Antiangiogenic Therapy for Advanced Hepatocellular Carcinoma

Edited by Ghassan K. Abou-Alfa, M.D., Melanie Thomas, M.D., and Alan Venook, M.D.

Worldwide, primary liver cancer is the sixth most common malignancy and the third most common cause of cancer-related death. In the US, an estimated 19,160 new cases of liver and intrahepatic bile duct cancer are expected in 2007, with 16,780 deaths from the disease[1]. HCC is commonly associated with viral hepatitis, alcoholism, and non-alcoholic steatohepatitis associated with diabetes and morbid obesity. Hepatitis C virus (HCV) – believed to infect 4 million Americans – is associated with most US HCC cases.

HCC tends to be particularly vascular and, like all solid tumors, requires angiogenesis to grow beyond a few millimeters in size. Angiogenesis is evident in early stage liver carcinoma and correlates with disease progression[2]. The primary stimulus for tumor angiogenesis is vascular endothelial growth factor (VEGF), an endogenous cytokine that induces capillary endothelial cell proliferation, migration and survival, and the induction of bone marrow-derived endothelial progenitor cells (EPCs) to the new vasculature.

VEGF is overexpressed in most solid tumors and may be further upregulated by external stimuli. In various *in vivo* tumor models, chronic alcohol exposure, a known risk factor for HCC and other cancers, has correlated with increased VEGF expression, tumor growth and tumor vessel density, suggesting that promotion of angiogenesis may be one possible mechanism of alcohol-induced tumor progression[3]. Other angiogenic factors, such as platelet-derived growth factor (PDGF) and basic fibroblast growth factor (bFGF), are also expressed in HCC.

Clinical Efficacy of Antiangiogenic Therapies for HCC

The inherent vascularity of HCC makes it a logical target for antiangiogenic therapy. **Sorafenib** (Nexavar) and **sunitinib** (Sutent) are orally administered small molecule tyrosine kinase inhibitors (TKIs) that bind competitively to the intracellular receptor domains for VEGF, PDGF, and other angiogenic growth factors. Based on positive phase 3 trial results, sorafenib is now approved for advanced, unresectable HCC in the U.S. and Europe; phase 2 data of sunitinib in advanced HCC have recently been presented. **Bevacizumab** (Avastin), a humanized monoclonal antibody that binds circulating VEGF, is also in phase 2 trials for advanced HCC.

Sorafenib

Sorafenib inhibits angiogenesis through targeting of VEGF receptors 1, 2, and 3 (VEGFR-1, -2, and -3), platelet-derived growth factor receptor-β (PDGFR-β), stem cell factor receptor (c-Kit), FLT-3 and RET. Additionally, sorafenib targets the Raf-1 kinase, part of the Raf/MEK/ERK signaling pathway involved in tumor cell proliferation and survival. In a phase 2 trial conducted in 137 patients with inoperable HCC, sorafenib 400 mg bid produced a median time-to-progression (TTP) and median overall survival (OS) of 4.2 mo. and 9.2 mo., respectively[4]. These findings provided the rationale for the randomized phase 3 Sorafenib HCC Assessment Randomized Protocol (SHARP) trial that compared sorafenib 400 mg bid to placebo in 602 patients with unresectable HCC who had not received prior systemic therapy. Median overall survival (OS) was 10.7 mo. for sorafenib vs. 7.9 mo. for placebo (P=0.00058; HR=0.69), making sorafenib the first systemic therapy to prolong survival in advanced HCC[5]. Median radiographic TTP in the sorafenib and placebo arms was 5.5 mo. vs. 2.8 mo. (P=0.000007; HR=0.58).

While only 7 (2.3%) of sorafenib-treated patients in SHARP achieved a partial response (PR), 71% had stable disease (SD). In the phase 2 sorafenib HCC study, SD correlated with central tumor necrosis in some sorafenib-treated patients, which occurred despite an increase in tumor size[4]. This finding may help to explain why a survival benefit is observed with sorafenib in the absence of evident tumor regression, although this hypothesis requires validation.

It should also be noted that most patients in SHARP (≥95%) had Child-Pugh A cirrhosis and good performance status, and only 48% who received sorafenib had underlying viral hepatitis. Future clinical studies will therefore need to evaluate the safety and efficacy of sorafenib in patients with more severe cirrhosis and worse liver function usually seen by medical oncologists.

Most recently, final outcome data were presented from a randomized phase 2 trial of sorafenib plus doxorubicin (dox) and dox plus placebo in chemotherapy-naïve HCC patients[6]. Median TTP in the sorafenib/dox and dox/placebo arms, respectively, was 8.6 mo. and 4.8 mo., median PFS 6.9 mo. and 2.8 mo., and median OS 13.7 mo. and 6.5 mo. These results warrant further investigation to explore the efficacy and tolerability of this combination.

Sunitinib

Sunitinib, a TKI with activity against VEGFR-1, -2, and -3, PDGFR, c-Kit, FLT-3 and RET, was evaluated in two recent open label phase 2 studies for advanced HCC. In the first trial, conducted in 37 patients with unresectable disease, sunitinib 50 mg/day (4 weeks on, 2 weeks off) produced major tumor necrosis in 48% of patients and a median TTP and OS of 5.2 mo. and 11.2 mo., respectively[7]. Similar results were obtained in a second trial using a 37.5 mg/day sunitinib dose—median PFS and OS among the 26 enrolled patients were 4.1 mo. and 11.6 mo., respectively, with a 42% disease control rate[8]. In addition, tumor permeability, as estimated by DCE-MRI, decreased by an average of 38% following 2 weeks of sunitinib therapy, and 11 of 18 patients had reduced circulating levels of soluble VEGFR-2, which are suggestive of an antiangiogenic response to therapy.

Bevacizumab

Bevacizumab (BV) has been evaluated for advanced HCC in several recent studies. In a phase 2 trial, 33 patients with advanced, unresectable HCC received BV 10 mg/kg in combination with gemcitabine/oxaliplatin (GEMOX)[9]. Of 30 evaluable patients, 6 (20%) had confirmed PR and 8 (27%) had SD with a median duration of response of 9 mo. (range, 4.5 to 13.7 mo.). Median PFS and OS were 5.3 mo. and 9.6 mo., respectively. The combination of BV 5 mg/kg and capecitabine/oxaliplatin (CapeOX) produced a PR in 4 (13%) and SD in 23 (77%) of 30 patients with advanced unresectable or metastatic HCC in a second phase 2 trial[10]. Median TTP and OS were 4.5 mo. and 10.3 mo., respectively.

As monotherapy, BV 5 or 10 mg/kg delayed disease progression in 67% of 24 evaluable patients with unresectable HCC, of which 3 (12.5%) had PR; this phase 2 trial is accruing additional patients at the 10 mg/kg BV dose[11]. Encouraging results were also reported from a single-arm phase 2 trial of BV in combination with **erlotinib** (Tarceva), an inhibitor of the epidermal growth factor receptor (EGFR), in 34 patients with unresectable HCC[12]. EGFR is overexpressed in many human carcinomas, although estimates of its expression in HCC vary widely[13]. Of 29 evaluable patients in this trial, median OS was 19 mo. and 21% of patients experienced a response, which is comparable to the response rate observed with BV plus GEMOX in the phase 2 study.

Metronomic Chemotherapy

Certain conventional chemotherapeutic agents may have antiangiogenic activity when administered in a metronomic dosing schedule. Metronomic chemotherapy is thought to suppress tumor growth in part by inhibiting mobilization of EPCs—high levels of circulating EPCs have been associated with disease progression in HCC and other tumors. A small, preliminary study enrolled 22 patients with advanced HCC to receive capecitabine (2000 mg/sq.mt.; 14 doses over 21 days) followed by metronomic capecitabine (1300 mg, uninterrupted)[14]. Whereas 5 patients were dismissed due to liver failure during the standard capecitabine therapy, only 2 developed liver failure during metronomic dosing. Among 6 evaluable patients who received metronomic capecitabine, 2 PR and 3 SD have been observed, suggesting the need for further evaluation of this dosing strategy.

Antiangiogenic Escape

The complex, highly heterogeneous nature of HCC makes it unlikely that targeting any one pathway will achieve optimal disease control. Furthermore, most tumors eventually compensate for (escape) therapy-induced VEGF interruption, resulting in tumor progression after an initial response. Proposed escape mechanisms include upregulation of VEGF and other growth factors, contribution of VEGF by host stroma proximal to the tumor, activation of alternate signaling pathways, co-option of existing vessels, and transformation of the tumor vasculature to a more mature, less VEGF-dependent phenotype[15, 16].

There are considerable data to support targeting both the VEGF and EGFR pathways simultaneously as a means to circumvent anti-VEGF escape[15]. For example, some preclinical evidence suggests that inhibiting EGFR may make tumors more angiogenesis dependent, and therefore more susceptible to VEGF inhibitors[15]. As previously discussed, encouraging results were obtained from a phase 2 study of BV plus erlotinib in advanced HCC, and this combination is being evaluated further in HCC and other tumor types.

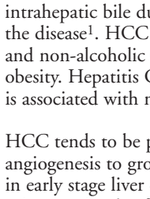
Side Effects of Antiangiogenic Therapy in HCC

The risk for bleeding, a concern in any HCC patient, is elevated in those undergoing treatment with a VEGF inhibitor. Six patients (20%) discontinued BV due to variceal hemorrhage, and 1 patient had grade 3 hemorrhagic ascites in the phase 2 study of single-agent BV for advanced HCC[11]. Hypertension is also a well-documented side effect of VEGF inhibition and can typically be managed with medication. The most frequent adverse events associated with sorafenib in the SHARP trial were fatigue, diarrhea, weight loss, rash/desquamation, hand-foot skin reaction, alopecia, anorexia, nausea and abdominal pain[17]. Although grade 3/4 bleeding in SHARP was very rare, clinicians should be aware of the potential for increased bleeding risk with sorafenib. Sunitinib was associated with grade 3/4 thrombocytopenia, neutropenia, anemia, asthenia, and ascites in a phase 2 HCC study[7]. Four patients had grade 5 bleeding, drowsiness, hepatic encephalopathy and renal failure attributed to sunitinib therapy.

Future Directions

Antiangiogenic therapies appear poised to markedly alter the treatment outlook for patients with advanced HCC. Combination therapies, new therapeutic targets, better patient selection based on tumor characteristics, and the adoption of imaging techniques that measure tumor perfusion are almost certain to provide further advances. Furthermore, pilot studies are underway to examine the potential roles of anti-VEGF therapy in adjuvant HCC treatment settings, post-resection, and post-chemoembolization for inoperable HCC.

Recently, positive data were presented from a randomized phase 2 study of **PI-88**, a heparin sulfate mimetic, for the prevention of HCC recurrence following curative resection[18]. PI-88, which inhibits angiogenesis by interfering with VEGF and fibroblast growth factor-1, -2 (FGF-1, -2) binding at the heparan sulfate domain, roughly doubled the time to disease recurrence in 'high-risk' HCC patients. A randomized phase 3 trial of this agent in 600 HCC patients is being initiated with the primary endpoint of disease-free survival following surgical resection. Because advanced HCC remains incurable, further study of innovative treatment strategies is very much needed, and clinicians should consider referring appropriate patients for participation in clinical trials.



From the Editor-in-Chief

The Angiogenesis Foundation is pleased to present this issue of *Targeting Tumor Angiogenesis* focused on advanced hepatocellular carcinoma. I have invited three preeminent experts, Drs. Ghassan K. Abou-Alfa, Melanie Thomas, and Alan Venook, to discuss the latest evidence on antiangiogenic therapies for advanced HCC and what the future holds for new therapeutic targets under investigation.
– *William W. Li, M.D., President, The Angiogenesis Foundation*

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Abbreviated References:

1. Jemal A (2007) 2. Yoshiji H (2004) 3. Gu JW (2005) 4. Abou-Alfa GK (2006) 5. Llovet J (2007) 6. Abou-Alfa GK (2007) 7. Faivre SJ (2007) 8. Zhu AX (2007) 9. Zhu AX (2006) 10. Sun W (2007) 11. Malka D (2007) 12. Thomas MB (2007) 13. Kannangai R (2006) 14. Brandi G (2007) 15. Bender JG (2004) 16. Casanovas O (2005) 17. Sorafenib PI (2007) 18. Garner J (2007)

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This CME activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the Joint Sponsorship of the Institute for Medical Studies (IMS) and The Angiogenesis Foundation.

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RELEASE AND EXPIRATION
Release date is December, 2007. Expiration is November, 2008.

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

EDUCATIONAL OBJECTIVES
- Describe angiogenesis targets and pathways in hepatocellular carcinoma
- Describe the paradigm shifts in cancer management accompanying antiangiogenic therapy
- Review clinical data regarding the use of antiangiogenic agents in treating advanced hepatocellular carcinoma

METHOD OF PARTICIPATION
Review the illustration and article(s) on this publication, and 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 to obtaining CME credits for this activity.

SPONSORSHIP
This CME activity is jointly sponsored by The Angiogenesis Foundation and The Institute for Medical Studies.

ACKNOWLEDGEMENT OF SUPPORT
This activity is supported by an educational grant from Bayer Onyx.

FACULTY DISCLOSURE
Ghassan K. Abou-Alfa, M.D. has a financial interest/relationship or affiliation in the form of:
- Grants/research support from Bayer Onyx
- Consultant to Genentech

Melanie Thomas, M.D. has a financial interest/relationship or affiliation in the form of:
- Grants/research support from Genentech

Alan Venook, M.D. has a financial interest/relationship or affiliation in the form of:
- Grants/research support from Genentech, Pfizer

William W. Li, M.D.
- Has no relationships to disclose that are germane to this CME activity

Written by Rod Smith, Medical Writer and Editor, The Angiogenesis Foundation
- Has no relationships to disclose that are germane to this CME activity

DISCUSSION OF UNLABELED USE
This CME activity contains discussion of published and/or investigational use of bevacizumab (Avastin), erlotinib (Tarceva), PI-88, sorafenib (Nexavar), and sunitinib (Sutent) for treatment of advanced hepatocellular carcinoma.

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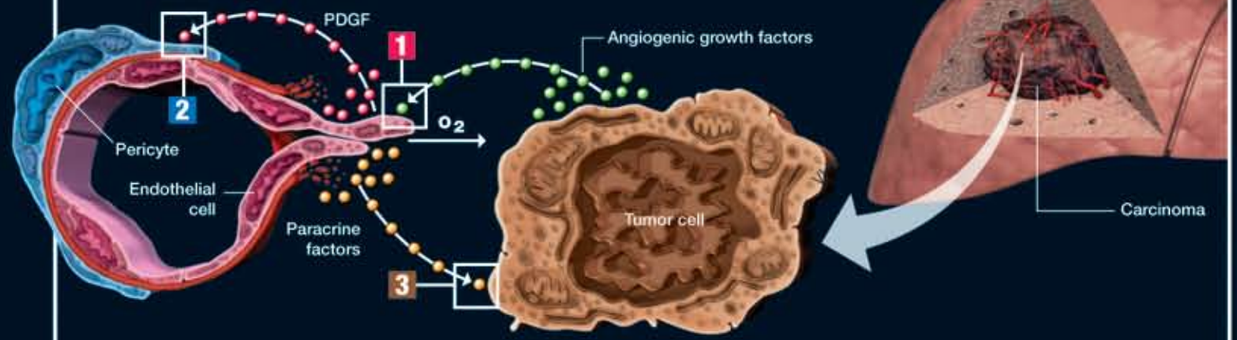
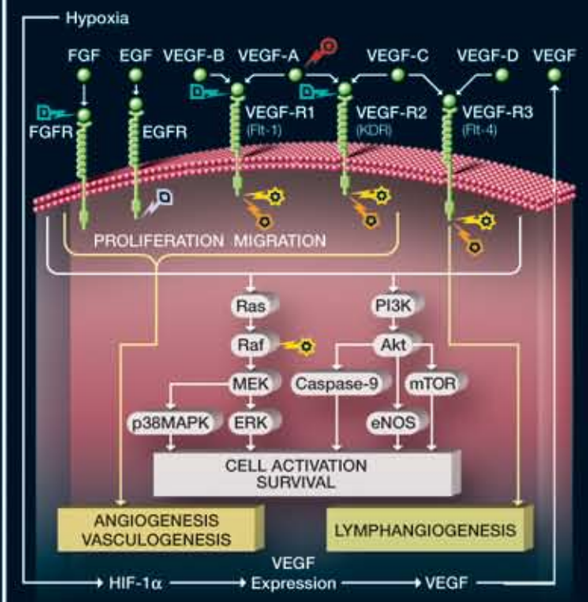
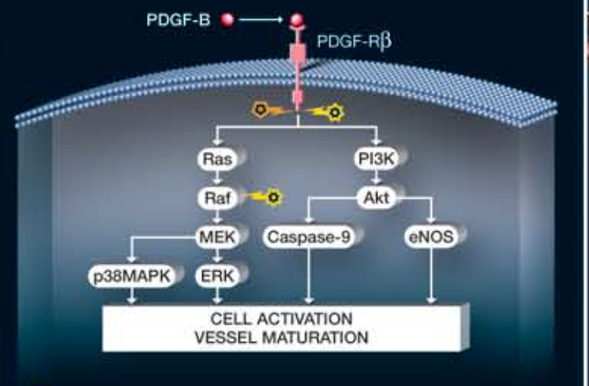
Targeting Cells and Pathways in Liver Cancer

During tumor angiogenesis, endothelial cells recruit pericytes to stabilize blood vessels perfusing tumors. Endothelial cells also provide paracrine factors to tumor cells which, in turn, release growth factors that sustain angiogenesis. Key pathways in each cell can be targeted for therapy.

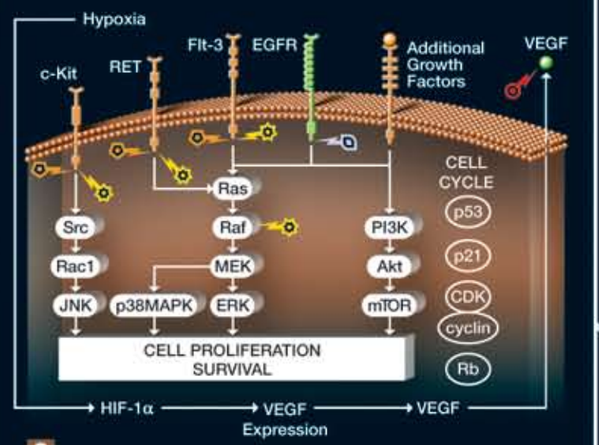




1 ENDOTHELIAL CELL The vascular endothelial growth factor (VEGF) family (A-D) binds to receptors VEGF-R1, VEGF-R2, VEGF-R3, activating signal transduction to promote angiogenesis,vasculogenesis, and lymphangiogenesis.



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)

- **Bevacizumab** (Avastin)
- **Erlotinib** (Tarceva)
- **PI-88**
- **Sunitinib** (Sutent)
- **Sorafenib** (Nexavar)

Targeting Tumor Angiogenesis

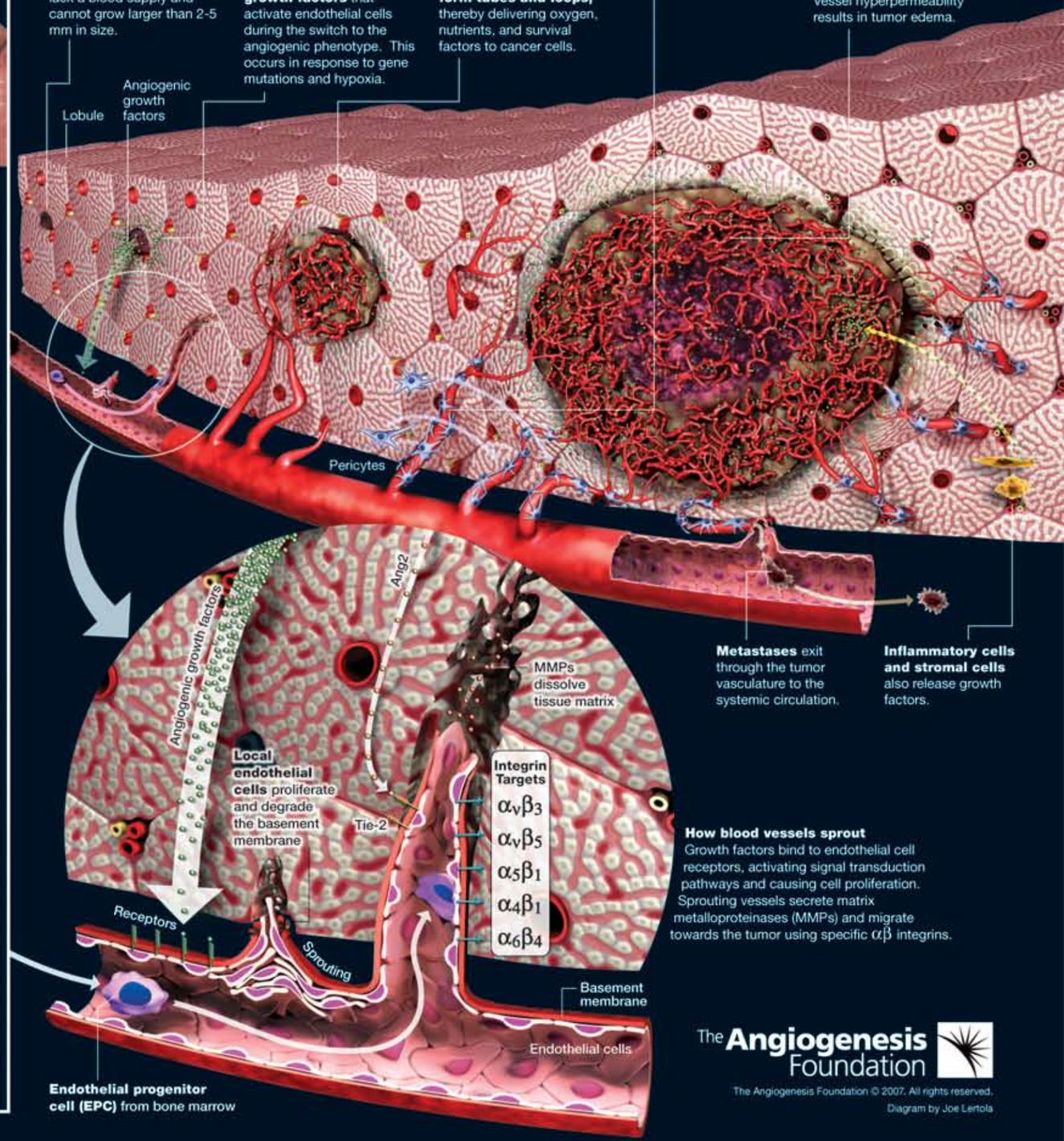
1 Incipient cancers lack a blood supply and cannot grow larger than 2-5 mm in size.

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.



Metastases exit through the tumor vasculature to the systemic circulation.

Inflammatory cells and stromal cells also release growth factors.

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.

The Angiogenesis Foundation

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Diagram by Joe Lertola