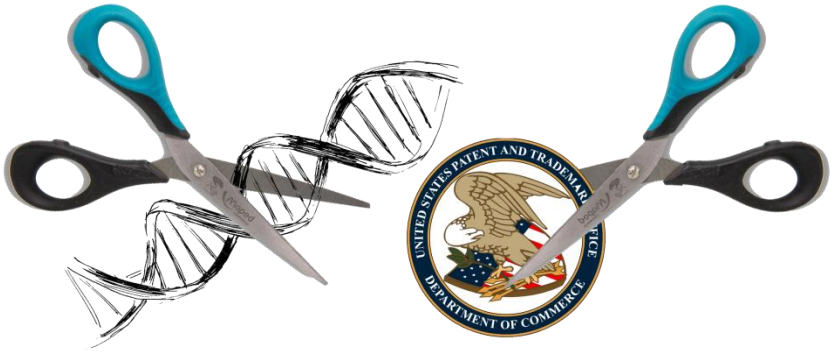
Integrity IP – Jan 2019

Parsing CRISPR Patent Claims

by Joseph Page, Integrity IP



Patent Scope

Among the most important mistakes made by laypersons considering patent claims relates to the *breadth* of protection. Non-experts often mistakenly see matter in a patent *specification* and conclude that is part of the protected concept. This is an error.

A patent ONLY protects that which is set forth in the claims. The claims are found at the very end of a patent. Still further, a very strict reading of that which is set forth as patent claims – constitutes the protection afforded to the inventor. The following presents 'a very strict reading' of a soon-to-be famous patent – the '*CRISPR patent*'[1].

Broad's Broad Claim

A most recent, and very important CRISPR patent claim reads precisely as follows:

> 1. A method of altering expression of at least one gene product comprising introducing into a eukaryotic cell containing and expressing a DNA molecule having a target sequence and encoding the gene product an engineered, non-naturally occurring Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)--CRISPR associated (Cas) (CRISPR-Cas) system comprising one or more vectors comprising: a) a first regulatory element operable in a

[1] Is it worth mentioning that Doudna was clearly first, however by omitting the teaching of CRISPR on eukaryotic cells, Broad Institute may have scooped the more powerful patent. Possibly a very critical error on the part of UC Berkeley patent team.

> eukaryotic cell operably linked to at least one nucleotide sequence encoding a CRISPR-Cas system guide RNA that hybridizes with the target sequence, and b) a second regulatory element operable in a eukaryotic cell operably linked to a nucleotide sequence encoding a Type-II Cas9 protein, wherein components (a) and (b) are located on same or different vectors of the system, whereby the guide RNA targets the target sequence and the Cas9 protein cleaves the DNA molecule, whereby expression of the at least one gene product is altered; and, wherein the Cas9 protein and the guide RNA do not naturally occur together.

This is in fact Broad Institute's Claim 1 of the 8,697,359 patent. We will examine this claim quite literally word-by-word to illustrate how to carefully consider a patent claim.

Method/Device

The claim reads: "*A method…*". This is important. Things that are not 'a method', are not protected by this claim[2]. Thus, a DNA molecule in perfect conformance with the entire description of the patent – is still not protected by this claim. If one is somehow able to bring into existence such CRISPR-Cas9 system without infringing the method, then the molecule system is not an infringement of claim 1. DNA is matter. DNA is not a method. CRISPR-Cas9 is a molecule system. It is also matter. Not method. Claim 1 ONLY protects a *method*. Claim 15 is drawn to a "CRISPR Cas9 system" – so that claim would be read with a view to *matter* rather than *method*.

Only One Claim at a Time

We are only considering Claim 1 for the moment. Claims must be considered strictly isolated without regard to what is found other claims, and further, precisely one at a time. One cannot infringe a combination of two claims. Each claim as it stands alone is either infringed – or not infringed. Precisely.

Word-by-word – *carefully*.

To properly analyze the claim, we proceed word-by-word. The next important words of claim 1 are "*altering expression*". The claimed method is strictly limited to methods for altering expression (of gene products). Using CRISPR-Cas9 for any other purpose at all – is totally fine and does not infringe this claim, so long as the use does not alter expression of gene product or products. One can use CRISPR-Cas9 all day long in any imaginable method whatever, so far as expression of gene products are not altered. If expression of gene products is the same before and after your application of CRISPR-Cas9 – then you have not altered expression and you have

[2] The patent includes 20 claims.

not infringed Claim 1. Thus any use of CRISPR-Cas9 is allowed, so long as such use does not result in an alteration of the expression of gene products.

Single Step Method

Claim 1 of the Broad patent only has a single step.

1) "*…introducing into a eukaryotic cell…*".

If you preform this step, then you have preformed the claimed method. When a CRISPR-Cas9 system is introduced to any cell type that is not '*eukaryotic*' – the method claim is NOT infringed. Any use of CRISPR-Cas9 with non-eukaryotic cells is permitted at least with regard to infringement of this claim. Accordingly, one must introduce (something) into a eukaryotic cell – strictly.

2) "*…containing and expressing a DNA molecule…* "

The method that is claimed in the patent, e.g. the *protected method* is only with regard to eukaryotic cells that are containing and expressing a DNA molecule. Cells that are not containing and expressing a DNA molecule are not included as protected methods.

Of course, this limitation might not be severe against the breadth of coverage. After all, the cells that don't contain and express a DNA molecule may not very interesting with regard to application of CRISPR-Cas9. Correct? Or maybe not. Is it possible to have a eukaryotic cell that is not yet *expressing* a DNA molecule – i.e. at the time of performing the 'introducing' step, but that might later then express a DNA molecule. In other words, the claimed method is strictly limited to eukaryotic cells that are 'expressing', rather than 'can later express'. Therefore, if someone uses a CRISPR-Cas9 on a eukaryotic cell that in not (yet) 'expressing' a DNA molecule – then they DO NOT INFRINGE.

It is unclear to this reviewer whether eukaryotic cells of interest exist that *contain* but do not '*express*' a DNA molecule. But it is not unclear - that if such condition occurs, the patent claim is not infringed. At the time of introduction of the CRISPR-Cas9, the eukaryotic cell must be expressing the DNA with the target sequence. Each word must be strictly taken literally, and the prejudice of any ambiguity is generally applied against the patentee – rather than the alledged infringer. This is due to the fact that the patentee alone was in control of word selection for the claim. Thus shortcomings arising from ambiguity are suffered by the patentee.

Without further scientific discussion on the precise notion of a cell '*expressing*' a DNA molecule, I only point that this claim limitation might offer some relief.

3) " *…DNA molecule having a target sequence and encoding the gene product…* "

The DNA molecule that is contained and expressed by the eukaryotic cell must have a target sequence and is the molecule that encodes the gene product of which expression is being 'altered'. Clearly this is not so limiting. Surely every instance where we might want to introduce some CRISPR-Cas9 into eukaryotic cells, those cells have DNA with a target sequence. We could ask ourselves: "is it always the case that the DNA molecule that has the target sequence is the molecule that does the encoding?". Maybe there is some system whereby the target sequence is part of a DNA molecule that is not the same as the molecule that encodes the gene product. Maybe there exists a system where a CRISPR-Cas9 manipulation at a target causes a 'nearby' or 'related' molecule to do the encoding after the manipulation is done. For example, if one knocks out a SNP or two and that causes encoding of a gene product from another molecule or portion of the molecule. Again, some scientific discussion would have to be done to determine whether that is sensible, but a most careful reading of the claim leaves open the possibility as the claim is specifically directed to the DNA molecule that has the manipulated target sequence AND does the encoding of the gene product.

4) " *…an engineered, non-naturally occurring Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)--CRISPR associated (Cas) (CRISPR-Cas) system…* "

What is 'introduced' to the eukaryotic cell? "An engineered, non-naturally occurring…". That phrase may sound somewhat strange to geneticists, however it is the result of some serious patent litigation from the past. People tried to patent pure genes previously. Even naturally occurring genes that they were first to discover. But correctly, the Patent Office does not allow patents for things that are naturally occurring. So, the future of all gene related patents will likely include this language: 'engineered, non-naturally occurring' to assure avoiding rejections based upon that principle.

Therefore, this claim is strictly limited to methods where *engineered* CRISPR is introduced into a eukaryotic cell. If you introduce a naturally occurring CRISPR-Cas9 system into a eukaryotic cell, you traverse the claim and do not infringe. I am not sure one can find such configuration that is useful, but *natural* CRISPR-Cas9 systems are not included as protected by this claim.

5) "(CRISPR-Cas) system comprising one or more vectors "

This limitation is not very helpful for traversing the claim. That is we must ask: "what is a CRISPR-Cas9 system – that has less than one vector"? To avoid infringing the claim, we could try to deploy a CRISPR-Cas9 system – without any vectors. But I am skeptical that such a configuration is sensible or exists in any real notion. So likely no help here. More detail on the precise nature as to what is a 'vector' is in order if this limitation were to be further resolved.

6) "…*vectors comprising: a) and b)…* "

We do know however that for the purposes of infringing this claim, a vector must have an 'a)' AND a 'b)'. It is not enough that a vector have an 'a)' OR a 'b)'. CRISPR-Cas9 systems that are introduced to eukaryotic cells must include vectors that have both 'a)' and 'b)' –

7) "…*a first regulatory element operable in a eukaryotic cell operably linked to at least one nucleotide sequence encoding a CRISPR-Cas system guide RNA that hybridizes with the target sequence…*"

The a) portion of the vector is 'a first regulatory element…'. This regulatory element is necessarily 'operable' in a eukaryotic cell. Thus, 'inoperable systems' are not considered included. ;)

This regulatory element is further 'operably linked' to a nucleotide sequence. The regulatory element is operably linked to a nucleotide sequence that encodes the guide RNA. The guide RNA that hybridizes with the target. That is, the first regulatory element is linked to a guide RNA. – not much opportunity to form a traverse here.

8) "…*a second regulatory element operable in a eukaryotic cell operably linked to a nucleotide sequence encoding a Type-II Cas9 protein…*"

The b) portion of the vector is the sequence that encodes the Cas9 protein. More specifically, a Type-II Cas9 protein. Thus, this claim does not cover any of the Type-I Cas9 proteins. Type-III Cas9 proteins are similarly not included (if there exists any Type-III, Type-IV, et cetera). Nor does the claim cover any of the Type-II Cas(N) proteins; where 'N' is any number other than 9. This claim is strictly limited to introduction of a Type-II Cas9 protein into an eukaryotic cell.

A bit of ambiguity might lie in the notion of these 'regulatory elements'. The claim says 'a regulatory element is *linked to*' a guide RNA and '*linked to*' sequence that encodes Cas9. This construct may be defective. The 'regulatory element' is therefor something that is *linked to* the

guide RNA and Cas9 encoding sequence. The claim does not state 'a guide RNA and Cas9 encoding sequence' – but rather it calls out some thing that is '*linked to*' these components. What is the physical nature of the 'first and second regulatory elements' that are linked to these well understood parts – I am uncertain. But these must be some real thing. It cannot be merely a guide RNA and a Cas9 encoding sequence. The claimed 'vector' describes that something is linked to those – more details on the 'some thing' would have to be gleaned from the specification. But the construct may be weak or even defective if there is an ambiguity as to the nature of this thing that is '*linked to*' the guide RNA and further to the encoding sequence for the Cas9.

9) "*…are located on same or different vectors of the system…* "

This is very good claims language limitation here: 'a) and b) are located on the same or different vectors of the system'. Can't beat that. This clause really doesn't restrict breadth at all. Therefore, no traverse possible in view of this clause.

10) "*…whereby the guide RNA targets the target sequence and the Cas9 protein cleaves the DNA molecule, whereby expression of the at least one gene product is altered; and, wherein the Cas9 protein and the guide RNA do not naturally occur together…*"

This portion of the claim can sometimes be considered 'surplusage'. "whereby, whereby, wherein," These words indicate that what follows describes some resulting thing – but not definition of additional structure or elements – of the method. Therefor, it necessarily occurs as a result of the previously set forth structure and detail. It can't be traversed. In most cases, this portion of the claim can be ignored.

Well, that is how to slice up a patent claim with a critical view to where the limitations lie and how to consider traversing them. Thankfully, slicing up DNA is now easier due to CRISPR than slicing up patent claims which still don't have a nice tool for assisting us to do that. If you would like me to help cutting up other patent claims – please contact me anytime.