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Recognition of tumor blood vessel normalization as a new antiangiogenic concept

To the editor:

We found the first evidence of drug-induced normalization of tumor blood vessels in 1970[1], and described it more definitively in 1972 (ref. 2). This was a new type of drug action. The drug we used was razoxane (ICRF 159; NSC 129943); by normalizing the characteristically chaotic tumor vasculature, it prevented tumor hemorrhages, blood-borne tumor-cell dissemination and metastasis[3].

It was clear from the outset that the concept of normalization of pathologic vasculatures, which sustain and extend diseases such as cancer, arthritis, diabetic retinopathy and others, could have widespread application. It was also obvious that normalization of blood vessels could improve the availability of drugs and oxygen to disease areas, and thus improve combination therapy[2]. Razoxane was therefore investigated in clinical trials, both as a single antiangiogenic and antimetastatic agent and in combination with cytotoxic drugs or radiotherapy. It proved to be highly effective in psoriasis[3,4], psoriatic arthropathy[5], Kaposi sarcoma[6] and Crohn disease[7]. It significantly delayed recurrences of Duke grade C colorectal cancer[9], and it potentiated radiotherapy[10] and some cytotoxic drugs[11]. All these results have been published in a series of papers, reviews[12,13] and abstracts.

It was surprising, therefore, that in an entirely hypothetical commentary by R.K. Jain[14] proposing normalization of tumor vasculature as a new rationale for antiangiogenic therapy, none of the papers in the fairly extensive literature on razoxane were thought to be relevant to the claims put forward in this article, as none were quoted. The justification for these omissions from the scientific record seems to be that the article was specifically about the possible potentiation of cytotoxic drugs or radiotherapy if they were combined with antiangiogenic agents such as TNP-470, STI-571, C225 or Herceptin—all of which (except TNP-470) are said to have shown vascular normalization, though this is not evident from the publications cited[14]. The evidence for vascular normalization by Herceptin comes from a brief report from Jain's laboratory[15].

Extensive clinical trials have examined the combination of Herceptin with cytotoxic drugs. In breast cancer, the combination of Herceptin and doxorubicin increases severe cardiotoxicity sixfold, and that of Herceptin and paclitaxel by fourfold (http://www.herceptin.com/herceptin/physician/pi.htm), with only a marginal increase in survival. In contrast, the D-isomer of razoxane (dexrazoxane; approved by the US Food and Drug Administration) was highly effective in reducing severe doxorubicin cardiotoxicity, and nearly doubled median survival time in very similar clinical trials[16].

Our original results showing razoxane normalization of tumor blood vessels have recently been fully confirmed by the National Cancer Institute in an extensive *in vitro* and *in vivo* investigation[17]. This shows that razoxane-induced changes in the tumor vasculature can provide the morphologic basis for improved delivery of therapeutics and for prevention of circulating tumor-cell escape.

COMPETING INTERESTS STATEMENT
The author declares that he has no competing financial interests.

Kurt Hellmann
Windleshaw House, Withyham, East Sussex, TN7 4DB, UK.

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Jain replies:

Hellmann's letter reminds us that the subject of normalization of tumor vasculature remains interesting and timely. In my 2001 Commentary[1], I tried to resolve an outstanding paradox: how can antiangiogenic therapy (which kills blood vessels) augment the response to cytotoxic or radiation therapies (which require blood vessels for delivering drugs and oxygen)? The rationale at that time was that combination therapy would target both cancer cells and endothelial cells, and there were ample data showing that antiangiogenic therapy could augment cytotoxic therapy[2]. However, other data showed that these two therapies could be antagonistic[3,4]. In 2001, it was becoming clear that antiangiogenic therapy alone might not be therapeutic, and would need to be combined with cytotoxic or radiation therapies. There were no published guidelines for optimizing this combination, especially in the absence of appropriate surrogate markers and suitable imaging technology.

In my Commentary, I suggested that antiangiogenic therapy can normalize tumor vasculature, improving drug delivery by pruning the immature and inefficient vessels and remodeling the remaining ones. I cited data from our laboratory to support this hypothesis[5–10]. We now have both clinical[11] and further preclinical evidence[12,13] showing that judicious blockade of vascular endothelial growth factor (VEGF) signaling or upregulation of endogenous inhibitors of angiogenesis (such as thrombospondin-1)[10] can induce structural, functional and molecular changes in the tumor vasculature, which lead to increased tumor oxygenation and improved drug penetration.

ICRF 159, the drug referred to in Hellmann's correspondence, is antimetastatic but not antiangiogenic. He states that treatment with ICRF 159 prevents pulmonary metastases, and posits that this occurs because malignant cells neither line nor penetrate the normalized blood vessels. The process by which tumor metastasis was slowed could not actually be observed using the methods described in his 1972 paper[14].

The potential mechanism of action of this drug remained unknown until after 2001—the year I wrote my Commentary. Although Hellmann does use the term 'normalization' in his 1972 paper, there were no actual measurements of vessel structure (vessel density, vessel diameter distribution, fractal dimensions, pericyte coverage or basement membrane investment) or vascular function (blood flow, microvascular permeability, or interstitial and microvascular pressure). Moreover, Rybak *et al.*[15] have recently shown that ICRF 159 blocks network formation from cancer cells, but not from endothelial cells in culture, suggesting that ICRF 159 targets cancer cells. They refer to ICRF 159 as an antivasocrine agent, rather than an antiangiogenic agent. Considering that a number of well-characterized antiangiogenic agents were in clinical trials in 2001, I cannot see how one could place ICRF 159 in the same category as the various direct and indirect VEGF blockers that were the topic of my 2001 Commentary.

As we move forward, it is essential that we characterize the molecular and cellular mechanisms of the normalization process, search for new drugs that restore the balance of pro- and antiangiogenic molecules required for a normalized vasculature, and develop new imaging tools that can identify, in a clinical setting, the 'normalization window of opportunity' for combination therapy[16].

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