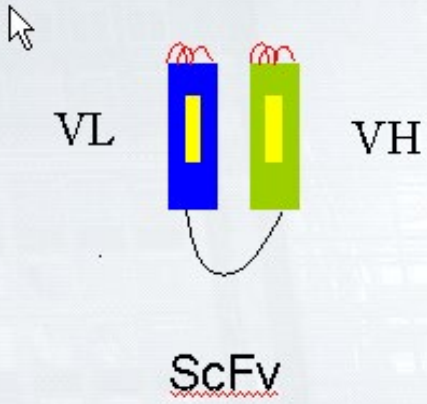
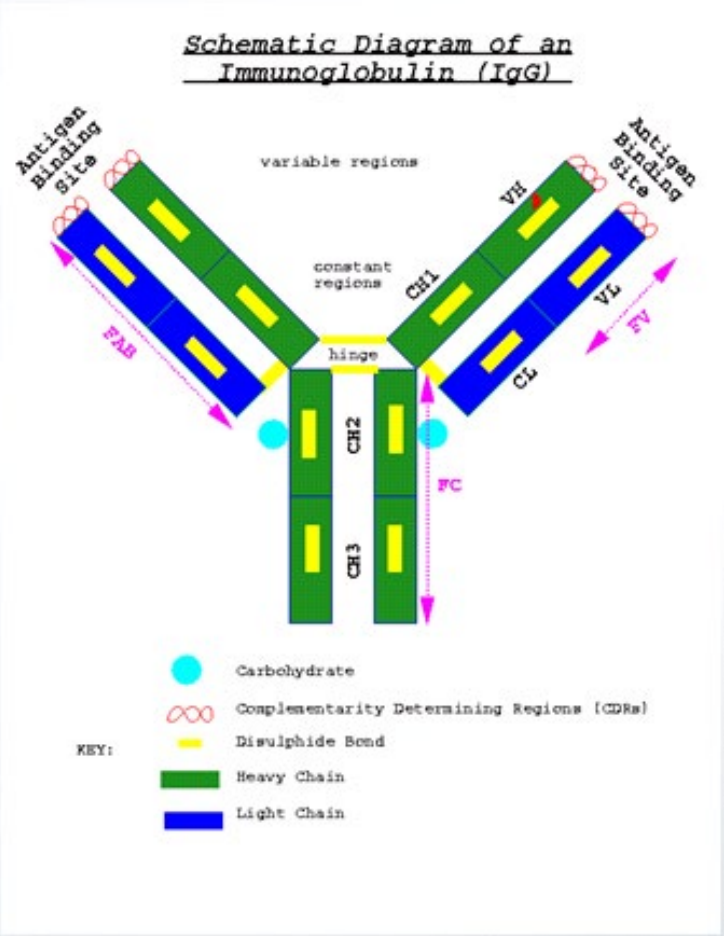
Written Description:
Antibodies

Bennett Celsa
TC 1600 QAS

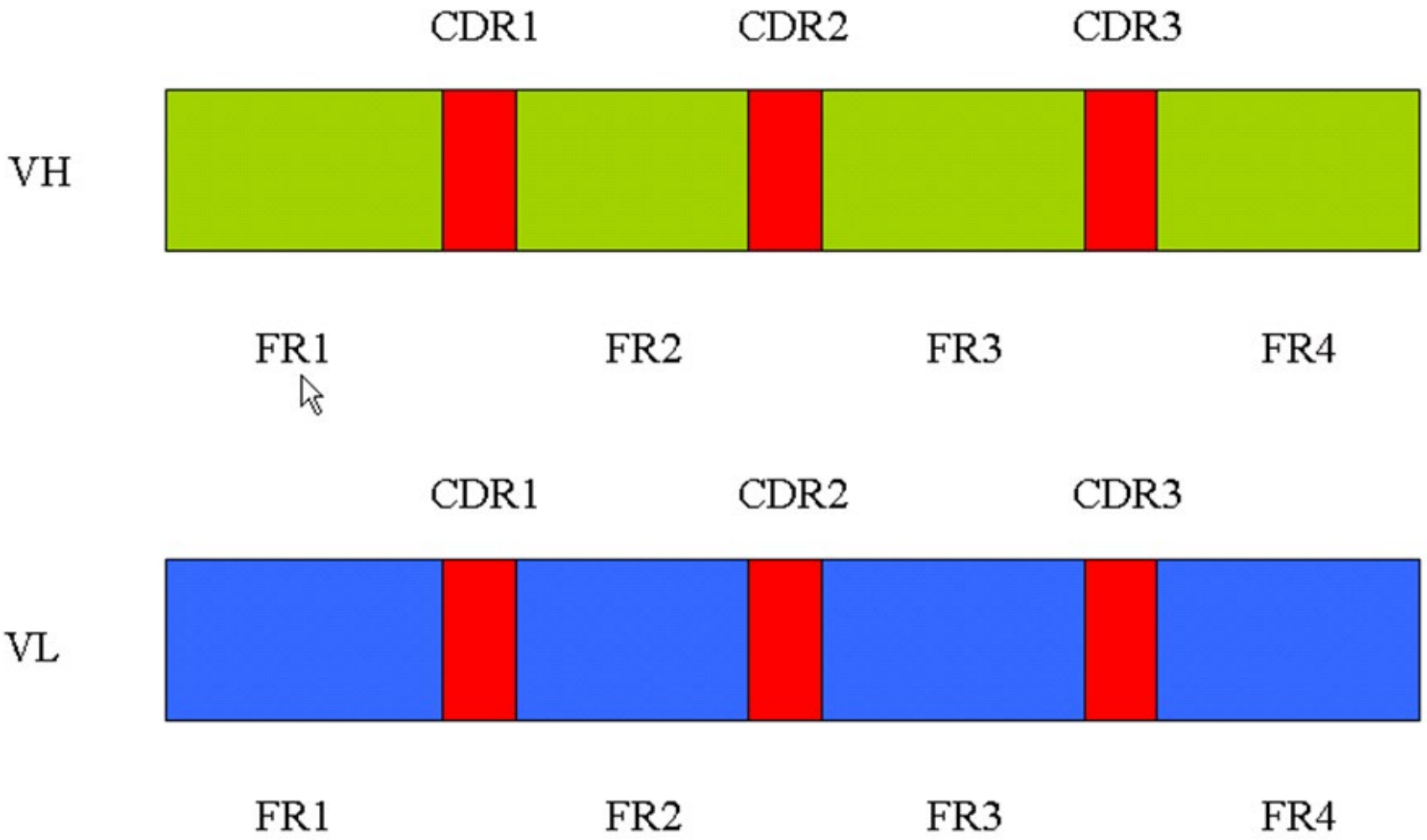
Antibody Structure



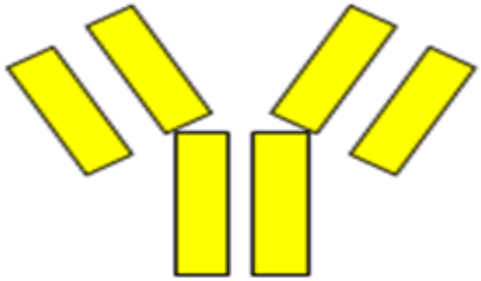


Adapted from people.cryst.bbk.ac.uk/~ubcg07s/gifs/igG.gif

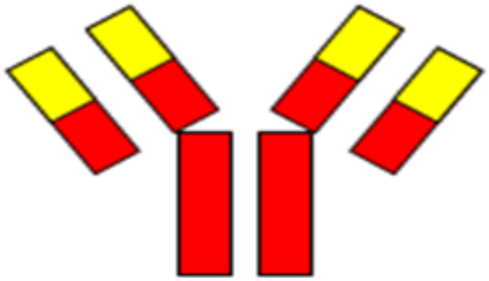
Antibody Variable Domains



Humanization of Antibodies



Mouse



Chimaeric

Humanized

Human

The W.D. Guidelines

- MPEP 2163: W.D. guidelines for complying with the written description requirement of 35 U.S.C. 112, 1st Para. that the "specification shall contain a written description of the invention. … ".

- This requirement is separate and distinct from the enablement requirement.

- Training Materials

  Written Description Training materials, Revision I , March 25, 2008 (available at http://www.uspto.gov/web/menu/written.pdf) (hereinafter Revised Training Materials)

The W.D. Requirement

- **"The 'written description' requirement implements the principle that a patent must describe the technology that is sought to be patented; the requirement serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed." *Capon v. Eshar*, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1084 (Fed. Cir. 2005); MPEP 2163.**

Written Description – Basics of Examiner's Analysis

- **Determine the scope of each claim as a whole**
  - **Broadest reasonable interpretation in light of and consistent with written description**
    - ***In re Morris*, 127 F.3d 1048, 44 USPQ2d 1023 (Fed. Cir. 1997); and MPEP 2163.**
  - **Consider the full scope of the claim**

Written Description –Basics of Examiner's Analysis (cont.)

- **Review entire application to understand how the applicant provides support for the claimed invention**
  - **Review includes consideration for each element and/or step claimed.**
  - **Review includes comparing the claim scope with the scope of the disclosure.**

- **The determination of compliance with WD is decided on a case-by-case basis.**

Considerations For Determining Compliance with WD

- Evaluate the following:

  a. Actual reduction to practice (e.g. Examples)

  b. Disclosure of drawings or structural chemical formulas

  c. Sufficient relevant identifying characteristics

  - Complete structure
  - Partial structure
  - Physical and/or chemical properties
  - Functional Characteristics when coupled with a known or disclosed correlation between function and structure

  d. Method of making the claimed invention

  e. Level of skill and knowledge in the art

  f. Predictability in the art.

See MPEP 2163(II)(A)(3) and page 1 of the "Revised Training Materials".

Written Description – Basics of Examiner's Analysis for Genus Claims

- **WD for claimed genus may be satisfied through sufficient description of a representative number of species**
  - **inverse function of the skill and knowledge in the art.**
  - **depends on whether one of skill in the art would recognize necessary common attributes or features possessed by the members of the genus.**
  - **generally, in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.**
- **See *Enzo Biochem, Inc. v. Gen-Probe, Inc.*,323 F.3d 956, 966, 63 USPQ2d 1609,1615 (Fed. Cir. 2002); *Noelle v. Lederman,* 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004); *Regents of the University of California v.Eli Lilly,* 119 F.3d at 1568, 43 USPQ2d at 1406 (Fed. Cir. 1997) .**

Revised Training Materials-Example 7 (Allelic Variants)

- **Claim 1. An isolated DNA that encodes Protein X having the amino acid sequence SEQ ID: 2. (Genus)**

- **Claim 2. An isolated allele of the DNA according to claim 1, which allele encodes Protein X having the amino acid SEQ ID: 2. (Subgenus)**

Revised Training Materials-Example 7

- **Specification:**
  - **Discloses a DNA, SEQ ID NO: 1 that encodes Protein X (SEQ ID NO: 2) which is a cell surface receptor for adenovirus.**
  - **No allelic sequence information is disclosed.**
  - **Allelic variants of SEQ ID NO: 1 can be obtained by hybridizing SEQ ID NO: 1 to a DNA library made from the same species that yielded SEQ ID NO: 1.**

Revised Training Materials-Example 7

- Claim 1. An isolated DNA that encodes Protein X having the amino acid sequence SEQ ID: 2.
  - Only one species in the claimed genus (SEQ ID NO: 1).
  - However, genetic code provides a known correlation between codon function and structure e.g. cDNA → protein.
  - One skilled in the art would have been able to readily envision all the DNAs capable of encoding SEQ ID NO: 2.
    - Conclusion: Claim 1 genus satisfies WD.

Revised Training Materials-Example 7

- **Claim 2. An isolated allele of the DNA according to claim 1, which allele encodes Protein X having the amino acid SEQ ID: 2.**
  - **"allele": native DNAs that encode protein X.**
  - **Actual reduction to practice: one species, SEQ ID NO: 1.**
  - **Structure of one allele does not provide guidance to the existence or structure of other alleles.**
  - **No information regarding the common attributes that allow one to identify an allele versus any DNA that encodes.**
  - **Accordingly, one member of this genus is not representative.**
  - **Conclusion: Claim 2 subgenus fails to satisfy WD.**

Revised Training Materials-Example 11

- **Claim 1. An isolated nucleic acid that encodes a polypeptide with at least 85% amino acid sequence identity to SEQ ID NO: 2. (Genus)**

- **Claim 2. An isolated nucleic acid that encodes a polypeptide with at least 85% amino acid sequence identity to a SEQ ID NO: 2; wherein the polypeptide has activity Y. (Subgenus)**

Revised Training Materials-Example 11

Example 11A (Specification):

- **Only nucleic acid SEQ ID NO: 1 encodes the polypeptide of SEQ ID NO: 2 with novel activity Y.**
- **SEQ ID NO: 2 has no significant sequence identity with any known polypeptide or polypeptide family.**

Example 11B: (Specification)- Additionally discloses:

- **Deletion studies identifying 2 domains critical to activity Y.**

- **Proposes: conservative mutations within the domains will retain activity while non-conservative substitutions will not.**
- **Proposes: most mutations outside of the domains will not affect activity Y.**

Revised Training Materials-Example 11

- Claim 1. An isolated nucleic acid that encodes a polypeptide with at least 85% amino acid sequence identity to SEQ ID NO: 2.
  - Actual reduction: single species i.e., SEQ ID NO: 1.
  - "at least 85% identity" is a partial structure e.g. up to 15% of the amino acids may vary from those in SEQ ID NO: 2.
- WD for claim 1: SEQ ID NO: 2 combined with the genetic code would have put one in possession of the genus of nucleic acids that encode SEQ ID NO: 2.

Revised Training Materials-Example 11

- Claim 2. An isolated nucleic acid that encodes a polypeptide with at least 85% amino acid sequence identity to a SEQ ID NO: 2; wherein the polypeptide has activity Y.

  - Encompasses NA's encoding SEQ ID NO: 2 and polypeptides having 85% sequence identity to SEQ ID NO: 2 that have activity Y.
  - SEQ ID NO: 2 and genetic code put one in possession of the genus of nucleic acids that encode SEQ ID NO: 2.
  - No known or disclosed correlation between a structure other than SEQ ID NO: 2 and activity X.
  - Accordingly, SEQ ID NO: 2 is not representative of other proteins having activity X.

- Claim 2 fails to satisfy WD (Ex. 11a result)

Revised Training Materials-Example 11

- **Claim 2. An isolated nucleic acid that encodes a polypeptide with at least 85% amino acid sequence identity to a SEQ ID NO: 2; wherein the polypeptide has activity Y.**

  - **proposes that conservative mutations within the domains will retain activity while non-conservative substitution will not.**
  - **proposes that most mutations outside of the domains will not affect activity Y.**

- **Claim 2 has WD (Ex. 11b result) by establishing structure-function correlation from deletion studies that identify two domains critical to activity Y.**

Revised Training Materials-Example 14

- Description of a mouse antigen provided support for antibodies binding that mouse antigen but, without more, did not support claims to antibodies binding the corresponding human antigen or a generic claim to antibodies binding a corresponding mammalian antigen genus.
- "as long as an applicant has disclosed a 'fully characterized antigen,' either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen" . *Noelle v. Lederman*, 355 F.3d 1343, 1349 (Fed. Cir. 2004).

In re Alonso : Use of Antibody Genus: Partially Characterized Antigen

- Based on: *In re Alonso*, 545 F3d 1015, 88 USPQ2d 1849 (Fed. Cir. 2008).

- **Claim. A method of treating neurofibrosarcoma in a human by administering an effective amount of a monoclonal antibody idiotypic to the neurofibrosarcoma of said human, wherein said monoclonal antibody is secreted from a human-human hybridoma derived from the neurofibrosarcoma cells.**

In re Alonso : Disclosure

- Claim. A method of treating neurofibrosarcoma in a human by administering an effective amount of a monoclonal antibody idiotypic to the neurofibrosarcoma of said human, wherein said monoclonal antibody is secreted from a human-human hybridoma derived from the neurofibrosarcoma cells.
- **Specification discloses a method of generating antibodies to tumor cell suspensions and screening them for the ability to cause tumor regression in a patient.**
- **Generated a single monoclonal antibody to a tumor cell suspension prepared from a patient tumor sample that bound a 221KD tumor surface antigen.**
- **Exemplified the regression of a patient's tumor with said monoclonal antibody.**

In re Alonso : Analysis

- Claim. A method of treating neurofibrosarcoma in a human by administering an effective amount of a monoclonal antibody idiotypic to the neurofibrosarcoma of said human, wherein said monoclonal antibody is secreted from a human-human hybridoma derived from the neurofibrosarcoma cells.
- **The claim encompasses a monoclonal antibody genus which is:**

  - Idiotypic to a neurofibrosarcoma of a human patient

  - Therapeutic
- **The prior art teaches that there is considerable antigenic heterogeneity of tumors between patients and metastatic sites within a single patient.**
- **Therefore, the antibodies falling within the claimed genus would be expected to vary substantially.**

In re Alonso : Analysis (Cont.)

- Claim. A method of treating neurofibrosarcoma in a human by administering an effective amount of a monoclonal antibody idiotypic to the neurofibrosarcoma of said human, wherein said monoclonal antibody is secreted from a human-human hybridoma derived from the neurofibrosarcoma cells.
- **A single therapeutic monoclonal antibody was reduced to practice.**
- **The antigen to which the disclosed monoclonal antibody binds was not fully characterized.**
- **Neither the specification nor the prior art provided information regarding which antibody structures predictably would function to treat neurofibrosarcoma.**

In re Alonso : Conclusion (Lack of WD)

- Claim. A method of treating neurofibrosarcoma in a human by administering an effective amount of a monoclonal antibody idiotypic to the neurofibrosarcoma of said human, wherein said monoclonal antibody is secreted from a human-human hybridoma derived from the neurofibrosarcoma cells.
- **A general method of making and identifying antibodies is not enough to describe the procedure for generating and determining whether a given antibody will function in the claimed method.**
- **The single disclosed antibody is insufficiently representative of the variable genus of antibodies encompassed by the claim.**

Summary: WD Antibody Genus/Subgenus Claims

Generic Antibody claim coverage:

- possible when a fully characterized antigen is claimed (*Noelle*).

E.g., An antibody that specifically binds antigen X of SEQ ID. NO.

Summary: WD Antibody Genus/Subgenus Claims (Cont.)

- **Functional Subgenus Antibody claim: may require:**
  - **representative species; and/or**
  - **additional identifying characteristics e.g. "structure, epitope characterization, binding affinity, specificity, or pharmacological properties …." (*Alonso*); and/or**
  - **a structure / function correlation**

using specification and/or state of the prior art.

- **A functional subgenus antibody claim (depending on the limitation) can result in a claim that does not meet WD, as in examples 7 and 11 of the Revised Training Materials.**

Example 1: (high affinity antibody subgenus)

- **Claim 1: An isolated antibody that binds human receptor X which comprises the heavy chain variable region of SEQ ID NO:1 and the light chain variable region of SEQ ID NO:2.**
- **Claim 2: An isolated antibody that exhibits an equilibrium dissociation constant (K_D) of less than 285pM with human receptor X and is comprised of a sequence at least 90% homologous to the heavy chain variable region of SEQ ID NO:1 and a sequence at least 90% homologous to the light chain variable region of SEQ ID NO:2.**
- **NOTE: Claim 2 is an antibody subgenus of claim 1 that includes only those claim 1 antibody compounds that have high affinity receptor X binding.**

Example 1: (Specification)

- Prior art teaches monoclonal and polyclonal antagonist antibodies to cytokine receptor X expressed on human inflammatory cells (e.g. mast cells) were useful in inhibiting inflammation and allergic responses.
- Instant application discloses an isolated high affinity antagonist (HAA) antibody to cytokine receptor X that exhibits an equilibrium dissociation constant (K_D) of less than 285 pM that contains a V_H of SEQ ID NO:1 and a V_L of SEQ ID NO:2.

Ex. 1 (Specification Cont.)

- Specification discloses that conventional phage library/panning techniques based on their HAA antibody can obtain additional antagonist antibodies.
- The instant application encompasses (but does not exemplify) fragments and analogs (deletion/addition/ substitution) that are >90% homologous (sequence identity) to their isolated antibody.

Ex. 1: Claim 1: Analysis/Conclusion

- Claim 1: An isolated antibody that binds human receptor X which comprises the heavy chain variable region of SEQ ID NO:1 and the light chain variable region of SEQ ID NO:2.
- Isolated VL and VH domains retain their antigen-binding activity as the Fv fragment. [1]
- Specification discloses a species within the instant claim scope.
- Prior art establishes a sufficient correlation between antibody (VL and VH) structure and antigen binding.
- Therefore, a claim that defines an antibody that binds receptor X as comprising a VH chain of SEQ ID NO:1 and a VL chain of SEQ ID NO:2 meets WD.

[1] Hayzer et al. Bioconjugate Chemistry 1991 Vol. 2. pp 301-3018.

Ex. 1: Claim 2 (Analysis)

- Claim 2: An isolated antibody that exhibits an equilibrium dissociation constant (K_D) of less than 285pM with human receptor X and is comprised of a sequence at least 90% homologous to the heavy chain variable region of SEQ ID NO:1 and a sequence at least 90% homologous to the light chain variable region of SEQ ID NO:2.
- Claim encompasses antibodies in which up to 10% of the amino acids may vary in both the VH and VL regions of SEQ ID 1 and SEQ ID 2 which would be deemed by one of ordinary skill to be essential to retain high affinity antagonistic binding (K_D of less than 285 pM).
- Discloses only a single species within the instant claim scope.
- There is no teaching identifying what amino acids can be varied within the VL or VH antibody regions and still retain high affinity (Kd< 285pM) antagonistic binding with human receptor X.

Ex.1: Claim 2 (Conclusion: lacks WD)

- Claim 2: An isolated antibody that exhibits an equilibrium dissociation constant (K_D) of less than 285pM with human receptor X and is comprised of a sequence at least 90% homologous to the heavy chain variable region of SEQ ID NO:1 and a sequence at least 90% homologous to the light chain variable region of SEQ ID NO:2.

- **Neither the prior art nor applicant's disclosure defines sufficient representative antibodies and/or sufficient structure/function correlation between modifying the VL or VH regions of their disclosed antibody and the retention of high affinity antagonistic binding to satisfy the WD requirement for claim 2.**

  -result is consistent with Revised Training Materials: example 11 (% identity).

Example 2: (Ab genus: modified CDR's)

- **Claim 3: An isolated antibody that binds to receptor X, said antibody comprises an amino acid sequence that is at least 90% homologous to the 3 heavy chain variable CDRs in SEQ ID NO:1 and an amino acid sequence that is at least 90% homologous to the 3 light chain variable CDRs in SEQ ID NO:2.**

- **CDRs: Complementarity Determining Regions.**

Ex. 2 (Disclosure)

- Claim 3: An isolated antibody that binds to receptor X, said antibody comprises an amino acid sequence that is at least 90% homologous to the 3 heavy chain variable CDRs in SEQ ID NO:1 and an amino acid sequence that is at least 90% homologous to the 3 light chain variable CDRs in SEQ ID NO:2.
- **Discloses prior art antagonist antibodies to cytokine receptor X that are expressed on human inflammatory cells (e.g. mast cells) for use in inhibiting inflammation and allergic responses.**
- **Applicant produces an isolated high affinity antagonist (HAA) antibody to cytokine receptor X with a (K_D) of less than 285 pM that contains a V_H of SEQ ID NO:1 and a V_L of SEQ ID NO:2.**

Ex. 2 (Disclosure cont.)

- Claim 3: An isolated antibody that binds to receptor X, said antibody comprises an amino acid sequence that is at least 90% homologous to the 3 heavy chain variable CDRs in SEQ ID NO:1 and an amino acid sequence that is at least 90% homologous to the 3 light chain variable CDRs in SEQ ID NO:2.
- Applicant identifies by sequence the 3 CDR regions within both the V_H and V_L chains of the HAA antibody.
- Specification discloses conventional phage library/panning techniques which can be used to screen for additional antagonist antibodies.
- Application encompasses (but does not exemplify) fragments and analogs (deletion/addition/ substitution) that are >90% homologous (sequence identity) to their isolated antibody including humanized antibodies.

Ex. 2 (State of the Prior Art)

- Well known that the heavy and light polypeptide chains each contribute three CDRs to the antigen binding region of the antibody molecule.
- The prior art[1] teaches humanization of antibodies by transfer of the 6 CDRs from a donor framework region to an acceptor framework region and retention of antigen binding.

[1]Queen et al., PNAS (1988) 86:10029-10033,

Riechmann et al., Nature (1988) 332:323-327

Ex. 2: (State of the Prior Art: Cont.)

- *Brown et al.* (J Immunol. 1996 May;156(9):3285-91 at 3290 and Tables 1 and 2), describes how a one amino acid change in the VH CDR2 of a particular antibody was tolerated whereas, the antibody lost binding upon introduction of two amino changes in the same region.
- *Vajdos et al.* (J Mol Biol. 2002 Jul 5;320(2):415-28 at 416) teach that amino acid sequence and conformation of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. Aside from the CDRs, the Fv also contains more highly conserved framework segments which connect the CDRs and are mainly involved in supporting the CDR loop conformations, although in some cases, framework residues also contact antigen.

Ex. 2 (Analysis)

- Claim 3: An isolated antibody that binds to receptor X, said antibody comprises an amino acid sequence that is at least 90% homologous to the 3 heavy chain variable CDRs in SEQ ID NO:1 and an amino acid sequence that is at least 90% homologous to the 3 light chain variable CDRs in SEQ ID NO:2.
- **Scope of the claim encompasses antibodies with 6 intact CDRs as well as a subgenus of antibodies that encompass up to 10% variation (fragments and/or analogs) in the 6 CDRs.**
- **Disclose a species within the instant claim scope.**
- **Prior art discloses 6 CDRs as being essential structure of the antibody's binding site, and thus when intact, would provide enough structure to define the antibody's binding site (structure / function correlation) e.g. where amino acid substitutions can be made so as to change (e.g. 6 CDR's) or retain (e.g. constant or variable framework) antigen binding.**

Ex. 2 (Analysis / Conclusion: Lacks WD)

- Claim 3: An isolated antibody that binds to receptor X, said antibody comprises an amino acid sequence that is at least 90% homologous to the 3 heavy chain variable CDRs in SEQ ID NO:1 and an amino acid sequence that is at least 90% homologous to the 3 light chain variable CDRs in SEQ ID NO:2.
- Prior art for humanization supports obtaining successful antigen binding by transferring the 6 intact CDRs from a donor framework to an acceptor framework.
- However, prior art teaches that variation(s) within the CDRs render antigen binding unpredictable.
- Therefore, a single antibody species would not be deemed by one of skill in the art to be representative of a claim that defines an antibody that binds antigen X comprising at least 90% homology to the 6 CDR of the VH and VL chains in SEQ ID NO:1 and SEQ ID NO:2.
- Accordingly, claim lacks WD.

Example 3: Single CDR-defined subgenus

- **Claim : An isolated antibody that binds to human antigen X, said antibody comprising a heavy chain variable domain and a light chain variable domain, said heavy chain variable domain comprises the CDR3 in SEQ ID NO:1 (VH).***

*** This Example mirrors an example in the lecture on "Enablement Issues in the Examination of Antibodies", given by Larry R. Helms (SPE, AU 1643) at the June 13, 2007 BCP (http://www.cabic.com/bcp/)**

Ex. 3: Specification

- Claim : An isolated antibody that binds to human antigen X, said antibody comprising a heavy chain variable domain and a light chain variable domain, said heavy chain variable domain comprises the CDR3 in SEQ ID NO:1 (VH).
- Discloses antigen X from human tissue which is over-expressed in cancer tissue vs. normal tissue.
- Applicant produced a series of anti-X antibodies which were not random combinations of VH and VL i.e., they had specific VH domains paired with specific VL domains.
- The VH domains are highly homologous (>75%) to each other and share not only CDR3 but are nearly identical in framework regions i.e. 3-6 amino acids differ out of 124 residues.
- The CDR1 and CDR2 regions of these antibodies share some identity: CDR1 (3/5 identical) and CDR2 (6/16 identical) regions.

Ex. 3: Specification Cont.

- **Claim : An isolated antibody that binds to human antigen X, said antibody comprising a heavy chain variable domain and a light chain variable domain, said heavy chain variable domain comprises the CDR3 in SEQ ID NO:1 (VH).**
- **Analysis of the VL sequences of these antibodies reveals that these domains are highly homologous (>75%) to each other.**
- **The framework regions are nearly identical and the VL domains are identical in CDR1 and CDR2 regions. The CDR3 (8/10 are identical) regions are highly homologous to each other.**

Ex. 3 (State of the Prior Art)

- Prior art methods for screening rely on a two step process where each step results in an antibody.
- However, each step requires one of the variable domains to be a defined sequence and the defined variable domain provides enough structure to obtain an antibody.
- See e.g. Klimka et al., British Journal of Cancer (2000) 83: 252-260; and Beiboer et al., J. Mol. Biol. (2000) 296:833-849.

Ex. 3 (State of the Prior Art: cont.)

- **Prior art methods do not result in an antibody solely by keeping CDR3 in the VH defined and randomizing the rest of the VH and VL domains.**
- **Prior art indicated that, in some instances, the CDR3 region is important. However, this region is not solely responsible for binding. The conformation of other CDRs, as well as framework residues influence binding.**
- **See e.g., MacCallum et al., J. Mol. Biol. (1996) 262: 732-745; Pascalis et al., the Journal of Immunology (2002) 169: 3076-3084; and Casset et al., BBRC (2003) 307, 198-205.**

Ex. 3 (Analysis)

- Claim : An isolated antibody that binds to human antigen X, said antibody comprising a heavy chain variable domain and a light chain variable domain, said heavy chain variable domain comprises the CDR3 in SEQ ID NO:1 (VH).

- **Claim is broadly drawn to any antibody that binds antigen X and comprises a heavy chain variable region comprising CDR3 in SEQ ID NO:1.**

- **Discloses a series of antibodies with highly homologous VH and VL domains and identical VH CDR3 regions.**

Ex. 3 (Analysis cont.)

- Claim : An isolated antibody that binds to human antigen X, said antibody comprising a heavy chain variable domain and a light chain variable domain, said heavy chain variable domain comprises the CDR3 in SEQ ID NO:1 (VH).
- **Neither the specification, nor the prior art provides any examples to support the premise that CDR3 of the VH or VL is solely responsible for antigen binding.**
- **Prior art does not support a definition of an antibody structure solely by defining the CDR3 sequence of a VH or VL.**
- **Therefore, the disclosed species would not be deemed by one of skill in the art to be representative of the claim scope.**

Ex. 3 (Conclusion: Lacks WD)

- **Based on this analysis a claim to an isolated antibody that binds to human antigen X, said antibody comprises a heavy chain variable domain and a light chain variable domain, said heavy chain variable domain comprises the CDR3 in SEQ ID NO:1, does not meet the requirements of 35 U.S.C. 112, first paragraph, for WD.**

Questions

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