

## Contents

**Foreword** xv

**Acknowledgments** xvii

<b>1</b>	<b>Antibacterial Carbohydrate Vaccines</b>	<b>1</b>
	<i>Federica Compostella, Laura Morelli, and Luigi Lay</i>	
1.1	Introduction	1
1.1.1	A Brief History of Vaccines	2
1.2	Carbohydrate-Based Vaccines	5
1.2.1	Mechanism of the Immune Response to Carbohydrate-Based Vaccines	12
1.3	Components of Glycoconjugate Vaccines	15
1.3.1	The Carbohydrate Antigen	16
1.3.2	Linkers for Carbohydrate–Protein Conjugation	19
1.3.3	The Carrier Protein	22
1.3.4	The Adjuvant	24
1.4	Technologies Employed for Production of Glycoconjugate Vaccines	25
1.4.1	Traditional Glycoconjugates	26
1.4.2	Glycoconjugates Based on Synthetic Carbohydrate Antigens	28
1.4.2.1	Site-Selective Protein Conjugation	29
1.4.3	Enzymatic and ChemoEnzymatic Approach	30
1.4.4	Bioengineered Glycoconjugates	31
1.4.5	Nanotechnology-Based Glycoconjugate Vaccines	33
1.4.5.1	Outer Membrane Vesicles (OMVs) and Generalized Modules for Membrane Antigens (GMMA)	33
1.4.5.2	Gold Nanoparticles, Liposomes, and Virus-Like Particles	34
1.4.6	Nonprotein-Based Glycoconjugates	36
1.4.7	Noncovalent Vaccines	36
1.5	Conclusion	37
	Acknowledgments	38
	References	39

<b>2</b>	<b>Antifungal Glycoconjugate Vaccines</b>	<b>57</b>
	<i>Linda del Bino, Maria R. Romano, and Roberto Adamo</i>	
2.1	Human Fungal Infections	57
2.2	Immunity Against Fungal Pathogens	59
2.3	Carbohydrate Antigens in Fungal Cell Wall	60
2.4	Glycoconjugate Vaccines Against <i>Candida albicans/Candida auris</i>	61
2.5	Glycoconjugate Vaccines Against <i>Cryptococcus neoformans</i>	64
2.6	Glycoconjugate Vaccines Against <i>Aspergillus fumigatus</i>	66
2.7	Universal Fungal Polysaccharide Antigens	68
2.8	Conclusions and Future Prospects	68
	References	69
<b>3</b>	<b>Carbohydrate-Based Antiviral Vaccines</b>	<b>73</b>
	<i>Adrián Plata and Alberto Fernández-Tejada</i>	
3.1	Introduction	73
3.2	Human Immunodeficiency Virus	74
3.2.1	Vaccine Constructs Derived from gp120 High-Mannose N-Glycan Cluster	75
3.2.1.1	Surface Oligomannose Cluster-Targeting bnAb: 2G12 Antibody	75
3.2.1.2	Synthesis and Immunological Evaluation of 2G12 Epitope Mimics	76
3.2.2	Vaccine Constructs Derived from gp120 First and Second Variable Loops (V1V2)	81
3.2.2.1	V1V2-Targeting bnAbs	81
3.2.2.2	Synthetic V1V2 N-Glycopeptide Antigens as bnAb Epitope Mimics	81
3.2.3	Vaccine Constructs Derived from gp120 Third Variable Loops (V3)	83
3.2.3.1	V3-Targeting bnAbs	83
3.2.3.2	Synthetic Glycoconjugates and N-glycopeptides as V3-Directed bnAb Epitope Mimics	83
3.2.3.3	Synthetic V3 Glycopeptides as bnAb Epitope Mimics	83
3.3	Influenza A Virus	85
3.3.1	Vaccine Constructs Based on Hemagglutinin (HA)	86
3.3.1.1	Hyperglycosylated HA Vaccines	87
3.3.1.2	$\alpha$ -Gal-Based Vaccine Constructs	87
3.3.2	Vaccine Constructs Based on Neuraminidase (NA)	88
3.3.3	Acetalated Dextran as Adjuvant Carrier	89
3.3.4	Multivalent Constructs as Anti-Influenza Inhibitors	89
3.4	Hepatitis C Virus	90
3.5	Ebola Virus	91
3.5.1	Glycoprotein-Based Vaccines	92
3.5.2	Monoclonal Antibodies and Carbohydrate Antiviral Agents as Therapeutics	92
3.6	SARS-CoV-2 Virus	94
3.6.1	Prospective Vaccine Constructs Based on $\alpha$ -Gal Epitope	94
3.6.2	RBD-Based Constructs for Vaccine Development	95

3.6.3	Saponins as Carbohydrate-Based Adjuvant Candidates for COVID-19 Vaccines	95
3.7	Conclusions and Outlook	96
	Acknowledgments	96
	References	97
<b>4</b>	<b>Bacterial Glycolipid Lipid As and Their Potential as Adjuvants</b>	<b>111</b>
	<i>Atsushi Shimoyama and Koichi Fukase</i>	
4.1	Introduction	111
4.2	Bacterial Glycolipid Lipid A: an Innate Immune Stimulant	113
4.3	Vaccines Containing Natural LPS as Adjuvants	117
4.3.1	Cholera Vaccines	117
4.3.2	<i>Salmonella enterica</i> Serovar Typhi Vaccines	117
4.3.3	Other Vaccines	118
4.4	LPS and Lipid A in the Environment or Fermented Foods as Adjuvants	118
4.5	Synthetic and Semisynthetic Lipid As as Adjuvants	120
4.6	Developing Novel Lipid A Adjuvants	121
4.6.1	Parasitic Bacterial Lipid As	121
4.7	Symbiotic Bacterial Lipid As	123
4.8	Lipid A-Based Self-Adjuvanting Vaccines	125
4.9	Conclusions	127
	References	127
<b>5</b>	<b>Antiadhesive Carbohydrates and Glycomimetics</b>	<b>131</b>
	<i>Jonathan Cramer, Lijuan Pang, and Beat Ernst</i>	
5.1	Introduction	131
5.1.1	Carbohydrate-Protein Interactions in Viral Adhesion to Host Cells	131
5.1.2	Bacterial Adhesins and Antiadhesion Therapy	132
5.1.3	Selected Examples	133
5.2	DC-SIGN-Mediated Viral Adhesion and Entry into Myeloid Cells	133
5.2.1	Introduction	133
5.2.2	DC-SIGN Ligands Employing Natural Carbohydrate Epitopes	136
5.2.2.1	Dendrimers	137
5.2.2.2	Nanoparticles	137
5.2.2.3	Polymers	138
5.2.2.4	Other Multivalent Scaffolds	138
5.2.3	DC-SIGN Ligands Employing Carbohydrate Derivatives or Glycomimetics	139
5.2.4	Conclusion and Perspectives	141
5.3	The Bacterial Adhesin FimH	143
5.3.1	UTIs and FimH	143
5.3.2	FimH CRD	143
5.3.3	FimH Antagonists	145
5.3.4	Conclusion and Perspectives	147

5.4	<i>Pseudomonas aeruginosa</i> Virulence Factors (PA-IL and PA-IIL)	148
5.4.1	Introduction	148
5.4.2	Mono- and Oligovalent Glycomimetic PL-Ligands	149
5.4.3	Conclusions and Perspectives	152
5.5	General Aspects	152
	References	153
<b>6</b>	<b>Targeting Carbohydrates in Cancer – Analytical and Biotechnological Tools</b>	<b>161</b>
	<i>Henrique O. Duarte, Joana Gomes, and Celso A. Reis</i>	
6.1	Aberrant Protein Glycosylation in Cancer	161
6.2	Detection and Mapping of Carbohydrate-Based Antigens in Human Neoplastic Tissues	164
6.3	Imaging Mass Spectrometry	164
6.4	<i>In Situ</i> Proximity Ligation Assay	166
6.5	Glycan Microarrays	169
6.6	Glycoengineered <i>In Vitro</i> , <i>In Vivo</i> , and <i>Ex Vivo</i> Models	171
6.7	Structural Elucidation of Glycoconjugates: Glycomic and Glycoproteomic Strategies	176
6.8	Concluding Remarks	182
	List of Abbreviations	183
	References	185
<b>7</b>	<b>Carbohydrate-Specific Monoclonal Antibody Therapeutics</b>	<b>201</b>
	<i>Matthew Lohman, Hannah Rowe, and Peter R. Andreana</i>	
7.1	Introduction	201
7.2	Types of Monoclonal Antibodies	202
7.2.1	IgG Antibodies	202
7.2.2	IgM Antibodies	203
7.2.3	ScFv and Fab Fragments	203
7.3	Humanization of Monoclonal Antibodies	204
7.3.1	CDR Grafting	204
7.3.2	Transgenic Animals	204
7.4	Breakthrough Research	205
7.5	mAbs from Preclinical to Clinical Studies	206
7.6	Globo Series	206
7.6.1	Blood Group	206
7.6.2	Mucin-Attached Glycans	207
7.7	New Treatment Options for Neuroblastoma	207
7.7.1	History of Unituxin	208
7.7.2	What is Unituxin?	209
7.7.3	Challenges with Unituxin	211
7.7.4	mAbs Binding to Neuroblastoma	211
7.7.5	Chimeric and Humanized Anti-GD2 Antibodies	212
7.7.6	Naxitamab as a Potential Alternative for High-Risk Patients	212

7.7.7	Chimeric Antigen Receptors (CARs) Targeting GD2	213
7.8	Summary	214
	List of Abbreviations	215
	References	216
<b>8</b>	<b>Carbohydrates in Tissue Engineering</b>	<b>223</b>
	<i>Laura Russo and Francesco Nicotra</i>	
8.1	Introduction	223
8.2	Biomaterials and Medical Devices: Natural and Synthetic Strategies	224
8.2.1	Carbohydrates as Building Blocks for Medical Device Formulation	224
8.2.1.1	Human Polysaccharides: Glycosaminoglycans (GAGs) and Proteoglycans (PGs)	225
8.2.1.2	Polysaccharides from Plants, Algae, Animal, and Microbial Fermentation	228
8.2.2	Carbohydrates as Signaling Molecules: Opportunities in Tissue Engineering and Regenerative Medicine	233
8.3	Carbohydrates in Animal-Derived Medical Devices: Friends or Foes?	234
8.4	Glycoengineering Application to Regenerative Medicine	235
8.5	Future Opportunities and Major Challenges	237
	Conflict of Interest	237
	References	237
<b>9</b>	<b>Carbohydrate-Based Therapeutics for Lysosomal Storage Disorders</b>	<b>245</b>
	<i>Camilla Matassini, Francesca Clemente, and Francesca Cardona</i>	
9.1	An Introduction to Lysosomal Storage Disorders (LSDs)	245
9.2	Available Treatments for LSDs: The Role of Carbohydrate-Based Therapeutics	248
9.2.1	Enzyme Replacement Therapy (ERT)	250
9.2.2	Substrate Reduction Therapy (SRT)	251
9.2.3	Pharmacological Chaperone Therapy (PCT)	252
9.2.4	Combined ERT/PC Therapy	254
9.3	Mucopolysaccharidoses	254
9.4	Sphingolipidoses	258
9.4.1	Fabry Disease	258
9.4.2	Gaucher Disease	262
9.4.3	Niemann–Pick	267
9.4.4	GM1 Gangliosidosis and Morquio B ( $\beta$ -Gal)	268
9.4.5	GM2 Gangliosidosis ( $\beta$ -Hexosaminidase)	272
9.4.6	Krabbe	275
9.5	Glycogen Storage Disorders	275
9.5.1	Pompe Disease	275
9.6	Glycoproteinoses	277
9.6.1	Fucosidosis	277
9.6.2	$\alpha$ -Mannosidosis	279

9.7	Conclusions	279
	Acknowledgments	282
	Abbreviations and Acronyms	283
	References	284
<b>10</b>	<b>Carbohydrates and Carbohydrate-Based Therapeutics in Alzheimer's Disease</b>	<b>293</b>
	<i>Ana M. Matos, João Barros, and Amélia P. Rauter</i>	
10.1	Introduction	293
10.2	O-GlcNAc Transferase (OGT) and O-GlcNAc Hydrolase (OGA) in Neurodegeneration	295
10.2.1	O-GlcNAc Cycling as a Therapeutic Target Against Alzheimer's Amyloid Plaques and Neurofibrillary Tangles	296
10.2.2	OGA Inhibitors	299
10.2.2.1	PUGNAc	301
10.2.2.2	GlcNAcstatins	305
10.2.2.3	Thiazoline Inhibitors	311
10.3	GalNAc in Neurodegeneration	322
10.4	Chitosan and Derivatives in AD Brain	324
10.5	Cholinesterase Inhibitors	325
10.6	Fyn Kinase Inhibitors	330
10.7	Amyloid Protein-Protein Interaction Inhibitors	334
10.8	Inhibitors of A $\beta$ o and/or Oxidative Stress-Induced Neurotoxicity	338
10.9	Carbohydrate-Protein Interactions as Potential Therapeutic Targets Against AD	341
10.9.1	Lipid-Raft Gangliosides as Membrane Accumulation Sites for Toxic A $\beta$ Aggregates	341
10.9.2	The Role of Microglial Cells in A $\beta$ Brain Clearance	342
10.10	Conclusion	343
	List of Abbreviations	344
	Acknowledgments	347
	References	347
<b>11</b>	<b>Carbohydrate-Based Antithrombotics</b>	<b>353</b>
	<i>Antonella Bisio, Marco Guerrini, and Annamaria Naggi</i>	
11.1	Introduction	353
11.2	Antithrombotic Drugs	354
11.3	Heparin	354
11.4	Mechanism of Interaction with Coagulation Factors	357
11.4.1	Antithrombin-Mediated Activity	357
11.4.2	Heparin Cofactor II Mediated Activity	360
11.4.3	Additional Factors	360
11.4.4	Adverse Effects of Heparin	360
11.4.4.1	Heparin-Induced Thrombocytopenia	361
11.4.4.2	Osteoporosis	361

11.5	Low Molecular Weight Heparins	361
11.5.1	Ultralow Molecular Weight Heparins	363
11.6	Drugs Based on Natural GAG Mixtures	363
11.6.1	The Role of Dermatan Sulfate	364
11.6.2	Sulodexide	364
11.6.3	Danaparoid	365
11.6.4	Mesoglycan	365
11.7	Defibrotide	366
11.8	Pentosan Polysulfate	367
11.9	Fondaparinux and Related Synthetic Oligosaccharides	367
11.10	Chemoenzymatic Synthesis of Oligosaccharides	369
11.11	Conclusions and Perspectives	369
	Acknowledgment	369
	References	370

<b>Index</b>	381
--------------	-----