**English summary**

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer-related deaths, with 5-year survival rates below 5%. Most patients present with locally advanced or metastatic disease at diagnosis, and standard chemotherapy treatments yield a limited disease control. The main reasons of this poor prognosis include invasive behavior and multifactorial chemoresistance. Therefore, there is an urgent need to develop novel approaches to inhibit PDAC invasiveness and its chemoresistance. In the current thesis, we focused on: (1) elucidating molecular mechanisms underlying the aggressiveness and chemoresistance of PDAC, in order to identify prognostic markers of treatment response; (2) the study of the therapeutic potential of novel anticancer agents; (3) identifying new treatment strategies that could be readily translated to the clinic.

In **chapter 1**, we provide an introductory overview about pancreatic cancer. In **chapter 2**, we show that EZH2 can play role as a prognostic factor for locally-advanced and metastatic PDAC. Our results showed that EZH2 expression correlated with survival and with the rs6958683 polymorphism in the first cohort of patients, but this polymorphism was not associated with survival in the larger cohorts.

In **chapter 3**, we review the role of miRNAs in initiation and progression of cancer. Moreover, since miRNAs are stable and detectable in human plasma, they could be useful diagnostic or prognostic markers.

In **chapter 4**, we describe the role of miR-211 in gemcitabine activity in PDAC cells with different migratory abilities. Moreover, we evaluated whether miR-211 might affect gemcitabine chemosensitivity and RRM2 expression. Our findings demonstrated that enforced expression of miR-211 with pre-miR-211 is associated with inhibition of the cell proliferation, as well as with reduction of migration and invasion of PDAC cells.

In **chapter 5**, we explored the biological role of galectin-4 (Gal-4) on invasive behavior of several representative primary PDAC cell cultures as well as its impact in regulation of Wnt/β-catenin pathway in pancreatic cancer cells. Our results demonstrated that overexpression of Gal-4 reduced migration and metastasis formation of pancreatic cancer. Moreover, we showed that high expression of gal-4 sensitized PDAC cell to the Wnt/β-catenin inhibitor ICG-001.

In **chapter 6**, the therapeutic potential of the novel Akt inhibitor perifosine in combination with gemcitabine was investigated in PDAC cells. Our findings demonstrated that perifosine inhibited cell growth and interacted synergistically with gemcitabine in PDAC cells with high expression of Akt, while an antagonistic interaction was observed in cells with low Akt expression. Moreover, perifosine enhanced gemcitabine-induced apoptosis in PDAC cells with high Akt expression.

In **chapter 7**, we evaluated the molecular mechanisms underlying the inhibition of lactate dehydrogenase A (LDH-A), using two of the most promising compounds among our new LDH-A inhibitors. We investigated the combination of these two inhibitors with gemcitabine in pancreatic cancer cells in normal and hypoxic conditions. Our results demonstrated that these inhibitors were effective against PDAC cells under hypoxic condition and their combination with gemcitabine was synergistic in PDAC cells under both conditions. In addition, inhibition of LDH-A by the new inhibitors leads to inhibition of cell proliferation, stemness, and migration properties of PDAC cells, especially under hypoxic conditions and increased apoptosis and disturbed cell cycle.

In **chapter 8**, we discuss the results presented in the current thesis and provided our view on the future perspectives in PDAC research.