Common Patent Myths and Tips for Biomarker Inventions

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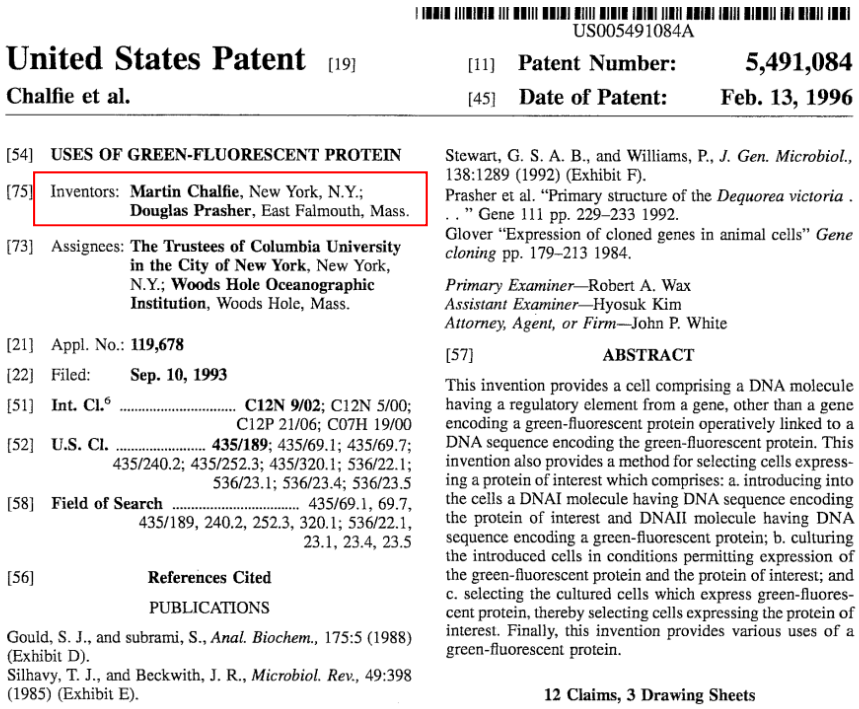
Common Patent Myths (U.S.)

Myth #1 – Authors of manuscript = Inventors



US005491084A

United States Patent [19]

Chalfie et al.

[11] **Patent Number: 5,491,084**

[45] **Date of Patent: Feb. 13, 1996**

[54] **USES OF GREEN-FLUORESCENT PROTEIN**

[75] Inventors: **Martin Chalfie**, New York, N.Y.; **Douglas Prasher**, East Falmouth, Mass.

[73] Assignees: **The Trustees of Columbia University in the City of New York**, New York, N.Y.; **Woods Hole Oceanographic Institution**, Woods Hole, Mass.

[21] Appl. No.: **119,678**

[22] Filed: **Sep. 10, 1993**

[51] **Int. Cl.**[6] **C12N 9/02**; C12N 5/00; C12P 21/06; C07H 19/00

[52] **U.S. Cl.** **435/189**; 435/69.1; 435/69.7; 435/240.2; 435/252.3; 435/320.1; 536/22.1; 536/23.1; 536/23.4; 536/23.5

[58] **Field of Search** 435/69.1, 69.7, 435/189, 240.2, 252.3, 320.1; 536/22.1, 23.1, 23.4, 23.5

[56] **References Cited**

PUBLICATIONS

Gould, S. J., and subrami, S., *Anal. Biochem.*, 175:5 (1988) (Exhibit D).

Silhavy, T. J., and Beckwith, J. R., *Microbiol. Rev.*, 49:398 (1985) (Exhibit E).

Stewart, G. S. A. B., and Williams, P., *J. Gen. Microbiol.*, 138:1289 (1992) (Exhibit F).

Prasher et al. "Primary structure of the *Dequorea victoria* . . . " Gene 111 pp. 229–233 1992.

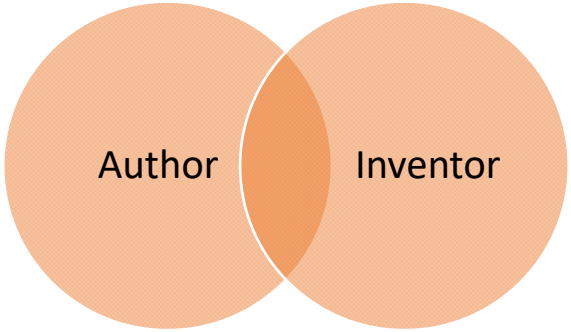
Glover "Expression of cloned genes in animal cells" *Gene cloning* pp. 179–213 1984.

Primary Examiner—Robert A. Wax
Assistant Examiner—Hyosuk Kim
Attorney, Agent, or Firm—John P. White

[57] **ABSTRACT**

This invention provides a cell comprising a DNA molecule having a regulatory element from a gene, other than a gene encoding a green-fluorescent protein operatively linked to a DNA sequence encoding the green-fluorescent protein. This invention also provides a method for selecting cells expressing a protein of interest which comprises: a. introducing into the cells a DNAI molecule having DNA sequence encoding the protein of interest and DNAII molecule having DNA sequence encoding a green-fluorescent protein; b. culturing the introduced cells in conditions permitting expression of the green-fluorescent protein and the protein of interest; and c. selecting the cultured cells which express green-fluorescent protein, thereby selecting cells expressing the protein of interest. Finally, this invention provides various uses of a green-fluorescent protein.

12 Claims, 3 Drawing Sheets



Inventor

1. Conceive a complete and definite idea of the invention

→ **Mental** act of coming up with the invention)

AND

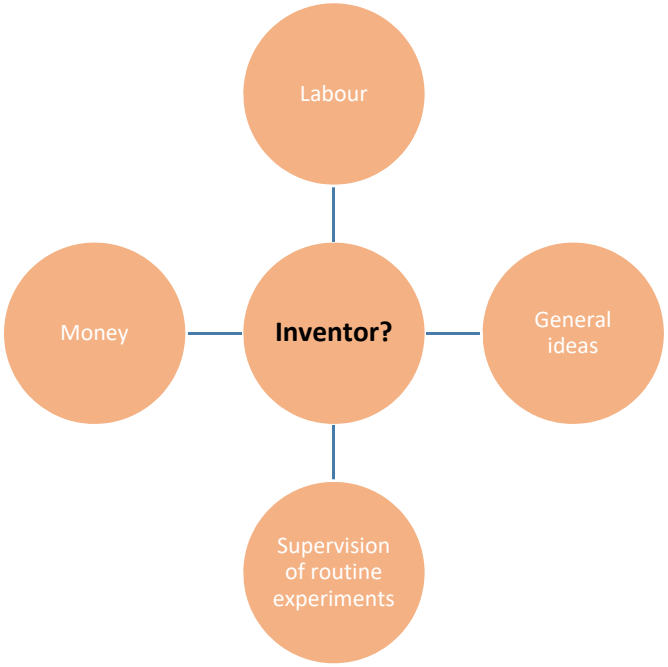
2. Reduce to practice of the conceived idea

→ **Physical** step of bringing the idea to physical fruition)

- Actual – Experiments/Prototypes, or
- Constructive – Filing patent app'l

Inventorship Determination

- Determined by patent attorney/agent based on one's contributions to the **claimed invention**.

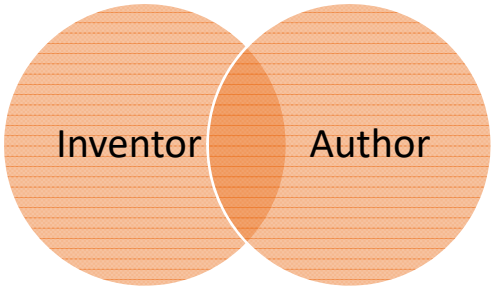


- A pen comprising A, B and C.
  - **X** conceived A, B & C and built the prototype.
  - **Y** contributed the money to build the prototype.
  - **Z** built the prototype with X under X's instruction.

- U.S. – False inventorship with deceptive intent may render a patent **unenforceable**.
- Always identify the right inventors & never omit a ture inventor!

What if I co-write the paper or patent app'l?

- Inventorship ≠ Authorship on scientific publication



- An **author** is a person who makes sufficient contribution to the **original expression** of the work (writing, drawing etc.)
- Authorship may or may not be relevant to "inventing"
  - e.g. write-up introduction/conclusion/findings
  - Title of paper, proofreading?

Myth #2 – I can withhold details of my invention to prevent others from copying

- Quid Pro Quo (Something for Something):
  - Patentee gets the **right to exclude** others for a period of time
  - Public gets **full disclosure** of the inventor's best ideas about how to make and use the invention

- Three distinct disclosure requirements (35 U.S.C. §112)

Written Description

- Describe in full, clear, concise and exact terms
- **Show possession** of full scope of an invention

Enablement

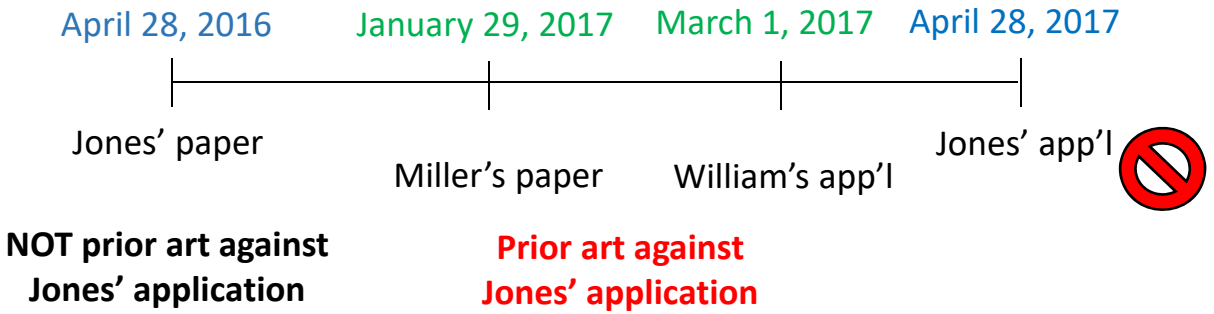
- Enable one skilled in the art to make and use the claimed invention without **undue experimentation**

Best Mode

- **Must** disclosure the best mode of making and using the invention as contemplate
- Do NOT need to point it out

Myth #3 – I am safe because my app'l was filed within the grace period

- Novelty – not publicly disclosed in U.S. or abroad
- Grace period (U.S. – 1 year)
  - Inventors can file a patent application after disclosure made by the inventors, or a third party who obtained the invention from the inventors.

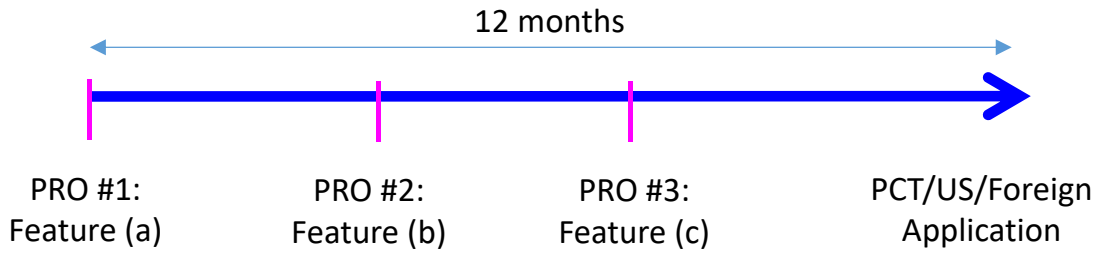


Take away:

- Grace period only saves you from your own disclosure, not others'.
- Don't be too confident about grace period, always file before disclosure!

Myth #4 – Brief description is sufficient for provisional app'l

- Never examined or published
- Need not be perfect but **can't be quick and dirty**
- Fewer formalities (e.g. background, abstract, claims, drawings)
- Must meet the full disclosure requirements to provide a useful priority date



- New data or ideas - file multiple PRO and claim multiple priority
- Secure earliest filing date for each feature, and flexibility in future filing

Myth #5 –
Patents give me an exclusive right to practice my invention

- NO. Patent is NOT a positive right but a right to exclude
- A patented invention ≠ Free of infringement problems

- Freedom to operate (FTO)
  - Whether an activity can be done without infringing IP rights of a third party?
  - Any valid IPs covering the components or activities essential for practicing your invention in a particular country ?

- Patent - iPSC
  - License or challenge?

- Takeaway: Time to time FTO base on actual product/process

專利，就是科技競爭力
廖和信，天下遠見出版社，2003

Biomarkers

Biomarkers

- Biomolecules that are indicators or predictors of medical states of a subject.

  e.g. nucleic acids, genes, antigens, enzymes, hormones, cells etc.

- Four main categories:
  1. Compositions or kits comprising the biomarkers
  2. Methods of producing the biomarkers
  3. Medicinal uses of biomarkers
  4. Diagnostic uses of biomarkers

- Patentability issues
  1. Written description
  2. Enablement
  3. Patentable subject matter

Patentable subject matter – China, Japan & Europe

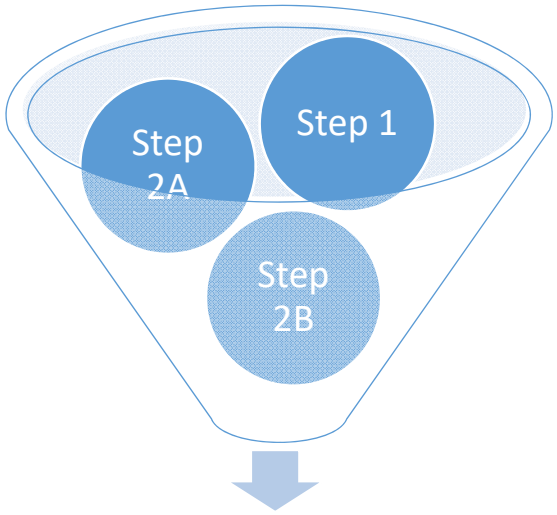
- Treatment claims practiced on ***living*** human bodies are not allowed
  - ✗ *Use of compound X for treating disease Y …*
  - ✓ *Use of compound X for the manufacture of a medicament for treating disease Y* (China/Japan)
  - ✓ *Compound X for use in the treatment of disease Y . . .* (Europe)

- Diagnostic claims are not allowed with limited exceptions
  - ✓ Diagnostic methods that are practiced on **dead bodies**
  - ✓ Europe: Diagnostic methods that are practiced on samples (e.g. tissues or fluids) taken from living bodies, as long as the samples are **not returned** to the same body
  - ✓ Japan: Methods of determining **susceptibility** to a disease by determining and comparing the gene sequence with a standard

Patentable subject matter – U.S.

- U.S. - Excluded subject matters under § 101
  - Law of nature
  - Natural phenomenon
  - Abstract idea
  - Product of nature

- Two-part test (*Alice*):
  - Additional element(s) that make the claim **significantly more than** the exception



Hypothetical Example

- You newly identified a human protein "Protein-S" which was found to be indicative of breast cancer. Data showed that the blood level of Protein-S in all tested breast cancer patients > 300 ng/ml, while the normal subjects had a level < 1 ng/ml.

- You created two **recombinant antibodies** against Protein-S.
  (1) Ab ONE – Having **native** amino acid sequence of the naturally-occurring antibody in human body (SEQ ID NO:1).
  (2) Ab TWO – **Artificial** variant of which the Fc region is replaced by a murine counterpart having a different sequence than the human Fc region (SEQ ID NO: 2).

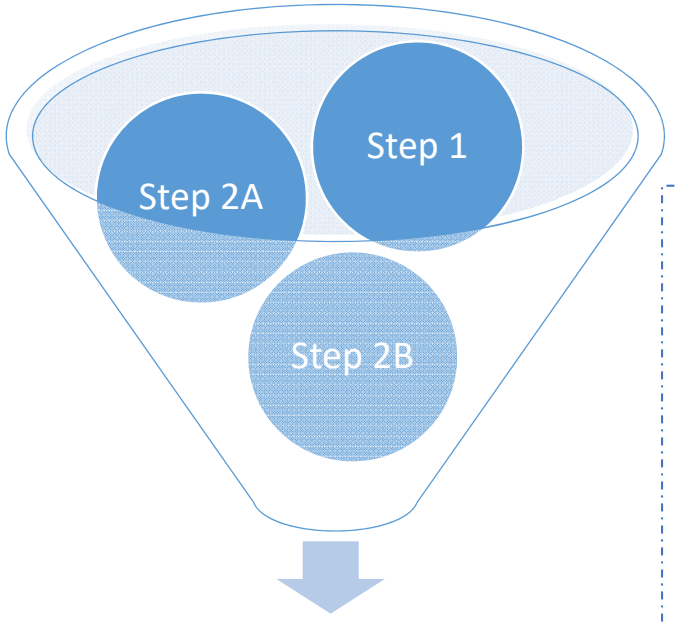
- Claimed inventions:
  (1) Product
  (2) Method of treatment
  (3) Method of diagnosis

https://www.giantmicrobes.com/us/products/antibody.html

A) Natural Product

Claim 1: A purified recombinant antibody binds to Protein-S.
Claim 2: The antibody of claim 1, wherein the antibody has a Fc region comprising an amino acid sequence of **SEQ ID NO: 2**. → Counterpart sequence from mice

Different aa sequence → Structurally different!



Patent eligible

Two-part test (*Alice*):

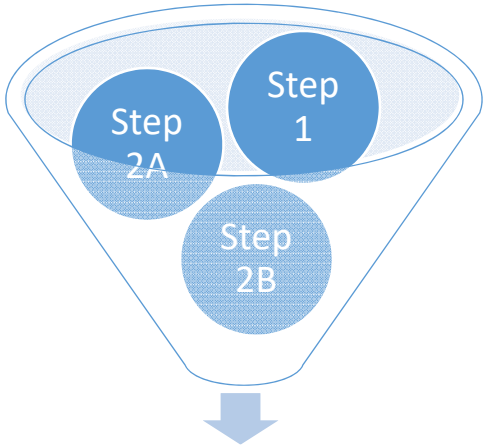
- Step 1: Composition of matter
- Step 2A: Element directed to -
  - Product of nature (natural Ab)
- Step 2B:
  - Any "**markedly different characteristics**"?
  - Change in structure, functions or other properties?
  - Yes → Patent eligible

A) Takeaway - Product claims of natural biomarkers

- Identify new functions or properties of the claimed product
- Explain why such product as a whole has a “marked difference” from the natural biomolecule
  - ✓ Recombinant vs Natural biomarker: subtle structural/functional difference?
  - ✓ Combination of natural products: characteristics that are different as compared to ***each*** of the natural products, and/or ***their combination*** exists in nature.

- Add artificial elements
  - ✓ Artificial version of the natural product (e.g. encapsulated and fluorescent-labelled, sustained-released formulation)
  - ✓ Effective ratio, or amount of the natural products that results in a significantly improvement (e.g. stability of Ab, accuracy of detection)

B) Medicinal Use of Biomarkers



- Step 1: Process
- Step 2A:
  - Whether the use seeks **to tie up the natural biomarker**?
  - No → NOT directed to product of nature
- Step 2B: N/A

1. A method of treating a disease caused by an excessive amount of Protein-S, comprising a step of administering to a subject a purified antibody that binds Protein-S. (X Too general → monopolize use of natural Ab)

2. A method of treating breast cancer, comprising a step of administering to a subject having breast cancer a daily dose of 1 ng of purified antibody that binds Protein-S for a period of 10 days. (√ practical app'l)

B) Takeaway - Medicinal Use of Biomarkers

- Should not be drafted at a high level of generality that appears to unreasonably block all the other potential uses of the natural products.
  - **X** A method of treating a cancer using compound A.

- Meaningful limitations
  - ✓ Dosage of the product (e.g. 5-10 ng/ml)
  - ✓ Time points for administration (e.g. once daily for a week)
  - ✓ Route of administration
  - ✓ Combination with other ingredients

C1) Diagnosis by detection of antigen (Natural phenomenon)

1. A method of detecting Protein-S in a subject, comprising the steps of:
   a) obtaining a test sample from the subject;
   b) contacting the test sample with an anti-Protein-S antibody; and
   c) measuring the binding between Protein-S and the antibody.

Well-understood, routine and conventional activities for detecting Ab
→ **NO inventive concept**

2. The method of claim 1, wherein the antibody is **Antibody-S1**.

√ Non-natural Ab: **Inventive concept**
Not asking a scientist to use *any detection technique* with *any generic* anti-Protein-S antibody

- Step 1: Process
- Step 2A: directed to -
  - Natural phenomena (i.e., natural occurrence of natural products)
- Step 2B:
  - Any other elements that make the claim **"significantly more than"** the exception?
  - **Inventive concept**, e.g. non-conventional steps to perform detection or diagnosis

C2) Diagnosis by comparing data (Natural correlation/Abstract idea)

- Steps of "comparing" and "analyzing": pure mental processes and fall within the scope of abstract ideas
  - X Comparing information from control group and treatment group
  - X Diagnosing an abnormal condition by performing clinical tests and "thinking about" the results
- Step 2A: Abstract idea
- Step 2B: "significantly more" element

1. A method of diagnosing breast cancer in a subject, comprising:
a) obtaining a sample from the subject;
b) contacting the sample with an anti-Protein-S antibody;
c) measuring the binding between Protein-S and the antibody; and
d) determining the level of Protein-S in the sample from the results of step (c),
wherein a level of Protein-S equals to or more than 300 ng/ml indicates that the subject has breast cancer.

Well-understood, routine and conventional activities for determining the level of Ab
→ **No inventive concept**

2. The method of claim 1, further comprising a step of administering an **effective amount of compound X** to the diagnosed subject.

√ More than asking the doctor to diagnose & treat patients *generally*

c) Takeaway - Diagnostic claims

- Diagnostic claims based on biomarkers need to include additional **"significantly more"** steps or elements to be eligible.

- Identify "significantly more" elements:
  1. A **known** step/technology but was **not routinely used** in the same class of invention at the time of filing maybe "non-conventional" (e.g. RNA vs DNA sequencing)

  2. Whether the method as a whole represents an improvement of the technology?

  3. Add artificial or non-conventional criteria/parameters:
     - Biomarker X and Y alone is indicative of a disease, they may have **different weight in the relevancy with the occurrence of the disease**

       → A <u>weighing system</u> that does not exist in nature!!

  4. Link the diagnosis with treatment (e.g. add an extra step of "treating the diagnosed subject with 10 ng of compound X" based on the diagnostic results).

Drafting tips to address 101 issues

1. Law may change. Be sure to include all possible embodiments of products and methods even if they merely "read-on" the natural products or natural correlations.

2. Identify and explain all potential differences between your invention and the natural products.

3. Identify elements that are **not** "well-understood, routine and conventional" for performing your steps. State so in your application with objective evidence.

4. Do not over limit your claims. Explore elements that may be added to limit the judicial exceptions in practical sense. Then draft a series of claims to add limitations one-by-one:

    1. A kit comprising a purified antibody bound to Protein-S.
    2. The kit of claim 1, wherein the antibody is a recombinant protein.
    3. The kit of claim 2, wherein the antibody is expressed in *E.coli*.
    4. The kit of claim 3, wherein the antibody has an amino acid sequence of SEQ ID NO: 2.
    5. The kit of claim 4, further comprises compound X.
    6. The kit of claim 5, wherein the antibody and compound X are provided in a molar ratio of 1:5.

5. Draft claims in different claim formats for each of the subject matter.

    e.g. Typical treatment claims vs Swiss-type claims

    Detection of antigen vs Diagnosis based on the presence of antigen

THANK YOU!