



Tyrosine Kinases as Targets for Cancer Therapy

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CME INFORMATION

OVERVIEW OF ACTIVITY

The annual San Antonio Breast Cancer Symposium (SABCS) is unmatched in its significance with regard to the advancement of breast cancer treatment. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year where published results from a plethora of ongoing clinical trials lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across all breast cancer subtypes. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of the rapidly evolving data sets in breast cancer. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest SABCS meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for breast cancer.

LEARNING OBJECTIVE

- Review the classes of tyrosine kinases, their activation mechanisms and the therapeutic drugs that target tyrosine kinase function.

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IN THIS ISSUE:

- Phase II: [Sorafenib shows trend to improved PFS with paclitaxel](#)
- Phase II: [Sorafenib improves PFS with capecitabine](#)
- Phase II: [Sunitinib has similar or inferior effect as capecitabine](#)
- Mechanism of action of TKIs: [Spectacular NEJM artwork](#) (best in the biz)

During a 2008 interview, I queried leukemia maven Dr Michael Keating about current clinical trials in CML. “Imatinib is the Big Dog, and while there are Phase III studies comparing it to second-generation TKIs, they’re trying to prove that something’s better than magic.” Nine years after the FDA approval of what sure seems like magic, last month at ASH nilotinib actually was shown to be superior to imatinib when using state-of-the-art CML RT-PCR and FISH assay technology. The unexpected bottom line is, in a disease that’s more than 90 percent “curable” with imatinib treatment, the rate of accelerated phase/blast transformation with nilotinib was 0.4 percent compared to 3.9 percent for imatinib. That, along with equal or better tolerability, might just be practice changing in the near future.

Meanwhile, investigators are desperately looking for TKIs in other cancers that come close to the Big Dog, and other than GIST, perhaps the greatest success has been in non-small cell lung cancer, in which first EGFR mutant tumors and now EML4-ALK fusion cancers seem to fit the oncogene addiction model and respond pretty well to TKIs.

On the angiogenic side of the equation, renal cell cancer seems to lead the way, with the VEGFR TKIs sunitinib and sorafenib benefiting many or most treated patients, although a long way from magic. In breast cancer, most of the encouraging TKI news has been with HER2-positive tumors, for which lapatinib has significant antitumor activity both with chemo and trastuzumab, and neratinib, another HER2 TKI, is demonstrating promising activity.

HER2-negative tumors are a different matter, and until San Antonio, it was difficult to get excited about what was seen. However, in back-to-back oral presentations, Bill Gradishar and then Jose Baselga reported two Phase II randomized trials demonstrating PFS advantages when sorafenib was added to paclitaxel in one study and capecitabine in another. Dermatologic toxicity was substantial, particularly when

sorafenib was combined with capecitabine, suggesting the need for dose/schedule adjustments in future trials.

At a breast cancer roundtable we hosted last week in our Miami studio with an impressive faculty of nine investigators, it was noted that sorafenib got its moniker partly in recognition of RAF inhibitory properties but that the agent is also known to inhibit PDGFR, along with what is thought to be its major effect on VEGF blockade. I shared with the group my recent surprise when another MD Anderson leukemia wizard, Dr Farhad Ravandi, told me that sorafenib is also being evaluated clinically as an FLT3 inhibitor in patients with AML.

The two Phase II sorafenib studies reported at San Antonio are part of an integrated set of four Phase II trials called the TIES program, and roundtable participant Cliff Hudis noted that Memorial and ACORN are participating in the effort by evaluating capecitabine or gemcitabine, with or without sorafenib. During the roundtable discussion Edith Perez stated she thought that this complex multitargeted TKI might end up having similar anti-angiogenic activity as bevacizumab but with the important option of oral administration, although the faculty was uncertain whether sorafenib will end up in daily breast cancer clinical practice.

As suggested by [our graphics slide set](#) on potential mechanisms of action of TKIs in cancer, there is an urgent need to dissect the specific pathways affected by the panoply of novel targeted agents like sorafenib. Only this will allow us to exchange our current organ-based cancer treatment strategy for a molecular one as we learn how to select the correct biologic agent for the appropriate patient.

Next up on 5-Minute Journal Club: More from San Antonio and a simultaneous *Lancet Oncology* publication on the SWOG node-positive Oncotype DX® study: No surprises, and more evidence to take action.

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Tyrosine Kinases as Targets for Cancer Therapy

Presentation discussed in this issue

Krause DS, Van Etten RA. Tyrosine kinases as targets for cancer therapy. *N Engl J Med* 2005;353(2):172-87. **Abstract**

Slides from a journal article and accompanying descriptive summary

Tyrosine Kinases as Targets for Cancer Therapy

Krause DS, Van Etten RA

N Engl J Med 2005;353(2):172-87.

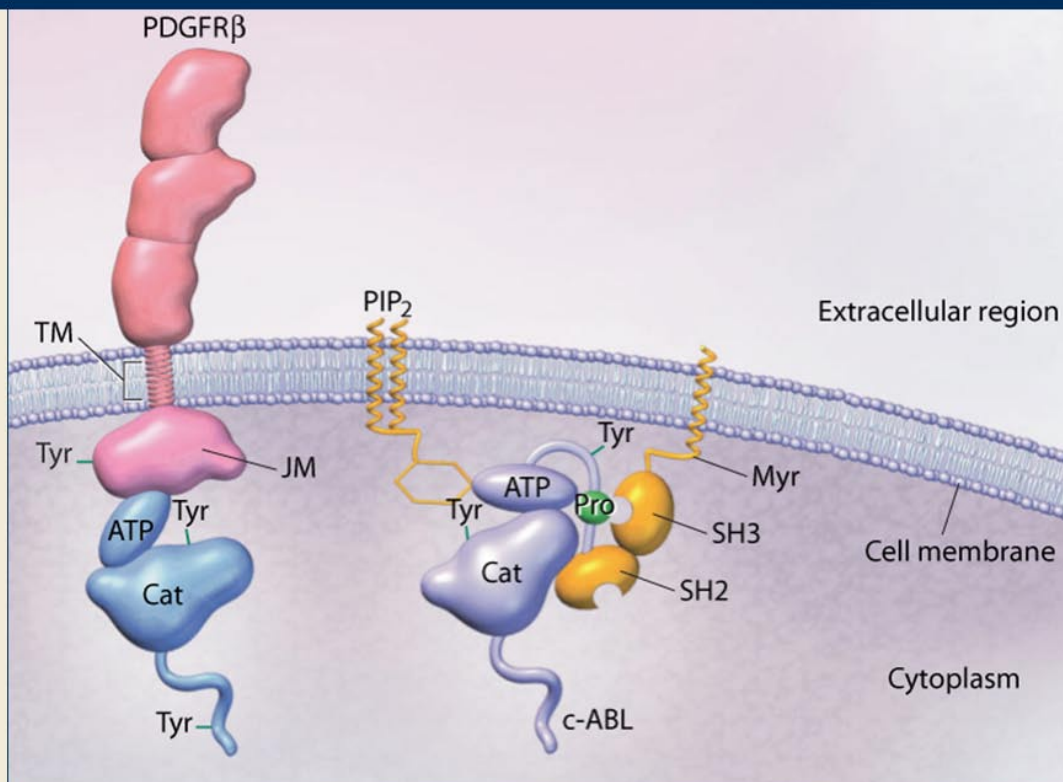
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Introduction

- Protein tyrosine kinases (TKs) catalyze the transfer of a phosphate group from ATP to tyrosine residues in proteins.
- There are two classes of TKs:
 - Receptor TKs-transmembrane proteins with extracellular ligand binding domains and intracellular kinase domains.
 - Nonreceptor TKs-lack transmembrane domains and are found in the cytosol, nucleus or near the plasma membrane
- Receptor TKs include EGF and VEGF receptors, PDGF receptors, FLT-3 and KIT.
- Nonreceptor TKs are typified by c-ABL.

Krause DS, Van Etten RA. *N Engl J Med* 2005;353(2):172-87.

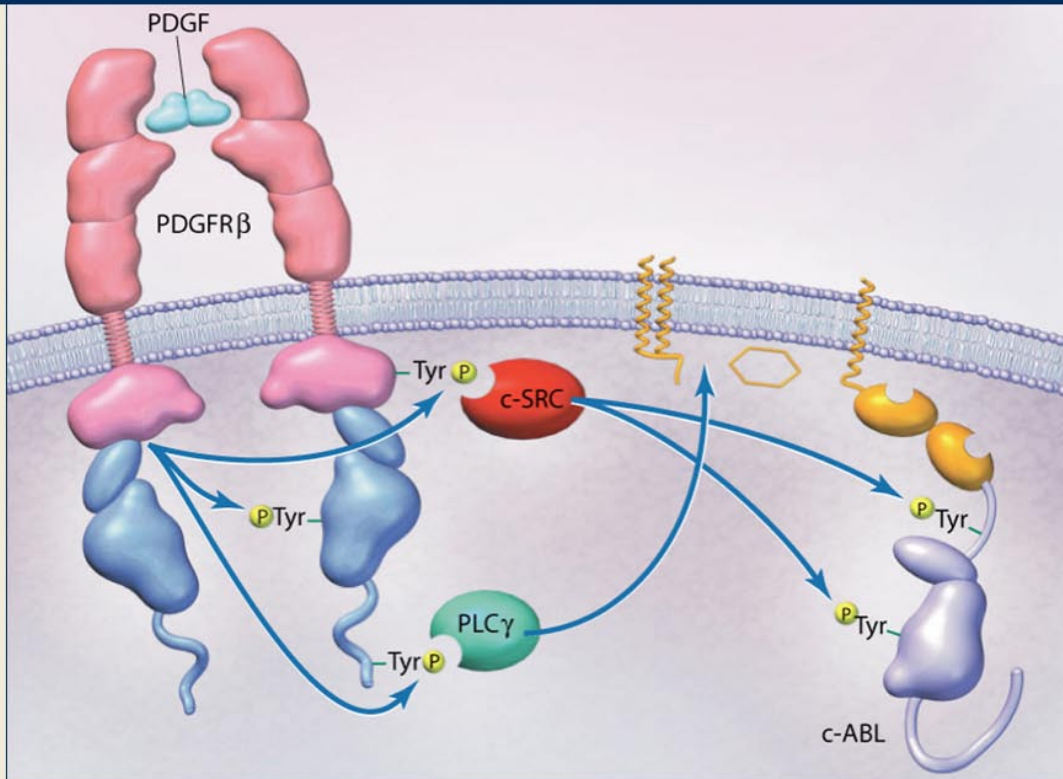
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Regulation of TK Activity-Inactive State

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Regulation of TK Activity-Activated State

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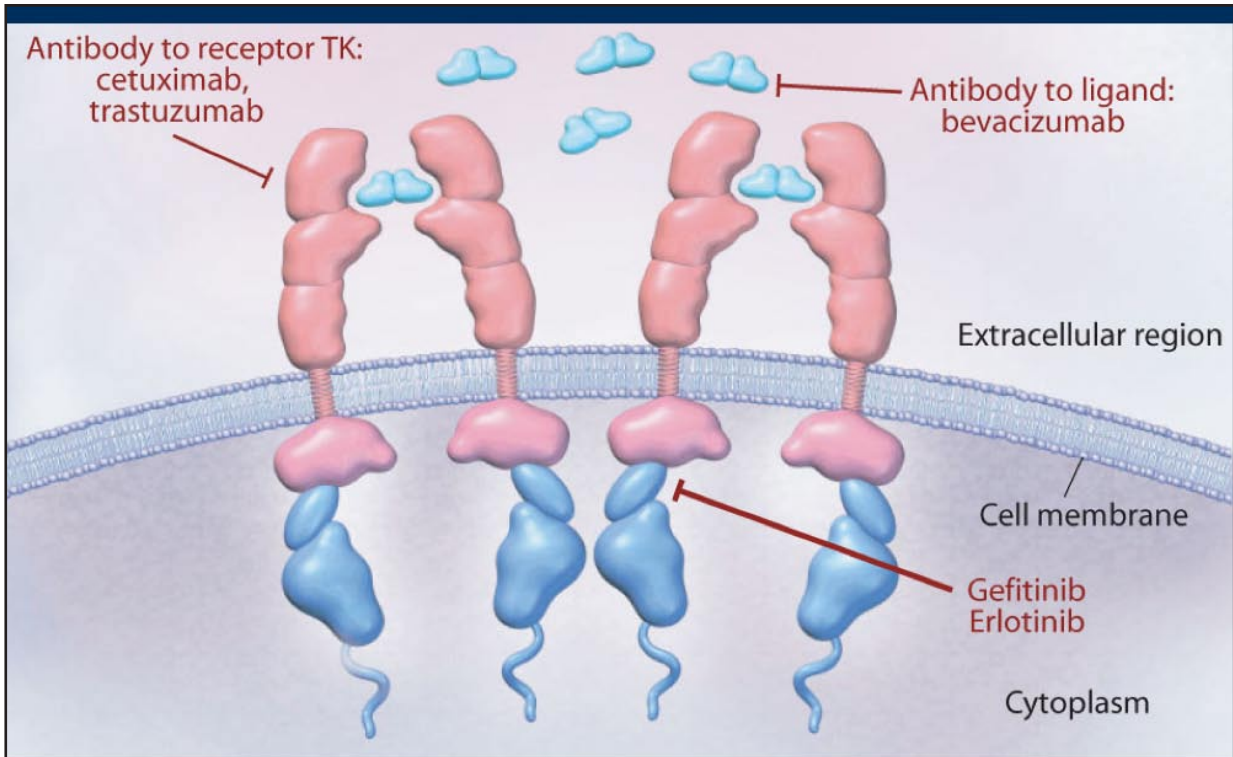
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TK Dysregulation in Cancer

- Dysregulation of TK activity may occur in several ways.
 - Increased expression of receptor TK and/or its ligand
 - Mutation that alters autoregulation of the TK
 - Fusion with a partner protein that results in constitutive activation of the TK
- Aberrant TK activation may result in increased cell survival and proliferation, and in drug resistance.
 - In tumors, increased angiogenesis and invasiveness may result.
- TKs can be inhibited pharmacologically through multiple mechanisms.

Krause DS, Van Etten RA. *N Engl J Med* 2005;353(2):172-87.

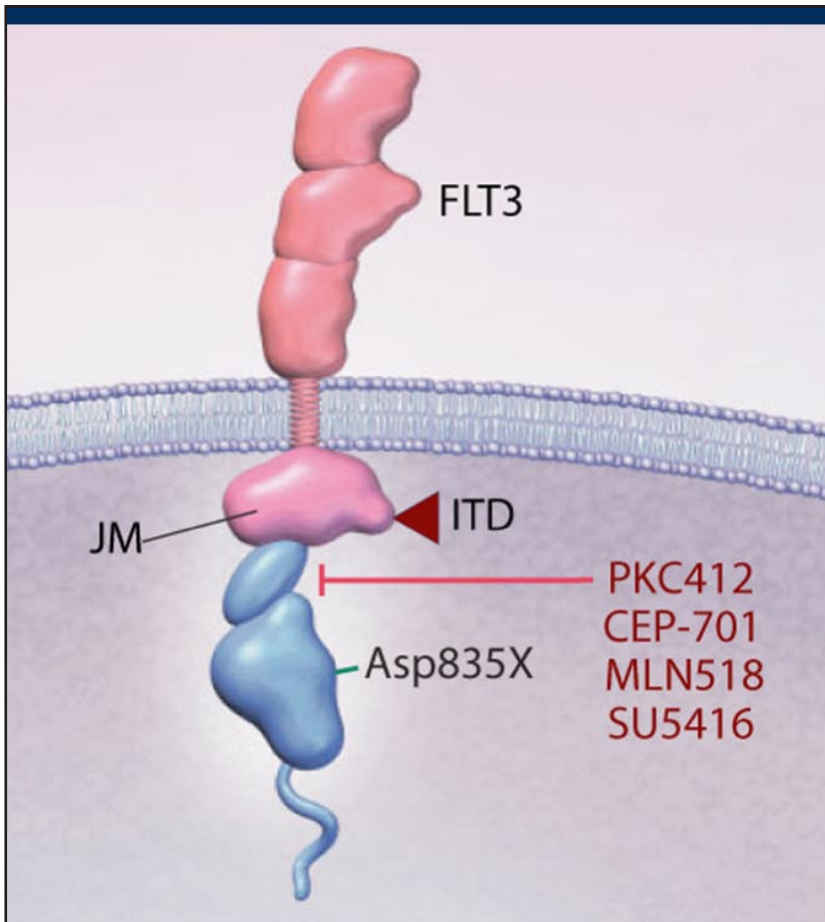
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Small Molecule Inhibitors of Receptor TKs

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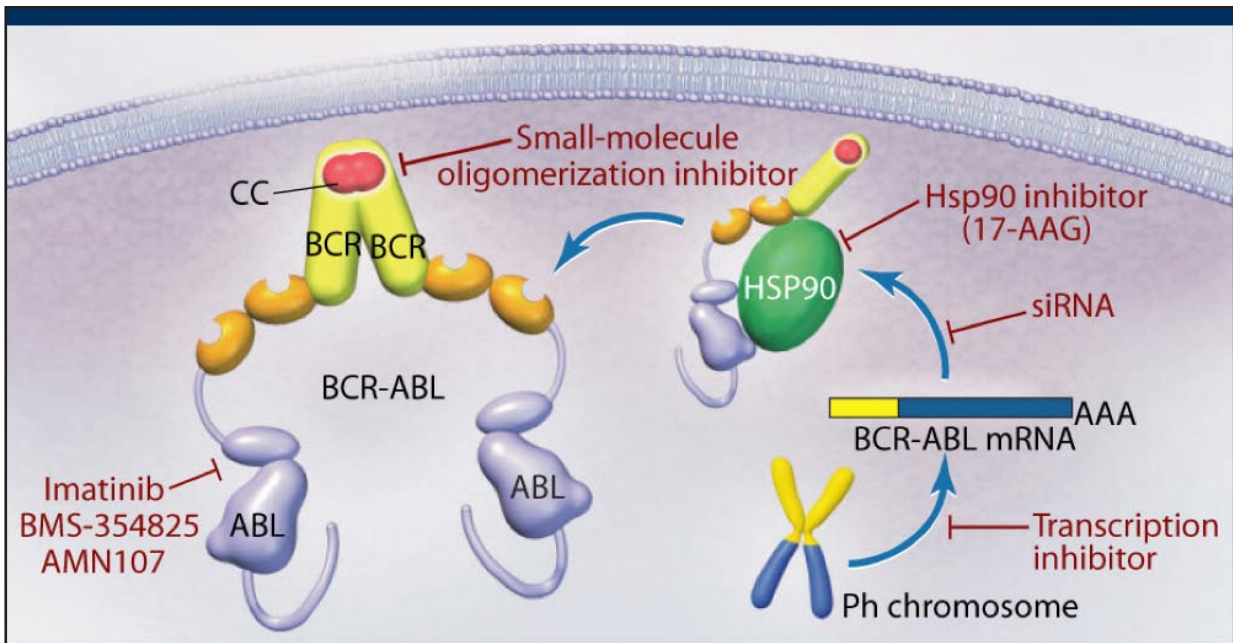
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Therapeutic Targeting of Constitutively Activated Receptor TKs

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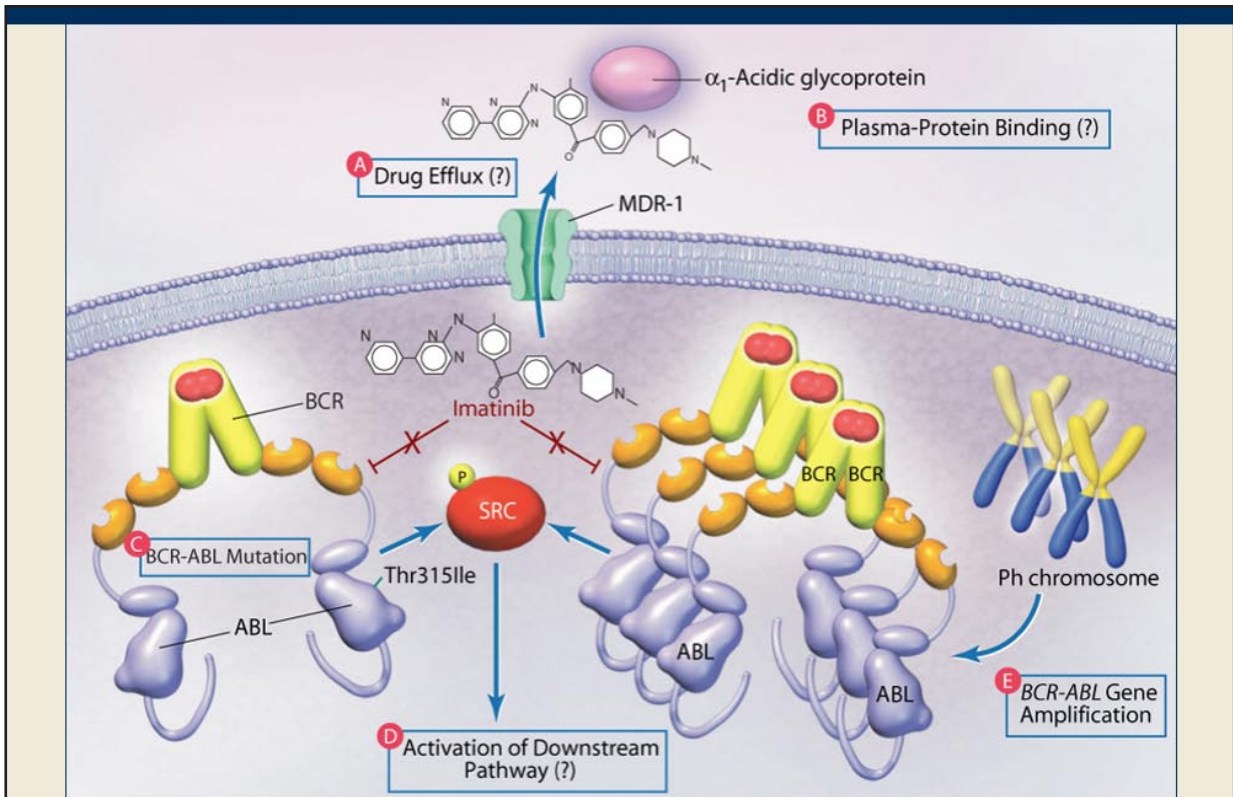
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Therapeutic Targeting of Activated Fusion TK Proteins

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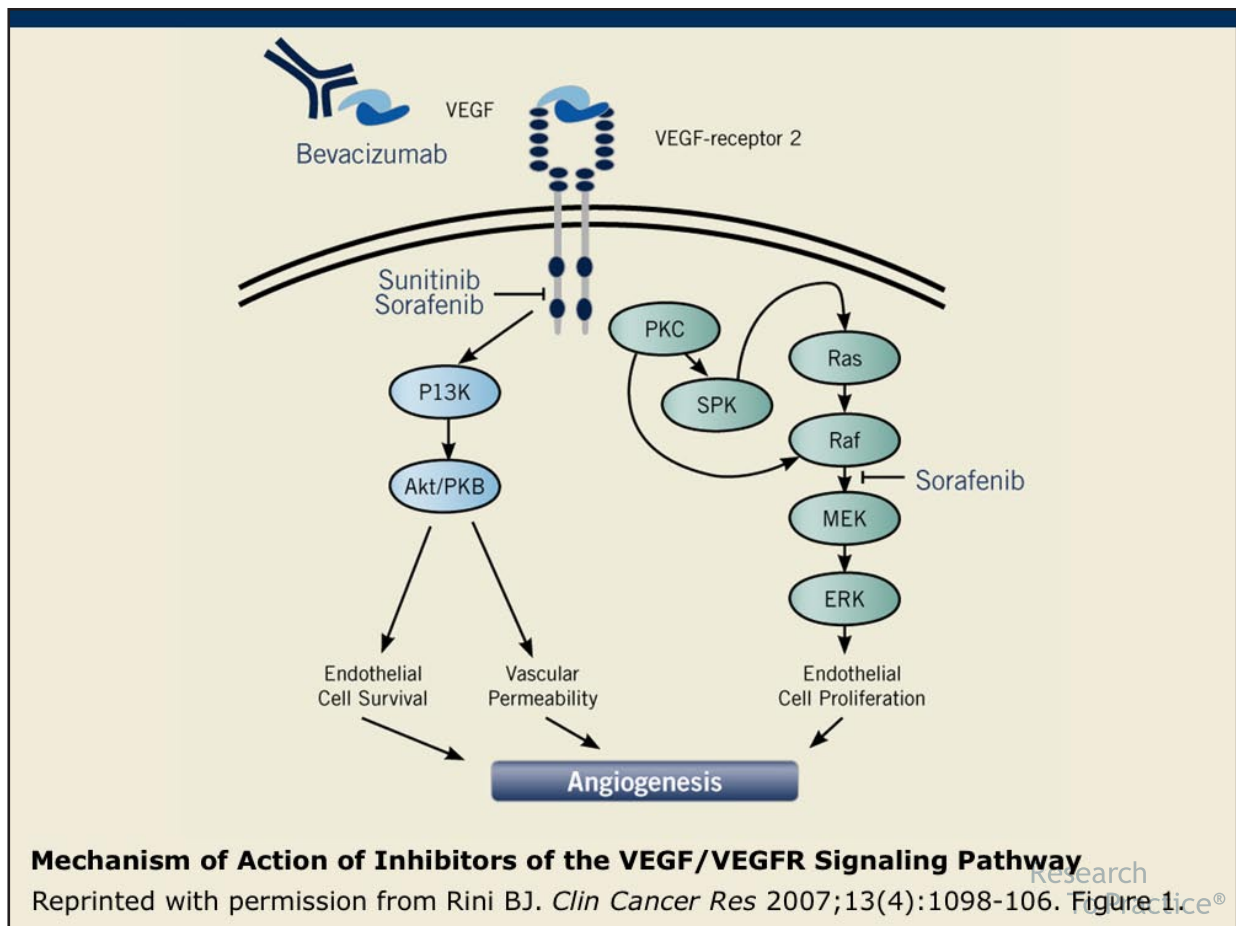
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Limitations of TK-Targeted Therapies: Development of Resistance

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Editor's Note: Though published in 2005, the *New England Journal* article by Krause and Van Etten on mechanisms of action of tyrosine kinase inhibitors (TKIs) remains a classic in oncology education, particularly the extraordinary graphic depictions of the *NEJM* artists. We reproduce these figures along with another graphic in an article by Rini et al on VEGF TKIs in another attempt to assist busy clinicians attempting to understand the rapidly evolving translational database that is permeating contemporary oncology.

Regulation of TK Activity-Inactive State: The inactive PDGFR- β receptor TK exists as a single membrane-spanning molecule in which the regulatory tyrosine (Tyr) amino acids are not phosphorylated.

The inactive nonreceptor TK c-ABL is tethered to the cell membrane by PIP2 that acts as an inhibitory molecule. Nonreceptor TKs are maintained in their inactive states through interactions with inhibitory lipids or cellular proteins.

Regulation of TK Activity-Activated State: After PDGFR- β binds its ligand, dimerization occurs, allowing phosphorylation of the regulatory tyrosine residues. The phosphorylated tyrosines are binding sites for other cell signaling proteins, such as c-SRC and phospholipase C- γ (PLC- γ), that function in initiating downstream signaling cascades. These signaling cascades regulate cellular processes, such as angiogenesis, cell proliferation and cell survival.

For nonreceptor TKs such as c-ABL, activation may occur in response to various intracellular signals that can lead to the dissociation of the inhibitory molecules and the phosphorylation of regulatory tyrosines. Similar to the receptor TKs, phosphorylation of the regulatory tyrosines also leads to the initiation of cellular signaling cascades affecting cell function.

Small Molecule Inhibitors of Receptor TKs: Several small molecules that inhibit the function of receptor TKs (indicated in red) have been developed. Gefitinib and erlotinib are intracellular inhibitors of EGFR that block EGFR phosphorylation and subsequent activation. Cetuximab and trastuzumab are antibodies targeted against receptor TKs. Bevacizumab is an antibody directed against the VEGF-A ligand that prevents the interaction of VEGF-A with its receptor, VEGFR.

Inhibition of receptor TK function blocks the downstream signaling cascades of cellular processes, such as angiogenesis and cell proliferation, that can promote the survival of tumor cells.

Therapeutic Targeting of Constitutively Activated Receptor TKs: FLT3 is a receptor TK that is expressed on blast cells in the majority of acute myeloid leukemia (AML) cases. It may become constitutively activated by internal tandem duplications (ITD) or by a point mutation (D835X) within the receptor TK. FLT3 is also among the receptor TKs that are targeted by sorafenib and sunitinib. Inhibitors of FLT3 kinase activity under development, such as midostaurin (PKC412), lestaurtinib (CEP-701), tandutinib (MLN518) and semaxanib (SU5416), are indicated in red.

Therapeutic Targeting of Activated Fusion TK Proteins: The activated TK fusion protein BCR-ABL is the only proven molecular target for chronic myeloid leukemia (CML). Examples of therapeutic agents targeting the activated TK fusion protein BCR-ABL are listed in red.

Imatinib is a specific inhibitor of several TKs, including ABL, c-KIT and PDGFR, that has been successful as a treatment for CML. Nilotinib is also a highly selective inhibitor of BCR-ABL kinase activity that has been recently shown to have superior efficacy compared to imatinib for the treatment of patients with CML in the chronic phase.

17-AAG interferes with binding to cellular chaperone proteins such as Hsp90. Small interfering RNAs (siRNA) act to promote the degradation of BCR-ABL mRNA and other agents act to block oligomerization or BCR-ABL transcription.

Limitations of TK-Targeted Therapies: Development of Resistance: Though advances in the development of TK-targeted therapies have been made, resistance to these therapies is a growing problem. Causes of imatinib resistance in chronic myeloid leukemia are depicted, but the mechanisms involved in the development of resistance are applicable to both small-molecule TK inhibitors and to monoclonal antibodies directed against receptor TKs.

(A) There may be increased efflux of the drug from the cancer cell mediated by membrane transporter proteins that result in a decreased intracellular concentration of the drug.

(B) Proteins in the blood plasma may bind the drug and decrease its effective concentration.

(C) The TK molecule targeted by the drug may gain a mutation that allows for it to escape the drug's action.

(D) Mutations may result in the activation of components of the signaling pathway downstream of the targeted TK.

(E) Amplification of the TK gene resulting in overproduction of the TK can confer relative resistance to an inhibitor.

Mechanism of Action of Inhibitors of the VEGF/VEGFR Signaling Pathway: In addition to bevacizumab, which targets the VEGF ligand, the VEGF/VEGFR signaling pathway can be inhibited by the small molecules sunitinib and sorafenib. These oral multikinase inhibitors interfere with the activation of VEGFRs 1 to 3 by preventing phosphorylation. Sorafenib also inhibits the activity of Raf-1 kinase that functions in the signaling pathway, which is initiated after VEGFR binds its ligand.