Dr. Mildred Scheel Memorial Lecture

Hamburg, June 18, 1988

In Memoriam Dr. Mildred Scheel

Klaus Munk

The Wilsede Meeting is also supported by the Wilsede Fellowship Programme of the Dr. Mildred Scheel Stiftung, which is part of the Deutsche Krebshilfe. Since that Foundation was established by Dr. Mildred Scheel, it is appropriate that we should reflect and comment on the great contribution which she made to cancer prevention, treatment and research.

Who was Mildred Scheel? What were her ideas and what did she achieve with her Foundation?

Mildred Scheel was born in Cologne in 1932, daughter of a physician and radiologist. She studied medicine and specialized in radiology. Later, she married Mr. Walter Scheel before he was appointed Minister for Foreign Affairs. When Mr. Scheel subsequently became President of the Federal Republic of Germany, she became the "First Lady" of this country. No doubt this helped her to fulfil her noble ambition to contribute to the fight against cancer. As a consequence of this, she founded the Deutsche Krebshilfe in 1974. From that time on, all her efforts were directed towards encouraging people to contribute money for this crucial purpose. She developed many significant ideas for organizing cancer prevention, early diagnosis and treatment that was applicable on a large scale. She initiated the establishment of the first five cancer centers in this country. Once they were functioning successfully, she was able to convince the Government to assume full responsibility for maintaining them. She then prepared to launch new undertakings. It became apparent to people that she had unique qualities that enabled her to initiate new ideas for fighting cancer, and this added significantly to her personal success. She also supported in particular the treatment of childhood cancer in many hospitals, and initiated the psychosocial after-care of patients and their families. In addition, she aided individuals who were economically affected by having cancer.

The Dr. Mildred Scheel Stiftung was established to promote and support cancer research. It supports a great number

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of research projects in many institutes and provides a fellowship programme for scientists to work and study at institutions abroad. Included in that programme is the Wilsede Fellowship Programme. The Dr. Mildred Scheel Stiftung is now an important body in the Federal Republic of Germany for the granting of fellowships. Many of Mildred Scheel's initiatives were not broadly accepted at first, but through her continued energy they are now accepted as common practices in the oncological field in this country.

When she had a particular goal in sight, no obstacles could prevent her from reaching it. Yet, for all her tenacity, Mildred Scheel was a warm, loving and sensitive person who had special understanding for cancer patients, together with a human touch. She was always very hard-working and enthusiastic, and stimulating for all of us. None of those who, like myself, had worked with her in the Foundation for over 10 years can remember her ever missing a meeting of the board or the scientific councils of the Deutsche Krebshilfe or the Dr. Mildred Scheel Stiftung, until the last few weeks of her life. During those meetings she listened carefully to the experts, although sometimes she came to her own conclusions when she was convinced that a particular step forward had to be made. She never lost her enthusiasm for helping others, even when she realized what would be the consequence of her own illness. She always seemed to be positive in her attitude and could always stimulate others with her spirit and her personality. She could have done so much more in the future and she is sadly missed by all of us. We all will always remember her with great devotion.

The Mildred Scheel Memorial Lectures are our tribute. The second lecture will be held by Axel Ullrich, a classic molecular biologist, who has made important contributions to the understanding of cancer in the field of molecular biology.

Growth Factor Receptors: Role in Normal Mitogenic Signalling and Oncogenesis

A. Ullrich [1] and J. Schlessinger [2]

Growth factors, differentiation factors, and polypeptide hormones are crucial components of the regulatory system that coordinates development of multicellular organisms. Many of these factors mediate their pleiotropic actions by binding to and activating cell surface receptors with an intrinsic protein tyrosine kinase (PTK) activity. Figure 1 presents a schematic representation of the known growth factor receptors that bear PTK activity. Growth factor receptors with PTK activity, or receptor tyrosine kinases (RTKs), have a similar molecular topology. All possess a large, glycosylated, extracellular, ligand-binding domain, a single hydrophobic transmembrane region, and a cytoplasmic domain which contains a PTK catalytic domain (Hanks et al., 1988; Yarden and Ullrich 1988, Schlessinger 1988; Williams 1989).

Primary sequence homology and distinct structural characteristics of different RTKs allow the classification of these receptors into subclasses (Fig. 1). The structural features characteristic of the four subclasses include two cysteine-rich repeat sequences in the extracellular domain of monomeric subclass I receptors, disulfide-linked heterotetrameric $\alpha_2\beta_2$ structures with similar cysteine-rich sequences in subclass II RTKs, and five or three immunoglobulin-like repeats in the extracellular domains of subclass III and IV RTKs, respectively. The tyrosine kinase domain of the latter is interrupted by hydrophilic insertion sequences of varying length. The availability of RTK cDNA clones has made it possible to initiate detailed structure-function analyses of the mechanisms of action of RTK family members. Numerous mutants of insulin, epidermal growth factor (EGF), platelet-derived growth factor (PDGF), insulin-like growth factor 1 (IGF-1), colony-stimulating factor 1 (CSF-1), and other receptors have been characterized in regard to their biological and biochemical properties. This has led to the establishment of a receptor domain function map and model for RTK-mediated signal generation (Fig. 2).

Ligand binding to the extracellular domain of the receptor results in conformational change and subsequent oligomerization [Schlessinger 1988]. Receptor oligomerization is a universal phenomenon among growth factor receptors. It has been detected in living cells, in isolated membranes, and in preparations of solubilized and purified receptors [Schlessinger 1986; Yarden and Schlessinger 1985, 1987 a, b; Cochet et al., 1988]. It may be induced by either monomeric ligands, such as EGF, which cause receptor oligomerization by inducing conformational changes [Greenfield et al. 1989] resulting in receptor-receptor interactions [Lax et al. 1990] or by bivalent ligands, such as PDGF and CSF-1, which mediate dimerization of neighboring receptors [Seifert et al. 1989; Heldin et al. 1989; Hammacher et al. 1989]. Oligomerized growth factor receptors possess elevated PTK activity [Yarden and

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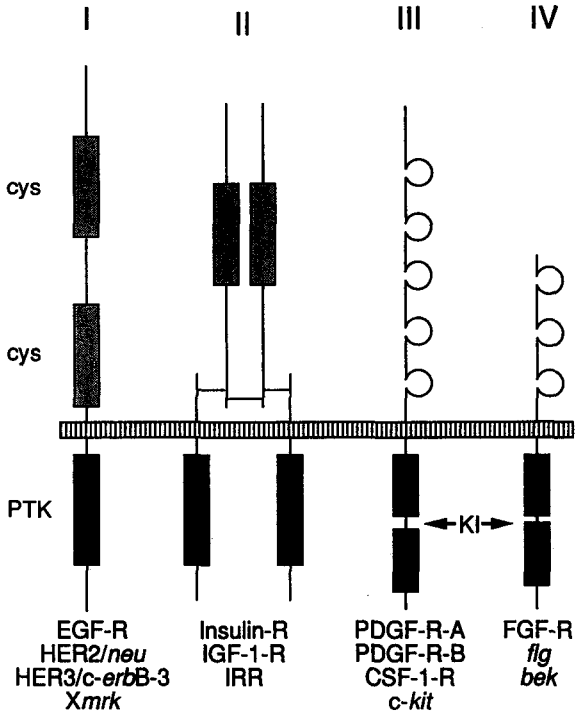

Fig. 1. Schematic representation of receptor tyrosine kinase subclasses. For details, see Ullrich and Schlessinger (1990)

Schlessinger 1987a, b; Böni-Schnetzler and Pilch 1987], which leads to phosphorylation of tyrosine residues of the receptor polypeptide chain and of cellular substrates.

Receptor phosphorylation releases an internal constraint by stabilizing a conformation that is competent to interact with and phosphorylate cellular substrates [Honegger et al. 1988a, b]. The recent observation that phosphorylation of EGF and insulin receptors can occur by intermolecular cross-phosphorylation both in vitro and in living cells [Honegger et al. 1989, 1990; Ballotti et al. 1989; Lammers et al. 1990] further supports the importance of receptor oligomerization in the process of receptor activation.

The chain of events that is initiated by tyrosine phosphorylation of cellular substrates is still poorly understood. Several RTK substates of potential biological importance have recently been identified (Figure 3). Both PDGF and EGF can induce tyrosine phosphorylation of phospholipase Cγ(PLC-γ) in vitro and in living cells [Margolis et al. 1989; Meisenhelder et al. 1989; Wahl et al. 1989]. In addition, PLC-γ was observed to associate with the activated receptor kinases in a ligand- and kinase-dependent manner [Margolis et al. 1989, 1990a; Kumjian et al. 1989]. However, growth factor-induced inositol triphosphate (IP_3) generation appears not to be the

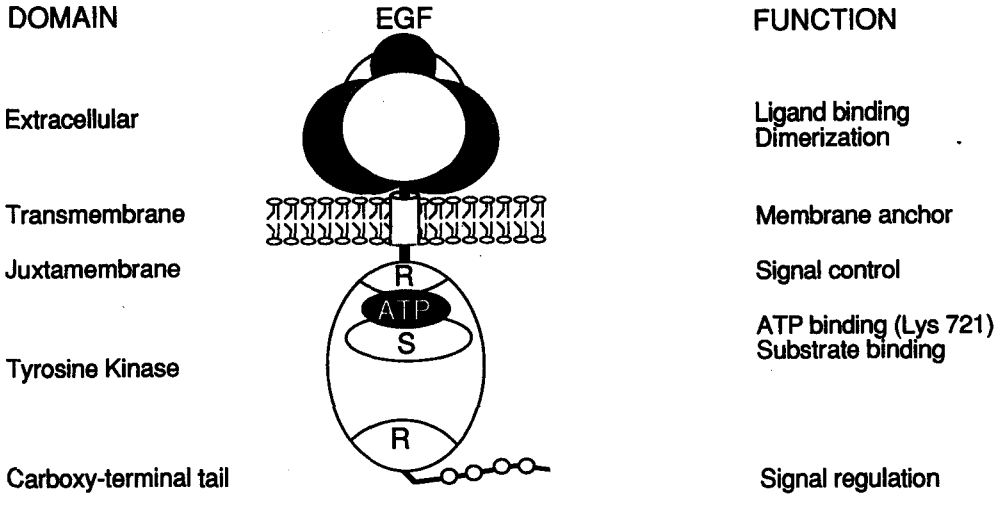

Fig. 2. Proposed structure-function topology of the EGF receptor. Subdomains II and IV (*stippled*) represent the cysteine-rich regions of the extracellular domain. Most of the structural determinants that define EGF binding affinity are proposed to be located in the cleft formed by subdomains I and III. The symbols *S* and *R* within the PTK domain represent proposed interaction sites for substrates and regulatory factors [Ullrich and Schlessinger, 1990]

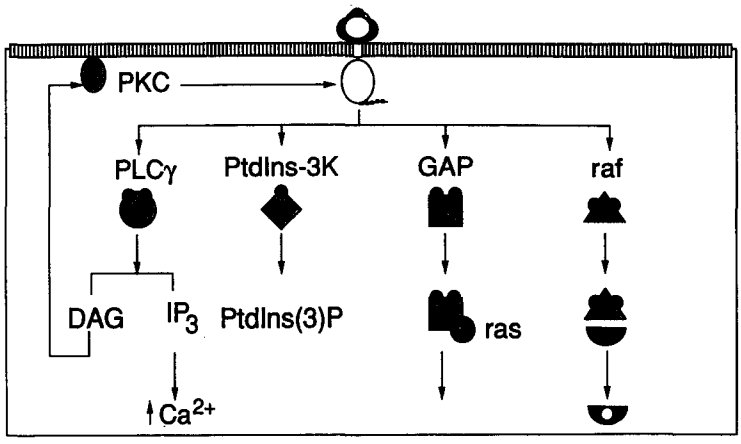

Fig. 3. Receptor-mediated multiple signalling pathways. Direct phosphorylation (*black dots* on symbols) of substrates, PLC-γ, PtdIns-3K, GAP, and *raf* leads to secondary events, including enzymatic activation and metabolite formation (DAG, IP_3, PtdIns(3)P), activation of enzymatic functions by association, and Thr/Ser phosphorylation (*white dot* on symbol) of substrates [Ullrich and Schlessinger, 1990]*PtdIns-3K:* phosphatidylinositol 3-kinase; *GAP:* GTPase-activating protein; *PtdIns(3)P:* phosphatidylinositol 3-phosphate

sole mechanism leading to the initiation of DNA synthesis [Downing et al. 1989], which is compatible with the notion that the phosphatidylinositol (PI) signalling pathway does not play an essential role in the mitogenic response [Lopez-Rivas et al. 1987; L'Allemain et al. 1989; Margolis et al. 1990b].

Other RTK substrates that have recently been identified include PI kinase and the *ras* binding protein GAP [Kaplan et al. 1987; Varticovski et al. 1989; Molloy et al. 1989] (Fig. 3). Similarly, it has been suggested that the c-*raf* protooncogene product becomes phosphorylated in response to PDGF receptor activation [Morrison et al. 1989]. Intriguingly, all proteins identified thus far as RTK targets are either components of second messenger pathways, protooncogene products, or factors that regulate the activity of protooncogene products.

The importance of allosteric regulation of receptor activation and signal transduction is further emphasized by the fact that a large variety of structural alterations found in RTK-derived oncogene products lead to constitutive kinase activation and, consequently, subversion of molecular control mechanisms and alteration of receptor signals. Thus, transforming RTK derivatives serve as valuable model systems not only for studying the mechanisms of oncogenesis but also for the analysis of normal structure-function relationships for these signal-transmitter molecules. Constitutive activation of RTK signalling functions can be achieved in a number of ways. For example, in the cases of v-*erb*-B and v-*kit*, deletion of the extracellular binding domain eliminates the negative control that this structure normally exerts on the cytoplasmic domain. Even point mutations within the extracellular domain can lead to intracellular activation, as in

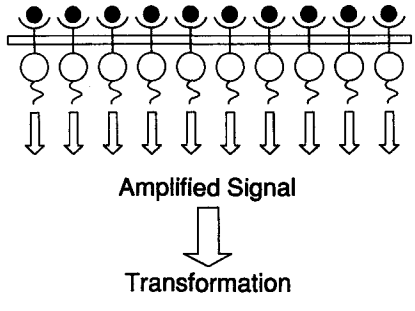

Fig. 4. Transformation by receptor amplification. Schematic representation of proposed transformation model by autocrine stimulation of overexpressed receptor tyrosine kinases. Ligand (*black dots*) is activating receptors in the plasma membrane of a tumor cell, resulting in an amplified transforming signal

the case of v-*fms* mutations at residues 301 and 374 [Woolford et al. 1988; Roussel et al. 1988] (Fig. 4). These mutations appear to induce and stabilize a conformational change equivalent to that triggered by ligand binding and possibly dimerization. Another dramatic effect of a single point mutation is exemplified by the Val/Glu conversion in the *neu* transmembrane domain [Bargmann et al. 1986], which suggests that this part of the putative receptor is involved in an overall conformational alteration that occurs upon interaction with the yet unidentified ligand. In this case, the transmembrane mutation results in constitutive receptor oligomerization [Weiner et al. 1989]. Another type of structural alteration has been identified in the EGF receptor/*erb*-B system and involves mutations in the PTK core region [Massoglia et al. 1990]. Despite the presence of an intact extracellular domain, these mutations render the EGF receptor competent for mitogenic and transforming signalling without autophosphorylation. RTK-derived oncogenes possess other structural lesions such as cytoplasmic point mutations, deletions, and C-terminal truncations which appear to enhance and modulate the transforming signal [Khazaie et al. 1988; Woolford et al. 1988].

For human cancer, activating RTK mutations appear to be of minor importance. The most common cellular lesion found in human cancers involves autocrine activation in conjunction with receptor overexpression (Fig. 4). Many tumors and tumor cell lines have been found to coexpress growth factors and their receptors, including TGF-α, PDGF-A, PDGF-B, acidic fibroblast growth

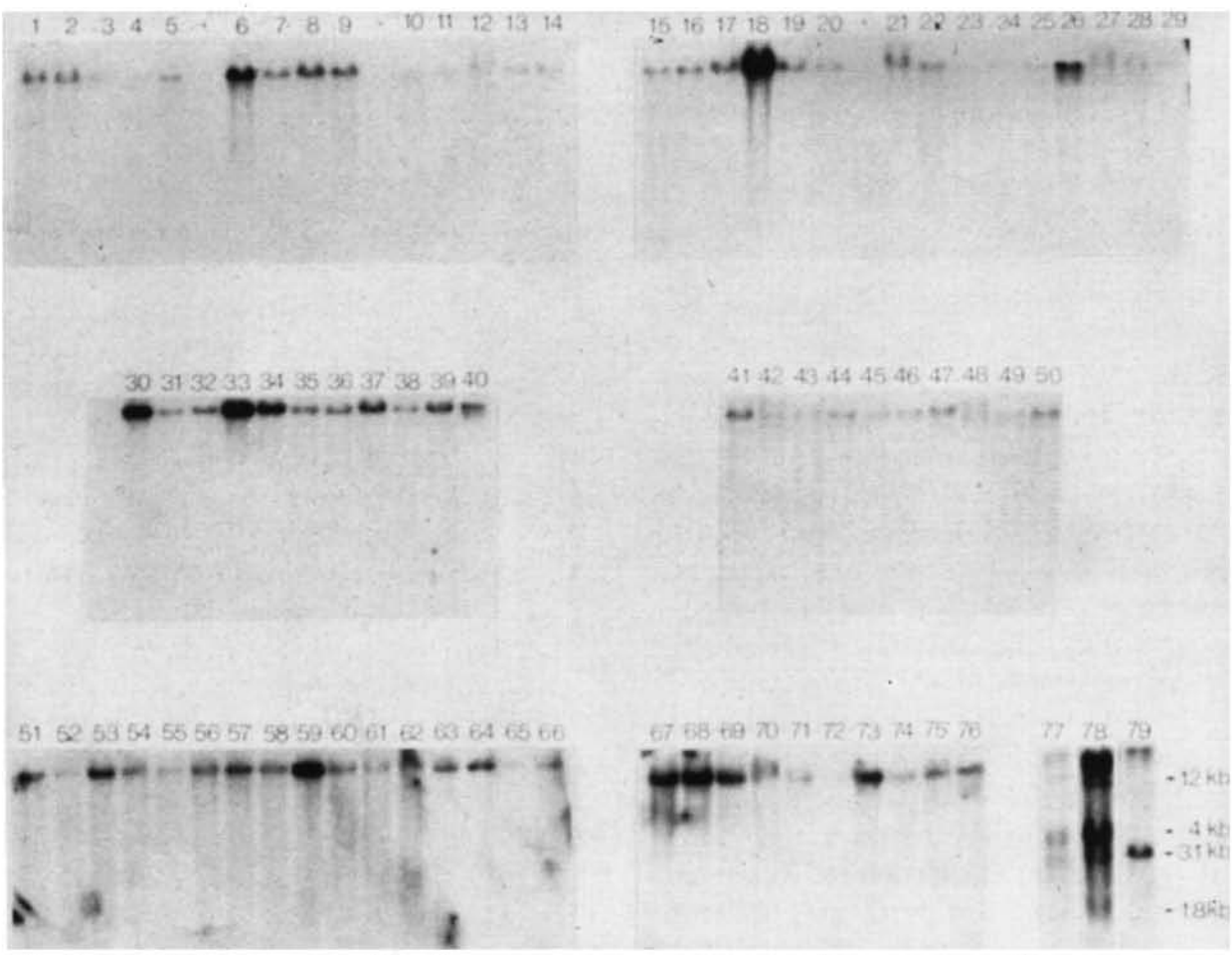

Fig. 5. HER2/*neu* gene amplification in mammary carcinoma. Southern blot hybridization analysis of chromosomal DNA from primary mammary carcinoma tumors [Slamon et al. 1987]

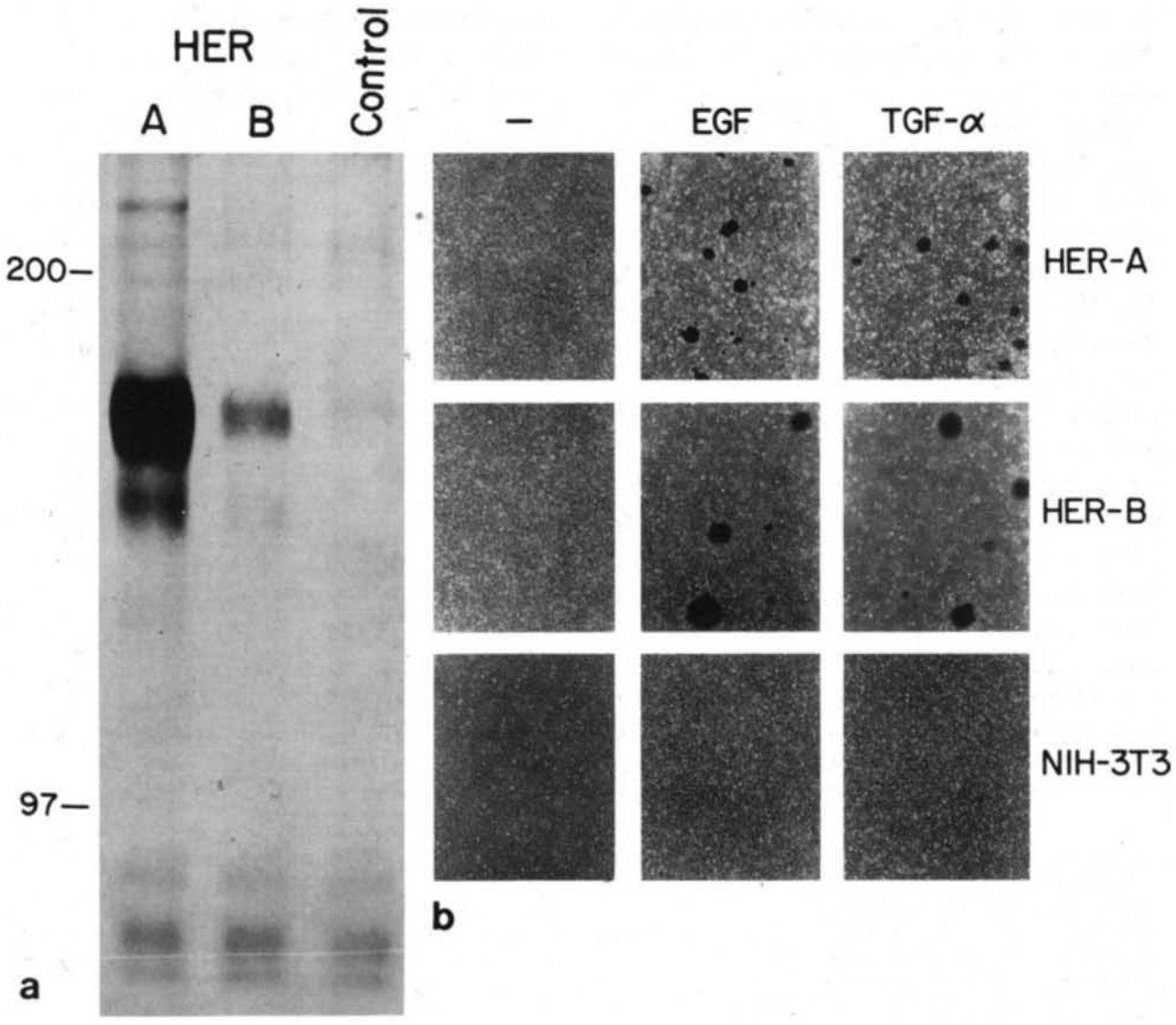

Fig. 6a,b. Cell transformation by EGF receptor overexpression. NIH-3T3 cell lines HER-A and HER-B overexpressing the human EGF receptor (**a**) were stimulating with EGF or TGF-α and tested for their ability to grow in soft agar (**b**)

factor (FGF), basic FGF, and their specific RTKs. Thus, autocrine receptor activation represents yet another scenario of subversion of normal growth control. For mammary and ovarian carcinoma, extensive studies have demonstrated a direct correlation between the extent of overexpression of $p185^{HER\,2/neu}$ and a patient's prognosis, a result which strongly suggests a critical role for this EGF receptor-like RTK in tumor progression and perhaps even tumor initiation [Slamon et al. 1989] (Fig. 5). This possibility is further supported by efficient induction of mammary carcinoma in mice by an activated *neu* gene product [Muller et al. 1988] and transformation of NIH-3T3 cells by overexpression of unaltered $p185^{HER\,2/neu}$ [Hudziak et al. 1987]. Analogous experiments with the EGF receptor indicated that autocrine stimulation of the overexpressed receptor was essential to achieve a transforming effect [Di Fiore et al. 1987; Velu et al. 1987; Riedel et al. 1988] (Fig. 6).

On the basis of these findings, strategies involving antireceptor antibodies were designed for the treatment of mammary and ovarian carcinoma. Monoclonal antibodies, such as the anti-HER2/*neu* antibody 4D5, are able to interfere with autocrine activation of the receptor, which results in inhibition of tumor cell growth in tissue culture and nude mouse models (Ullrich et al., unpublished).

In principle, every receptor with PTK activity has oncogenic potential. One can anticipate that many more types of activating mutations, as well as specific instances of RTK overexpression, will be detected in animal and human tumors. The molecular identification and characterization of these mutants will not only provide important insights into fundamental mechanisms underlying receptor activation and normal growth control, but may also enhance our understanding of oncogenesis and open new avenues for diagnosis and therapy.

References

1. Ballotti R, Lammers R, Scimeca JC, Dull T, Schlessinger J, Ullrich A, Van Obberghen E (1989) Intermolecular transphosphorylation between insulin receptors and EGF-insulin receptor chimerae. EMBO J 8:3303–3309
2. Bargmann CI, Hung MC, Weinberg RA (1986) Multiple independent activations of the neu oncogene by a point mutation altering the transmembrane domain of p185. Cell 45:649–657
3. Böni-Schnetzler M, Pilch PF (1987) Mechanism of EGF-receptor autophosphorylation and high affinity binding. Proc Natl Acad Sci USA 84:7832–7836
4. Cochet C, Kashles O, Chambaz EM, Borrello I, King CR, Schlessinger J (1988) Demonstration of epidermal growth factor-induced receptor dimerization in living cells using a chemical covalent cross-linking agent. J Biol Chem 263:3290–3295
5. Di Fiore PP, Pierce JH, Fleming TP, Hazan R, Ullrich A, King CR, Schlessinger J, Aaronson SA (1987) Overexpression of the human EGF receptor confers an EGF-dependent transformed phenotype to NIH 3T3 cells. Cell 51:1063–1070
6. Dionne C, Crumley G, Bellot F, Kaplow J, Searfoss G, Ruta M, Burgess W, Jaye M, Schlessinger J (1990) Cloning and expression of two distinct high-affinity receptors cross-reacting with acidic and basic fibroblast growth factors. EMBO J 9:2685–2692
7. Downing JR, Margolis BL, Zilberstein A, Ashmun RA, Ullrich A, Sherr CJ, Schlessinger J (1989) Phospholipase C-γ, a substrate for PDGF receptor kinase, is not phosphorylated on tyrosine residues during the mitogenic response to CSF-1. EMBO J 8:3345–3350
8. Greenfield C, Hils I, Waterfield MD, Federwisch M, Wollmer A, Blundell TL, McDonald N (1989) EGF binding induces a conformational change in the external domain of its receptor. EMBO J 8:4115–4124
9. Hammacher A, Mellstrom K, Heldin CH, Westermark B (1989) Isoform-specific induction of actin reorganization by PDGF suggests that the functionally active receptor is a dimer. EMBO J 8:2489–2495
10. Hanks SK, Quinn AM, Hunter T (1988) The protein kinase family: conserved features and deduced phylogeny of the catalytic domains. Science 241:45–52
11. Heldin C-H, Ernlund A, Rorsman C, Ronnstrand L (1989) Dimerization of the B type PDGF-receptor occurs after ligand binding and is closely associated with receptor kinase activation. J Biol Chem 264:8905–8912
12. Honegger A, Dull TJ, Bellot F, Van Obberghen E, Szapary D, Schmidt A, Ullrich A, Schlessinger J (1988 a) Biological activities of EGF-receptor mutants with individually altered autophosphorylation sites. EMBO J 7:3045–3052
13. Honegger A, Dull TJ, Szepary D, Komoriya A, Kris R, Ullrich A, Schlessinger J (1988 b) Kinetic parameters of the protein tyrosine kinase activity of EGF-receptor mutants with individually altered autophosphorylation sites. EMBO J 7:3053–3060
14. Honegger AM, Kris RM, Ullrich A, Schlessinger J (1989) Evidence that autophosphorylation of solubilized EGF-receptors is mediated by intermolecular cross phosphorylation. Proc Natl Acad Sci USA 86:925–929
15. Honegger AM, Schmidt A, Ullrich A, Schlessinger J (1990) Evidence for EGF induced intermolecular autophosphorylation of the EGF-receptor in living cells. Mol Cell Beiol 10:4035–4044
16. Hudziak RM, Schlessinger J, Ullrich A (1987) Increased expression of the putative growth factor receptor p $185^{HER\,2}$ causes transformation and tumorigenesis of NIH 3T3 cells. Proc Natl Acad Sci USA 84:7159–7163

17. Kaplan DR, Whitman M, Schaffhausen B, Pallas DC, White M, Cutley L, Roberts TM (1987) Common elements in growth factor stimulation and oncogenic transformation: 85 Kd phosphorylation and phosphatidylinositol kinase activity. Cell 50:1021–1029
18. Khazaie K, Dull TJ, Graf T, Schlessinger J, Ullrich A, Beug H, Vennstrom B (1988) Truncation of the human EGF receptor leads to differential transforming potentials in primary avian fibroblasts and erythroblasts. EMBO J 7:3061–3071
19. Kornbluth S, Paulson KE, Hanafusa H (1988) Novel tyrosine kinase identified by phosphotyrosine antibody screening of cDNA libraries. Mol Cell Biol 8:5541–5544
20. Kraus MH, Issing W, Miki T, Popescu NC, Aaronson SA (1989) Isolation and characterization of ERBB3, a third member of the ERBB/epidermal growth factor receptor family: evidence of overexpression in a subset of human mammary tumors. Proc Natl Acad Sci USA 86:9193–9197
21. Kumjian DA, Wahl MI, Rhee SG, Daniel TO (1989) Platelet-derived growth factor (PDGF) binding promotes physical association of PDGF receptor with phospholipase C. Proc Natl Acad Sci USA 86:8232–8236
22. L'Allemain G, Seuwen K, Velu T, Pouyssegur J (1989) Signal transduction in hamster fibroblasts overexpressing the human EGF-receptor. Growth Factors 1:311–321
23. Lammers R, Van Obberghen E, Ballotti R, Schlessinger J, Ullrich A (1990) Transphosphorylation as a possible mechanism for insulin and EGF receptor activation. Biol Chem 265:16886–16890
24. Lax I, Mitra AK, Stroud RM, Ravera C, Givol D, Hurwitz DR, Ullrich A, Schlessinger J (1990) EGF-induced oligomerization of soluble, extracellular, ligand binding domain of EGF receptor Biol Chem (in press)
25. Lee PL, Johnson DE, Cousens LS, Fried VA, Williams LT (1989) Purification and complementary DNA cloning of a receptor for basic fibroblast growth factor. Science 245:57–60
26. Lopez-Rivas A, Mendoza SA, Nanberg E, Sinnett-Smith J, Rozengurt E (1987) Ca^{+2} mobilizing actions of PDGF differ from those of bombesin and vasopressin in Swiss 3T3 mouse cells. Proc Natl Acad Sci USA 84:5768–5772
27. Margolis BL, Rhee SG, Felder S, Lyall R, Levitski A, Ullrich A, Zilberstein A, Schlessinger J (1989) EGF induces phosphorylation of phospholipase C-II: a potential mechanism for EGF-receptor signalling. Cell 57:1102–1107
28. Margolis B, Bellot F, Honegger AM, Ullrich A, Schlessinger J, Zilberstein A (1990a) Tyrosine kinase activity is essential for the association of phospholipase C-γ with EGF-receptor. Mol Cell Biol 10:435–441
29. Margolis B, Zilberstein A, Franks C, Felder S, Kreamer S, Ullrich A, Rhee SG, Skorecki K, Schlessinger J (1990b) Effect of phospholipase c-γ overexpression on PDGF-induced second messengers and mitogenesis. Science 248:607–610
30. Massoglia S, Gray A, Dull TJ, Munemitsu S, Kung H-J, Schlessinger J, Ullrich A (1990) Epidermal growth factor receptor cytoplasmic domain mutations trigger ligand-independent transformation. Mol Cell Biol 10:3048–3055
31. Meisenhelder J, Suh P-G, Rhee SG, Hunter T (1989) Phospholipase C-γ is a substrate for the PDGF and EGF receptor protein-tyrosine kinases in vivo and in vitro. Cell 57:1109–1122
32. Molloy CJ, Bottaro DP, Fleming TP, Marshall MS, Gibbs JB, Aaronson SA (1989) PDGF induction of tyrosine phosphorylation of GTPase activating protein. Nature 342:711–714
33. Morrison DK, Kaplan DR, Escobedo JA, Rapp UR, Roberts TM, Williams LT (1989) Direct activation of the serine/threonine kinase activity through tyrosine phosphorylation by the PDGF β receptor. Cell 58:649–657
34. Muller WJ, Sinn E, Pattengale PK, Wallace R, Leder P (1988) Single-step induction of mammary adenocarcinoma in transgenic mice bearing the activated c-neu oncogene. Cell 54:105–109
35. Riedel H, Massoglia S, Schlessinger J, Ullrich A (1988) Ligand activation of overexpressed epidermal growth factor receptors transforms NIH 3T3 mouse fibroblasts. Proc Natl Acad Sci USA 85:1477–1481
36. Roussel MF, Downing JR, Rettenmier CW, Sherr CJ (1988) A point mutation in the extracellular domain of the human CSF-1 receptor (c-fms proto-oncogene

product) activates its transforming potential. Cell 55:979–988
37. Ruta M, Howk R, Ricca G, Drohan W, Zabelshansky M, Laureys G, Barton DE, Francke U, Schlessinger J, Givol D (1988) A novel protein tyrosine kinase gene whose expression is modulated during endothelial cell differentiation. Oncogene 3:9–15
38. Ruta M, Burgess W, Givol D, Epstein J, Neiger N, Kaplow J, Crumley G, Dionne C, Jaye M, Schlessinger J (1989) Receptor for acidic FGF is related to the tyrosine kinase encoded by the fms like gene (flg). Proc Natl Acad Sci USA 86:8722–8726
39. Schlessinger J (1986) Allosteric regulation of the epidermal growth factor receptor kinase. J Cell Biol 103:2067–2072
40. Schlessinger J (1988) Signal transduction by allosteric receptor oligomerization. Trends Biochem Sci 13:443–447
41. Seifert RA, Hart CE, Phillips PE, Forstrom JHW, Ross R, Murray MJ, Bowen-Pope DF (1989) Two different subunits associate to create isoform-specific PDGF-receptors. J Biol Chem 264:8771–8778
42. Shier P, Watt VM (1989) Primary structure of a putative receptor for a ligand of the insulin family. J Biol Chem 264:14605–14608
42a. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL (1987) Human breast cancer: Correlation of relapse and survival with amplification of the HER-2/*neu* oncogene. Science 235:177–182
43. Slamon DJ, Godolphin W, Jones LA, Holt JA, Wong SG, Keith DE, Levin WJ, Stuart SG, Udove J, Ullrich A, Press MF (1989) Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science 244:707–712
44. Varticovski L, Druker B, Morrison D, Cantley L, Roberts T (1989) The colony stimulating factor-1 receptor associates with and activates phosphatidylinositol-3 kinase. Nature 342:699–702
45. Velu TJ, Beguinot L, Vass WC, Willingham MC, Merlino GT, Pastan I, Lowy DR (1987) Epidermal growth factor-dependent transformation by a human EGF receptor protooncogene. Science 237:1408–1410
46. Wahl M, Nishibe S, Suh P-G, Rhee SG, Carpenter G (1989) Epidermal growth factor stimulates tyrosine phosphorylation of phospholipase C-II independently of receptor internalization and extracellular calcium. Proc Natl Acad Sci USA 86:1568–1572
47. Weiner DB, Liu J, Cohen JA, Williams WV, Greene M (1989) A point mutation in the neu oncogene mimics ligand induction of receptor aggregation. Nature 339:230–231
48. Williams LT (1989) Signal transduction by the PDGF-receptor. Science 243:1564–1570
49. Wittbrodt J, Adam D, Malitschek B, Maueler B, Raulf F, Telling A, Robertson SM, Schartl M (1989) Novel putative receptor kinase encoded by the melanoma-inducing T4 locus in Xiphophorus. Nature 341:415–421
50. Woolford JW, McAuliffe A, Rohrschneider LR (1988) Activation of the feline c-fms protooncogene: multiple alterations are required to generate a fully transformed phenotype. Cell 55:965–977
51. Yarden Y, Schlessinger J (1985) EGF receptor self-phosphorlyation is mediated by an intermolecular allosteric process. In: Growth factors in biology and medicine. Pitman, London, pp 23–45
52. Yarden Y, Schlessinger J (1987a) Self-phosphorylation of epidermal growth factor receptor: Evidence of a model of intermolecular allosteric activation. Biochemistry 26:1434–1442
53. Yarden Y, Schlessinger J (1987b) Epidermal growth factor induces rapid, reversible aggregation of the purified epidermal growth factor receptor. Biochemistry 26:1443–1451
54. Yarden Y, Ullrich A (1988) Growth factor receptor tyrosine kinases. Annu Rev Biochem 57:443–478