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Immunoglobulins – Basic considerations

■ **Abstract** Immunoglobulins (Igs) or antibodies (Abs) are the principal operators of the adaptive humoral immune response. For optimum functional activity they acquire an optimized structure for antigen (Ag) recognition, precipitation, agglutination, phagocytosis (IgG1/3 and IgA), cytotoxicity (IgG1/3), transport through mucosa (IgA and IgM) and placenta (IgG1/3), complement activation (IgG1/3 and IgM) and release of inflammatory mediators (IgE). A diversity with potentially up to 10^{15} different Ab specificities is generated during Ag-independent B cell development in the bone marrow by combinatorial V-D-J joining, creation of junctional diversity, and

combinatorial association of L and H chains. Furthermore, Ab variety is created during Ag-dependent B cell maturation in peripheral lymphatic tissues by isotype class switching and somatic hypermutation. Two types of enzymes play a key role in Ab diverseness, i. e., the products of recombination-activating genes RAG1 and RAG2 and the affinity induced deaminase (AID). The prevailing adult-type B2 cells provide the basis for the acquired humoral immune response characterized by Ab production, Ag processing and presentation, immunological memory and tolerance along with the generation of the anti-idiotypic network, whereas the fetal-type B1 cells may play a role in innate immunity and autoimmunity. Impairment of B cell immunity includes immunodeficiency (agammaglobulinemia), malignant transformation (leukemia, lymphoma, plasmocytoma) and immune dysregulation (allergy, autoimmunity). The diagnostic

relevance of Abs comprises classical serology (immunoprecipitation, agglutination, complement binding, RIA, ELISA), immunocytochemistry and immunohistochemistry, immunofluorescence (microscopic and flow cytometric), cytotoxicity tests, immunoblots, immunospot assays and immunoabsorption (affinity chromatography). Therapeutic application of Abs (passive immunization) is directed against infections, intoxications, solid tumors, leukemias and lymphomas, graft rejection and graft-versus-host reaction, hemolytic anemia, and autoimmune diseases. The generation of genetically engineered monoclonal Abs (mAbs) has revolutionized the diagnostic and therapeutic potential of Abs in almost all disciplines of modern medicine.

■ **Key words** B cells · antibody structure · antibody genetics · antibody diagnostics · antibody therapy · monoclonal antibodies

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Introduction – history

The hallmark of immunity is specificity of recognition. In body fluids (“humor”) antibodies (Abs) recognize small antigenic structures, the antigens (Ags), which they neutralize and eliminate by various mechanisms. The discovery of this so-called humoral immunity dates back to the 1890s, when Emil von Behring and

Shibasaburo Kitasato discovered that serum of animals immunized to *Corynebacterium diphtheriae* could prevent diphtheria in un-immunized animals and attenuate the disease in humans. The chemical nature of the responsible serum component(s) that neutralize and precipitate toxins as well as agglutinate and lyse bacteria was unknown at that time, but in 1907 Svante August Arrhenius undertook the first mathematical approach to disclose physical and chemical principles of Ag-Ab in-

teractions in a publication entitled “Immunochemistry: The application of the principles of physical chemistry to the study of the biological antibodies”. It was Karl Landsteiner, the discoverer of the blood groups, who in the 1930s provided closer insight into the specificity of Ab recognition by analyzing immunoprecipitation on a molecular level. He named it a “serological reaction”. Michael Heidelberger, Oswald Avery and Forrest Kendall quantified the Ag and Ab components of *pneumococcus* polysaccharide (PS)-Ab-complexes. They observed that both Ags and Abs are multivalent and that respective Abs are proteins in nature, which could exist in two forms featuring different mass and sedimentation rates (7S and 19S). These types of Abs are now called immunoglobulins (Igs) G and M (IgG and IgM).

A great enigma of early immunology was the origin of immune specificity. Two major theories tried to explain the phenomenon. The instructional theory, which was postulated among others by Linus Pauling, proposed that Abs upon binding to an antigenic template acquire a complementary configuration to the particular Ag. In contrast, Paul Ehrlich proposed a selective theory according to which preformed “side-chain” receptors bind an infectious agent that induces the release of more side-chain receptors of the same specificity. In the 1950s, the work of Niels Kay Jerne, David W. Talmage and Macfarlane Burnet suggested that a naïve lymphocyte expresses receptors displaying the identical unique specificity and that binding of the complementary Ag would lead to clonal proliferation of such activated lymphocytes. Thereby, Ehrlich’s selective theory was established in a modified form, known as the clonal-selection theory. It is widely accepted as the prevailing theory of acquired immunity, although the concept of Ab diversity still holds aspects of the instructional theory, especially when considering the Ag-driven somatic hypermutation (see below).

It became apparent that Abs are glycoproteins or γ -globulins (according to their electrophoretic mobility) synthesized by mature B cells and plasma cells in response to Ag-stimulation. Their structures were elucidated by Rodney R. Porter [12] through enzymatic cleavage (by papain) and by Gerald M. Edelman [4] through reduction of interchain disulfide bonds (by mercaptoethanol) as being composed of two light (L) and two heavy (H) polypeptide chains in their monomeric form. Subsequently, they were named Igs. In humans five Ig-classes (IgG, IgM, IgA, IgD and IgE) could be identified according to structural markers of the H chains and their multimeric assembly. The structure of the least abundant Ig, IgE, was resolved by precipitation of serum derived from an allergic patient with antisera to the hitherto known IgG, IgA, IgM and IgD by Kimishige and Teruko Ishizaka [6]. Independently, the group of Hans Bennich and S. Gunnar O. Johansson [14] analyzed the serum of a rare IgE plasmocytoma using

the Prausnitz-Küstner reaction, thereby confirming the structural evidence. Since then, especially with the advent of monoclonal Abs (mAbs) by the revolutionary hybridoma technique [8], Igs have become an inevitable tool for research, diagnostics and therapy in modern biology and medicine.

Structure and function of Igs

The basic structure of Igs comprises four polypeptide chains (two L and two H chains), which are connected by disulfide bridges. In humans, the L chains contain one variable and one constant region (domain), whereas the H chains are composed of three (IgG, IgA, IgD) or four (IgM and IgE) constant regions (Fig. 1).

The N-terminal variable and constant region of one L and one H chain constitute the Fab fragment (named according to “Ag binding”), whereas the remaining two to three constant domains of the two H chains constitute the C-terminal Fc-fragment (named according to “crystalline”). Structural differences in the Fc fragments are the basis for five different isotype classes of human Igs, i. e., IgG, IgM, IgA, IgD and IgE. IgG comprise four subclasses (IgG1, IgG2, IgG3 and IgG4) and IgA two subclasses (IgA1 and IgA2). In mice, the nomenclature of IgG subclasses differs from the human one. According to their function, murine and human IgG subclasses correspond to each other as follows:

<u>Human</u>	<u>Mouse</u>
IgG1	IgG2a
IgG2	IgG3
IgG3	IgG2b
IgG4	IgG1

Human IgM occurs commonly as pentamer or hexamer and IgA as dimer both with an additional j-chain (from “join”). The constant regions of the human L chains determine two types of L chains, i. e., κ chains and λ chains, that occur in a proportion of about 2:1 within the whole Ig repertoire. Pepsin digestion of Igs results in fragmentation of the Fc residue and persistence of two prolonged Fab residues, connected by one disulfide bond and forming the $F(ab')_2$ fragment. The basic function of the $F(ab')_2$ fragment is the binding of antigenic epitopes via complementarity determining regions (CDRs). Low affinity of one binding site in multimeric IgA or IgM can be compensated for by an increase of avidity, which is important for neutralization of thymus-independent (TI) PS-Ags that contain repetitive epitopes. The principle functions of the Fc fragment are the following (see also Table 1):

- receptor-mediated phagocytosis (IgG1/3 and IgA), cytotoxicity (IgG1/3) and release of inflammatory mediators (IgE),

bone marrow itself (in mice, rats and primates), in the gut-associated lymphoid tissue (of rabbits and ungulates) or in the bursa of Fabricius, an outpouching of the intestine of birds. The term B cells originates from bursa and bone marrow, respectively. In 1954 Bruce Glick and co-workers [5] observed by accident a missing Ab production to *Salmonalle typhimurium* in chicken after removal of the bursa, suggesting that bursa-derived lymphocytes are responsible for Ab formation. Based on this finding and due to the fact that in some rodents and in all primates the bone marrow was identified as bursa-equivalent organ, the term “B cell” was introduced to distinguish the cells responsible for the humoral immune response from the later recognized thymus-derived lymphocytes (T cells), which are responsible for the cellular immunity. In the peripheral lymphoid tissue (lymph nodes, spleen, GALT, BALT) naïve, but antigenically committed immunocompetent B cells mature to Ab-producing B cells and plasma cells, when contact to complementary Ags occurred. They can also develop to memory B cells; either in conjunction with T helper cells (thymus-dependent Ags, TD Ags) or uncontrolled from T cell help (thymus-independent Ags, TI Ags). Another phenomenon of B cell development is that early during ontogenic evolution so-called fetal-type B1 cells arise, whereas later in life adult-type B2 cells predominate. The characteristic features of both B1 and B2 cells are summarized in Table 2.

The function of maintained B1 cells in adult life is poorly understood, but certain clues point to a role in innate (“natural”) immunity and autoimmunity [9]. B cell maturation into Ab producing cells is regulated through the CD40/CD40L receptor-ligand pair, manifesting direct cell-cell contact with T helper cells, and by stage-dependent release of cytokines such as interleukin

1 (IL1) derived from macrophages, IL2 and interferon- γ (IFN- γ) derived from T helper 1 (Th1) cells, IL4, IL5 and IL6 derived from Th2 cells and transforming growth factor- β (TGF- β) derived from Th3 cells. The different cytokine patterns of Th1 and Th2 cells promote different Ig isotype class switching. In mice, via IFN- γ activation Th1 cells inhibit IgG1 production and enhance IgG2a production, whereas Th2 cells induce IgG1 and IgE production by IL4 release. B cells themselves also produce cytokines, such as IL6, IL10 and TGF- β , which interfere with both the humoral and cellular immune response. The final Ag-dependent B cell maturation is initiated by binding of Ag either in context with the major histocompatibility complex (MHC) class II molecules on T helper cells (for TD Ags) or in soluble form (for TI Ags) [10]. There are two types of TI Ags, i. e., the B cell mitogen lipopolysaccharide (LPS) (TI1 Ag), which activates immature and mature B1 and B2 cells, and bacterial PS containing repetitive sequences (TI2 Ags) that activate only mature B1 cells. TD Ag-dependent B cell activation requires cross-linking of B cell receptors that are composed of the Ag-recognizing 4-chain Ab molecule containing truncated H chains and of the signal-transducing invariant Ig α and Ig β chains. Additional Ag binding to the co-receptor complex CD19:CD21:CD81 augments activation signaling by a factor of more than 1,000. The intracellular signal cascades are induced by tyrosine phosphorylation of the intracellular domains of Ig α and Ig β that contain immune receptor tyrosine-based activation motifs (ITAMs) and of the CD19 molecule. Subsequently, MAP kinase, Ca⁺⁺ and protein kinase C (PKC) pathways are induced. They activate in turn the transcription factors AP1, NFAT and NF κ B, respectively. Thereby, genes are transcribed that promote final B cell differentiation into Ab producing B cells and plasma

Table 2 Properties of fetal-type B1 cells and adult-type B2 cells

Property	B1 cells	B2 cells
Location	Mainly epithelial	Everywhere
Self renewal	<i>in situ</i>	Bone marrow
Autonomous proliferation	yes (chronic lymphatic leukemia)	No
Life span <i>in vivo</i>	Long	Short or long
Hyperexpression of <i>c-myc</i>	Yes	No
CD5 expression	Yes	No
V region repertoire	Restricted	Diverse
Somatic hypermutation	No	Yes
Autonomous Ig production	High	Low
Memory	No	Yes
T cell help needed	No	Yes or no
Ig isotypes	IgM	IgM, IgG, IgA, IgD, IgE
Protein specificity	Rare	Frequent
Carbohydrate specificity	Frequent (TI2)	Rare
Anti-idiotypic antibody production	Frequent	Rare
Autoantibody production	High	Low

cells or into B memory cells that express high affinity membrane Abs. In addition, during all stages of B cell development there exists an essential cross-talk of the Ca^{++} and PKC pathways with the CD19 activated phosphoinositide 3-kinase (PI3K) pathway that is mediated by the Bruton type tyrosine kinase (Btk). TD Ag binding to the B cell receptor not only induces Ab production, but it can also result in Ag internalization, processing and presentation to Th1 cells. The TI1 Ag LPS stimulates polyclonal B cell activation via complex formation with LPS-binding protein (LBP), toll-like receptor 4 (TLR4) and CD14, whereas the TI2 Ags preferentially induce an IgM response of low affinity through the conventional B cell receptor of B1 cells.

Ag stimulation induces Abs with complementary Ag binding sites (paratopes) within the V region of Igs containing sequences (idiotypes) either within the paratope or outside the Ag binding site (see Fig. 1). The sum of idiotypes (idiotype) is unique for the Ab and can in turn induce anti-idiotypic Abs, which provide internal images of the primary (stimulating) antigenic epitopes. Based on this finding Nils Kay Jerne proposed in 1974 [7] a network theory of the immune system with the central assumption that idiotypic stimulation leads to formation of anti-idiotypic Ab1, which in turn stimulates formation of anti-anti-idiotypic Ab2 and so forth. However, anti-idiotypic Abs may not only exhibit stimulatory, but also inhibitory and suppressive properties, so that the anti-idiotypic Ab network may limit itself by decreasing Ab production after successive activation steps. Generally, the anti-idiotypic regulation should also apply to T cell receptors and may thereby stabilize the internal homeostasis of the immune system exerting regulatory influence on the immune response to both exogenous and endogenous Ags. The network theory has contributed to explanation of various immune phenomena such as explanation of self-nonsel self discrimination, repertoire selection, immunological tolerance, immunological memory, and mechanism of action of intravenous Ig (IVIg) therapy. Furthermore, anti-idiotypic vaccines hold promise for protection from infectious diseases as immunization with pathogenic Ags can be avoided.

■ Monoclonal Abs

In order to obtain high (potentially unlimited) quantities of pure Abs of one defined specificity, Köhler and Milstein [8] modified the somatic cell hybridization technique for the production of so-called monoclonal Abs (mAbs). They fused normal mouse B cells with non-Ab producing cancerous plasma cells (myeloma cells) and propagated the resulting B cell hybridomas in a suitable selection medium. After several steps of subculturing at single cell density, hybridomas of one specificity were obtained. They grew indefinitely and

produced large quantities of mAbs, which were screened for their specificity, e. g., by conventional ELISA. In the meantime genetic engineering techniques allow for production of mAbs, also in the human system (see "Application of Igs").

Diversity of Igs

Acquired humoral immunity is essentially based on Ab diversity and selection. The diversity, which potentially provides with Abs of more than 10^{15} different specificities, is generated by various mechanisms being active at different Ag-independent and Ag-dependent stages of the B cell development that are:

■ Combinatorial V-D-J joining

In humans, the germ-line V region of the Ig H chain is coded by the V_H (from "variable"), D (from "diversity") and J_H (from "joining") gene segments located on chromosome 14. The L chain V regions are coded only by V_L and J_L segments located on chromosome 2 for the κ chain and on chromosome 22 for the λ chain, respectively. Each type of gene segment exists in several variants that are combined in the pro-B cells and pre-B cells by a process named rearrangement. The rearrangement starts with the binding of products from recombination-activating genes RAG1 and RAG2, whose expression is unique to lymphoid progenitor cells and some cells of the central nervous system, to recombination signal sequences (RSSs) flanking each V, D and J gene segment. The complete recombinase complex includes next to RAG1 and RAG2 the ubiquitously present DNA-dependent protein kinase (DNA-PK), DNA-ligase IV, Ku70:Ku80 and terminal deoxynucleotidyl transferase (TdT). Its activity results in formation of a chromosome with rearranged V, D and J gene segments. Successful $V_H D J_H$ rearrangement in late pro-B cells is followed by transition into large pre-B cells, which proliferate under the influence of bone marrow stromal cells. $V_L J_L$ rearrangement occurs in pre-B cells, which develop to immature B cells that express first IgM exclusively and later in addition dominating IgD. At this stage of B cell development, apoptotic deletion of self-reactive B cells takes place and leads to selection of self tolerant B cells that are exported to the periphery, prepared for Ag-driven maturation.

■ Generation of junctional diversity

In the majority of cases, $V_H D J_H$ and $V_L J_L$ segments do not join in phase with the reading frame, resulting in non-productive rearrangements and, if both alleles are af-

ected, apoptosis of B cells. The remaining productive rearrangements allow for translation of complete V region polypeptides in about 8% of pre-B cells that leave the bone marrow as mature immunocompetent B cells. However, the joining process of the coding sequences is imprecise, thus, generating different productive combinations, especially in the CDR3 hypervariable region. In this region, addition of so-called N- and P-nucleotides through TdT activity increases the Ab diversity significantly. Allelic exclusion ensures that only one V_LJ_L unit and one V_HDJ_H unit are expressed in functional B cells.

■ Combinatorial association of L and H chains

The third Ag-independent mechanism of Ab diversity generation is based on the variable combination of H and L chains. Although not all V_H and V_L genes are used with the same frequency and combine to stable Ig molecules, the number of productive H-L combinations may account for 10^6 – 10^7 possibilities.

■ Isotype class switching

After Ag stimulation of mature IgD and IgM coexpressing B cells, isotype class-specific recombination occurs at the intronic switch sites between the V_HDJ_H unit and the C_H gene segment. This process is influenced by T helper cell-derived cytokines (see “Production of Igs”) and ensures the production of Abs of only one Ig subtype per B cell and plasma cell, respectively.

■ Somatic hypermutation

In response to Ag stimulation, T helper cell-derived signals lead to point mutations through base exchanges in all three CDRs of the Ig V regions. The number of these mutations increases during secondary and tertiary Ab response thereby enhancing the chance to generate high affinity Abs. B cell clones with high affinity Igs are preferentially expanding, giving rise to so-called affinity maturation of Abs. One enzyme is essentially involved in both isotype class switching and somatic hypermutation, i.e., the affinity induced deaminase (AID) that deaminates cytosine to uracil of ssDNA during transcription. AID plays, therefore, another key role for promotion of Ab diversity besides RAG1 and RAG2.

Pathology of Igs

Pathological situations related to inappropriate Ab response can be classified as follows:

■ Immunodeficiencies

- X-linked agammaglobulinemia of Bruton type (BTK deficiency)
- Severe combined immunodeficiency (SCID), e.g., caused by lack of RAG, TdT or AID

■ Malignant transformation

- Chronic lymphocytic leukemia (most frequently of CD5⁺ B1-cell type)
- Hodgkin’s disease and non-Hodgkin’s lymphoma (derived from B cells of different developmental stages)
- Multiple myeloma, Waldenström’s macroglobulinemia, monoclonal gammopathy of undetermined significance (MGUS)

■ Immunodysregulation

- In response to exogenous Ags (allergy), hypersensitivity reactions according to the classification of Robin R. A. Coombs and P. G. H. Gell [3] are the following:
 - Type I: IgE-mediated anaphylactic hypersensitivity (atopy), e.g., in hay fever, asthma, and allergic reactions to drugs such as penicillin
 - Type II: Ab-mediated cytotoxic hypersensitivity (IgG- or IgM-mediated), e.g., in blood transfusion reaction, erythroblastosis fetalis (Rhesus disease), and hemolytic anemia
 - Type III: Immune complex-mediated hypersensitivity (IgG or IgM with soluble Ags), e.g., in localized Arthus reaction, and generalized serum sickness

Type IV represents Ab-independent cell-mediated hypersensitivity. However, there are two more Ab-dependent hypersensitivity reactions:

- Stimulatory Ab reactions (IgG-mediated), e.g., in hyperthyroidism of Grave’s disease
- Ab-dependent cellular cytotoxicity (ADCC), e.g., in AIDS and schistosomiasis
- In response to endogenous Ags (autoimmune diseases), many self-reactive auto-Abs are detected in normal healthy individuals. Their incidence increases with growing age; however, no pathological consequences are obvious. Therefore, auto-Abs may only be regarded as pathogenic, if they fulfill the Witebsky-Rose-Koch criteria for autoimmune diseases:
 - Demonstration of the inciting auto-Ag and the auto-Ab in the disease-specific lesions

- Demonstration of reactivity of the auto-Ab with the auto-Ag at 37 °C
- Induction of auto-Ab production and disease by immunisation with the auto-Ag
- Induction of the disease by auto-Ab transfer to normal subjects

The first successful transfer of a neurological disease into normal mice by patients' Igs was demonstrated by Toyka et al. [15] in myasthenia gravis. Other examples of autoimmune diseases with a significant contribution of auto-Abs to the pathogenesis are systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and insulin-dependent diabetes mellitus (IDDM).

Application of Igs

■ Diagnostics

Abs and especially mAbs are indispensable tools for diagnostic purposes in almost all medical disciplines. Among others, they serve as probes for the typing of blood groups, histocompatibility Ags, CDR3-sequences of T cell receptors, and markers of leukemias and lymphomas. Innumerable analytical and preparative techniques depend on the use of Abs such as

- Immunocytochemistry and immunohistochemistry (aspirates, biopsies)
- Immunofluorescence (microscopy and flow cytometry)
- Immunoassays (agglutination, complement binding, radioimmunoassay, enzyme-linked immunosorbent assay, immunospot, immunoblot, cytotoxicity test)
- Immunoprecipitation
- Immunoabsorption (affinity chromatography)

Main clinical situations that require Ab analysis of body fluids or on cells and tissues are:

- Infections and intoxications
- Hemolytic anemia
 - anti-Rh (D) Abs: detection by anti-Ig antiserum (Coombs' reagent)
 - on fetal erythrocytes (direct Coombs test) or
 - in maternal serum (indirect Coombs test)
 - anti-drug Abs on erythrocytes: detection by anti-Ig antiserum (Coombs' reagent)
- Transplantation
 - preformed Abs
 - acute graft rejection
- Allergic diseases: detection of specific IgE Abs *in vivo* by
 - prick test
 - scratch test
 - patch test
- Autoimmune diseases

■ Therapy

Therapeutic application of Abs bases on the properties of their main components, i. e., the F(ab')₂-fragments block and agglutinate (neutralise) bacteria and extracellular viruses, and the Fc-fragments enhance phagocytosis (opsonation), act cytotoxic (via complement activation and Ab-dependent cellular cytotoxicity (ADCC)) and immunomodulate. First clinical trials with Ab therapy date back to the 1890s, when Emil von Behring and Shibasaburo Kitasato treated patients suffering from diphtheria with sera of animals immunized to *Corynebacterium diphtheriae*, and when Jules Héricourt and Charles Robert Richet treated cancer patients with antisera raised in animals that received the patients' cancer cells. Since then, major indications for Ab treatment, also called passive immunization, have been:

- infections, e. g., rabies,
- intoxications, e. g., snake bite,
- solid tumors, e. g., colon and breast cancer,
- leukemia and lymphoma, e. g., chronic lymphocytic leukemia and non-Hodgkin lymphoma,
- transplantation, e. g., chronic graft rejection and graft-versus-host reaction,
- hemolytic anemia, e.g., Rh incompatibility (anti-D prophylaxis),
- autoimmune diseases, e. g., RA, SLE, Crohn's disease, chronic inflammatory demyelinating polyneuropathy (CIDP) and multiple sclerosis (MS).

A major challenge of Ab treatment still is cancer therapy, since early trials with individual tailor-made animal-raised (xenogenic) antisera have yielded inconsistent and contradictory results. These antisera contained a mixture of polyclonal Abs directed against cancer cells as well as normal tissue cells, therefore limiting the anti-tumor efficacy and giving rise to serious adverse effects. Moreover, they could even promote tumor growth (enhancing Abs of IgG type). A new era began with the advent of mAbs that minimized the risk of harmful side-effects by using different strategies for their production and modification. In order to mediate the killing of target cells, the mAbs were conjugated to toxins (immunotoxins) or radionuclides and genetically engineered to become bispecific hybrid Abs (Fig. 2). Furthermore, the immunogenicity of xenogenic (rodent) mAbs has been reduced due to the construction of chimeric Abs (homologous recombination) consisting of rodent Fab-fragments and a human Fc-fragment. In transgenic mice, so-called humanized mAbs have been generated by reshaping or CDR-grafting. They contain only the Ag-binding site (CDR, idiotope) of mice, whereas all other parts of the Ab are of human origin. Finally, phage-display library technique allows for generation of complete human mAbs of any specificity. However, there still remain constraints, even of human anti-tumor mAbs, i. e.,

Fig. 2 Target cell destruction by toxin-conjugated and bispecific Abs

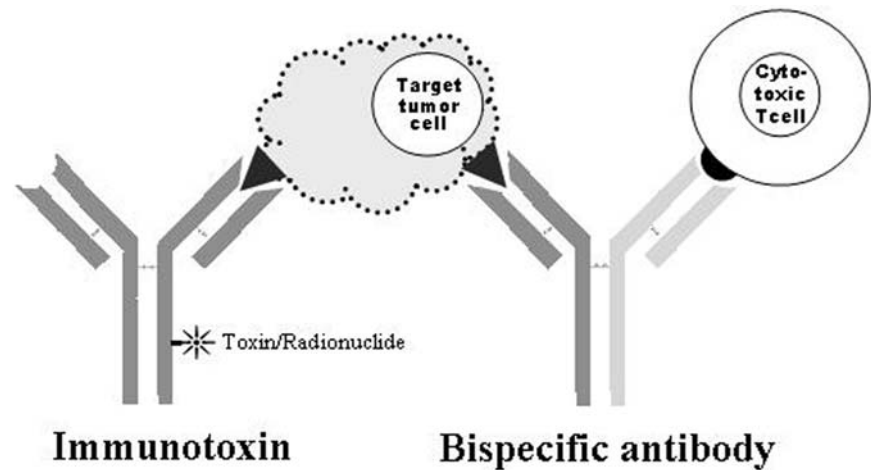


Table 3 Recombinant mAbs currently used in therapeutical trials

Name	Target	Characteristics	Indication
Abciximab	GPIIb/IIIa	chimeric	Angina pectoris and myocardial infarction
Alemtuzumab	CD52	humanized	B cell leukemia and lymphoma, Wegener's granulomatosis, graft-versus-host disease, MS
Basiliximab	CD25	chimeric	Transplant rejection (kidney)
Bevacizumab	VEGF	humanized	Colon cancer
Cetuximab	EGFR	chimeric	Colon cancer
Daclizumab	CD25	humanized	Leukemias, transplant rejection (kidney/liver)
Efalizumab	CD11a	humanized	Psoriasis
Gemtuzumab	CD33	humanized (toxin-conjugated)	Acute myeloid leukemia
Ibritumomab	CD20	mouse (radionuclid-conjugated)	Lymphoma, RA
Infliximab	TNF	chimeric	RA, Crohn's disease
Natalizumab	β 4-Integrin	humanized	MS, RA, Crohn's disease, colitis ulcerosa
Omalizumab	IgE	humanized	Allergic rhinitis and asthma
Rituximab	CD20	chimeric	B cell lymphoma, RA, SLE
Trastuzumab	EGFR2/HER2	humanized	Breast cancer

the lack of tumor-specific Ags and the short half-lives of allogenic Igs.

One of the first humanized mAbs assigned for commercial development was CAMPATH-1H. The name is derived from *Cambridge, pathology* and *humanized*. It was constructed by inserting six hypervariable loops of a rat mAb displaying specificity for CD52, a surface marker of B and T cells, into a human Ab framework [13]. This Ab has been proven to be highly effective in treatment of B cell leukemia (chronic lymphocytic leukemia) and lymphoma (non-Hodgkin lymphoma). Due to its high affinity binding to B and T cells, it has also beneficial effects in graft-versus-host and autoimmune diseases. Currently it is being tested in patients with early active relapsing-remitting MS in a comparative study with IFN- β [2]. Alternatively, mAbs for treat-

ment of MS are directed to the T cell receptor such as the T cell depleting humanized anti-V β 5.2/5.3 T cell receptor-specific mAb ATM-027 [11]. On the other hand, a high affinity chimeric human-mouse anti-CD20 mAb that was originally generated to treat non-Hodgkin B cell lymphoma has recently been considered highly promising for the treatment of autoimmune diseases that are mainly Ab-mediated such as RA and SLE [1].

The therapeutic mAbs are designated according to the scheme: Proper name – characteristics (“mo” = mouse, “xi” = chimeric, “zu” = humanized, “mu” = human) – monoclonal Ab (mab), e. g. Alemtuzumab stands for CAMPATH-1H. An overview on recombinant mAbs currently tested in clinical trials is given in Table 3.

Great promise holds another therapeutic form of Abs, i. e. the IVIg therapy, which has been used over the

past two decades extensively in the treatment of a variety of primary immunodeficiencies, infectious diseases and autoimmune disorders.

The current state-of-the-art of IVIg therapy is the topic of following articles of the present special issue of

Journal of Neurology. They cover fields such as basic considerations regarding the mechanism of action, indications for application in neurological disorders, and safety considerations of respective uses of IVIg.

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