

Index

a

- Abl inhibition 359
- absorption, distribution, metabolism, and elimination (ADME), of drug 45, 142, 144, 346, 414
- ACE inhibitors 10, 12
- acetaminophen 176, 374
 - inhibitors, protects against hepatotoxicity *in vivo* 376
 - liver damage 125
 - overdose 110
- acetylation 89
- acetylators 89
- acetylcysteine (AC) 110, 113, 115
- acetylhydrazine 89
- acetyl isoniazid 89
- acne 341, 342, 344, 380, 458
- action potential 258
 - AP/QT prolongation
 - as a torsadogenicity biomarker 320
 - duration 304
 - estimation of proarrhythmic hERG occupancy levels based on 304
 - nontrappable blockers 305
 - trappable blockers 304
 - isomorphic lengthening 298
 - normal AP and proarrhythmic abnormalities 296
 - abnormal calcium channel reopening triggers 298–300
 - blocker-induced loss of baseline I_{Kr} , cause EADs 301
 - effects of hERG dysfunction 301
 - molecular mechanisms 296
 - reduction in baseline I_K levels over supra-AP timescales 300
 - state transitions of hERG determine instantaneous I_{Kr} current 296
 - voltage-gated ion channel state transitions 297, 298
 - prolongation 298
 - simulated cardiac, in M cells 297, 299, 300
 - simulations 303, 304, 320
 - stratification of AP timings 301
 - supra-AP timescales 300
 - waveform 298, 304
- activity-based protein profiling (ABPP) 390
- acute coronary syndrome (ACS) 281, 331, 337
- acute liver injury (ALI) 88, 96, 110, 115–118, 120
- acute lymphoblastic leukemia (ALL) 332, 333, 377, 401
- acylcarnitines 112, 115, 116
- administration route, of drugs 52, 53
- $\alpha 2$ adrenergic receptor ($\alpha 2$ AR) 22
- adrenergic receptor antagonists 10
- β -adrenergic receptors (β -ADRs) 35, 235
- adrenocorticotrophic hormone (ACTH) 465
- ADRs. *See* adverse drug reactions (ADRs)
- adverse drug reactions (ADRs) 3, 4, 6–8, 14, 15, 457
 - as a drug-induced disease 30
 - as drug-induced diseases 29
 - multiscale models of 30, 31
 - primary toxicity profiles 30
 - psychiatric 12
- adverse effects, incidence of 95
- Adverse Event Reporting System (AERS) 30
- afatinib 388
- aflatoxin B1 (AFB1) 136
- agranulocytosis 58, 66
- akathisia 5, 65, 460
- Akt inhibitors 12, 425
 - enzyme inhibition data 424
- Akt overexpression 424

- Akt1 selectivity
 - Ala230 425, 426, 428
 - residue differences and structural consequences 426
- alanine aminotransaminase 110–112
- alanine aminotransferases (ALT) 33, 88, 89, 91, 92, 94, 95, 96, 98, 107–109, 111, 112, 114, 116, 171–173, 175, 176, 179–186, 373, 375, 376
- albumin 91, 96, 112, 139, 140, 280
- aldosterone 439, 443, 447
 - reproducible *in vitro* screening models 440
 - safety risk 447–448
 - torcetrapib, effect of 441–444
 - torcetrapib induction, molecular mechanism of 439, 440
- aldosterone synthase (AS) 438
- aldosterone synthase overexpression (AS^{hi/hi})
 - mouse model of 448
- alfuzosin 260
- ALI. *See* acute liver injury (ALI)
- alkaline phosphatase (ALP) 92, 95, 100, 111–113
- ALL. *See* acute lymphoblastic leukemia (ALL)
- allosteric inhibitors 359
- allosteric kinase inhibitors 10
- allosteric modulator sites 12
- almotriptan 68
- ALT. *See* alanine aminotransferases (ALT)
- Alzheimer's disease 467
 - Lewy bodies 471
- aminotransferase 91
- amlodipine 245
- AMP-activated protein kinase (AMPK) 407
- amphetamine 57, 467, 469
- amrinone 218
- anacetrapib 438, 448
 - application of *in vitro* models 440, 441
 - BP/aldosterone preclinical models 448–449
 - chemical structure and physicochemical properties 438
- anemone toxin II (ATXII) 257
- angiotensin-converting enzyme (ACE) 442
- angiotensin II antagonists 10, 14
 - AT1 receptor 14, 439
- angiotensin inhibitors 12
- angiotensin receptor antagonist FAERS
 - profiles 12
- ankyrin-G 256
- anorexia 377
- anthracyclines 284
- anticancer drugs 202
- antidepressants 12
 - smoking cessation 471
 - target primarily 5-HT transporter 69
- antiepileptic drugs 472
- antigen-presenting cells (APCs) 144
- antihistamines 52
- antihypertensive adrenergic receptor
 - blockers 12
- antihypertensive drugs 9, 15
- antimigraine medications 67
 - contraindications 68
 - warnings 69
- antipsychotics 58, 65
 - second-generation 67
- anti-ribosomal emetine 21
- “antitarget” effects 83
- antitubercular therapy 87
- antiulcer drug 33
- anxiety 5, 285, 342, 459–461, 463, 464, 467, 470, 471
 - with D₁ and D₅ antagonists 460
- AO. *See* action potential
- aortic pressure 210
- apoptosis 84, 116, 181, 244, 281, 338, 339, 340, 347, 382, 424
 - cardiomyocyte 52
 - caspase-dependent 138
 - K18 attributed to 117
 - myocyte 448
 - quantification of 117
 - -resistant phenotype 140
 - trastuzumab and lapatinib leading 407
- appetite-reducing agents 61
- aripiprazole 66, 67
 - antipsychotic drugs 461
 - postmarketing psychiatric side effect profile of 462
- ARREST study 254
- arrhythmias 52, 69, 201, 202, 239, 245, 253, 257, 260, 281, 346
- ARRY-380 (ONT-380) 420–424
 - kinases with minimal inhibition 423
 - optimization path 421
 - proposed binding mode 422
- arterial blood pressure 225
- arteriosclerosis 203
- artificial intelligence 36
- aspartate aminotransferases (AST) 33, 87, 88, 92, 95, 100, 111, 127, 128, 175, 176, 183, 287, 373, 376
- aspirin 27, 126
- AST. *See* aspartate aminotransferases (AST)
- atenolol 10, 218, 226
- atherogenic lipid profile 67

atherosclerosis 68
 atomoxetine 467
 ATP binding domain 370
 ATP cleft 414, 418, 419, 422–424, 428
 ATP-competitive inhibitors 305
 ATP-competitive KI, IC₅₀ values for 390
 ATP synthesis 179, 180, 183, 390
 atrial natriuretic peptide (ANP) 282
 atrioventricular (AV) node 235
 autism 66, 242, 247
 autoregulation 205, 206, 464
 Avastin 334
 avidity 205, 206
 axitinib 333, 344, 346, 347, 351, 366, 371, 373, 377

b

BCR-ABL fusion protein 371
 BCR-Abl inhibitors 347, 408
 BCR-ABL targeting KIs nilotinib 384
 benfluorex (Servier) 58, 61–63
 benzothiazepine (BTZ) 245
 bevacizumab 9, 47, 49, 331, 334, 347, 408
 bile acid-mediated toxicity module 184
 – bosentan 187
 – pioglitazone 184
 – SimPopsTM simulation 188, 189
 – telmisartan 187
 – troglitazone 184
 bile salt export pump (BSEP) 47, 136, 160–163, 181, 188, 189
 – competitive inhibitors 160
 – drug interaction with 160
 – role in drug development 162, 163
 – troglitazone sulfate as inhibitor 161
 bile salts 47, 159, 160, 181
 bilirubin 33, 87, 91, 92, 99, 112, 143, 176, 341, 373, 374
 biliverdin 96
 bioactivity databases 25
 bioinformatics 22, 23, 25
 biomarkers
 – in animal models 376
 – for assessment of DILI 111–113
 – for beta cell mass 469
 – blood-based 110
 – COX-1 therapeutic 32
 – efficacy 221
 – genomic 285, 286
 – NIH defined as 109
 – novel investigational, for DILI 113, 114
 – NT-proBNP 285
 – ROC curve 99

– surrogate 371
 – torsadogenicity 320
 – translational 288
 biotransformation 131
 bipolar disorders 66
 – depressive episodes associated with 70
 birth defects 384
 bisphosphonates 9
 BLAST 21
 bleeding diathesis 47
 β -blockers 28, 219, 226
 blood–brain barrier (BBB) 458
 blood pressure (BP)
 – activation of 5-HT_{1A} receptors 464
 – aldosterone 443
 – CP-532,623 444, 445
 – dalcetrapib 445
 – ketanserin 466
 – safety risk 447–448
 – small-molecule inhibitors of kinases: side effects 341, 342
 – sustained increase 441, 442
 – tissue mRNA analysis 442, 443
 – torcetrapib 437, 443, 444
 – – effect of 437, 438, 441–444, 445
 – – molecular mechanisms of 444–447
 – – -positive inotropism 446–447
 blood–retinal barrier damage 388
 bone morphogenetic proteins (BMPs) 379
 bone toxicity 379–380
 bosentan 160, 187
 – hepatotoxicity 189
 – simulations 187
 bosutinib 11, 333, 344, 346, 351, 354, 357, 366
 B-Raf, comparable binding modes
 – x-ray crystal structures 417
 BRaf inhibitor 333, 340
 BRaf mutation 356, 407
 bromocriptine 62, 461
 bronchoconstrictory reflex 210
 bulimia nervosa 70
 bupropion 471

c

cabergoline 58, 62, 461
 cabozantinib 333, 344, 347, 352, 366, 387, 389
 Ca channel antagonist 445
 Ca channel blockers 10, 12
Caenorhabditis elegans 35
 Ca²⁺ion 209, 235, 246
 calcineurin–nuclear factor of activated T cells (NFAT) signaling pathway 243
 calcium–calmodulin complex 243

- calcium/calmodulin-dependent protein kinase II (CaMKII) 256
- calcium channels 235
 - antagonist 226
- calcium homeostasis 133
- calcium-induced calcium release (CICR) 235
- CaMKII phosphorylation 264
- Cancer and Leukemia Group B (CALGB) protocol 401
- cancer drug 357, 358, 402
 - and cardiotoxicity 402, 403
 - evaluation of various cancer cell lines 414
 - inhibitor of Akt as 424
- cannabis 462
- Cannabis sativa* 462
- capecitabine–DPD 27
- carbamazepine 472
- carcinogenesis 137
- cardiac action potential (AP). *See* action potential
- Cardiac Arrhythmia Suppression Trials (CAST) 253
- cardiac biomarkers 280
- cardiac cycle 206
- cardiac dysfunction 409
- cardiac enzymes 402
- cardiac function 203, 213
 - definition 203
 - dual EGFR/ErbB2 inhibition 406
 - general principle 203
 - methods available to assess 213–217
 - sensitive marker of 284
- cardiac inotropy 214
- cardiac $\text{Na}^+/\text{Ca}^{2+}$ exchange pump 254
- cardiac output (CO) 205
- cardiac rhythm 262
- cardiac side effect 404
- cardiac sodium current (*Nav1.5*)
 - approaches, to interrogate effects of emerging compounds on 265, 266
 - animal-based 265
 - cellular- and tissue-based 265
 - ionic currents 265
 - organ-based 265
 - *in silico*/binding 265
 - current density, in ventricular myocytes 268
 - DI–DII cytoplasmic linker 264
 - heterogeneous population of 256
 - molecular biology 255
 - multiple pools of 257
 - structure and functional characteristics 256
 - three voltage-gated sodium channels 261
 - use of human stem cell-derived cardiomyocytes 266–268
- cardiac-specific kinase antitargets 404
 - clinical outcome predictions 409–410
 - heart, clinical findings 404
 - Bcr–Abl inhibition 408
 - c-Kit Inhibition 408
 - dual ErbB2/EGFR inhibitor 406, 407
 - EGFR inhibition 406
 - ErbB2 inhibition 404–406
 - JAK/STAT inhibition 407–408
 - MEK inhibitor 407
 - PDGFRs 408
 - rapidly accelerated fibrosarcoma (Raf) kinase 407
 - VEGFR inhibition 408–409
 - preclinical findings 404
 - preclinical safety 409–410
- cardiac stem cells 402, 403
- cardiac toxicities 202
- cardiac troponins 205, 206, 209, 280–282
 - binary and ternary complexes 282
 - biological half-life 281
 - epitopes of 281
 - hemolysis 282
 - immunoassays 281
 - nonclinical use 287
 - absence of increase in cTnT and/or cTnI values 288
 - BQRT in nonclinical drug development studies 286, 288
 - regulatory perspective 286–288
- cardiomyocytes 214, 246, 255, 257, 266, 285, 404, 409, 471
 - action potentials 52
 - Cav1.2, derived from iPS cells 246, 247
 - regulation of CICR in 244
 - Timothy syndrome ventricular-like 247
 - use of human stem cell-derived 266–268
 - *in vitro* iPS-derived cardiomyocytes (iPS-CMs) 246
- cardiomyopathy 213
- CardioTox 30
- cardiotoxicity 224, 286, 403
 - kinase inhibitors 401
 - zebrafish, use 410
- cardiovascular adverse events (AEs) 202
- cardiovascular disease (CVD) 437, 438, 448
- cardiovascular-related drug 201
- cardiovascular safety 203
- cardiovascular side effects 202
- cardiovascular toxicity 380
 - evaluation of 286

- case study
 - cardiac side effects associated
 - with kinase proteins and signaling pathways 401, 402
 - importance of identifying residues that frequently neglected in 418
- caspase-1 132, 147
- catalepsy 65, 66
- Ca_v1.2 antagonists 245
 - impact on electromechanical functions 245, 246
- Ca_v1.2 calcium channels 235
 - and cardiac diseases 244
 - function in cardiac tissue 237–239
 - implication on heart physiology 238
 - modulation of 240
 - inactivation 242
 - indirect regulation of 243, 244
 - regulation by calmodulin 242, 243
 - sympathetic stimulation and kinase regulation 241, 242
 - voltage- and calcium-dependent facilitation 241
 - role in conduction and contractility 239, 240
 - structure 235, 236
 - α -subunit of 236
 - β -subunit of 236, 237
- Cav1.2 off-target liability, prediction of 246
- cell death 128, 133
- cell polarity 130
- cellular ATP model 183, 187
- cellular depolarization 235
- cellular energy 173
- cell viability 142
- central nervous system (CNS) drugs 33
- cetuximab 8, 9, 406
- channel interactive proteins (ChiPs) 255
- ChEMBL 21, 30
 - database 22, 25
- Chemically Advanced Template Search (CATS) fingerprints 23
- chemoinformatic literature 21
- chemotherapeutic agents 116, 129
 - cytotoxic 365, 391, 403
- Cheng–Prusoff equation 390
- chlorotrianisene 32
- chlorpromazine 65, 66, 145
- cholestasis 160, 161
- cholesterol-lowering drugs 9
- cholesteryl ester transfer protein (CETP) 437
 - CETP-proficient monkey 444
 - CETPtg mouse 443
 - inhibitors (CETPi) 437
- chronic hepatitis C 98
- chronic myeloid leukemia (CML) 346, 377, 403
- chronotropy 219
- chylomicrons (CM) 450
- cinchophen 142
- citalopram 27, 70
 - suicidal ideation in teenagers 467
- c-Jun N-terminal kinase (JNK) pathway 408
- Claviceps purpurea* 60, 68
- clozapine 29, 30, 58, 65, 71
 - atypical antipsychotic 466
 - contraindication 67
 - D₂–5-HT₂ antagonist, antipsychotic doses 461
 - as inverse 5-HT_{2A} agonist 66
 - patients with schizophrenia 67
 - reserved for use in 30
 - side effects 29, 66
 - therapeutic doses 66
 - vs. chlorpromazine 66
- cMet inhibitor 355
- CNS receptors 5
 - associated neurological/psychoactive effects 5, 6
 - involved in psychoactive effects 5
 - potentially involved in psychoactive effects
 - agonism 5, 6
 - antagonism 5, 6
- coagulopathies 47
- cocaine 467
- coherent datasets 21
- colchicine 34
- cold intolerance 377
- collagenase 131
- colon carcinoma, non-small cell lung cancer (NSCLC) 332–337, 403
- colorectal cancer 408
- combination therapy, evidence for 358
- competitive intelligence 4
- complementary functional databases 28
- computer-readable datasets 36
- computer science 36
- conformations 24, 242, 305, 413, 415
 - low-energy 24
- contraction–relaxation cycle 235
- Conus magus* 472
- ‘convulsive ergotism’ 60
- coronary syndromes, acute 403
- coronary vasospasm 245
- corticosterone 442, 465
- covalent inhibitors 354
- COX-1 inhibitors 32

creatine kinase 280
 crizotinib 11, 355, 356, 388
 cryopreservation 131
 crystallization 58, 63
 – 5-HT_{1B} and 5-HT_{2B} receptors 63
 CTD–Pfizer dataset 30
 cutaneous toxicities 380, 381
 – clinical management of 383
 – mechanistic basis of 381
 – preclinical evaluation of 381–383
 cyclases 235
 cyclooxygenase-2 (COX-2) inhibitors 19
 cyclophosphamide 403
 CYP3A enzymes 374
 Cyp11B2 439
 – expression in human adrenocortical cells 441
 – messenger RNA (mRNA) coding 438
 – mRNA, reproducible *in vitro* screening models 440
 CYP-generated metabolites 142
 CYP-mediated metabolism 373
 cysteine 116, 354, 390
 cytarabine 401
 cytochrome P450 enzymes 129, 141, 142
 cytokines 129
 cytotoxicity 135
 – assays 133
 – endpoints 132

d

dabrafenib 407
 dacarbazine 138
 D₂ agonists 5, 341, 460, 461, 463
 dalcetrapib 438, 449
 – BP and aldosterone preclinical models 448–449
 – chemical structure and physicochemical properties 438
 – compound 440
 – -treated CM, uptake of 450
 – *in vitro* models, application 440, 441
 dal-HEART phase III clinical trial program 437
 danger hypothesis, for immune-mediated idiosyncratic hepatotoxicity 145
 “danger” priming the immune system 144
 D₁ antagonism 460
 D₂ antagonism 460
 D₅ antagonism 461
 dasatinib 346, 371
 – BCR-ABL inhibitors 373
 – cardiotoxicity 402

 – heart failure 408
 – KI targeting BCR-ABL 377
 – multikinase inhibitor 371
 – trabecular bone volume 379
 databases 21
 – FAERS 7
 – NCBI 26
 – StARlite 25
 data interpretation 52
 data mining 30
 data resources 26
 DA transporter 59
 D₂/D₃ receptors 66
 dementia 471
 – -related psychosis 67
 depression
 – with D₁ and D₅ antagonists 460
 – treatment of 467
 dexfenfluramine 62
 DFG-out channel 414
 DHP-sensitive channels 245
 diabetic ketoacidosis (DKA) 67
 diastolic arterial pressure (DAP) 226
 diastolic function 206, 209, 214
 diclofenac 138, 145
 differentiated pluripotent stem cells 137
 – embryonic stem cells 137, 138
 – induced pluripotent stem cells 138, 139
 dihydroindene analogues 427
 DILI. *See* drug-induced liver injury (DILI)
 DILIsym®
 – bosentan PBPK model 187
 – current version 175
 – mechanistic modules, version 3A 175
 – – bile acid-mediated toxicity 181–184
 – – innate immune responses 178, 179
 – – mitochondrial toxicity 179–181
 – – oxidative stress-mediated toxicity 175–178
 – mechanistic, multiscale model of DILI 173
 – multiscale structure of 174
 – overall structure and mechanistic representation 175
 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfofophenyl)-2H-tetrazolium (MTS) 142
 dizziness 5, 6, 12, 51, 202, 341, 342, 460, 461, 472
 dobutamine infusion 402
 docking 23
 dopamine D₁/D₂/D₃ receptor 64, 458–464
 dopamine D₄ receptor 35
 dopaminergic system 458

- dopamine transporter (DAT) 32, 470
 - dose-related liver injury 85
 - doxorubicin 403
 - DRAK1 kinase 355
 - D₂ receptors 62
 - dromotropy 219
 - Drosophila* model 19
 - drowsiness 5, 341, 460, 461, 463
 - drug activity, large-scale prediction of 20
 - drug attrition
 - due to DILI 108
 - in the pharmaceutical industry 107
 - DrugBank 21
 - drug–BSEP interactions 161
 - susceptibility factors for 161, 162
 - drug design 4, 9
 - drug discovery 3, 35
 - ADR prediction during 4
 - application of ESCs 138
 - cardiovascular 214
 - challenge facing 128
 - correct use of MedDRA terminology at 48
 - metabolism-mediated toxicity in 141, 149
 - objectives, cardiac safety liability and their alignment to 220
 - precision-cut human liver slices in 140
 - drug–disease associations 29
 - drug–drug interactions 10
 - drug effects on *I*_{NaF} 261, 262
 - models of block and classification schemes
 - based on antiarrhythmic drug effects 263, 264
 - use-dependent block (and tonic block) 262, 263
 - voltage-dependent block 262
 - drug efficacy 109
 - drug-induced cardiotoxicity 279, 285
 - drug-induced cholestasis 161
 - drug-induced injury 96
 - drug-induced liver injury (DILI) 83, 91, 372
 - acetaminophen-induced 376
 - cause of 109
 - clinicopathological presentation
 - and proposed mechanisms 126
 - dose–response relationship for idiosyncratic DILI 128
 - drug attrition due to 108
 - efforts from the US-based DILIN and the Spanish Hepatotoxicity Registry 119
 - efforts to aid identification, validation, and qualification novel TSBM 110
 - idiosyncratic 108, 145, 148
 - improved biomarkers 109
 - current status for assessment 111–113
 - novel investigational biomarkers 113, 114
 - validation/biological qualification 109, 120
 - incidence in TGZ-treated patients 185
 - incidence of 108
 - Innovative Medicines Initiative MIP-DILI 114
 - “intrinsic” 108
 - key questions, for development of new mechanistic biomarkers 118
 - mechanistic modules in DILIsym® version 3A 175
 - mechanistic, multiscale model 173
 - mechanistic safety biomarkers 107–110
 - mitochondria as critical cellular components in 179
 - serum ALT activity 120
 - as significant ADR for currently used medicines and 108
 - structure and mechanistic representation of DILIsym® 175
 - treatment and management 95
 - *in vitro* models for prediction 125–130
 - clinicopathological presentation/proposed mechanisms 126
 - screening strategy 129
 - drug-induced negative inotropic effect 214
 - drug-induced parkinsonism 65
 - drug-induced toxicity, and liver 110, 111
 - drug–protein complexes 20
 - drug repositioning 4
 - drug safety 109
 - assessment 214
 - ICH S7A guidance 218
 - drugs computationally, for rapid comparison 23
 - drug screening 21, 26, 71
 - drug–target–ADR (DTA) 32
 - drug–target characterization 21
 - duloxetine 70
 - DXG sequence 418
 - dyskinesia 5, 29, 65, 460, 461, 469
 - dystonic reactions 65
- e**
- EC dysfunction 408
 - echocardiography 213, 214, 224, 285, 409, 410, 446
 - noninvasive 214
 - ecopipam, dopamine D_{1,5} receptor antagonist 461
 - eDISH programming 96, 98, 99, 100, 120

- elasticity modulus 205
 - eletriptan 68
 - encainide 253
 - end-diastolic pressure (EDP) 205
 - end-diastolic ventricular diameter 216
 - end-diastolic volume (EDV) 205
 - endocannabinoid system 462
 - endogenous damage-associated molecular patterns (DAMPs) 129
 - endothelial cells 19, 62, 126, 129, 178, 389, 408
 - endothelin-1 (ET1) 442
 - endothelin-converting enzyme 442
 - endothelin receptor antagonists 203
 - endothelins 219
 - enzyme inhibition
 - pyrrolopyridine analogues, selectivity ratio 426
 - for representative AKT inhibitors 424
 - for representative B-Raf inhibitors 416
 - epidermal growth factor receptor (EGFR) 331, 334, 371, 381, 420–423
 - ARRY-380 modeled, into X-ray coordinates 422
 - ATP binding cleft 421
 - Cys775, rotamer population 422
 - EGFR-deficient mice 381
 - EGFR-target KI 384
 - inhibitors 7, 337, 366, 380, 388
 - – FAERS representation of side effects 8
 - knockout mice 384
 - signaling 382, 383
 - x-ray crystal structure of 421
 - epidermal hyperplasia 381
 - epidermal necrolysis 374
 - epithelial cells 131
 - ErbB receptor and isoform
 - deletion of ErbB2 406
 - EGFR, clinical effect 423
 - ErbB2-activating ligand neuregulin (Nrg1) 406
 - ErbB2 and ErbB3, heterodimers 420
 - ErbB2 as upstream trigger 407
 - ErbB2 ATP binding cleft 421
 - ErbB (HER) family of receptor tyrosine kinases 420–423
 - ErbB1 inhibitors 8, 404
 - ErbB program 420
 - ErbB1 (EGFR, HER1) receptor 8
 - kinases involved in cardiovascular risks 9
 - x-ray crystal structures of 423
 - Erbtux 334
 - ergonovine 60
 - ergot alkaloids 59, 60
 - ergotamine 59, 60, 62, 68, 69
 - ergotism 60
 - erlotinib
 - epidermal growth factor receptor (EGFR) 371
 - -induced hepatotoxicity 373
 - therapy 388
 - escitalopram 70
 - escitalopram oxalate, suicidal ideation in teenagers 467
 - ethambutol 86
 - ethylenediaminetetraacetic acid (EDTA) 282
 - European Medicines Agency (EMA) 457
 - evacetrapib 438
 - application of *in vitro* models 440, 441
 - chemical structure and physicochemical properties 438
 - development 440
 - EXTEND clinical trials 127
 - extrapyramidal side effects 65
- f**
- famotidine 146
 - fast sodium current (I_{NaF}) 258, 259
 - fatigue 90, 211, 342–346, 377, 378, 423
 - KI-induced 378
 - FDA Adverse Event Reporting System (FAERS) 7, 8, 12, 14, 15, 48, 49, 462, 463
 - felbamate 138
 - felodipine 245
 - fenfluramine 14, 15, 59, 61, 62, 467, 469
 - Fen-Phen disaster 63
 - fexofenadine HCl 14
 - fibrosis 129, 331
 - flame-retardant polybrominated hydrocarbons 450
 - flecainide 253, 260
 - flecainidesodium channel blocking drugs 254
 - fludarabine 401
 - fluoxetine 70, 467
 - fluvoxamine maleate 467
 - forward perturbation 33
 - forward synthetic behavior
 - in cell 33
 - direct target prediction and 34, 35
 - fostamatinib 225
 - Frank–Starling curve 205, 206
 - frovatriptan 68
 - functional annotation datasets 27
- g**
- gabapentin 472
 - G alpha (s) signaling events 28

- gangrenous ergotism 60
- gastrointestinal graft 402
- gastrointestinal stromal tumor (GIST) 403
- gastrointestinal toxicity 385
- gatekeeper residue 413
- GDC-0068 (Ipatasertib)
 - discovery 424–428
 - x-ray crystal structure of 428
- gefitinib 371, 384, 388
- gene expression 130
- gene *gnrr-1* 35
- gene ontology (GO) term 28
- genetic interaction maps 35
- genetic–phenotypic associations 28
- genome-wide screening 439
- genomic biomarkers 285, 286
 - facilitate mechanistic understanding 286
 - *Spp1* and *Timp1* 286
 - utility of 285
- Gilbert's syndrome 374
- glibenclamide 143
- glioblastoma 420
- glutamate dehydrogenase (GLDH) 112, 114, 115
- glutathione depletion 340
- glutathione (GSH) synthesis 173
- glycoprotein 160
- G-protein-coupled receptors (GPCRs) 57, 235, 458, 460
 - dopamine D_{1/2} receptors (DRD1/2) 458–464
 - 5-HT_{2A} (HTR2A) 465–466
 - serotonin (5-HT_{1A}) receptor (HTR1A) 464–465
- G proteins 235
- h**
- halogenated hydrocarbons vs. potent CETPi 449–451
- haloperidol 65, 66
- hand–foot skin reaction 380
- H1 antihistamines 3
- hazard identification 219–221
 - of kinase inhibitor using *in vitro* pharmacological profiling 222
- heart fatty acid-binding protein (HFABP) 285
- heart rate 31, 203, 205, 216, 217, 227, 317, 342, 464
- heat shock protein 70 (HSP70) 147
- hematopoietic stem cells 387
 - pathways and networks 386
- hematopoietic system 385
- hematopoietic toxicity 385
 - clinical manifestations of 385
 - mechanistic basis of 385–387
 - preclinical evaluation of 387
- HepaRG cells 136
- heparins 112, 282
- hepatic ATP dynamics 176
- hepatic immune system 147
- hepatic slices 140
- hepatic toxicants 130
- hepatic toxicity 127, 139, 141, 142, 144, 148, 149, 345, 372–373
- hepatitis C infection 117, 160
- hepato-cellular carcinoma (HCC) 346
- hepatocellular necrosis 84
- hepatocyte growth factor 138
- hepatocyte-like cells (HLCs) 138
- hepatocyte necrosis 110
- hepatocytes 96, 129, 130, 131, 159
 - dedifferentiation 94, 96, 110, 113, 115, 129, 131, 132, 133, 135, 138, 140, 148, 159, 173, 180, 183, 376
 - immortalized 141
 - iPSC-derived 139
 - primary 130, 131
 - cell culture conditions 131, 132
 - limitations of cultures 133, 134
 - toxicity endpoints 132, 133
 - uninjured 96
- HepatoTox 30
- hepatotoxicity 47, 84, 85, 373
 - attempts to standardize terminology 91, 92
 - Common Terminology Criteria for Adverse Events (CTCAE) 92
 - diagnostic test evaluation 93, 94
 - poor positive test value 94
 - validation 93
 - genetic risk factors 375
 - idiosyncratic 111, 114
 - immune-mediated (*See* immune-mediated hepatotoxicity)
 - likely cause of liver abnormalities, determination of the 94, 95
 - metabolism/clearance pathways roles 373–375
 - neutrophil-mediated 129
 - “normal” range/“upper limit of normal” 92, 93
 - preclinical evaluation of 376–377
 - prediction of serious, dysfunctional liver injury 90, 91
 - problems of postmarketing 89, 90
 - severity of liver injury, and aminotransferase elevations 91

- treatment and management of DILI in practice 95
 - of tyrosine kinase inhibitors 373
 - voluntary monitoring ,after approval for marketing 90
 - hepatotoxins 85
 - HepG2 cells line 135, 146
 - Herceptin 334, 423
 - hERG blockade 295
 - dynamics of 301–303
 - simulations of human cardiac AP 303, 304
 - time-dependent 296
 - hERG channel occupancy 296
 - hERG dysfunction/blockade 296–301
 - in promoting early after depolarization 296
 - hERG mitigation/circumvention
 - limitations of 295
 - hERG safety 295, 296
 - assessment, implications in findings 313
 - – hERG mitigation strategies 320
 - – k_{off} -driven potency at subphysiological gating frequencies 307, 308, 311, 313
 - – safety margins for trappable/nontrappable blockers 323
 - HER1/HER2 inhibitor 161
 - hESC differentiation protocol 138
 - high-density lipoprotein cholesterol (HDL-C) 437
 - high-mobility group box-1 (HMGB1) 112, 116
 - high-mobility group protein B1 (HMGB-1) 147
 - high-throughput screening 28
 - hinge-binding pyridine nitrogens 419
 - hinge-interacting pyridine nitrogen 418
 - histamine H4 receptor 22
 - HIV reverse transcriptase inhibitor 22
 - Hofmann's account 61
 - homeostasis 159
 - homozygous G(1019) allele 464
 - H295R cell line 439, 440
 - 5-HT_{1A} agonists 57
 - 5-HT_{2A} agonists 58, 61, 465, 466
 - 5-HT₆ antagonism 58
 - 5-HT_{1A} receptors
 - central activation of 464
 - side effects 464
 - 5-HT_{2B} activation 51
 - 5-HT_{1B/1D} agonism 69
 - 5-HT_{2B} receptor 15, 50, 58, 61, 62
 - blocker 285
 - 5-HT_{2C} agonist 62
 - 5-HT₃ channel 51
 - 5-HT_{2C} receptor 58
 - 5-HT₂/Dopamine D2 Link 65
 - 5-HT₃/5-HT₄ receptor links 63
 - gastrointestinal and antiemetic indications 63–65
 - 5-HT pharmacology 57
 - 5-HT₁₋₇ receptor families 57, 65, 66
 - 5-HT₃ receptors 58, 59
 - 5-HT₄ receptors 59
 - 5-HT releasers 61
 - 5-HT syndrome 58, 59, 69
 - 5-HT transporter 57, 70
 - in depression 70
 - human adrenal corticocarcinoma cell line H295R model 440
 - human embryonic stem cells (hESCs) 137
 - human leukocyte antigen (HLA) 375
 - human oxytocin receptor 35
 - Huntington's disease 469
 - hydergine 60
 - hydrazine 89
 - derivatives, of pyridine carbonic acids 85
 - hydrophobic aryl ring 415
 - hypercholesterolemia 375
 - hyperprolactinemia 461
 - hypophosphatemia 379
 - hypothyroidism 341, 377–379, 378
 - KI-induced 378
 - hypoventilation 211
 - hypoxia 211
 - Hy's law 89, 112
- i*
- ICD-9 codes 27
 - “idiosyncratic” adverse reactions 4
 - idiosyncratic DILI (iDILI) 373
 - dose-response relationships 128
 - ILD-like effects 388
 - imatinib 346, 355, 356, 359, 402, 403, 408
 - BCR-ABL fusion protein 371
 - chronic myeloid leukemia (CML) 403
 - CML, treatment of 371
 - hypothyroidism 377
 - -resistant gastrointestinal stromal tumor (GIST) 371
 - therapy 388
 - toxic side effects 403
 - immune-mediated hepatotoxicity 144, 145
 - inflammatory cofactors, use of 145, 146
 - innate immune system
 - – and inflammasome 147, 148

- inadvertent hERG binding function, causes
 - of 305
 - electrostatic attraction with ion conduction pathway 305
 - predicted solvation properties of ion conduction pathway 305, 306
- I_{NaL} blocking agents 259
- indirect modulation, of I_{NaF} 264, 265
- indomethacin 32
- induced pluripotent stem cells (iPSCs) 139, 246
- inferring adverse reactions 31
 - finding side effects sans targets 33
 - from off-targets to antitargets 31
 - systematic antitarget prediction and testing 32, 33
- inflammasome 147, 148
- INH-induced hepatitis 87
- INH prophylaxis 88
- innate immune system 147
- Innovative Medicines Initiative MIP-DILI 114
- inotropy 203, 204, 215, 219
 - and ventricular function 203
- interstitial lung disease (ILD) 388
- intracellular Ca^{2+} homeostasis 246
- intrinsic inotropic state 214
- in vitro* pharmacological data 45
- in vitro* safety pharmacology 4
- iodine uptake 378
- ipatasertib 427
- ipilimumab 358
- isoniazid 85, 86, 138
 - derivatives, chemical structures of 89
- isonicotinic acid 85
- isonicotinyl hydrazide 85
- isotope-labeled ligands 53
- isovolumic systole 214
- itraconazole 218

- j**
- JAK signaling 407
- JNK inhibition 376

- k**
- keratin 18 (K18) 112, 116, 117
- kidney 20, 114, 220, 283
 - failure 342
 - KIs affect 389
 - problems 344
 - toxicity 389
- kinase, clinical evidence
 - animal genetics – KO (OMIM) 9
 - animal toxicity 9
 - human safety (information based on FDA label) 9
 - target 9
- kinase inhibitors 10, 12, 21, 354
 - adverse effects of 372
 - bone toxicity 379–380
 - cardiovascular toxicity 380
 - clinical safety of 371–372
 - cutaneous toxicity 380–383
 - gastrointestinal toxicity 385
 - hematopoietic toxicity 385–387
 - hepatic toxicity 372–373
 - non-kinase target-related promiscuity of 11
 - ocular toxicity 387–388
 - pulmonary toxicity 388–389
 - renal toxicity 389
 - reproductive toxicity 383–385
 - thyroid toxicity 377–379
 - tooth toxicity 379–380
 - toxicity, derisking strategies 389–391
- kinase insert domain receptor (KDR) 47
- kinases 405, 406
 - in disease, commonly targeted 338–340
 - involved in cardiovascular risks 9
 - signaling 365
- kinome 334
- KI-related cutaneous toxicities 381
- KI therapy 384
- knowledge-based fingerprints 24
 - performance of 24
- Kupffer cells 129, 148
- Kyoto Encyclopedia of Genes and Genomes (KEGG) 28

- l**
- lacidipine 245
- lactic acidosis 129
- lamotrigine 472
- lapatinib 388
 - ditosylate 8
 - -induced, in serum ALT 375
- large-molecule inhibitors of kinase pathway, approved 334
- late (or residual or slow) sodium current (I_{NaL}) 259–261
- lecozotan 465
- left atrial pressure (LAP) 209
- left ventricular ejection fraction (LVEF) 401
- left ventricular end-diastolic pressure (LVEDP) 215, 216

- increase in 216
- indicator of preload 216
- left ventricular pressure (LVP) 205, 210
 - signal 446
- lercanidipine 245
- levodopa 461
- levofloxacin 146
- Lewy bodies 471
- life-threatening serotonin syndrome 69
- lipophilic drugs 128
- lipopolysaccharide (LPS) 146
- lisuride 62, 461
- liver biopsy 109, 113
- liver damage 125, 127
- liver-derived cell lines 135
 - HepaRG cells 136
 - HepG2 line 135
- liver failure 87, 88, 94, 108, 110, 113, 117, 127, 128, 184, 374
- liver function tests 127
 - monitoring 127
- liver injury 128. *See also* hepatotoxicity
- liver-like model, *in vivo* hepatotoxic
 - liability 377
- liver necrosis 127
- liver safety data management tool. *See* eDISH programming
- liver tests 88
- logging capability 30
- long QT syndromes (LQTS) 244, 256, 257
 - congenital, SCN5A mutations related to 256
 - sodium channel inactivation 260
 - gain-of-function mutations 260
- lorcaserin 62
- low-density lipoprotein cholesterol (LDL-C) 444
- lowest level term (LLT) 48
- LQTS. *See* long QT syndromes (LQTS)
- L-type Ca channel 447
 - antagonists 439
 - mRNA levels 440
- Lucentis 334
- lumiracoxib 143
- lusitropy 207, 209, 214
 - definition 207
 - importance 207
 - incompetence 211
 - manifestation(s) of 208
 - modified Wiggers diagram 208
 - negative state 210
- lysine–glutamate pair 418

m

- mAb kinase inhibitors 12
- macrophage receptor with collagenous structure (MARCO) 450
- macrophages 450
- Macugen 334
- major depressive disorder (MDD) 70
- MAO inhibitors 57, 69, 70
- MAPK pathway 414
- MATLAB computing platform 173
- maximum tolerated doses 127
- MDL keys 24
- MedDRA. *See* Medical Dictionary for Regulatory Activities (MedDRA)
- Medical Dictionary for Regulatory Activities (MedDRA) 4, 46
 - association of ADRs with targets 49
 - correct use of terminology, at different phases 48–50
 - high level group term (HLGT) 47
- MEK inhibitor 340, 387, 388, 407
- melfalan 401
- meromyosin cross-bridges cycling 206
- metabolomics 27
- MetaCyc 28
- (±)-3,4-methylenedioxymethamphetamine (MDMA) 466
- methylergonovine 62
- methyl group 420
- microRNA-122 (miR-122) 112, 117, 118
- microRNAs (miRNAs) 285
- midazolam, coadministration 374
- mitochondrial DNA 129
- mitochondrial toxicity 161, 175, 179–181
 - troglitazone-induced 161
- mitoxantrone 401, 402
- mitral valve 209
- model compounds 309, 310
- models to mitigate hepatocyte
 - dedifferentiation 140
 - liver slices 140, 141
 - selective engineering of metabolism 141–144
- modifying factors, for data interpretation 52, 53
- molecular descriptors (fingerprints) 23
- molecular interactions 20
- monoamine oxidase 468
 - inhibitors (MAOIs) 466
- monoamine oxidases A and B (MAO A and B) 57
- monoamine transporters 70
- monoclonal antibodies (mAbs) 3, 404

- MTD robust PD effects 427
 mTOR inhibitors 388
 multidrug resistance-associated protein 2 (MRP2) 161
 multikinase inhibitors 19
 multiple kinase nodes 358
 multiscale inquiry, resources for 25
 – adverse reactions as drug-induced diseases 29, 30
 – functional and biological annotations (diseases) 27, 28
 – ligands to targets 25
 – perturbing biological systems (phenotypes) 25, 27
 multiscale models, of adverse drug reactions 30, 31
 multitarget virtual screening 23
 mutations
 – of BRAF gene 414
 – BRaf V600E 357
 – EGFR 357
 – hyperactivated BCR-Abl 357
 – in K18 117
 – kinase inhibitors treating resistance 357
 – SCN5A mutations related
 – – to congenital long QT syndromes 256, 257
 myocardial contraction 205
 – mechanism of 204
 myocardial fibers 205
 – contractility estimation 204, 205
 – from pressure–volume loop 206, 207
 myocardial hypoxia 209
 myocardial infarction (MI) 280, 281, 403
 myocardial oxygen consumption (MVO₂) 205
 myocyte 236, 239, 256–258, 267, 280, 448
 – damage 409
- n**
- NA/5-HT uptake blockers 59
 Na–K ATPase 264
 natriuretic peptides (NP) 282–285
 – ANP and BNP, role in 283
 – in anthracycline-induced cardiotoxicity 284
 – BNP and NT-proBNP assays 283–285
 – membrane receptors for 283
 – role in diagnosis and monitoring of 284, 285
 natural killer T (NKT) cells 148
 nausea 5, 51, 71, 341, 343, 345, 459, 463, 470, 472
 NC-IUPHAR Committee 464
 NCX blockers 219
 NET. *See* norepinephrine, transporter (NET)
 networks, of known and new target activity 21
 neural-type voltage-gated calcium channel 471, 472
 neurokinin 1 (NK1) receptor antagonist 285
 neurological disorders 458
 neuronal nicotinic receptors (nAChRs) 469–471
 NeuroTox 30
 neurotoxin 259
 neurotransmitters 468
 new molecular entity (NME) 4
 niacin 85
 nicardipine 245, 402
 nicotinic $\alpha\beta 2$ 471
 nicotinic acetylcholine receptors
 – agonists/activators of 470
 nicotinic acid 85
 nicotinic receptor agonists 470
 nifedipine 245, 445
 nilotinib 346, 401
 – cardiotoxicity 401
 – causes anterior chamber 388
 – CML, treatment of 371
 nimodipine 245
 nisoldipine 245
 nitrendipine 245
 nitric oxide (NO) bioavailability 442
 nivolumab 358
 Nod-like receptors (NLRs) 147
 nonalcoholic steatohepatitis (NASH) 117
 nonclinical testing, of drugs 217
 non-dihydropyridines 245
 non-kinase target-related promiscuity, of selected kinase inhibitors 11
 non-oncology indications 403
 non-small cell lung cancer (NSCLC) 403
 nonsteroidal anti-inflammatory drugs (NSAIDs) 372, 472
 nontoxic diacetylhydrazine 89
 norepinephrine 69, 213, 470
 – transporter (NET) 468, 470
 norfenfluramine 53, 62
 NP. *See* natriuretic peptides (NP)
- o**
- obsessive compulsive disorder (OCD) 70
 ocular toxicity
 – mechanistic basis 387–388
 – preclinical evaluation of 388
 OFFSIDES and TWOSIDES datasets 30
 “off-target” activity 20
 off-target promiscuity 53
 olanzapine 58, 67, 70, 466
 oncogenesis 404

- oncology 358, 360
- Online Mendelian Inheritance in Man (OMIM)
 - reports 28
- opioid 472
- organic anion transporters 159, 160
- organic anion transporting polypeptide (OATP) 159, 160
- organic cation transporter 1 (OCT1) 161
- organ transplantation 163
- oxcarbazepine 472
- oxidative stress 110, 129, 133, 260
- oxytocin 465
 - receptor 35
- P**
- pacemaker 235
- PAI-1 inhibitors 220
- palliative medications 358
- pancreatic carcinomas 420
- panic disorder 70
- panitumumab 7, 8, 334
 - adverse effects/toxicity 8
 - *-k*-RAS 27
 - ventricular dysfunction 406
- para*-aminosalicylic acid 86
- Parkinsonian heart 52
- Parkinson-like syndrome 461
- Parkinson's disease (PD) 458, 461, 468
- paroxetine 69, 70, 467
- patch clamp techniques 258
- pathogen-associated molecular patterns (PAMPs) 147
- pazopanib 375
 - coadministration 374
 - hypothyroidism 377
 - -treated patients 375
- PDE3 inhibition 50
 - data 50
 - effects of 50
- PDGFR KI-mediated inhibition of 378
- PDGFR kinases 371
- pegaptanib 334
- pegaptinib 383
- pergolide 58, 461
- pericardial pressure 205
- pericytes 19
- Perjeta 334
- peroxisome proliferator-activated receptor γ (PPAR γ) 19
- pertuzumab 334
- pharmacokinetics 27, 45
 - data 223
 - properties 440
 - warfarin–CYP2C9, 27
- pharmacological interaction 3
- pharmacological profiling, *in vitro* functional tests 221
- pharmacological promiscuity
 - of antihypertensive drugs 10
 - of marketed drugs 9
- pharmacology modeling 173
- pharmacovigilance analysis 12
- Phe595, backbone NH 418
- Phe583/Gly593, in B-Raf 419
- phenoxypyridine moiety 422
- phone's embedded sensors 30
- phosphate donor substrate 370
- phosphodiesterases (PDEs) 235
 - inhibitors 203
- phospholipase C (PLC γ) pathway 420
- physiologically based pharmacokinetic (PBPK) model 173
 - for telmisartan 189
- PI3K–Akt–mTOR pathway 424
- pimavanserin 66
- pimobendan 218
- pioglitazone 176, 184, 186, 187
- PKA-dependent phosphorylation 264
- platelet aggregation 32
- platelet-derived growth factor receptor (PDGFR) 52
- pleural or pericardial pressure (P_{pl}) 205
- plexxikon 356
- p38 MAP kinases inhibition 415
- polychlorinated biphenyls (PCBs) 449
- polychlorinated compounds 449
- polyfluorinated compounds 449
- polypharmacological compounds 20
- polypharmacology 355
 - by serendipity 20
- polypharmacy 9
- ponatinib 346
- positron emission tomography (PET) 468
- postmarketing pharmacovigilance 6–8
- posttranslational modifications 256, 258
- potassium channel openers 203
- potent CETPi vs. halogenated hydrocarbons 449–451
- pramipexole 461
- predicting drug off-targets
 - by statistical chemical similarity 21
 - – similarity ensemble approach 21–23
 - – structure-based virtual screens 23
- prediction of mechanisms 33
- Predictive Safety Testing Consortium (PSTC) 109, 113

- pregabalin 472
- pregnanc 383
- proarrhythmia for drugs 254
- progesterone metabolites 161
- prolactin 465
- Protein Data Bank 20
- protein degradation 256
- protein kinase B (PKB) pathway 420
- protein kinases 365
 - adenosine triphosphate (ATP) 365
 - inhibitors 413
 - mutations and dysregulation 365
- protein P08588, 28
- protein phosphatases 235
- proteomics 27, 28
- prothrombin 96, 112
- proton pump inhibitor 33
- Prozac 22
- pseudoephedrine HCl 14
- pseudolarix acid B 34
- psychotropic agents 10
- PTEN-null xenograft models 424
- public databases 29
- public–private consortia 109
- PubMed 373
- pulmonary edema 211
- pulmonary toxicity 388–389
- Purkinje fibers 258
- pyrazinamide 86
- pyridinylpyrazoles 414
- pyrrolopyridine analogues 426
- pyrrolopyrimidine template 424

- q**
- QTc prolongation 403
- “quantified self” movement 30
- quantitatively “fingerprinting” compounds, by
 - phenotype 34
 - HCS data 34
- quantitative structure–activity relationship (QSAR) methods 33
- quantitative systems pharmacology
 - analyses 28, 36
- quetiapine 66, 67
- quinazolines 414, 424, 425
- quinoline 34

- r**
- rabeprazole 33
- RADIANCE data
 - *post-hoc* analysis of 446
- Raf-1, heart-specific knockdown 407
- Raf inhibitor 407
- Raf isoforms 415
- ranibizumab 334
- ranitidine 145, 146
- rapamycin 356, 359, 387
- Ras/Raf/MEK/ERK (MAPK) signal
 - transduction pathway 414
- Rauwolfia serpentina* 469
- reactive oxygen species (ROS) 376
- receiver operating characteristic (ROC)
 - analysis 285
 - curves 98
 - hypothetical biomarker 99
 - miR-133a 285
- receptor–drug gaps 22
- receptor kinases 19
- regulatory guidance, on testing of drugs
 - animal models focusing on cardiovascular effects 218
 - data from nonclinical studies 218
 - drug-induced alterations in QT of infrahuman mammals 218
 - ICH S7A guidance 218
 - in models of general or safety pharmacology 217
 - toxicology studies 218
- renal cell carcinoma (RCC) 346, 371, 403
- RenalTox 30
- renal toxicity 389
- renin–angiotensin–aldosterone system (RAAS) 442, 443
- renin behavioral syndromes *in vivo* 465
- representing drugs, computationally for rapid
 - comparison 23
- reproductive toxicity
 - clinical management of 384–385
 - developmental 383
 - preclinical evaluation of 384
- Rescriptor 22
- reserpine 469
- RET
 - KI-mediated inhibition of 378
 - kinase inhibitors 19
 - proto-oncogenes 52
 - thyroid toxicity 378
- retinal vein occlusion (RVO) 388
- rheumatic disease 359
- rheumatoid arthritis (RA) 331, 356, 372
 - Janus kinase inhibitors tofacitinib 413
- rifampin 86
- rimonabant
 - cannabinoid CB1 receptors 463
 - FAERS data segment representing psychiatric disorders 463

risk assessment 219, 221–224
 – matrix 223
 risk management 224, 225
 risk mitigation 219, 225–227
 risperidone 58, 67, 466
 rizatriptan 68
 rosiglitazone 19
 ruxolitinib 356

S

Safer and Faster Evidence-Based Translation (SAFE-T) consortium 109, 110, 113
 safety assessment, within drug development 109
 SB-204,741, antihypertrophic effect 284, 285
 SB-216,763, glycogen synthase kinase inhibitor 285
 schizophrenia 66, 458, 470
 – treatment-resistant 466
 Scitegic's Extended Connectivity FingerPrint (ECFP) 23, 24
 SCN5A gene 255
 SEA. *See* similarity ensemble approach (SEA)
 sedation 460
 Seldane 279
 selective 5-HT_{1B/1D} receptor agonist 67, 68
 selective platelet-derived growth factor receptor (PDGFR) inhibition 331
 selective serotonin/norepinephrine reuptake inhibitors (SNRIs) 69
 selective serotonin reuptake inhibitors (SSRIs) 22, 27, 69, 71, 465
 SERCA blockers 219
 serine–threonine kinase 424
 serotonergic system 467
 serotonin 57
 – 5-HT_{1A} receptor (HTR1A) 464–465
 – syndrome 60, 466
 – – symptoms 71
 – transporter 14, 53, 467, 470
 – – polymorphism 467
 – – SLC6A4, 466–467
 sertraline
 – suicidal ideation in teenagers 467
 serum aspartate aminotransferase (AST) 87, 88
 serum hepatocellular enzyme 88
 SH2 peptides 391
 sibutramine 5-HT reuptake inhibitor 468
 Side Effect Resource (SIDER) 29
 SIDER's prevalence data 30
 signal transduction 28
 silibinin 160
 similarity ensemble approach (SEA) 21–23, 35
 – predictions on human pharmacological data 35
 Similarity Metrics 24
 SimPopsTM simulation 173, 188
 – ALT elevations 189
 – ATP loss in telmisartan-treated 190
 – for bosentan and telmisartan 188
 – minimum average liver ATP 189
 – PK variability 189
 single-nucleotide polymorphism (SNP) 27
 – gene coding for glycine dehydrogenase 27
 – glycine dehydrogenase SNP's association with citalopram 27
 sinoatrial (SA) node 235
 sirolimus 384, 388
 skin graft 402
 skin lesions 383
 skin physiology 381
 SLC6A4 gene 466
 SLC18A2 gene 468
 small-molecule inhibitors of kinases
 – approved 332, 333
 – phase II and III, late-stage 335–337
 – properties, approved 348–353
 – side effects, approved 341–346
 small-molecule KDR inhibitors 47
 small-molecule kinase inhibitors
 – adverse effects 366–369
 smoking cessation 471
 smooth muscle contraction 465
 social media 36
 sodium channels 255, 259
 – cardiac, evidence for multiple functional types 257, 261
 – heterogeneous distribution 257
 – neuronal-type 261
 – noncardiac-type 260
 – voltage-gated 261
 sodium homeostasis 255
 sodium taurocholate cotransporting polypeptide (NTCP) 159, 160
 solubility 45
 Sonic hedgehog 379
 sorafenib 356, 407
 Sprague-Dawley rats 377, 444
 Src family kinases 377
 SSRIs (selective serotonin reuptake inhibitors) 57
 staurosporine 359
 steatohepatitis 129
 sterile inflammation 129, 147

- steroid hormone mimetic (SHM-1121X) 443
- steroid hormones 439
- Stevens–Johnson syndrome 374
- stiffness 205
- streptomycin 86
- stroke volume (SV) 205
- structure–activity models 128
- structure–activity relationship (SAR) 221, 359, 414
 - methods 45
- structure-based pharmacophores 23
- structure-based virtual screens 23
- sudden cardiac arrest (SCA) 254
- suicidal behavior 457
 - serotonergic system 467
- suicidal ideation, with D₁ and D₅ antagonists 460
- suicidal intent 458
 - in adolescent
 - – ADHD (atomoxetine) 467
 - G-protein-coupled receptors 458
 - – dopamine D_{1/2} receptors (DRD1/2) 458–464
 - – 5-HT_{2A} (HTR2A) 465–466
 - – serotonin (5-HT_{1A}) receptor (HTR1A) 464–465
 - neural-type voltage-gated calcium channel 471, 472
 - neuronal nicotinic receptors (nAChRs) 469–471
 - norepinephrine transporter (NET) 468
 - serotonin transporter (SLC6A4) 466–467
 - targets 458
 - vesicular monoamine transporter (VMAT2) 468–469
- suicidality, targets associated 459, 460
- sulfanilamide 86
- sumatriptan 58, 68
- sunitinib 11, 19, 47
 - antithyroid autoantibodies 378
 - hypothyroidism 377
 - renal cell carcinoma 408
- symptoms
 - determination, associated with a target 50–52
 - organ-based classification
 - – and biomarker behavior 46, 47
- synergy 53, 355
- synthetic behaviors 35
- systemic arterial pressure 211
 - afterload 212, 213
 - – estimated by 213
 - – important for 213
 - components 211, 212
 - importance 211
- system organ class (SOC) 45, 46
- systolic function 205
 - and inotropy 205, 206
- systolic pressure 212
- t**
- tacrine 112
- TALE proteins 220
- Tanimoto coefficient (Tc) 24
- tardive dyskinesia
 - D₂ agonists 460
 - tetrabenazine 469
- target–ADR network 47, 48
- target interactions 53
- targets associated
 - with possible ADRs, in particular organ class 48
 - with suicidality 459, 460
- T-cells 129, 144
 - function 387
- telemetry 214
- telmisartan 12, 14, 176, 184, 187–190
- temsirolimus 388
- terfenadine 279
- test validation, and qualification 100, 101
- tetrabenazine 469
 - extrapyramidal disorders 469
- δ-9-tetrahydrocannabinol (THC)
 - CB1 receptor 463
 - sensory perception 463
- 1,2,3,4-tetrahydroquinoline scaffold 440
- tetrodotoxin (TTX) 259
 - -sensitive (non-Nav1.5) isoforms 257
- TGZ-mediated hepatotoxicity 186
- thiosemicarbazones 86
- THLE cell lines 142
 - parental 141, 142
- Thr211 Akt1 possesses 425
- thrombotic microangiopathy 47
- thyroid gland 378
- thyroid hormones 378
 - replacement therapy 377
- thyroid toxicity 377
 - clinical management of 378–379
 - mechanistic basis of 378
- Timothy syndrome 247
- TLR4 receptors 147
- tofacitinib 356, 359, 387
- tolcapone 143
- toll-like receptors (TLRs) 146, 147
- tooth toxicity 379–380

- torcetrapib 439
 - on aldosterone production *in vitro* 439
 - blood pressure, effect of 437, 438, 441
 - chemical structure, and physicochemical properties 438
 - ILLUMINATE study 438, 441
 - *in vitro* studies 438
 - *in vivo* cardiovascular safety studies 444
- torcetrapib-induced BP
 - molecular mechanisms of 444–447
- torsade de pointes arrhythmia (TdP)
 - arrhythmia 295
- total bilirubin (TBL) 87, 88, 92, 96, 99, 100, 102, 111–113
- Tourette's disease 469
- Tourette's syndrome 458
- Tox21 4
- ToxCast 4
- toxicity profiles 30
- toxicology 355
- trametinib 340, 356, 388
 - hematopoietic effects 387
- transformation, of antitarget effect into clinical phenotype 51
- translational medicine 358
- translation of effects on I_{NaF} 268, 269
 - relation to conduction velocity and proarrhythmia 268, 269
- translation of nonclinical findings, to humans 217–219
- translation safety biomarkers (TSBM) 110
- transmembrane crystallography 23
- transportation optimization 36
- trastuzumab 9, 334, 404, 406, 407, 420, 423
 - ventricular dysfunction 404
- tremor 5, 29, 32, 53, 459, 460, 466, 469
- triazolopyridine 422
- tricyclic antidepressants 59
- triglyceride 129
- triptans 58, 68, 69
- troglitazone 160
 - induced liver injury 161
 - inhibiting BSEP 161
 - mediated hepatotoxicity 186
- troponins. *See* cardiac troponins
- trovaflaxacin 145, 146
- tuberculosis 87
- Tversky index 24
- tyrosine kinase inhibitors (TKIs) 202
 - congestive heart failure (CHF) 402
 - hepatotoxicity of 373
- u**
 - UDP-glucuronosyltransferase 374
 - ulcerative colitis 372
 - unselective RET kinase inhibitors 19
 - urodilatin 282
- v**
 - validation compounds 143
 - Valine 600 414
 - valproate 472
 - valproic acid 138
 - vandetanib 11, 20, 388
 - varenicline 471
 - vascular endothelial growth factor receptor 1-3 (VEGFR1-3) 52
 - KI-mediated inhibition of 378
 - vascular insufficiency 203
 - vascular necrosis 203
 - vasopressors 402
 - Vectibix 7, 8, 334
 - vemurafenib 356, 407
 - venlafaxine 70
 - veno-occlusive disease 129
 - ventilation 211
 - ventricular action potentials 235
 - ventricular conduction 258
 - ventricular function 204
 - ventricular repolarization 254, 261
 - ventricular tachycardia 247
 - verapamil 52, 53
 - vesicular dopamine 468
 - vesicular monoamine transporter (VMAT2) 468–469
 - inhibition 53
 - knockout mouse 468
 - vilazodone 70
 - viral hepatitis C 98
 - viral infections 96
 - visual disturbance 388
 - voltage clamp-based approaches 258, 259
 - voltage-dependent block 262
 - voltage-gated sodium channels 255, 258
 - voltage-gated T-type Ca channel
 - antagonism 439
 - vomiting 5, 51, 64, 341–345, 459, 460, 467
 - vortioxetine 70
 - v-wave 209
- w**
 - warfarin 27
 - web search prioritization 36
 - whole-organism model systems 33, 34
 - Wnt signaling 137, 379

x

xenobiotics 141
– clearance mechanisms 130
xerosis 381
ximelagatran 127, 375

z

ZD6126, in preclinical models 225, 226
zebrafish 35

– with an orthogonal ligand 35
– in cardiotoxicity studies 410
– –CNS compounds 35
– as a model organism 35
ziconotide 472
zinc finger proteins 220
ziprasidone 67
zolmitriptan 68
Zucker diabetic fatty rat (ZDFR) 442

