Evi/Gpr177 as new target in Wnt signaling pathway for treating various cancer types (P-975)

Key facts
The Wnt secretion protein Evi/Grp177

- is upregulated in various cancer types such as astrocytic astrocytoma and its high expression correlates with poor prognosis
- supports tumor cell proliferation, invasion and tumor initiation and prevents apoptosis
- constitutes a validated target for glioma treatment and glioma diagnostics.

Background
Malignant astrocytomas constitute most primary brain tumors with poor prognosis for glioma patients and low long-term survival rates. Glioblastoma, the most aggressive form, are characterized by invasive behavior and a high degree of apoptosis resistance leading to limited treatment options. Despite highly aggressive multimodal therapy, including surgical resection followed by combined radio- and chemotherapy, the median survival of glioblastoma patients has remained as low as 12-14 months throughout the past decade. Lowering the rate of recurrence after tumor removal would greatly improve the poor prognosis for glioma patients.

The Technology
DKFZ inventors now identified the Wnt secretion protein Evi/Gpr177, which is strikingly upregulated during glioma tumorigenesis in a WHO stage-independent way and which correlated with poor prognosis (p = 0.013). SiRNA- and lentiviral shRNA-based silencing of Evi/Gpr177 significantly inhibited glioma cell proliferation and migration (please see Figures below). Additionally an inhibitory antibody against Evi/Gpr177 was invented that significantly reduced Wnt target gene response.

Development Stage
Functional analyses in glioma and glioblastom-derived cancer stem-like cells identified the target molecule as an essential regulator of glioma tumorigenesis. In the following animal studies will be performed, confirming the capability of Evi/Gpr177 as new target for glioma treatment.

Advantages and Commercial Opportunity
Evi/Gpr177 is a core Wnt signalling component and a specific regulator of pan-Wnt protein secretion, affecting both canonical and non-canonical signalling. This fact assigns the protein as vulnerable target for glioma treatment. Additionally its localization in the membrane facilitates the accessibility to antibodies and compounds. Apart from the role as target, Evi/Gpr177 also can be used as diagnostic marker.

Inventors
The invention was jointly conceived by Iris Augustin and Michael Boutros of German Cancer Research Center Heidelberg (DKFZ).

Intellectual Property
A PCT patent application was published as WO 2012/143382, which was nationalized in Europe (EP 2699599) and USA (granted as US 9,062,114)

Reference
1) "The Wnt secretion protein Evi/Gpr177 promotes glioma tumourigenesis." in EMBO Mol Med. 2012 Jan; 4(1): 38-51. by Iris Augustin et al.

2) "Wnt secretion is required to maintain high levels of Wnt activity in colon cancer cells." in Nat Commun. 2013 Oct 28 by Voloshanenko O, Erdmann G, Dubash TD, Augustin I, Metzig M, Moffa G, Hundsrucker C, Kerr G, Sandmann T, Anchang B, Demir K, Boehm C, Leible S, Ball CR, Glimm H, Spang R, Boutros M.

DKFZ Contact:
Dr. Frieder Kern
Deutsches Krebsforschungszentrum
Office of Technology Transfer T010
Email: f.kern@dkfz.de
Tel.: +49-(0)6221-42-2952
Fax: +49-(0)6221-42-2956

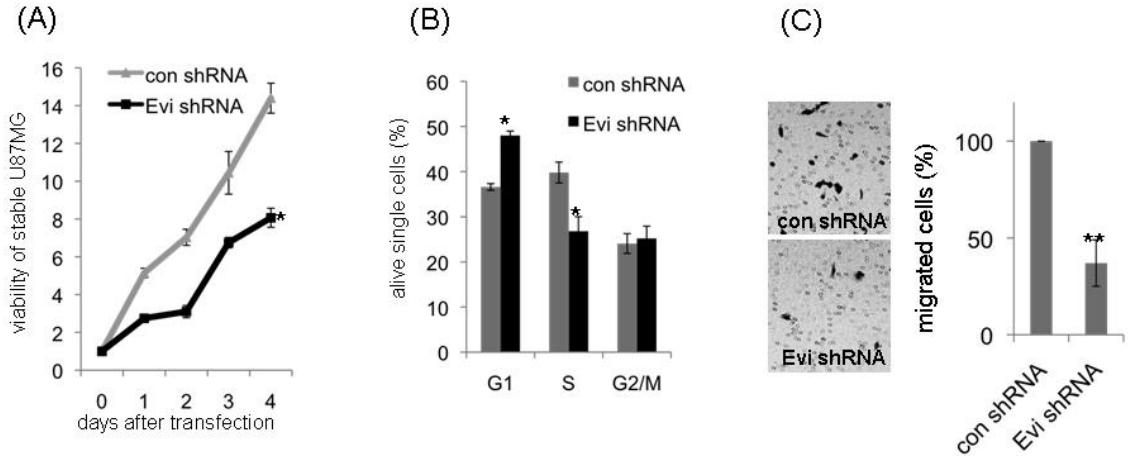

Figure 1: Silencing of the target protein Evi/Gpr177 with shRNA in glioblastoma cells affects proliferation (A), cell cycle (B) and cell migration (C) in comparison to control (con).

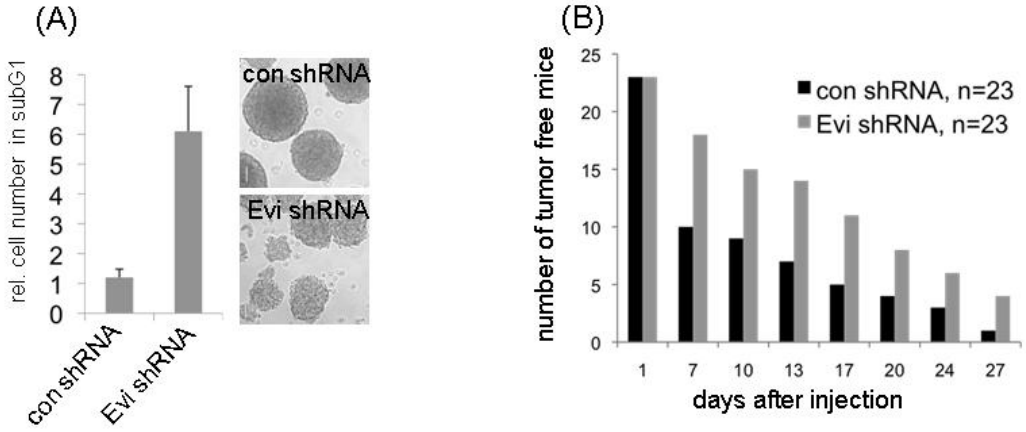

Figure 2: Target validation demonstrated by (A) apoptosis of glioblastoma cancer stem-like cells after Evi/Gpr177 silencing and (B) tumor formation of U87MG cells as xenotransplantation in Nod/Scid mice.

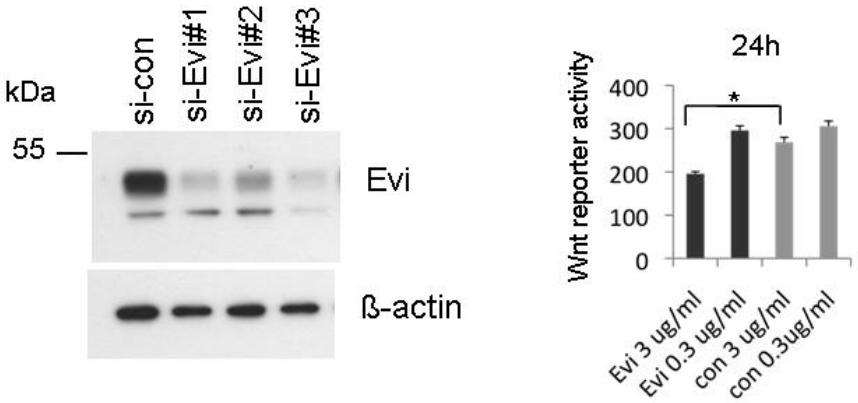

Figure 3: Evi/Gpr177 antibodies reduce Wnt reporter activity.