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**United States Patent** [19][11] **Patent Number:** **5,554,638****Dewhirst et al.**[45] **Date of Patent:** **Sep. 10, 1996**[54] **METHODS FOR IMPROVING THERAPEUTIC EFFECTIVENESS OF AGENTS FOR THE TREATMENT OF SOLID TUMORS AND OTHER DISORDERS**[75] Inventors: **Mark W. Dewhirst**, Chapel Hill; **Robert E. Meyer**, Cary; **Joseph Bonaventura**, Beaufort, all of N.C.; **Joseph DeAngelo**, Hamtramck, Mich.[73] Assignees: **Duke University**; **Apex Bioscience, Inc.**, both of Durham; **North Carolina State University**, Raleigh, all of N.C.[21] Appl. No.: **246,882**[22] Filed: **May 20, 1994****Related U.S. Application Data**

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[51] **Int. Cl.**<sup>6</sup> ..... **A61K 31/22**; A61K 31/415[52] **U.S. Cl.** ..... **514/398**; 514/560; 514/565; 514/551; 514/411; 514/456[58] **Field of Search** ..... 514/565, 560, 514/551, 398, 411, 456[56] **References Cited****U.S. PATENT DOCUMENTS**

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*Primary Examiner*—Robert W. Ramsuer*Assistant Examiner*—John Peabody*Attorney, Agent, or Firm*—Pennie & Edmonds[57] **ABSTRACT**

The present invention is directed to the use of an inhibitor of NO activity, such as a nitric oxide scavenger or an NO synthase inhibitor, as an antitumor therapy to reduce tumor blood flow and oxygenation. The invention is also directed to administration of a nitric oxide scavenger or a nitric oxide synthase inhibitor to enhance the effectiveness of tumor therapy with hypoxic or acidic chemotherapeutic agents or hyperthermia. The invention is also directed to the administration of a nitric oxide synthase substrate to a subject previously administered a nitric oxide synthase inhibitor, in order to selectively inhibit tumor perfusion. In a specific example, administration of cell free hemoglobin, a nitric oxide scavenger, in conjunction with mitomycin C, a hypoxic cytotoxin, results in a significant delay in tumor growth of a human tumor xenograft in a mouse compared to mitomycin C alone. In another example, the administration of an inhibitor of nitric oxide synthase followed by the administration of a substrate of the enzyme causes a specific irreversible reduction of tumor blood flow, while normal blood flow is restored.