BG TARGETED TUMOR THERAPY

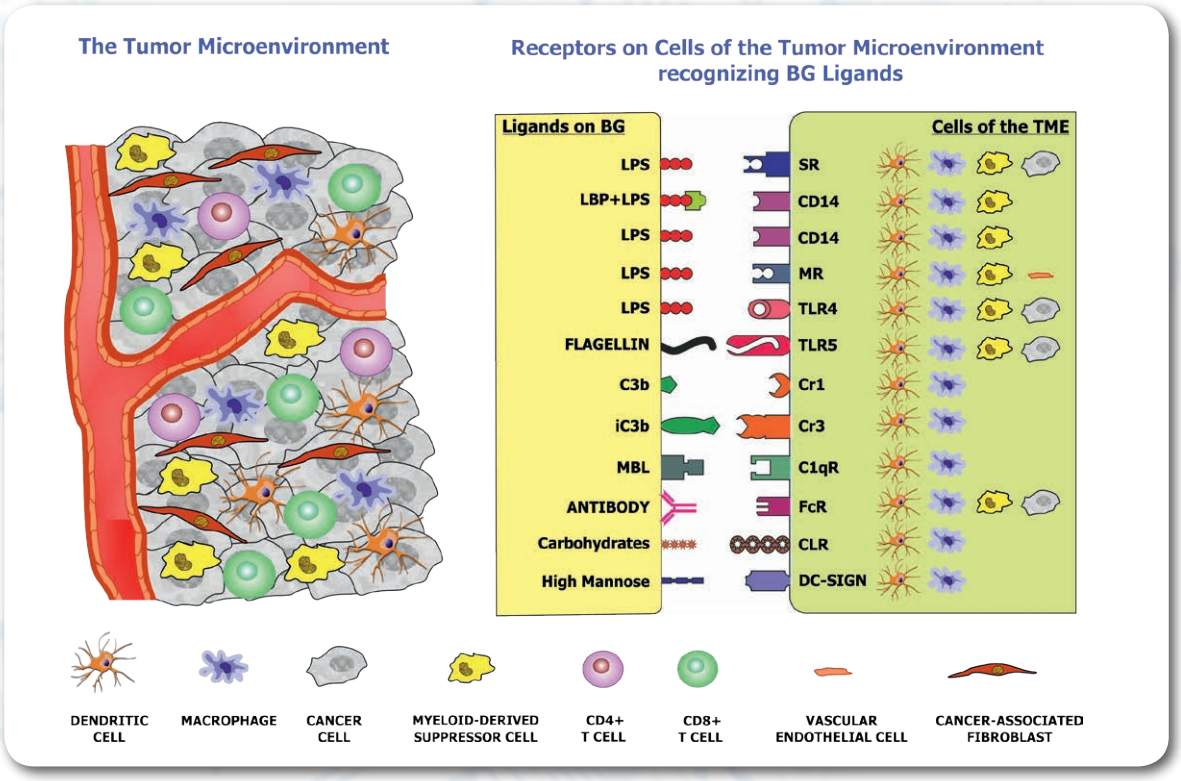
BIRD-C is developing therapeutic cancer vaccines based on personalized dendritic cells-based cancer immunotherapy and on targeting the tumor microenvironment by Bacterial Ghosts (BGs) to stimulate effective anti-tumor T cell immune responses. BGs are empty intact non-living bacterial envelopes of Gram-negative bacteria generated by a proprietary production process.

The aim of BIRD-C tumor therapy strategy is to (re)stimulate the patient's immune system to revert the tumor evasion and to build up strong cellular and humoral immune responses against patient's specific tumor antigens.

TARGETING THE TUMOR MICROENVIRONMENT

Tumors represent complex heterogenous systems built up by cancer cells and distinct non-malignant cell populations including immune cells, cancer-associated fibroblasts, angiogenic vascular cells, lymphatic endothelial cells and other cells actively participating on disease progression all together forming so called tumor microenvironment (TME). The effect of BGs on the TME has been investigated in different animal models and resulted in a provisional EU and US patent application – BGs for the treatment of cancer.

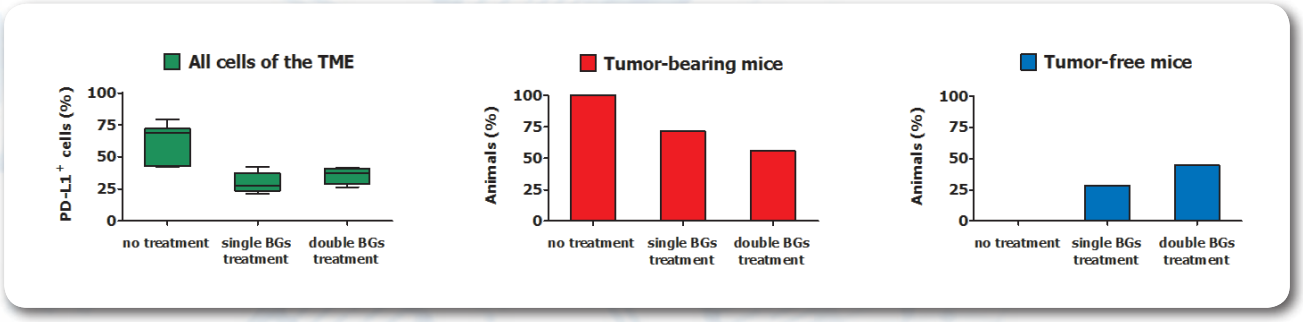
Receptors present on cells within the TME recognize BGs.



In proof of concept studies it was shown that the treatment of intraperitoneal CT-26 (colorectal carcinoma) tumor bearing animals with *E. coli* BGs markedly reduced number of both cancer cells and non-malignant cells expressing immune checkpoint PD-L1 (ligand for programmed cell death protein 1) within the TME and increased numbers of tumor infiltrating helper T cells and dendritic cells which positively correlated with increased treatment doses. Overexpression of PD-L1 is related to poor prognosis and escape of cancer cells from immune surveillance.
Decreased expression of PD-L1 should restore or prime effective anti-tumor immune response. It is assumed, that changes in the TME induced by BGs led to the reduction of tumor burden and immune-mediated eradication of tumors as described in the following graphs.

BG, Bacterial Ghost; CLR, C-type Lectin Receptor; CR, Complement Receptor; DC-SIGN, Dendritic Cell-Specific Intercellular Adhesion Molecule-3 Grabbing Non-integrin; FcR, Fc Receptor; LPS, Lipopolysaccharide; LBP, Lipopolysaccharide Binding Protein; MBL, Mannose Binding Lectin; MR, Mannose Receptor; PD-L1, Ligand for programmed cell death protein 1; SR, Scavenger Receptor; TLR, Membrane-Associated Toll-Like Receptor; TME, Tumor Microenvironment

Targeting the TME: Down-regulation of PD-L1 Expression and Tumor Burden Reduction



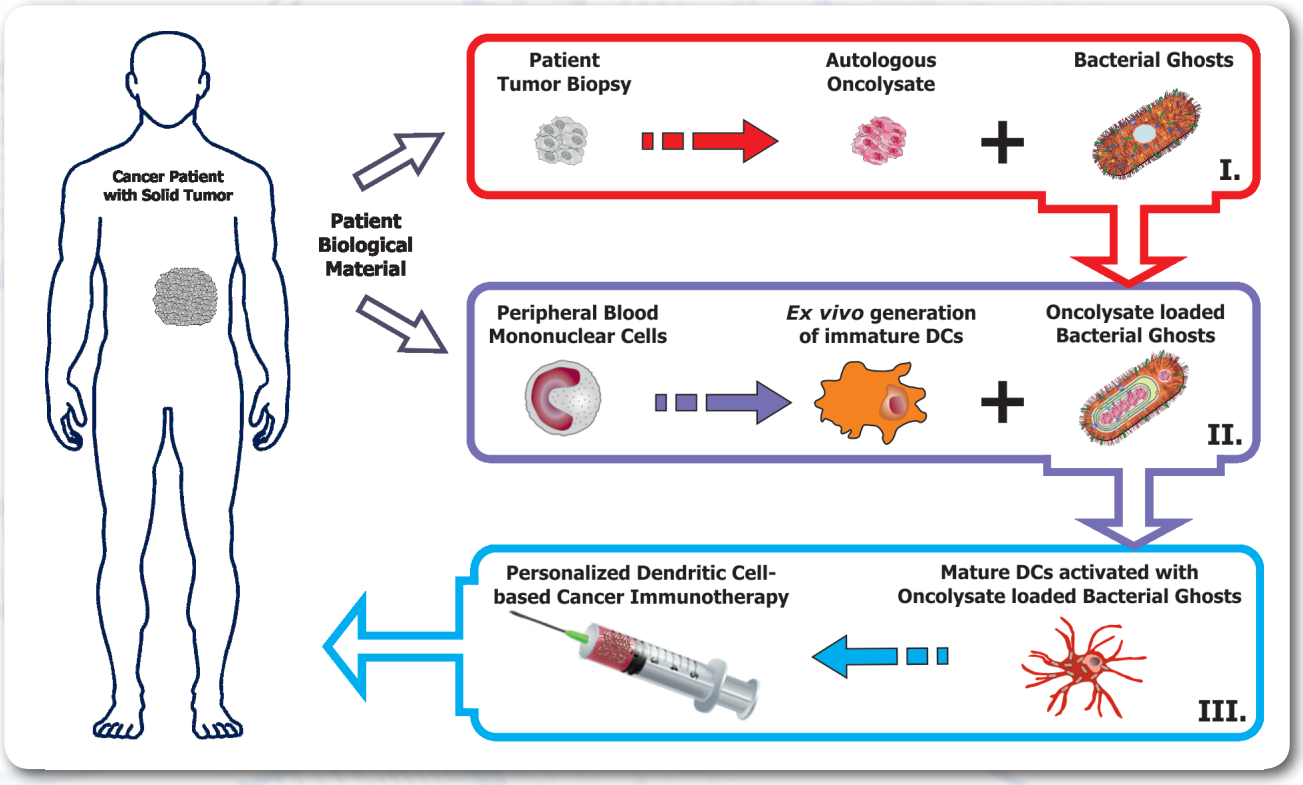
Animals at the section day showed no tumor presence in two out of eight animals, who received single treatment with BGs and no tumor presence in four out of nine animals who received two doses treatment with BGs. All animals from control group without the treatment had fully developed tumors at the section day.

PRECISION MEDICINE: Personalized Dendritic Cell-based Cancer Immunotherapy

Our preclinical data will lead to development of advanced personalized dendritic cell-based cancer immunotherapy for patients with late-stage cancer (patent EP 2 591 798 B1 – Vaccine for tumor immunotherapy).

Ex vivo results confirmed that this one-step BGs mediated antigen delivery and maturation-inducing platform generates dendritic cells capable of inducing prominent proliferation of autologous T helper and cytotoxic T cells that efficiently recognize oncolysate-derived tumor-associated antigens expressed on the surface of native human tumor cells. Combining BGs with tumor antigens present within the oncolysate generated from patient's tumor, real time highly mutated neo-antigens, significantly enhance chances to stimulate effective qualified cytotoxic T cells.

Targeted BG Cancer Immunotherapy: Personalized Dendritic Cell-based Immunotherapy



Sensitization of patient's peripheral blood-generated immature dendritic cells (II) by BGs loaded with the oncolysate obtained from patient tumor biopsy (I) in the presence of IFN-alpha and GM-CSF enhances maturation process of dendritic cells indicated by increased expression of maturation markers and co-stimulatory molecules, and leads to high production of IL-12. Vaccination of patients with *ex vivo* generated autologous mature dendritic cells (III) stimulates effective T cell response against broad spectrum of self highly mutated neo-tumor-associated antigens presented in oncolysate.

BG, Bacterial Ghost; GM-CSF, Granulocyte-Macrophage Colony-Stimulating Factor; IFN, Interferon; IL, Interleukin