The angiome: a new concept in cancer biology

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Angiogenesis is a key process in cancer biology, and justifies focus on the endothelium. Separate studies have looked at different aspects of angiogenesis and vascular biology, primarily focusing on certain laboratory and imaging techniques that generally reflect one particular aspect of the assessment of the endothelium. These techniques include the secretion/release of molecules (such as growth factors) into the plasma, by the presence of mature and progenitor endothelial cells themselves in the circulation, but also by examination of peripheral blood flow and the local circulation of the tumour, and cells of the tumour itself. However, a limitation of this approach is that these methods, although themselves being useful, have often been viewed in isolation and thus can provide only a part of the vascular picture. The authors submit that this approach is weak, and introduce ‘the angiome’ as a term which fuses several different aspects of endothelial and tumour biology into a single concept. The authors suggest that the adoption of the concept of the angiome will bring improved insights into angiogenesis and thus cancer cell biology. In justifying this concept, the authors review the current understanding of endothelial biology and the methods of its assessment, and hypothesise that a more multifactorial approach to the angiome will be a crucial determinant of outcomes of and treatment strategies for diseases, in particular anti-angiogenics for cancer therapy.

INTRODUCTION
Over the last three decades, much insight has been gained into the central role of the endothelium in health and in various diseases, and for which various assessment tools for assessing its function have emerged. Whether as a target (as in coronary artery disease and hypertension) or a facilitator of disease processes (eg, tumour growth and metastasis), endothelial activity is crucial to many if not all disease processes, and its assessment, directly or indirectly, is a valuable tool both in patient care and in clinical research.1–3 Broadly, ‘pathological’ endothelial processes either promote neovascular and neo-lymphatic formation (ie, angiogenesis, as in cancer and the synovium in rheumatoid arthritis) or restrict vessel growth (eg, endothelial damage, as is central to the pathophysiology of atherosclerosis). Current tools used to assess these activities may be classified into four broad classes: (1) those that examine circulating plasma markers, (2) others that measure cellular markers, (3) a third that focuses on growth factors, and (4) fourth, an array of imaging techniques (CT, MRI, ultrasound, etc) to more precisely view vascular supply to a tumour.4–5 Some methods are used to generate epidemiological and cell-physiology data on the role of the endothelium in large populations, but the importance of these tools in monitoring clinical disease progression and its treatment is slowly becoming accepted.

Therapies designed to modulate angiogenesis are an exciting new addition to the range of oncological drugs, and potential surrogate markers of its effectiveness, such as circulating endothelial cells (CECs) and plasma levels of angiogenic growth factors themselves, are the focus of a number of research studies.6–10 Unfortunately, clinical application of many of these cellular tests is limited by factors such as the lack of standardised methodology and concerns of sensitivity and specificity, although measurement of plasma markers, inevitably by ELISA, is more robust. Given the importance of the endothelium, much work is needed in improving current methods, but more importantly, no one tool on its own can provide a complete picture of the role of this organ in health and disease. In developing a concept of a more comprehensive view of vascular biology in cancer, we first review the current aspects of the endothelium and new blood-vessel formation (angiogenesis) in particular the tools used for their assessment. By identifying the limitations to these tests and prospective surrogates, we aim to provide insight into areas that would benefit from future studies. We will use these to introduce a new concept that advocates a multifactorial approach to its assessment specifically in cancer and demonstrate its importance as a crucial determinant of disease progression and treatment strategies. This concept we name the ‘angiome.’

VASCULAR BIOLOGY
The endothelium is the largest organ in the body and forms the intima of blood vessels. In the adult, it comprises 1.6×1015 cells, weighs approximately 1 kg and covers a surface area of approximately 4000–7000 m2.11 The endothelium has a number of functions in maintaining vascular haemostasis, vessel wall permeability, appropriate blood flow and lumen patency.11–12 Several of these are regulated through intricate paracrine, endocrine and autocrine activities of mediators (such as nitric oxide), and some are directly secreted by the endothelium. Shear stress, blood pressure and oxygen tension stimulate the release of endothelial derived vasoactive factors which regulate blood flow and organ perfusion, the mechanisms of which are yet to be fully elucidated.13–14 A healthy endothelium resists platelet adhesion and promotes fibrinolysis (so maintaining vessel patency), has antioxidant and anti-inflammatory properties, and inhibits leukocyte adhesion and migration, and smooth muscle proliferation and migration, all of which are important in vascular integrity (table 1).15–16

PLASMA MARKERS OF ENDOTHELIAL ACTIVITY/FUNCTION
Unfortunately, many potential markers (such as those listed in table 1) are difficult and expensive to measure, and/or are not specific for the endothelium. However, of those that are endothelial-specific and have acceptable assay characteristic, two are worthy of mention.17

E-selectin
Endothelial cell activation by inflammatory cytokines results in the increased expression of adhesion molecules such as E-selectin, intercellular adhesion molecule-1 and vascular endothelial growth factor-1,
although the latter are not specific for the endothelium.18–20 E-selectin (CD62E) is synthesised by endothelial cells in response to stimuli such as lipopolysaccharide, Interleukin 1 and tumour necrosis factor-z.20 Its ligands include several diverse and structurally distinct molecules on haematopoietic and neoplastic cells.21–23 Expression in postcapillary venules of skin, bronchi and bone implicates E-selectin in inflammation and metastasis of carcinomas.24 A soluble form of E-selectin (sE-selectin) can be detected in the plasma, with increased levels in various cancers,18–20 25 and which may have angiogenic activity.25 However, in a study of breast cancer, sE-selectin and inflammatory markers failed to correlate with tumour size, lymph-node involvement, response to chemotherapy or hormone therapy, and survival, although sE-selectin was higher in the presence of liver metastasis.26 In others, raised sE-selectin was associated with reduced tumoral angiogenesis (leading to the hypothesis that the shedding of sE-selectin may inhibit tumour progression), and sE-selectin failed to predict those women with breast cancer whose disease progressed, although elsewhere, levels did reflect invasive breast cancer.16 19 20 In renal cell carcinoma, levels of sE-selectin above median were associated with a poor prognosis.27

Von Willebrand factor

This high-molecular-weight multimeric endothelial product participates in haemostasis, is stored in Weibel–Palade bodies, and is released from the endothelium by a number of factors that include IL-1, tumour necrosis factor and hypoxia.30 31 The Von Willebrand factor (vWF) may have a role in tumour cell dissemination, as significantly higher levels have been reported in metastatic cancers.32–36 In addition, the release of thrombin by tumour cells may induce vWF production in endothelial cells and enhance the adhesion of tumour cells.37 vWF is also used histologically to define intra- and peritumoral microvessel density (MVD), and in this respect, a high vWF-positive microvessel number marks an unfavourable prognosis in patients with stage II and stage III colorectal cancer.38 A direct interaction between vWF and neoplastic cells has been demonstrated, while the expression of platelet surface glycoproteins GpIb and GpIIb–IIIa complex, some of the adhesive ligands for vWF, has been reported in tumour cells,37–39 which may contribute to the metastatic process by promoting the binding of tumour cells to platelets via plasma vWF. Moreover, such interaction results in heterotypic cell aggregates, which are not easily recognised by the immune system and are more capable of adhering to an endothelial surface than are single tumour cells.37–40 A positive correlation between Dukes’ stage and plasma vWF in patients with colorectal cancer was recently reported,39 although the relationship between vWF levels and survival in metastatic colorectal cancer remains unclear. The possibility that vWF may be influenced by inflammation,40 41 and that systemic inflammation is often present in cancer,42 43 further justifies interest in this molecule. Indeed, the evidence implicating raised vWF in thrombosis has helped fuel the argument of the development of a therapy that targets the interaction between vWF and platelets.44

**CELLULAR MARKERS**

At the end of their lifespan, mural endothelial cells are lost from the intima and can be found in plasma as CECs. These cells may be replaced from a pool of endothelial progenitor cells (EPCs), which can also be found in the plasma. Both CECs and (reparative) EPCs may be surrogates of vascular damage and repair.46

**CECs**

Endothelial-like cells in peripheral whole blood smears were first reported in the 1970s, although the true definition of CECs was established 20 years later by the presence of cell surface molecule CD146.47 48 More recently, several techniques have been developed to characterise and/or isolate these cells, and increased numbers, probably reflecting the extent of vascular insult, have been reported in a number of conditions including infectious and cardiovascular disease, inflammatory connective tissue disease and cancer.47–49 However, these reports are diverse in the conditions studied, and in the fine tuning of the methods of isolation and detection techniques employed, which impact markedly on CEC numbers. Recent strategies have increased the accuracy of detection by the use of more than one monoclonal antibody (eg, to CD133), lectins (eg, from Ulex Europeus) and the application of cell sorters.40–42 However, the small numbers of CECs contribute to poor inter- and intraobserver reproducibility and large coefficients of variation, so that the accurate detection of CECs remains a challenge.

**EPCs**

As EPC development has paralleled that of CECs, similarities are present, most notably the variety of technical methods. EPCs have been defined by diverse cell surface markers, and a further difficulty is the variety in descriptive terms given to these cells: are EPCs the same as circulating endothelial progenitors (tables 2, 3)? EC precursors were originally defined to be circulating vascular endothelial growth factor (VEGF) receptor 2-expressing (VEGFR2) cells mobilised from the bone marrow by VEGF.47 52 However, the co-expression of these factors by subsets of haemopoietic cells and mature ECs/CECs has led to much debate and difficulty in distinguishing EPCs from these subsets. This has led some to suggest that a spectrum of cells exists between an immature haemopoietic stage (EPCs being the intermediate stage) and the completely differentiated mature endothelial cell.53–56

The rationale for a role of the EPC in cancer must be put into context of the development of the vascular system whereby mesodermal precursors differentiate into vascular endothelial cells to form a primaryplexus of neovessels (ie, vascularogenesis). This process, thought to be restricted to embryological or prenatal stage of life, was challenged when CD34+ cells from peripheral blood, umbilical cord blood and bone marrow of in vitro and in vivo mice models differentiated into endothelial and blood vessels.57

### Table 1 Substances produced by endothelial cells

<table>
<thead>
<tr>
<th>Substance</th>
<th>Activities</th>
</tr>
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<tbody>
<tr>
<td>Prostacyclin</td>
<td>Vasodilatation; inhibits platelet aggregation</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>Vasodilatation; inhibits platelet adhesion and aggregation</td>
</tr>
<tr>
<td>Tissue plasminogen activator</td>
<td>Promotes fibrinolysis</td>
</tr>
<tr>
<td>Thrombomodulin</td>
<td>Anticoagulant activity</td>
</tr>
<tr>
<td>Thromboplatin</td>
<td>Promotes blood coagulation</td>
</tr>
<tr>
<td>Platelet-activating factor</td>
<td>Activation of platelets and neutrophils</td>
</tr>
<tr>
<td>Von Willebrand factor</td>
<td>Promotes platelet adhesion and activation of blood coagulation</td>
</tr>
<tr>
<td>Tissue factor</td>
<td>Promotes coagulation</td>
</tr>
<tr>
<td>Plasminogen-activator inhibitor</td>
<td>Inhibits fibrinolysis</td>
</tr>
</tbody>
</table>
studies showed the process of incorporating bone marrow-derived cells to occur in blood vessels of tumours, healing wounds, myocardial infarcts and those denuded of endothelium, justifying EPCs as possible contributors to angiogenesis and thus tumour vascularisation. Despite this high level of scientific enquiry, the general area of CEC and EPC research suffers from the lack of consensus as to the defining characteristics of these cells (tables 2, 3).

GROWTH FACTORS
The importance of soluble factors (such as growth factors) originating from tumours and other cells, with the ability to promote cell growth and angiogenesis, has long been recognised and is now an established feature of cancer research. Principal among these growth factors are VEGF, placental growth factor, angiopoietin and fibroblast growth factor, raised plasma levels of which have been described in numerous neoplasia and that may also mark metastatic development. Notably, several of these growth factors have also been shown to have an intimate association with EPCs, leading to the hypothesis that upregulation of growth factors mobilising these cells from the bone marrow, which then home to developing vessels and so promote vascularisation, has been taken to imply participation in (and possible regulation of) tumour development and satisfies long-held and current hypotheses on tumour biology. A corollary of the hypothesis that overproduction or hyper-responsiveness to growth factors is a major factor in oncology has led to clinical strategies to suppress this process. Indeed, following informative in vitro and animal models, several strategies for the inhibition of the release of growth factors, and their attachment to their receptors, have been developed with the objective of diagnosing, stratifying and treating human cancer, and other vasculo-proliferative conditions such as diabetic retinopathy, macular degeneration and proliferative nephropathy.

### Table 2 Cell-surface molecules of interest in the study of endothelial progenitor cells

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Function/synonym/distribution</th>
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<tbody>
<tr>
<td>CD14</td>
<td>Receptor/signalling. LPS receptor, monocytes, macrophages and neutrophils</td>
</tr>
<tr>
<td>CD31</td>
<td>Adhesion. PECAM-1, very widely distributed</td>
</tr>
<tr>
<td>CD34</td>
<td>Adhesion (precise function unclear), present on leucocytes at various stages of differentiation, especially haemopoietic or endothelial progenitors; also on numerous neoplastic cells</td>
</tr>
<tr>
<td>CD45</td>
<td>Signalling, leucocyte common antigen, present on ‘mature’ and neoplastic leucocytes</td>
</tr>
<tr>
<td>CD69E</td>
<td>Adhesion; E-selectin, endothelial cells</td>
</tr>
<tr>
<td>CD105</td>
<td>Signalling, TGF-β receptors, endothelial cells, activated monocytes, pre-B lymphocytes</td>
</tr>
<tr>
<td>CD133</td>
<td>Unclear, promin-1, heamopoietic stem cells, endothelial progenitor cells, some neuronal cells</td>
</tr>
<tr>
<td>CD144</td>
<td>Adhesion and signalling. VE-Cadherin, endothelial cells</td>
</tr>
<tr>
<td>CD146</td>
<td>Adhesion, Mel-CAM/MUC-18, mature endothelial cells, T lymphocytes, some neoplastic cells</td>
</tr>
<tr>
<td>CD202b</td>
<td>Signalling, Tie-2 (angiopoietin receptor), endothelial cells</td>
</tr>
<tr>
<td>CD309</td>
<td>Signalling, VEGFR2/KDR/Fk-1, endothelial cells</td>
</tr>
</tbody>
</table>

### Table 3 Endothelial progenitor cell pseudonyms

<table>
<thead>
<tr>
<th>Name of cell</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angioblast</td>
<td>—</td>
</tr>
<tr>
<td>Blood outgrowth endothelial cell</td>
<td>BOEC</td>
</tr>
<tr>
<td>Circulating angioblast</td>
<td>CAC</td>
</tr>
<tr>
<td>Circulating angiogenic cell</td>
<td>CEC</td>
</tr>
<tr>
<td>Circulating endothelial cell</td>
<td>CEC</td>
</tr>
<tr>
<td>Circulating endothelial progenitor cell</td>
<td>CEC</td>
</tr>
<tr>
<td>Endothelial cell colony-forming unit</td>
<td>CFU-EC</td>
</tr>
<tr>
<td>Culture-modified mononuclear cells</td>
<td>CMMC</td>
</tr>
<tr>
<td>Circulating progenitor cell</td>
<td>CPC</td>
</tr>
<tr>
<td>Endothelial cell</td>
<td>EC</td>
</tr>
<tr>
<td>Endothelial-like cell</td>
<td>ELC</td>
</tr>
<tr>
<td>Endothelial colony-forming cell</td>
<td>ECFC</td>
</tr>
<tr>
<td>Endothelial progenitor cell</td>
<td>EPC</td>
</tr>
<tr>
<td>Endothelial outgrowth cell</td>
<td>EOC</td>
</tr>
<tr>
<td>Haemopoietic precursor cell</td>
<td>HPC</td>
</tr>
<tr>
<td>Haemopoietic stem cell</td>
<td>HSC</td>
</tr>
<tr>
<td>Multipotent adult progenitor cell</td>
<td>MAPC</td>
</tr>
</tbody>
</table>

The problem facing vascular biologists is the extent to which their colleagues are using different names to describe the same cell, and vice versa.

**PHYSIOLOGY OF BLOOD FLOW**

Central to the general hypothesis of tumour growth and metastatic potential is an appropriate blood supply. It follows that detailed study of the vasculature local to the tumour may be profitable in searching for strategies to assess angiogenesis.

**Flow-mediated dilatation**

In health, a temporary restriction to arterial blood flow (such as of the brachial artery), followed by release, causes a temporary increase in blood flow down that artery. A normal endothelium will respond to this increased blood flow by releasing mediators such as nitric oxide that dilate the artery, facilitating more extensive blood flow. Failure of a downstream artery to dilate in this manner is taken to imply endothelial dysfunction. This physiological vascular response, assessable in the laboratory by ultrasound scanning, is called flow-mediated dilatation (FMD). The technique probably represents the gold standard for clinical research on conduit artery endothelial biology, but practical challenges to its suitability for use include the need for highly trained operators, the expense of the equipment and also the care required to minimise the effect of environmental or physiological influences, such as exercise, eating, caffeine ingestion and variations in temperature. Although pioneered in cardiovascular disease, it is becoming used in cancer, where it can assess vascular responses to chemotheraphy.

**Pulse-wave analysis and velocity**

Analyses allied to FMD include pulse-wave analysis, pulse-wave velocity, reactive hyperaemia and digital pulse amplitude tonometry. These methods have been validated as measures of nitric oxide bioavailability and have been shown to change with exposure to risk factors and with atherosclerotic disease, and may complement FMD testing. The relative contribution of structural alterations in the vessel wall and endothelial dependent biology remains uncertain. Reproducibility in different age groups and stages of disease, as well as clarification of their relationships with other established measures of endothelial function, is needed. An allied technique assesses arterial stiffness, changes in which can be measured with pulse-wave analysis by radial artery tonometry or pulse contour analysis by digital photoplethysmography.

**Other imaging**

The relationship between angiogenesis, tumour growth and metastasis in addition to monitoring of the tumours treatment can be imaged non-invasively with a number of more complex techniques: x-rays, CT, MRI, positron emission tomography, single photon tomography, ultrasound and near-infrared optical imaging. While several imaging techniques are able to assess the angiogenic status of tumours, both CT and MRI have the advantage of good spatial resolution.
often equal to that of the corresponding morphological features and, when combined with contrast media, give important features of the microcirculation. These techniques, being quick and minimally invasive, and involving little patient risk, mean that they can be incorporated into routine patient studies with a view to assessing angiogenesis, even at the level of the individual patient.

**SUMMARY OF VASCULAR FUNCTION**

We have noted different aspects of vascular function (box 1). The most specific and potentially useful plasma markers are vWf and sE-selectin, while CECs and EPCs seem likely to inform, respectively, on damage to, and repair of, the intimal monolayer. Interest in growth factors such as VEGF follows from their role as mediators of angiogenesis, while advances in imaging allow a more direct view, and assessment of, the physiology and pathology of blood vessels. Once excised, the general vascularity to a tumour, and possibly its own localised microcirculation, can be assessed by counting the number of microvessels, hence MVD. Although seemingly independent, there are several examples in cancer research of overlaps between these areas, but few where several have been evaluated at the same time, and none where all four are co-examined.

**ANGIOME**

Given the above observations, there would seem to be ample justification for assuming that the vascular infrastructure of a tumour is worthy of further study. Indeed, we hypothesise that a more comprehensive study of the endothelium will bring benefits in terms of basic cancer biology and in clinical oncology. Many of the features we have noted are already present in a wide range of cancers, including ovarian cancer, which we can take as a model. Raised levels of plasma vWf and soluble E-selectin, and vWf-defined microvessels are present, while VEGF and its receptor, and other growth factors have been studied.

Increased angiogenesis (defined by vWf-microvessel counts or CD31) confers a disadvantage and anti-VEGF therapy that reduces MVD has been reported. Furthermore, there is an established cancer marker (CA-125) and several imaging studies using different technologies have been reported.

Ideally, the (non-invasive and non-surgery/biopsy requiring) latter will replace historical MVD counting of excited tumours as a method for assessing ‘real time’ angiogenesis in an individual patient. Su et al. recently reported raised EPCs in ovarian cancer that correlated with VEGF, and antiangiogenic therapy has been attempted.

There are many putative components of the oncogenic vasculature with both stromal and tumour interaction. Collectively, these components might be best viewed and studied as the ‘angiome’. We contend that the angiome represents the true in vivo status of a tumour in an individual, and that this status can be assessed by a combination of a plasma marker of the endothelium (vWf, sE-selectin), plasma levels of a growth factor (VEGF, FGF, PlGF), an imaging-based assessment of angiogenesis (ultrasound, MRI, CT, PET) and an assessment of CECs and/or EPCs (box 1).

**CONCLUSIONS**

Given that angiogenesis is critical to tumour growth and metastasis, its assessment is crucial to prognostic predictions, and new methods are demanded. The demonstration that neutralising anti-VEGF antibodies are efficacious in prolonging survival in metastatic colon and renal cancer has been the tour de force of antiangiogenic drug development and so may be seen as a justification for a wider view of the endothelium in cancer biology.

We have outlined a number of techniques in clinical practice used to assess angiogenesis which include circulating plasma factors, radiological imaging techniques, immunohistochemistry of tumour specimens and circulating endothelial cells. Together we describe these as the angiome.

While the concept of the multifactorial assessment model of endothelial activity and angiogenesis is not new, studies in cancer that have taken a more global approach to this assessment are lacking. Though the fundamental limitation to some tests (eg, for CEC and EPC enumeration) is a lack of standardisation (tables 2, 3), a number of studies have primarily used cellular and plasma treatment. The vascular view of this tumour model certainly appears to lend support to observations made over the last two decades with regard to surgery and chemotherapy interactions.

These concepts lead to a generic hypothesis, that is, that the angiogenic state of a tumour is a fundamental biological characteristic, and also to several subhypotheses. One may speculate that tumours demonstrate a spectrum of angiogenic activity, that a positive angiomic (A+) state equates to a well-vascularised, well-oxygenated tumour, while a negative angiomic (A−) state equates to a poorly vascularised hypoxic tumour. It follows that A+ tumours have a high growth potential but high chemosensitivity, while A− tumours have a low growth potential and increased tendency to develop chemoresistance. It is also possible that surgery might alter angiogenic status. These hypotheses in turn generate some fairly essential basic questions: What are the relative components of the angiome for a specific tumour type? Is the angiome generic or specific to tumour type (and stage)? How might one define a positive and negative angiome? How does it alter with time and/or interventions? And, crucially, does it predict outcome and/or response?

**Box 1 Aspects of vascular biology**

- Plasma markers
  - Soluble E-selectin
  - Von Willebrand factor
- Circulating endothelioid cells
- Circulating endothelial cells
- Endothelial progenitor cells
- Physiological blood-vessel responses
  - Flow-mediated dilatation
  - Arterial stiffness, pulse wave analysis and velocity
- Angiogenic growth factors
  - Vascular endothelial growth factor
  - Basic fibroblast growth factor
  - Angiopoietins
- Excised tumours
  - Microvessel density

**POTENTIAL CLINICAL VALUE OF THE ANGIOME**

The eventual goal would, of course, be to manipulate the angiome with therapeutic intent, so that drugs which target and inhibit angiogenesis might be seen to inhibit growth. Conversely, they may also lead to hypoxia and development of drug resistance. Agents that promote tumour angiogenesis paradoxically may allow greater penetration of cytotoxic agents, improved oxygenation and increased vulnerability to cytotoxic cell kill. Viewed simplistically, one could argue that optimal surgical cytoreduction removes hypoxic and hypovascular tumour, and the remaining ‘microscopic’ disease (well served by the tumour microvasculature) is sensitive to adjuvant
markers to reflect endothelial activity in the presence of various cancers. Indeed, a strength of our hypothesis is the increasingly frequent publication of what we consider ‘preangiome’ data—that is, those that use a panel of different markers of the endothelium. For example, Willett et al. used blood flow, MVD, CECs and plasma VEGF to assess outcome following anti-VEGF therapy; Yu et al. co-measured EPCs and VEGF in hepatocellular cancer; Norden-Zfoni et al. looked at VEGF, its soluble receptor and mature CECs in gastrointestinal cancer; while Fischer et al. focused on histology, EPCs and VEGF in small-cell lung cancer. This underlines a multiparametric assessment of vascular biology involving histological, circulating and imaging markers in monitoring the effects of an antiangiogenic agent prior to the appearance of overt changes in tumour size.

As our understanding of endothelial activity and angiogenesis continues to evolve, such as in the in vitro and animal data suggesting that vWF is directly involved in angiogenesis, newer therapies will emerge and are likely to require more accurate assessment tools. There is a number of limitations to current assessors, the most notable being a lack of standardised methodology. While a number of newer tools are emerging, what is clear is that further studies towards improving the accuracy of current tests of endothelial function and angiogenesis are required for translation to clinical application. Furthermore, larger disease-specific studies with more stringent exclusion criteria will be necessary. Most notably, the benefits seen from recent clinical data on the efficacy of anti-VEGF therapy for metastatic cancer will continue to drive research into other modulators of angiogenesis. With the expected rise in clinically validated angiogenic modifiers, the demand for better surrogate markers, rather than the maximum tolerated dose to optimise drug doses and schedules, may also increase. To date, despite newer technologies, no single marker fulfils this requirement, but recent reports advocate the use of circulating cellular markers (CECs, EPCs), despite limitations of (in)accurate enumeration. However, the importance of the multiparametric assessment strategy of the effects of antiangiogenic agent (including histological, circulating and imaging markers) is that it ‘predicts’ the tumour’s response. Nevertheless, it is expected that as newer treatments to target angiogenesis emerge, more accurate measures of endothelial activity will be crucial to disease staging and, more importantly, will influence and monitor treatment strategies in the future.

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**REFERENCES**


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