

Index

Page numbers in *italics* refer to information in figures or tables.

a

- abatacept *11, 158, 181*
- abciximab *167*
- absorption *28, 29*
- acetylation, PSA *97*
- acetylcholinesterase *234*
- N-acetylgalactosamine *81*
- N-acetylglucosamine *81, 83*
- 5-N-acetylneuraminic acid *101*
- ACHIEVE 1 trial *231, 240, 241*
- acromegaly *10, 42*
- acrylic acid *318*
- activated partial thromboplastin time (aPTT) *196, 199, 202*
- activated protein C *5*
- activin receptor-like kinase-1 (ALK1)-Fc *159*
- acute lymphoblastic leukemia *10, 42*
- Adagen® *10, 41, 42, 46*
- ADAMTS-Fc *159*
- adenosine deaminase *10, 41*
- administration, distribution, metabolism and excretion (ADME) *13*
- administration route *29, 30*
 - PEGylated proteins *51*
- adverse effects
 - IL-2 *305, 306*
 - interferon products *131*
 - and liposomes *301, 302*
 - TNF- α *302*
 - *see also* safety; toxicity
- Affibody molecules *274, 275, 276–278*
- afibercept *11, 158, 180*
- African green monkey (COS-7) cells *88*
- aggregation resistance, AlbuAb™ *258, 259*
- alanine scanning epitope mapping *253, 254*
- albiglutide *229, 230*
- albinterferon alpha-2b (alb-IFN) *11, 14, 230, 231, 232, 240, 241*
- Albu tagging technology *291–294*
- AlbuAb™ *249–266*
 - albumin interactions *255, 256*
 - bio-analytical characterization *256–259*
 - biodistribution *260–265*
 - key considerations *252, 253*
 - production of fusions *259*
 - purification *260*
- albuferon, *see* albinterferon alpha-2b (alb-IFN)
- Albufluor *292*
- albumin *285–289*
 - challenges, as a target *253, 254, 255*
 - coupling *9*
 - FcRn recycling *147, 148, 273*
 - FcRn transport of *149, 150*
 - half-life *144, 227, 285*
 - homeostasis *143–145*
 - recycling *35, 36*
 - structure *286, 287*
 - *see also* AlbuAb™; human serum albumin (HSA); recombinant albumin fusion proteins; recombinant human albumin (rHA); serum albumin
- albumin binders *285–289*
- albumin binding *9, 11, 14, 15*
 - covalent *250*
 - FcRn *146, 147, 227, 273, 285*
 - HES conjugates *123*
 - insulin derivatives *289, 290, 291*
 - through ABDs *269–279*
 - through small molecules *285–294*
 - transient *250*

- albumin-binding domains (ABDs) 269–279
 - bispecific 278, 279
 - engineered derivatives 270–272
 - half-life extension *in vivo* 272–276
 - immunogenicity 277, 278
 - PEG mimetics 75
 - scDb 16, 17, 18
 - *see also* AlbuAb™
 - albumin fusion 8, 11, 223–242
 - to complex proteins 233, 234
 - *see also* recombinant albumin fusion
 - albumin fusion proteins, *see* recombinant albumin fusion proteins
 - albutropin 230, 237–240
 - aldonic acid 124
 - alefacept 11, 158, 168
 - alkylation, reductive 46, 47
 - alternative scaffolds 250
 - Alzheimer's amyloid beta (A β) peptide 150
 - Amber technology 48
 - amination, *see* reductive amination
 - amino acid polymers
 - elastin-like 64, 69, 70, 77
 - gelatin-like 64, 68, 69, 77
 - genetic 64, 70, 71, 77
 - homo-amino-acid 64, 72, 73, 77
 - PAS polymers 64, 73–75, 77
 - polyanionic 64, 70, 77
 - in recombinant PEG mimetics 65–67, 76, 77
 - amino acid sequences
 - naturally occurring 67, 68
 - PEG mimetics 64
 - 3-amino-propionaldehyde-diethylacetal 125
 - 2-aminoethyl methacrylate hydrochloride 318
 - amylopectin 118
 - anaphylactoid reaction 122
 - anemia 4, 10, 42, 89, 127, 193, 230
 - animal species
 - albumin as a target 252, 253, 254
 - albumin fusion proteins 238, 239
 - mammalian cell expression 175
 - anionic polymerization 321, 326
 - anthrax toxin receptor 159
 - anti-coagulants 5
 - anti-drug antibody 76
 - anti-TNF Fab 10
 - antibodies 5
 - anti-drug 76
 - bispecific 15, 16
 - domain antibodies 251, 252
 - elimination half-life 55
 - engineering 170, 207–216
 - Fab fusions 170, 171
 - Fc-mediated functions 166, 167
 - FcRn inhibitors 215
 - heavy chain 252, 255, 256, 259, 262
 - pharmacokinetics 28
 - PSA and 95–108
 - without the FC region 171, 172
 - antibody-dependent cellular cytotoxicity 165, 166
 - antibody fragments 5, 43, 157
 - Albu tagging 292–294
 - clinical applications 158
 - from IgG–FcRn engineering 213–215
 - polysialylation 107
 - antigen 13 repeats 64, 67, 68
 - Aranesp® 10, 127, 128, 129, 130
 - area-under-the-concentration-time curve (AUC) 26, 27, 78
 - albumin fusion proteins 238, 239
 - EPO 129, 130
 - Epo-Fc 193, 194
 - HES-IFN α 135, 136
 - rFIXFc 194, 196, 198
 - scDb 17
 - arginase 10
 - asialoglycoproteins (ASGP) 84, 103
 - asparaginase 10, 106
 - asparagine residue 81, 82
 - astrocytomas 99
 - atomic force microscopy (AFM) 100
 - autoimmunity 215
 - average steady state concentration ($C_{ss,av}$) 27
 - asymmetric flow field flow fractionation (aFFFF) 132, 133
 - azapropazone 288
 - azo-components 334, 335
- b**
- B-type natriuretic factor (BNP) 230
 - B7.1-Fc 159, 180
 - barbourin 230
 - basiliximab 158
 - BB fragment 272, 277, 278
 - Benefix® 196, 232, 238, 239
 - β 2-microglobulin (B2M) 143, 145, 147
 - bifunctional linker approaches 126
 - bilirubin 286
 - binding affinity
 - ABD derivatives 271
 - AlbuAb™ 252
 - IgG and albumin to FcRn 145–147, 191

- bioavailability (*F*) 24, 25, 27
 - oral 28
 - PEGylated proteins 51
- biodegradability
 - biopolymers 95
 - nanoparticles 323, 333
 - PEG mimetics 77
 - PEGylated proteins 117
- biodegradable/recombinant tails 250
- biodistribution
 - AlbuDAb™ 260–265
 - IL-2-liposomes 305
 - PEGylated proteins 54
 - TNF- α liposomes 303
- biopolymers 95
- biotropin 91
- bispecific albumin-binding domains 278, 279
- bispecific antibodies 15, 16
- blood–brain barrier (BBB) 150, 210, 315, 330
- bone marrow-derived cells 147, 148
- bone marrow microvascular endothelial cells 330
- bone repair 319
- Bowman’s capsule 65
- BP1700-Fc 159
- BR3 11, 159
- brain
 - blood–brain barrier 150, 210, 315, 330
 - FcRn expression in 148, 150, 210
- breast cancer 43, 170, 172, 180, 274
- briobacept 11
- butyrylcholinesterase (BChE) 230, 232, 234
- c**
- calcitonin 4
- Campostar® 43
- cancer 10
 - Fc fusion proteins 180
- cancer therapy 4, 10, 11
 - albumin technology 230
 - antibody constructs 170, 171
 - G-CSFs 276
 - PEGylated liposomes 301, 302–306
 - PEGylated proteins 43
 - polyanionic polymers 70
 - PSA and 99
 - scDbs 15–18, 273, 274
 - *see also specific cancers*
- carbohydrate chains, glycosylation 81, 82
- carboxyl-terminal peptide (CTP) 84, 85, 86–92
- catabolism 144
 - hypercatabolism 143, 145, 148, 190
- cation exchange-HPLC 50
- cationic polymerization 321, 323
- CCL21 chemokine 99, 100
- CCR5 160
- CCR7 99
- CD4 158, 180, 269, 272
- CD16a 165
- CD22-Fc 159, 179
- CD23 165
- CD32 164
- CD36 98
- CD44 179
- CD47-Fc 159, 169
- CD64 164
- CD68-Fc 159
- CD89 165
- CD99-Fc 159
- CEA-Fc 159
- cell adhesion molecules (CAMs) 179
- chemical conjugation 8, 9, 250, 257, 259, 289
 - regioselective 124, 126, 127, 134
- chimeric genes
 - construction 86
 - expression 86, 87
- chimeric mAb 158
- Chinese hamster ovary (CHO) cells 86, 87, 226, 235, 239
- Cimzia® 10, 12, 42, 48, 107
- circulation lifespan, PEGylated proteins 54, 55
- CKR-7 160
- clathrin 213
- clearance (*CL*) 24, 25, 27
 - PSA 96, 104, 106, 107
 - *see also* hepatic clearance; pharmacokinetics; renal clearance
- clotting assay 236, 240
- clotting factor Fc fusions 194–202
 - *see also* factors
- CNTO 530 159
- coagulation factors, *see* factors
- cocaine hydrolase 230, 232, 234
- codon optimization 174
- colominic acid 12, 13
- colon cancer 273
- complement-dependent cytotoxicity 165, 166
- complementary DNA (cDNA) 226
- complex oligosaccharides 81

- concentration in the blood (C_{\max})
 - drugs 23
 - Epo-Fc 193, 194
 - HES-IFN α 135, 136
 - rFIXFc 194, 196, 198
 - confocal laser scanning microscopy 329, 330, 331
 - congestive heart failure 230
 - convective extravasation 26, 30
 - copolymerization 317, 318, 319
 - costs of production 75, 228
 - CR2-Fc 159
 - Crohn's disease 10, 42
 - cross-reactivity 252, 253, 254
 - CTLA-4 5, 11, 158, 181
 - cysteine-specific PEGylation 47, 48
 - cystic fibrosis 5, 160
 - cytokines
 - albumin fusion with 231, 232
 - Fc fusion 159–162
 - immunocytokines 167, 180
 - serum stability and half-life 167–172
 - traps 178
 - cytopathic effect (CPE) assay 134, 135
- d**
- daclizumab 158
 - darbepoetin alfa 12
 - daunorubicin 301
 - 5-deamino-3,5-dideoxyneuraminic acid 101
 - degree of polymerization (DP), PSA 100, 102
 - dendritic cells 148, 150, 210
 - denileukin diftitox 223
 - diabetes 4, 10, 11, 229, 230, 289, 290
 - diabodies 171, 172
 - dialysis 66
 - diazepam 288
 - diclofenac 288
 - dimeric Epo-Fc 192, 193, 194
 - dimeric Fc fusion 168, 169, 172–174
 - dimeric rFIXFc 195, 196, 197
 - direct (oil-in-water) miniemulsion 317
 - distribution, *see* volume of distribution (V)
 - disulfide bonds, PEGylation 48
 - DNase 5
 - DNase-Fc 160
 - dogs
 - FIX-deficient 198
 - rFVIII Fc PK and PD 201, 202
 - dolichol 82
 - domain antibodies 251, 252
 - dosage regimen 23, 24
 - dose rate (D/τ) 28
 - double emulsion 323
 - doxorubicin 301, 303, 304, 306
 - drug delivery
 - Fc fusion proteins 179
 - liposomes 299–311
 - nanoparticles 315–335
 - drug disposition
 - FcRn 35, 36
 - target-mediated 34, 35, 249
 - drug sites 1 and 2 287, 288, 291
 - drugs
 - albumin binding 288, 289
 - concentration in blood and plasma 23
 - conjugation of HES to 123–127
 - peptides 289
 - dual marker nanoparticles 333
 - dynammin 320
- e**
- efficacy
 - AlbuDAbTM fusions 262–265
 - recombinant albumin fusions 239–241
 - elastin-like polymers 64, 69, 70, 77
 - ELC-Fc 160
 - electron microscopy
 - PSA 100
 - TEM 326, 327, 328
 - elimination 31–35
 - half-life of antibodies 55
 - PEGylated proteins 51–54
 - elimination rate constant (K) 26, 27
 - encapsulation
 - markers 327–333
 - nanoparticles 323–327
 - endocytosis 30, 33, 211–213
 - receptor-mediated 34, 215, 320
 - endoplasmic reticulum (ER) 81, 82
 - endothelial cells 31, 32, 209, 210, 211, 212
 - engineered Fc 8
 - enhanced permeability and retention (EPR) effect 70
 - enzyme-linked immunosorbent assay (ELISA) 135, 193, 196, 202, 235
 - enzymes 5
 - gastrointestinal 28, 32
 - epidermal growth factor receptor (EGFR) 160
 - epilepsy 99
 - epitope mapping 253, 255
 - Epogen[®] 127
 - ErepoXen 10
 - erythroid burst forming colonies (BFU-E) 89

erythropoietin (EPO) 4, 10, 12, 84, 85, 86, 87, 89, 90
 – albumin fusion 230
 – HES-modified
 — chemistry of 127, 128
 — *in vitro* activity 128, 129
 — *in vivo* activity 129, 130
 – marketed products 127
 erythropoietin-Fc (Epo-Fc) 160, 170, 179
 – dimer and monomer 192, 193, 194
 – prototype construct 193, 194
 erythropoietin mimetic peptides (EMPs)
 10, 159
Escherichia coli 69–71, 73
 – AlbuDAb fusions 259
 – as expression host 174, 175
 – PSA in 97, 101
 etanercept 11, 158, 168, 178, 181, 223
 exenatide 229
 exocytosis 211–213
 expression hosts 174–176
 expression sites
 – FcRn 148, 209, 210
 – *see also specific sites*
 expression vectors 86, 87
 extendin-4 229, 230
 extravascular tissues 54
 eyes, FcRn expression in 148, 150

f

F-actin 320
 Fab fragments 4
 – anti-TNF Fab 10
 – clinical applications 158
 – IgG 162
 – in PEG mimetics 73, 74
 – PEGylated 47, 48, 55
 – PSA 107
 Fab fusions, antibodies 170, 171
 Fabry disease 5
 factors 4
 – factor VIIa 4, 230, 232–235, 238–240
 — with PEGylated liposomes 309, 310
 – factor VIII 4, 11, 194, 195, 200, 233
 — FVIII-Fc 160, 200–202
 — with PEGylated liposomes 307–309
 – factor IX 4, 10, 11, 194, 195
 — albumin fusion 230, 232, 234–236, 238–240
 – factor IX-Fc 11, 160, 170, 194, 195–200
 – factor Xa 173
 familial hypercatabolic hypoproteinaemia (FHH) 190
 fatty acids 11, 286, 288, 290, 291

Fc-alpha receptors (Fc α R) 163, 164, 165
 Fc-epsilon receptors (Fc ϵ R) 163, 164, 165, 166
 Fc fusion 8, 11, 13, 14, 157–182
 – clotting factor 194–202
 – cytokine/protein examples 159–162
 – dimeric 168, 169, 172–174
 – monomeric 169, 170, 189–203
 Fc fusion proteins
 – applications 178–181
 – construction 172–174
 – *in vitro* and *in vivo* activity 177
 – monomeric 192–202
 – peptibodies 170
 – pharmacokinetics 177
 – plasmid vectors 169, 172, 173
 – purification 176
 – traditional 191, 192
 Fc-gamma receptors (Fc γ R) 163, 164, 165, 166
 Fc-mediated antibody functions 166, 167
 Fc receptors (FcR) 163–166
 Fc regions 163
 – antibodies without 171, 172
 – clinical applications 158
 Fc-X fusion vector 169, 173
 FcRn, *see* neonatal Fc receptor (FcRn)
 fibronectin 293
 flow cytometry 322
 FLSC 160
 fluorescein 292
 fluorescence activated cell sorting 329
 fluorescent labeling 328–331
 follicle-stimulating hormone (FSH) 4, 83, 85, 86–88, 160
 FreeStyle 293 cells 175
 furosemide 288
 fusion proteins 5, 223
 – advantages of technology 225
 – *see also* Fc fusion proteins; recombinant albumin fusion proteins
 Fv fragment 162
 – *see also* single-chain Fv (scFv)

g

G-CSF, *see* granulocyte-colony-stimulating factor (G-CSF)
 gadolinium-DTPA 292
 galactosidase 5
 gastrointestinal enzymes 28, 32
 gastrointestinal mucosa 28, 32
 Gaucher disease 5
 gelatin-like polymers 64, 68, 69, 77
 Gelofusine® 68

gene therapy 178, 179
 genetic fusion 8, 9, 250
 – AlbuDAb 257, 259
 – PEG mimetics 63–78
 genetic polymers 64, 70, 71, 77
 glomerular filtration 32, 33
 – PEG mimetics and 65–67
 – PEGylated proteins 52
 glomerular filtration barrier 6
 glucagon 4
 glucagon-like peptide (GLP) 4, 11, 179, 229, 230
 glucocerebrosidase 5
 α -glucosidase 5
 glutathione S-transferase (GST) 67
 glycans
 – polysialylation 102
 – proteoglycans 81
 glycine-rich homo-amino-acid polymers 72, 73
 glycolipids, PSA in 97, 102
 glycoproteins (GP) 81, 83, 84
 – asialoglycoproteins 84, 103
 – crystallographic diagram 85
 – glycoprotein gp120 180
 – glycoprotein VI 160
 – long-acting agonists of 84–92
 – myelin oligodendrocyte 161
 – PSA in 97–99, 102, 103
 N-glycosylation 8, 10, 12, 82
 – scDb 16, 17
 O-glycosylation 8, 12, 81–92
 5-N-glycoylneuraminic acid (Neu5Gc) 101
 Glymera™ 70
 gout 10, 42
 granulocyte-colony-stimulating factor (G-CSF) 4, 10, 230, 276
 – hF-CSF 51
 – M-CSF 34
 – PEG mimetics 68, 70, 71
 – PEGylated 46
 – PEGylated liposomes 310
 granulomatosis 4
 granulosa cell aromatase induction 87
 growth factors 4
 – EGFR 160
 – IGF-1 4, 240
 – VEGF 11, 158, 162, 180
 growth hormone (GH) 85, 86, 87, 90–92
 – *see also* human growth hormone (hGH)

h

half-life 6, 24, 26, 27
 – albumin 144, 227, 285
 – albumin fusion proteins 238, 239
 – cytokines 167–172
 – IgG 35, 144, 190
 – plasma proteins 6, 144
 – rFIXFc 198, 200
 – terminal 4, 5
 half-life extension
 – albumin binding through ABDs 269–279
 – albumin binding through small molecules 285–294
 – Fc fusion 157–182
 – O-glycosylation 81–92
 – HESylation 117–137
 – liposomes 299–311
 – nanoparticles by miniemulsion 315–335
 – PEGylation 41–56
 – platform technologies 249, 250, 251
 – recombinant albumin fusion 223–242
 – recombinant PEG mimetics 63–78
 – scDb 15–18
 – therapeutic proteins 10, 11
 half-life modulation 7, 8, 9
 HAP polymers 64
 heavy chain antibodies (VHHs) 252, 255, 256, 259, 262
 HeLa cells 319, 320
 Hematide 10
 hematocrit levels 89, 90, 129, 130
 hematopoietic cells 209, 210
 hemoglobin, HES conjugates 123
 hemophilia 194–202
 hemophilia A 4, 11, 194, 200–202, 230, 232, 233, 299, 307–310
 hemophilia B 4, 10, 11, 194–196, 198, 230, 232, 234
 hemophilic arthropathy 194, 195
 hepatic clearance
 – EPO–HES conjugates 128
 – PEGylated proteins 51, 53
 hepatic protein metabolism 33, 34
 hepatitis C virus (HCV) 4, 10, 11, 42
 – Albuferon 240, 241
 – IFN α 168, 231
 – PEG-IFN 130
 HER2-specific Affibody 274, 275
 HER2+HER3 specific single-chain Fv 11
 HES, *see* hydroxyethyl starch (HES)
 Hespan® 120
 HESylation 8, 13, 77, 117–137
 – conjugation of HES to drug substances 123–127

- hexosamine biosynthesis pathway (HBP) 83
- high affinity Fc receptors 164, 166
- high-mannose oligosaccharides 81
- high performance liquid chromatography (HPLC) 49, 50, 132, 133
- hirudin 5, 230
- histidine residues, in FC molecule 145
- histone-1 (H1) 101
- HIV infection 89, 158, 160, 161, 180, 272
- homeostasis, albumin and immunoglobulins 143–145, 190
- homo-amino-acid polymer (HAP) 64, 72, 73, 77
- hormones 4
- *see also* follicle-stimulating hormone (FSH); growth hormone (GH)
- HRM polymers 64
- human chorionic gonadotropin beta (hCG β) subunit 83, 84
- human embryonic kidney (293) cells 88, 235, 239
- human FcRn 147, 166, 208, 209, 214
- human granulocyte colony stimulating factor (hF-CSF) 51
- human growth hormone (hGH) 4, 10, 46, 91, 230, 237
- hGHR-Fc 160
- PEGylated 53, 54
- human serum albumin (HSA) 6, 226, 227, 229, 249, 251, 253, 254
- ABD interactions 271
- affinity to 257, 258
- domains 255, 256
- FcRn-mediated recycling 13–15
- kidney filtration 66
- scDb 16, 17
- structure 287
- humanized mAb 158
- humanized VEGF-Fc 158
- hyaluronidase 10
- hybrid oligosaccharides 81
- hybrid repetitive motif (HRM) 64, 68, 77
- hydrodynamic radius 7–9, 249, 250
- PEG mimetics 65, 73, 74
- protein standards, PEG reagents and PEGylated proteins 52, 53
- PSA 96, 106
- strategies to increase 9, 10, 11, 12, 13
- hydrophilic liquids, encapsulation 325
- hydrophobic liquids, encapsulation 323, 324, 325
- hydroxyapatite (HAP) 318, 319
- hydroxyethyl starch (HES) 13
- clinical uses 120, 121
- erythropoietin polymer conjugates 127–130
- interferon α polymer conjugates 130–136
- metabolism and toxicology 122, 123
- non-oxidized 125, 127
- parameters 119, 120, 121
- production and characteristics 118, 119
- protein coupling 123
- site-specific functionalization 124, 125, 126
- viscosity 135, 136, 137
- *see also* HESylation
- hypercatabolism 143, 145, 148, 190
- hyperproteinemia 145, 148
- hyperuricemia 5
- hypoalbuminemia 143, 148, 150
- hypogammaglobulinemia 143
- hypoglycemia 4
- i**
- ibuprofen 288
- iduronate-2-sulfatase 5
- IFN, *see* interferon α (IFN α); interferon β (IFN β)
- IgG, *see* immunoglobulin G (IgG)
- Igs, *see* immunoglobulins (Igs)
- ILs, *see* interleukins
- immune cells, FcRn in 148, 150, 151
- immune thrombocytopenia 151
- immunocytokines 167, 180
- immunogenicity
- ABDs 277, 278
- albumin fusion proteins 228
- Fc fusion proteins 180, 181
- PEG mimetics 68, 76, 77, 78
- PEGylated proteins 55
- PSA 106
- immunoglobulin A (IgA) 162, 163, 164, 165
- immunoglobulin E (IgE) 162, 163, 164
- immunoglobulin G (IgG) 5, 6, 35, 36, 158, 162–167
- ABDs 249, 250
- binding 8
- clinical applications 158
- domain antibodies 251
- Epo-Fc linked to 193
- Fc fusion 157, 163
- Fc-mediated antibody functions 166, 167
- Fc receptors 163–166
- Fc regions 163
- FcRn binding to 145, 146, 147, 191, 214

- FcRn interactions 189–191, 208, 209
 - engineering 213–215
 - FcRn recycling 13, 14, 147, 148
 - FcRn transport 149, 150
 - general structure 163
 - half-life 35, 144, 190
 - intracellular transport 210–212
 - in mucosal immune 150, 151
 - immunoglobulin M (IgM) 162, 164
 - immunoglobulins (Igs)
 - five major classes 162
 - homeostasis 143–145, 190
 - intravenous 151, 152, 215
 - renal filtration 66
 - immunoliposomes 302
 - immunomodulation 230, 306
 - immunoreceptor tyrosine-based activation motifs (ITAM) 166
 - in vitro* activity
 - EPO–HES conjugates 128, 129
 - Fc fusion proteins 177
 - rhIFN α -2b 134, 135
 - in vivo* activity
 - ABDs 272–276
 - albumin fusion proteins 238, 239
 - drug instability in 189
 - EPO–HES conjugates 129, 130
 - Fc fusion proteins 177
 - IgG–FcRn engineering 213–215
 - in vivo* fluorescein angiography 292
 - indomethacin 288
 - infertility 4
 - infestin-4 230
 - insect cell expression 175
 - insulin 4, 10, 11, 230
 - albumin-binding derivatives 289, 290, 291
 - pharmacokinetics 28
 - resistance 83
 - insulin aspart 290
 - insulin detemir 11, 14, 15, 290, 291
 - insulin glarginine 290
 - insulin-like growth factor 1 (IGF-1) 4, 240
 - insulin lispor 290
 - interfacial polymerization 323, 324, 325, 326
 - interferon α (IFN α) 4
 - albumin fusion 230, 231, 232
 - Fc monomers 194
 - HES conjugates 130–136
 - IFN α -Fc 161, 168, 178
 - interferon α -2b (IFN α -2b) 10, 11, 52, 53
 - AlbuDAb™ fusions 263, 264
 - HESylation 131–133
 - *in vitro* activity 134, 135
 - PEGylated 52, 53, 130, 131, 134, 135, 241
 - pharmacokinetics 135, 136
 - viscosity 135, 136
 - *see also* albinterferon alpha-2b (alb-IFN)
 - interferon β (IFN β) 4, 43, 194, 230
 - IFN β -Fc 161
 - interferon γ (IFN γ) 4
 - interleukin-1 receptor (IL-1R) 11, 178
 - interleukin-1 receptor antagonist (IL-1ra) 262, 264
 - interleukin-2 (IL-2) 230
 - adverse effects 305, 306
 - IL-2-Fc 160, 180
 - in PEGylated liposomes 304–306
 - interleukins 4, 5
 - IL-4-Fc 161
 - IL-10-Fc 161
 - IL-15-Fc 160
 - IL-18bp-Fc 161
 - IL-29 10
 - viral interleukin 10 178, 179
 - intestines
 - enzymes 28, 32
 - FcRn expression in 148, 149, 150, 190
 - intraluminal metabolism 32, 33
 - intramuscular (i.m.) administration 29, 51
 - intraperitoneal (i.p.) administration 51
 - intravenous (i.v.) administration 29, 30, 51
 - intravenous immunoglobulin (IVIg) 151, 152, 215
 - Intron® A 130, 134, 135
 - inverse (water-in-oil) miniemulsion 317
 - ion exchange chromatography 50, 132
 - IP-10-Fc 161
 - IP-17R-Fc 161
 - isoelectric point 96, 214, 215
- k**
- ketoprofen 288
 - KGLP-1/HSA 229
 - kidneys
 - FcRn expression in 148, 149, 150, 191, 210
 - protein metabolism 32, 33
 - renal failure 89
 - *see also* renal clearance
 - Krystexxa® 10, 42
- l**
- lactonization, HES 124, 126
 - Lenercept 158
 - leukaemia inhibitory factor (LIF05) 161
 - leukopenia 131

- LFA-3 5, 11, 158, 168
- ligands
- albumin binders 288
 - receptor interactions 179
- “linkerless” approaches 124, 126
- linkers, Fc fusion design 173
- liposomes 299–311, 316
- drug carriers 13, 300–302
- liraglutide 11
- liver
- FcRn expression in 148, 191
 - protein metabolism 33, 34
 - *see also* hepatic clearance
- liver cancer 10
- low affinity Fc receptors 164, 165, 166
- lung cancer 99
- lungs, FcRn expression in 148, 149, 191, 193, 194
- lutropin 4, 83
- lymphatic system, in protein therapeutics 29, 30
- lysines, in PEGylation 46, 47
- lysosomes 33, 191
- m**
- macrophage colony-stimulating factor (M-CSF) 34
- macrophages, and HES storage 122
- macular degeneration 11, 167
- magnetic resonance imaging (MRI) 292, 326
- magnetite nanoparticles 331–333
- maize starch 118, 119
- major histocompatibility complex class I (MHC-I) 143, 145, 190
- maleimide-activated PSA 105, 107
- mammalian cell expression 175
- markers, encapsulation 327–333
- mass spectroscopy
- PEG mimetics 75
 - PEGylated proteins 50
- matrix assisted laser desorption/ionization time-of-flight (MALDI-TOF) 49
- maximum daily dose, HES 121
- mean molecular weight, HES 119, 120, 121
- membrane bound FcR 166
- metabolism
- HES 122, 123
 - *see also* protein metabolism
- methotrexate 228
- miniemulsion 317–335
- encapsulation of markers 327–333
 - nanocapsule formation 323–327
 - polyreactions 321, 323
 - process of 317
 - radical polymerization 317–321, 322
 - release of materials 333, 334, 335
- Mircera® 10, 42, 46, 128, 129, 130
- MLV-IL-2 306
- molar specific activity 235, 236
- molar substitution, HES 120, 121
- molecular mass (kDa) 4, 5
- PEGylated proteins 51–53
 - plasma proteins 6
 - PSA 96
 - and renal filtration 66
 - scDb 17
- monkeys
- cynomolgus 193, 194
 - FIX-deficient 198
- monodispersity, PEG mimetics 75, 77
- monomeric Epo-Fc 192, 193, 194
- monomeric Fc fusion 169, 170, 189–203
- monomeric Fc fusion proteins 192–202
- monomeric rFIXFc 195, 196, 197, 198
- mouse FcRn 147, 200, 208, 209, 214, 216, 273, 274
- mouse rFVIII Fc clotting activity 201
- mouse serum albumin (MSA) 253, 254, 260, 261, 262
- mucopolysaccharidose 5
- mucosal immune cells 148, 150, 151
- multifocal plane microscopy (MUM) 211, 212
- multiple sclerosis 4, 43, 181
- mutagenesis polymerase chain reaction (PCR) 86
- myelin oligodendrocyte glycoprotein (MOG) 161
- myocardial infarction 5
- myotonic dystrophy 148
- myristic acid 290, 291
- n**
- N-hydroxy-succinimide (NHS) esters 46
- N-linked oligosaccharides 81, 82
- N-terminal PEGylation 46, 47
- nanobodies 43
- nanocapsules 323–327
- nanocytes 321, 322
- nanodroplets 317
- nanoexplosion temperature 334, 335
- nanoparticles 9, 13, 315–335
- cellular uptake 316, 319, 320
 - detection in biological systems 327–333
 - polymeric 317

- radical polymerization and functionalization 317–321, 322
 - release of materials 333, 334, 335
 - nanoprecipitation 324, 326
 - natalizumab 181
 - native chemical ligation 125
 - negative charge 76, 78, 96, 97
 - Neisseria meningitidis* 97, 101
 - neonatal Fc receptor (FcRn) 166, 250
 - albumin binding to 146, 147, 227, 273, 285
 - biochemistry 145–147
 - biology of 143–152
 - cell biology 210–212
 - characterization and expression patterns 207, 208
 - in drug disposition 35, 36
 - FcRn-Fc 160
 - IgG interactions, *see* immunoglobulin G (IgG)
 - inhibitors of 215
 - knockout and transgenic mice 200
 - mucosal immune 148, 150, 151
 - sites of expression 148, 209, 210, *see also specific sites*
 - therapeutics 151–152
 - transport 149, 150, 212, 213
 - *see also* Fc fusion; mouse FcRn
 - neonatal Fc receptor (FcRn) recycling 3, 6, 7, 147–149
 - modulation strategies 8, 9
 - strategies implementing 13–15
 - Neulasta® 10, 42, 46, 276
 - neural cell adhesion molecule (NCAM) 98–100, 102
 - neuraminidases 102, 103, 107
 - neuroendocrine tumors 99
 - neutropenia 4, 10, 42, 230
 - neutrophilin-2 receptor (NRP-2) 98, 99
 - neutrophins 100
 - NKTR-181 262
 - noncovalent binding, proteins and PEGylated liposomes 307–310
 - novel erythropoiesis stimulating protein (NESP) 90
 - NovoSeven® 233, 238
 - nuvance 158
- O**
- O-linked oligosaccharides 81, 82
 - in glycoprotein agonist design 85, 86
 - in glycoprotein functions 83, 84
 - Oncaspar® 10, 42, 46
 - Opaxio™ 70
 - oral bioavailability 29
 - organ accumulation, PEG mimetics 75
 - organophosphorus (OP) 232, 234
 - osteoporosis 4
 - OX40L-Fc 161
 - Oxymera™ 70
- P**
- paclitaxel 70
 - palmitic acid 286
 - parathyroid hormone 4
 - PAS polymers 64, 73–75, 77
 - passive immunity 190
 - PBA nanoparticles 331
 - PD-L1-Fc 161
 - PEG, *see* polyethylene glycol (PEG)
 - PEG mimetics, *see* recombinant PEG mimetics
 - Pegasys® 10, 42, 44, 46, 50, 131
 - pharmacokinetics 135, 136
 - PEGIntron® 10, 42, 46, 50, 131
 - PEGylated G-CSF 46
 - PEGylated IFN α 52, 53, 130, 131, 134, 135, 241
 - PEGylated IFN β -1a 43
 - PEGylated liposomes 299, 300, 301–310
 - PEGylated proteins 44–50
 - biodegradability 117
 - biodistribution 54
 - characterization 50
 - circulation lifespan 54, 55
 - FDA approved 41, 42, 43
 - hydrodynamic radius 52
 - pharmacokinetics 43, 44, 50–55
 - purification 48, 49
 - safety 55, 56, 117
 - viscosity 44, 45, 135, 136, 137
 - PEGylation 8, 9, 10, 12, 41–56, 250
 - drawbacks to 224, 225
 - random 45, 46
 - scDb 16
 - site-specific 46–48
 - peptibody 170
 - peptidases 32
 - peptides
 - drugs 289
 - pharmacokinetics 28
 - *see also specific peptides*
 - periodate oxidation 104, 105
 - peritubular extraction 33
 - pFUSE-Fc 169, 172, 173
 - pH
 - albumin–FcRn binding 146
 - IgG–FcRn binding 145, 191, 214

- pharmacodynamics
 - EPO 89
 - PEG mimetics 78
 - rFVIIIc 201, 202
- pharmacokinetics 27–35
 - AlbuDAb™ fusions 262–265
 - albumin fusion protein 224
 - drugs, and albumin binding 288, 289
 - Epo-Fc 194
 - Fc fusion proteins 177
 - growth hormone 91
 - IFN α -2b and Pegasys 135, 136
 - IL-2-liposomes 305
 - liposomal carriers 300–302
 - PEG-LipFVIIa 310
 - PEG-LipFVIII 308, 309
 - PEGylated proteins 43, 44, 50–55
 - primary parameters 24, 25
 - PSA and 95–108
 - recombinant albumin fusion proteins 238, 239
 - rFIXFc 194, 195–200
 - rFVIIIc 201, 202
 - secondary parameters 24, 25–27
 - TNF- α liposomes 303, 304
- phase separation 323, 324
- phenprocoumon 239
- phenylalanine ammonia lyase 10
- phenylketonuria 10
- Pichia pastoris* 68, 69, 226, 232, 255
- pinocytosis 146, 211, 320
- placenta, FcRn expression in 148, 149, 190
- plaque psoriasis 5, 11
- plasma concentration–time profile 23, 25, 26
- plasma proteins 143
 - half-life 6, 144
 - turnover 144
 - *see also* albumin; immunoglobulins (Igs)
- plasma volume substitutes 120
- plasmatic α -amylase 118, 119, 122
- plasmid vectors, Fc fusion 169, 172, 173
- podocytes 149, 150
- polyaddition 326
- polyanionic polymers 64, 70, 77
- poly(*n*-butylcyanoacrylate) (PBCA) 321, 326, 330
- poly(ϵ -caprolactone) (PCL) 332
- polydendrocyte (NG2) cells 98
- polydispersity
 - HES 119, 120, 132, 133
 - PEG reagents 49
- polyethylene glycol (PEG) 9, 12, 44
 - PEG-IL-2 305, 306
 - PEG-LipFVIIa 310
 - PEG-LipFVIII 308, 309
 - PEG propionaldehyde 125
 - PEG-SN38 43
- polyethylene glycol (PEG) reagents 44–48
 - characterization 49
 - hydrodynamic radius 52
- polyglutamate 70
- polyglycine 72, 73
- poly(D,L-lactide-coglycolide) (PLGA) 332
- polymerase chain reaction (PCR) 86, 172
- polymeric nanoparticles 317
- polymerization
 - anionic 321, 326
 - cationic 321, 323
 - copolymerization 317, 318, 319
 - degree of 100, 102
 - interfacial 323, 324, 325, 326
 - radical 317–321, 322
- polymers, *see* amino acid polymers; biopolymers
- polysialic acid (PSA) 12, 77, 95–108
 - biosynthesis 101–103
 - conjugation 103–108
 - in nature 97–101
 - pharmacological effects 103
 - structure 105
- polysialylation 8, 10, 12, 13, 95, 96
 - therapeutic applications 103–108
 - *see also* polysialic acid (PSA)
- polysialyltransferases (SIATs) 102, 108
- polysorbate 80 330
- polystyrene nanoparticles 319, 320, 329, 331, 332
- polyurethane nanocapsules 327, 334
- Polyxen® 104
- Pompe disease 5
- potency, AlbuDAb™ 257, 258
- pPIC9-Fc fusion vector 169, 173
- primary pharmacokinetic parameters 24, 25
- PRO542 158
- progressive multifocal encephalopathy (PML) 181
- protein binding 31
- protein metabolism 31, 32
 - hepatic 33, 34
 - receptor-mediated 34, 35
 - renal 32, 33
- protein scaffolds, PEGylation 43
- protein therapeutics, *see* therapeutic proteins
- proteoglycans 81

- proteolysis 31, 32, 249
 – PEGylated proteins 53, 54
 PSA, *see* polysialic acid (PSA)
 PSK92 101, 104
 PT-Fc 161
- q**
- quantitative whole body autoradiography
 (QWBA) 260, 261, 262
 quantum dots (QDs) 330
- r**
- Rab GTPases 213
 radical polymerization 317–321, 322
 radiotherapy 303
 random PEGylation 45, 46
 ranibizumab 167
 rat serum albumin 253, 254, 261, 262
 receptor ligand interactions 179
 receptor-mediated clearance 249
 receptor-mediated endocytosis 34, 215, 320
 receptor-mediated protein metabolism
 34, 35
 recombinant albumin fusion 223–242
 – technology 234–237
 recombinant albumin fusion proteins
 225–233
 – advantages 228
 – challenges 228
 – clinical efficacy 240, 241
 – mode of action 227
 – pharmacokinetics 238, 239
 – practical applications 227, 228
 – preclinical efficacy 239, 240
 – therapeutic potential 229–233
 recombinant factor VIII-Fc (rFVIII-Fc) 11,
 200–202
 recombinant factor IX-Fc (rFIX-Fc) 11, 194,
 195–200
 recombinant human albumin (rHA) 225,
 226, 229
 recombinant Ig-like transcript
 (rILT3-Fc) 161
 recombinant PEG mimetics 8, 63–78
 – characteristics of 77
 – overview 64
 – renal filtration and 65–67, 76
 reductive alkylation 46–47
 reductive amination
 – HES 125, 127, 131, 134
 – PSA 104, 105, 106–107
 regioselective conjugation, HES 124, 126,
 127, 134
 releasable PEGylation 45
 release mechanisms, nanoparticles 333,
 334, 335
 renal cell carcinoma 4
 renal clearance 3, 6, 7, 249
 – in O-glycosylation 84
 – PEG mimetics 65–67, 76
 – PEGylated proteins 51–53
 – PSA 96–97
 renal failure 89
 renal protein metabolism 32, 33
 reverse phase-HPLC 49, 50, 132, 133
 rheumatoid arthritis 4, 5, 11, 42, 168, 178,
 181, 202
 Ribavirin® 131
 rilonacept 11, 178
 rituximab 165
 Roferon® 130
 romiplostim 11, 170
- s**
- Saccharomyces cerevisiae* 231, 237
 safety
 – FSH-CTP 88
 – HES 121
 – PEGylated proteins 55, 56, 117
 – *see also* adverse effects; toxicity
 salicylate 288
 SAPA repeats 64
 scDb, *see* single-chain diabody (scDb)
 scFv, *see* single-chain Fv (scFv)
Schistosoma japonicum 67
 secondary pharmacokinetic parameters 24,
 25–27
 selectins 97, 179
 serogroup B capsular PSA (PSB) 101, 104
 serogroup C capsular PSA (PSC) 101, 104
 serum albumin 286
 – *see also* human serum albumin (HSA);
 mouse serum albumin (MSA); rat serum
 albumin
 serum residence time 249, 251
 serum stability, cytokines 167–172
 severe combined immunodeficiency disease
 (SCID) 10, 42
 shed acute phase antigen (SAPA)
 64, 67, 68
 sialic acid
 – in EPO conjugates 127, 128
 – *see also* polysialic acid (PSA)
 sialylation
 – in glycoproteins 84
 – *see also* polysialylation
 side effects, *see* adverse effects
 siglec family 97

- sIL-4R-Fc 158
 single-chain diabody (scDb) 15–18, 230, 273, 274, 276, 293, 294
 single-chain Fv (scFv) 11, 73
 – Albu tagging 293, 294
 – albumin fusion 230
 – Fc fused 161
 – polysialylation 106, 107
 single-chain TNF (scTNF) 321
 site-specific PEGylation 46–48
 size-exclusion chromatography (SEC) 49, 132
 – HES conjugates 132
 – PEGylation 47, 49, 50
 – scDb 17, 18
 size-exclusion chromatography-multi-angle laser light scattering (SEC-MALLS) 120, 132, 258
 sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) 17, 50, 87, 177, 232
 soluble complement receptor 1 (sCR1) 272, 273
 soluble FcR (sFcR) 166
 solution state, AlbuAbTM 258
 Somavert[®] 10, 42, 46
 stability, AlbuAbTM 252
 staphylococcal protein A 176
 starch, *see* hydroxyethyl starch (HES); maize starch
 sterically stabilized liposomes (SSL) 299, 303–306
 streptococcal protein G (SpG) 176, 270, 271–273
 styrene 318
 subcutaneous (s.c.) administration 29, 30, 51
 substitution pattern, HES 120, 121
 succinylated gelatin 68
 sulfathiazole 288
 SuliXen 10
 superoxide dismutase 51
 surface charge 319, 320
 surface-functionalized nanoparticles 318
 surface plasmon resonance (SPR) 255
 surfactants 317, 318, 319, 321
 SynCAM1 98
 syndecan-Fc 161
 SynFusionTM 179
 systemic exposure 24, 26, 27
- t**
 T-cell leukemia 5
 t-PA 5
 tandem Fv (taFv) 230
 target-mediated drug disposition 34, 35, 249
 targeted lipid-coated particles (TLPs) 321, 322
 terminal half-life 4, 5
 TheraPEGTM 48
 therapeutic proteins 3, 4, 5
 – drawbacks 315
 – half-life, *see* half-life
 – half-life extension, *see* half-life extension
 – pharmacokinetics, *see* pharmacokinetics
 – recombinant albumin fusion, *see* recombinant albumin fusion proteins
 – *see also* Fc fusion proteins; glycoproteins (GP)
 thermal stability, AlbuAb 258, 259
 thiols
 – in PEGylation 47
 – PSA conjugation 104, 105, 107
 thioredoxin 230
 thrombin 4, 173
 thrombocytopenia 4, 5
 thrombolytics 5, 230
 thrombopoietin (TPO) 170
 thymosin- α 1 230
 thyroid cancer 88
 thyrotropin (TSH) 83, 85, 88, 89
 Tim-3-Fc 162
 TMP-Fc 5
 TNF, *see* tumor necrosis factor (TNF)
 total anterior circulation infarct (TACI) 162
 total internal reflection fluorescence microscopy (TIRFM) 211
 toxicity
 – cytotoxicity 165, 166
 – HES 122, 123
 – TNF- α 302–304
 – transfection agents 320
 – *see also* adverse effects; safety
 TPO-mimetic peptide 11
 trans-sialidase 67, 68
 TransceptorTM 179
 transcytosis 213
 transfection agents 320
 transferrin 143, 144, 148
 transmission electron microscopy (TEM) 326, 327, 328
 trastuzumab 73, 273
 TrkB-Fc 162
 tropoelastin 69
Trypanosoma cruzi 67, 68
 trypsin digestion 53, 54
 tubular reabsorption 33

- tubulovesicular transport containers (TCs) 211
 - tumor necrosis factor (TNF)
 - nanocytes 321, 322
 - receptors 5, 11, 158, 162, 168, 178, 181
 - TNFR75-Fc 158
 - tumor necrosis factor alpha (TNF α)
 - 230, 232
 - in PEGylated liposomes 302–304
 - two-compartment pharmacokinetic model 30, 54
 - Type I/II targeted liposomes 301
- u**
- ultrafiltration 66
 - urate oxidase 5
 - uricase 10
 - UT-7 cells 128, 129
- v**
- valproate 288
 - vascular endothelial growth factor (VEGF)
 - 11, 158, 162, 180
 - vascular endothelium 147, 148, 190
 - VCP-Fc 162
 - versatility, AlbuDAb™ 252, 256, 257
 - VHHs, *see* heavy chain antibodies (VHHs)
- viral interleukin 10 (vIL-10) 178, 179
 - viscosity, PEGylated proteins 44, 45, 135, 136, 137
 - vitamin K 233, 235
 - Volplex® 68
 - volume of distribution at steady state (V_{ss}) 25, 30
 - volume of distribution (V) 24, 25, 26
 - therapeutic proteins 29, 31
 - volume of the central compartment (V_c) 25
- w**
- warfarin 288
 - weight gain, and growth hormone 91
 - Western blot analysis 87, 177
 - whole blood clotting time (WBCT) 196, 198, 199, 201, 202
 - WST-1 viability assay 129
- x**
- xolair 158
 - XTEN polypeptides 64, 71, 72, 77
- y**
- yeast cell expression 176, 228, 231, 237
- z**
- zidovudine 89