Available online at www.sciencedirect.com
ScienceDirect
Biochemical and Biophysical Research Communications 356 (2007) 323–328
BBRC
www.elsevier.com/locate/ybbrc

Mini Review

# Sunitinib: A VEGF and PDGF receptor protein kinase and angiogenesis inhibitor

Robert Roskoski Jr. *

*Blue Ridge Institute for Medical Research, 3754 Brevard Road, Suite 116A, Box 19, Horse Shoe, NC 28742, USA*

Received 28 February 2007
Available online 7 March 2007

**Abstract**

Sunitinib (SU-11248, Sutent) inhibits at least eight receptor protein-tyrosine kinases including vascular endothelial growth factor receptors 1–3 (VEGFR1–VEGFR3), platelet-derived growth factor receptors (PDGFRα and PDGFRβ), stem cell factor receptor (Kit), Flt-3, and colony-stimulating factor-1 receptor (CSF-1R). VEGFR1 and VEGFR2 play key roles in vasculogenesis and angiogenesis. PDGFRβ, which is found in pericytes that surround capillary endothelial cells, plays a pivotal role in stabilizing the vascular endothelium. Sunitinib inhibits angiogenesis by diminishing signaling through VEGFR1, VEGFR2, and PDGFRβ. Renal cell cancers that have metastasized, or spread from the primary tumor, exhibit extensive vascularity, and sunitinib is approved for the treatment of these neoplasms. Activating Kit mutations occur in about 85% of gastrointestinal stromal tumors and activating PDGFRα mutations occur in about 5% of these tumors. Sunitinib is approved for the treatment of those tumors that are resistant to imatinib (STI-571, Gleevec), another Kit and PDGFRα protein-tyrosine kinase inhibitor. Both sunitinib and imatinib bind reversibly to the ATP binding site of their target kinases and thereby inhibit their catalytic activity.


*Keywords:* Bevacizumab; Cancer therapy; Colorectal cancer; Flt-3; Gastrointestinal stromal tumors; Leukemia; Renal cell cancer; SU-5416; SU-6668; SU-10944; SU-11248; Tyrosine kinase inhibitors

Protein kinases are enzymes that play a key regulatory role in nearly every aspect of cell biology. These enzymes catalyze the following reaction:

$$\mathrm{MgATP^{1-}} + \text{protein-OH} \rightarrow \text{protein-OPO}_3^{2-} + \mathrm{MgADP} + \mathrm{H^+}$$

Based upon the nature of the phosphorylated –OH group, these enzymes are classified as protein-serine/threonine kinases and protein-tyrosine kinases. The 58 human receptor protein-tyrosine kinases are divided into about 20 families [1]. The PDGFR family includes the colony-stimulating factor-1 receptor (CSF-1R, or Fms, where Fms refers to viral feline McDonough sarcoma virus), Flt-3 (Fms-like tyrosyl kinase-3), Kit (the stem cell factor receptor), and the platelet-derived growth factor receptors (PDFGRα and PDFGRβ). An extracellular segment containing five immunoglobulin-like domains, a single transmembrane segment, a juxtamembrane domain, a cytoplasmic kinase domain that contains an insert of about 70 amino acid residues, and a carboxyterminal tail characterizes the PDGF receptor family. The VEGF receptor family includes VEGFR1 (Flt-1), VEGFR2 (Flk-1/KDR, Fetal liver kinase-1/kinase domain-containing receptor), and VEGFR3 (Flt-4). The VEGF receptors, which have seven immunoglobulin-like extracellular domains, have an architecture that parallels that of the PDGF receptor family.

Neovascularization, or new blood vessel formation, is divided into two components: vasculogenesis and angiogenesis. Embryonic or classical vasculogenesis is the process of new blood vessel formation from hemangioblasts

*Abbreviations:* CSF-1R, colony-stimulating growth factor-1 receptor; FGF-R1, fibroblast growth factor receptor-1; PDGFR, platelet-derived growth factor receptor; PlGF, placental growth factor; VEGF/VPF, vascular endothelial growth factor/Vascular permeability factor.

* Fax: +1 828 890 8130.
*E-mail address:* rrj@brimr.org

0006-291X/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.bbrc.2007.02.156

that differentiate into blood cells and mature endothelial cells [2]. In contrast, angiogenesis is the process of new blood vessel formation from pre-existing vascular networks by capillary sprouting. During this process, mature endothelial cells divide and are incorporated into new capillaries. Angiogenesis, which is regulated by both endogenous activators and inhibitors, is under stringent control [3].

## The VEGF and PDGF family of ligands and receptors

The ligands for the VEGF and PDGF receptor families, all of which are polypeptide dimers, and their respective receptors are listed in Table 1. VEGFR2 is the predominant mediator of VEGF-stimulated endothelial cell migration, proliferation, survival, and enhanced vascular permeability that occur during vasculogenesis and angiogenesis. VEGF was originally described as a vascular permeability factor [2]. Although, many first messengers including cytokines and growth factors participate in angiogenesis and vasculogenesis, the VEGF family is of paramount importance.

The PDGF/PDGFR family plays a supporting role in angiogenesis [4,5]. PDGF stimulates the proliferation of many cells of mesenchymal origin such as fibroblasts and vascular smooth muscle cells. Vascular endothelial cells produce PDGF, and the surrounding mural cells, which include pericytes and vascular smooth muscle cells, express PDGFRβ. PDGF-BB, a PDGF-B homodimer, regulates pericyte and fibroblast functions in the supporting matrix of tumors. Thus, inhibition of both PDGF and VEGF signaling promises to be more effective in blocking tumor angiogenesis than targeting either system alone [4,5].

*FLT3* mutations occur in humans with acute myelogenous leukemia (15–35% of patients), myelodysplasia (5–10%), and acute lymphoblastic leukemia (1–3%), thereby making *FLT3* one of the most frequently mutated genes in hematological malignancies [8]. Many cancers of the breast and female reproductive tract express CSF-1R, which may be stimulated by CSF-1 produced by tumor cells, the tumor-supporting matrix, or tumor-associated macrophages.

## Therapeutic inhibition of VEGF action

When experimental tumors reach a size of 0.2–2.0 mm in diameter, they become hypoxic and limited in size in the absence of angiogenesis [2]. There are more than two dozen endogenous pro-angiogenic factors and more than two dozen endogenous anti-angiogenic factors. In order to increase in size, tumors undergo an angiogenic switch where the action of pro-angiogenic factors predominates, resulting in angiogenesis and tumor progression [3]. Neoplastic growth thus requires new blood vessel formation, and Folkman proposed in a ground-breaking paper in 1971 that inhibiting angiogenesis might be an effective anti-tumor treatment [10]. Strategies for restraining tumor

Table 1
Functions of receptor targets of sunitinib

| Receptor | Polypeptide ligands | Receptor functions and properties | Actual and potential therapeutic targets | Citations |
|---|---|---|---|---|
| VEGFR1 | VEGF, VEGF-B, PlGF | Vasculogenesis, angiogenesis, and monocyte/macrophage motility | Vascular endothelial cells/monocytes | [2] |
| VEGFR2 | VEGF, VEGF-C, VEGF-D, VEGF-E | Vasculogenesis, angiogenesis, and endothelial cell motility | Vascular endothelial cells | [2] |
| VEGFR3 | VEGF-C, VEGF-D | Vascular and lymphatic development and maintenance | Vascular and lymphatic endothelial cells | [2] |
| PDGFRα | PDGF-AA, PDGF-AB, PDGF-BB, PDGF-CC | Proliferation, chemotaxis | Lung, prostate, renal cell carcinomas; chronic myelomonocytic leukemia; glioblastoma | [4,5] |
| PDGFRβ | PDGF-BB, PDGF-DD | Expressed in pericytes and smooth muscle cells of developing and mature vasculature; proliferation, chemotaxis | Pericytes; lung, prostate, renal cell carcinomas; chronic myelomonocytic leukemia; glioblastoma | [4,5] |
| Kit | Stem cell factor (SCF) | Gametogenesis, hematopoiesis, mast cell development and function, and melanogenesis | Acute myelogenous leukemia; gastrointestinal stromal tumors; mastocytomas; small cell lung cancer; seminoma/dysgerminoma; T-cell lymphoma | [6,7] |
| Flt-3 | Flt ligand (FL) | Proliferation and development of hematopoietic stem cells; expressed in myeloid and lymphoid progenitor cells, dendritic cells, and natural killer cells | Acute myelogenous leukemia, myelodysplasia, acute lymphocytic leukemia | [8] |
| CSF-1R | Colony-stimulating factor-1 | Differentiation, proliferation, survival, and function of macrophages. Stimulates tumor-associated macrophages that facilitate angiogenesis, extracellular-matrix breakdown, and metastasis | Breast and other carcinomas | [9] |