Index

Note: 'Page numbers followed by "f" indicate figures and "t" indicate tables and "b" indicate boxes.'

Α	Administration costs, 706–707
AABB. See American Association of Blood Banks	Adoption of innovation, 673–674
(AABB)	Adoptive cell therapy, 56, 69–73, 80, 363–364
AAV. See Adeno-associated virus (AAV)	Adoptive T cell therapy, 377–378, 396–397,
Abiraterone, 42	583–584
Abiraterone acetate, 359–360	Adult acute lymphoblastic leukaemia (Adult ALL),
ABR. See Annual bleeding rate (ABR)	309–315
Academia industry partnerships, 344–348	Adult haemoglobin (HbA), 410
Acellular tissue matrix, 248–249	Adult roundworm (Caenorhabditis elegans), 451
Act on Safety of Regenerative Medicine (RM Act),	Adult stem cells, 246–247
132, 133t	AdV. See Adenovirus (AdV)
Activating receptors of NK cells, 95–96	Advanced Biohealing, 652
Activation-induced cell death (AICD), 46	Advanced therapies, 200–201
Acute leukocytic leukaemia, 652–653	affordability of, 708–709
Acute lymphoblastic leukaemia (ALL), 7–8,	Advanced Therapies Manufacturing Action Plan,
304–305, 530, 750	671–672
Acute lymphocytic leukaemia (ALL), 19-20, 508	Advanced therapy medicinal products (ATMPs),
Acute myeloblastic leukaemia (AML), 19–20	587–588, 597–598, 598t, 649, 669–671
Acute myeloid leukaemia (AML), 326-327	regulation, 587–588
AD. See Alzheimer's disease (AD)	Advanced Therapy Treatment Centres (ATTCs),
ADA. See Adenosine deaminase (ADA)	681–682
ADA-SCID. See Adenosine deaminase severe	Advanced Tissue Sciences (ATS), 649-650
combined immunodeficiency (ADA-SCID)	Adverse events (AEs), 325
Adaptimmune NY-ESO-1 programme, 378	AEs. See Adverse events (AEs)
Adaptimmune therapeutics, 332–333, 378	Affinity purification, 614
Adaptive immunity, 493–494	Afibromer technology, 418–419
ADCC. See Antibody-dependent cell-mediated	Ageing, 449–450, 453–455
cytotoxicity (ADCC)	human cell senescence and immortalisation, 452
Adeno-associated virus (AAV), 18, 215-216, 229,	human tissue regeneration regulation, 453-455
286, 291	perspectives, 456–458
AAV-based gene therapy medicinal products,	therapeutic strategies for, 455-456
292	Agency for Healthcare Research and Quality
vectors, 414–415	(AHRQ), 725b
Adenosine deaminase (ADA), 18–19, 659–660	Aggregated hyperphosphorylated tau, 472
deficiency, 287	AHRQ. See Agency for Healthcare Research and
Adenosine deaminase severe combined	Quality (AHRQ)
immunodeficiency (ADA-SCID), 18–19,	AI. See Artificial Intelligence (AI)
715–716, 725b	AICD. See Activation-induced cell death (AICD)
Adenovirus (AdV), 17–18, 286, 288, 291	Alanine aminotransferase (ALT), 415
AdV5, 288	Aldesleukin, 377
Adicet Bio, Inc., 55–56	Alipogene tiparvovec. See Glybera
Adipocytes, 700–701	Alkylamines, 45

Alkylphosphates, 45	Annuity. See Amortisation
ALL. See Acute lymphoblastic leukaemia (ALL);	Anti-CD19 receptor, 747–748
Acute lymphocytic leukaemia (ALL)	Anti-CTLA-4. See Anticytotoxic T lymphocyte
Allen Cell Explorer, 198–199	antigen 4 (Anti-CTLA-4)
Allocation in healthcare context, 591	Anti-HIV CAR-T cells, 633
Allogene therapeutics, 644	Anti-KIR antibody, 43
Allogeneic	Anti-PD-1/PD-L1 therapies, 551-552
allogeneic cell-based therapies, 584	Anti-PD1. See Antiprogrammed death protein 1
bone marrow transplantation, 71	(Anti-PD1)
CAR-T, 637-638	Anti-T cell immunoglobulin 3 (Anti-TIM-3),
cell replacement, 176–177	525-527
MSCs, 10–11	Anti-VEGF bevacizumab, 556–557
NK cells, 110–111	Antibody, 214
transplantation, 124	anti-KIR antibody, 43
off-the-shelf replacement nerve tissue, 278-279	antibody-dependent cellular cytotoxicity,
products, 599-601	118–120
$\gamma\delta$ T cell therapy, 50–51	antibody-dependent NK-mediated tumour
T cells, 700	killing, 118
therapies, 599-601, 602t-604t	DC101, 695–696
treatments, 251	exception, 702
Alpha thalassaemia Major. See Haemoglobin Bart's	KDR-1121, 695–696
ALT. See Alanine aminotransferase (ALT)	Antibody-dependent cell-mediated cytotoxicity
Alternative payment models, 730	(ADCC), 42–43, 95–96, 110–111,
Alzheimer's disease (AD), 216, 469, 708	118–120
therapeutic opportunities for, 470–474	Anticancer immunotherapy development, 103
AMA. See American Medical Association (AMA)	Anticytotoxic T lymphocyte antigen 4
Amazon, 426–427, 756	(Anti-CTLA-4), 525–527
American Association of Blood Banks (AABB),	Antigen, 491–492, 639
727	classes targetable by TCRs, 383t
American Medical Association (AMA), 723b	loading, 496
American Society for Blood and Marrow	processing, 494
Transplantation (ASBMT), 724	Antigen-presenting cells (APC), 490, 525–527
American Society of Clinical Oncology (ASCO),	Antigens, loading-up with, 497–498
43, 305–306	Antiprogrammed death protein 1 (Anti-PD1),
American Society of Haematology (ASH), 305–306	525–527
Aminobisphosphonates (N-BP), 45	'Antiresistance' strategies, 548–550
AML. See Acute myeloblastic leukaemia (AML);	AP. See Artificial pancreas (AP)
Acute myeloid leukaemia (AML)	APC. See Antigen-presenting cells (APC)
Amortisation payment model, 421–423, 729	Approval processes of CAR-T therapy, 772
AMT-060 gene therapy, 416–418	Archaeoglobus fulgidus, 220
AMT-061 gene therapy, 416–418	Artificial Intelligence (AI), 183–200
Analytic hierarchy process, 619	AI for drug discovery, development and
Analytical reprogramming, 456	repurposing, 192f
Angiogenesis, 517–518	deep learning, 187–189
Animal models, 175	machine learning, 186–187
Anisotropy creation in cellular hydrogels, 272–273	neural networks, 188–189
Annual bleeding rate (ABR), 414–415	structured and unstructured data, 189
2017 Annual meeting of American Society for	Artificial pancreas (AP), 158
Hematology (ASH2017), 633-634	Artificial restriction enzymes, 585

ASBMT. See American Society for Blood and	Bacille Calmette-Guérin vaccine, 581
Marrow Transplantation (ASBMT)	Bacteriostatic-bacteriocidal antibiotic, 558-559
ASCO. See American Society of Clinical	Baculovirus, 286
Oncology (ASCO)	BamH1 enzyme, 232
ASCT. See Autologous stem cell transplant (ASCT)	Barriers to innovation, 663-669
Aseptic technique, 257–258, 260	B-associated transcript 3 (BAT3), 100
ASH. See American Society of Haematology	BAT3. See B-associated transcript 3 (BAT3)
(ASH)	4–1BB, 695–696
ASH2017. See 2017 Annual meeting of American	BBSRC. See Biotechnology and Biological
Society for Hematology (ASH2017)	Sciences Research Council (BBSRC)
Asymptote, 655	BCMA. See B-cell maturation antigen (BCMA)
Atezolizumab, 545–547	Bellicum Pharmaceuticals, 605, 635-636, 644
Athersys, 649–651	Benefit-risk assessment, 587
ATMPs. See Advanced therapy medicinal products	Best price, 427
(ATMPs)	Beta cells, 161, 166, 175
ATS. See Advanced Tissue Sciences (ATS)	effective insulin production by, 166
ATTCs. See Advanced Therapy Treatment Centres	endogenous insulin-producing, 157-158
(ATTCs)	pancreatic progenitor cells, 174-176
Autograft replacement, 274–276	T1D recipients and, 161
EngNT to, 276–278	Beta thalassaemia, 411–412
Autologous	cell and gene therapies for, 413t
adoptive cell transfer, 582	Bevacizumab, 545–547
CAR-expressing cells, 700	Big data, 184-200, 185f-186f
CAR-T cell therapies, 753	Big datasets, 190–200
NK cells, 105–110	Allen Cell Explorer, 198–199
products, 397-398, 599-601	automated image analysis algorithms, 199–200
stem cells, 278	business models, 191
T cell therapy, 72–73, 82	working with 'Omics Insights', 191-196
γδ T cell therapy, 49–50	cell barcoding, 198
therapies, 599–601, 602t–604t	deriving genomic insights in oncology, 195–196
developers, 607–608	deriving novel pathway insights, 190–191
transplantation, 123–124	drug
Autologous stem cell transplant (ASCT), 390	discovery and development, 190–191
Autolus, 636, 645	disease interactions, 190–191
Automating, 344–348	Human Cell Atlas, 197–198
Axicabtagene ciloleucel, 377, 583–584, 706–707,	machine learning to predict phenotype of stem
720	cells, 198–199
Azidothymidine (AZT), 559–560	mechanobiology, 199
AZT. See Azidothymidine (AZT)	network linkages, 191
	omics Data to Cell Therapies, 194–195
В	revealer, 195–196
B-cell	single-cell sequencing of large populations,
aplasia, 82–83, 338–339, 639	196–198
lymphoma, 357	structural databases to design molecules, 190
malignancies, 82–83	(Bio)ethical research, 582
CAR-T cell therapy in, 83–84	Biocompatible material, 270–271
B-cell maturation antigen (BCMA), 326–328	BioCurate Pty Ltd. in Australia, 750–751
B2B. See Business to business (B2B)	Bioengineered trachea, 244–245
B2P. See Business to provider/patient (B2P)	Bioengineering, 244

Bioethics, 592–593	Blastic plasmacytoid dendritic cell neoplasm
Bioindustry Association Regenerative Medicine	(BPDCN), 637–638
Industry Group, 681	Bleeding disorders, 413–420
Biological safety cabinet (BSC), 260	Blood oxygen level dependent signal (BOLD
Biologics, 214–215	signal), 474
Biologics, 527-530, 533-536, 565	Blood triglycerides, 716–717
Biologics License Application (BLA), 623	Bluebird Bio, 378, 605, 643
Biomarkers, 340–344, 394–396	Bluebird biosciences, 634
biomarker-based diagnostics, 525	BM. See Bone marrow (BM)
biomarker-based personalised	BMN 270. See Valoctocogene roxaparvovec
medicines, 736	BMT. See Bone marrow transplant (BMT)
current status in field of biomarker use, 344	Body-on-a-chip systems, 561
immune	Boggs chamber, 162
contexture, 396	BOLD signal. See Blood oxygen level dependent
regulation, 395–396	signal (BOLD signal)
predicting efficacy of CAR-T cells, 341-342	Bone marrow (BM), 313
predicting toxicity, 342–344	Bone marrow transplant (BMT), 71, 287, 707
response assessments, 396	BPD. See Bipolar disorder (BPD)
T cells, 396	BPDCN. See Blastic plasmacytoid dendritic cell
target antigen expression, 395	neoplasm (BPDCN)
Biomaterials, 247–256	Brain, 461–462
implanted scaffolds, 248-250	Brazil ANVISA, 358
3D bioprinting, 250	Breakthrough designation, 392-393
acellular tissue matrix, 248–249	Breakthrough Therapy, 325
manufactured scaffolds, 249-250	BrHPP. See Bromohydrin Pyrophosphate (BrHPP)
types in tissue and organ regeneration, 248t	Bromohydrin Pyrophosphate (BrHPP), 42–43,
Biomimetic approach, 272	48–49
BioResource, 660	Bruton's tyrosin kinase, 117
Biosafe Group, 655	BSC. See Biological safety cabinet (BSC)
Biosimulation for disease prevention and	Burden of illness, 718–720
prediction, 198–200	Business models, 191
Biotechnology and Biological Sciences Research	Business to business (B2B), 752-757
Council (BBSRC), 667–668	Business to provider/patient (B2P), 752-757
Bipolar disorder (BPD), 462-465	
and facilitating drug development pipeline,	C
464–468	C-lectin-related genes (Clr genes), 95
lithium reveals BPD brain architectural	C# programming, 622
abnormalities, 469–470	CAB. See Conditionally Active Biologics (CAB)
using lithium to gain insight into, 463-464	Cadaver-derived islets for T1D, 158-159
mania, 468f	Caenorhabditis elegans. See Adult roundworm
research workflow from patient cells to novel	(Caenorhabditis elegans)
proteomic insight, 465f	CALR. See Calreticulin (CALR)
Bispecific T cell engagers (BiTEs), 527-529,	Calreticulin (CALR), 525-527
540-541	Cancer, 69-71, 83-84, 287-288, 515-520. See also
Bisphosphonates, 52	Solid tumour oncology
BiTEs. See Bispecific T cell engagers (BiTEs)	cells, 689
BLA. See Biologics License Application (BLA)	cancer cell-targeting drugs, 117-118
'Black box' opaque, 189, 462	hallmarks, 520-525, 522f-524f
Black swan risk, 6	immunity cycle, 394–395

immunology, 41	CD34+ cell, 104–105
immunosurveillance theory, 581	CD40 receptor, 554–555
immunotherapy, 111, 551	CD44 receptor, 538–539
genome-editing technologies in, 584–586	CD80 receptor, 529
γδ T cells in, 48–53	CD94/NKG2 family, 95
incidence and mortality, 516f	CD123 receptor, 326
inflammation and, 517f	CD133 receptor, 538–539
NK cells and, 94–102	CD138 receptor, 326–327
role in cancer immunosurveillance and	CDMO/CMO industry. See Contract
immunoediting, 100–102	Development Manufacturing Organisation
Cancer Genome Atlas, 195–196	industry (CDMO/CMO industry)
Cancer-testis antigen (CTAs), 332	CDRs. See Complementarity-determining regions
Capacity planning decision-making, 605,	(CDRs)
607–608	CEA. See Carcinoembryonic antigen (CEA)
Capital expenditure (CAPEX), 605	Celgene Corporation, 378, 643
CAR. See Chimeric antigen receptor (CAR)	Cell
CAR-BCMA. See Chimeric antigen	barcoding, 198
receptor-BCMA (CAR-BCMA)	biosimulation for disease prevention and
CAR-T. See Chimeric antigen receptor T cell	prediction, 198–200
(CAR-T)	cell-based products, 747, 778–780
Carcinoembryonic antigen (CEA), 389, 584	
	cell-derived principles, 437
Cardiomyocytes, 251–252	cell-derived therapeutics, 438f
Cardiovascular disease, 287	cell-inspired principles, 437
Carisma therapeutics, 644	in cellular and tissue therapies, 245–247
Carma therapeutics. See Carisma therapeutics	adult stem cells, 246–247
Cartesian approach, 91	ESCs, 246
Caspase 9 (Cas9), 222, 636	perinatal stem cells, 247
endonuclease technology, 585	infrastructure for cGMP Compliance, 260
Catapult Centres, 676, 678t	manufacturing strategies, 52–53, 396–399,
Catapult programme, 669–672	584
CCAM. See Classification Commune des Actes	replacement therapy, 158
Médicaux (CCAM)	suspension infusions, 261–262
CCRM. See Commercialization of Regenerative	Cell and Gene Therapy Catapult, 679
Medicine (CCRM)	Cell death protein 1 (PD1), 331
CD3 zeta chain, 695	Cell Design Labs, 635
CD4+ T cell line, 73–74	Cell therapies, 4–5, 7–10, 250–251, 269, 409–410,
CD4ζ-modified CD4+ and CD8+ T cells,	649–651, 675–676, 708–709, 712–713,
303–304	748, 749f. See also Engineered T cell
CD8 receptor, 74–75	therapy
CD8+T cells. See Cytotoxic T lymphocytes	using cadaver-derived islets and immune
(CTL)	suppression for T1D, 158–159
CD19 (cell surface protein), 326–327, 333–334,	challenges in commercialisation, 599
348–357, 747–748	factors affecting innovation in, 666f
CD19-targeted therapies, 82–83	for haemophilia in preclinical and clinical phases
CD20 receptor, 326	417t
CD22 receptor, 326	innovative payment models, 424t
CD28 (endogenous protein), 76, 80–81, 693,	iPSC as source material for, 173-174
695–696	manufacturing, 261–262
CD33 receptor, 326	payment models for, 764–766, 765t

Cell therapies (Continued)	cGMP. See Current good manufacturing practices
perspectives, 428–429	(cGMP)
potential of immune system	cGTPs. See Current Good Tissue Practices
industry, 54–57	(cGTPs)
obstacles to development and implementation	Checkpoint blockers, 121–123, 529, 531f
of $\gamma\delta$ T cell therapies, 53–54	Checkpoint inhibitors, 559–560
perspectives, 57–58	successes in, 544–547
potential for γδ T cells as primary effectors, $48-53$	Chemistry, manufacturing and controls (CMC), 358–359
regulatory $\gamma\delta$ T cells, 48 $\gamma\delta$ T cells and recognition of malignant	Chemokine (C–X–C motif) ligand 10 (CXCL10), 525–527
disease, 44–58	Chemotherapies, 559-560, 689. See also Cancer
$V\delta1+T$ cells, 46–48	Children's Hospital Of Philadelphia (CHOP),
$V\delta 2+T$ cells, 45–46	315–320
for SCD and beta thalassaemia, 413t	Chimeric antigen receptor (CAR), 69, 73–77, 80,
and value-based pricing implementation in	94, 124, 378–379, 507–509, 583, 747–748
United States, 420–428	CAR-expressing immune cells, 691
Cell Therapy Technology and Innovation Centre	CAR-NK cells, 136, 511, 527–532, 540–541,
(TIC), 660	547, 559–560, 562f–563f
CellChain platform, 757	clinical development status, 136, 139t
Cellectis, 637–638, 644	CAR-functionalised cell therapy in
CELLforCURE in France, 750	glioblastoma, 508–511
Cell-related encephalopathy syndrome (CRES),	Chimeric antigen receptor T cell (CAR-T), 4–5,
393–394	41, 201–202, 224–226, 251, 291, 303,
Cellular biomaterials, 271–272	461–462, 509, 525–527, 530–532, 551, 605,
Cellular Biomedicine Group in China, 750	652-653, 715-716, 747, 778-780
Cellular hydrogels	academia industry partnerships, 344-348
anisotropy creation in, 272-273	access and responsibility, 766-771
stabilisation of aligned, 273-274	allogeneic CAR-T, 637–638
Cellular self-alignment process, 273	arrival of leukapheresis material, 755f
Cellular switches, 635–636	biomarkers, 340–344
Cellular therapy, 83, 659–660	Current Status in Field of Biomarker Use, 344
cells in, 245–247	predicting efficacy of CAR-T cells, 341-342
cellular/tissue apoptosis, 214	predicting toxicity, 342–344
Celularity, 644	cell therapy companies, 640t–641t
Center for Advanced Cellular Therapeutics,	challenges with CAR-T cell therapies, 333-340
750	clinical outcome of CD19 targeted CAR-T cells,
Center for Medicare and Medicaid services (CMS),	306–326
420, 427–428, 723b, 724	clinical trials with, 304–333, 305t
Central nervous system (CNS), 391, 461–462,	collaborating with hospitals, 757–761
507	critical innovation chunks of CAR-T S-Curve,
Central processing unit (CPU), 186-188	9–11, 10f
Centralised payer and provider systems, 728–729	customer/business model, 753–757
Centre for Islet Transplant Registry (CITR),	financing history of leading companies, 642
158–159	first-generation CAR-T therapies, 633–634
Cephalon, 651	for GBM, 509–511
Cetuximab, 119	global clinical development and regulatory
CFRs. See Codes of Federal Regulation (CFRs)	approval, 751–752
CGD. See Chronic granulomatous disease (CGD)	healthcare systems and societal value, 762-763

history, 633	China
incumbents, 642–644	CAR-T cell research in, 348–357
induced toxicities, 335-339	clinical trials, 349t–356t
CRS, 335–338	immune cell therapy development status in,
insertional oncogenesis, 339	132–133, 135t
neurological toxicity, 338	CHOP. See Children's Hospital Of Philadelphia
replication-competent viruses, 339	(CHOP)
on target toxicity, 338–339	Christmas disease. See Haemophilia B (FIX
initial trials of, 303–304	deficiency)
insufficient migration and infiltration, 540-541	Chronic granulomatous disease (CGD), 19–20
limitations in ability, 539–540	Chronic immunosuppressive therapy, 161
manufacturing challenges, 339–340	Chronic lymphocytic leukaemia (CLL), 114,
Novartis journey to, 748–751, 758f	306–309, 307t
optimisation to improve antitumour efficacy, 331	Chronic myeloid leukaemia (CML), 748
patient and clinical value, 762	Chronic obstructive pulmonary disorder (COPD),
payment models for cell and gene therapies,	517–518
764–766, 765t	'Chunk theory' method, 520–521
perspectives, 362–365, 645, 771–773	Chylomicron levels, 716–717
platform, 635–638	CITR. See Centre for Islet Transplant Registry
from process to product, 752–761	(CITR)
regulatory challenges and solutions, 357–359	Claims, 691
research in China, 348–357	Class I HLA molecules, 379–382, 380f
clinical trials, 349t–356t	Class II HLA molecules, 379–382, 380f
rising stars, 644–645	Classical gene editors, 216–218, 217f
safety considerations, 639–642	Classification Commune des Actes Médicaux
in situ reprogramming, 638	(CCAM), 724–726
in solid tumours, 329–333	Clinical manufacturing, translating bench research
therapeutics, 136	to, 256
therapy, 69, 80–81, 583–584	Clinical responsibility, 768
academia/industry collaboration to	Clinical trial application (CTA), 176
commercialising, 345t–346t	
adoptive cell therapy, 69–73	Clinical trial design, 29 Clinical value, 762
CAR, 73–77	CliniMACS Prodigy, 614
clinical trials, 303–304	CLL. See Chronic lymphocytic leukaemia (CLL)
commercial, value and access challenges, 359–362	Closed-loop concept, 158
	Clargenes. See C-lectin—related genes (Clr genes)
perspectives, 83–84	Cluster Analyses, 187
T cell engineering timeline, 70f	Clustered regularly interspaced short palindromic
targeting antigens, 326–329	repeat (CRISPR), 220–221, 292, 582,
transforming T cell therapies into commercial	585
reality, 81–83	systems as genome editing tools, 222–223
viral vector-based gene transfer, 77–80	Clustered regularly interspaced short palindromic
traditional, linear medicine manufacturing and	repeats/CRISPR-associated protein 9
distribution model, 754f	(CRISPR/Cas9), 32–33, 224, 292–293,
value, 761–766	412, 563–564, 582, 585–586, 637–638
workflows, 638–639	collection, 232–233
Chimeric antigen receptor-BCMA	engineered cell-based therapies, 778–780
(CAR-BCMA), 327–328	gene, 196, 222, 332–333
Chimeric DNA, 692–693	as gene editing therapeutic, 227

Clustered regularly interspaced short palindromic	Compassionate use program (CUP), 22
repeat (Continued)	Complementarity-determining regions (CDRs),
nucleases therapeutics, 232, 234t-235t	382
system, 213–214, 221, 477–478	Complete remission (CR), 306
therapeutic formulations, 228-230	Complete response (CR), 633-634
CMC. See Chemistry, manufacturing and controls	Complex integrated automation devices, 263
(CMC)	Concanavalin-A, 52–53
CML. See Chronic myeloid leukaemia (CML)	Conditionally Active Biologics (CAB), 636
CMS. See Center for Medicare and Medicaid	Conditioned media, 443–444
services (CMS)	Conditioning induction regimen, 548–557
CMV. See Cytomegalovirus (CMV)	Consumer loan, 422
CNS. See Central nervous system (CNS)	Contract Development Manufacturing
Codes of Federal Regulation (CFRs), 258	Organisation industry (CDMO/CMO
COGs modelling. See Cost of goods modelling	industry), 654–655
(COGs modelling)	Contract research services, 655
Coley's toxins, 527	Conventional malignant tumour treatments,
Collaborator, 680	558–559
Collagen, 272–273, 275, 278	Conventional textile techniques, 250
Collapsin response mediator protein-2 (CRMP2), 464–468, 470–472	Convergence innovation in inflammation and oncology, 525–530
lithium influences CRMP2 phosphorylation,	Cooley's Anaemia. See Thalassaemia Major
470–474	COPD. See Chronic obstructive pulmonary
methamphetamine treatment effect, 468f	disorder (COPD)
Combination chemotherapy, 548–550	CoreHEM consortium, 717
Combination therapy, 94, 251–252, 559–560. See	Cost analyses, 618
also Gene therapy (GT)	Cost of goods modelling (COGs modelling),
in cancer, 548–557, 549f	606
landscape analysis of targets of anti-PD-1/L1	Cost per m ² estimates method, 616
combination trials, 552f	'Cost-plus' pricing models, 761
with NK cell-based immune therapy, 114-123	Costimulatory
antibody-dependent cellular cytotoxicity,	CD28 as molecule, 80–81
118–120	domain, 75
cancer cell-targeting drugs, 117-118	ligands, 494
checkpoint blockers, 121–123	NKG2D ligation, 46
cytokine combination, 114–116	receptors, 72
radiotherapy, 116–117	'Costs of resistance', 521–523
targeting immune suppressive signalling,	Cotherapies, 698–699
120–121	COX-2 inhibitors. See Cyclooxygenase-2
Combinatorial antigen-sensing circuits, 635	inhibitors (COX-2 inhibitors)
Combined ATMPs, 587	CpG-oligodeoxynucleotides (CpG-ODN), 499
Commercial CAR-T therapies, 757, 768	CPT. See Current procedural terminology (CPT)
Commercial innovation, 752	CPU. See Central processing unit (CPU)
Commercialisation, 243–244, 258, 264–265	CQAs. See Critical quality attributes (CQAs)
of innovation, 674	CR. See Complete remission (CR); Complete
Commercialization of Regenerative Medicine	response (CR)
(CCRM), 655	Cre/loxP system, 477–478
Common Terminology Criteria for Adverse Events	CRES. See Cell–related encephalopathy syndrome
Version 4.0 (CTCAE), 335–337	(CRES)
Comparator selection, 718–720	Crick Centre in London, 676

CRISPR. See Clustered regularly interspaced short	Cytokine(s), 54, 103, 105, 114, 342–343, 490
palindromic repeat (CRISPR)	combination, 114–116
CRISPR/Cas9. See Clustered regularly interspaced	therapy, 377
short palindromic repeats/CRISPR-	Cytomegalovirus (CMV), 510-511
associated protein 9 (CRISPR/Cas9)	Cytoplasmic sensors, 500
Critical limb ischaemia, 722	Cytotherapies, 705, 708
Critical quality attributes (CQAs), 396	Cytotoxic T cells, 303–304
Crmp2-Knockout mouse (CRMP2-KO mouse),	Cytotoxic T lymphocytes (CTL), 41, 492
469–470, 471f	Cytotoxic T-lymphocyte-associated antigen 4
CRMP2. See Collapsin response mediator	(CTLA-4), 122, 545
protein-2 (CRMP2)	Cytotoxicity, 119
Cross-border access of CAR-T therapy, 773	of NK cells, 93
Cross-reactivity, 47–48	
CRS. See Cytokine release syndrome (CRS)	D
Cryopreservation, 755	Damage-associated molecular patterns (DAMPs),
Cryotanks, 755	490, 493
CTA. See Clinical trial application (CTA)	DAMPs. See Damage-associated molecular patterns
CTAs. See Cancer-testis antigen (CTAs)	(DAMPs)
CTCAE. See Common Terminology Criteria for	DAPI. See 4',6-Diamidine-2'-phenylindole
Adverse Events Version 4.0 (CTCAE)	dihydrochloride (DAPI)
CTL. See Cytotoxic T lymphocytes (CTL)	Data
CTL019 cell, 43	mining, 621
CTLA-4. See Cytotoxic T-lymphocyte-associated	privacy of CAR-T therapy, 772
antigen 4 (CTLA-4)	processor, 191
CUP. See Compassionate use program (CUP)	Daudi Burkitt's lymphoma, 46
Curative treatments, payment and reimbursement	DC. See Dendritic cells (DC)
for, 27–28	DC101 antibody, 695–696
Current good manufacturing practices (cGMP),	Deal terms for CAR therapies, 652–653, 653t
161	Deaminase enzymes to Cas9, conjugation of, 226
cell and tissue manufacturing infrastructure for	Decellularisation, 249, 271–272
compliance, 260	Decellularized scaffolds, 248–249
Current Good Tissue Practices (cGTPs), 258	Decentralised payer and provider systems, 728–729
Current procedural terminology (CPT), 723b	Decision makers, 668–669
Customer value, 778–780	Decision making, 668–669
Customer/business model, 753–757	Decision Trees, 187
CXCL10. See Chemokine (C-X-C motif) ligand	Decisions in development lifecycle of cell and gene
10 (CXCL10)	therapies
CXCR3 receptor, 98	assumptions and constraints, 614–616
CYAD-101, 637–638	autologous vs. allogeneic products, 599–601
Cyclic GMP-AMP, 500	cell and gene therapy products, 624t
Cyclin-dependent kinase-5, 472	challenges in commercialisation of cell and gene
Cyclooxygenase-2 inhibitors (COX-2 inhibitors),	therapies, 599
519	critical decisions, 625–626
Cyclosporine, 244	decision variables, parameters and assumptions,
Cystic fibrosis, 288	610–614
Cytokine release syndrome (CRS), 306, 315–319,	decisional or decision-support tools, 598,
335–338, 344, 362–363, 393–394, 532,	606–622, 609f
541-544, 633-634, 639, 759	handling of risks and uncertainties, 619-621
grading scale, 336t	implementation, 621–622

Decisions in development lifecycle of cell and gene	Dimension Therapeutics, 652–653
therapies (Continued)	2,3-Dioxygenase (TDO), 533–536
objectives, 606-608, 607t	'Disease in a dish' approach, 464-465
partnering and capacity planning decisions, 605	Divestment, 601
perspectives, 622–626	DLBCL. See Diffuse large B-cell lymphoma
product withdrawal and divestment, 601	(DLBCL)
regenerative medicine approvals, 600f	DLI therapy. See Donor lymphocyte infusions
'servitisation' of therapies, 625	therapy (DLI therapy)
solution method, 616–619	DMD. See Duchenne muscular dystrophy (DMD)
systems, 608–610	DNA. See Deoxyribonucleic acid (DNA)
techniques and algorithm, 617t	DNA-barcode-Conjugation, 196
Deep learning, 187–189	Donor lymphocyte infusions therapy (DLI
'Defensive' strategies, 548–550	therapy), 51, 303
Delirium, 639	L-dopa, 473–474, 483
Demand goal, 611	Double-chain chimeric antibody receptor, 9–10
Dendritic cells (DC), 44-45, 489, 491f	Downstream operations process parameters,
adaptive immunity, 493–494	611–614, 612f
antigens for presentation, 491-492	DP. See Drug product (DP)
combination therapies, 500-501	DRG. See Diagnosis-related group (DRG)
cross-presentation, 494-495	DRI approach. See Drug resistant immunotherapy
dual function, 492-494	approach (DRI approach)
ex vivo APC generation, 496	Drug
generation of potent, 496-497	combinations, 565
techniques of antigen loading, 497f	developers, 718
in immune system network, dual role of,	development pipeline, 464–468
489–490	discovery and development, 190-191
innate immunity, 493–494	drug/disease interactions, 190-191
initiation of, 492–493	Drug product (DP), 168–169
strategies to employ activated, 496f	Drug resistant immunotherapy approach (DRI
targeting patrolling DC and releasing natural	approach), 56–57
potential, 498–500	Drug substance (DS), 168-169
targeting cytoplasmic sensors, 500	'Drugome' approaches, 563–564
targeting TLR agonists, 498-500	DS. See Drug substance (DS)
therapeutic strategies using, 495	DSM. See Design structure matrix (DSM)
therapy product, 136	Duchenne muscular dystrophy (DMD), 709
vaccine therapy, 377	Duration of effect, 715–716
in vivo antigen loading of, 498	
in vivo expansion of, 498	E
Deoxyribonucleic acid (DNA), 15-16	E:T ratio. See Effector cells versus tumour cells
Design structure matrix (DSM), 618	ratio (E:T ratio)
Deterministic modelling, 619–620	Early ADA-SCID gene therapy, 18–19
Device Master File (MAF), 171–172	Early endosomes, 493
Device optimisation, 164–165	Early gene therapy failures, 19–20
Diabetes, unmet medical need of, 157–158	Early Phase process development, 257
Diagnosis-related group (DRG), 723, 726	Eat-me signals, 489–490, 492
4',6-Diamidine-2'-phenylindole dihydrochloride	EBV. See Epstein-Barr virus (EBV)
(DAPI), 249	ECM. See Extracellular matrix (ECM)
Diffuse large B-cell lymphoma (DLBCL), 321–322,	EcoRV enzyme, 232
324, 357, 583–584, 751	Ectosomes, 439–441

'Edmonton Protocol', 158	EngNT-CTX, 278-279
Effector cells versus tumour cells ratio (E:T ratio),	Enterprise Investment Scheme (EIS), 682, 684
104	Enterprise risk factors, 620
EFT. See Embryonic-foetal transition (EFT)	Environment, 659–663
EGFR. See Epidermal growth factor receptor	Enzalutamide, 42
(EGFR)	Enzymatic agents, 249
EGFR vIII. See Epidermal growth factor receptor variant III (EGFR vIII)	Enzyme replacement therapy (ERT), 19, 290 Epidermal growth factor receptor (EGFR),
EIS. See Enterprise Investment Scheme (EIS)	538–539, 584
Electrospinning technology, 271–272	Epidermal growth factor receptor variant III
ELIANA trial, 756–757	(EGFRvIII), 330–331, 509, 511
EMA. See European Medicines Agency (EMA)	Epimorphosis, 453
Embryo, 269–270	Episode-of-care reimbursement, 723–727
Embryonic stem cells (ESCs), 159, 216, 246	Epistemological revolution, 461–462
Embryonic-foetal transition (EFT), 453	Epithelial-to-mesenchymal transition (EMT), 515
EMT. See Epithelial-to-mesenchymal transition	EPSRC. See Engineering and Physical Sciences
(EMT)	Research Council (EPSRC)
Encapsulation, 161–162, 163t, 176–177	Epstein–Barr virus (EBV), 103
limitations, 165–168	Equipment-factored estimates, 616
macroencapsulation, 162–165	Erlotinib, 548–550
microencapsulation, 162–165	ERT. See Enzyme replacement therapy (ERT)
Encaptra device, 164–165, 165f, 167	Escherichia coli, 220
host vascularisation of, 169f	ESCRT. See Endosomal sorting complex required
ENCODE. See Encyclopaedia of DNA Elements	for transport (ESCRT)
(ENCODE)	ESCs. See Embryonic stem cells (ESCs)
Encyclopaedia of DNA Elements (ENCODE),	Eteplirsen, 717
193–194	EU. See European Union (EU)
Endogenous insulin-producing beta cells, 157–158	European Medicines Agency (EMA), 15, 28–29,
Endogenous MSCs, 10–11	288, 290, 324, 358, 415, 435–436, 479–480,
Endosomal sorting complex required for transport	587-588, 597-598, 634, 673-674, 748
(ESCRT), 439–441	and gene therapies, 30t
Engineered AAV vectors, 18	European Union (EU), 22, 597–598, 653–654,
Engineered immune effector cells, 551, 559–560	673–674
Engineered neural tissue (EngNT), 273–274, 276f,	EV. See Extracellular vesicle (EV)
278	Evidence, 709–710, 712, 718, 728
to replace autograft, 276–278	gap, 768
Engineered Platelet gene therapy for haemophilia	Ex vivo APC generation, 496
A, 419	loading-up with antigens, 497-498
Engineered T cell therapy, 303, 377–378, 401.	Ex vivo delivery, 15–16
See also Chimeric antigen receptor T cell	Exosomal therapy, 439–442
(CAR-T);T cell receptors (TCRs)	Exosome(s)
initial three studies of, 385-389	engineering, 442
MAGE-A3 experiences, 391-392	large-scale manufacturing of, 442
NY-ESO-1 studies, 389–390	Express Scripts, 427–428
perspectives, 399–402	Expressive aphasia, 639
studies without preinfusion conditioning, 392	External cell, 261
Engineering and Physical Sciences Research	Extracellular matrix (ECM), 244-245, 261
Council (EPSRC), 667–668	Extracellular vesicle (EV), 439, 441
EngNT. See Engineered neural tissue (EngNT)	biogenesis, 440f

F	Funding, 664–667
F1 Oncology, 636	FVIII deficiency. See Haemophilia A (FVIII
Facility costs, 616	deficiency)
FACS. See Fluorescent-activated cell sorting	
(FACS)	G
FBC. See Foreign body capsule (FBC)	GammaDelta Therapeutics, Ltd., 56
FCB Pharmicell, 435	Gammavirus, 286
FcγRs receptor, 120	GBM. See Glioblastoma multiforme (GBM)
FDAMA. See Food and Drug Administration	GCN4 (yeast transcription factor), 697-698
Modernisation Act (FDAMA)	GD2, 330–331, 584
FDIs. See Foreign direct investments (FDIs)	GDP. See Gross domestic profit (GDP)
FHCRC. See Fred Hutchinson Cancer Research	GE. See General Electric (GE)
Center (FHCRC)	Gefitinib, 548–550
Financial markets, 668	Genalyte, 638–639
Financial-based risk sharing, 765t	Gendicine, 20, 294t
Financing history of leading companies, 642	Gene therapy (GT), 15–22, 201–202, 285, 409–410,
First-generation CAR-T therapies, 633–634	659–660, 675–676, 708–709, 712–713,
First-generation CARs, 583, 692–693	747–748, 749f, 751–752
design, 74–75	challenges in commercialisation of, 599
T cells, 74–75	companies, 652–653
First-line cancer chemotherapy, 548–550	early ADA-SCID gene therapy, 18–19
Fiscal measures, 681–682	early development, 16–18
FIX deficiency. See Haemophilia B (FIX	vector development, 17–18
deficiency)	early gene therapy failures, 19–20
FIX-Padua, 416-418	European Medicines Agency and, 30t
FL. See Follicular Lymphoma (FL)	factors affecting innovation in, 666f
Flat organs, 262	FDA and, 31t
'Flexible voucher' system, 28	first approvals, 20–22
Fluorescent proteins to Cas nucleases, conjugation	future research funding, 29–32
of, 226–227	for haemophilia in preclinical and clinical phases,
Fluorescent-activated cell sorting (FACS), 196,	417t
614	innovative payment models, 424t
Follicular Lymphoma (FL), 321–322	limited patient population, 28–29
Fondazione Telethon, 22–23	major events in, 33f
Food and Drug Administration Modernisation Act	medicinal products, 293f
(FDAMA), 426–427	payment models for, 764–766, 765t
Foreign body capsule (FBC), 167-168	perspectives, 293–295, 428–429
Foreign body reaction, 167–168	for SCD and beta thalassaemia, 413t
Foreign direct investments (FDIs), 683-684	second innovation wave, 292–293
Foundation for Biomedical Research and	Strimvelis development, 22–28
Innovation, 750	technology, 32–34
Fourth-generation CARs, 697–699	time for success, 290–292
Fraunhofer Institute for Cell Therapy, 750	trials, 649–650
Fraunhofer-Gesellschaft in Germany, 669-671	history, 287–290
Fred Hutchinson Cancer Research Center	and value-based pricing implementation in
(FHCRC), 306, 308–309, 313, 322, 343–344	United States, 420–428
Free market prices, 668	vector types, 286–287
Functional agent, 462	for VWD, 419–420
Functional avidity of T cell, 382	worldwide gene therapy approvals, 21t

Gene Therapy Advisory Committee, 674	Glioblastoma, 47–48
Gene therapy medicinal products (GTMPs), 587	Glioblastoma multiforme (GBM), 507,
Gene transfer, 77	525–527
Gene-based therapies, 7-10, 251	CAR-functionalised cell therapy in, 508-511
Gene-editing	CAR-T therapy, 509-511
approaches, 82	Chimeric antigen receptor, 507–509
and drug discovery, 214	selection of clinical trials deploying, 510t
nucleases, 215	chimeric antigen receptor-functionalised NK
revolution, 233	cell therapy, 511
technologies, 581–582	immunosuppression, 507–508
adoptive T cell therapy, 583–584	GLP. See Good Laboratory Practice (GLP)
findings, 586–591	Glucocorticoid-induced tumour necrosis factor
genome-editing technologies in cancer	receptor (GITR), 533-536
immunotherapy, 584–586	Glybera, 22, 292–295, 294t, 597–598, 751–752
materials and method, 582	Glybera, 706, 716–719
perspectives, 591–593	Glycogen-synthase kinase 3-beta (GSK3β), 472
principle of autonomy, 589-591	O-glycosylation, 530–532
principle of beneficence/nonmaleficence,	GM-CSF. See Granulocyte-macrophage colony
586–589	stimulating factor (GM-CSF)
principle of justice, 591	GmbH, 699
technology description, 582-586	GMP. See Good Manufacturing Practice (GMP)
Gene-modified CD4+ and CD8+T cells, 303-304	Good Clinical Practices, 477–478, 588
Gene-modified cells, 445	Good DNA, 285
Gene-modified haematopoietic cells, 16-17	Good Laboratory Practice (GLP), 171-172,
General Electric (GE), 655	477–478, 588
General practice physician (GP), 722-723	Good Manufacturing Practice (GMP), 103, 278,
Genetic algorithms, 187	442, 477–478, 588, 616
Genetic disorders, 100	Good Tissue Practices, 477–478
Genetic engineering, 82, 700–701	Google, 426–427
tools, 213–214	Google Charts, 622
Genetic modifications, 251	GP. See General practice physician (GP)
Genetically engineered MSCs, 10–11	Graft-versus-host disease (GvHD), 41-42, 94, 251,
Genetically engineered T cell therapy, 69	303, 540–541, 585, 651–652
Genetix Pharmaceuticals, 643	Graft-versus-leukaemia effect (GVL effect), 303
Genome editing tools, 177	Graft-versus-tumour effect, 41–42
Genome-editing approach, 213–214	Granulocyte-macrophage colony stimulating factor
Genome-wide association studies (GWAS),	(GM-CSF), 343, 718–719
192–193	gRNAs. See Guide RNAs (gRNAs)
10x Genomics, 638–639	Gross domestic profit (GDP), 660
Genyzme, 651–652	GSK. See GlaxoSmithKline (GSK)
Germ line cells, 586	GSK3β. See Glycogen-synthase kinase 3-beta
Germ line/soma dichotomy, 449–450, 450f	(GSK3β)
German Institute for Quality and Efficiency in	GSK3β inhibitors, 479–480
Healthcare (IQWiG), 718-719	GT. See Gene therapy (GT)
Gilead, 642	GTMPs. See Gene therapy medicinal products
GITR. See Glucocorticoid-induced tumour	(GTMPs)
necrosis factor receptor (GITR)	Guide RNAs (gRNAs), 218, 228, 585
GlaxoSmithKline (GSK), 15, 26, 378	GvHD. See Graft-versus-host disease
Glialign project, 279	(GvHD)

GVL effect. See Graft-versus-leukaemia effect (GVL effect)	professionals, 759 systems, 762–763
GWAS. See Genome-wide association studies (GWAS)	Heat shock protein 70 (HSP70), 441 hEG cells. <i>See</i> Human embryonic germ cells (hEG cells)
Н	Hemophilia A, 709
HACA. See Human antichimeric antibody	Hepatitis C virus (HCV), 708–709
(HACA)	Hepatocellular carcinoma (HCC), 545
Haematologic malignancies, 45–46	HER2. See Human epidermal growth factor
Haematological malignancies	receptor 2 (HER2)
CAR-T cell therapies targeting antigens other	Her2/neu, 584
than CD19 for, 326–329	Hereditary persistence of foetal haemoglobin
clinical outcome of CD19 targeted CAR-T cells	(HPFH), 412
in B-cell, 306–326	Herpes Simplex Virus (HSV), 286
Haematopoietic stem cell transplantation (HSCT),	hESCs. See Human embryonic stem cells (hESCs)
41–42, 290, 659–660	Heterodimer CD94/NKG2A, 123
allogeneic γδ T cell therapy in setting, 50–51	HFEA. See Human Fertilisation and Embryology
HSCT-based therapies, 724	Authority (HFEA)
Haematopoietic stem cells (HSCs), 4–5, 17, 72–73,	HIF-1A. See Hypoxia-inducible factor 1α
104, 287	(HIF-1A)
Haemoglobin Bart's, 410–411	High mobility group box 1 (HMGB-1), 525-527
Haemoglobin H disease, 410-411	High performance Integrated Virtual Environment
Haemoglobinopathies, 410-413	(HIVE), 359
Haemophilia, cell and gene therapies for, 417t	High-cost transformative therapies, 736
Haemophilia A (FVIII deficiency), 413-414, 419	outcomes-based arrangements for, 729
Engineered Platelet gene therapy for, 419	High-throughput screening employing, 479
Haemophilia B (FIX deficiency), 413-414, 416	HindIII, 232
HAMA. See Human antimurine antibody (HAMA)	hiPSCs. See Human induced pluripotent stem cells (hiPSCs)
Harvard Pilgrim, 427–428	Histone deacetylases (HDAC), 545–547
HAVCR2. See Mucin domain-3 protein (TIM-3)	HIV. See Human immunodeficiency virus (HIV)
Hayflick Limit, 452	HIVE. See High performance Integrated Virtual
HbA. See Adult haemoglobin (HbA)	Environment (HIVE)
HCC. See Hepatocellular carcinoma (HCC)	HLA. See Human leucocyte antigen (HLA)
HCT/Ps. See Human cells, tissues and cellular-and	HMGB-1. See High mobility group box 1
tissue-based products (HCT/Ps)	(HMGB-1)
HCV. See Hepatitis C virus (HCV)	Hollow spherical organs, 262
HDAC. See Histone deacetylases (HDAC)	Homologous directed recombination (HDR), 213
HDR. See Homologous directed recombination	Homologous recombination, 585
(HDR)	Hospital onboarding team, 760
Head-to-head trials, 770	Hospital Outlier Payment mechanisms, 726–727
Health assessment technology bodies, 426	Hospital readmission, 423–425
Health Canada, 358	Hospital Supplemental Outlier Payment, 727
Health Research Authority (HRA), 674	House of Lords, 674
Health technology assessment (HTA), 712–713,	HPFH. See Hereditary persistence of foetal
716, 718, 729	haemoglobin (HPFH)
Healthcare	HPV. See Human papillomavirus (HPV)
planning, 663	HRA. See Health Research Authority (HRA)
products and services, 721	HSCs. See Haematopoietic stem cells (HSCs)

HSCT. See Haematopoietic stem cell	Hydroxyurea, 411–412
transplantation (HSCT)	Hypothetical case studies, 620–621
HSP70. See Heat shock protein 70 (HSP70)	Hypoxia, 507–508
HSV. See Herpes Simplex Virus (HSV)	Hypoxia-inducible factor 1α (HIF-1A), 519-520
HTA. See Health technology assessment (HTA)	Hypoxic microenvironment, 507-508
hTERT. See Human telomerase reverse	
transcriptase (hTERT)	1
Human anti-CD19 CAR-T cells, 80	I-PREDICT study, 563–564
Human antichimeric antibody (HACA), 542-544	IBM, 426–427
Human antimurine antibody (HAMA), 4-5	Ibrutinib, 117
Human Cell Atlas, 197–198	'iCas9'. See Inducible Cas9 ('iCas9')
Human cell senescence, 452	ICD. See Immunogenic cell death (ICD)
Human cells, tissues and cellular-and tissue-based	ICER. See Institute for Clinical and Economic
products (HCT/Ps), 259	Research (ICER)
Human embryonic germ cells (hEG cells), 453	ICER Policy Summit. See Institute for Clinical and
Human embryonic stem cells (hESCs), 104-105,	Economic Review Policy Summit (ICER
159–160, 270–271, 453	Policy Summit)
cell lines, 453	IDO. See Indoleamine-2,3-dioxygenase (IDO)
pluripotency of, 457f	IFM Therapeutics, Inc., 701
Human epidermal growth factor receptor 2	IFN. See Interferon (IFN)
(HER2), 119, 509-511	Ig-like external domains, 95
Human Fertilisation and Embryology Authority	Ig-like lectins, 95
(HFEA), 675	IL13Rα2. See Interleukin receptor-13Rα2
Human immune system, 69–71	$(IL13R\alpha2)$
Human immunodeficiency virus (HIV), 290–291,	Imaging technologies, 101
303–304, 635	Imatinib, 748–750
HIV1, 17	IMid drug. See immunomodulatory drug (IMid
pools, 224–226	drug)
Human induced pluripotent stem cells (hiPSCs),	Imlygic, 292–295, 294t
462–464, 469	Imlygic, 377, 718–719
cell type stages of reprogramming and associated	Immatics US, Inc., 56
variables, 478t	Immature progenitor cells, 165–166
issues in applying, 477t	Immortalisation, 452–453
technical, regulatory and business factors,	Immortality, 452
476–481	Immune cells, 71
Human leucocyte antigen (HLA), 173, 378–379,	therapy development status, 124–136
538–539	China, 132–133, 135t
Human NK cells, 104–105	Japan, 132, 133t
Human papillomavirus (HPV), 332	Korea, 133–136, 137t–138t
Human peripheral blood, NK cells in, 93	Immune checkpoints, 121
Human pluripotent stem cell lines, 453	blockade, 546f
Human telomerase reverse transcriptase (hTERT),	receptors, 550
559–560	Immune/immunity
Human tissue regeneration regulation, 453–455	balance control, 92
Huntington's disease, 709	contexture, 396
Hydrogels, 250, 270–272	immune-controlled intervention, 140
encapsulation, 270–271	regulation, 395–396
Hydrops fetalis. See Haemoglobin Bart's	against staphylococcal and streptococcal Cas9, 230
4-Hydroxytamoxifen (4-OHT), 278	suppression for T1D, 158–159

Immuno-oncology (IO), 94, 339-341, 377, 544	Inflammatory diseases, 557-558
Immunogenic cell death (ICD), 525-527	Informed consent, 589–590
Immunogenic tumour cell death, 537f	Informed decision-making on cost of production,
Immunoglobulins, 96	623
Immunohistochemistry, 161	Inherited monogenic diseases, 287
Immunomedics, Inc., 701	Inhibitory receptors of NK cells, 94–95
Immunomodulation, 437	Initial Public Offering (IPO), 637-638
immunomodulatory drug (IMid drug), 117	Innate immune cells, 44
Immunoreceptor tyrosine-based inhibition motifs	Innate immunity, 493–494
(ITIMs), 94–95, 123	and adaptive immunity, 490
Immunosuppression, GBM, 507-508	initiation of, 492–493
Immunosuppressive drugs, 244	Innate lymphocytes, 44
Immunosuppressive microenvironment, 509	Innate Pharma, 42–43, 54
Immunosuppressive TME, 527, 533–536	Innovate UK, 681
Immunotherapeutic methods, 91	Innovation, 664–667, 669–672, 778–780
Immunotherapy, 41, 69, 507, 581–582, 633, 689	barriers to, 663–669
expansion and manipulation of NK cell for	chasms, 663–664
clinical practice, 103-105, 107t-108t	infrastructure, 676–679
NK cell-based, 103-105	legislation and policies, 672-676
In situ reprogramming, 638	Innovation S-curves, 3, 461–462, 467–468,
In situ RNA hybridisation (RNAish), 395	470-472, 481-482
In situ vaccination, 536	big pharmas and radical innovation adoption,
In vivo activation and expansion of $\gamma\delta$ T cells, 48–49	6–8
In vivo delivery, 15–16	black swan risk, 6
In vivo modification, 498–500	bottom-line impact of successful adoption of
antigen loading of DC, 498	radical innovation, 5
expansion of DC, 498	patterns in industrial product emergence, 4-5
In-process packaging, 169	perspectives, 11
IND. See Investigational new drug application	hurdles and catalysts of market access, 12f
(IND)	policies and regulatory frameworks as
Indefinite replicative capacity. See Immortality	accelerators, 8–9
Independent Research and Technology	predicting technological progress, 9-11
Organisations (IRTOs), 678t	Innovative payment models for cell and gene
India National Institute of Biologicals (NIB), 358	therapies, 424t
Individualised CAR-T immunotherapy, 750	Innovative therapy developers, 717
Indoleamine-2,3-dioxygenase (IDO), 102, 533-536	Inpatient BMT-based gene therapy for Ultrarare
Induced pluripotent stem cells (iPSCs), 104–105,	immunodeficiency disorder, 725b
173, 194, 216, 246, 269–270, 455, 464–465,	Inpatient Prospective Payment System (IPPS),
481–483	725b, 726–727
perspectives, 481–483	Inpatient reimbursement codes and payment
as source material for cell therapy, 173–174	models, 723–724
Induced tissue regeneration (iTR), 456	Input parameters, 611, 613t, 615t
Inducible Cas9 ('iCas9'), 697	Insertional oncogenesis, 339
Industrial Strategy Challenge Fund (ISCF), 681–682	Insight deriver, 191
Industrial Technology Research Institute in Taiwan,	Institute for Clinical and Economic Research
669–671	(ICER), 715–716
Inflammation	Institute for Clinical and Economic Review Policy
and cancer, 517f	Summit (ICER Policy Summit), 422
convergence innovation in, 525–530	Insulin, 157–158

insulin-delivering cell therapy, 171	ISO. See International Organization for
insulin-producing cells, 160	Standardization (ISO)
INT. See Integrated bioprocess platform (INT)	Isopentenyl pyrophosphate (IPP), 45
Integrated bioprocess platform (INT), 614	Issued claims, 695
Intellectual property (IP), 661–663	ITIMs. See Immunoreceptor tyrosine-based
Inter partes review, 695	inhibition motifs (ITIMs)
Interfering RNA approach, 215–216	iTR. See Induced tissue regeneration (iTR)
Interferon (IFN), 96–97, 377	
IFN α -2b, 527	J
IFN-γ, 119, 306–308, 321–322, 493	JAK/STAT pathway, 533-536
Interferon regulatory factor 3 (IRF3), 500	Janus kinases (JAKs), 533–536
Interleukin receptor-13R α 2 (IL13R α 2), 509–510, 584	Japan, Immune cell therapy development status in 132, 133t
Interleukins (ILs)	Japan Ministry of Health, Welfare and Labour/
	Pharmaceutical and Medical Devices
IL1β, 525–527	
IL-2, 71–72, 114–116, 303–304, 539–540	Agency, 358
IL-6, 306–308, 342–343	Japanese Pharmaceuticals and Medical Devices
IL-6/JAK/STAT-3 signalling cascade, 533–536	Agency (PMDA), 132
IL-12, 115–116	Juno Therapeutics, 325–326, 363–364, 378, 643
IL-15, 105–110, 115	K
IL-18, 115–116	
IL-21 receptor, 114	K562 cells, 103
International Organization for Standardization	KDR-1121 antibody, 695–696
(ISO), 258	Keytruda. See Pembrolizumab
Internet bubble, 649–650	KFDA. See South Korea Ministry of Food and
Intratumoural heterogeneity, 532	Drug Safety (KFDA)
Intravenous infusion, 748	Kidney transplantation, 244
Investigational new drug application (IND), 171–172, 319–320, 358–359	Killer immunoglobulin receptors (KIRs), 43, 94 mismatch principle, 110–111
IO. See Immuno-oncology (IO)	Kite Pharma, 378, 642
Ionic detergents, 249	Kite Pharmaceuticals, 321, 323-324, 332-333,
IP. See Intellectual property (IP)	344–348
Ipilimumab, 43, 122, 529, 533-536, 544	Knowledge economy, 669
IPO. See Initial Public Offering (IPO)	Korea, immune cell therapy development status in
IPP. See Isopentenyl pyrophosphate (IPP)	133–136, 137t–138t
IPPS. See Inpatient Prospective Payment System	KTE-C19, 323-324
(IPPS)	Kymriah, 293–295, 294t, 321, 605, 623
iPSCs. See Induced pluripotent stem cells (iPSCs)	·
IRF3. See Interferon regulatory factor 3 (IRF3)	L
Irradiated EBV-transformed lymphoblastoid cell	Laboratory-produced tissue-engineered organs,
line, 104	244–245
Irradiated feeder cells, 120	Labour costs, 616
IRTOs. See Independent Research and Technology	LAG. See Lymphocyte activation gene (LAG)
Organisations (IRTOs)	Lambert agreement models, 680
ISCF. See Industrial Strategy Challenge Fund (ISCF)	Lang Factor, 616
Islet	Late-Phase process development and technology,
cell types, 175	257–258
discoveries enabling renewable source of,	Latin hypercube sampling, 620
159–161	Leasing model. See Amortisation
	2

'Lego-like' approach, 564	Luxturna. See Voretigene neparvovec
Lenalidomide, 117	LV. See Lentivirus (LV)
Lentiviral technology, 79–80	LVV. See Lentiviral vector (LVV)
Lentiviral vector (LVV), 79, 287	Ly49 gene, 95
Lentivirus (LV), 17, 215-216, 286, 290-291, 445	Ly49a receptor, 95
Leukapheresis, 584	Ly49b receptor, 95
Levodopa, 473–474	Lymph node (LN), 494
Lex specialis, 587–588	Lymphocyte activation gene (LAG), 532
Licences, 651	Lymphocyte subsets, 41
Life Sciences Industrial Strategy, 671–674	Lymphodepleting chemotherapy, 625
Life-threatening side effects, 105	7 1 1 0 17
LILR family, 95	M
Limited patient population, 28–29	M&A decisions. See Merger and acquisition
Liponanoparticles (LNPs), 215–216, 229	decisions (M&A decisions)
Lipoprotein lipase (LPL), 22	MA. See Marketing authorisation (MA)
Lipoprotein lipase deficiency (LPLD), 706	mAb. See Monoclonal antibodies (mAb)
Lithium, 462	Machine learning, 186–187
biological processes and downstream substrates,	to predict phenotype of stem cells, 198–199
464f	MACI, 597–598
drug discovery and drug development pipeline	Macrocellular evolutionary mechanisms, 532
timeline, 467f	Macroeconomics headwinds, 650–651
to gain insight into bipolar disorder, 463-464	Macroencapsulation, 162–165, 163t
influences CRMP2 phosphorylation, 470–474	Macrophages, 98–99
mechanism of action to treat lithium BPD, 464f	MACS. See Magnetic-activated cell sorting
reveals bipolar disorder brain architectural	(MACS)
abnormalities, 469–470	MAF. See Device Master File (MAF)
Living drugs, 583	MAGE, 391
LN. See Lymph node (LN)	MAGE-A12 expression patterns, 391
LNPs. See Liponanoparticles (LNPs)	MAGE-A3 experiences, 391-392
Logarithmic scale, 3	'Magic bullet' design, 530–532
Logistical and regulatory barriers, 423-427	Magnetic-activated cell sorting (MACS), 614
best price, 427	Major histocompatibility complex (MHC), 41-42,
capturing, integrating and analysing RWE,	93-94, 380f, 507-508, 691
426–427	MHC-I, 491
definition of value, 423-425	'Make-to-order' model, 625
LOH. See Loss of heterozygosity (LOH)	Malignant disease recognition, 44-58
Long Terminal Repeat (LTR), 289	Mantle cell lymphoma, 321–322
Long-term follow-up component (LTFU	Manufacturing, 103
component), 22	capacity, 753
Longitudinal health records, 780	COGs, 607
Loss of heterozygosity (LOH), 395	costs, 706–707
LPL. See Lipoprotein lipase (LPL)	manufactured scaffolds, 249-250
lpl gene, 22	MAPCs. See Multipotent adult progenitor cells
LPLD. See Lipoprotein lipase deficiency (LPLD)	(MAPCs)
LTFU component. See Long-term follow-up	Market access, critical parameters for, 709-720
component (LTFU component)	Marketing authorisation (MA), 597-598
LTR. See Long Terminal Repeat (LTR)	application, 324
Luciferase, 79	process, 588
LUXTURNA, 292–295	Markets in Europe, 728–729

MATLAB, 622 methodologies, 257 Mature NK cells, 97 Minimal residual disease-negative CR MDSC. See Monocyte-derived suppressor cells (MDSC); Myeloid-derived suppressor cells (MDSC) (MDSC) (MIATA), 340–341 Mechanism of action (MoA), 94 Mitochondrial replacement therapies (MRT), 67	
MDSC. See Monocyte-derived suppressor cells (MDSC); Myeloid-derived suppressor cells (MDSC) (MDSC) (MDSC) (MIATA), 340–341 Mechanism of action (MoA), 94 Mitochondrial replacement therapies (MRT), 67	
(MDSC); Myeloid-derived suppressor cells (MDSC) (MIATA), 340–341 Mechanism of action (MoA), 94 Minimum Information About T cell Assays (MIATA), 340–341 Mitochondrial replacement therapies (MRT), 67	
(MDSC) (MIATA), 340–341 Mechanism of action (MoA), 94 Mitochondrial replacement therapies (MRT), 67	
Mechanism of action (MoA), 94 Mitochondrial replacement therapies (MRT), 67	
	75
Mechanobiology, 199 MLD. See Metachromatic leukodystrophy (MLD	
Medical and clinical field in CAR-T therapy, 771 MLMT. See Multiluminance mobility test	ŕ
Medical Research Council (MRC), 667–668 (MLMT)	
Medicare Provider and Analysis Review MLV. See Murine leukemia virus (MLV)	
(MedPAR), 725b MM. See Multiple myeloma (MM)	
Medicare Severity-DRG (MS-DRG), 725b MoA. See Mechanism of action (MoA)	
MedPAR. See Medicare Provider and Analysis moDC. See Monocyte-derived DC (moDC)	
Review (MedPAR) Model validation, 621	
Membrane vesicles, 439–441 Modern governmental industrial strategy, 669–6	84
Memorial Sloan Kettering Cancer Center encouraging investment, 681–684	
(MSKCC), 306, 308–309, 314–315, 318, innovation infrastructure, 676–679	
330–331, 696–697 innovation legislation and policies, 672–676	
6-Mercaptopurine, 548–550 investing in science, research and innovation,	
Merger and acquisition decisions (M&A decisions), 669–672	
strengthening strategic capabilities, 679–681	
Mesenchymal stem/stromal cells (MSCs), 4–5, UK innovation landscape assets, 677f	
54, 216, 246–247, 251, 270, 436–437, 441, Moloney virus gene coding, 78	
536–538, 599–601, 651 Monalizumab, 123	
new ideas, 437–445 Monoclonal antibodies (mAb), 6–7, 110–111, 37	77,
next generation therapies, 438f 525, 601, 607–608, 691	
therapy, 435 Monocyte-derived DC (moDC), 497	
allogeneic, 435–436 Monocyte-derived human macrophages cells	
conditioned media, 443–444 (MOTO-CAR cells), 552–554	
exosomal therapy, 439–442 Monocyte-derived suppressor cells (MDSC), 54	
gene-modified cells, 445 Monokines, 116	
perspectives, 445 Monorhaphis chuni, 450	
Mesoblast, 649–650 Monte Carlo simulation, 620	
Mesothelin cMet, 584 Moore's law, 183	
Metabolically hostile microenvironment, for semiconductor electronics, 3	
536–538 Mortality, 423–425	
Metachromatic leukodystrophy (MLD), 23 MOTO-CAR cells. See Monocyte-derived hun	nan
Metastasis, 517–518 macrophages cells (MOTO-CAR cells)	
Methotrexate, 548–550 Mouse NK cells express, 101	
2-Methyl-3-butenyl-1-pyrophosphate MRC. See Medical Research Council (MRC)	
(2M3B1-PP), 49–50 MRD-CR. See Minimal residual disease-negative	ve
MHC. See Major histocompatibility complex CR (MRD-CR)	
(MHC) MRT. See Mitochondrial replacement therapies	
MIATA. See Minimum Information About T cell (MRT)	
Assays (MIATA) MS-DRG. See Medicare Severity-DRG	
Microbiology, 558–559 (MS-DRG)	

MSH2. See MutS homologue 2 (MSH2)	Natural killer cells (NK cells), 4–5, 41–42, 91–92,
MSKCC. See Memorial Sloan Kettering Cancer	490, 507–508, 511, 637–638, 691
Center (MSKCC)	activation mechanisms, 96–97
Mucin 1 (MUC1), 530–532	adoptive transfer, 123–124
Mucin domain-3 protein (TIM-3), 122, 525–527,	allogeneic, 110–111
533–536	attack, 394
Multi-attribute decision-making, 618–619	autologous, 105–110
Multicellular organisms, 450	and cancer, 94–102
Multilayer flasks, 614	characteristics, 92–93
Multilingual service team, 756–757	clinical development status of CAR natural
Multiluminance mobility test (MLMT), 716	killer, 136, 139t
Multiple CAR-NKs, 511	perspectives, 140
Multiple endocrine hormones, 175	combination therapy with NK cell-based
Multiple myeloma (MM), 327–329, 390	immune therapy, 114–123
Multipotent adult progenitor cells (MAPCs),	deficiency, 100–101
270	development, 93
Multispecific antigen approaches, 511	function, 93–94, 97
Multistem, 651	future development approach, 94
Multivesicular bodies (MVBs), 439	immune cell therapy development status in Asia,
Murine leukemia virus (MLV), 289	124–136
Murine-based γRV, 16–17	line, 111, 112t–113t
Mutagenic clonal expansion, 19–20	NK cell-based immunotherapy, 102–111
MutS homologue 2 (MSH2), 46	NK-92 cell, 43
MVBs. See Multivesicular bodies (MVBs)	ongoing clinical trials, 123–136, 125t–127t
Mycobacterium tuberculosis, 220	receptors and ligands, 94–96
MyD88/CD40 activation switch, 635–636	activating receptors, 95–96
Myeloablative preparative regimen, 390	inhibitory receptors, 94–95
Myelodysplastic syndrome, 19–20	role in cancer immunosurveillance and
Myeloid cells, 97–99	immunoediting, 100–102
Myeloid-derived suppressor cells (MDSC), 99, 532	in tumour microenvironment, 97–100
suppression of NK cell activity by, 99	Natural killer complex (NKC), 95
suppression of the centuctivity by, >>	Natural killer T cells (NKT cells), 490
N	Natural Language Processing (NLP), 189
N-BP. See Aminobisphosphonates (N-BP)	Natural materials, 249–250
NAMD. See National Association of Medicaid	NCI. See National Cancer Institute (NCI)
Directors (NAMD)	NCR, 96
Nanorobotics (NR), 229	NCSC. See Neural crest stem cells (NCSC)
NanoString panels, 395	Neoantigens, 330–332, 538–539
Nanovesicle exosomes (NV exosomes), 229	Neoblasts, 451
National Association of Medicaid Directors	Neovascularisation inhibitors, 559–560
(NAMD), 708–709	Nerve tissue regeneration
National Cancer Institute (NCI), 73,	allogeneic off-the-shelf replacement nerve tissue,
306, 385	278–279
National Health Service (NHS), 669	cellular biomaterials, 271–272
National Institute for Health and Care Excellence	cellular hydrogels
(NICE), 675-676, 713-714	creating anisotropy in, 272-273
National Institute for Health Research (NIHR),	stabilisation of aligned, 273-274
660	EngNT to replace autograft, 276-278
National Marrow Donor Program (NMDP), 727	peripheral nerve tissue engineering, 274-276

perspectives, 279	NKRP1 receptor, 96
stem cell therapy	NKT cells. See Natural killer T cells (NKT cells)
applications of materials to, 270-271	NLP. See Natural Language Processing (NLP)
for neuronal regeneration, 269	NMDP. See National Marrow Donor Program
stem cells and mechanisms of action, 269-270	(NMDP)
Net present value (NPV), 607	Non hereditary diseases, 229–230
Network linkages, 191	Non Hodgkin's lymphoma (NHL), 46, 315–318,
Neural crest stem cells (NCSC), 276–278	321–326
Neural networks, 187–189	clinical outcome reported with CD19-targeted
Neural stem cells (NSCs), 269–270	CAR-T cells, 316t
Neuro-Linguistic Programming (NLP). See	Non-small cell lung cancer (NSCLC), 55, 523,
Natural Language Processing (NLP)	524f
Neurofibrillary tangles (NFTs), 472	Nonadoption consequences of radical
Neurological diseases, 462	innovation, 6
Neurological toxicity, 338	•
	Noncancer targets, 700–701
Neuronal regeneration, stem cell therapy for, 269	Noncurative bridge-to-BMT treatment scenario,
Neurons, 469	715–716
Neuroscience, 763	Nonhomologous end joining (NHEJ), 213
Neurotoxicities, 532	Nonionic detergents, 249
Neurotoxicity, 362–363	Nonpeptide alkylphosphates, 45–46
New Diagnostic and Treatment Methods	Nonpeptide antigens, 45
Regulation reimbursement (NUB	Nonstandard payment models, 728–729
reimbursement), 726	Nonviral vectors, 18, 286, 292
New Technology Add-on Payment (NTAP),	Novartis, 344–348, 378, 427–428, 591, 605, 642
726–727	CAR-T therapy, 759
New York oesophageal squamous cell carcinoma-1	journey to CAR-T therapy, 748–751
(NY-ESO-1), 332, 389–390, 538–539	NPV. See Net present value (NPV)
Next-generation	NR. See Nanorobotics (NR)
CAR-T, 635, 642	NSCLC. See Non-small cell lung cancer
gene editor, 218, 219f	(NSCLC)
NFTs. See Neurofibrillary tangles (NFTs)	NSCs. See Neural stem cells (NSCs)
NHEJ. See Nonhomologous end joining (NHEJ)	NTAP. See New Technology Add-on Payment
NHL. See Non Hodgkin's lymphoma (NHL)	(NTAP)
NHS. See National Health Service (NHS)	Nucleic acids, 500, 696
NIB. See India National Institute of Biologicals (NIB)	polymer, 694
NICE. See National Institute for Health and Care	Nusinersen, 716–717
Excellence (NICE)	NV exosomes. See Nanovesicle exosomes (NV
NIH. See United States National Institutes of	exosomes)
Health (NIH)	NY-ESO-1. See New York oesophageal squamous
NIHR. See National Institute for Health Research	cell carcinoma-1 (NY-ESO-1)
(NIHR)	
Nivolumab, 529, 533–536, 717–718	0
NK cells. See Natural killer cells (NK cells)	Objective response rate (ORR), 525–527
NKC. See Natural killer complex (NKC)	OECD. See Organisation of Economic
NKG cell line, 111	Cooperation and Development (OECD)
NKG2 receptor, 95	Off-target
NKG2D, 637–638	activity, 394
ligands, 46	edits, 585
receptor, 96	effects, 227–228, 231
1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	, -, -

Off-the-shelf	Outcome-based payments, 763
CAR-T cells, 344–348, 584	models, 735t
products, 398	Outcome-based pricing. See Value-based pricing
therapy, 41–42, 54–55, 344–348	(VBP)
treatment. See Allogenic treatments	Outcome-based risk-sharing models, 764, 765t
'Off-tumour/on-target' toxicity, 329–330	Outpatient cell therapy for critical limb ischaemia,
Offensive strategies, 548–550	723b
Office of Inspector General (OIG), 727	Overall response (OR), 634
4-OHT. See 4-Hydroxytamoxifen (4-OHT)	Overall response rate (ORR), 306–308, 325
OIG. See Office of Inspector General (OIG)	Overall survival (OS), 309–313, 711
Olovnikov hypothesis, 452	OX40 antibody, 556, 695–696
Omics	,
data to cell therapies, 194–195	P
working with omics insights, 191–196	p53 gene, 20
AI for drug discovery, development and	Paediatric acute lymphoblastic leukaemia (pALL),
repurposing, 192f	315–321,764
deriving, 192–194, 193f	Palisade Risk 6, 621
On target toxicity, 338–339	pALL. See Paediatric acute lymphoblastic
'On target/off tumour' toxicity, 338–339	leukaemia (pALL)
'On-target, off-tumour' toxicity, 393–394, 639	PAM. See Protospacer adjacent motif (PAM)
Oncology, 564. See also Solid tumour oncology	Pamidronate, 45–46
checkpoint blockade to enhance antitumour	PAMP. See Pathogen-associated molecular patterns
immunity, 528f	(PAMP)
convergence innovation in, 525–530	Pancreatic adenocarcinoma (PDAC), 519–520
therapy, 559–560	Pancreatic hormones, 175
Oncolytic viruses, 559–560	Pancreatic progenitor
therapy, 377, 538–539	cells advantages, 174–176
Opdivo. See Nivolumab	pancreatic progenitor–derived in vivo
Operationen-und Prozedurenschlüssel (OPS),	differentiated grafts, 161
724–726	Panitumumab, 717–718
Ophthalmology, 763	pAPCs. See Professional antigen-presenting cells
OPS. See Operationen-und Prozedurenschlüssel	(pAPCs)
(OPS)	Paracrine
OR. See Overall response (OR)	activity of MSCs, 443
Organ	effects, 436–437
failure, 243	mediators, 436–437, 443
inflammation, 17–18	Parallel induction regimen, 548–557
Organisation of Economic Cooperation and	Paraplatin, 548–550
Development (OECD), 660	Parkinson's disease (PD), 473–474
Oriental medicine, 91	epistemic and clinical breakthroughs, 474f
Ornithine transcarbamylase deficiency (OTC	revisiting established functional agent Levodopa,
deficiency), 288	473–474
Orphan Act, 778–780	Partial reprogramming, 456
ORR. See Objective response rate (ORR); Overall	Partial response (PR), 306
response rate (ORR)	Partnering, 605
OS. See Overall survival (OS)	PASS. See Postauthorisation safety study (PASS)
Osiris, 651–652	Patent Cooperation Treaty (PCT), 689–690
OTC deficiency. See Ornithine transcarbamylase	Patent Trial and Appeal Board (PTAB),
deficiency (OTC deficiency)	695–696

Patents, 690	PD1. See Cell death protein 1 (PD1)
in CAR technology, 691-699	PDAC. See Pancreatic adenocarcinoma (PDAC)
first-generation CARs, 692-693	pDC. See Plasmacytoid DC (pDC)
second-generation CARs, 694-697, 694f	PEC-01 cells, 171-172
third-and fourth-generation CARs, 697-699	PEG. See Polyethylene glycol (PEG)
genetic engineering and 'universal'	Pembrolizumab, 529, 544–545, 717–718
CAR-expressing cells, 700–701	Peptide-bound Major Histocompatibility (pMHC),
noncancer targets, 700–701	331–332
perspectives, 701–703	Peptide-HLA complex (pHLA), 379
and process, 690–691	Peptides, 491
U.S. Patent No. 4,224,237, 691	Performance-based plans, 27–28
U.S. Patent No. 7,190,446, 694	Performance-based pricing Value-based pricing
U.S. Patent No. 7,465,741, 692	(VBP)
U.S. Patent No. 8,465,743, 695–696	Perinatal stem cells, 247
U.S. Patent No. 9,020,587, 696	Peripheral blood mononuclear cells (PBMNC),
Pathobiology of cancer, 558	52–53, 103
Pathogen-associated molecular patterns (PAMP),	Peripheral mononuclear cells (PBMC),
490, 493	496–497
Patient	Peripheral nerve injury (PNI), 274
access schemes, 728	Peripheral nerve tissue engineering, 274–276
approaches to addressing patient's immune	Personalised combination therapy treatment,
system, 176–177	563–564
autonomy, 589	Personalised medicine, 15
diagnostics, 393	PGE2. See Prostaglandin E2 (PGE2)
patient-and payer-centric approach, 780–781	Pharmaceutical
patient-derived leukocytes, 71	companies, 769
population stratification, 717–718	responsibility, 768
responsibility, 766–767	developers, 712
value, 762	expenditures, 770
Patient-reported outcomes (PROs), 714	industry, 777–778
Pattern recognition receptors (PRR), 490	Phase 1/2 clinical trial, 172–176
'Pay as you go' model, 707	Phase 2 JULIET study, 325
Pay-for-performance arrangements, 729, 765t	Phase 3 KEYNOTE-426 clinical
Payers, 713	trial, 550
acceptance, 721	Phenylketonuria, 709
Payment	pHLA. See Peptide-HLA complex (pHLA)
challenges and models, 727–730	Phospho-inositol-3 kinase (PI3K), 533-536
for curative treatments, 27–28	Phosphorylation, 464–465
models for cell and gene therapies, 764-766,	PHS. See Public Health Service (PHS)
765t	Phylogenetic trees, 201
schemes, 729	PI3K. See Phospho-inositol-3 kinase (PI3K)
PBMC. See Peripheral mononuclear cells (PBMC)	PIDs. See Primary immunodeficiency diseases
PBMNC. See Peripheral blood mononuclear cells	(PIDs)
(PBMNC)	piggyBac transposon systems, 477-478
PCT. See Patent Cooperation Treaty (PCT)	Planar culture flasks, 614
PD. See Parkinson's disease (PD)	Plasmacytoid DC (pDC), 499
PD-1. See Programmed cell death-1 (PD-1)	Plastic compression, 273–274
PD-1/PD-L1 receptor/ligand system, 500–501	PLGA. See Poly-dl-lactide-co-glycolide
PD-6. See Programmed cell death 6 (PD-6)	(PLGA)

Pluripotent stem cell–derived islet replacement therapy	Primary immunodeficiency diseases (PIDs), 16–17 Primary mediastinal large B-cell lymphoma
advantages of pancreatic progenitor cells, 174–176	(PMBCL), 324
approaches to addressing patient's immune	Primary mode of action (PMOA), 171
system, 176–177	PRIME. See Priority Medicines (PRIME)
cell therapy using cadaver-derived islets and	Principle
immune suppression, 158–159	of autonomy, 589–591
discoveries enabling renewable source of islets,	of beneficence/nonmaleficence, 586–589
159–161	of justice, 591
encapsulation initiating circumvent requirement,	Priority Medicines (PRIME), 8–9, 392–393,
161–162, 163t	415–416
foreign body reaction and vascularisation, 167–168	Private businesses, 661–663
iPSC as source material for cell therapy, 173–174	Procedural codes, 724–727
perspectives, 177	Procedural reimbursement codes, 722–723
preclinical studies and regulatory submission,	Process development, 256–258
171–172	phases, 257–258
first clinical step, 172–176	Process economics, 618
product manufacturing, 168–171	Process simulations, 257–258
unmet medical need of diabetes, 157–158	Process validation, 256
Pluripotent stem cells, 4–5, 159, 246	Prochymal/chondrogen, 651–652
PMBCL. See Primary mediastinal large B-cell	Product
lymphoma (PMBCL)	complexity, 261–262
PMDA. See Japanese Pharmaceuticals and Medical	development
Devices Agency (PMDA)	costs, 607
PMDA Act (2014), 8–9	systems, 608
pMHC. See Peptide-bound Major	engraftment, 172
Histocompatibility (pMHC)	manufacturing, 168–171
PMOA. See Primary mode of action (PMOA)	risk factors, 620
PNI. See Peripheral nerve injury (PNI)	type, 610
Poly-DL-lactide-co-glycolide (PLGA), 559–560	value demonstration considerations, 712–713
Polyclonal T cells, 72–73	withdrawal, 601
Polyethylene glycol (PEG), 162	Proefficacy, 548–550
microencapsulation approach, 164	Professional antigen-presenting cells (pAPCs),
Polyhormonal endocrine cells, 160	44–45, 493
Positive externality, 668	Programmed cell death 6 (PD-6), 441
Postauthorisation obligations, 587–588	Programmed cell death-1 (PD-1), 122, 500–501
Postauthorisation safety study (PASS), 23	blockade, 533–536
Postsurgical infections, 581	function, 545
PR. See Partial response (PR)	PD-1/PD-L1inhibitors, 551–552
Precision	Proinflammatory cytokines, 552–554
medicine, 717–718	Proof-of-Principle/-Concept/-Activity/-Safety,
oncology, 563–564	778–780
Prednisone, 548–550	Proof-of-Relevance, 778–780
Preinfusion conditioning, 394	PROs. See Patient-reported outcomes (PROs);
Pricing, 427–428, 727–730. See also Value-based	Public Research Organisations (PROs)
pricing (VBP)	Prostaglandin E2 (PGE2), 533–536
modality, 421	Prostate-specific membrane antigen (PSMA),
system, 761	330–331
examples of pricing	Protein-engineered AAV, 18
- -	=

Protospacer adjacent motif (PAM), 221, 637–638	Rat Schwann cells, 278
Provenge, 42, 359–360, 377, 719	RBCs. See Red blood cells (RBCs)
Proximity ligation, 196	RBD. See Rare congenital bleeding disorders
PRR. See Pattern recognition receptors (PRR)	(RBD)
PSMA. See Prostate-specific membrane antigen	RCC. See Renal cell carcinoma (RCC)
(PSMA)	RCR/RCL. See Replication-competent retrovirus
PSREs. See Public Sector Research Establishments	or lentivirus (RCR/RCL)
(PSREs)	RCTs. See Randomised controlled trials (RCTs)
PTAB. See Patent Trial and Appeal Board (PTAB)	RDBMS. See Relational database management
Public Health Service (PHS), 258	software (RDBMS)
Public Research Organisations (PROs), 678t	Real world data. See Real-world evidence (RWE)
Public Sector Research Establishments (PSREs),	Real-world evidence (RWE), 420-421, 426
678t	approaches, 718
Public servants, 668	capturing, integrating and analysing, 426–427
PubMed, 481–482, 563–564	RECIST. See Response evaluation criteria in solid
PubMed-NCBI database, 582	tumours (RECIST)
Punctuated stochastic phase, 521-523	Recombinant DNA Advisory Committee (RAC),
-	332–333
Q	Reconstructive surgery, 243
Quality control (QC), 616, 753	Red blood cells (RBCs), 410-411
Quality of life (QoL), 320-321	Red face test, 781
Quality Systems Regulations, 477–478	Reexamination, 693
Quality-adjusted life year (QALY), 715-716	Regenerative Medicine, 7–9, 11, 183, 194,
Quantum Cell Expansion System, 263	243–244, 251, 453, 597, 652, 705,
	778–780
R	clinical translation changing paradigm, 263-265
R&D. See Research and development (R&D)	trials, 710–711
r/r. See Relapsed or refractory (r/r)	Regenerative Medicine Advanced Therapies
RAC. See Recombinant DNA Advisory	(RMATs), 8-9, 392-393
Committee (RAC)	Regenerative Medicine Programme, 681
Radiation therapy, 689	Regents of University of California, 696
Radical innovation	REGENXBIO, 652–653
big pharmas and adoption, 6-8	D 1 1 754 750
	Regulatory approval, 751–752
bottom-line impact of adoption, 5	Regulatory approval, 751–752 Regulatory T cells (Tregs), 46, 99, 507–508, 532,
commercial emergence	
commercial emergence barriers to innovation, 663–669	Regulatory T cells (Tregs), 46, 99, 507–508, 532,
commercial emergence	Regulatory T cells (Tregs), 46, 99, 507–508, 532, 584 Reimbursement, 409–410, 420, 422, 426, 428–429 for cell and gene therapies, 599
commercial emergence barriers to innovation, 663–669 factors affecting innovation in cell and gene therapies, 666f	Regulatory T cells (Tregs), 46, 99, 507–508, 532, 584 Reimbursement, 409–410, 420, 422, 426, 428–429
commercial emergence barriers to innovation, 663–669 factors affecting innovation in cell and gene	Regulatory T cells (Tregs), 46, 99, 507–508, 532, 584 Reimbursement, 409–410, 420, 422, 426, 428–429 for cell and gene therapies, 599 codes, 721–722 and payment models for therapies
commercial emergence barriers to innovation, 663–669 factors affecting innovation in cell and gene therapies, 666f modern governmental industrial strategy, 669–684	Regulatory T cells (Tregs), 46, 99, 507–508, 532, 584 Reimbursement, 409–410, 420, 422, 426, 428–429 for cell and gene therapies, 599 codes, 721–722 and payment models for therapies affordability of advanced therapies, 708–709
commercial emergence barriers to innovation, 663–669 factors affecting innovation in cell and gene therapies, 666f modern governmental industrial strategy,	Regulatory T cells (Tregs), 46, 99, 507–508, 532, 584 Reimbursement, 409–410, 420, 422, 426, 428–429 for cell and gene therapies, 599 codes, 721–722 and payment models for therapies
commercial emergence barriers to innovation, 663–669 factors affecting innovation in cell and gene therapies, 666f modern governmental industrial strategy, 669–684	Regulatory T cells (Tregs), 46, 99, 507–508, 532, 584 Reimbursement, 409–410, 420, 422, 426, 428–429 for cell and gene therapies, 599 codes, 721–722 and payment models for therapies affordability of advanced therapies, 708–709 burden of illness, 718–720 considerations, 721–727
commercial emergence barriers to innovation, 663–669 factors affecting innovation in cell and gene therapies, 666f modern governmental industrial strategy, 669–684 organisational competencies, 665f perspectives, 684–685 UK cell and gene therapy industry, 661f	Regulatory T cells (Tregs), 46, 99, 507–508, 532, 584 Reimbursement, 409–410, 420, 422, 426, 428–429 for cell and gene therapies, 599 codes, 721–722 and payment models for therapies affordability of advanced therapies, 708–709 burden of illness, 718–720 considerations, 721–727 critical parameters for market access, 709–720
commercial emergence barriers to innovation, 663–669 factors affecting innovation in cell and gene therapies, 666f modern governmental industrial strategy, 669–684 organisational competencies, 665f perspectives, 684–685 UK cell and gene therapy industry, 661f nonadoption consequences of, 6	Regulatory T cells (Tregs), 46, 99, 507–508, 532, 584 Reimbursement, 409–410, 420, 422, 426, 428–429 for cell and gene therapies, 599 codes, 721–722 and payment models for therapies affordability of advanced therapies, 708–709 burden of illness, 718–720 considerations, 721–727 critical parameters for market access, 709–720 inpatient reimbursement codes and payment
commercial emergence barriers to innovation, 663–669 factors affecting innovation in cell and gene therapies, 666f modern governmental industrial strategy, 669–684 organisational competencies, 665f perspectives, 684–685 UK cell and gene therapy industry, 661f nonadoption consequences of, 6 Radiotherapy, 116–117, 559–560	Regulatory T cells (Tregs), 46, 99, 507–508, 532, 584 Reimbursement, 409–410, 420, 422, 426, 428–429 for cell and gene therapies, 599 codes, 721–722 and payment models for therapies affordability of advanced therapies, 708–709 burden of illness, 718–720 considerations, 721–727 critical parameters for market access, 709–720 inpatient reimbursement codes and payment models, 723–724
commercial emergence barriers to innovation, 663–669 factors affecting innovation in cell and gene therapies, 666f modern governmental industrial strategy, 669–684 organisational competencies, 665f perspectives, 684–685 UK cell and gene therapy industry, 661f nonadoption consequences of, 6 Radiotherapy, 116–117, 559–560 RAFT absorbers, 273–274	Regulatory T cells (Tregs), 46, 99, 507–508, 532, 584 Reimbursement, 409–410, 420, 422, 426, 428–429 for cell and gene therapies, 599 codes, 721–722 and payment models for therapies affordability of advanced therapies, 708–709 burden of illness, 718–720 considerations, 721–727 critical parameters for market access, 709–720 inpatient reimbursement codes and payment
commercial emergence barriers to innovation, 663–669 factors affecting innovation in cell and gene therapies, 666f modern governmental industrial strategy, 669–684 organisational competencies, 665f perspectives, 684–685 UK cell and gene therapy industry, 661f nonadoption consequences of, 6 Radiotherapy, 116–117, 559–560 RAFT absorbers, 273–274 Randomised controlled trials (RCTs), 29, 718	Regulatory T cells (Tregs), 46, 99, 507–508, 532, 584 Reimbursement, 409–410, 420, 422, 426, 428–429 for cell and gene therapies, 599 codes, 721–722 and payment models for therapies affordability of advanced therapies, 708–709 burden of illness, 718–720 considerations, 721–727 critical parameters for market access, 709–720 inpatient reimbursement codes and payment models, 723–724 manufacturing and administration costs, 706–707
commercial emergence barriers to innovation, 663–669 factors affecting innovation in cell and gene therapies, 666f modern governmental industrial strategy, 669–684 organisational competencies, 665f perspectives, 684–685 UK cell and gene therapy industry, 661f nonadoption consequences of, 6 Radiotherapy, 116–117, 559–560 RAFT absorbers, 273–274	Regulatory T cells (Tregs), 46, 99, 507–508, 532, 584 Reimbursement, 409–410, 420, 422, 426, 428–429 for cell and gene therapies, 599 codes, 721–722 and payment models for therapies affordability of advanced therapies, 708–709 burden of illness, 718–720 considerations, 721–727 critical parameters for market access, 709–720 inpatient reimbursement codes and payment models, 723–724 manufacturing and administration costs,

Reimbursement (Continued)	Ribonucleic acid (RNA), 18, 198–199, 492
precision medicine and patient population	RIOs. See Research and Innovation Organisations
stratification, 717–718	(RIOs)
pricing and payment challenges and models,	Risk, 586, 588, 619-621, 664
727–730	factor, 588-589
procedural and episode-of-care-based	sharing or managed entry agreements, 728
reimbursement codes, 724–727	Rituximab, 5, 42-43, 120
procedural reimbursement codes, 722-723	RM Act. See Act on Safety of Regenerative
regenerative and advanced therapy clinical	Medicine (RM Act)
trials, 708f	RMATs. See Regenerative Medicine Advanced
with transformative and curative intent,	Therapies (RMATs)
728–730, 731t–734t	RMB. See Rocking motion bioreactor (RMB)
program, 26	RNA. See Ribonucleic acid (RNA)
for curative treatments, 27–28	RNA interference (RNAi), 215
Reinsurance, 422	RNA-guided endonucleases (RGENs), 221–223
Relapse, 333–335	RNAi. See RNA interference (RNAi)
strategies to manage CD19-negative relapse,	RNAish. See In situ RNA hybridisation (RNAish)
334–335	ROCKET trial, 314–315, 338, 361–363
Relapsed or refractory (r/r), 751	Rocking motion bioreactor (RMB), 619
Relational database management software	RPE. See Retinal pigment epithelium (RPE)
(RDBMS), 622	RPE cells. See Retinal pigmental epithelial cells
Renal cell carcinoma (RCC), 111, 550	(RPE cells)
Replication-competent retrovirus or lentivirus	RPE65-mediated inherited retinal disease, 720
(RCR/RCL), 339	RQR8, 636
Replication-competent viruses, 339	Ruxolitinib, 118
Replication-deficient HIV-based vectors. See	RV. See Retroviral/retrovirus (RV)
Lentiviral vector (LVV)	RVs. See Retroviral vectors (RVs)
Replication-deficient viral vectors, 78	RWE. See Real-world evidence (RWE)
Representative claim, 692–693, 695–696	RW E. See Real-World evidence (RWE)
	S
Research and development (R&D), 28–29, 660	
Tax Credit scheme, 672–673, 682–683	S-curves, 3, 614
Research and Innovation Organisations (RIOs),	Saccharomyces cerevisiae, 563–564
676, 678t, 679	Safety, Tolerability and Efficacy of VC-01
Response assessments, 396	Combination Product in Type One
Response evaluation criteria in solid tumours	Diabetes trial (STEP ONE trial). See Phase
(RECIST), 396	1/2 clinical trial
Retinal pigment epithelium (RPE), 716	San Raffaele Telethon Institute for Gene Therapy
Retinal pigmental epithelial cells (RPE cells),	(SR-Tiget), 15, 22–23, 290
269–270	SB-FIX gene therapy, 418
Retrospective cohort studies, 556–557	SBS technology. See Sequencing by Synthesis
Retroviral vectors (RVs), 285	technology (SBS technology)
transduction, 79–80	Scaffold
Retroviral/retrovirus (RV), 16–17, 77, 286, 288,	design, 247–248
290–291	implanted, 248–250
gene transfer, 77	manufactured, 249–250
γ -Retrovirus (γ RV), 16–17, 20	materials, 247–248
Revealer, 195–196	Scale, 611
RGENs. See RNA-guided endonucleases	scale up for manufacturing, 262-263
(RGENs)	Scar tissue, 557–558

Scavenger receptors, 492	perspectives, 233
SCD. See Sickle cell disease (SCD)	purposes as tool for drug discovery, 223
scFv. See Single-chain variable fragment (scFv)	small molecules, 214
scFv-based fusion proteins, 76–77	stem cell therapy, 216
Schmidtea mediterranea, 450	therapeutic interventions, 230–231
Schwann cells, 276–278	Second-generation anti-CD19 CAR, 80
SCID. See Severe combined immunodeficiency	Second-generation CARs, 76–77, 583, 694–697,
(SCID)	694f
SCID-Bg immune knockout mouse model, 160	Second-generation cell-based therapies
SCID-X1. See X-linked severe combined	AI, 184–200
immunodeficiency (SCID-X1)	big data, 184–200
Science, 669–672	big datasets, 190–200
SCR. See Stressed cell response (SCR)	perspectives, 200–202
sCTMPs. See Somatic cell therapy medicinal	Secure ordering, 757
products (sCTMPs)	Securities and Exchange Commission (SEC), 44,
SD. See Stabilisation of disease (SD)	651–652
SEC. See Securities and Exchange Commission	Seed Enterprise Investment Scheme (SEIS), 684
(SEC)	Seizures, 639
Second generation cell therapies, 41	Self-antigens, 330–331
Second generation genome editing technologies	Self-inactivating LV vector (SIN LV vector), 17
background, 218–220	Sendai virus (SeV), 18, 445
biologics, 214–215	Senescence, 454–455
Cas9, 222	Senolysis, 455
classical gene editors, 216–218	Sensitivity analysis, 620
conjugation	Sensors, 490
of deaminase enzymes to Cas9, 226	Sentinels, 490
of fluorescent proteins to Cas nucleases,	Sequencing by Synthesis technology (SBS
226–227	technology), 184
CRISPR, 220–221	Sequential induction regimen, 548–557
based transcriptional activation and repression,	Servitisation of therapies, 625
223–226	SeV. See Sendai virus (SeV)
systems as genome editing tools, 222-223	Severe combined immunodeficiency (SCID),
CRISPR Cas	18–19, 287, 339, 659–660
collection, 232-233	sgRNA. See Small guide RNA (sgRNA)
CRISPR Cas9 variants, adaptations, 223	Shareholder responsibility, 768–769
CRISPR-Cas9 as gene editing therapeutic,	Shotgun cytotoxic chemotherapeutic agents,
227	559–560
nucleases therapeutics, 232	Sickle cell disease (SCD), 410-412
systems, 225f	cell and gene therapies for, 413t
therapeutic formulations, 228–230	Sickle RBCs, 410–411
gene editing and drug discovery, 214	Sigilon Therapeutics, 418–419
immunity against staphylococcal and	Signal transducer and activator of transcription 3
streptococcal Cas9, 230	(STAT-3), 533-536
interfering RNA approach, 215–216	Silent carrier state, 410–411
modes of delivery in context of therapeutics,	Silico systems, 183
228–230	Simulation platforms, 621-622
next generation gene editor, 218	SIN LV vector. See Self-inactivating LV vector
NHEJ introduction of mutations, 228	(SIN LV vector)
off-target effects, 227-228	Singapore Health Sciences Authority, 358

Single-arm trial approaches, 719–720	macrocellular evolutionary mechanisms, 532
Single-cell	metabolically hostile microenvironment,
genomic sequencing, 196	536–538
measurement, 196-198	perspectives, 557–565
sequencing of large populations, 196-198, 197f	successes in checkpoint inhibitors, 544-547
Single-chain variable fragment (scFv), 74-75,	therapeutic combinations road map, 562f-563f
308–309, 692, 696	Solid tumours, 584
Single-nucleotide polymorphisms (SNPs),	cancers, 45–46
192–193, 410	CAR-T cells in, 329–333
Single-objective decision-making, 618-619	addition of safety switch to manage toxicity,
Sipuleucel-T. See Provenge	331
Site-specific integration of CAR gene, 586	exploring potential target antigens, 330-331
Skin grafting, 244–245	optimisation of CAR-T cell to improve
Sleeping Beauty transposon, 419	antitumour efficacy, 331
SMA. See Spinal muscular atrophy (SMA);	TCR gene therapy, 331–333
Supplementary Motor Area (SMA)	Solution method, 616–619
Small guide RNA (sgRNA), 222–223	DSM, 618
Small molecules, 214, 527–529, 533–536, 559–560,	process economics, 618
565	single-objective vs. multi-attribute decision-
Small-and medium-sized enterprises (SMEs),	making, 618–619
669–671	value systems modelling, 618
SMEs. See Small-and medium-sized enterprises	'what-if' scenario analysis, 618
(SMEs)	Somatic cell therapy medicinal products (sCTMPs)
SNPs. See Single-nucleotide polymorphisms	587
(SNPs)	SOPs. See Standard Operating Procedures (SOPs)
Societal pressures, 777–778	South Korea Ministry of Food and Drug Safety
Societal responsibility, 769–771	(KFDA), 358
Societal value, 762–763	South Korean FDA. See South Korea Ministry of
Society's responsibility, 769–771	Food and Drug Safety (KFDA)
SOCS. See Suppressor of cytokine signalling	Spark Therapeutics, 409, 415–416, 652–653
(SOCS)	Specificity, 696–697
Sofosbuvir, 708–709	Spinal cord injury, 216
Solid and functioning healthcare system, 769	Spinal muscular atrophy (SMA), 716
Solid organs, 262	SR-Tiget. See San Raffaele Telethon Institute for
Solid scaffolds, 250	Gene Therapy (SR-Tiget)
Solid tumour oncology	Stabilisation of disease (SD), 306
CAR-T cells	Standard Operating Procedures (SOPs), 257–258
insufficient migration and infiltration,	Staphylococci, 227, 230
540–541	Staphylococcus aureus, 558–559
limitations in ability, 539–540	STAT-3. See Signal transducer and activator of
challenges in, 530–544	transcription 3 (STAT-3)
beyond checkpoint blockade, 531f	Stem cells, 159, 245–246
combination therapies, 548–557	and mechanisms of action, 269–270
enhanced killing capabilities, 541–542	applications of materials to, 270–271
few tumour-associated antigens targets, 538–539	stem cell-based study, 462, 463f
immunosuppressive tumour microenvironment,	therapy, 216
533–536	therapy for neuronal regeneration, 269
improved safety profile, 542–544	transplant, 18–19
intratumoural heterogeneity, 532	transplantations, 762–763

Stempeucel, 435–436	genes, 83
Stepwise gradual phase, 521–523	phosphoantigen BrHPP, 52
Stimulator of interferon genes (STING), 500	polymers, 249–250
STN. See Subthalamic nucleus (STN)	Synthetic Notch receptor (synNotch receptor),
Stochastic modelling, 619–620	635
Strategic alliances	System boundary, 608–610
deal, 655–656	manufacturing and supply chain systems,
landscape in 2017–18, 652–655	608–610
2000s landscape, 649–650	product development systems, 608
2010s landscape, 650–652	Systems pharmacology, 563–564
perspectives, 656	7 1 377
Strategic checklist for new pharmaceuticals,	T
778–780, 779f	αβT cell depleted grafts (αβTCD grafts), 50
Strategy for UK Life Sciences, 669, 684–685	T cell depletion (TCD), 51
Streptococci, 227, 230, 581	T cell engineering. See also Tissue engineering
Streptococcus pyogenes, 585	and CAR-T cell therapy development, 69,
Stressed cell response (SCR), 493	80–81
Striatum, 474	adoptive cell therapy, 69–73
Strimvelis, 293–295, 294t, 597–598, 706–707,	CAR, 73–77
716–717, 720	perspectives, 83–84
business, 26	transforming T cell therapies into commercial
development, 22–28	reality, 81–83
efficacy, 23	viral vector-based gene transfer, 77–80
payment and reimbursement for curative	timeline, 70f
treatments, 27–28	αβ T cells, 41–42, 584
factors in treatment value and cost of drug, 27t	γδ T cells, 44–58
registry, 23–24, 24t	obstacles to development and implementation o
strategic alliance, 22–23	therapies, 53–54
success	potential for $\gamma\delta$ T cells as primary effectors,
collaboration and division of expertise, 25–26	48–53
treatment manufacturing, 26	allogeneic $\gamma\delta$ T cell therapy in setting of
vector improvement, 25	HSCT, 50–51
Structural databases to design molecules, 190	autologous γδ T cell therapy, 49–50
Structured data, 189	cell manufacturing strategies, 52–53
Substantia nigra pars compacta, 474	DLI therapy, 51
Subthalamic nucleus (STN), 474–476	in vivo activation and expansion, 48–49
Suicide switch, 697	
	γδ T cell-based immunotherapies, 54
Sumitomo Dainippon Manufacturing Plant, 194 Sunitinib, 550	T helper 1 cells (TH1 cells), 97 T lymphocyte, 696
	, , ,
Supplementary Motor Area (SMA), 474	T-bodies, 41, 583, 691
Supply chain in TCR-engineered T cells, 396–399	T cell receptor–engineered T cells. See also
Suppressor of cytokine signalling (SOCS), 533–536	Engineered T cell therapy
Swissmedic FDA, 358	biomarkers and improving responses,
Switches, 697–698	394–396
synNotch receptor. See Synthetic Notch receptor	clinical development considerations, 392–394
(synNotch receptor)	clinical experience with, 385–392
Synthetic	initial three studies, 385–389
biology approaches, 564	manufacturing and supply chain, 396–399
gene circuits, 635	therapy studies, 386t–388t

T cell receptors (TCRs), 44-45, 72, 92, 331-332,	Technology adoption curve, 673-674, 673f
378-379, 492, 530-532, 692, 698. See also	'Technology Appraisals' network, 675–676
Engineered T cell therapy	Tekniikan edistämiskeskus (TEKES), 669-671
chains, 382	TEMCELL HS, 435–436
classes of antigens targetable by, 383t	TERT, 452
gene therapy to treat solid tumours, 331-333	Tetrahymena, 450
identifying targets and development, 383–385	TFL. See Transformed follicular lymphoma (TFL)
mutation frequencies, 384t	TFP. See Total productivity factor (TFP)
and peptide–MHC interface, 380f	TGF-β. See Transforming growth factor β
population coverage with multiple, 381f	(TGF-β)
structure and function, 379–382	TH1 cells. See T helper 1 cells (TH1 cells)
TCR-engineered T cell therapy, 538-539	β-Thalassaemia, 10–11
TCR-driven recognition, 530-532	Thalassaemia Intermedia, 411–412
T cells, 4-5, 378-379, 396, 583-584, 691. See also	Thalassaemia Major, 411–412
Chimeric antigen receptor T cells (CAR-T	Thalassaemia Minor, 411–412
cells)	Thalassaemia trait, 410–411
engineering, 584	The Cancer Genome Atlas (TCGA), 194
growth factor, 71–72	TheraCyte device, 162, 167
persistence, 71–72	Therapeutic antitumour immunity, 121
therapy, 377	Therapeutic gene (transgene), 15–16
transforming into commercial reality, 81–83	6-Thio-2'-deoxyguanosine (6-thio-dG), 559–560
T-flasks, 614	Third-generation
T1D. See Type 1 diabetes (T1D)	ADV vectors, 17–18
TAA. See Tumour-associated antigens (TAA)	CARs, 697–699
TAAT cells. See Tumour-associated antigen T cells	Third-Party/government financing, 422–423
(TAAT cells)	Three-dimension
TALENs. See Transcription activator-like effector	architecture, 247–248
nucleases (TALENs)	bioprinting, 250
Talimogene laherparepvec. See Imlygic	printing, 271–272
TAMs. See Tumour-associated macrophages	Throughput, 611
(TAMs)	TIC. See Cell Therapy Technology and Innovation
TAN. See Tumour associated neutrophils (TAN)	Centre (TIC)
TAP. See Transporter associated with antigen	TILs. See Tumour-infiltrating lymphocytes (TILs)
processing (TAP)	TIM-3. See Mucin domain-3 protein (TIM-3)
Target antigens, 330–331	Tisagenlecleucel, 377, 583–584, 589, 706–707, 720
expression, 395	Tissue engineering, 243–245, 271–272. See also T
Targeted therapies, 548–550, 552–554, 558–560,	cell engineering
749–750	biomaterials, 247–256
Targeting	cells in cellular and tissue therapies, 245–247
immune suppressive signalling, 120–121	elements of, 245f
patrolling DC and releasing natural potential,	key considerations in applications, 245
498–500	manufacturing, 258–263
Task precedence constraint methodology, 614–615	cell and tissue manufacturing infrastructure,
TCD. See T cell depletion (TCD)	260
TCGA. See The Cancer Genome Atlas (TCGA)	cell therapy manufacturing and product
TCR. See αβ T cell receptor (TCR)	complexity, 261–262
TCRs. See T cell receptors (TCRs)	clean room environmental classification, 261t
TDO. See 2,3-Dioxygenase (TDO)	regulatory environment, 258–260
Technological progress prediction, 9–11	scale up for manufacturing, 262–263

process development, 256-258 Transformative therapy, 719, 721–722 regenerative medicine clinical translation developers and manufacturers, 736 changing paradigm, 263-265 Transformative value, 713-717 translating bench research to clinical Transformed follicular lymphoma (TFL), 324 Transforming growth factor β (TGF- β), manufacturing, 256 98, 525 upcoming technologies, 250–252 secretion, 120 allogenic treatments, 251 combinatorial therapies, 251–252 transgene. See Therapeutic gene (transgene) Translational infrastructure, 669-671 genetic modifications, 251 tissue-engineered products with scaffolds, 252 Transporter associated with antigen processing (TAP), 379 vascularisation of engineered organs, 252 tissue-engineered products, 253t-255t Trastuzumab, 119 Tissue manufacturing infrastructure for cGMP Tregs. See Regulatory T cells (Tregs) Compliance, 260 Trial and error process, 160 Tissue therapy, cells in, 245–247 2,4,6-Trinitrophenyl (TNP), 74 Tissue-engineered products, 587 TRX518, 533-536 with scaffolds, 252 tSCs. See Tumour-initiating stem cells (tSCs) TKIs. See Tyrosine kinase inhibitors (TKIs) Tuberculosis vaccine, 581 TLR. See Toll-like receptors (TLR) Tubular hollow organs, 262 TLS. See Tumour lysis syndrome (TLS) Tumour associated neutrophils (TAN), TME. See Tumour microenvironment (TME) 519-520 Tumour lysis syndrome (TLS), 306-308, 335 TML. See Tumour mutational load (TML) Tmunity, 636, 644 Tumour microenvironment (TME), 507–508, TNF. See Tumour necrosis factor (TNF) 517-518, 520-521, 536-538, 545-547, TNF-related apoptosis-inducing ligand (TRAIL), 552-554 immunosuppressive, 533–536 TNFRS. See Tumour necrosis factor receptor Tumour microenvironment, NK cells in, 97–100 superfamily (TNFRS) NK cells activity regulation by tumour cells, TNO. See Toegepast Natuurwetenschappelijk 99-100 Onderzoek (TNO) regulatory T cell, 99 TNP. See 2,4,6-Trinitrophenyl (TNP) suppression of natural killer cell activity by Tocilizumab, 759 **MDSC**, 99 Toegepast Natuurwetenschappelijk Onderzoek suppressors effect in, 99–100 (TNO), 669-671 Tumour mutational load (TML), 507–508 Toll-like receptors (TLR), 498–500 Tumour necrosis factor (TNF), 93, 321–322 TONIC clinical trial, 525-527 TNFα, 96-97, 525-527 Total productivity factor (TFP), 668 Tumour necrosis factor receptor superfamily (TNFRS), 554-555 Toxicity considerations, 393–394 Tracking platform, 757 Tumour-associated antigen T cells (TAA T cells), Tracking role of mechanical forces on cell 303 behaviour, 199 Tumour-associated antigens (TAA), 41 Traditional pharmaceuticals, 747 targets, 538-539 TRAIL. See TNF-related apoptosis-inducing Tumour-associated macrophages (TAMs), 519-520 ligand (TRAIL) Tumour-infiltrating lymphocytes (TILs), 16-17, Transcription activator-like effector nucleases (TALENs), 214, 292–293, 585–586, 71–72, 78, 385, 533–536, 554–555, 637-638 659-660 Transcyte, 597, 599, 649–650 Tumour-initiating stem cells (tSCs), 529 Transformative effect, 713-714 sensitisers, 559-560

Tumours, 515–517	Upstream operations process parameters, 611-614,
tumour cells, NK cells activity regulation by,	612f
99–100	US FDA. See United States Food and Drug
tumour-derived cytokines, 98	Administration (US FDA)
tumour-derived inhibitory factors, 54	USPTO. See United States Patent and Trademark
tumour-specific CAR, 695	Office (USPTO)
tumour-specific T cells, 73	UTRs. See Untranslated regions (UTRs)
21st Century Cures Act, 8–9, 778–780	Vaccinia, 286
Type 1 diabetes (T1D), 157–158	'Valleys of death', 663–664
cell therapy using cadaver-derived islets and	Valoctocogene roxaparvovec, 415
immune suppression, 158–159	Value, 423–425
Type 2 diabetes (T2D), 157	of CAR-T therapies, 761–766
Tyrosine kinase inhibitors (TKIs), 545–547	societal, 762–763
	systems modelling, 618
U	Value-based pricing (VBP), 420–421, 423
UAB. See University of Alabama at Birmingham	implementation in United States, 420–428
(UAB)	logistical and regulatory barriers, 423–427
UCART123, 637–638	Vascular endothelial growth factor (VEGF),
UCB. See Umbilical cord blood (UCB)	507–508, 538–539, 557
UK. See United Kingdom (UK)	Vascularisation, 167–168
UK Cell Therapy Manufacturing Centre, 679	VBA. See Visual basic for application (VBA)
UK Regenerative Medicine Platform (UKRMP),	VBP. See Value-based pricing (VBP)
660, 680	VC-01 STEP ONE clinical trial, 176
UL-16 binding proteins (ULBP1–6), 46	VCTs. See Venture Capital Trusts (VCTs)
Umbilical cord blood (UCB), 19, 104	Vectibix. See Panitumumab
UCB-derived NK cells, 104	Vectors
Uncertainties, 619–621, 712	development, 17–18
Unencapsulated pancreatic progenitor cell implants,	of gene therapy, 286–287
164	improvement in Strimvelis, 25
UniQure, 416–418	VEGF. See Vascular endothelial growth factor
United Kingdom (UK), 661, 713	(VEGF)
innovation infrastructure, 676	'Vein-to-vein' cell journey, 756
treasury department, 682	Venture capital
United States Food and Drug Administration (US	incentives, 672–673
FDA), 15, 358, 583–584, 587, 633	investment, 683–684 Venture Capital Trusts (VCTs), 682
FDA-approved CAR-T therapies, 634t United States National Institutes of Health (NIH),	Very good partial response (VGPR), 327–328
54–55, 194, 332–333	Vesicular stomatitis virus (VSV), 78–79
United States Patent and Trademark Office	VGPR. See Very good partial response (VGPR)
(USPTO), 690, 701–702	Vincristine, 548–550
Universal CAR-T cell (U CAR T 19 cell). See	Viral gene transfer, 80
'Off-the-self' CAR-T cells	Viral gene translet, 60 Viral vectors, 286, 292, 755–756
'Universal' CAR-expressing cells, 700–701	viral vector-based gene transfer, 77–80
'Universal' donor approaches, 82	viral vector–based gene translet, 77 66 viral vector–mediated methods of GT, 32–33
University of Alabama at Birmingham (UAB), 51,	'Virtual patient' concept, 780
56–57	Virus
Unmanipulated allogeneic T cell therapy, 41–42	production, 78–79
Unstructured data, 189	virus-infected cells, 47–48
Untranslated regions (UTRs), 222	Virus-like particles (VLP), 499
	I

Visual basic for application (VBA), 621
Vitruvian networks, 655
VLP. See Virus-like particles (VLP)
von Willebrand disease (VWD), 413–414, 419
gene therapy for, 419–420
Voretigene neparvovec, 427–428
Voretigene neparvovec, 706–707, 716, 718–719
Voretigene neparvovec-rzyl. See LUXTURNA
VSV. See Vesicular stomatitis virus (VSV)
VWD. See von Willebrand disease (VWD)
Vγ9Vδ2+ T cells, 46
Vδ1+ T cells, 46–48
Vδ2+ T cells, 45–46

W

WAS. See Wiskott–Aldrich syndrome (WAS)
Weighted sum technique, 619
Weismann barrier, 450, 451f
Weismann hypothesis, 450
Western medicine', 91
'What-if' scenario analysis, 618
White blood cells, 747–748
WHO. See World Health Organization (WHO)
William's antagonistic pleiotropy, 451–452
Wiskott–Aldrich syndrome (WAS), 19–20
World Health Organization (WHO), 463–464, 777–778

X

X-linked severe combined immunodeficiency (SCID-X1), 19–20, 288, 290 gene therapy trial, 289 Xenogeneic antigen, 249 Xenograft breast tumour model, 119

Υ

Yamanaka protocol, 477–478 YESCARTA, 293–295, 693

Z

Zalmoxis, 293–295, 294t
Zidovudine, 559–560
Zinc finger nucleases (ZFNs), 214, 292, 412, 585–586, 637–638
Ziopharm Oncology, 635–636
Zoledronate, 45–46
Zoledronate alone and in combination with IL-2 (ZOL/IL2), 48–49
Zolgensma, 293–295
ZUMA-1 trial, 323–324, 341, 362–363
ZUMA-3 trial, 314–315
Zwitterionic detergents, 249
Zynteglo, 293–295
Zytiga. See Abiraterone acetate