Biotech/Chem/Pharm Customer Partnership Meeting

Personal Medicine

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Overview

- What is Personal Medicine?
- Legal/Examination Issues Facing Personal Medicine Claims
- Claim examples

Personal Medicine – A Growing Approach

- Personal vs. Personalized medicine
- Treatments tailored/optimized to individual subject's genome
  - Natural genetic variations play a role in the risk of getting a disease and in the effectiveness of treatments
  - A move away from "one size fits all" treatments
  - Examples: cancer immunotherapy or biotherapy
- Improved genetic sequencing and biomarker prediction have helped open up this approach
- In some cases is a shift from reacting to a disease to prevention
  - Can sometimes predict susceptibility to disease, improved detection, preempt progression

Personal Medicine – A Growing Approach

- **Recent successes in the news:**
  - FDA approval (8/30/2017) of CAR T-cell therapy for acute lymphoblastic leukemia

  " …a new frontier in medical innovation…" – FDA Commissioner

- **Recent example showing success**
  - Ott et al., "An Immunogenic Personal Neoantigen Vaccine for Patients with Melanoma," Nature 22991:1-21 (2017).
  - All 6 melanoma patients enrolled in trial (2 were metastatic) exerienced complete tumor regression

Legal Landscape and Examination Issues

- Somewhat challenging
- Faces similar issues as other related life science technologies
- Some examples, immunotherapy or biotherapy
  - Boosting the body's immune system
  - Train the immune system to attack cancer cells
- Claims sets may include;
  - Diagnostic assays
  - Tailored therapeutic compositions unique to each patient
  - Methods of making personal therapeutic compositions
  - Methods of treatment

Legal Landscape and Examination Issues

- The 101 landscape impacts Personal Medicine
- *Mayo* & *Myriad* have impacted diagnostics & laws of nature/natural products
  - Personal Medicine can involve:
    - Identifying a subject's biomarkers by way of a diagnostic assay
    - Using a subject own immune system/response to target disease/cancer
- Enablement
  - The treatment compositions are unique/customized to the patient
  - *Wands* factors - Number of examples
- Written Description
  - How to best describe & protect treatment compositions when they are different for each individual
- Divided Infringement issues

Typical Claim Sets

Diagnostic assay claims

- Focusing on the biomarker or unique aspect of the subjects genome in order to customize a treatment
- Faces similar 101 "law of nature" issues as other diagnostics
- A novel/new method of measuring the biomarker likely eligible
- What about a combination of biomarkers identified and used together to assess a susceptibility to disease or likelihood of a specific treatment?
- What about using specific probes to create "man-made" samples?

Typical Claim Sets

Therapeutic Compositions

- May be a man-made combination of “natural products”
- Compositions might be man-made combination of antigens or specific proteins to invoke an immune response
- Compositions might include adjuvants that modify the effect of antigens or suppress unwanted reactions
- Product-by-process claims - are still products, potentially protective for products that can’t be made by another process
  - Original intent was for products which could only be described by how they are made

Typical Claim Sets

Methods of making personal therapeutic compositions

- e.g., customized cancer specific T cells
- Do methods of making face fewer 101 hurdles?
- Do methods of making face fewer Written Description and/or Enablement hurdles?
- Non-naturally occurring product
- What is the impact of the method being *ex vivo* or *in vivo*?

Typical Claim Sets

Methods of treatment

- e.g., screening a patient for a biomarker followed by active treatment/application step
- Adding steps with “substantially more” can avoid 101 issues
- Awareness of possible divided infringement issues, i.e. method being performed by two different entities
- *Akamai v. Limelight* cases – the performance of all of the steps might be attributable to a single actor
  - Can be a factor in claim drafting

Challenges for Personal Medicine/Diagnostic Companies

Finding of Induced Infringement: Divided Infringement

Limelight: Supreme Court considered whether there can be induced infringement where separate entities perform separate steps of a method claim (joint/divided infringement)

Holding: "A defendant is not liable for inducing infringement under §271(b) when no one has directly infringed under §271(a) or any other statutory provision."

- *Reverses en banc Federal Circuit decision*

Induced infringement under 35 U.S.C. § 271(b) limited to cases where direct infringement under §271(a) has occurred.

34. A content delivery method, comprising:

distributing a set of page objects across a network of content servers managed by a domain other than a content provider domain, wherein the network of content servers are organized into a set of regions;

for a given page normally served from the content provider domain, tagging at least some of the embedded objects of the page so that requests for the objects resolve to the domain instead of the content provider domain;

in response to a client request for an embedded object of the page:

resolving the client request as a function of a location of the client machine making the request and current Internet traffic conditions to identify a given region; and

returning to the client an IP address of a given one of the content servers within the given region that is likely to host the embedded object and that is not overloaded.

Performed by Limelight

Performed by Limelight's Customers

- Limelight provides instructions to Customers on how to tag

Performed by Limelight

U.S. Patent No. 6,108,703

Possible Rejections

Enablement – 112(a)

- Using patient/cancer/tumor-specific antigen
- What evidence will be sufficient to establish enablement?
- Customized patient-specific treatment composition will have limited use on other patients
- Getting both Enablement & 103 rejections:
  - Office sometimes makes103 combinations of prior art, saying the combination is "enabled" for one of ordinary skill - and also rejects the application's disclosure as not enabled to support the scope of the claims
  - Is it a claim scope issue? What if these rejections are on the same claims?
  - An *improper* squeeze?

Possible Rejections

Written Description – 112(a)

- How much structure-function relationship is required for compositions?
  - e.g., compositions capable of causing an immune response
  - What types of structural properties can be used to define a structure?
    - Binding affinity, length/molecular weight of peptides – to induce an immune response?

- Claim scope in Written Description rejections
  - Sometimes scope of claim(s) broader than supported disclosure
  - Sometimes Genus being claimed without a representative number of species
    - Can the same above noted structural properties define a genus?

Issues with Written Description and Personal Medicine Claims

- How to claim a therapeutic composition with sufficient description to show possession when the specific embodiments of the composition are reduced to practice on a patient by patient basis?
  - e.g., properties of the composition, such as binding affinity or classes of protein mutations, can be described, but specific protein sequences as determined on a patient by patient basis.

- How to claim a therapeutic composition with sufficient description to show possession when the specific components of the composition are tailored for each patient?
  - e.g., specific sequences containing mutations are unique for each patient.

- What is a sufficient number of species to describe a claimed genus when the genus theoretically includes billions of species?

Example 1 - Antibodies

Claim: An isolated humanized monoclonal antibody that binds to amino acids 25-35 of [a specific] antigen with an affinity of 100 nM or less.

- **Sequences of variable regions of Ab not necessary?**

- Disclosure:
  - No structural properties of Ab variable domains disclosed
  - Identity and region of antigen to which the Ab binds disclosed

- Antibody "exception" of written description
  - USPTO guideline: claim for an isolated antibody binding to an antigen satisfies the written description requirement even when the specification only describes the antigen and does not have working or detailed prophetic examples of antibodies that bind to the antigen. (*Revised Interim Written Description Guidelines Training Materials* at 59–60 (1999); *Written Description Training Materials, Revision 1* at 45–46 (2008)).
  - When the inventor sufficiently described a protein (antigen) to warrant the patent rights for the protein, the USPTO advised examiners to grant patents for monoclonal antibodies that specifically bind to such protein, even when failed to show possession of the antibodies. *Id* at 59-60.
  - In *Noelle v. Lederman*, the Federal Circuit held that a claim for an antibody that is defined by its specific binding affinity to an antigen can satisfy the written description requirement with the specification that discloses a "fully characterized antigen," thereby approving the antibody exception in the USPTO Guidelines. (355 F.3d 1343, 1349 (Fed. Cir. 2004)).

Example 1 - Antibodies

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

- Single mAb example was insufficient to show possession of the broad genus of antibodies claimed. *In re Alonso* (Fed.Cir. 2008).

Disclosure:

- Only a single mAb example disclosed

- See also:
  - Very recenlty, CAFC held that later-developed antibody species may be evidence that a claimed antibody genus is invalid for lack of written description, and casts doubt on the "antibody exception." *Amgen Inc. v. Sanofi*, No. 2017-1480 (Fed. Cir. October 5, 2017).

Example 2 - Isolated Protein - U.S. Patent No. 5,344,915

Claim: A purified and isolated TNFα-binding protein which has a molecular weight of about 42,000 daltons and has at the N terminus the amino acid sequence

Xaa Thr Pro Tyr Ala Pro Glu Pro Gly Set Thr Cys Arg Leu Arg Glu

where Xaa is hydrogen, a phenylalanine residue (Phe) or the amino acid sequences Ala Phe, Val Ala Phe, Gln Val Ala Phe, Ala Gln Val Ala Phe, Pro Ala Gln Val Ala Phe or Leu Pro Ala Gln Val Ala Phe.

- Federal Circuit held that a claim to an isolated protein described by its partial amino acid sequence satisfies written description when the partial sequence is combined with other identifying characteristics of the protein. (*Yeda Research and Development Co., Ltd. v. Abbott GMBH & Co. KG*, Slip Op. 2015-1662 (Fed. Cir. 2016))

- Under the doctrine of inherent disclosure, "when a specification describes an invention that has certain undisclosed yet inherent properties, that specification serves as adequate written description to support a subsequent patent application that explicitly recites the invention's inherent properties." Slip Op. at 6. The court determined that the doctrine applied because it was "undisputed that the invention described in an earlier application was the exact invention claimed by the later patent." *Slip Op*. at 7.

Example 3 - Copaxone - US 6,939,539

Sole amendment made during prosecution:

Claim: A copolymer-1 composition comprising a mixture of polypeptides composed of glutamic acid, lysine, alanine and tyrosine, wherein the mixture has an average molecular weight of about 4 to about 9 kilodaltons, ~~and~~ wherein the mixture of polypeptides is non-uniform with respect to molecular weight and ~~constitution~~ sequence, and wherein the composition is suitable for treating multiple sclerosis.

Rejection	Applicant response
Specification is not enabling for "polypeptides composed of glutamic acid, lysine, alanine and tyrosine"; this is extremely broad and inclusive of all polypeptides of alanine, glutamic acid, lysine and tyrosine having a molecular weight between 5 and 9 kilodaltons, irrespective of the relative molar proportions of each amino acid. Specification does enable use of copolymer-1 (COP-1); spec provides no guidance for preparing mixtures of polypeptides of alanine, glutamic acid, lysine and tyrosine having the requisite biological activity of treating MS, other than COP-1 (the only species used in the working examples).	Amended claims to recite "copolymer-1"
The term "constitution" is unsupported by the specification.	Replaced "constitution" with "sequence" which they say is a "synonymous, non-narrowing term in the context of the specification."
No support in spec for "about 4 to about 9 kilodaltons"	Pointed to support in spec for "about 5 to about 9 kilodaltons."

Example 3 - Copaxone - US 7,199,098

1. A copolymer-1 composition comprising a mixture of copolymers of alanine, glutamic acid, lysine and tyrosine, the copolymer species in the mixture being non-uniform with respect to molecular weight and sequence, wherein over 75% of the copolymers in the mixture, on a molar fraction basis, have a molecular weight in the range of 2 kDa to 20 kDa and less than 5% of the copolymers have a molecular weight above 40 kDa, and wherein the composition is suitable for treating multiple sclerosis.

19. A copolymer-1 composition comprising a mixture of polypeptides composed of glutamic acid, lysine, alanine and tyrosine, wherein the mixture has an average molecular weight of 4 to about 8.6 kilodaltons, wherein the mixture of polypeptides is non-uniform with respect to molecular weight and sequence, and wherein the composition exhibits lower toxicity than a copolymer-1 composition having an average molecular weight greater than about 8.6 kilodaltons.

Example 4 - Patient-Specific Peptide Vaccine

Method of Treatment

Claim: A method of treating cancer in a subject comprising
administering to a subject a plurality of personal peptides
each peptide comprising
(a) a mutation expressed specifically by a cancer cell of the subject
(b) 5-100 contiguous amino acids, and
(c) an epitope that binds to a cell surface protein expressed by the subject.

Composition

Claim: A personal immunogenic composition comprising
(1) an adjuvant; and
(2) a plurality of personal peptides, each peptide comprising
(a) a mutation expressed specifically by a cancer cell of the subject,
(b) 5-100 contiguous amino acids, and
(c) an epitope sequence that binds to a cell surface protein expressed by the subject.

Example 4 - Patient-Specific Peptide Vaccine

- Claim to a genus of peptides with specific binding and mutation properties.
- An adjuvant to improve/support the immune reaction
- Composition activates the immune response
  - Is the breadth of the claims beyond the “possession’ in the disclosure?
  - Do the structural-functional properties of peptides in the specification support the “functional” genus?

Issue: Each peptide set for a given individual patient will be different than that for another individual

Disclosure:

- How to identify nucleotide sequences comprising a cancer specific mutation.
  - 200+ exemplary peptide sequences
- How to identify peptides that bind to a cell surface protein expressed by the subject
  - 50+ exemplary peptides
- How to identify peptides that are immunogenic
  - 2 exemplary immunogenic peptides

Example 4 - Patient-Specific Peptide Vaccine

What structural-functional properties of peptides are required?

- Specific mutations? Specific proteins?
- Peptide length
- Other structural features that lead to binding to cell surface protein unknown
- Other structural features that lead to immune cell interaction with cell surface protein-peptide complex unknown
- Other structural features that lead to activation of immune response unknown
- Differences in requirements for method vs composition claims?

In Closing

For discussion:

- How can these challenges be avoided or addressed?
- What have you experienced in your practices?
- What is the path forward for treatments compositions in this important technology?