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

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, which concerned 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 and is discussed only very briefly below.

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 adjourned 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 were 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 a 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 has a function.

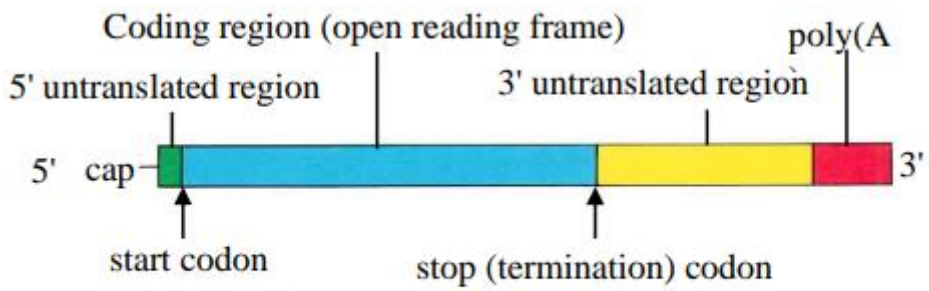

Figure 6: Structure of a typical mature eukaryotic mRNA

The "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 to certain plateauing and masking effects.

The Patents

The Patents claimed 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/Sufficiency

Meade J addressed this by reference to three questions: (1) is the technical effect disclosed in the Patents?; (2) is it plausible across the scope of the claims?; and (3) is the technical effect possessed by substantially all mRNAs covered by the claims (i.e. sufficiency in fact)?

1. Is the technical effect disclosed in the Patents?

It is known that the patentee is afforded some flexibility in framing its technical contribution, but it must disclose such a contribution to the skilled person. In this instance, CureVac 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. However, Meade J did not consider this contribution to be 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 answer to the first question should be found incorrect on appeal, Meade J went on to consider whether the alleged technical effect was plausible across the scope of the claims. CureVac argued that the skilled person would, based on their CGK, understand that the addition of a linker (splitting the poly(A) tail) would act as a roadblock and disrupt the mRNA degradation pathway. 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, he concluded that it was not plausible that insertion of a linker in the poly(A) tail would improve protein expression.

3. Sufficiency in fact

Meade J completed his analysis by considering whether, assuming the technical effect was plausible, it was possessed by substantially all of the mRNAs falling within the claims i.e. whether they benefited from improved protein expression. Significant amounts of experimental data were submitted by way of *in vivo* and *in vitro* litigation experiments and CEA notices. Meade J concluded that the technical effect was 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

The prior art, Thess was a PCT application which disclosed that combinations of a poly(A) sequence and a histone stem loop sequence (another type of mRNA sequence) synergistically improve protein expression. It included ambiguous language as to the proposed combinations and repetition of the sequences. Meade J agreed with BioNTech/Pfizer that in light of Thess. the skilled person would be motivated to test different combinations of the sequences to explore their 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 were held to be obvious over Thess.

Added matter

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