Targeting Cancer Initiating Cells in Pancreatic Cancer
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Introduction
Pancreatic ductal adenocarcinoma (PDAC) is the most lethal tumor of the gastrointestinal tract1. The American Cancer Society predicts 37,390 deaths and 43,920 new cases of PDACs in 20172. Currently, surgical resection is the only therapy which can provide a 5-year survival and even with a complete surgical resection, and an adjuvant therapy, the actual 5-year survival is only 12%. The majority of patients succumb to the disease within 20-24 months from their diagnosis3.

The cancer stem cell theory predicts the presence of a subpopulation of cancer cells, the cancer initiating cells (CICs), which has the potential to initiate and sustain tumor progression4. In patients, these cells are thought to be responsible for local recurrence and distant metastases and they have to be eradicated in order to cure a malignant disease5.

Recent studies have demonstrated that a subpopulation of PDAC cells which expresses high levels of aldehyde-dehydrogenase1A1, ALDH1A1, cells, can be identified as a pancreatic cancer initiating population6. These findings underlines the urgent need of anticancer therapeutic strategies which have the potential to target differentiated cancer cells as well as CICs.

To address this need, we have recently focused our attention on a new cancer-specific antigen, the glucose-regulated protein 94 kDa (Grp94). Grp94 is a member of the heat shock protein 90 family and is selectively expressed on the cell surface of cancer cells, but not on normal cells6.

To target this antigen we have generated a fully human monoclonal antibody (mAb), W9, which recognizes an extracellular epitope of Grp94.

Hypothesis
mAb W9 specifically targets pancreatic cancer cells as well as cancer initiating cells and inhibits their growth.

Specific Aims
1. Testing whether mAb W9 selectively stains human PDAC lesions, but not normal human tissues.
2. Determining if Grp94 is expressed in PDAC cell lines.
3. Evaluating the ability of mAb W9, alone or in combination with other chemotherapeutic agents, to inhibit the in vitro proliferation of cancer cells and a subpopulation of pancreatic cancer initiating cells, ALDH1A1 cells.

Conclusions
1. mAb W9 selectively stains human PDAC lesions, but not normal human tissues.
2. Grp94 is overexpressed on the cell surface membrane of several human PDAC cell lines.
3. mAb W9 significantly inhibits the in vitro proliferation of differentiated cancer cells as well as a subpopulation of CICs, ALDH1A1 cells, alone or in combination with other chemotherapeutic agents, such as 5-FU, radiotherapy and cyclopamine (a sonic hedgehog pathway inhibitor).

Methods
Generation of fully human antibody W9
mAb W9 was isolated from a phage display library with human heavy chain and lambda light chain variable region genes. scFv W9 light chain variable region and kappa light chain variable region cDNAs were subcloned into the pGEM-T vector and expressed in bacteria. The supernatant of bacteria expressing scFv W9 light chain variable region and kappa light chain variable region was used as an immunogen and purified antibodies were generated by hybridoma technology.

References