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Angiogenesis Inhibition Target Could Generate Cancer Drugs

By Sharon Kingman

BioWorld International Correspondent

LONDON - The discovery of the receptor for a highly active angiogenesis inhibitor raised the prospect of being able to develop a new generation of anticancer agents.

Because angiogenesis plays an important role in many other diseases, however, such drugs could be used to treat conditions as diverse as atherosclerosis, rheumatism, psoriasis, endometriosis and obesity.

Arjan Griffioen, professor of experimental oncology at the University of Maastricht in the Netherlands, told BioWorld International: "Now that we have found the receptor for this very active angiogenesis inhibitor, we have the tools to further study the biology of tumor growth and find compounds to treat cancer more effectively."

Griffioen is a founder of Peptx Inc., of St. Paul, Minn., and sits on the company's scientific advisory board. Peptx is looking for partners to help it develop anginex, a peptide that inhibits tumor growth by specifically inhibiting angiogenesis.

Having developed anginex and worked on the compound since 1998, Griffioen and his colleagues recently decided to try to discover what molecule it interacts with. The starting point for anginex had been a chemical scaffold known to be present in chemokines, which was tailored until the required activity - inhibition of angiogenesis - appeared.

So the team worked backward to engineer a gene that would encode anginex and then used that genetic code in a yeast two-hybrid screen to pull out other proteins that interacted with anginex in mammalian endothelial cells.

The approach allowed them to pinpoint the gene encoding a protein called galectin-1 (gal-1). The study is reported in the Oct. 16, 2006, issue of Proceedings of the National Academy of Sciences in a paper titled "Galectin-1 is essential in tumor angiogenesis and is a target for antiangiogenesis therapy." The first author is Victor Thijssen.

"Our first task was to validate that gal-1 and anginex bind to each other," Griffioen said. Their studies showed that anginex interacts with gal-1 in order to inhibit angiogenesis by endothelial cells, and furthermore, that gal-1 was vital for angiogenesis to occur.

The next step was to investigate what happens when the gene encoding gal-1 is knocked out in mice. "We were lucky here," Griffioen said. "The knockout mouse for gal-1 had already been made, in Paris. We intended to inject tumors, and when they reached a certain size, we would treat them with anginex in the expectation that the treatment would not work because the receptor was not present in these mice."

But to their surprise, the tumors injected did not even grow in the knockout mice. "We concluded from this that gal-1 was so important to tumor growth that the tumors would not even grow in these mice," Griffioen said. "We thought this was very interesting because the world is waiting for targets we can use to design new compounds for angiogenesis inhibition."

The next experiment involved knocking out the gene encoding gal-1 in a zebrafish model where all blood vessels are labeled fluorescently. In those animals, the researchers could see that the vasculature developed in a completely disorganized way.

"This finding suggested to us that gal-1 is probably also important in vascular guiding," Griffioen said.

Now that researchers know the identity of the receptor for anginex, they can study how the two interact and potentially design compounds with a higher affinity for gal-1 than anginex. Griffioen added: "We are going to attempt to do this in two ways. First, we want to mutate anginex and make shorter molecules to interact with gal-1, and secondly we will try to make peptidomimetics of anginex."

Writing in the Proceedings of the National Academy of Sciences, the team concluded that the results of various studies, including those by other groups, suggested that the increased expression of gal-1 in tumors makes it an "excellent target" for diagnostic or therapeutic purposes.