Antibodies, Patents and Freedom to Operate: The Monoclonal Maze

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Strategists and Advisors specializing in the protection, transfer and enforcement of Intellectual Property Rights.
Why is FTO important?

- The commercial market for therapeutic antibodies has increased dramatically
- The number of patents to antibody technologies has also increased
- A thorough understanding of the patent landscape and FTO issues is essential
- Do not want to spend many years and $$$ developing technology only to find out blocked from commercializing that technology by a third party patent
- Potential investors and partners generally consider FTO as important as or more important than a dominant IP portfolio
FTO Fundamentals

- **Patentability ≠ freedom to operate**
  - Patent is only a grant of the *right to exclude others* from making, using, or selling the patented invention
  
  - Patent does **not** give patent owner the affirmative right to do anything
    - No affirmative right to make, use, sell own invention

- **KEY**: A company can receive a patent for its technology and still be blocked from practicing that technology by a broader (dominant) patent
FTO Fundamentals

- Dominant patents vs. subordinate patents
  - Example:
    - Company A may receive a patent to a specific anti-CD20 humanized antibody, but may be blocked from making, using or selling that antibody by Company B’s patent to basic humanization technology and Company C’s patent broadly directed to any recombinant antibody that binds CD20.
    - Holder of subordinate patent may need license under each dominant patent to practice its own technology!
FTO Fundamentals

• BUT – subordinate patent can still have value
  – If subordinate patent is directed to improvement in the technology that is considered essential or particularly advantageous
    • Example: PDL’s Queen patents on humanization technology

• Valuable subordinate/improvement patent can be tool to clear FTO (e.g., through cross-license)
The FTO Search

- **Documents searched**
  - *Issued patents* – must consider impact now
    - Exclusive rights already granted
    - Consider expiration dates
  - *Pending patent applications* – no infringement now but potential problem if issue as patent
    - Good way to identify potential competitors and what might be coming down the road
    - Continuations often filed to pursue broader claims
The FTO Search

- **KEY:** must look at *claims* of third-party patents, not just specification
  - **Issue:** Assuming claim is valid (or will issue if appl.), will it hinder commercialization of my technology?

- **KEY:** compare claims to what you are actually doing or plan to do
  - Your patents may not reflect company’s current R&D

- **Search should not be limited to final product (i.e., MAb)**
  - Must consider IP surrounding:
    - target, antibody discovery techniques (e.g., phage display), humanization techniques, cell lines, expression systems, delivery, methods of treatment, etc.
    - Consider alternative terminology (e.g., antigen binding molecule)
The FTO Search

- **Scope of Search**
  - **U.S. only**
    - Will not identify potentially relevant patents and applications in other jurisdictions
  - **Worldwide**
    - Most comprehensive
  - **Major Markets**
    - **U.S. and PCT (Patent Cooperation Treaty)**
      - Minimum recommended
The FTO Search

• **Caveats**
  – No guarantee that all relevant patents will be identified
    • Delay in U.S. between filing and publication
      – Nonprovisional → at least 4 months
      – Provisional → more than a year
    • Some applications never publish before issuance
  – No guarantee that pending applications will issue with published claims
    • Often filed with extremely broad claims that have little chance of issuing
    • Moving target
Strategies for Clearing FTO

- **Noninfringement/Design Around Analysis**
  - Determine whether claims actually cover contemplated commercialization activity
  - Consider alternatives that will avoid claims (i.e., “design around”)
  - Carefully review prosecution history
    - Prosecution history can be roadmap to design-around strategies
      - Limitation on doctrine of equivalents (Festo)
Strategies for Clearing FTO

• Invalidity Analysis
  – Consider whether claims anticipated by or obvious over prior art
    • Broad claims more difficult to obtain now (but not impossible – see Noelle)

  – Consider whether claimed subject matter adequately described and enabled?
    • Application must fully describe claimed subject matter
    • Application must teach how to make and use claimed invention in manner that reasonably correlates with scope of claims
    • Lack of WD is most common rejection of broad antibody claims at USPTO
Strategies for Clearing FTO

- **Licensing**
  - Consider whether taking license is desirable/possible
    - Particularly if noninfringement/design around/invalidity positions uncertain
  - License more likely to be granted where patent holder is not competitor and does not plan to exploit technology in your intended field of use
    - BUT – must keep in mind *royalty stacking problem* (particularly in antibody space)
      - Allow for need for possible licenses in future
Select IP in the Antibody Space

- **Antibody Humanization**
  - Winter Patents (MRC) (e.g. U.S. 5,225,539)
    - Dominant humanization patent
    - Covers basic CDR grafting technology
  - Queen Patents (PDL) (e.g., U.S.)
    - Subordinate patent
    - Covers technique for improving binding affinity of humanized antibodies through “back mutations” (i.e., replacing acceptor framework residues with donor framework residues)
  - Example of where subordinate patent is as valuable or more valuable than dominant patent
Select IP in the Antibody Space

- **Antibody Expression**
  - Cabilly II Patent (Genentech)
    - U.S. 6,331,415
    - Broad claims to method for expressing recombinant antibodies in host cells
  - Has led to development of alternative expression systems
    - Polycistronic vector systems – potential design around?
Select IP in the Antibody Space

- Phage Display Technology
  - CAT
  - Morphosys

- Transgenic Mice
  - Abgenix
  - Medarex

- Examples of where FTO cleared in part by cross-licensing technology with competitor
New Patenting Opportunities and Perils

• The antibody field is rapidly developing

• New and improved antibody technologies create opportunities for broad claim protection

• Companies and institutions must understand patent landscape when venturing into new technology areas
Examples of the New Antibody IP

• Caveat – Exemplary only. No opinion on validity or enforceability. Pending claims may not issue.

• Fc Engineering
  – U.S. Pat. Pub. 20040132101 (Xencor)
    • Claim 1:
      – An antibody comprising an Fc variant portion comprising at least one amino acid modification in the Fc region of said parent Fc polypeptide, wherein said Fc variant modulates binding to an FcγR as compared to the parent Fc polypeptide

  – U.S. Pat. Pub. 20050064514 (MacroGenics)
    • Claim 1:
      – A polypeptide comprising a variant Fc region, wherein said variant Fc region comprises at least one amino acid modification relative to a wild-type Fc region, such that said polypeptide binds to an FcγR with an altered affinity relative to a polypeptide comprising a wild-type Fc region, provided that said at least one amino acid modification is not at the interface region of Fc-FcγR.
Examples of the New Antibody IP

- **Antibody Expression**
  - U.S. Pat. No. 5,639,947 (Scripps)
    - Claim 1:
      - A transgenic plant comprising: (a) plant cells containing nucleotide sequences encoding immunoglobulin heavy- and light-chain polypeptides that each contain an immunoglobulin leader sequence forming a secretion signal; and (b) immunologically active immunoglobulin molecules encoded by said nucleotide sequences.

- U.S. Pat. Pub. 20040261148 (Biolex)
  - Claim 1:
    - A recombinant monoclonal antibody having effector function, wherein said recombinant monoclonal antibody is produced by expression in duckweed.
Examples of the New Antibody IP

- **Modified Antibody Structures**
  - U.S. Pat. No. 5,260,203
    - Claim 1:
      - A single chain polypeptide having binding affinity for a given antigen, said polypeptide comprising (a) a first polypeptide comprising the antigen binding portion of an antibody; (b) a second polypeptide comprising the antigen binding portion of the heavy chain variable region of an antibody; and (c) at least one peptide linker linking said first and second polypeptides (a) and (b) into a single chain polypeptide having binding affinity for said given antigen
  - U.S. Pat. No. 5,837,821 (City of Hope)
    - Claim 1:
      - A *minibody* consisting essentially of the light and heavy chain variable domains of an antibody fused to, in sequence, the hinge region of an antibody, and amino acid linker and the CH$_3$ domain of an immunoglobulin molecule.
Examples of the New Antibody IP

• Increased Therapeutic Efficacy
    • Claim 9:
      – A modified therapeutic antibody of class IgG with an in vivo elimination half life of at least about 1.3-fold longer than that of the corresponding unmodified IgG antibody.

• Combination Therapies
  – U.S. Pat. No. 6,811,779 (ImClone)
    • Claim 1: A method for reducing tumor growth in a mammal in need thereof comprising treating the mammal with an effective amount of a combination of a monoclonal antibody which specifically binds to an extracellular domain of a VEGF receptor and radiation.
Examples of the New Antibody IP

- **New Targets**
  
  - U.S. Pat. No. 7,144,990 (Genentech)
    
    - Issued Dec. 5, 2006
    
    - Claim 1: An isolated antibody that specifically binds to the polypeptide shown in FIG. 16 (SEQ ID NO:16).
Other Important FTO Issues

- The FDA Safe Harbor
  - 35 U.S.C. § 271(e)(1)
    - Exempts from infringement activity conducted “solely for uses reasonably related to the development and submission of information” for purposes of FDA approval

- *Merck KGaA v. Integra* (U.S. 2005)
  - Interpreted statute as giving “wide berth” to use of patented drugs in activities related to FDA approval
Other Important FTO Issues

- **Merck KGaA v. Integra**
  - S. Ct. construed safe harbor to encompass *all uses* of patented inventions
    - So long as reasonably related to the development and submission of *any* information under the FDCA
      - Including preclinical

- Effect on research tools unclear
  - FN 7

- Case on remand to Fed. Cir.
Other Important FTO Issues

- **Offshoring**
  - Companies moving antibody development/manufacturing offshore until blocking patents expire
  - 35 U.S.C. § 271(g) – makes importation of product made abroad by process patented in U.S. an infringing act
  - *But See Bayer v. Housey* (Fed. Cir. 2004)
    - Only extends to importation of products, not data (e.g., screening data)
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Thank You

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