

Melanoma season is coming – so are better treatments for it

Better drug combinations to treat late-stage melanoma are on their way thanks to research published today by Centenary Institute scientists in Sydney.

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As we head into another Australian summer, many are now aware of the very real risk of skin cancer that comes with it. Prevention is working, but we need to get better at treating melanoma. Melanoma affects some 10,000 Australians every year. Nowadays, because of better prevention, many of these cancers are caught early and cut out before they metastasise or spread.

But some get through the net. And it is these late-stage melanomas, which kill about 1430 Australians each year, that Centenary researchers are targeting. Metastasising cancers are typically difficult to treat.

Earlier this year, two new anti-melanoma drugs were approved in the US, but tumours build up resistance to them after a few months, allowing the cancer to come back. Dr Nikolas Haass, PhD student Nethia Mohana-Kumaran and their colleagues at the Centenary Institute thought that using combinations of another group of drugs could offer a way forward.

This second group of potential drugs encourages cancer cells to kill themselves. This works fine for some leukaemias but melanomas and many other common cancers are resistant. The Centenary scientists have been exploring how to make this approach work in melanoma.

In today's publication in the journal *Clinical Cancer Research*, the researchers showed – in the test-tube - that when they stimulated certain parts of the cancer cells' suicide mechanism prior to treatment with this second group of drugs melanoma lose their resistance and become 100 times more sensitive to the drug. When they followed this up with trials with mice, however, they found the new drugs were not soluble enough to penetrate deep into the tumour and destroy all the cells.

So Dr Haass and the team are now investigating ways to get around this by trying a different similar drug combination that is potentially better at penetrating the tumour. There are no quick solutions in melanoma research, but if everything goes well this approach could extend the usefulness of the new drugs to a much wider range of cancers, including melanoma and other hard cases.

“This shows fundamental research can provide clues to treating a cancer that is known to so many Australians,” says Centenary Institute Executive Director Professor Matthew Vadas.

Australia's new Health Minister Tanya Plibersek met with Dr Haass and discussed his research during her visit to Centenary Institute on Wednesday, ahead of her swearing in by the Governor General.

- For interviews contact: Dr Nikolas Haass +61 2 9565 6245
- For paper and full release go to: <http://www.scienceinpublic.com.au/centenary> or call Andrew Wight on +61 3 9398 1416.

Background information, citation, abstract and about the author

Melanoma Facts:

- Australia (along with NZ) has the world's highest incidence rate for melanoma.
- In 2008, there were more than 10,300 cases diagnosed and 1430 deaths from melanoma.
- Early detection and surgical removal is the main therapy for early stage melanoma.
- For late-stage melanomas, there is no routine therapy, but there are many drugs undergoing clinical trials to change this.
- Five year survival for people diagnosed with melanoma is 92%, rising to 99% if the melanoma is detected before it has spread. If spread, the five year survival is 65%, dropping to 15% if the disease is widespread.

Source: <http://bit.ly/hpdgzs>

Citation

Modulation of NOXA and MCL-1 as a strategy for sensitizing melanoma cells to the BH3-mimetic ABT-737

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Abstract

Purpose: Drug resistance in melanoma is commonly attributed to ineffective apoptosis pathways. Inhibiting antiapoptotic BCL-2 and its relatives is an attractive strategy for sensitizing lymphoid malignancies to drugs but it has been largely unsuccessful for melanoma and other solid tumors. ABT-737, a small-molecule BH3-mimetic, selectively inhibits BCL-2, BCL-XL and BCL-w and shows promise for treating leukemia, lymphoma and small cell lung cancer. Melanoma cells are insensitive to ABT-737 but MCL-1 inhibition reportedly increases the sensitivity of other tumors to the compound.

Experimental Design: The efficacy of MCL-1 and BFL-1 inhibition for sensitizing melanoma cells to

ABT-737 was investigated by shRNA-mediated knockdown or overexpression of their antagonist NOXA in two-dimensional cell culture, a three dimensional organotypic spheroid model, and an *in vivo* model.

Results: *MCL-1* downregulation or *NOXA* overexpression strongly sensitized melanoma cells to ABT-737 *in vitro*. NOXA-inducing cytotoxic drugs also strongly sensitized melanomas to ABT-737 although, surprisingly, not *vice versa*. The drugs most suitable are not necessarily those normally used to treat melanoma. Resistance to ABT-737 occurred quickly in 3D melanoma spheroids through reduced NOXA expression although experiments with both xenografts and 3D spheroids suggest that penetration of ABT-737 into tumor masses may be the principal limitation, which may be obviated through use of more diffusible BH3-mimetics.

Conclusion: Sensitization of tumors to BH3-mimetics by cytotoxic drugs that induce NOXA is a therapeutic strategy worth exploring for the treatment of melanoma and other solid cancers.

About Nickolas Haass

Dr Nickolas Haass is a dermatologist and cell biologist who leads Centenary Institute's Melanoma research project. Nickolas and his team are looking at ways to improve existing late-stage melanoma therapies.

About the Centenary Institute:

Centenary Institute's dedicated scientists conduct fundamental research to understand the work of the body's genes, cells and proteins. Centenary's affiliation with the RPA Hospital and the University of Sydney means they can translate directly the discoveries in the lab to prevent diseases that affect so many of us.

More at: <http://www.centenary.org.au/>