
TABLE OF CONTENTS

Abstract.....	i
Resumen.....	iii
Resum.....	v
Acknowledgement.....	vii
List of abbreviations.....	ix
Table of content.....	xi
Objectives.....	xiv
Chapter 1. Introduction.....	1
1.1. Historical Overview of Polymer Therapeutics.....	1
1.2. Biomedical Applications of Polyamino Acids within Polymer Therapeutics Field.....	3
1.3. Advanced Design of Polypeptide-based Conjugates.....	7
1.3.1. Design of Structural Components.....	7
1.3.1.1. The Polymeric Matrix.....	7
1.3.1.2. Side-chains modifications: The Linking Moiety.....	8
1.3.1.3. Crosslinking strategies to stabilize self-assembly polypeptide-based therapeutics.....	9
1.3.1.4. Surface Decoration.....	11
1.3.2. Design of Physicochemical Parameters.....	13
1.3.2.1. Effect of Size.....	13
1.3.2.2. Effect of Charge.....	15
1.3.2.3. Effect of Conformation.....	17
1.3.2.4. Effect of Geometry.....	21
1.4. Merging Supramolecular and Polymer Chemistry as a Strategy to Control Polymer Morphology.....	22
1.4.1. Supramolecular Polymers: Principles and Design.....	23
1.5. References.....	26
Chapter 2. Towards Self-Assembling Polyglutamates.....	31
2.1. Introduction.....	31
2.2. Synthesis and Self-assembly of BTA-based Oligophenylalanines.....	34
2.2.1. Synthesis of Oligophenylalanines Blocks.....	34
2.3. Self-assembly Studies.....	37
2.4. Study of BTA-oligophenylalanines with Mono and Diglutamate Termini.....	40
2.5. Study of BTA-oligophenylalanine-based Polyglutamates.....	44
2.6. Understanding the Mechanism of Assembly.....	53
2.7. Self-assembly Studies of F3-based Star-polyelectrolytes including Different Amino Acid Sequences.....	57
2.8. Effect of Counterions on Self-assembly of F3E10.....	61

2.9. Conclusion.....	65
2.10. Supplementary information.....	66
2.11. References.....	73
Chapter 3. Role of aminoacid nature and order on the aqueous self-assembly of BTA-derivatives and corresponding polymers.....	75
3.1. Introduction.....	75
3.2. Synthesis and Self-assembly of Dipeptide Derivatives of BTA.....	76
3.3. Synthesis and Self-assembly of star-PGAs with cores based on Dipeptide Derivatives of BTA.....	82
3.4. Self-assembling of Tripeptide Derivatives of BTA.....	84
3.5. Synthesis and Self-assembly of star-PGAs with cores based on tripeptide Derivatives of BTA.....	92
3.6. Self-assembling of tetrapeptide derivatives of BTA.....	93
3.7. Self-assembly of Tripeptide-derivatives of BTA with Different Chiralities.....	97
3.8. Conclusion.....	98
3.9. Supplementary information.....	99
3.10. References.....	113
Chapter 4. Role of core and chain structure variations on star-PGA self-assembly.....	114
4.1. Introduction.....	114
4.2. Self-assembly of BTA Derivatives with Aromatic Insertions.....	115
4.2.1. Self-assembly of BTA Derivatives with Aromatic Insertions as Hydrochloric Salts.....	115
4.2.2. Self-assembly of stPGA based on ABA-F2 and AIP-F2.....	125
4.3. Effect of Aliphatic Chain Hydrophobicity on Self-assembly of BTA-based Diphenylalanines.....	128
4.3.1. Self-assembly of stPGA Based on F2C2 and F2C12.....	133
4.4. Self-assembly of Complex BTA-based Derivatives.....	135
4.5. Effect of Charge Density on Self-assembly of BTA-based PGAs.....	138
4.6. Conclusion.....	142
4.7. Supplementary Information.....	143
4.8. References.....	152
Chapter 5. Development of poly-l-glutamate based combination conjugates designed as triple negative breast cancer therapy.....	153
5.1. Introduction.....	153
5.2. Optimization of PGA-Fasudil Conjugates as Anticancer Therapeutics.....	155
5.2.1. Synthesis and Characterization of PGA-Fasudil Conjugates - Polymer-drug Linker Optimization.....	155

5.2.2. Drug Release Kinetics of PGA-Fasudil Conjugates.....	159
5.2.3. <i>In vitro</i> Studies of PGA-Fasudil Conjugates.....	160
5.2.4. Synthesis and Characterization of PGA-Fasudil Conjugates – Architectural Optimization.....	163
5.2.5. Plasma Stability of Selected Conjugates.....	164
5.2.5.1. Method Validation.....	165
5.2.5.1.1. Linearity.....	165
5.2.5.1.2. Stability.....	165
5.2.5.1.3. Selectivity.....	166
5.2.5.1.4. Precision and Accuracy.....	166
5.2.5.1.5. Matrix Effect.....	168
5.2.5.1.6. Recovery.....	168
5.2.5.1.7. Process Efficiency.....	168
5.2.5.2. Plasma Stability of the PGA-SS-FAS Conjugate.....	169
5.2.6. <i>In vivo</i> Studies of the PGA-SS-FAS Conjugate.....	170
5.3. Optimization of PGA-Dinaciclilb Conjugates.....	172
5.3.1. Synthesis and Characterization of the Conjugates - Optimization of Polymer-drug Linkers.....	172
5.3.2. Cell Viability studies with PGA-Dinaciclilb Conjugates.....	176
5.3.3. Drug Release Kinetics of Selected PGA-Dinaciclilb Conjugates.....	177
5.4. Optimization of a Polymer-Based Combination Conjugate.....	178
5.5. Conclusion.....	179
5.6. Supplementary information.....	180
5.7. References.....	187
Chapter 6. Supramolecular Stabilization And Crosslinking.....	189
6.1. Introduction.....	189
6.2. Hydrophobic Stabilization of Supramolecular Polymers.....	190
6.3. Polyelectrolyte Crosslinking in Water.....	200
6.4. Conclusion.....	208
6.5. Supplementary Information.....	209
6.6. References.....	211
Chapter 7. General discussion.....	213
Annex. List of compounds.....	224