



HARRY PERKINS INSTITUTE
OF MEDICAL RESEARCH



PERKINS Seminar Series

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TUESDAY 16 FEBRUARY



Associate Professor Nikolas Haass

Principal Research Fellow

The University of Queensland Diamantina Institute

"Dynamic melanoma heterogeneity and cell cycle-specific drug resistance"

Nikolas Haass is an Associate Professor at The University of Queensland Diamantina Institute/Translational Research Institute, Honorary Associate Professor at The University of Sydney and Adjunct Associate Faculty member at the Centenary Institute. After obtaining his PhD at the German Cancer Research Center/Heidelberg University, he trained as a dermatologist with a focus on cutaneous oncology at the University Hospital Hamburg-Eppendorf, Germany. He then spent five years at the Wistar Institute (University of Pennsylvania) in Philadelphia, as a post-doctoral fellow funded by the German Research Foundation. As a Cameron Melanoma Research Fellow from October 2007 to February 2013, he headed the group, 'Experimental Melanoma Therapy' at the Centenary Institute. In March 2013 he commenced his current position at UQDI. Using cutting-edge technology, such as real-time imaging of melanoma cells in 3D culture and *in vivo*, he and his team investigate the biology of tumour heterogeneity and the role of differential subpopulations of melanoma cells in melanomagenesis with the goal to develop novel therapeutic approaches by simultaneously targeting these differential subpopulations.

ABSTRACT

Metastatic melanoma is still highly therapy-resistant. Targeted therapy with signalling pathway inhibitors holds great promise but suffers from rapid onset of drug resistance. It is conceivable that this relates, in part, to tumour heterogeneity. Tumour heterogeneity is a feature of solid cancers that are typically composed of irregular regions of cells actively undergoing cell cycle, zones of quiescent cells, and other areas where cells invade into the surrounding tissues. The principal goal of our research has been and is to achieve a better understanding of this aspect of melanoma biology that will eventually put us in a position to contribute to the development of better anti-melanoma drugs.

Cutting-edge imaging technology and the fluorescent cell cycle indicator, FUCCI, revealed that 3D melanoma spheroids *in vitro* and melanoma xenografts *in vivo* display two distinct proliferative phenotypes characterised by differential subcompartmental distribution of G₁-arrested and cycling cells. We discovered that the master regulator of melanocyte biology, Microphthalmia-associated Transcription Factor (MITF), regulates this tumour subcompartmentalisation and thus dynamic heterogeneity. It is conceivable that neoplastic cells exhibit differential drug sensitivity based on their residence in specific cell cycle phases. In fact, we have demonstrated that G₁-arrested melanoma cells, irrespective of the underlying cause mediating G₁-arrest, are resistant to apoptosis induced by the proteasome inhibitor bortezomib or the alkylating agent temozolomide. In contrast, G₁-arrested cells were more sensitive to MAPK pathway inhibitor-induced cell death. Of clinical relevance, pre-treatment of melanoma cells with a MAPK pathway inhibitor, which induced G₁-arrest, resulted in resistance to temozolomide or bortezomib. On the other hand, pre-treatment with temozolomide, which induced G₂-arrest, did not result in resistance to MAPK pathway inhibitors. In summary, we have (1) established a model to study the effects of the cell cycle on drug sensitivity and (2) that cell cycle phase-specific drug resistance is an escape mechanism of melanoma cells that has implications on the choice and timing of drug combination therapies.

Therefore, we postulate that if we can understand how MITF drives cell cycle subcompartmentalisation within melanoma we will have better control of cancer progression by targeted therapy. We will use our model to test new therapy approaches and drug combinations.

Future plan: Over the next 5 years we will expand both research and clinical foci by optimizing our existing and developing new models and translate the work into the clinics. To do so, we have already established active collaborations: A/Prof H. Schaidt (UQ), Prof M. Herlyn (Philadelphia, USA), Prof. C. Wellbrock (Manchester, UK), Prof B. Gabrielli (UQ) & Prof W. Weninger (Centenary), dynamic melanoma heterogeneity, cell cycle and drug resistance; Prof P. Leedman (UWA), targeting miR-7-5p/RelA/NF-κB signalling; Prof P. Hersey (USyd), Prof D. Huang (WEHI) & Dr J. Allen (Garvan), targeting the intrinsic apoptosis pathway; Prof J. Rasko & A/Prof J. Holst (Centenary), targeting glutamine transport; Prof S. Menzies (USyd), high-risk melanoma clinic. Our work also provides important links with the pharmaceutical industry. We have/had industrial collaborations with Astra Zeneca, Abbott/AbbVie, Roche/Plexxikon, Genentech, OncoBeta, Novogen.

3:30pm till 4:30pm

SEMINAR ROOM G24, HARRY PERKINS INSTITUTE OF MEDICAL RESEARCH, NORTH CAMPUS

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Aberdare Rd

To Perth

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Your Guide to the



HARRY PERKINS INSTITUTE OF MEDICAL RESEARCH

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E

F

Campsie St

Verdun St

Kingston St

Geiradner Dr

Hospital Ave

Winthrop Ave

Kings Park

Child Care
Under Construction

Under Construction

Lions Eye Inst

Under Construction

Staff Car Park 4

HARRY PERKINS INSTITUTE

PathWest

Hollywood Private Hospital

Visitor Car Park 3A

Car Park 7B

Staff Car Park 6



Western Power Sub Station

Staff Car Park 3

Staff Car Park 7A

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UWA Car Park

Under Construction (New Children's Hospital)

To Stirling Hwy

Monash Ave

Visitor Car Park 7 8.00am - 4.00pm

Emergency Helipad

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Emergency Helipad

Visitor Car Park 1

Visitor and Staff Multi Deck Car Park (Entry off Winthrop Ave Only)

To Harry Perkins

Main Entrance

E Street

G Street

Main Entrance & Admissions

EMERGENCY

Waiting Walk

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Staff Car Park 7A

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