The VDR Nuclear Receptor is a Novel Proxy for MTSS1 and MTUS1 in Breast , Bladder and Colorectal Cancers

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Abstract

Metastasis Suppressor 1 (MTSS1) is a gene encoding the protein Missing In Metastasis (MIM). MIM is large (circa 750 residues, 82kDa), with an actin-binding motif near its C-terminus. MTSS1 has been implicated in breast, ovarian and fallopian tube carcinomas, as well as gastric, colon, bladder and lung cancers. MIM acts on the actin cytoskeleton, although the mechanism is not completely understood. There is no drug available which directly targets MTSS1. However, recent studies have shown that MTSS1 is principally expressed by the activated VDR Nuclear Receptor.

We have been investigating the VDR-agonist Olmesartan in a clinical trial focused on subjects with autoimmune and chronic inflammatory diseases, and our clinical data raises the possibility that a VDR-agonist may well have a profound direct effect on the incidence of metastatic cancers. During seven years of data collection in a cohort of over 700, many of whom have been totally disabled by their inflammatory disease, no cases of metastatic carcinoma, and only two confirmed carcinomas, have been reported. One breast ductal carcinoma in-situ (1.1cm in size) was reported, with all lymph nodes negative for metastatic carcinoma. The subject refused chemotherapy, continuing with the VDR-agonist study regime. Following resection 31 months ago, no recurrence has been observed. A high grade non-invasive papillary transitional-cell bladder carcinoma was found in another subject, who also refused chemotherapy in favor of the VDR-agonist. Following a transurethral resection, there has been no recurrence in the subsequent 30 months. Both of these carcinomas were judged to have most probably been present before the subjects were enrolled in the VDR-agonist trial.

It must be noted that expression of the Mitochondrial Tumor Suppressor 1 (MTUS1) is down-regulated by the VDR. However, this may be offset by Olmesartan's direct action on the Angiotensin signaling pathways, which seem to be a primary target of MTUS1.

Our initial clinical data shows that the VDR-agonist Olmesartan may be useful in the prevention of metastatic carcinomas, probably via up-regulation of MTSS1 expression, and more study is warranted.

Biography:

Prof. Trevor Marshall graduated from the University of Adelaide, South Australia, in 1973. After a year teaching in Papua New Guinea, he joined Curtin University, in Western Australia, lecturing in electronic and computer design. His Masters thesis was accepted in 1978 and he moved to the University of Western Australia to commence PhD studies in Bio-Engineering. Early clinical research focused on reversing male and female infertility using pulsatile infusions of LHRH and GnRH. Moving to the California in 1982, he designed a number of powerful computer arrays, including one which was used in the early P.E.T. scanners from Hamamatsu Photonics, of Japan. Pharmacokinetic data collected while a Visiting Scientist at the Hospital for Sick Children, in Toronto, formed the basis of his studies in diabetes, for which he was awarded a PhD by the University of Western Australia in 1985. The emergence of *in silico* biology in the late 1990's allowed his expertise in powerful scientific computers to be leveraged into the study of chronic human disease. He is currently Director of the Californian Autoimmunity Research Foundation, which he joined in 2004. Prof. Marshall is the holder of several patents, and was awarded two orphan designations by the US FDA for minocycline and clindamycin in the treatment of sarcoidosis. West China Hospital recently signed a collaboration agreement which will result in a number of joint research projects.

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