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Review

SRC as a target for anti-cancer drugs

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Introduction

Protein tyrosine kinases (PTKs) play a key role in normal cell division and abnormal cell proliferation. Enhanced PTK activity has been associated with proliferative diseases such as cancer (Bishop, 1987), atherosclerosis (Ross, 1933) and with psoriasis (Elder *et al.*, 1989). The involvement of well-identified PTKs in certain diseases has been documented over the past decade. For example, in mammary carcinoma and ovarian carcinoma, the amplification and overexpression of the HER-2/c-erbB2 proto-oncogene correlates with the severity of disease and poor prognosis (Slamon *et al.*, 1987, 1989). In human chronic myelogenous leukemia (CML), enhanced tyrosine kinase activity (Lugo *et al.*, 1990) and altered substrate specificity (Anafi *et al.*, 1992) which underlies the disease is a consequence of the activation of the cell c-*abl* proto-oncogene by its fusion with the *bcr* element from another chromosome. The involvement of defined PTKs has also been documented in other diseases. For example, the release of platelet-derived growth factor (PDGF) by platelets and of other cytokines at the damaged surface of the endothelium layering the internal surface of blood vessels results in stimulation of PDGF receptor on vascular smooth muscle cells, leading to enhanced inflammatory proliferation and consequent generation of the atherosclerotic plaque (Ross, 1993). The accelerated form of the disease restenosis is also mediated by PDGF, its receptor and inflammatory cytokines whose activities are also mediated by a variety of PTKs (Ross, 1993). Another example is psoriasis, in which the overexpression of transforming growth factor α (TGFα) and the persistent autocrine stimulation of the keratinocyte through the epidermal growth factor (EGF) receptor seem to play a major role in this condition (Elder *et al.*, 1989).

The identification of signal transduction pathways which play a key role in various cancers as well as in other proliferative diseases is a prerequisite for signal transduction therapy (Levitzki, 1990; Powis & Workman, 1994). It seems that different cancers utilize a specific signal transduction pathway or a set of such pathways for their survival, proliferation and eventually for metastasis. During its evolution, the tumor modifies the repertoire of pathways on which it depends. It seems, however, that certain normal signal transduction elements which exist in every cell, and which are active some of the time in normal cells, become persistently active in tumor cells and appear to be active in most tumors. These include Ras proteins, Raf proteins, MAPK, MAPKK, PKC isozymes, PI-3′ kinase, etc. This is why these signal transducers have also become popular targets for anti-cancer drugs [for reviews, see Levitzki (1992, 1994), Powis &

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Workman (1994) and Levitzki & Gazit (1995)]. In this short review, I will try to make the case that pp60$^{c\text{-}src}$ is also activated in many tumors and may qualify as a universal target for cancer therapy.

The involvement of pp60$^{c\text{-}src}$ in the oncogenic signal transduction of HER-2 and of EGFR/HER-1

Recent findings show that in 100% of breast cancer cases the level of tyrosine kinase activity is elevated up to 25-fold over normal breast tissue, where 70% of this elevation is attributed to the activity of activated pp60$^{c\text{-}src}$ kinase (Ottenhofkalff *et al.*, 1992). Similarly, mammary tumors in transgenic mice carrying the *neu* oncogene possess 7-fold higher c-src kinase activity as compared to the normal neighboring epithelium (Muthuswamy *et al.*, 1994). Other studies on lung cancer (Mellstrom *et al.*, 1987; Mazurenko *et al.*, 1992) and on colon cancer also show that tumor specimens exhibit a high level of tyrosine kinase activity, mostly due to pp60$^{c\text{-}src}$ kinase (Bolen *et al.*, 1987; Desau *et al.*, 1987; Cartwright *et al.*, 1990; Weber *et al.*, 1992). All these surveys suggest that src kinase is involved in tumor initiation, progression and metastasis. In one study, it was claimed that the level of expression of the Src protein as well as of its homologue Yes (p62$^{c\text{-}yes}$) is elevated and the level of expression seems to be the main reason for elevated src kinase (Park *et al.*, 1993). In other studies, it is stressed that it is the specific activity of the Src protein which is elevated and not its level of expression. It was also pointed out that the level of pp60$^{c\text{-}src}$ kinase activity increases with the progression of colon cancer from the early stages to the liver metastatic stage (Weber *et al.*, 1992).

Interestingly, so far no oncogenic mutant src variants have been identified in human tumors, although such variants may be discovered in the future. Thus, so far, in those cases in which elevated src kinase activity is found, it is that of normal cellular c-src, predominantly of pp60$^{c\text{-}src}$.

Since we were intrigued by the finding that HER-2 overexpressors exhibit elevated pp60$^{c\text{-}src}$ kinase activity and such a finding was not reported for EGF receptor overexpressor tumors, we have searched for possible differences between these two receptors *vis-à-vis* src activation. In this context, one must recall that EGFR and HER-2 are highly homologous (~80%; Coussens *et al.*, 1985) at the kinase domain, yet HER-2 is much more transforming (Di Fiore *et al.*, 1990). Furthermore, certain tyrphostins preferentially inhibit one or the other kinase (Gazit *et al.*, 1991, 1993; Osherov *et al.*, 1993), pointing to differences in substrate specificity and/or affinity towards intracellular substrates. Additionally, the fact that src type kinases are constitutively activated in HER-2 and HER 1-2 overexpressors in a ligand-independent manner (Osherov, 1995; Figure 1) and in EGFR overexpressors in an EGF-dependent manner (Osherov & Levitzki, 1994; Osherov, 1995) may point to a potential difference in the signaling of the two receptors. The extent of pp60$^{c\text{-}src}$ activation by EGF depends on the level of EGFR expression where low expressors are devoid of src activation (Osherov & Levitzki, 1994; Osherov, 1995). We also showed that A431 cells which overexpress EGFR as well as TGFα possess constitutive src activation (Osherov, 1995; and Figure 1). The functional activation of src has also been reported by others for a different cell system (Oude Weernink *et al.*, 1994). A physical EGFR to pp60$^{c\text{-}src}$ association in A431 has also been recently reported (Suto *et al.*, 1995). Luttrell *et al.* (1994) have reported that GST fusion proteins of src SH2/SH3 domains physically associate with phosphorylated EGFR and HER-2 *in vitro*. Stover *et al.* (1995) also reported that EGFR and pp60$^{c\text{-}src}$ can associate when co-expressed. The relationship between HER-1/EGFR and src is also strengthened by studies using NRK cells infected with a temperature-sensitive mutant of Rous sarcoma

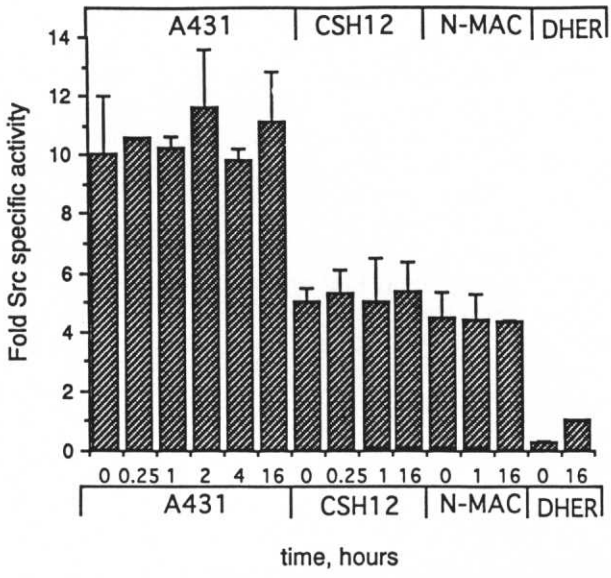


Figure 1 Activation of pp60$^{c\text{-}src}$ by HER-2, HER 1-2, EGF receptor and PDGF receptor. Four cell lines were examined for the state of pp60$^{c\text{-}src}$ activation: A431 epidermoid carcinoma cells which overexpress EGFR as well as its ligand TGFα; DHER cells, also known as HER 14 cells, which are NIH 3T3 cells which overexpress EGFR but are not expressing any EGFR ligand; N-MAC cells which are NIH 3T3 cells which overexpress the HER-2; and CSH which are NIH 3T3 cells which overexpress the chimera EGFR/HER-1 (out)/HER-2(in) and do not express any EGFR ligand. It can be seen that in the cells which express HER-2 and HER 1–2, pp60$^{c\text{-}src}$ is constitutively active. In A431, but not in DHER, pp60$^{c\text{-}src}$ is constitutively active. Activation of pp60$^{c\text{-}src}$ in DHER occurs only upon addition of EGF (not shown, see Osherov & Levitzki, 1994). Data are reproduced with permission from Osherov (1995)

virus. It was found that 10 nM epiderstatin, a glutarimide antibiotic which was found by screening for inhibitors of the signal transduction of EGF, reverses the transformed phenotype to the normal phenotype of NRK cells. The cell cycle progression of v-src(ts)-NRK cells was blocked at the G_0/G_1 phase, which was caused by the inhibition of biosynthesis of p60$^{v\text{-}src}$ (Osada *et al.*, 1995).

Whereas in NIH3T3 cells which overexpress EGFR the activation of pp60$^{c\text{-}src}$ is EGF dependent, in NIH 3T3 cells which overexpress HER-2 pp60$^{c\text{-}src}$ activation is ligand independent (Osherov, 1995; Figure 1). These findings, taken together, point to a stronger link between HER-2/neu and pp60$^{c\text{-}src}$ than between EGFR and pp60$^{c\text{-}src}$, and may suggest why HER-2 is more oncogenic.

The connection between PDGF receptor and pp60$^{c\text{-}src}$ as well as with Fyn and Yes is well established, and so is the connection between CSF-1 receptor and pp60$^{c\text{-}src}$ (for a review, see Heldin & Westermark, 1991). In both cases, it has been shown that activation of the receptor leads to the activation of the src protein by binding to a tyrosine-phosphorylated site on the activated receptor (Kypta *et al.*, 1990; Courtneidge *et al.*, 1993), most probably without dephosphorylation of the inhibitory tyrosine 527. Activation of the src protein is most probably by the association of the SH2 domain of the src kinase with the phosphorylated site of the receptor, thus relieving the inhibitory conformation

in which the SH2 domain is bound to the phosphorylated tyrosine 527 (in $pp60^{c\text{-}src}$).

In the normal cells which respond to PDGF or CSF-1, src is activated only transiently. In many tumors, PDGF receptor is co-expressed with PDGF and therefore tumor growth is largely driven by an autocrine PDGF/PDGF receptor loop (Heldin & Westermark, 1991). It is likely that in these tumors $pp60^{c\text{-}src}$ and perhaps other src proteins are persistently active. Similarly, tumors with activated CSF-1 receptor are likely to possess persistently activated src. Although these assumptions are reasonable, they have not been directly examined experimentally.

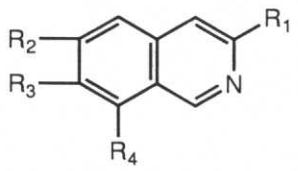
In conclusion, it seems that in tumors in which HER-2, EGF receptor, PDGF receptor and CSF-1 receptor play an important driving role, $pp60^{c\text{-}src}$ is a major signal transducer. We would like to suggest that an intensive effort should be devoted to establishing the oncogenic role of src kinases in human tumors. Since current data already strongly suggest that src kinases, especially $pp60^{c\text{-}src}$, may play a major role in many important human tumors (Table I), efforts to generate selective src kinase blockers should be intensified. Such blockers can become universal chemical agents to treat a large number of cancers, in combination with more selective agents to be determined according to the tumor.

Inhibition of $pp60^{c\text{-}src}$ leads to the reversal of the transformed phenotype in model systems

In two studies, it has been demonstrated that the inhibition of activated src kinase activity causes reversal of the transformed phenotype. Tyrphostins were found to reverse the transformed phenotype of NIH 3T3 cell transformed with $pp60^{c\text{-}src/F\ 527}$ (Agbotounou *et al.*, 1994). Similarly, chicken lens cells transformed with chicken temperature-sensitive (*ts*) v-src can reverse to the normal non-transformed phenotype at normal temperatures (Volberg *et al.*, 1992) in the presence of this family of tyrphostins. This class of compounds, however, are only effective at relatively high concentrations (10–100 μM) and are not very selective. Other studies suggest that certain closed-ring tyrphostins are more selective towards $p56^{lck}$ than EGF receptor (Figure 2; Burke *et al.*, 1992) in a biochemical assay, but this line of investigation has not yet been completed. These derivatized isoquinolines have not been examined against $pp60^{c\text{-}src}$ kinase. Furthermore, EGFR selective receptor kinase inhibitors, such as AG 1478, and PDGF receptor selective inhibitors such as AG 1295/6, do not inhibit $pp60^{c\text{-}src}$ (Kovalenko *et al.*, 1994;

Table I Examples of tumors in which src kinase is known or is likely to be elevated

Cancer	*Receptor overexpressed and/or activated by autocrine loop*	*Evidence for src activation*
Breast	HER-2	Yes
Ovary	HER-2	None but likely
Non-small cell lung	HER-2	Yes
Epidermoid carcinoma	EGFR	Yes
Colon	EGFR	Yes
Gliomas	EGFR	None but likely
Head and neck cancer	EGFR	None but likely
Glioblastomas	PDGFR	None but likely
Ovary	PDGFR	None but likely



	$p56^{lck}$ IC_{50},μM	EGFR
R1=CONH  R2=OH R3=OH R4=H	>1000	3.1
R1=CONH2 R2=H R3=OH R4=OH	0.5	>100

Figure 2 Isoquinoline tyrphostins as selective src type kinase inhibitors *in vitro*

Osherov, 1995). We and, most likely, other groups are actively seeking novel and specific src type blockers.

Isoquinolines are closed-ring tyrphostins where the nitrile group is incorporated into a second ring (Burke *et al.*, 1992). Substitutions on the two rings can lead to different specificities, as depicted in Table I. A limited study on such compounds has yielded compounds with differential selectivities towards p561ck and EGFR (Burke *et al.*, 1992), as depicted in the example given. While this review was being written, a novel src family inhibitor with a pyrazoso pyridine pharmacophore has been described (Hanke *et al.*, 1996).

How to use src kinase blockers in cancer therapy?

Since c-src is a cytoplasmic kinase and possesses a different kinase domain than growth factor receptors (Courtneidge *et al.*, 1993), it is likely that it interacts and/or phosphorylates only a partially overlapping set of intracellular signal transducers as compared to the receptor tyrosine kinases (Erpel & Courtneidge, 1995). Thus, it is likely that when src kinase-directed blockers are used in addition to selective receptor kinase blockers, a synergistic effect may be achieved. In view of the recent finding that activation of $pp60^{c\text{-}src}$ occurs at the G_2/M phase of the cell cycle (Roche *et al.*, 1995) and the action of growth factor receptors is at G_1, G_1/S and early S phase of the cell cycle, such a combination may indeed be rather useful. Since $pp60^{c\text{-}src}$ seems to be activated in many tumors it is likely that src blockers can become universal anti-cancer agents to be used in many cancers in conjunction with other signal interceptors, the nature of which will depend on the tumor. For example, in EGFR-overexpressing tumors, one could use quinazoline-type inhibitors like AG 1478 (Osherov & Levitzki, 1994) in combination with src blockers; in PDGF receptor-overexpressing tumors, one would use quinoxaline-type blockers like AG 1295 (Kovalenko *et al.*, 1994) in combination with src inhibitors. It remains a challenge to the medicinal chemist to generate such selective drugs. The surprising finding that c-Abl kinase shows a different substrate specificity to the oncogenic protein Bcr-Abl (Anafi *et al.*, 1992) is encouraging.

Other potential uses of src kinase blockers

The src family has 10 members with overlapping and non-overlapping selectivities (for a review, see Courtneidge *et al.*, 1993). In principle, it is possible to explore the possibility of generating kinase blockers selective for one or more src kinases. Thus, for example, $pp60^{c\text{-}src}$ seems to be more involved with tumors, whereas others are more related to the immune cells. src kinases like $p56^{lck}$, $p59^{lyn}$, $p59^{fyn}$ and Hck function in immune reactions. Thus, src kinase blockers may also be useful to manage inflammatory conditions such as sepsis (Novogrodsky *et al.*, 1994; Varichkin *et al.*, 1996), rheumatoid arthritis and tissue rejection. This avenue of research may hold great promise for therapies of various indications.

References

AGBOTOUNOU, W.K., LEVITZKI, A., JACQUEMIN-SABLON, A. & PIERRE, J. (1994). Effects of Tyrphostins on the activated c-src protein in NIH/3T33 cells. *Molecular Pharmacology*, **45**, 922.

ANAFI, M., GAZIT, A., GILON, C., BEN-NERIAH, Y. & LEVITZKI, A. (1992). Selective interactions of transforming and normal abl protein with ATP, tyrosine copolymer substrates and tyrphostins. *Journal of Biological Chemistry*, **267**, 4518.

BISHOP, J.M. (1987). The molecular genetics of cancer. *Science*, **335**, 305.

BOLEN, J.B., VEILLETTE, A., SCHWARTZ, A.M., DESEAU, V. & ROSEN, N. (1987). Activation of $pp60^{c\text{-}src}$ protein kinase activity in human colon carcinoma. *Proceedings of the National Academy of Sciences (USA)*, **84(8)**, 2251.

BURKE, T.R., JR, FORD, H., OSHEROV, N., LEVITZKI, A., STEFANOVA, I., HORAK, I.D. & MARQUEZ, V.E. (1992). Arylamides of hydroxylated isoquinolines as protein-tyrosine kinase inhibitors. *Bioorganic and Medicinal Chemistry Letters*, **12**, 1771.

CARTWRIGHT, C.A., MEISLER, A.I. & ECKHART, W. (1990). Activation of the $pp60^{c\text{-}src}$ protein kinase is an early event in colonic carcinogenesis. *Proceedings of the National Academy of Sciences (USA)*, **87**, 558.

COURTNEIDGE, S.A., DHAND, R., PILAT, D., TWAMLEY, G.M., WATERFIELD, M.D. & ROUSSEL, M. (1993). Activation of Src family by colony stimulating factor-1, and their association with its receptor. *EMBO Journal*, **12**, 943.

COUSSENS, L., YANG-FENG, Y.T., LIAO, Y.C., CHEN, E., GRAY, A., MCGRATH, J., SEEBURG, P.H., LIBERMAN, T., SCHLESSINGER, J., FRANCKE, U., LEVINSON, A. & ULLRICH U. (1985). Tyrosine kinase receptor with extensive homology to EGF receptor shares chromosomal location with neu oncogenes. *Science*, **230**, 1132.

DESEAU, V., ROSEN, N. & BOLEN, J.B. (1987). Analysis of $pp60^{c\text{-}src}$ tyrosine kinase activity and phosphotyrosylphosphatase activity in human colon carcinoma and normal human colon mucosal cells. *Journal of Cellular Biochemistry*, **35**, 113.

DI FIORE, P.P., SEGATTO, O., TAYLOR, W.G., AARONSON, S.A. & PIERCE, J.H. (1990). EGF receptor and erbB-2 tyrosine kinase domains confer cell specificity for mitogenic signaling. *Science*, **248**, 79.

ELDER, G.T., FISHER, G.J., LINDQUIST, P.B., BENNET, G.L., PITTELKOW, M.R., COFFEY, R.J., ELLINGSWORTH, L., DENRYNCK, R. & VOORHEES, G.G. (1989). Overexpression of transforming growth factor in promatic epidermis. *Science*, **243**, 811.

ERPEL, T. & COURTNEIDGE, S.A. (1995). Src family tyrosine kinases and cellular signal transduction pathways. *Current Opinion in Cell Biology*, **7**, 176.

GAZIT, A., YAISH, P., GILON, C. & LEVITZKI, A. (1991). Tyrphostins II: Heterocyclic and a-substituted benzonemalononitrile tyrphostins as potent inhibitors of EGF receptor and erbB-2/neu tyrosine kinases. *Journal of Medicinal Chemistry*, **34**, 1987.

GAZIT, A., OSHEROV, N., POSNER, I., BAR-SINAI, A., GILON, C. & LEVITZKI, A. (1993). Tyrphostin 3. Structure activity relationship studies of 5-S-aryl a-substituted benzylidenemalononitrile tyrphostins. *Journal of Medicinal Chemistry*, **36**, 3556.

HANKE, J.H., GARDINER, J.F., DOW, R.L., CHANGELIAN, P.S., BRISSETTE, W.H., WERINGER, E.J., POLLOCK, B.A. & CONNELLY, P.A. (1996). Discovery of a novel src family-selective tyrosine kinase inhibitor. *Journal of Biological Chemistry*, **271**, 695.

HELDIN, C.H. & WESTERMARK, B. (1991). Platelet-derived growth factor and autocrine mechanisms of oncogenic processes. *CRC Critical Reviews in Oncogenesis* **2**, 109.

KOVALENKO, M., GAZIT, A., BOHMER, A., RORSMAN, C., RONNSTRAND, L., HELDIN, C.-H., WALTENBERGER, J., BOHMER, F.-D. & LEVITZKI, A. (1994). Selective platelet-derived growth factor receptor kinase blockers reverse cis-transformation. *Cancer Research*, **54**, 6106.

KYPTA, R.M., GOLDBERG, Y., ULUG, E.T. & COURTNEIDGE, S.A. (1990). Association between the PDGF receptor and members of the src family of tyrosine kinases. *Cell*, **62**, 481.

LEVITZKI, A. (1990). Tyrphostins—potential antiproliferative agents and novel molecular tools. *Biochemical Pharmacology*, **40**, 913.

LEVITZKI, A. (1992). Tyrphostins: tyrosine kinase blockers as novel antiproliferative agents and dissectors of signal transduction. *FASEB Journal*, **6**, 3275.

LEVITZKI, A. (1994). Signal transduction therapy: a novel approach to disease management. *European Journal of Biochemistry*, **226**, 1.

LEVITZKI, A. & GAZIT, A. (1995). Tyrosine kinases inhibition: An approach to drug development. *Science*, **267**, 1782.

LUGO, T.G., PENDERGAST, A.M., MULLER, A.J. & WITTE, O.N. (1990). Tyrosine kinase activity and transformation potency of bcr-abl oncogene products. *Science*, **247**, 1079.

LUTTRELL, D.K., LEE, A., LANSING, T.J., CROSBY, R.M., JUNG, K.D., WILLARD, D., LUTHER, M., RODRIGUEZ, M., BERMAN, J. & GILMER, T.M. (1994). Involvement of $pp60^{c\text{-}src}$ with two major signaling pathways in human breast cancer. *Proceedings of the National Academy of Sciences (USA)*, **91**, 83.

MAZURENKO, N.N., KOGAN, E.A., ZBOROVSKAYA, I.B. & KISSELJOV, F.L. (1992). Expression of $pp60^{c\text{-}src}$ in human small cell and non-small cell lung carcinomas. *European Journal of Cancer*, **28**, 372.

MELLSTROM, K., BJELFMAN, C., HAMMERLING, U. & PAHLMAN, S. (1987). Expression of c-src in cultured human neuroblastoma and small-cell lung carcinoma cell lines correlates with neurocrine differentiation. *Molecular and Cellular Biology*, **7**, 4178.

MUTHUSWAMY, S.K., SEGEL, P.M., DANKORT, D.L., WEBSTER, M.A. & MULLER, W.J. (1994). Mammary tumors expressing the neu proto-oncogene possess elevated c-src tyrosine kinase activity. *Molecular and Cellular Biology*, **14**, 735.

NOVOGRODSKY, A., VANICHKIN, A., PATYA, M., GAZIT, A., OSHEROV, N. & LEVITZKI, A. (1994). Prevention of lipopolysaccharide-induced lethal toxicity by tyrosine kinase inhibitors. *Science*, **264**, 1319.

OSADA, H., SASAKI, M., SONODA, T. & ISONO, K. (1995). Epiderstatin induces the flat reversion of NRK cells transformed by temperature-sensitive Rous sarcoma virus. *Bioscience Biotechnology Biochemistry*, **56**, 1801.

OSHEROV, N. (1995). PhD Thesis, The Hebrew University of Jerusalem, Jerusalem, Israel.

OSHEROV, N. & LEVITZKI, A. (1994). Epidermal growth factor dependent activation of Src family kinases. *European Journal of Biochemistry*, **225**, 1047.

OSHEROV, N., GAZIT, A., GILON, C. & LEVITZKI, A. (1993). Selective inhibition of the EGF and HER-2/Neu receptors by Tyrphostins. *Journal of Biological Chemistry*, **268**, 11134.

OTTENHOF-KALFF, A.E., RIJKSEN, G., van BEURDEN, A.C.M., HENNIPMAN, A., MICHELS, A.A. & STAAL, G.E.J. (1992). Characterization of protein tyrosine kinases from human breast cancer—involvement of the c-src oncogene product. *Cancer Research*, **49**, 4773.

OUDE WEERNINCK, P.A., OTTENHOFF-KALFF, A.E., VENDRIG, M.P., VAN BEURDEN, E.A., STAAL, G.E. & RIJKSEN, G. (1994). Functional interaction between the epidermal growth factor receptor and c-Src kinase activity. *FEBS Letters*, **352**, 296.

PARK, J., MEISLER, A.I. & CARTWRIGHT, C.A. (1993). c-Yes tyrosine kinase activity in human colon carcinoma. *Oncogene*, **8**, 2627.

POWIS, G. & WORKMAN, P. (1994). Signaling targets for the development of cancer drugs. *Anti-Cancer Drug Design*, **9**, 263.

ROCHE, S., FUMAGALLI, S. & COURTNEIDGE, S.A. (1995). Requirement for Src family protein tyrosine kinases in G2 for fibroblast cell division. *Science*, **269**, 1567.

ROSS, R. (1993). The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature*, **362**, 801.

SATO, K., SATO, A., AOTO, M. & FUKAMI, Y. (1995). Site-specific association of c-Src with epidermal growth factor receptor in A431 cells. *Biochemical and Biophysical Research Communications*, **210**, 844.

SLAMON, D.J., CLARK, G.M., WONG, S.G., LEVIN, J.W., ULLRICH, A. & MCGUIRE, W.L. (1987). Human breast cancer correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science*, **235**, 177.

SLAMON, D.J., GODOLPHIN, W., JONES, L.A., HOLT, J.A., WONG, S.G., KEITH, D.E., LEVIN, W.J., STUART, S.G., UDOVE, J., ULLRICH, A. & PRESS, M.F. (1989). Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science*, **244**, 707.

STOVER, D.R., BECKER, M., LIEBETANZ, J. & LYDON, N.B. (1995). Src phosphorylation of the epidermal growth factor receptor at novel sites mediates receptor interaction with Src and P85 alpha. *Journal of Biological Chemistry*, **270**, 15591.

VARICHKIN, A., PATYA, M., GAZIT, A., LEVITZKI, A. & NOVOGRODSKY, A. Late administration of lipophilic tryphostins prevents lipopolysaccharide toxicity. *Infectious Disease*, in press.

VOLBERG, T., ZIK, Y., DROR, R., SABANAY, I., GILON, C., LEVITZKI, A. & GEIGER, G. (1992). The effect of tyrosine specific protein phosphorylation on the assembly of adhesin type junctions. *EMBO Journal*, **11**, 1733.

WEBER, T.K., STEELE, G. & SUMMERHAYES, I.C. (1992). Differential $pp60^{c\text{-}src}$ activity in well and poorly differentiated human colon carcinomas and cell lines. *Journal of Clinical Investigation*, **90**, 815.