

QIMR Seminar

Genetics and Population Health Division
Cancer and Cell Biology Division



Dr Nikolas Konstantin Haass

Cameron Melanoma Research Fellow, Centenary Institute of Cancer Medicine and Cell Biology, Newton, NSW

Dr has obtained his PhD in 1998 through the Department of Cell Biology, German Cancer Centre, Heidelberg, Germany with a thesis on gene structure, expression and intracellular localisation of pantophysin. In 1999 he took up residency in the Department of Dermatology and Venerology at the University Hospital Hamburg-Eppendorf until moving to the United States in 2003 where he undertook a Postdoctoral Fellowship at the Wistar Institute in Philadelphia. He has been a Cameron Melanoma Research Fellow and Senior Lecturer at the Faculty of Medicine/Dermatology, Royal Prince Alfred Hospital, The University of Sydney, NSW, Australia, and at the Centenary Institute of Cancer Medicine and Cell Biology in Sydney since 2007.

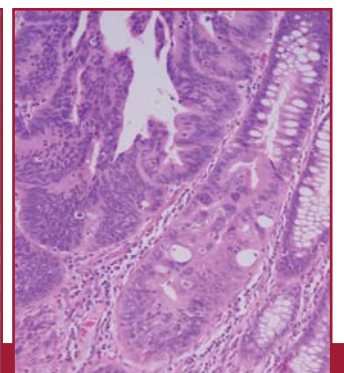
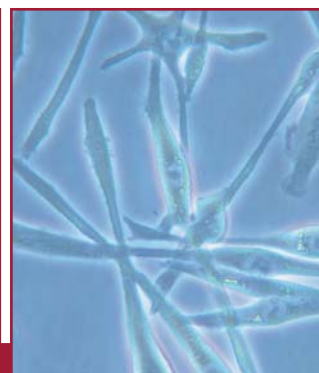
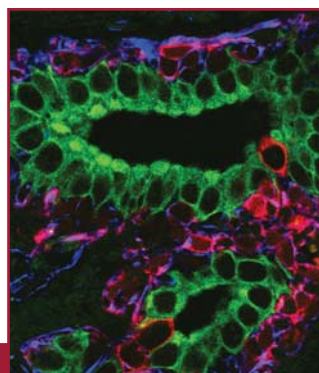
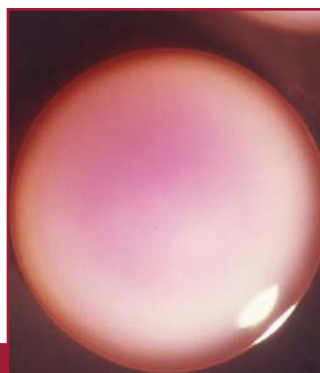
Targeted therapy of melanoma: Novel kinase inhibitors with potent and specific anti-melanoma activity

The findings that the mitogen-activated protein kinase (MAPK) pathway is constitutively active in melanoma and that 66% of melanomas harbour the activating B-RafV600E mutation has raised expectations for targeting this pathway for therapy. As preclinical studies *in vitro* often poorly predict the outcome of clinical studies we have developed a novel culture model which better compares to the *in vivo* situation: melanoma cells grown as three-dimensional spheroids are implanted into collagen to mimic tumour architecture and microenvironment. We investigated the anti-melanoma activity of the MEK1/2 inhibitor AZD6244 and the specific B-RafV600E inhibitor PLX4720 in our 3D model and *in vivo*. AZD6244 is cytostatic as a monotherapy in melanoma, but cytotoxic when combined with the taxane docetaxel *in vitro*. AZD6244 fully inhibits tumour growth at well-tolerated doses and causes tumour regression when combined with docetaxel *in vivo*. PLX4720 blocks proliferation exclusively in melanoma cells harbouring the B-RafV600E mutation and leads to tumour regression *in vitro* and *in vivo*.

We show here inhibitors that directly target the MAPK pathway in melanoma to correlate *in vitro* and *in vivo* data. Given their better potency and specificity these novel drugs are important candidates as second generation small molecule therapeutics.



Queensland Institute of
Medical Research



1.00 pm Thursday 17 July 2008

Westpac Auditorium, Bancroft Centre, QIMR