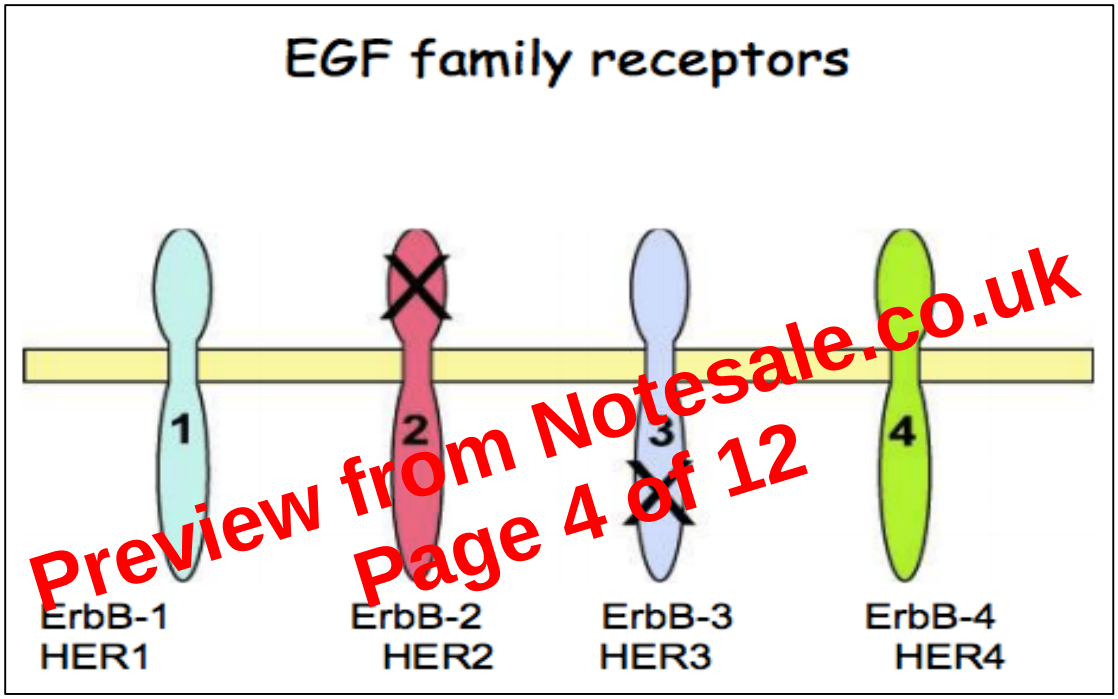
EGF Family receptor Signalling:

1. EGFR are the first RTKs to be characterised – EGFR sequencing by Waterfield's lab revealed homology to v-erbB (one of two oncogenes carried by the avian erythroblastosis virus).
2. **V-erbB** is a truncated form of the avian EGFR gene (ErbB1).
3. EGFR/ErbB-1 is the prototype receptor tyrosine kinase.
4. EGF family receptors are expressed in almost all types of tissue. There are four types:
    - ErbB-1 (EGFR)
    - ErbB-2
    - ErbB-3
    - ErbB-4



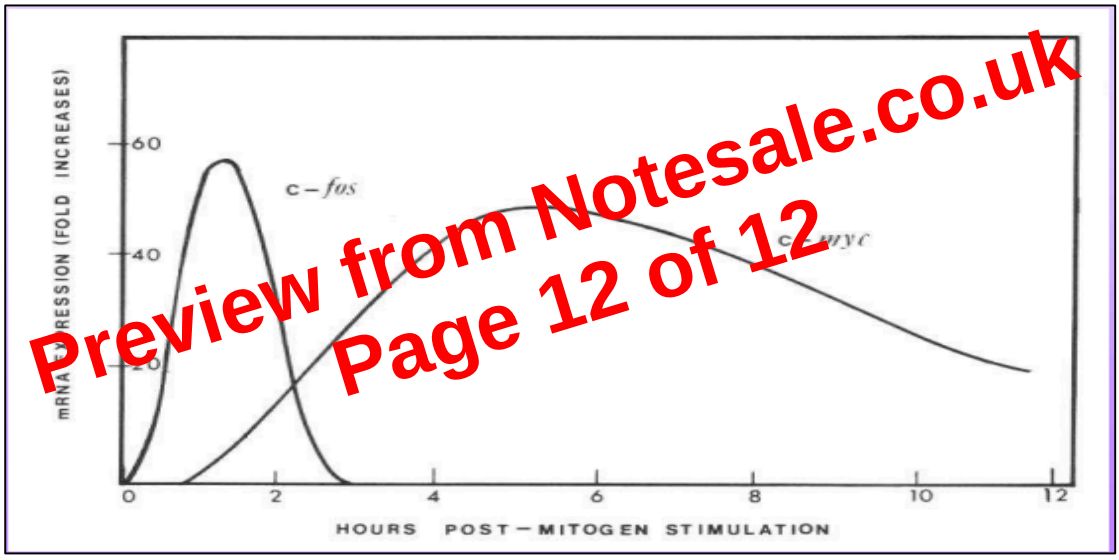
→ ErbB-2/HER2 has no obvious/known ligand binding region.
→ ErbB-3/HER3 has no kinase activity.

- Activation of Receptor by EGF:
    1. EGF is a monomeric growth factor ligand – therefore, it binds to **2 separate sites** on the receptor, i.e. the receptor requires two EGF molecules.
    2. Binding of EGF changes the conformation of the receptor and allows *dimerization* to occur.
    3. Ligand-stabilized conformation – the binding of the ligand to its binding site stabilizes the receptor.
    4. Ligand-induced activated dimers – refers to the dimerization event that produces two phosphorylation events to occur.

4. SH2 and SH3 domains are found in numerous other signalling molecules that are essential for building up signalling complexes.
5. SH2 domains contain one binding site of phosphotyrosine and another binding site for the **amino acid side chain.**
6. This adds another level of *specificity* of the molecule because different proteins have different sequences and thus different amino acid side chains.

Beyond the Receptor:

1. PDGF stimulation was found to cause a large, rapid increase in *c-myc expression in fibroblasts.*
2. This is the first piece of evidence linking **different proto-oncogenes in a common pathway.**
3. A direct response occurring even in the presence of protein synthesis inhibitors.
4. An even more rapid response was later found for *fos* and *jun.* I.e. increased transcription occurs within minutes.



→ Stimulation of one proto-oncogene leads to the stimulation of another.

5. Because *fos, jun* and *myc* are switched on by growth factors, even in the presence of a protein synthesis inhibitor, they are called **"immediately early"** genes.
6. Inhibition of Fos or Myc expression with **anti-sense constructs** or by micro-injecting antibodies, blocks growth factor stimulation of DNA synthesis.
7. I.e. **induction is essential for mitogenesis.**