

ASX ANNOUNCEMENT

NATURE PUBLICATION FOR CELLMID'S MIDKINE IN CANCER

- Findings that midkine plays an essential role in the metastatic spread of malignant melanomas were published in the prestigious journal *NATURE*
- Cellmid holds the most significant global IP portfolio around midkine globally
- This high quality independent study provides strong validation of Cellmid's cancer therapeutic and diagnostic programs targeting midkine

SYDNEY: Monday, 3 July 2017, Cellmid Limited (ASX: CDY) is pleased to advise that the highest ranked paper *Nature* has published the results of a significant study showing for the first time that midkine, around which the Company holds extensive intellectual property rights, is a crucial agent in the promotion of melanoma metastasis.

The paper, entitled "*Whole-body imaging of lymphovascular niches identifies pre-metastatic roles of midkine*", by Professor Marisol Soengas and her group based in CNIO in Madrid, describes how midkine drives the often-fatal metastatic spread of melanoma cells from the primary tumour in the skin to distant organs such as liver, lung, bone and brain.

This independent study published in *Nature* is highly significant for Cellmid for four key reasons:

- It provides strong validation for Cellmid's cancer therapeutic and diagnostic programs, which use the Company's proprietary midkine antibodies;
- It adds to the considerable data on the prognostic value of detecting midkine in different cancer types, where elevated midkine levels in various tissues correspond with poor therapeutic outcomes;
- It significantly increases visibility and credibility of Cellmid's cancer therapeutic programs targeting midkine; and
- As the holder of the most significant intellectual property and antibody assets around midkine globally the publication places the Company in a unique position for partnerships.

The Company's antibodies against midkine have already shown considerable promise in reducing tumour growth and restricting new blood supply to different solid tumours (some of these results have been released in ASX announcements on 3 October 2013 and 5 October 2016). Together with these new discoveries around metastasis, inhibiting midkine for better treatment of melanoma becomes a compelling drug development program for Cellmid.

While most conventional anti-cancer treatments aim to kill rapidly dividing tumour cells, the ability to stop the spread of metastatic tumour cells would be of immense benefit for many advanced cancer patients with diverse tumour types.

It is widely accepted that lymphatic vessels are often the escape route for cancer cells to spread initially to nearby lymph nodes, followed by metastasis to more distant vital organs. The sprouting of new lymphatic vessels from the tumour into surrounding lymph nodes was thought to facilitate this step-wise metastatic spread via a process called lymphangiogenesis.

However, the group at CNIO in Madrid used a sophisticated mouse model to demonstrate that the primary tumour induces aberrant lymphangiogenesis in lymph nodes and organs located at considerable distances from the tumour, creating a pre-metastatic niche for tumour cells to lodge in.

Importantly, midkine release from the tumour was found to stimulate distant lymphangiogenesis, creating a route for cancer cells to colonize sites throughout the body independent of local spread into lymph nodes adjacent to the primary tumour.

Midkine also enhanced the ability of tumour cells to adhere to lymphatic vessels. Therefore, midkine not only promotes lymphangiogenesis, but also tumour cell colonization in newly formed lymphatic vessels.

These actions of midkine extend Cellmid's current knowledge about midkine's role in tumours as well as in blood vessel formation and cellular interactions throughout the body. Together with previous studies, the current findings provide strong rationale for Cellmid's oncology program targeting midkine with therapeutic antibodies.

In their *Nature News and Views* commentary on the study, Hoshino and Lyden from Weill Cornell Medicine in New York describe how "...MDK (*midkine*) downregulation in an aggressive melanoma led to drastic inhibition of lymphangiogenesis, and reduced number of metastases", concluding that this work "...might open a door to diagnostic and therapeutic strategies that aim to deal with metastases before they arise".

David Olmeda, lead author on the Nature paper, lends further support for Cellmid's midkine program in oncology "...we focussed on... *MIDKINE*, because it was new and could represent an alternative therapeutic target".

Details of the study and results

An engineered mouse model was used to conduct the study that incorporates a very sensitive bioluminescent reporter called luciferase with the *Vegfr3* gene that specifically mediates lymphangiogenesis. This model enables researchers to track aberrant lymphatic vessel formation by imaging internal light generation in living tissues of mice in the presence of implanted tumours that have different metastatic potentials.

Detailed *in vivo* imaging of melanoma tumour-bearing mice revealed distinct patterns of new lymphatic development, with lymph vessel formation at distant sites proceeding independently of lymphangiogenesis around the primary tumour. In addition, the ability of tumour cells to colonize distal lymph nodes and organs was not linked to lymphangiogenesis in the proximity of the tumour. These findings represent fundamental new paradigms in understanding metastatic spread from primary tumours and are likely a general feature of many cancer types.

Removal of primary tumours dampened distal lymphangiogenesis, indicating that factors released by melanoma cells drive pre-metastatic niche formation. However, presence of VEGFC in the tumour - the most likely angiogenic factor to control lymphangiogenesis - did not influence distal lymphangiogenesis and metastases, suggesting that other tumour-derived factors may be involved.

The lack of correlation between VEGFC and melanoma tumour metastasis led the researchers to perform proteomic profiling to compare the factors released by melanoma cells with high versus low metastatic potential. The most highly ranked candidate that had not previously been studied in this context was identified as midkine.

While midkine has been extensively investigated in other tumour types and has been shown to promote metastasis by blood vessel growth, inflammatory signalling and cell proliferation, it has not previously been linked to lymphangiogenesis.

Marisol Soengas and colleagues carried out gain and loss-of-function experiments to manipulate midkine expression in melanomas with low or conversely high metastatic and lymphangiogenic potential to demonstrate that midkine is essential for creation of the pre-metastatic niche in aberrant lymphatic vessels at distal sites. The cellular action of midkine in mediating lymphangiogenesis and tumour cell adhesion to lymphatic vessels was then examined *in vitro* by examining the attachment and spreading of tumour cells in the presence of confluent monolayers of lymphatic endothelial cells.

Treatment with midkine protein stimulated the movement of melanoma cells across and through the lymphatic cell layer, indicating that midkine secreted by tumour cells into circulating lymph and/or blood may influence tumour cell colonization of distal premetastatic niches.

Further evidence for the ability of midkine to influence dynamic interactions between tumour cells and the lymph node microenvironment was obtained by intravital multiphoton imaging. Melanoma cells expressing midkine were observed actively invading lymphatic vessels, while the same tumour cells in which midkine had been silenced were static and showed no dynamic interaction with lymph cells.

The group then explored the clinical relevance of these experimental findings by showing that high midkine levels in lymph nodes taken from melanoma patients was prognostic for poor outcomes. Kaplan-Meier survival curves comparing melanoma patients stratified for high vs low midkine showed that more than twice the number of patients with low midkine were disease free at 8 years compared to patients with high midkine expression in lymph nodes ($p=0.0243$).

As disease-free survival was defined as the time interval between diagnosis and the development of the earliest metastasis detected at any anatomical site, this analysis combined with hazard ratios of 2.76 ($p=0.005$) by Cox regression univariate model shows a strong association between midkine and metastasis in melanoma patients. Multivariate modelling showed the prognostic value of midkine was independent of other factors such as age, gender and Breslow score, a prognostic measure of how deeply the tumour has invaded into the skin.

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Cellmid Limited (ASX: CDY)

Cellmid is an Australian life sciences company with lead programs in multiple disease indications. The Company, through its wholly owned subsidiaries, Lyramid, Kinera and Advangen, develops and markets innovative novel therapies and diagnostic tests for fibrotic diseases, cancer, ischemic diseases of the heart and hair loss. Cellmid holds the largest and most comprehensive portfolio of intellectual property relating to the novel targets midkine (MK) and FGF5 globally. Intellectual property pertaining midkine is being exploited through wholly owned subsidiaries Lyramid and Kinera. Advangen, Cellmid's consumer health business, sells its FGF5 inhibitor hair growth products in Australia, Japan and the USA and currently expanding distribution in other territories. For further information, please see www.cellmid.com.au and www.evolisproducts.com.au.

Investment in life sciences companies

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