Pharma Session 4
Antibodies and epitope / competitive claims
Presenters

Michele Wales (US)

Graeme Boocock (CA)

Li Caihui (CN)

Osamu Yamamoto (JP)

Moderator: Jürgen Meier
Introduction

Jürgen Meier
Patent Attorney
Partner, Vossius & Partner
Why do we need to talk about antibody patents?

• Antibodies/antibody constructs/ drugs with antibody parts account for 10 out of the top 15 pharmaceutical products by worldwide sales in 2018, including the number one best-selling drug Humira® (containing the antibody adalimumab) and Opdivo® (nivolumab), Keytruda® (pembrolizumab), Enbrel® (etanercept), Herceptin® (trastuzumab), Avastin® (bevacizumab), Rituxan®/MabThera® (rituximab), Eylea® (aflibercept), Remicade® (infliximab), and Stelara® (ustekinumab)

• Since 2016, the first “biosimilars” are approved and are entering the market (16 antibody biosimilar approvals by the FDA up to July 2019)
General Antibody Structure and Function

© http://opig.stats.ox.ac.uk/webapps/newsabdab/sabdab/about/
General Antibody Structure and Modifications

- fully mouse
- chimeric
- humanized
- fully human

Antibody domains can be combined by genetic engineering

Suurs et al., Pharmacology and Therapeutics 2019, Vol 201, p.103-119
Even more antibody “derivatives” have been developed:

Brinkmann et al., MABS 2017, Vol 9, NO. 2, 182-212;
... and are in use...

Brinkmann et al., MABS 2017, Vol 9, NO. 2, 182-212;
Claiming Antibodies in Europe

Jürgen Meier
Patent Attorney
Partner, Vossius & Partner

www.aippi.org
Antibody claims may be directed to an target, may be “functionally defined” and do not have to be narrow...

T 1300/05, "RET screening assay/PROGENICS"
1. A monoclonal antibody generated against a cell-line susceptible to infection by macrophage-tropic HIV-1 isolates, and derived from the HuT 78 T lymphoblastoid cell line, wherein said antibody inhibits HIV-1 envelope glycoprotein mediated membrane fusion between Hela-envJR-FL and said cell-line, but does not inhibit HIV-1 envelope glycoprotein mediated membrane fusion between Hela-envLAI and Sup-T1 cells or between HelaenvLAI and Hela-CD4+ cells.

2. Use of a monoclonal antibody according to claim 1 for the preparation of a medicament for the treatment of HIV-1 infection.
The Technical Board:

The examining division came to a conclusion of lack of clarity of [...] on the ground that the claimed antibodies may have been better defined by technical features: sequence, epitopes and accession number. Yet, the sequence of an antibody is not likely to provide any useful information as to its characteristics, the determination of epitopes is a downstream development of the isolation of the monoclonal antibody per se and an accession number is not suited to characterize a family of antibodies. Thus, this approach to clarity cannot be followed.

(section 6)
T 1300/05, “RET screening assay/PROGENICS”

The Technical Board:

The examining division denied sufficiency of disclosure for the reason that it would be undue burden to obtain all antibodies falling within the scope of the claims. As explained above, it is the board's opinion that all necessary information for doing so is contained within the application. Thus, assuming for the sake of discussion that the skilled person would ever want to isolate all of the antibodies falling within the scope of the claims, the possibly undue amount of work involved would not stem from deficiencies in the way the invention was described but rather from the task which he/she chose to accomplish (section 17)
Antibody claims may be defined by decisive sequences and/or function and do not have to be narrow...

T 617/07, "Monoclonal NGF-antagonist antibodies/LAY LINE"
20. Monoclonal antibody, synthetic and biotechnological derivatives thereof, able to recognise and bind the high affinity tyrosine kinase receptor of NGF (Nerve Growth factor), named TrkA, and act as antagonist for the binding of NGF to TrkA, and which prevents the functional activation of TrkA by NGF, and characterised by at least one CDR selected from: light chain CDRs defined by aa 46-55 of SEQ ID No 2, aa 71-77 of SEQ ID No 2 and aa 110-119 of SEQ ID No 2 and heavy chain CDRs defined by aa 176-185 of SEQ ID No. 2, aa 200-216 of SEQ ID No 2 and aa 249-262 of SEQ ID No 2.

Note the functional limitation and the single CDR used for definition!
The Technical Board:

It is not an undue burden to identify antibodies that have the combination of the structural and functional features set forth in claim 20; (sections 22. to 26., 28. and 32 of decision).
Antibody claims may be defined by negative features and do not have to be narrow...

T 2332/10 „Antibody to C5 and C5a/GENENTECH“
An antibody or fragment thereof that binds to C5 and C5a, but does not prevent the activation of C5 and does not prevent formation of or inhibit the activity of C5b.
T 2332/10, “Antibody to C5 and C5α/GENENTECH”

The Technical Board:

- **Claim construction, section 6.**: antibody does not interfere with convertase.

- **Novelty, section 14.2**: the disclosure of a peptide to generate an antibody thereto does not amount to an unambiguous disclosure of an antibody to the three dimensional antigen having a particular function: section 14.1 and 14.2.

- **Inventive step, sections 20., 24. and 27.**: "the assessment of inventive step is purpose driven"!
Antibody claims may be defined by structural and functional features, which may be necessary in light of the prior art...

T 648/13, “Anti-αOPGL-1 antibody/AMGEN”
Inventive Step in „Selection Inventions“

**Inventive step – effect**

Claimed selection linked to a particular technical effect?

- yes
- no

Purposive selection

- yes
- no

Selection & effect suggested by prior art?

- yes
- no

Obvious selection

- Yes
- No

Not obvious selection

- Yes
- No

**No inventive step**

Inventive step

- No inventive step
1. An antibody, comprising a heavy chain and a light chain, wherein:
   the heavy chain comprises:
   an amino acid sequence as set forth in SEQ ID NO: 13;
   and
   the light chain comprises:
   an amino acid sequence as set forth in SEQ ID NO: 14;
   and
   wherein the antibody binds to an osteoprotegerin ligand (OPGL) and inhibits binding of OPGL to an osteoclast differentiation and activation receptor (ODAR).

Note the functional limitation does not define a “high affinity and binding specificity”!
T 648/13, “Anti-αOPGL-1 antibody/AMGEN”

- The Technical Board:
  • **novel**: whereas the cited prior art had disclosed antibodies that block the interaction between OPGL and its receptor ODAR, these prior art antibodies do not unambiguously and inevitably have the same amino acid sequences as those of the claims; (sections 31. to 35.);
  • **inventive**: the claimed antibody exhibited an unexpected and surprisingly high affinity and binding specificity for OPGL; (sections 46. and 47.)
Antibody claims may be merely defined by functional features, but an *enabling* teaching must be provided in the specification

T1389/13, “YKL-40 monoclonal antibodies/BIO-Y”
T1389/13, “YKL-40 monoclonal antibodies/BIO-Y”

1. An antibody, antigen binding fragment or recombinant protein thereof, which is specific for human YKL-40 (SEQ ID NO: 1), said antibody, antigen binding fragment or recombinant protein thereof capable of inhibiting growth of a cell upon binding to an epitope on YKL-40, wherein the cell is an YKL-40 expressing cancer cell.
T1389/13, “YKL-40 monoclonal antibodies/BIO-Y”

The Technical Board:

The patent failed to provide a single (reliable) analytical measuring method allowing the person skilled in the art to carry out the invention as claimed, i.e. to arrive at an anti-YKL-40 antibody which inhibits growth of a cell. A number of passages throughout the description of the patent in suit emphasize and distinguish different possible biological activities of the compounds of the invention, including the inhibition of growth of cells (which is the functional feature comprised in the claim), induction of apoptosis of cells, and a ‘growth repressive effect’. However, the methods in the patent were considered as failing to distinguish between inhibition of the growth of cells and the induction of apoptosis. (sections 19 and 25)
Antibody claims may be merely defined by structural features, but an *plausible teaching* must be provided in the specification that the claimed antibody is inventive.

T 605/14 “Anti-angiopoietin-2 antibodies/MEDIMMUNE”
An antibody or antigen binding fragment thereof comprising a variable light chain having a sequence defined by SEQ ID NO:81 and a variable heavy chain having a sequence defined by SEQ ID NO:79.
Claim is directed to an antibody comprising specific variable light and heavy chains, which were those of the specific, singled-out monoclonal antibody (mAb) 3.19.3, an anti-Ang-2 antibody provided in the patent.

The patentee relied in the defense of this antibody, inter alia, on Biacore binding affinity data as originally disclosed in the patent specification and argued that the single antibody claimed shows a higher (advantageous) preferential binding for Ang-2 versus Ang-1.

The Technical Board:

High-resolution Biacore measurements are reproducible, the values themselves are not considered reliable in the application. Indeed, the Board concluded that the technical effect of a higher preferential binding affinity of mAb 3.19.3 for Ang-2 versus Ang-1 is not derivable from the application as filed (section 11)
In the EPO, in contrast to the USPTO:

NO “STRUCTURAL NON-OBVIOUSNESS”
"While it is established case law that claims can validly cover broad subject-matter, the question of the allowability of a broad claim versus the requirement of sufficiency of disclosure is one which is strictly assessed on a case-by-case basis, influenced by the extent to which the information in the patent in suit could be used to develop further embodiments without a major conceptual leap; e.g. decision T 636/97 [...]" (section 22)
Thanks for your attention!
Overview – Antibody Patenting

• Patent Eligibility Unlikely to Block Patentability
• Written Description is Key Issue in United States
• New Grounds for Invalidity Challenges
  – New 103/112 Squeeze
  – Consider need for license
  – Effect on Litigation
Patent Eligible Subject Matter Not an Issue

• Can the Antibody be found in Nature?
  – Selection against self-antibodies during development
  – Examiner needs to provide evidence of existence
    • “mere possibility” is not enough
  – Most antibodies are artificially created in laboratory
How to Argue Over Patent Eligible Rejections

• Any Structural or Functional Difference
  – Sequence Differences
    • Chimeric, Humanized, Fragments
  – Manufacturing/Glycosylation Differences

• Methods of Using

• “Purified” or “Isolated” not enough
Obsolete Written Description Standard: Well-Characterized Antigen

*Noelle v. Lederman*, 355 F.3d 1343 (Fed. Cir. 2004)

- Written Descriptions satisfied if antigen to which antibody binds was well characterized.
  - Sequence information (or even generation of an antibody) not needed.
  - Stark contrast to standard for Small Molecules

- Therapeutic Antibodies – US Industry Boomed

• Amgen sued Sanofi/Regeneron - Infringement of Praluent™
  – Cholesterol treatment which lowers high LDL levels
  – Amgen’s antibody - Repatha™
An isolated monoclonal antibody, wherein, when bound to PCSK9, the monoclonal antibody binds to at least one of the following residues: S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of SEQ ID NO:3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR.

No Antibody Sequence Recited In Claim
Specification disclosed 22 different antibodies with function
Well-Characterized Antigen Standard **Eliminated**

- Newly characterized antigen test “flouts basic legal principles of the written description requirement” and that Congress “has not created a special written description requirement for antibodies as it has, for example, for plant patents.”

- Representative Number of Species of **Sequenced** Antibodies
  - Standard now consistent with small molecules
  - Inconsistent with other jurisdictions
  - Applies retroactively
  - USPTO issued guidance in February 2018 that “well characterized antigen” no longer satisfies written description
# How to Obtain Allowable Antibody Claims

<table>
<thead>
<tr>
<th></th>
<th>Sequence Data</th>
<th>No Sequence Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target/Antigen</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Domains</strong> - CDRs, Humanized, Chimeric, Fragment, Light Chain, Heavy Chain</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Functional</strong> - Agonist, Antagonist</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Functional</strong> - Binds to Epitope, Competitive Binding and/or Specificity</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Method of Treatment</strong></td>
<td>Yes</td>
<td>No</td>
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</tbody>
</table>
Best Practices

• Claim Antibodies by Sequences
  – CDR/Heavy/Light/Full Length Sequences
    • All six CDRs are necessary for function/utility
  – Claims to variants (% identity) if CDRs are maintained
    • Variation limited to in framework sequences

*An antibody or fragment thereof comprising SEQ ID NO: 2*

*An antibody comprising HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 wherein HCDR1 comprises SEQ ID NO: 3, HCDR2 comprises SEQ ID NO: 4, HCDR3 comprises SEQ ID NO: 5, LCDR1 comprises SEQ ID NO: 6, LCDR2 comprises SEQ ID NO: 7, LCDR3 comprises SEQ ID NO: 8.*
• Functional Language Requires Exemplified Antibodies
  – Inherent Function and therefore may be unnecessary
    • An antibody comprising SEQ ID NO:1.
    • An antibody comprising SEQ ID NO:1 wherein said antibody inhibits binding of antigen X to its receptor Y.
    • An antibody comprising SEQ ID NO:1 which binds to amino acids 110, 156, 190 and 203 of SEQ ID NO:2 {antigen}.

– Needed if Variants are Being Claimed
  • An antibody comprising the amino acid sequence at least 90% identical to SEQ ID NO:1, wherein said antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 wherein HCDR1 comprises SEQ ID NO: 3, HCDR2 comprises SEQ ID NO: 4, HCDR3 comprises SEQ ID NO: 5, LCDR1 comprises SEQ ID NO: 6, LCDR2 comprises SEQ ID NO: 7, LCDR3 comprises SEQ ID NO: 8, and wherein said antibody has function X.
Invalidity Challenges

• 103/Written Description Squeeze
  – If antigen published – then all antibodies obvious
  – Need Ab sequence before written description satisfied
  – Claims will be limited to specific antibody plus a reasonable scope of variation

• Review License Agreements to Generic Antibodies
  – May no longer be valid

• Additional grounds of attack in litigation
Thanks for your attention!
Antibody Patenting:
A Canadian Perspective

Graeme Boocock, PhD
Senior Patent Agent
Borden Ladner Gervais LLP
General Considerations

• Formal jurisprudence from Canadian courts in this technical area is [almost] non-existent.

• The Canadian Intellectual Property Office (CIPO) relies on a series of decisions of the Patent Appeal Board (PAB) and Commissioner of Patents for its policies.
  – Some of this was written into CIPO’s examination manual, the Manual of Patent Office Practice (MOPOP), in 2017.

• However, some key practice points remain formally unpublished.
A Strict Beginning
Commissioner’s Decision 1206 - 1995 ("Pasteur")

• Application filed in 1987.
• Claimed monoclonal antibodies that had not been made.
• Taught they could be made using “traditional techniques”.
• PAB relied on U.S. law and out of context statements from Dr. James Goding in an academic textbook:
  – “If the preparation of monoclonal antibodies were routine... the field of immunology would routinely produce all kinds of cures.”
• Claims denied for lack of sufficient description/enablement.
• Decision applied by CIPO for the next ~15 years!
Modern Objections Reflect History

Common bases for objection today include:

– **Support/Claim Scope**: Section 84 of the *Patent Rules*
  “The claims... shall be fully supported by the description...”

– **Sufficiency/Enablement**: Subsection 27(3) of the *Patent Act*
  “The specification of an invention must (a) correctly and fully describe the invention... (b) set out clearly... the method of constructing, making, compounding, or using a... composition of matter... as to enable any person skilled in the art...”

– **Utility/Sound Prediction**: Section 2 of the *Patent Act*
  Requires a factual basis, a sound line of reasoning for inferring claim scope, and proper disclosure.
Chipping Away at *Pasteur*

Commissioner’s Decision 1283 (2008)

- Faced with critical affidavit from Dr. Goding:
  
  “...the precedential value of Pasteur has been diminished in respect of its findings on the enablement requirement...” → but no change in policy

Considerations for Enablement:
- whether the applicant actually prepared a monoclonal antibody,
- where a monoclonal antibody had not been prepared,
  - whether the target antigen to which the monoclonal antibody specifically binds was fully characterized,
  - the availability and/or ease of production of the antigen,
- whether the scope of an antibody claim with respect to the antigen is appropriate.

Considerations for Written Description:
- whether there was a full characterization of the target antigen to which the monoclonal antibody specifically binds;
- if not, whether the applicant actually prepared the monoclonal antibody and provided a full characterization thereof;
- if not, whether the applicant prepared a monoclonal antibody and deposited a hybridoma which produces the antibody...; and
- whether the scope of an antibody claim with respect to the antigen is appropriate.
Chipping Away at *Pasteur*

**Commissioner’s Decision 1296** (2009)

- Application filed in 1990.
- Inventors produced murine mAb and deposited hybridoma.
- No antibody sequences provided.
- Claims to **non-exemplified chimeric antibodies** allowed.
- Claims to **non-exemplified humanized antibodies** denied.
Chipping Away at Pasteur

Commissioner’s Decision 1302 (2010)

- Inventors described novel epitope.
- Claims to non-exemplified monoclonal antibodies allowed.

“… the skilled person would appreciate that monoclonal antibodies can be adequately described based on a combination of a structural description of the antigen, functional identity [i.e. specific immunoreactivity] between the antibody and antigen, and knowledge of predictable production methods.”

⇒ CIPO policy change, but only for monoclonal antibodies.
Chipping Away at *Pasteur*

Commissioner’s Decision 1398 (2016)

- Application filed in 2002.
- Inventors made murine mAbs and described novel epitope.
- No antibody sequences disclosed.
- Claims to non-exemplified humanized antibodies allowed.

“The evolution of [common general knowledge] is an important factor for assessing whether the disclosure in this case is sufficient to enable a person skilled in the art to practice the invention as claimed without… undertaking undue experimentation as of the relevant date.”

“…[CD1296] leaves open the possibility that a humanized antibody can be described in ways other than by providing the amino acid sequences of the CDRs… Canadian examination practice with respect to antibodies has also evolved since [CD1296].”
Humanized and chimeric Antibodies (17.07.03)

CGK timeline

1992 Monoclonal antibody
2000 Human antibody (mouse, phage display)
2002 Humanized antibody

• Evaluate 27(3)(a) and 27(3)(b) as for monoclonal antibodies

Adapted from: http://www.mbl.co.jp/e/ir/glossary.html

https://ipflyonthewall.files.wordpress.com/2017/01/a-2016-00719_0001-english.pdf
Enablement – 27(3)(b)

- Antibody prepared? – 27(3)(b) compliant
- Antibody not prepared? - evaluate
  - CGK and DIS must be taken into account

<table>
<thead>
<tr>
<th>Ab produced?</th>
<th>Ag fully characterized?</th>
<th>Indication that would be unable to produce?</th>
<th>Indication that undue experiment or core step adaption required?</th>
<th>27(3)(b) compliant?</th>
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Correct and full description – 27(3)(a)

- Ag defined by:
  - Structure, formula, chemical name, physical properties
  - aa SEQ of antigenic polypeptide
  - Similar fully characterized protein

<table>
<thead>
<tr>
<th>Ag fully characterized?</th>
<th>Ab prepared and fully characterized?</th>
<th>Ab prepared and hybridoma deposited?</th>
<th>27(3)(a) compliant?</th>
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https://ipflyonthewall.files.wordpress.com/2017/01/a-2016-00719_0001-english.pdf
Example 2 – claim 3

Claim 3. An antibody that competes for specific binding to RF with monoclonal antibody M1 produced by the hybridoma having accession number IDAC 022612-11.

- Competing Ab claim
  - M1 novel and non-obvious
  - competing Ab likewise novel and non-obvious
  - POSITA can identify competing Abs, therefore enabled

<table>
<thead>
<tr>
<th>Compliant?</th>
<th>27(3)(a)</th>
<th>27(3)(b)</th>
<th>28.2</th>
<th>28.3</th>
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Today: A Very Favourable Situation

• With a novel epitope, one can claim a range of non-exemplified antibody sub-types, including:
  – Monoclonal,
  – Bi-specific,
  – Chimeric, and
  – Humanized antibodies.

• If an epitope was known → obviousness asserted during examination for a claim to a *general class* of antibodies.

• If a murine monoclonal was known → obviousness asserted for claim to *general* humanized antibody.

• However, claims to *specific* antibodies may still be available.

• Applicants have sometimes faced surprising policy reversals!
Accepted Claiming Conventions

• One can claim antibodies in terms of, e.g.,:
  a) a well-defined epitope,
  b) a full set of intact CDR sequences,
  c) a biological deposit, or
  d) competition for specific binding with an antibody defined by (b) or (c).

• Post-CD1398, CIPO examiners have greater discretion to be positively responsive to the state of the art when assessing sufficiency-enablement.
**Functional Features**

- Examiners require *structural* definitions in independent claims.
  - Functional features may be present in addition or in dependent claims.
  - Functional features may be more acceptable when the point of invention is not the antibody *per se* (e.g., “use” inventions).

- *May* be possible to claim an antibody in terms of the *full* target molecule (less precise than an epitope) if functional features are also recited.

- Functional features can be expected to garner scrutiny:
  “Cases in which more detailed support may be required... include:
  - where the applicant is claiming a particular monoclonal antibody reciting particular functional characteristics that go beyond the simple interaction with the target...”
  - MOPOP 17.07.02a
Policy-based Sticking Points Remain

• It is not permitted to claim sequences of (or encoding) an unsequenced biological deposit.

• Claims to non-exemplified CDR variants are [nearly] impossible to obtain.
  – Consider that competitive binding claims may provide similar coverage.

• Antibodies defined by discontinuous or conformational epitopes can be more challenging.
  – CIPO is still most familiar with “classic” epitopes.
  – Examiners are usually susceptible to technical argument.
A Word on Sound Prediction

• If claims cover embodiments for which utility has not been demonstrated at filing, the inventors must have been in a position to make a “sound prediction” of their utility.

• This requires:
  – factual basis (e.g. experimental evidence),
  – articulable and sound line of reasoning for inferring claim scope, and
  – proper disclosure of these elements.

• Supreme Court of Canada has stated that sound prediction:
  – “cannot mean a certainty”, but
  – cannot be based on speculation alone.  Apotex Inc v Wellcome Foundation Ltd 2002 SCC 77

• Objections may parallel EP plausibility + technical effect issues.
• Post-filing evidence is generally not considered.
Thanks for your attention!
Patent on antibodies in China

Cahui Li
3S Bio Inc.
Patent on antibodies in China

Patentability of antibodies in China

Invalidation of patent on antibodies in China
Patent on antibodies in China

Patentability of antibodies in China

- Epitope
- Antibodies
- Usage
Patent on antibodies in China

Patentability of antibodies in China

- Epitope
  - sufficient disclosure
  - identification of the epitope
  - technical effect of the epitope
Claim disclosed: A functional epitope of osteopontin, wherein the functional epitope is NXPY, and wherein X=A or G, and Y=S, T, N or P.

Claim issued: A functional epitope of osteopontin, where in the functional epitope is NAPS.
Epitope: sufficient disclosure

**CN103509086B**

- **Claim disclosed:**
  A botulinum toxin BoNT/B Hc functional epitope FYQ*I*, wherein * may be an arbitrary amino acid.

- **Claim issued:**
  An anti-botulinum toxin antibody, wherein the AA sequence of VH is SEQ ID NO.16 and the AA sequence of VL is SEQ ID NO.18.
Patent on antibodies in China

Patentability of antibodies in China

- Antibodies
  - Antibodies restricted by binding affinity difficult to be issued: **sufficient disclosure**
Antibodies restricted by structure

- CDRs
- VH\VL
- full sequences of light chain and heavy chain

sufficient disclosure + inventive step
Patent on antibodies in China

Patentability of antibodies in China

Usage

• Single usage (mechanism-usage)
• Combination (1+1>2)
• Dosage (difficult to be issued)
Patent on antibodies in China

Invalidation of patent on antibodies in China

- AA sequence
- ZL 93121424.6
  - hybridoma $\rightarrow$ antibody restricted by VH\VL
  - Sufficient disclosure
Patent on antibodies in China

Invalidation of patent on antibodies in China

➤ Usage

ZL 00811372.6

Rituxan + CHOP for treatment of DLBCL (diffuse large B cell lymphoma)

Inventive step
Patent on antibodies in China

Thanks for your attention!
Claiming Antibodies in Japan

Osamu Yamamoto
Patent Attorney
Partner, YUASA AND HARA
Agenda

- How to claim antibodies
  Structure / Function

- Support / Enablement requirements
  Breadth of Claims and Support by Examples

- Inventive Step
  Post-filing Data

- Litigation
  Invalidity defense
How to claim antibodies

Structural feature(s), e.g., a sequence, is definitely of use.

Functional feature(s) may be of use.

Possible to define antibodies by their target/antigen, if antigen X is new and inventive, and is structurally described.

“An antibody which binds to antigen X”

When a target is found to have a previously unappreciated role in a disease:

“A pharmaceutical composition for treating a disease X, which comprises an antibody directed against target Y.”
How to claim antibodies

A claim may define an antibody by its ability to bind to a particular epitope. In a majority of cases an epitope must be defined by its exact sequence.

**JP No. 6165713**

Claim 1   *An isolated monoclonal antibody specific for IGF-1, wherein the antibody binds to an epitope consisting of amino acids 76-84 (SEQ ID NO: 3) of IGF-1 precursor (SEQ ID NO: 1).*

Difference at a binding site or an epitope alone is unlikely to suffice to establish inventive step, but if that difference gives rise to particular advantageous effects, the difference could be persuasively asserted in support of inventive step.
How to claim antibodies

Possible to define by its ability to bind to a particular epitope.

“An antibody specific to target X having a same epitope as an antibody produced by a hybridoma deposited under ATCC -----.”

Possible to define by reference to a target affinity / cross-reactivity, etc.

“A monoclonal antibody binding to protein A, having a dissociation constant of $10^{-13}$ M or more and $10^{-12}$ M or less.”

“A monoclonal antibody which binds not to antigen B but to antigen A.”
How to claim antibodies

An antibody directed to a known target may be claimed with reference to a particular sequence.

The extent of a sequence required varies depending on the case; for example, a full length, to whole variable regions, or to all CDRs.

Indication of all 6 CDRs recognized as a minimum requirement.

However, increasing appreciation of relevance of framework regions to target binding exists.

Generally, it is not permissible to claim sequence variation in CDRs unless variation has been experimentally exemplified in the specification.
Support / Enablement

The number of examples must be sufficient to enable a person skilled in the art to carry out the invention in its full scope as claimed without undue burden.

Amgen Inc. v Sanofi
Hei 29 Gyo-ke 10225 and 10226 (December 27, 2018)

Sanofi filed invalidation trials against P1 on January 18, 2016, and against P2 on May 31, 2016.

Decisions on both cases were issued on August 10, 2017. P1 was maintained with a correction of the claims. Sanofi brought the case to the IP high court. The IP High Court upheld the JPO decisions.

In parallel, the infringement case was before the Tokyo District Court. A decision favorable to Amgen was issued on January 17, 2019.
Corrected Claim 1 reads as follows:

_An isolated monoclonal antibody, which can _neutralize_ binding of PCSK9 and LDLR protein, and which is _competitive_ for binding to PCSK9 with the antibody including a heavy chain variable region consisting of an amino acid sequence shown as SEQ ID No. 49, and a light chain variable region consisting of an amino acid sequence shown as SEQ ID No. 23._
Support / Enablement

- Screening -
3104 hybridomas: antigen specific
2441 hybridomas: stable production of monoclonal antibody
85 antibodies: strong neutralizing activity of binding of PCSK9/LDLR protein
3 antibodies: strongest binding activity with PCSK9
21B12, 31H4, 16F12

- Epitope Binning -
31H4 / 16F12 similar, 21B12 different conformational epitope
19 / 39 antibodies: competing with 21B12
10 / 39 antibodies: competing with 31H4
The IP High Court upheld the JPO decisions.

Sanofi argued that Claim 1 includes *merely functional or characteristic definitions*, and therefore the claimed invention encompasses an enormous number of antibodies or a wide variety of structures; while in the specification only a limited number of antibodies is disclosed.

Amgen argued that the specification includes *detailed descriptions* of how to prepare the claimed monoclonal antibody based on results of experiments, and that as of the filing date desired antibodies can be obtained by a screening test based on known characteristics.

It is worth drafting a claim that is defined only by a functional feature(s).
Inventive Step

Structural difference over prior art antibodies is not sufficient.

It is necessary to show that a new antibody to a known target provides “an unexpected effect.”

Appeal No. 2016-8151 (July 6, 2017)

Claim 1 reads:

An isolated antibody that binds TAT425 comprising:

(a) a CDR-L1 sequence of SEQ ID NO:10;
(b) a CDR-L2 sequence of SEQ ID NO:13;
(c) a CDR-L3 sequence of SEQ ID NO:16;
(d) a CDR-H1 sequence of SEQ ID NO:19;
(e) a CDR-H2 sequence of SEQ ID NO:23; and
(f) a CDR-H3 sequence of SEQ ID NO:27,

wherein the TAT 425 comprises amino acid sequence of SEQ ID NO:2 or its extracellular domain.
Citation 1 discloses the same antigen TAT425 sequence, and refers to an isolated antibody that binds to TAT polypeptides including TAT 425.

The patent applicant / appellant argued:

(1) none of the cited documents discloses an antibody defined by CDRs, and
(2) the Examples show that the claimed antibodies were bound to different extracellular epitopes, etc.

Against the above arguments, the board found that:

(1) it was routine to analyze amino acid sequence of an antibody, and it would be an easy to produce antiTAT425 monoclonal antibody, and thus simple identification of an amino acid sequence does not provide inventive step;
(2) as the TAT425 is a larger polypeptide, it is not surprising that the TAT425 comprises a plurality of epitopes that do not compete for binding to a plurality of antibodies; and,
(3) the cited documents also disclose that both primary human prostate cancer and metastatic prostate cancer showed positive for expression of TAT 425, and thus it would be within reasonable expectation of a person skilled in the art.
Post-filing Data

At present, the JPO accepts late-filed experimental data in support of inventive step over cited documents, so long as the effects shown by the data can be inferred from descriptions in the specification.

*Hei 29 Gyo-ke 10106 (October 22, 2018)*

Whether unexpected effects are produced by the claimed invention.

The Appeal Board found “yes”

- Patients treated according to the above therapeutic regimen will display improved overall survival and/or reduced time to tumor progression (TTP).

The IP High Court disagreed:

- The application discloses its effects, but does not mention what other regimen and to what extent the claimed invention will produce an improved survival rate and/or reduced TTP.
- The data could be considered only to the extent indicative of “qualitative effects”, and the court declined to consider beyond “qualitative effects”.
Alleged infringer can challenge validity of patent

The court usually construes the claim for invalidity to be commensurate with the scope for infringement.

It is important to start an infringement law suit, after careful review of scope of the claims and validity of the claims, especially in the case of a functionally defined claim.
There are many ways to define antibody inventions.

Various factors, including what is already known, what is found by an inventor, and how many data inventor has at the time of filing, should be considered at each stage of drafting the claims, prosecuting the application, and litigation.
Thanks for your attention!
## Summary and Discussion

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FURTHER READING

Antibody Patenting
A Practitioner’s Guide to Drafting, Prosecution and Enforcement

-HOT FROM THE PRESS!

- AIPPI LAW SERIES BOOK (5th volume)

- 23 JURISDICTIONS COVERED!

- 35 AIPPI AUTHORS!