**MEDI0639 Targets Dll4**

**Jenkins et al.**

Agents that target the Delta-like ligand 4 (Dll4)-Notch interaction have emerged as a new generation of molecules targeting tumor vasculature. Disrupting this interaction stimulates overdevelopment of the tumor vasculature, decreasing the effective blood supply to the tumor cells and restricting tumor growth. The work by Jenkins and colleagues describes an investigational human therapeutic antibody, MEDI0639, which binds a functional epitope on Dll4 that has not been described previously. Targeting this epitope results in potent modulation of endothelial cell function in vitro and modifies human vessels in vivo, establishing MEDI0639 as a new potential therapeutic to target Dll4.

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**A Glut1 Inhibitor Reduces Cancer Growth In Vitro and In Vivo**

**Liu et al.**

Glucose transporter 1 (Glut1) is upregulated in almost all cancer cells. By coupling chemical synthesis with glucose uptake and cell proliferation assays, Chen and his colleagues identified a Glut1 inhibitor, WZB117. WZB117 was shown to inhibit glycolysis and ATP synthesis, to block Glut1-mediated glucose transport, and to induce cell cycle arrest and senescence. Daily intraperitoneal injection of WZB117 led to significant reduction in the size of tumors grafted on nude mice. WZB117 and drugs cisplatin and paclitaxel show significant synergistic anticancer effects. All these indicate that Glut1 is a potential anticancer target and WZB117 is a candidate for developing anti-Glut1 anticancer drugs.

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**DZNeP/Gemcitabine Combination in Pancreatic Cancer**

**Avan et al.**

Enhancer of Zeste Homolog 2 (EZH2) is upregulated in pancreatic cancer and has been associated with gemcitabine chemoresistance and poor prognosis. To explore its role as a novel therapeutic target, Avan and colleagues evaluated the interaction of the EZH2-inhibitor DZNeP with gemcitabine in pancreatic cancer cells, including primary cultures and spheroids growing in cancer stem cells selective medium. This study shows that DZNeP modulates EZH2/H3K27me3 expression and interacts synergistically with gemcitabine through reduction of CD133+ cells, enhancement of nucleoside transporters hENT1/hCNT1 expression, and inhibition of cell migration. These results provide a scientific rationale for future studies on this novel approach for treatment of pancreatic cancer.

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**BKM120 Alters Microtubule Dynamics at High Concentrations**

**Brachmann et al.**

The pan-phosphoinositide 3-kinase (PI3K) inhibitor BKM120 was found, at high concentrations, to cause cell death in various cellular systems, irrespective of their level of PI3K addiction. Transcriptional and biochemical profiling studies were used to identify the origin of these unexpected and apparently PI3K-independent effects. Brachmann and colleagues show that BKM120, at high concentrations, can act as a microtubule destabilizer via direct tubulin binding. Further analysis of clinical data, such as the assessment of mitotic markers in tumor biopsies from patients treated with BKM120, will be required to fully confirm that the compound off-target activity is not clinically relevant.