Kluwer Patent Blog

Split poly(A) tail mRNA patents invalid for insufficiency and obviousness

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On 8 October 2024, Mr Justice Meade handed down judgment in BioNTech SE and Pfizer Inc., (together, **BioNTech/Pfizer**) v CureVac SE. Meade J found CureVac's patents, relating to split poly(A) tails in mRNA, invalid for obviousness and insufficiency due to (i) lack of plausibility and (ii) because the purported technical effect does not in fact exist over substantially the whole scope of the claims. BioNTech/Pfizer's added matter attack failed.

BioNTech/Pfizer, the developer and supplier of the Comirnaty COVID-19 mRNA vaccines, issued proceedings seeking to revoke three patents owned by CureVac: (1) EP (UK) 1 865 122 (**EP 122**); (2) EP 3 (UK) 708 668 (**EP 668**); and (3) EP (UK) 4 023 755 (**EP 755**). Infringement was not disputed if the patents were held to be valid. Issues pertaining to the plausibility of EP 122 were hived off for a separate hearing (which is discussed further below), so the trial was limited to the revocation of EP 668 and EP 755. Both EP 668 and EP 755 (collectively, the **Patents**) concern mRNA molecules comprising split poly(A) tails, which was said to improve protein expression, use of said mRNAs as vaccines and intramuscular administration of said mRNAs. The priority date was 12 December 2014.

Technical background

mRNA copies information from DNA in the cell's nucleus and migrates to the cytoplasm where it is translated by cellular machinery (known as ribosomes) to form polypeptides. At the priority date, mRNA was being explored for vaccine applications. The idea was to administer mRNA, that encodes a viral protein, which would be translated by the patient's ribosomes to express the viral protein. This protein would then stimulate an immune response, which would be induced if the patient were exposed to the virus in future.

mRNA is made up of nucleic acid bases: adenine, cytosine, guanine and uracil (and minor variations thereon). mRNAs have a typical structure, which is depicted in Figure 6 of the judgment (copied below). The mRNA structure is important because each section of has a function, e.g. to initiate translation of the polypeptide, to encode the polypeptide gene or to prevent degradation of mRNA by enzymes in the cytosol.

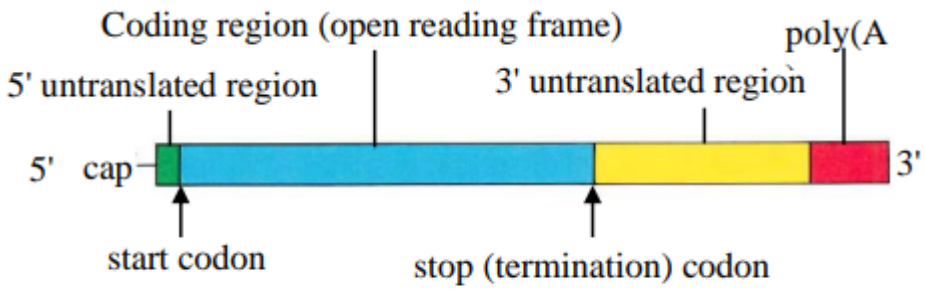

Figure 6: Structure of a typical mature eukaryotic mRNA

"Poly(A) tail" refers to multiple adenine residues at the 3' end of the mRNA. The poly(A) tail was understood to prevent RNA degradation, which increases the half-life of the mRNA and therefore protein expression. However, the precise mRNA degradation pathways were not well understood at the priority date. Generally speaking, the longer a poly(A) tail, the greater the expression from the mRNA construct, although this was known to be subject certain plateauing and masking effects.

The Patents

The Patents claim an mRNA comprising a split poly(A) tail, defined as "*comprising at least two separate poly(A) sequences, wherein a poly(A) sequence is a sequence of 20 to 400 adenine nucleotides, wherein at least one poly(A) sequence comprises at least 70 adenine nucleotides and wherein a first and/or a second poly(A) sequence comprises at least 60 adenine nucleotides…*". The linker, which splits the poly(A) sequences, is defined in the specification as being from 1 to 200 nucleotides in length. Taken together, the claims were to an extremely broad class of mRNA molecules.

Plausibility

Meade J addressed plausibility in three stages: (1) is the technical effect disclosed in the patent; (2) is it plausible across the scope of the claims; and (3) is the technical effect possessed by substantially all mRNAs covered the claims (i.e. sufficiency in fact).

1. Is the technical effect disclosed in the patent?

The patentee is afforded flexibility in framing its technical contribution, but it must disclose such a contribution to the skilled person. In this instance, CurVac alleged that its technical contribution was the introduction of a linker to produce an mRNA with a split poly(A) tail, which improves protein expression, Meade J did not consider that the contribution was disclosed in the Patents. Examining the data in the Patents, Meade J found that the skilled person would consider that plateauing and masking effects account for protein expression levels, rather than a split poly(A) tail.

2. Is the technical effect plausible across the scope of the claims?

In the event that his finding should be found incorrect on appeal, Meade J continued to the second question. CureVac argued that the skilled person would understand that the addition of a linker (splitting the poly(A) tail) would act as a roadblock and disrupt the mRNA degradation pathway based on their CGK. However, Meade J found that whilst potential mRNA degradation models

were known, there was uncertainty about which system was correct. The topic was highly complex and incompletely understood. Further, it was possible that the linker could have a functional effect which alters expression. Accordingly, it was not plausible that insertion of a linker in the poly(A) tail would result in improved expression.

3. Sufficiency in fact

Meade J completed his analysis by considering sufficiency in fact. Did substantially all of the mRNAs within the claims benefit from improved expression? Significant amounts of experimental data were submitted from *in vivo* and *in vitro* litigation experiments and CEA notices. Meade J concluded that the technical effect is not enjoyed across substantially the whole claim; the technical effect was demonstrated in some mRNAs, but often it was not present. Ultimately, the data was not able to support such a broad claim.

Obviousness

Thess is a PCT application which discloses that combinations of a poly(A) sequence and a histone stem loop sequence (another type of mRNA sequence) synergistically improves protein expression. It includes ambiguous language as to the proposed combinations and repetition of the sequences. Meade J agreed with BioNTech/Pfizer that the skilled person would be motivated to test different combinations of the sequences to explore the synergistic effects. As part of this testing, the skilled person would test a poly(A)-histone stem loop-poly(A) sequence, in which the histone stem loop effectively acts as a linker and splits the poly(A) tail, thereby arriving at the claimed invention. Accordingly, the Patents are obvious over Thess.

Added matter

Finally, BioNTech/Pfizer's added matter attack against the introduction of "*wherein a poly(A) sequence is a sequence of 20 and 400 adenine nucleotides*" into the claim failed on the basis that Meade J considered there is an individualised disclosure of the features of the granted claim in the application.

Comment

Readers will be aware that, following the Court of Appeal's decision in the apixaban litigation, the UK is somewhat of an outlier in its standard for plausibility compared to the rest of Europe. Whilst *BioNTech/Pfizer* is indeed another decision invalidating a patent for lack of plausibility, regard should be given to the facts of the case. The CureVac patents claimed a broadly defined platform technology; there was no disclosure in the application that the split poly(A) tail improved expression levels, let alone any reason why it would do so; and the CGK was not robust enough to support the plausibility of such a broad claim. Arguably, this is the type of patent that the Justices of the Supreme Court had in contemplation when laying down the test in *Warner-Lambert v Actavis**[1]*.

There may be some reason for cheer for patentees, however. In considering the application of *Warner-Lambert*, Meade J said "*It must also be possible, I think, that a patent may be adequately plausible if it presents a brand new idea for the first time which, once articulated, the skilled person would understand would work purely from the CGK. I expect that is a lot more likely in the mechanical field than in life sciences and especially second medical uses, which is what the Supreme Court were considering at (7). In any event, such a scenario is miles from the present*

case." Some may view this as movement from the UK courts on the topic of plausibility, marginally rowing back from the position taken in apixaban. More likely, however, is that Meade J is simply restating the law as it stands: a patent will be plausible under the *Warner-Lambert* criteria in circumstances where it teaches the skilled person a new idea which is supported adequately by the CGK.

In any case, it seems that CureVac is not content with the state of the law on plausibility in the UK. Despite arguing that two of its patents were valid under *Warner-Lambert* (EP 668 and EP 755), in the context of its third patent (EP 122, which was not the subject of this trial) CureVac indicated that it intends to argue on appeal to the Supreme Court that the law on plausibility should change. Watch this space…

[1] [2018] UKSC 56

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