bacteria. Thus, the mixture does not have markedly different characteristics from what occurs in nature, and is a "product of nature" exception. Accordingly, the claim is directed to an exception (*Step 2A: YES*). Because the claim does not include any additional features that could add significantly more to the exception (*Step 2B: NO*), the claim does not qualify as eligible subject matter, and should be rejected under 35 U.S.C. § 101.

The inoculant of claim 1 was held to be ineligible subject matter in *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 131 (1948):

> Discovery of the fact that certain strains of each species of these bacteria can be mixed without harmful effect to the properties of either is a discovery of their qualities of non-inhibition. It is no more than the discovery of some of the handiwork of nature and hence is not patentable. The aggregation of select strains of the several species into one product is an application of that newly-discovered natural principle. But however ingenious the discovery of that natural principle may have been, the application of it is hardly more than an advance in the packaging of the inoculants. Each of the species of root-nodule bacteria contained in the package infects the same group of leguminous plants which it always infected. No species acquires a different use. The combination of species produces no new bacteria, no change in the six species of bacteria, and no enlargement of the range of their utility. Each species has the same effect it always had. The bacteria perform in their natural way. Their use in combination does not improve in any way their natural functioning. They serve the ends nature originally provided and act quite independently of any effort of the patentee.

Recently, the Supreme Court looked back to this claim as an example of ineligible subject matter, stating that "the composition was not patent eligible because the patent holder did not alter the bacteria in any way." *Myriad*, 133 S. Ct. at 2117.

Claim 2: Eligible. In nature, *R. phaseoli* only infects garden beans, and *R. californiana* only infects lupine. When mixed together as claimed, the combination now infects a third species of plant: *R. californiana* infects both lupine and wild indigo, but *R. phaseoli* continues to only infect garden beans. The combination of species thus has changed *R. californiana* such that, when combined with *R. phaseoli*, it has a different characteristic (biological function) than it had in nature, *i.e.*, the claimed combination infects a new group of leguminous plants (wild indigo) as compared to the naturally occurring bacteria by themselves. This functional difference rises to the level of a marked difference, and accordingly the claimed mixture is not a "product of nature" exception. Note that unless the examiner can show that this particular mixture of bacteria exists in nature, this mere possibility does not bar the eligibility of this claim. *See, e.g., Myriad*, 133 S. Ct. at 2119 n.8 ("The possibility that an unusual and rare phenomenon *might* randomly create a molecule similar to one created synthetically through human ingenuity does not render a composition of matter nonpatentable" (emphasis in original)). Thus, the claim is not directed to an exception (*Step 2A: NO*), and qualifies as eligible subject matter.

7. Nucleic Acids

This example illustrates that changes in genetic information/structure (claims 2 and 4), or physical structure (claim 3), as compared to a product's natural counterpart can demonstrate markedly different characteristics.

Background: Virginia nightshade is a naturally occurring plant that grows wild in the Shenandoah Valley of Virginia. When damaged, the leaves of Virginia nightshade produce a hormone called Protein W, which activates chemical defenses against herbivores. Protein W is naturally encoded by Gene W, which is part of chromosome 3 in Virginia nightshade and has the nucleic acid sequence disclosed as SEQ ID NO: 1. The specification also discloses substitution modifications of Gene W, *e.g.*, nucleic acids having one or more nucleotide bases that are substituted with different bases relative to SEQ ID NO: 1. For

example, one of the disclosed modifications changes a naturally occurring adenine to a guanine, *e.g.*, the first nine nucleotides are "TAC GGG AAA" in naturally occurring Gene L and "TAC GGG AAG" in the modified nucleic acid. Some of the modifications are silent, meaning that no change occurs in the encoded protein. It is known in the art that some silent modifications affect characteristics of nucleic acid such as transcription rate and splicing, and that some do not. No substitution modifications of Gene W are known to occur in nature. The modified nucleic acids have 90% or greater identity to SEQ ID NO: 1. The specification discloses labeling the nucleic acids, *e.g.*, with a fluorescent or radioactive label.

The specification discloses vectors comprising SEQ ID NO: 1 and a heterologous nucleic acid. The specification defines "heterologous" nucleic acid sequences as nucleic acid sequences that do not naturally occur in Virginia nightshade, *e.g.*, sequences from other plants, bacteria, viruses, or other organisms. Disclosed heterologous nucleic acids include plant viral vectors such as tobacco mosaic virus, and viral promoters such as the cauliflower mosaic virus (CaMV) 35S promoter. The viral promoters cause different expression of Gene W as compared to its natural expression levels in Virginia nightshade, *e.g.*, Gene W is expressed all the time (constitutively) as opposed to only in response to leaf damage.

Claims:

1. Isolated nucleic acid comprising SEQ ID NO: 1.
2. Isolated nucleic acid comprising a sequence that has at least 90% identity to SEQ ID NO: 1 and contains at least one substitution modification relative to SEQ ID NO: 1.
3. The isolated nucleic acid of claim 1, further comprising a fluorescent label attached to the nucleic acid.
4. A vector comprising the nucleic acid of claim 1 and a heterologous nucleic acid sequence.

Analysis of Claims:

These claims are analyzed for eligibility in accordance with their broadest reasonable interpretation. Because all of the claims are directed to a statutory category, *e.g.* a composition of matter (*Step 1: YES*), and are nature-based products (a nucleic acid), the markedly different characteristics analysis is used to determine if the nature-based products are exceptions.

Claim 1: Ineligible. The claimed nucleic acid has a different structural characteristic than naturally occurring Gene W, because the chemical bonds at each end were severed in order to isolate it from the chromosome on which it occurs in nature, but has the same nucleotide sequence as the natural gene. The claimed nucleic acid has no different functional characteristics, *i.e.*, it encodes the same protein as the natural gene. Under the holding of *Myriad*, this isolated but otherwise unchanged nucleic acid is not eligible because it is not different enough from what exists in nature to avoid improperly tying up the future use and study of naturally occurring Gene W. In other words, the claimed nucleic acid is different, but not markedly different, from its natural counterpart in its natural state (Gene W on chromosome 3), and thus is a "product of nature" exception. Accordingly, the claim is directed to an exception (*Step 2A: YES*). Because the claim does not include any additional features that could add significantly more to the exception (*Step 2B: NO*), the claim does not qualify as eligible subject matter, and should be rejected under 35 U.S.C. § 101.

Claim 2: Eligible. The claim is limited to nucleic acids in which the nucleotide sequence has been changed to contain at least one non-naturally occurring substitution modification relative to SEQ ID NO: 1. All of the claimed nucleic acids have different structural characteristics than the naturally occurring nucleic acid, *e.g.*, one or more nucleotides have been changed relative to the natural sequence. Some of the claimed nucleic acids may have different functional characteristics, *e.g.*, they may encode a different protein than the natural gene. Because the structural differences between the claimed nucleic acids and their natural counterparts are enough to ensure that the claim is not improperly tying up the future use of naturally occurring Gene W, they rise to the level of a marked difference, and so the claimed nucleic acids

are not a "product of nature" exception. Thus, the claim is not directed to an exception (*Step 2A: NO*), and qualifies as eligible subject matter.

Claim 3: Eligible. The claim is limited to a molecule that includes a nucleic acid and a fluorescent label, which combination does not occur in nature as a single molecule. The claimed molecule thus has different structural characteristics than the naturally occurring nucleic acid and label (single molecule vs. two separate molecules). It also has different functional characteristics (the labeled nucleic acid is now fluorescent, whereas the natural gene is not). These differences rise to the level of a marked difference, and so the claimed molecule is not a "product of nature" exception. Thus, the claim is not directed to an exception (*Step 2A: NO*), and qualifies as eligible subject matter.

Claim 4: Eligible. The claim is limited to vectors comprising a non-natural combination of Gene W (SEQ ID NO: 1) with a sequence from another organism, and thus does not read on the naturally occurring chromosome in Virginia nightshade. This non-natural combination results in the vectors having a different genetic structure and sequence than the naturally occurring nucleic acids, *i.e.*, different structural characteristics. Some of the claimed vectors may have different functional characteristics, depending on the selected heterologous sequence. These differences rise to the level of a marked difference, and so the claimed vector is not a "product of nature" exception. Thus, the claim is not directed to an exception (*Step 2A: NO*), and qualifies as eligible subject matter.

8. Antibodies

This example illustrates that products created by human manipulation of natural processes (claims 2 and 3), as well as products that are changed in structure as compared to a product's natural counterpart (claims 4 and 5), can have markedly different characteristics.

Background: Newly discovered *Staphylococcus texana* bacteria have an antigen called Protein S on their outer surface. The specification describes the discovery of naturally occurring antibodies to Protein S in mice and wild coyotes living in Texas. No human antibodies to Protein S are naturally occurring. Antibodies have two types of domains: (1) constant domains such as the Fc domain, which are unvarying in antibodies of a particular class (*e.g.*, IgA) within a species; and (2) variable domains comprising complementarity determining regions (CDRs) that bind to an antigen and that vary from antibody to antibody.

The specification describes multiple types of antibodies to Protein S, including:

- murine antibodies, that were created by injecting laboratory mice with Protein S;
- human antibodies, that were created by injecting transgenic mice with Protein S;
- chimeric antibodies (defined as antibodies that have murine variable domains and human constant domains);
- humanized antibodies (defined as antibodies having murine CDRs but are otherwise human); and
- antibodies with variant Fc domains (defined as antibodies having an Fc domain that is engineered to comprise at least one amino acid modification relative to a wild-type Fc domain).

It is well-known in the art that murine antibodies have different constant domains than human and coyote antibodies, and that murine antibodies may cause allergic reactions and anaphylactic shock when administered to humans or coyotes. The specification discloses a particular murine antibody created by applicants, comprising SEQ ID NOs: 7-12 as its six CDR sequences. There is no naturally occurring antibody that has this particular combination of CDR sequences. It is well-known in the art that chimeric and humanized antibodies are less immunogenic to humans than murine antibodies. It is also well-known that antibodies with variant Fc domains may exhibit different characteristics (*e.g.*, increased cytotoxicity and/or serum half-life) than antibodies with wild-type Fc domains.

Claims:

1. An antibody to Protein S.