Assessing Compliance with the Utility Requirement of 35 U.S.C. § 101 based on the Sequence Homology

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Presentation Outline

Overview

Utility Guidelines

- Three-pronged Test & Definition

Patenting Isolated Nucleic Acid or Encoded Protein

Examples of potential claimed isolated nucleic acid or polypeptide
Historical Trend

Types of Information relevant to claimed isolated nucleic acid or encoded protein

- Sequence Alignment
- Domain Analysis
- Sequence Annotation
- Additional Evidence

Examples

Acknowledgment

Question or Comments

Overview

- **Virtually Every Art Area in Work Groups 1630-1660 has Applications relating to Protein or DNA:**
  - Protein
  - DNA
  - Antibodies
  - DNA/Protein Assays
  - Drug Design and Drug Screening Assays
  - Antibody Assays
  - Therapy (Proteins)
  - Gene Therapy
  - BioInformatics
  - Gene Chips/Arrays
  - Transgenic Animals

Overview (cont.)

- Invention must be useful to be patentable under 35 U.S.C. §101
- *Brenner v. Manson*, 383 U.S. 519 (1966):
- Does the invention have a utility that is
  - specific
  - substantial
  - credible

Utility Guidelines

- Federal Register
- (http://www.access.gpo.gov/su_docs/aces/aces140.html)
- 1242 Official Gazette 162 (January 30, 2001)
- See also MPEP §2107

- Three-pronged Test
  - Specific
  - Substantial
  - Credible

"Specific Utility"

- Must be specific to the subject matter claimed
- How specific??
  - All mice can be snake food
  - All proteins can be amino acid sources

"Substantial Utility"

- is defined as a "real world" use

- Utilities that require carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities

"Credible Utility"

- An assertion is credible unless
  - the logic underlying the assertion is seriously flawed, or
  - the facts upon which the assertion is based are inconsistent with the logic underlying the assertion
- *Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility.*

Patenting Isolated Nucleic Acid or Encoded Protein

- **Examples of claimed isolated nucleic acid or polypeptide**
  - An isolated nucleic acid encoding SEQ ID NO: 1
  - An isolated enzyme comprising the sequence of SEQ ID NO: 1
  - An isolated receptor comprising the sequence of SEQ ID NO: 1
  - An isolated polypeptide that modulates human sweet taste, said polypeptide having the sequence of SEQ ID NO: 20
  - An FGF-like polypeptide as set forth in SEQ ID NO: 1

Examples of Inventions Having Utility

- A therapeutic method of using the claimed nucleic acid or polypeptide in treating a known or newly discovered disease

- An assay having one or specified physical steps, wherein the assay measures the presence of a claimed nucleic acid or polypeptide which has a stated correlation to a predisposition to the onset of a particular disease condition

Examples of Inventions Lacking Utility

- A method of using a claimed polypeptide to treat an unspecified disease

- A method of making a claimed nucleic acid that itself has no specific, substantial and credible utility

Historical Facts

- An application may disclose:
  - Full Open Reading Frame (ORF)
  - Member of a family of protein that is already known based upon amino acid sequence homology, i.e., comparison of entire sequence or determination of a consensus sequence
  - The disclosure more often than not does not provide information pertaining to fully characterized nucleic acid including expression of any encoded protein and full functional analysis of the protein

Historical Facts (cont'd)

- An application may also disclose:
  - Sequence alignment
  - Domain Analysis
  - Sequence Annotation
  - Additional Supporting Evidence

Sequence Alignment

- Points to Consider:
  - The extent of identity between a claimed sequence and a known putative sequence
  - Knowledge of a certain function of the claimed sequence, e.g., information pertaining to known sequences with similar regions and known functions

Domain Analysis

- Points to Consider:
  - Highly conserved domains are indicative of structures with a particular function or different function
  - Knowledge about domain structures with known functions must be elaborated further
- Examples of the knowledge of domain structures:
  - Polypeptides with “death domains” such as TNF receptors are involved in apoptosis (Hoffmann, K., et al., FEBS Letter. 1995, 371, 321-323)
  - The presence of a helix-loop-helix domain in a polypeptide indicates that it is involved in DNA binding, but may not necessarily indicate a particular function, since the roles of such polypeptides are highly diverse (Aravind, L., et al., FEMS Microbiology Reviews 2005, 29, 231-262)

Sequence Annotation

- Sequence annotation is the identification of particular regions in a polypeptide based on known structures that are common to many polypeptides

- Sequence annotation identifies such elements as hydrophobic regions that are indicative of a signal sequence or a membrane-spanning region

- Examples of features that may be identified include:

  – ATP binding sites that may be typical of kinases
  – SH2 regions that may indicate a particular type of signal transduction pathway

Additional Supporting Evidence

- Additional supporting evidence may have information that supports or teaches away from the utility that is asserted based on sequence comparisons
- Examples of types of information include:
  - Chromosomal localization: does the gene map to a region known to be important for the asserted function?
  - Tissue-specific expression: is this information consistent with the asserted function?
  - Biochemical data: was the polypeptide asserted to have a particular activity, for example, isolated from an extract that exhibited that activity?

Example I: Receptors Having Utility

- **Claim**:

  – An isolated polypeptide that modulates human sweet taste, said polypeptide having the sequence of SEQ ID NO: 20

Facts

- **Are sequence alignments provided?**
  - A single sequence alignment to a known protein is provided
  - The claimed protein exhibits 70% identity to rTIR5
  - rTIR5 is known to be a sweet taste receptor
  - Taste receptors as a family exhibit 30-70% identity (Hoon et al., Cell, 1999, 96, 541-551)

Facts

- **Are domains identified?**
  - A domain comparison is provided
  - The domain comparison indicates that the protein has a sucrose-binding domain
  - the domain structure is well characterized and the required sequence of amino acids has been identified (Xu et al., Proc. Nat. Acad. Sci. 2004, 101(39), 14258-14263)

Facts

- **Is sequence annotation provided?**
  - The sequence annotation indicates that the protein is a G-protein coupled receptor (GPCR)
  - Known sweet taste receptors are GPCR(s) (Hoon et al., Cell, 1999, 96, 541-551)

Facts

- **Is any supporting evidence provided?**
  - Chromosomal localization
  - Tissue-specific expression
- The additional evidence of chromosomal localization to a locus known to be involved in sweet taste and the tissue-specific expression in taste buds is consistent with the asserted utility

Conclusion

- The additional evidence of its specific expression in taste buds couples with the above fact finding analysis makes it more likely than not that the polypeptide is a sweet taste receptor

- Thus, the claimed polypeptide is found to have a specific, substantial and credible utility as asserted by Applicant

Example 2: Growth Factors Lacking Utility

- **Claim:**
  - An isolated Fibroblast Growth Factor (FGF)-like polypeptide as set forth in SEQ ID NO: 1

Facts

- **The specification:**
  - SEQ ID NO: 1 is structurally similar to known members of the Fibroblast Growth Factor (FGF) family
  - The highest sequence identity is 32% identity to FGF-5a and 28% identity to FGF-7b

Facts

- **The specification discloses a number of asserted utilities including**:
  - May provide benefits in the stimulation of cells within or near the liver
  - May regulate intestinal cell activity
  - May stimulate the growth on pancreatic beta islet cells
  - May regulate neuronal cells
  - May stimulate or inhibit angiogenesis
  - May regulate hematopoeitic cells
  - May regulate pulmonary cells
  - Maybe used as a therapeutic to treat inflammatory bowel disease, Crohn's disease, etc.

Facts

- **Are sequence alignments provided?**
  - SEQ ID 1 has 32% identity to FGF-5a and 28% identity to FGF-7b
  - FGF-5a and FGF-7b are known FGF proteins; however, they exhibit distinct biological functions
  - FGF-5a has a role in hair growth (Qiao et al., Development 126:547-555, 1999)
  - FGF-7b has a role in kidney development (Hebert et al., Cell 78:1017-12025, 1994)

Facts

- **Are domains identified?**
  - A core domain characteristic of FGFs is identified
  - The domain contains 28 highly conserved residues and six identical amino-acid residues (Ornitz and Itoh, Genome Biology 2(3):3005.1-3005-12, (2001)
  - The FGF super family comprises a very large number of FGFs, many of which contain the core domain but exhibit a broad range of biological activities
  - Accordingly, the presence of a core FGF domain does not indicate *per se* that SEQ ID NO: 1 exhibits a function like hFGF-5 or FGF-7

Facts

- **Is sequence annotation provided?**
  - Annotation indicates a signal sequence
  - However, this is characteristic of a membrane-bound or secreted protein and does not indicate any particular function

Facts

- **Is any supporting evidence provided?**
  - As discussed above, northern hybridization data indicate higher expression of mRNA in adult liver compared to fetal liver

Conclusion

- Presence of the core domain cannot be reliably used to predict the function of the protein
- Sequence comparison results do not provide support for any specific function
- The teachings in the specification are mere suggestions for experimental investigation to determine what activities the FGF-like sequence of SEQ ID NO: 1 might have, and what practical use may be derived from such activities
- Therefore, the sequence information provided does not establish that the polypeptide has a credible, specific and substantial utility

Example III: Enzymes Lacking Utility

- **Claim:**
  - An isolated polypeptide comprising an amino acid sequence which is at least 95% identical to the amino acid sequence of SEQ ID NO:1, wherein the polypeptide cleaves a polypeptide comprising SEQ ID NO:2

Facts

- **The specification discloses:**
  - SEQ ID NO:1 is one of seven proteins isolated from a partially purified proteolytic fraction which cleaves polypeptides comprising SEQ ID NO:2
  - SEQ ID NO:1 is identified as a new member of a family of enzymes possessing a glutaminase homology domain
  - The domain contains four short, conserved sequences that are art-recognized as the defining characteristics of the glutaminase homology domain (Guy, et al., J. Biol. Chem. 1995, 270(5), pp. 2190-2197)

Facts

- **The specification discloses:**
  - Other members of the family include amidohydrolases, L-glutaminases, and glycosylglutaminases
  - To date, no family members have been shown to have endopeptidase activity
  - No data regarding whether the disclosed polypeptide actually has an endopeptidase activity, i.e., cleaving a polypeptide comprising SEQ ID NO:2, are present in the specification

Facts

- **The specification discloses:**
  - The polypeptide is an endopeptidase enzyme from the proteolytic fraction which cleaves SEQ ID NO:2
  - SEQ ID NO:2 is cleaved as an essential step during a herpes virus infection
  - The specification indicates that the polypeptide is useful for in a screening assay for possible herpes virus therapeutics
  - No working examples of a screening assay are disclosed in the specification

Facts

- **Are sequence alignments provided?**
  - No sequence alignment is provided

Facts

- **Are domains identified?**
  - The specification does provide a generic description of the glutaminase homology domain based upon four conserved sequences and indicates the location of the domain in the claimed polypeptide
  - Based upon the PTO's sequence search results, the glutaminase homology domain appears to be present in the claimed polypeptide
  - However, the asserted endopeptidase activity being ascribed to the claimed polypeptide has not previously shown to be possessed by other family members of glutaminase enzymes

Facts

- **Is sequence annotation provided?**
  - No sequence annotation is provided

Facts

- **Is any supporting evidence provided that favors or disfavors the utility that is asserted based on sequence comparisons?**
  - The additional evidence that the polypeptide was isolated from a proteolytic fraction which contains seven proteins
  - One or more of the other isolated proteins, or an unisolated protein from the fraction, might have/possess the proteolytic enzyme
  - This evidence is neutral with regard to specifically assigning the proteolytic function ascribed to the disclosed polypeptide

Conclusion

- The claimed polypeptide appears to possess a glutaminase homology domain
- However, the identification of the claimed polypeptide as a proteolytic enzyme which cleaves a polypeptide comprising SEQ ID NO:2 is not supported by the analysis
- There is no additional evidence that conclusively supports the asserted function of the polypeptide required for the asserted utility
- Therefore, the claimed polypeptide is not found to have a specific, substantial and credible utility asserted by the disclosure

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Thank You

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