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New compound shows promise in treating multiple human cancers

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A new compound, discovered jointly by international pharmaceutical company Servier, headquartered in France, and Vernalis (R&D), a company based in the UK, has been shown by researchers at the Walter and Eliza Hall Institute and Servier to block a protein that is essential for the sustained growth of up to a quarter of all cancers.

The research presents a new way to efficiently kill these cancerous cells and holds promise for the treatment of blood cancers such as acute myeloid leukaemia, lymphoma and multiple myeloma, as well as solid cancers such as melanoma and cancers of the lung and breast. It is published online today in the journal *Nature*.

The Servier compound - S63845 - targets a protein of the BCL2 family, called MCL1, which is essential for the sustained survival of these cancer cells.

Institute scientist Associate Professor Guillaume Lessene, who led the Walter and Eliza Hall Institute's research team in Melbourne, Australia, said the work provided the first clear preclinical evidence that inhibiting MCL1 was effective in targeting several cancer types.

"MCL1 is important for many cancers because it is a pro-survival protein that allows the cancerous cells to evade the process of programmed cell death that normally removes cancer cells from the body," Associate Professor Lessene said. "Extensive studies performed in a variety of cancer models have shown that S63845 potently targets

cancer cells dependent on MCL1 for their survival."

The institute team of Associate Professor Lessene worked with haematologist Associate Professor Andrew Wei and Dr Donia Moujalled from The Alfred Hospital and Servier scientists, to demonstrate that not only was S63845 effective against several cancer types, but that it could also be delivered at doses that were well tolerated by normal cells.

Dr Olivier Geneste, Director of Oncology Research at Servier, said this preclinical research represented major findings regarding the druggability of MCL1, a valuable and highly challenging target. "S63845 was discovered through collaboration with the fragment and structure based discovery expertise at Vernalis," he said. "As part of the ongoing Servier / Novartis collaboration on this target class, clinical development of a MCL1 inhibitor should be launched in the near future."

Associate Professor Lessene said the research provided further evidence of the usefulness of a new class of anti-cancer drugs called BH3 mimetics. "BH3 mimetics inhibit a group of proteins known as the 'pro-survival BCL-2 proteins'," he said. "MCL1 is a member of this protein family, and inhibiting it activates the process of programmed cell death. Walter and Eliza Hall Institute researchers revealed the role of BCL-2 in cancer more than 28 years ago and the essential role of MCL1 for the survival of malignant cells four years ago."

More information: András Kotschy et al. The MCL1 inhibitor S63845 is tolerable and effective in diverse cancer models, *Nature* (2016). DOI: 10.1038/nature19830

Provided by Walter and Eliza Hall Institute