ASX ANNOUNCEMENT

CELLMID'S MIDKINE ANTIBODIES SHOW ANTI-TUMOUR ACTIVITY AGAINST BRAIN CANCER

- **Midkine antibodies slow glioblastoma cell growth and reduce brain tumour size**
- **Data adds to findings that midkine antibodies are effective against multiple tumour types alone or in combination with other therapies**
- **New clinical development and collaboration opportunity for Cellmid**

SYDNEY, 5 Oct 2016: Cellmid Limited (ASX: CDY) is pleased to report the results of its preclinical collaboration with Complutense University, Spain, showing anti-midkine antibodies (MK antibodies), produced by its wholly owned subsidiary LYRAMID, are effective in improving tetrahydrocannabinol (THC) treatment response in animal models of cannabinoid resistant glioblastoma multiforme; one of the most common and aggressive forms of brain cancer.

Currently, there is no effective treatment for glioblastoma, with tumours recurring even after the most intensive combination of surgery, radio- and chemotherapy. Existing treatments only extend survival from three months to just over a year, with very few glioblastoma patients surviving beyond three years. Cellmid's collaborators at Complutense University in Madrid have previously shown that high levels of MK were found to be associated with aggressive tumours and poor survival in glioblastoma patients.

Medicinal cannabis has a number of benefits in cancer treatment including relieving pain and nausea, and improving appetite. There is sound scientific evidence that distinct chemical components of cannabis called cannabinoids are potent anti-cancer agents, with direct anti-tumour actions including induction of cancer cell death. However, as for many cancer drugs, tumours can develop resistance to cannabinoids.

In the current study Cellmid's collaborators, led by Professor Guillermo Velasco, observed that MK antibodies, in combination with the cannabinoid THC, inhibited tumour growth in gliomas that are resistant to THC. Overcoming THC resistance highlights a potential treatment strategy using MK antibodies to enhance glioblastoma sensitivity to treatment, and provides a strong rationale for the continued clinical development of MK antibodies to treat brain cancer in combination with cannabinoids.

The results of the study add to the already significant intellectual property assets ready for clinical development by LYRAMID. Furthermore, it provides additional collaboration opportunities with companies focused on improving their existing therapeutic approaches using cannabinoids in the treatment of glioblastoma multiforme.

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Details of the study and results. Evidence for the efficacy of MK antibodies was first obtained from detailed experiments using cultured Glioma Initiating Cells (GICs), a subset of chemo- and radiotherapy resistant tumour cells that are implicated in the recurrence of glioblastoma following treatment. These specialized cells were originally derived from glioma patient tumours and have features of cancer stem cells. Importantly MK levels are very high in GICs compared with other glioma cell cultures. *In vitro* experiments using GICs can help researchers to understand the factors that enable their survival and self-renewal despite anti-cancer treatments.

Treatment of GICs with MK antibodies or the cannabinoid THC separately had only a modest effect on their viability. However, the combination of THC with N-terminal MK antibodies led to dramatically reduced GIC proliferation with significantly less viable GICs ($p<0.01$). In particular, one of the LYRAMID antibodies was very effective at sensitising GICs to THC with almost no glioma cells surviving at the highest dose.

Further experiments comparing four different MK antibodies confirmed that the N-domain antibodies were consistently the most potent in reducing GIC viability when used in combination with THC. Final confirmation of the efficacy was provided by an assay to test capacity of GICs to form neurospheres, which is a proxy for the ability for tumour self-renewal. In combination with THC, the N-terminal binding antibody inhibited the generation of neurospheres to a greater extent than MK antibody or THC treatments alone ($p<0.05$).

To test whether the results using GICs in cell culture conditions would translate into reduced *in vivo* tumour growth Professor Velasco implanted the GICs into mice, and in an effort to mirror the disease in humans allowed the tumors to grow to a detectable size before starting treatment. Mice with tumors were treated with MK antibody and THC treatments and tumour growth was tracked for a further 12 weeks.

While the glioblastoma tumours in mice administered THC alone continued to grow steadily, tumours treated with both THC and the N-domain midkine antibody IP10 grew much slower for the 12-week treatment period and were significantly smaller by the end of the experiment ($p<0.01$). Therefore, in accord with the data from *in vitro* experiments, MK neutralization with N-domain MK antibodies sensitizes tumours to the anti-tumour action of THC.

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Cellmid Limited (ASX: CDY)
Cellmid is an Australian life sciences accelerator 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 to this novel target 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 and Japan, and currently expanding distribution in other territories. For further information, please see www.cellmid.com.au and www.evolisproducts.com.au.

Midkine (MK)
Midkine is a growth factor that is highly expressed during embryonic development. Midkine modulates many important biological interactions such as cell growth, cell migration and cellular adherence. These functions are relevant to cancer, inflammation, autoimmunity, ischemia, nerve growth/repair and wound healing. Midkine is barely detectable in healthy adults and only occurs as a consequence of the pathogenesis of a number of different disorders. Midkine expression is often evident very early in disease onset, even before any apparent physical symptoms. Accordingly, midkine is an important early marker for diagnosing cancers and autoimmune diseases. Finally, midkine is only evident in a disease context, and targeting midkine is not expected to harm normal healthy tissues.

Investment in life sciences companies
There are a number of inherent risks associated with the research, development and commercialisation of pharmaceutical products. Investment in companies specialising in these activities carry specific risks which are different to those associated with trading and manufacturing businesses. As such, these companies should be regarded as highly speculative. Cellmid recommends that investors seek professional advice before making an investment in its shares.

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