DOCTORAL THESIS

Luminescent bioprobes for imaging and inhibition of EBV associated cancers

Jiang, Lijun

Date of Award:
2017

ABSTRACT

The high incidence rate of Nasopharyngeal Carcinoma (NPC) in southern China, including Hong Kong, has attracted worldwide attention. According to the Center for Health Protection in Hong Kong, there were 841 new cases of NPC, with 655 cases of males and 186 cases of females in 2013. The development of NPC is highly associated with the infection of one human herpes virus, the Epstein-Barr virus (EBV). Given that the homodimerization of one of the EBV endogenous protein-Epstein-Barr Nuclear Antigen 1 (EBNA1) is essential for both viral genome maintenance and infected-cell survival, thus the interference of EBNA1 homodimerization would be a novel strategy for the inhibition of EBV-positive tumours. In this thesis we devote to conjugate several kinds of organic fluorophores with various EBV-specific peptides in order to achieve the highly responsive and selective imaging, as well as the effective inhibition of EBV-positive tumours *in vitro* and *in vivo*. The first research focused on the conjugation of a styrene pyridine fluorophore with two EBNA1-specific peptides, aiming to develop a dual-probe for the imaging and inhibition of EBV-positive tumour cells. Then we tried to introduce a Nuclear Localization Sequence into the EBNA1-specific peptide, and used an Intra-molecular Charge Transfer characterized fluorophore for the following second research, it showed an impressively responsive signal when the probe binds with EBNA1 both *in vitro* and *in vivo*, more importantly, only 4 μg probe can inhibit 92.8% of growth inhibition of an EBV-positive tumour. Along this line, our last research centred on the further improvement of the imaging by taking advantage of lanthanide.

TABLE OF CONTENT

LIST OF TABLES ix

LIST OF SCHEMES x

LIST OF FIGURES xi

LIST OF SYMBOLS xxix

LIST OF ABBREVIATIONS xxx

CHAPTER 1 INTRODUCTION 1

1.1 Epstein-Barr Virus 2

1.2 Epstein-Barr Nuclear Antigen 1 8

1.3 Molecular imaging 21

1.4 Objective of this thesis 30

1.5 References 32

CHAPTER 2 EBNA1-SPECIFIC LUMINESCENT SMALL MOLECULES FOR THE IMAGING AND INHIBITION OF LATENT EBV-INFECTED TUMOR CELLS 39

2.1 Introduction 40

2.2 Results and Discussion 45

2.3 Conclusion 56

2.4 References 57

CHAPTER 3 TARGETING EBNA1: A THERAPEUTIC APPROACH FOR EBV-RELATED TUMOURS WITH TAILORED RESPONSIVE OPTICAL IMAGING 61

3.1 Introduction 62

3.2 Results and discussion 70

3.3 Conclusion 118

3.4 References 120

CHAPTER 4 EMISSIVE LANTHANIDE PROBES FOR THE IMAGING AND INHIBITION OF EBV-ASSOCIATED DISEASES 124

4.1 Introduction 125

4.2 Results and Discussion 130

4.3 Conclusion 140

4.4 References 142

Chapter 5 EXPERIMENTAL PROCEDURES 144

5.1 Experimental procedures for chapter 2 145

5.2 Experimental procedures for chapter 3 151

5.3 Experimental procedures for chapter 4 167

LIST OF PUBLICATIONS 193

CURRICULUM VITAE 195