# Bulletin Board

## SapC-DOPS shows promise in the treatment of brain tumors

According to a study published in a recent issue of the journal *Molecular Therapy*, the nanovesicle drug saposin-C dioleoylphosphatidylserine (SapC-DOPS) can selectively target and kill cancer cells in the brain. The research, conducted by scientists from Ohio State University Comprehensive Cancer Center – Arthur G James Cancer Hospital and Richard J Solove Research Institute (OH, USA), supports the future development of the drug for the treatment of brain tumors.

The research team used both *in vitro* and *in vivo* studies to demonstrate the ability of SapC-DOPS to cross the blood–brain–tumor barrier, block the growth of tumor blood vessels and cause apoptosis in cancer cells. Using two brain tumor models, including one of glioblastoma multiforme, the specific targeting of the drug was found to be dependent on the presence of phosphatidylserine (PtdSer) in the membrane of cancer cells. This molecular mechanism of targeting was established from studies that included the increase of cell surface expression of PtdSer, a more effective killing capacity of SapC-DOPS, blocking of exposure to PtdSer and inhibition of tumor targeting *in vivo*. Furthermore, the study revealed that, in contrast to traditional chemotherapy, hypoxic cells were more sensitive to cell death induced by SapC-DOPS.

"Few drugs have the capacity to cross the tumor–blood–brain barrier and specifically target tumor cells. Our preclinical study indicates that SapC-DOPS does both and inhibits the growth of new tumor blood vessels, suggesting that this agent could one day be an important treatment for glioblastoma and other solid tumors," commented Balveen Kaur, leader of the study (Ohio State University Comprehensive Cancer Centre).

"Based on our findings, we speculate that SapC-DOPS could have a synergistic effect when combined with chemotherapy or radiation therapy, both of which are known to increase the levels of exposed PtdSer on cancer cells," Kaur explained.

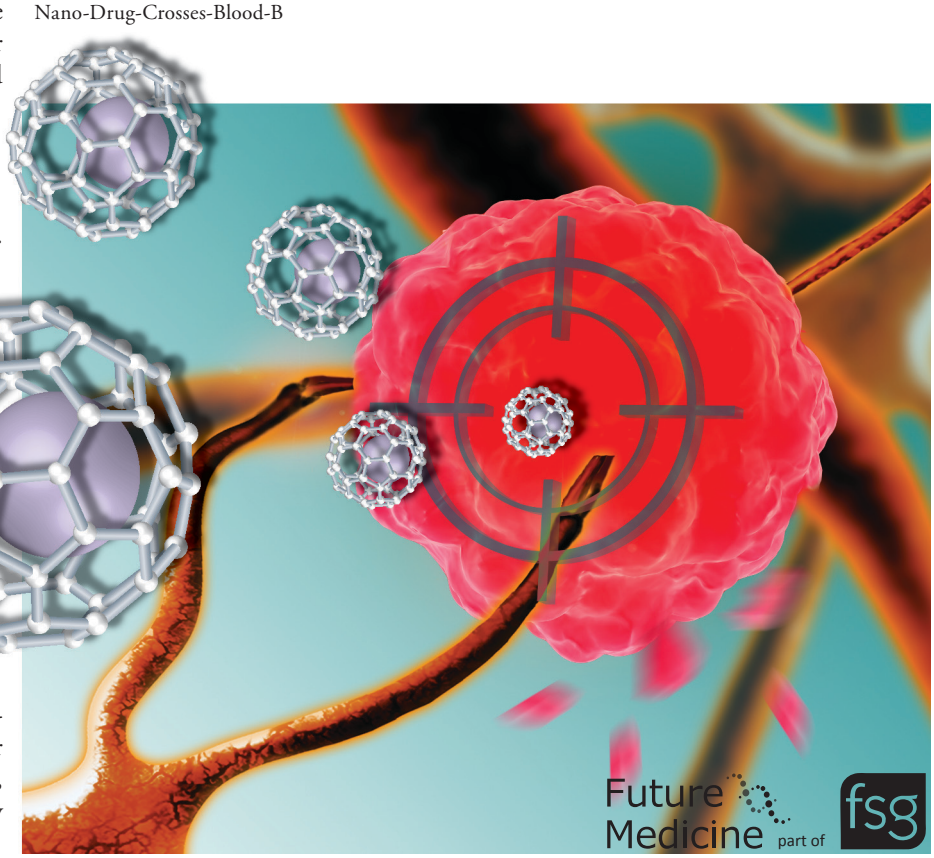
Following this research, it is hoped that SapC-DOPS can be further developed to become a novel anti-tumor and antiangiogenic drug used in the treatment of brain tumors.

– Written by Emma Elliston

Sources: Wojton J, Chu Z, Mathsyaraja H *et al.* Systemic delivery of SapC-DOPS has antiangiogenic and anti-tumor effects against glioblastoma. *Mol. Ther.* doi:10.1038/mt.2013.114 (2013) (Epub ahead of print); Ohio State University Comprehensive Cancer Center press release: http://cancer.osu.edu/mediaroom/releases/Pages/Nano-Drug-Crosses-Blood-B

## in the news...





# European Medicines Agency grants full marketing authorization for pazopanib

GlaxoSmithKline (GSK; London, UK) has announced that the European Medicines Agency has agreed to remove the conditional status of the marketing authorization for Votrient® (pazopanib) and convert it to a full marketing authorization. Granted a conditional licence in the EU in 2010, the specific obligations of the conditional approval included a noninferiority study (COMPARZ) to evaluate the efficacy and safety of pazopanib versus sunitinib.

As presented at the European Society of Medical Oncology Conference 2012, the noninferiority of pazopanib compared with sunitinib (Sutent®) in terms of progression-free survival has been shown.

The Committee for Medicinal Products for Human Use issued a positive opinion on these results in addition to data from other ongoing studies of pazopanib in advanced renal cell carcinoma, and granted full approval for pazopanib's marketing authorization. The decision was ratified by the European Commission in June 2013.

Discussing the decision, Paul Nathan, (Mount Vernon Cancer Centre, Northwood, UK) commented: "We welcome the European Medicines Agency's decision to convert the marketing authorization for pazopanib to a full approval, which is based on emerging clinical data that supports doctors, nurses and patients to make informed choices in the treatment of advanced renal cell carcinoma."

The most common adverse events in the COMPARZ study for pazopanib compared with sunitinib, respectively, included diarrhea (63 vs 57%); fatigue (55 vs 63%); hypertension (46 vs 41%); nausea (45 vs 46%); decreased appetite (37 vs 37%); ALT increase (31 vs 18%); hair colour changes (30 vs 10%); hand–foot syndrome (29 vs 50%); taste alteration (26 vs 36%); and thrombocytopenia (10 vs 34%).

The General Manager of GSK UK, Erik van Snippenberg, commented: "GSK is delighted that the European Medicines Agency has lifted the conditional nature of pazopanib's licence. This is based on the strength of the COMPARZ head-to-head results, which demonstrate that pazopanib is not less effective than sunitinib with a differentiated tolerability profile."

Having received a positive Technology Appraisal Guidance from NICE in February 2011, pazopanib is currently available on the National Health Service (NHS) in England. Pazopanib is also available from NHS Scotland following advice issued by the Scottish Medicines Consortium in March 2011.

– Written by Dominic Chamberlain

Source: GlaxoSmithKline Press release. EMA lifts conditional status for GSK's Votrient® (pazopanib) and grants full approval: www.medicinesresources.nhs.uk/upload/documents/News/2013/GSK%20press%20release.pdf

## About the News

The News highlights some of the most important events and research. If you have newsworthy information, please contact: Francesca Lake, Commissioning Editor, *Future Oncology*, f.lake@futuremedicine.com

# *APOBEC* mutations in the genome have potential to cause cancer

A group of proteins naturally found in the body and involved in immune defense has been implicated in the process of causing cancer. APOBEC cytidine deaminases inactivate viruses and prevent translocations that can disrupt the human genome; however, new findings by researchers from the National Institute of Environmental Health Sciences (NC, USA) in collaboration with a team from the Broad Institute of MIT and Harvard (MA, USA), suggest that APOBEC proteins can induce mutation clusters in human tumors. They examined approximately 1 million mutations in 2680 cancer exomes from 14 different types of cancer, including bladder, cervical, breast, head and neck, and lung cancers, using The Cancer Genome Atlas database. By using APOBEC's distinctive mutation pattern signature they discovered that 68% of all mutations were caused by APOBEC in some types of cancer.

Furthermore, they discovered that in breast cancer HER2 tumors were significantly enriched with the *APOBEC* mutation signature, indicating that *APOBEC* mutagenesis is functionally linked to the development of cancer. The mutational pattern of *APOBEC* was also found in cancer-associated genes, suggesting that *APOBEC*-mediated mutagenesis is carcinogenic.

Steven Roberts, first author of the study, hypothesized that because APOBECs are regulated by the immune system, which is amenable to environmental factors, *APOBEC* mutagenesis could be significantly linked to the environment. He commented: "We hope that determining the environmental link to these mutations will lead to viable cancer prevention strategies."

The team plan to tackle why APOBEC mutagenesis only appears in some cancer types and not in others in future studies.

– Written by Janet Lee

Sources: Roberts SA, Lawrence MS, Klimczak LJ *et al.* An *APOBEC* cytidine deaminase mutagenesis pattern is widespread in human cancers. *Nat. Genet.* doi:10.1038/ng.2702 (2013) (Epub ahead of print); NIH. NIH scientists find that proteins involved in immunity potentially cause cancer: www.nih.gov/news/health/jul2013/niehs-14.htm

# First 3D-guided breast biopsy performed in the USA

The first 3D-guided breast biopsy in the USA was recently performed by radiologists at Magee-Womens Hospital of University of Pittsburgh Medical Center (UPMC; PA, USA). UPMC is now the first center in the USA that offers its patients this advanced biopsy technique. The 3D-guided biopsy system, which has been approved by the US FDA, was developed by Hologic, Inc. (MA, USA). The 3D biopsy procedure has various advantages over the more traditional stereotactic biopsy procedures, such as faster lesion targeting, reduced patient procedure time and reduced radiation exposure.

New 3D-guided biopsies can be beneficial for detecting breast cancers as they allow the localization and precise targeting of regions of interest using 3D mammography. This results in a complete reconstruction of the breast, enabling radiologists to identify particular abnormalities that could otherwise be difficult to detect if only traditional screening techniques were available. Jules Sumkin, chief of radiology at Magee-Womens Hospital, highlighted the potential importance of the 3D biopsy technique: "This biopsy option is especially valuable for women with breast lesions that are hard to reach with standard biopsy procedures, as well as for women with arthritis or other physical issues that make traditional biopsy difficult".

Magee-Womens Hospital is expecting to see the number of women routinely screened for breast cancer increase due to women being offered the latest available technology in mammography and breast biopsies. This may be particularly beneficial as the stage at which breast cancer is detected will influence the chances of survival in the patient. If the cancer is detected early, the 5-year survival rate is 98%. Breast cancer is the second-leading cause of cancer death in women (the leading cause being lung cancer) and statistics suggest that one in eight women will develop the disease in their lifetime.

The new 3D biopsy system complements existing 3D breast cancer screening equipment, which Magee-Womens Hospital radiologists helped to develop, and is known as breast tomosynthesis. The researchers are currently the most widely published group in the USA on this 3D technology, and much of the initial research on the 3D technique was carried out at the hospital: "The ability for us to provide 3D-guided biopsy to our patients represents an exciting new example of our leadership in this area," said Sumkin. "Magee radiologists continue to play a pivotal role in the development and advancement of this technology."

– Written by Jodie Frosdick

Source: UMPC Press release: www.upmc.com/media/NewsReleases/2013/Pages/magee-performs-first-3D-guide

## Priority Paper Alerts

**Parker C, Nilsson S, Heinrich D *et al.* Alpha emitter radium-223 and survival in metastatic prostate cancer. *N. Engl. J. Med.* doi:10.1056/NEJMoa1213755 (2013) (Epub ahead of print).** In this Phase III, randomized, double-blind, placebo-controlled study, the authors randomly assigned 921 patients who had received, were not eligible to receive or declined docetaxel, in a 2:1 ratio, to receive six injections (one injection was administered every 4 weeks) of radium-223 (at a dose of 50 kBq/kg intravenously) or matching placebo. The primary end point was overall survival. The main secondary efficacy end points included time to the first symptomatic skeletal event and various biochemical end points. A prespecified interim analysis, conducted when 314 deaths had occurred, assessed the effect of radium-223 versus placebo on survival. An updated analysis, when 528 deaths had occurred, was performed before crossover from placebo to radium-223. The authors observed at the interim analysis, which involved 809 patients, that radium-223, as compared with placebo, significantly improved overall survival (median: 14.0 vs 11.2 months), which was confirmed by the updated analysis involving 921 patients. Secondary efficacy end points also showed a benefit of radium-233 as compared with placebo. Additionally, radium-223 was associated with low myelosuppression rates and fewer adverse events. The study, which was terminated for efficacy at the prespecified interim analysis, demonstrated that radium-223 improved overall survival.

**Ko AH, Tempero MA, Shan YS *et al.* A multinational Phase 2 study of nanoliposomal irinotecan sucrosofate (PEP02, MM-398) for patients with gemcitabine-refractory metastatic pancreatic cancer. *Br. J. Cancer* doi:10.1038/bjc.2013.408 (2013) (Epub ahead of print).** In this study, the researchers enrolled 40 eligible patients who had metastatic pancreatic adenocarcinoma, Karnofsky Performance Status ≥70, and had progressed following gemcitabine-based therapy. Participants were given an intravenous injection of PEP02 120 mg/m2 every 3 weeks. Simon two-stage design was used and the primary objective was 3-month survival rate. The most common severe adverse events included: abdominal pain, diarrhea, neutropenia and asthenia. Three patients achieved an objective response, with an additional 17 demonstrating stable disease for a minimum of two cycles. Ten out of the 32 patients with an elevated baseline CA19-9 had a greater than 50% biomarker decline. The study met its primary end point with a 3-month survival rate of 75%, with median progression-free survival and overall survival of 2.4 and 5.2 months, respectively. The authors concluded that PEP02 demonstrates moderate anti-tumor activity with a manageable side effect profile for metastatic, gemcitabine-refractory pancreatic cancer patients. A Phase III trial of PEP02 (MM-398), referred to as NAPOLI-1, is currently underway given the limited treatment options available to this patient population.