Abstract

The First International Conference on Vascular Targeting focused on vascular targeting agents (VTAs) that occlude or destroy the pre-existing blood vessels of solid tumors. The VTAs cause a rapid shutdown in the blood supply to the tumor that kills tumor cells by depriving them of oxygen and nutrients. The VTAs are distinct from antiangiogenic agents, which prevent new blood vessel formation. Two major types of VTAs are being developed for cancer: the ligand-directed VTAs that use antibodies, peptides, and growth factors to deliver toxins, procoagulants, and pro-apoptotic effectors to tumor endothelium, and the small molecule VTAs that do not specifically localize to tumor endothelium but exploit pathophysiological differences between tumor and normal tissue endothelia to induce acute vascular shutdown in tumors. Both approaches were described at the meeting and highlighted the variety of VTAs in preclinical development, their selectivity for tumor endothelium, their rapid antitumor effects, and the improved activity seen when combined with other anticancer approaches (antiproliferative chemotherapeutic drugs, radiation, radiolabeled antibodies, nitric oxide synthetase inhibitors, and antiangiogenic agents). Early clinical studies were summarized for the small molecule VTAs: the antitubulin drugs, combretastatin A4 phosphate (CA4P) and ZD6126, and the flavonoid, 5,6-dimethylxanthenone-4-acetic acid (DMXAA). The agents lacked the bone marrow and gastrointestinal toxicities associated with antiproliferative chemotherapy. As a marker of biological effect, blood flow reductions in tumors were measured using magnetic resonance imaging or positron emission tomography for all of the agents tested, and single-agent clinical activity was seen. These agents are now being evaluated in combined modality studies to see whether the impressive results obtained in experimental models can be translated into humans.

Introduction

The late Juliana Denekamp outlined the concepts behind VTAs for cancer treatment in the early 1980s. In a series of papers, she showed that physical occlusion of the blood supply to tumors in rodents leads to tumor regressions (1, 2). She showed that endothelial cells proliferate more rapidly in tumors than in normal tissues and suggested that the properties of tumor endothelium may be different sufficiently for VTAs to be constructed that selectively occlude or destroy tumor blood vessels. Subsequent studies validated the VTA approach by showing that a toxin targeted by an antibody specific for tumor blood vessels caused tumor regressions in mice (3, 4) and that antitubulin drugs have inherent VTA activity (5). VTAs exert their primary action on the pre-existing blood vessels of solid tumors and differ from antiangiogenic agents that prevent new blood vessel formation. There are thought to be a number of advantages of VTAs over other cancer therapies. First, a single vessel provides the nutrition for and facilitates removal of waste products of metabolism from hundreds or thousands of tumor cells and has to be damaged at only one point to block blood flow upstream and downstream. Second, endothelial cell killing is not required. A change of shape or local initiation of blood coagulation may be sufficient. Third, the endothelial cell is adjacent to the blood stream ensuring adequate drug delivery. Fourth, the target is a normal diploid cell that is unlikely to acquire genetic mutations that render it drug resistant. Fifth, a surrogate marker of biological activity, i.e., blood flow, is measurable in the clinic. Sixth, temporary effects on vascular function may be sufficient: studies indicate that >99% of tumor cells in vivo can be killed during a 2-h period of ischemia (6). Finally, unlike angiogenesis inhibitors, VTAs should require only intermittent administration to synergize with conventional treatments rather than chronic administration over months or years.

Two types of VTAs are currently being developed for cancer treatment: the ligand-directed VTAs, which use antibodies and peptides to target toxins, procoagulants, and pro-apoptotic effectors to tumor endothelium; and the small molecules that do not specifically localize to tumor endothelium, but which exploit pathophysiological differences between tumor and normal tissue endothelia to induce selective occlusion of tumor vessels (Table 1). The term VTA is used in the field to include drugs that do not bind selectively to tumor vessels, but which act similarly to ligand-directed VTAs to cause acute vascular shutdown in tumors. Both types of VTAs produce a characteristic pattern of necrosis after administration to mice and rats with solid tumors (7–10). They cause a widespread central necrosis that can extend to as much as 95% of the tumor. A thin rim of viable tumor cells usually survives at the periphery of the tumor at which point the tumor cells obtain nutrients from unaffected blood vessels in

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1 The Meeting was held June 12–14, 2002, at the Royal Sonesta Hotel, Cambridge, MA. It was sponsored by The University of Texas Southwestern Medical Center at Dallas and supported by unrestricted educational grants from AstraZeneca, Aventis Pharmaceuticals, and Oxigene. In addition to the organizers [P. E. T., D. J. C., D. C. B.], the meeting attendees included Drs. Bruce Baguley (University of Auckland, Auckland, New Zealand), Neal Bander (Cornell University, New York, NY), Marie-Christine Bissery (Aventis Pharmaceuticals, Paris, France), Rolf Brekken (The Hope Heart Institute, Seattle, WA), Robert Kerbel (University of Toronto, Toronto, Ontario, Canada), Pat LoRossio (Wayne State University School of Medicine, Detroit, MI), Dario Neri (Institute of Pharmaceutical Sciences, Zurich, Switzerland), Peter O’Dwyer (University of Pennsylvania, Philadelphia, PA), Barbara Pedley (Royal Free Hospital School of Medicine, London, United Kingdom), Sophia Ran (University of Texas Southwestern Medical Center, Dallas, TX), Michael Rosenblum (The University of Texas M. D. Anderson Cancer Center, Houston, TX), Gordon Rustin (Mount Vernon Cancer Centre, Northwood, United Kingdom), Jan Schnitzer (Sidney Kimmel Cancer Center, San Diego, CA), Ben Seon (Roswell Park Cancer Institute, Buffalo, NY), Dietmar Siemann (Shands Cancer Center, Gainesville, FL), and Yasuo Tsutsumi (Faculty and Graduate School of Pharmaceutical Sciences, Osaka, Japan).

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3 The abbreviations used are: VTA, vascular targeting agent; TF, tissue factor; VEGF, vascular endothelial growth factor; IL, interleukin; TNF, tumor necrosis factor; PS, phosphatidylserine; MTD, maximum tolerated dose; CA4P, combretastatin A4 phosphate; FAA, flavone acetic acid; DMXAA, 5,6-dimethylxanthenone-4-acetic acid; NO, nitric oxide; MRI, magnetic resonance imaging; scFv, single-chain Fv; VCAM-1, vascular cell adhesion molecule-1.
the surrounding normal tissues. As described below, combinations of VTA s with therapies that attack the outer rim can be curative (11, 12).

**Ligand-directed VTAs**

Ligand-directed VTAs use a targeting moiety that binds to markers that are selectively expressed on tumor endothelium to deliver an effector specifically to the tumor vasculature. The targeting moiety is most commonly an antibody, peptide, or growth factor. Target molecules that are up-regulated on tumor vessels as compared with vessels in normal tissues include: (a) molecules associated with angiogenesis and vascular remodeling (e.g., VEGF receptors, fibronectin-ED-B domain, \( \alpha_\beta_3 \) integrin); (b) cell adhesion molecules induced by inflammatory mediators that are secreted by tumor cells and host cells that infiltrate the tumor (e.g., VCAM-1, E-selectin); and (c) molecules associated with prothrombotic changes that occur on vascular endothelium in tumors (e.g., PS). The effector can act by inducing thrombosis of tumor blood vessels directly, by inducing vascular injury or apoptosis that later leads to thrombosis, by redirecting host defenses to attack the tumor vessels, or by causing endothelial cell shape changes that physically block tumor vessels.

Rapid thrombosis and major tumor regressions in mice were described using human coagulation-inducing protein TF targeted to tumor endothelium. Targeting was achieved with monoclonal antibodies directed against MHC class II (an experimentally induced marker), the cell adhesion marker VCAM-1 (P. Thorpe) and with human scFv (L19) directed against the fibronectin-ED-B isofrom (D. Neri). The extracellular domain of TF is not a coagulant while free in the blood circulation, but it becomes a powerful and specific coagulant once bound to a ligand to the tumor vasculature. These VTAs homed selectively to tumor vessels, and, within a few hours, vessels throughout the tumor were packed with platelet aggregate, erythrocytes, and fibrin. By 24 h, tumor cells showed pyknotic changes that became progressively more marked. By 72 h, the entire central region of the tumors had degenerated into amorphous debris.

Impressive preclinical activities were reported when toxins and other cytotoxic agents were selectively targeted to tumor vasculature. Marked antitumor effects were described for the human VEGF121 fused to the plant toxin gelonin (M. Rosenblum), the chemical conjugate of ricin A-chain linked to monoclonal antibodies to mouse endoglin (B. Seon), the cytoxic agent neocarzinostatin conjugated to the monoclonal antibody TES-23 directed against a CD44-related tumor endothelial cell marker (Y. Tsutsumi), and an immunotoxin directed against the VEGF-receptor complex (R. Brekken).

Successful efforts to enhance the antitumor activity of cytokines by targeting the extracellular matrix that surrounds tumor vessels were described (D. Neri). IL-12 is a heterodimeric cytokine with potent immunostimulatory activity and antiangiogenic properties. Marked antitumor activity was reported for L19 scFv fused to IL-12 or TNF-\( \alpha \), attributed to the high affinity of the L19 scFv and the abundance of the target marker in tumor vasculature. Because L19 scFv recognizes the human fibronectin ED-B domain as well as that of other species, it is a prime candidate for clinical trials.

“Naked antibody” VTAs were described (S. Ran, P. Thorpe) that recognize PS, a phospholipid that becomes exposed on the surface of tumor endothelium, probably as a result of its exposure to hypoxia, inflammatory cytokines, acidity, and thrombin. On normal vessels, PS is segregated to the internal surface of the plasma membrane, where it is unavailable for antibody binding. Treatment of mice with the antibodies suppressed the growth of tumors without causing apparent toxicity. Vascular damage to tumor vessels was mediated possibly through host effectors.

Vascular-targeted gene therapies that cause the selective apoptosis of tumor endothelial cells are producing impressive antitumor effects.

J. Hood described the use of a cationic nanoparticle coupled to an \( \alpha_\beta_3 \) integrin-targeting ligand to deliver a mutant gene, ATP\( ^{32} \)-Raf, to tumor blood vessels in mice. The ATP\( ^{32} \)-Raf gene blocks endothelial signaling and angiogenesis in response to multiple growth factors. Treatment of mice with the targeted gene caused apoptosis of the tumor endothelium and sustained regression of established primary and metastatic tumors. G. Dougherty described the development of adenoviral vectors to deliver DNA, encoding Flk-1 (the receptor for VEGF) fused to the proapoptotic protein Fas, to tumor vasculature. It is expected that, in the tumor microenvironment, VEGF will activate the chimeric cell surface receptor and induce cell death. *In vitro* studies support this expectation.

Powerful new techniques are being developed for finding markers that are specifically and homogeneously expressed on tumor vessels. At the meeting, J. Schnitzer described a physical method for isolating the luminal plasma membrane from vascular endothelium in intact animals, which he used to generate a monoclonal antibody against a caveolar protein expressed in rat lung microvascular endothelium. The antibody targets the lungs after i.v. injection into rats and is transported into the adjoining epithelium. It could potentially be used to target drugs or even genes to normal and malignant lung epithelial cells.

**Small Molecule VTAs**

**Tubulin-binding Agents.** A number of tubulin-binding agents that destabilize the tubulin cytoskeleton, such as colchicine, vincristine, and vinblastine, disrupt the vasculature of a tumor, but only at doses close to their MTD. This limitation was overcome by the development of second-generation tubulin depolymerizing agents, which disrupt the tumor vasculature at doses well below their MTD. The mechanism of action of these agents involves rapid changes in endothelial cell shape that disrupt the endothelial cell layer surrounding blood vessels and expose underlying basement membranes. This leads to blood vessel congestion and loss of blood flow. It remains to be established whether coagulation and thrombus formation caused by exposure of the underlying basement membrane is critical for these events. The loss of blood flow, as in the biological approaches above, leads to a loss of nutrient supply and waste removal, and the tumor cells supported by the affected vessels undergo necrosis.

The lead agents in this class, CA4P (D. Chaplin; Ref. 9) and

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<tr>
<th>VTAs described at the Meeting</th>
<th>Compound</th>
<th>Comments</th>
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<tbody>
<tr>
<td><strong>Ligand-directed</strong></td>
<td>Anti-TF</td>
<td>TF induces coagulation</td>
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<td></td>
<td>Anti-VCAM-1/TF</td>
<td>VCAM-1 is a cell adhesion marker</td>
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<td></td>
<td>L19 scFv-TF</td>
<td>L19 scFv targets fibronectin ED-B domain</td>
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<td></td>
<td>VEGF-gelonin</td>
<td>Gelonin is a plant toxin</td>
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<td></td>
<td>Anti-endoglin linked to ricin A</td>
<td>Antibody-toxin</td>
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<td>Anti-TES-23 linked to neocarzinostatin</td>
<td>Antibody-cytotoxic</td>
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<td></td>
<td>L19 scFv-IL-12</td>
<td>Antibody-cytokine</td>
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<td>L19 scFv-TNF-( \alpha )</td>
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<td></td>
<td>Anti-PS</td>
<td>Naked antibody</td>
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<td>Targeted ATP( ^{32} )-Raf gene</td>
<td>Gene therapy, blocks signaling</td>
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<td></td>
<td>DNA encoding Flk-1 fused to Fas</td>
<td>Gene therapy, induces apoptosis</td>
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<tr>
<td><strong>Small molecules</strong></td>
<td>CA4P</td>
<td>Phosphatase prodrug of CA4P</td>
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<td></td>
<td>ZD6126</td>
<td>Phosphatase prodrug of N-acetylglucosamine</td>
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<tr>
<td></td>
<td>AVE8062A</td>
<td>Combretastatin analogue</td>
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<td>Ox4503</td>
<td>Combretastatin analogue</td>
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<td></td>
<td>DMXAA</td>
<td>Flavonoid</td>
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ZD6126 (D. Blakey; Ref. 8), cause rapid (within 40 min) cell shape changes in proliferating immature endothelial cells in culture, whereas quiescent mature endothelial cells are resistant to these changes. This difference in sensitivity provides a rationale for the selective effects on tumor vasculature, given the much higher proportion of proliferating or immature endothelial cells in tumor blood vessels as compared with normal vessels. Direct experimental support for a selective effect on tumor endothelial cell shape leading to tumor vessel occlusion was demonstrated for ZD6126 by using immunohistochemistry and by electron microscopy of a mouse tumor model (8).

The effects of both agents on cell shape are rapidly reversible on drug removal and, coupled with short in vivo exposure, may contribute to tumor selectivity. Agents such as colchicine dissociate slowly, and even short exposure leads to significant cytotoxicity via disruption of the tubulin cytoskeleton of cells in normal tissues. The importance of a short exposure for the tumor selectivity of ZD6126 was demonstrated by the finding that continuous low-level administration of ZD6126 reduced tumor activity but enhanced bone marrow and gastrointestinal toxicity.

The combretastatin analogues, AVE8062A (formerly AC-7700) and Oxi4503 (a diphosphate derivative of combretastatin A1) were more effective as single agents than CA4P or ZD6126 (M-C. Bissery). This may be because they are more cytotoxic and act as both a VTA and a cytotoxic drug, with the latter activity leading to cell killing of the surviving viable rim. It is not yet known whether the increased cytotoxicity of AVE8062A and Oxi4503 limits or enhances their antitumor activity in humans.

**Flavonoids.** TNF-α disrupts tumor vasculature, but its toxicity to normal tissues precludes its use as an anticancer agent in humans. One approach to increasing the antitumor selectivity of TNF-α is to induce its synthesis in tumors in situ. FAA was the first agent reported to have such activity. In murine tumor models, FAA causes vascular disruption leading to tumor necrosis at doses close to its MTD. However, FAA induced TNF-α production only in murine cells, which prompted the search for new agents having a similar effect on human cells. DMXAA (10) is an analogue that acts on human cells. It acts through induction of TNF-α, and probably also of serotonin (B. Baguley). DMXAA may trap TNF-α produced in the tumor microenvironment and stimulate further TNF-α production. However, in preclinical tumor models, DMXAA retains a narrow therapeutic margin, possibly because of toxicity caused by the escape of TNF-α from the tumor into the circulation.

**Combination with Other Agents.** Improved antitumor effects are observed when VTAs are combined with other therapies that kill the viable rim of tumor cells that repopulates tumors. D. Siemann described the increased tumor cell killing when CA4P, ZD6126, or DMXAA are combined with cisplatin. Improved activity was seen with biologically active doses of CA4P and ZD6126 that are well below the MTD, but only at doses approaching the MTD of DMXAA. Giving the cytotoxic drug before the VTA rather than concurrently improved activity. It is possible that VTAs disrupt blood flow, preventing the cytotoxic drug from reaching tumor cells, which, although hypoxic, eventually survive. Although limited data are available, there was no evidence of enhanced bone marrow toxicity when combining cytotoxic agents with VTAs. Other successful combinations were to give VTAs with angiogenesis inhibitors (D. Siemann), radiation, or hyperthermia (M. Horsman), or 131I-radio labeled antibody to carcinoembryonic antigen (B. Pedley).

P. Davis described a combination treatment of CA4P with NO synthetase inhibitors. CA4P was active against a low-NO-producing tumor (CaNT) but showed little activity against a high-NO-producing tumor (SaS). NO synthetase inhibitors, e.g., L-(omega)-nitro-L-arginine, enhanced CA4P activity in the CaNT tumor and made SaS sensitive to the action of CA4P. NO thus appears to protect tumors from the action of CA4P, possibly by inducing vasorelaxation by NO or by effects on cytochrome c oxidase leading to increased survival under low oxygen.

The key message from these combination studies was that the VTAs can kill the central, poorly perfused, hypoxic regions of the tumor, whereas antiproliferative agents such as cisplatin, radiation, and radioiodinated antibodies kill the well-perfused, well-oxygenated, rapidly proliferating rim of the tumor. The combination can kill both populations, and it is likely that maximal clinical benefit of VTAs will be achieved when used in combination with a wide range of existing and experimental cancer therapeutic approaches.

**Clinical Studies**

CA4P. P. O’Dwyer reviewed the clinical experience with CA4P from three completed Phase I studies that included approximately 100 patients. The drug was given every 3 weeks, every week, or on a schedule involving five daily doses, and the dose-limiting toxicities were acute cardiac syndrome, reversible ataxia, and tumor pain, respectively. Blood flow reductions were measured, by using either MRI or positron emission tomography, in all three studies. Bone marrow toxicity, which is associated with cytotoxic therapies, was not observed with CA4P even after prolonged administration. One complete tumor response was observed in a patient with an anaplastic thyroid cancer, with the patient free from disease 33 months later, and three patients had no tumor progression for periods of >1 year. On the basis of this clinical experience, and on the shutdown in blood flow observed in tumors at achievable doses, a combination Phase Ib study using CA4P with carboplatin has been initiated. Several other Phase Ib and Phase II studies should begin in the near future.

ZD6126. J. Eveloch described preclinical studies using gadolinium-enhanced MRI to measure the effects of ZD6126 on tumor and normal tissue (muscle) blood flow in a mouse tumor model. A dose-dependent reduction was seen in tumor blood flow, without significant effects on the blood flow in muscle. In a Phase I clinical trial (P. LoRusso), 31 patients received ZD6126 every 21 days. Dose-limiting toxicities were abdominal pain and gastrointestinal symptoms. Changes in blood pressure and asymptomatic cardiac toxicities (rise in troponin/decreased ejection fraction) were seen, but there was no myelosuppression. Significant reductions in tumor blood flow were documented with MRI. Stable disease lasting four or more cycles was seen in three patients, and in another patient there was a minor response lasting 19 cycles. New studies are in progress to identify the minimum dose of ZD6126 that consistently reduces tumor blood flow for combined-modality clinical trials.

**DMXAA.** The results from two Phase I clinical trials for DMXAA were summarized (G. Rustin). A combined total of 109 patients were accrued, and dose-limiting toxicities were transient confusion, tremor, slurred speech, visual disturbance, anxiety, vomiting, malaise, and left ventricular failure. Significant reductions in tumor blood flow were measured using MRI, and dose-dependent increases in the plasma levels of the serotonin metabolite 5-hydroxyindoleacetic acid were observed. Although no increases in serum TNF-α levels were detected, local TNF-α production was detected in one of three tumor biopsies performed.

**Recommendations for Future Research**

**Ligand-directed VTAs.** Future research should identify new, more specific tumor endothelial markers. Currently available markers are often undetectable on vessels in resting normal tissues but are present on vessels in angiogenic normal tissues (e.g., ovary), healing wounds, or inflamed tissues. There are some powerful techniques for...
searching for new markers, such as serial analysis of gene expression and in vivo phage display. Other ways to improve tumor vessel specificity might use bispecific VTAs that recognize two differently regulated tumor vessel markers, because endothelial cells in normal tissues might express one, but not the other, marker. It might be possible to target tumor cell markers that bind to the adjacent tumor endothelium. In parallel, efforts are required to identify novel effectors. Human effectors, such as ILs and coagulant proteins, are attractive because of their inherently low immunogenicity. Naked antibody VTAs that direct host defenses to attack tumor vessels are also attractive because of their simplicity. The early successful targeting of apoptosis-inducing genes to tumor vasculature that was described at the meeting will undoubtedly be refined further. Angiogenesis-related promoters also need additional investigation because they raise the possibility of restricting gene expression more completely to sites of tumor angiogenesis. Ligand-coated liposomes should be explored as VTAs because of their ability to deliver a large payload of diverse effectors. Finally, in studies reported at the meeting, treatment with ligand-based VTAs caused little or no toxicity at therapeutic doses, suggesting that such experimental therapies could be safely translated into clinical treatments. The early clinical assessment of ligand-based VTAs, therefore, is recommended for future research.

**Small Molecule VTAs.** Future research should aim to increase our understanding of the preclinical and clinical toxicity (including cardiovascular effects) associated with the current lead agents. This research might identify ways of reducing unwanted side effects to maximize the clinical impact of the first generation compounds and should aid the future development of both the present and the second-generation agents. In addition, further work is needed to explore approaches for controlling/killing the surviving peripheral rim of tumor cells to provide guidance for future combination trials. In the longer term, and given the encouraging clinical validation of the approach, identification of new small molecule agents that exploit other pathophysiological differences between tumor and normal tissue vasculature should provide alternative vascular targeting strategies. Agents that disrupt cell-cell adhesion that might lead to selective acute apoptosis of tumor endothelial cells is one area worthy of further exploration.

**Clinical Studies.** The clinical studies completed to date with the small molecule VTAs are encouraging. The surrogate marker of activity, i.e., blood flow reduction within the tumor, has been observed with all of the agents tested. In addition, clinical activity was seen despite preclinical data suggesting that there would be no tumor responses with the administration of a VTA alone. Progression into combination studies has begun and should establish whether the exciting preclinical data obtained when VTAs are combined with cytotoxic chemotherapy, radiation, antibody therapeutics, and antiangiogenic agents can be translated into humans.

**VTAs for Nonmalignant Diseases and Organ-specific Drug Delivery.** Future research should explore the use of VTAs for treating nonmalignant diseases, including diabetic retinopathy, psoriasis, arthritis, and other angiogenic diseases. Vascular endothelium in these diseases has phenotypic similarities to tumor endothelium. Indeed, CA4P has produced benefit in a murine model of diabetic retinopathy (13). MRI agents might be incorporated into ligand-directed VTAs for detecting and monitoring disease. Vascular endothelium in normal brain, lung, and lymphoid tissues express selective markers, which suggests that ligands against these markers might be used to construct VTAs for specific drug delivery to these organs.

**REFERENCES**

The First International Conference on Vascular Targeting: Meeting Overview
Philip E. Thorpe, David J. Chaplin and David C. Blakey


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