Method of Inhibiting Growth of Malignant Tumors is Determined by Scientists at The Scripps Research Institute

La Jolla, CA. April 22, 1994 — A novel and potentially powerful method of inhibiting the growth and metastases of virtually all types of malignant tumors has been developed by investigators at The Scripps Research Institute (TSRI) in La Jolla, California. The strategy involves literally starving tumors by cutting off their blood supply. Moreover, they suggest it may be possible to do this with nothing more than an antibody that targets blood vessels entering tumors.

A paper describing the experimental observations that led to this concept was published in the April 22 issue of Science magazine by Drs. David A. Cheresh, and Peter C. Brooks, in the Department of Immunology at TSRI, and their collaborator, Richard Clark, Jr., M.D., in the Department of Dermatology at the State University of New York at Stony Brook.

In order to grow, thrive, and, ultimately, metastasize, malignant tumors must attract and become pervaded with a rich supply of blood to provide nourishment and remove wastes. This is achieved, in part, by the secretion of factors that promote new blood vessel growth in the direction of and into the tumor, a process known as angiogenesis.

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Unfortunately, extensive efforts over the past three decades to devise ways to block the production or activity of tumor-produced angiogenic factors have been disappointing. Because many different molecules, from both normal and tumor cells, are capable of inducing new blood vessel growth, it has been difficult to block angiogenesis, although a number of compounds currently are being examined for their effects on the process.

Now, however, Cheresh and Brooks suggest that blocking angiogenesis may after all be a highly effective means of combating cancer. Rather than blocking or inhibiting the angiogenic signals from the tumor, they propose to block the reception or "reading" of those signals by blood vessel cells, thereby preventing angiogenesis from occurring at all.

According to Cheresh, "By inhibiting the process of angiogenesis, we can choke the tumor from its needed blood supply. When this happens, you can expect the total annihilation of the tumor. While work in this area is ongoing, preliminary studies seem to bear this out."

The idea arose from their studies of a family of receptor molecules called the integrins. Found on all tissues, integrins receive and respond to molecular signals of many different kinds, and in turn control a wide range of cellular functions. In blood vessels, Cheresh and Brooks found that one particular integrin, known as VNR, is expressed primarily on newly growing blood vessel sprouts but not at all on adjacent, established vessels. This integrin presumably stimulates vessel growth by promoting adhesion and motility of the cells in the vessels to their surroundings and to tumor tissue.

"We had found something distinct and unique on these new vessels, and this gave us the idea to attempt to block the function of this integrin receptor," Cheresh said. In earlier studies, Cheresh and his colleagues had developed a monoclonal antibody that specifically

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blocks the function of the VNR integrin.

When this antibody was applied to a chicken embryo experimental model containing fragments of human tumor they observed that it virtually prevented blood vessel growth toward the tumor without any effect on the normal vessels feeding the embryo. Cheresh and Brooks believe that this model of angiogenesis might predict what would occur in a cancer patient when a tumor begins to grow.

According to Cheresh, "The concept is that a monoclonal antibody or other inhibitor of the VNR integrin might prove to be a novel form of cancer therapy, since it is not directed at the ever-changing tumor cells as is the case with current drugs, but rather at normal tissues feeding the tumor."

Since the Science paper was written, Cheresh and Brooks, together with their TSRI colleague, Mauricio Rosenfeld, have shown that this monoclonal antibody and other inhibitors of VNR can block blood vessel growth toward tumors of the lung, colon, and pancreas. Also, they have begun to test their strategy in other preclinical models containing human tumors.

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