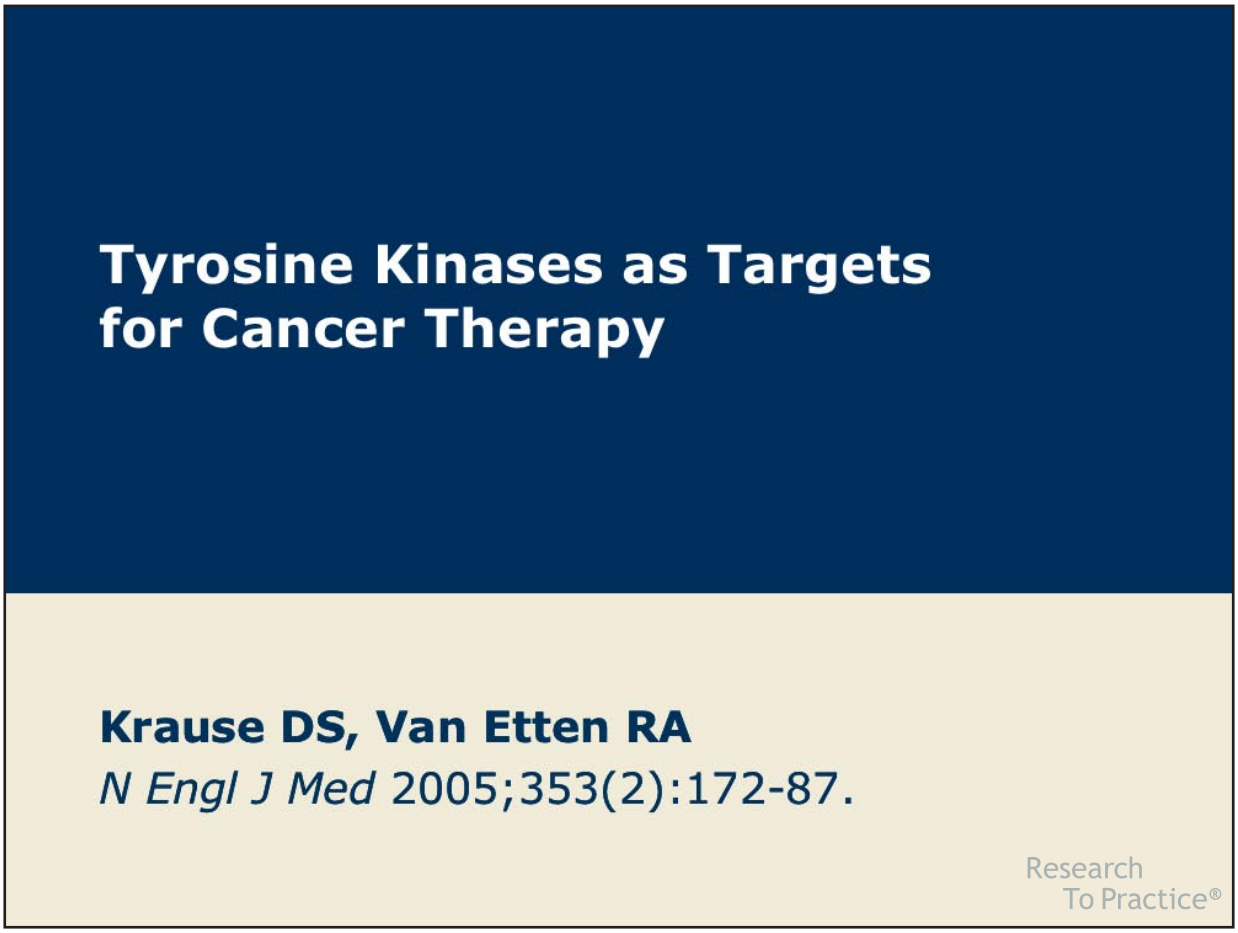
Tyrosine Kinases as Targets for Cancer Therapy

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



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.

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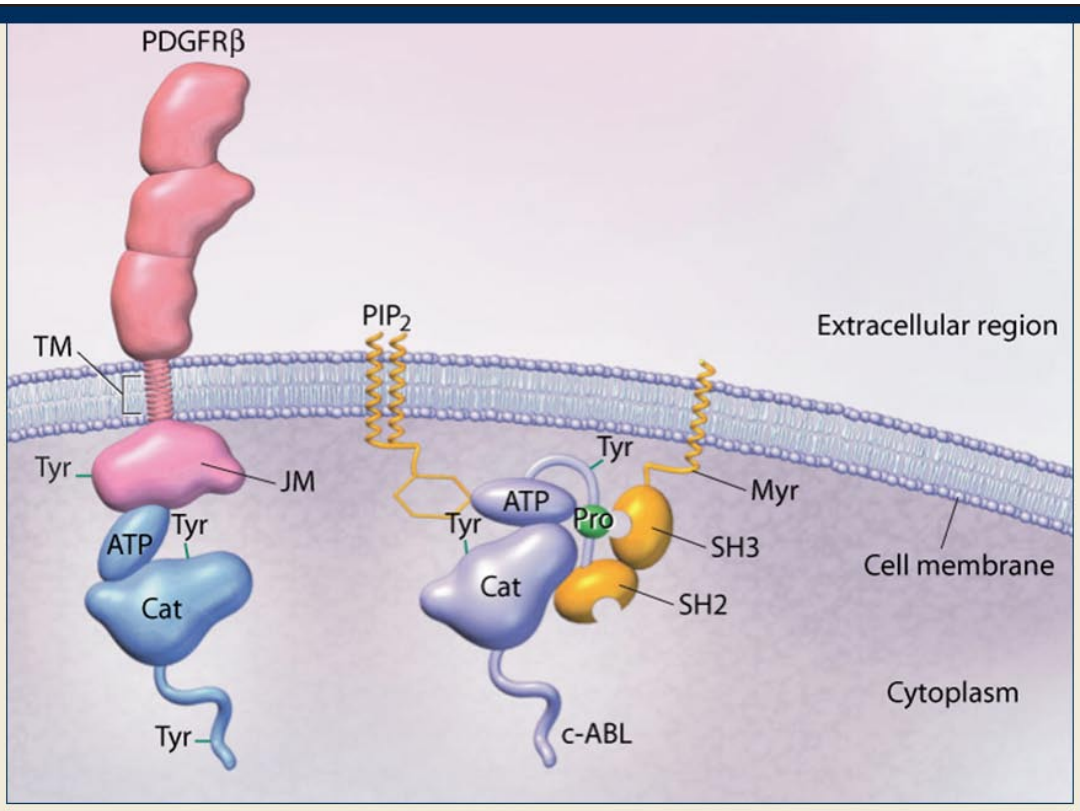

Regulation of TK Activity-Inactive State

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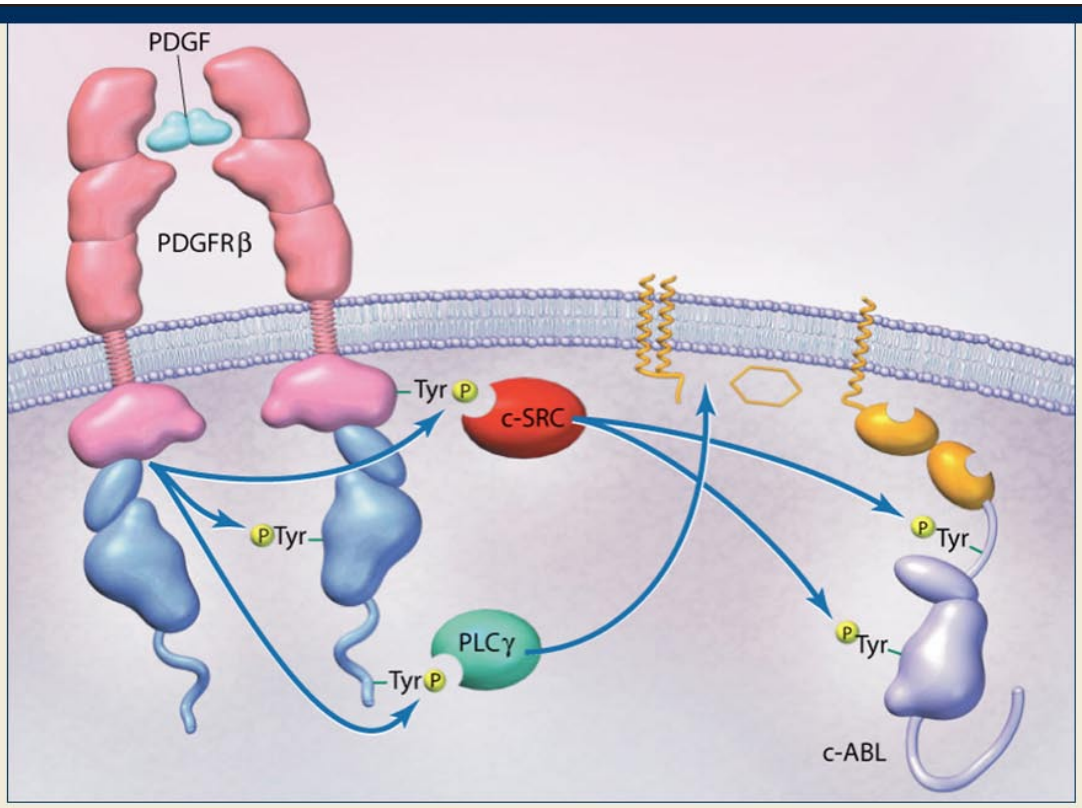

Regulation of TK Activity-Activated State

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.

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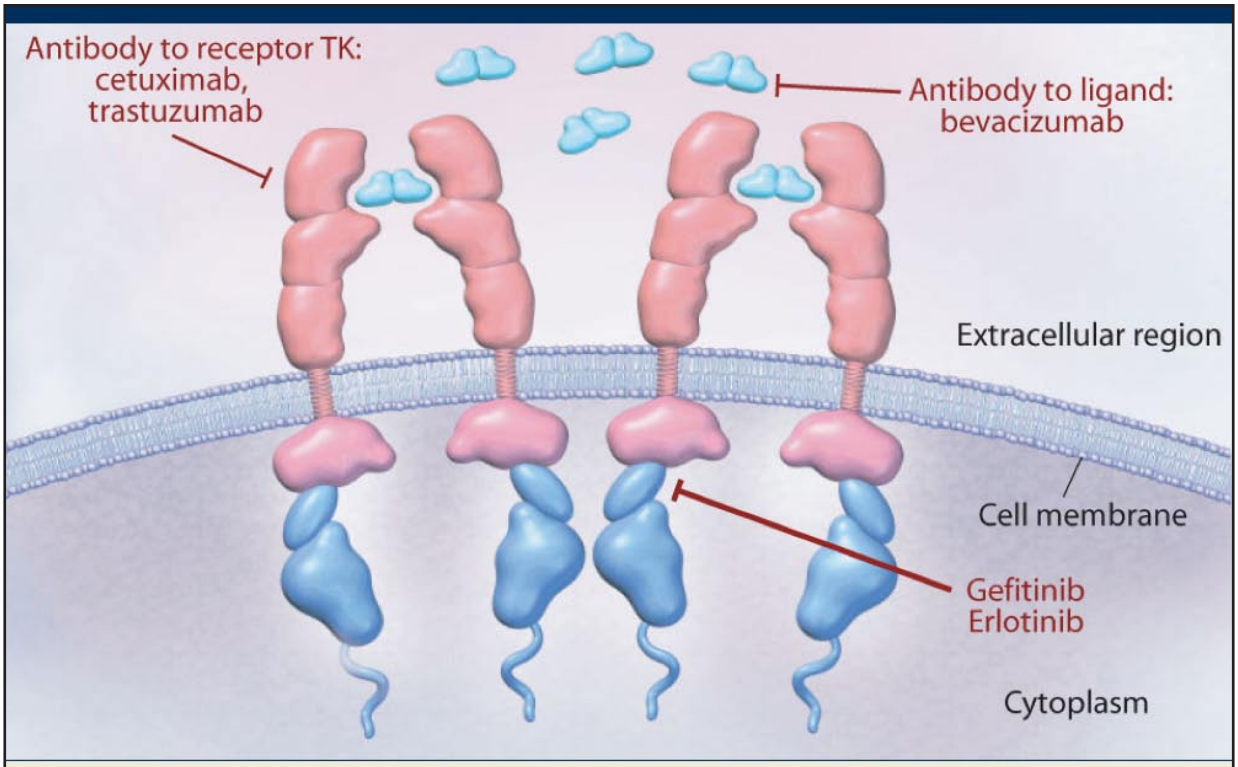

Small Molecule Inhibitors of Receptor TKs

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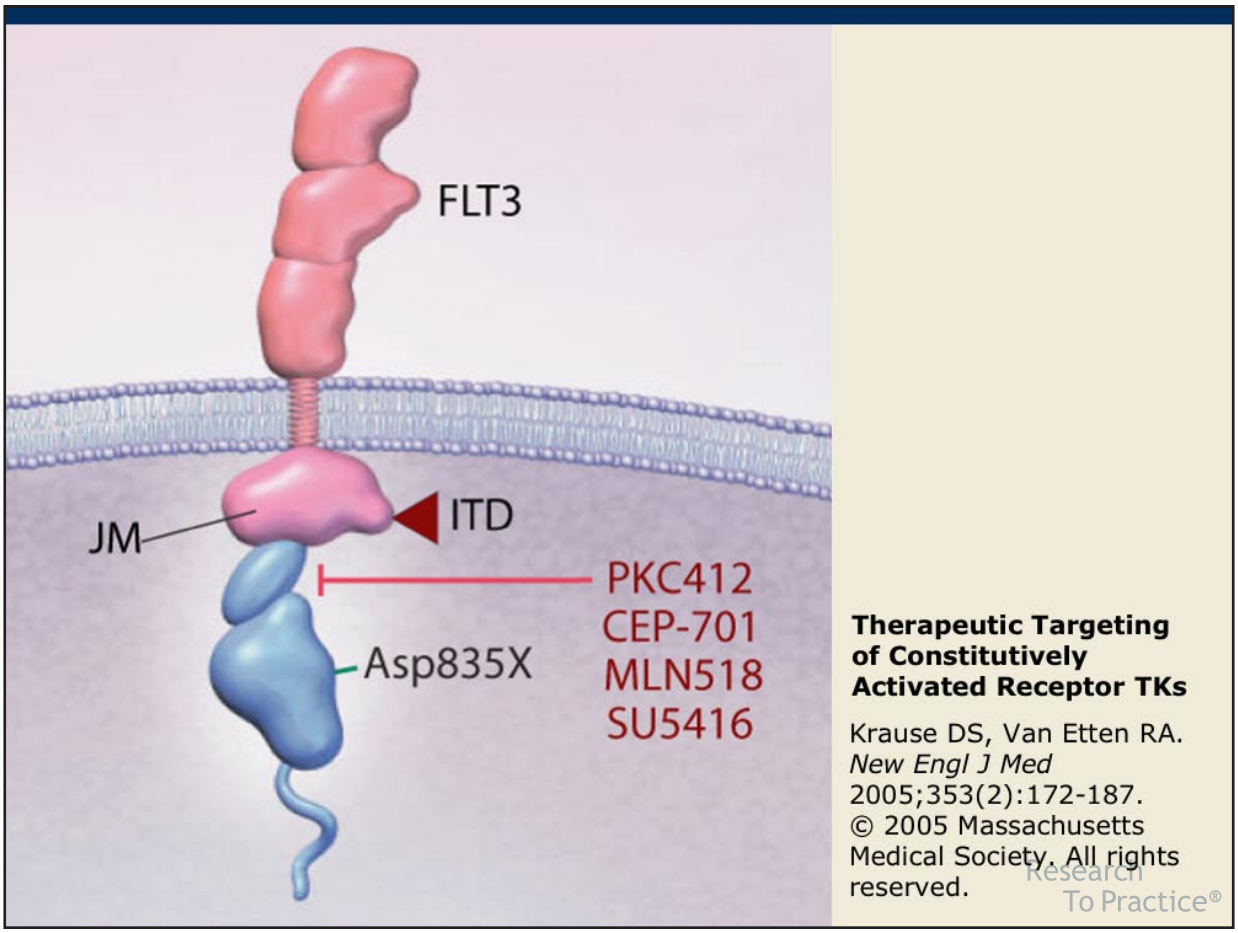

Therapeutic Targeting of Constitutively Activated Receptor TKs

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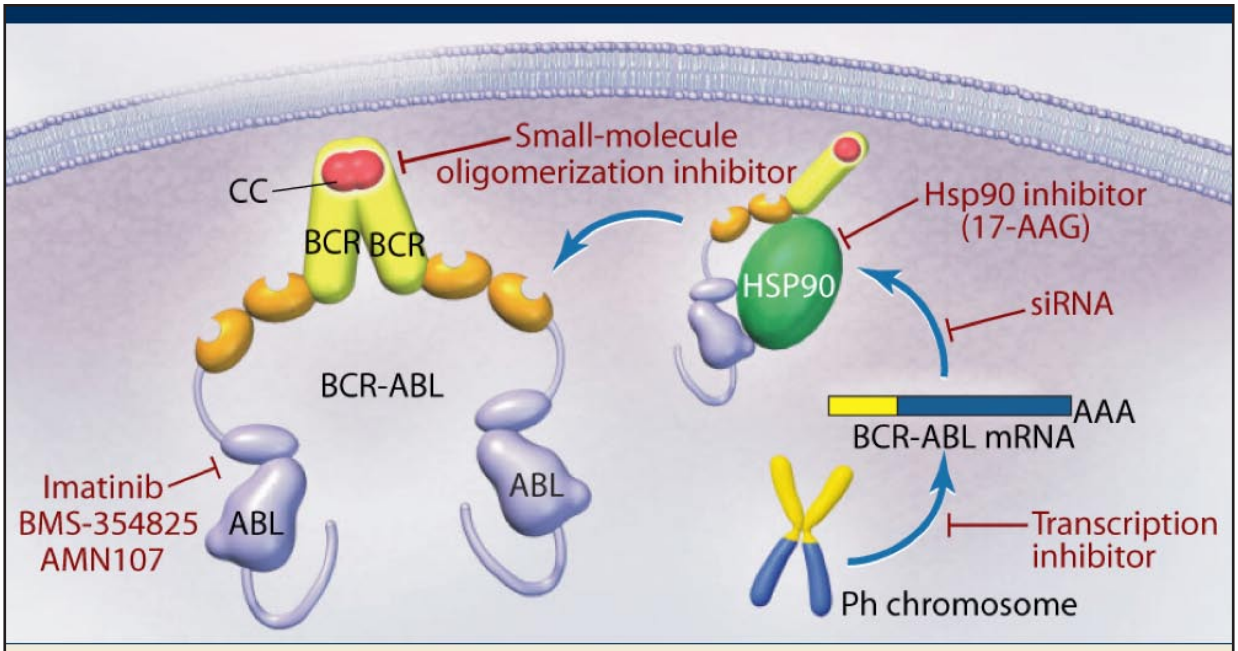
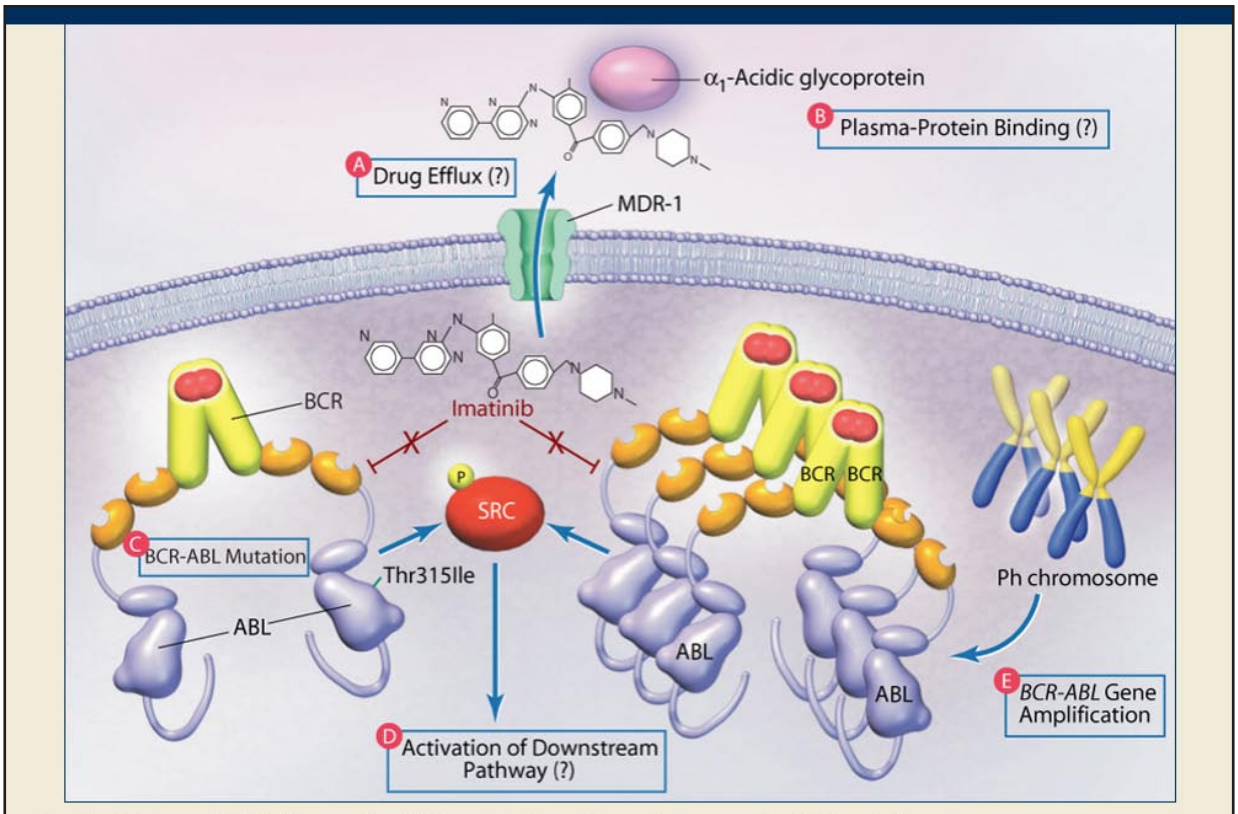
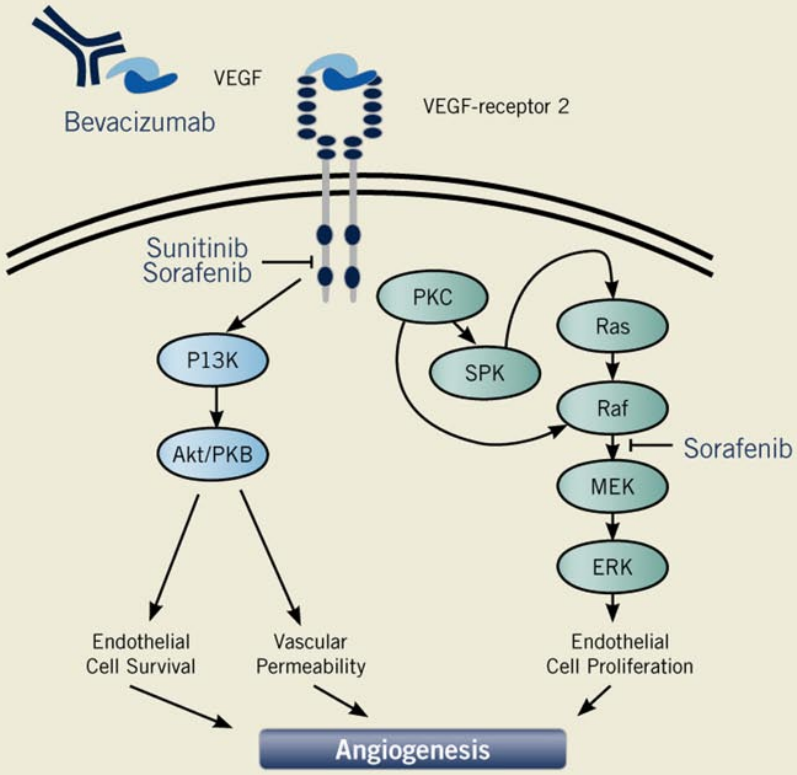


Therapeutic Targeting of Activated Fusion TK Proteins



Limitations of TK-Targeted Therapies: Development of Resistance



Mechanism of Action of Inhibitors of the VEGF/VEGFR Signaling Pathway

Reprinted with permission from Rini BJ. *Clin Cancer Res* 2007;13(4):1098-106. Figure 1.