

August 15, 2008

Prototype Test for Predicting Clinical Outcome for Melanoma Patients Gene signature prognostication of rapid progression from Stage III to Stage IV

Investigators from the Melbourne Centre of the international Ludwig Institute for Cancer Research (LICR) and Pacific Edge Biotechnology Ltd today reported that they have developed a test to predict whether a patient will progress rapidly from Stage III melanoma to metastatic Stage IV cancer and death.

More than 70% of patients with Stage III melanoma — melanoma that has spread to the lymph nodes — will typically have a rapid time to progression (TTP) to Stage IV melanoma, and succumb to their disease within five years of their diagnosis. However, the remaining <30% of patients will have a slow TTP to Stage IV and will have prolonged survival. Not being able to distinguish between these patient subtypes means that some patients might undergo aggressive, often toxic, treatments unnecessarily. The unpredictable and significant discrepancies in TTP and survival could also cloud the interpretation of results from clinical trials of new melanoma therapies.

The LICR Melbourne team, together with collaborators from Pacific Edge Biotechnology Limited in New Zealand, has developed a prototype test that can distinguish between these two patient subtypes with 85-90% accuracy. However, the team cautions that these findings must be validated in a larger number of patients before the test can be applied routinely as a prognostic tool.

According to the senior author of the study, LICR's Professor Jonathan Cebon, M.D., the predictive test could assist patients and their health care teams in making treatment decisions. Perhaps most importantly, being able to distinguish between the subtypes could have a tremendous impact on the development of new melanoma therapies. "One of the major problems we have in clinical trials for new melanoma therapies is that we can't identify the people who are going to have a slower disease progression no matter what they receive in a clinical trial," says Professor Cebon. "When new treatments are tested it is necessary to show clinical benefit by comparing patients who receive the new therapy with those who do not. Although patients might all have the same type of cancers, there can be big differences in their survival simply because their cancers behave differently - and this may have nothing to do with the treatment. If we are able to identify the good players and the bad players up-front, it becomes a whole lot easier figuring out whether good results are due to the new treatment or not. Most importantly far fewer patients would be needed for the clinical trials. It's partly because we can't clinically identify subtypes of patients that we have to do very large and very expensive trials. And, of course, this increases the time it takes to test the clinical benefit of potential new therapies."

The joint Australian/New Zealand team used microarrays to measure the expression of more than 30,000 genes in lymph node sections taken from 29 patients with Stage III melanoma. There were 2,140 genes differentially expressed in the sections from people who had already had a "poor" outcome (average TTP of just four months) and patients that had had a "good" outcome (average TTP of 40+ months). Using statistical analyses, the team identified 21 genes that could be used to differentiate

between the two subtypes of patients in the retrospective analysis. This gene signature was then used to prospectively analyze another 10 patients, with the clinical outcome for nine of the 10 (90%) patients proving to be predicted accurately. The one patient who was incorrectly predicted to have a “good” prognosis did have a rapid TTP to Stage IV. However, this patient went on to have a prolonged survival of six years. The team also applied the test to published data sets and showed they could get a prediction accuracy of 85%, even though data was not available for all 21 genes in the published literature.

This study, published in *Clinical Cancer Research*, was conducted under the auspices of the Hilton – Ludwig Cancer Metastasis Initiative. It was led by investigators from: LICR Melbourne Center, Austin Health, Melbourne, Australia; Department of Biochemistry, University of Otago, Otago, New Zealand; Pacific Edge Biotechnology Limited, Dunedin, New Zealand, and; Department of Statistics, University of Auckland, Auckland, New Zealand.