

PAT-SM6 Kills Human Multiple Myeloma Cells

- *In vitro* “proof of concept” for anti-cancer PAT-SM6
- PAT-SM6 kills multiple myeloma cells through two different mechanisms: programmed cell death and complement dependent cytotoxicity

Melbourne, Australia; 8 May, 2013: Patrys Limited (ASX: PAB), a clinical stage biopharmaceutical company, is pleased to announce the publication of a new scientific article in the current edition of the Public Library of Science (PLOS ONE) journal regarding its lead anti-cancer candidate PAT-SM6.

The study confirms both the anti-cancer properties of PAT-SM6 as seen in earlier research and also points to the mechanism by which this occurs in patients with multiple myeloma.

“This is an important study that not only shows that our lead drug candidate (PAT-SM6) actively targets and kills cancerous multiple myeloma cells, it explains the mechanism behind this,” said Dr Marie Roskrow, Chief Executive Officer, Patrys.

“We can see how PAT-SM6 binds to the glucose-regulate protein 78 (GRP78) which is abnormally attached to the outside of multiple myeloma cells and not on the inside as occurs in healthy, non-cancer causing cells. This further validates the potential of PAT-SM6 as an anti-cancer therapy for patients with multiple myeloma.”

The study was conducted in collaboration with the Institute of Pathology, University of Würzburg, Germany.

Lead researcher, Dr. Stephanie Brändlein, examined whether Patrys’ IgM antibody, PAT-SM6, can effectively kill multiple myeloma cells. This study confirmed that PAT-SM6 induces killing of multiple myeloma cells (cytotoxicity). Further, it showed that PAT-SM6 induces cytotoxicity in multiple myeloma cells but not normal cells by interacting with glucose-regulated protein 78 (GRP78).

In a normal cell GRP78 is located inside the cell and plays a crucial role in cell growth and survival. In a malignant multiple myeloma cell, it has been shown that isoforms of GRP78 can exist outside the cells on the cell surface. These isoforms of GRP78 are important for the multiple myeloma cell survival, metastasis and resistance to chemotherapeutics. PAT-SM6 binds to this isoform of GRP78 resulting in inhibition of cell survival and specific killing of the cancer cells.

Laboratory experiments reveal strong binding of PAT-SM6 to the surface of multiple myeloma cell lines and cancer cells isolated from the bone marrow of newly diagnosed as well as relapsed patients. This binding of PAT-SM6 results in killing of the cells through a mechanism called programmed cell death, without releasing any harmful substances. PAT-SM6 shows significant induction of this killing mechanism resulting in high levels of cell death in cells extracted from both newly diagnosed patients and those with refractory and relapsed disease.

PAT-SM6 was also seen to have an additional anti-cancer effect. It was shown to be capable of killing multiple myeloma cells through an additional mechanism called complement dependent cytotoxicity (CDC).

CDC is the immune process by which the binding of PAT-SM6 to the cancer cell activates a cascade of proteins and events inside the cell that ultimately results in their destruction. Compared to the induction of programmed cell death, CDC appears to be moderate, but represents an important additive effect to the main killing mechanism.

“This is an exciting study that demonstrates the ability of PAT-SM6 to effectively kill multiple myeloma cells and strongly supports Patrys’ current Phase I/IIa clinical trial of PAT-SM6 in patients with relapsed and refractory multiple myeloma,” said Dr. Stephanie Brändlein, senior author of the paper.

A summary of the article is available for download at: <http://dx.plos.org/10.1371/journal.pone.0063414>.

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About Patrys Limited:

Based in Melbourne, Australia, Patrys (ASX: PAB) is focused on the development of natural human antibodies as therapies for cancer and other major diseases. Patrys has a deep pipeline of anti-cancer natural human antibodies that enable both internal development and partnering opportunities. More information can be found at www.patrys.com.

About PAT-SM6:

The natural human antibody PAT-SM6 has been shown to have potent anti-cancer properties in a large number of laboratory and animal studies. More specifically, Patrys has now screened PAT-SM6 against more than 200 tumours from individual patients with various cancers, and the product binds to over 90% of the tumours screened regardless of cancer type or patient age, gender or disease stage. With respect to multiple myeloma PAT-SM6 has shown particularly strong promise. Patrys has filed patent applications to cover the PAT-SM6 antibody molecule, disease target, and the mechanism of action. Patrys has successfully completed a Phase I clinical trial to evaluate PAT-SM6 as a therapy for melanoma. In November 2012, Patrys commenced a PAT-SM6 clinical trial in patients with multiple myeloma. Multiple myeloma is a type of bone marrow cancer that affects approximately 1,200 Australians each year with 39% five-year survival rate.

About GRP78 and LDL:

Patrys’ clinical candidate PAT-SM6 binds to a form of Glucose-regulated protein 78 (GRP78), which is expressed on the surface of cancer cells but not detected on the surface of healthy cells. The second target for PAT-SM6 is oxidised low density lipoprotein (oxLDL) and very low-density lipoprotein (VLDL). More specifically, experiments have shown that PAT-SM6 binds to oxLDL, then binds to GRP78 expressed on the surface of cancer cells, and "imports" the oxLDL into the cancer cell, causing intracellular deposition of lipids. Once bound, the PAT-SM6/LDL/GRP78 complex is then internalised into cancer cells inducing apoptosis and cell death. The anti-cancer activity of PAT-SM6 is enhanced in the presence of oxLDL. The potential of GRP78 as a target for cancer therapy is supported by extensive third party literature that has reported several roles played by GRP78 with respect to promoting tumour proliferation, tumour survival, metastasis and resistance to a wide variety of existing anti-cancer therapies. As a result, GRP78 expression has been correlated with an adverse prognosis in melanoma, breast, lung, gastric, hepatocellular and prostate cancer, and drug resistance in breast cancer. Given GRP78's reported roles with respect to several cancers, a molecule such as PAT-SM6 presents a promising anti-cancer treatment to the extent it interferes with the function of GRP78 in cancer.



About Multiple Myeloma:

Multiple myeloma is a type of bone marrow cancer arising from plasma cells, and new therapies are desperately needed to treat patients who become resistant to established chemotherapeutics. There is an estimated 200,000 cases worldwide and the incidence is increasing. The five-year survival of patients is approximately 30% (at 10 years ~20%). Despite new marketed therapies, multiple myeloma remains largely incurable and fatal. The multiple myeloma market is dominated by three major products: Revlimid, Velcade and Thalidomide with combined net sales greater than US\$4.4 Billion in 2011.