



Society for Industrial
Microbiology
and Biotechnology

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United States Patent and Trademark Office

RE: New Guidelines for Determining Subject Matter Eligibility Of Claims Reciting Or Involving Laws of Nature, Natural Phenomena, & Natural Products

The Society for Industrial Microbiology and Biotechnology (SIMB) is the principal organization that represents the interests of scientists and engineers that specialize in the isolation, characterization, and commercial development and production of natural product chemicals (NPs) in the United States. Half of the members of SIMB work in pharmaceutical/biotech/fuels and chemicals companies. The other half is composed of academics (faculty, research scientists, postdocs, students, etc.). On behalf of the membership, the officers of SIMB would like to offer this comment to the USPTO on the draft guidelines issued by the United States Patent and Trademark Office (USPTO) on March 4, 2014 in the “*2014 Procedure for Subject Matter Eligibility Analysis of Claims Reciting or Involving Laws on Nature/Natural Principles, Natural Phenomena and/or Natural Products*”.

Whereas the SIMB does not question or comment on the recent U.S. Supreme Court rulings in either the *Association for Molecular Pathology v. Myriad Genetics, Inc.* (2013) or *Mayo Collaborative Services v. Prometheus Laboratories Inc.* (2012) whether unaltered sequences of the human genetic code should not, in principle, be patentable. However, we would like to raise the point that the USPTO concept of “equivalence” between unaltered genomic DNA (sequence) and unaltered natural products is, in our judgment, simply too broad to accurately apply in most cases.

Natural Products in their Native State

NPs are low molecular weight chemicals whose structures are determined by a set of enzymes that are employed by the host in step-wise biochemical pathways. The sets of enzymes are encoded by corresponding sets of genes in the genomic DNA. From the early 1990s, it has been established that the genes encoding the biosynthesis of NPs are clustered in the genome. Recent major advances in bioinformatics (connecting gene sequences to enzyme functions) have enabled accurate prediction of some biochemical pathways, as well as the chemical structure of the corresponding NP, simply by “reading” the DNA sequence of previously characterized NPs or closely-related analogs. DNA sequencing technology has also advanced to the point where the sequence of the entire genome of a microorganism can be obtained in a matter of days. To date, genomic sequences have been determined for more than 50,000 fungi and bacteria of the phylum *Actinobacteria* (actinomycetes) that are known to produce NPs classified as secondary metabolites (compounds that have bioactivity, e.g. antibiotics, anti-tumor agents, anti-parasitic agents, etc.). Genomic sequencing of strains of these bacteria that had been previously discovered to

produce antibiotics (e.g. erythromycin or vancomycin) revealed the presence of many other clusters encoding NPs. At the Annual Meeting of SIMB last week in St. Louis, the company Warp Drive Bio reported that it had sequenced the genomes of 145,000 *Actinobacteria* species and determined that each genome contains on average 26 NP clusters. Many of the clusters are likely to produce previously undiscovered NPs with novel structures and a broad range of potential biological activity. In essence, bioinformatics approaches give us clues where to look, but do not readily inform us about the exact nature of the different structures that each biosynthetic cluster will produce, or when in the life cycle the NP will be produced, if it is produced at all. And, bioinformatics approaches cannot yet reliably predict the presence or nature of previously undefined clusters.

Bacteria and fungi, many of which produce antibiotics or other NPs, live in "communities" in the soil and other environments, which can be referred to as the "native state". Of the thousands of antibiotics or other NPs identified from soil organisms (only after laboratory cultivation), only a single recent report has indicated the presence of antibiotic activity in the soil, and neither the structure of the compound(s) nor the identity of the organism(s) in the community that produced the compound was determined. We contend that it is not possible to make either determination in the "native state". NPs cannot be amplified by PCR from the native state. While it may be possible to amplify segments of a gene cluster from the native state corresponding to a given NP detected in the soil, current technology is not yet sufficiently advanced to enable the prediction of the structure of the NP from reading DNA sequences amplified from the soil, particularly if the compound was subsequently found to be novel. In such cases, there would be no precedent for the DNA sequences encoding the NP. The basis for enabling one to predict the chemical structure of the NP from reading the DNA sequence comes from the prior knowledge culled from similar DNA sequences determined previously. For novel compounds, this knowledge is completely missing. In reality, therefore, the only way we can know if a given antibiotic is present in the soil is to have that compound in hand so that it can be used for comparative purposes.

In addition, because the microorganisms live in communities, it is also not currently possible to link the NP found in nature to the individual strain that produced it. Amplified DNA from the community of microbes might reveal NP biosynthesis genes, but unless one separates the community into single cell samples, without cultivating them (which is a significant technical challenge), current technology does not permit a determination of which cell in the population produced the NP. Finally, because most fungi and *Actinobacteria* in the soil are normally present as spores, which are metabolically inactive, it is most likely that the NPs detected in the soil would have been produced before the cells entered the sporulation stage, making the connection between the NP and the producing host even more difficult to establish.

Although NPs can be detected in the soil on rare occasions, we contend that these limited events do not warrant the conclusion that all of the more than the 5 million (i.e. >195,000 x 26) NP clusters predicted by DNA sequencing produce their corresponding NPs in the native state. It is well established that NP biosynthesis genes are very

tightly regulated and that, even under laboratory controlled conditions, many of the biosynthetic pathways involved are activated only when the cells are treated with elicitors (chemicals) or mutagens. Furthermore, biosynthesis genes corresponding to antibiotics or other NPs can be deleted from cells without an apparent effect on growth or survivability in the laboratory, raising the question of whether they even need to be produced in the native state. On these bases, therefore, we argue that one cannot *a priori* predict the native state of an NP before it is identified and characterized. One also cannot predict *a priori* the native state of the host with respect to production of the NP. Hence, we assert that, at this point in our understanding, there is not yet enough information to conclude that (1) there is a common native state of all NPs, (2) the native state of a yet to be discovered NP is known or can be predicted, and (3) the native state can only be determined after the NP is isolated and characterized. Until such information becomes available, SIMB contends that the isolation of the organism and the cultivation of the host, often under non-predictable conditions, to ultimately produce a novel NP alone represent sufficient and significant hand-of-man intervention to justify composition of matter claims re a novel NP compound, as well as claims re the use of the host that produces it.

In developing the subject matter eligibility guidelines, the US Patent Office has taken the position that natural products (NPs) are not patent-eligible when the claimed NP “appears to be a natural product that is not markedly different in structure from naturally occurring products”. However, this overly-rigid position is not consistent with Supreme Court precedent, including the *Myriad* case. In contrast to DNA, which predictably encodes a protein sequence as in the *Myriad* case, as we have pointed out, in many instances, particularly identifying, isolating, purifying (and eventually synthesizing) NPs is not routine or trivial. Implementation of a *per se* rule that NPs do not constitute patent-eligible subject matter would be great setback for the industries that investigate NPs to identify improved medicines and other products as well as for the patients and other consumers who would benefit from the advances these industries provide. Without the possibility of patent protection to ensure a limited period of exclusivity, it is unlikely that companies will put forth the necessary level of investment to identify and develop NPs into usable products. It would likely destroy any chance of discovering the new antibiotics necessary to combat the growing spread of multidrug resistance that has given rise to “superbugs” that are now impossible to treat.

In conclusion, we contend that there is no common, single native state for all natural products, and that the native state of an NP yet to be discovered cannot be determined or predicted. Hence, we believe that the new guidance provided to patent examiners on the patentability of new NPs is not warranted by current evidence or understanding and respectfully request that the USPTO reconsider its position on Natural Products.

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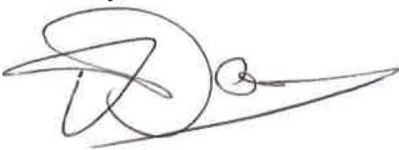
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