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Gut check: microbiome patent update

By Mark James FitzGerald, PhD

Bacteriophage are receiving significant attention as an alternative to antibiotics for clinical and agricultural use, and a rapidly growing number of companies are focusing on bacteriophage-based approaches to control bacterial targets.

From a patent perspective, bacteriophage are subject to many of the same challenges as other microbiome-related IP. Where bacteriophage, like bacterial microbiota, are naturally occurring, a first hurdle to clear for obtaining patent protection is that natural products, in and of themselves, are not patent eligible subject matter in the U.S. under § 101 of the patent statute. This issue can be addressed in the same manner as it is for bacterial microbiota by claiming, for example, formulations containing the bacteriophage or methods of using the bacteriophage.

Another challenge with a close parallel in bacterial microbiome-related IP is how to define and describe the bacteriophage—under § 112 of the patent statute, the patent needs to describe how to make and use the invention in a manner commensurate in scope with what is claimed, and the claims need to describe the invention in definite terms so that competitors can tell whether a given product or method falls within the scope of the claims. If described too narrowly, it may be easy for competitors to identify another bacterium or bacteriophage that performs the same function. If described too broadly, the claims may be found invalid if, for example, they encompass the prior art, or if they encompass species that the description has not adequately described how to obtain. For technology relating to bacteria, these requirements can be met, for example, by reference to 16S sequence identity, encoded enzyme or metabolic pathways, genomic sequence or some combination of these that bear on the desired function of the bacteria. Indeed, one can obtain fairly broad coverage for a class of bacteria that perform a given function by describing the structure, i.e., the enzymes and/or genes encoding the enzymes that provide that function. However, where bacteriophage lack 16S rRNA and take advantage of the bacterial host's metabolic machinery to replicate, there is no close parallel for broadly defining bacteriophage in patent claims. The two most common approaches for defining bacteriophage in patents are (1) reference to a deposit with a recognized international patent depositary authority under the Budapest Treaty, and (2) reference to genomic sequence of the bacteriophage. The following looks at some of the advantages, disadvantages, and details of each, with reference to issued bacteriophage patent claims.

U.S. Patent 10,822,590

- Issued: November 3, 2020
- Titled: Bacteriophage and composition comprising same
- Assignee: CJ Chieljedang Corp. (Seoul, KR)

Claim of Interest:

- 1. A method for preventing an infectious disease caused by avian pathogenic *Escherichia coli*, the method comprising: administering bacteriophage ΦCJ25 deposited as accession number KCCM11463P to birds.

This patent refers to an isolated phage deposited under the Budapest Treaty with the Korean Culture Center for Microorganisms (KCCM) under the noted accession number. Reference to a patent deposit satisfies the enablement and written description requirements under § 112 of the U.S. patent statute. The deposited material becomes publicly available upon issue of the patent, but of course, one cannot use the deposited bacteriophage in the claimed method without infringement liability as long as the patent remains valid and in force.

Reference to a deposit is an effective way to obtain patent coverage around use of the deposited strain of phage. That coverage is likely limited to the specific strain deposited. In this instance, the patent specification notes that the genomic sequence of the isolated bacteriophage strain is 95% identical to that of another strain known in the art (*Enterobacteria* phage EcoDS1), but where the broadest claim refers to "the bacteriophage ΦCJ25 deposited as accession number KCCM11463P," that specific strain is likely to be all that the patent covers. This is not necessarily a bad thing—patent coverage for a specific commercially useful strain, combined with the need, for example, for regulatory approval around a given product, can create a significant hurdle for competitors to isolate and commercially exploit similar, but non-identical strains.

Interesting to note: the claim does not require that the recited bacteriophage strain actually *infects* the avian pathogenic *E. coli*. The specification does describe such infection by the bacteriophage.

U.S. Patent 10,722,544

- Issued July 28, 2020
- Titled: *Streptococcus iniae* bacteriophage Str-INP-1 and use of the same for inhibiting proliferation of *Streptococcus iniae*.
- Assignee: Intron Biotechnology, Inc. (Gyeonggi-Do, KR)

Claim of interest:

- 1. A pharmaceutical composition for inhibiting or treating the infections of *Streptococcus iniae* comprising an effective amount of a *Siphoviridae* bacteriophage Str-INP-1 as an active ingredient, wherein said *Siphoviridae* bacteriophage is isolated from the nature and can kill *Streptococcus iniae* cells specifically, wherein the genome of said *Siphoviridae* bacteriophage comprises the nucleotide sequence of SEQ ID NO: 1, and wherein said pharmaceutical composition is formulated in the form of a bath treatment agent or a feed additive.

This patent is drawn to the use of phage that infect and kill the fish pathogen *Streptococcus iniae*. The patent specification refers to a deposit under the Budapest Treaty, but the claims refer only to genomic sequence and the ability to kill the target bacteria. In this instance, the deposit serves to

satisfy the requirement that the patent describes how to make and use the claimed invention under the enablement and written description provisions of § 112 of the patent statute, but the issued claims are *not expressly limited to the deposited strain*. Rather, the issued claims are expressly limited to bacteriophage comprising the nucleotide sequence of SEQ ID NO: 1, which is the full genomic sequence of the deposited phage. Thus, in this instance, it is somewhat more clear that if a competitor independently isolates a phage that happens to have the same sequence as that recited in the claim, the competitor's formulation of that phage as a bath treatment agent or feed additive will likely infringe this claim.

So does that mean that a competitor who either intentionally changes one nucleotide of a bacteriophage obtained from a deposit, or a competitor who independently isolates a bacteriophage that happens to have a single nucleotide change would not be liable for infringement of such a claim? The answer, unfortunately, is the lawyer's cliché "it depends."

In the U.S., it is possible to infringe a patent for which a competitor's product or process does not literally satisfy all elements of the claims under the so-called doctrine of equivalents. Entire treatises have been written on the ins and outs of the doctrine of equivalents, and the finer details are beyond the scope of this article, but in brief, if a product or process does not literally include an element recited in a claim, but includes an element that performs substantially the same function in substantially the way and achieves substantially the same result—the so-called "function, way, result test"—a court can find infringement under the doctrine of equivalents.

An important limit on the doctrine of equivalents relates to what transpired between the Applicant and the Patent Office during the examination of the patent application. The courts have ruled that one cannot re-capture by equivalents claim scope that was given up in order to obtain the patent. Thus, if an Applicant originally claims their invention broadly, but narrows their claims, for example, to avoid prior art identified by the Examiner, such an amendment can abrogate the scope of equivalents available to that element of the claims. This effect is one type of so-called prosecution history estoppel. Given this factor, then, although Applicants will generally want the broadest coverage possible, it can sometimes be beneficial to focus claims more narrowly from the outset in order to preserve at least the potential of coverage under the doctrine of equivalents. Claims drawn to bacteriophage may be one of those times.

In the '544 patent, the Applicant included the reference to the genomic sequence of SEQ ID NO: 1 in the claims from the outset. There was no narrowing of that element during prosecution, so it is arguable that an independently isolated phage that has only minor variations in sequence could be found to infringe under the doctrine of equivalents, as long as the variation does not match phage sequences known in the prior art.

U.S. Patent 10,898,531

- Issued: January 26, 2021
- Titled: Vibrio parahaemolyticus bacteriophage Vib-PAP-5 and use thereof for suppressing proliferation of Vibrio parahaemolyticus bacteria
- Assignee: Intron Biotechnology, Inc. (Gyeonggi-do, KR)

Claim of interest:

- 1. A method for treating a Vibrio parahaemolyticus infection, the method comprising: administering to an animal other than a human a composition comprising an isolated

Myoviridae bacteriophage Vib-PAP-5 (Accession number: KCTC 13029BP) that can kill Vibrio parahaemolyticus specifically as an active ingredient, wherein the Myovirdae bacteriophage Vib-PAP-5 is prepared by bacterial culture with inoculum of bacteriophage Vib-PAP-5 and comprises a genome encoded by the nucleotide sequence of SEQ ID NO:1, wherein the composition is administered as a feed additive or a medicine bath agent.

This patent refers to the subject bacteriophage by **both** deposit accession number **and** genomic sequence in the broadest claim. The broadest original claims as filed referred to the accession number and the genome of SEQ ID NO: 1. As there were no narrowing amendments made to the way the bacteriophage is defined in the independent claim during the examination process, and where the independent claims do recite the bacteriophage genomic sequence, it is likely that the claims would be found to encompass phage with minor variations in genomic sequence—again, as long as the variation does not match phage known in the prior art.

U.S. Patent 10,898,530

- Issued: January 26, 2021
- Titled: Phage therapy
- Assignee: Pherecydes Pharma (France)

Claim of interest:

- 1. An antibacterial composition comprising at least two bacteriophages having lytic activity against a Pseudomonas aeruginosa (P. aeruginosa) strain and a pharmaceutically acceptable excipient or carrier, said at least two bacteriophages being selected from the bacteriophages having a genome comprising a nucleotide sequence of any one of SEQ ID NOs: 1 to 7 or a sequence having at least 99% identity thereto; and said pharmaceutically acceptable excipient or carrier comprising a preservative in an amount effective to preserve the activity of the bacteriophages.

This composition claim requires at least two different bacteriophage selected from a group of 7 bacteriophages defined by genomic sequence. The claims as issued refer to the subject phage by genomic sequence "or a sequence having at least 99% identity thereto." That is, on its face the claim encompasses combinations of bacteriophage with up to 1% variation from the reference sequences.

Looking at the prosecution file history, it's interesting to note that the applicants originally sought claims reciting "at least 90% identity thereto," but the Patent Office rejected those claims as overbroad. Briefly, the Office argued that the claims encompass a large genus of bacteriophages that can comprise up to 10% difference in sequence relative to the reference sequences, but that the disclosure did not describe which sequences could be changed and still provide the functional activity of, for example, lytic infection of *P. aeruginosa*. The applicants responded by narrowing the claims to recite 97% sequence identity, but the Office maintained the same argument. Only when the applicant narrowed to 99% identity and argued that bacteriophage replication has inherently low fidelity, with natural sequence variation on the order of 1%, and that one of ordinary skill in the art would understand which gene sequences can and cannot tolerate change, did the Office allow the claims.

By starting at 90% genomic sequence identity and narrowing to 99%, the applicants surrendered literal claim scope between 90% and 99%. Further, under the current application of the doctrine of

equivalents, while there are limited circumstances for rebuttal, it is likely that a court would find that there is no range of equivalents available to the 99% identity limitation. Thus, it is likely that the claims would not be found to encompass a competitor's product with phage genomes 98.5% identical to the reference genomes under the doctrine of equivalents. That said, where, as but one example, the phage genome of SEQ ID NO: 1 is about 64,000 bases in size, the claims would reasonably encompass any phage that infects *P. aeruginosa* and varies by about 640 nucleotides or less relative to that reference. Given the 7 genome sequences to choose from, even without relying upon equivalents, there appears to be a reasonable scope of protection provided by the approach taken by this applicant.

It is worth considering that if an applicant can describe the bacteriophage protein sequences that determine host specificity for a particular target bacterial species, specific reference to those sequences in the claims may permit broader protection than claims that refer to the entire phage genome.

Conclusion

Bacteriophage present unique challenges to meeting the patent disclosure requirements in a manner that provides broad protection, but bacteriophage claims are nonetheless issuing at a rapid pace. Regardless of whether applicants rely upon biological deposit, genome sequence, physical characteristics of the phage, some combination of these, or some combination of these with functional characteristics, it is important to consider the impact that filing strategy can have on interpretation and scope of the claims, both literally and under the doctrine of equivalents.

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