Neu receptor dimerization

SIR—The probable mechanism by which the binding of the (as yet unidentified) ligand to the rat growth factor receptor encoded by the *neu* gene (which is closely related to the gene for epidermal growth factor receptor) is that binding promotes receptor dimerization, which activates the cytoplasmic tyrosine kinase (TK) domain of the Neu receptor[1]. Starting from the observation that mutations that convert the valine residue at position 664 (Val 664) of the Neu receptor into glutamate, glutamine or aspartate result in the constitutive activation of TK, and hence the conversion of *neu* into an oncogene that transforms cells, our molecular modelling now explains the effect of the mutations in terms of the dimerization of the transmembrane α-helix of the Neu receptor. Very recently, Weiner *et al.* have shown that the presence of Glu 664 in Neu leads to receptor aggregation[2].

We have previously proposed[3] a model for aggregation based on the formation of a dimer of Neu receptor transmembrane α-helices. Our more recent stereochemical modelling considered the following sequences:

Residue	661	662	663	664	665
neu oncogene	-Ala-	Thr-	Val-	Glu-	Gly-
neu gene	-Ala-	Thr-	Val-	Val-	Gly-
Position(P)	0	1	2	3	4

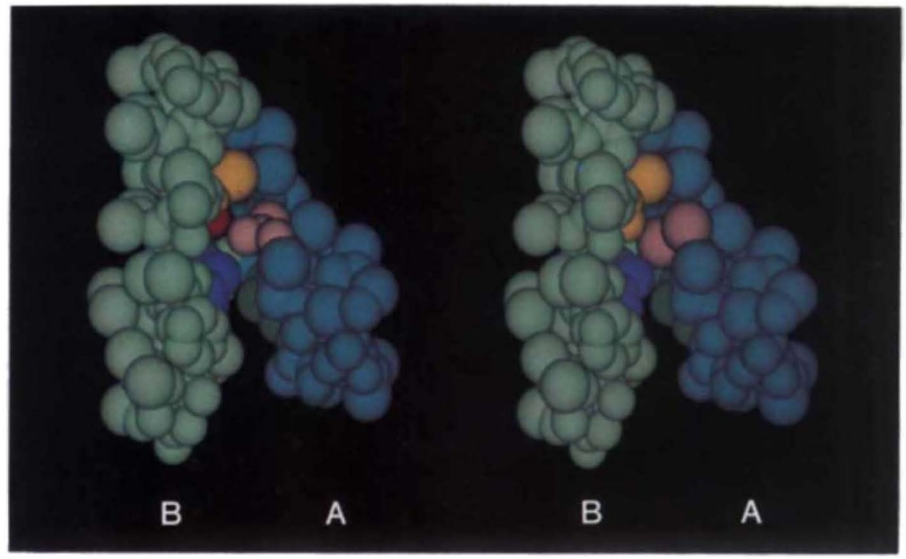
In the hydrophobic membrane, Glu and Asp side chains in oncogenic Neu will be protonated and may form a hydrogen bond with the other helix, stabilizing dimerization. One possibility[3] is that the Glu side chains are extended and form carboxyl–carboxylate hydrogen bonds. An alternative interaction involves a symmetric helix packing in which the carboxyl group of Glu 664 in one helix (helix A, left-hand figure) forms a hydrogen bond with the carbonyl oxygen of Ala 661 in the other (helix B, left-hand figure). The carbonyl oxygen of Ala 661 still forms the main-chain hydrogen bond in α-helix B. A second, symmetric hydrogen bond is formed between Glu 664 in B and the oxygen of Ala 661 in A. The helical axes lie at about $-50°$, a favoured orientation[4], permitting extracellular/extracellular and intracellular/intracellular domain associations. In normal Neu (righthand figure) the same transmembrane helical arrangement would pack Val 664 (P3) in A against Gly 665 (P4) in B. The helix packing is mediated by small side chains at P0 and P4.

Enhanced dimerization of the *neu* oncogene product, which may mimic the aggregation of growth factor receptors induced by their ligands, probably accounts for its constitutive TK activation. Activation can be explained stereochemically. Two inter-helical hydrogen bonds can be formed in the Glu mutant of Neu, promoting dimerization and higher TK activity. In normal Neu, the same packing can occur but this is stabilized only by van der Waals forces leading to fewer dimers and lower constitutive TK activity. The Gln and Asp mutations may form weaker inter-helical hydrogen bonds consistent with the lower levels of activity observed. A similar model would explain why Glu and Asp mutations at the equivalent position in c-*erbB*-2 (the human equivalent of *neu*) are also activating[5].

Helix association may also be a component of TK activation in other growth factor receptors. In 18 of the 20 transmembrane regions of such receptors[6–8] we have examined, we find a sequence motif analogous to that required for the packing in Neu. P0 requires a small side chain (Gly, Ala, Ser, Thr or Pro); P3 an aliphatic side chain (Ala, Val, Leu or Ile) and P4 only the smallest side chains (Gly or Ala). From the observed residue frequencies in the 20 transmembrane regions, the probability that the pattern occurs by chance in 18 out of the 20 sequences is only 0.0005.

Mutations at P3 to Glu, Asp, Gln or Asn might lead to increase in TK activity in some of these receptors. In all 17 reported DNA sequences, a single base change at P3 could produce one of these mutations. Indeed, in the epidermal growth factor receptor the mutation of Val to Glu at P3 leads to some increase in transforming activity, although this requires the presence of the ligand[9]. However, our model for Neu dimerization involves a highly specific inter-helical interaction and may not extend to other receptors.

It will be interesting to test whether peptides corresponding to the Neu transmembrane region, particularly those with a transforming mutation, can specifically inhibit TK activity by forming a non-productive complex. If so, and if dimerization is a more general phenomenon, such peptide inhibitors may represent a novel therapeutic strategy for cancer cells whose transformed state is dependent on unregulated growth factor receptor activity.



Space-filling models for the packing of part of the transmembrane α-helices in Neu. In both cases, the left helix (B) is mainly in light green, the right (A) in light blue. In helix B, Ala 661 is in yellow, Gly 665 in dark blue. In helix A, Gly 665 is in dark green. Left, oncogenic Neu with Glu 664 in helix A in pink forming the proposed hydrogen bond with the carbonyl oxygen (red) of Ala 661 of B. Right, normal Neu with Val 664 in helix A in pink packing against Gly 665 in B.

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Erratum

In the Scientific Correspondence by William Fowler on cold fusion in the 1 June issue of *Nature* (p.345), the 4th line of the second paragraph should read: "Nevertheless, I prefer to express my results in terms of transition widths. . .". The 5th line from the end of the same paragraph should read: ". . . $^5S_2 \rightarrow {}^5D_0$, of the nuclear states. . .".

On the same page, equation (4) should read:

$$\Gamma_\pi = \frac{1}{375\pi}\alpha^2 Z^2 \frac{E_\pi^5}{(\hbar c)^4} a_\pi^4 f_\pi$$