₁₆₅ variant (nm)	Docking score (arbitrary unit)	
			VEGF ₁₆₅ /RNV66:del5-1	VEGF ₁₆₅ /V7t1:del5-1
1	2.0	3.0	-1585.66	-1332.31
2	2.0	4.0	-1406.98	-1462.43
3	2.0	5.0	-1453.60	-1500.75
4	2.0	6.0	-1661.58	-1414.71
5	2.0	7.0	-1459.98	-1371.72
6	2.0	8.0	-1419.21	-1462.75
7	2.0	9.0	-1501.44	-1379.47
8	2.5	3.0	-1376.38	-1332.15
9	2.5	4.0	-1340.17	-1314.57
10	2.5	5.0	-1394.24	-1441.49
11	2.5	6.0	-1418.07	-1459.87
12	2.5	7.0	-1491.36	-1442.13
13	2.5	8.0	-1394.94	-1323.66
14	2.5	9.0	-1460.88	-1494.86
15	3.0	3.0	-1533.36	-1358.27
16	3.0	4.0	-1467.09	-1428.88
17	3.0	5.0	-1468.25	-1446.66
18	3.0	6.0	-1490.43	-1429.68
19	3.0	7.0	-1428.29	-1409.06
20	3.0	8.0	-1483.33	-1438.75
21	3.0	9.0	-1421.65	-1520.67
22	3.5	3.0	-1359.34	-1482.53
23	3.5	4.0	-1367.87	-1509.37
24	3.5	5.0	-1411.33	-1484.80

25	3.5	6.0	-1472.44	-1525.07
26	3.5	7.0	-1426.56	-1436.94
27	3.5	8.0	-1398.79	-1484.69
28	3.5	9.0	-1426.25	-1504.26
29	4.0	3.0	-1528.69	-1357.21
30	4.0	4.0	-1495.14	-1455.48
31	4.0	5.0	-1610.47	-1574.14
32	4.0	6.0	-1464.47	-1473.17
33	4.0	7.0	-1472.31	-1473.99
34	4.0	8.0	-1450.83	-1522.74
35	4.0	9.0	-1621.94	-1413.32
36	4.5	3.0	-1426.16	-1447.03
37	4.5	4.0	-1472.15	-1397.56
38	4.5	5.0	-1493.81	-1509.98
39	4.5	6.0	-1448.33	-1446.58
40	4.5	7.0	-1583.54	-1404.61
41	4.5	8.0	-1518.56	-1380.32
42	4.5	9.0	-1531.82	-1480.95
43	5.0	3.0	-1380.37	-1335.54
44	5.0	4.0	-1382.32	-1340.19
45	5.0	5.0	-1454.60	-1585.07
46	5.0	6.0	-1496.28	-1416.07
47	5.0	7.0	-1431.18	-1464.41
48	5.0	8.0	-1305.42	-1384.47
49	5.0	9.0	-1377.28	-1386.00
50	5.5	3.0	-1636.68	-1470.79
51	5.5	4.0	-1425.01	-1379.53
52	5.5	5.0	-1329.79	-1430.80
53	5.5	6.0	-1380.04	-1347.92
54	5.5	7.0	-1349.97	-1356.03
55	5.5	8.0	-1358.41	-1459.56
56	5.5	9.0	-1347.19	-1423.12
57	6.0	3.0	-1400.87	-1474.10
58	6.0	4.0	-1323.23	-1479.43

59	6.0	5.0	-1238.59	-1362.00
60	6.0	6.0	-1384.32	-1305.59
61	6.0	7.0	-1301.92	-1491.21
62	6.0	8.0	-1287.77	-1307.84
63	6.0	9.0	-1413.63	-1300.23
64	6.5	3.0	-1438.00	-1357.71
65	6.5	4.0	-1401.28	-1273.88
66	6.5	5.0	-1376.03	-1422.60
67	6.5	6.0	-1470.37	-1313.39
68	6.5	7.0	-1344.00	-1384.46
69	6.5	8.0	-1465.69	-1342.57
70	6.5	9.0	-1358.48	-1387.27
71	7.0	3.0	-1525.94	-1342.41
72	7.0	4.0	-1298.53	-1245.42
73	7.0	5.0	-1424.56	-1368.05
74	7.0	6.0	-1413.82	-1290.63
75	7.0	7.0	-1259.39	-1322.03
76	7.0	8.0	-1335.68	-1435.95
77	7.0	9.0	-1361.75	-1368.25
78	7.5	3.0	-1260.05	-1209.06
79	7.5	4.0	-1372.79	-1294.95
80	7.5	5.0	-1297.33	-1240.71
81	7.5	6.0	-1365.60	-1378.54
82	7.5	7.0	-1227.52	-1327.40
83	7.5	8.0	-1371.70	-1286.71
84	7.5	9.0	-1320.48	-1286.48

Table S2. Docking scores for VEGF₁₆₅/RNV66, VEGF₁₆₅/V7t1, and VEGF₁₆₅/del5-1. For each of the 7 variants resulting from the 7 VEGF₁₆₅ conformations and one aptamer conformation, the top 3 poses with the highest docking scores were selected.

Pose no.	VEGF ₁₆₅ variant (nm)	Docking score (arbitrary unit)		
		VEGF ₁₆₅ /RNV66	VEGF ₁₆₅ /V7t1	VEGF ₁₆₅ /del5-1
1	3.0	-1111.94	-1130.62	-1385.42
2	3.0	-1107.25	-1112.98	-1334.28
3	3.0	-1104.16	-1081.71	-1327.89
4	4.0	-1095.65	-1091.89	-1436.74
5	4.0	-1084.58	-1082.79	-1429.98
6	4.0	-1065.09	-1076.22	-1339.94
7	5.0	-1240.33	-1176.38	-1321.24
8	5.0	-1160.47	-1094.93	-1314.01
9	5.0	-1159.65	-1093.58	-1292.39
10	6.0	-1158.57	-1075.13	-1392.07
11	6.0	-1112.22	-1071.39	-1274.14
12	6.0	-1105.28	-1045.00	-1273.14
13	7.0	-1127.28	-1077.80	-1292.16
14	7.0	-1093.09	-1058.36	-1264.45
15	7.0	-1083.60	-1046.37	-1225.48
16	8.0	-1049.06	-1015.12	-1249.85
17	8.0	-1026.48	-994.86	-1198.54
18	8.0	-1026.01	-986.45	-1182.81
19	9.0	-1079.94	-1073.30	-1252.40
20	9.0	-999.11	-1071.73	-1223.78
21	9.0	-987.24	-1065.54	-1199.53

Table S3. Binding free energy (ΔG) values of the top 10 complex structures for each of the five types of VEGF₁₆₅/aptamer complexes.

Complex no.	ΔG (kcal/mol)				
	VEGF ₁₆₅ /RNV66:del5-1	VEGF ₁₆₅ /V7t1:del5-1	VEGF ₁₆₅ /RNV66	VEGF ₁₆₅ /V7t1	VEGF ₁₆₅ /del5-1
1	−237.3	−237.2	−106.9	−152.4	−140.1
2	−234.8	−216.0	−86.4	−150.7	−137.6
3	−226.2	−209.0	−70.6	−120.3	−136.3
4	−218.5	−203.6	−69.6	−116.3	−133.5
5	−207.2	−199.0	−61.4	−116.3	−117.9
6	−205.8	−194.0	−59.1	−104.1	−114.2
7	−194.7	−190.4	−57.7	−90.1	−111.8
8	−194.6	−188.6	−56.0	−88.6	−109.0
9	−184.8	−188.3	−55.5	−88.1	−108.5
10	−184.6	−187.3	−55.2	−81.4	−94.0
Average	−208.9 ± 18.6	−201.3 ± 15.1	−67.84 ± 16.0	−110.8 ± 24.1	−120.3 ± 14.8

Table S4. Binding poses for the top ten complex structures of each VEGF₁₆₅/aptamer complex type.

Complex no.	VEGF ₁₆₅ /RNV66:del5-1	VEGF ₁₆₅ /V7t1:del5-1	VEGF ₁₆₅ /RNV66	VEGF ₁₆₅ /V7t1	VEGF ₁₆₅ /del5-1
1	Sandwich	Sandwich	Sandwich	Hug	Sandwich
2	Sandwich	Sandwich	Side	Sandwich	Sandwich
3	Sandwich	Side	Hug	Sandwich	Sandwich
4	Sandwich	Sandwich	Sandwich	Side	Sandwich
5	Side	Sandwich	Sandwich	Sandwich	Sandwich
6	Sandwich	Sandwich	Sandwich	Sandwich	Sandwich
7	Sandwich	Sandwich	Sandwich	Sandwich	Sandwich
8	Side	Sandwich	Sandwich	Sandwich	Sandwich
9	Sandwich	Hug	Hug	Sandwich	Hug
10	Sandwich	Sandwich	Sandwich	Sandwich	Sandwich