7 SUMMARY
The peripheral benzodiazepine receptor (PBR) is a mitochondrial transmembrane protein. It is associated with the permeability transition pore complex which participates in mitochondrial apoptosis pathways. PBR is overexpressed in various tumor entities and may be of functional relevance for tumorigenesis and tumor progression. Thus, the modulation of PBR by specific exogenous ligands represents a promising strategy for the development of innovative drug therapies and for the elucidation of PBR’s function. The aim of this study was to investigate this approach using esophageal carcinoma as a model, which is known for its very poor prognosis and the lack of curative treatment modalities. Experiments were performed using two established esophageal cancer cell lines representing the two different histologies, squamous cell and adenocarcinoma, as well as primary cell cultures of human esophageal carcinoma.

The expression of the mitochondrial PBR was shown both in KYSE-140 (squamous cell) and OE-33 (adenocarcinoma) cell lines, all primary cell cultures, and tissues of esophageal carcinoma. One third of the histological sections displayed an overexpression of PBR in the tumor tissue versus normal mucosa. In KYSE-140 cells, the specific knockdown of PBR by antisense technology led to growth inhibition. Thus, PBR may regulate the proliferation of esophageal cancer cells.

PBR ligands were shown to inhibit the proliferation of esophageal cancer cells in a time- and dose-dependent manner. The drug effects were due to an induction of apoptosis and an arrest of the cell cycle at the G1/S checkpoint. The mechanism of PBR-ligand-induced apoptosis and cell cycle arrest was then elucidated: A disruption of the mitochondrial membrane potential precedes and is required for caspase-3 activation elicited by PBR ligands. Caspase-3-activation then leads to p38MAPK activation which in turn induces DNA fragmentation and G1/S cell cycle arrest.

The antiproliferative effects of PBR ligands were found to be associated with transcriptional alterations of genes involved in the regulation of apoptosis and cell cycle: Using cDNA microarrays and semi-quantitative RT-PCR, a strong up-regulation of the growth arrest and DNA-damage-inducible genes gadd45 and gadd153 was observed in response to PBR ligands. The expression of gadd genes was shown to be regulated by p38MAPK. Gadd genes are known regulators of apoptosis and cell cycle.

Moreover, a PBR-ligand-mediated activation of the mitogenic and anti-apoptotic ERK1/2 was demonstrated. The inhibition of ERK1/2 activation led to an over-additive increase of
apoptosis and cell cycle arrest caused by PBR ligands. The activation of ERK1/2 by PBR ligands may help to design combination therapies in the future.

In conclusion, PBR represents an interesting target for the innovative pharmacological treatment of esophageal carcinoma. The transfer of these innovative therapeutic concepts to the clinical situation should be evaluated \textit{in vivo} and in clinical studies in the future.