Addressing The Many Challenges of Antibody Patent Prosecution

October 19, 2007

Jane E. Remillard

(617) 994-0774 jer@lahive.com
INTRODUCTION

1. The Monoclonal Antibody - From Mouse to Human

2. Antibody Products in the Marketplace

3. Strategic Claim Considerations
   - scope considerations
   - sample claims
   - problems associated with claiming structure and function (e.g., in US, EP, China and Korea)

4. Practice Tips: How to Get Breadth on Antibody Claims
THE MONOCLONAL ANTIBODY - FROM MOUSE TO HUMAN

mouse antibody (IgG)

1975

1983

chimeric antibody (variable region is exchanged)

humanized antibody (CDRs are exchanged)

1986

1988

humanized antibody (2nd generation) (CDRs / FW residues exchanged)

1990s

fully human antibody

yellow = mouse / donor
blue = human / acceptor

= FW substitution

= CDRs

= frame works (FW)

= target antigen

variable region (CDR + FW)

light chain

heavy chain

VL

VH

CH1

CH2

CH3

CL
1. ORTHOCLONE OKT3  
anti-CD3 for graft rejection  
Ortho Biotech / J&J 1986

2. PANOREX  
anti-EpCAM for colon cancer  
Centocor 1995

3. ZEVALIN  
anti-CD20 for radioimaging non-Hodg.  
Biogen Idec / Schering 2002

1. REOPRO  
anti-platelet receptor for anti-clotting  
Centocor / Eli Lilly 1995

2. RITUXAN  
anti-CD20 for non-Hodg.  
Genentech / Biogen Idec / Roche 1997

3. REMICADE  
anti-TNFα for Crohn’s  
Centocor / Schering 1998

4. SIMULATECT  
anti-IL-2 for graft rejection  
Novartis 1998

5. ERBITUX  
anti-EGFR for colon cancer  
Imclone / BMS 2004

1. ZENAPAX  
anti-CD25 for transplant reject.  
Roche 1997

2. SYNAGIS  
anti-RSV for RSV infection  
MedImmune 1998

3. HERCEPTIN  
anti-HER-2 for breast cancer  
Genentech / Roche 1998

4. MYLOTARG  
anti-CD33 for AML  
Celltech / Wyeth 2000

5. CAMPATH  
anti-CD52 for CLL  
ILEX / Schering / Millennium 2001

6. XOLAIR  
anti-IgE Fc for allergy / asthma  
Tanox / Genentech / Novartis 2002

7. AVASTIN  
anti-VEGF for colon cancer  
Genentech 2004
STRATEGIC CLAIM CONSIDERATIONS

• PROTECT COMPETITIVE SPACE

• PROTECT PROPRIETARY PRODUCTS
STRATEGIC CLAIM CONSIDERATIONS

1. Claim antibody by broad function or class or use
   - binding to a specific protein
   - falling within a particular class (e.g., chimeric, humanized, human)
   - useful for treating a particular indication

2. Claim antibody by specific function
   - combine multiple functions
   - specify dosage protocol, combination therapies, etc.

3. Claim antibody by epitope
   - binding to a specific epitope (or competing for binding with a particular antibody defined by, e.g., sequence or deposit)
STRATEGIC CLAIM CONSIDERATIONS

1. Claim antibody by broad structure
   - VH CDR3 only
   - full length variable region with at least 80% identity
   - consensus sequences
   - germ line sequences

2. Claim by specific structure
   - all three CDRs or full length variable regions
   - heavy chain only, light chain only - and heavy and light chains combined
SAMPLE CLAIMS

CLAIM ANTIBODY BY BROAD FUNCTION, CLASS OR METHOD OF USE

1. An isolated antibody which binds to integrin B protein having the amino acid sequence of SEQ ID NO: 1 (e.g., novel antigen).

2. An isolated antibody which binds to amino acid residues 55-135 of human matrilipase having the amino acid sequence of SEQ ID NO:2 (e.g., novel epitope).

3. An isolated humanized antibody which binds to CD4 (e.g., known antigen).


5. Use of antibody which binds IL-15 in the manufacture of a medicament to treat psoriasis.
SAMPLE CLAIMS

CLAIM ANTIBODY BY SPECIFIC FUNCTION, EPITOPE OR METHOD OF USE

1. An isolated human antibody that dissociates from human TNFα with a Kd of 10-8 M or less and a Koff rate constant of 10-3 s-1 or less, both determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard in vitro L929 assay with an IC50 of 10-7 M or less.

2. An isolated antibody against IL-15 that prevents IL-15 from transducing a signal through either of the β- or γ-subunits of the IL-15 receptor complex, wherein the monoclonal antibody interferes with binding of (a) amino acid Asp56 of the IL-15 molecule to the β-subunit of the IL-15 receptor complex or (b) amino acid Gln156 of the IL-15 molecule to the γ-subunit of the IL-15 receptor complex.
SAMPLE CLAIMS

3. An isolated antibody that binds to an epitope on hepatitis C virus (HCV) recognized by an antibody having a heavy chain variable region comprising SEQ ID NO:1 and a light chain variable region comprising SEQ ID NO2.

4. An isolated antibody that competes for binding to hepatitis C virus (HCV) with antibody 4D10 having ATCC accession number 324478.

5. A method of treating psoriasis comprising administering an antibody that binds to IL-15, wherein the antibody is administered in a dosage range of 0.05 to 100 mg per kilogram of body weight per day.
SAMPLE CLAIMS

CLAIM ANTIBODY BY BROAD STRUCTURE  CDR3 – only

1. An isolated antibody that binds HCV comprising at least the VH CDR3 having amino acids 98-106 of SEQ ID NO:4.

2. An isolated human monoclonal antibody that binds IL-8, wherein the antibody comprises:
   a heavy chain variable region comprising CDR1, CDR2, and CDR3 sequences; and
   a light chain variable region comprising CDR1, CDR2, and CDR3 sequences, wherein
   the heavy chain variable region CDR3 sequence comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 2, 3, and conservative sequence modifications thereof, and
   the light chain variable region CDR3 sequence comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 5, 6, and conservative sequence modifications thereof.
SAMPLE CLAIMS

CLAIM ANTIBODY BY BROAD STRUCTURE  Germline

1. An isolated antibody capable of binding human CTLA4, which antibody comprises: (a) a heavy chain variable region of a human VH 3-30.3 gene; and (b) a light chain variable region of a human VK A-27 gene.

2. An isolated monoclonal antibody that specifically binds to CTLA-4, comprising a heavy chain variable region amino acid sequence that comprises a contiguous amino acid sequence from within an FR1 sequence through an FR3 sequence that utilizes a human VH 3-33 family gene and that comprises at least one of the amino acid substitutions in any one of SEQ ID NO: 74-79 and 81-84 as compared to SEQ ID NO: 72.

3. An isolated human monoclonal antibody that binds to human AILIM, wherein a V region DNA encoding a heavy chain variable region of said human monoclonal antibody is from human immunoglobulin heavy chain V gene segment 1-02 or 3-13.
SAMPLE CLAIMS

CLAIM ANTIBODY BY BROAD STRUCTURE  % Homology

1. An isolated antibody that binds interferon gamma protein and includes an antigen binding region comprising all or part of a heavy chain variable region consisting of an amino acid sequence at least 90% homologous to SEQ ID NO:7.

2. An isolated antibody which binds IL-8 comprising, a heavy chain variable region having CDRs comprising the amino acid sequences SEQ ID NO:8 (CDR1), SEQ ID NO:9 (CDR2), and SEQ ID NO:10 (CDR3), or sequences at least 90% homologous therewith.
SAMPLE CLAIMS

CLAIM ANTIBODY BY BROAD STRUCTURE  Consensus Sequence

1. An isolated human monoclonal antibody which binds to human IL-8 comprising a VH CDR3 domain having the amino acid sequence:
   Asp-X4-Val-Gly-X5-Phe-Asp-Tyr,
   wherein X4 is Lys, Arg, or His, and X5 is Gly, Ala, Val, Leu, or Ile.

2. An isolated monoclonal antibody that binds to Z, wherein the antibody comprises:
   a heavy chain variable region comprising CDR1, CDR2, and CDR3 sequences; and
   a light chain variable region comprising CDR1, CDR2, and CDR3 sequences, wherein
   the heavy chain variable region CDR1 comprises the amino acid sequence R-A-S-Q-X-X-S-
   S-X-L-A (SEQ ID NO:11), the heavy chain variable region CDR2 comprises the amino acid
   sequence A-S-X-X-S/T (SEQ ID NO:12), and the heavy chain variable region CDR3 comprises
   the amino acid sequence Q-Q-X-X-S/N-X-P/S (SEQ ID NO:13), wherein X is any amino acid.
SAMPLE CLAIMS

CLAIM ANTIBODY BY SPECIFIC STRUCTURE

1. An isolated antibody which binds to IL-8 and comprises:
   a heavy chain variable region CDR1 comprising SEQ ID NO:26;
   a heavy chain variable region CDR2 comprising SEQ ID NO:27;
   a heavy chain variable region CDR3 comprising SEQ ID NO:28;
   a light chain variable region CDR1 comprising SEQ ID NO:29;
   a light chain variable region CDR2 comprising SEQ ID NO:30;
   a light chain variable region CDR3 comprising SEQ ID NO:31.

2. An isolated antibody which binds to human VEGF receptor Flt-1,
said antibody comprising a heavy chain variable region comprising the
amino acid sequence of SEQ ID NO:32, and a light chain variable region
comprising the amino acid sequence of SEQ ID NO:33.
STRATEGIC CLAIM CONSIDERATIONS

1. CLAIM ANTIBODY BY BROAD FUNCTION
   ● capture the competitive space of antibodies that bind a given target antigen or have a particular therapeutic use
   ● can be a good offensive claim, particularly if functions are ones that most therapeutic products would have
   ● more resistant to design around
   ● can be a difficult claim to prosecute in US and abroad (e.g., requires sufficient number of representative species)

2. CLAIM ANTIBODY BY SPECIFIC FUNCTION OR EPITOPE
   ● not as good, but still covers reasonably broad subgenus of functionally equivalent antibodies
   ● can be a good offensive and defensive claim
   ● can still be difficult to prosecute in US and abroad

3. CLAIM ANTIBODY BY BROAD STRUCTURE (e.g., CDR3 ONLY, FULL LENGTH VR WITH AT LEAST 80% IDENTITY, CONSENSUS SEQUENCES, DERIVED FROM A PARTICULAR GERM LINE)
   ● likely only protects a limited subgenus (e.g., product), but may impede design around
   ● easier to prosecute in US and abroad

4. CLAIM ANTIBODY BY SPECIFIC STRUCTURE (e.g., ALL 3 CDRS OR FULL LENGTH VRS)
   ● likely only protects particular species
   ● can be good defensive claim
   ● more resistant to being defeated in litigation
   ● easy to prosecute in US and abroad
PROBLEMS WITH CLAIMING STRUCTURE AND FUNCTION

1. **US** - written description and enablement issues

2. **EP** - inventive step issues (if known target) structure does not generally impart inventive step
   
   - problem solution approach / show either that
     a) special, unexpected difficulties were overcome in obtaining the antibody, or
     b) the antibody has special, unexpected properties

   - sufficiency (enablement) requirement generally satisfied if specification describes at least one antibody having the specified functional features together with the VL & VH sequences of that antibody, or details of a deposited hybridoma producing that antibody

3. **Korea** - KIPIO Guidelines 2000; require claiming antibody by sequence unless target is novel, in which case antibody can be defined by target sequence
4. China – Guidelines for Examination (2006); product claims should be defined by structure or method of production

- stipulate that a monoclonal antibody can be (often interpreted as “should be”) defined by deposited hybridoma producing that antibody

- claiming antibody by sequence is often viewed as lacking sufficiency of disclosure under Article 26(3) (e.g., a skilled artisan still could not reproduce the antibody) – frequently applies to claims defining all CDR sequences

- patentability is highly dependent on the specific epitope or antigen that the antibody bind to

- for a known antigen, only antibodies having superior effects are considered patentable under Article 22(3)
5. Japan - Examination Guidelines for patent and Utility Model in Japan (Part VII: Monoclonal Antibodies);

- stipulate that a claim directed to an antibody may be defined by specifying the antigen recognized by it, hybridoma that produces it, or cross-reactivity

- for a known antigen, must show unexpected properties or difficulty in obtaining the antibody

- if an antibody is claimed by sequence (e.g., a recombinant humanized antibody), then all CDRs generally are required
PRACTICE TIPS: HOW TO GET BREADTH FOR ANTIBODY CLAIMS

1. combine multiple functions alone or in combination with structure
2. claim % homology
3. define by epitope
4. define by germline sequence
5. define by consensus sequences
6. claim conservative substitutions
PRACTICE TIPS: HOW TO GET BREADTH ON ANTIBODY CLAIMS

1. include as many examples as possible
   ● disclose several representative species

2. sequence as many antibodies as possible
   ● allows drafting of consensus and germline claims
   ● inexpensive relative to value of broader patent protection

3. include mutational analysis (e.g., VR, CDR and/or FW regions)

4. map epitopes for as many antibodies as possible/perform cross-competing studies

5. disclose as many functional characteristics as possible
   ● e.g., binding affinity/dissociation rates, cross reactivity, stability / thermal characteristics, functional effect on targets, inhibition, up regulation, neutralization, etc.

6. include data supporting nexus between functional characteristics & therapeutic use

7. establish level of skill/predictability in the art at the time of filing

8. submit scientific declarations during prosecution
THANK YOU