Therapeutic Angiogenesis: Hope or Hype

To the Editor:

Grines et al \(^1\) assert that the vascular endothelium and/or the myocardium can incorporate a human, replication-deficient adenovirus vector (Ad5–FGF4) in which one gene is replaced with the human FGF4 gene that is delivered by intracoronary infusion. This, according to the authors, allows sustained in situ production of “angiogenic growth factors.” The data show, however, that the vector was detected in the pulmonary artery and later in the venous blood. Thus, the alleged lack of systemic exposure to the unidentified growth factors is not convincing.

The observation that 2 patients (3%) were diagnosed with malignancies 69 days (brain) and 267 days (colon) after the treatment was dismissed as unrelated occurrences. Furthermore, the report does not discuss the more general angiogenesis-neoplasia link, described initially nearly 100 years ago. In 1971, Folkman advanced the now well accepted postulate that tumor growth and metastasis are angiogenesis-dependent, and hence blocking angiogenesis could be an effective strategy to arrest tumor proliferation. \(^2\) Not surprisingly, in 2000, the journal Cancer and Metastasis Review published nearly 200 pages of contributions on the angiogenesis-neoplasia association. \(^3\) In addition, neovascularization of untreated tissues may initiate or aggravate other pathological states with serious clinical consequences, such as rheumatoid arthritis, retinopathies (including macular degeneration), psoriasis, and hemangiomias. In a critical essay, Epstein et al \(^4\) emphasized the still overlooked serious side effects resulting from administration of angiogenic agents and concluded explicitly, “We are not seduced by hype and we judge the merits of this potential important and novel therapeutic approach to obstructive arterial disease in a dispassionate and objective manner.” A more specific critical appraisal by Ungvary et al \(^5\) cautions that angiogenesis induction may “promote the vascularization of developing tumors, thus supporting their growth and metastasis.” They assert that a minimum of 10 years of study is imperative to ascertain such potential. There is also a long history of studies on the prognostic value of tumor vascularization.

In an attempt to evaluate the current hope and hype claims in angiogenesis research, it is obvious that inhibition of angiogenesis to suppress cancer growth (advocated by oncologists) or stimulation of angiogenesis to ameliorate ischemic heart disease (endorsed by cardiologists) represent a basic biological contradiction and irreconcilability. It is an example of oversimplification and a myopic view of a very complex, not very well predictable problem. Extended experimental assessment before the initiation of large clinical trials is unquestionably essential before a clinical disaster materializes. In our era of narrow medical specialization, it is time for cardiologists to start communicating with oncologists for the well being of our patients.

Emile G. Bliznakov, MD
Biomedical Research Consultants
2821 North Course Dr (H-205)
Pompano Beach, FL 33069

Response

Dr Bliznakov combines different statements in the text of the Angiogenic Gene Therapy (AGENT) trial publication \(^1\) to infer assertions or conclusions we did not formulate. The AGENT publication does not refer to any unidentified growth factors or to lack of systemic exposure. We showed the detection of Ad5FGF-4 in Figure 1 and stated that estimated first-pass extraction across the coronary circulation in dose groups 3 through 5 was 87%. We also stated that the absence of circulating Fibroblast Growth Factor-4 in patient plasma is also supportive of relatively selective cardiac gene delivery.

Regarding the observation that 2 patients were diagnosed with cancer, we did not dismiss the occurrence as unrelated to treatment; we presented the facts. In the case of the patient with renal and colon cancer who had 3 first-degree relatives with colon cancer, we stated, “Although an effect of product administration on clinical course cannot be excluded, the cancer was considered unlikely to have been caused by the product, and PCR assay conducted on the tumor was negative.” \(^6\) In the other case of a patient with a brain tumor, an independent neurological oncologist review indicated that the tumor was almost certainly present at the time of product administration on the basis of size and doubling time. The tumor was negative for Ad5FGF-4 DNA and mRNA. In the article quoted by Bliznakov, the authors discussed the potential risk for tumor growth with long term (>10 years) systemic simvastatin treatment in the elderly. \(^7\) This is not relevant to the AGENT trial, in which patients received a one-time treatment by subselective intracoronary injection.

We did not overlook or minimize the risks related to the virus vector or the growth factor gene; on the contrary, we expressed our concern about adenovirus propensity for hepatotoxicity and concern in delivery of growth factor genes. A recent review concluded, however, that clinical trials of cardiovascular gene therapy have thus far disclosed no evidence indicative of inflammatory or other complications, including death, directly attributable to the vector used, and that there is little evidence that (selective) administration of angiogenic growth factors is sufficient to stimulate the growth of neoplasms. \(^8\)

We believe that a long-term follow-up and a larger database are necessary to make a more realistic evaluation of angiogenic gene therapy in patients with coronary artery disease; these studies are now in progress.

Cindy L. Grines, MD
Director, Cardiac Catheterization Laboratories
William Beaumont Hospital
Cardiology Administration/3rd Floor
3601 West Thirteen Mile Rd
Royal Oak, MI 48073-6769


Correspondence

Robert Engler, MD
President and Chairman
Collateral Therapeutics
San Diego, Calif

Jeffrey Brinker, MD
Jeffrey Rade, MD
Johns Hopkins Hospital
Baltimore, Md

Gregory Helmer, MD
Minnesota Heart Clinic
Minneapolis, Minn

Jonathan Marmur, MD
Mount Sinai Medical Center
New York, NY

William Penny, MD
UCSD San Diego VA Medical Center
San Diego, Calif

Matthew W. Watkins, MD
Fletcher Allen Health Center
Burlington, Vt

Pran Marrott, MD
Berlex Laboratories, Inc
Montville, NJ

H. Kirk Hammond, MD
Professor of Medicine
VA San Diego
San Diego, Calif

Andrew West, MD
Heart and Vascular Institute of Texas
San Antonio, Tex