ASX ANNOUNCEMENT

SIGNIFICANT NEW FINDINGS PUBLISHED ON MIDKINE

- **Recently published study findings show Cellmid's midkine antibodies prevented heart muscle damage and preserved function**
- **To date there is no established, safe therapy for chronic inflammatory heart disease – urgent clinical need to develop new therapies**
- **The publication is the most recent result of the Midkine Symposia – platform for multiple partnerships and collaborations with leaders in science and clinic**
- **Reviewed by Chief Editor of Nature Reviews Cardiology, giving the Company its second exposure to the high-ranking journal family**
- **Cellmid now plans to validate further findings, the subject of a patent application, using its antibodies for autoimmune myocarditis triggered by checkpoint inhibitors as cancer treatments**

SYDNEY: Thursday, 7 February 2019, Cellmid Limited (ASX: CDY) is pleased to advise that the prestigious *Journal of Experimental Medicine* has published a significant study showing for the first time that midkine, around which the Company holds extensive intellectual property rights, promotes cardiac muscle inflammation associated with the occasionally fatal autoimmune disease, myocarditis. Cellmid's midkine antibodies prevented cardiac muscle damage due to rampant inflammation, thereby reducing fibrosis and preserving cardiac function.

The paper, entitled "*Midkine drives cardiac inflammation by promoting neutrophil trafficking and NETosis in myocarditis*", by Cellmid collaborators Dr Ludwig Weckbach and Professor Barbara Walzog based at the Biomedical Center und Klinikum der Universitat, Ludwig Maximillian University (LMU), describes how midkine is key to the inflammatory processes of myocarditis leading to cardiomyopathy and end-stage heart failure.

This highly significant publication is yet another example of the value and importance of the Company's biennial Midkine Symposia, most recently held in Munich and hosted by Dr Weckbach and his team from LMU, and delivers critical benefits for Cellmid as follows:

- The data published further validates the Company's patent application covering the use of midkine antibodies for the treatment of myocarditis (filed Jan 2018);
- By showing efficacy in a clinical indication with urgent need for treatment it increases the value, visibility and credibility of Cellmid's midkine assets;
- As the holder of the most significant intellectual property assets around midkine globally, the publication provides the Company with exposure to and a strong platform for partnerships.

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Chief Editor of *Nature Reviews Cardiology*, Dr Gregory Lim, released Editorial Comment on the findings, reinforcing the potential of the efficacy of Cellmid's midkine antibodies. In his *Editorial Comment,* Dr Lim explained the significance of identifying neutrophil extracellular traps (NETs) for the first time in cardiac biopsies from patients with myocarditis, as well as from mice with experimental autoimmune myocarditis. He has also outlined the molecular detail by which midkine promotes neutrophil recruitment and NETosis involving the low-density lipoprotein receptor-related protein 1, pointing to a clear mechanism of action by which Cellmid's reagents provide therapeutic benefit in myocarditis.

The role of neutrophils in NETosis is becoming accepted as a critical initiating step in many chronic inflammatory disorders. By providing the experimental evidence for midkine's contribution to the early development of myocarditis, the current publication extends previous clinical studies that found elevated cardiac midkine in myocarditis patients.

Cellmid's antibodies against midkine have already shown considerable promise in other inflammatory and autoimmune disorders including chronic kidney disease and a model of multiple sclerosis called experimental autoimmune encephalitis (ASX announcements: 1 December 2015, 18 January 2017 and 12 September 2018). The common feature of these studies is that blocking midkine modifies the behaviour of immune and inflammatory cells that perpetuate the destructive tissue injury and organ dysfunction associated with several chronic diseases.

Support for the role of midkine in inflammatory processes came from previous studies by Dr Weckbach, who demonstrated that midkine is critical for recruitment of neutrophils into the inflamed tissue. The current study extends these findings with detailed analysis of the molecular and cellular interactions through which midkine promotes neutrophil accumulation in heart tissue.

The finding that Cellmid's midkine antibodies restrict neutrophils from undergoing NETosis in myocarditis places midkine at a pivotal step in progression from the initial acute phase of cardiac muscle injury to chronic heart failure that is a significant cause of mortality in children and young adults. The ability of midkine antibodies to not only limit neutrophil recruitment but also NET formation reinforces the potential of Cellmid's drug development program in inflammatory heart failure.

"*To date, there is no established therapy for patients with chronic inflammatory cardiomyopathy other than non-specific immunosuppression with limited benefit and severe side effects*", said Dr Ludwig Weckbach. "*Blocking midkine or NETs could represent novel and promising therapeutic options for patients with myocarditis*" he added.

As explained by Professor Barbara Walzog: "*We demonstrated that antibody-mediated inhibition of midkine indeed reduced neutrophil infiltration into the heart tissue and led to a significant improvement in heart function. This intervention protected the tissue from undergoing fibrotic remodelling, a process which is a major contributor to heart failure*."

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Important further studies planned as a result of the publication

The findings of midkine's role in autoimmune myocarditis may be relevant to a dangerous side effect of the block-buster new cancer drugs that boost the immune system to combat tumours. By taking the breaks off the immune system, checkpoint inhibitors often cause immune related adverse events that can develop rapidly and, in the case of autoimmune myocarditis, are fatal in approximately one to four percent of all patients treated with checkpoint inhibitors.

While interventions with standard steroidal anti-inflammatory drugs provide some benefit, there is an urgent unmet need to counter the significant problem of immune related adverse events, especially as cancer patients are increasingly treated with combination immunotherapies.

"*The potential of Cellmid's midkine antibodies to alleviate the heart failure experienced by cancer patients may lead to deploying our midkine assets as an adjunct therapy in oncology to work alongside immuno-oncology drugs*" said Head of R&D at Cellmid, Dr Graham Robertson.

Cellmid's midkine antibodies have already demonstrated anti-metastatic and anti-tumour benefits (ASX announcement 3 July 2017). Cellmid plans to explore whether the midkine antibodies will not only improve myocarditis induced by checkpoint inhibitors in cancer patients, but also have a direct anti-cancer action in limiting the spread of primary tumours to other organs.

Details of the study and results

In a series of 14 patients with myocarditis confirmed by endomyocardial biopsy (EMB) and reduced cardiac function assessed by echocardiographic left ventricular ejection fraction, NETs were detected in EMBs of two patients with evidence of parvovirus infection and eight patients with evidence of parvovirus. The presence of polymorphonuclear neutrophils was shown in all 14 biopsies by standard immunohistochemistry while NETs were identified by colocalization of the H2A-H2B-DNA complex, myeloperoxidase and citrullinated histone 3 (H3Cit).

An experimental mouse model of myocarditis (EAM mice) involving injection of myosin heavy chain peptide to elicit autoimmune responses was used to obtain further evidence for the presence of NETs in inflamed cardiac tissue. H3Cit and neutrophil elastase were readily detected amongst extra-cellular DNA 21 days after induction of EAM when inflammatory infiltrate is maximal.

EAM mice were treated with reagents (DNase or Cl-amidine) that block NET formation to elucidate the functional relevance of NET formation for cardiac inflammation. These treatments reduced the EAM inflammatory score ($p<0.05$ DNase vs. vehicle; $p<0.01$ Cl-amidine vs. vehicle) alongside normalised heart/body weight ratio ($p<0.05$) indicating that NETs are required for cardiac inflammation and remodelling.

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Midkine expression was increased 8-fold in the hearts of EAM mice relative to sham mice ($p<0.05$), consistent with midkine's role in neutrophil recruitment. Blocking midkine with a Cellmid antibody that recognizes the midkine protein dramatically reduced the number of neutrophils from 768/mm^2 to 158/mm^2 ($p<0.001$) in heart muscle, together with a 5-fold decrease in the percentage of neutrophils that colocalised with NETs, ($p<0.001$), demonstrating that midkine contributes to both formation of NETs as well as enhancing neutrophil recruitment.

Examination of total inflammatory infiltrate by immunohistochemistry and specific inflammatory cell populations by flow analysis revealed that treatment with the Company's midkine antibody reduced the EAM inflammatory score ($p<0.05$) and diminished the recruitment of leukocytes ($p<0.001$), neutrophils (p,0.05) and T-cells ($p<0.001$), but not macrophages.

In the chronic stage of heart failure in the EAM mice, treatment with Cellmid's midkine antibody out to day 63 attenuated the development fibrosis ($p<0.05$) and improved echocardiographic parameters of heart performance fractional shortening ($p<0.05$) and left ventricular ejection fraction ($p<0.05$).

Detailed mechanistic studies using molecular and cell-based experiments were carried out to show that treatment with Cellmid's midkine antibody blocked leukocyte adhesion, but not rolling, in blood vessels, the essential first step for extravasation of neutrophils into damaged tissue.

The involvement of the potential midkine receptor LRP1 in general leukocyte and neutrophil trafficking was dissected in both in vitro and in vivo experiments that showed an absolute requirement for the interaction between midkine and LRP1 for neutrophil recruitment.

These findings and planned future studies support the therapeutic application of Cellmid's midkine antibodies in the treatment of myocarditis, including myocarditis resulting from injury to the myocardium by toxins, therapeutic agents and other drugs, infectious agents and other autoimmune diseases/conditions.

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Cellmid Limited (ASX: CDY)

Cellmid is an Australian life sciences company with a consumer health business and biotech assets in development. Advangen is Cellmid's wholly owned subsidiary engaged in the development and sale of first in class, best in class, clinically validated anti-aging products for hair, skin and body. Advangen has a range of FGF5 inhibitor hair growth products which are sold in Australia, Japan, USA and China. Advangen has a rich portfolio of hair growth and anti-aging hair care assets which include formulations of products on market, trademarks, patents and patent applications, proprietary assays and manufacturing processes. For further information, please see www.cellmid.com.au and www.myevolis.com.au.

Cellmid also has two wholly owned subsidiaries, Lyramid and Kinera, which develop innovative novel therapies and diagnostic tests for fibrotic diseases, cancer and ischemic diseases of the heart. Cellmid holds the largest and most comprehensive portfolio of intellectual property relating to the novel targets midkine (MK) globally.

Forward looking statements

This announcement may have forward-looking statements that are subject to risks and uncertainties. Such statements involve known and unknown risks that may cause the actual results, performance or achievements of Cellmid to be materially different from the statements in this announcement. Actual results could differ materially depending on factors such as the availability of resources, regulatory environment, the results of marketing and sales activities and competition.

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