Reductionist's Reticent Rhetoric

Alas, a Vast Morass, Avastin

by Jim Duke, PhD

James Duke received his PhD in Botany from the University of North Carolina, moving on to postdoctoral studies at Washington University and the Missouri Botanical Garden where he assumed professor and curator duties, respectively. Dr. Duke spends a signficant amount of his time exploring the ecology and culture of the Amazonian Rain Forest. In addition to a distinguished 30-year career with the United States Department of Agriculture, Dr. Duke sits on the board of directors and advisory councils of numerous organizations involved in plant medicine and the rainforest. He is also an accomplished musician, poet, and songwriter.

On Feb 26/27/2004 the TV was promoting the vastly overrated newly approved colon-cancer drug Avastin. The breaking news stirred up my counterreductionist's feelings and sent me surfing the vast outback of PubMed abstracts for information on Avastin. Since it sounded like the TV announcer was hinting that it might be an antiangiogenic compound, I first did a search for Avastin AND Angiogenesis. The news implied that this was the first antiangiogenic drug approved after a long search, involving many dead ends. It is!

How well I remember my visit with Dr. Jude Volkman at Boston Children's Hospital about a decade ago. He had a huge incubator with hundreds of petri dishes, each with a pulsating chicken egg splayed out in the dish, with radiating blood vessels. He was studying angiogenesis and its inhibition, not only for cancer but also for pediatric hemangiomas. By dropping in a potential antiangiogenic compound, he could readily measure inhibition of angiogenesis. It was he who first told me of the antiangiogenic activity of Thalidomide, formerly *public enemy numero uno*, and of the more acceptable genistein, which my associates and I have now identified in significant quantities in 75 types of beans including Native American black beans, kidney beans, lima beans, pinto beans and the Oriental soybean and kudzu. While there is no proof of *in vivo* activity, epidemiological data advancing the case of genistein in soybeans should be applicable to equal amounts of genistein in other legumes, other things being equal. If they praise soy for preventing hormone-dependent cancers, maybe the praise should be spread across all the equally rich legume sources (most of which also contain anticancer phytates, phytosterols, other estrogenic isoflavones, and Bowman-Birk Inhibitors. Peanuts even contain a little resveratrol. I was visiting Dr Volkman at the expense of a patron who suffered prostatic cancer and who was funding research on antiangiogenics and potential antimetastatics. Genistein looked good to bean-loving Jim Duke, (being genetically targeted for colon cancer by family history)

Avastin is, as the news today suggested, also an antiangiogenic compound. Avastin is described as a Vascular Endothelial Growth Factor (VEGF) inhibitor, a special type of angiogenesis inhibitor. I then did a search for VEGF AND genistein and, even more amusing to me, found many more titles and abstracts. So I reckoned my reductionistic searching would yield a bigger field if I went for VEGF-inhibitor, one type of angiogenesis-inhibitor. I went to my database, to see which plants or phytochemicals I had scored as VEGF-Inhibitors. Only 4 (boswellic acid, EPA, genistein and selenium) were in my limited database near the end of 2003; I'll wager I could come up with dozens more today with a focused search, but then I would have another Rhetorical Reductionistic Review in the making. All were previously discussed in John Boik's work (2001). Boik offered an entire chapter on angiogenesis, a process

"With nutritional genomics, proteomics, and metabolomics, scientists are able to simultaneously elucidate the biological effects of dietary constituents on cell function and global gene expression."

Go B & Wong 2003, Diet, nutrition, and cancer prevention: the postgenomic era *J Nutr.* **133(11 Suppl 1):3830S-3836S**

which is good when you want a wound to heal, but bad when you don't want a cancer to metastasize. Then he had another chapter on natural inhibitors of angiogenesis. "Metastasis will not happen until angiogenesis has occurred" (Boik 2001). VEGF is produced when tissue oxygen is low (local hypoxia), characteristic of the central region of solid tumors. Several other growth factors stimulate angiogenesis, and yet other variables including cytokines can also inhibit angiogenesis So there are several reductionistic targets for the Avastin mimics and next year's competitors, another vegetable soup of atavistic acronyms.

So Anti-EGF, Anti-PDGF, Anti TGF-beta, and/or AntiTNF activity = AntiVEGF activity = Decreased Vascular Permeability = Antiangiogenic activity = Antimetastatic activity = Increased Cancer Survival. Adding a few more acronyms, Boik suggests there may be synergy between protein kinase C (PKC-) and protein tyrosine kinase (PTK-) inhibitors as VEGF inhibitors, making their combination potentially more powerful. PKC-Inhibitors (e.g. procyanidins, verbascosides, yuanhuacine) may reduce angiogenesis by lowering or inhibiting collagenase. The collagenase enzymes (and matrix metalloproteinases or MMPs) are also involved in metastasis by degrading the extracellular matrix. Boik speculates that saponin containing herbs (*Aesculus; Centella*, *Ruscus*, none normally considered foods) and common food phytochemicals like anthocyanidins and proanthocyanidins, noted for inhibiting vascular permeability, may selectively be added to my soup, as they too make their contribution to antiangiogenesis. Then Boik suggests that COX-2-Inhibitors and lipoxygenase inhibitors and NF- kB-inhibitors might also contribute to antiangiogenesis. That makes my 5-year old Cox-2-Inhibitade also look good for antiangiogenesis. I invented that when I first predicted that Celebrex or Vioxx would be recalled within a decade. It may probably be several years before the pharmacophiles will conjure up an expensive synergistic synthetic antiangiogenic cocktail of a dozen different synthetic compounds inhibiting one or the other at slightly different levels slowing metastasis. I could probably conjure up an inexpensive alphabet vegetable soup rich in a dozen or so natural inhibitors of VEGF which I think may have more promise of extending the life of a colon cancer patient (maybe even me one of these days), as Avastin alone or in synergy with other expensive pharmaceuticals. I may be wrong, but we'll never know until we clinically compare them. That may never happen. What a hypothetical headline!: "Heads-on on Clinical Trial between $10,000 Drug Avastin and $1 Alphabet Soup for the Prevention of Metastasis of Colon Cancer."

Meanwhile those colon cancer patients who can't wait for them to develop the pharmaceuticals they cannot afford might want to give the soup a try: All food plants!

Relax first with deep breathing and a cup of green tea for its antiangiogenic activity, sweetened with licorice for its antiangiogenic phytochemical (isoliquiritin). I suppose we better pass on ephedra which only recently

Avastin Factoid

Bevacizumab (Avastin: Genetech Inc, CA) is a humanized recombinant monoclonal antibody to vascular endothelial growth factor, which is a major regulator of angiogenesis and hence target for antimetastatic drug therapy. Like the many dozens of investigational antiangiogenic agents currently in phase 1 and II testing, Avastin initially had very disappointing results in clinical trials. In February 2004 it was suddenly given "fast-track" approval by the FDA for treatment of metastatic colorectal cancer when coadministered with IFL (ironotecan, 5-FU and leucovorin aka the Salz regime). This approval was granted on the basis of a single unpublished clinical trial by Genetech on 800 patients. No peer review or expert critique of the data was available prior to the licensing by the FDA. In fact the drug combination did not lead to remission or cure, but apparently it extended life expectancy by about four months against IFL alone, an average of 20.3 months from 15.6 months. Avastin has pronounced safety and toxicity issues: in the combo regime licensed by the FDA, serious or fatal hemoptysis occurred in 31% of squamous cell lung cancer patients, hypertension in 60% of all patients including 7% with hypertensive crises, proteinuria was common, requiring dialysis in two cases, one of whom died from renal failure in the trial. Minor side effects are also numerous. The cost of the drug is around $4,400.00 per month per patient. As Ralph Moss has pointed out, the licensing of the Martha Stewart drug Erbitux, and of Avastin, tell us more about the politics of how big Pharma can get the FDA to approve a dangerous and unproven drug treatment without rigorously designed published clinical trials submitted to peer review journals, than of effective regulation. Genetech stock has more than tripled in value since the approval of Avastin.
Jonathan Treasure

was demonstrated to be antiangiogenic in vitro. [Maybe it's even antilegal these days.] Basic for the main course, alphabet soup, will be a mixed bag of beans with their genistein, curry with its curcumin, garlic with its selenium, milk thistle with its silymarin and silybin, pot marigold for its lupeol, hazelnuts for their homeopathic levels of taxol, Mexican bamboo for its emodin and resveratrol, peanuts (in red testa) for resveratrol, celery for its apigenin, tabasco pepper for its luteolin, and onion for its quercetin. Feed the patient, starve the metastasis.

References

Boik J 2001, *Natural Compounds in Cancer Therapy*. Oregon Medical Press, Princeton, MN

Here's one of my "food farmacy" formulae for Inhibit-ADE – a food farmaceutical for those afraid of Celebrex or Vioxx. Recipe as of Christmas 2004: 5 parts chamomile for apigenin; 5 parts cinnamon for cinamaldehyde, 4 parts clove for eugenol; 5 parts ginger for gingerol, paradol, and shogaol; 5 parts grape for resveratrol; 5 parts lemon balm for rosmarinic-acid; 3 parts oregano for rosmarinic-acid; 5 parts peppermint for rosmarinic-acid; 2 parts rosemary for oleanolic, rosmarinic and ursolic acids; 1 part sage for oleanolic, rosmarinic and ursolic acids; 4 parts spearmint for rosmarinic-acid; 1 part thyme for ursolic acid; and 5 parts turmeric or curry for curcumin and turmerone. I rarely measure this closely myself, and would not cry if I were short one or two ingredients. Brave souls might add hot pepper sauce to the Inhibit-ADE above or the curried celery below. Two of my associates found curcumin or curried celery as efficacious as Celebrex for their arthritis. The curried celery could embrace some of the better mixing tea herbs above as well. Certainly black pepper should be added as its piperine significantly enhances uptake of COX-2-I, curcumin. Dare I add hot pepper for its capsaicin, said to be as potent as Vioxx? (See *Natural Pharmacy*; Dec., 2004) Jim Duke, Dec. 2004, with Vioxx gone and Celebrex barely hanging on)