Proteins driving tumor cell death discovered with new cancer drug

February 8 2011

Sheffield researchers have identified two proteins that play a crucial role in the destruction of tumours in patients being treated with a promising new group of cancer drugs.

University of Sheffield researchers Dr. Chryso Kanthou and Professor Gillian Tozer have discovered that the proteins Rho Kinase and Nitric Oxide Synthase play an important role in driving cell death in tumors that are being treated with the drug Combretastatin A-4-phosphate, currently in clinical trials.

Combretastatin is one of a large group of new cancer drugs known as Vascular Disrupting Agents (VDAs) that selectively damage tumour blood vessels by cutting off their blood supply, starving them of oxygen and nutrients. The Sheffield researchers have been awarded nearly £200,000 from medical research charity, Yorkshire Cancer Research, to investigate further how they can improve these new drugs, particularly Combretastatin, following previous research published in the scientific journal *Clinical Cancer Research*.

The scientists will be focusing on how the drugs interact with Rho kinase and Nitric Oxide Synthase in the tumour in order to identify areas or other molecules to target so as to improve how VDAs work in general for the benefit of cancer patients worldwide.

Dr. Kanthou of the Tumor Microcirculation Group in the Department of Oncology at the University of Sheffield said: "Tumors need blood

vessels in order to grow and spread and several promising treatments with Vascular Disrupting Agents (VDAs) are now being developed to specifically destroy tumor blood vessels. "VDAs are a group of new drugs in clinical trials that cause rapid, extensive and selective damage to tumour blood vessels by stopping blood flow to the tumour and therefore they indirectly kill tumor cells by starving them of oxygen and nutrients.

"However, these drugs do not currently eradicate tumors completely and blood flow gradually recovers and tumor cells re-grow from cells that escape the treatment, especially around the tumor rim. "Our research, funded by Yorkshire Cancer Research, will aim to understand the precise mechanisms through which tumor vessels are damaged by VDAs and how they eventually resist treatment, re-grow and recover. "We will be using our funding to investigate further the role of the proteins Rho Kinase and Nitric Oxide Synthase, which we have recently discovered drive tumor cell death when the lead VDA, Combretastatin, is used. "We must identify the molecules and proteins that are involved in these processes so that VDAs can be made more effective treatments for all forms of cancer."

More information: Tozer GM, et al. Nitric oxide synthase inhibition enhances the tumor vascular-damaging effects of combretastatin A-4 3-O-phosphate at clinically relevant doses. *Clin Cancer Res* 2009;15:3781-90.

Provided by Yorkshire Cancer Research