

Index

A

- Abatacept, 9, 52–53, 162, 302, 304
- Adaptive autoimmunity, autoantibodies as
 - biomarkers of, 5–7
- ADAR (adenosine deaminases acting on RNA), 117
- Adenovirus, 20, 22, 123
- Adoptive Treg-cell therapy, 284–285
- Age of onset, 39
- AIRE (autoimmune regulator), 50–51, 276
- Alefacept, 41–42, 44, 282, 285, 300, 302
- α cells, lack of autoimmunity to, 86–87
- α -galactosylceramide (GalCer), 67
- Alternative splicing, 121–122
- Anergy, 110, 152–155, 216, 277, 330
- Animal models
 - advancing, 61–75
 - NOD (nonobese diabetic) mice (*see* NOD mice)
- Anti-CD3 antibody. *See also* Teplizumab
 - FcR-nonbinding (FNB), 282–283, 300, 325, 329–332
 - OKT3, 327–331
 - preclinical models advance of next-generation, 329–330
 - second-generation, 330–333
- Anti-CTLA-4 mAb, 265–266
- Antidrug antibodies, 315, 321
- Antigen presentation function, 176–177
- Antigen-presenting cells (APCs)
 - antigen delivery to, 315–316, 320–321
 - autoantigen-specific immunotherapy (ASI) safety, 320–321
 - B cells as, 157–158
 - CD4 and CD8 co-engagement, 202
- Antigens in T1D
 - classification of antigen-specific T cells, 241
 - introduction, 227–229
 - review, 227–242
 - targeted by islet-associated autoantibodies, 229
- Antigen spreading, 311
- Anti-IL-21 monoclonal antibody, 303
- Antisense oligonucleotides, 316
- Antithymocyte globulin (ATG), 8–9, 282, 285, 299–300, 302–304
- APS1 (autoimmune polyglandular syndrome type 1), 50–51
- ASI. *See* Autoantigen-specific immunotherapy
- ATF6, 101–103
- ATG (antithymocyte globulin), 8–9, 282, 285, 299–300, 302–304
- Autoantibodies
 - B cells and, 156–157
 - biomarkers of adaptive autoimmunity, 5–7

- prediction of disease risk, 5–7
- screening, 7

- Autoantigen-specific immunotherapy (ASI)
 - biomarkers, 321
 - challenges to development, 320
 - examples of types developed, 313
 - historical perspective, 312–314
 - key knowledge gaps, 321–322
 - mode of actions, 317–320
 - optimization strategies, 315–317
 - progress in T1D, 314–320
 - review, 311–321
 - routes of administration, 315–316
 - safety, 320–321
- Autoimmune polyglandular syndrome type 1 (APS-1), 276
- Autoimmunity, benign islet, 85–87, 240–241

B

- BabyDiab and Babydiet studies, 24–25
- BACH2, 118
- BAFF blockade, 67, 162
- BANDIT trial, 92
- Baricitinib, 92, 103, 269, 303
- B-cell anergy, 152–155
- B-cell depletion, 283
- B-cell receptor (BCR), 152
- B cells (B lymphocytes)
 - anergy, 152–154
 - as antigen-presenting cells, 157–158
 - association of genetic risk alleles with B cells, 155–156
 - autoantibodies and, 156–157
 - breakdown of B-cell tolerance in T1D, 152–154
 - depletion with rituximab, 161–163
 - evidence for B-cell-targeted treatment stratification, 160
 - introduction, 151–152
 - in pancreatic tissue, 159–160
 - regulatory, 158–159
 - review, 151–163
 - targeted therapeutic strategies, 161–163
- BCR retrogenic mice, 74
- Benign islet autoimmunity, 85–87, 240–241
- β -cell function, clinical interventions to preserve
 - challenges, 296–300
 - sites of action, 301
 - summary of interventions showing efficacy, 300
- β -cell function, markers of, 298–299
- β -cell identity, 138
- β -cell mass, 137–138

Index

- β-cell protection therapies
 - baricitinib, 92
 - combination, 92
 - IFN signaling inhibitors, 92
 - imatinib, 91–92
 - liraglutide, 92
 - verapamil, 90–91
 - β-cell replacement. *See* Islet transplantation
 - β-cell risk genes
 - defective immune system, 116–118
 - IFIH1* (Interferon Induced with Helicase C Domain 1), 116–117
 - MDA5* (Melanoma Differentiation-Associated Protein 5), 116–117
 - PTPN2*, 116
 - β cells
 - biology of, 86
 - cross talk with immune cells, 85–93
 - as easy target for autoimmunity, 118–120
 - as initiator versus contributor to autoimmune attack, 117
 - maturation in vitro, 346
 - role in pathophysiology, 137–138
 - susceptibility to autoimmunity, 86
 - T_{FH} interactions, 202
 - β-cell senescence, 100, 103–105
 - β-cell-specific CD8 T cells
 - as cellular players in T1D pathogenesis, 194–195
 - differentiation, 194–200
 - IL-21 signaling, 202–203
 - phenotypes and functional states, 195–197
 - population heterogeneity, stemness and differentiation, 198–200
 - proposed model of differentiation, 198
 - TOX expression, 197
 - β-cell-specific T cells
 - epigenetic programs, 220
 - functional persistence, 216
 - genetics and epigenetics, 215–222
 - hierarchical order of antigens recognized by, 231
 - β-cell stress
 - β-cell vulnerability, 101
 - clinical agents targeting, 106–109
 - immune surveillance of stressed β-cells, 109–110
 - interactions between responses in T1D, 105–106
 - introduction, 99–101
 - mechanism of immune surveillance, 106
 - review, 99–110
 - senescence, 100, 103–105
 - senolytics, 108–109
 - UPR (unfolded protein response), 101–103
 - UPR targeting agents, 107–108
 - β-cell tolerance, failure of, 2
 - β2m* (β-2-microglobulin), 105
 - BET inhibitors, 104, 108
 - BIM*, 122
 - Biodiversity hypothesis, 27–28
 - Biomarkers
 - application of omics in T1D, 251–253
 - autoantigen-specific immunotherapy (ASI), 321
 - β-cell function, 298–299
 - definition, 250
 - examples in T1D, 250
 - exhausted CD8 T cells as functional, 254–255
 - follicular helper T (T_{FH}) cells, 255–256
 - functional, 249, 252–256
 - pharmacodynamic (PD), 250–251, 254, 315
 - Biomarker signatures, 253–254
 - Biorepository, nPOD, 133
 - B-regulatory (Breg) cells, 158–159, 317
 - Bystander immunoregulation, 311–312, 315, 317, 319, 321–322
 - Bystander suppression, 278–279
- ## C
- Carbonylation, 238
 - Cathelicidin-related antimicrobial peptide (CRAMP), 173, 175, 178
 - Cathepsin D (CatD), 236
 - CD3. *See also* Anti-CD3 antibody
 - CD3ε, 328–329
 - history as target for immune modulation, 327–328
 - CD25, 280, 284
 - CD28, 52, 203, 277–281
 - Cd101*, 64–65
 - CD205, 315
 - CD226, 67
 - CD20 B cells, 160
 - CD40-CD40L, 201–202
 - CD4 T cells
 - antigen specificities, 200–201
 - B cells as antigen-presenting cells to, 157–158
 - benign autoimmunity, 85–87
 - as cellular players in T1D pathogenesis, 194–195
 - differentiation of, 194–195, 200–204
 - differentiation of β-cell-specific CD8 T cells, 200
 - DNA methylation, 219
 - epigenetic modifications, 219–220
 - epitopes, 200, 228
 - HIP-specific, 200–201
 - histone modifications, 219–220
 - NOD mice, 66–70
 - polarization states, 200–201
 - priming and effector phase of CD8 T cells, role during, 201
 - Tregs (*see* Tregs)
 - CD8 T cells
 - B cells as antigen-presenting cells to, 157–158
 - benign autoimmunity, 85–87
 - β-cell-specific (*see* β-cell-specific CD8 T cells)
 - in CPI-DM, 265
 - epigenetic modifications, 220
 - epitopes, 70, 228, 230, 233
 - exhaustion, 53, 193, 195–197, 200, 204, 254–255
 - molecular programs and factors associated with autoimmune CD8 T-cell state, 197
 - NOD mice, 66–73
 - Qa-1-restricted, 89
 - stem-like, 198–200, 204–205

- Celiac disease, 17
 - Cell-free DNA (cfDNA), 252
 - Central tolerance, 50–51, 276–277
 - Checkpoint inhibitor-induced diabetes (CPI-DM)
 - cellular mechanisms, 264–265
 - definition, 262
 - diagnosis, 262
 - epidemiology and natural history, 262–264
 - future opportunities for treatment and prevention, 269
 - genetic determinants, 264
 - insulin therapy, 267
 - mechanisms, 264–267
 - monitoring, diagnosis, and treatment, 267–269
 - NOD mouse studies, 265–266
 - review, 261–270
 - schematic of natural history of, 268
 - selectivity of one CPI versus another, 265–267
 - ChgA, 234
 - Chimeric antigen receptors (CARs), 285
 - Citrobacter rodentium*, 184
 - Citrullination, 121, 237
 - COVID-19, 4, 19
 - Cow's milk, 19, 22, 29
 - Coxsackie B viruses (CVBs), 20, 22, 30, 117, 123–124
 - C-peptide
 - epitopes, 233
 - preservation with rituximab, 161–162
 - relapse as measured by loss, 41
 - response to teplizumab, 332, 334
 - specific CD4 T cells, 233
 - T-cell recognition of, 231–232
 - values predictive for clinical benefits after islet transplants, 298
 - C-peptide (AUC) area under the curve, 7–8, 297–298
 - C-peptide levels
 - as outcomes for drug approval, 297
 - preservation by baricitinib, 92
 - preservation by liraglutide, 92
 - preservation by verapamil, 91
 - progression of diabetes, 7–8
 - CPI-DM. *See* Checkpoint inhibitor-induced diabetes
 - CRAMP (cathelicidin-related antimicrobial peptide), 173, 175, 178
 - Crinosomes, 231
 - Cross talk between β cells and immune cells
 - β -cell susceptibility to autoimmunity, 86
 - extracellular HLA class I forms, 88
 - HLA-E, 89–90
 - introduction, 85–86
 - nonclassical HLA class I molecules, 90
 - outlook, 92
 - PD-1/PD-L1, 88–89
 - receptor/ligand pairs favoring T-cell/ β -cell cross talk, 87–88
 - receptor/ligand pairs inhibiting T-cell/ β -cell cross talk, 88–90
 - review, 85–93
 - surface HLA class I, 87–88
 - CTLA-4 (cytotoxic T-lymphocyte-associated protein 4)
 - anti-CTLA-4 mAb, 265–266
 - CD80 and CD86 blockade, 221
 - immune checkpoint inhibition of, 277
 - CTLA-4 inhibitors, CPI-DM following, 261–262, 265–266, 269
 - CTLA4* locus
 - histone modification of, 219
 - Idd* locus effects, 64–65
 - CVBs. *See* Coxsackie B viruses
 - Cyclosporine, 326–327
 - Cytokine release syndrome (CRS), 328, 333
 - Cytokines
 - proinflammatory, 173
 - UPR influence on production, 101
 - Cytomegalovirus (CMV), 22
- ## D
- Daclizumab, 342
 - DAISY study, 24–25
 - Damage-associated molecular patterns (DAMPs), 171
 - Defective ribosomal products (DRiPs), 5, 121, 238
 - DEFEND-1 study, 333
 - Dendritic cells (DCs)
 - antigen presentation function, 176–177
 - inflammatory cytokines, 173
 - licensing by CD4 T cells, 201–202
 - NOD mice, 67
 - pancreatic islet infiltration, 170
 - secondary immune activation signals, 177
 - Diabetes Control and Complications Trial (DCCT), 8, 297
 - Diabetes distress, 296
 - Dietary factors
 - DIPP study, 23, 27
 - TEDDY study, 21–22
 - DiMe sibling cohort study, 24–25
 - DIPP (Diabetes Prediction and Prevention) study
 - dietary factors, 23, 27
 - infectious agents, 22–23
 - overview, 22
 - summary of findings, 24–25
 - DNA delivery technologies, 312, 316
 - DNA methylation
 - inhibition of, 222
 - overview, 219–220
 - T cells, 221–222
 - Dosing
 - precision, 250–251
 - treat-to-target (T2T) strategies, 251
 - DRiPs (defective ribosomal products), 5, 121, 238
- ## E
- EAE (extrinsic experimental autoimmune encephalomyelitis) model, 316–317
 - EBV (Epstein–Barr virus), 3, 221, 332–333
 - EDIC trial, 8, 297

Index

- Edmonton Protocol, 342–343, 352
Eisenbarth, George, 130, 325
Embryonic stem cells (ESCs), 345, 348, 351–352
Encapsulation
 adaptive rejection and recurrent autoimmunity, 350–351
 biomechanical signals, influence of, 350
 encapsulated PECs (pancreatic endoderm cells), 351
 encapsulated PSC-derived islets, 351–352
 engineering tailored cell transplantation sites, 348–351
 fibrosis response, 348–349
 molecular transport, impact on, 349–350
Endocrine pancreas in T1D, 137–140
Endotypes, 6, 9, 42, 135, 143, 160, 262, 264, 304
End points, 295–298, 305
Enteroviruses
 coxsackie B viruses (CVBs), 20, 22, 30, 117, 123–124
 detection in pancreas, 26–27
 DIPP study, 22–24
 as environmental factors in T1D, 3–4, 15, 19–30
 findings in prospective studies, 20–25
 polio hypothesis, 28
 proving causality, 29–30
 TEDDY study, 4, 20–21, 24
Environmental Determinants of Islet Autoimmunity (ENDIA) study, 142
Environmental factors
 balance between risk and protective factors, 18
 candidate factors, 18–19
 challenges in identification of, 17
 dietary, 21–23, 27
 evidence for influence, 16–19
 explanation for increase in T1D incidence, 27–28
 genetic susceptibility interaction, 38
 infectious agents, 20–23
 introduction, 15–16
 nature of factors that could modulate risk of T1D, 17–18
 pancreas tissue studies, 26–27
 pathogenesis, 2–4, 15–31
 prospective studies, 19–26
 proving causality, 28–30
 review, 2–4, 15–31
 role of, 16
 tolerance loss, 280
EOMES, 216–217, 255
Epidemiology of Diabetes Interventions and Complications (EDIC) study, 8, 297
Epigenetics, 219–220
Epitopes
 enzymatic PTMs, 237
 essential versus nonessential, 240–241
 hybrid insulin peptides (HIPs), 234–236
 indispensability for T cells to respond, 239
 neoepitopes in T1D, 236–238
 nonenzymatic PTMs, 237–238
 pathogenic versus nonpathogenic mimotopes, 238–240
 T-cell hierarchy in T1D, 227–242
Epitope spreading, 311
Epstein–Barr virus (EBV), 3, 221, 332–333
ER stress
 β -cell as easy target for autoimmunity, 118–120
 JAK/STAT signaling, 101–103
 posttranslational modifications (PTMs) of β -cell proteins, 120
 TUDCA as chemical reliever of, 120
 UPR to mitigate, 101–103
ESCs (embryonic stem cells), 345, 348, 351–352
Etanercept, 343
Exocrine pancreas, 140–143
Extracellular matrix, 350
- F**
- FcR-nonbinding (FNB) anti-CD3, 282–283, 300, 325, 329–332, 344
Follicular helper T (T_{fh}) cells. *See* T_{fh} CD4 cells
Forkhead Box P3 (FOXP3), 51–52, 203, 219, 222, 276–277, 286
- G**
- GAD65
 alum conjugated, 314
 autoantibody, 221, 229, 263, 283
 autoantigen-specific immunotherapy (ASI), 314–315
 deaminated, 121
GAD (glutamic acid decarboxylase)
 antibody, 70, 156, 263, 326
 NOD mice, 70, 74
GADA (glutamic acid decarboxylase autoantibodies), 5–6, 9, 21–22, 139, 253
Genetic factors
 CPI-DM, 264
 environmental interaction, 38
 HLA associations, 2, 37–38
 INS associations, 38
 polymorphisms, 2
 single gene mutations, 2
 tolerance loss, 279–280
Genetic risk score (GRS), 2, 7, 251
Genetics
 association of genetic risk alleles with B cells in T1D, 155–156
 basis for T1D development in NOD mice, 63–66
 genetic dysfunctions of innate immune cells, 175–176
 T regulatory cell disorders, 51–52
Genomics, 251
Glucagon, 139
Glucose transporter 1 (GLUT1), 221
Glutamic acid decarboxylase autoantibodies (GADA), 5–6, 9, 21–22, 139, 253
Gluten, 21, 23
G6PC2, 122
Gut
 innate immune dysfunction in, 179–181
 microbiota, 181–182

- ## H
- HbA1c levels
 - IFN signaling, 92
 - islet transplantation, 298, 343, 352
 - outcome assessment, 297–299
 - target levels, 267
 - teplizumab, 331–332, 334
 - Herpes viruses, transient reactivation of chronic, 221
 - HIPs. *See* Hybrid insulin peptides
 - Histone deacetylases (HDACs), 222
 - Histone modifications, 219–220
 - HLA-A, 87–88
 - HLA (human leukocyte antigen) alleles
 - central tolerance, role in, 277
 - CPI-DM, 264
 - DR3, 2, 6, 22, 29, 38, 115, 155–156, 193, 229, 253, 264, 279, 314
 - DR4, 2, 6, 22, 29, 38, 115, 155–156, 229, 253, 264, 267, 279
 - genetic association, 2, 16, 38
 - genetic basis for T1D development in NOD mice, 63
 - humanized NOD mice, 72
 - immune tolerance, influence on, 279–280
 - as risk factor, 115–116, 155
 - HLA-B, 87–88
 - HLA class I
 - cross talk between β cells and immune cells, 87–88, 90
 - extracellular, 88
 - hyperexpression in, 137
 - surface, 87–88
 - up-regulation of surface, 87–88
 - HLA class II
 - aberrant expression in, 137
 - risk-conferring, 101
 - HLA-E, 89–90
 - HLA-F, 90
 - HLA-G, 90
 - Homeostasis, restoration of, 41–44
 - Human Islet Research Network (HIRN), 137
 - Humanized NOD mice, 71–74
 - Human leukocyte antigen. *See* HLA alleles
 - Human Pancreas Analysis Program (HPAP), 139
 - Hyaluronan, 140
 - Hybrid insulin peptides (HIPs)
 - CatD-mediated formation, 236
 - CD4 T cells, HIP-specific, 200–201
 - HIP11, 239
 - neoantigen, 120
 - NOD mice, 69–70
 - role in T1D, 234–237
 - Hygiene hypothesis, 1–3, 27
 - Hypersensitivity reactions, 321
- ## I
- IA2 autoantibodies, 229, 283, 326
 - ICR mice, 62
 - Idd* genes, 63–65
 - IFH1*, 124
 - IFN. *See* Interferon
 - IGRP-specific CD8 T cells, 265
 - IL-2
 - Il2* gene, 64–65
 - muteins, 284
 - therapy, 67, 283–284, 286, 302–303
 - Treg receptor for, 178–179
 - IL-10, 314–319
 - IL10* gene, 317, 320
 - IL-21 signaling, 202–203
 - Imatinib, 91–92, 107–108
 - Immune cells, cross talk with β cells, 85–93
 - Immune checkpoint inhibitor-induced diabetes. *See* Checkpoint inhibitor-induced diabetes (CPI-DM)
 - Immune checkpoint inhibitors
 - of CTLA-4, 277
 - introduction, 161–262
 - of PD-1, 277
 - tolerance breakdown, 39, 123, 277
 - Immune polyendocrinopathy X-linked (IPEX), 51–52
 - Immune-related adverse event (irAE), 256, 262–264, 269
 - Immune suppression, systemic side effects of chronic, 344
 - Immune surveillance, of stressed β cells, 109–110
 - Immune system
 - cross reaction of viral proteins, 124
 - interplay with β -cell in T1D, 115–125
 - islet-infiltrating immune cells, 133–137
 - rebalancing, 275–286
 - Immune system, balanced
 - central tolerance, 276–277
 - introduction, 275–276
 - loss of tolerance in T1D, 279–282
 - peripheral tolerance, 277–278
 - rebalancing in T1D, 282–286
 - Tregs, role of, 278–279
 - Immune tolerance. *See* Peripheral immune tolerance; Tolerance
 - Immunomodulators
 - advanced trail designs, 305
 - broad, 300–302, 304
 - precision, 302–303, 305
 - review, 295–305
 - targeting β -cell–immune systems interactions, 303
 - timing and choice, 303–305
 - Immunotherapy approaches, 300–303
 - Inborn errors of immunity (IEI), 50
 - Incidence increase and environmental factors, 2–4, 16, 27–28
 - Induced pluripotent stem cells (iPSCs), 345, 354
 - Inflammation
 - initiation and amplification of pancreatic, 170–173
 - innate effector mechanisms contributing to response in islets, 173, 175
 - viral infection, 123
 - Inflammatory secretomes, 101
 - Infliximab, 269

Index

- Inhibitory checkpoint blockade, 196, 199, 218, 256
- Innate immunity
- adaptive immunity tolerance against β cells by innate cells in lymph nodes, 177–179
 - antigen presentation function, 176–177
 - distant effect on islet autoimmunity, 179–184
 - dysfunction in the gut, 179–181
 - early recruitment of effectors to islets, 169–170
 - enforcement of immune tolerance by innate cells, 179
 - genetic dysfunctions of immune cells, 175–176
 - initiation and amplification of pancreatic inflammation, 170–173
 - innate cells as direct immune effectors in pancreas, 169–176
 - innate cells as modulators of adaptive immunity in pancreas, 176–179
 - innate effector mechanisms contributing to inflammatory response in islets, 173, 175
 - intra-islet adaptive immunity support by innate cells, 177
 - review, 169–184
 - secondary activation signals, 177
- Innate lymphoid cells, 170
- Innervation, altered pancreatic, 139
- INS genetic association, 10, 38, 155
- Instant blood-mediated inflammatory reaction (IBMIR), 347
- Insulin
- autoantibodies, 229
 - discovery, 341
 - variable number of tandem repeats (VNTRs) gene element, 230–231
- Insulin therapy
- as blessing and a curse, 296
 - CPI-DM, 267
 - difficulty achieving glycemic control, 295–296
- Insulinitis
- micrograph of, 68
 - NOD mice, 62, 66–68, 71–74
- Interferon (IFN)
- HLA-B up-regulation, 87–88, 92
 - IFN- γ , role in CPI-DM, 265, 269
 - signaling inhibitors, 92
 - type I and β -cell stress, 103
- Intestine, alterations of innate immunity in, 181
- Intraportal islet cell transplants, 342, 347, 352
- Invariant NK T cells (iNKT), 67, 105, 109–110, 170, 178, 319–320
- IPEX (immune polyendocrinopathy X-linked), 51–52
- Ipilimumab, 265
- irAE (immune-related adverse event), 256, 262–264, 269
- IRE1 α , 101–103, 106–108
- Islet autoimmunity, benign, 85–87, 240–241
- Islet transplantation
- clinical trials with encapsulated PSC-derived pancreatic grafts, 351–352
 - controlled trials, 343–344
 - effects of environment on PSC-derived graft function, 346–347
 - engineering tailored cell transplantation sites, 348–351
 - evolution of, 342–343
 - future direction, 353–354
 - long-term outcomes, 343–344
 - pluripotent stem cells to manufacture islets, 345–346
 - review, 341–355
 - transplant sites, 347–348
 - universal grafts, 352–353

J

- JAK inhibitor (JAKi), 54, 92, 269
- JAK/STAT signaling
- β -cell stress, 101–103
 - ER stress, 101–103
- Joslin Medalist Study, 8
- Juvenile Diabetes Research Foundation (JD RF), 130

K

- KLRG1, 216, 255

L

- LAG3, 262
- Lantidra, 343
- LFA-3, 282
- Life expectancy, loss of
- Liposomes, 285, 316
- Liraglutide, 92
- Liver-resident invariant natural killer T cells (LiNKT), 319–320
- Longevity of effect, demonstrating, 299–300
- Lyp (lymphoid tyrosine phosphatase), 155

M

- Macrophages
- β -cell death, influence on, 175
 - CVB infections of, 123
 - inflammatory cytokines, 173
 - pancreatic islet infiltration, 170
- Major histocompatibility complex (MHC)
- genetic basis for T1D development in NOD mice, 63
 - humanized NOD mice, 72–73
 - NLRC5 mutation effects, 264
- Makino, Susumu, 62–63
- MDA5 (Melanoma Differentiation-Associated Protein 5), 116–117
- Methylpseudouridine, 316
- MHC. *See* Major histocompatibility complex
- Microbiome
- DIPP study, 22–23
 - influence of, 4
 - innate immunity link, 181–182
 - TEDDY study, 21
- MIDIA study, 24–25
- Mimetic cells, 276
- Mimotopes, 238–240

- Monogenic type 1 diabetes
 - AP51/AIRE, 50–51
 - definition, 50
 - immune dysregulation in, 50
 - introduction, 49–50
 - IPEX/FOXP3, 51–52
 - JAK/STAT pathway defects, 53–54
 - peripheral tolerance defects, 53
 - review, 49–54
- mRNA vaccine, 316
- Mtv3*, 65
- Multiple sclerosis, 3, 283, 296, 316, 321
- Murine models
 - disease progression, 40–41
 - NOD (*see* NOD mice)
- N**
- Nanoparticle (NP) packaging, 235, 312, 315–317, 319–320
- Natural killer (NK) cells
 - invariant NK T cells (iNKT), 67, 105, 109–110, 178
 - pancreatic islet infiltration, 170
- Navacims, 317
- NCG mice, 71
- Neoantigens
 - citrullinated peptides, 121
 - defective ribosomal products (DRIPs), 121, 238
 - formed by alternative splicing, 121–122
 - GAD5, deaminated, 121
 - HIPs, 120
 - PTMs, 120
 - RNA splice variants, 238
- Neoepitopes, 236–238. *See also* Neoantigens
- Network for Pancreatic Organ Donors with Diabetes (nPOD). *See* nPOD
- Neuritis, 71
- Nfkbid*, 64–65
- NIDDK TrialNet, 333–334
- Nivolumab, 265
- NK. *See* Natural killer cells
- NKG2/CD94 receptors, 89
- NLRC5, 264
- NOD mice
 - β -cell senescence, 103–105
 - β -cell-specific T cells, 218
 - benefits of model, 326
 - B lymphocytes in T1D, 151–152, 156–162
 - CD4 and CD8 T cell responses, 194–196, 198–203
 - CD3 antibody studies, 330
 - CPI-DM studies, 265–266
 - disease progression, 40–41
 - DNA methylation inhibition, 222
 - genetic basis for T1D development, 63–66
 - humanized, 71–74
 - insulinitis, 62, 66–68, 71–74
 - origins of, 62–63
 - pathophysiology, 66–71
 - PD-L1 pathway, 89
 - review, 61–75
- NON (nonobese nondiabetic) mice, 63
- Nonobese diabetic mice. *See* NOD mice
- nPOD
 - abnormalities of accessory cells in pancreas, 140
 - antigen specificity of CD4 and CD8 T-cell lines, 232–233
 - biorepository, 133
 - functional analysis of tissues, 139
 - history of genesis, 130
 - introduction, 129–130
 - key questions and future opportunities, 135
 - NOD mice, 67–68
 - organizational structure, 131
 - overview of program, 130–133
 - pancreas processing, 132
 - questions to address going forward, 142–143
 - scientific impact of program, 133
 - T1D immunology, 133–137
 - timeline of program evolution, 134
- NRG mice, 71–72
- NSG mice, 71–72
- Nucleic acid technologies, 315–316
- O**
- Off-target effects, 108–109, 321
- OKT3, 327–331
- Omega-3 fatty acids, 25–26
- Omics
 - applications in T1D, 251–253
 - biology learned from, 253–254
 - introduction, 249
- Otelixizumab, 332
- Outcome assessments
 - in early (stage 1 or stage 2) T1D, 298–299
 - in new-onset (stage 3) T1D, 296–299
- Outcomes, clinically relevant, 296–297
- P**
- PAD (protein arginine deiminase), 38, 43, 237
- Pancreas
 - abnormalities in T1D, 134, 136
 - B cells in tissue, 159–160
 - changes in pancreas morphology and function, 141–142
 - innate cells as direct immune effectors in, 169–176
 - innate cells as modulators of adaptive immunity in pancreas, 176–179
 - size and weight in T1D, 140
 - tissue studies and environmental factors, 26–27
- Pancreas processing schematic, nPOD, 132
- Pancreatic endoderm cell (PEC), 346–348, 351–353
- Pancreatic lymph nodes, innate immunity and, 171, 176–179, 183–184
- Pathogenesis
 - CD8 and CD4 T cells as cellular players in, 194–195
 - environmental factors, 2–4, 15–31
 - epitope hierarchy, 227–242
 - general model, 4–5

Index

- Pathogenesis (*Continued*)
genetic background, 2
implications of studies on initiation and progression, 8–9
introduction, 1–2
progression after clinical diagnosis, 8
review, 1–10
stages of diabetes, 7–8
- Pathophysiology, in NOD mice, 66–71
- Pattern-recognition receptors (PRRs), 101, 171
- PD-1 (programmed cell death 1), 53, 88–89, 277
- PD-1 inhibitors, and CPI-DM, 262, 265–267, 269
- PD-L1 (programmed death ligand 1)
CPI-DM, 262, 265–267, 269
elimination of senescent cells, 109
inhibited by TYK2 inhibitor, 92
inhibition of T-cell/ β -cell cross talk, 88–89
knockin, 353
- PEC (pancreatic endoderm cell), 346–348, 351–353
- PEC-Direct device, 348, 351, 353
- Peptide MHCII (pMHCII), 317, 319–321
- Peripheral immune tolerance
breakdown and repair, 37–45
progression, 38–41
serial loss of, 42–44
susceptibility, 37–38
- Peripheral tolerance, 277–278
- Peripheral tolerance defects, 53
- PERK (pancreatic ER kinase), 101–103, 106, 118–119
- Personalized medicine, 54, 110, 249, 254, 256
- Pharmacodynamic (PD) biomarkers, 250–251, 254, 315
- PLN (pancreatic lymph nodes), as reservoir of stem-like T cells, 198–199
- Pluripotent stem cells (PSCs)
clinical trials with encapsulated PSC-derived pancreatic grafts, 351–352
effects of transplantation environment on PSC-derived graft function, 346–347
future of PSC grafts and devices, 353
to manufacture islets, 345–346
universal grafts, 352–353
- Polio hypothesis, 28
- Polygenic risk score (PRS), 251
- Poly(lactic-co-glycolic acid) (PLGA) microparticles, 315–316
- Posttranslational modifications (PTMs)
citruinated peptides, 121
enzymatic PTMs, 237
ER stress consequence, 120
hybrid insulin peptides, 120, 279
insulin B-chain peptides, 232
neoantigen formation, 120
nonenzymatic PTMs, 237–238
peripheral immune tolerance, 39–41, 43
role of neoepitopes in T1D, 236–238
- Predisposition, genetic, 38–39
- Pre-proinsulin, role in T1D, 230–234
- Prevalence, projected, 3
- Probiotics, 21, 29, 315
- Progression
after clinical diagnosis, 8
implications of studies on, 8–9
NOD mouse strain, 40–41
peripheral immune tolerance, 38–41
stages, 326
- Proinsulin
autoantibodies, 229
expression patterns and processing, 138
- Prospective studies of environmental factors
conclusions from, 26
DIPP, 22–26
importance, 19–26
TEDDY, 19–22
- PROTECT trial, 333–334, 344
- Protégé trial, 332–333
- Proteomics, 253
- Provocative tests, to assess β -cell function, 8
- PRRs (pattern-recognition receptors), 101
- PSCs. *See* Pluripotent stem cells
- PTEN, 155–156
- PTMs. *See* Posttranslational modifications
- PTPN2* (Protein Tyrosine Phosphatase, Nonreceptor Type 2), 116, 155
- Ptpn22*, 65
- pTregs (peripherally induced Tregs), 277–279, 314
- ## Q
- Qa-1-restricted CD8⁺ T cells, 89
- ## R
- Rapamycin, 315
- Rat insulin promoter, 62
- Rebalancing the immune system
B lymphocyte depletion, 283
boosting Tregs, 283–285
future directions, 285–286
next-generation Tregs for T1D, 285–286
purging effectors, 282–283
T-cell depletion and inactivation, 282–283
- Regulatory B cells (Bregs), 158–159
- Regulatory T cells. *See* Tregs
- Rejection, adaptive, 350–351
- Reprogramming T cells, 42, 221–222
- Rheumatoid arthritis, 38, 41, 44, 237, 296
- Rituximab, 66–67, 161–163, 300, 302
- RNA-binding proteins, 121–122
- RNA delivery technologies, 312, 316
- RNA splice variants, 238
- ## S
- SARS-CoV-2, 19, 21, 29, 124–125
- Scottish Diabetes Research Network Type 1 Bioresource (SDRNT1BIO) Study, 297
- SEARCH for Diabetes in Youth Study, 3

- Secondary activation signals, 177
 - Senescence, and β -cell stress, 100, 103–105
 - Senescence-associated secretory phenotype (SASP), 103–105
 - Senolytics, 108–109
 - Sequential multiple assignment randomized trials (SMART), 305
 - Signal transducer and activator of transcription 1 (STAT1), 53–54
 - Signal transducer and activator of transcription 3 (STAT3), 53
 - Single-cell technologies, 100, 105, 125, 205
 - Splice variants, 238
 - Stages of diabetes, 7–8
 - Stem cell–derived islets. *See* Islet transplantation
 - Stem cells
 - embryonic stem cells (ESCs), 345, 348, 351–352
 - induced pluripotent stem cells (iPSCs), 345, 354
 - pluripotent stem cells (PSCs), 342, 345–347, 351–354
 - Stem-like T cells, 193–194, 198–200, 204–205
 - Susceptibility, genetic, 37–38
 - “Swiss” mice, 62
 - Systemic lupus erythematosus, 41, 237
- T**
- Tauroursodeoxycholic acid (TUDCA), 103, 107, 120
 - TBET, 203
 - T-cell differentiation
 - β -cell-specific CD8 T cells, 194–200
 - CD4 T cells, 194–195, 200–204
 - introduction, 193–194
 - review, 193–205
 - spatially restricted in lymph nodes, 199
 - T-cell exhaustion
 - CD8 T cells, 53, 193, 195–197, 200, 204, 254–255
 - chronic antigen exposure, 277
 - as functional biomarker, 254–255
 - low-dose ATG, 282
 - teplizumab, 39, 41–42
 - as therapeutic target, 221–222
 - viral infection, 216
 - T-cell factor 1 (TCF1), 198–199
 - T-Cell Multipotency Index, 220
 - T cells
 - classification of antigen-specific T-cells, 241
 - data from nPOD program, 134–137
 - depletion to rebalance immune system, 282–283
 - DNA methylation, 221–222
 - epitope hierarchy in T1D, 227–242
 - genetic and epigenetics of self-reactive, 215–222
 - heterogeneous autoreactive subsets in T1D, 216–219
 - regulation-resistant effector T cells, 281
 - stem-like, 193–194, 198–200, 204–205
 - Tcf7*, 219
 - TCR (T-cell receptor)
 - antigen specificity of individual, 234
 - CD8 expressed, 233
 - data from nPOD donors, 135, 137
 - humanized NOD mice, 72–74
 - omics studies, 254
 - public, 137
 - self-reactive, 276–277
 - T-cell development, 276
 - TCR affinity, 197, 204, 232, 239–240
 - TCR signal strength, 197, 201, 203–204, 281
 - TEDDY (The Environmental Determinants of Diabetes in the Young) study
 - dietary factors, 21–22
 - environmental factors, 280
 - infectious agents, 20–21
 - order of autoantibody appearance, 229
 - overview, 19–20
 - pathogenesis of T1D, 4, 6, 9
 - proteomics study, 253
 - summary of findings, 24–25
 - transcriptomic study, 252
 - Teplizumab
 - approval of, 100, 325, 334
 - birth of, 330–333
 - as broad immunomodulator, 300
 - C-peptide level increase, 216
 - for delay of clinical T1D diagnosis, 1–2
 - immune tolerance repair, 39, 41–42, 44
 - impact on stem-like T-cell population, 218
 - introduction of, 300
 - in islet transplantation, 344
 - long-term response, 200
 - NOD mouse model, 61
 - rebalancing immune system, 282–283
 - rebirth in prediabetic stage 2 individuals, 333–334
 - reducing T-cell effector functions, 221
 - road map, 335
 - saga, 325–336
 - T-cell exhaustion, 39, 41–42
 - Treg sparing, 285
 - with verapamil, 304
 - Tfh CD4 cells
 - autoantigen-specific immunotherapy (ASI), role in, 317, 319–320
 - as biomarker of worse outcome, 255–256
 - role in pathogenesis, 201–204
 - T helper (T_H)
 - lineages, 201
 - T_H1 CD4 T cells, 202
 - Therapy. *See also specific agents*
 - adoptive Treg-cell therapy, 284–285
 - antigen-specific inactivation of effector cells, 285
 - β -cell stress targeted agents, 106–109
 - B-cell-targeted strategies, 161–163
 - challenges of developing disease-modifying, 296–300
 - clinical immunologic interventions, 295–305
 - combinations, 286, 304
 - epigenetic reprogramming, 221–222
 - harnessing of β -cell protection, 90–92
 - homeostasis restoration, 41–44

Index

Therapy (*Continued*)

- IL-2, 283–284, 286, 302–303
 - immunomodulators, 295–305
 - immunotherapy approaches, 300–303
 - rebalancing immune system, 282–286
 - senolytics, 108–109
 - targets and agents, 93
 - T-cell suppression, strategies for, 220–222
 - tolerization, 42–45, 200, 220–222
 - Treg cells, 203–204
 - UPR targeting, 107–108
- Thioredoxin-interacting protein (TXNIP), 90–91, 101–102, 107, 118, 353
- Thymic negative selection, 67
- TIGIT, 216–217, 255
- TNF. *See* Tumor necrosis factor
- Tnfrs9*, 65
- Tofacitinib, 269
- Tolerance. *See also* Peripheral immune tolerance
- breakdown of B cell, 152–154
 - central, 276–277
 - infectious, 278
 - operational, 314, 316
 - peripheral, 277–278
- Tolerance loss
- environmental factors, 280
 - genetic factors, 279–280
 - regulation-resistant effector T cells, 281
 - Treg defects, 280–281
- Tolerization therapy, 42–45, 200, 220–222
- TOX, 197, 204
- Tr1. *See* T-regulatory type 1 (Tr1) cells
- Transcription factor (TCF-1), 218
- Transcriptomic studies, 251–252
- Transglutaminase 2 (TG2), 237
- Transplantation. *See* Islet transplantation
- Treat-to-target (T2T) strategies, 251
- Tregs
- adoptive Treg-cell therapy, 284–285
 - boosting, 283–285
 - defects, 280–281
 - development and differentiation, 203–204
 - ex vivo expansion, 344
 - mechanisms of suppression, 278
 - next-generation, 285–286
 - peripherally induced (pTregs), 277–279
 - persistence, 280, 284–285, 321
 - resistance to control by, 281
 - role of, 278–279
 - tTregs (thymic), 276, 278
- T-regulatory type 1 (Tr1) cells, 314–321
- TrialNet, 7–8, 344
- TrialNet Pathway to Prevention Study, 326
- TRIGR (trial to reduce insulin-dependent diabetes mellitus in the genetically at risk) study, 18–19; summary of findings, 24–25
- tTregs (thymic), 276, 278, 314
- TUDCA (tauroursodeoxycholic acid), 103, 107, 120
- Tumor necrosis factor (TNF)
- anti-TNF- α , 329
 - CPI-DM, role in, 265, 269
- Twins, identical, 2–3
- TXNIP, 90–91, 101–102, 107, 118, 353
- Type 2 diabetes (T2D), 99–100
- Tyrosine kinase 2 (TYK2) gene, 119
- Tzield. *See* Teplizumab

U

- UPR (unfolded protein response), 101–103, 107–108
- Ustekinumab, 303, 305

V

- Valproic acid, 222
- Verapamil, 90–91, 107, 304
- VER-A-T1D trial, 91
- Viral infections. *See also specific agents*
 - herpes viruses, transient reactivation of chronic, 221
 - innate response triggers, 171
 - T-cell exhaustion, 216
 - triggers of T1D development, 123–125

Z

- ZnT8 (zinc transporter 8) autoantibodies, 229, 283, 326