



# TARGETING THE TUMOUR MICROVASCULATURE ENHANCING THE EFFECTS OF VASCULAR DISRUPTING AGENTS

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Colorectal cancer (CRC) is the second most frequent cancer in Australia, resulting in over 4,000 deaths annually, with liver metastasis being the predominant cause. Recent strategies for treatment have focussed on selective targeting of the tumour vasculature, either alone or in combination with systemic chemotherapy. Two types of anti-angiogenic agents have been developed to specifically target the tumour vasculature. The first includes the angioinhibitory agents (AIA) that target immature vessels and inhibit the development of new vessels. The second includes the vascular disruptive agents (VDAs) that specifically target the mature tumour vasculature. We have

previously tested the efficacy of a novel VDA Oxi4503 (Oxigene), in a model of colorectal liver metastases. VDAs reduce the bulk of the tumour mass. However, a consistent finding and cause of tumour recurrence is the persistence of a viable rim of tumour tissue at the periphery of the tumour-host interface. The characterisation of the microvasculature and cellular characteristics of this persistent viable rim forms the basis of this project. Our aim is to determine the reasons behind the persistence of the viable tumour cells at the periphery of the original tumour after treatment with VDAs, and to overcome this limitation by strategies which target the remaining rim to enhance overall tumour eradication.

## Techniques:

Animal models  
Angiogenesis assays  
FACS analysis  
Immunostaining  
Laser Doppler flowmetry  
Laser Confocal in vivo microscopy  
Microvascular casting and SEM  
RT-PCR  
Western blots

## Projects

1. Demonstration of key differences between the peripheral and central tumour microenvironments.
2. Characterising pro-angiogenic and molecular changes in the viable rim following VDA Oxi4503 treatment.
3. The effect of angioinhibitory agents on the tumour vasculature- Ultrastructure study.
4. Tumour growth and survival following combination AIA and VDA therapy.
5. Changes in tumour microcirculation and angiogenic growth factors in the viable rim following AIA and VDA therapy.

## Publications:

Chan, L et al. Targeting the tumour vasculature. (Review) (Accepted 5/08) ANZ J Surgery.

Chan LS, Malcontenti-Wilson C, Muralidharan V, Christophi C. Alterations in the Vascular Architecture and permeability following Oxi4503 Treatment. *Anticancer Drugs*. 2008 Jan;19(1):17-22.

Malcontenti-Wilson C, Chan L, Nikfarjam M, Daruwalla J, Muralidharan V, Christophi C. Treatment of Colorectal Liver Metastases with Vascular Targeting Agent Oxi4503. *Journal of Gastroenterology & Hepatology*, Epub ahead of print June 2007.