Issues in Patenting Proteins

Jon P Weber, SPE 1657

Issues in Patenting Proteins

- Fundamentally patenting proteins is like patenting anything – must meet the criteria under four main laws:
  - **101 – Utility including eligible subject matter**
  - **112, first and second paragraph – enablement, written description including best mode, and clarity**
  - **102 - novelty**
  - **103 – obviousness**

Issues in Patenting Proteins
35 USC 101

- Does the protein meet utility requirements?
  - Is the utility credible? and
  - Is the utility specific? and
  - Is the utility substantial?

  or
  - Is the utility well-established?

Issues in Patenting Proteins 35 USC 101

- Is the utility Credible?
- An asserted utility is credible unless:

  1. the logic underlying the assertion of utility is seriously flawed, or

  2. the facts upon which the assertion is based are inconsistent with the logic underlying the assertion

  - Asserted utilities that conflict with long-established and tested scientific theories would not be credible
  - A credible utility is assessed on the totality of the evidence from the standpoint of the person having ordinary skill in the art

Issues in Patenting Proteins 35 USC 101

- Is the utility specific (as opposed to general)?
- The utility must be specific to the subject matter claimed.
  - Asserted Utility: Protein is used to generate Ab
    - All proteins can generate antibodies – not a specific utility
  - Asserted Utility: Protein is used to detect cancer
    - The protein is over-expressed in cancer cells – specific utility
- If there is a clear association in the relationship of specific protein to its asserted utility, it is expected that the test is met

Issues in Patenting Proteins 35 USC 101

- 1. An isolated polypeptide consisting of SEQ ID NO: 2
  - Fact pattern – The polypeptide has been shown by a yeast two hybrid assay and co-immunoprecipitation of the endogenous proteins to bind to a specific kinase with known utility
  - Specific utility of the polypeptide derives from the utility of the kinase

Issues in Patenting Proteins
35 USC 101

- Is the utility substantial?
- A substantial utility describes a “real world” use
- Utilities that require further research to identify or confirm a “real world” use are not substantial
- A protein with no known function and no known ligand (an orphan) would not have a substantial utility

Issues in Patenting Proteins
35 USC 101

1. An isolated polypeptide consisting of SEQ ID NO: 2.
   - Fact pattern – The polypeptide has been shown by a yeast two hybrid assay and co-immunoprecipitation of the endogenous proteins to bind to a specific kinase with known utility
   - Additional fact – the binding reaction to the kinase can be used to identify overexpression that occurs in certain cancers
   - Substantial utility exists

Issues in Patenting Proteins 35 USC 101

- **Alternatively, is the utility well-established?**

  Often, assertions of well-established utility rely on the sequence of a gene encoding the claimed protein as well as a recognition in the art of activity associated with the sequence, i.e., specific enzyme, growth factor

- **Sites that provide information on structure and function**
  - **BLAST - http://www.ncbi.nlm.nih.gov/blast/Blast.cgi**
  - **PFAM - http://pfam.sanger.ac.uk**
  - **ClustalW2 - http://www.ebi.ac.uk/Tools/clustalw2/index.html**
  - **Prosite - http://ca.expasy.org/prosite/**
  - **SBase - http://hydra.icgeb.trieste.it/sbase/**
  - **Motif Search - http://motif.genome.jp/**

Issues in Patenting Proteins 35 USC 101

- 1. An isolated polypeptide consisting of SEQ ID NO: 4.
  - Fact pattern – BLAST analysis finds motifs for dehydrogenase, kinase and a ligase, but the closest sequence identity to any protein is 30%. Asserted utility as a dehydrogenase.
  - Credible? – No, motif insufficient because it could just as well be a ligase or a kinase by motif analysis. If the top percent identity proteins were all dehydrogenases, then there might be sufficient evidence.
  - Specific? – No, the substrate is not identified, generic dehydrogenase is asserted.
  - Substantial? – No, If the substrate had been identified, then the dehydrogenase would have had a well-established utility.

Issues in Patenting Proteins 35 USC 101

- 1. An isolated polypeptide consisting of SEQ ID NO: 6.
  - Fact pattern – PFAM analysis suggests that protein belongs to family of proteins known to bind to a class of enzymes, but the specific binding partner is not identified. Asserted utility is to modulate these enzymes.
  - Credible? Yes, the family of proteins has a common property of binding to this class of enzymes.
  - Specific? Maybe. If additional evidence suggests that the family proteins that bind to this class of enzymes are modulators, then probably yes.
  - Substantial? Maybe. If the modulation is suggested to treat a laundry list of diseases, then probably not. Correlation not established.

Issues in Patenting Proteins 35 USC 101

- Is the protein a product of nature?
  - Claims must clearly indicate the hand of man to distinguish from the naturally occurring protein.
    - Fusion polypeptide
    - "Recombinant" may be insufficient by itself
    - Non-naturally occurring variants
    - Isolated or purified
- 1. A polypeptide with disharmony activity obtainable from *Psuedobogus bacterii.*
  - Fix by adding isolated or purified, if supported by the specification

Issues in Patenting Proteins 35 USC 112, 1st Paragraph

- 112, first paragraph – Is the disclosure enabling?
  - Are sufficient properties to make and use the protein provided? How many are enough?
    - Activity and active ligand
    - Physical or chemical properties: molecular weight, pI, source, catalytic properties, binding properties
    - Structure – sequence, crystal
    - Product-by-process
      - Isolated a specific way
      - Encoded by a nucleic acid w/ SEQ ID NO:
    - State of the prior art

Issues in Patenting Proteins 35 USC 112, 1st Paragraph

- 112, first paragraph - Is the protein adequately described?
  - May have possession of genus but not subgenus
    - Arises primarily when a protein is claimed by % identity to a SEQ ID NO: and having an identified function.
    - Example – the protein with SEQ ID NO: 2 has a specific identified function, however, the claims are drawn to a % identity of less than 100% and claiming the specific function. The disclosure does not identify which residues can be varied and still retain the claimed activity. Lacks written description. Without a claimed activity, written description is met.

Issues in Patenting Proteins 35 USC 112, 1st Paragraph

- Percent identity of sequences and folding
  - Protein must fold correctly and retain desired activity
  - RUBIK'S CUBE ® analogy – thousands of incorrect, but only one correct solution
  - Change critical residues to folding or reactivity or interaction?
    - Can claimed protein tolerate much sequence change?
    - Belongs to well known family?
    - Identify more than just motifs?
    - Relationship between primary structure and function of proteins is very complex and is an unsolved problem.
    - Hb examples: sickle cell; helix contact – Gly(B6)-(E8)

Issues in Patenting Proteins 35 USC 112, 1st Paragraph

- 1. An isolated polypeptide having 90% sequence identity with SEQ ID NO: 8.
  - Fact pattern – Polypeptide has identified activity. Sequence alignment shows the closest identity to any polypeptide is 35% but to a totally different activity polypeptide. The sequence does not identify a family of related proteins. No additional characterization of critical residues or regions is performed.
  - Written description met because one can contemplate all variations
  - Enablement – how to use, not met, because the effect of the 10% variation cannot be determined from disclosed information

Issues in Patenting Proteins 35 USC 112, 1st Paragraph

- 1. An isolated polypeptide having 90% sequence identity with SEQ ID No: 8.
  - Fact pattern – Protein has demonstrated function and belongs to a family of related proteins, ten of which have been sequenced. Sequence alignment provided insights into highly conserved as well as moderately conserved residues, but the closest family member only has 88% sequence identity. Site directed mutagenesis and alanine scanning have identified several additional critical residues.
  - Written description met because one can contemplate the 10% variation
  - Enablement probably met because sufficient structural information has been provided

Issues in Patenting Proteins 35 USC 112, 2nd Paragraph

- 112, second paragraph – Is it clear?
  - Have terms been defined in the specification?
  - Applicants can be their own lexicographer
  - Exemplification is not a definition
  - Indefinite vs definite articles
    - Indefinite “a” or “an” is open
    - Definite “the” or “said” is closed
    - Frequently an issue with sequences

Issues in Patenting Proteins Prior Art

- Does the protein distinguish over the art, 102 and 103?
  - Classic biochemistry vs Molecular Biology
    - Sequence may only provide new property of old protein; properties are inherent in a product
    - Must provide sufficient distinguishing properties
  - New alleged use of old protein might be inherent
    - Administered the same way to the same population
    - Example: administering insulin to diabetics to control appetite

Issues in Patenting Proteins

THANK YOU

Jon P Weber, SPE 1657

jon.weber@uspto.gov

571-272-0925