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Antiangiogenic Therapy for Advanced Renal Cell Carcinoma

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Renal cell carcinoma (RCC) afflicted an estimated 51,190 Americans and resulted in 12,890 deaths in the United States in 2007[1]. Most forms of RCC are diagnosed in an advanced stage and are highly resistant to cytotoxic chemotherapy. Roughly 10% of patients with metastatic RCC (mRCC) respond to immunotherapy using low-dose interferon-α or interleukin-2 (IL-2). While a small minority of patients obtain durable remissions from high-dose IL-2, this therapy carries high toxicities necessitating intensive supportive care.

In a succession of landmark studies, three different antiangiogenic agents, **sunitinib** (Sutent), **sorafenib** (Nexavar), and **temsirolimus** (Torisel), demonstrated significantly greater anti-tumor effects in patients with mRCC than either immunotherapy or placebo. These therapies, now FDA-approved for advanced RCC, capitalize on new understandings of the cellular signaling pathways underlying renal tumor angiogenesis and growth.

Both hereditary and sporadic forms of clear cell renal carcinoma are driven by mutations in the von Hippel-Lindau (*VHL*) tumor suppressor gene. In normal cells, the wild-type VHL protein prevents uncontrolled angiogenesis by promoting the degradation of hypoxia-inducible factor-1α (HIF-1α), a transcription factor activated in response to tissue hypoxia. In renal tumors with mutated *VHL*, HIF-1 accumulates in the cells, triggering production of potent proangiogenic growth factors, most notably vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). These proteins bind to specific endothelial cell surface receptors (VEGFR, PDGFR), activating signaling pathways downstream of the receptors that induce endothelial cell proliferation, migration, and capillary tube formation.

Clinical Evidence for Antiangiogenic Agents in mRCC

Tyrosine Kinase Inhibitors

Sunitinib and sorafenib are oral multi-kinase inhibitors that exert antiangiogenic effects through intracellular targeting of VEGFR and PDGFR. Sorafenib additionally inhibits Raf-1, an enzyme involved in tumor cell proliferation. In a pivotal phase 3 trial involving 750 previously untreated mRCC patients, sunitinib (50 mg/day) more than doubled median progression-free survival (PFS) compared to interferon (11 mo. vs. 5 mo., $P<0.001$)[2]. Sorafenib improved PFS compared with placebo in a phase 3 trial (TARGET) in 903 cytokine-refractory mRCC patients (median PFS = 5.5 mo. vs. 2.8 mo., $P<0.001$)[3]. Overall survival (OS) at the final analysis was non-significant between the two arms: 17.8 mo. vs. 15.2 mo. ($P=0.146$)[4]. Although both sunitinib and sorafenib are broadly approved for advanced RCC, sorafenib has thus far failed to improve upon interferon for PFS in the front-line setting[5].

Other TKIs being evaluated for advanced or mRCC include **axitinib** (AG-013736), an inhibitor of VEGFR-1, -2, and -3; **pazopanib** (GW786034), which targets VEGFR-1, -2, and -3, PDGFR-α and –β, and c-Kit; and **cediranib** (AZD2171, Recentin), an inhibitor of VEGFR-1 and -2, c-Kit, and PDGFR-β. Each of these agents has produced responses in phase 2 trials in advanced RCC: Axitinib induced tumor regression in 55% of 62 sorafenib-refractory patients in a single-arm trial[6]; pazopanib controlled disease in 73% of 225 mRCC patients, most of whom were treatment-naïve[7]; and cediranib produced confirmed partial responses (PR) in 6/16 (38%) and tumor control in 12/16 (75%) treatment-naïve mRCC patients[8].

Monoclonal Antibodies

Monoclonal antibodies prevent activation of endothelial cell receptors by neutralizing growth factors circulating outside the cell. **Bevacizumab** (BV; Avastin), a VEGF-targeting monoclonal antibody, was evaluated in a randomized phase 3 trial (AVOREN) in 641 previously untreated mRCC patients. The addition of BV to interferon significantly increased median PFS (10.2 mo. vs. 5.4 mo., $P<0.0001$) and improved response rates (31% vs. 12%, $P<0.0001$) vs. interferon plus placebo[9]. Antibodies that target the epidermal growth factor receptor (EGFR), such as **erlotinib** (Tarceva), have thus far shown limited utility in mRCC. In a phase 2 study, the addition of erlotinib to BV failed to significantly improve PFS vs. BV/placebo (9.9 mo. vs. 8.5 mo., $P=0.58$) or tumor response in treatment naïve mRCC patients[10].

Antibodies are also being developed that target integrins, molecules that enable cells to adhere to and migrate through surrounding connective tissue. The α5β1 integrin binds to fibronectin in the matrix surrounding blood vessels and promotes endothelial cell proliferation, migration and survival. **Volociximab** (M200), a monoclonal antibody that blocks fibrinectin binding to α5β1, was evaluated in an open-label phase 2 study in 40 heavily pretreated mRCC patients[11]. At the time of analysis, 80% of patients had stable disease (SD) and there was 1 confirmed PR. OS was 79% at 6 months and 68% at 22 months. As therapeutic targets in RCC, integrins show promise, but require further investigation.

Inhibitors of mTOR

mTOR (mammalian target of rapamycin) is a serine/threonine kinase that controls numerous cellular activities through the function of two main protein complexes, TORC1 and TORC2. TORC1 regulates expression and stability of HIF-1 along with key proteins involved in endothelial cell proliferation[12]. TORC2 is implicated in the regulation of cell morphology and adhesion, and also phosphorylates and activates the *Akt* oncogene, a potent stimulator of angiogenesis and tumorogenesis[12, 13]. Alterations in the PI3K/Akt pathway occur in many cancer types and result in increased proangiogenic cell signaling through mTOR and other proteins[12]. **Temsirolimus** (Torisel, CC1-779), a derivative of rapamycin, binds to the intracellular protein FKBP-12 to form a complex that disrupts mTOR signaling in TORC1. This mechanism suppresses the production of proteins, such as HIF-1, that stimulate cell proliferation and angiogenesis.

In a pivotal phase 3 trial, 626 previously untreated mRCC patients with poor prognosis (3 risk factors) were randomized to receive interferon, temsirolimus, or both drugs together[14]. Median OS was significantly prolonged vs. interferon in patients treated with single-agent temsirolimus (10.9 mo. vs. 7.3 mo.), but not with combination therapy (8.4 mo.). A high incidence of adverse events (AEs), treatment dropouts, and reduced dosing may have hindered efficacy in the combination arm. At ASCO 2008, results were presented from a randomized Phase 3 trial of the mTOR inhibitor everolimus (RAD001) in patients with advanced RCC who had progressive disease ≤6 mo. of receiving sunitinib and/or sorafenib[15]. This trial, RECORD-1, was halted when interim data showed a doubling of PFS among patients who received everolimus compared with placebo (4.0 mo. vs. 1.9 mo., $P<0.001$). Based on these results, everolimus should be a viable option for mRCC patients who fail TKI therapy with a VEGFR inhibitor.

Antiangiogenic Escape and Treatment Strategies

Both laboratory and clinical research has demonstrated that most tumors eventually compensate for VEGF interruption through a number of proposed mechanisms, including upregulation of VEGF and other growth factors in response to treatment, co-option of existing vessels that are less VEGF-dependent, and transformation of the tumor vasculature to a more mature, less VEGF-dependent phenotype[16]. The mechanisms behind resistance to TKIs are less clear due to the multiple signaling pathways affected by these agents, but may include amplification of an oncogenic kinase gene, production of a drug-resistant variant of the targeted kinase, upregulation of alternate signaling pathways, and drug efflux, among other postulated escape routes[17].

Treatment strategies to combat antiangiogenic escape include the use of dual agents that hit different angiogenic targets, and sequential therapy. A number of studies using various combinations of agents have been initiated, but results are quite preliminary. In a small study in 12 mRCC patients, the combination of temsirolimus and BV produced PR in 8 patients and SD in 3; a phase 2 trial using this combination has been initiated[18]. Because different angiogenesis inhibitors often hit overlapping targets, which may have important implications regarding efficacy, toxicities and resistance, more research is required before combination therapy can be endorsed for mRCC.

Some mRCC patients who relapse on front-line therapy have achieved a clinical response by switching to a different angiogenesis inhibitor. Several recent analyses, for example, have suggested that sequential therapy with sunitinib and sorafenib is feasible in patients who relapsed on the alternate agent[19, 20, 21]. Responses have also been observed in mRCC patients treated with sunitinib after experiencing disease progression on BV therapy[22]. Axitinib, as discussed previously, produced clinical benefit in a majority of sorafenib-refractory mRCC patients, including a subset of patients who also received prior sunitinib[6].

Side Effects of Antiangiogenic Therapy

While anti-VEGF therapies are generally well tolerated, they have distinct side effect profiles requiring careful administration and monitoring. Common toxicities with sunitinib and sorafenib therapy include diarrhea, fatigue, nausea, stomatitis, hypertension, hand-foot skin reaction—a condition in which painful, symmetrical hyperkeratotic lesions develop on the palms and soles of the feet—rash, hair changes, and mucosal inflammation[23]. Of these, fatigue and skin toxicities are most likely to cause interruption or discontinuation of sunitinib and sorafenib therapy, respectively. A recent study documented abnormal thyroid function tests and/or clinical symptoms (fatigue) in nearly 85% of mRCC patients receiving sunitinib[24]. Therefore, thyroid monitoring of patients on sunitinib is now advised, and thyroid hormone replacement may be required for some patients. Recently, the FDA amended the sunitinib labeling to include risks for reduced left ventricular ejection fraction (LVEF) and QT interval prolongation associated with rare reports of LV dysfunction, ventricular arrhythmias, and congestive heart failure[25]. Cardiac monitoring may therefore be warranted for patients on sunitinib, particularly those with a history of cardiac events.

Hypertension is a well-documented side effect of VEGF inhibitors, including BV, and is presumably due to decreased nitric oxide production by targeted endothelial cells. Less frequent AEs observed with BV therapy include thromboembolic events and GI perforations; reversible posterior leukoencephalopathy and nasal septum perforation have also been reported. mRCC patients who received temsirolimus in the phase 3 trial had a significant incidence of hyperglycemia, hypercholesterolemia and hyperlipidemia, reflecting inhibition of mTOR-regulated glucose and lipid metabolism[14]. These metabolic effects can be readily managed with lipid- and glucose-lowering agents.

Future Directions

While angiogenesis inhibitors represent the first major advancement over cytokine therapy for advanced or mRCC, new agents, treatment strategies, and screening tools will be needed to continue this trend. Gene expression profiling may have some utility for predicting treatment response in renal cancer, given the reliance of this malignancy on mutated *VHL*. In the largest study of its kind to date, *VHL* mutation status was not predictive of either PFS or OS in mRCC patients treated with antiangiogenic agents, although "loss of function" mutations (defined as those mutations thought to disrupt VHL protein function) was correlated with a higher response rate[26]. Finally, recent studies have suggested that certain inflammation markers, such as elevated platelet and neutrophil counts, may foretell poor prognosis in mRCC patients on VEGF inhibitors, and thus warrant further investigation[27].

Abbreviated References:

1. Jemal A (2007) 2. Motzer RJ (2007) 3. Escudier B (2007) 4. Bukowski RM (2007) 5. Szczylik C (2007). 6. Rini BI (2007) 7. Hutson TE (2007) 8. Sridhar SS (2007) 9. Escudier B (2007) 10. Bukowski RM (2006) 11. Yazji S (2007) 12. Corradetti MN (2006) 13. Inoki K (2006) 14. Hudes G (2007) 15. Motzer RJ (2008) 16. Kerbel RS (2005) 17. Arteaga CL (2007) 18. Merchan JR (2007) 19. Dham A (2007) 20. Tamaskar I (2006) 21. Escudier B (2007) 22. George DJ (2007) 23. Robert C (2005) 24. Rini BI (2007) 25. Sutent PI (2007) 26. Choueiri TK (2007) 27. Choueiri TK (2007)

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From the Editor-in-Chief

The Angiogenesis Foundation is pleased to present this CME issue of *Targeting Tumor Angiogenesis* focused on new findings in antiangiogenic therapies for advanced RCC. I have invited three preeminent experts, Dr. Gary Hudes, Dr. Brian Rini, and Dr. Sandy Srinivas, to discuss the latest clinical evidence for antiangiogenic treatments for advanced RCC and current strategies for optimizing its therapy.

– *William W. Li, M.D., President, The Angiogenesis Foundation*

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RELEASE AND EXPIRATION
Release date is August 2008. Expiration is August 2009.

INTENDED AUDIENCE
Practicing oncologists and oncology nurses in the U.S.

EDUCATIONAL OBJECTIVES
At the conclusion of this educational activity, clinicians will be able to:
- Describe angiogenesis targets and pathways in cancer.
- Describe the paradigm shifts in cancer management accompanying antiangiogenic therapy.
- Review clinical data regarding the use of antiangiogenic agents in treating advanced renal cell carcinoma.

METHOD OF PARTICIPATION
Review the illustration and article(s) on this publication, then visit www.angio.org and click on CME Information for additional content, CME registration and evaluation. There you can access additional program content, related articles, and detailed instructions for obtaining CME credits for this activity.

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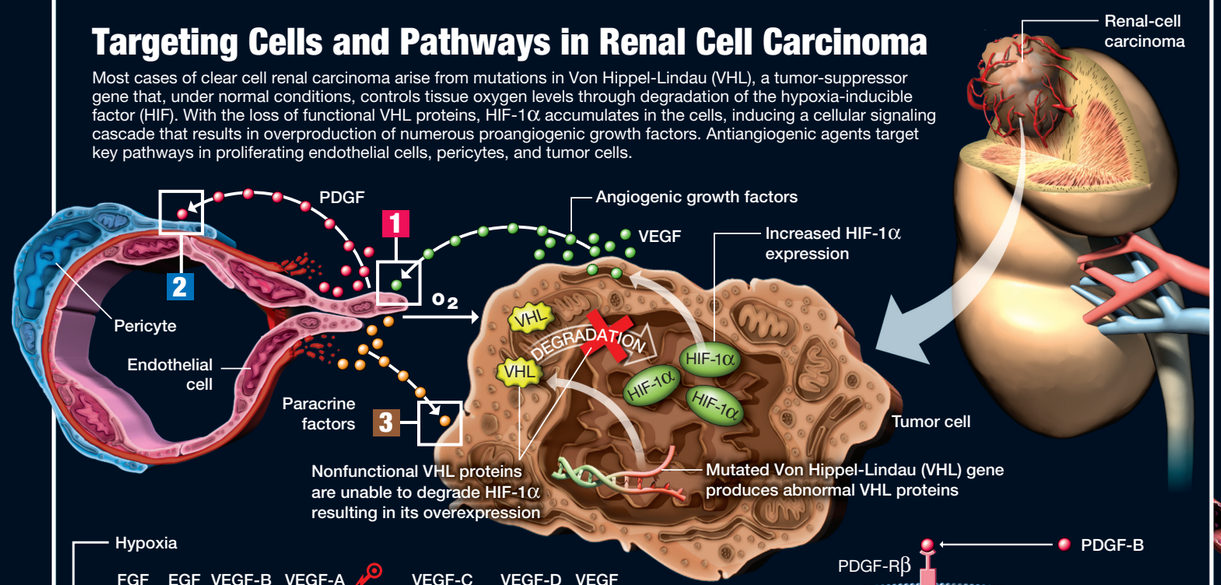
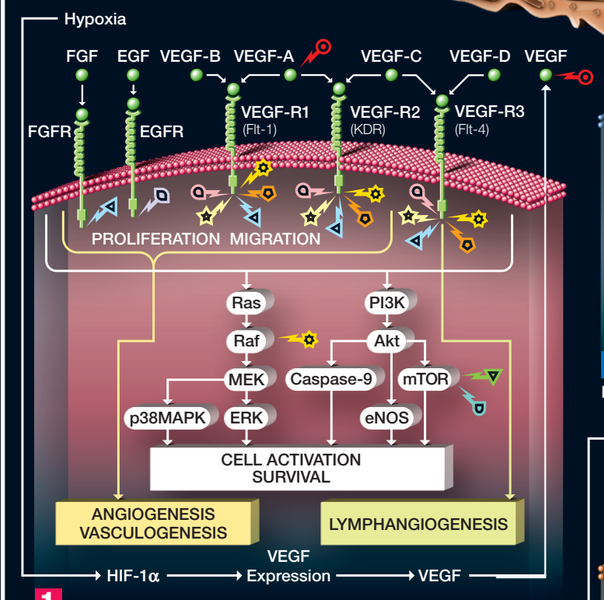
Medical Writer: Roderick Smith, M.S. has nothing to disclose with regard to commercial interests.

DISCUSSION OF UNLABELLED USE
This CME activity contains discussion of published and/or investigational use of axitinib, AZD2171 (Recentin), bevacizumab (Avastin), erlotinib (Tarceva), everolimus, pazopanib, and volociximab.

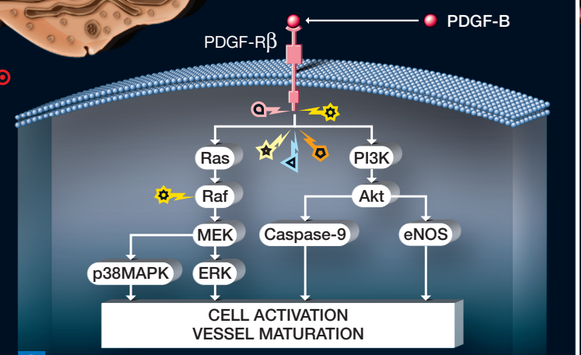
Targeting Cells and Pathways in Renal Cell Carcinoma

Most cases of clear cell renal carcinoma arise from mutations in Von Hippel-Lindau (VHL), a tumor-suppressor gene that, under normal conditions, controls tissue oxygen levels through degradation of the hypoxia-inducible factor (HIF). With the loss of functional VHL proteins, HIF-1α accumulates in the cells, inducing a cellular signaling cascade that results in overproduction of numerous proangiogenic growth factors. Antiangiogenic agents target key pathways in proliferating endothelial cells, pericytes, and tumor cells.

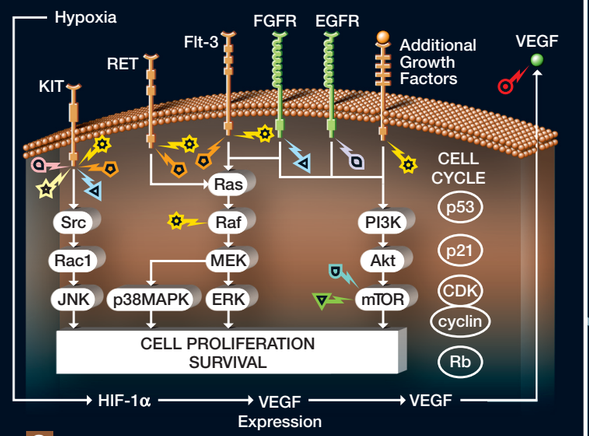




1 ENDOTHELIAL CELL The vascular endothelial growth factor (VEGF) family (A-D) binds to receptors VEGF-R1, VEGF-R2, VEGF-R3, activating signal transduction to promote angiogenesis,vasculogenesis, and lymphangiogenesis.



2 PERICYTE Platelet-derived growth factor (PDGF) and its receptor PDGF-Rβ mediate vessel maturation.



3 TUMOR CELL Multiple growth factors and receptors activate signal transduction and cell cycle pathways to stimulate tumor cell growth.

Targeted Agents

(Targets shown in diagram above and to the right)

- **Axitinib** (AG-013736)
- **AZD2171** (Recentin)
- **Bevacizumab** (Avastin)
- **Erlotinib** (Tarceva)
- **Everolimus** (RAD001)
- **Pazopanib** (GW786034)
- **Sunitinib** (Sutent)
- **Sorafenib** (Nexavar)
- **Temsirolimus** (Torisel)
- **Volociximab** (M200)

Targeting Tumor Angiogenesis

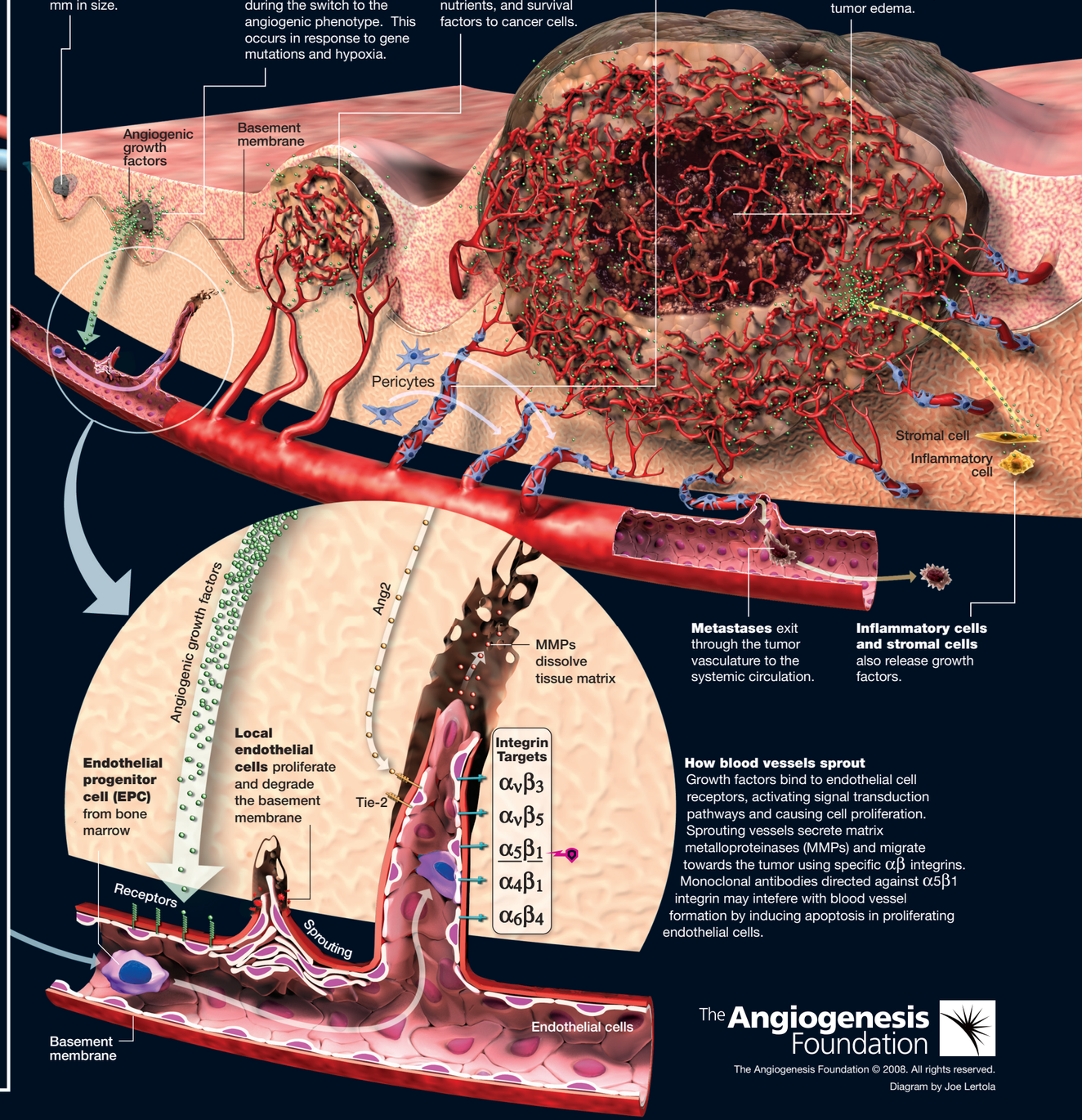
1 Incipient cancers lack a blood supply and cannot grow larger than 2-5 mm in size.

2 Cancer cells release growth factors that activate endothelial cells during the switch to the angiogenic phenotype. This occurs in response to gene mutations and hypoxia.

3 Angiogenic vessels form tubes and loops, thereby delivering oxygen, nutrients, and survival factors to cancer cells.

4 Vessels mature as pericytes are recruited by endothelial cells to stabilize new capillaries.

5 Unabated angiogenesis enables tumor expansion and local invasion. Abnormal blood flow leads to central hypoxia. Vessel hyperpermeability results in tumor edema.



How blood vessels sprout

Growth factors bind to endothelial cell receptors, activating signal transduction pathways and causing cell proliferation. Sprouting vessels secrete matrix metalloproteinases (MMPs) and migrate towards the tumor using specific αβ integrins. Monoclonal antibodies directed against α5β1 integrin may intefere with blood vessel formation by inducing apoptosis in proliferating endothelial cells.

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Diagram by Joe Lertola