Subject Index

ABCpred, 84
Acid alpha-glucosidase (GAA), 38
Activated coagulation FIX (FIXa), 148
Activated partial thromboplastin time (aPTT), 208–209, 211
Activated prothrombin complex concentrate (APCC), 37, 157–159
Acute coronary syndrome (ACS), 227
Adaptive immune system, 3–5, 76–77
AERx® iDMS, 142–143
Aggregates and array structures, 99–103
Alfa4-integrin antagonist, 39
American Association of Pharmaceutical Sciences (AAPS), 70
Anemia, 117
Anti-antibodies, 199–200
Anti-antibody responses (AARs), 103
Antibodies detection assays, 58, 69
Anti-EPO antibodies
  ELISAs for, 116
  neutralizing capacity, 116
  radioimmunoprecipitation assay (RIPA), 115–116
  SPR analysis, 116
Anti-GA antibodies, 40–41
Antigen presenting cells (APCs), 16–18
  antigen uptake, processing and presentation by, 5–8
Antigen processing and presentation, 9–11
Anti-infliximab antibodies, 198
Anti-natalizumab antibodies, 181–182
Antithrombin (AT), 206
Anti-TNF antibody constructs, 190–194
  immunogenicity of, 194–200
Anti-Xa assay, 208
Apidra®, 138
Argatroban, 225–227
AT-thrombin complex (TAT), 206–207
Avonex, 42, 44, 130
B-cells, 5, 76
  epitope identification, protein immunogenicity and, 82–84
  receptors (BCRs), 4, 13, 16
Bechterew's disease, 190
Bepipred, 84
Bet v 1 homologues, in vegetables, 88
Betaferon, 42–44, 130
Betaseron®, 130
BIAcore analysis, 116
Binding Abs (BAbs), 128
  binding assays for, 131–132
  and NAbs, 131
Binding assays
  antibody positive samples, confirmation of, 63
  biosensor-based immunoassays, 62
  immunoassays, 58–61
  radioimmunoprecipitation assays (RIPA), 61
Bioinformatics, immunogenicity prediction and, 84–89
Biopharmaceuticals, immunogenicity
  causes
    aggregates and array structures, 99–103
    patient-related factors, 103–104
    product-related factors, 103
    structural characteristics of biomacromolecule, 97–99
  clinical aspects
    adverse drug reactions, 39–40
    drug efficacy, reduction in, 31–35
    endogenous protein, cross-reaction with, 35–36
    in gene-defective hosts, 36–39
    glatiramer acetate (GA), 40–41
    growth hormone, 27–29
    insulin, 29–31
    interferon-β (IFNβ), 41–42
    neutralizing antibodies (NAbs), *see* Neutralizing antibodies (NAbs)
  danger model, self *versus* non-self, 16–18

methods for reduction of
biomacromolecule, modification of, 103–104
clinical measures, 105–106
formulation improvement, 104–105
structure optimization, 102–103
Biosensor-based immunoassays, 62
Biosimilars
development, 106–107
and innovator product, potential differences between, 107–108
Bivalirudin, 219–225
Blocking assay, natalizumab antibody characterization in, 176–177
Blood coagulation factor VIII (FVIII), immunogenicity
concentrates, 149–150
and haemophilia A, 147–149
inhibitors, clinical features and treatment principles in haemophilia patients with, 156–161
inhibitory antibodies development, in haemophilia A, 150–155
B lymphocytes, 3, 195
T-cell-independent activation of, 13
Bovine insulins, 30–31
B19 parvovirus, 118
Bridging assay, 61

Carbohydrate epitope αGal (Galα1-3Galβ1–4GlcNAc-R), 99
$CD4^+$ T helper (Th) cells, 4
$CD8^+$ cytotoxic T lymphocytes (CTL), 4
Cell-based neutralization assays
format and design, appropriateness of, 64–65
neutralizing antibody assay, development and design, 65–68
Central tolerance mechanism, 13–15
Chemokine receptors (CCR), 6
12C4, high-affinity anti-natalizumab monoclonal antibody, 177
Chronic hepatitis C, IFNα-2a for, 34
Chronic kidney disease (CKD), 117–118
Chronic renal failure (CRF), 117
Cimzia™ CDP870, 191
Citrulline, 104
Clinical isolated syndrome (CIS), 46
CLIP (*cl*ass II-associated *i*nvariant chain *p*eptide), 9
Colony stimulating factors, 115–116
Continuous erythropoiesis receptor activator (CERA), 115
Continuous subcutaneous insulin infusion (CSII), 137
Copolymer-1, *see* Glatiramer acetate (GA)
Coumarins, 229
CpG motifs, 99
Crohn's disease, 174, 189–190, 192
Cytopathic effect (CPE) assay, 132–133
for NAbs, basic principle, 134

Danaparoid, 227–228
"Danger signals", 7, 100–101, 105
Danger model and biopharmaceuticals, self *versus* non-self, 16–18
Deep vein thrombosis (DVT), 205, 210–212
Dendritic cells (DCs), 2, 5–8, 76–77, 81
maturation, MHC regulation and, 11–12
priming of lymphocytes by, 12–13
Diabetes, insulin immunogenicity and, 137–138
children and adolescents with, 140–141
pregnant women with, 141
DiscoTope algorithm, 87
Disseminated intravascular coagulation (DIC), 214–215
Drug reactions, adverse, 39–40

Electrochemical luminescence (ECL) detection systems, 58, 61
ELISPOT assay, 82
EMEA guideline, 240
on antibody assays, 70
on biosimilar medicinal products containing recombinant erythropoietins, 120–122
Enbrel™, 191
Endocytosis, receptor-mediated, 8
End-stage renal disease (ESRD) therapy, 117
Enzyme-linked immunosorbent assays (ELISAs), 58, 61, 82, 131–132, 196
for detection of anti-EPO antibodies, 116
natalizumab antibody detection by, 175–176
Epitope mapping by phage, 83–84
Epoetin β, 114
Eprex-associated PRCA, 119
Erythropoietin (EPO), 35–36
biosimilars, 120–122
clinical relevance and therapeutic consequences, 117–120
manufacturers of variants and rhEPO, 114–115
structure and function, 113–114
Erythropoietin receptor (EPOR), 114
Exubera®, 142–143

"Fast-acting" insulin analogues, 31
Fc receptors (FcR), 7
FcγRIIa receptor, 212–213
Federal Food, Drug, and Cosmetic Act (FFDCA), 107
Feedback-restrained molecular dynamics (FRMD), 83
Fondaparinux, 227

Glatiramer acetate (GA), 40–41
Granulocyte macrophage colony stimulating factor (GM-CSF), 17, 32–33, 69–70, 78

Haemophilia A, 36–38, 98
  blood coagulation factor VIII and, 147–149
  inhibitory antibodies development in, against FVIII, 150–155
Haemophilia B, 36–38, 98
Helper T-cells (T_h-cells), 76–77
Hematite™, 115
"Heparin resistance," 209
Heparin-induced platelet aggregation assay (HIPA), 217
Heparin-induced thrombocytopenia (HIT), 205
  administration, 208
  chemistry and source, 206
  clinical presentation of, 214
  definition, 214
  diagnosis, 215–217
  dosing, 209
  heparin resistance, 209
  history of, 213
  incidence of, 213
  indications, 206
  low molecular weight heparins (LMWHs), 210–212
  mode of action, 206–207
  monitoring, 208
  presentation, patterns of, 215
  treatment, 217
    argatroban, 225–227
    bivalirudin, 219–225
    coumarins, 229
    danaparoid, 227–228
    fondaparinux, 227
    lepirudin, 218–219
    re-exposure to heparin, 229–230
Heparin-induced thrombocytopenia and thrombosis syndrome (HITTS), 213
Hepatitis B and C virus, 128
Hirudo medicinalis, 218
Humalog®, 138–139
Human anti-chimeric antibodies (HACA), 197
Human anti-human antibodies (HAHAs), 103
Human IgG1-kappa constructs, 196
Human insulin (HI), 31, 138–141
Human leukocyte antigen (HLA), 9–10
Humira, 103, 191

IFN-alpha receptor (IFNAR), 128, 132, 135
IFN-stimulated regulatory elements (ISRE), 128, 133
IgM and IgG antibody, 41, 76
Immune tolerance induction (ITI) therapy, 156, 160
Immunoassays, 58–61
  See also Specific types
Immunoblotting techniques, 131
Immunogenicity
  of anti-TNF antibody constructs, 194–200
  of blood coagulation factor VIII (FVIII), *see* Blood coagulation factor VIII (FVIII), immunogenicity
  of insulin, *see* Insulin, immunogenicity
  mechanisms
    adaptive response, 76–77
    innate response, 75–76
  natalizumab, *see* Natalizumab, immunogenicity
  prediction, bioinformatics and, 84–89
  prediction using
    bioinformatics, 84–89
    in vitro techniques, 80–84
  risk assessment, *see* Immunogenicity risk assessment
  of therapeutic proteins, 77–78
    testing, using animals, 78–80
Immunogenicity, of biopharmaceuticals
  causes
    aggregates and array structures, 99–103
    patient-related factors, 103–104
    product-related factors, 103
    structural characteristics of biomacromolecule, 97–99
  clinical aspects
    adverse drug reactions, 39–40
    drug efficacy, reduction in, 31–35
    endogenous protein, cross-reaction with, 35–36
    in gene-defective hosts, 36–39
    glatiramer acetate (GA), 40–41
    growth hormone, 27–29
    insulin, 29–31
    interferon-β (IFNβ), 41–42
    neutralizing antibodies (NAbs), *see* Neutralizing antibodies (NAbs)
  methods for reduction of
    biomacromolecule, modification of, 103–104
    clinical measures, 105–106
    formulation improvement, 104–105
    structure optimization, 102–103
Immunogenicity risk assessment, 239
  common deficiencies, 251–253
  key questions for, 241–251
  regulatory guidance, 240
  risk evaluation, 241
  risk factors identification, 240
  risk management, 241
Immunoglobulin (IgG) antibodies, 118, 139, 151
Immunological tolerance
  central, 13–15
  peripheral, 15–16
Innate cells, impact of proteins, 81

Innate immune system, 2–3, 75–76
Insulin, immunogenicity
  diabetes mellitus and, 137–138
  pulmonary, 141–143
  in special populations, 140–141
  subcutaneously administered, 139
  treatment with insulin analogues, 139–140
Insulin replacement therapy, 29
$\alpha_4\beta_1$-Integrin, 174
Interferon alfa (IFNα), 33–34
Interferon beta (IFNβ), 34–35, 41–42, 46, 104, 127
  clinical relevance and therapeutic consequences, 135
  detection methods
    BAbs, binding assays for, 131–132
    NAbs, bioassays for, 132–135
  efficacy, effects of NAbs on, 43–45
  immune reactions against, 130
  structure and function, 128–130
Interferon (IFN)-γ, 12, 33, 77
Interleukin-10 (IL-10), 152

JAK-STAT-signal pathway, 114

Kawade assay, 133

Lantus®, 138, 140
Leachables, 104
Lepirudin, 218–219
Levemir®, 138, 140
"Long-acting" insulin analogues, 31
Low molecular weight heparins (LMWHs), 210–212, 215, 217, 229–230
Lymphocyte activation
  MHC regulation upon DC maturation, 11–12
  priming, by DC, 12–13
  T-cell-independent, 13

Macrophage-colony stimulating factor (M-CSF), 81
Macrophage inflammatory protein (MIP), 6
Macrophages, 5, 76, 81
Macropinocytosis, 8–9
Macugen®, 104
Major histocompatibility complex (MHC), 4, 77, 152
  regulation, DC maturation and, 11–12
Megakaryocyte differentiation and growth factor (MDGF), 35, 57
Methionyl-rhGH, 29
MHC class I/II-restricted antigen presentation, 9–10
β2-Microglobulin, 43–44
MPID-T database, 88
Multiple daily injections (MDI) of insulin, 137
Multiple sclerosis (MS), 40, 46
  IFNβ for, 34
  natalizumab in, action mechanism of, 173–174
  pivotal phase III trials, 180
  symptoms, 135
  treatment, in patient with antibodies against IFNβ, 41–46
Multiple sequence alignment algorithm (PILEUP), 83
Myelin basic protein (MBP), 40
Myxovirus resistance protein A (MxA) assay, 43, 132–133, 135

Naïve antigen-specific T-cells, 7
Natalizumab, immunogenicity
  bioanalytical assays for, 175–178
  data from preclinical and clinical studies, 179–181
  efficacy, 182–183
  in MS, action mechanism, 173–174
  pharmacodynamics, 181
  pharmacokinetics, 181–182
  safety, 183–184
  use, 174
Natural killer (NK)-cells, 6–7, 33
Neopterin, 43–44
Neulasta®, 104
Neutralizing antibodies (NAbs), 128
  assays, 58, 64–65
    development and design, 65–68
  BAbs and, 131
  bioassays for, 116
  dynamics, 42–43
  effects, on IFNβ Efficacy, 43–45
  elimination, 45
  IFN-beta, 132–135
  prevent formation of, 45–46
Neutral protamine Hagedorn (NPH) insulin, 138, 140
3-Nitrotyrosine, 104
N-methionine-free rhGH, 29
NOD-like receptors (NLRs), 2–3
Novastan, *see* Argatroban
NovoRapid®, 138, 140–141, 143
NovoSeven®, 158
Nucleotide-binding oligomerization domain (NOD), 2

Oral antidiabetic drugs (OADs), 137

Pathogen-associated molecular patterns (PAMPs), 2–3, 7
Pattern recognition receptors (PRRs), 2, 7

PEGylation, 115, 244
of amino groups, 104
of liposomes, 100
Peripheral tolerance, 15–16
Phage-displayed oligopeptides, immunoscreening, 83
Phagocytosis, 9
Plasma-derived factor VIII (pdFVIII), 149
See also Blood coagulation factor VIII (FVIII), immunogenicity
Plasmapheresis, 230
Platelet factor, 4 (PF4), 212
Polyethylene glycol (PEG), 100, 103–104
Pompe disease, 38–39
Porcine FVIII, 157
Porcine insulins, 30–31
Programmed cell death 1 (PD1), 16
Progressive multifocal leukoencephalopathy (PML), 174
Proteasome, 10
Public Health Safety Act (PHSA), 107
Pulmonary embolism (PE), 205
Pulmonary insulin, 141–143
Pure red cell aplasia (PRCA), 35–36, 118–120, 122

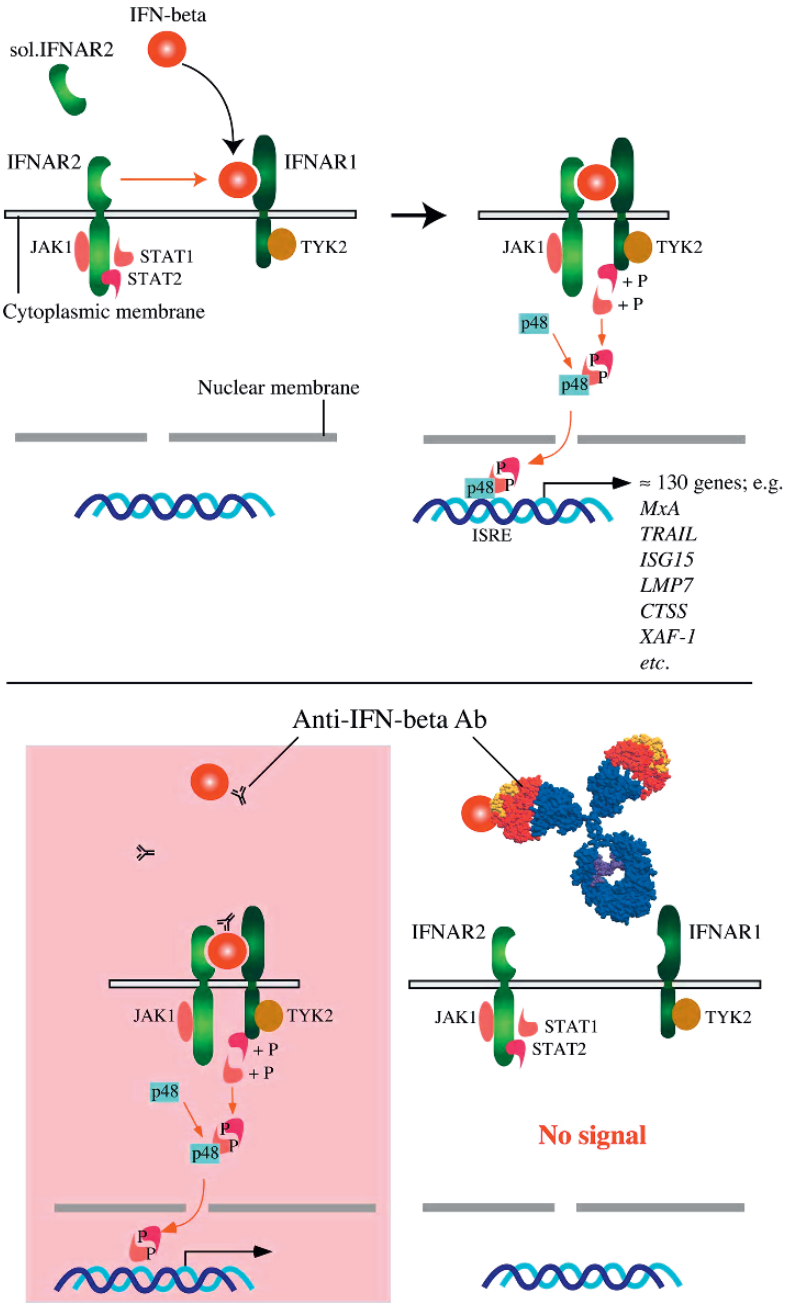
Radioimmunoprecipitation assays (RIPA), 61, 251–252
anti-EPO antibodies analysis by, 115–116
Rebif®, 130
Recombinant factor VIII (rFVIII), 149–150, 158–160
Recombinant forms of human growth hormone (rhGH), 27–29
Recombinant human erythropoietin (rhEPO), 35–36
manufacturers of, 114–115
See also Erythropoietin (EPO)
Relapsing-remitting multiple sclerosis (RR-MS), 41, 43
See also Multiple sclerosis (MS)
Remicade™, 191
Renal cell carcinoma, IFNα-2a for, 34
Rheumatoid arthritis (RA), 190, 192

Saccharomyces cerevisiae, 218
Sandoz's Omnitrope, as biosimilar, 107
Serotonin release assay (SRA), 217
Serum sickness syndrome, 245
Small interfering RNA (siRNA), 3, 99
SPA algorithm, 84
Surface plasmon resonance (SPR), 58
for anti-EPO antibodies detection, 116

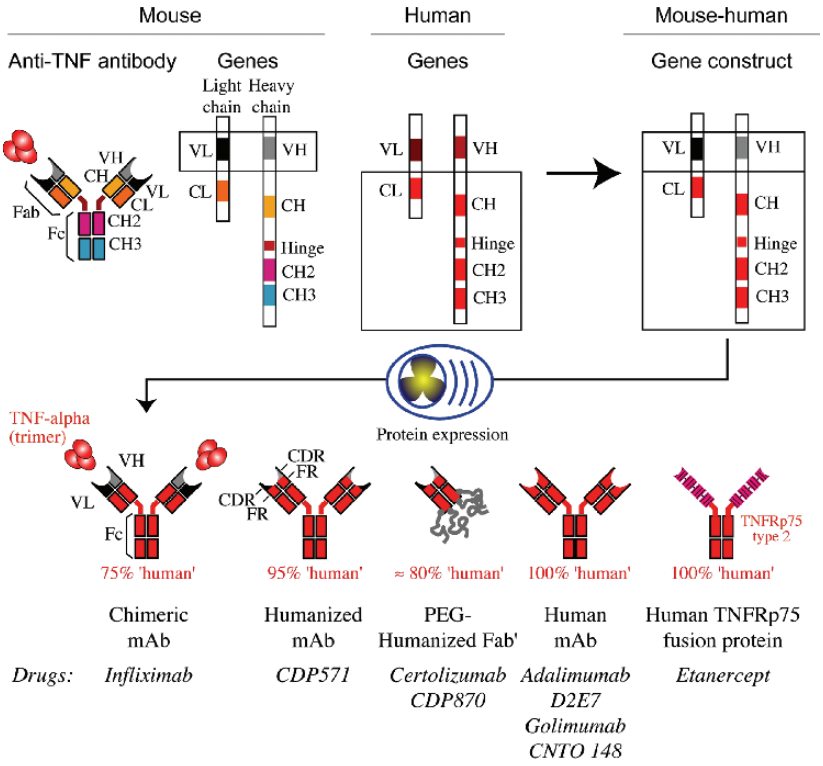
T-cell epitope
identification, protein immunogenicity and, 81–82
mapping, based on amino acid motifs, 88–89
T-cell receptors (TCR), 4, 13, 15
Theiler's virus model of demyelinating disease, 41
Therapeutic proteins, immunogenicity of, 77–78
testing, using animals, 78–80
Thrombocytopenia, 35
Thrombotic thrombocytopenia purpura (TTP), 215
TNF receptor (TNFR), 191
Toll-like receptors (TLRs), 2–3, 7
Tumor necrosis factor (TNF)-α/β, 77, 152, 190
Type II HIT, *see* Heparin-induced thrombocytopenia and thrombosis syndrome (HITTS)
Type I interferons (IFNs), 33–35, 128, 133
signaling, 129

Vascular cell adhesion molecule-1 (VCAM-1), 174
Venous limb gangrene (VLG), 214
Venous thromboembolism (VTE), 205, 209–211
von Willebrand factor (VWF), 148

X_a inhibition assay, 208
Xase complex, 148, 151



Color Plate 1 Type 1 IFN signaling and anti-IFN-beta BAb/Nabs.
The example shows IFN-beta signaling through IFN-alpha receptors 1 and 2 (IFNAR1 and IFNAR2). The *upper panel* shows ligand–receptor binding, association of the two receptor chains and intracellular signaling and activation of genes through IFN-stimulated regulatory elements (ISRE). The *left lower panel* shows anti-IFN-beta BAbs (non-neutralizing) as they are often depicted. The *right lower panel* shows the correct size relations.



Color Plate 2 Genetically engineered anti-TNF antibody constructs.
The upper panel shows the light and heavy chain genes spliced together from TNF-alpha-immunized murine splenocytes (VL and VH segments) and from human IgG1 (CL, CH, Hinge, CH2, and CH3 segments). The chimeric protein, infliximab, is produced when the gene constructs are expressed in antibody-secreting immortalized myeloma cells.
Abbreviations: VL and VH: variable regions of IgG on light and heavy chains, respectively; CL, CH, CH2, and CH3: constant regions of IgG on light and heavy chains, respectively; Fab: fragment antigen binding, including the variable parts of IgG; Fc: human IgG1 Fc region; CDR: complementarity-determining regions; FR: framework regions; mAb: monoclonal antibody; PEG: polyethylene glycol; TNF: tumor necrosis factor; TNFRp75: tumor necrosis factor receptor type 2.