Antibodies-related patent applications

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Basic Background-Antibodies

Diagram of an antibody with labels:
- Idiotopes
- Idiotype
- Fab
- VH
- VL
- Paratope
- Antigen
- Epitope
- L-chain
- Fc
- H-chain
Basic Background - Terminology

Therapeutic Antibodies and Fusion Proteins: Terminology

- Murine Ab
  - Muromonab
  - Rituximab
  - Infliximab

- Chimeric Ab
  - "ximab"
  - Trastuzumab
  - Omalizumab
  - Efalizumab
  - Bevacizumab

- Humanized Ab
  - "zumab"

- Human Ab
  - "umab"
  - Adalimumab
  - Panitumumab

PK/PD Predictions for monoclonal Antibodies, October 09, 2008, Genentech
A variant IgG comprising a human IgG V_H region comprising one or more amino acid substitutions relative to a wild-type human IgG V_H region at one or more of amino acid residues 17, 19, 57, 66, 70, 79, 81, 82a, 82b, numbered according to the EU index as in Kabat, wherein the variant IgG has altered binding to Staphylococcus aureus protein A.
Inventive step

Patent case I

EXAMPLES

1. Anti-Her2 Variants-mutagenesis of the VH domain
2. Binding of anti-Her2 variants to protein A (ELISA)
   - All variants retained the same binding affinity to Her2 as wild-type
   - Certain variants show reduced binding to protein A
   - Others show increased binding or essentially the same level of binding
Is It involve Inventive step?

Patent case I

A variant IgG comprising a human IgG VH region comprising an amino acid substitution relative to a wild-type human IgG VH region at an amino acid residue position selected from the group consisting of amino acid residues 70, 79, and 82b, numbered according to the EU index as in Kabat, wherein the variant IgG has increased binding to *Staphylococcus aureus* protein A compared to a wild-type human IgG VH region, wherein the variant IgG is useful for treating a patient with *Staphylococcus aureus* infection.
Inventive step - second use

Patent case I

- The claimed "useful for treating" antibody may be used for additional uses and therefore the claimed antibody is identical to the antibody of the prior art, known from D1, capable to bind the same epitope.

- Any antibody that comprises the claimed IgG VH region will be identical to the parent antibody and capable of binding to the same epitope

- By formulation of the claims to a second use claims, the claims may be accepted.
Inventive step-specific amino acid sequences

Patent case II

CLAIMS:

1. An antibody, or antigen-binding fragment thereof, that binds endoglin, comprising a heavy chain variable region having an amino acid sequence set forth as SEQ ID NO: 89 and a light chain variable region having an amino acid sequence set forth as SEQ ID NO: 93.

8. Use of an antibody or antigen-binding fragment thereof, of claim 1, in the formulation of a medicament for the treatment of an angiogenesis-related disease.
Inventive step-specific amino acid sequences

Patent case II

- Document D1 teaches that anti-endoglin antibody that is use for antiangiogenic therapy. D1 does not disclose a humanized and de-immunized anti endoglin antibody.

- In light of D1, in combination with common general knowledge regarding de immunization approaches, it would be obvious to the person skilled in the art, to provide the claimed antibody.
Inventive step-specific amino acid sequences

- D1 describes a mouse monoclonal antibody produced by conventional hybridoma-techniques.
- D1 does not provide any rationale for arriving at any modified sequence that results in a humanized and de-immunized sequence.
- The applicant has found that when the anti-endoglin antibody comprises specific VH and VL humanized and de-immunized sequences, angiogenesis is inhibited.
- Non-obviousness is recognized.
1. A variant of a reference monoclonal anti-TNFα antibody or an anti-TNFα antigen binding fragment, said reference monoclonal anti-TNFα antibody or an anti-TNFα antigen binding fragment comprising:

   a CDR-H1 amino acid sequence of D Y A M H (SEQ ID NO:5);
   a CDR-H2 amino acid sequence of A I T W N S G H I D Y A D S V E G (SEQ ID NO:6);
   a CDR-H3 amino acid sequence of V S T L S T A S S L D Y (SEQ ID NO:7);
   a CDR-L1 amino acid sequence of R A S Q G I R N Y L A (SEQ ID NO:8);
   a CDR-L2 amino acid sequence of A A S T L Q S (SEQ ID NO:9); and
   a CDR-L3 amino acid sequence of Q Y R N R A P Y T (SEQ ID NO:10),

   wherein the variant comprises at least one CDR-L1 amino acid substitution selected from Q4G, Q4H, Q4R, G5S, A11G, and A11S, and up to 5 additional CDR substitutions as compared to the CDRs of said reference monoclonal anti-TNFα antibody or said anti-TNFα antigen binding fragment.
Patent case III

- D1 discloses an anti-TNFα antibody (designated D2E7) from which the variants are presently claimed, and laboratory procedures for genetic engineering of antibodies against specific epitopes are known, e.g., in D2.
- In view of D1 in combination with D2, the present claims lacks an inventive step.
Patent case III

- Certain mutations in the CDRs of D2E7, particularly CDR-L1, result in a reduction in immunogenicity while preserving useful binding.
- D1 does it mention trying to reduce the immunogenicity of D2E7
- D2 does not disclose nor suggest a method to reduce immunogenicity of an antibody that is already humanized or fully human
- Non-obviousness is recognized
CM-24, a humanized immune-modulating antibody that binds CEACAM1.

CM-24's effect is elicited by its ability to block the binding of CEACAM1 on cancer cells to CEACAM1 on certain immune cells. This abrogates the immunosuppressive function of CEACAM1, promoting cell killing by T cells and NK cells. The effect of CEACAM1 blockade does not lead to general immune activation, but to anti-cancer-specific activation.
Summary

Changes in Amino acid sequence to improve function

Medi-557 [Numax-YTE]
- Engineering the variable domain to lower the isoelectric point to decrease elimination of IgG

Cimzia
- Fab (monovalent format with short serum half life) or Fab-PEG (monovalent format with increased serum half life) fragments

Lucents
- Modulate antigen specificity and binding affinity (affinity maturation) of the variable domain

Zevalin, Bexxar, SGN-35, T-DM1
- Disulfide bond
- Hinge

Antitope platform
- Eluys platform

Fc-fusion proteins and peptides
- Pepobody
- Monobody
- Single-chain Fv-Fc
- Small modular immunopharmaceuticals
- One-armed antagonist antibody
- IgG4-derived unibody

Immunoconjugates and toxins
- Radioactive nuclides
- Chemotherapeutics
- Toxins, cytokines and enzymes

Modulate binding to Fc receptors
- Increased complement activation (increased complement component C3 binding by isotype chimerism)
- Enhanced ADCC (low levels of fucose and/or mutations that lead to increased FcγRIIIA or decreased FcγRIIB binding)
- Enhanced anti-inflammatory properties (addition of sialylated glycans)
- Increased serum half life [increased binding to FcRn]

Teplizumab (MGA031; MacroGenics/Eli Lilly)
- Otelixizumab (TRX4; Tolerex/GlaxoSmithKline)
- Xencor, Biowa [MEDI-563], Potelligent, GA-101 [Glycart]
Thank you