

Index

a

AA3H, 75, 211
acid sphingomyelinase (ASMase), 30, 145, 241
activated cell-permeable peptide dendrimer (ACPPD), 187
agrobacterium-mediated gene transfer, 381
 α,α -disubstituted amino acids (dAAs), 30, 31, 79, 84–87, 212, 214, 384
 α -aminoisobutyric acid (Aib), 85
 α/β -peptides, 81, 82, 83
 α/γ -peptides, 83, 84
 α -helical peptides, 57–62, 123
 α -peptide, 80, 85
AMAL therapeutics, 374
2-aminoacyclohexylcarboxylic acid (ACHC), 212, 215
6-aminohexanoic acid (Ahx), 149, 268, 269, 375
aminoisobutyric acid (Aib), 30
amphiphatic cationic peptides, 45
amphiphatic cell-penetrating peptides (CPPs), 20
 α -helical peptides, 57–62
 β -sheet peptides, 62–63
M918, 64–65
p14ARF, 64
Pep-1, 64
polyproline type II helical peptides, 63–64
pVEC, 64
amphiphatic peptide (AMP), 57–65, 85, 150, 210, 224, 245, 246, 317
amphiphatic peptide-based method, 230–231
amphiphilic α -helical antimicrobial peptide, 45
amphiphilic CPPs, 382, 383, 384, 387, 388, 389
anionic peptides, 20, 64, 393
antimicrobial peptides (AMPs), 47, 84, 113, 150, 166, 187, 209
antisense oligomers, 263, 265, 267
antisense oligonucleotides (ASO), 237, 263, 375
 delivery system, for myotonic dystrophy, 34
anti-TOMM20 antibody, 36

APTstat3 cell-permeable peptide (APTstat3-9R), 190
Arabidopsis thaliana, 382, 384, 385, 387–389, 393
Arg4-Arg5-dNal6 (D- β -naphthylalanine)-Arg7-Fpa8 (L-4-fluorophenylalanine), 129
arginine-rich cell-penetrating peptides (CPPs), 20, 29, 206
 with α,α -disubstituted α -amino acids (dAAs), 30
 assembly system, 33–34
 bacterial cells, 149
 cell membrane penetration, 30
 cellular uptake mechanisms of, 141–151
 cytosolic delivery of functional molecules, 150
 endocytosis mechanisms of, 143–144
 enhanced cytosolic release systems, 36
 enhanced membrane penetration of, 148–149
 for extracellular vesicles and exosomes, 36–38
 gene interaction, 34
 genes and oligonucleotides delivery, 34–35
 ion-pairing and hydrogen bonding, 141, 142
 membrane penetration mechanisms of, 144–147
 molecular coating, 35–36
 multilamellar formation of membranes for, 148
 toxicity, 149–150
 with unnatural amino acids, 30–31
arginine-rich peptides, 121, 123, 124, 125, 142, 143, 145, 146, 150
arginine-rich R7W peptide, 125
arginine-terminated nanoparticles with quantum dots, 36
aromatic oligoamide foldamers, 88
artificial cyclized helix-loop-helix (HLH) peptides, 32

- aR7W2 peptide, 144
 AVB-620, 23, 194, 376
 azurin, 62, 63
- b**
- Bac₁₅₋₂₄, 63
 benzylpenicillin, 209, 210
 β-amino acids, 80–83
 β/γ-peptides, 81, 82
 β-hairpin arginine peptides, 31
 β-peptide, 80–83
 β-peptide foldamers, 215
 β-sheet peptides, 62–63
 β-, γ- or δ-amino acids, 79
 bicyclic dodecaarginine (R12) preparation, 32
 biotinylated CPPs, 22
 blood-brain barrier (BBB), 37, 186, 209, 230, 294, 323, 357
 blood–cerebrospinal-fluid-barrier (BCSFB), 294
 bombinins, 117–120
 boron neutron capture therapy (BNCT), 151
 bovine serum albumin (BSA), 35, 249, 384
 BP100, 47, 48, 382, 383, 387, 392
 BP100(KH)₉, 47, 228
 (BP100)₂K₈, 47
 bPrP₀, 60
- c**
- CADY, 61, 241
 CADY/siRNA complexes, 61
 cancer-targeting cell-penetrating peptides, 32–33
 CAP18 (106–121)-derived sC18 peptides, 38
 5-carboxyfluorescein (FAM), 144
 5- or 6-carboxyfluorescein (FAM), 206
 cargo molecules, 62, 69, 72, 143, 150, 205–207, 211, 212, 347, 386, 388, 392
 18 kDa cationic antimicrobial peptide cathelicidin (CAP18), 47
 cationic CPP oligoarginines, 22
 cationic CPPs, 17, 19–22, 45, 47, 64, 75, 85, 86, 161, 163, 231, 239, 241, 267, 277, 317, 322, 324, 333, 348, 356, 384, 386, 388, 389
 cationic peptide-based method, 229–230
 caveolae, 160
 caveolin-mediated endocytosis, 111, 240, 246
 Cecropin A, 116
 cell drinking process, 160
 cell-penetrating peptides (CPPs), 1, 57, 219, 315, 315–316, 331, 367, 381
 applications, 323–324, 349
 artificial, 383–385
 cellular internalization, 317, 319–320
 characteristics of, 239
 chemical structures, 21–22
 classification, 18
 clinical trial, 367–376
 conjugated polymer micelles, 285–286
 conjugates for nucleic acid delivery, 242–243
 CPP-PMO, 243
 CPP-PNA, 242–243
 design and availability, 382–383
 direct translocation, 241
 electrophysiological analysis of the direct penetration of, 113–128
 endocytosis-dependent mechanism, 239, 241
 experimental readout, 344–345
 functionalization, 247–250
 histidine-rich CPPs, 48–51
 homing peptide sequences, 250
 improvement, 324
 internalization mechanism, 239–241, 386–389
 intestinal barrier, 347
 mucus, 347
 transepithelial transport, 347–349
 intestinal injection, 344
 intracellular delivery of drugs, 207
 in vivo distribution of, 184
 in vivo methods, 343
 oral gavage, 343–344
 lipid-grafting, 248–249
 lists of, 2
 for liver targeting, 323
 lysine-rich CPPs, 45–48
 modified lipid nanoparticles, 321–324
 molecular dynamics (MD)
 simulation, 129–131
 molecular imaging, 183
 nanoparticles for nucleic acid delivery, 243–247
 oral administration safety, 345–346
 oral delivery of biopharmaceuticals, 331
 carriers, 333–342
 challenges, 331–333
 formulation, 342
 transepithelial cargo absorption, 333, 341
 origins, 22–23
 PEGylation, 249
 pharmacokinetics of, 184–185
 physical and chemical properties and structures of, 111
 physicochemical properties, 17, 19–21
 polymer micelles, 287
 polypeptide-based carriers, 389–393
 region-dependent CPP-mediated intestinal absorption, 342
 reporting and statistical analysis, 346
 in situ administration, 344

- solid-state NMR analysis of the direct penetration of, 128–129
 for tumor targeting, 322–323
 types, 317
 typical classifications, 111, 112
 cellular internalization, 124, 223, 240, 241, 245, 315, 316, 317, 319–322
 C-end Rule (CendR), 32, 33
 central nervous system (CNS), 209, 294
 charge flux, 117–120
 chimeric CPPs, 22, 23
 chimeric peptides, 72, 243, 317, 383
 ciprofloxacin, 212, 214
 c-Jun N-terminal kinase inhibitor 1 (D-JNK-1), 371, 372
 clathrin and caveolin-independent endocytosis, 111
 clathrin-coated vesicles, 160
 clathrin-mediated endocytosis, 111, 144, 160, 161, 162, 319, 321, 387
 Clavanin A, 115
 conjugating CPPs, 183
 covalent conjugation, of oligoarginine, 38
 covalent methods, 223
 chemical method, 224, 227
 genetic method, 224
 CPP-conjugates
 for cancer treatment, 190–196
 for CNS disorders, 186–187
 for infectious diseases, 187–189
 CPP-PMO, 243
 CPP-PNA, 242–243
 C-terminal structures, 17, 22
 C105Y, 73, 317
 cyclic arginine-rich peptides, 31–32, 243
 cyclic-R9 peptide-decorated nanoparticles, for oral delivery, 31
 Cyclorasin 9A5, 129
 cyclosporin A (CsA), 208, 209
 cysteine perfluoroarylation reaction, 32
 cystic fibrosis, 277
 cystic fibrosis transmembrane conductance regulator (CFTR), 277
 Cyt c⁷⁷⁻¹⁰¹, 47
 Cytosolic Tat, 164
- d**
- deep learning approach, 269
 deferoxamine, 209
 dendrimer structures, of arginine-rich peptide, 35
 D-formed octaarginine (r8), with stearyl moiety, 37
 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC), 128
 1,2-dimyristoyl-*sn*-glycero-3-phospho-(1'-*rac*-glycerol) (sodium salt) (DMPG), 129
 dioleoyl phosphatidylcholine (DOPC), 130, 131, 146
 dioleoyl phosphatidylcholine (DOPC) bilayer membrane, 124
 dioleoyl phosphoethanolamine (DOPE), 321–322
 1, 2-dioleoyl-*sn*-glycero-3-phosphoethanolamine (DOPE), 128
 1,2-dioleoyl-*sn*-glycero-3-phospho-*rac*-(1-glycerol) sodium salt, 62
 direct plasma membrane translocation, 159, 171
 direct translocation, 239, 241, 245, 269, 348
 dodeca (R12)-arginine-conjugated exosomes, 38
 D-oligoarginines, 21
 doxorubicin (Dox), 33, 206, 207, 208, 210, 211, 323, 374
 dppz-Xentry peptide, 34
 droplet contact method, 113, 114
 droplet interface bilayer, 113
 drug delivery
 amphipathic peptides, 210
 Arg-rich peptides, 206–209
 cationic peptides, 209, 210
 foldamers, 212–215
 hydrophobic peptides, 211–212
 water solubility of, 205
 drug delivery system (DDS) tools, 20, 23
 D-Tat, 21
 Duchenne muscular dystrophy (DMD), 237, 243, 264, 275–276, 278
- e**
- electroporation, 149, 224, 265, 266
 endocytic pathway, 160–162, 166–172, 174, 175, 227, 270, 294, 319
 endocytic uptake, 126, 144, 159, 162, 171, 173, 174, 273, 348
 endocytic vesicles, 160, 166, 167
 endocytosis, 319
 CPPs, 161–162
 endocytic pathway, 160–161
 types of, 160
 endocytosis-dependent internalization, 240, 241, 246, 319
 endocytosis-dependent mechanism, 239, 241, 246
 endocytosis-independent entry, 317, 319
 endocytosis mechanisms, of arginine-rich cell-penetrating peptides, 143

- endosomal escape
 direct modification of, 173
 disadvantage, 174–175
 endocytic pathway, 170–171
 endocytosis, 160–162
 evidence
 non-toxic, 169
 toxic, 168–169
 mechanisms of, 163
 leaky fusion, 162–165
 membrane destabilization/
 permeabilization, 165–166
 proton sponge effect, 166–167
 membrane leakage, 171–172
 small molecules, 173–174
 toxic or not, 170
 Endosomal Sorting Complexes Required for
 Transport (ESCRT) complex, 170, 174
 EpN18 peptide, 148, 149
 EPR effect, 287, 292, 297, 301, 302, 322
- f**
 fallypride, 209
 fluorescein isothiocyanate (FITC), 73, 186, 211
 fluorescence microscopy, 162, 168, 171,
 172, 267
 fluorescent dye, 23, 196, 367, 376
 fluorophore-conjugated CPPs, 23
 fluorophores, 23, 173
 foldamers
 α,α -disubstituted amino acids (dAAs), 84–86
 aromatic oligoamide foldamers, 88
 β -amino acids, 80–83
 γ -amino acids, 83–84
 oligoureas, 87
 poly-N-substituted glycine oligomers, 86
 F4R4 peptides, 34
 fusogenic peptides, 165, 241, 246, 322, 324
- g**
 GALA peptide, 20, 61, 246, 322–324
 γ -amino acids, 83–84
 γ -peptide, 83, 84
 Gaussian accelerated molecular dynamics
 (GaMD) simulation, 385
 Generally Regarded as Safe (GRAS), 249
 genetic disease, 251, 264, 270, 275–277
 genetic method, 222, 224
 giant plasma membrane vesicles (GPMVs), 145
 glutathione (GSH), 207, 227, 285, 288, 294, 297
 glycosaminoglycans (GAGs), 60, 63, 125, 126,
 142, 146, 239
 gold nanoparticles (AuNPs), 35
 BSA-r8 coating, 36
 GST-Grb2 SH2-MTS1 fusion protein,
 72
- h**
 hCT(9-32)-br, 73
 hCT(18-32)-br, 74
 hexaarginine-conjugated Van derivatives, 188
 1,1,1,3,3-hexafluoro-2-propanol, 58
Hibiscus cannabinus, 385
 histidine-rich CPPs, 45, 48–51, 49
 HIV-1 Nef DNA delivery, 35
 HIV Tat peptide, 266, 267
 HL6 peptide, 50
 homing peptide sequences, 250
 host-directed PPMOs, 273
 Hutchinson-Gilford progeria syndrome
 (HGPS), 276–277
 hyaluronic acid (HA), 193
 hydrazone, 207
 hydrophobic CPPs, 20
 AA3H, 75
 C105Y, 73
 examples of, 70
 hCT(9-32)-br, 73
 hCT(18-32)-br, 74
 hydrophobic MPS, 72
 L1-7, 75
 M918, 74
 membrane-translocating sequence, 72
 MPG, 69
 MTS1, 72
 P4, 74–75
 Pep-7, 73
 Pept1, 74
 PFV, 74
 substance P analog, 72
 TP10, 72–73
 translocation motif (TLM), 73
 hydrophobic MPS, 72
- i**
 inflamed tissue, 287, 301–304, 307
 instantaneous membrane defect, 115
 intracellular delivery systems, 29, 39
 intranasal administration, 355
 bioavailability, 355
 ion channel/pore-forming peptides, 113
- k**
 KAI Pharmaceuticals, 371
 KALA, 62, 246
 K16ApoE, 186, 187
 K-homology splicing regulatory protein
 (KHSRP), 273
- l**
 LAH4, 51, 61
 L17E, 61

- leaky fusion, 162–165
 leucine (L)-lysine (K) sequence, 120
 levofloxacin, 212, 214
 LH peptide, 50
 linear CPPs, 21
 lipid-grafting, 248–249
 lipid nanoparticles (LNPs), 315–316, 321–324
 types, 320–321
 lipopeptides, 34, 249
 liraglutide (LRT), 32
 L8K6, 120–122
 L12K9, 120, 121
 L16K12, 120–122
 LK peptides, 120, 122, 123
 LL-37, 116
 low-molecular-weight (LMW) drugs, 367, 374–375
 L-peptide bombinin H2, 117
 LTP peptides, 35
 lysine-rich CPPs, 38, 45–48, 382, 389
 lysophosphatidylcholine (LPC), 164
 lysosomal-associated membrane protein 1 (LAMP1), 161
- m**
- M918, 35, 64–65, 74
 machine learning, 268, 269
 macropinocytosis, 29, 36, 37, 38, 60, 61, 65, 74, 141, 142, 143, 160–162, 169, 228, 240, 241, 285, 286, 292, 319, 321, 386, 387
 macropinocytosis-inducible exosomal system, 37
 macropinocytosis pathway, 29, 292, 386
 macropinosomes, 161, 162
 Magainin 1, 114, 116
 melittin, 20, 128, 348, 349
 membrane destabilization/permeabilization, 165–166
 membrane penetration mechanisms, of arginine-rich peptides, 144–147
 membrane repair, 165, 170, 171, 241
 membrane-translocating sequence, 72
 messenger RNAs (mRNAs), 23, 237, 238, 264, 271, 276, 375
 methicillin-resistant *Staphylococcus aureus* (MRSA), 188, 212
 miniprotein structures, 269
 Mitoparan (INLKKLAKL(Aib)KKIL), 47
 M-lycotoxin, 61
 model amphiphatic peptide (MAP), 20, 22, 45, 47, 58, 60, 85, 184, 317
 molecular dynamics (MD) simulation, 112, 129–131, 146, 149, 164, 387
 monomers, 79, 80, 114, 386
 Montal-Mueller/painting methods, 113
 MPG, 22, 35, 62, 69
 MTSI, 72
 multilamellar formation of membranes for membrane penetration of arginine-rich peptides, 148
 multiple/stable pBLMs, 113
 muscle-specific peptide (MSP), 243
- n**
- nanocarriers with R9 peptides, 33
 nano DDS, 21, 23
 NickFect70, 51
 non-arginine-containing P9W, 124
 non-cationic cell-penetrating peptide (AA3H), 211
 noncovalent conjugation method, 222
 noncovalent method, 223, 224, 228–229
 non-proteinogenic amino acids, 22, 79–80, 85, 86, 89
 nose-to-brain drug delivery, 294–297, 357–358
 by coadministration with CPPs, 357–358
 mechanistic insight, 358–360
 therapeutic effects, 360–362
 NRP-1-targeted peptide, 33
 nuclear localization sequences (NLS), 35, 50, 72, 242, 248, 250
 nucleic acid delivery, 243–244
 PepFect family, 245
 RALA family, 246–247
 WARP family, 245–246
 nucleic acids (NAs), 21–23, 45, 51, 57, 58, 62, 69, 79, 161, 165, 167, 183, 237, 265, 285, 286, 295–297, 304, 315, 320, 321, 362, 367, 375–376
- o**
- octa (R8)-arginine-conjugated exosomes, 38
 octa-arginine peptide, 45
 octa-D-arginine (r8), 208
 oligoamide foldamers, 88, 89
 oligoarginines, 19, 21, 22, 29, 38, 85, 86, 141, 144, 145, 150, 206, 209, 212, 228, 231, 268, 285, 286, 292, 316, 317, 333, 386
 with exosomal membrane proteins, 38
 oligonucleotides (ONs), 34–35, 62, 69, 173, 237–238, 268, 269, 273, 297
 oligoprolines, 83, 124
 oligourea foldamer, 87–89
 oligoureas, 87
 oral delivery, 1, 31, 304–307, 331–350
- p**
- P4, 74–75
 Pardaxin P5, 116
 p14ARF, 35, 64, 74

- parylene double-well (PDW) chip, 113
 pDNA delivery, 88, 245, 249, 288–292
 PEGylation, 248–249, 287, 288, 301
 Penetratin, 17, 22, 45, 57, 184, 241, 242
 Pep-1, 64
 Pep-7, 73, 317
 PepFect 3 (PF3), 245
 PepFect family, 240, 245
 Pept1, 74
 peptide-based nanoparticles (PBNs), 238
 peptide development, 241, 267–270
 peptide lengths, range of, 21
 peptide-modified exosomes, cellular uptake of, 38
 peptide nucleic acids (PNAs), 23, 60, 74, 231, 242
 peptide–PMO (PPMO)
 bacteria and protists, 273–275
 genetic disease, 275–277
 peptide development, 267–270
 platform technology, 270–278
 viruses, 270–273
 peptide receptor radionuclide therapy (PRRT), 250
 peptoids, 86
 PFV, 74
 pharmacokinetics
 of CPP-conjugates for cancer treatment, 190–196
 of CPP-conjugates for CNS disorders, 186–187
 of CPP-conjugates for infectious diseases, 187–189
 of CPP-conjugates for inflammatory diseases, 189–190
 of CPPs, 184, 185
 pH-low insertion peptides (pHLIP), 242
 phosphorodiamidate morpholino oligomers (PMOs), 263, 375
 phosphorodiamidate morpholino oligonucleotides (PMOs), 32, 243
 phosphorylated epidermal growth factor receptor (EGFR), 72
 PICsome, 393
 planar bilayer lipid membrane (pBLM), 113–114
 plasmid DNAs (pDNAs), 22, 23, 31, 60, 85, 237, 285, 319, 375, 386
 poly(ethylene glycol) (PEG), 33, 188, 287, 320
 polyelectrolyte complex (PEC), 292
 polyethylene glycol-phosphatidylethanolamine (PEG-PE), 164
 polyhistidine peptides (PHPs), 50, 383
 poly ion complex micelles (PICs), 287
 polylysine, 47, 242, 246
 polymer micelles, 287
 multifunctional peptide-conjugated, 297
 poly-N-substituted glycine oligomers, 86
 poly-proline-arginine (poly-PR), 149
 polyproline-containing arginine-rich peptide P9R7W, 124
 polyproline II (PPII) helix, 123–125, 128
 polyproline II (PPII) helix structure, 123, 126
 polyproline type II helical peptides, 63
 poly(chloro-*p*-xylylene) (parylene)
 separator, 113
 pore-forming peptides, 113, 114, 128, 166
 positive charge-independent histidine-rich CPPs, 50
 ppTG1, 60
 ppTG20, 60
 Pro-Arg-rich antimicrobials, 63
 progerin, 276, 277
 proline-based γ -amino acids, 83
 proline-rich peptides, 123, 124
 protein-derived CPPs, 21–22
 protein kinase C-alpha (PKC α), 143
 proteinogenic amino acids, 21
 protein pharmaceuticals, 373
 protein–protein interactions (PPIs), 32, 190, 223
 protein transduction domains (PTDs), 1, 316
 proton sponge effect, 50, 51, 162, 163, 166–167, 241, 286, 297, 299
 PsorBan, 367, 371
 pVEC, 64, 130, 184, 210
- r**
- Rab7, 144, 161, 164
 - RALA family, 246–247
 - RA therapy, 301
 - r7-conjugated CsA, 208, 209
 - REDV-TAT-NLS-H12, 50, 51
 - R₁LS (1st generation dendritic arginine), 34
 - R₂LS (2nd generation dendritic arginine), 34
 gene transfection efficacy, 34
 - R₃LS (3rd generation dendritic arginine), 34
 - R16-modified exosomes, with saporin encapsulation, 38
 - RNA interference (RNAi), 238, 286
 - ruthenium (II) dipyridophenazine (dppz), 34
 - R₆W₃, 60
- s**
- Sarepta Therapeutics, 237, 375
 - sC18, 38, 47
 - siRNA delivery, 88, 246, 285–307
 - SL-37, 116
 - small interfering RNAs (siRNAs), 23, 61, 74, 85, 190, 237, 238, 248, 249, 285, 292, 304, 323, 375, 392

- SNIPER, 230
Solanum lycopersicum, 383
 solid phase peptide synthesis (SPPS), 248
 solid-state NMR analysis, of direct penetration of CPPs, 128–129
 spinal muscular atrophy (SMA), 238, 276
 stable nucleic acid lipid particles (SNALPs), 321
 stearylated CPPs, 22
 stearyl-r8-Exo induced macropinocytosis, 37
 structure-activity relationship (SAR), 47, 173, 243, 246, 268
 substance P analog, 72
 surfactant-like peptides (SLPs), self-assembly of, 33
 survival motor neuron 1 protein (SMN1), 238
 sweet arrow peptide (SAP), 63
 SynB-conjugated doxorubicin, 210
 synthetic CPP, 22, 73
- t**
 Tat-conjugated polymer micelles, 288
 tetramethylrhodamine (TMR), 164
 TH peptide, 48
 TK peptide, 47, 48
 TP10-conjugated vancomycin, 212, 213
 transacting activator of transcription (TAT) peptide, 219, 316
- transactivator of transcription (Tat) protein, 1, 19, 22, 219, 285
 translocation motif (TLM), 73
 transmembrane peptide structures, 114
 sporotran, 17
 transportan, 20, 60, 72, 73, 195, 242, 317, 383, 389
 transportan 10 (TP10), 60, 72–73, 184, 188, 211, 212, 245
 Trojan peptides, 1, 316
 tumor-homing CPPs, 33
 tumor-homing peptides, 194, 196
 tumor-penetrating peptides (TPPs), 32, 33
 tumor tissue, 48, 184, 190, 193–196, 289, 291, 292, 297–301
- v**
 vancomycin (Van), 187–189, 212
 vascular endothelial growth factor (VEGF), 292
 VT5, 20, 62
- w**
 WRAP family, 245–246
- z**
 Zolgensma (Novartis), 238

