

Index

Locators in *italics* refer to figures.

- 3' untranslated region. *See* 3' UTR
- 3' UTRs, 13, 30, 42, 68, 114, 127
 7-mer sequence in, 31
BAF53a and, 104
 docking site on mRNAs and, 28
 in the human transcript, 151
 miR-223 and, 32
 octopus protein-coding transcripts of, 130
 of a protein-coding gene, 20
 of *Limk 1*, 121
 of *lin-14*, 17–19
 of mRNAs, 114, 116
 of mRNAs and developmental timing, 22
 of the *KCNQ2* transcript, 154
 of transcripts, 31, 136
 sequence and surrogate gene, 22
 site for miR-122, 180
- 5' UTR, 181
- 5-ccAttGtcAcaCtcCa-3, 183
- 7-mer. *See* mer sequence
- absence epilepsy, 141, 203
- actin, 113, 116
 controlling in the spine, 122
 depolymerizing agent of, 122, 123
- actinomycin D, 73
- action potentials, 109–11, 122, 124, 126, 169
 delays in firing of, 154
 drugs and, 145
 firing of, 143, 171, 196, 233
 frequency of, 111
 hippocampus and, 158
 pre-miR-134 and, 121
 triggering new, 112
 triggering of, 153
 up phase of, 199–201
- acute anti-seizure effect, of antimir, 149
- ACUUU sequence, 117
- acyl-protein-thioesterase 1 (APT1), 121
- ADARs (adenosine deaminase acting on RNA), 170–1
 in human hippocampal samples, 171–3
- adeno-associated virus (AAV), 193–4, 206
 AAV-335 mice and seizures, 204
 AAV9, 194
 AAV9 as microRNA, 204
 as a gene therapy, 196
 mutant HTT-targeting microRNA sequence, 195
 programmed with cell promoters, 236
- adenosine kinase (ADK), 157
- adenosine triphosphate (ATP), 6, 8
- adults
 microRNA function and system repair, 82
 microRNAs in, 243
 resistant epilepsy in, 141
 suppression of microRNAs functions in, 82
- ageing
 effect of removing microRNAs, 7
 microRNAs and, 132, 243–4
- AGOs, 62, 115–16, 218–19, 239
- AGO protein and PAZ, 74
- AGO proteins, 64–5, 66
- AGO proteins and microRNA-mediated actions, 66
- AGO proteins and microRNAs, 50, 75
- AGO proteins and TRBP mice lacking the, 61
- AGO proteins from plasma samples, 218
- AGO2 (Argonaute 2), 59, 106, 151, 170, 218
- AGO2 and hepatitis C (HCV), 181–2
- AGO2-FLAG, 228
- Ago2*-null embryo studies, 79
- crystal structure of AGO2, 68
- degradation of AGO protein, 75
- live interactions with microRNA and, 66–9
- mice lacking the *Ago2* gene, 64
- microRNA-loaded AGO protein, 67
- microRNAs and, 117
- variants of the *Ago2* gene, 64
- versus exosome, 221
- Allen Brain Institute, 105
- ALS, 137, 224
 microRNA-based medicine for, 210
- alternative splicing process, 13, 50
- Alzheimer's disease, 46, 141, 216, 219–20, 221, 224
- AGO2 and, 223
- diagnosis and amyloid deposits, 213
- early-onset, 228
- extracellular β -Amyloid plaques in, 241
- medicines and, 175
- pathology of, 220
- Amanita phalloides*, 52
- Ambros, Victor, 17, 20
- American Journal of Clinical Genetics, 168
- amine group (NH_3), 6, 14
- amino acids, 6, 7, 10, 13, 50, 56, 68
- growing chain of, 14
- mapping of key, 56
- phosphates and, 62
- stable isotope labelling, 31
- triplet code for, 16
- ubiquitin and, 72
- AMPA receptor, 171
- amygdala, 133, 152
- fear and stress response, 134–5
- loss of Dicer from, 134

Index

- amyloid deposits, Alzheimer's
 diagnosis and, 213
 amyotrophic lateral sclerosis
 (ALS), 137, 224
 microRNA-based medicine
 for, 210
 Angelman, Harry, 165
 Angelman syndrome, 165–8
 reduced ataxia in Angelman
 mice, 167
 animal evolution, 41
 microRNA gene expansion
 and, 39
 animal genomes, 26
 microRNAs and, 23
Anolis carolinensis, 38
 antimir/antimirs, 121, 123,
 125, 191
 blocking miR-335 and, 203
 editing with, 172
 in animal trials, 188
 targeting miR-2392, 238
 understanding, 149–51
 antimir-122,
 levels of microRNAs, 184
 taking it to clinical trial,
 184–6
 antimir-134,
 result of use of in mice, 190
 therapy, 191
 anti-psychotics, 135
 anti-seizure medications
 (ASMs), 145, 155, 187,
 212, 226
 and dogs, 190
 organised and systematic
 discovery of, 145
 sodium channels as
 targets, 196
 work in rodents, 188
 antisense, 18
 antisense inhibitors, 125
 antisense
 oligonucleotides, 182
 antisense sequences, 236
 antisense strand, 10, 18, 21
 antisense drug, 191
 platforms, 182
anxiolytic effect, 134
 Arabidopsis, 43, 74
 microRNAs, 27
 Arabidopsis thaliana, 48, 49
 and Physcomitrella
 patens, 44
 archaea, 40, 217
 Argo journey, 58
 Argonaute
 how it works, 65
 microRNAs
 interaction, 64–6
 name, 49
 Argonaute 2. *See* AGOs
 ARHGAP32 gene, 124
 Aronica, Eleonora, 147
 ASOs, 123, 175, 198
 astrocytes, 80, 104, 111,
 148, 159
 activator of, 157
 differentiation, 104
 atomic force microscopy, 121
 ATP, 158
 A-U Watson-Crick match, 64
 Avery, Oswald, 10
 axon initial segment, 126
 axon terminals, 129
 axons, 104, 111, 116, 142
 bundle of, 142
 changes to, 143
 ganglion cells and, 85
 insulation of, 101
 of the human neurone, 200
 bacteriophages, 78, 192
 BAF53a, 104
 Baram, Tallie, 191
 Bartel, David, 25–6, 27
 targets of microRNAs
 and, 28
 Baulcombe, David, 21
 BDNF (brain-derived
 neurotrophic factor),
 117, 129
 signalling system fault, 129
 Belt, 58
 Berlin Institute for Medical
 Systems Biology, 130
 biogenesis, 51–2
 blocked, 73
 of a microRNA, 69–72
 pathway, 28, 77, 80, 81, 216
 pathway and rules of
 engagement, 232
 pathway in *C. elegans*, 83
 process for microRNAs,
 234–5
 biomarkers, 230, 231
 Alzheimer's disease and,
 219
 biofluid-based, 242
 blood-based microRNA, 225
 categories of, 212–13
 circulating, 229–30
 circulating microRNAs as,
 228–9
 identification of, 221
 in human brain fluid, 223
 less-invasive sources of,
 219–21
 microRNA, 215–16, 230,
 231, 243
 microRNAs as, 213–18
 bipolar disorder, 136
 miR-124 and, 240
 miR-134 and, 226
 predisposition to, 137
 birth weights, 97
 blood samples, 211
 children exposed to
 childhood trauma
 and, 134
 epilepsy motoring, 224
 FLAG-AGO2 in a, 228
 from dogs with epilepsy,
 191
 from rats with brain
 injuries, 146
 in human studies, 225
 microRNAs in, 211
 patients with drug-resistant
 epilepsy, 198
 temporal lobe epilepsy
 patients, 209
 blood, for disease
 biomarkers, 221
 blood-based microRNAs
 biomarkers of, 225
 dementia and, 220
 blood–brain barrier, 189
 circulation in, 188, 216
 BMAL 1, 241–2
 body clock(s), 241–2
 bortezomib, 72
 brain cells, 6, 45, 70, 102,
 106, 111
 ASO-based microRNA drugs
 and, 236
 complementary actions
 and, 103
 creation of realistic living
 systems and, 241
 death of, 79
 during sleep, 241
 inflammatory responses to,
 155–6
 lost in Parkinson's
 disease, 99
 maturing, 104
 microRNAs in, 73, 139

Index

- brain cells (cont.)
 microRNAs to repress transcripts, 133
 non-brain cell proteins and, 30
 reaction to injuries, 163
 RISC component in, 228
 signalling and, 109
 UPS system is activated in, 72
 brain development, 100–5, 109, 130, 141
 abnormal, 83
 brain-enriched microRNAs, 114
 cell elimination during, 104
 early, 79
 effect of gene variation on, 76
 epilepsy and, 165
 last part to develop, 105–6
 levels of transcript and, 45
 microRNAs switched on during, 28
 regulation of, 46
 transgenerational effects on, 97, 99
 brain diseases, 127, 133, *See also* mental health problems as conveyors of microRNAs in, 221–4
 biomarkers of, 224–7
 nasal epithelium samples and, 241
 brain injury
 blood microRNAs changes and, 225
 development of epilepsy following, 149
 epilepsy development after a, 227
 microglia and, 156
 reactions to, 162
 traumatic, 156, 157, 188
 brain samples, 105, 133, 141
 analysis of, 204
 dendritic morphology in, 150
 editing and, 171
 from the epilepsy patients, 157
 measuring miR-134 in, 166
 miR-1202 and, 136
 miR-134 and, 151
 miR-27a present in, 54
 obtaining, 45
 patients consent to collect, 201
 temporal lobe epilepsy patients, 150
 brain size, 45
 brain tissue samples
 from temporal lobe epilepsy patients, 148
 temporal lobe epilepsy patients, 148
 brain, the
 circulating microRNAs and, 227–8
 controlling the excitability of, 153–5
 hyperexcitability in, 195
 macro-level functions of, 133–5
 microRNA enrichment in, 114–15
 microRNA system, 139
 microRNAs in human brain fluid, 223
 miR-134 and brain power, 128
 RNA editing and, 171
 special microRNAs in, 114
 brain-derived neurotrophic factor (BDNF), 117, 129
 signalling system, 129
 brain-related functions, 97
 Brennan, Gary, 191
 Brenner, Sydney, 16
 bulk analysis, 130

C. elegans, 56, 83
 and the discovery of microRNAs, 18
C. elegans study, 26
 development of, 21
 C/G-value paradox, 39
 C19MC, 54
 CA1 pyramidal neurones, 199
 CA1 region, 142
 CA3 subfield, 142
 CACNB2, 137
 Caenorhabditis, 18
 Caenorhabditis elegans (*C. elegans*), 15–19
 Cajal institute, 123
 calmodulin-dependent kinase II (CaMKII), 113
 Cambrian explosion, 38
 CaMKII, 120
 CAMKII, transcript for, 127

 canine hippocampus, miR-14 in, 191
 cannabis sativa plant, 197
 carbamazepine, 146, 196
 carboxyl group (COOH), 6, 14
 cardiac hypertrophy, 187
 cardiac phenotypes, in mice lacking miR-1, 84
 Cardior Pharmaceuticals, 187
 Caspase-I, 157–8
 role of, 158
 CD4, 237
 cDNA sequences, 25
 Cell paper, 15, 64, 99
 cell suicide programme, 104
 cells, 5
 cell-to-cell communication, 34, 44, 109–11, 216, 218, 231
 cellular features, 99
 cellular senescence, 244
 Center for RNA Medicine, 182
 Centre for Human Genetics at Saarland University, 234
 cerebellum, 123
 cerebral cortex forms, 102
 cerebrospinal fluid, 221
 cervical cancer, HeLa cells and, 24, 178
 Chargaff, Erwin, 10
 charge difference, 109
 Chernobyl, 228
 children
 psychosis and Dutch, 97
 chromatin, 8, 12
 chronic stress
 miR-15a protection against, 135
 circadian rhythm, 241
 circulating biomarkers, 229–30
 clinical trials
 animal trial for microRNA therapy for treating epilepsy, 188–91
 antimir-122 and, 184–6
 drugs and, 176
 microRNA drugs and, 235
 CLOCK, 241
 CLOCK-BMAL1 complex, 242
 CNS gene therapy, 193
 coding sequence/CD, 13
 codon, 7
 cofilin, 122
 Cold Spring Harbor, 59
 communication, microRNAs and synapses, 125–7

Index

- complex brain disorder, 137
 contralateral hippocampus, 158
 COOH, 6
 corticotropin-releasing factor (CRF), 134
 Covid-19 pandemic, 191, 238
 circulating microRNAs and, 238
 home tests and, 230
 mRNA vaccines and, 2, 6
 Cre system, 79
 CREB, 125
 miR-132 levels and neuronal activity, 117
 CREB protein, 117–18
 CREB transcript, 129
 Creutzfeldt-Jakob disease, 226
 Crick, Francis, 16
 CRISPR, 61, 236, 241
 Cry genes, 242
 CSF1R receptor, 156–7
 Ctenophores, 40
 C-terminus, 14
 Cullen, Brian, 27
 cut-like homeobox 1 (CUX1), 177
 cyclic AMP (cAMP), 117
 cysteine, 6
 cystic fibrosis (CF), 206
 cystic fibrosis trans-membrane conductance regulator gene (*CFTR*), 206
 cytokines, 155, 157
 inflammatory, 192
 cytosol, 59, 70

 D. melanogaster, 16, 25, 56
 Daegu Gyeongbuk Institute of Science and Technology, 154
 Dana-Farber Cancer Institute, 229
 Daphnia, 38
 death cap mushroom, 52
 DeFelipe, Javier, 123
 degenerative diseases
 edited miR-376a and, 173
 Delanty, Norman, 148
 dementia
 blood-based microRNA and, 220
 dendrites, 111
 changes to, 143
 Dicer and AGO proteins in, 116
 simulation of Dicer in, 119
 dendritic complexity, synaptic connectivity, 136
 dendritic spine function, control of, 124
 dendritic spines, 111, 112, 112, 121, 129
 Denisovans, genome of, 46
 dentate granule neurones, 142
 dentate gyrus, 142
 deoxyribonucleic acid (DNA), 6
 deoxyribose, 8
 depolarisation block, 144
 developmental disorders, 105
 developmental timing, regulation of, 22
 Dgcr 8, mutant mice, 136
 DGCR8, 56–9, 135
 production of mature microRNAs, 56
 DHX 36, 117
 DHX 9, 117
 diagnosis
 future of, 242–3
 journey of, 212
 use of microRNAs in, 211–13
 Dicer, 25, 115–16, 238
 AGO and, 235
 deleted from brain cells, 80
 deletion of, 95
 dendrites and, 116
 disappearing, 151–2
 how it works, 63
 independent pathway, 222
 loss of from the amygdala, 134
 microRNA maturation and, 60
 stimulation in the dendrite, 119
 TRBP and, 61–2
 Dicer (RNase III enzyme), 59–61
 Dicer required adenosine triphosphate (ATP)
 Dicer and, 60
 differentiation process
 brain cells and, 103–4
 dominant microRNAs and, 103
 DiGeorge syndrome, 135
 direct-acting antivirals (DAAs), 186
 diseases
 rare and single-gene causes of, 236
 disulphide bridge, 6
 DNA
 chemical structure of, 9
 history of, 8–10
 structure of, 8
 DNA code
 reading of, 10–13
 DNA-based nanoswitches, 239
 dogs
 animal trials with epilepsy and, 190–1
 treatment of drug-resistant epilepsy in, 210
 dopamine, 79
 dorsolateral prefrontal cortex, 106
 double-stranded RNA (dsRNA), 20–1, 44, 55, 56–9, 60, 235
 ADARs and, 171
 Drosha and, 59
 synthetic, 23
 TRBP actions and, 62
 Dravet syndrome, 141, 168–9, 196
 cannabidiol (CBD) for treating, 197
 CBD-based drug, Epidiolex for, 197
 sodium channel activity and, 206
 Dravet, Charlotte, 168
 Drosha, 55–9
 DGCR8 act, 238
 RNA cutting activity of, 56
 Drosophila melanogaster, 55
 Drosophila, gene silencing in, 60
 drug development, 183, 184
 for epilepsy, 187
 UPS used in, 72
 drug-resistant epilepsy, 148
 in dogs, 210
 Duncan, Janet, 145, 155
 DYKDDDDK (FLAG tag), 228

 Edinburgh Medical and Surgical Journal, 145, 155
 electrical storm, triggering, 124
 electroencephalogram (EEG), 123
 EMBO journal, 48
 embryonic nervous system, 101
 endoribonuclease, 55

Index

- energy-hungry pathways, 173
 Engel, Tobias, 72, 158
 enhancer, 12
 entorhinal cortex, 142
 Epidiolex, 197
 epileptogenesis, 162
 epilepsy
 animal trial for microRNA
 therapy for treating, 188–91
 biomarker of, 213, 221
 causes of, 141
 circadian gene expression
 in, 242
 development after a brain
 injury, 227
 diagnostic journey, 212
 disease-modifying therapies
 for, 191
 drug-resistant, 148
 excitability of the brain in,
 155–60
 history of, 140
 microRNA biogenesis
 machinery and, 140
 microRNA studies and,
 160–3
 microRNAs and, 146–8
 microRNAs and the human
 epileptic brain, 169–70
 microRNAs as medicines
 for, 187–8
 microRNAs for, 195–8
 mutations of KCNQ2 gene
 and, 154
 temporal lobe, 141–2
 therapy, 155
 treating, 145–6
 treating genetic epilepsies,
 163–8
 treatment-resistant, 140
 UPS and, 72
 what it is, 141
 epilepsy models, microRNAs
 targeted in preclinical, 189
 epilepsy therapy screening
 programme (ETSP), 188
 EpimiRNA project, 123, 169,
 171, 195, 197, 221
 eukaryotes, 40
 cells of, 8
 eukaryotic cells, 8
 evolutionary genetics, 103
 excitability, 127
 concentration and
 movement of potassium
 of, 153–5
 miR-335 and, 205–6
 spine changes on, 122
 excitability, neuronal
 seizures and, 154
 excitatory and inhibitory
 neurones, 196
 excitatory neurones, 111, 113,
 143, 191, *See also*
 inhibitory neurones
 excitatory
 neurotransmission, 125
 excitatory synapse, 111
 excitatory synaptic activity, 150
 exons, 13
 exoribonuclease 1 (XRN1), 69
 exosomes, 217, 218
 versus AGO, 221
 experimental temporal lobe
 epilepsy, microRNA
 changes in, 160–3
 Exportin/Exportins, 59,
 63
 Exportin-5, 50, 59
 extracellular vesicles, 217

 Farrell, Michael, 148
 Filipowicz, Witold, 73
 Fire, Andrew, 26
 FLAG sequence, detecting, 228
 FLAG tag, 228
 fluorescence resonance energy
 transfer (FRET), 66
 focal seizure syndromes, 196
 fragile X syndrome, 27
 Franklin, Rosalind, 10
 Fukushima Daiichi Nuclear
 Power Plant, 228
 FutureNeuro, 197, 208

 GABA, 143–4, 152
 releasing neurones, 126
 GABA (gamma-amino butyric
 acid), 111
 GABA inhibitory
 neurotransmission
 system, 141
 GABA receptors, 198
 GABA signalling, 203
 GABA-releasing cells, 194
 GABA-releasing inhibitory
 neurone, 144
 GADD45, 92
 Gallus gallus, 38
 gametes, 96
 microRNAs, 94–5
 Gareth, 195

 gene, 7
 to protein, 10–13
 gene activation, stress-
 related, 134
 gene expression, 37, 232
 coordination of, 107
 gene expression patterns, 243
 gene expression
 programmes, 243
 gene expression, in the
 hippocampus, 242
 gene mutations, 163
 gene programmes, 108
 gene silencing, 23, 64
 in *Drosophila*, 60
 microRNAs and, 70
 gene therapy/therapies, 192,
 204, 205, 207, 236
 adeno-associated virus
 (AAV) as, 196
 clinically approved, 193
 concerns with, 237
 controlling, 236
 human trial of, 192
 microRNAs and, 195–8
 next generation of, 210
 PPI panel and, 208–9
 temporal lobe epilepsy
 and, 152
 trial for Dravet, 207
 trials of and *UBE3A*, 165
 use of, 193
 gene turn-off process, 173
 generation sperm, 98
 genes switching, 107
 genetic code, 7–10
 genetic epilepsies, treating,
 163–8
 genetic epilepsy, 141
 genetic risks, 240
 genetics
 and modelling, 240–1
 evolutionary, 103
 genetics, 16
 genome
 gene-making and, 7
 genome biology, 224
 genome sequence
 in gametes, 97
 geromirs, 243
 Glasgow Royal Infirmary, 145
 glia, 111
 glia cells, 111
 glial cells, 142
 gliogenesis, 106
 globus pallidus, 152

Index

- glutamate receptor, 198
 glycine, 6
 Golgi apparatus, 217
 Gorter, Jan, 147
 Gothenburg university, 217
 great-ape specific
 microRNA, 46
 Greene, Catherine, 206
 Greengard, Paul, 79
GRIA2 transcript
 editing of, 171
 Gross, Nina, 169
 guanine triphosphate
 (GTP), 59
guide, 64
 GW, 197
 GW182, 69
- Hannon, Gregory, 59
 hepatitis C (HCV)
 principles about miR-122
 and, 180–1
 Harvard University, 229
 HCV. *See* hepatitis C (HCV)
 heart disease
 death from, 175
 heart failure
 miR-132 and, 187
 Heiland, Mona, 197
 HEK293 cells, 61
 HeLa cells, 24, 30, 31, 235
 foreign microRNA and, 31
 let-7 and, 60
 miR-124 and, 30
 hepatitis C (HCV), 178–80
 and AGO2, 181–2
 direct-acting antivirals for
 treating, 186
 effects of miravirs on, 186
 miR-122 and, 179
 miravirs for treating, 178
 using miR-122 to treat,
 182–4
 herpes simplex virus, 193
 heterochronic genes, 17
 Hill, Tom, 197
 hippocampus
 epilepsy-causing
 injuries, 191
 gene expression in the, 242
 miR-146a in, 147
 pyramidal neurones in
 the, 123
 hippocampus, the, 142, 142–3
 Hippocrates, 140
 histones, 8
- Howard Hughes Medical
 Institute (Duke
 University), 27
 Hox genes, 93–4, 102
 microRNAs and, 94
 HUGO nomenclature, 7
 human brain. *See also*
 brain, the
 development of the last part,
 105–6
 neurones in, 108
 human brain diseases, 105,
 See also brain diseases
 human diseases, 27, 46, 171,
 175, 194, 231
 diagnostic tests for
 various, 71
 gene sequences to treat, 193
 microRNA therapy and, 176
 model in an animal, 202
 risks for, 153
 statistics on death from, 175
 testing on non-human
 primates, 184
 treatment by gene
 transfer, 192
 human genome, 6
 human neurones, miR-335
 and, 202
 humans, microRNAs in, 38
 Huntington's disease, 194
 hybridisation, 29, 198
- IL1 β , 157–8
 microRNA link and, 157
 IL1 β pathway, 157
 Imanishi, Takeshi, 182
 immune system
 cell-to-cell communication
 in the, 216
 Importins, 59
 individual-nucleotide
 resolution cross-linking
 and immunoprecipitation
 (iCLIP), 169
 induced pluripotent stem cells
 (iPSCs), 88
 inflammation
 anti-inflammatory
 drugs, 157
 early inflammatory reactions
 and, 156
 microRNAs influence on,
 155–60
 information
 action potentials and, 111
- inhibitory neurones, 102, 109,
 111, 113, 122, 126–7, 141,
 142–3, 152, 165, 191, 196
 GABA neurotransmitter
 and, 143–5
 NaV 1.1 and, 169
 inhibitory neurones, 205
 inhibitory synapses, 111
Integrator controls, 235
 intergenerational effects, 95
 interleukin 1 β (IL1 β), 155
introns, 13, 50
 iPSCs, 241
- Janus kinases (JAKs), 104
 Jimenez-Mateos, Eva, 146, 198
 Johns Hopkins University,
 86, 240
- KA receptor, 147
 kainic acid, 147, 150
 in animal studies, 224
 in mice models, 148
 Kandel, Eric, 129
 Kauppinen, Sakari, 182–3
KCNQ2 gene, 153
KCNQ2 transcript, 154, 225
 Kjems, Jorgen, 160, 161, 169
 Kosik, Kenneth, 106
 Krook-Magnuson, Esther, 166
 Kv7.2 protein, 154
 Kyoto University, 237
- Lacks, Henrietta, 24
 lamotrigine, 196
 latrunculin A, 123
 Lau, Kelvin, 171
 Lederberg, Joshua, 192
 Lee, Rosalind, 26
 Lennox-Gastaut syndrome, 196
 lentivirus, 193
let-7, 27, 37, 60
 HeLa cells and, 60
 production of mature
 microRNA, 60
 Levene, Phoebus, 8
 levetiracetam, 145, 203
Limk1, 122, 151, 170
 3' UTR of, 121
 inhibitor, 150
 regulating, 122
lin-14, 17–19
 lin-4,
 mutations and loss of, 17
 liver
 miR-122 in liver cells, 180

Index

- liver (cont.)
 miR-122 microRNA in the, 177–80
 long-term depression (LTD), 119
 loop ‘quencher’ region, 118
 LYPLA 1, 121
- MacRae, Ian, 61, 68, 181
 magnetic resonance imaging (MRI) scanner, 189
 Mamad, Omar, 190
 mass spectrometry, 31
 Massachusetts Institute of Technology (MIT), 25
 maternal grandmother, 97
 maternal stress
 unpredictable, 97
 maternal stress and diet, transgenerational effects of, 96
 Max Planck Institute for Brain Research, 23, 59, 113
 mediator, 12
 medicines
 essential, 175
 for human diseases, 175
 microRNAs as, 175–6
 using miR-122 to treat HCV, 182–4
 Meischer, Friedrich, 10
 Mello, Craig, 60
 membrane potential, 109
 Memorial Sloan Kettering Cancer Center (New York), 81
 mental health problems, microRNA imbalances and, 135
 mer sequence, 31
 7-mer or 8-mer sites, 32
 7-mer sequence, 31
 messenger RNA (mRNA), 6–7
 metabolic processes, shutting down, 173
 METriC, 191
 microarray technology, 30
 microglia, 111
 microglial processes, 156
 natural function of, 156
 microprocessor, 56–9, 78, 135, 238
 how it works, 57
 microRNA biogenesis, 235
 pathway, 77, 80, 81
 standard or ‘canonical’ pathway for, 62
 steps in, 50
 microRNA biomarkers, 215–16, 230, 243
 blood-based, 225
 effects of, 231
 human brain fluid and, 223
 microRNA datasets, 105
 microRNA decay, 73–4
 microRNA degradation, 74,
 See also microRNAs decay
 enzymes involved in, 74–5
 microRNA evolution, 38, 41, 43, 44
 human-specific, 47
 introns and, 46
 microRNA functions, 41, 71, 81–2, 115, 127, 177
 a virus that disabled, 28
 controlling, 214
 disordered, 137
 in health and disease, 72
 investigation of *in vitro* and *in vivo*, 122
 single cell resolution of, 234
 synaptic activity and, 119, 120
 TRBP and, 62
 microRNA inhibitor, 201
 microRNA pathway, 235
 microRNA production, 76
 microRNA sequences, conservation of, 41
 microRNA system
 adult brain and, 139
 microRNA systems, 34
 microRNA therapies, 191–3, 207, 235–6
 clinical trial of, 177–80
 dogs with epilepsy and the, 190–1
 for epilepsy animal trials, 188–91
 microRNA transcription
 on signals for, 52–4
 microRNA turnover, 73
 microRNAs, 7
 aging and, 243–4
 AGO-loaded, 117
 aligning to mRNA and AGO’s search mode, 67
 altering the sequences of, 170–3
 and target co-evolution, 42, 47
 as a biomarker, 213–16
 as a suitable biomarker, 229–30
 as biomarkers, 227
 as medicine, 175–6
 at the synapse(s), 115–16, 120
 biogenesis genes, 136
 biogenesis of, 69–72
 biogenesis process for, 234–5
 biomarkers, 231
 biomarkers and, 216–18
 blood-based, 220
 brain activity and, 127–8
 brain diseases and, 135–7
 brain-enriched, 224
 cell-type specific, 130–3
 changes in biogenesis machinery and epilepsy, 140
 circulating as biomarkers, 228–9
 completion of the work, 72–3
 connecting to synaptic activity, 117–18
 consensus on the numbers of, 234
 control of neuronal structure and function and, 155–60
 coupling synaptic activity to production of, 118–20
 detection and deployment of, 239–40
 development of more, 41–2
 development of the field, 232
 diagnosis of diseases and use of, 211–13
 Dicer and, 64
 differentiation of brain cells and, 103–4
 discoveries leading to medicine, 207
 discovery of the first, 18
 drug programmes, 235–6
 early discoveries on, 15
 editing in the brain, 171
 editing of, 171–3
 effect of on RNAi pathway, 77
 effect on the spine, 124–5
 effects of, 33
 effects of failure of, 232
 embedded among Hox genes, 94
 enriched at synapses, 139

- enrichment in the brain, 114–15
- epilepsy and, 146–8, 160–3
- evolution of, 37–40
- exosomes or AGO2 in, 223
- fertilisation, 95–9
- function in health and disease, 72
- function of, 7
- future diagnostics and, 242–3
- gametes and, 94–5
- gene silencing and, 64
- gene therapy and, 195–8
- great-ape specific, 46
- history of editing of, 171
- human datasets of, 198
- human epileptic brain and, 169–70
- human-specific, 45
- IL1 β link and, 157
- in Ctenophores, 40
- in gametes, 98
- in the animal kingdom, 37
- inhibitors, 182
- inter-species trafficking of, 44
- journey of, 69–72
- life cycle of, 75
- links with disease, 240–1
- macro-level brain functions and, 133–5
- maturation at a single synapse, 119
- measuring mRNA levels and, 234
- medicines for epilepsy, 187–8
- microRNA-based switches, 236–8
- microRNA-loaded AGO interactions, 66–9
- microRNA-OFF switch, 237
- microRNA-ON switch, 237
- migration of cells and, 103
- motor control, 137–9
- movement controls and in seizures, 152–3
- number of in humans, 38
- overview of, 8
- plants, 42–4
- point-of-care and circulating, 229–30
- production of mature, 56
- production of mature *let-7*, 60
- proving they are in the brain, 227–8
- ratio of mRNA, 33
- replication of, 33–4
- role of in brain disease, 221–4
- role of in evolution, 37–40
- serum, 224–7
- silence gene expression and, 70
- silencing complex, 169
- single cell resolution of function of, 234
- smartness and, 130
- sperm and, 99, 243
- structure of, 22
- suppression of in adults, 82
- switch-on during brain development, 101
- synapse control story and, 125–7
- synapse-localised, 126
- synapses and, 121–2
- target match-up, 29–32
- temporal lobe epilepsy and, 146
- the future of, 27–9
- treating genetic epilepsies by targeting, 163–8
- uses of, 108–9
- virus-host battles and, 238
- what makes human and, 44–7
- what they do, 232
- where found, 244
- why they are needed, 34–5
- microRNAs
- 3' UTRs and octopus, 131
- and the puzzle of life, 232
- gene expansion and animal evolution, 39
- Hox genes and, 93–4
- miR-1, cardiac arrest in mice lacking, 84
- miR-106b, 154, 226
- miR-1202, 136
- miR-122, 177–80
- hepatitis C (HCV) and, 179
- hepatitis C (HCV) and interactions with, 180–1
- miR-124, 31, 106, 138, 191, 240
- HeLa cells and, 30
- microRNAs in the brain, 114
- miR-128, 103, 114
- deficiency of, 153
- miR-132, 124
- heart failure and, 187
- miR-134, 114, 122, 124
- anti-seizure effects of inhibiting, 190
- bipolar disorder and, 226
- blocking, 127
- blocking *in vivo*, 123
- brain samples and, 166
- hippocampal gene expression, 151
- human brain samples and, 151
- in canine hippocampus, 191
- inhibition of, 167
- nucleotides
- complementary, 121
- precursor molecule of, 117
- preventing seizures by blocking, 148–9
- synapses and, 116
- miR-134 inhibitor, antimir and, 149
- miR-134 molecules, 121–2
- miR-137, 240
- mutant mice and, 136
- miR-138, 105, 124, 127
- miR-146a, 148
- Alzheimer's disease, 226
- inflammatory responses and, 147
- miR-15a, 134
- chronic stress and, 135
- miR-16, 218
- miR-181, production of mature, 118
- miR-181a, 124, 129
- miR-1908, 136
- miR-196, expression, 93
- miR-2115, 46
- miR-218, 138
- miR-219, 105
- miR-22 gene, 159
- blocking, 159
- miR-2392, antimir targeting, 238
- miR-335, 195, 198–9, 205
- changing seizures and, 203–4
- linking to sodium channels, 199–201
- regulator of excitability, 205–6
- targets sodium channels, 202
- miR-338, 105
- miR-376a
- editing of, 172

Index

- miR-451, 64, 222
 cerebrospinal fluid and, 222
 miR-499, 136, 137
 miR-7, 95
 miR-9, 103, 222
 miR-92, 47
 miravirsin, 178, 186–7, 236
 effect on patients with
 HCV, 186
 SPC3649 as, 183
 miRNA inhibitor, 207
 mirtrons, 62–4
 Mitchell, Kevin, 76
 mitochondria, 238, 242
 molecular biology, 16
 molecular weights, 25
 molecule
 types of, 8
 Moloney Leukemia Virus
 (MOV), 120
 Mooney, Catherine, 222, 224
 Morris, Gareth, 123–4, 199
 motoneurons, 137, 138,
 See also neurones
 motor neurone disease, 137
 MOV 10, 165
 MOV10 protein, 120
 movement, control of, 152–3
 mRNA, 14
 3' UTR of the, 116
 copying DNA to make, 10
 protein-coding, 63
 mRNA decay, 69
 mRNA levels, measuring, 234
 mRNA transcript, non-coding
 portion of, 30
 mTOR pathway, 188
 Müller cells, 73
 multiple sclerosis, AGO2
 and, 223
 mutant Dicer (hets), 77
 myelination, 102
 myelination process, 104–5

 NANOg, 89, 92–3, 99, 103
 nasal epithelium, 241
 National Institute of
 Neurological Disorders
 and Stroke (NINDS), 187
Nature, 23, 156
Nature Cell Biology, 217
Nature Communications, 187
Nature Genetics, 77, 78
Nature Neuroscience, 156, 224
 a catalogue, 106
 NaV, 6, 169, 207

 NCT 05350969, 187
 neurodegeneration, 193
 neurodegenerative diseases
 progressive, 137
 neurogenesis, 45, 101,
 102–3, 105
 peak, 106
 neuroinflammation, 143
 neuromuscular system,
 diseases of the, 138
 neuronal activity, microRNA
 activity and, 118
 neuronal excitability, 154
 neurone loss, 142
 neurones, 106, 111
 editing with antimirs, 172
 elimination during brain
 development, 104
 excitatory, 111
 neurophysiology, 109–11
 neuropsychiatric disease
 microRNAs and, 136–7
 neurotransmitter, 110–11
 dopamine, 79
 release of, 85
 neurotransmitter GABA, 143
 New England Journal of
 Medicine, 183, 194
 trial, 187
 next generation, microRNAs
 and the, 243
 Nirenberg, Marshal, 10
 NMDA receptors, 118, 124, 126
N-methyl-D-aspartate, 118
 nocturnal epilepsy, 155
 non-canonical pathway, 62
 non-coding RNA, 10
 Novo Nordisk, 182
 Novozymes, 182
 N-terminal, 14
 nuclear factor kappa light chain
 enhancer of activated
 B cells (NFkB), 155
 nuclear medicine applications,
 228–9
 nuclear pore complex, 59
 nuclear power plant
 disasters, 228
 nucleases, 13
 nucleotide, 8
 nucleotides
 conversion of, 170–3
 insertion and/or deletion of,
 170–3
 microRNA degradation
 and, 74

 O'Brien, Donncha, 148
 O'Shaughnessy, William
 B., 197
 occipital lobe, 109
 Oct 4, 89, 92–3, 99, 103
 octopus
 microRNAs and the, 131
 protein-coding
 transcripts, 130
 oligodendrocyte precursor
 cells, conversion of, 105
 oligodendrocytes, 104, 111
 oligodendroglia, 102
 OpenArray, 222
 Oregon Health and Sciences
 University, 173
 outer subventricular zone
 (OSVZ), 45
 Oxford-Astrazeneca Covid-19
 vaccine, 192

 p250GAP, 124
P2rx7 gene, 159
 P2X receptors, 158–60
 paralysis, 137
 Parkinson's disease, 79, 99,
 226
 passenger strand, 42
 Pasterkamp, Jeroen, 160, 169
 paternal copy, 165
 patients, listening to their
 needs, 207–10
 PAZ domain/region, 61,
 66, 68
 perforant pathway, 142
 petit mal epilepsy, 141
 pharmacodynamics, 176
 pharmacokinetics, 176
 phenobarbital, 145, 187
 phenotypes and traits
 heritability of, 35
 phenytoin, 187, 196
 phosphatase and tensin
 homolog (Pten), 103
 phosphate, 8
 Physcomitrella patens vs
 Arabidopsis thaliana,
 44
 PIWI, 66
 plant microRNAs, 42–4
 plasma, as brain disease
 biomarkers, 224–7
 plasticity, proteins of, 112–14
 point-of-care, circulating
 microRNAs and, 229–30
 Pol II, 51–2, 54, 63, 235

Index

- microRNAs transcription, 54, 55
 transcription of pri-microRNAs, 58
 Pol III, 51
 role of, 54
 polio vaccine, 24
 polymerase II (RNAP II. *See also* Pol II)
 potassium
 leak of potassium ions, 109
 potassium
 channelopathies, 153
 potassium ions, 110
 regulating, 153–5
 potassium channels
 variants of, 153
 precision therapy, 165
 prefrontal cortex, 105, 136
 Prehn, Jochen, 160
 pre-microRNA, 59
 cytosol and, 59
 cytosol and pri-microRNA, 59–61
 in Dicer, 62
 pre-miR-134, 117
 increase in level of, 121
 pre-miR-181a, 118
 primate evolution, 45
 PRIME project, 209
 pri-microRNA molecule, 29, 51–2, 54–8, 64
 original, 59
 processing activity, 56
 primordial cells, 45
 Proceedings of the National Academy of Sciences of the United States of America, 38
 pro-enzymes, 157
 programmed cell death, 104
 prokaryotes bacteria, 40
 promoter, 12
 promoter escape, 12
 protein stromal cell-derived factor 1 α (SDF1 α), 95
 protein/proteins, 5–6
 at synapses, 113
 control on, 14–15
 interactions with
 microRNAs, 234–5
 naming conventions for, 15
 of plasticity, 112–14
 RNA binding, 61–2
 transportation of, 59
 protein-coding genes, 38, 44
 protein-coding sequence (CDS), 68
 proteomic analysis, 31
 psychiatric disorder, 135
 psychogenic non-epileptic seizures (PNES), 212, 226
 psychosis, 202
 PTZ model, 201–3
 Public Patient Involvement (PPI), 208
 Purkinje neurones, 123
 pyramidal neurones, 142
 in the hippocampus, 123
 Qingdao University, 225
 Quintana, Rodrigo, 190
 radioactivity
 as a diagnostic tool, 228–9
 threat to life from, 228
 Ran protein, 59
 Raoof, Rana, 221, 224
 rapamycin, 188
 RCSI, 206
 red blood cells, 6
 Regulus, 182, 186
 research
 effect of Covid-19 pandemic on, 191
 resilience
 of microRNAs, 35–7
 reverse engineering
 approach, 195
 ribonucleases, 54–5
 ribonucleic acid (RNA), 5
 ribosomal RNA (rRNA), 13
 ribosomes, 6, 13
 RISC
 components of, 234
 RISC activity, 120
 RISCs, 239
 RNA
 A-to-I editing, 170
 composition and different forms of, 11
 RNA binding proteins (RBPs), 6, 61–2
 RNA editing, 170–3
 RNA interference, 20
 RNA molecules, 53, 55, 62
 insertion and/or deletion of nucleotides, 170–3
 RNA polymerase, 51
 RNA polymerase II (RNAP II). *See*
 RNA polymerases, 12, 18
 DNA and, 10
 RNA transcription
 blocking of, 73
 RNAi, 20
 natural function of, 21
 RNAi pathway, 25, 27, 29, 59, 77, 81, 204
 gene silencing and, 60
 in mammals, 64
 research on the, 59
 triggering, 44
 RNAP II, 51
 RNase III, 55
 cutting domains, 61
 domains, 61, 77
 enzyme (Dicer), 59–61
 nuclear-localised, 55
 ROC analysis, 222
 Roche, 186
 Rockefeller University, 177
 Rosenow, Felix, 160
 Rosetta Inpharmatics, 29
 Rous sarcoma virus, 192
 Russian Federation, 228
 Ruvkun, Gary, 17, 20, 26
 and colleagues, 17, 19, 23
 discovery of a second small RNA, 21
 let-7, 23
 Salk, Jonas, 24
 Sanfeliu, Albert, 198
 Santaris, 182, 183–4, 186
 published tests, 184
 Sarnow, Peter, 178
 and colleagues, 180
 Schaefer, Anne, 79, 156, 228
 schizophrenia, 135–6, 202, 241
 miR-124 and, 240
 treatments for, 135
 Schorge, Stephanie, 123, 160
 Schratt, Gerhard, 53, 116, 121, 123, 165
 and colleagues, 121, 122, 123, 127, 166
 Schuman, Erin, 113
 Science, 152
 Science Advances, 239
 Science Foundation
 Ireland, 208
 Science papers, 26
 Science Translational Medicine, 195, 229
 SCN1A, 169, 198, 206
 transcript, 170
 Scripps Research Institute, 181

Index

- SEISMIC study, 226
 seizures, 141, 143–5, *See also*
 epilepsy
 causes of, 140
 changing miR-335 and
 changing, 203–4
 Dravet syndrome and, 168
 history of seizure models,
 201–3
 microRNA controls motor,
 152–3
 microRNA-based test, 229
 miR-134 blocking and,
 148–9
 onset of after injection of
 PTZ, 203
 sense strand, 10
 Seoul University, 235
 serum microRNAs, 229
 as brain disease biomarkers,
 224–7
 Severo Ochoa Centre, 220
 sex differences, 106
 Sharp, Philip, 27
 Shope papilloma virus, 192
 short interfering RNAs
 (siRNA), 29
 side chain, 6
 signal transducer and activator
 of transcription proteins
 (STATs), 104
 signal transfer process, 111
 SILAC study, 31, 32
 Simon, Roger, 72, 173
SIRT1 gene, 128
SIRT1-mutant mice, 129
 small RNAs
 degrading nucleases
 (SDNs), 74
 doubling of, 21–3
 small temporal RNAs, 23
 small temporal RNAs, in
 C. elegans, 25
 smartness
 how microRNAs influence,
 127–8
 microRNAs and, 130
 sodium channel blockers,
 196, 236
 sodium channels, 141, 168,
 195–6, 198, 205
 as targets of anti-seizure
 medicines, 196
 linking miR-335 to, 199–201
 loss of activity, 206
 miR-335 and, 202
 sodium, overload of, 147
 sodium-potassium
 ATPase, 109
 Soreq, Hermona, 195
 SOX family, 104
 SOX 2, 92, 99, 103
 SOX4 transcription
 factor, 105
 SPC3649, human trials of,
 183, 185
 sperm and egg cells, 94
 sperm, microRNAs in, 98, 243
 spike. *See* action potentials
 spine density, synaptic
 connectivity and, 136
 spine heads, 121
 shrinkage of the, 122
 spine/spines
 effect of microRNAs on,
 124–5
 effect on with injection of
 miR-134, 123
 fault in, 128–9
 spines. *See also* dendritic spines
 spinomuscular atrophy (SMA),
 138, 192
 stable isotope labelling, 31
 Stanford University, 178
 status epilepticus, 222, 227
 episode of, 222
 stem cells, 45
 embryonic, 28, 89, 90–3,
 98, 103
 germline, 94
 haematopoietic, 228
 induced pluripotent, 237
 microRNAs to create,
 99–100
 mutant embryos, 77
 neural, 103
 Stevens-Johnson
 syndrome, 146
 stoichiometry, 131
Streptomyces bacteria, 73
 striatum, 126
 stroke
 death from, 175
 gene turn-off and protection
 from, 173
 microRNA test, 229
 paralysis and, 137
 protecting the brain
 from, 173
 UPS system and a, 72
 substance P, 143
 surrogate gene, 22
 survival motor neurone gene
 (SMN), 138
 Swiss Federal Institute of
 Technology (ETH), 116
 synapses, 111–12
 effect of on structure of the
 brain, 127–8
 localised microRNAs
 and, 126
 microRNA control at, 120
 microRNA maturation
 at, 119
 microRNAs and, 115–17
 microRNAs enriched at, 139
 proteins at, 113
 signposting of the, 116–17
 structure of and microRNAs,
 121–2
 synapsin1 gene (hSYN1), 204
 synaptic activity
 coupling to microRNA
 production, 118–20
 excitatory, 150
 microRNAs and, 117–18
 synaptic homeostasis, 156
 synaptic plasticity, 109
 synaptic transmission, 110, 111
 Szybalski, Wacław, 192
 T box brain protein 2
 (TBR2), 103
 T6B, switching of, 82
 target co-evolution
 microRNAs and, 42, 47
 Targetscan, 28, 32
 Tatum, Edward, 192
 TDMD process, 75
 Temin, Howard, 192
 temporal lobe epilepsy, 141–2
 cross-linked RNAs in
 patients with, 198
 Dravet syndrome and, 169
 hippocampus and, 142
 microRNA-based
 treatments, 143
 microRNAs and, 146,
 169–70
 microRNAs control gene
 networks and, 147
 miR-146a and, 147
 pathophysiology of, 144
 TGF-beta pathway and, 164
 temporal lobes, 109, 133, 142
 terminal uridyl transferases
 (TUTs), 74
 Thum, Thomas, 187

Index

- TNRC 6, 69
 protein, 81
 toll-like receptors (TLRs), 155
 transcribed mRNA, 15
 transcription, 10–13, 117
 by RNA polymerases, 12
 Drosha and the sites of, 58
 transcription factors, 12, 17
 transcription repressors, 12
 transcription factors, 103
 host gene and, 28
 transcripts, 10, 116, 138
 3' UTRs of, 136
 after blocking miR-122, 177
 dendrites and, 113
 transfer RNA (tRNA), 14
 transgenerational concept, 96
 transgenerational effects
 in humans, 97–8
 of maternal stress and
 diet, 96
 translational repression, 69
 TRBP (TAR-RNA binding
 protein), 61–2
 as a bridge, 61
 treatment-resistant epilepsy,
 140, 142, 208, 226
 brain tissue from, 156
 in adults, 141
 inflammation and, 157
 treatment-resistant temporal
 lobe epilepsy, 146
 ADARs in patients with,
 171–3
 miR-314 and, 151
 triangulation methods, 195

 tridione, 203
 trinucleotide repeat containing
 adaptor 6 (TNRC6), 69
 triple whammy, 23–7
 Tuschl, Thomas, 23–5

 UBE3A, 165–6
 ubiquitin-protease system
 (UPS), 72
 University of Bonn, 189
 University of California, 46, 86
 University of California
 (Berkeley), 61
 University of California
 (Davis), 146
 University of California
 (Irvine), 191
 University of California
 (Riverside), 74
 University of California (San
 Diego), 186
 University of California (San
 Francisco), 84
 University of California (Santa
 Barbara), 106
 University of Glasgow, 190
 University of Utah, 188

 vaccines, 6, 191
 mRNA, 2
 Oxford-Astrazeneca Covid-
 19, 192
 Venø, Morten, 161, 169
 Ventura, Andrea, 81
 veterinary trials, 191
 viral vectors, 195, 204, 205, 236

 advantages of, 192
 miR-335 and, 209
 tools, 193
 virally delivered gene-
 replacement
 treatment, 192
 viruses, 40
 choosing for lab work,
 193–5
 gene delivery and, 192
 microRNAs and, 238
 Vollum Institute, 117, 125,
 127
 voluntary muscles, role of
 microRNAs in motor
 control of, 137–9

 Watson, James, 59
 Watson-Crick base-pairing
 principles, 29
 with cytidine, 170
 Wedge, 58
 Wengel, Jesper, 182
 Wilcox, Karen, 188
 worm development, 17

 Yamanaka, Shinya, 99
 Yamanaka factors, 99–100

 Zamore, Phillip, 60, 64
 artificial duplexes, 64
 zebrafish, 94
 zolgensma, 192
 zonisamide, 196
 ZSWIM 8, 75
 α -helices, 6