New Patent Issues Surrounding Therapeutic Antibodies

by

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**Antibodies: Cutting Edge for Legal Developments**

- **Therapeutic antibodies have come of age...** By early 2006:
  - 18 mAbs approved by FDA
  - approximately 350 in clinical trials
  - >$10B in revenues
  - Six mAbs → global revenues > $500M
  - Market expected to grow by 20% per year by 2010
  - $45B market by 2009
  - Better toxicity profiles/ faster approval
## Therapeutic Indications

<table>
<thead>
<tr>
<th>Indications</th>
<th>Drugs</th>
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<tr>
<td>Colorectal cancer</td>
<td>Avastin, Erbitux</td>
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<tr>
<td>Lymphomas</td>
<td>Rituxan, Bexxar, Zevalin</td>
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<tr>
<td>Leukemias</td>
<td>Campath, Mylotarg</td>
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<td>Lung Cancer</td>
<td>Cotara</td>
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<td></td>
<td>...and Panitumumab, Ovarex,</td>
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<td></td>
<td>Zanolimumumab, Galiximab,</td>
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<td></td>
<td>Velociximab, Proxinium</td>
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<td></td>
<td>etc</td>
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Case Law on Antibody Patents

- The case law has evolved as antibody technology has evolved
- The cases tend to lag the technology
  - Many of cases today deal with technologies first developed 10 or more years ago
- Early cases – hybridoma technology and immunoassays (mid-1970s)
- More recent cases – technologies for making chimeric, humanized, and human antibodies (early-mid 1980s)
In re Strahilevitz (C.C.P.A. 1982)

- **Claims:** method for removing a hapten (e.g. drug) or antigen from blood using an immunodialysis process
  - Claims not limited to specific haptens/antibodies
- **Facts:** Application lacked specific examples; no human treatment data, no dialysis or adsorption data
- **Issue:** Did application enable claims?
- **Held:** claims enabled
  - Preparing antibodies to specific antigens and haptens was well known in art
  - Selection of matrix, dialysis membrane and flow rate for dialysis well known.
Enablement: Wands

- **In re Wands** (Fed. Cir. 1988)
  - **Claims**: Immunoassay for detection of HBsAg using high-affinity IgM mAbs (covered any IgM mAb)
  - **Facts**:
    - Applicants had deposited a single cell line
    - Exr. Had rejected for lack of enablement
  - **Issue**: Were claims enabled?
  - **Held**: enabled
    - Deposit not necessary if cell lines obtainable from readily available sources/materials
    - Preparing/screening hybridomas was well known in art
    - **Need for some experimentation is OK, as long as not undue**
    - Wands factors: look at (1) quantity of experimentation, (2) amount of direction or guidance, (3) working examples, (4) nature of invention, (5) state of art, (6) relative skill in art, (7) predictability of art, (8) breadth of claims
Enablement - Scope

- **Johns Hopkins Univ. v. Cellpro, Inc. (Fed. Cir. 1998)**
  
  - **Claims**: Purified suspensions of stem cells and mAbs used to produce the suspensions
  
  - **Facts**:
    - Civin had discovered My-10 antigen expressed on immature stem cells, but not mature cells; claimed anti-My-10 mAbs
    - CellPro produced similar suspension with antibody to CD34
    - My-10 and CD34 recognized by OSA as same antigen
  
  - **Issues**: Did CellPro infringe? Claims enabled?
  
  - **Held**: CellPro infringed and claims enabled
    - Court construed claims to cover all antibodies that bind CD34
    - Fact that CellPro mAbs bound different epitope on CD34 irrelevant
    - Using methods taught, one skilled in the art could make many more anti-CD34 mAbs w/out undue experimentation
**Obviousness**

- **Hybritech Inc. v. Monoclonal Antibodies, Inc. (Fed. Cir. 1986)**
  - **Claims**: Sandwich assay utilizing mAbs with affinity of at least $10^8$ liters/mole
  - **Issue**: Were claims invalid as obvious?
  - **Facts**: Prior Art:
    - method of making mAbs (Kohler & Milstein), use of mAbs to map epitopes, high affinity antibodies, and “predicted” use of mAbs in immunoassays
  - **Held**: Not obvious
    - prior art was “invitation to experiment” only
    - Commercial success of Hybritech kits was evidence of nonobviousness
Anticipation

- **Nichols Institute Diagnostics v Scantibodies Clinical Labs (Fed Cir 2006)**
  - **Claims**: An Ab or Ab fragment that selectively binds a peptide of hPTH selected from the group consisting of SEQ IDs Nos 1-6
  - **Issue**: Were claims invalid as anticipated?
  - **Facts**: Prior Art:
    - Serum inherently containing an Ab of the claim although no mention that it selectively binds hPTH peptides
  - **Held**: Anticipated: Prior art was sufficient even in the absence of selectivity property or its significance.
**The Present Battlefield: Written Description**

- **Noelle v. Lederman** (Fed. Cir. April 2004)
  - **Claimed Technology:**
    - Antibodies to CD40CR antigen found on T cells
    - Antibody blocks binding of antigen to CD40 receptor on B cells and prevents B cell activation
  - **Facts:**
    - Noelle had claims to genus of any CD40CR mAb, as well as the murine, chimeric, humanized and human forms of the mAb
    - Noelle application only disclosed murine CD40CR antigen
      - No disclosure of human antigen or any CD40 antigen other than murine
  - **Issue:** Did application *adequately describe* claimed subject matter?
To prevail in interference, Noelle had to show claimed subject matter was described in earliest applications

*Held:* Priority application supported claims to mouse mAbs, but not to genus or human CD40CR mAbs

- Can broadly claim antibody by binding affinity for antigen, but only if application discloses a “fully characterized antigen”
- Noelle did not describe human CD40CR antigen (e.g. by structure, formula, chemical name, etc.)
- Disclosure of single mouse antigen, not enough to support claim to genus
  - Needed to disclose more species to claim genus
**Written Description (II)**

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<tr>
<th>• Chiron Corp. v. Genentech, Inc. (Fed. Cir. March 2004)</th>
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<tr>
<td>- <strong>Chiron’s ‘561 Claims</strong>: A monoclonal antibody that binds to human c-erbB2 antigen</td>
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<td>- <strong>Facts:</strong></td>
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<td>• Chiron sued Genentech alleging Herceptin infringed Chiron patent</td>
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<td>• ‘561 patent based on application filed 1995</td>
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<td>• The 1995 application claimed priority to 3 applications filed in 1984, 1985(CIP), and 1986(CIP)</td>
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<td>• To prevail Chiron had to show priority appls supported claims</td>
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Chiron v Genentech (cont’d)

- 1984 application – one murine mAb that binds HER2; produced by hybridoma method
  - Hybridoma deposited but appl. does not identify antigen by structure, function, etc.

- 1985 CIP application – six more murine mAbs; hybridomas for all; antigen identified by mol. wt.
  - No mention of chimeric or humanized but says mAb not limited by source or manner made

1986 CIP application – six more murine mAbs; three hybridomas deposited
  - No mention of chimeric or humanized but says mAb not limited by source or manner made
Chiron v Genentech (cont’d)

Issue: Whether priority applications supported (i.e., described and enabled) a broad construction of the term “monoclonal antibody” to include chimeric or humanized?

Held: No support – claims invalid
  • Ct. construed '561 claim to cover chimeric and humanized mAbs as well as murine…but
  • Such construction did not relate back to the earliest priority documents….thus
  • Claims invalid over intervening prior art under Section 102
Chiron v Genentech (cont’d)

- Nascent technology requires “specific and useful” teaching to enable
- 1984 appl. – no need to enable chimeric/humanized mAbs, but did not describe
- 1985 appl. – no specific/useful teaching of chimeric or humanized → not enabled
- 1986 appl. - no specific/useful teaching of chimeric or humanized → not enabled
  - Follow-on applications need to be updated
More Herceptin Battles: 
*Hudziak v Ring (Board 2005)*

- **Count:** A Mab that binds HER2
- **Count** is generic to murine, humanized, chimeric antibodies
- Earliest Chiron document described Ab 454C11; did not show it bound HER2; inherently, however, 454C11 does
- **HELD:** The 454C11 Ab prevents Genentech from obtaining patent protection for its own AB.
- **No one got protection**
Written Description: Capon v Eshhar (CAFC 2005)

- Claims to chimeric genes comprising
  - A first gene segment encoding a single-chain Fv domain of a specific Ab
  - A second gene segment encoding partially or entirely the transmembrane and cytoplasmic, and optionally the extracellular, domains of an endogenous protein
- Claims found enabled, but...
- Board rejected for lack of WD of the full scope of the chimeric DNA, by lack of reference to “structure, formula, chemical name or physical properties” citing Fiers, Lilly, Amgen, Enzo
The Road Back to Wands: The “Capon Factors”

- CAFC reversed
- WD is to be tested by reference to the “nature and scope of the invention at issue and with the scientific and technologic knowledge already in existence.”
- Application of the law “will vary with differences in the state of knowledge in the field and differences in the predictability of the science.”
- “Determination of what is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter”
The “Capon” Factors (cont’d)

• While “for biochemical processes relating to gene modification, protein expression and immune response, success is not assured… generic inventions are not thereby invalid.”

• “The record does not show [the concept of selecting and combining gene sequences into a single activation protein] to be in the prior art, and includes experimental verification as well as potential variability in the concept.

• Written description is OK even if some testing and verification!
Written Description and Actual Reduction to Practice

- **Falkner v Inglis** (CAFC May 2006)
- Poxviruses for vaccine production
- Written description can be complied with by generic descriptions of viral constructs
- No DNA sequence need be described if it is in the prior art
- No example is needed to comply with WD
- No actual reduction to practice is needed to comply with WD
- Decision relies heavily on **Capon v Eshhar**
Hot Issues: Subgeneric claims

• One of our recent interferences had two counts:
  – Count 1: A MAb that selectively binds receptor of SEQ ID No1 and that is an agonist
  – Count 2: A MAb that selectively binds receptor of SEQ ID No1 and that is an antagonist

• Issue: Since difference is functional, is description of both antibodies sufficient by describing the antigen and a screening method?
Hot Issues: Selection of candidate leads

- Is early selection of Ab candidates exempt from infringement?
- Issue: Is the screening of populations of Abs to find a few leads using patented methods an infringement or is it exempt under 35 USC 271(e)(1) and *Integra v Merck*
- And if it is an infringement, how is it compensable?
- Reach through value?
The state of the law on Abs

- Enablement, inherent anticipation and inherent support are stable areas of the law
- Written description is in major flux...
  - The scope-based holding of *Lilly* is being re-evaluated (e.g. *Capon* and *Falkner*) and seems to be getting closer to an enablement standard
- Obviousness may soon be the next battlefield
New Patent Issues...

Thank You

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