

TABLE OF CONTENTS

Abstract.....	i
Resumen.....	iii
Resum.....	v
Acknowledgment.....	vii
List of abbreviations.....	ix
Table of Contents.....	xv
Objectives.....	xviii
Chapter 1. Introduction.....	1
1. Pediatric Brain Tumor (BT).....	1
1.1. Classification and Staging of Pediatric BT.....	2
1.2. Statistics: Incidence, Mortality and Survival Rate.....	4
1.3. Genetic and Environmental Risk Factors.....	5
1.4. Clinical Management of Pediatric Brain Tumor.....	8
2. Nanomedicine – a Promising Tool to Improve the Efficacy of Standard Chemotherapy.....	12
2.1 Polymer Therapeutics.....	17
2.2 Polymer-drug Conjugates: Promising Concept to Increase Therapeutic Effectiveness.....	18
2.3 Polypeptide-based Nanomedicine: a Decent Alternative to PEGylation and Liposomes.....	20
2.3.1. Synthetic Strategies for Functionalised Polypeptide Synthesis.....	21
2.3.1.1. NCA-ROP - The Mechanism and Recent Advances.....	22
2.3.1.2. The Protecting Groups for Direct Fabrication of Polypeptides via NCA-ROP.....	24
2.3.1.3. Covalent Drug Linkage – the Strategic Advantage of Polypeptide-drug Conjugates.....	27
2.3.1.4. Direct Conjugation via Side-chain Available Group.....	28
2.3.1.5. Acid-labile Linkers in Polyglutamate (PGA) Conjugates.....	29
2.3.1.6. Redox responsive linkers in PGA conjugates.....	32
2.3.1.7. Aminoacid or Peptide Spacer as a Linker Strategy for PGA.....	33
2.3.2. Rational Design of Polypeptide-drug conjugates for Cancer Treatment..	34
2.3.2.1. Molecular Weight/size.....	34
2.3.2.2. Polymer Architecture.....	35
2.3.2.3. Surface Charge of Nanoparticles.....	37
2.3.2.4. Ligand Density.....	37
3. Strategies for Brain Drug Delivery.....	37
3.1. Intravenous Administration: Crossing the BBB.....	41
3.2. Local Drug Delivery to the Brain: Intratumoral, Intrathecal, Intracavitary, and Convection-enhanced Therapies.....	43
3.3. Intranasal Administration.....	45
3.3.1. Mechanisms of Intranasal Drug Delivery to the Brain.....	45
3.3.2. Strategies to Increase Mucus Penetration/diffusion of Drug Delivery Systems.....	48
4. Nanomedicine for Brain Tumor Therapy.....	49
4.1. Inorganic Nanomedicines for Brain Tumor Therapy.....	49
4.2. Organic Nanomedicine for Brain Tumor Therapy.....	50
5. References:.....	53
Chapter 2. Rational Design of a Polyglutamate-based Intranasal Platform for Brain Delivery.....	71
2.1. Introduction.....	71
2.2. Results and Discussion.....	75
2.2.1. Synthesis and Characterization of Linear and Star PGA-based Carriers	75

2.2.2. Establishing an Ex Vivo Model for the Study of Mucosal Permeation.....	79
2.2.3. Ex vivo Permeation Studies of Linear and Star Polyglutamates.....	82
2.2.4. Functionalization of StPGA with the Lectin Binding Peptide.....	85
2.2.5. Functionalization of StPGA with the Hyaluronic acid.....	93
2.2.6. LinPGA and StPGA Functionalization with Docosahexaenoic Acid....	101
2.2.7. Exploring the Impact of Crosslinking on Mucosal Permeation.....	105
2.2.8. In vivo Preliminary Biodistribution Data of Selected Intranasal Platforms.....	108
2.3. Conclusions.....	110
2.4. Supplementary Information.....	111
2.5. References.....	140
Chapter 3. Development of Well-defined Poly-L-Glutamate-Palbociclib Conjugates for Pediatric Glioma Treatment.....	147
3.1. Introduction.....	147
3.2. Results and Discussion.....	152
3.2.1. Synthesis of pH-responsive PGA-palbociclib Conjugates using a pH- Sensitive Hydrazone Linker.....	153
3.2.2 Design and Development of Redox-responsive PGA-palbociclib Conjugates using a Disulfide Linker.....	155
3.2.2.1 Synthesis and Physico-chemical Characterization of PGA-SS- Palbociclib Conjugates.....	156
3.2.2.2 Conjugate Solution Conformation Dictates Palbociclib Release Kinetics in a Reducing Environment.....	169
3.2.2.3 Biological Evaluation of PGA-SS-palbociclib Conjugates.....	171
3.2.3 Design and Development of Self-immolative Peptidic Linker for PGA- palbociclib Conjugates.....	177
3.2.3.1 Synthesis and Physico-chemical Characterization of PGA-ValCit- palbociclib Conjugates.....	178
3.2.3.2 Biological Evaluation of PGA-ValCit-palbociclib Conjugates.....	192
3.2.4. Evaluation of a Combination Therapy to Improve the Efficacy of PGA- palbociclib Conjugates.....	198
3.2.5. Encapsulation Strategy with Poloxamers as an Option for the Intranasal Administration of the Combination Therapy PGA-Palbociclib Conjugate: Inavolisib.....	200
3.2.6. In vivo Preliminary Data of Conjugate Biodistribution after Intranasal Administration.....	204
3.3. Conclusions.....	206
3.4. <i>Supplementary Information</i>	207
3.5 References.....	251
Chapter 4. General Discussion.....	258
4.1. A strategy to Improve the Effectiveness of Pediatric Brain Tumor Treatment...	259
4.1.1. Development of an Intranasal Drug Delivery Platform.....	259
4.1.2. In vivo Preliminary Validation of the Intranasal Platform.....	261
4.1.3. Rational Design and Synthesis of Polyglutamates-based Palbociclib Conjugates.....	262
4.1.4. Effect of Physico-chemical Characteristics of Polyglutamates-based Palbociclib Conjugates on their Biological Activity.....	266
4.1.5. Evaluation of the Combination Therapy to Increase the Efficacy of Palbociclib.....	268
4.2. References.....	268
Chapter 5. Final Conclusions.....	270