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News

Cutting off cancer's supply lines

Targeting the blood vessels that feed tumours is not the silver bullet once hoped for, but refinements to the strategy may suggest further ways to treat the disease. Erika Check Hayden reports.

Erika Check Hayden

Drugs that aim to choke off a tumour's blood supply, known as angiogenesis inhibitors, have been hailed as opening a new era in cancer therapy. But a flurry of animal studies suggests that such drugs may in certain situations actually accelerate the spread of cancer.

"We're just finding the limitations of these types of agents in the clinic," says John Ebos, a cancer researcher at the University of Toronto, Canada. "I don't think it's unique — various types of therapies, such as chemotherapy and radiation, also have limitations. It's just a question of how we can overcome it."



Network of blood vessels surrounding a tumour — a potential target for therapy.

CLOUDS HILL IMAGING LTD/SPL

This is a key time in the long and controversial history of these drugs. In May, the US Food and Drug Administration (FDA) is expected to decide whether to expand use of bevacizumab, the first angiogenesis inhibitor. This monoclonal antibody, sold as Avastin by South San Francisco-based Genentech, was approved in 2004 for treating metastatic colon cancer in combination with chemotherapy. It has since been approved in the United States and elsewhere for other uses, and on 31 March an FDA advisory committee recommended the drug also be approved for glioblastoma, a deadly brain cancer for which few other treatments are available. The agency's decision is expected in May.

"I think there's been that growing feeling of why aren't they working better, and we're now uncovering some explanations."

According to regulatory papers filed in January, Genentech may before then reveal results of a clinical trial to test the use of bevacizumab as an 'adjuvant' used with chemotherapy in patients whose colon tumours have been surgically removed. The 2,710-patient phase III trial investigated whether those who take bevacizumab are more likely to survive without recurrence of their disease than patients who do not take the drug.

"There are tens of thousands of patients with early colorectal cancer who don't get Avastin right now," says Geoffrey Porges, an analyst with Sanford C. Bernstein in New York City. Success as an adjuvant therapy "would open up a market at least as large as the current metastatic market", he thinks, noting that trials testing the drug as an adjuvant for other cancers are under way. Last year, the drug racked up \$4.8 billion worldwide in sales; its wholesale price is about \$50,000 per year of treatment.

The original idea behind bevacizumab and other angiogenesis inhibitors was championed by Judah Folkman of Harvard Medical School. In 1971, Folkman wrote in the *New England Journal of Medicine*¹ that all tumours depend on the constant growth of new blood vessels, a process called angiogenesis, and that blocking it should eliminate the cancer. The popularity of the idea waned in the early 2000s following disappointing results in clinical trials of two anti-angiogenic compounds,

angiostatin and endostatin, that were discovered in Folkman's lab. It regained ground when bevacizumab was approved.

Since 2004, two other angiogenesis inhibitors have been approved in major markets worldwide: sunitinib, sold as Sutent by Pfizer, for use in advanced kidney cancer and gastrointestinal stromal tumours, and sorafenib, sold as Nexavar by Bayer, for use in kidney and liver cancer. Both are small-molecule drugs that target kinases, in particular vascular endothelial growth factor, or VEGF, which is also targeted by bevacizumab. Many more such compounds are in late-stage clinical trials (see [table](#)).

ANGIOGENESIS INHIBITORS IN LATE-STAGE CLINICAL DEVELOPMENT*

Drug	Maker	Being tested in which cancers
Bevacizumab (Avastin)	Genentech	Kidney, ovarian, brain, prostate, liver, pancreas, lymphoma, gastric, gastro-oesophageal
Sunitinib (Sutent)	Pfizer	Breast, kidney, liver, lung
Sorafenib (Nexavar)	Bayer	Lung, melanoma, pancreas
Pazopanib	GlaxoSmithKline	Kidney, soft-tissue sarcoma, lung, ovarian
Axitinib	Pfizer	Kidney (pancreas suspended)
XL647	Exelixis	Metastatic thyroid cancer
BIBF1120	Bioscience Resource	Lung, gallbladder
Cediranib (Bectin)	AstraZeneca	Colorectal, brain, ovarian
Aflibercept (VEGF trap)	Regeneron, Sanofi-Aventis	Lung, prostate, pancreatic, colorectal
Briwanib	Bristol-Myers Squibb	Liver, colorectal
Vandetanib (Zactima)	AstraZeneca	Lung

*Phase III trials that target the VEGF pathway.
 Drugs shown in colour are already FDA approved for some cancers; see text for details.

[Click for larger image.](#)

But these drugs have not been the magic bullet that Folkman envisaged. In major cancers, such as breast and colon, they have helped patients to survive longer when given with chemotherapy, but not when given alone. The drugs seem to grant most patients slower progression and a few extra months of survival — a real benefit, but not a cure.

The tumours fight back

That has led researchers to ask whether the drugs are working as Folkman hypothesized. Some, such as Rakesh Jain of the Massachusetts General Hospital in Boston, have suggested that the drugs "normalize" blood-vessel growth around tumours. Cancer blood vessels are normally leaky and chaotic; by correcting this, angiogenesis inhibitors may turn the vessels into a more efficient pipeline for delivering chemotherapy, Jain suggests.

Some physicians who treat patients with cancer have also noticed that when the disease does return after treatment aimed at angiogenesis, it is more aggressive than in patients not treated with the drugs. Other researchers now have evidence that may validate this observation. In mouse studies [\(bibr id='b2 b3'/>](#), researchers have reported that the drugs can speed the spread of tumours to nearby tissues and distant organs.

Reporting recently in *Cancer Cell*, two teams investigated the effects of angiogenesis-inhibiting drugs and of knocking out the gene encoding VEGF. One team, led by Douglas Hanahan of the University of California, San Francisco, and Oriol Casanovas of the Catalan Institute of Oncology in Barcelona, Spain, reported that tumours spread faster and more often to both near and distant organs in mice treated with drugs or lacking the *VEGF* gene². The other group, led by Robert Kerbel of the University of Toronto, reported similar effects³, and found that in some situations the treated mice actually died earlier than untreated animals.

Kerbel's group further studied how metastasis changed depending on when the drugs were given. When given either before or long after metastatic tumour cells were injected into the mice, or after primary tumours had been surgically removed, the drugs hastened metastasis. But when given while the mice were still carrying primary tumours — those that had yet to metastasize — the drugs actually helped shrink the tumours. If the data hold true in humans, they suggest that the timing of drug delivery can have a major impact on a patient's response.

“What they're

A third paper⁴, published online in *Nature Medicine* on 22 March, suggested

telling us is that there are other targets that need to be considered if you're going to mess with the blood supply."

that such effects might also occur for a class of drugs called integrin inhibitors. These block the activity of integrins, which are proteins that trigger angiogenesis, among other things. Researchers led by Kairbaan Hodivala-Dilke at Queen Mary, University of London, studied the effects of two integrin inhibitors, one of which, cilengitide, is in phase III clinical trial to treat brain cancer. They found that, when given in low doses in mice, the drugs paradoxically seemed to promote angiogenesis and tumour growth.

Ebos, the first author on the Kerbel-group paper, says that, taken together, these studies don't mean anti-angiogenesis drugs are a disappointment, simply that they have limitations. "I think there's been that growing feeling of why aren't they working better, and I think we're now uncovering some of the explanations," he says.

For instance, Hanahan and Casanovas's team studied whether choking off some blood vessels, and thereby inducing oxygen deprivation (hypoxia), might be driving the tumours to search elsewhere for sustenance. When they stained cancer cells in mice with a marker for hypoxia, it showed up in the cancer cells of animals treated with angiogenesis inhibitors.

The oxygen connection

To Casanovas, this provides a link to earlier studies indicating that hypoxia can boost tumour invasiveness, and shows that the lack of oxygen caused by angiogenesis inhibitors actually induces cancerous cells to leave the tumour site in search of it. Casanovas says that his and Kerbel's teams have together found enough evidence to suggest that such effects probably occur with many angiogenesis inhibitors in many different tumour types. "Between us, we have tested five different compounds, including small molecules and antibodies, so we think the effect could be more general than strictly what we've seen in these two papers, and the same thing applies for different types of tumours," Casanovas says.

Donald McDonald, a vascular biologist at the University of California, San Francisco, suggests that the new studies are delivering a broader message. "What they're telling us is that there are other targets [in addition to VEGF] that need to be considered if you're going to mess with the blood supply." Drug companies are already developing compounds that may address some of the problems raised by the papers.

McDonald notes that researchers six years ago reported⁵ that hypoxic cancer cells ramped up production of a protein called Met, which binds and activates another protein called hepatocyte growth factor. This growth factor also goes by the name of scatter factor because it triggers cells to move — precisely the effect seen in the *Cancer Cell* papers. Administered with anti-angiogenesis drugs; Met inhibitors — the focus of development by drug and biotechnology companies — might offset the effects reported in the *Cancer Cell* papers, McDonald suggests.

And Hodivala-Dilke's team noted that simply using some drugs differently might improve their effectiveness. Clinical trials of cilengitide have delivered mixed results so far, and the team says its study points to a possible reason for this. They found that integrin inhibitors slowed the degradation of proteins that promote angiogenesis. These longer-lived proteins then recruited cells that make up blood-vessel walls to the tumour site, where they built new blood pipelines to the tumour. Because the effect occurred only at very low doses, the team suggests that the drugs should be delivered continuously, rather than at a high dose followed by drug-free days, as was done in the clinical trials. That way, levels would stay above those that seemed to promote angiogenesis in the study.

Porges says that the new studies have not dampened enthusiasm among drug companies who are developing angiogenesis inhibitors, integrin inhibitors and inhibitors of other growth factors thought to be involved in cancer. They expect that eventually patients will be given combinations of inhibitor: with or without chemotherapy.

Because of this, McDonald says that the angiogenesis-inhibitor story is far from over. "We have learned that what these drugs do is more complicated than the original idea, which was that they would stop tumour growth by stopping blood-vessel growth," he says. "Avastin is chapter one of angiogenesis inhibition, and we're going to move on to chapter two and chapter three. And with each chapter there will be more clinical benefit as we get a better understanding of the underlying biology." ■

See Editorial, [page 679](#).

CORRECTED: This article, and the table accompanying it, should have said that Nexavar (sorafenib) is co-developed worldwide by Bayer and Onyx Pharmaceuticals.

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#69

Based on the progress made so far it is hoped that the scourge of cancer if not totally eradicated will surely be taken control of in a few decades from now. While certainly, much progress (pertaining to several types of cancers) has been made so far, yet much still remains to be done in this discipline. Moreover, rapid advancements in gene related technologies have improved our understanding of the causes of cancer at the foundational level and also to some degree in totality. Though much progress has been made, yet in general by large the traditional approach of scientists in the study of cancer reminds one of: It was six men of Indostan, learning much inclined, Who went to see the elephant, (Though all of them were blind), That each by observation Might satisfy his mind. The first approached the elephant, And happening to fall Against his broad and sturdy side, At once began to bawl: "God bless me! But the elephant Is very like a wall!" The second, feeling of the tusk, Cried: "Ho! What have we here, So very round and smooth and sharp? To me 'tis very clear, This wonder of an elephant Is very like a spear!" The third approached the animal, And happening to take The squirming trunk within his hands, Thus boldly up and spake: "I see," quoth he, "the elephant Is very like a snake!" The fourth reached out an eager hand, And felt about the knee. "What most this wondrous beast is lik

 Is might plain," quoth he; "Tis clear enough the elephant Is very like a tree." The fifth, who chanced to touch t ear, Said: "E'en the blindest man Can tell what this resembles most: Deny the fact who can, This marvel of an elephant Is very like a fan." The sixth no sooner had begun About the beast to grope, Than seizing on the swinging tail That fell within his scope, "I see," quoth he, "the elephant Is very like a rope." And so these men Indostan Disputed loud and long, Each in his own opinion Exceeding stiff and strong. Though each was partly right, All were in the wrong.

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Posted by: **Upinder Fotadar** | 2009-04-08 06:42:57 I



#69

Dear Sir/Madame: Despite its pitfalls, inhibiting angiogenesis doubtlessly possesses great potential to shrink the bulk of the tumor in glioblastoma multiforme and constitutes an option for therapy worthwhile pursuing. However, the method remains symptomatic treatment. This horrible disease will only be beat, once the molecular signaling mechanisms are understood that induce astrocytes and microglia to divide. I have writter about glioblastoma in more detail here: <http://brainmindinst.blogspot.com/2008/06/glioblastoma-multiforme-octopus-in.html>

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Posted by: **Peter Melzer** | 2009-04-11 10:24:59 I



#70

This report neglect to mention our previous observation, published in 2007 (Cervi et al, Blood, 109(5):2139-46), in which we demonstrated inhibition of leukemogenesis in a transgenic mouse model overexpressing VEGF. In this paper we have shown that, if VEGF overexpression was induced before tumor initiation, VEGF alters microenvironment resulting in the inhibition of cancer progression. I believe this is the first evidence to suggest a negative role for VEGF in tumor progression. Unfortunately, none of the recent papers demonstrati similar results were sited our publication.

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Posted by: **Yaacov Ben-David** | 2009-04-17 03:31:43 I



#159:

When you get rid of VEGF with Avastin, the body cranks out other types of blood vessel growth/survival facto

The problem with Avastin is the same thing that was a problem with AZT for HIV/AIDS. Early results, then rapid resistance. Solution was combination therapy to attack different targets. With cancer, it's going to take combination antivasular therapy to make a difference.


Tumor vasculature needs VEGF to survive. Avastin removes VEGF, killing blood vessels. But other proangiogenic factors can substitute: FGF, PDGF, ephrin A1, angioprotein 1, IL-8 etc. We need to attack these other targets, as well.

If you can achieve this, then you may not even need the other drugs, which don't get into the tumor so well. B angiogenic attack provides true selective toxicity, something which is sorely lacking with all of the other treatments.

Perhaps Avastin "sensitive" tumors secrete relatively low levels of VEGF. Tumors which secrete relatively low levels of VEGF might be more susceptible to an agent which works by blocking VEGF.

While vasculogenic mimicry – some types of cancers form channels that carry blood, but are not actual blood vessels – with co-option, instead of growing new blood vessels, tumor cells can just grow along existing blood vessels. This process cannot be stopped with drugs that inhibit new blood vessel formation.



 The consistent and specific cure or control of cancer will require developing and using a set of drugs, given in combination, targeted to patterns of normal cellular machinery related to proliferation and invasiveness.

A sufficient number of independent methods of cell killing must be employed so that it is too improbable for a cancer cell to evolve that can escape death or inactivation. It must examine every cell in the body and must do so for a prolonged period of time.

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Posted by: **Gregory Pawelski** | 2010-11-23 11:17:45 A

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