

Index

a

- ABL gene 148
- acetylation 10
- acetylcholinesterase (AChE) inhibitors 211
- actionable targets, by clinical molecular profiling 157
 - actionable mutations in different tumor types 158
 - actionable primary resistance mutations, identification 173–175
 - actionable secondary resistance mutations
 - identification and treatment, strategies for 169–173
 - genes in OncoCarta Panel 159
 - OICR/PMH experience 157–163
 - challenge and opportunity for NGS 166, 169
 - distribution of tumor types, and mutations in molecular profiling study 161
 - instruments 154
 - resistance mutations identified/targeted oncology therapies 167, 168
 - treatment impacted by 162
 - understanding and targeting resistance mutations 166
 - workflow of MP study 160
- AD. *See* Alzheimer's disease (AD)
- AGC kinases 272–275
 - protein kinase C (PKC) (*See* PKC)
 - Rho-associated coiled coil containing protein kinase (ROCK) (*See* ROCK)
- airway hyperresponsiveness (AHR) 255
- ALK gene 26
- ALK translocation partners 73
- allosteric inhibitor 354
- Alzheimer's disease (AD) 211, 227
 - amyloid plaques as biomarker 212–214
 - cerebral β -amyloid (A β) deposition 212, 213, 220
 - disease risk 212
 - drug candidates failed 212
 - etiology 212
 - quantification of specific proteins 212
 - theranostics 219, 220
- 2-amino-5-aryl-3-benzoxypyridine scaffold 74, 75
- amyloid aggregates 214, 215, 218, 219. *See also* Alzheimer's disease (AD)
- amyloid plaques as biomarker in AD 212–214
 - detection 214–218
 - development of amyloid chemical probes 218
 - ^{18}F -labeled tracer, use for 216, 217
 - medicinal chemistry perspective 215
 - BTA-1 215
 - thioflavin-T (ThT) 215
 - perspectives 220–222
 - PET imaging 214
 - agents 217
 - SAR campaign
 - identified hydroxylated derivative 215, 216
 - trial of benzothiazole amyloidimaging agent 216
 - use of polymeric nanoparticles 218
- amyloid precursor protein (APP) 213
- anacetrapib 12, 17
- anaplastic lymphoma kinase (ALK) 72
 - activators 72
 - role in 73
- angiogenesis 14, 42, 45
 - Kras 42
 - modulators 44
 - promoting factor 23
- animal models, LRRK2 function 233–234
 - dopamine replacement drugs 233
 - preclinical testing 233
 - dopaminergic neurons 233
 - dopaminergic system 234

- kinase-dead knock-in mouse 234
 - kinase-dead mutation 233
 - nonselective LRRK2 kinase inhibitor 233
 - pathological phenotypes 234
 - antiangiogenic agents 23
 - antibacterial agents 8
 - antibody–drug conjugates 2
 - approach 15
 - anticancer drugs 5, 14, 23, 28
 - discovery of predictive biomarkers (See predictive biomarkers)
 - anti-inflammatory cotreatment 15
 - apoptosis 6, 37, 79, 83, 121, 123, 197, 231, 276, 316
 - AS1410 122, 124
 - Asthma
 - classifying methods 255
 - clinical study 256
 - clinical symptoms 255
 - etiology 255
 - genetic testing 255, 256
 - pathophysiology 256
 - patient categories 255
 - ataxia telangiectasia 185
 - mutated 185
 - atherosclerosis 320
 - ATM/ATR pathways 123
 - ATP-mimetic therapies 34
 - automation technology 2
 - autoradiography 290
 - Avastin 23
- b**
- bapineuzumab 212, 219, 318
 - basal-cell carcinomas (BCCs) 102, 113
 - hedgehog 102
 - vismodegib treatment, clinical study 112–114
 - BCR-ABL* fusion oncogene 24, 147
 - BCR* gene 5, 148
 - bioinformatic analyses, genome sequence 343
 - biomarkers 8, 212
 - amyloid plaques as the biomarker in AD 212–214
 - angiogenetic 13
 - challenges associated with identifying 23
 - determine/modulate antiangiogenic drug activity
 - for agents targeting VEGF axis 43
 - diagnostic 9
 - discovery using cell line models 29, 30
 - drug efficacy 9
 - imaging 289
 - for novel oncology drugs 22
 - pharmacodynamic 9
 - in drug developments 289
 - predictive, for cancer drug therapy 23
 - and targeted therapies 213
 - in targeting patients 9
 - blood–brain barrier (BBB) 212, 215, 292, 293, 294, 300, 308, 320, 324
 - BMSG-SH-3 124
 - bortezomib 354
 - BRACO-19 compound 123, 124
 - BRAF* gene 27, 148
 - B-Raf inhibitor 148, 172, 345
 - BRAF* inhibitors 27, 41, 72, 91, 92
 - B-RAF kinase 345
 - BRAF* (V600)-mutated metastatic melanoma 92
 - Btk 266
 - BTK gene, mutation 266
 - X-linked agammaglobulinemia 266
 - clinical development 266
 - cytoplasmic protein tyrosine kinase 266
 - expression 266
 - ibrunitib (PCI-32765), an irreversible inhibitor 266
 - clinical trials 266
 - immunosuppressant effect 266
 - important role 266
- c**
- camptothecin 4, 5, 16
 - cancer
 - cancer stem cells 204
 - FDG-PET MIP images 316
 - G-quadruplexes as therapeutic targets in (See quadruplexes)
 - identifying actionable targets 147
 - immunotherapy 23
 - multiple genetic changes 183
 - types of driver genome alterations in human 149
 - cancer cell lines
 - challenges/limitations of cell line models 32, 33
 - genomic characteristics 31
 - historical application, in cancer research 28, 29
 - as models of human cancer 31
 - as model system for discovery predictive biomarkers 28
 - properties with primary tumors 32
 - Cancer Genome Project 30
 - case studies 194

- APE1 198
 - Chk1-DNA repair 197
 - DNA ligases 198
 - DNA-PK-mTOR 197, 198
 - MGMT 199
 - MLH1/MSH2 194
 - p53-ATM 197
 - RAD51 199
 - WEE1 198
 - catalytic carbonylation 301
 - nucleophilic attack with 302
 - palladium-mediated 301
 - rhodium-mediated 302, 303
 - CDK1 (cyclin-dependent kinase 1) 192
 - Cdk1/cyclin B complex 198
 - cell death 51, 121, 186, 189, 201
 - assay 231
 - CETP inhibitors 12
 - clinical trials 12
 - Charcot-Marie-Tooth disease 352
 - chemical genomics 10
 - Chk1 inhibitor 41
 - chromosomal aberrations 21
 - chromosomal translocations 24, 26
 - chronic myelogenous leukemia (CML) 5, 24, 147
 - *BCR-ABL* fusion gene, actionable mutation 148
 - cancer therapeutics, and driver mutations 150
 - chromosomal translocation 346
 - drugs to target secondary mutations 170
 - FDA-approved and investigational kinase inhibitors 27
 - genomic alteration 54
 - imatinib-resistant 34, 37
 - resistance to Gleevec 7
 - treatment with ABL tyrosine kinase inhibitor 24
 - cisplatin 162, 188, 195, 197, 291
 - c-Kit 268, 269
 - allergen-induced asthma murine models 269
 - c-Kit/SCF pathways 269
 - inhibition 269
 - clinical trials 269
 - important role 269
 - inhibitors, multikinase activity 268
 - structure 269
 - investigation 269
 - kinase domain 120
 - mouse studies 269
 - multikinase activity 268
 - stem cell factor (SCF) 268
 - tyrosine kinase family, member of 268
 - clinical imaging biomarkers 290
 - clinical validation 156, 290, 325
 - PET tracer 324
 - c-myc* oncogene 119
 - c-myc* promoter 120, 125
 - collagen-induced arthritis (CIA) model 259
 - Committee for Medicinal Products for Human Use (CHMP) 234
 - copy number variations (CNVs) 148
 - CP529414 17
 - CP-690550. *See* tofacitinib
 - CPT drug 16
 - CRAF inhibitor 92
 - crizotinib 26, 28, 73, 74
 - *ALK* abnormalities to 26
 - *ALK*-derived pharmacological effects 79
 - 2-amino-3-benzoyloxy pyridine series, scaffold for 83
 - autoinhibitory conformation of MET 78
 - bind MET kinase domain 76
 - BioLume Ames assay 80
 - cocrystal structure 76, 79
 - discovery of 74, 76
 - dose-dependent antitumor efficacy 79
 - human clinical efficacies of 80-83
 - inhibition of MET signaling by 83
 - kinase selectivity of 77, 78
 - PHA-665752 76, 77
 - pharmacokinetic parameters of 80
 - pharmacology 78-80
 - potently inhibited NPM-*ALK* phosphorylation 79
 - stabilizing interactions to Tyr-1230 residue 78
 - TKI drugs, cancers develop resistance to 82
 - CRTH2 receptor antagonist 349
 - crystallization techniques 4
 - cyclic peptide cRGD 13
 - cyclopamine 103
 - as SMO antagonist 102, 103
 - cycloposine 103
 - CYP3A4 inhibitor 75
 - cytokines 45
 - cytotoxic drug 14
 - cytotoxicity 14, 17, 122, 197, 199
- d**
- dabrafenib 92
 - dalcetrapib 12, 17
 - dasatinib 7, 17
 - deacetylation 10
 - demethylation

- of histone lysines/histone arginines 350
 - and oxidation provided vemurafenib 97
 - designer 33-mer peptide Anginex 13
 - deubiquitination 353, 354
 - dicarboxypropyl)ureidopentanedioic acid (DUPA) 14, 15
 - DNA “bar code” 3
 - DNA damage 41, 183
 - double-strand breaks 185
 - induced nuclear RAD51 foci 205
 - major DNA damage response proteins 184
 - repair proteins and typical lesions repaired for 185
 - response 184, 185
 - DNA damage response (DDR) 183
 - pathways 183, 204
 - DNA encoded library technology 3
 - DNA-mediated toxicity 117
 - DNA methylation 9, 10
 - DNA modifications 10
 - DNA repair 185
 - base excision repair (BER) 184
 - direct repair 184
 - homologous recombination (HR) 185
 - mismatch repair 184
 - nonhomologous end joining (NHEJ) 185
 - nucleotide excision repair (NER) 184
 - proteins 188
 - dopamine replacement therapy 228
 - doxorubicin 14, 17, 162
 - drug delivery systems 4
 - designing 12, 13
 - drug design 11, 12
 - drug differentiation 11
 - drug discovery 1, 211
 - Gleevec 5
 - drug–drug interactions 15, 16, 75, 237
 - potential 109
 - drug efficacy 11
 - druggable genome 343
 - drug-likeness 3
 - drug resistance 22, 37, 38, 40, 72
 - mechanisms and markers, for targeted agents 35, 36
 - mutations 345
 - rational combination approaches 37
 - second-generation therapies 37
 - through activation of alternative pathways 34
 - transporters 310
 - drugs design 1, 11, 189
 - computer-assisted 344
 - hydrophobic core designing 14
 - structure-based 3
 - drugs targeting kinases 344–347
 - drugs targeting phosphatases 347, 348
 - drug–target networks 343
 - drug target superfamilies 353, 354
 - dual ALK/MET kinase inhibitor 26
 - dual erbB1 and erbB2 tyrosine kinase inhibitor (Tykerb) 9
- e**
- 4E-BP protein 231
 - genetic studies, *Drosophila* 231
 - hLRRK2 overexpression 231
 - impact of LRRK2 kinase inhibitors 232
 - phosphorylation 231
 - EGFR 267, 268
 - activation, EGFR *in vitro* 268
 - pharmacological effects 268
 - EGF expression elevation 267
 - EGFR immunoreactivity elevation 267
 - ErbB receptors 267
 - expression 267
 - erythroblastic leukemia viral oncogene homolog, (ErbB) family 267
 - kinase inhibitors 22
 - normal human airway epithelial (NHBE) cells 268
 - recent investigations 268
 - small-molecule ErbB inhibitors, cancer treatment 267
 - clinical trials 267
 - dual EGFR/ErbB2 inhibitors (lapatinib) 267
 - erlotinib 267
 - selectively targeting EGFR (gefitinib) 267
 - structure 268
 - *in vitro* study 268
 - asthmatic bronchial mucosa 268
 - EGFR mutations 26
 - EML4-ALK fusion gene 73
 - epigenetic regulation 350–352
 - epigenetics 9, 10
 - modifications 10
 - epigenomics 1
 - ERBB2 gene 25
 - erbB2 receptor 5
 - ERK 260, 261
 - activation 261
 - inhibitors
 - indolizines 260
 - naphthyridine-dione 261
 - isoforms 260
 - ERK1 260
 - ERK2 260

- MEK1 inhibitors 260
- erlotinib 22, 26, 27, 36, 150, 166, 172, 267, 268, 346
- with onartuzumab 26
- ertiprotafib 347

f

- FLT3-inhibitor 346
- fragment-based drug discovery 3
- Friedreich's ataxia 352

g

- galectin-1 inhibitor 13
- GDC-0449. *See* vismodegib
- gefitinib 22, 27, 35, 71, 150, 171, 267
 - resistance 37
- gene amplification 37
 - ALK fusion 82
- BCR-ABL oncogene 34
- gene expression signatures 22
- genetic aberrations 147
- genetic alterations 45
- genetic polymorphisms 12
- genome-wide association study (GWAS) 8, 279
- genomics 11
- genomic sequencing 147, 148, 163, 175–177
 - high-throughput 166
- impact on identification of actionable mutations 149, 151, 154–157
- genotype–phenotype relationships 8
- GG211 16
- Gleevec 2, 7, 16, 24, 29, 120, 269
 - for CML patients 7
- efficacy 6
- molecular targets of 5, 6
- Glivec 5
- glycogen synthase kinase-3 (GSK-3) 277, 278
 - function 277
- GSK-3 α 277
 - important role 277
 - GSK-3 β
 - allergic airway inflammation, treatment 278
 - chemical inhibition 277
 - future studies 278
 - important role 277
 - knockout mice 278
 - mice study 277
 - role in asthma patients 278
 - role in neurological disease 278
 - structure 278

- TGF β 1-driven extracellular matrix production 278
- Gorlin syndrome 102
- GW572016 17

h

- HDAC6 inhibitor 352
- HDAC inhibitors
 - in clinical testing 352
- HDAC3-selective drug 352
- healthcare 1, 16, 217, 260, 267, 275
- hedgehog (Hh) pathway 101
 - aberrant activation 102
- genes 24
 - inhibitor (*See* vismodegib)
 - leading to FDA drug approval 25
 - potencies and screening pharmacological properties of inhibitors 106
 - signaling pathway, representation 102
- hepatocyte growth factor receptor (HGFR) 71
- HER2 amplification 27
- Herceptin 2
 - estimation of overall survival 25
- exceptional efficacy 5
- to paclitaxel 25
- HER2/HER3-directed therapies 30
- HER2 kinase 30
- HER2 signaling 25
- HGF/MET signaling 72
 - pathway 72
- histone 10, 55
- histone deacetylases 351, 352
- histone demethylases 350
- histone-modifying enzymes 350
- host gene–microbe interactions 8
- hTERTgene 135
- hypoxia 45

i

- IGFR signaling network 7
- IGF signaling computational analysis 7
- I κ B kinase (IKK) 275, 276
 - composition 275
 - expression 275
 - I κ B-NF- κ B protein complex 275
 - activation 275
 - nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) 275
 - phosphorylation 275
 - selective IKK- β inhibitors 275
 - asthma treatment 275
 - clinical development 276
 - development 275

- IMD-0354 275, 276
- knockout mice 275
- tissue specific deletion, bronchial tissue 275
- IKK. *See* IκB kinase (IKK)
- imatinib 5, 16, 24, 27, 82, 148, 171, 346
- immune pathways, activation 261
- immunomodulation 8
- inhaled corticosteroids (ICSs) 255
- inhibitors, of mutationally activated kinases 22
- in silico*-based lead discovery in GPCR family 348–350
- in silico* drug testing approach 12
- insulin receptor (IR) 72
- interactome 11
- International Cancer Genome Consortium (ICGC) 31
- IPI-926. *See* saridegib
- ITK 265, 266
 - clinical study 265
 - function 265
 - important role 265
- ITK polymorphisms 266
- ITK susceptibility 266
- nonreceptor tyrosine kinases,
 - TEC family 265
- selective small-molecule ITK inhibitors 265
 - BMS-509744 265
 - 31 single-nucleotide polymorphisms (SNPs) 266

j

- JAK 264, 265
 - allergic asthma 264
 - pathogenesis 264
 - critical role, signal transduction 264
- cytokine signaling regulation 264
- expression 264
- JAK3
 - biological response regulation 264
 - clinical study 264
 - important role 264
 - nonreceptor protein tyrosine kinases family 264
- small-molecule JAK inhibitors 264, 265
 - tofacitinib (CP-690550) 264, 265
- jervine 103
- JNK 259, 260
 - corticosteroid-resistant subjects 260
- inhibitors 259
 - CEP-1347 (KT-7515) 260
 - SP-600125 259, 260
 - isoforms 259
- JTT-705 17

k

- kinase inhibitors 9
 - FDA-approved and investigational inhibitors 27, 28
- future aspects 279
- kinase inhibitors, tested in clinical trials 345
- kinase mutants, resistant to drug treatments 344
- kinase-targeted drug treatments 21. *See also* oncogene addiction
- KINOMEScan technology 346

l

- lapatinib 17, 150, 267, 345
- late-stage melanoma 256
 - diagnostics 256
 - treatment 256
- Lck 263, 264
 - Bruton's tyrosine kinase inhibitor 264
 - PCI-32765 264
 - inhibitors 263
 - family 263
 - nonselective Lck inhibitors 263, 264
- on-target systemic Lck inhibition 263
 - consequences 263
 - toxicities 263
- protein tyrosine kinase inhibitor 264
- Dasatinib (Sprycel) 264
- selective Lck inhibitors 263
- challenge 263
- signaling cascade initiation 263

T-cell activation 263

leukocyte tyrosine kinase (LTK) 72

liposomes 13

– dual targeted 13

long-acting beta-2 agonists (LABAs),
inhaled 255

LRRK2-associated PD

– biomarker strategies 235

challenge, using imaging biomarkers 235

clear LRRK2-associated biomarker

absence 234, 235

clinical studies 234–236

clinical trial, novel LRRK2 inhibitor 236

DATATOP study 235

disease modification, demonstration 234

disease-modifying treatments 234

disease-modifying, two-step procedure 234

ethical challenges 235, 236

¹⁸F-DOPA, assessing striatal DAT

function 235

future prospects 236

imaging study, LRRK2-targeted treatment 235

- lengthy clinical trials 235
- LRRK2 population 236
- multiyear study 235
- mutation prevalence rate 236
- pathogenic LRRK2 mutation 236
- single-agent therapy 235
- treatment perspective 234
- LRRK2-familial PD 228
- vs. sporadic PD 228
- LRRK2 function
 - animal models (*See* animal models, LRRK2 function)
 - biochemical studies 229, 230
 - cellular studies 230–233
 - biomarkers discovery 230
 - kinase function
 - *in vitro* monitoring 231
 - *in vivo* monitoring 231
 - wild type 233
 - LRRK2 kinase domain, structural models 237, 238
 - homology modeling 237
 - inhibition profile-based approach in template selection 237
 - kinome phylogenetic tree analysis 237
 - ROCK1-derived model 238
 - ROCK1/H-1152 crystal structure 238
 - ROCK1 kinase inhibitors 238
 - Roco4 kinase domain crystal structures 238
 - structural understanding 237
 - three-dimensional models 237
 - tyrosine kinase-like (TKL) subfamily 237
 - LRRK2 kinase inhibitors 240
 - ATP-competitive kinase inhibitors 240
 - high-throughput kinase profiling 241
 - blood-brain barrier 245
 - broad-spectrum kinase inhibitors 238
 - structures 239
 - B_u/P_u ratios 246
 - CNS-targeted kinase programs 246
 - diaminopyrimidine inhibitors 245
 - disease-modifying effect 238
 - extensive PK profiling,
 - diaminopyrimidines 245
 - future prospect 246
 - G7080 245
 - Genentech’s 2011 patent application 244
 - GSK2578215A 243
 - physicochemical properties 243
 - kinase selectivity 243
 - LRRK2 autophosphorylation inhibition,
 - Ser1292 245
 - LRRK2 toxicity 238
 - *in vivo* protection 238
 - medium- to high-throughput screening 242
 - inhibitors discovered 242
 - mouse PK experiments 243
 - *in vitro* cellular studies, GSK2578215A 243
 - MRCT-Genentech-published patent applications 243
 - docking models 244
 - GNE diaminopyrimidine HTS hit (magenta) 244
 - selective lead G7080 (cyan) 244
 - docking studies 244
 - nonselective kinase inhibitors screening 238
 - quantitative chemoproteomics method 240
 - CZC-25146/CZC-54252 discovery 240
 - properties 240
 - strategies used to identify 238–246
 - structural diversity 246
 - structures 239
 - TAE684 241
 - favorable mouse PK profile 242
 - increased total brain penetration 242
 - multiple kinases inhibition 242
 - properties 241, 242
 - *in vivo* inhibition, LRRK2 autophosphorylation 245
 - in vivo* pharmacokinetic profiles 241
 - LRRK2 mutant 231
 - ectopic expression 231
 - LRRK2 protein 230
 - autophosphorylation
 - catalytic activity 230
 - demonstration, mass spectrometry 230
 - sites as biomarkers, kinase activity 232
 - brain-penetrable LRRK2 inhibitors 232
 - composition 229
 - dose-dependent dephosphorylation 232
 - exonic variants 228
 - genetic association with PD 229
 - gnotyping studies 228
 - GTPase activity, ROC domain 230
 - GTP binding, affects 230
 - kinase activity 229
 - *in vitro* kinase assay 230
 - *in vitro* studies 229, 230
 - kinase activity reduction 231
 - kinase inhibitors
 - cellular potency and selectivity, modification of 231
 - CZC-25146 231
 - inhibition constants 232
 - knockout mouse 230, 231
 - large genome-wide association studies 228

- LRRK2 inhibitors development 229
 - LRRK2 PD mutations 230
 - LRRK2[pSer1292] 232
 - antibodies against of 233
 - overexpression 231
 - phosphorylation 232
 - as biomarker 232
 - protein structure, confirmed familial PD mutations and risk factors 228
 - transgenic mice studies 232
 - variants 232
 - associated with familial PD 229
 - LRRK2 small-molecule inhibitors 236, 237
 - ATP-competitive kinase inhibitors 237
 - cellular studies 237
 - discovering new medicines 236
 - druggability 237
 - LRRK2[G2019S] protein 236
 - necessary 237
 - therapeutic strategy 236
 - LRRK2-associated PD treatment 236
 - *in vivo* experiments 237
 - lysine demethylases inhibitors 351
- m**
- magnetic resonance imaging (MRI) techniques 290
 - malignant melanoma 27
 - MAP kinase (MAPK) cascade 27
 - MAPK pathways 7, 9
 - medicinal chemistry 1, 2, 14
 - MEK inhibitor 28
 - memantine 211
 - metabolomics 1
 - metagenomics 8
 - metal binding proteins 3
 - MET* amplification 26
 - metastatic medulloblastoma 25
 - methylation 10, 55, 297, 299
 - MET* inhibitor 74
 - *N*-substituents on the 5-pyrazol-4-yl group 75
 - MET* TKI inhibitors in cancer patients 83
 - midkine (MK) 72
 - mitogen-activated protein kinases (MAPK) 256–261
 - inflammatory response, external triggers 256
 - Mitogen-activated protein kinase (MAPK) pathway 257
 - stress-activated protein kinase 257
 - *c-Jun* *N*-terminal kinase (JNK) (*See* JNK)
 - extracellular regulating kinase (ERK) (*See* ERK)
 - p38MAP kinase (p38) (*See* p38)
 - MK0859 17
 - molecular aberration 24
 - molecular design, evolution 4–6
 - molecular profiling, identifying secondary/ novel mutations 165
 - monoclonal antibody 25, 317
 - anti-HER2 receptor 25
 - phase II clinical study 26
 - mutations 6, 21, 22
 - BRAF 91
 - BRCA1/2 189
 - C1156Y 82
 - driver/passenger mutations 148
 - EGFR 72
 - EGFR T790M 22
 - G1269A 82
 - G1202R 82
 - HSP110* 54
 - IDH* 149
 - KRAS 82
 - L1196M 82
 - MEK 37
 - MET 72, 83
 - NRAS 37
 - oncogenic mutations 148
 - p53 42, 45
 - PIK3CA* 27
 - PTCH1* 24
 - Rad6* 188
 - Rad18* 188
 - RAS 149
 - SMO* 24
 - S1206Y 82
 - T790M
 - gatekeeper 26, 82
 - V600E 96
 - myeloid lineage 5
- n**
- nanoparticles 2, 13
 - dual targeted 13
 - liposomal 13
 - optimization along with target potency, and efficacy 14
 - nanotechnology 13
 - neurite outgrowth cellular assay 231
 - neurodegenerative diseases 211
 - nonreceptor protein tyrosine kinases 261–266
 - Bruton's tyrosine kinase (Btk) (*See* Btk)
 - IL-2-inducible Tcell kinase (ITK) (*See* ITK)

- The Janus kinase (JAK) (*See* JAK)
- Lymphocyte-specific protein tyrosine kinase (Lck) (*See* Lck)
- Spleen tyrosine kinase (Syk) (*See* Syk)
- non-small cell lung cancer (NSCLC) 26
- abnormal ALK gene 73
- de novo* highly MET-amplified patient 83
- MET amplification and stromal HGF, role in resistance to 83
- mutations affecting various receptor tyrosine kinases 26
- mutation spectrum in 30
- ROS1* rearrangements 83
- Novartis tertiary amine library (TAM) 349
- NSCLC. *See* non-small cell lung cancer (NSCLC)
- o**
- onartuzumab 26, 28
- oncogene addiction 22, 24. *See also* predictive biomarkers
- defined 24
 - role of 27
 - utility of predictive biomarkers 24
- p**
- p38 257–259
- future medicine strategy prospects 259
- inhibitors 257
- catalytic activity inhibition 257
 - losmapimod 258, 259
 - ML3403 257
 - pyridazine 259
 - SB203580 257, 258
 - UR-13870 258
 - urea 259
- isoforms 257
- p38 α 257
- development 257
 - inhibitors 257
 - proinflammatory cytokines, synthesis regulation 257
- Palau Pharma's p38 inhibitor 279
- pan- and isoenzyme-selective HDAC inhibitors 352
- Parkinson's disease 15
- Parkinson's disease (PD) 15, 227
- genetic cause 228
- origin 228
- symptoms 227
- PARP inhibitors 42, 188
- case study 188, 189
 - clinical development 190–192
 - clinical trials 193
 - discovery 189, 190
 - nicotinamide-derived PARP inhibitors 190
 - perspectives 192, 194
 - patched homolog 1 (PTCH1) protein 101
 - PD. *See* Parkinson's disease (PD)
 - PD-related neurodegeneration 231
 - personalized medicines 1
 - in autoimmune/inflammatory diseases 8 - diagnostic/biomarker-based codiscovery 11
 - rapid progress in 15–18
 - PF-02341066. *See* crizotinib
 - PGDFR 269, 270
 - asthma, study for 269 - biological effects 269
 - family 269
 - genetic study 269, 270
 - inhibitor 270
 - PDGF/PDGFR signaling route 269
 - PDGFR- α promoter polymorphism 270
 - P-glycoprotein 109
 - PHA-665752 74
 - pharmacodynamics (PD) 290
 - phenotypic screening 3
 - Philadelphia chromosome 5
 - phosphatase inhibitors, structure-guided design 348
 - Phosphatidylinositol-3 kinases 270–272
 - activation 271 - broad-spectrum inhibitor 271
 - mouse study 271, 272 - classification 271
 - clinical studies 272
 - dual PI3K γ / δ inhibitor 272
 - TG100-115 272 - function 270, 271
 - genetic deletions study 271
 - results 271 - intracellular signal transducer enzymes, family of 270, 271
 - isoforms 271
 - expression pattern 271
 - pharmacological inhibition study 271
 - results 271
 - PI3K δ inhibitor 271
 - structure 271
 - PI3K δ signal transduction pathway 271
 - clinical studies 271
 - selective inhibition, IC87114 271
 - PI3K γ inhibitor 271
 - AS-604850 272
 - asthma, examined for 272
 - mouse study 272

- structure 271
 - phosphorylation
 - MET 74
 - p53 56
 - PI3K inhibitors 28
 - PI3K signaling 7, 27
 - PKC 272, 273
 - advanced PKC inhibitors 273
 - 4-amino-3-cyanopyridine 273
 - clinical trials 273
 - sotrastaurin 273
 - staurosporine analogs 273
 - challenges 273
 - isoforms 272
 - atypical isoforms 273
 - classical isoforms 272
 - novel isoforms 273
 - serine/threonine kinases family 272
 - in vitro* studies 273
 - planar scintigraphy 290
 - pleiotrophin (PTN) 72
 - PLX4032. *See* Vemurafenib
 - poly(ADP-ribose) polymerases 352, 353
 - polyamides 117
 - polypharmacy 1, 15
 - positron emission tomography (PET) 290
 - cameras 291
 - $^{11}\text{C}/^{18}\text{F}$ -labeled PET tracers, development
 - of 292–294
 - in cardiology 319, 320
 - detection of photons 291
 - imaging
 - in clinic, research, and drug development 315
 - neuroimaging 317–319
 - in oncology 315–317
 - positron-emitting radionuclides
 - from cyclotron products/cyclotron products 291
 - properties 290
 - tracer kinetic modeling for quantification
 - of tracer uptake 320–325
 - posttranslational modifications 55, 56
 - predictive biomarkers
 - cancer cell lines, as a model system for discovery 28
 - for cancer drug therapy 23
 - current challenges in discovering 51, 52
 - access to tumor cells, limited during treatment 51–53
 - drivers and passengers 53, 54
 - epigenetic regulation, and complexity 54, 55
 - regulatory posttranslational modifications 55, 56
 - discovery for antiangiogenic agents 42, 43
 - challenges 43, 44
 - on-treatment effects, as a surrogate of drug efficacy 45
 - pathway activity, as predictor of drug efficacy 44, 45
 - predicting inherent resistance 45
 - discovery, in context of treatment combinations 38–42
 - combination analysis 38, 39
 - Loewe additivity model 39
 - gene expression signatures as 47
 - diagnostic development: 48, 50
 - signature discovery: unsupervised clustering 47–49
 - modeling drug resistance to discover 33, 34, 37, 38
 - experimental approaches 33
 - random mutagenesis screens 34
 - rational combinations, include targeted agents with 41
 - prodrug strategy 14
 - advantages 15
 - ligand-targeted 14
 - PSMA (prostate-specific membrane antigen)-targeted 14
 - Protein Data Bank (PDB) 344
 - protein kinases 256
 - protein tyrosine phosphatases (PTPs) 347
 - proteomics 1, 11
 - PTEN expression 27
 - purified LRRK2 *in vitro* 230
 - optimized substrate sequence, WWRFYTLRRA (Nictide) 230
 - peptide substrate sequence 230
 - iterative optimization 230
- q**
- quadruplexes
 - as anticancer targets 123–125
 - developing superior binding ligands 130–134
 - fundamentals 117–119
 - genomic 119, 120
 - G-quadruplex small molecules 124
 - antitumor efficacy 124
 - G-quartet, core hydrogen-bonding motif 118
 - in human telomeres 120–123
 - informatics studies, location to nonhuman species 119
 - overrepresentation 119, 120
 - native structures 125–130

- crystal structure (PDB ID 3QXR) 127
- mixed parallel/antiparallel topologies 126
- molecular dynamics-derived structure 129
- NMR (PDB ID 2O3 M) 127
- NMR structures determined for a c-myc promoter complex 132
- selected crystal and NMR structures 128, 129
- quadruplex approach, advantages in 135
- small-molecule structures 130
- crystal structure, tetrasubstituted naphthalene diimide compound 131
- structures of representative quadruplex-binding small molecules 122
- quarflorin 122, 124
- quizartinib 346

r

- radiolabeling compounds, with ^{11}C 294
 - ^{11}C and basic reactive intermediates, preparations 294, 295
- ^{11}C methylations 295, 296
 - formation of ^{11}C -C bond 297, 298
 - formation of ^{11}C -X bond 295, 296
 - heteroatom methylation using 296
 - Pd-mediated 297
 - Pictet-Spengler reaction 296
 - Suzuki and Stille cross-coupling 298
 - Wittig synthesis 298
- ^{11}CO , reactions with 301-303
- $^{11}\text{CO}_2$, reactions with 299-301
- H^{11}CN , reactions with 303, 304
- radiolabeling compounds, with ^{18}F 304
 - aliphatic nucleophilic ^{18}F -fluorination 306-309
- aromatic nucleophilic ^{18}F -fluorination 309-313
- C- ^{18}F bond, formation of 304-306
- electrophilic ^{18}F -fluorination 313, 314
- ^{18}F -Al, Si, B bond, formation of 314, 315
- radiological imaging techniques 289
- RAF kinases 91
- receptor-mediated endocytosis 15
- receptor tyrosine kinase (RTK) 71
 - activation 71
 - inhibitors 71
 - molecular architecture 71
- receptor tyrosine kinases (RTKs) 266-270
 - c-Kit (*See* c-Kit)
 - definition 266, 267
- Epidermal growth factor receptor (EGFR) (*See* EGFR)
- platelet-derived growth factor (PDGF) (*See* PDGF)
- role in asthma pathophysiology 267
- tyrosine kinase receptor 267
- vascular endothelial growth factor (VEGF) (*See* VEGF)
- rheumatoid arthritis 15
- RHPS4 compound 122, 123
- RNA sequencing 163
- ROCK 273-275
 - activation 274
- aminofurazan-based inhibitor GSK269962A 274
- function 273, 274
- implication 274
- inhibitors 274
 - development 274
 - fasudil 274
 - shortcomings 274
 - Y-27632 274
- myosin phosphatase phosphorylation 274
- ROCK1 273
- ROCK2 273
- serine-threonine protein kinases, AGC superfamily 273
- treatment 274
- in vivo* biological findings 274, 275
- ROS expression 73
- ROS kinase 73

s

- Saccharomyces cerevisiae* 187, 199
- saridegib 103
- selective inhibitors, of Jak kinases 346
- semagacestat 212
- serine/threonine-protein kinases 185
- serine/threonine-protein kinases ATR 185
- signaling inhibitors 7
- single-photon emission computed tomography (SPECT) 290
- smoothened homolog (SMO) protein 101
 - optimization 103
- small-molecule inhibitors 103-107
- structure-activity relationship 104, 105
- somatostatin receptor subtype 5 (SSTR5) 349
- sorafenib 95, 164
 - multitargeted kinase inhibitor 92
- SP-600125 259, 260
 - clinical test results 259, 260
- sphingosine kinase (Sph K) 276, 277
 - allergic asthma, preclinical models 277
- clinical trials 276
- function 276

- inhibitors 277
 - *N,N*-dimethylsphingosine (DMS) 277
 - SK-I 277
 - *in vivo* studies 277
 - MAPK pathway 276
 - signaling pathway 276
 - sphingolipid metabolic pathway 276
 - regulation 276
 - sphingosine-1 phosphate (S1P) 276, 277
 - in vitro* study 276
 - Sprycel 17
 - staurosporine analog K252a 74
 - steroidal alkaloids 103
 - STI571 5, 16
 - structural bioinformatics 12
 - Structural Genomics Consortium (SGC) 344
 - Syk 261–263
 - caveat 262, 263
 - excellair™, large-molecule antisense
 - oligonucleotide 261
 - clinical trials 261
 - IgE-mediated response, role 261
 - immunoreceptor signaling, mediator 261
 - inhibitors 261
 - BAY 61-3606 262
 - limitations 262
 - P505-15, selective inhibitor 263
 - structure 262
 - inhibitor therapy 262
 - knockout mice 261
 - pharmacologically inhibition 261
 - R343 inhaled Syk inhibitor 261, 262
 - clinical trials 261
 - R406 inhaled Syk inhibitor 262
 - allergic asthma treatment 262
 - functional role 262
 - scaffold-specific mutagenicity risk 263
 - selective Syk inhibition 261
 - synthetic lethality 185–188
 - with drug molecule 187
 - screening for 199–202
 - contextual screening 203
 - methodologies 199
 - MRN 203
 - RAS 202
 - synthetic lethal screen against mutation Y 201
 - VHL 202, 203
 - selected structures
 - of agents in clinical trials 200
 - of preclinical agents 201
 - systems chemical biology 10
 - combined with structural bioinformatics 12
- t**
 - tankyrase inhibitors 353
 - TBI medicine 12
 - T-cell tyrosine protein phosphatase (TC-PTP) 347
 - TDM-1 18
 - T-DM1 for treatment of cancer 15
 - telomerase 120–123
 - telomestatin 122, 123
 - tetrasubstituted naphthalene diimide 122
 - theranostics 12, 219, 220
 - limitations 12, 13
 - thrombospondins 45
 - tofacitinib 264, 265, 346
 - structure 265
 - treatment 265
 - topoisomerase poison 188
 - topotecan 16
 - torcetrapib 12, 17
 - toxicity 4, 12, 28, 343
 - transmembrane proteins 101
 - trastuzumab 25, 27
 - emtansine 18
 - resistance 37
 - traumatic brain injury (TBI) 11
 - tumorigenesis 8
 - tumors
 - angiogenesis 44
 - promoting factor 23
 - BRAF signaling 27
 - BRCA1/BRCA2 proteins 189
 - CALU-6 107
 - pharmacodynamic evaluation of inhibitors 107
 - growth factor-driven resistance 72
 - with *HER2* overexpression 25
 - host interactions 23
 - inflammatory myofibroblastic 73
 - lacking *HER2* amplification 30
 - PAM50 multigene expression 50
 - ROS aberrantly expressed in 73
 - specimens linked to drug-based clinical trials 24
 - suppressor genes, aberrant methylation 55
 - U87 glioblastoma xenograph tumor
 - model 75
 - Tykerb 17
 - tyrosine kinase 5
- u**
 - ubiquitination 10, 353, 354
 - ubiquitin-like peptides 353
 - ubiquitin–proteasome system 353

v

vascular endothelial cell growth factor (VEGF) 23
 – genetic variations (SNPs) in VEGF pathway genes 45
 ligand levels 44
 V600E *BRAF*-mutated melanoma 27
 VEGFA transcriptional signatures 44
 VEGFR 270
 – activation 270
 angiogenic factor 270
 asthma, studies for 270
 clinical study 270
 genetic polymorphism 270
 preclinical studies 270
 receptor tyrosine kinase, ligand for 270
 vemurafenib 27, 28, 37, 72, 91, 148
 – 7-azaindole scaffold 92, 93
 clinical efficacy 96
 cobas 4800 diagnostic assay 96
 cocrystallized with mutated p38 kinase 93
 cocrystal structure with *BRAF*^{V600E} kinase domain 95
 discovery/development 92–95
 optimization
 – 5-position of azaindole core 94
 – sulfonamides with 93
 – pharmacokinetic properties 94
 pharmacology 95
 safety 96
 synthesis 96
 – Aldol coupling 96
 – 5-bromoazaindole 96

– 5-bromo-7-azaindole 96
 – 4-chlorophenylboronic acid 96
 – commercially available building blocks 96
 – 2,4-difluoroaniline 96
 – Friedel–Crafts reaction 97
 – process route 97, 98
 – Suzuki coupling 96, 98
 – utility of bioisosteric replacement 93
in vitro profiling 95
in vivo studies 95
 viral vector-mediated expression
 – LRRK2[G2019S] 233
 virtual screening 3, 11
 vismodegib 24, 101, 103
 – biotransformation 108
 clinical experience in phase I 112–114
 – basal-cell carcinoma 113
 – drug–drug interaction potential 109
 preclinical characterization of 107
 – blood plasma partitioning 107, 108
 – plasma protein binding 107, 108
 – preclinical pharmacokinetics 109, 110
 predicted human pharmacokinetics 110–112
 – allometric scaling 111
 – *in vitro*/exploratory *in vivo* metabolism 108

w

warfarin 344
 – genotype variants 344
 World Wide Web Consortium (W3C) 11

z

ZINC database 134

