# CONTENTS

## Chapter 1: INTRODUCTION

Pancreatic cancer, an introductory overview  
1.1. General introduction  
1.2. Pancreas anatomy  
1.3. Epidemiology  
1.4. Risk factors  
1.5. Clinical presentation, diagnosis and management of PDAC  
1.6. Treatment  
1.7. Tumor biology  
1.7.1. Pathogenesis of PDAC  
1.7.2. Genetic alterations  
1.8. Preclinical PDAC models  
1.9. Conclusions and future prospects  
1.10. Outline of the thesis  
1.11. References

## Part 1: GENETICS AND EPIGENETICS FACTORS (Chapters 2-6)

### Chapter 2: Prognostic factors in gemcitabine/cisplatin polychemotherapy regimens in pancreatic cancer: XPD-Lys751Gln polymorphism strikes back

### Chapter 3: A polymorphism in the promoter is associated with EZH2 expression but not with outcome in advanced pancreatic cancer patients

### Chapter 4: An analysis of human equilibrative nucleoside transporter-1, 6 ribonucleoside reductase subunit M1, ribonucleoside reductase subunit M2, and excision repair cross-complementing gene-1 expression in patients with resected pancreas adenocarcinoma: Implications for adjuvant treatment

### Chapter 5: MIRN211 (microRNA 211)

### Chapter 6: High-throughput microRNA (miRNAs) arrays unravel the prognostic role of miR-211 in pancreatic cancer

## Part 2: DRUGS TARGETING KEY SIGNALING PATHWAYS IN NEW MODELS OF PANCREATIC CANCER (Chapters 7-10)

### Chapter 7: Molecular mechanisms involved in the synergistic interaction of the EZH2 inhibitor 3-deazaneplanocin A (DZNeP) with gemcitabine in pancreatic cancer cells

### Chapter 8: Impact of AKT/PI3K signalling pathway in pancreatic cancer and synergistic interaction of the novel Akt inhibitor perifosine with gemcitabine in pancreatic cancer cells
Chapter 9: MET as a potential therapeutic target for the treatment of upper gastrointestinal cancers: characterization of novel c-Met inhibitors for therapeutic intervention

Chapter 10: Enhancement of the antiproliferative activity of gemcitabine by modulation of c-Met pathway in pancreatic cancer

Part 3: NOVEL IN VIVO MODELS TO IMPROVE PROGNOSTIC AND THERAPEUTIC STRATEGIES (Chapters 11-12)

Chapter 11: Crizotinib inhibits metabolic inactivation of gemcitabine in c-Met-driven pancreatic carcinoma

Chapter 12: CYB5A role in pancreatic cancer prognosis and autophagy modulation

Chapter 13: DISCUSSION

Scope 1: Identification of prognostic or predictive markers of treatment response
1.1. XPD-Lys751Gln polymorphism as a prognostic factor
1.2. EZH2 is a prognostic factor for locally-advanced and metastatic
1.3. Do observational studies provide a strong rationale for future trials to validate the best markers for personalized treatment of PDAC patients?
1.4. MicroRNA-211 as a prognostic factor in resected PDAC

Scope 2: Therapeutic potential of novel anticancer agents in treatment of PDAC
2.1. Inhibition of EZH2
2.2. Inhibition of Akt/PI3K signaling pathway
2.3. Antitumor activity of novel c-Met/ALK inhibitor crizotinib

Scope 3: Development of new patient-derived orthotopic mouse PDAC models
3.1. Crizotinib and gemcitabine in c-Met-driven pancreatic carcinoma
3.2. CYB5A as a novel prognostic factor

Conclusions and Future Directions

Chapter 14: English Summary, Samenvatting and Persian summary

English Summary
Samenvatting
Persian summary

Curriculum Vitae

List of publications/Meeting proceedings

Acknowledgements